Alcohol consumption and health in Chinese adults: the China Kadoorie Biobank (CKB)



Pek Kei Im

Balliol College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy

Hilary 2020

Acknowledgements

First and foremost, I wish to express my deepest gratitude and appreciation to my supervisors - Dr Iona Millwood, Dr Ling Yang, and Professor Zhengming Chen - for their invaluable guidance and support in my application for the DPhil and over the course of my DPhil.

I would like to thank the participants, staff, and funders of the China Kadoorie Biobank (CKB) for their contribution to the CKB study. I am also grateful to the Nuffield Department of Population Health for funding me to undertake my DPhil. Furthermore, I would like to thank Dr Christiana Kartsonaki for sharing her extensive statistical knowledge. Thanks also to my friends, colleagues, and the Science Shuttle drivers who have made this DPhil journey an enjoyable and inspiring experience that kept me going.

A special thanks goes to Priscilla Lam for her constant encouragement and support, especially in difficult times. Last but not least, I would like to express my deep and sincere gratitude to my parents and my brother for their unwavering love, patience, and support.

Abstract

Alcohol consumption and health in Chinese adults: the China Kadoorie Biobank (CKB)

Pek Kei Im, Balliol College, University of Oxford, DPhil, Hilary Term 2020

Background: Alcohol intake has been associated with poor mental health and increased risks of certain cancers and liver diseases. Evidence is limited from China, where disease rates, drinking patterns, and individuals' tolerability of alcohol differ importantly from Western populations.

Methods: The prospective China Kadoorie Biobank recruited >512,000 adults (41% men) aged 30-79 years from 10 diverse areas during 2004-2008. Detailed information about alcohol consumption, mental health, and other characteristics were recorded by questionnaire, with follow-up through linkage with death and disease registries and electronic hospital records. Logistic regression yielded adjusted odds ratios relating problem drinking patterns to mental health. Cox regression yielded adjusted hazard ratios (HRs) relating usual alcohol consumption to disease risks.

Results: At baseline, 33% of men drank alcohol regularly (i.e., at least weekly). Among male regular drinkers, the prevalence of heavy episodic drinking (>60g/session) increased between baseline and the second resurvey (30% vs. 35%; 8 years apart), particularly among younger men born in the 1970s (41% vs. 47%). 24% of male regular drinkers reported problem drinking at baseline, which was positively associated with stressful life events, poor mental health (e.g., depression, anxiety, sleep problems), and increased risks for all-cause mortality, hospitalisation, and injuries. Alcohol intake showed positive dose-response associations with risks of incident cancers of the oesophagus (655 events; HR=1.98 [95%CI: 1.79-2.18] per 280g/week higher usual alcohol intake), mouth and throat (236; 1.74 [1.48-2.05]), liver (573; 1.52 [1.31-1.76]), colon and rectum (575; 1.19 [1.00-1.43]), gallbladder (107; 1.60 [1.16-2.22]), and lung (1017; 1.25 [1.10-1.42]), with similar associations among never- and ever-regular smokers. The associations for oesophageal cancer and lung cancer appeared greater among men with low alcohol tolerability. There were also dose-response relationships between alcohol intake and incident liver cirrhosis (408; 1.87 [1.65-2.12]), alcoholic liver disease (ALD) (211; 2.02 [1.79-2.28]), and non-alcoholic fatty liver disease (208; 1.78 [1.42-2.22]). The risks were greater for oesophageal cancer and ALD among daily drinkers, and for liver cancer, liver cirrhosis, and ALD among men usually drinking without meals, compared with their counterparts. Very few women (~2%) drank alcohol regularly which limited the capacity to assess associations with health.

Conclusion: Among Chinese men, alcohol consumption was associated with poor mental health, premature death, cancers at multiple sites, and major chronic liver diseases. Certain drinking patterns may further exacerbate the risks.

Declaration and Statement of Contribution

This thesis is my own work except where otherwise stated, and I have acknowledged all sources used and have cited these in the reference section.

The idea to study the relationships between alcohol consumption and health in Chinese adults was conceived by my supervisors (Dr Iona Millwood, Dr Ling Yang, and Professor Zhengming Chen). I was awarded a scholarship from the Nuffield Department of Population Health to undertake my DPhil research project. I led the research presented in this thesis, developed the analysis plans, conducted the literature review, analysed the data, interpreted the results, and wrote all the chapters, under the supervision of my supervisors. I am the first author on each of the four manuscripts that have been written based on the research presented (Chapters 5 to 8) in this thesis (two published, one under review, one in preparation; see Appendix A). Co-authors have read and provided advice on the drafts of the corresponding manuscripts.

Table of Contents

Acknowledgements ..... **i**

Abstract ..... **ii**

Declaration and Statement of Contribution ..... **iii**

List of Figures ..... **x**

List of Tables ..... **xvi**

List of Abbreviations ..... **xxiv**

Chapter 1. Introduction **1**

1.1 Levels and trends of alcohol drinking 1

1.1.1 Prevalence of alcohol drinking 1

1.1.2 Level of alcohol consumption 2

1.1.3 Patterns of alcohol consumption 3

1.1.4 Alcohol tolerability 5

1.1.5 Heavy episodic drinking 6

1.2 Burden of deaths and diseases 7

1.2.1 Leading causes of mortality and morbidity 7

1.2.2 Cancers 8

1.2.3 Liver diseases 16

1.2.4 Mental health 18

1.3 Alcohol-attributable disease burden 19

1.4 Conclusions 21

Chapter 2. Literature review **29**

2.1 Alcohol and cancers 30

2.1.1 Mouth and throat cancer 31

2.1.2 Oesophageal cancer 33

2.1.3 Colorectal cancer 36

2.1.4 Liver cancer 38

2.1.5 Breast cancer 40

2.1.6 Lung cancer 41

2.1.7 Stomach cancer 44

2.1.8 Other cancers 46
2.2 Alcohol and liver diseases 50
2.2.1 Total liver disease 50
2.2.2 Liver cirrhosis and ALD 52
2.2.3 NAFLD 56
2.3 *ALDH2*-rs671, cancers and liver diseases 57
2.4 Other mechanisms 60
2.5 Summary of findings and gaps in existing evidence 61
2.5.1 Alcohol and cancers 61
2.5.2 Alcohol and liver diseases 62
2.5.3 *ALDH2*-rs671, cancers and liver diseases 63
2.5.4 Limitations of existing studies 63
2.5.5 Conclusions 65

Chapter 3. Aim and Objectives 119
3.1 Aim 119
3.2 Objectives 119

Chapter 4. Study design, population and methods 120
4.1 Study design and population 120
4.2 Data collection 121
4.2.1 Baseline survey 121
4.2.2 Assessment of alcohol consumption 122
4.2.3 Assessment of other major lifestyle factors 125
4.2.4 Assessment of medical history, mental health and wellbeing 126
4.2.5 Physical measurements and blood collection 127
4.2.6 Resurveys 129
4.3 Long-term follow-up of health outcomes 130
4.4 Genotyping measurements 131
4.5 Statistical methods 132
4.6 Baseline characteristics of CKB participants 133
4.7 Characteristics of resurvey CKB participants 134
4.8 Conclusions 135

Chapter 5. Prevalence, patterns and trends of alcohol drinking 141
5.1 Introduction 141

5.2 Aims and Objectives 142
5.3 Methods 143
5.3.1 Classifications of alcohol consumption 143
5.3.2 Classifications of major correlates and subgroups 144
5.3.3 Statistical analyses 145
5.4 Results 148
5.4.1 Baseline prevalence and patterns of alcohol consumption 148
5.4.2 Baseline drinking characteristics by consumption level and drinking patterns 150
5.4.3 Trends in alcohol consumption across surveys 151
5.4.4 Patterns and trends of alcohol consumption by population subgroups 152
5.4.5 Factors associated with reducing drinking 156
5.4.6 Regression dilution 157
5.5 Discussion 158
5.5.1 Summary of findings 158
5.5.2 Comparison with previous studies in China and elsewhere 159
5.5.3 Strengths and limitations 163
5.5.4 Research implications 165
5.5.5 Conclusions 167

Chapter 6. Problem drinking, mental health and mortality risk 199

6.1 Introduction 199
6.2 Aims and objectives 200
6.3 Methods 200
6.3.1 Assessment of problem drinking patterns 200
6.3.2 Assessment of stressful life events, wellbeing and mental health 201
6.3.3 Prospective outcome definitions 202
6.3.4 Statistical analyses 203
6.4 Results 205
6.4.1 Prevalence and determinants of problem drinking 205
6.4.2 Drinking characteristics of problem drinkers 206
6.4.3 Cross-sectional associations of stressful life events and problem drinking 207
6.4.4 Cross-sectional associations of problem drinking with wellbeing and mental health 208

6.4.5 Problem drinking and risks of all-cause mortality and hospitalisations. 209
6.4.6 Subgroup analyses 210
6.4.7 Sensitivity analyses..... 211
6.5 Discussion..... 212
6.5.1 Summary of findings 212
6.5.2 Comparison with previous studies 213
6.5.3 Mechanisms 220
6.5.4 Strengths and limitations 220
6.6 Conclusions 221

Chapter 7. Alcohol consumption and risks of cancers 245

7.1 Introduction 245
7.2 Aims and Objectives 246
7.3 Methods 246
7.3.1 Assessment of alcohol consumption 246
7.3.2 Assessment of cancer outcomes 247
7.3.3 Genotyping data..... 247
7.3.4 Statistical analyses 248
7.4 Results..... 251
7.4.1 Incidence rates and correlates of cancers 251
7.4.2 Alcohol drinking status and risks of cancers..... 253
7.4.3 Amount of alcohol consumption and risks of cancers..... 253
7.4.4 Subgroup analyses 255
7.4.5 Drinking patterns and risks of cancers 256
7.4.6 Sensitivity analyses..... 257
7.4.7 Genetic analyses 257
7.4.8 Population attributable fraction..... 260
7.5 Discussion..... 261
7.5.1 Summary of findings 261
7.5.2 Overall cancer 261
7.5.3 IARC alcohol-related cancers..... 262
7.5.4 Lung cancer 265
7.5.5 Other cancers..... 266
7.5.6 Effect modification by other factors..... 268

7.5.7 Drinking patterns 269
7.5.8 Gene-alcohol interactions and potential mechanisms 271
7.5.9 Strengths and Limitations 273
7.6 Conclusions 274

Chapter 8. Alcohol consumption and risks of liver diseases 310
8.1 Introduction 310
8.2 Aims and Objectives 311
8.3 Methods 312
8.3.1 Assessment of HBsAg, alcohol consumption and genotypes 312
8.3.2 Assessment of liver disease outcomes 312
8.3.3 Statistical analyses 313
8.4 Results 315
8.4.1 Incidence rates and correlates of liver diseases 315
8.4.2 Alcohol drinking status and risks of liver diseases 316
8.4.3 Amount of alcohol consumption and risks of liver diseases 317
8.4.4 Subgroup analyses 317
8.4.5 Drinking patterns and risks of liver diseases 318
8.4.6 Sensitivity analyses 319
8.4.7 Genetic analyses 320
8.4.8 Population attributable fraction 321
8.5 Discussion 322
8.5.1 Summary of findings 322
8.5.2 Total liver disease 322
8.5.3 Liver cirrhosis and ALD 324
8.5.4 NAFLD 325
8.5.5 Effect modification by other factors 327
8.5.6 Drinking patterns 328
8.5.7 Causal inference and potential gene-alcohol interactions 330
8.5.8 Potential mechanisms 331
8.5.9 Strengths and limitations 332
8.6 Conclusions 332

Chapter 9. General Discussion 352
9.1 Summary of findings 352

9.2 Findings in the context of existing literature and the thesis 354
9.2.1 Patterns and trends of alcohol consumption 354
9.2.2 Problem drinking, mental health and mortality risk 355
9.2.3 Alcohol consumption and risks of cancers and liver diseases 356
9.2.4 Causal relevance of alcohol and gene-alcohol interactions on risks of cancers and liver diseases 359
9.3 Strengths and limitations 360
9.3.1 Representativeness 361
9.3.2 Reverse causation 362
9.3.3 Measurement errors 363
9.3.4 Residual confounding 364
9.3.5 Statistical power 365
9.4 Future research 366
9.4.1 Further analyses including other risk factors and cancer subtypes 366
9.4.2 Multi-omics biomarkers 367
9.4.3 Mendelian randomisation 368
9.4.4 Burden of alcohol-related diseases in China 369
9.5 Public health and clinical implications 369
9.6 Conclusions 371

References 377

A. List of publications, presentations and awards 404

B. Supplementary methods on literature review 406

C. CKB Baseline questionnaire 411

D. Additional information on CKB cancer endpoint data and resurvey subsets 430

E. Additional results on alcohol drinking patterns and trends 434

F. Additional results on problem drinking, mental health and mortality risk 448

G. Additional results on alcohol consumption and risks of cancers 471

H. Additional results on alcohol and risks of liver diseases 508

List of Figures

Figure 1.1. Time trends of prevalence of current drinking, alcohol per-capita consumption and prevalence of heavy episodic drinking between 1990 and 2030 in WHO regions and China 24

Figure 1.2. Genetic variants affecting alcohol metabolism in East Asians 25

Figure 1.3. Distribution of incident cancer cases for the 10 most common cancers in 2018, by sex 26

Figure 1.4. Age-standardised incidence and mortality rates of cancers in China in 2014, by rural and urban regions 27

Figure 1.5. Distribution of global alcohol-attributable deaths and disability-adjusted life years in 2016, by broad disease category 28

Figure 4.1. Locations of the ten study sites of the China Kadoorie Biobank 140

Figure 5.1. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort 193

Figure 5.2. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by age group* 194

Figure 5.3. Proportions of types of alcohol consumed in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort 195

Figure 5.4. Prevalence of alcohol consumption in men at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas 196

Figure 5.5. Proportions of types of alcohol consumed in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas 197

Figure 5.6. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health-related risk factor index 198

Figure 6.1. Alcohol drinking status and problem drinking categorisation among men in the China Kadoorie Biobank 233

Figure 6.2. Prevalence of current regular drinking and problem drinking among all men 234

Figure 6.3. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by age group in men 235

Figure 6.4. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by ten study areas in men 236

Figure 6.5. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by rural and urban areas in men 237

Figure 6.6. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in male current regular drinkers 238

Figure 6.7. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, in male current regular drinkers 239

Figure 6.8. Prospective associations of problem drinking with events due to interntional self-harm and transport accidents, in male current regular drinkers..... 240

Figure 6.9. Cross-sectional associations of problem drinking with poor wellbeing and mental health, by rural and urban areas in male current regular drinkers 241

Figure 6.10. Cross-sectional associations of problem drinking with poor wellbeing and mental health, by household income level in male current regular drinkers..... 242

Figure 6.11. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, by rural and urban areas in male current regular drinkers..... 243

Figure 6.12. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, by household income level in male current regular drinkers 244

Figure 7.1. Incidence rates (per 100,000 person-years) of site-specific cancers, in men and women..... 286

Figure 7.2. Age-standardised incidence rates (per 100,000 person years) of site-specific cancers, by rural and urban areas..... 287

Figure 7.3. Associations of alcohol consumption with common cancers, in male current regular drinkers 288

Figure 7.4. Associations of alcohol consumption with colon cancer and rectal cancer, in male current regular drinkers 289

Figure 7.5. Associations of alcohol consumption with less common cancers, in male current regular drinkers..... 290

Figure 7.6. Associations of alcohol consumption with other less common cancers, in male current regular drinkers 291

Figure 7.7. Associations of alcohol consumption with IARC alcohol-related cancers and other cancers, by smoking status in male current regular drinkers 292

Figure 7.8. Associations of alcohol consumption with overall cancer, by smoking status in male current regular drinkers 293

Figure 7.9. Adjusted HRs per 280g/week higher usual alcohol intake for IARC alcohol-related cancers, other cancers and overall cancer, by population subgroups in male current regular drinkers..... 294

Figure 7.10. Associations of alcohol consumption with lung cancer, by smoking status in male current regular drinkers 295

Figure 7.11. Adjusted HRs per 280g/week higher usual alcohol intake for site-specific IARC alcohol-related cancers, by population subgroups in male current regular drinkers 296

Figure 7.12. Adjusted HRs per 280g/week higher usual alcohol intake for stomach cancer, lung cancer and pancreatic cancer, by population subgroups in male current regular drinkers 297

Figure 7.13. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by HBsAg seroprevalence in male current regular drinkers 298

Figure 7.14. Adjusted HRs per 280g/week higher usual alcohol intake for oesophageal cancer, by high-risk and other study areas in male current regular drinkers 299

Figure 7.15. Adjusted HRs for site-specific IARC alcohol-related cancers associated with drinking patterns, in male current regular drinkers 300

Figure 7.16. Adjusted HRs for other cancers and overall cancer associated with drinking patterns, in male current regular drinkers 301

Figure 7.17. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by beverage type in male current regular drinkers 302

Figure 7.18. Adjusted HRs for major cancers associated with duration of regular drinking, in male current regular drinkers 303

Figure 7.19. Adjusted HRs per 280g/week usual alcohol intake for major cancers, by flushing status in male current regular drinkers 304

Figure 7.20. Associaton of alcohol consumption with oesophageal cancer and lung cancer, by flushing status in male current regular drinkers 305

Figure 7.21. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by *ALDH2*-rs671 genotype in male current regular drinkers 306

Figure 7.22. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancers by *ALDH2*-rs671 genotype in male current regular drinkers 307

Figure 7.23. Associations of alcohol consumption with mouth and throat cancer, oesophageal cancer and lung cancer, by *ALDH2*-rs671 genotype in male current regular drinkers 308

Figure 7.24. Associations of alcohol consumption with colorectal cancer, liver cancer and stomach cancer, by *ALDH2*-rs671 genotype in male current regular drinkers 309

Figure 8.1. Incidence rates (per 100,000 person-years) of liver diseases, in men and women 341

Figure 8.2. Incidence rates (per 100,000 person-years) of liver diseases, by rural and urban areas 342

Figure 8.3. Associations of alcohol consumption with liver diseases, in male current regular drinkers 343

Figure 8.4. Adjusted HRs per 280g/week higher usual alcohol intake for total liver disease, by population subgroups in male current regular drinkers 344

Figure 8.5. Adjusted HRs per 280g/week higher usual alcohol intake for major chronic liver diseases, by population subgroups in male current regular drinkers 345

Figure 8.6. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by HBsAg seroprevalence in male current regular drinkers 346

Figure 8.7. Adjusted HRs for liver diseases associated with drinking patterns, in male current regular drinkers 347

Figure 8.8. Associations of alcohol consumption with liver diseases, by mealtime drinking habits in male current regular drinkers 348

Figure 8.9. Adjusted HRs for liver diseases associated with duration of drinking, in male current regular drinkers 349

Figure 8.10. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by flushing status in male current regular drinkers 350

Figure 8.11. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by *ALDH2*-rs671 genotype in male current regular drinkers 351

Figure B 1. Flow diagram for the literature review on alcohol consumption and site-specific cancers 409

Figure B 2. Flow diagram for the literature review on alcohol consumption and liver diseases 410

Figure E 1. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health-related risk factor index (hypertension removed) 447

Figure F 1. Cross-sectional associations of problem drinking (excluding negative emotions indicator from the definition of problem drinking) with depression and anxiety, in male current regular drinkers 466

Figure F 2. Cross-sectional associations of problem drinking (with different definitions of low-risk and high-risk drinkers) with poor wellbeing and mental health, in male current regular drinkers 467

Figure F 3. Prospective associations of problem drinking (with different definitions of low-risk and high-risk drinkers) with all-cause mortality, any hospitalisation and events due to all external causes, in male current regular drinkers 468

Figure F 4. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in men 469

Figure F 5. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, in men 470

Figure G 1. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancer, in female current regular drinkers 498

Figure G 2. Associations of the joint effects of alcohol consumption and smoking with IARC alcohol-related cancers, other cancers and overall cancer, in male current regular drinkers 499

Figure G 3. Associations of the joint effects of alcohol consumption and smoking with major cancers, in male current regular drinkers 500

Figure G 4. Associations of the joint effects of alcohol consumption and body mass index with major cancers, in male current regular drinkers 501

Figure G 5. Associations of the joint effects of alcohol consumption and body mass index with IARC alcohol-related cancers, other cancers and overall cancer, in male current regular drinkers 502

Figure G 6. Associations of alcohol consumption with major cancers, by drinking frequency in male current regular drinkers 503

Figure G 7. Associations of alcohol consumption with major cancers, by heavy episodic drinking status in male current regular drinkers 504

Figure G 8. Associations of alcohol consumption with mouth and throat cancer, colorectal cancer and liver cancer, by flushing status in male current regular drinkers 505

Figure G 9. Association of alcohol consumption with stomach cancer, by flushing status in male current regular drinkers 506

Figure G 10. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancer, by flushing status in male current regular drinkers507

Figure H 1. Association of alcohol consumption with total liver disease, in female current regular drinkers 530

Figure H 2. Associations of the joint effects of alcohol consumption and smoking with liver diseases, in male current regular drinkers 531

Figure H 3. Associations of alcohol consumption with alcoholic liver disease, by body mass index in male current regular drinkers 532

Figure H 4. Associations of the joint effects of alcohol consumption and body mass index with liver diseases, in male current regular drinkers 533

Figure H 5. Associations of the joint effects of alcohol consumption and HBsAg seropositivity with liver diseases, in male current regular drinkers 534

Figure H 6. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by high-risk and other study areas in male current regular drinkers 535

Figure H 7. Associations of alcohol consumption with liver diseases, by drinking frequency in male current regular drinkers 536

Figure H 8. Associations of alcohol consumption with liver diseases, by heavy episodic drinking status in male current regular drinkers 537

Figure H 9. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by beverage type in male current regular drinkers 538

Figure H 10. Associations of alcohol consumption with liver diseases, by flushing status in male current regular drinkers 539

Figure H 11. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases by HBsAg seroprevalence (after exclusion of unclear or missing HBsAg test results), in male current regular drinkers 540

Figure H 12. Associations of alcohol consumption with liver diseases, by *ALDH2*-rs671 genotype in male current regular drinkers 541

List of Tables

Table 1.1. Top ten causes of deaths in 2017 22

Table 1.2. Top ten global risk factors for disability-adjusted life years in 2017..... 23

Table 2.1. Meta-analyses on alcohol consumption and risks of cancers of the mouth and throat, and UADT 66

Table 2.2. Prospective studies on alcohol consumption and risks of cancers of the mouth and throat, and UADT 68

Table 2.3. Meta-analyses on alcohol consumption and oesophageal cancer risk 69

Table 2.4. Prospective studies on alcohol consumption and oesophageal cancer risk . 71

Table 2.5. Meta-analyses on alcohol consumption and colorectal cancer risk 74

Table 2.6. Prospective studies on alcohol consumption and colorectal cancer risk..... 76

Table 2.7. Meta-analyses on alcohol consumption and liver cancer risk 80

Table 2.8. Prospective studies on alcohol consumption and liver cancer risk..... 83

Table 2.9. Meta-analyses on alcohol consumption and female breast cancer risk 85

Table 2.10. Prospective studies on alcohol consumption and female breast cancer risk 87

Table 2.11. Meta-analyses and pooled analyes on alcohol consumption and lung cancer risk 89

Table 2.12. Prospective studies on alcohol consumption and lung cancer risk..... 92

Table 2.13. Meta-analyses on alcohol consumption and stomach cancer risk..... 93

Table 2.14. Prospective studies on alcohol consumption and stomach cancer risk..... 97

Table 2.15. Meta-analyses on alcohol consumption and risks of other cancers 100

Table 2.16. Prospective studies on alcohol consumption and risks of other cancers.. 106

Table 2.17. Meta-analyses on alcohol consumption and risks of liver diseases..... 112

Table 2.18. Prospective studies on alcohol consumption and risks of liver diseases .. 114

Table 4.1. Definitions of main alcohol drinking pattern variables..... 137

Table 4.2. Socio-demographic characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014) 138

Table 4.3. Lifestyles and health-related characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)..... 139

Table 5.1. Definitions of changes in drinking status between baseline and the second resurvey..... 168

Table 5.2. Prevalence of alcohol consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014), by sex 169

Table 5.3. Patterns of alcohol consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014) among current regular drinkers, by sex 170

Table 5.4. Baseline drinking characteristics of male current regular drinkers by level of alcohol drinking 171

Table 5.5. Baseline drinking characteristics of male current regular drinkers by frequency of drinking 172

Table 5.6. Baseline drinking characteristics of male current regular drinkers by heavy episodic drinking status 173

Table 5.7. Baseline drinking characteristics of male current regular drinkers by mealtime drinking habits 174

Table 5.8. Baseline drinking characteristics of male current regular drinkers by beverage type 175

Table 5.9. Mean alcohol consumption among male current regular drinkers at baseline (2004-2008) and the two resurveys (2008, 2013-2014), by beverage type 176

Table 5.10. Cross-tabulation of types of beverage reported on a typical drinking day and on the last drinking day among male current regular drinkers at baseline (2004-2008) and the two resurveys (2008, 2013-2014) 177

Table 5.11. Associations of blood pressure with alcohol consumption in a typical drinking week 178

Table 5.12. Associations of blood pressure with alcohol consumption on the last drinking day 179

Table 5.13. Changes in alcohol consumption between baseline and the second resurvey at the individual level among men who were current regular drinkers at both time points 180

Table 5.14. Prevalence and mean levels of alcohol consumption among men at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics 181

Table 5.15. Drinking patterns among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics . 182

Table 5.16. Drinking patterns among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas 183

Table 5.17. Drinking patterns in a typical drinking week among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics 184

Table 5.18. Prevalence of problem drinking among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort and study area 185

Table 5.19. Correlates of alcohol consumption among men at baseline 186

Table 5.20. Prevalence and mean levels of alcohol consumption among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health and lifestyle risk factors 187

Table 5.21. Drinking patterns among male current regular drinkers at baseline (2004-2008) and second resurvey (2013-2014), by health and lifestyle risk factors 188

Table 5.22. Changes in drinking status among men from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and health factors 189

Table 5.23. Reasons for stopping drinking among previous regular drinkers at the second resurvey (2013-2014), by socio-demographic characteristics and health factors 190

Table 5.24. Reasons for stopping drinking among previous regular drinkers at the second resurvey (2013-2014) in men and women, by socio-demographic characteristics and health factors 191

Table 5.25. Estimated regression dilution ratios of alcohol intake among subset of participants involved in all three surveys 192

Table 6.1. Baseline characteristics of male current regular drinkers by problem drinking status 223

Table 6.2. Drinking characteristics of male current regular drinkers by problem drinking status 224

Table 6.3. Drinking characteristics of male current regular drinkers by problem drinking status, in rural and urban areas 225

Table 6.4. Drinking characteristics of male problem drinkers reporting specific problem drinking indicators 226

Table 6.5. Cross-sectional associations of stressful life events with problem drinking, in male current regular drinkers 227

Table 6.6. Cross-sectional associations of problem drinking indicators with poor wellbeing and mental health, in male current regular drinkers 228

Table 6.7. Prospective associations of problem drinking indicators with all-cause mortality, any hospitalisation and events due to external causes, in male current regular drinkers 230

Table 6.8. Cross-sectional associations of stressful life events with problem drinking, by rural and urban areas in male current regular drinkers 231

Table 6.9. Cross-sectional associations of stressful life events with problem drinking, by household income level in male current regular drinkers 232

Table 7.1. Number of incident cancer cases reported in men and women in the CKB 276

Table 7.2. Baseline characteristics of participants by incident cancer outcome, in men and women 277

Table 7.3. Adjusted HRs for incident cancers associated with alcohol drinking status, in men 278

Table 7.4. *ALDH2*-rs671 and *ADH1B*-rs1229984 genotype and allele frequencies across the ten study areas in the CKB 279

Table 7.5. Prevlanece and patterns of alcohol drinking by *ALDH2*-rs671 and by *ADH1B*-rs1229984 genotype, in men and women 280

Table 7.6. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, in men 281

Table 7.7. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, by drinking status in men 282

Table 7.8. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in men 283

Table 7.9. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, by drinking status in men 284

Table 7.10. Population attributable fraction of ever regular drinking on cancers in men in the CKB 285

Table 8.1. Baseline characteristics of participants by incident liver disease outcome, in men and women 334

Table 8.2. Adjusted HRs for incident liver diseases associated with alcohol drinking status, in men 335

Table 8.3. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in men 336

Table 8.4. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in men 337

Table 8.5. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, by drinking status in men 338

Table 8.6. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, by drinking status in men 339

Table 8.7. Population attributable fraction of ever regular drinking on liver diseases in men 340

Table 9.1. Summary of existing evidence and CKB findings on associations of alcohol drinking and health outcomes 373

Table 9.2. Estimated numbers of incident cancer cases at $p<0.05$ for the effects of heavy drinking in male current regular drinkers 375

Table 9.3. Estimated numbers of alcoholic liver disease events at $p<0.05$ for the interaction effects of alcohol intake level and flushing status and BMI in male current regular drinkers 376

Table D 1. Distribution of cancer incidents in the CKB by reporting source 430

Table D 2. Baseline socio-demographic characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014) 431

Table D 3. Baseline lifestyles and health-related characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)..... 432

Table D 4. Baseline drinking patterns of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)..... 433

Table E 1. Baseline drinking characteristics of female current regular drinkers by level of alcohol drinking..... 434

Table E 2. Baseline drinking characteristics of female current regular drinkers by frequency of drinking..... 435

Table E 3. Baseline drinking characteristics of female current regular drinkers by heavy episodic drinking status..... 436

Table E 4. Baseline drinking characteristics of female current regular drinkers by mealtime drinking habits..... 437

Table E 5. Baseline drinking characteristics of female current regular drinkers by beverage type..... 438

Table E 6. Prevalence of alcohol consumption of the subset of participants involved in all three surveys, by sex..... 439

Table E 7. Patterns of alcohol consumption of the subset of participants involved in all three surveys, by sex..... 440

Table E 8. Prevalence and mean levels of alcohol consumption among women at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics..... 441

Table E 9. Changes in drinking status among men from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and baseline health factors (based on baseline information)..... 442

Table E 10. Changes in drinking status among women from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and health factors 443

Table E 11. Estimated regression dilution ratios of alcohol intake among the subset of participants involved in all three surveys, by selected population subgroups..... 444

Table F 1. Details of main analytic models..... 448

Table F 2. Adjusted odds ratios (ORs) for poor wellbeing and mental health associated with per increase in the number of problem drinking indicators, in male problem drinkers..... 449

Table F 3. Cross-sectional associations of problem drinking with sleep problems, in male current regular drinkers..... 450

Table F 4. Adjusted hazard ratios (HRs) for prospective outcomes associated with per increase in the number of problem drinking indicators, in male problem drinkers.... 451

Table F 5. Cross-sectional associations of stressful life events with problem drinking, in male current regular drinkers - in sequentially adjusted models..... 452

Table F 6. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in male current regular drinkers - in sequentially adjusted models.... 454

Table F 7. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to external causes, in male current regular drinkers - in sequentially adjusted models 456

Table F 8. Baseline characteristics of men by alcohol drinking and problem drinking status 458

Table F 9. Prevalence of current regular drinking and problem drinking in women ... 459

Table F 10. Baseline characteristics of female current regular drinkers by problem drinking status 460

Table F 11. Cross-sectional associations of stressful life events with problem drinking, in female current regular drinkers 461

Table F 12. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in female current regular drinkers 462

Table F 13. Prospective associations of problem drinking indicators with all-cause mortality, any hospitalisation and events due to external causes, in female current regular drinkers 463

Table F 14. Comparison of problem drinking and AUD definitions in the CKB and commonly used screening tests and diagnostic criteria 464

Table G 1. Age-standardised incidence rates (per 100,000 person-years) of major cancers, by ten study areas in men 471

Table G 2. Age-standardised incidence rates (per 100,000 person-years) of major cancers, by ten study areas in women 472

Table G 3. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol drinking categories in men 473

Table G 4. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol drinking categories in women 474

Table G 5. Adjusted HRs for cancer mortality associated with alcohol drinking status, in men 475

Table G 6. Adjusted HRs for incident cancers associated with alcohol drinking status, in women 476

Table G 7. Adjusted HRs for incident cancers associated with ever regular drinking status, in women 478

Table G 8. Adjusted HRs for incident cancers associated with drinking status and amount, in men 479

Table G 9. Adjusted HRs for cancer mortality associated with amount of alcohol consumption, in male current regular drinkers 481

Table G 10. Adjusted HRs for cancer mortality associated with drinking status and amount, in men 482

Table G 11. Adjusted HRs per 280g/week higher usual alcohol intake for incident cancers, in male current regular drinkers – in sequentially adjusted models 484

Table G 12. Adjusted HRs for incident cancers associated with amount of alcohol consumption, in female current regular drinkers 485

Table G 13. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol consumption and smoking status in male current regular drinkers 486

Table G 14. Adjusted HRs for major cancers associated with daily drinking, by weekly alcohol intake level in male current regular drinkers 487

Table G 15. Adjusted HRs for major cancers associated with heavy episodic drinking, by weekly alcohol intake level in male current regular drinkers 488

Table G 16. Adjusted HRs for IARC alcohol-related cancers, other cancers and overall cancer associated with alcohol drinking status after various exclusions of participants, in men 489

Table G 17. Adjusted HRs for IARC alcohol-related cancers, other cancers and overall cancer associated with amount of alcohol consumption after various exclusions of participants, in male current regular drinkers 490

Table G 18. Adjusted HRs for major cancers associated with *ALDH2-rs671* genotype, in men – in sequentially adjusted models 491

Table G 19. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, by drinking status in men – in sequentially adjusted models 492

Table G 20. Adjusted HRs for major cancers associated with the joint effects of *ALDH2*-rs671 genotype and alcohol consumption, in male current regular drinkers 494

Table G 21. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in men – in sequentially adjusted models 495

Table G 22. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, in women – in sequentially adjusted models 496

Table G 23. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in women – in sequentially adjusted models 497

Table H 1. Proportions of participants who developed incident liver diseases during follow-up, by baseline HBsAg test results 508

Table H 2. Baseline prevalence of HBsAg seropositivity in the CKB 509

Table H 3. Age-standardised incidence rates (per 100,000 person-years) of liver diseases, by ten study areas in men and women 510

Table H 4. Crude and standardised incidence rates (per 100,000 person-years) of liver diseases, by alcohol drinking categories 511

Table H 5. Adjusted HRs for liver disease mortality associated with drinking status, in men 512

Table H 6. Adjusted HRs for incident liver diseases associated with drinking status, in women 513

Table H 7. Adjusted HRs for incident liver diseases associated with regular drinking status, in women 514

Table H 8. Adjusted HRs for liver disease mortality associated with amount of alcohol consumption, in male current regular drinkers 515

Table H 9. Adjusted HRs for incident liver diseases associated with amount of alcohol consumption, in female current regular drinkers 516

Table H 10. Adjusted HRs for liver diseases associated with daily drinking, by weekly alcohol intake level in male current regular drinkers..... 517

Table H 11. Adjusted HRs for liver diseases associated with heavy episodic drinking, by weekly alcohol intake level in male current regular drinkers..... 518

Table H 12. Adjusted HRs for liver diseases associated with drinking status (after exclusion of unclear or missing HBsAg test results), in men 519

Table H 13. Adjusted HRs for liver diseases associated with amount of alcohol consumption (after exclusion of unclear or missing HBsAg test results), in male current regular drinkers 520

Table H 14. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, in male current regular drinkers – in sequentially adjusted models 521

Table H 15. Adjusted HRs for liver diseases associated with drinking status and amount, in men..... 522

Table H 16. Adjusted HRs for liver diseases associated with alcohol drinking status after various exclusions of participants, in men 523

Table H 17. Adjusted HRs for liver disease associated with amount of alcohol consumption after various exclusions of participants, in male current regular drinkers 524

Table H 18. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in men – in sequentially adjusted models 525

Table H 19. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in men – in sequentially adjusted models..... 526

Table H 20. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in women – in sequentially adjusted models..... 527

Table H 21. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in women – in sequentially adjusted models..... 528

Table H 22. Adjusted HRs for alcoholic liver disease per 280g/week higher alcohol intake by flushing status and body mass index in male current regular drinkers, with application of overall and group-specific regression dilution ratios 529

List of Abbreviations

ADH	Alcohol dehydrogenase
ALD	Alcoholic liver disease
ALDH	Aldehyde dehydrogenase
AUD	Alcohol use disorder
AUDIT	Alcohol Use Disorder Identification Test
BMI	Body mass index
CDC	Centre for Disease Control and Prevention
CHNS	China Health and Nutrition Survey
CI	Confidence interval
CIDI-SF	Composite International Diagnostic Interview - Short Form
CKB	China Kadoorie Biobank
COex	Exhaled carbon monoxide
COPD	Chronic obstructive pulmonary disease
CYP2E1	Cytochrome P450 2E1
CPSS	Chinese Prospective Smoking Study
DALY	Disability-adjusted life year
DCHS	Diet, Cancer and Health Study
EAC	Oesophageal adenocarcinoma
EPIC	European Prospective Investigation into Cancer and Nutrition
ESCC	Oesophageal squamous cell carcinoma
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAD	General anxiety disorder
GBD	Global Burden of Disease
H. pylori	*Helicobacter pylori*
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HED	Heavy episodic drinking
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, 10th Revision
KVHS	Korean Veterans Health Study
MDE	Major depressive episode
MET	Metabolic equivalent tasks
MR	Mendelian Randomisation
MWS	Million Women Study
NAFLD	Non-alcoholic fatty liver disease
NCD	Non-communicable disease
NHIC	National Health Insurance Corporation
OR	Odds ratio
PAF	Population attributable fraction
RDR	Regression dilution ratio
RR	Risk ratio
SCS	Shanghai Cohort Study
SD	Standard deviation
SDI	Socio-demographic Index
SE	Standard error
SLR	Systematic Literature Review
SNP	Single nucleotide polymorphism
UADT	Upper-aerodigestive tract
UK	United Kingdom
US	United States
WCRF	World Cancer Research Fund
WHO	World Health Organisation

Chapter 1. Introduction

Alcohol, which is widely consumed worldwide, is a leading risk factor for global deaths and disability. The cultures and patterns of alcohol drinking including the purpose (e.g., rituals, interpersonal relations, intoxication), beverage types, integration of drinking with meals, regularity of drinking, and alcohol-related harms vary within and across countries. Both alcohol production and consumption have been increasing in China, which is undergoing rapid social and economic development. This chapter aims to set out the importance of assessing the major health risks associated with alcohol drinking in China by providing an overview, globally and in China, on the recent trends of alcohol consumption and the leading causes of deaths and disability, with a description of the major disease burden attributable to alcohol drinking.

1.1 Levels and trends of alcohol drinking

1.1.1 Prevalence of alcohol drinking

According to the Global Status Report on Alcohol and Health by the World Health Organisation (WHO), 2.3 billion (43%) people aged 15 years and above consumed alcohol at least once in the previous 12 months in 2016, which was more common in men than in women (54% vs. 32%).[1] The prevalence of past-year alcohol drinking varied enormously across regions, ranging from 3% in the Eastern Mediterranean Region to 54-60% in Europe, the Americas, and the Western Pacific.[1] In China, an estimated 69% of men and 43% of women drank alcohol at least once in the past 12 months in 2016, which was less prevalent than in high-income countries (78% in men,

57% in women).[1] Over the past three decades, the prevalence of alcohol drinking in the Western Pacific has risen steadily and is forecasted to further increase, mainly driven by the upward trend in China, in contrast to the relatively stable or declining trends observed in other regions (Figure 1.1A).[1,2]

Within China, alcohol use varies substantially across population subgroups, with a particularly striking gender difference in the prevalence of regular alcohol drinking (i.e., drinking at least once a week). According to the China National Nutrition and Health Survey in 2002, the prevalence of regular drinking was 39.6% in men and only 4.5% in women.[3] Moreover, there is also large geographical variation in alcohol use, which is particularly evident when it is observed at a regional level. The China Chronic Disease and Risk Factor Surveillance, an ongoing nationally representative survey, showed little difference in the past-year drinking prevalence at a rural-urban level in 2007 (36.4% vs. 34.6% for men and women combined, rural vs. urban).[4] Another nationwide study in 2008 also reported broadly similar prevalence of drinking alcohol at least 3 times a week across rural and urban areas (9.3% vs. 6.8%); however, at a more refined regional level, the percentages ranged from 2.2% in the north-west to 12.7% in the east.[5]

1.1.2 Level of alcohol consumption

The level of alcohol consumption varies markedly worldwide, with the highest per-capita consumption traditionally observed in European and American countries and the lowest in Asian countries.[2] However, over the past few decades, there has been a rapid increase in per-capita alcohol consumption in South-East Asia and the Western

Pacific, particularly in India and China, despite the declines in Europe and the stable trends in other regions (Figure 1.1B).[1,2] In China, although the total per-capita alcohol consumption in 2016 was lower than in many high-income countries (11.7L vs. 18.4L in men, 2.5L vs. 4.8L in women; China vs. the United Kingdom [UK]), the consumption level among drinkers (17.0L in men, 6.0L in women) was comparable to that in high-income countries (19.6L in men, 6.9L in women).[1]

As with drinking prevalence, the amount of alcohol consumption varies enormously by sex and geographical area within China. According to Chronic Disease and Risk Factor Surveillance in 2007, male drinkers consumed on average 47.8g of alcohol per drinking day compared with 19.1g among female drinkers.[4] Various previous nationwide surveys in China have also consistently reported a higher mean consumption in rural than in urban regions (50.4 vs. 43.1g per drinking day in men),[4,6] as well as 2-3 fold variations across different urban and rural areas.[6]

1.1.3 Patterns of alcohol consumption

In addition to prevalence and amount, the patterns of alcohol consumption (e.g., beverage types, mealtime drinking habits, age started drinking) also vary greatly both between different countries and between different regions within countries, especially in China.

For beverage types, spirits are the most consumed alcohol type globally and in Asia, while beer is the most consumed beverage type in the Americas and Europe, with wine consumption being particularly common in Europe.[1] In China, alcohol is mainly consumed in the form of spirits, including “strong” distilled liquor (over 50% v/v

ethanol) and "weak" liquor (30-40% ethanol).[1,7] Beer, rice wine, unrecorded medicinal and home-brewed alcohol and, to a much lesser extent, grape wine are also consumed in China.[1,7] Within China, the types of alcohol consumed vary hugely across geographical regions, partly depending on the local alcoholic beverage production, and across age groups. In particular, beer drinking is more common in younger drinkers in China, with an increasing beer drinking prevalence and beer production reported over the past two decades.[3,8-10]

Unlike in most Western countries, in China alcohol is commonly consumed during meal times and social activities, such as festivals and celebrations.[7] Particularly among men, alcohol is often considered as an important means to maintain good relations and to engage in business activities.[7] These cultural differences between different populations towards alcohol drinking (e.g., whether alcohol is consumed together with meals, or whether one is under pressure to drink to excess regardless of one's alcohol tolerability; more in following sections) may have impacts on health consequences.

Early onset age of first drinking has been associated with higher risks of heavy alcohol use and developing alcohol-related disorders in Western populations.[11-13] The adolescent drinking prevalence in China was shown to be lower than that in Western societies (past-month drinking prevalence: 15-45% in China in 2004-2013 vs. 57-65% in the UK and European countries in 2011).[14,15] Recently, a decline in adolescent drinking prevalence has been observed in the UK.[16] In contrast, an increasing trend in adolescent drinking in China, which may partly be due to the influx of Western culture, has been suggested.[17,18]

1.1.4 Alcohol tolerability

The major alcohol metabolism pathway involves the breakdown of alcohol to acetaldehyde by alcohol dehydrogenase (ADH), mainly ADH1, and then the conversion of acetaldehyde to acetate by aldehyde dehydrogenase (ALDH), mainly ALDH2 (Figure 1.2). Acetaldehyde, a major toxic metabolite and a Group 1 carcinogen, is formed primarily in the liver where 90% of ingested alcohol is oxidised and also in other tissues, e.g., gastrointestinal tract.[19,20] When the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, the surplus acetaldehyde accumulates and causes discomfort at sufficient concentrations.[19-21] Therefore, fast conversion of alcohol to acetaldehyde or/and, particularly, slow clearance of acetaldehyde can limit one's alcohol tolerability and hence alcohol consumption level.

There are genetic variants that importantly affect acetaldehyde formation and breakdown. In China and other East Asian countries, a substantial proportion of the population cannot metabolise alcohol effectively due to a common loss-of-function variant of the *ALDH2* gene (rs671).[22] Approximately 30-50% of East Asian populations carry at least one copy of the *ALDH2* loss-of-function variant which is rare in other populations (e.g., 0% in Caucasians).[22,23] In China, approximately 5% of the population are homozygous and 33% are heterozygous for the *ALDH2* loss-of-function variant.[24] The *ALDH2* loss-of-function variant encodes an inactive subunit of ALDH2 that results in reduced ALDH2 enzyme activity. This leads to the accumulation of acetaldehyde after drinking a small amount of alcohol, causing unpleasant physiological response (including facial flushing and nausea) known as the "Asian flushing response".[25] A genetic variant of the *ADH1B* gene (rs1229984), which encodes a more active form of

enzyme ADH that accelerates the conversion of alcohol into acetaldehyde, is also highly prevalent in East Asian populations (~90% carrying at least one copy) but is uncommon in populations of European and African descent.[22,26] Both genetic variants, *ALDH2*-rs671 and *ADH1B*-rs1229984, involve a G → A mutation, with the A allele associated with lower alcohol intake.

With a stronger influence on alcohol consumption and acetaldehyde levels than *ADH1B*-rs1229984,[24] the *ALDH2*-rs671 genetic variant is particularly relevant for studying alcohol-related health effects in East Asian populations. The enzyme activity in *ALDH2*-rs671 AA homozygotes and *ALDH2*-rs671 AG heterozygotes is nearly 0% and 17-38%, respectively, of the normal ALDH2 activity seen in *ALDH2*-rs671 GG homozygotes.[27] On one hand, the severe unpleasant flushing response may prevent *ALDH2*-rs671 A allele carriers, particularly *ALDH2*-rs671 AA homozygotes, from habitual alcohol drinking and heavy drinking. Paradoxically, the increased levels of acetaldehyde after alcohol consumption may predispose *ALDH2*-rs671 A allele carriers who drink habitually, particularly *ALDH2*-rs671 AG heterozygotes who experience a less severe manifestation of the flushing response, to higher susceptibility to diseases which possibly involve acetaldehyde in their aetiology, such as cancers and liver diseases.[19-21]

1.1.5 Heavy episodic drinking

Heavy episodic drinking (HED) is defined as consuming at least 60g or more of pure alcohol on at least one single occasion for at least once per month,[1] with a lower cut-off for women classified in some guidelines (e.g., 40g).[28-30] Given the rapidly elevated

blood alcohol level which results, HED is a harmful pattern of alcohol use and an important risk factor for acute consequences of alcohol use, such as intoxication and injuries.[31] The WHO estimated that one million people globally (29.2% vs. 7.2%, men vs. women) engaged in HED in 2016.[1] Although the prevalence of HED in China in 2016 (22.7% overall [36.3% vs. 8.6%, men vs. women] and 40.7% of all drinkers as estimated by WHO) is still lower than that in countries with strong HED culture, e.g., Russia and some Eastern European countries (~40% overall, ~60% of all drinkers), an increasing trend has been observed and is further projected in the Western Pacific, especially in China, despite the declining trends in Western populations (Figure 1.1C).[1,2]

1.2 Burden of deaths and diseases

1.2.1 Leading causes of mortality and morbidity

Over the past three decades, the epidemiological transition has been reflected in the global trends of mortality, characterised by a decline in deaths from communicable, maternal, neonatal, and nutritional diseases (33.1% vs. 18.6% of total deaths, 1990 vs. 2017) but a substantial increase in non-communicable diseases (NCDs) (57.7% vs. 73.4%) as shown in the Global Burden of Disease (GBD) Study.[32,33] In 2017, the leading causes of deaths globally were cardiovascular diseases (17.8 million, 32% of total deaths) and cancers (9.6 million, 17%).[33] In the past decades, the age-standardised mortality rates have declined globally, largely due to improvements in health-care and treatment.[32] However, the consequent longer life expectancy and ageing populations have led to a substantial increase in the absolute number of NCD deaths, as well as a growing burden from non-fatal disability and morbidity such as mental disorders.[32,34]

The epidemiological transition has also taken place in China, where the number of NCD deaths has increased from 5.8 to 9.4 million (71.8% vs. 89.5% of total deaths) between 1990 and 2017.[33] The leading causes of deaths in China differ importantly from those in countries with high Socio-demographic Index (SDI), which is a summary measure of development status developed by GBD researchers and is strongly correlated with health outcomes. Overall, China was classified as a high-middle SDI country in 2017, although the SDI varied from low-middle to high at the province level within China.[35] In China, the top ten leading causes of deaths in 2017 were cardiovascular diseases (stroke, ischemic heart disease, hypertensive heart disease), cancers (lung, liver, stomach, oesophagus), chronic obstructive pulmonary disease (COPD), Alzheimer's disease, and road injuries.[33] Four cancers contributed to this list compared with only two cancers (lung, colon-rectum) in high-SDI countries (Table 1.1). Importantly, China shares a substantial portion of the global burden of cancers and liver diseases.

1.2.2 Cancers

According to the GBD study, the number of incident cancer cases increased by 28% globally between 2006 and 2016.[36] In the GLOBOCAN project, the International Agency for Research on Cancer (IARC) estimated there were 18.1 million new cancer cases and 9.6 million cancer deaths globally in 2018.[37] Importantly, with ~20% of the world population, China shares a substantial portion of the global burden of cancers by contributing to 24% of global cancer cases and 30% of global cancer deaths.[38]

In China, the number of cancer deaths increased by 73.8% between 2000 and 2011.[39] Despite the decline in age-standardised mortality rates for overall cancer, the age-

standardised incidence rates were stable for men with significant upward trends observed for women.[39] The National Central Cancer Registry of China, based on data collected from 339 population-based cancer registries, reported a total of 3.8 million new cancer cases and 2.3 million cancer deaths in 2014, with higher age-standardised incidence and mortality rates in men than in women (208.3 vs. 166.4 per 100,000 persons for incidence, 138.3 vs. 75.2 per 100,000 persons for mortality).[40] The age-standardised incidence rate was higher in urban than in rural areas (191.6 vs. 179.2 per 100,000 persons) but the converse was true for cancer mortality rate (102.5 vs. 110.3 per 100,000 persons), which may indicate poorer cancer prognosis related to late diagnosis and poor clinical treatment in rural areas.[40]

There are substantial differences in the distribution of cancer types between China and high-income countries, particularly the smaller burden of prostate cancer in men but the larger burden of cancers with infection involved in their aetiology such as oesophageal cancer, stomach cancer, and liver cancer in China than in high-income countries (Figure 1.3).[38] The aetiology and risk factors vary across site-specific cancers, with alcohol drinking being identified as one of the major cancer risk factors among others such as smoking, obesity, insufficient physical activity, dietary factors, infection, and family history of cancer.[41] The following sections provide an overview of the most common site-specific cancers globally and in China.

1.2.2.1 Lung cancer

As the leading cause of cancer incidence and mortality worldwide, lung cancer caused 2.1 million new cancer cases and 1.8 million deaths globally in 2018, representing

almost 1 in 5 cancer deaths.[37] Between 2006 and 2016, there were general declines in the age-standardised incidence rates among men in high and high-middle income countries, mostly reflecting the decreasing tobacco consumption there, while increases in age-standardised incidence rates were reported among women.[36] Almost 40% of global lung cancer occurrence now occurs in China.[38] In China between the 2000s and 2010s, the age-standardised incidence rates changed little in men but increased slightly among women, with upward trends observed particularly in rural areas in both sexes.[39,42] In 2014, the age-standardised incidence and mortality rates were 36.6 and 28.3 per 100,000 persons in China, with almost twofold-higher rates in men than in women but similar rates in rural and urban areas (Figure 1.4).[40] Nevertheless, due to the ageing population, the crude incidence rates in both men and women increased sharply between 2000 and 2014.[42]

Heavy alcohol consumption has been suggested to be associated with increased lung cancer risk by the World Cancer Research Fund (WCRF), based on evidence from different populations.[41] However, the causal relevance of alcohol has not been established by IARC due to possible residual confounding by smoking, which is the principal cause of lung cancer.[19,20] Other established risk factors include passive smoking, occupational and environmental lung carcinogens (e.g., asbestos, radon, indoor air pollution), and pre-existing lung disease (e.g. emphysema, chronic bronchitis, tuberculosis, pneumonia), while vegetables and fruit intake and physical activity are suggested to be protective factors for lung cancer.[43]

1.2.2.2 Female breast cancer

As the most common female cancer diagnosed globally and in China, breast cancer was estimated to cause 2.1 million new cancer cases and 0.6 million deaths worldwide in 2018, accounting for 1 in 4 cancer cases among women.[37] Over the past two decades, while the global age-standardised incidence rate of breast cancer remained stable, there were increasing trends particularly in middle SDI countries and in China.[36,39] In China, the age-standardised incidence and mortality rates were 28.8 and 6.4 per 100,000 persons in 2014, and were higher in urban than in rural areas (Figure 1.4).[40]

Alcohol consumption is an established risk factor for breast cancer, for which the evidence, mostly based on Western population, is considered as convincing and strong by both IARC and WCRF.[19,20,41] Other known risk factors include genetic factors, menstruation, reproduction, exogenous hormone intake, and postmenopausal obesity, whereas breastfeeding and physical activity are known protective factors.[37,44]

1.2.2.3 Colorectal cancer

Ranked as the third most commonly diagnosed cancer and second leading cause of cancer mortality globally, colorectal cancer was estimated to cause 1.8 million new cancer cases and 881,000 deaths in 2018, accounting for 1 in 10 cancer cases and deaths.[37] Colorectal cancer is considered a clear marker of socio-economic development, given its link with Western lifestyles and a 3-fold higher incidence rate in high-income than in low-middle and low-income countries.[37,45] Between the 2000s and 2010s, the age-standardised incidence rates decreased in high SDI countries, but increased in other countries including China.[36,37,39] In China, colorectal cancer was the

fifth most common cancer in 2014, with the age-standardised incidence and mortality rates being 17.5 and 7.9 per 100,000 persons, which were higher in men and in urban areas (Figure 1.4).[40]

Alcohol consumption, especially heavy drinking, is an established risk factor for colorectal cancer as indicated by IARC and WCRF, largely based on evidence from Western countries and high-income Asian countries (e.g., Japan, Singapore).[19,20,41] Other established risk factors include smoking, red and processed meat intake, obesity, and inflammatory bowel disease, whereas protective factors include physical activity and dietary fibre intake.[46]

1.2.2.4 Stomach cancer

Stomach cancer is the fifth most common cancer diagnosis but the third most deadly cancer globally, with markedly high incidence rates in East Asia.[37] There were 1 million new cancer cases and 783,000 deaths caused by stomach cancer in 2018, with half of the global stomach cancer deaths occurring in China.[37] Globally and in China, the age-standardised incidence rates of stomach cancer have dropped substantially over time,[36,39] yet stomach cancer remains the third most common cancer in China.[40] In China, the age-standardised incidence and mortality rates were 19.5 and 13.3 per 100,000 persons in 2014, and were higher in men and in rural areas (Figure 1.4).[40]

Stomach cancer can be classified according to anatomical site of origin into gastric cardia cancer (near gastro-oesophageal junction) and gastric non-cardia cancer (more distal regions), with the latter being more common and most prevalent in Asia.[37,47] Alcohol consumption is a probable risk factor for stomach cancer as indicated by WCRF

based on evidence from different populations, but IARC noted no conclusive evidence due to possible residual confounding by dietary deficiencies.[19,20,41] Other established risk factors for stomach cancer include smoking, high-salt food and salt-preserved foods, and low fruit intake.[37,47] In particular, *Helicobacter pylori* (*H. pylori*) infection, which is highly prevalent in Asia, is the main risk factor for gastric non-cardia cancer.[37,47] For gastric cardia cancer which is increasingly common particularly in high-income countries, important risk factors include obesity, gastroesophageal reflux disease, and possibly Barrett oesophagus.[37,47]

1.2.2.5 Liver cancer

Liver cancer is the sixth most common cancer diagnosis but ranks fourth in terms of mortality, causing an estimated 841,000 new cancer cases and 782,000 deaths globally in 2018.[37] Between the 2000s and 2010s, the age-standardised incidence rates of liver cancer increased in high, high-middle, and middle SDI countries, but decreased in low and low-middle SDI countries.[36] Although both age-standardised incidence and mortality rates have decreased in China,[39] approximately half of global liver cancer cases and deaths currently still occur in China.[38] In 2014, the age-standardised rates of liver cancer in China were 17.8 and 15.3 per 100,000 persons for incidence and mortality, respectively, with higher rates in men and in rural areas (Figure 1.4).[40]

The most common type of liver cancer is hepatocellular carcinoma, accounting for ~90% of all liver cancer cases with the rest being intrahepatic cholangiocarcinoma and other rare types.[48] Heavy alcohol consumption is an established risk factor for liver cancer as indicated by both IARC and WCRF based on evidence from different

populations, but prospective evidence from China is limited.[19,20,41] Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the strongest risk factors for liver cancer, with HBV infection playing a predominant role in China and Africa while HCV infection is predominant in high-income countries (e.g., Japan, Western countries).[49] Other established risk factors include liver cirrhosis, aflatoxin exposure (especially in China and Africa), smoking, obesity, and type 2 diabetes.[37,48,50]

1.2.2.6 Oesophageal cancer

As the seventh most commonly diagnosed cancer and the sixth deadliest cancer globally, oesophageal cancer caused an estimated 572,000 cancer cases and 509,000 deaths in 2018.[37] The rates of oesophageal cancer declined globally and in China between the 2000s and 2010s.[36,39] However, oesophageal cancer remains the sixth most common cancer and the fourth leading cause of cancer deaths in China, which accounts for >50% of global oesophageal cancer occurence.[38,40] In China, the age-standardised incidence and mortality rates were 12.2 and 8.8 per 100,000 persons in 2014, with higher rates in men than in women.[40] The occurrence of oesophageal cancer exhibits significant regional variation in China, with particularly high rates in several rural areas, such as Linxian in the Henan province and Yanting in the Sichuan province, where incidence rates reached 80 to 100 per 100,000 persons in 2011.[40,51]

There are two major histologic subtypes of oesophageal cancer: oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma (EAC). While ESCC remains the most prominent type of oesophageal cancer globally and particularly in China (>90% of oesophageal cancer cases), EAC has risen sharply in incidence and is

the main histological subtype in Western countries.[37,52,53] Alcohol consumption is a well-established risk factor for ESCC as indicated by both IARC and WCRF, based on evidence from different populations including China.[19,20,41] Other established risk factors for ESCC include smoking, human papilloma virus infection, betel quid chewing, and drinking very hot beverages.[37] For EAC, risk factors include obesity, gastroesophageal reflux diseases, and Barrett oesophagus.[54] Physical activity and consumption of vegetables and fruit intake are suggestive protective factors for oesophageal cancer.[54]

1.2.2.7 Other cancers

Prostate cancer is the second most commonly diagnosed cancer in men globally (age-standardised incidence rate=29.3 per 100,000 persons in 2018),[37,38] with relatively low incidence rate in China (2.9 per 100,000 persons in 2014).[40] However, the incidence rate of prostate cancer has increased rapidly in China between 2000 and 2011, possibly reflecting early detection by screening and increasingly westernised lifestyles.[39] The link between alcohol consumption and prostate cancer is not clear, with existing evidence mainly based on Western populations.[55] Apart from body fatness, developmental factors (marked by adult attained height), and genetic susceptibility (e.g., African heritage, family history), little is known about the risk factors for prostate cancer.[37,55]

Although with relatively low incidence rates (4.8 per 100,000 persons in 2018), pancreatic cancer is the seventh deadliest cancer globally.[37,38] Between 2000 and 2011, the incidence and mortality rates of pancreatic cancer increased among men in China,

among whom pancreatic cancer was the sixth deadliest cancer in 2014.[39,40] Established risk factors for pancreatic cancer include obesity, smoking, and pancreatitis; however, accumulating evidence from Western countries and more recently from China have also suggested that heavy alcohol consumption is a risk factor for pancreatic cancer.[19,56,57]

Cancers of the mouth, pharynx, and larynx combined (i.e., mouth and throat) are among the ten most common and also deadliest types of cancers globally and in China.[37,38] These cancers are more common in South-Central Asia compared with other regions.[58] Alcohol consumption is an established risk factor for these cancers as indicated by both IARC and WCRF, based on evidence from different populations but with no prospective evidence from China.[19,20,41] Other established risk factors are generally similar to those of oesophageal cancer.[19,58]

1.2.3 Liver diseases

According to the GBD study, liver disease was estimated to cause over 2 million deaths worldwide in 2017, with 1.3 million due to liver cirrhosis which is the tenth leading cause of global deaths, and a further 1 million due to viral hepatitis and liver cancer.[33] In China, approximately 300 million people are affected by chronic HBV infection and other chronic liver diseases, and China accounts for half of worldwide liver cancer incidents and deaths.[38,59]

Liver diseases come in a wide spectrum of severity with various aetiologies and risk factors. The most common causes of chronic liver diseases are chronic HBV and HCV infections, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD),

all of which may progress into end-stage liver diseases including liver cirrhosis and liver cancer.[60] ALD comprises a spectrum of stages ranging from the relatively mild and reversible alcoholic hepatic steatosis (fatty liver) and alcoholic hepatitis, to alcoholic fibrosis and sclerosis of the liver, and further to alcoholic liver cirrhosis and alcoholic hepatic failure.[61] NAFLD refers to fat accumulation in >5% of hepatocytes, in the absence of other competing liver disease aetiologies and without excessive alcohol consumption.[62] NAFLD is strongly associated with obesity and the metabolic syndrome.[62] Both "alcoholic" and "non-alcoholic" fatty liver diseases share similar histopathological patterns. The basic distinction between the two is based on alcohol drinking history for which the threshold varies between countries, e.g., 30g and 20g of alcohol intake per day for men and women according to European and American guidelines, 140 and 70g per week for men and women in Asian-Pacific countries.[63]

Between 1990 and 2017, the number of global liver cirrhosis deaths increased, while the age-standardised mortality rates declined globally and in China.[33] Conventionally, ALD and HCV are the most common causes of liver cirrhosis-related deaths in Western countries, while HBV is the main cause of liver cirrhosis-related deaths in China and most other East Asian countries.[64] However, changes in the epidemiology of liver disease appears to be taking place in China. In China, the overall prevalence of HBV infection declined from 9.8% to 7.2% (<1% at young age, i.e., <5 years) between 1992 and 2006 largely due to the introduction of a universal HBV immunization programme among new-born babies, while the anti-HCV seroprevalence declined from 3.2% to 0.43% following the implementation of mandatory HCV screening for blood transfusion in the 1990s.[59,65] Meanwhile, the prevalence of ALD and NAFLD is rising at

an alarming rate in China, possibly reflecting the increasing prevalence of alcohol consumption and obesity.[59] Regional surveys suggested an increase in the prevalence of ALD from 2.3% to 8.7% between 2000 and 2015 in China.[66] Similarly, a study in Beijing showed a 33% increase in hospitalisations from alcoholic cirrhosis between 2006 and 2010, in parallel with a decline in hospitalisations from viral hepatitis-related cirrhosis.[67] Consistent with the global rise in NAFLD prevalence,[68] the prevalence of NAFLD increased from 5%-13% in the 1990s to 21% in the 2010s in China, in parallel with the increased prevalence of overweight and obesity resulting from urbanisation and lifestyle changes, with dramatic variation across regions (e.g., 13% vs. 43%, rural vs. urban).[69,70]

Overall, alcohol consumption is an established risk factor for liver cirrhosis, based on evidence from different populations.[71-73] Emerging evidence from Western populations have also suggested that certain drinking patterns, e.g., drinking without meals and drinking daily, may also increase risks of ALD and liver cirrhosis.[74,75] Although alcohol consumption appears to be a direct cause only for ALD, it may interact with liver diseases involving other aetiologies, e.g., HBV infection and NAFLD, to accelerate disease progression and increase mortality.[61,76]

1.2.4 Mental health

With the shift of the global health burden to chronic diseases, increasing disability-free years of life becomes as important as increasing life expectancy. Mental and addictive disorders, which are largely neglected, are the leading contributors to the non-fatal health burden, accounting for ~20% of years lived with disability and affecting 1 billion

people according to GBD 2016.[34,77] In 2016, the leading mental disorders were depression and anxiety disorders, which were more prevalent in women than in men and accounted for 47% of all years lived with disability related to mental and addictive disorders.[34]

Alcohol use disorder (AUD), including alcohol dependence and harmful patterns of alcohol use, is a mental health condition resulting from chronic problematic use of alcohol.[1] AUD was the leading addictive disorder in 2016 and is often associated with other common mental disorders, especially depression and anxiety, based on findings mainly from Western populations.[34,78-83] Importantly, both mental disorders and AUD are associated with considerable excess mortality from suicides and self-harms.[77,84] According to WHO, the global prevalence of AUD among persons aged 15+ years was 5.1% in 2016, with higher prevalence in men than in women (8.6% vs 1.7%) and the highest prevalence in Europe (14.6% in men, 3.5% in women) and the Americas (11.5% and 5.1%) across WHO regions.[1] In China, previous multi-site surveys showed a dramatic increase in the prevalence of alcohol dependence from 0.016% to 0.68% between the 1980s and 1990s.[7] In 2016, the WHO estimates of 12-month prevalence of AUD in China were 8.4% in men and 0.2% in women based on population surveys.[1]

1.3 Alcohol-attributable disease burden

In 2017, alcohol use was the seventh leading risk factor worldwide for premature deaths and disability, after high systolic blood pressure, smoking, high fasting plasma glucose, high body mass index (BMI), short gestation for birthweight, and low birthweight for gestation (Table 1.2).[85]

The WHO estimated that alcohol consumption was responsible for 3 million deaths (5% of all deaths) and 130 million disability-adjusted life years (DALYs) (5% of all DALYs) worldwide in 2016, with a disproportionately high burden among men (75% of alcohol-attributable deaths).[1] The major causes of alcohol-attributable deaths and DALYs were injuries, digestive diseases (mainly liver cirrhosis), cardiovascular diseases, infectious diseases, cancers, and AUD (Figure 1.5).[1] For populations aged 15-49 years, the leading causes of the alcohol-attributable burden were AUD, injuries, and tuberculosis.[86] However, for populations aged 50 years and older, cancers which have been causally linked to alcohol consumption by IARC (i.e., cancers of the mouth and throat, oesophagus, liver, colon and rectum, and female breast)[19] were the leading causes of alcohol-attributable deaths (19% of alcohol-attributable deaths in men, 27% in women), followed by stroke and chronic liver diseases.[86]

Alcohol consumption accounts for 48% of deaths from liver cirrhosis globally.[1] Alcohol consumption is also responsible for a high proportion of deaths from injuries (e.g., 18% of self-harms, 27% of road injuries) and cancers of the upper-aerodigestive tract (UADT) (22%-31% for mouth and throat, 17% for oesophagus), as well as deaths from cancers of the colon and rectum (11%), liver (10%), and female breast (5%).[1]

In China, the GBD study estimated that 10% of deaths in men and 1.2% in women were attributable to alcohol consumption in 2016.[86] These estimates were, however, based mainly on relative risks derived from prospective studies in Western countries and focused primarily on mortality rather than incidence. These relative risk estimates may not be directly applicable to China, where the prevalence and patterns of alcohol

drinking, disease rates, other modifying factors (e.g., diet, smoking, HBV infection), and importantly alcohol tolerance differ greatly from those in Western populations.[1,87]

1.4 Conclusions

As a result of the epidemiological transition, the focus of public health goals has shifted to preventing premature deaths and also reducing non-fatal disability from NCDs and mental and addictive disorders. Alcohol consumption is an important contributor to the global burden of premature deaths and disability, especially for liver diseases, cancers, injuries, AUD, and mental health conditions. In China, alcohol consumption and the prevalence of AUD have increased substantially over recent decades. There is a substantial disease burden associated with alcohol drinking in China, where specific drinking patterns and low alcohol tolerability may have implications for the harmful effects of alcohol. Therefore, understanding the roles of alcohol consumption and drinking patterns on both mental health and chronic diseases, especially cancers and liver diseases, in Chinese populations may provide valuable insights into disease aetiology, which will be helpful for improving public health burden estimation and for informing timely disease prevention strategies.

Table 1.1. Top ten causes of deaths in 2017

Rank	Global	High-SDI countries	China*
1	Ischemic heart disease	Ischemic heart disease	Stroke
2	Stroke	Alzheimer's disease	Ischemic heart disease
3	COPD	Stroke	COPD
4	Lower respiratory infection	Lung cancer	Lung cancer
5	Alzheimer's disease	COPD	Alzheimer's disease
6	Lung cancer	Lower respiratory infection	Liver cancer
7	Neonatal disorder	Colorectal cancer	Stomach cancer
8	Diarrheal disease	Chronic kidney disease	Hypertensive heart disease
9	Diabetes	Diabetes	Road injuries
10	Liver cirrhosis	Liver cirrhosis	Oesophageal cancer

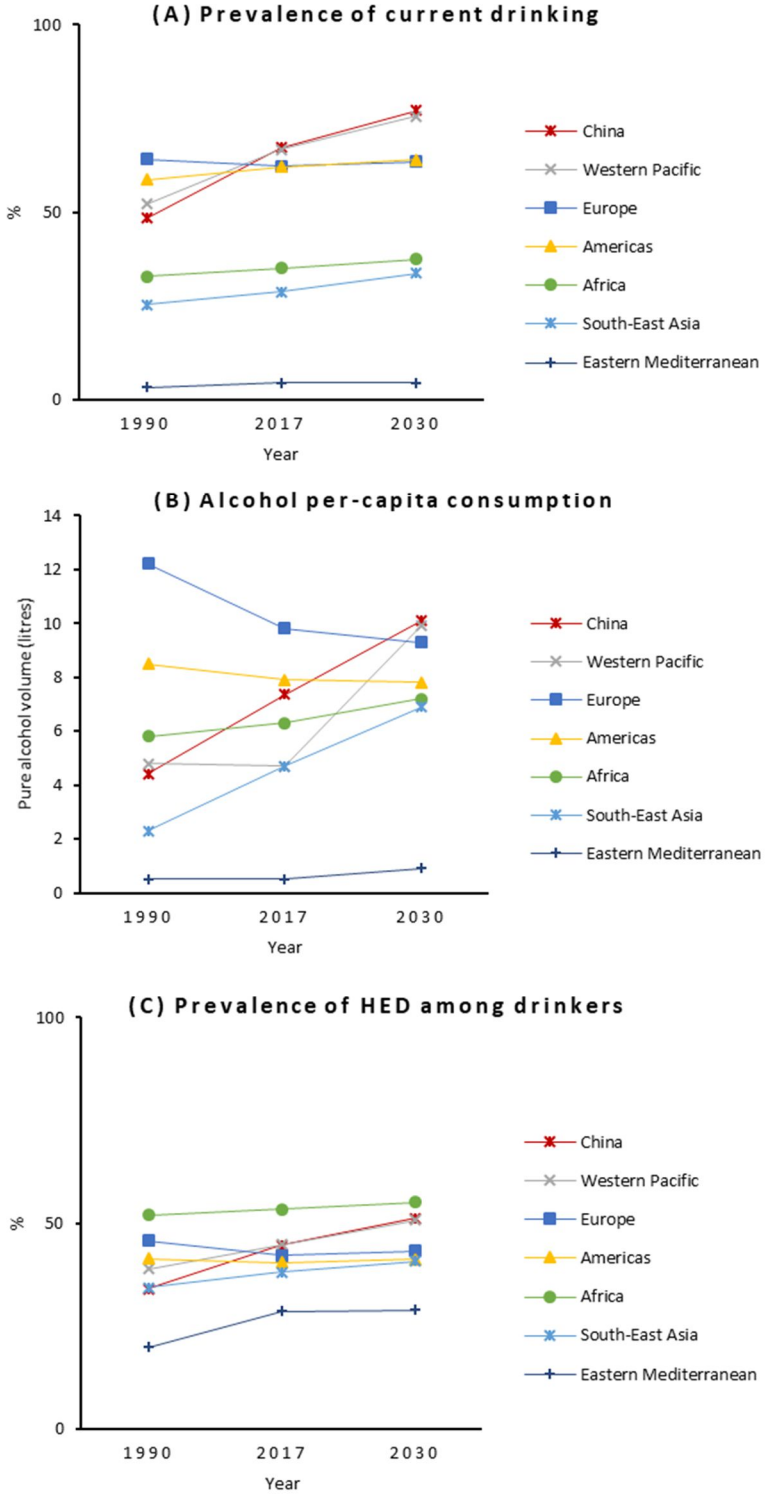
SDI, socio-demographic index; COPD, chronic obstructive pulmonary disease.
Data are obtained from the Global Burden of Disease Study 2017.[33]
SDI is a summary measure of a geography's socio-demographic development developed by researchers of the Global Burden of Disease Study, based on average income per person, educational attainment, and total fertility rate.[86]
*China belongs to the high-middle SDI category.

Table 1.2. Top ten global risk factors for disability-adjusted life years in 2017

Rank	Overall	Males	Females
1	High systolic blood pressure	Smoking	High systolic blood pressure
2	Smoking	High systolic blood pressure	High fasting plasma glucose
3	High fasting plasma glucose	High fasting plasma glucose	High body mass index
4	High body mass index	Alcohol use	Short gestation for birthweight
5	Short gestation for birthweight	Short gestation for birthweight	Low birthweight for gestation
6	Low birthweight for gestation	High body mass index	Child wasting
7	Alcohol use	Low birthweight for gestation	High LDL cholesterol
8	High LDL cholesterol	High LDL cholesterol	Low whole grains
9	Child wasting	Ambient particulate matter	Ambient particulate matter
10	Ambient particulate matter	Low whole grains	Smoking

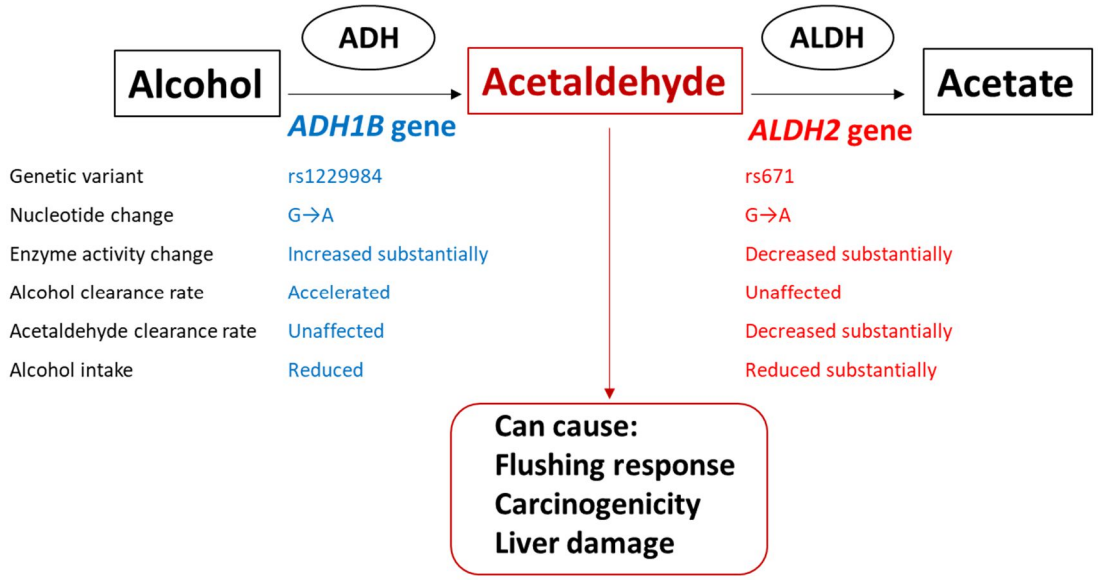
LDL, low-density lipoprotein.
Data are obtained from the Global Burden of Disease Study 2017.[85]

Figure 1.1. Time trends of prevalence of current drinking, alcohol per-capita consumption and prevalence of heavy episodic drinking between 1990 and 2030 in WHO regions and China



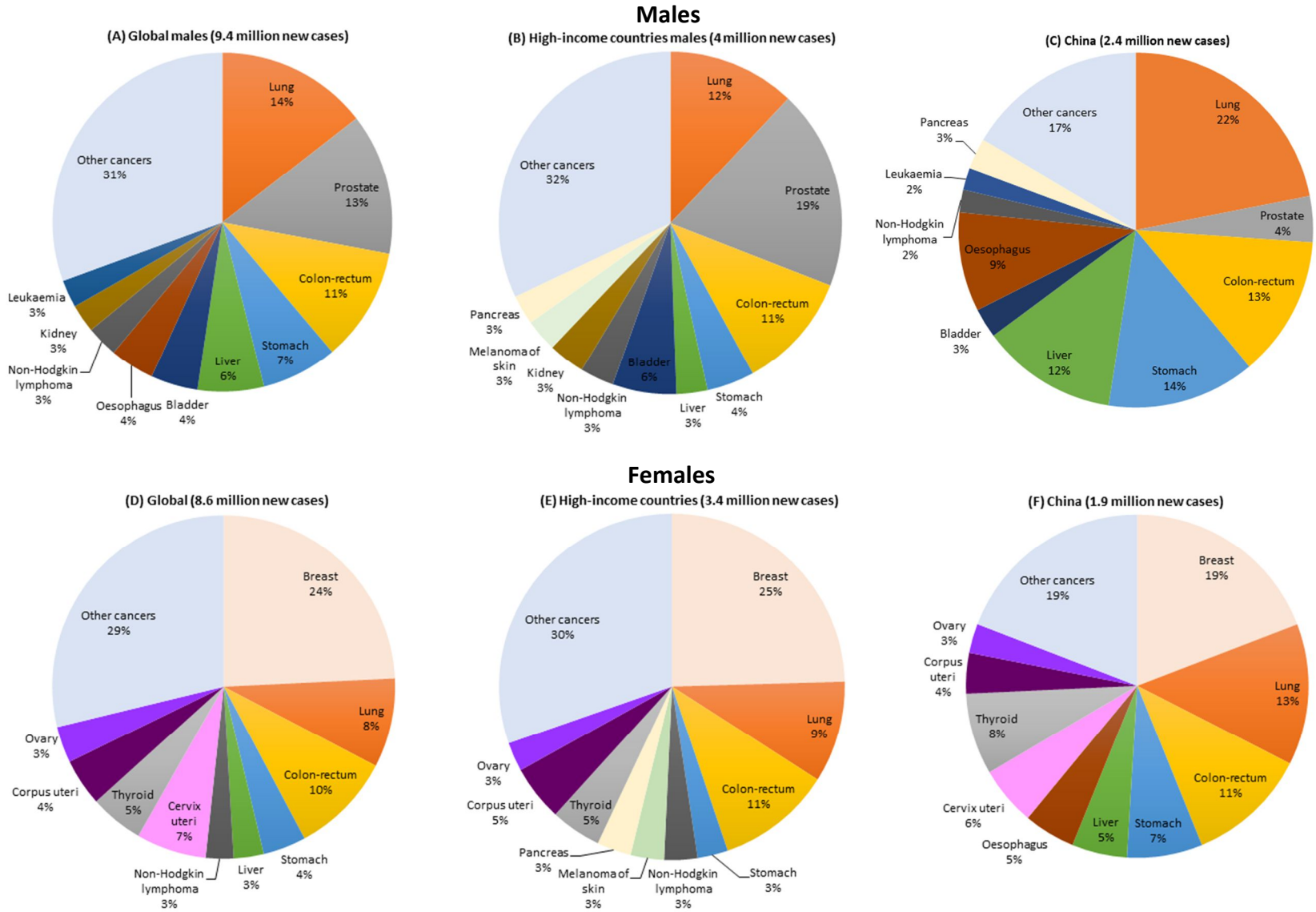
Data are obtained from a modelling study by Manthey et al 2019, based on country-validated data up to 2016 with forecasts up to 2030.[2] (A) displays the prevalence of current drinking (i.e., drinking alcohol at least once in the past 12 months) among adult population aged 15 years or above; (B) displays the total alcohol per-capita consumption (in litres per adult) among adult population aged 15 years or above; (C) displays the prevalence of HED among adult current drinkers. WHO, World Health Organisation; HED, heavy episodic drinking.

Figure 1.2. Genetic variants affecting alcohol metabolism in East Asians



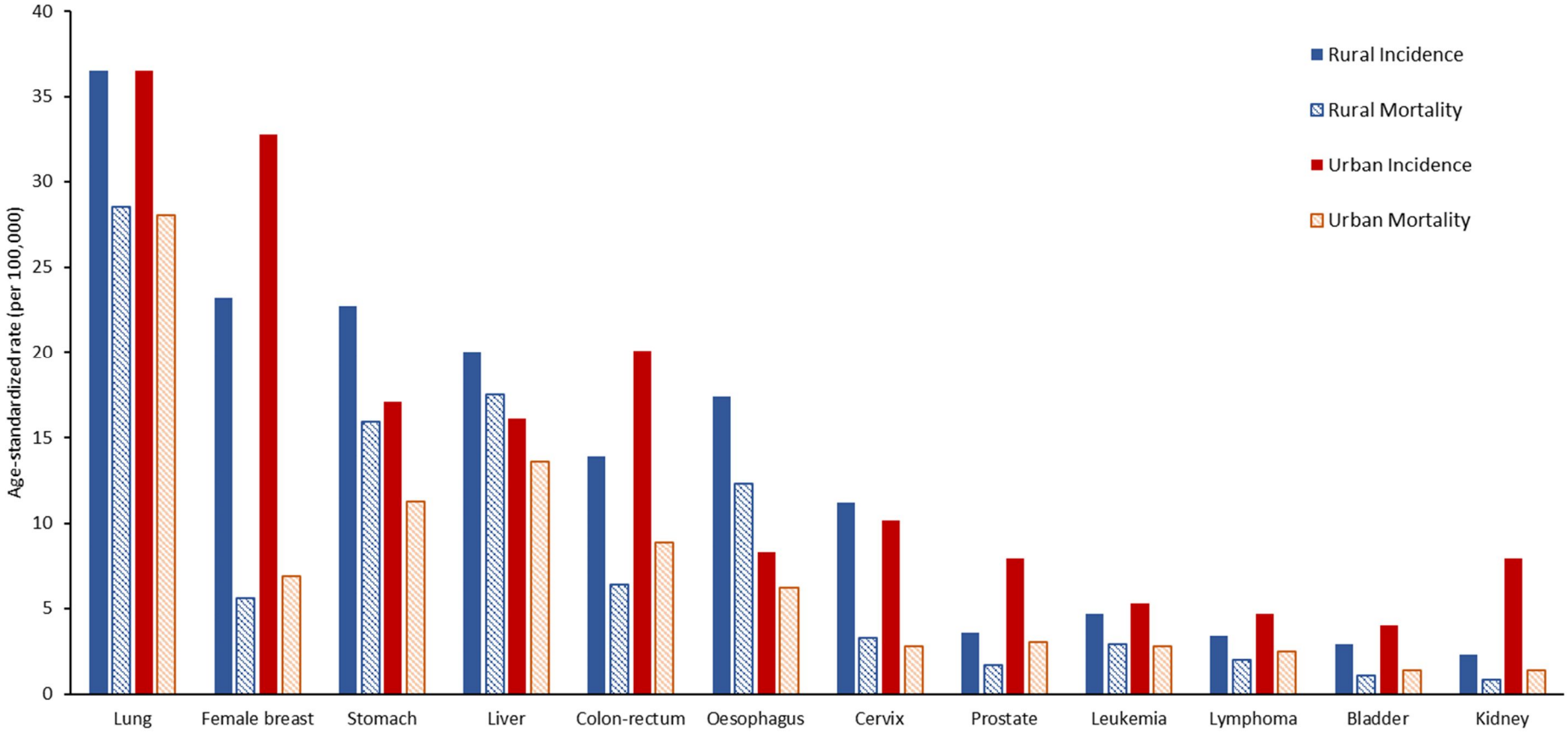
ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase.

Figure 1.3. Distribution of incident cancer cases for the 10 most common cancers in 2018, by sex



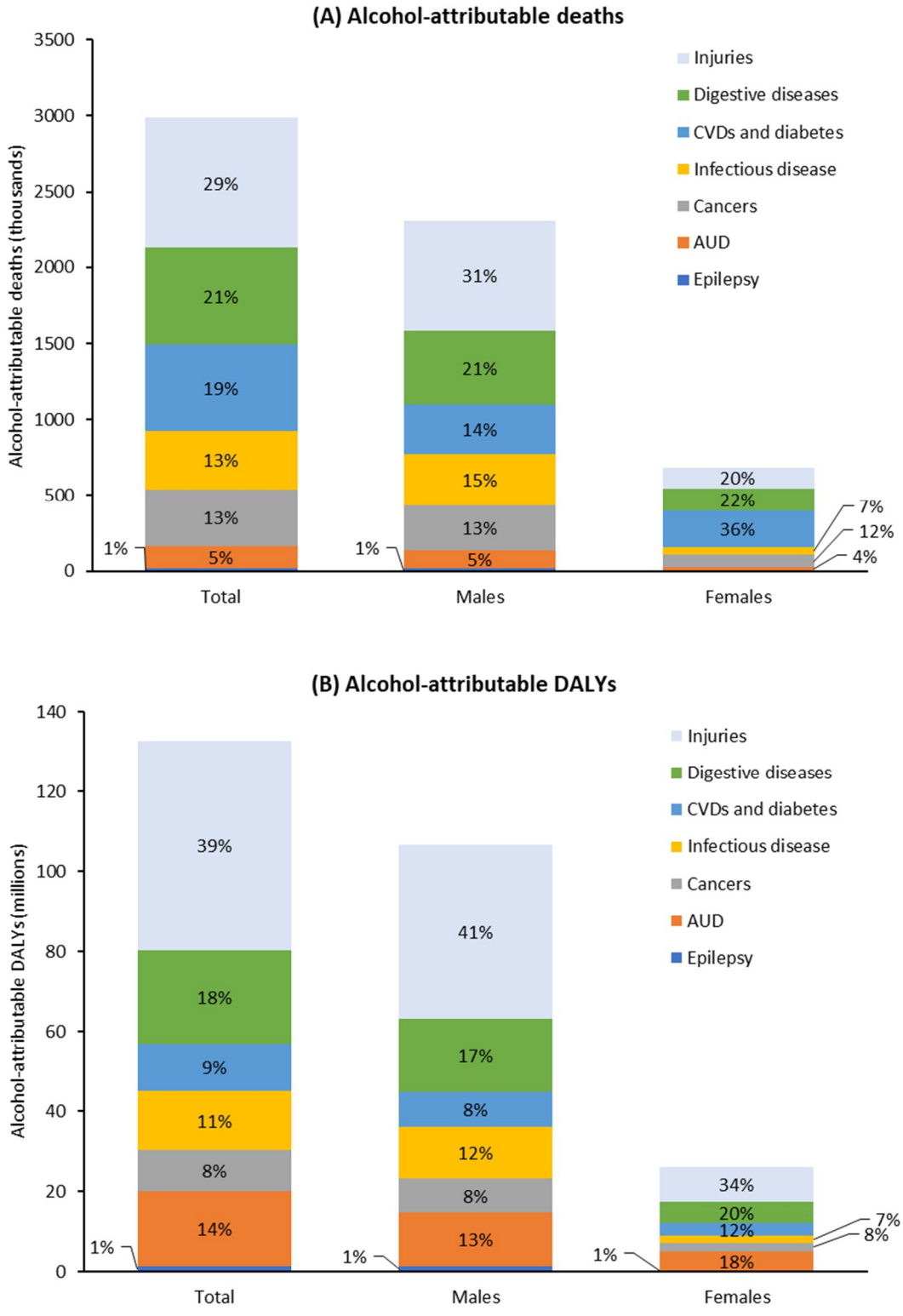
Data were obtained from GLOBOCAN 2018.[38] (A)-(C) refers to cancer incidence among males, (D)-(F) refers to cancer incidence among females.

Figure 1.4. Age-standardised incidence and mortality rates of cancers in China in 2014, by rural and urban regions



Data are obtained from the National Central Cancer Registry of China based on 339 cancer registries.[40]

Figure 1.5. Distribution of global alcohol-attributable deaths and disability-adjusted life years in 2016, by broad disease category



Data were obtained from the World Health Organisation's Global Status Report on Alcohol and Health 2018.[1] CVD, cardiovascular disease; AUD, alcohol use disorder; DALY, disability-adjusted life year.

Chapter 2. Literature review

This chapter provides a narrative review of published literature from large-scale prospective cohort studies and meta-analyses of prospective or case-control studies on the associations between alcohol consumption and risks of cancers and liver diseases, with an emphasis on relevant literature from China.

As the starting point for assessing the associations of alcohol consumption with risks of cancers, the IARC Monographs (2010 and 2012),[19,20] the WCRF Systematic Literature Reviews (SLRs),[88-99] and a comprehensive meta-analysis by Bagnardi et al published in 2015[100] were reviewed. The WCRF SLRs included dose-response meta-analyses of prospective cohort studies on site-specific cancers in relation to alcohol consumption as part of the ongoing Continuous Update Project.[41] The meta-analysis by Bagnardi et al investigated the dose-response associations of alcohol intake with 23 cancer types based on a total of 572 studies (163 cohorts and 409 case-control studies) from worldwide including 490,000 cancer cases.[100] Subsequently published meta-analyses and large-scale prospective cohort studies (sample size >10,000) published after the most recent meta-analysis relevant to the corresponding site-specific cancer were also reviewed. Regarding evidence from China, a meta-analysis by Li et al published in 2011 summarised the existing evidence of the associations between alcohol consumption and 13 cancer types from 4 cohorts and 116 case-control studies conducted in Chinese populations.[101] This meta-analysis by Li et al and large-scale prospective studies conducted in China, though already included in the meta-analyses reviewed, were discussed separately due to their close relevance to this thesis.

Similar review methodology was used for liver diseases by reviewing the most recent meta-analyses plus subsequently published large-scale prospective cohort studies. The search strategies and flow diagrams are presented in Appendix B. At the end of this chapter, the evidence gap in the existing literature is discussed.

2.1 Alcohol and cancers

The IARC Working Groups have concluded that alcohol consumption and acetaldehyde are Group 1 carcinogens and are causally related to cancers of the oral cavity, pharynx, larynx, oesophagus (mainly ESCC), liver, colon and rectum, and female breast,[19,20] consistent with the WCRF Third Expert Report in 2018 which concluded that alcohol consumption is a convincing cause of these cancers.[41] These cancers are henceforth referred to as "IARC alcohol-related cancers" in this thesis. WCRF further concluded that alcohol consumption is a probable cause of stomach cancer at intakes above 45g of ethanol per day, and with suggestive evidence that alcohol may also increase the risks of lung cancer at >40g/day and pancreatic cancer at >45g/day.[41] In contrast, IARC stated that there is evidence suggesting a lack of carcinogenicity of alcohol for kidney cancer and non-Hodgkin lymphoma given the mostly null or inverse associations observed,[19,20] while WCRF suggested that alcohol consumption probably protects against kidney cancer.[41] The following sections review the epidemiological evidence on the relationships between alcohol consumption and risks of IARC alcohol-related cancers, other common cancers (e.g., lung, stomach), and briefly less common cancers suggested to be related to alcohol.

2.1.1 Mouth and throat cancer

Overall, the existing literature has consistently shown that alcohol consumption is associated with increased risks of cancers of the mouth and throat (i.e., mouth, pharynx, and larynx), and that the risks increase in a dose-response manner.[19,20,96,100]

Although no summary comparisons were made between overall drinkers and never drinkers, the WCRF SLR 2016 reported clear dose-response associations with relative risks (RRs) per 10g/day increase in ethanol intake of 1.15 (95% confidence interval [CI]: 1.09-1.22) for oral cancer (5617 cases; 6 cohorts), 1.19 (1.10-1.30) for oral and pharyngeal cancer (954 cases; 5 cohorts), and 1.09 (1.05-1.13) for laryngeal cancer (781 cases; 6 cohorts) (Table 2.1).[96] The associations were generally consistent in men and women, with no clear evidence of differential effects by the type of beverage.[96] While several studies included in the WCRF SLR reported an attenuation of the effects of alcohol among never smokers, the tests for interaction between alcohol drinking and smoking were inconclusive and were limited by the low numbers of cases among non-drinkers and non-smokers.[96] Likewise, in the meta-analysis by Bagnardi et al, strong positive dose-response associations were observed.[100] In that meta-analysis, the risk of oral and pharyngeal cancer (18,837 cases; 5 cohorts, 47 case-control studies) was significantly higher at all levels of alcohol consumption, with the pooled RRs increasing from 1.13 (1.00-1.26) in light drinkers to 5.13 (4.31-6.10) in heavy drinkers compared with non-drinkers and occasional drinkers.[100] For laryngeal cancer (9634 cases; 3 cohorts, 38 case-control studies), a significantly increased risk was observed in moderate (RR=1.44 [1.25-1.66]) and heavy drinkers (2.65 [2.19-3.19]) but not light drinkers.[100] There was no significant heterogeneity by sex or different

populations, although a significant excess risk of oral and pharyngeal cancer among light drinkers was observed in Asian studies only.[100]

No subsequently published prospective studies have been identified for site-specific cancers of the mouth and throat, except for overall UADT cancers which included mouth and throat cancer as well as oesophageal cancer (Table 2.2). All of these studies investigated the associations by categories of drinking level without reporting on the overall associations with current drinkers versus never drinkers, while some reported on the risk estimates for ex-drinkers. A prospective study of 124,000 participants with 18 years of follow-up in the United States (US) reported a significantly higher UADT cancer risk associated with former drinking (hazard ratio [HR]=2.9 [95% CI: 1.9-4.6]; 552 cases) and most levels of alcohol consumption (2.5 [1.7-2.8] for ≥3 drinks/day) compared with lifelong abstinence.[102] The study further showed that the association with heavy drinking was consistent across beverage types.[102] In Asia, the prospective Korean Veterans Health Study (KVHS) involving 108,000 men with relatively short follow-up (~5 years) reported a strong dose-response association between alcohol intake and UADT cancer mortality risk (HR=1.63 [1.39-1.91] per 5 drinks/week; 199 deaths), and further showed a significant additive interaction between low BMI and high alcohol intake.[103]

In China, the meta-analysis by Li et al of case-control studies reported that alcohol drinking was associated with significantly increased risks of nasopharyngeal cancer (odds ratio [OR]=1.21 [99%CI: 1.00-1.46]; 1698 cases; 4 studies) and oral cancer (1.71 [1.20-2.44]; 347 cases; 3 studies), but had no available information for investigation into the dose-response relationships (Table 2.1).[101] Existing relevant prospective

studies were based on Shanghai and Hong Kong, two of the most developed and Westernised cities in China (Table 2.2). In these studies, the risks tended to be higher among regular drinkers and increased with the amount consumed.[72,104] The Shanghai Cohort Study (SCS) of 18,000 men reported a 3.7-fold (RR=3.72, p<0.01; 64 deaths) higher risk of UADT cancer mortality among men drinking ≥29 drinks/week versus non-drinkers.[72] Likewise, a cohort study of 67,000 elderly men and women in Hong Kong (65+ years) also reported a 2.6-fold (HR=2.58 [1.00-6.67]; 134 deaths) higher risk of head and neck cancer mortality among those with high alcohol intake (defined as >30g/day in men and >20g/day in women in the study) compared with never drinkers.[104] The association was significant in men but could not be investigated among women due to the lack of events in female heavy drinkers.[104]

2.1.2 Oesophageal cancer

Overall, existing studies have consistently shown higher risks of oesophageal cancer associated with alcohol consumption, which increase in a dose-response manner and are largely restricted to the subtype of ESCC but not EAC.[19,20,94,100]

The WCRF SLR 2015 including 17 cohort studies with 6618 cases reported an RR of 1.24 (1.16-1.33) for overall oesophageal cancer per 10g/day increase in alcohol intake (Table 2.3).[94] Similarly, a subsequently published meta-analysis of 8 case-control studies by Jayasekara et al, which focused on lifetime and long-term exposure of alcohol consumption in order to capture possible variation of alcohol use during the course of life, also reported a significant dose-response association for oesophageal cancer ($RR_{\text{highest vs. lowest category}}$=6.71 [4.21-10.70]).[105]

For ESCC, the WCRF SLR reported an RR of 1.25 (1.12-1.41) per 10g/day increase in alcohol intake (6 studies), which was consistent across studies from Asia, Europe, and North America (Table 2.3).[94] A significantly increased risk of ESCC was observed in the highest versus lowest consumption levels of beer (RR=2.56 [1.18-5.57]) and spirits (3.41 [2.16-5.38]), but no associations were observed for wine intake owing to the limited number of cases in the high-intake category.[94] Similarly, Bagnardi et al also reported that all levels of alcohol consumption were associated with significant excess risk of ESCC which increased in a clear dose-response relationship (14,318 cases; 13 cohorts, 41 case-control studies).[100] There was 26% (RR=1.26 [1.06-1.50]) higher risk for light drinkers to almost 5-fold (4.95 [3.86-6.34]) higher risk for heavy drinkers compared with non-drinkers and occasional drinkers, with the significantly increased risk among light drinkers observed in Asian studies only.[100]

Findings from prospective studies in Asia, where ESCC is the predominant pathological subtype (>90% in South Korea and China), also showed clear links between alcohol consumption and oesophageal cancer (Table 2.4). In studies from South Korea, significantly higher risks have consistently been shown at all levels of regular drinking. Both the Korean National Health Insurance Corporation (NHIC) study including 23 million participants with ~9000 cases ($HR_{\geq 30g/day\ vs.\ non\text{-}drinkers}$=3.13 [2.95-3.32])[106] and the KVHS with 108 deaths (HR=1.81 [1.53-2.14] per 5 drinks/week)[103] reported strong dose-response relationships between alcohol intake and oesophageal cancer. The NHIC study further reported a synergistic effect between alcohol consumption and current smoking, while both studies suggested interactions between alcohol consumption and low BMI on oesophageal cancer risk.[103,106] In addition, another NHIC

analysis reported a positive association between drinking frequency and risk of oesophageal cancer, with a 2.8-fold higher risk associated with daily drinkers versus never drinkers; however, it is not clear whether the analysis had adjusted for total amount of alcohol intake, which might have confounded the observed association.[107]

In China, the meta-analysis by Li et al including 2 cohorts and 34 case-control studies reported an approximately 80% (OR=1.78 [1.38-2.30]; 10,189 cases) higher risk of oesophageal cancer for drinkers versus non-drinkers, which was significant only in men and in case-control studies (Table 2.3).[101] In contrast, a prospective study of 1958 ESCC cases in Linxian, a well-known high-risk rural area of oesophageal cancer in China, reported no significant associations for past-year drinkers compared with past-year non-drinkers (RR=0.92 [0.82-1.03]) (Table 2.4).[108] This may be due to reverse causation (e.g., the reference group [past-year non-drinkers] may have included ex-drinkers who stopped drinking due to latent cancer and thus had high cancer risk) and confounding by other unknown major risk factors in the local area. Other prospective studies in China have shown expected positive associations between alcohol consumption and oesophageal cancer, but the risk estimates varied greatly across different studies. The nation-wide Chinese Prospective Smoking Study (CPSS) of 0.2 million men with 848 deaths reported a 25% (HR=1.25 [1.07-1.47]) higher risk of oesophageal cancer mortality among all current drinkers and a 63% (1.63 [1.12-2.39]) higher risk among the heaviest drinking group (i.e., 700+g/week) compared with non-drinkers,[73] whereas the much smaller study of elderly population in Hong Kong reported a 6-fold (HR=6.63 [2.92-15.02]; 115 deaths) higher mortality risk for those drinking >30g/day (>20g/day in women) versus never drinkers.[104] Similarly, the SCS reported 3- to 5-fold higher risks

in men drinking 4+ drinks/day versus non-drinkers for overall oesophageal cancer (HR=3.74 [2.12-6.59]; 101 cases) and ESCC (4.64 [2.31-9.30]; 68 cases).[109] The SCS also explored other aspects of drinking, reporting significant trends for age started drinking and duration of regular drinking and an apparently stronger association for spirit drinkers than for beer and rice wine drinkers.[109] These findings, however, are limited by statistical power and are likely to be confounded by the total amount of alcohol consumed.

For EAC, both the WCRF SLR and Bagnardi et al meta-analysis reported no significant associations with alcohol consumption (Table 2.3).[94,100]

2.1.3 Colorectal cancer

Previous studies in different populations have shown that alcohol consumption increases the risk of colorectal cancer, with some reporting excess risks only at relatively high intake levels (e.g., >30g/day only).[19,20,98,100]

The WCRF SLR 2016 of 16 prospective studies, largely conducted in Western countries and Japan, reported a 7% (RR=1.07 [1.05-1.09]; 15,896 cases) higher risk of colorectal cancer per 10g/day increase in alcohol intake, with a non-linear relationship where the risk started to increase from 30g/day.[98] The RRs per 10g/day were similar for colon cancer (1.07 [1.05-1.09]; 12,051 cases) and rectum cancer (1.08 [1.07-1.10]; 7763 cases) and across subgroups defined by sex, geographic location, and beverage type (Table 2.5).[98] Similarly, the meta-analysis by Bagnardi et al of 33 cohorts and 33 case-control studies with 41,715 cases showed a dose-response relationship between alcohol intake and colorectal cancer, with a 21%-53% higher risk in moderate (RR=1.21

[1.11–1.32]) and heavy drinkers (1.53 [1.30–1.80]) compared with non-drinkers and occasional drinkers among men, whereas no detrimental effects were observed among light drinkers and women.[100]

Subsequently published prospective studies in Western populations also reported modest associations between increasing alcohol consumption and colorectal cancer, with significantly increased risks mostly starting from moderate or high intake levels, while no formal comparisons were made between overall drinkers and never drinkers. Overall, there was a 2-8% higher risk of colorectal cancer per 10g/day increase in alcohol intake reported by the Melbourne Collaborative Cohort Study (HR=1.08 [1.04-1.12]; 922 cases),[110] the Multi-ethnic Cohort Study in the US (HR=1.02 [1.01-1.03]; 4923 cases),[111] and the UK Biobank (HR=1.08 [1.04-1.12]; 2609 cases) (Table 2.6).[112] In these three studies, the associations did not appear to differ substantially across beverage types. However, higher risks were reported for rectal cancer than for colon cancer,[110,112] and for distal than for proximal colon cancer.[112]

In Asia, two prospective cohort studies in South Korea also reported significantly increased risks of colorectal cancer associated with current alcohol consumption in men but not in women.[106,113] Among men, the Korean Multi-center Cancer Cohort study with 112 colorectal cancer cases reported an HR of 1.70 (1.05-2.76) in current drinkers, among whom the risk increased in a dose-response manner with amount of alcohol consumption, compared with never drinkers.[113] The study also reported a positive association with duration of alcohol drinking; however, the observed association may be confounded by the total amount consumed which was not taken into account in the analysis.[113] The large Korean NHIC study with 155,000 cases did not

report on the risk estimate for overall drinkers compared with non-drinkers, but reported significantly increased colorectal cancer risk both among men drinking <30g/day (HR=1.12 [1.10-1.13]) and ≥30g/day (1.32 [1.30-1.35]).[106] The NHIC study further indicated that the association was consistent across BMI categories and smoking status, with no significant interactions observed.[106]

In China where colorectal cancer incidence has increased steadily in the past few decades, the existing evidence about its relationship with alcohol consumption is limited to studies conducted in the late 1980s and early 1990s and is inconsistent. The meta-analysis by Li et al including 10 case-control studies in Chinese populations showed no significant associations between alcohol drinking and colorectal cancer ($OR_{drinkers\ vs.\ non\text{-}drinkers}$=1.58 [0.90-2.76]; 4311 cases) (Table 2.5).[101] None of the previous cohort studies in China, which included the CPSS (193 deaths),[73] the SCS (29 deaths),[72] the study on elderly population in Hong Kong (944 deaths),[104] and the Jiashan study based on a high-risk area of colorectal cancer in China (242 cases),[114] reported significant associations between colorectal cancer and alcohol consumption or drinking frequency (Table 2.6).

2.1.4 Liver cancer

Overall, existing studies have shown that ever alcohol consumption is positively associated with risks of liver cancer, with some reporting significant excess risks among heavy drinkers only.[19,20,88,100]

The WCRF SLR 2014 reported an RR for liver cancer of 1.04 (1.02-1.06) per 10g/day increase in alcohol intake based on 14 prospective studies and the Asian Pooling

Project (6372 cases), noting a significant risk increase starting at >45g/day (Table 2.7).[88] The association was apparent across sex and geographic locations, but was stronger for incidence (RR=1.12 [1.05-1.18] per 10g/day; 1738 cases) than mortality (1.02 [1.01-1.03]; 3912 cases).[88] In a meta-analysis of 11 cohorts and 32 case-control studies, the risk of liver cancer was significantly higher for ever drinkers (RR=1.29 [1.16-1.42]) and former drinkers (2.06 [1.31-2.81]) compared with never drinkers, and among current drinkers there was a significant dose-response association.[115] Similarly, the meta-analysis by Bagnardi et al based on 9 cohorts and 27 case-control studies (12,965 cases) also showed a dose-response association between alcohol intake and liver cancer, with a significant excess risk observed only in heavy drinkers (RR=2.07 [1.66-2.58]) compared with non-drinkers and occasional drinkers.[100]

In Western populations, the recently published Liver Cancer Pooling Project of 14 US-based prospective cohorts including 1.5 million participants with 1423 cases showed a J-shaped relationship between alcohol intake and risk of hepatocellular carcinoma (Table 2.8).[116] No comparisons between overall drinking and never drinking were made, and with limited statistical power the study found no obvious difference across beverage types.[116]

In China, the meta-analysis by Li et al involving 18 case-control studies with 3812 cases reported a 56% (OR=1.56 [1.16-2.09]) excess liver cancer risk in drinkers compared with non-drinkers, which was significantly in men only (Table 2.7).[101] However, prospective evidence in China is limited. Single-region prospective cohort studies in Shanghai (102 deaths), Hong Kong (590 deaths), and Haimen City (1092 deaths), which is within the area of the highest liver cancer mortality in China, did not find significant

associations between alcohol intake and liver cancer mortality (Table 2.8).[72,104,117] The large CPSS reported no significant associations for overall drinkers but a 38% (HR=1.38 [1.11-1.73]; 1115 deaths) excess risk among those drinking 420-699g/week compared with non-drinkers.[73]

A few East Asian studies have examined the joint effects of alcohol use and hepatitis B surface antigen (HBsAg), an indicator of current HBV infection. The Taiwan Screening Project (115 incidents) and the Korean Cancer Prevention Study of 1 million participants (3800 deaths) showed that the highest risks of liver cancer were observed among HBsAg positive alcohol drinkers, who had up to 18 to 28-fold excess risk compared with HBsAg negative non-/light drinkers.[118,119] However, both studies as well as the Haimen City Cohort in China found no significant multiplicative interactions.[117-119] Prospective evidence on the potential interactions between alcohol consumption and diabetes, smoking, and BMI is limited. A significant interaction between alcohol consumption and diabetes on liver cancer risk has been reported, based mainly on US populations, but not between alcohol consumption and smoking.[115,116] A significant interaction between alcohol use and BMI/obesity on liver cancer risk was also reported in a cohort study in Taiwan (305 cases) but not in the US Liver Cancer Pooling Project study.[116,120]

2.1.5 Breast cancer

Existing evidence, mostly based on Western populations, has shown clear linear associations between alcohol intake and female breast cancer risk.[19,20,97,100]

The WCRF SLR 2017 reported a 11% (RR=1.11 [1.06-1.16]; 33,415 cases; 29 cohorts) higher risk of breast cancer per 10g/day increase in alcohol intake in postmenopausal women and a 3% (1.03 [0.99-1.07]; 4426 cases; 18 cohorts) higher risk in premenopausal women, with significant excess risks observed in Western populations only (Table 2.9).[97] Similarly, Bagnardi et al also reported a 4-61% higher risk of breast cancer associated with all levels of alcohol consumption compared with non-drinkers and occasional drinkers (165,750 cases; 43 cohorts, 75 case-control studies), with the evidence more apparent in Western than in Asian populations.[100] Subsequently published large prospective cohort studies from Western populations, although without direct comparisons between overall drinkers and never drinkers, generally confirmed the positive dose-response associations, with an 8% (RR=1.08 [1.05-1.11]; 29,005 cases) excess risk per 10g/day increase in alcohol intake in postmenopausal women reported in the updated Million Women Study (MWS) (Table 2.10).[121]

Few studies in East Asian populations were able to reliably study the associations of alcohol drinking with breast cancer because alcohol consumption is rare and at low levels in Asian women. In China, the meta-analysis by Li et al including 4 case-control studies with 1655 cases reported an inverse relationship between alcohol drinking and female breast cancer ($OR_{\text{drinkers vs. non-drinkers}}$=0.76 [0.60-0.97]),[101] with no relevant evidence from large prospective cohort studies available.

2.1.6 Lung cancer

There is some suggestive evidence that alcohol consumption is associated with increased risks of lung cancer, in J-shaped associations.[92,100] However, residual

confounding by smoking cannot be excluded even after adjustment due to the strong correlation between smoking and alcohol consumption. For studies focusing on non-smokers, the number of non-smoking heavy drinkers and the number of lung cancer cases among them are often too small to conduct a reliable assessment.[122-125]

The WCRF SLR 2015, based on 26 prospective studies with 21,940 cases, reported an RR for lung cancer of 1.03 (1.01-1.05) per 10g/day increase in alcohol intake, with the risk increase mainly starting at 40g/day (Table 2.11).[92] The association did not appear to differ by sex, lung cancer subtype, and geographic location.[92] Further analyses suggested that the association appeared to differ by beverage type, with an inverse association for wine (RR=0.87 [0.76-0.98] per 10g/day; 2701 cases) and suggestive positive associations for beer (1.04 [0.93-1.16]; 3481 cases) and spirits (1.03 [0.98-1.10]; 2920 cases).[92] The positive association with total alcohol intake was greatly attenuated with adjustment for smoking, and no significant associations were observed when stratified by never smokers (RR=0.96 [0.92-1.00] per 10g/day; 1350 cases) and current smokers (1.01 [0.97-1.02]; 4255 cases).[92] The meta-analysis by Bagnardi et al of 18 cohorts and 16 case-control studies with 38,423 cases reported a J-shaped relationship between alcohol consumption and lung cancer, with a significantly increased risk observed only in heavy drinkers (RR=1.15 [1.02-1.30]) compared with non-drinkers and occasional drinkers.[100]

No comparisons between overall drinkers and never drinkers were made in subsequently published studies, and the findings on the associations with amount consumed are somewhat inconsistent. A recent pooled analysis from the International Lung Cancer Consortium and the SYNERGY study of 1 cohort and 21 case-control

studies with 19,149 cases, mostly from Western populations, showed a U-shaped relationship between alcohol consumption and lung cancer with an inverse association observed up to 20g/day.[126] The pooled analysis also reported a significant multiplicative interaction between alcohol consumption and smoking intensity on lung cancer risk.[126] In contrast, in a prospective study of 1989 lung cancer cases in the US, there were no associations observed at low-intake levels but a 30% excess risk for those drinking ≥3 drinks/day (HR=1.3 [1.1-1.6]) compared with lifelong abstainers, which was significant for spirits and beer (Table 2.12).[102]

Pooled studies and meta-analyses focusing on never smokers, mostly based on case-control studies, generally showed no significant associations between total alcohol intake and lung cancer (Table 2.11). The International Lung Cancer Consortium and the SYNERGY study including 2548 cases in never smokers reported an inverse association at all levels of alcohol consumption, with a ~20% significantly lower risk associated with low and moderate drinking (<20/day) compared with non-drinking, which was significant for wine and spirits but not beer.[122] In contrast, two other studies showed no significant associations between alcohol consumption and lung cancer among never smokers, including a pooled analysis of 6 case-control studies in Spain ($OR_{\text{drinking vs. non-drinkers}}$=1.22 [0.83-1.80]; 438 cases)[123] and a meta-analysis of 1 pooled analysis, 3 cohorts, and 6 case-control studies (HR=1.01 [0.92-1.10] per 10g/day; 1913 cases).[124] Conversely, a strong significant dose-response association between alcohol intake and lung cancer among male never smokers has been reported in a pooled analysis of 7 Western cohorts, which however is based on a limited number of events (n=74).[125]

In China, existing evidence is inconsistent and limited. Both the meta-analysis by Li et al of 2 cohorts and 4 case-control studies ($OR_{drinkers\ vs.\ non\text{-}drinkers}$=1.39 [0.93-2.07]; 1104 cases) and the CPSS ($HR_{drinkers\ vs.\ non\text{-}drinkers}$=1.03 [0.90-1.18]; 1082 deaths) found no significant associations between overall drinkers and lung cancer (Tables 2.11-2.12).[73,101] However, when considering the amount consumed, both the CPSS ($HR_{420\text{-}699g/week\ vs.\ non\text{-}drinkers}$=1.30 [1.03-1.63])[73] and the study of elderly population in Hong Kong ($HR_{high\text{-}intake\ vs.\ never\ drinkers}$=1.39 [1.01-1.90]; 1958 deaths)[104] reported J-shaped associations for lung cancer mortality, whereas the much smaller SCS with only 147 deaths reported no significant associations.[72] None of these studies further explored the associations separately by smoking status.

2.1.7 Stomach cancer

Overall, existing studies have suggested weak positive associations between alcohol consumption and stomach cancer, particularly at high consumption levels.[95,100]

The WCRF SLR 2015 involving 23 prospective studies (including 10 from Korea and Japan) reported a small excess risk of stomach cancer per 10g/day increase of alcohol consumption (RR=1.02 [1.00-1.04]; 11,926 cases), and the risk appeared to increase more markedly at >45g/day (Table 2.13).[95] The risk estimates appeared stronger in ever smokers ($RR_{highest\ vs.\ lowest\ intake}$=1.84 [1.42-2.36]) than in never smokers (1.23 [1.03-1.46]).[95] However, most studies included in the WCRF SLR did not adjust for important dietary factors (e.g., intake of fresh fruit and vegetables) and none adjusted for *H. pylori*. Similar to the WCRF SLR, the meta-analysis by Bagnardi et al of 19 cohorts and 20 case-control studies with 25,958 cases reported a significantly increased risk of

stomach cancer in heavy drinkers only (RR=1.21 [1.07−1.36]) compared with non-drinkers and occasional drinkers, with no significant heterogeneity observed across sex or region.[100] Subsequently published meta-analyses and pooled analysis, mostly based on case-control studies, reported no significant associations among overall drinkers but significant excess risks among those with high levels of alcohol intake.[127-129] The associations appeared to be consistent across *H. pylori* status,[127] and were significant in spirit and beer drinkers but not wine drinkers.[127,129] However, two subsequently published prospective studies in the US showed no significant associations between any level of alcohol consumption and stomach cancer (Table 2.14).[102,130]

In Asia, the recent Korean NHIC study with 135,382 cases reported significant dose-response associations between alcohol intake and stomach cancer in the overall study population and in men ($HR_{<30g/day\ vs.\ non\text{-}drinkers}$=1.06 [1.05-1.08], $HR_{>30g/day\ vs.\ non\text{-}drinkers}$=1.26 [1.24-1.29]), which were consistent across BMI and smoking categories.[106] Existing evidence in China is however mixed. The meta-analysis by Li et al involving 2 cohorts and 29 case-control studies (8645 cases) reported a 40% (OR=1.40 [1.20-1.64]) excess risk of stomach cancer in drinkers versus non-drinkers (Table 2.13).[101] The CPSS study with 1137 stomach cancer deaths reported no significant associations with overall drinkers, but a weak J-shaped association with a non-significant 15% ($HR_{\geq 700g/week\ vs.\ non\text{-}drinkers}$=1.15 [0.85-1.57]) excess mortality risk among the heaviest drinkers compared with non-drinkers (Table 2.14).[73] Likewise, in the SCS with 391 stomach cancer cases, there were no significant excess risks among overall regular drinkers compared with non-drinkers, but an almost 50% (HR=1.46 [1.05-2.04]) higher risk in those drinking 4+ drinks/day.[131] No clear associations with age started drinking

or duration of drinking were further observed in the SCS.[131] In contrast, the study of elderly population in Hong Kong (335 deaths) reported no significant associations between alcohol drinking and stomach cancer mortality.[104] A seemingly protective effect of past-year drinking for gastric cardia cancer (RR=0.84 [0.72-0.97]; 1089 cases) was reported in a study conducted in Linxian, a region with high incidence and mortality rates of gastric cardia cancer, which however might be due to reverse causation or confounding by other unknown risk factors.[108]

2.1.8 Other cancers

For pancreatic cancer, there has been accumulating evidence that heavy alcohol intake appears to be associated with modestly increased risks (Tables 2.15-2.16).[19,20,99,100] The WCRF SLR 2011 involving 9 prospective studies with 3096 pancreatic cases reported no clear overall associations with alcohol consumption (RR=1.00 [0.99-1.01] per 10g/day), although the risk of pancreatic cancer appeared to increase significantly at high intake levels, i.e., >3 drinks/day ($RR_{highest\ vs.\ lowest}$=1.29 [1.13-1.48]).[99] Similarly, a meta-analysis of 21 cohorts reported no significant associations with overall drinkers but a 15% higher risk of pancreatic cancer among heavy drinkers compared with non-drinkers (RR=1.15 [1.06-1.25]; 11,846 cases),[132] with a similar risk estimate reported by Bagnardi et al (RR=1.19 [1.11-1.28]; 27,326 cases).[100] In both meta-analyses, the associations were significant in men only.[100,132] Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) study of ten European countries involving 1283 pancreatic cancer cases reported a small excess risk (HR=1.06 [1.02-1.10]) per 12g/day increase in lifetime alcohol intake among male drinkers, with a markedly increased risk at intake of ≥60g/day compared with 1-5g/day (1.77 [1.06-

2.95]).[133] In contrast, subsequently published individual cohort studies in Melbourne (239 cases)[134] and the US (535 cases)[102] did not find any significant associations with former drinking or any levels of alcohol consumption. In China, the meta-analysis by Li et al of 5 case-control studies reported a 71% (OR=1.71 [1.32-2.20]; 1612 cases) higher risk of pancreatic cancer among male drinkers compared with non-drinkers.[101] More recently, a prospective study involving 0.5 million adults from the China Kadoorie Biobank (CKB) reported a 33% (HR=1.33 [1.11-1.58]; 340 cases) higher risk of pancreatic cancer among male current regular drinkers compared with abstainers, with no excess risks among light to moderate drinkers but an approximately 70% (1.69 [1.21-2.37]) higher risk among men drinking ≥420g/week.[56]

A weak link has been suggested between alcohol consumption and prostate cancer, but existing evidence is mostly based on Western populations and remains largely inconsistent.[90,100,135] The WCRF SLR 2014 involving 25 prospective studies (23 from Western populations) showed no significant associations between prostate cancer and alcohol intake (RR=1.01 [0.99-1.02] per drink/day; 36,942 cases).[90] However, a meta-analysis of 16 cohorts and 11 case-control studies (all from Western populations except 1 from Japan) reported an 8% (RR=1.08 [1.01-1.17]; 49,898 cases;) higher risk of prostate cancer among drinkers compared with abstainers.[135] Both this meta-analysis and Bagnardi et al (42,658 cases; 20 cohorts, 23 case-control studies) also reported progressively increasing risks with amount consumed, although the risk increase was modest (from 4% excess risk in light drinkers to 18% in heavy drinkers compared with non-drinkers and occasional drinkers).[100,135] In contrast, no significant associations between alcohol consumption and prostate cancer were observed in studies from Asia,

including the meta-analysis by Li et al (569 cases, 4 case-control studies),[101] the Asia Cohort Consortium (367 deaths; 11 cohorts),[136] and the study of elderly population in Hong Kong (181 deaths).[104]

For kidney cancer[91,100,137,138] and non-Hodgkin lymphoma,[100,139,140] previous large meta-analyses and pooled-analyses involving mainly Western populations tended to show inverse associations with alcohol drinking. The WCRF SLR 2015 with >3500 cases suggested a probable inverse relationship between alcohol intake and kidney cancer (RR=0.92 [0.86-0.97] per 10g/day), but there was insufficient evidence at higher intake levels (i.e., >30g/day).[91] No direct comparisons between overall drinkers and never drinkers were made in the identified studies, but inverse dose-response associations have been consistently reported in the large meta-analysis by Bagnardi et al (8-20% lower risk in drinkers; 12,893 cases; 6 cohorts, 11 case-control studies)[100] and another meta-analysis (HR=0.94 [0.92-0.95] per 5g/day; 5503 cases; 7 cohorts and 1 pooled-analysis of 12 cohorts).[137] The EPIC study (931 cases) also reported an inverse association of light lifetime alcohol consumption with renal cancer ($HR_{6\text{-}12g/day\ vs.\ 0\text{-}6/day}$=0.73 [0.57-0.93]), but there were no clear dose-response relationships at higher intake levels.[138] In contrast, no significant associations between kidney cancer and former or current alcohol intake were reported in a US cohort (383 cases).[102] There are no WCRF SLR reports on the associations between alcohol consumption and haematological cancer. Nevertheless, a meta-analysis of 14 cohort studies (11,381 cases) reported an 11% (RR=0.89 [0.83-0.95]) lower risk of non-Hodgkin lymphoma among ever drinkers versus never drinkers and a further inverse dose-response association with amount of alcohol intake.[139] Bagnardi et al also reported a similar

inverse association with a 12-25% lower risk among drinkers versus non-drinkers and occasional drinkers (14,124 cases; 9 cohorts, 15 case-control studies).[100] In the Melbourne Collaborative Cohort Study (538 cases), a ~20% lower risk of non-Hodgkin lymphoma was associated with all lifetime alcohol consumption categories compared with lifetime abstinence, but there was no evidence of a dose-response relationship.[140] There are no relevant large prospective studies from China.

For gallbladder cancer, overall no significant associations with alcohol consumption were reported in the WCRF SLR (RR=1.07 [0.98-1.17] per 10g/day; 417 cases; 3 cohorts).[93] However, the meta-analysis by Bagnardi et al of 4 cohorts and 4 case-control studies reported a 2.6-fold (RR=2.64 [1.62-4.30]; 880 cases) higher risk of gallbladder cancer in heavy drinkers compared with non-drinkers and occasional drinkers, mostly based on studies from Japan and South Korea.[100] In China, the meta-analysis by Li et al suggested an inverse relationship between alcohol drinking and gallbladder cancer ($OR_{drinkers\ vs.\ non\text{-}drinkers}$=0.70 [0.49-1.00]; 467 cases), which however was based on only 2 case-control studies and may be due to reverse causation.[101] For bladder cancer, existing large-scale studies including the Bagnardi et al meta-analysis[100] (10,663 cases), the WCRF SLR 2014[89] (2673 cases), the EPIC study[141] (1802 cases), and the Japan Public Health Center-based Prospective Study[142] (354 cases) showed no significant associations with regular alcohol consumption or amount consumed. No relevant large prospective studies on these minor cancers are available from China.

2.2 Alcohol and liver diseases

Although alcohol consumption is a major risk factor for liver diseases, especially in European populations, little prospective evidence exists from Chinese population where liver diseases are predominantly related to HBV infection. Existing evidence on the associations between alcohol consumption and NAFLD is inconsistent, with some studies reporting inverse associations with low to moderate alcohol intake.[143,144] There are also emerging evidence from Western populations linking drinking patterns to risks of liver cirrhosis and ALD.[74,75] As the evidence on liver cancer has been reviewed in previous section (Section 2.1.4), the following sections review existing meta-analyses (Table 2.17) and large prospective studies (Table 2.18) on the associations of alcohol intake with non-neoplastic liver diseases (broadly covering International Classification of Diseases, 10th Revision [ICD-10]: K70-K77, unless specified otherwise), focusing on liver cirrhosis, ALD, and NAFLD.

2.2.1 Total liver disease

Most studies on the associations of alcohol consumption with overall liver disease (broadly covering ICD-10: K70-K77, with some studies also covering liver cancer) made no comparisons on liver disease risks between overall drinkers and never drinkers. Nevertheless, existing studies have consistently reported significant dose-response associations with alcohol intake levels, with some reporting J-shaped associations.[103,145-147]

A study of 27,086 Finnish men with 20 years of follow-up (213 deaths) reported a significant trend between alcohol consumption and total liver disease mortality, with

HRs of 2.06 (1.22-3.50) for those drinking 5-20g/day and 6.68 (4.16-10.71) for >20g/day compared with 0-5g/day (Table 2.18).[145] A much larger US study of 0.5 million participants with 11 years of follow-up reported a J-shaped association between alcohol intake and liver disease mortality (defined as ICD-10: K70, K73, K74 in the study; 789 deaths).[146] The US study reported an approximately 6-fold (HR=5.84 [4.81-7.10]) higher risk for those drinking >3 drinks/day compared with <1 drink/day, with a 2-fold (1.88 [1.55-2.28]) higher risk for non-drinkers who likely included ex-drinkers who stopped drinking due to poor health.[146] In Asia, the KVHS reported a strong linear association between alcohol consumption and liver disease mortality among regular drinkers (HR=1.65 [1.49-1.84] per 45g/week; 338 deaths).[103]

Several prospective studies have investigated the potential interactions between alcohol consumption and BMI, but the findings are inconsistent and are based on relatively small numbers of cases. A small cohort study on 9559 Scottish men with 29 years of follow-up (80 liver disease deaths, 196 liver disease cases including liver cancer) reported a significant supra-additive interaction between alcohol consumption and higher BMI on liver disease.[148] A study of 95,126 post-menopausal women in England with 5 years of follow-up also reported higher HRs of liver-related events (325 cases including liver cancer) among those with higher BMI, but no significant interactions were found.[147] In contrast to Western findings, the KVHS (also with ~5 years of follow-up) reported a significant supra-additive interaction on liver disease mortality between high alcohol intake and lower BMI.[103] While the findings might reflect potential differences between Asian and Western populations (e.g., aetiology of liver diseases), it might also be explained partly by the short follow-up period and the

use of mortality outcome in the KVHS. It is possible that individuals might have experienced weight loss by the time of baseline due to undetected severe liver diseases which have poor short-term prognosis, and this could lead to reverse causation in the findings from the KVHS.[149] It is also possible that certain factors and conditions linked to low BMI (e.g., socio-economic deprivation, smoking, nutritional status) may have adverse effects on the short-term prognosis and mortality risk in people with severe liver diseases.

2.2.2 Liver cirrhosis and ALD

Similar to overall liver disease, existing studies on liver cirrhosis have consistently shown clear dose-response associations with amount of alcohol consumption, with some studies reporting J-shaped relationships when including non-drinkers.[71,74,75,103,150,151]

A meta-analysis by Rehm et al involving 1.5 million participants with 3384 cases from 14 cohorts and 3 case-control studies, mostly based on the US and European populations, reported significant dose-response relationships between alcohol consumption and risk of liver cirrhosis and ALD (Table 2.17).[71] In that meta-analysis, more pronounced impacts were observed for mortality than morbidity and in women than in men ($RR_{60+g/day\ vs.\ lifetime\ abstainers}$=22.7 [17.2-30.1] for mortality and 6.1 [4.6-8.0] for morbidity in women; 14 [11.7-16.7] for mortality and 5.0 [3.9-6.4] for morbidity in men).[71] For morbidity, the risk appeared to increase starting from >2 drinks/day in women and >3 drinks/day in men, while no thresholds were observed for mortality. This might be explained by the detrimental effects of alcohol drinking on existing liver

diseases, e.g., via worsening the immune system, which might accelerate the progression to end-stage liver diseases and deaths.[71] Subsequently published prospective studies in Western populations have also reported J-shaped associations between alcohol consumption and risks of liver cirrhosis and ALD (Table 2.18). The MWS previously reported a ~40% (RR=1.41 [1.23-1.61]) excess risk of liver cirrhosis and ALD among never and former drinkers compared with women drinking 1-2 units/week (2105 cases among all women; 6 years of follow-up).[150] Among drinkers, a more recent MWS analysis with 15 years of follow-up reported a clear dose-response relationship, with a 3.5-fold (RR=3.43 [2.87-4.10]; 1560 cases) higher risk associated with drinking >15 drinks/week versus 1-2 drinks/week.[75] In addition, there were a significant multiplicative interaction between higher alcohol consumption and smoking[150] and also an additive interaction between higher alcohol consumption and higher BMI on risk of liver cirrhosis and ALD.[152] Similarly, the Danish Diet, Cancer and Health Study (DCHS) of 56,000 participants with 15 years of follow-up also reported a higher risk of alcoholic cirrhosis in current abstainers compared with those drinking ≤14 drinks/week (HR=7.58 [3.39-16.9]; 257 cases among men), with a strong dose-response relationship observed among current drinkers.[74] A recent meta-analysis of 7 cohorts and 2 case-control studies (5505 cases), which was published after the completion of this literature review chapter, reported no excess risks of liver cirrhosis in occasional drinkers but an approximately 3-fold higher risk in former drinkers compared with lifetime abstainers.[153] The meta-analysis also reported a dose-response association with amount of alcohol intake, which appeared stronger in women than in men.[153]

Several prospective studies in Asia have also reported positive associations between alcohol consumption and mortality of ALD and liver cirrhosis. The Singapore Chinese Health Study reported no excess risks of liver cirrhosis mortality at <20g/day but a 7-fold (HR=7.07 [4.01-12.47]; 114 deaths) higher risk in those drinking 20+g/day compared with non-drinkers.[151] The KVHS reported a clear dose-response association between alcohol intake and ALD mortality (HR=1.67 [1.45-1.93] per 45g/week; 178 deaths), with a supra-additive interaction observed between high alcohol intake and low BMI.[103] In China, the CPSS (418 deaths) reported no significant associations for overall drinking with liver cirrhosis mortality compared with non-drinkers.[73] However, both the CPSS ($HR_{\geq 700g/week\ vs.\ non\text{-}drinkers}$=1.74 [1.22-2.48])[73] and the SCS ($RR_{\geq 29\ drinks/week\ vs.\ non\text{-}drinkers}$=2.99, p<0.01; 35 deaths)[72] reported significantly increased mortality risks of liver cirrhosis among heavy drinkers. There are no prospective studies quantifying the association between alcohol consumption and ALD in China.

As well as alcohol amount consumed, the effects of drinking patterns on liver cirrhosis and ALD have also been increasingly explored in Western populations. The DCHS reported a 3.6-fold (HR=3.65 [2.39-5.55]) higher risk of alcoholic cirrhosis, given amount consumed, associated with daily drinking compared with drinking 2-4 days/week in men.[74] Likewise, the recent MWS analysis showed that daily drinking was associated with a 61% (RR=1.61 [1.40-1.85]) excess risk of liver cirrhosis and ALD compared with non-daily drinking, after adjusting for total weekly intake, mealtime habits, and beverage types.[75] Conversely, although the study outcomes were not specifically liver cirrhosis or ALD, some small cohort studies have shown detrimental effects of HED frequency on risks of liver diseases after controlling for volume of

drinking, including the Finland Health 2000 Study ($HR_{\text{weekly binge vs. <monthly binge}}$=3.45 [1.71-6.94]; 84 cases) and a general population survey in the US ($HR_{\text{daily risk drinking vs. never risk drinking}}$= 4.76 [2.29-9.88]; ~130 cases).[154,155] However, these findings should be interpreted with caution given the small numbers of cases. Moreover, these comparisons were made based on the frequency of HED, e.g., those who engaged in HED frequently (e.g., ≥weekly) vs. those who never or rarely engaged in HED (e.g., <monthly). The huge disparity in terms of total alcohol intake and drinking frequency between the comparison groups might have confounded the results.

Regarding the effect of meals, the MWS reported a 31% (RR=0.69 [0.62-0.77]) decreased risk of liver cirrhosis and ALD associated with drinking with meals versus drinking without meals after adjusting for total weekly intake,[75] as also suggested in a previous small cross-sectional study in Italy.[156] Findings on the effects of beverage types are however mixed. The DCHS showed that wine drinkers had a lower risk of alcoholic cirrhosis than beer and liquor drinkers up to moderate weekly amounts,[74] as shown in previous studies in Denmark.[157] However, the MWS reported similar risk estimates among wine-only drinkers and drinkers of a mixture of alcoholic beverages.[75]

No prospective studies on drinking patterns and liver diseases are available from China, although a small cross-sectional study in Xi'an city with 83 ALD cases reported a higher prevalence of ALD in drinkers who usually drank outside mealtimes than those who drank only at mealtimes, especially for those who drank strong spirits only or multiple types of alcoholic beverages.[158]

2.2.3 NAFLD

For all stages of liver diseases from hepatic steatosis (fatty liver) to cirrhosis, the basic distinction between “alcoholic” and “non-alcoholic” is based on the history of alcohol intake, usually at cut-points of 20g/day for women and 30g/day for men.[144] However, the usefulness of such a distinction into “alcoholic” and “non-alcoholic”, at least for fatty liver, has been questioned due to the uncertainty of the relationship between alcohol intake and fatty liver and possible underreporting of alcohol consumption in clinical settings.[159] Given this, this section reviews evidence from meta-analyses and prospective studies which studied either NAFLD or fatty liver as study outcomes.

No direct comparisons were made between overall drinkers and never drinkers in the identified studies. Existing meta-analyses, based mainly on cross-sectional studies, tend to show inverse associations with low and moderate drinkers compared with non-drinkers, and there is insufficient evidence to assess the associations with heavy drinking. A meta-analysis by Cao et al including 16 studies, of which 13 were cross-sectional studies and 9 were from Japan, with 76,608 participants reported a significantly lower risk of fatty liver disease associated with low to moderate drinking (<280g/week) compared with non-drinking (OR=0.77 [0.69-0.86]) (Table 2.17).[143] The findings concerning heavy drinking compared with non-drinking were however conflicting; Cao et al reported a significantly lower risk in Japanese studies (OR=0.67 [0.58-0.77]; 6 studies) but a higher risk in German studies (1.79 [1.06-3.00]; 2 studies).[143] Similarly, another meta-analysis involving 25,662 cases from 18 studies (mostly cross-sectional studies and/or in Japanese populations) reported a significantly lower risk of fatty liver disease associated with drinking <20g/day compared with non-

drinking in studies from Japan (RR=0.75 [0.71-0.79]; 14 studies) but not other countries (1.05 [0.86-1.30]; 8 studies).[144]

Recently, the Whitehall II study involving 5407 participants in the UK with 30 years of follow-up showed that both former drinking (OR=2.09 [1.55-2.85] in men, 1.68 [1.08-2.67] in women) and sustained heavy drinking (2.04 [1.53-2.74] in men, 2.24 [1.08-4.55] in women) were associated with a higher fatty liver index, which is a proxy for fatty liver disease, compared with stable low-risk drinking (i.e., 8-168g/week in men, 8-112g/week in women) (Table 2.18).[160] However, the Whitehall II study found no significant associations among stable low-risk drinkers compared with non-drinkers, suggesting that the previously reported protective associations of low-risk drinking for fatty liver, most of which are based on cross-sectional studies, may be due to recall bias and reverse causation.

In China, a small cross-sectional study with 9432 male retirees (3169 cases) in Shiyan City also reported positive dose-response relationships between NAFLD risk and moderate alcohol consumption, as well as duration of drinking.[161] Yet, no prospective studies on fatty liver and alcohol consumption are available from Chinese populations.

2.3 *ALDH2*-rs671, cancers and liver diseases

Among East Asian populations, the *ALDH2*-rs671 A allele which causes the "Asian flushing response" deters its carriers from alcohol consumption, especially individuals with the *ALDH2*-rs671 AA genotype, which may protect them against risks of certain cancers and liver diseases. However, there is increasing evidence that the *ALDH2*-rs671 A allele may also contribute to increased susceptibility to carcinogenesis and may

modify the associations between alcohol drinking and certain cancer risks, especially in habitual drinkers with the *ALDH2*-rs671 AG genotype who experience a dramatically elevated acetaldehyde level after moderate alcohol consumption. A recent meta-analysis by Zuo et al involving 66 case-control studies with 25,682 cancer cases reported a significantly lower risk of overall cancer associated with the *ALDH2*-rs671 AA compared with the GG genotype (OR=0.85 [0.72-0.99]), whereas a significantly higher risk was associated with the AG versus the GG genotype (1.32 [1.14-1.52]).[162] The *ALDH2*-rs671 AG genotype was also associated with significantly higher risks of oesophageal cancer (OR=1.79 [1.28-2.49]) and oral cancer (1.37 [1.00-1.88]) compared with the GG genotype.[162] Previous studies, mostly of case-control studies but also a recent prospective study based on the CKB, have consistently reported synergistic interactions between *ALDH2*-rs671 genotype and alcohol consumption on cancers of the oesophagus and mouth and throat, with higher risks observed in drinkers with the *ALDH2*-rs671 AG than drinkers with the GG genotype, given the same volume of alcohol consumption.[163,164] Other than UADT cancers, Zuo et al did not find any significant associations between *ALDH2*-rs671 genotype and other cancers including cancers of the liver, colon and rectum, breast, lung, pancreas, and stomach.[162] A few case-control studies have reported possible synergistic interactions between *ALDH2*-rs671 genotype and alcohol consumption for liver cancer, colorectal cancer, and stomach cancer,[163,165] but the overall evidence remains sparse and inconclusive.

The accumulation of acetaldehyde, a major toxic metabolite in the liver where >90% of alcohol is metabolised, may also increase susceptibility to liver injury after alcohol consumption.[166] Animal studies have suggested that ALDH2 deficiency may confer

resistance to early-stage alcoholic fatty liver but stimulate hepatic inflammation and fibrosis following alcohol consumption.[167] However, evidence from epidemiological studies is limited and tends to reflect the strong protective effect of the *ALDH2*-rs671 A allele on heavy drinking and thus the risks of liver diseases. In contrast, there has been little investigation into the potential interactions between *ALDH2*-rs671 genotype and alcohol consumption on risks of liver diseases. A meta-analysis of 12 case-control studies with 1003 cases reported a decreased alcoholic cirrhosis risk in individuals with the *ALDH2*-rs671 AG than those with the GG genotype (OR=0.78 [0.61-0.99]).[168] Similarly, a subsequently published case-control study of 281 ALD patients in Beijing reported a significantly lower prevalence of the *ALDH2*-rs671 AG genotype in ALD patients than in healthy controls.[169] However, among ALD patients, the duration of drinking and amount consumed were lower in those with the *ALDH2*-rs671 AG than those with the GG genotype.[169] The findings therefore suggest that among *ALDH2*-rs671 AG drinkers, the ALD risk increase may start at a lower alcohol intake level than that in *ALDH2*-rs671 GG drinkers, as a result of acetaldehyde accumulation due to reduced ALDH2 enzyme activity.[169] However, there were no formal tests for interaction between *ALDH2*-rs671 genotype and alcohol intake on ALD risk in the study. Recently, two small studies in Japan have reported increased risks of fatty liver disease associated with the *ALDH2*-rs671 AA and AG versus the GG genotype, which however are based on small sample size (n<1600) and are in specific populations (e.g., non- or moderate drinkers, alcohol dependent men).[170,171]

2.4 Other mechanisms

Apart from the action of alcohol via acetaldehyde which is a Group 1 carcinogen,[19,20] other potential mechanisms by which alcohol may contribute to the development of various cancers and liver diseases are not well established. Several plausible general mechanisms have been proposed.

In addition to the ADH-mediated ethanol oxidation pathway, ethanol can also be oxidized by microsomal enzyme cytochrome P450 2E1 (CYP2E1), which is found mainly in the liver and also many other tissues (e.g., oesophagus, pancreas, lung, breast, brain).[20,172] CYP2E1 is induced by chronic alcohol consumption and produces reactive oxygen species that can cause DNA damage (e.g., through lipid peroxidation), which may relate to most cancer types but particularly to liver diseases and liver cancer.[20,41,172] In addition, ethanol may act as the solvent for cellular penetration of environmental carcinogens, especially tobacco for cancers of the upper digestive and respiratory tract.[173] Alcohol consumption may also alter sex hormone levels (e.g., increased levels of oestrogen) and related signalling pathways for sex-specific cancers, e.g., breast cancer.[172,173] While folate is essential for DNA synthesis, repair, and methylation, alcohol consumption may inhibit folate absorption and lead to folate deficiency, which may promote carcinogenesis in different tissues, especially in the colon and rectum.[41,173,174] Moreover, chronic alcohol consumption may result in impaired immune surveillance and suppressed immune response against tumour cells, therefore facilitating cancer development and progression.[172] The mechanisms for the inverse associations between alcohol intake and kidney cancer are uncertain. One potential explanation is that the improved insulin sensitivity associated with low to

moderate alcohol intake might protect against kidney cancer, given that diabetes and hyperinsulinemia have been linked to increased kidney cancer risks.[175,176] A further potential mechanism relates to the diuretic effects of alcohol and the resulting increased urine volume, which may reduce the concentration of carcinogens and the duration of carcinogen exposure in the kidney; however, the relationship between total fluid intake and kidney cancer has not been established.[175]

Heavy alcohol consumption can induce changes in lipid metabolism and result in fatty liver.[177] Furthermore, heavy alcohol consumption may induce inflammation and fibrosis leading to liver cirrhosis and pancreatitis, which may develop into liver cancer and pancreatic cancer, respectively.[172,173] For example, chronic alcohol consumption can cause hepatocyte death, inhibit liver regeneration, and suppress anti-fibrotic effects.[178] Also, chronic high alcohol consumption can cause intestinal dysbiosis, which leads to weakened gut barrier function and gut leakiness of bacterial products. This may induce chronic inflammation which has been associated with liver diseases, liver cancer, and colorectal cancer.[41,179] Moreover, heavy drinking may interact with chronic viral hepatitis (e.g., via enhanced viral replication, weakened immune response) to accelerate progression to liver cirrhosis and liver cancer.[180,181]

2.5 Summary of findings and gaps in existing evidence

2.5.1 Alcohol and cancers

Existing studies have shown consistent positive associations between amount of alcohol consumption and cancers of the mouth and throat, oesophagus, colon and rectum, liver, and female breast, with apparent excess risks at higher intake levels only

for cancers of the colon-rectum and liver. There is also suggestive evidence that heavy alcohol consumption is associated with higher risks of lung cancer, stomach cancer, and pancreatic cancer. However, these associations may be partly due to potential residual confounding by smoking and other factors. In particular, few studies are large enough to assess reliably the associations between alcohol and lung cancer in never smokers. Also, few studies on stomach cancer adjusted for dietary factors (e.g., fresh fruit and vegetable intake). For other cancers, previous studies have reported inverse associations of alcohol consumption with kidney cancer and non-Hodgkin lymphoma, mostly up to moderate intake levels, but the underlying mechanisms are uncertain. There is limited evidence for positive associations of alcohol intake with gallbladder cancer and prostate cancer.

There is no clear evidence that the associations of alcohol with most cancer types differ by beverage types. However, the associations of other important drinking patterns (e.g., drinking daily, drinking without meals, HED) with site-specific cancers have not been assessed reliably and systematically.

2.5.2 Alcohol and liver diseases

Current non-drinkers (who may include former drinkers) have been consistently associated with excess risks of liver diseases compared with light drinkers, which is likely due to reverse causation. Among regular drinkers, previous studies have consistently shown positive dose-response relationships between alcohol consumption and overall liver disease, ALD, and liver cirrhosis. The relationship between alcohol

consumption and fatty liver disease (including NAFLD) is unclear, as existing evidence is mostly based on cross-sectional studies and is inconsistent across populations.

Emerging evidence from Western populations have shown that drinking daily and drinking without meals may further exacerbate the risks of liver cirrhosis and ALD, independent of the total amount consumed, but there is no clear evidence of differential effects by beverage types. Few prospective studies have investigated the interactions between alcohol consumption and other factors (e.g., BMI, HBV infection) on risks of liver diseases; for those that did, the numbers of cases are limited and the results are inconsistent.

2.5.3 *ALDH2*-rs671, cancers and liver diseases

A number of case-control studies have reported potential interactions between alcohol drinking and *ALDH2*-rs671 genotype on risks of UADT cancers. However, evidence is uncertain for other major cancer types and liver diseases.

2.5.4 Limitations of existing studies

The majority of previous studies have involved Western populations and high-income East Asian populations (e.g., Japan, South Korea). Given the substantial cancer and liver disease burden in China and the differences in drinking patterns, other risk factor exposures, and genetic background between Chinese and these high-income populations, relevant evidence from China is important to advance knowledge about the aetiology of these diseases and inform public health policy. However, most prospective studies in China covered only a single high-risk area or urban city, involved small sample size, had limited information on alcohol consumption (e.g., no

information on past drinking or drinking patterns), and were conducted at least 30 years ago (since then alcohol consumption has increased substantially, see Chapter 1). Furthermore, most studies in China involved disease mortality only, which precluded the investigation of less common (e.g., mouth and throat cancer, kidney cancer, prostate cancer) and less fatal disease outcomes (e.g., NAFLD). Importantly, the associations of alcohol consumption with cancer and liver disease mortality may be confounded by a number of other factors (e.g., disease severity, access to healthcare, treatment), whereas the associations with disease incidence would be more informative in understanding the role of alcohol in disease development and informing disease prevention.

Almost all prospective studies reviewed excluded participants with known cancers or other pre-existing conditions from the analyses. However, most studies (especially those in Chinese populations) directly compared different alcohol consumption levels with non-drinkers, who may include people who had stopped drinking due to early signs of disease or abstained in the first place because of underlying poor health (i.e., "sick-quitters/sick non-starters").[182,183] This may lead to reverse causation and residual confounding in the findings, complicating the interpretation of the null or inverse associations of low alcohol intake observed for some outcomes. Furthermore, most existing studies had only one baseline measure of alcohol intake, which may not accurately reflect an individual's true "usual" alcohol intake because of random measurement error and changes over time. The use of a single measurement of alcohol exposure (where within-person variation in alcohol intake is unaccounted for)

may lead to an underestimation of the true risk association (i.e., “regression dilution bias”).[184]

2.5.5 Conclusions

Although alcohol consumption has been associated with certain cancers (mouth and throat, oesophagus, liver, colon and rectum), ALD, and liver cirrhosis, evidence in Chinese populations and for other cancers and liver diseases, which is in part constrained by the limitations in existing studies, is less clear. How different drinking patterns and alcohol tolerance might affect the risks of different cancers and liver diseases remains to be further explored. Given the major differences in drinking patterns, genetics, lifestyles, and environmental risk factors between China and Western countries, reliable assessment of the associations of alcohol consumption and drinking patterns with incident site-specific cancers and liver diseases in a large well-designed prospective study in Chinese population could help advance the understanding of disease aetiology and inform public health policy.

Table 2.1. Meta-analyses on alcohol consumption and risks of cancers of the mouth and throat, and UADT

Authors, year	Location	No of cases	Cancer site	Reference category	No of studies & study design	Subgroup	Exposure category	RR or OR (95% CI)*
Li et al, 2011[101]	China	1698	Nasopharynx	Non-drinkers	4 C-C	Overall	Drinkers	1.21 (1.00-1.46)
		347	Oral		3 C-C	Overall	Drinkers	1.71 (1.20-2.44)
Bagnardi et al, 2015[100]	Worldwide	18837	Oral cavity and pharynx	Non-drinkers and occasional drinkers	52 (5 cohorts, 47 C-C)	Overall	Light	1.13 (1.00-1.26)
							Moderate	1.83 (1.62-2.07)
							Heavy	5.13 (4.31-6.10)
					29	Men	Light	1.20 (1.06-1.35)
							Moderate	2.01 (1.69-2.40)
							Heavy	5.33 (4.28-6.63)
					9	Women	Light	1.00 (0.78-1.27)
							Moderate	1.67 (1.25-2.22)
							Heavy	5.70 (3.75-8.66)
					18	European	Light	0.95 (0.80-1.12)
							Moderate	1.51 (1.22-1.89)
							Heavy	5.41 (3.79-7.72)
					15	North American	Light	1.09 (0.92-1.29)
							Moderate	2.02 (1.74-2.34)
							Heavy	5.58 (4.35-7.15)
					12	Asian	Light	1.33 (1.06-1.68)
							Moderate	2.18 (1.64-2.91)
							Heavy	3.02 (1.93-4.73)
		9634	Larynx		41 (3 cohorts, 38 C-C)	Overall	Light	0.87 (0.68-1.11)
							Moderate	1.44 (1.25-1.66)
							Heavy	2.65 (2.19-3.19)
					25	Men	Light	0.85 (0.61-1.19)
							Moderate	1.50 (1.23-1.83)
							Heavy	2.77 (2.15-3.57)
					3	Women	Light	0.89 (0.62-1.29)
							Moderate	1.59 (1.06-2.38)
							Heavy	1.55 (0.45-5.34)
					20	European	Light	0.83 (0.41-1.67)

Authors, year	Location	No of cases	Cancer site	Reference category	No of studies & study design	Subgroup	Exposure category	RR or OR (95% CI)*
							Moderate	1.36 (1.12-1.65)
							Heavy	2.71 (2.02-3.63)
					15	North American	Light	0.90 (0.67-1.21)
							Moderate	1.54 (1.20-1.98)
							Heavy	2.74 (2.15-3.48)
					4	Asian	Light	0.72 (0.34-1.50)
							Moderate	1.57 (0.78-3.16)
							Heavy	1.63 (0.70-3.79)
WCRF SLR, 2016[96]	Worldwide	5617	Oral		6	Overall	Per 10g/day	1.15 (1.09-1.22)
					5	Men	Per 10g/day	1.13 (1.04-1.22)
					4	Women	Per 10g/day	1.24 (1.07-1.45)
		954	Oral/pharynx		5	Overall	Per 10g/day	1.19 (1.10-1.30)
					3	Men	Per 10g/day	1.09 (1.04-1.15)
					2	Women	Per 10g/day	1.28 (1.16-1.41)
		781	Larynx		6	Overall	Per 10g/day	1.09 (1.05-1.13)
					5	Men	Per 10g/day	1.09 (1.05-1.12)
					4	Women	Per 10g/day	1.22 (1.03-1.45)
		1826	UADT		9	Overall	Per 10g/day	1.18 (1.10-1.26)
					6	Men	Per 10g/day	1.17 (1.08-1.27)
					3	Women	Per 10g/day	1.19 (0.95-1.49)
Jayasekara et al, 2016[105]	North America, Europe, Australia, Asia		UADT	Lowest category (usually non-drinkers)	16 (3 cohorts, 13 C-C)	Overall	Highest category	2.83 (1.73-4.62)
			Oral cavity and pharynx			Overall	Highest category	4.84 (2.51-9.32)
			Larynx			Overall	Highest category	2.25 (1.49-3.42)

UADT, upper-aerodigestive tract; RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review.
*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.2. Prospective studies on alcohol consumption and risks of cancers of the mouth and throat, and UADT

Authors, year	Location; cohort	Baseline period (mean/median follow-up)	Age	No of case/ sample size	Cancer site	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Yi et al, 2016[103]	Korea; KVHS	2004 (to 2010)	Mean 58.8	199 deaths / 107735 men	UADT	<1 drink (~9g)/week	Overall	1-6 drinks/week 7-13 drinks/week 14-27 drinks/week ≥28 drinks/week Per 5 drinks/week	1.10 (0.71-1.68) 1.39 (0.85-2.28) 2.44 (1.60-3.71) 3.08 (2.00-4.75) 1.63 (1.39-1.91)	Age at enrolment, smoking, physical activity, income, BMI	Significant additive interaction between low BMI and high alcohol intake.
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	552 incidents / 124193	UADT	Lifelong abstainers	Overall	Ex-drinkers <1 drink/day 1-2 drinks/day ≥3 drinks/day	2.9 (1.9-4.6) 1.1 (0.8-1.6) 1.5 (1.1-2.3) 2.5 (1.7-2.8)	Age, race, education, BMI, marital status, smoking	Consistent cross beverage types.
Yuan et al, 1997[72]	Shanghai, China; SCS	1986-1989 (6.7 years)	45-64	64 deaths / 18244 men	UADT	Lifelong non-drinkers	Men	1-28 drinks/week ≥29 drinks/week	1.49 3.72	Age, education, smoking	1 drink ≈ 13g of ethanol. Significant for ≥29 drinks/week.
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	134 deaths / 66820	Head and neck	Never drinkers	Overall	Ex-drinkers Social (<1/week) Weekly social Weekly moderate Weekly high	0.88 (0.51-1.54) 0.64 (0.35-1.18) 1.32 (0.41-4.27) 1.10 (0.51-2.36) 2.58 (1.00-6.67)	Age, exercise, sex, SES, BMI, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).

UADT, upper-aerodigestive tract; HR, hazard ratio; RR, risk ratio; CI, confidence interval; KVHS, Korean Veterans Health Study; BMI, body mass index; US, United States; SCS, Shanghai Cohort Study; SES, socio-economic status.
All studies (except Yi et al and Shen et al who did so in subgroup or sensitivity analyses) excluded prior cancers at baseline.
All studies measured alcohol consumption at baseline only.

Table 2.3. Meta-analyses on alcohol consumption and oesophageal cancer risk

Authors, year	Location	No of cases	Outcome	Reference category	No of studies & study design	Subgroup	Exposure category	RR or OR (95% CI)*
Li et al, 2011[101]	China	10189	Oesophageal cancer	Non-drinkers	34 C-C, 2 cohorts	Overall	Drinkers	1.78 (1.38-2.30)
						Men	Drinkers	1.82 (1.49-2.22)
						Women	Drinkers	0.91 (0.47-1.77)
						Cohort	Drinkers	1.08 (0.94-1.23)
						C-C	Drinkers	1.79 (1.47-2.17)
Bagnardi et al, 2015[100]	Worldwide	14318	ESCC	Non-drinkers and occasional drinkers	54 (13 cohorts, 41 C-C)	Overall	Light	1.26 (1.06-1.50)
							Moderate	2.23 (1.87-2.65)
							Heavy	4.95 (3.86-6.34)
					13	Cohort	Light	1.20 (0.84-1.71)
							Moderate	1.92 (1.44-2.58)
							Heavy	3.56 (2.25-5.64)
					41	C-C	Light	1.29 (1.07-1.55)
							Moderate	2.34 (1.87-2.92)
							Heavy	5.43 (4.04-7.32)
					31	Men	Light	1.39 (1.11-1.74)
							Moderate	2.25 (1.78-2.85)
							Heavy	4.69 (3.49-6.31)
					9	Women	Light	1.14 (0.87-1.49)
							Moderate	2.18 (1.42-3.35)
							Heavy	8.32 (2.95-23.45)
					13	European	Light	1.05 (0.79-1.38)
							Moderate	1.91 (1.32-2.77)
							Heavy	4.76 (2.69-8.41)
					13	North American	Light	1.07 (0.84-1.37)
							Moderate	2.95 (2.38-3.67)
							Heavy	7.63 (5.34-10.91)
					23	Asian	Light	1.54 (1.18-2.00)
							Moderate	2.20 (1.65-2.94)
							Heavy	4.24 (2.93-6.14)

Authors, year	Location	No of cases	Outcome	Reference category	No of studies & study design	Subgroup	Exposure category	RR or OR (95% CI)*
		5727	EAC and gastric cardia		25	Overall	Light	0.86 (0.76−0.98)
							Moderate	0.97 (0.78−1.22)
							Heavy	1.15 (0.95−1.39)
WCRF SLR, 2015[94]	Worldwide	6618	Oesophageal cancer		17	Overall	Per 10g/day	1.24 (1.16-1.33)
					11	Men	Per 10g/day	1.34 (1.22-1.47)
					4	Women	Per 10g/day	1.25 (1.14-1.37)
					9	Asia	Per 10g/day	1.34 (1.19-1.49)
					4	Europe	Per 10g/day	1.16 (1.01-1.33)
					4	North America and Europe	Per 10g/day	1.17 (1.07-1.28)
					3	Not adjusted for smoking	Per 10g/day	1.24 (1.00-1.53)
					14	Adjusted for smoking	Per 10g/day	1.25 (1.15-1.36)
					7	Not adjusted for body fatness	Per 10g/day	1.34 (1.17-1.54)
					10	Adjusted for body fatness	Per 10g/day	1.20 (1.09-1.31)
			ESCC		6	Overall	Per 10g/day	1.25 (1.12-1.41)
			EAC		6	Overall	Per 10g/day	1.00 (0.98-1.02)
Jayasekara et al, 2016[105†]	North America, Europe, Australia, Asia		Oesophageal cancer	Lowest category (usually non-drinkers)	8 C-C	Overall	Highest category	6.71 (4.21-10.70)

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); ESCC, oesophageal squamous cell carcinoma; EAC: oesophageal adenocarcinoma; WCRF, World Cancer Research Fund; SLR, Systematic Literature Review.

*For Li et al, the effect size and CIs correspond to OR (99%CI).

†Included only studies with exposure of lifetime/long-term alcohol consumption.

Table 2.4. Prospective studies on alcohol consumption and oesophageal cancer risk

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	RR or HR (95% CI)	Adjustment	Notes
Choi et al, 2017[106]	South Korea; NHIC	2009-2012 (5.4 years)	20+	9171 incidents / 23323730	Oesophageal cancer	Non-drinkers	Overall	<30g/day	1.52 (1.45-1.60)	Age, sex, smoking, exercise, income, BMI, diabetes	Synergistically increased risks between excessive drinking and current smoking, and low BMI.
								≥30g/day	3.13 (2.95-3.32)		
							Men	<30g/day	1.55 (1.47-1.63)		
								≥30g/day	3.17 (2.99-3.37)		
							Women	<30g/day	1.16 (0.95-1.41)		
								≥30g/day	2.45 (1.50-4.03)		
Yi et al, 2016[103]	South Korea; KVHS	2004 (to 2010)	Mean 58.8	108 deaths /107735 men	Oesophageal cancer	<1 drink (~9g) /week	Overall	1-6 drinks/week	1.40 (0.74-2.64)	Age at enrolment, smoking, physical activity, income, BMI	Significant additive interaction between low BMI and high alcohol intake.
								7-13 drinks/week	2.23 (1.13-4.40)		
								14-27 drinks/week	3.51 (1.90-6.47)		
								≥28 drinks/week	5.14 (2.79-9.47)		
								Per 5 drinks/week	1.81 (1.53-2.14)		
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	115 deaths / 66820	Oesophageal cancer	Never drinkers	Overall	Ex-drinkers	1.53 (0.85-2.73)	Age, sex, SES, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Insufficient study power in women. Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).
								Social (<1/week)	1.34 (0.75-2.38)		
								Weekly social	0.73 (0.10-5.34)		
								Weekly moderate	3.15 (1.62-6.09)		
								Weekly high	6.63 (2.92-15.02)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	RR or HR (95% CI)	Adjustment	Notes
Yang et al, 2012[73]	China; CPSS	1990-1992 (15 years)	40-79	848 deaths / 218189 men	Oesophageal cancer	Non-drinkers	Men	Non-drinkers	1.00 (0.91-1.10)	Age, area, smoking, education	Floated CIs are presented. NS trend with alcohol amount among drinkers.
								All drinkers	1.25 (1.07-1.47)		
								<140g/week	1.19 (0.93-1.53)		
								140-279g/week	1.28 (1.00-1.65)		
								280-419g/week	1.11 (0.84-1.46)		
								420-699g/week	1.38 (0.99-1.94)		
								≥700g/week	1.63 (1.12-2.39)		
Fan et al, 2008[109]	Shanghai, China; SCS	1986-1989 (10.2 years)	45-64	101 incidents / 18244 men	Oesophageal cancer	Non-drinkers	Men	Regular drinkers	2.02 (1.31-3.12)	Age, baseline year, BMI, residence, education, preserved food intake, fresh fruits intake, fresh vegetable intake, years of smoking; (for specific beverage type) consumption of other alcoholic beverages	1 drink ≈ 13g. Significant trend with amount, duration, and lifetime consumption. Risks appeared higher for spirits vs. wine or rice wine intake. Joint effect analysis showed the highest risk in long-term smokers (>40 years) drinking 4+ drinks/day (vs. non-drinking non-smokers), but *p*-interaction was NS.
								<1 drink/day	1.22 (0.62-2.44)		
								1- <2 drinks/day	1.87 (0.99-3.53)		
								2- <4 drinks/day	2.01 (1.13-3.59)		
								4+ drinks/day	3.74 (2.12-6.59)		
							Age started drinking	30+ years	1.58 (0.92-2.71)		
								20-29 years	2.37 (1.41-3.98)		
								<20 years	2.54 (1.36-4.74)		
							Years of drinking regularly	<20 years	1.33 (0.68-2.59)		
								20-39 years	2.02 (1.23-3.32)		
								40+ years	3.22 (1.77-5.86)		
							Beer	<1 drink/day	1.46 (0.75-2.85)		
								1+ drinks/day	1.71 (0.66-4.42)		
							Rice wine	<1 drink/day	1.39 (0.66-2.90)		
								1- <2 drinks/day	3.51 (1.73-7.13)		
								2+ drinks/day	1.82 (0.82-4.01)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	RR or HR (95% CI)	Adjustment	Notes
							Spirits	<2 drinks/day	1.02 (0.45-2.30)		
								2- <4 drinks/day	2.87 (1.48-5.58)		
								4+ drinks/day	4.93 (2.60-9.36)		
				68	ESCC		Overall	>4 drinks/day	4.64 (2.31-9.30)		
Tran et al, 2005[108]	China; Linxian General Population Trial	1986-1991 (15 years)	40-69	1958 incidents / 29584	ESCC	Past-year non-drinkers	Overall	Past-year drinking	0.92 (0.82-1.03)	Age, gender	

HR, hazard ratio; RR, risk ratio; CI, confidence interval; NHIC, National Health Insurance Corporation; BMI, body mass index; KVHS, Korean Veterans Health Study; SES, socio-economic status; CPSS, Chinese Prospective Smoking Study; NS, non-significant; SCS, Shanghai Cohort Study; ESCC, oesophageal squamous cell carcinoma.
All studies (except Yi et al and Shen et al who did so in subgroup or sensitivity analyses) excluded prior cancers at baseline.
All studies measured alcohol consumption at baseline only.

Table 2.5. Meta-analyses on alcohol consumption and colorectal cancer risk

Authors, year	Location	No of cases	Cancer site	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*
Li et al, 2011[101]	China	4311	CRC	Non-drinkers	10 C-C, 1 cohort	C-C	Drinkers	1.58 (0.90-2.76)
Bagnardi et al, 2015[100]	Worldwide	41715	CRC	Non-drinkers and occasional drinkers	66 (33 cohorts, 33 C-C)	Overall	Light	0.99 (0.95-1.04)
							Moderate	1.17 (1.11-1.24)
							Heavy	1.44 (1.25-1.65)
					33	Cohort	Light	1.01 (0.95-1.06)
							Moderate	1.20 (1.12-1.29)
							Heavy	1.41 (1.23-1.63)
					33	C-C	Light	0.97 (0.89-1.06)
							Moderate	1.14 (1.05-1.25)
							Heavy	1.46 (1.15-1.86)
					37	Men	Light	1.05 (0.95-1.16)
							Moderate	1.21 (1.11-1.32)
							Heavy	1.53 (1.30-1.80)
					25	Women	Light	0.95 (0.89-1.01)
							Moderate	1.07 (0.99-1.16)
							Heavy	1.24 (0.68-2.25)
					13	European	Light	1.03 (0.97-1.10)
							Moderate	1.17 (1.07-1.29)
							Heavy	1.22 (0.98-1.52)
					27	North American	Light	0.96 (0.90-1.03)
							Moderate	1.14 (1.05-1.24)
							Heavy	1.29 (1.01-1.66)
					24	Asian	Light	1.03 (0.91-1.18)
							Moderate	1.24 (1.08-1.42)
							Heavy	1.73 (1.39-2.16)

Authors, year	Location	No of cases	Cancer site	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*
WCRF SLR, 2016[98]	Worldwide	15896	CRC		16	Overall	Per 10g/day	1.07 (1.05-1.09)
					14	Men	Per 10g/day	1.08 (1.06-1.10)
					10	Women	Per 10g/day	1.04 (1.00-1.08)
					7	Asia	Per 10g/day	1.07 (1.06-1.08)
					5	Europe	Per 10g/day	1.05 (1.02-1.08)
					4	North American	Per 10g/day	1.06 (1.01-1.12)
					6	Wine	Per 10g/day	1.04 (1.01-1.08)
					5	Beer	Per 10g/day	1.08 (1.05-1.11)
					4	Liquor	Per 10g/day	1.08 (1.02-1.14)
		12051	Colon		14	Overall	Per 10g/day	1.07 (1.05-1.09)
					12	Men	Per 10g/day	1.08 (1.06-1.10)
					10	Women	Per 10g/day	1.05 (1.02-1.09)
					8	Asia	Per 10g/day	1.08 (1.07-1.10)
					3	Europe	Per 10g/day	1.03 (1.00-1.07)
					3	North American	Per 10g/day	1.07 (0.99-1.16)
		7763	Rectum		11	Overall	per 10g/day	1.08 (1.07-1.10)
					10	Men	Per 10g/day	1.09 (1.06-1.12)
					8	Women	Per 10g/day	1.09 (1.04-1.15)
					7	Asia	Per 10g/day	1.07 (1.05-1.10)
					3	Europe	Per 10g/day	1.09 (1.05-1.12)
					1	North American	Per 10g/day	1.13 (1.08-1.19)
Jayasekara et al, 2016[105†]	North America, Europe, Australia		CRC	Lowest category (usually non-drinkers)	7 (2 cohorts, 5 C-C)	All	Highest category	1.49 (1.27-1.74)
						Cohort	Highest category	1.86 (1.47-2.36)
						C-C	Highest category	1.35 (1.17-1.57)

RR, risk ratio; OR, odds ratio; CI, confidence interval; CRC, colorectal cancer; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review.

*For Li et al, the effect size and CIs correspond to OR (99%CI).

†Included only studies with exposure of lifetime/long-term alcohol consumption.

Table 2.6. Prospective studies on alcohol consumption and colorectal cancer risk

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Bradbury et al, 2019[112]	UK; UKB	2006-10 (5.7 years)	40-69	2609 incidents / 475581	<1g/day	Overall	1-7g/day	1.02 (0.90-1.16)	Age, sex, regions, SES, smoking status, WC, height, physical activity, family history of CRC, aspirin or ibuprofen use, vitamin D supplement use, folate supplement use; (women only) parity, menopause, OCA use, HRT use; (sensitivity analyses) red and processed meat intake	Significant heterogeneity by sex, and by proximal vs. distal colon.
							8-15g/day	1.06 (0.93-1.20)		
							≥16g/day	1.24 (1.10-1.40)		
							Per 10g/day	1.08 (1.04-1.12)		
				1504		Men	Per 10g/day	1.12 (1.08-1.17)		
				1105		Women	Per 10g/day	0.99 (0.93-1.06)		
						Beer	Per 10g/day	1.11 (1.06-1.18)		
						Wine	Per 10g/day	1.05 (1.00-1.10)		
						Spirits	Per 10g/day	1.08 (0.90-1.31)		
						Beer (colon)	Per 10g/day	1.09 (1.02-1.16)		
						Beer (rectal)	Per 10g/day	1.16 (1.07-1.27)		
						Proximal colon	Per 10g/day	1.00 (0.94-1.06)		
						Distal colon	Per 10g/day	1.12 (1.05-1.19)		
Park et al, 2019[111]	Hawaii and California; MEC	1993-1996 (16.7 years)	45-75	4923 incidents / 190698	0g/day	Overall	0.1-4.9g/day	0.99 (0.91-1.07)	Sex, race/ethnicity, age, family history of CRC, history of colorectal polyps, BMI, pack-years of cigarette smoking, multivitamin use, NSAID use, physical activity, HRT use, daily energy intake (excluding alcohol),	Significant heterogeneity by anatomical subsite, BMI, dietary fibre, and folate intake, but NS heterogeneity by smoking.
							5-14.9g/day	0.94 (0.84-1.05)		
							15-29.9g/day	1.12 (1.00-1.26)		
							≥30g/day	1.24 (1.11-1.37)		
							Per 10g/day	1.02 (1.01-1.03)		
						Men	Per 10g/day	1.02 (1.01-1.03)		
						Women	Per 10g/day	1.01 (0.98-1.04)		
						Beer	Per 10g/day	1.04 (1.02-1.05)		
						Wine	Per 10g/day	1.08 (1.01-1.14)		
						Liquor	Per 10g/day	1.02 (0.98-1.06)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
						Right colon	Per 10g/day	1.01 (0.99-1.03)	red meat, dietary fibre, calcium, folate, vitamin D	
						Left colon	Per 10g/day	1.02 (1.00-1.04)		
						Rectum	Per 10g/day	1.02 (1.00-1.04)		
Choi et al, 2017[106]	South Korea; NHIC	2009-2012 (5.4 years)	20+	154970 incidents / 23323730	Non-drinkers	Overall	<30g/day	1.12 (1.10-1.13)	Age, sex, smoking, exercise, income, BMI, diabetes	Dose-response associations consistent across BMI and smoking, but NS interaction.
							≥30g/day	1.32 (1.30-1.35)		
						Men	<30g/day	1.18 (1.16-1.20)		
							≥30g/day	1.40 (1.37-1.43)		
						Women	<30g/day	0.98 (0.96-1.01)		
							≥30g/day	0.95 (0.87-1.04)		
Jayasekara et al, 2017[110]	Melbourne; MCCS	1990-1994 (14.6 years)	40-69	922 incidents / 38149	Lifetime abstention	CRC	>0-19g/day	1.03 (0.87-1.22)	Age, sex, education, country of birth, SES, smoking, physical activity, total red meat intake, energy from food (excluding alcoholic beverages), dietary fibre intake, dietary folate intake	For men, the effect was stronger for beer than wine.
							20-29g/day	1.24 (0.95-1.60)		
							30-39g/day	1.24 (0.90-1.70)		
							≥40g/day	1.50 (1.15-1.95)		
							Per 10g/day	1.08 (1.04-1.12)		
						Men	Per 10g/day	1.06 (1.02-1.11)		
						Women	Per 10g/day	1.10 (1.00-1.21)		
				596		Colon	Per 10g/day	1.00 (0.96-1.05)		
				326		Rectum	Per 10g/day	1.08 (1.03-1.14)		
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	2148 incidents / 124193	Lifelong abstainers		Ex-drinkers	1.1 (0.9-1.4)	Age, race, education, BMI, marital status, smoking	
							<1 drink/day	1.1 (1.0-1.3)		
							1-2 drinks/day	1.2 (1.0-1.4)		
							≥3 drinks/day	1.4 (1.1-1.7)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Cho et al, 2015[113]	South Korea; KMCC	1993-2005 (11.2 years)	20+	(112 men, 108 women) incidents / 18707	Never drinkers	Men	Former drinkers	0.92 (0.43-1.96)	Age, BMI, moderate physical activity, smoking	NS in women.
							Current drinkers	1.70 (1.05-2.76)		
						Duration (men)	<15 years	0.31 (0.04-2.27)		
							15-29 years	1.32 (0.72-2.44)		
							≥30 years	1.93 (1.17-3.18)		
						Amount (men)	<10g/day	1.28 (0.71-2.31)		
							10-29g/day	1.77 (0.96-3.26)		
							≥30g/day	2.24 (1.31-3.84)		
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	944 deaths / 66820	Never drinkers	Overall	Ex-drinkers	1.11 (0.89-1.37)	Age, sex, SES, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).
							Social (<1/week)	0.96 (0.78-1.18)		
							Weekly social	1.24 (0.75-2.06)		
							Weekly moderate	0.79 (0.54-1.16)		
							Weekly high	1.25 (0.68-2.30)		
Yang et al, 2012[73]	China; CPSS	1990-1991 (15 years)	40-79	193 deaths / 218189 men	Non-drinkers	Men	Non-drinkers	1.00 (0.82-1.22)	Age, area, smoking, education	Floated CIs are presented. NS trend with alcohol amount among drinkers.
							All drinkers	0.90 (0.65-1.24)		
							<140g/week	1.26 (0.79-2.02)		
							140-279g/week	0.60 (0.33-1.08)		
							280-419g/week	0.88 (0.53-1.45)		
							420-699g/week	0.77 (0.38-1.55)		
							≥700g/week	1.06 (0.55-2.06)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Chen et al, 2005[114]	Jiashan county, China	1989-1990 (10.6 years)	30+	242 incidents / 64100	Non-drinkers	CRC	Ex-drinkers	0.21 (0.03-1.54)	Age, sex, smoking status, occupation, education level, marital status	
							Occasional	1.13 (0.79-1.64)		
							Daily drinkers	1.11 (0.74-1.67)		
						Colon	Ex-drinkers	0.37 (0.05-2.75)		
							Occasional	1.06 (0.61-1.83)		
							Daily drinkers	0.97 (0.52-1.78)		
						Rectum	Occasional	1.20 (0.73-1.98)		
							Daily drinkers	1.24 (0.71-2.14)		
Yuan et al, 1997[72]	Shanghai, China; SCS	1986-1989 (6.7 years)	45-64	29 deaths / 18244 men	Lifelong non-drinkers	Men	1-28 drinks/week	0.8	Age, education, smoking	NS. 1 drink ≈ 13g.
							≥29 drinks/week	1.3		

HR, hazard ratio; RR, risk ratio; CI, confidence intervals; CRC, colorectal cancer; UK, United Kingdom; UKB, UK Biobank; SES, socio-economic status; WC, waist circumference; OCA, oral contraceptive agent; HRT, hormone replacement therapy; MEC, Multi-ethnic Cohort Study; BMI, body mass index; NSAID, Nonsteroidal anti-inflammatory drugs; NS, non-significant; NHIC, National Health Insurance Corporation; MCCS, Melbourne Collaborative Cohort Study; US, United States; KMCC, Korean Multi-centre Cancer Cohort; CPSS, Chinese Prospective Smoking Study; SCS, Shanghai Cohort Study.
All studies (except Yi et al and Shen et al who did so in subgroup or sensitivity analyses) excluded prior cancers at baseline.
Except Jayasekara et al who measured usual lifetime alcohol consumption (between age 20 to the decade of baseline age) and Bradbury et al who accounted for regression dilution bias with multiple measures, all other studies measured alcohol consumption at baseline only.

Table 2.7. Meta-analyses on alcohol consumption and liver cancer risk

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
Li et al, 2011[101]	China	3812	Non-drinkers	18 C-C	Overall	Drinkers	1.56 (1.16-2.09)	
					Men	Drinkers	1.56 (1.01-1.62)	
					Women	Drinkers	1.93 (0.81-4.57)	
Bagnardi et al, 2015[100]	Worldwide	12965	Non-drinkers and occasional drinkers	36 (9 cohorts, 27 C-C)	Overall	Light	1.00 (0.85-1.18)	
						Moderate	1.08 (0.97-1.20)	
						Heavy	2.07 (1.66-2.58)	
				9	Cohort	Light	0.85 (0.74-0.97)	
						Moderate	1.00 (0.87-1.17)	
						Heavy	1.12 (1.02-1.23)	
				27	C-C	Light	1.31 (0.97-1.78)	
						Moderate	1.15 (0.97-1.35)	
						Heavy	2.79 (2.00-3.87)	
				16	Men	Light	1.05 (0.84-1.32)	
						Moderate	1.08 (0.88-1.32)	
						Heavy	1.59 (1.21-2.09)	
				9	Women	Light	0.81 (0.59-1.12)	
						Moderate	1.24 (0.88-1.75)	
						Heavy	3.89 (1.60-9.48)	
				9	European	Light	0.92 (0.58-1.46)	
						Moderate	0.83 (0.70-0.97)	
						Heavy	2.00 (1.07-3.74)	
				8	North American	Light	1.24 (0.73-2.10)	
						Moderate	1.23 (0.97-1.56)	
						Heavy	3.40 (2.54-4.55)	
				18	Asian	Light	1.02 (0.83-1.26)	
						Moderate	1.14 (0.97-1.33)	
						Heavy	1.59 (1.27-2.00)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
WCRF SLR, 2014[88]	Worldwide	5650		14	Overall	Per 10g/day	1.04 (1.02-1.06)	
		6372		17	Overall + Asian pooling project	Per 10g/day	1.04 (1.02-1.06)	
		4132		8	Men	Per 10g/day	1.03 (1.01-1.05)	
		637		4	Women	Per 10g/day	1.19 (1.04-1.35)	
		1738		9	Incidence	Per 10g/day	1.12 (1.05-1.18)	
		3912		5	Mortality	Per 10g/day	1.02 (1.01-1.03)	
		4720		11	Asia	Per 10g/day	1.04 (1.02-1.07)	
		930		3	North America and Europe	Per 10g/day	1.08 (1.00-1.16)	
Chuang et al, 2015[115]	Worldwide	Not specified in the study	Never/very low frequency drinkers	43 (11 cohorts, 32 C-C)	Overall	Ever	1.29 (1.16-1.42)	Significant dose-response relationship with amount. Evidence of synergistic effects of alcohol (drinking status) with hepatitis (but NS for hepatitis B), and diabetes, which however may be subject to publication bias. NS synergistic effects of alcohol with smoking.
						Current	0.85 (0.68-1.01)	
						Former	2.06 (1.31-2.81)	
				11	Cohort	Ever	1.07 (0.87-1.27)	
						Current	0.86 (0.74-0.97)	
						Former	1.87 (1.13-2.62)	
				32	C-C	Ever	1.46 (1.27-1.65)	
						Current	1.55 (0.38-2.73)	
						Former	4.16 (1.55-6.76)	
				14	Men	Ever	1.14 (0.95-1.34)	
						Current	0.98 (0.73-1.24)	
						Former	2.16 (1.09-3.23)	
				6	Women	Ever	1.45 (1.01-1.90)	
						Current	0.76 (0.50-1.01)	
						Former	1.78 (0.66-2.90)	
				11	Adjusted for hepatitis and smoking	Ever	1.50 (1.22-1.79)	
				32	Without full adjustment of hepatitis and smoking	Ever	1.22 (1.08-1.37)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
Turati et al, 2014[185]	Worldwide	4445 incidents; 5550 deaths	Non-drinkers	16 (5 nested C-C, 10 cohorts, 1 PA of 4 cohorts)	Overall	Moderate	0.91 (0.81-1.02)	
						Heavy	1.16 (1.01-1.34)	
					Cohort	Moderate	0.91 (0.81-1.03)	
						Heavy	0.88 (0.62-1.26)	
					Nested C-C	Moderate	1.08 (0.98-1.19)	
						Heavy	2.63 (1.62-4.28)	
					Men	Moderate	0.90 (0.76-1.07)	
						Heavy	1.14 (0.96-1.34)	
					Women	Moderate	0.89 (0.71-1.12)	
						Heavy	N/A	
					Asia	Moderate	0.97 (0.86-1.08)	
						Heavy	1.17 (1.00-1.37)	
					Other regions	Moderate	0.66 (0.52-0.84)	
						Heavy	1.13 (0.75-1.71)	
					Adjusted for hepatitis	Moderate	0.92 (0.77-1.10)	
						Heavy	1.08 (0.88-1.33)	
					No hepatitis adjustment	Moderate	0.91 (0.78-1.07)	
						Heavy	1.25 (1.01-1.55)	
					Incidence	Moderate	0.84 (0.67-1.05)	
						Heavy	1.70 (0.89-2.93)	
					Mortality	Moderate	0.97 (0.88-1.07)	
						Heavy	1.11 (1.03-1.21)	

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review; NS, non-significant; PA, pooled analysis.
*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.8. Prospective studies on alcohol consumption and liver cancer risk

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Petrick et al, 2018[116]	US; LCPP (14 cohorts)	N/A	N/A	1423 HCC incidents / 1518741	Non-drinkers	HCC	>0-0.5 drink/day 0.5-1 drink/day 1-3 drinks/day 3-5 drinks/day 5-7 drinks/day 7+ drinks/day	0.77 (0.67-0.89) 0.57 (0.44-0.73) 0.71 (0.58-0.87) 1.04 (0.79-1.36) 1.00 (0.68-1.49) 1.87 (1.41-2.47)	Sex, age, race, cohort, BMI, diabetes, smoking, smoking intensity, education	For HCC, significant interaction was shown between heavy drinking and diabetes, but NS for alcohol with smoking, BMI, or gender. Insufficient study power for subgroup analyses by beverage type.
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	213 incidents / 124193	Lifelong abstainers	Overall	Ex-drinkers <1 drink/day 1-2 drinks/day ≥3 drinks/day	1.9 (1.0-3.7) 1.0 (0.6-1.5) 1.5 (0.9-2.5) 1.5 (0.8-2.7)	Age, race, education, BMI, marital status, smoking	
					<1 drink/day	Wine Liquor Beer No preponderant choice	≥3 drinks/day ≥3 drinks/day ≥3 drinks/day ≥3 drinks/day	1.0 (0.3-3.6) 0.4 (0.1-1.7) 2.0 (0.5-6.5) 2.3 (1.2-4.4)		
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	590 deaths / 66820	Never drinkers	Overall	Ex-drinkers Social (<1/week) Weekly social Weekly moderate Weekly high	1.28 (0.99-1.65) 0.81 (0.62-1.06) 1.15 (0.63-2.12) 1.16 (0.79-1.71) 1.12 (0.52-2.40)	Age, sex, SES, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Yang et al, 2012[73]	China; CPSS	1990-1991 (15 years)	40-79	1115 deaths / 218189 men	Non-drinkers	Men	Non-drinkers All drinkers <140g/week 140-279g/week 280-419g/week 420-699g/week ≥700g/week	1.00 (0.91-1.09) 1.12 (0.98-1.28) 0.98 (0.76-1.25) 1.13 (0.94-1.37) 1.02 (0.84-1.25) 1.38 (1.11-1.73) 1.21 (0.92-1.09)	Age, area, smoking, education	Floated CIs are presented. NS trend with alcohol amount among drinkers.
Evans et al, 2002[117]	Haimen City, China; Haimen City Cohort	1992-1993 (8 years)	25-64	1092 deaths / 83794	<4 drinks/week	Men Women	≥4 drinks/week ≥4 drinks/week	0.8 (0.7-0.9) 0.6 (0.3-1.3)	Age	NS across beverage types. NS interaction between alcohol and HBsAg.
Yuan et al, 1997[72]	Shanghai, China; SCS	1986-1989 (6.7 years)	45-64	102 deaths / 18244 men	Lifelong non-drinkers	Men	1-28 drinks/week ≥29 drinks/week	0.68 0.84	Age, education, smoking	NS. 1 drink ≈ 13g.

HR, hazard ratio; RR, risk ratio; CI, confidence intervals; US, United States; LCPP, Liver Cancer Pooling Project; HCC, hepatocellular carcinoma; BMI, body mass index; NS, non-significant; ICC, intrahepatic cholangiocarcinoma; SES, socio-economic status; CPSS, Chinese Prospective Smoking Study; HBsAg, hepatitis B surface antigen.
Except Evans et al, all studies (except Yi et al, Shen et al and Petrick et al who did so in subgroup or sensitivity analyses) excluded prior cancers at baseline.
Most studies in Petrick et al and all other studies measured alcohol consumption at baseline only.

Table 2.9. Meta-analyses on alcohol consumption and female breast cancer risk

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95%CI)*	Notes
Li et al, 2011[101]	China	1655	Non-drinkers	4 C-C	Overall	Drinkers	0.76 (0.60-0.97)	
Bagnardi et al 2015[100]	Worldwide	165750	Non-drinkers and occasional drinkers	118 (43 cohorts, 75 C-C)	Overall	Light	1.04 (1.01-1.07)	
						Moderate	1.23 (1.19-1.28)	
						Heavy	1.61 (1.33-1.94)	
				43	Cohort	Light	1.06 (1.03-1.10)	
						Moderate	1.22 (1.17-1.27)	
						Heavy	1.50 (1.19-1.89)	
				75	C-C	Light	1.04 (0.99-1.09)	
						Moderate	1.23 (1.16-1.32)	
						Heavy	1.78 (1.27-2.50)	
				41	European	Light	1.03 (0.98-1.10)	
						Moderate	1.19 (1.10-1.28)	
						Heavy	1.82 (1.14-2.89)	
				57	North American	Light	1.06 (1.03-1.10)	
						Moderate	1.25 (1.20-1.31)	
						Heavy	1.67 (1.33-2.09)	
				9	Asian	Light	0.89 (0.72-1.11)	
						Moderate	1.44 (1.21-1.71)	
						Heavy	3.44 (0.47-25.14)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95%CI)*	Notes
WCRF SLR, 2017[97]	Worldwide	117399			Any breast cancer:			
				35	Overall	Per 10g/day	1.07 (1.05-1.10)	
				4	Asia	Per 10g/day	1.13 (0.89-1.43)	
				7	Europe	Per 10g/day	1.08 (1.04-1.11)	
				11	North America	Per 10g/day	1.07 (1.05-1.10)	
		4426			Premenopausal:			
				18	Overall	Per 10g/day	1.03 (0.99-1.07)	
				1	Asia	Per 10g/day	1.05 (0.97-1.13)	
				4	Europe	Per 10g/day	1.04 (0.98-1.11)	
				5	North America	Per 10g/day	1.07 (1.02-1.12)	
		33415			Postmenopausal:			Significant for wine, for current and never hormone therapy users, and for ER+PR+ and ER+PR- only.
				29	Overall	Per 10g/day	1.11 (1.06-1.16)	
				1	Asia	Per 10g/day	1.01 (0.87-1.18)	
				9	Europe	Per 10g/day	1.08 (1.04-1.12)	
				12	North America	Per 10g/day	1.11 (1.07-1.15)	

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review; ER, oestrogen receptor; PR, progesterone receptor.
*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.10. Prospective studies on alcohol consumption and female breast cancer risk

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95%CI)*	Adjustment	Notes
Key et al, 2018[121]	UK; MWS	2000-2004 (12 years)	Post-menopausal	29005 incidents / 691571		Overall	Per 10g/day	1.08 (1.05-1.11)	Year of birth, region, calendar year, dietary energy intake, SES, BMI, height, smoking, age at menarche, strenuous exercise, parity, age at first birth, education, ever use of HT for menopause	NS heterogeneity by ER status.
Kim et al, 2017[186]	US; Nurses' Health Study II	1991 (to 2011)	27-44	2866 incidents / 93835		Overall	Per 10g/day	1.06 (1.00-1.12)	Age, calendar year, oral contraceptive use, parity, age at first birth, age at menarche, menopausal status, HT use, BMI, personal history of benign breast disease, height, smoking, family history of breast cancer, intakes of red meat and folate	NS when alcohol consumption was analysed in categories.
						No family history	Per 10g/day	1.04 (0.97-1.10)		
						Had family history	Per 10g/day	1.16 (1.03-1.30)		
						High folate intake	Per 10g/day	1.02 (0.95-1.10)		
						Low folate intake	Per 10g/day	1.11 (1.02-1.21)		
White et al, 2017[187]	US; Sister Study (All participants had a sister who had been diagnosed with breast cancer)	2003-2009 (6.4 years)	35-74	1843 incidents / 50884	<60 drinks/year	Lifetime consumption	60-229 drinks/year	1.19 (1.06-1.33)	Age, race/ethnicity, education, age at menarche, age at first birth, parity, use of hormonal birth control, smoking, use of postmenopausal hormones, age at menopause and menopausal status, BMI	NS for current drinking levels, duration of drinking, age started drinking, or former consumption.
							≥230 drinks/year	1.35 (1.15-1.58)		
					Low-level drinkers		Ever binge	1.29 (1.15-1.45)		
							Current binge	1.38 (1.19-1.61)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95%CI)*	Adjustment	Notes
Williams et al, 2017[188]	US; African AMBER Consortium (2 cohorts, 2 C-C)	N/A	20+	5108 incidents / 22338	0-4 drinks/ week		Never Past drinkers 4-6 drinks/week 7-13 drinks/week ≥14 drinks/week	1.12 (1.02-1.24) 1.04 (0.93-1.17) 1.04 (0.86-1.25) 1.07 (0.88-1.32) 1.33 (1.07-1.64)	Age, study, time period, geographic region, education, age at menarche, BMI, menopausal status, HT use, parity, smoking status, duration of oral contraceptive use	Consistent across breast cancer subtypes. No effect modification by oral contraceptive use, smoking, or menopausal status.

HR, hazard ratio; RR, risk ratio; CI, confidence interval; UK, United Kingdom; MWS, Million Women Study; SES, socio-economic status; BMI, body mass index; HT, hormone therapy; NS, non-significant; ER, oestrogen receptor; US, United States; AMBER, American Breast Cancer Epidemiology and Risk; C-C, case-control(s).

*HR (99%CI) for Key et al; OR (95%CI) for Williams et al.

All studies (except Williams et al) excluded prior cancers at baseline.

All studies either measured lifetime consumption or used multiple measures to take account of within-person variation.

Table 2.11. Meta-analyses and pooled analyes on alcohol consumption and lung cancer risk

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
Li et al, 2011[101]	China	1104	Non-drinker	4 C-C, 2 cohorts	Overall	Drinkers	1.39 (0.93-2.07)	No data was reported separately for women.
					Men	Drinkers	1.19 (0.91-1.54)	
					Cohort	Drinkers	1.27 (0.85-1.91)	
					C-C	Drinkers	1.59 (0.86-2.94)	
Bagnardi et al, 2015[100]	Worldwide	38423	Non-drinkers and occasional drinkers	34 (18 cohorts, 16 C-C)	Overall	Light	0.84 (0.79-0.88)	
						Moderate	0.98 (0.92-1.05)	
						Heavy	1.15 (1.02-1.30)	
				18	Cohort	Light	0.85 (0.82-0.89)	
						Moderate	0.97 (0.91-1.04)	
						Heavy	1.07 (0.93-1.25)	
				16	C-C	Light	0.71 (0.57-0.89)	
						Moderate	1.03 (0.87-1.21)	
						Heavy	1.33 (1.07-1.66)	
				22	Men	Light	0.86 (0.82-0.91)	
						Moderate	0.98 (0.89-1.08)	
						Heavy	1.14 (1.00-1.31)	
				11	Women	Light	0.85 (0.77-0.93)	
						Moderate	1.01 (0.89-1.15)	
						Heavy	1.20 (0.75-1.92)	
				4	European	Light	0.80 (0.76-0.85)	
						Moderate	0.88 (0.83-0.94)	
						Heavy	0.96 (0.74-1.26)	
				14	North American	Light	0.87 (0.80-0.94)	
						Moderate	1.06 (0.98-1.15)	
						Heavy	1.26 (1.10-1.45)	
				12	Asian	Light	0.81 (0.69-0.94)	
						Moderate	0.93 (0.80-1.08)	
						Heavy	0.92 (0.87-0.98)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
WCRF SLR, 2015[92]		21940		26	Overall	Per 10g/day	1.03 (1.01-1.05)	Not possible to exclude residual confounding by smoking.
		24630		32	Overall plus Asian Pooling Project	Per 10g/day	1.03 (1.02-1.05)	
		1350		4	Never smokers	Per 10g/day	0.96 (0.92-1.00)	
		4255		5	Current smokers	Per 10g/day	1.01 (0.97-1.02)	
		11727		21	Men	Per 10g/day	1.04 (1.02-1.06)	
		12102		16	Women	Per 10g/day	1.01 (0.98-1.05)	
		15081		23	Incidence	Per 10g/day	1.04 (1.01-1.06)	
		9549		9	Mortality	Per 10g/day	1.03 (1.00-1.06)	
		808		3	Small cell carcinoma	Per 10g/day	1.03 (0.97-1.10)	
		1477		4	Squamous cell carcinoma	Per 10g/day	1.00 (0.93-1.09)	
		1827		6	Adenocarcinoma	Per 10g/day	1.06 (1.02-1.09)	
		3481		7	Beer	Per 10g/day	1.04 (0.93-1.16)	
		2701		5	Wine	Per 10g/day	0.87 (0.76-0.98)	
		2920		6	Spirits	Per 10g/day	1.03 (0.98-1.10)	
				11	Asia	Per 10g/day	1.04 (1.01-1.06)	
				7	Europe	Per 10g/day	1.04 (0.99-1.07)	
				14	North America and Europe	Per 10g/day	1.03 (1.00-1.07)	
				4	No smoking adjustment	Per 10g/day	1.15 (1.02-1.31)	
				5	Adjusted for smoking status only	Per 10g/day	1.03 (0.99-1.03)	
				10	Adjusted for smoking status, intensity	Per 10g/day	1.02 (0.99-1.05)	
				11	Adjusted for smoking status, intensity, duration	Per 10g/day	1.04 (1.01-1.08)	
				28	Excluding studies that did not adjust for smoking	Per 10g/day	1.03 (1.01-1.04)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR or RR (95% CI)*	Notes
Brenner et al, 2019[126]	Worldwide (ILCCO and the SYNERGY consortium study) (mostly Western countries)	19149	Non-drinkers	21 C-C and 1 cohort (EPIC)	Overall	0-4.9g/day 5-9.9g/day 10-19.9g/day 20-29.9g/day 30-44.9g/day >45g/day	0.79 (0.72-0.87) 0.85 (0.74-0.96) 0.78 (0.67-0.91) 0.98 (0.85-1.12) 0.92 (0.82-1.04) 0.94 (0.77-1.15)	Association varied little by beverage types (although beer appeared to be more harmful for SCC). Significant multiplicative interaction between alcohol and smoking.
Never smokers only								
Garcia et al, 2018[123]	Spain	438	Non-drinkers	6 C-C	Never smokers	Drinkers	1.22 (0.83-1.80)	Significantly increased risks for spirits drinkers and drinkers consuming all wine types, but NS for beer or specific wine type (e.g., red, white).
Fehringer et al, 2017[122]	Worldwide (ILCCO and SYNERGY study) (mostly Western countries)	2548	Non-drinkers	21 C-C and 1 cohort (EPIC)	Never smokers	>0-4.9g/day 5-9.9g/day 10-19.9g/day 20-29.9g/day 30-44.9g/day 45+g/day	0.80 (0.70-0.90) 0.82 (0.69-0.99) 0.79 (0.65-0.96) 0.82 (0.62-1.09) 0.68 (0.47-0.99) 0.91 (0.65-1.29)	Inverse associations observed for wine and liquor compared with non-drinkers, but not beer.
Bagnardi et al, 2011[124]	Worldwide (mostly Western countries)	1913	Non-drinkers	10 (3 cohorts, 6 C-C, 1 PA of 7 cohorts)	Never smokers	Drinkers Per 10g/day	1.21 (0.95-1.55) 1.01 (0.92-1.10)	No heterogeneity across study design, geographic area, or gender.

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review; ILCCO, International Lung Cancer Consortium; EPIC, European Prospective Investigation into Cancer and Nutrition; SCC, squamous cell carcinoma; PA, pooled analysis.

*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.12. Prospective studies on alcohol consumption and lung cancer risk

Authors, year	Location; cohort	Baseline period (mean/median follow-up)	Age	No of cases/ sample size	Reference category	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	1989 incidents / 124193	Lifelong abstainers	Ex-drinkers <1 drink/day 1-2 drinks/day ≥3 drinks/day	1.2 (0.9-1.5) 1.0 (0.9-1.2) 1.0 (0.8-1.2) 1.3 (1.1-1.6)	Age, race, education, BMI, marital status, smoking	Significantly increased risk at >3 drinks/day (vs. <1 drink/day) for liquor and beer.
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	1958 deaths / 66820	Never drinkers	Ex-drinkers Social (<1/week) Weekly social Weekly moderate Weekly high	0.93 (0.81-1.08) 0.85 (0.74-0.98) 0.83 (0.57-1.21) 0.93 (0.75-1.16) 1.39 (1.01-1.90)	Age, sex, SES, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).
Yang et al, 2012[73]	China; CPSS	1990-1991 (15 years)	40-79	1082 deaths / 218189 men	Non-drinkers	Non-drinkers All drinkers <140g/week 140-279g/week 280-419g/week 420-699g/week ≥700g/week	1.00 (0.92-1.09) 1.03 (0.90-1.18) 0.86 (0.66-1.11) 0.92 (0.75-1.13) 1.02 (0.84-1.24) 1.30 (1.03-1.63) 1.25 (0.97-1.62)	Age, area, smoking, education	Floated CIs are presented. Significant trend with alcohol amount among drinkers.
Yuan et al, 1997[72]	Shanghai, China; SCS	1986-1989 (6.7 years)	45-64	147 deaths / 18244 men	Lifelong non-drinkers	1-28 drinks/week ≥29 drinks/week	0.76 0.94	Age, education, smoking	NS. 1 drink ≈ 13g.

HR, hazard ratio; RR, risk ratio; CI, confidence intervals; US, United States; BMI, body mass index; SES, socio-economic status; CPSS, Chinese Prospective Smoking Study; SCS, Shanghai Cohort Study; NS, non-significant.
All studies (except Shen et al who did so in sensitivity analyses) excluded prior cancers at baseline.
All studies measured alcohol consumption at baseline only.

Table 2.13. Meta-analyses on alcohol consumption and stomach cancer risk

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR of RR (95% CI)*	Notes
Li et al, 2011[101]	China	8645	Non-drinkers	29 C-C, 2 cohorts	Overall	Drinkers	1.40 (1.20-1.64)	
					Men	Drinkers	1.12 (0.78-1.59)	
					Women	Drinkers	1.97 (1.02-4.43)	
					Cohort	Drinkers	1.14 (0.99-1.32)	
					C-C	Drinkers	1.40 (1.19-1.64)	
Bagnardi et al, 2015[100]	Worldwide	25958	Non-drinkers and occasional drinkers	39 (19 cohorts, 20 C-C)	Overall	Light	0.99 (0.92-1.06)	
						Moderate	0.97 (0.90-1.04)	
						Heavy	1.21 (1.07-1.36)	
				19	Cohort	Light	0.94 (0.87-1.03)	
						Moderate	0.96 (0.88-1.06)	
						Heavy	1.15 (1.03-1.28)	
				20	C-C	Light	1.08 (0.93-1.26)	
						Moderate	0.98 (0.89-1.08)	
						Heavy	1.22 (0.97-1.54)	
				20	Men	Light	1.00 (0.92-1.10)	
						Moderate	1.07 (1.00-1.14)	
						Heavy	1.20 (0.99-1.45)	
				7	Women	Light	1.08 (0.76-1.54)	
						Moderate	0.90 (0.66-1.22)	
						Heavy	3.23 (0.80-13.07)	
				12	European	Light	0.98 (0.84-1.15)	
						Moderate	0.90 (0.79-1.04)	
						Heavy	1.21 (1.04-1.42)	
				8	North American	Light	0.95 (0.75-1.22)	
						Moderate	0.90 (0.76-1.06)	
						Heavy	1.42 (0.86-2.34)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR of RR (95% CI)*	Notes
				16	Asian	Light	1.01 (0.94-1.08)	
						Moderate	1.01 (0.91-1.12)	
						Heavy	1.08 (0.93-1.26)	
WCRF SLR, 2015[95]		11926		23	Overall	Per 10g/day	1.02 (1.00-1.04)	
				13	Men	Per 10g/day	1.03 (1.01-1.05)	
				5	Women	Per 10g/day	1.02 (0.90-1.15)	
				16	Incidence	Per 10g/day	1.01 (0.98-1.04)	
				7	Mortality	Per 10g/day	1.02 (1.00-1.04)	
				14	Asia	Per 10g/day	1.03 (1.01-1.04)	
				7	Europe	Per 10g/day	1.02 (0.98-1.06)	
				2	North America and Europe	Per 10g/day	0.98 (0.87-1.11)	
				3	No smoking adjustment	Per 10g/day	1.02 (0.97-1.07)	
				20	Adjusted for smoking	Per 10g/day	1.02 (1.00-1.04)	
				11	Not adjusted for BMI	Per 10g/day	1.02 (1.00-1.04)	
				12	Adjusted for BMI	Per 10g/day	1.02 (1.00-1.05)	
				6	Never smokers	Highest intake	1.23 (1.03-1.46)	
				6	Current & former smokers	Highest intake	1.84 (1.43-2.36)	
				6	GCC	Per 10g/day	1.01 (0.99-1.03)	
				7	GNCC	Per 10g/day	1.03 (0.97-1.09)	
Wang et al, 2017[129]	Worldwide	Not specified	Lowest category	73 (56 C-C, 17 cohorts/nested C-C)	Overall	Highest category	1.25 (1.15-1.37)	Consistent across study design, countries, cancer site, sex, smoking, *H. pylori* infection, and confounder adjustment (BMI, smoking, fruit &
						Per 12.5g/day	1.04 (1.01-1.07)	
				17	Cohort/nested C-C	Highest category	1.19 (1.06-1.34)	
				56	C-C	Highest category	1.28 (1.15-1.43)	
				24	Beer	Highest category	1.13 (1.03-1.24)	
						Per 12.5g/day	1.07 (1.01-1.13)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR of RR (95% CI)*	Notes
				28	Liquor	Highest category	1.22 (1.06-1.40)	vegetable, socio-economic status).
						Per 12.5g/day	1.03 (0.98-1.09)	
				26	Wine	Highest category	0.99 (0.84-1.16)	
						Per 12.5g/day	0.99 (0.93-1.06)	
				18	GNCC	Highest category	1.19 (1.01-1.40)	
				15	GCC	Highest category	1.16 (0.98-1.39)	
He et al, 2017[128]	Worldwide	22545	Non-drinkers	22 cohorts	Overall	Drinkers	1.03 (0.99-1.08)	Consistent across sex, countries, mortality/incidence, and adjustment of BMI/education/physical activity.
						Light	0.95 (0.88-1.02)	
						Moderate	1.05 (0.98-1.13)	
						Heavy	1.13 (1.06-1.21)	
					Men	Drinkers	1.04 (0.97-1.12)	
						Light	0.96 (0.90-1.03)	
						Moderate	1.06 (0.97-1.14)	
						Heavy	1.13 (1.06-1.22)	
					Women	Drinkers	1.01 (0.79-1.30)	
						Light	0.74 (0.57-0.98)	
						Moderate	1.30 (0.90-1.87)	
						Heavy	1.33 (0.79-2.24)	
Rota et al, 2017[127]	Worldwide (StoP)	9669	Never drinkers	20 C-C	Overall	Ever drinkers	1.10 (0.99-1.21)	Stronger association for GCC than GNCC. Similar across *H. pylori* infection status. Similar across regions but J-shaped for Asia. Significantly increased risk in spirit drinkers
						≤1 drink/day	1.00 (0.86-1.16)	
						1- 4 drinks/day	1.11 (1.01-1.23)	
						4- 6 drinks/day	1.26 (1.08-1.48)	
						>6 drinks/day	1.48 (1.29-1.70)	
					Men	<1 drink/day	1.02 (0.85-1.22)	
						1- 4 drinks/day	1.10 (0.98-1.24)	
						>4 drinks/day	1.44 (1.24-1.68)	

Authors, year	Location	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	OR of RR (95% CI)*	Notes
					Women	<1 drink/day	0.99 (0.83-1.18)	only, although non-significant increased risks were also observed for beer and wine drinkers.
						1- 4 drinks/day	1.11 (0.92-1.33)	
						>4 drinks/day	1.41 (0.97-2.06)	
					Never smokers	<1 drink/day	1.03 (0.82-1.28)	
						1- 4 drinks/day	1.14 (0.97-1.33)	
						>4 drinks/day	1.87 (1.35-2.58)	
					Former smokers	<1 drink/day	1.10 (0.86-1.40)	
						1- 4 drinks/day	1.41 (1.09-1.83)	
						>4 drinks/day	1.64 (1.10-2.44)	
					Current smokers	<1 drink/day	0.91 (0.76-1.10)	
						1- 4 drinks/day	0.93 (0.78-1.12)	
						>4 drinks/day	1.14 (0.93-1.40)	
					Drinking duration	<20 years	1.02 (0.84-1.23)	
						20 - 40 years	1.28 (1.08-1.51)	
						>40 years	1.13 (0.97-1.33)	
					GCC	<1 drink/day	0.97 (0.65-1.44)	
						1- 4 drinks/day	1.00 (0.81-1.24)	
						>4 drinks/day	1.61 (1.11-2.34)	
					GNCC	<1 drink/day	0.98 (0.84-1.15)	
						1- 4 drinks/day	1.16 (0.94-1.44)	
						>4 drinks/day	1.28 (1.13-1.45)	
			Current drinkers		Years since quitting	<5 years	1.93 (1.39-2.68)	
						5-10 years	1.00 (0.66-1.53)	
						>10 years	0.84 (0.56-1.25)	

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review; BMI, body mass index; GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer; *H. pylori, Helicobacter pylori*; StoP, Stomach cancer Pooling Project.

*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.14. Prospective studies on alcohol consumption and stomach cancer risk

Authors, year	Location; cohort	Baseline period (mean/median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Wang et al, 2018[130]	US; NIH-AARP diet and health cohort	1995-1996 (15.5 years)	50-71	(662 GCC & 713 GNCC) incidents / 490605	Never drinkers	GCC	0-1 drink/day	0.86 (0.70-1.05)	Age, sex, race/ethnicity, health status, education, BMI, smoking status, self-reported diabetes, the Healthy Eating Index 2010 score; (analyses of beverage type) other beverage types	1 drink ≈ 13-14g. NS for beverage types and subgroups by sex, ethnicity, education, or smoking.
							1-3 drinks/day	0.91 (0.70-1.17)		
							>3 drinks/day	1.06 (0.80-1.42)		
						GNCC	0-1 drink/day	0.81 (0.67-0.97)		
							1-3 drinks/day	0.96 (0.76-1.23)		
							>3 drinks/day	0.73 (0.53-1.01)		
Choi et al, 2017[106]	South Korea; NHIC	2009-2012 (5.4 years)	20+	135382 incidents / 23323730	Non-drinkers	Overall	<30g/day	1.05 (1.04-1.06)	Age, sex, smoking, exercise, income, BMI, diabetes	Consistent dose-response relationships across BMI and smoking, but NS interaction.
							≥30g/day	1.24 (1.21-1.26)		
						Men	<30g/day	1.06 (1.05-1.08)		
							≥30g/day	1.26 (1.24-1.29)		
						Women	<30g/day	1.00 (0.97-1.02)		
							≥30g/day	1.06 (0.95-1.20)		
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	403 incidents / 124193	Lifelong abstainers		Ex-drinkers	1.1 (0.7-1.8)	Age, race, education, BMI, marital status, smoking	
							<1 drink/day	0.9 (0.7-1.2)		
							1-2 drinks/day	0.8 (0.6-1.4)		
							≥3 drinks/day	0.8 (0.5-1.3)		
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	335 deaths / 66820	Never drinkers		Ex-drinkers	0.89 (0.62-1.30)	Age, sex, SES position, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).
							Social (<1/week)	0.73 (0.50-1.05)		
							Weekly social	0.55 (0.17-1.73)		
							Weekly moderate	1.18 (0.71-1.95)		
							Weekly high	0.53 (0.13-2.15)		

Authors, year	Location; cohort	Baseline period (mean/median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Yang et al, 2012[73]	China; CPSS	1990-1991 (15 years)	40-79	1137 deaths / 218189 men	Non-drinkers	Men	Non-drinkers	1.00 (0.92-1.09)	Age, area, smoking, education	Floated CIs are presented. Significant trend with alcohol amount among drinkers.
							All drinkers	0.96 (0.84-1.10)		
							<140g/week	0.87 (0.68-1.11)		
							140-279g/week	0.95 (0.77-1.19)		
							280-419g/week	0.96 (0.77-1.20)		
							420-699g/week	1.00 (0.75-1.34)		
							≥700g/week	1.15 (0.85-1.57)		
Moy et al, 2010[131]	Shanghai, China; SCS	1986-1989 (19 years)	45-64	391 incidents / 18244 men	Non-drinkers	Men	Regular drinkers	1.03 (0.83-1.26)	Baseline age, year of baseline interview, neighbourhood of residence, education, BMI, years of smoking, summed intakes of preserved food items, fresh fruits, fresh vegetables; (for analyses on beverage type) amount drunk of other beverage types	1 drink ≈ 13g. Further adjustment of *H. pylori* serology and other biomarkers does not materially change the results. NS interaction between alcohol and smoking.
						Amount	<4 drinks/day	0.94 (0.76-1.18)		
							4+ drinks/day	1.46 (1.05-2.04)		
						Age started	30+ years	0.94 (0.72-1.23)		
							20-29 years	1.10 (0.84-1.45)		
							<20 years	1.10 (0.76-1.58)		
						Years of drinking regularly	<20 years	0.87 (0.63-1.22)		
							20-39 years	1.14 (0.89-1.46)		
							40+ years	0.97 (0.69-1.38)		
						Daily ethanol intake	<20g/day	0.88 (0.67-1.16)		
							20-40g/day	1.16 (0.86-1.58)		
							40+g/day	1.15 (0.85-1.55)		
						Lifetime consumption	<300kg	0.94 (0.74-1.20)		
							200-800kg	1.11 (0.81-1.49)		
							800+kg	1.37 (0.91-2.06)		

Authors, year	Location; cohort	Baseline period (mean/median follow-up)	Age	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
						Beer	<1 drink/day	0.83 (0.60-1.16)		
							1+ drinks/day	1.21 (0.79-1.84)		
						Rice wine	<1 drink/day	1.11 (0.80-1.53)		
							1 - <2 drinks/day	1.05 (0.68-1.61)		
							2+ drinks/day	1.14 (0.80-1.63)		
						Spirits	<2 drinks/day	1.13 (0.83-1.56)		
							2 - <4 drinks/day	1.19 (0.81-1.74)		
							4+ drinks/day	1.40 (0.92-2.14)		
						Joint effect of alcohol and smoking:				
						Never smokers	Non-drinkers	1		
							<4 drinks/day	1.20 (0.81-1.78)		
							4+ drinks/day	1.80 (0.73-4.46)		
						Smokers	Non-drinkers	1.81 (1.36-2.41)		
							<4 drinks/day	1.49 (1.11-2.00)		
							4+ drinks/day	2.43 (1.66-3.56)		
Tran et al, 2005[108]	Linxian, China; Linxian General Population Trial	1986-1991 (15 years)	40-69	(1089 GCC & 363 GNCC) incidents / 29584	Past-year non-drinkers	GCC	Any past-year drinking	0.84 (0.72-0.97)	Age, gender	
						GNCC	Any past-year drinking	0.79 (0.61-1.02)		

HR, hazard ratio; RR, risk ratio; CI, confidence interval; US, United States; NIH-AARP, National Institutes of Health-American Association of Retired Persons; GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer; BMI, body mass index; NS, non-significant; NHIC, National Health Insurance Corporation; SES, socio-economic status; CPSS, Chinese Prospective Smoking Study; SCS, Shanghai Cohort Study; *H. pylori, Helicobacter pylori*.
All studies (except Shen et al who did so in sensitivity analyses) excluded prior cancers at baseline.
All studies measured alcohol consumption at baseline only.

Table 2.15. Meta-analyses on alcohol consumption and risks of other cancers

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
Li et al, 2011[101]	China	Pancreas	1612	Non-drinkers	5 C-C	Overall	Drinkers	1.15 (0.97-1.37)	
						Men	Drinkers	1.71 (1.32-2.20)	
						Women	Drinkers	1.16 (0.52-2.60)	
		Prostate	569		4 C-C	Overall	Drinkers	1.17 (0.84-1.62)	
		Gallbladder	467		2 C-C	Overall	Drinkers	0.70 (0.49-1.00)	
Bagnardi et al, 2015[100]	Worldwide	Pancreas	27326	Non-drinkers and occasional drinks	39 (18 cohorts, 21 C-C)	All	Light	0.95 (0.89-1.01)	
							Moderate	1.03 (0.97-1.09)	
							Heavy	1.19 (1.11-1.28)	
					20	Men	Light	0.98 (0.86-1.11)	
							Moderate	1.08 (1.00-1.15)	
							Heavy	1.16 (1.06-1.27)	
					15	Women	Light	0.93 (0.86-1.01)	
							Moderate	1.04 (0.93-1.17)	
							Heavy	1.17 (0.98-1.40)	
					11	European	Light	0.90 (0.85-0.96)	
							Moderate	0.97 (0.90-1.04)	
							Heavy	0.79 (0.50-1.24)	
					16	North American	Light	0.99 (0.89-1.09)	
							Moderate	1.03 (0.95-1.12)	
							Heavy	1.17 (1.08-1.28)	
					9	Asian	Light	1.01 (0.71-1.45)	
							Moderate	1.19 (0.97-1.46)	
							Heavy	1.18 (0.96-1.44)	
		Prostate	42658		43 (20 cohorts, 23 C-C)	Men	Light	1.04 (1.01-1.08)	
							Moderate	1.06 (1.01-1.11)	
							Heavy	1.09 (0.98-1.21)	

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
					11	European	Light	1.02 (0.94-1.11)	
							Moderate	1.00 (0.90-1.11)	
							Heavy	0.95 (0.75-1.21)	
					24	North American	Light	1.05 (1.01-1.09)	
							Moderate	1.09 (1.02-1.16)	
							Heavy	1.20 (1.09-1.31)	
					5	Asian	Light	0.91 (0.70-1.19)	
							Moderate	1.05 (0.85-1.31)	
							Heavy	1.00 (0.58-1.72)	
		Kidney	12893		17 (6 cohorts, 11 C-C)	Overall	Light	0.92 (0.86-0.99)	
							Moderate	0.79 (0.72-0.86)	
							Heavy	0.80 (0.57-1.14)	
					11	Men	Light	0.99 (0.87-1.11)	
							Moderate	0.83 (0.71-0.97)	
							Heavy	0.88 (0.29-2.63)	
					9	Women	Light	0.85 (0.78-0.92)	
							Moderate	0.65 (0.52-0.81)	
							Heavy	N/A	
					7	Europe	Light	1.01 (0.86-1.17)	
							Moderate	0.81 (0.69-0.94)	
							Heavy	0.75 (0.60-0.93)	
					6	North America	Light	0.89 (0.80-1.00)	
							Moderate	0.80 (0.69-0.92)	
							Heavy	0.98 (0.68-1.41)	
					2	Asia	Light	0.63 (0.35-1.13)	
							Moderate	1.07 (0.18-6.41)	
							Heavy	0.88 (0.16-4.92)	

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
		NHL	14124		24 (9 cohorts, 15 C-C)	Overall	Light	0.88 (0.80-0.97)	
							Moderate	0.87 (0.81-0.95)	
							Heavy	0.75 (0.64-0.88)	
					9	Men	Light	0.96 (0.78-1.18)	
							Moderate	0.91 (0.76-1.08)	
							Heavy	0.87 (0.52-1.43)	
					8	Women	Light	0.90 (0.78-1.04)	
							Moderate	0.86 (0.72-1.03)	
							Heavy	N/A	
					9	European	Light	0.97 (0.83-1.12)	
							Moderate	0.95 (0.82-1.12)	
							Heavy	0.97 (0.71-1.34)	
					10	North American	Light	0.87 (0.77-0.99)	
							Moderate	0.84 (0.76-0.94)	
							Heavy	0.77 (0.59-1.00)	
					3	Asian	Light	0.75 (0.41-1.36)	
							Moderate	0.77 (0.61-0.98)	
							Heavy	0.62 (0.50-0.78)	
		HL	1335		9 (2 cohorts, 7 C-C)	Overall	Light	0.73 (0.59-0.89)	
							Moderate	0.73 (0.60-0.87)	
							Heavy	0.63 (0.41-0.97)	
		Bladder	10663		19 (3 cohorts, 16 C-C)	Overall	Light	0.99 (0.89-1.10)	
							Moderate	1.01 (0.91-1.12)	
							Heavy	0.95 (0.75-1.20)	
					12	Men	Light	1.13 (0.97-1.32)	
							Moderate	1.07 (0.95-1.22)	
							Heavy	1.24 (0.87-1.78)	

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
					7	Women	Light	0.88 (0.70-1.12)	
							Moderate	0.93 (0.72-1.20)	
							Heavy	0.81 (0.38-1.73)	
					8	European	Light	1.09 (0.85-1.40)	
							Moderate	1.07 (0.89-1.28)	
							Heavy	1.23 (0.76-1.99)	
					9	North American	Light	0.95 (0.84-1.09)	
							Moderate	0.96 (0.84-1.09)	
							Heavy	0.80 (0.56-1.14)	
					2	Asian	Light	1.00 (0.64-1.56)	
							Moderate	1.49 (0.54-4.09)	
							Heavy	0.89 (0.51-1.54)	
		Gallbladder	880		8 (4 cohorts, 4 C-C)	Overall	Light	1.23 (0.84-1.83)	
							Moderate	0.88 (0.68-1.13)	
							Heavy	2.64 (1.62-4.30)	
WCRF SLR, 2011[99]		Pancreas	3096		9	Overall	Per 10g/day	1.00 (0.99-1.01)	
					3	Never smokers	Per 10g/day	1.02 (0.96-1.09)	
					2	Ever smokers	Per 10g/day	0.99 (0.95-1.02)	
					5	Men	Per 10g/day	1.02 (0.99-1.04)	
					3	Women	Per 10g/day	0.99 (0.95-1.02)	
WCRF SLR, 2014[90]		Prostate	36942		25	Overall	Per drink/day	1.01 (0.99-1.02)	1 drink =12.5g.
					7	Advanced/high grade cancer	Per drink/day	1.00 (0.96-1.03)	
					7	Non-advanced/low grade	Per drink/day	1.00 (0.97-1.03)	

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
WCRF SLR, 2015[91]		Kidney	3525		7	Overall	Per 10g/day	0.92 (0.86-0.97)	
			4179		15	Overall + Pooling Project	Per 10g/day	0.88 (0.79-0.97)	
					3	Men	Per 10g/day	0.92 (0.84-1.00)	
					5	Women	Per 10g/day	0.81 (0.68-0.96)	
WCRF SLR, 2014[89]		Bladder	2673		7	Overall	Per 10g/day	0.97 (0.91-1.04)	
					3	Men	Per 10g/day	1.01 (0.94-1.08)	
					3	Women	Per 10g/day	1.02 (0.74-1.41)	
WCRF SLR, 2015[93]		Gallbladder	417		3	Overall	Per 10g/day	1.07 (0.98-1.17)	
Wang et al, 2016[132]	Worldwide (mostly Western countries)	Pancreas	11846	Lowest level/ no intake	21 cohorts	Overall	Drinkers	1.02 (0.95-1.08)	NS in women. Significantly increased risks associated with heavy intake of liquor but not beer or wine, and in North America only.
							Low (0-12g/day)	0.97 (0.89-1.05)	
							Moderate (12-24g/day)	0.98 (0.93-1.03)	
							Heavy (≥24g/day)	1.15 (1.06-1.25)	
						Men	Drinkers	1.03 (0.91-1.17)	
							Low (0-12g/day)	0.98 (0.84-1.15)	
							Moderate (12-24g/day)	0.93 (0.80-1.09)	
							Heavy (≥24g/day)	1.18 (1.00-1.39)	

Authors, year	Location	Cancer site	No of cases	Reference category	No of studies & study design	Subgroup	Exposure category	HR or RR (95% CI)*	Notes
Zhao et al, 2016[135]	Worldwide (mostly Western countries)	Prostate	49848	Abstainers	27 (16 cohorts, 11 C-C)	Men	Any drinkers	1.08 (1.01-1.17)	
							Former drinkers	1.10 (0.97-1.25)	
							Occasional (<1.3g/day)	0.95 (0.85-1.06)	
							Low (1.3 - <25g/day)	1.08 (1.04-1.11)	
							Medium (25-<45g/day)	1.07 (1.02-1.12)	
							High (45 - <65g/day)	1.14 (1.08-1.22)	
							Higher (65+g/day)	1.18 (1.10-1.27)	
Fowke et al, 2015[136]	Asia; Asia Cohort Consortium	Prostate	367	1-155g/week	11 cohorts	Men	No intake	1.02 (0.78-1.34)	
							Heavy (>156g/week)	1.00 (0.74-1.35)	
Psaltopoulou et al, 2018[139]	Worldwide (mostly Western countries)	NHL	11381	Never or non-drinkers	14 cohorts	Overall	Ever or current drinkers	0.89 (0.83-0.95)	Significantly reduced risk of NHL with beer intake. NS for HL.
							Light (≤12.5g/day)	0.93 (0.87-1.00)	
							Moderate (12.5-50g/day)	0.85 (0.80-0.90)	
							Heavy (≥50g/day)	0.73 (0.60-0.89)	
Xu et al, 2015[137]	Worldwide (mostly in Western countries)	Kidney	5503	Non-/ occasional drinkers	8 (7 cohorts and 1 PA of 12 cohorts)	Overall	Per 5g/day	0.94 (0.92-0.95)	
						Men	Per 5g/day	0.95 (0.93-0.97)	
						Women	Per 5g/day	0.91 (0.88-0.94)	
						Wine	Per 5g/day	0.94 (0.90-0.99)	
						Beer	Per 5g/day	0.89 (0.85-0.93)	
						Liquor	Per 5g/day	0.96 (0.92-0.99)	

RR, risk ratio; OR, odds ratio; CI, confidence interval; C-C, case-control(s); WCRF, World Cancer Research Fund; SLR, Systematic Literature Review; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; NS, non-significant; PA, pooled analysis.

*For Li et al, the effect size and CIs correspond to OR (99%CI).

Table 2.16. Prospective studies on alcohol consumption and risks of other cancers

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Shen et al, 2013[104]	Hong Kong	1998-2001 (10.5 years)	65+	Pancreas	242 deaths / 66820	Never drinkers	Overall	Ex-drinkers	1.63 (1.10-2.41)	Age, sex, SES position, BMI, exercise, health status, smoking, smoking*sex, smoking*age	Moderate (≤30g/day[men], ≤20g/day[women]). High (>30g/day[men], >20g/day[women]).
								Social (<1/week)	1.15 (0.77-1.71)		
								Weekly social	1.49 (0.54-4.08)		
								Weekly moderate	0.54 (0.20-1.48)		
								Weekly high	1.71 (0.53-5.53)		
				Prostate	181 deaths / 66820	Never drinkers	Men	Ex-drinkers	1.12 (0.74-1.69)		
								Social (<1/week)	0.92 (0.61-1.39)		
								Weekly social	0.83 (0.26-2.64)		
								Weekly moderate	0.87 (0.46-1.63)		
								Weekly high	0.77 (0.19-3.15)		
Pang et al, 2018[56]	China; CKB	2004-2008 (9 years)	30-79	Pancreas	340 incidents / 209290 men	Abstainers	Men (drinking status)	Abstainers	1.00 (0.79-1.27)	Age-at-risk, area, baseline age, education, smoking, BMI, total physical activity	Floated CIs are presented except for analysis on HED (where conventional CIs are used for two-way comparison).
								Occasional	1.04 (0.83-1.30)		
								Monthly	0.95 (0.53-1.73)		
								Reduced intake	1.06 (0.67-1.69)		
								Ex-regular	1.32 (0.87-2.02)		
								Current regular	1.33 (1.11-1.58)		
						Abstainers	Men (drinking amount)	Abstainers	1.00 (0.77-1.29)		
								1-140g/week	1.12 (0.81-1.55)		
								140-280g/week	1.09 (0.78-1.53)		
								280-420g/week	1.14 (0.76-1.70)		
								≥420g/week	1.69 (1.21-2.37)		
						No HED	Regular drinkers	HED	1.60 (1.12-2.30)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Klatsky et al, 2015[102]	US	1978-1985 (17.8 years)	Mean 41	Pancreas	535 incidents / 124193	Lifelong abstainers	Overall	Ex-drinkers	1.3 (0.8-2.0)	Age, race, education, marital status, BMI, smoking	
								<1 drink/day	0.9 (0.7-1.2)		
								1-2 drinks/day	1.1 (0.8-1.5)		
								≥3 drinks/day	1.0 (0.7-1.5)		
				Prostate	3408 incidents / 124193	Lifelong abstainers	Overall	Ex-drinkers	1.1 (0.9-1.3)		
								<1 drink/day	1.1 (0.9-1.2)		
								1-2 drinks/day	1.1 (1.0-1.3)		
								≥3 drinks/day	1.1 (1.0-1.4)		
				Bladder	813 incidents / 124193	Lifelong abstainers	Overall	Ex-drinkers	1.3 (0.9-2.0)		
								<1 drink/day	1.2 (0.9-2.6)		
								1-2 drinks/day	1.3 (0.9-1.7)		
								≥3 drinks/day	1.1 (0.8-1.6)		
				Kidney	383 incidents / 124193	Lifelong abstainers	Overall	Ex-drinkers	1.3 (0.8-1.2)		
								<1 drink/day	1.0 (0.7-1.4)		
								1-2 drinks/day	0.9 (0.6-1.4)		
								≥3 drinks/day	1.0 (0.6-1.6)		
Jayasekara et al, 2019[134]	Melbourne; MCCS	1990-1994 (20.2 years)	40-69	Pancreas	239 incidents / 38472	Abstainers	Lifetime consumption	<19g/day	1.23 (0.90-1.69)	Age, sex, BMI, country of birth, smoking, diabetes, education, physical activity, energy from food; (for baseline intake) former drinking	
								20-39g/day	0.96 (0.59-1.57)		
								>40g/day	1.30 (0.76-2.23)		
								Per 10g/day	1.01 (0.93-1.09)		
							Baseline consumption	Former drinkers	1.46 (0.94-2.27)		
								<19g/day	1.18 (0.85-1.65)		
								20-39g/day	0.94 (0.57-1.55)		
								>40g/day	1.21 (0.70-2.08)		
								Per 10g/day	0.98 (0.90-1.06)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Naudin et al, 2018[133]	Europe; EPIC	1992-2000 (14 years)	35-70	Pancreas	1283 incidents / 476106	0.1-4.9g/day	Men (Lifetime consumption)	Non-drinkers	0.53 (0.16-1.74)	Study centre, age, smoking, BMI, diabetes, education, physical activity, height; (for lifetime alcohol consumption) duration of drinking, time since quitting; (for beverage type) energy intake from other alcohol sources	J-shaped association with baseline consumption in men. NS for both baseline and lifetime consumption in women. Subgroup analyses by beverage types and smoking status are based on baseline consumption. NS heterogeneity across smoking status.
								Ex-drinkers	1.78 (0.75-4.22)		
								5-14.9g/day	1.22 (0.82-1.81)		
								15-29.9g/day	1.26 (0.84-1.90)		
								30-59.9g/day	1.42 (0.93-2.17)		
								≥60 g/day	1.77 (1.06-2.95)		
								Per 12g/day	1.06 (1.02-1.10)		
							Men (Baseline consumption)	Per 12g/day	1.05 (1.01-1.09)		
							Men Beer	Per 12g/day	1.09 (1.02-1.15)		
							Men Wine	Per 12g/day	0.97 (0.90-1.05)		
							Men Spirits	Per 12g/day	1.17 (1.04-1.32)		
							Men never smokers	Per 12g/day	1.06 (0.98-1.15)		
							Men current smokers	Per 12g/day	1.05 (1.00-1.11)		
Dickerman et al, 2016[189]	Finland; Older Finnish Twin Cohort	1975-1981 (30 years)	Mean 40.1	Prostate	(601 incidents & 110 deaths) / 11372	Light drinkers (≤3 drinks/week)	Incidence	Abstainers	1.27 (0.94-1.71)	Age, BMI, smoking, social class, education, physical activity	1 drink=12g. Moderate (3-14 drinks/week). Heavy (>14 drinks/week).
								Moderate	1.20 (0.99-1.46)		
								Heavy	1.46 (1.12-1.91)		
							Mortality	Abstainers	1.90 (1.04-3.47)		
								Moderate	1.22 (0.76-1.97)		
								Heavy	1.32 (0.66-2.62)		
						Non-binge	Incidence	Binge	1.28 (1.06-1.55)		
							Mortality	Binge	0.87 (0.52-1.45)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Jayasekara et al, 2018[140]	Melbourne; MCCS	1990-1994 (19.3 years)	40-69	NHL	538 incidents / 37990	Lifetime abstainers	Overall (lifetime alcohol intake)	<20g/day	0.81 (0.66-0.99)	Age, sex, education, SES, smoking, BMI, energy from food, country	
								20-39g/day	0.79 (0.58-1.08)		
								≥40g/day	0.79 (0.54-1.15)		
								Per 10g/day	0.97 (0.92-1.03)		
							Beer	Per 10g/day	0.91 (0.83-1.00)		
							Wine	Per 10g/day	1.03 (0.94-1.12)		
							Spirits	Per 10g/day	1.06 (0.83-1.37)		
Wozniak et al, 2015[138]	Europe; EPIC	1992-2000 (11.5 years)	35-70	Kidney	931 incidents / 477325	0-6g/day (men); 0-3g/day (women).	Average lifetime consumption	Non-drinkers	1.44 (0.99-2.08)	Age, sex, BMI, hypertension, smoking status, waist-to-hip ratio; (for analysis of alcoholic beverage) intake from other alcoholic beverages	Significant inverse associations with baseline consumption across sexes, but NS for hypertensive participants or smokers. NS trends when stratified by beverage types.
								Former drinkers	1.05 (0.70-1.57)		
								6-12 (men) / 3-12 (women) g/day	0.73 (0.57-0.93)		
								12-24g/day	0.86 (0.66-1.11)		
								24-60g/day	0.76 (0.57-1.00)		
								>60g/day	0.94 (0.61-1.44)		
							Baseline consumption	Non-drinkers	1.21 (0.91-1.59)		
								6-12 (men) / 3-12 (women) g/day	0.78 (0.62-0.99)		
								12-24g/day	0.82 (0.64-1.04)		
								24-60g/day	0.70 (0.55-0.90)		
								>60g/day	0.91 (0.63-1.30)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Botteri et al, 2017[141]	Europe; EPIC	1992-2000 (13.9 years)	35-70	Bladder	1802 incidents / 476160		Overall (Lifetime consumption)	Per 12g/day	1.02 (0.99-1.05)	Age at recruitment, gender, study centre, smoking, energy, BMI, physical activity, education level	Results reflected lifetime alcohol consumption unless otherwise specified. Significantly higher risks for baseline heavy drinking in men and smokers, and lifetime drinking at >24g/day for spirits consumption in men & smokers (might be related to residual confounding by smoking).
							Men	Per 12g/day	1.02 (0.99-1.05)		
							Women	Per 12g/day	0.98 (0.85-1.14)		
							Never smokers	Per 12g/day	0.93 (0.81-1.06)		
							Smokers	Per 12g/day	1.02 (0.99-1.05)		
							Overall (Baseline consumption)	Per 12g/day	1.03 (1.00-1.06)		
						0-6g/day (men); 0-3g/day (women).	Overall (Lifetime consumption)	Non-drinkers	0.89 (0.63-1.26)		
								6-12 (men)/ 3-12 (women) g/day	0.94 (0.79-1.12)		
								12-24g/day	1.05 (0.88-1.29)		
								24-60g/day	1.01 (0.83-1.22)		
								60-96 (men)/ >60 (women) g/day	1.09 (0.81-1.49)		
								>96 (men) g/day	1.35 (0.91-2.00)		

Authors, year	Location; cohort	Baseline period (mean/ median follow-up)	Age	Cancer site	No of cases/ sample size	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Masaoka et al, 2017[142]	Japan; JPHC	1990, 1993-1994 (18.2 years)	40-69	Bladder	(354 men & 110 women) incidents / 95915	Non-/ occasional drinkers	Overall	Regular drinkers	1.14 (0.91-1.41)	Age at baseline, study area, smoking	NS trends. Inverted U-shaped association in men flushers but not in men non-flushers.
								1-150g/week	1.08 (0.82-1.42)		
								151-300g/week	1.26 (0.95-1.67)		
								301-450g/week	1.10 (0.79-1.54)		
								>450g/week	1.08 (0.75-1.55)		
							Men	Regular drinkers	1.15 (0.91-1.44)		
								1-150g/week	1.08 (0.80-1.46)		
								151-300g/week	1.30 (0.97-1.73)		
								301-450g/week	1.09 (0.78-1.54)		
								>450g/week	1.06 (0.73-1.53)		
							Women	Regular drinkers	1.05 (0.56-1.95)		
								1-150g/week	1.16 (0.61-2.20)		
								>150g/week	0.50 (0.07-3.68)		

HR, hazard ratio; RR, risk ratio; CI, confidence interval; SES, socio-economic status; BMI, body mass index; CKB, China Kadoorie Biobank; HED, heavy episodic drinking; US, United states; MCCS, Melbourne Collaborative Cohort Study; EPIC, European prospective investigation into cancer and nutrition cohort; NHL, non-Hodgkin lymphoma; NS, non-significant; JPHC, Japan Public Health Centre-based Prospective Study.
All studies (except Shen et al who did so in sensitivity analyses) excluded prior cancers at baseline.
Most studies (except Masaoka et al, Shen et al, and Klatsky et al who measured alcohol consumption only at baseline, and Pang et al who used only baseline measurement in the analyses) analysed lifetime consumption or used multiple alcohol consumption measures over a timespan to take account of within-person variation.

Table 2.17. Meta-analyses on alcohol consumption and risks of liver diseases

Authors, year	Locations	No of cases	Outcome	Reference	No of studies & study design	Subgroup	Exposure category	RR (95% CI)	Notes
Rehm et al, 2010[71]	9 US, 4 Italy, 2 Denmark, 1 Japan, 1 China	3384	Liver cirrhosis and ALD (K70, K74) mortality	0g/day	17 (14 cohorts, 3 C-C)	Men	>0-12g/day	1.0 (0.6-1.6)	
							12-24g/day	1.6 (1.4-2.0)	
							24-36g/day	2.8 (2.3-3.4)	
							36-48g/day	5.6 (4.5-7.0)	
							48-60g/day	7.0 (5.8-8.5)	
							≥60g/day	14 (11.7-16.7)	
						Women	>0-12g/day	1.9 (1.1-3.1)	
							12-24g/day	5.6 (4.5-6.9)	
							24-36g/day	7.7 (6.3-9.5)	
							36-48g/day	10.1 (7.5-13.5)	
							48-60g/day	14.7 (11.0-19.6)	
							≥60g/day	22.7 (17.2-30.1)	
			Liver cirrhosis and ALD (K70, K74) morbidity			Men	>0-12g/day	0.3 (0.1-0.9)	
							12-24g/day	0.3 (0.2-0.4)	
							24-36g/day	0.7 (0.5-1.0)	
							36-48g/day	2.0 (1.5-2.7)	
							48-60g/day	2.3 (1.7-3.2)	
							≥60g/day	5.0 (3.9-6.4)	
						Women	>0-12g/day	0.4 (0.1-1.2)	
							12-24g/day	1.0 (0.5-1.9)	
							24-36g/day	2.4 (1.8-3.2)	
							36-48g/day	1.9 (1.4-2.6)	
							48-60g/day	5.9 (3.7-9.3)	
							≥60g/day	6.1 (4.6-8.0)	

Authors, year	Locations	No of cases	Outcome	Reference	No of studies & study design	Subgroup	Exposure category	RR (95% CI)	Notes
Cao et al, 2016[143]	2 US, 1 Brazil, 9 Japan, 1 HK, 1 Argentina, 2 Germany	Not specified	Fatty liver disease	Non-drinkers	16 (13 cross-sectional, 2 cross-sectional following longitudinal studies; 1 cohort)	All	Light to moderate (≤40 g/day)	0.77 (0.69-0.86)	
						Men	Light to moderate	0.77 (0.66-0.91)	
						Women	Light to moderate	0.70 (0.63-0.78)	
						BMI <25kg/m^2	Light to moderate	0.79 (0.72-0.87)	
						BMI ≥25kg/m^2	Light to moderate	0.69 (0.51-0.93)	
						All	Light (<20g/day)	0.75 (0.67-0.83)	
						All	Moderate (20-40g/day)	0.80 (0.66-0.98)	
						All	Heavy (>40 g/day)	0.82 (0.59-1.12)	
						Japan	Heavy	0.67 (0.58-0.77)	
						Japan men	Heavy	0.69 (0.63-0.74)	
						Japan women	Heavy	0.87 (0.55-1.36)	
						Germany	Heavy	1.79 (1.06-3.00)	
Roerecke et al, 2016[144]	11 Japan, 7 form the US, Germany, Finland, Italy, Spain, China	25662	Hepatic steatosis (fatty liver)	Non-drinkers	18 (6 cohorts, 12 cross-sectional studies)	All studies	<20g/day	0.85 (0.75-0.96)	Dose-response relationships: (Japan) inverse in men, J-shaped in women; (Germany): detrimental in men; inverse in women.
						All men	<20g/day	0.80 (0.68-0.95)	
						All women	<20g/day	0.74 (0.66-0.83)	
						Japan	<20g/day	0.75 (0.71-0.79)	
						Japan men	<20g/day	0.73 (0.68-0.78)	
						Japan women	<20g/day	0.72 (0.62-0.83)	
						Other countries	<20g/day	1.05 (0.86-1.30)	
						Other countries men	<20g/day	1.68 (1.26-2.23)	
						Other countries women	<20g/day	0.80 (0.61-1.04)	

RR, risk ratio; CI, confidence interval; C-C, case-control(s); US, United states; ALD, alcoholic liver disease; BMI, body mass index.

Table 2.18. Prospective studies on alcohol consumption and risks of liver diseases

Authors, Year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Trembling et al, 2017[147]	England; UKCTOCS	2001-2005 (5.1 years)	50-74	325 incidents / 95126 post-menopausal women	Liver-related event (K70, K73, K74, K76, I85, Z94.4, C22.0)	Non-drinkers	Overall	1-15 units/week	0.78 (0.61-1.00)	Smoking, Index of Multiple Deprivation 2007, hypertension, heart disease, hypercholesterolaemia, diabetes, BMI	NS interaction between alcohol and BMI.
								16-20 units/week	0.97 (0.52-1.82)		
								≥21 units/week	1.83 (0.97-3.44)		
							Joint effect by alcohol and BMI:				
							BMI <25kg/m^2	None	1		
								1-15 units/week	0.91 (0.56-1.47)		
								16-20 units/week	1.03 (0.35-2.99)		
								≥21 units/week	1.93 (0.66-5.62)		
							BMI 25-30 kg/m^2	None	1.46 (0.85-2.50)		
								1-15 units/week	1.34 (0.71-1.83)		
								16-20 units/week	1.61 (0.61-4.26)		
								≥21 units/week	3.32 (1.25-8.81)		
							BMI ≥30 kg/m^2	None	2.28 (1.35-3.86)		
								1-15 units/week	1.58 (0.96-2.61)		
								16-20 units/week	1.67 (0.39-7.15)		
								≥21 units/week	2.86 (0.67-12.21)		
Yi et al, 2016[103]	South Korea; KVHS	2004 (to 2010)	Mean 58.8	338 deaths / 107735 men	Any liver disease mortality (K70-K76)	<1 drink (~9g) /week	Non-neoplastic liver diseases	1-6 drinks/week	0.90 (0.64-1.26)	Age at enrolment, smoking, physical activity, income, BMI	Significant trend with alcohol amount across BMI levels. Significant interaction between lower BMI and high alcohol intake.
								7-13 drinks/week	1.53 (1.07-2.19)		
								14-27drinks/week	1.92 (1.38-2.67)		
								≥28 drinks/week	2.92 (2.12-4.02)		
								Per 5 drinks/week	1.65 (1.49-1.84)		
				178 deaths / 107735 men	ALD mortality (K70)	<1 drink (~9g) /week	ALD	1-6 drinks/week	1.32 (0.81-2.18)		
								7-13 drinks/week	2.45 (1.48-4.07)		
								14-27drinks/week	2.77 (1.71-4.50)		
								≥28 drinks/week	4.03 (2.51-6.46)		
								Per 5 drinks/week	1.67 (1.45-1.93)		

Authors, Year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Schwartz et al, 2013[145]	Finland; ATBC Study	1985-1988 (to 2009)	50-69	213 deaths / 27086 men	Any liver disease mortality (K70-K77)	<5g/day	Mortality	5-20g/day >20g/day	2.06 (1.22-3.50) 6.68 (4.16-10.71)	Age, education, BMI, smoking, diabetes, study arm (a-tocopherol, b-carotene, both, neither).	
Persson et al, 2013[146]	US; NIH-AARP Diet and Health Study	1995-1996 (10.5 years)	50-71	789 deaths/ 494743	Liver disease mortality (K70, K73, K74)	<1 drink/day	Mortality	None 1-3 drinks/day >3 drinks/day	1.88 (1.55-2.28) 2.03 (1.63-2.52) 5.84 (4.81-7.10)	Age, sex, race, education, smoking, body mass index, diabetes	Consistent trend across folate intake, but NS interaction.
Dawson et al, 2008[155]	US; NESARC	2001-2002 (to 2004-2005)	18+	~130 incidents / 21200 drinkers	Any liver disease incident (i.e., cirrhosis and other liver disease; ICD-10 code not specified)	Never risk drinking	Overall	<1 risk drinking /month 1-3 risk drinking/month 1-2 risk drinking /week 3-4 risk drinking /week Daily or near daily risk drinking	1.21 (0.62-2.35) 1.62 (0.79-3.32) 2.78 (1.32-5.85) 2.40 (0.47-12.23) 4.76 (2.29-9.88)	Age, sex, race/ethnicity, marital status, BMI, employment, education, health status, smoking, drug use, mood/ anxiety disorder, personality disorder, family history of alcoholism, ethanol intake, duration of drinking	Risk drinking was defined as 5+ and 4+ drinks on a single day for men and women, respectively.
Simpson et al, 2018[75]	UK; MWS	1996-2001 (15 years)	50-64	1560 incidents / 401806 weekly drinkers	ALD and liver cirrhosis incidence (K70, K74)	1-2 drinks/ week	All	>15 drinks/week	3.43 (2.87-4.10)	Birth year, baseline year, deprivation quintile, regions, smoking, oral contraceptive use, HRT use, BMI; (for analyses on patterns, where appropriate) number of baseline drinks, beverage types, mealtime habits, frequency	Consistent associations across BMI and smoking. Limited power to investigate across specific beverage types.
						W/o meals	All	With meals	0.69 (0.62-0.77)		
						W/o meals	Wine only	With meals	0.69 (0.56-0.85)		
						W/o meals	Other beverage types	With meals	0.72 (0.63-0.82)		
						Non-daily	All	Daily	1.61 (1.40-1.85)		

Authors, Year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Askgaard et al, 2015[74]	Denmark; DCHS	1993-1997 (15 years)	50-64	(257 men & 85 women) incidents / 55917	Alcoholic cirrhosis incidence (K70.3)	0-14 drinks/ week	Men	Current abstainers	7.58 (3.39-16.9)	Age, smoking, education, waist circumference; (for drinking frequency) alcohol amount; (for lifetime consumption) early age alcohol amount and/or baseline alcohol amount	1 drink = 12g. No cases in lifetime abstainers. Recent but not lifetime alcohol consumption is the strongest predictor. Lower risks in wine drinkers compared to beer and liquor drinkers up to moderate weekly amount.
								14-28 drinks/week	2.33 (1.52-3.58)		
								28-42 drinks/week	6.98 (4.65-10.5)		
							Women	Current abstainers	3.21 (0.77-13.4)		
								14-28 drinks/week	3.49 (2.00-6.12)		
								28-42 drinks/week	16.2 (9.16-28.7)		
						2-4 drinking days/week	Men	Current abstainers	10.0 (4.32-23.0)		
								<1 day/week	1.34 (0.67-2.67)		
								1 day/week	1.30 (0.59-2.87)		
								5-6 days/week	1.43 (0.84-2.43)		
								7 days/week	3.65 (2.39-5.55)		
							Women	Current abstainers	4.03 (0.91-17.8)		
								<1 day/week	1.45 (0.71-2.96)		
								1 day/week	0.81 (0.29-2.24)		
								5-6 days/week	2.30 (1.14-4.67)		
								7 days/week	1.73 (0.85-3.52)		
Goh et al, 2014[151]	Singapore; Singapore Chinese Health Study	1993-1998 (14.7 years)	45-74	114 deaths / 63275	Liver cirrhosis mortality	Non-drinkers	Overall	<20 g/day	0.72 (0.39-1.35)	Age, sex, dialect, smoking, education, recruitment year, BMI, diabetes history, physical activity	
								20+ g/day	7.07 (4.01-12.47)		

Authors, Year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Britton et al, 2019[160]	UK; Whitehall II study	1985-1989 (30 years)	35-55 years	1552 incidents/ 5407 civil servants	High fatty liver index (>60)	Stable low-risk, i.e., <168g/ week (men)	Men 30-year typologies	Stable non-drinkers	1.21 (0.73-1.96)	Age, socio-economic position, ethnicity, and smoking.	
								Unstable low-risk	1.24 (0.95-1.65)		
								Stable heavy	2.04 (1.53-2.74)		
								Unstable heavy	1.64 (1.26-2.15)		
								Former drinkers	2.09 (1.55-2.85)		
						Stable low-risk, i.e., <112g/ week (women)	Women 30-year typologies	Stable non-drinkers	1.50 (0.86-2.63)		
								Unstable low-risk	1.11 (0.72-1.75)		
								Stable heavy	2.24 (1.08-4.55)		
								Unstable heavy	0.75 (0.45-1.25)		
								Former drinkers	1.68 (1.08-2.67)		
						Low-risk	Men cross-sectional	Non-drinkers	0.99 (0.62-1.53)		
								Former drinkers	1.71 (1.37-2.15)		
								Heavy	1.43 (1.23-1.67)		
						Low-risk	Women cross-sectional	Non-drinkers	1.44 (0.91-2.26)		
								Former drinkers	1.62 (1.18-2.22)		
								Heavy	0.95 (0.67-1.35)		
Yang et al, 2012[73]	China; CPSS	1990-1991 (15 years)	40-79	418 deaths / 218189 men	Liver cirrhosis mortality	Non-drinkers	Men	Non-drinkers	1.00 (0.87-1.16)	Age, area, smoking, education	Floated CIs are presented.
								All drinkers	1.15 (0.93-1.42)		
								<140g/week	1.12 (0.76-1.64)		
								140-279g/week	0.84 (0.59-1.21)		
								280-419g/week	1.16 (0.85-1.56)		
								420-699g/week	1.22 (0.83-1.79)		
								≥700g/week	1.74 (1.22-2.48)		

Authors, Year	Location; cohort	Baseline period (mean/ median follow-up)	Age	No of cases/ sample size	Outcome	Reference category	Subgroup	Exposure category	HR or RR (95% CI)	Adjustment	Notes
Yuan et al, 1997[72]	Shanghai, China; SCS	1986-1989 (6.7 years)	45-64	35 deaths / 18244 men	Hepatic cirrhosis mortality	Lifelong non-drinkers	Men	1-28 drinks/week ≥29 drinks/week	0.46 2.99	Age, education, smoking	1 drink ≈ 13g. Significant at ≥29 drinks/week.

HR, hazard ratio; RR, risk ratio; CI, confidence interval; UKCTOCS, United Kingdom Collaborative Trial of Ovarian Cancer Screening; BMI, body mass index; NS, non-significant; KVHS, Korean Veterans Health Study; ALD, alcoholic liver disease; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; US, United States; NIH-ARRP, National Institutes of Health-American Association of Retired Persons; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; ICD-10, international classification of diseases, 10th revision; UK, United Kingdom; MWS, Million Women Study; W/o, without; HRT, hormone replacement therapy; DCHS, Diet, Cancer and Health Study; CPSS, Chinese Prospective Smoking Study; SCS, Shanghai Cohort Study.

All prospective studies (except the Whitehall II study which included both cross-sectional and prospective analyses, and Yi et al, Goh et al, and Shen et al who excluded prior relevant diseases or early events in subgroup or sensitivity analyses) excluded prior relevant diseases at baseline.

Most studies (except the UK studies, e.g., MWS and Whitehall II, and Askgaard et al) measured alcohol consumption only once at baseline.

Chapter 3. Aim and Objectives

3.1 Aim

The main aim of this thesis is to examine the associations of alcohol drinking with major chronic diseases, specifically cancers and liver diseases, and mental health among Chinese adults from the CKB prospective cohort study.

3.2 Objectives

Specific objectives of the thesis are to:

1. Examine the recent patterns and trends in alcohol consumption and the factors associated with stopping alcohol drinking within the CKB population;
2. Examine the cross-sectional associations of problem drinking with mental health and wellbeing, and the prospective associations of problem drinking with overall mortality, any hospitalisation, and events due to external cause;
3. Assess the prospective associations of alcohol consumption and drinking patterns with incidence of overall and site-specific cancers;
4. Assess the prospective associations of alcohol consumption and drinking patterns with incidence of overall and major chronic liver diseases.

Chapter 4. Study design, population and methods

This chapter describes the study design and population, assessments of exposures, covariates and outcomes, and characteristics of the CKB study participants.

4.1 Study design and population

The CKB is a blood-based large prospective cohort study of 0.5 million middle-aged adults recruited from 10 diverse areas across China during 2004-2008. The CKB study involved collection of questionnaire data, physical measurements, and blood samples at the baseline survey, complemented by subsequent periodic resurveys and follow-up for cause-specific mortality and morbidity and for any hospital admission. It was established to investigate both the established and emerging genetic and non-genetic causes, and their complex interplay, of common chronic diseases in the Chinese population. Details of the CKB design, survey methods, and population have been discussed previously.[190,191]

Prior to the baseline and subsequent resurveys, ethical approvals were obtained from the ethics committees of the University of Oxford and the Chinese Centre for Disease Control and Prevention (CDC). In addition, approvals were also obtained from institutional research boards at the local CDCs in each of the 10 areas. All participants provided written informed consent which allowed access to their medical records and long-term storage of blood for anonymised and non-specified medical research purposes.

The 10 geographically defined study sites (5 urban and 5 rural) of CKB were selected to maximize geographic and socio-economic diversity and to cover a wide spectra of risk

factor exposures and disease patterns, while taking account of logistic convenience such as population stability, quality of death and disease registries, and local commitment and capacity (Figure 4.1). The study population was not intended to be representative of China as a whole. A Regional Coordinating Centre and survey team, consisting of about 15 full-time staff with medical qualifications and fieldwork experience, were established in each of the ten study areas.

All permanent, non-disabled residents aged 35-74 years from 100-150 administrative units (rural villages or urban residential committees) selected within each study area were identified through official residential records and invited to participate. Invitation letters and study information leaflets were delivered door-to-door by local community leaders or health workers following extensive publicity campaigns. To encourage participation, individuals attending the baseline survey who were slightly outside the target age range (30-34 or 75-79 years) were not turned away (n~10,000). Overall, 512,891 men and women aged 30-79 years were enrolled in the CKB study. Participants are broadly representative of the geographically defined areas from which they were sampled, with an average response rate of ~30% across the ten study areas.

4.2 Data collection

4.2.1 Baseline survey

The baseline survey took place between June 2004 and July 2008, during which data collection was performed in temporary assessment clinics specially set up in the local communities for the CKB study. At local assessment clinics, trained health workers administered a laptop-based questionnaire to collect information on socio-

demographic status, lifestyle factors (e.g., alcohol drinking, smoking, tea drinking, diet, physical activity), exposure to passive smoking and domestic indoor air pollution, wellbeing and mental health (e.g., self-reported health status, life satisfaction, stressful life events, sleep patterns, symptoms of depression and anxiety), personal and family medical history, and reproductive history (for women only).

A range of physical measurements (e.g., blood pressure, anthropometry) were undertaken, and a 10 ml non-fasting blood sample was collected for onsite blood tests including random plasma glucose and HBsAg and for long-term storage. The CKB baseline questionnaire is shown in Appendix C.

4.2.2 Assessment of alcohol consumption

Alcohol intake was self-reported by participants at the baseline questionnaire. Participants were asked how often they had drunk alcohol during the past 12 months (never or almost never, occasionally, only at certain seasons, every month but less than weekly, usually at least once a week). Those who had not drunk alcohol at least weekly in the past 12 months were asked if there was a period of at least a year prior to that when they had drunk some alcohol at least once a week.

Those who had drunk alcohol at least once a week in the past 12 months were asked further questions about their drinking patterns including: frequency of drinking (1-2, 3-5, or 6-7 days per week); types of beverage (beer, grape wine, rice wine, weak spirits with <40% alcohol content, strong spirits with ≥40% alcohol content) and amount consumed for each beverage type (reported by number of small [250 ml] or large [640 ml] bottles of beer, and number of liang [50g] for wines and spirits) on a typical

drinking day, on special occasions, and the last time they drank; time of drinking in relation to meals (usually drinking with meal, usually drinking between or after the meals, no regular patterns); age started drinking in most weeks; whether the alcohol consumption of the participants had changed significantly in the past few years (about the same as before, increased a lot, decreased a lot); and the experience of flushing or dizziness after drinking (soon after first mouthful, after drinking small amount of alcohol, after drinking large amount of alcohol, no flushing). They were also asked about their experience of problem drinking indicators related to alcohol use in the past month, including: ever drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing of control after drinking (i.e., negative emotions); being unable to stop drinking; and having shakes when stopping drinking.

For this thesis, participants were classified into five main drinking categories based on the frequency of alcohol drinking during the past year and prior to the past year, according to the method described in Millwood et al (2013):[87] (1) abstainers – who had never or almost never drunk alcohol in the past 12 months and had not drunk at least weekly in the past; (2) ex-regular drinkers – who had not drunk alcohol in most weeks in the past 12 months but did so in the past; (3) reduced-intake drinkers – who had drunk alcohol in the past 12 months only occasionally, at certain seasons, or monthly but less than weekly, but had drunk at least weekly in the past; (4) occasional drinkers – who had drunk alcohol in the past 12 months only occasionally, at certain seasons, or monthly but less than weekly, and had not drunk at least weekly in the past; and (5) current regular drinkers – who had drunk alcohol at least weekly in the past 12

months. These drinking categories are broadly in line with those discussed in the WHO guide for monitoring alcohol consumption,[28] with additional information on the past drinking habits of participants which allows former regular drinkers to be distinguished from never regular drinkers for assessing reliably the health effects of alcohol consumption.

Level of alcohol consumption was calculated as grams of pure alcohol, based on the beverage type and amount drunk in the reported drinking scenario (a typical drinking day, special occasions, or the last time they drank), assuming the following alcohol content by volume (v/v) typically seen in China:[7] beer 4%, grape wine 12%, rice wine 15%, weak spirits 38%, and strong spirits 53%. Total weekly level of alcohol consumption was calculated as grams per week by multiplying the consumption on a typical drinking day by the frequency of drinking (taken as the median of the reported frequency intervals, i.e., 1.5 for 1-2 days/week, 4 for 3-5 days/week, 6.5 for 6-7 days/week).

Among current regular drinkers, “daily drinking” was defined as drinking 6-7 days per week. “Heavy episodic drinking (HED)” was defined as consuming more than 60g of alcohol on one occasion for men and more than 40g for women, in line with WHO guidelines.[28] “Problem drinking” was defined by the report of one or more of the five problem drinking indicators (ever drinking in the morning, unable to do anything, negative emotions, unable to stop drinking, having shakes when stopping drinking) measured in the baseline survey. Those who reported usually drinking with meals were classified as “drinking with meals”, whereas those who reported usually drinking between or after meals, or had no regular patterns, were categorised as “drinking

without meals". "Duration of regular drinking" was calculated as the difference in years between baseline age and age started drinking alcohol in most weeks. Participants who reported experiencing hot flushes or dizziness soon after the first mouthful or after drinking a small amount of alcohol were classified as "having the flushing response".

Detailed definitions of the various parameters of alcohol consumption are shown in Table 4.1. Further classifications of alcohol exposure specific to the research questions are described in the relevant chapters.

4.2.3 Assessment of other major lifestyle factors

Detailed information related to smoking including frequency, amount, type of tobacco smoked, the age at which participants started smoking regularly and stopped smoking, and the main reason for smoking cessation were collected. Based on a combination of these information, smoking status was classified as never smokers (did not smoke at baseline and had smoked <100 cigarettes in lifetime), ex-regular smokers (had smoked ≥100 cigarettes or equivalent but had quit smoking at least six months before baseline by choice), occasional smokers (did not meet the criteria for never or ex-regular smoker, and had not stopped smoking completely for at least six months before baseline), and current regular smokers (ever smoked ≥1 cigarettes or equivalent daily for at least six months, or stopped for at least six months before baseline due to ill health).

Detailed information on tea drinking including frequency, amount, types, and temperature was collected by questionnaire. Dietary data covering 12 major food

groups (rice, wheat products, other staple foods [e.g., corn, millet], meat, poultry, fish, eggs, dairy products, fresh vegetables, preserved vegetables, fresh fruit, soybean products) were collected in terms of the frequency of habitual consumption during the past 12 months (Daily, 4-6 days per week, 1-3 days per week, monthly, never/rarely).

Questions on physical activity were adapted from validated questionnaires used in several other studies in Western[192] and Chinese populations,[193] with some additional modifications after a CKB pilot study. Participants were asked about their usual type and duration of physical activities related to occupation, commuting, housework, and leisure-time exercise during the past year. Metabolic equivalent tasks (METs) from the 2001 update of a major compendium of physical activities were used to quantify the amount of physical activity.[194] The MET value for a particular type of physical activity represents the ratio of the energy expended per kilogram of body weight per hour during that activity to that expended when sitting quietly. The number of hours spent per day participating in each activity was multiplied by the MET score for that activity, and the daily amount of physical activity was obtained by summing the MET-hours for activities related to occupation, commuting, housework, and non-sedentary leisure-time activities.

4.2.4 Assessment of medical history, mental health and wellbeing

Participants were asked to rate their health status (excellent, good, fair, poor) and to report whether they had ever been diagnosed by a doctor of a range of health conditions, including: diabetes, chronic heart disease, stroke or transient ischaemic attack, tuberculosis, cancers (lung, oesophagus, stomach, liver, intestine, breast, prostate, cervix, other), emphysema or bronchitis, cirrhosis or chronic hepatitis, peptic

ulcer, gallstone or gallbladder disease, kidney disease, rheumatoid arthritis, hypertension, asthma, rheumatic heart disease, psychiatric disorders, neurasthenia, fracture, and head injury. Participants were also asked to report any family history (father, mother, siblings, children) of major chronic diseases including stroke, heart attack, diabetes, mental disorder, and cancer (no information of cancer type was collected).

Indicators of wellbeing and mental health (e.g., life satisfaction, sleep problems, depression, anxiety) and experience of ten stressful life events were also assessed by baseline questionnaire, which are discussed in detail in Chapter 6.

4.2.5 Physical measurements and blood collection

A range of physical measurements including height, weight, hip and waist circumference, blood pressure, pulse rate, lung function, and exhaled carbon monoxide (COex) were measured using standard instruments and protocols and with regular calibrations. All anthropometric measurements were measured by trained technicians while participants were wearing light clothes and no shoes, usually to the nearest 0.1 cm or 0.1 kg.[195] Standing height was measured using a stadiometer. Waist circumference and hip circumference were measured with a soft non-stretchable tape. Waist circumference was measured at the midway between the lowest rib and the iliac crest, while hip circumference was measured around the maximum circumference of the buttocks.[196] Weight was measured by using a body composition analyser (TANITA-TBF-300GS, Tanita Corporation, Tokyo, Japan), with subtraction of weight of clothing according to season. BMI was calculated as weight (in kg) divided by the square of standing height (in m). Waist-to-hip ratio was the ratio of waist circumference to hip

circumference. Blood pressure was measured twice using a UA-779 digital sphygmomanometer (A&D Instruments; Abingdon, UK) after participants had remained at rest in a seated position for at least 5 minutes.[197] Spirometry was performed to measure forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) using a portable handheld "Micro spirometer" (Micro Medical Limited, Rochester, Kent, England) following recommended procedures. Screen-detected COPD was defined based on the modified Global Initiative for Chronic Obstructive Lung Disease criteria (prebronchodilator FEV1/FVC <0.7) as previously reported.[198] To help validate smoking exposure, COex was measured by a hand-held battery operated meter (CareFusion MicroCO meter, Chatham, UK).[199]

In addition, a 10 ml non-fasting blood sample was collected into an ethylene diamine tetraacetic acid vacutainer (BD Hemogard™, US) for long-term storage for future research. A small sample of this was used for on-site testing on HBsAg using rapid test strips (ACON Biotech), which gave either negative, positive, or unclear results.[200] On-site blood test was also carried out for random plasma glucose using the SureStep Plus System (Johnson & Johnson, California, US). Individuals with a plasma glucose level between 7.8 and 11.1 mmol/L were invited back for a fasting plasma glucose test the following day. Among those without self-reported diabetes, screen-detected diabetes was defined as having a measured random plasma glucose level ≥7.0mmol/L with time since last food intake ≥8 hours, or ≥11.1mmol/L with time since last food intake <8 hours, or a fasting plasma glucose level ≥7.0mmol/L on subsequent testing.[201]

4.2.6 Resurveys

Following completion of the baseline survey, two periodic resurveys were conducted between May and October 2008 (i.e., first resurvey, response rate ~80%) and between August 2013 and September 2014 (i.e., second resurvey, response rate ~75%). Each of the two resurveys involved ~5% of randomly selected surviving participants using administrative unit as the basic sampling unit. The resurveys serve two important purposes: (1) to provide repeat measurements of risk exposures (for this thesis, alcohol consumption) to correct for regression dilution bias, which allows unbiased assessment of the prospective associations between long-term "usual" levels of risk exposures and diseases; and (2) to enable calibration and enhancement of risk factor exposures measured at baseline.[190] Similar data collection and survey procedures were used as in the baseline survey, with a few additional more detailed questions (e.g., reasons for stopping alcohol drinking) and enriched physical measurements.

Alcohol intake was re-assessed in the same way among a subset of participants at the first resurvey, and with minor changes and a few additional questions at the second resurvey. At baseline and the first resurvey, participants were allowed to report up to three beverage types on "special drinking occasions" and "the last time they drank", but only one beverage type on "a typical drinking day". However, at the second resurvey, participants were allowed to report up to three beverage types for all of the three drinking scenarios. Also at the second resurvey only, ex-regular drinkers and reduced-intake drinkers were asked about their main reason for stopping drinking in most weeks (existing physical illness, money, health concerns about future illness, family disapproval, doctor's advice, other reasons).

4.3 Long-term follow-up of health outcomes

The vital status of participants was monitored through China's Disease Surveillance Points system via reviews of death certificates. For the few deaths (~5%) without recent medical attention, standardised verbal autopsy was used to determine probable causes of deaths from symptoms or signs described by relevant informants (usually family members). In addition, information on non-fatal outcomes of four major diseases (diabetes, cancer, ischemic heart disease, stroke) and any episode of hospitalisation were collected through linkage, via unique national identification, with disease registries and the Chinese National Health Insurance claim databases (>98% coverage across the ten study areas). Participants were lost to follow-up if: (1) their permanent registered residence moved out of the study area; (2) they could not be contacted after at least three reasonable attempts within 1 year; or (3) they could be contacted but the new residence was out of the jurisdiction of the Regional Coordinating Centre. To minimise loss to follow-up and underreporting of events, annual active follow-up through local residential, medical, health insurance, and administrative records was also performed. All events were coded using ICD-10 by trained staff blinded to baseline information.

In the CKB, some regions had not yet set up a cancer registry and others had a varied quality of data collection, and the reporting of incident cancer events from cancer registries was incomplete (covering 45% of all cancer incidents recorded, see Table D1). Death registries and the national health insurance system were the main reporting sources of cancer and liver disease events in the CKB (covering >94% of all cancer incidents and 99% of all liver disease events), with cancer registries serving as

an additional data source. The cancer mortality rate in the CKB has been shown to be consistent with that from the National Central Cancer Registry, while the cancer incidence rate was much higher in the CKB.[202] This is because the comprehensive and complete cancer monitoring via different active and passive systems allowed the CKB to capture cancer incidents which would otherwise be missed out based on data from cancer registries only. This suggests good data quality and completeness for cancer endpoint detection in the CKB. Nevertheless, there are more tertiary hospitals in urban areas than in rural areas in China, and people living in deprived and rural areas or with lower socio-economic status may be less likely to seek medical services in tertiary hospitals due to the high costs involved. This may potentially result in regional differences in the completeness of endpoint assessment, especially for liver diseases. As there are huge regional variations in alcohol consumption (see Chapter 5), *ALDH2* and *ADH1B* genotypes (see Chapter 7), and other risk factors, potential variation in the completeness of endpoint detection between study areas may generate spurious associations with alcohol. To account for the heterogeneity across study sites, all analyses in this thesis are adjusted for the ten study areas (see Section 4.5 and Method sections in each chapter).

By 1 January 2017 (censoring date for the main prospective analyses in Chapter 7-8; ~10 years of follow-up), 44,037 (8.6%) participants had died and 4781 (0.9%) were lost to follow-up.

4.4 Genotyping measurements

Genotyping was conducted in a subset of individuals using a custom-designed 800K single nucleotide polymorphism (SNP) array (Axiom; Affymetrix) or a 384-SNP array

(GoldenGate; Illumina). To date, 167,924 participants were genotyped for the two alcohol metabolism variants (*ALDH2*-rs671, *ADH1B*-rs1229984), of whom 151,164 participants were population-based and the remainder were from nested case-control studies of cardiovascular diseases and COPD. Further details of the subset of participants with genotype data for *ALDH2*-rs671 and *ADH1B*-rs1229984 are presented in Chapter 7.

4.5 Statistical methods

Prevalence and mean values of baseline characteristics and drinking characteristics were calculated separately in men and women. Where appropriate, prevalence and mean values across subgroups were directly standardised to the age and study area structure of the CKB population. The associations between alcohol drinking parameters and baseline characteristics were assessed using multinomial logistic regression for categorical outcome variables, logistic regression for binary variables, and linear regression for continuous variables, and were adjusted for age and study area where appropriate. Cancer and liver disease incidence rates were presented as per 100,000 person-years. Incidence rates were calculated separately in men and women, and were standardised by the age and study area structure of the CKB population where appropriate. The cross-sectional associations of problem drinking patterns with mental health and wellbeing were assessed using logistic regression. Cox proportional hazards models were used to assess the prospective associations of usual alcohol consumption and drinking patterns with mortality and disease risks among participants with no history of relevant diseases at baseline. The underlying time scale was time since entry into the study (i.e., time at entry to time at diagnosis, death, loss

to follow-up, or censoring date, whichever occurred first). Cox regression models were stratified by age-at-risk group (in five-year intervals) and study area (ten regions) to account for any heterogeneity across age-at-risk groups and the ten study areas in the baseline hazard function of health outcomes, and were further adjusted for relevant covariates specific to the analyses. For exposure variables involving more than two exposure categories, floating standard errors (SEs) were used to estimate group-specific variances and CIs of log ORs or log HRs for all categories including the reference group, enabling comparison between any two categories rather than simply pairwise comparisons with the reference category.[203,204] For two-way comparisons of exposure categories, conventional SEs and CIs were used. Heterogeneity across strata was assessed with a chi-squared test. Further details of analytical methods are covered in the relevant chapters. All analyses were performed in SAS version 9.4 and all figures were plotted in R version 3.6.1.

4.6 Baseline characteristics of CKB participants

Of the 512,891 participants recruited at baseline, the mean age was 52 years (standard deviation [SD] 10.7), and 41% were men and 56% were from rural areas (Table 4.2). Approximately half of participants had at least 6 years of education, and the proportion was higher in men than in women. Most participants (90%) were married at baseline.

Striking sex difference was seen in the prevalence of smoking, which reflects the cultural norm in China where certain unhealthy behaviours are more acceptable in men than in women. At baseline, 61% of men were current regular smokers as opposed to only 2% of women (Table 4.3). 28% of participants consumed fresh fruit

regularly (i.e., at least 4 days/week), which was less common in men than in women (23% in men vs. 32% in women), whereas the opposite was observed for daily tea drinking (41% vs. 16%). The mean level of physical activity was 22.0 MET hours/day in men and 20.4 MET hours/day in women.

The mean level of systolic blood pressure at baseline was slightly higher in men than in women (133 mmHg vs. 130 mmHg), while the mean BMI was similar in both sexes (23.4 kg/m^2 vs. 23.8 kg/m^2). 46% of participants reported having good or excellent health (49% in men vs. 43%, in women), and almost 70% were satisfied with life (70% vs. 68%). About 22% of participants had at least one prior major chronic disease (23% in men vs. 22% in women), 0.5% had prior cancer (0.5% in both sexes), and 1.2% had prior cirrhosis or chronic hepatitis (1.7% vs. 0.8%).

4.7 Characteristics of resurvey CKB participants

The subsets of participants resurveyed at the first resurvey in 2008 (n=19,788) and the second resurvey in 2013-2014 (n=24,996) were broadly representative of the baseline study population in terms of the distribution of their socio-demographic characteristics, lifestyles, and health-related factors recorded at the time of baseline (Tables D2-D3). Baseline alcohol drinking prevalence and patterns were also broadly similar between the entire study population and the two resurvey subsets (Table D4). Looking at the characteristics of subset participants at the time of the resurveys, the proportion of participants with household income of >35,000 yuan/year was progressively higher at the resurveys than at baseline (18% vs. 29% vs. 60%, baseline vs. 1st resurvey vs. 2nd resurvey) (Table 4.2), possibly reflecting the rapid economic development in China. For major lifestyles and health-related factors, there were little

fluctuation between the baseline survey and the first resurvey, but notable differences at the second resurvey (Table 4.3). The proportions of participants reporting regular fresh fruit consumption and being satisfied with life were higher at the second resurvey than at baseline. Conversely, the prevalence of current regular smoking among men was progressively lower across the resurveys (61% vs. 58% vs. 51%). As the study population became older, indications of poor health, such as high systolic blood pressure (mean 131 mmHg vs. 137 mmHg, baseline vs. 2nd resurvey) and the proportion of participants with prior chronic disease (22% vs. 33%), were also more prevalent at the second resurvey than at baseline.

4.8 Conclusions

The CKB is the largest ever blood-based prospective cohort study in China. The diverse study population, the prospective study design, the rich data on alcohol consumption as well as other major lifestyles and health-related indicators, the repeat measurements in resurveys among representative subsets, and the wide range of incident diseases identified through extensive electronic health record linkage illustrates CKB to be the best resource to date for reliable assessments of the relationships between alcohol consumption and health in Chinese adults. In particular, the representative resurvey subsets offer the opportunity to examine the temporal trends in drinking prevalence and patterns in Chinese adults over the last decade. More importantly, the extensive data collected in the CKB allows comprehensive adjustment for potential confounding factors, evaluation of reverse causation bias, and the estimation of “usual” alcohol intake for the prospective assessment of alcohol for disease risks. Finally, the availability of genetic data on the two important alcohol

metabolism genetic variants makes CKB a unique resource to explore the causal role of alcohol, as well as potential gene-alcohol interactions, in different cancers and liver diseases.

Table 4.1. Definitions of main alcohol drinking pattern variables

Drinking parameters	Description
Drinking status	
Abstainers*	Past 12 months: Never drank alcohol. In the past: Had not drunk at least weekly.
Ex-regular drinkers	Past 12 months: Never drank alcohol. In the past: Had drunk at least weekly.
Reduced-intake drinkers	Past 12 months: Had drunk alcohol but less than weekly. In the past: Had drunk at least weekly.
Occasional drinkers	Past 12 months: Had drunk alcohol but less than weekly. In the past: Had not drunk at least weekly.
Current regular drinkers	Past 12 months: Drank alcohol at least weekly (i.e., drank alcohol in most weeks). In the past: N/A.
Drinking patterns	
Drinking frequency	1-2 days/week; 3-5 days/week; daily or almost every day.
Mean consumption†	Calculated based on the beverage type and amount drunk (g of pure alcohol/session), and frequency of drinking (for total amount in a typical drinking week). Alcohol content by volume (v/v) of each beverage type are assumed as the following:[7] beer 4%, grape wine 12%, rice wine 15%, weak spirits 38% and strong spirits 53%.
Types of alcohol†	Strong spirit (≥40% alcohol) only; weak spirit (<40% alcohol) only; wine (rice wine & grape wine) only; beer only; mixed (more than one type, available in resurveys only).
Heavy episodic drinking (HED)†	Men: Consumption of >60 g of alcohol per session. Women: Consumption of >40 g of alcohol per session.
Problem drinking	Reporting one or more of the following in the past month: (i) ever drinking in the morning; (ii) being unable to work or do anything due to drinking; (iii) feeling depressed, irritated or losing control due to drinking; (iv) being unable to stop drinking; (v) having shakes when stopping drinking.
Flushing response	Experiencing hot flushes or dizziness soon after first mouthful or after drinking small amount of alcohol.
Drinking with/outside meals	Usually drinking with meals vs. usually drinking between or after meals/no regular patterns.

*Past-year abstainers

†Data available on a typical drinking day, on special occasions, and the last time the participants drank.

Table 4.2. Socio-demographic characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Overall			Men			Women		
Characteristics	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**
Number of participants	512891	19788	24996	210259	7770	9569	302632	12018	15427
Mean age, years	51.5	54.1	59.0	52.4	54.9	59.7	51.0	53.6	58.5
Birth cohorts, %									
<1940	11.7	12.5	9.7	13.8	15.1	11.6	10.3	10.8	8.6
1940-1949	21.3	22.8	23.0	22.4	23.6	24.2	20.6	22.3	22.2
1950-1959	31.6	32.2	33.8	30.9	30.2	32.9	32.2	33.5	34.4
1960-1969	29.9	28.5	29.3	27.9	27.0	27.5	31.3	29.5	30.5
1970s	5.4	4.0	4.2	4.9	4.0	3.9	5.7	4.0	4.3
Rural area, %	55.9	58.8	56.9	56.6	60.5	56.8	55.4	57.7	57.1
Highest education, %									
No formal education	18.6	18.6	20.2	8.9	8.5	9.2	25.3	25.0	27.1
Primary school	32.2	34.9	32.1	33.3	36.6	33.4	31.4	33.8	31.4
Middle/high school	43.4	40.1	41.9	49.9	46.0	49.2	38.8	36.2	37.4
≥Technical school/college	5.9	6.5	5.7	7.9	8.8	8.2	4.4	5.0	4.2
Household income (yuan/year), %									
<10,000	28.2	17.6	8.7	26.0	16.3	8.2	29.8	18.4	9.0
10,000-19,999	29.1	27.2	12.3	28.3	25.9	11.2	29.6	28.1	13.0
20,000-34,999	24.7	26.4	19.3	25.4	25.7	17.9	24.2	26.8	20.2
35,000+	18.0	28.8	59.7	20.2	32.1	62.7	16.5	26.7	57.8
Married, %	90.6	90.5	87.1	92.9	93.5	91.9	89.0	88.6	84.1

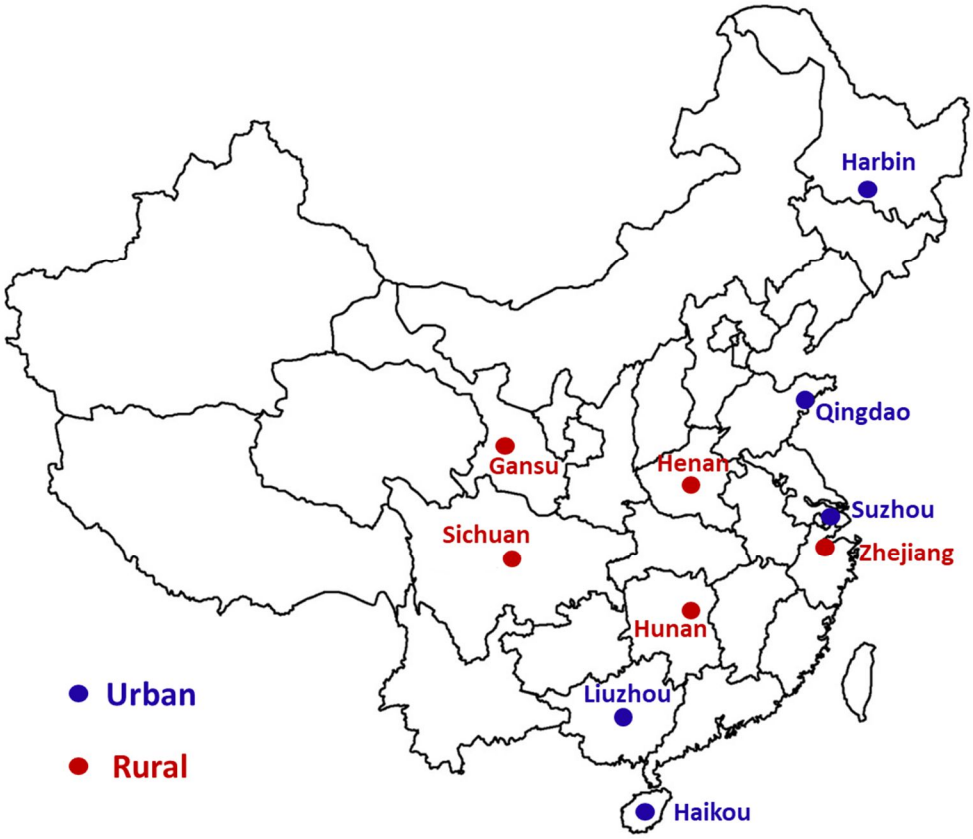
Characteristics are based on the characteristics of the participants collected at each of the baseline survey and the resurveys.

Table 4.3. Lifestyles and health-related characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Overall			Men			Women		
Characteristics	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**
Number of participants	512891	19788	24996	210259	7770	9569	302632	12018	15427
Lifestyle factors									
Regular smoking, %	26.4	24.0	20.5	61.1	57.6	51.0	2.4	2.3	1.6
Regular fruit intake, %	28.2	30.4	45.0	23.0	24.7	39.0	31.8	34.1	48.8
Physical activity, mean MET hours/day	21.1	20.0	19.4	22.0	21.1	21.1	20.4	19.3	18.4
Daily tea drinking, %	26.1	22.6	24.0	40.8	36.5	40.4	15.9	13.5	13.9
Physical measurements									
Mean SBP, mmHg	131.1	126.4	136.5	132.8	127.6	136.9	129.9	125.7	136.3
Mean DBP, mmHg	77.8	75.3	78.3	79.2	76.6	79.6	76.8	74.5	77.5
Mean heart rate, beats/minute	78.9	78.4	77.6	77.7	77.4	76.6	79.7	79.0	78.2
Mean BMI, kg/m^2	23.7	23.6	24.2	23.4	23.2	24.0	23.8	23.8	24.3
Mean WHR	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Mean standing height, cm	158.7	158.6	157.8	165.2	165.4	164.7	154.1	154.2	153.5
Self-reported wellbeing, health and medical history									
Satisfied with life*, %	68.5	70.3	81.2	69.7	72.6	82.4	67.7	68.8	80.5
Self-reported good health†, %	45.8	43.4	43.8	49.2	44.9	47.0	43.3	42.4	41.8
Prior chronic disease‡, %	22.3	23.0	33.1	22.6	23.7	31.7	22.1	22.5	33.9
Prior coronary heart disease, %	3.0	3.3	5.9	2.7	3.0	5.5	3.2	3.4	6.2
Prior stroke or TIA, %	1.7	2.2	3.4	2.3	2.9	4.3	1.3	1.6	2.9
Prior cancer, %	0.5	0.7	1.2	0.5	0.7	1.1	0.5	0.6	1.2
Prior cirrhosis or chronic hepatitis, %	1.2	1.2	1.3	1.7	1.6	1.6	0.8	1.0	1.1
Prior emphysema or bronchitis, %	2.6	2.4	4.4	3.1	3.0	4.9	2.2	2.1	4.1
Prior diabetes, %	3.2	4.5	7.4	2.9	4.2	6.6	3.3	4.7	7.9
Prior psychiatric disorder, %	0.4	0.3	0.5	0.3	0.2	0.2	0.4	0.3	0.7

MET, metabolic equivalent task; S/DBP, systolic/diastolic blood pressure; BMI, body mass index; WHR, waist-hip ratio; TIA, transient ischaemic attack.
Characteristics are based on the characteristics of the participants collected at each of the baseline survey and the resurveys.
*Reporting being satisfied or very satisfied with life.
†Reporting good or excellent self-rated health.
‡Diagnosed with one or more of: coronary heart disease, stroke or TIA, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Figure 4.1. Locations of the ten study sites of the China Kadoorie Biobank



Chapter 5. Prevalence, patterns and trends of alcohol drinking

5.1 Introduction

In China, the prevalence of alcohol drinking is lower than in many Western populations, particularly among women,[1] which may reflect differences in social, cultural, and also genetic factors (primarily ALDH2-deficiency common in East Asians).[7,23,205] Despite this, there have been dramatic increases in alcohol availability, production, and per-capita consumption in China over recent decades, probably driven mainly by rapid economic development and urbanisation.[7,206,207] Questions remain, however, about changes in patterns of alcohol drinking (e.g., drinking frequency, HED, beverage types) in adult Chinese populations, which may affect various alcohol-related conditions differently.

Most published studies on the prevalence of alcohol drinking in Chinese general populations tended to have small sample sizes, were conducted before 2010, or lacked detailed investigation of drinking patterns.[3-6,8,208-212] Moreover, heterogeneity in the geographical regions covered and definitions used (e.g., cut-off values for defining heavy drinking, HED) complicates comparison across previous studies. The CKB study previously reported the prevalence of alcohol drinking and extensively on the drinking patterns in 0.5 million participants across ten diverse areas based on the baseline survey in 2004-2008,[87] but was yet to report the changes in alcohol drinking prevalence and patterns in subsequent resurveys.

Previous longitudinal studies from Western populations have shown that alcohol drinking varies with age throughout the life-course.[213-215] Understanding and taking account of the within-person variation of alcohol consumption and age-related quitting will greatly improve the assessment of the relationships between alcohol consumption and risks of chronic diseases. Yet, there are no studies investigating changes in drinking behaviour at the individual level in China. Furthermore, as stopping drinking may reduce the risk of alcohol-related harm in the long-term,[216] understanding the motivations for alcohol cessation among ex-drinkers could help to inform the development of effective alcohol drinking interventions. However, evidence on the factors and reasons for stopping alcohol drinking in China is limited. Large-scale longitudinal surveys, such as the CKB cohort, are therefore needed to provide new evidence on the recent trends of alcohol consumption and drinking patterns, as well as factors associated with stopping drinking in China.

5.2 Aims and Objectives

Using data from the baseline survey in 2004-2008 and the two resurveys in 2008 and 2013-2014 of the CKB, this chapter aims to assess:

1) The baseline prevalence and patterns of alcohol drinking in the CKB population;
2) The temporal trends in the prevalence and patterns of alcohol drinking between the baseline survey in 2004-2008 and the second resurvey in 2013-2014;
3) The socio-demographic, health, and other factors associated with changes in drinking prevalence and patterns over this time period;

4) The extent of within-person variation in alcohol consumption level over the three surveys.

5.3 Methods

5.3.1 Classifications of alcohol consumption

Detailed questionnaire assessment and classifications of various alcohol consumption parameters in the CKB study have been described in Chapter 4. Given the substantial difference in the amount of alcohol consumption between men and women in the CKB, current regular drinkers were classified into four consumption categories in men (<140, 140-279, 280-420, 420+g/week) and three categories in women (<70, 70-139, 140+g/week) using different cut-off points.

For this chapter, all parameters of alcohol consumption listed in Chapter 4 were compared across baseline and resurveys at an overall level. Major parameters including drinking status, amount consumed, major drinking patterns (drinking frequency, HED [>60g/session in men, >40g/session in women], mealtime drinking habits, beverage type) and experience of problem drinking indicators were compared across surveys at both an overall level and at subgroup levels (more in Sections 5.3.2-5.3.3).

To describe changes in drinking status at the individual level between the baseline survey and the second resurvey (rationale in Section 5.3.3), six categories were defined: stable non-drinkers; starters; stable drinkers; stoppers; decreased-intake drinkers; and increased-intake drinkers (detailed definitions shown in Table 5.1). Among ex-regular and reduced-intake drinkers at the second resurvey, the reported

reasons for stopping or reducing drinking were re-categorised as followings given the low numbers of participants reporting certain reasons: existing physical illness; money; future health concerns ("future health concerns" and "doctor's advice" combined); and "other" reasons ("family against" and "other" combined).

5.3.2 Classifications of major correlates and subgroups

Detailed questionnaire assessment of socio-demographic characteristics, lifestyle risk factors, and health-related factors has been described in Chapter 4.

In this chapter, participants were classified into major socio-demographic subgroups according to ten-year birth cohorts (<1940, 1940-1949, 1950-1959, 1960-1969, 1970s), rural or urban areas, ten study areas, highest education level (no formal education, primary school, middle or high school, technical school/college or above), annual household income (<10,000, 10,000-19,999, 20,000-34,999, 35,000+ yuan/year), and marital status (married vs. not married). For analyses among current regular drinkers where sample sizes within subgroups were small, education (primary school or below vs. middle school or above) and income (<20,000 vs. 20,000 yuan/year) were collapsed into two levels.

In this chapter, smoking status was classified into current regular smoking versus other smoking categories (never, ex-regular, occasional). Lack of regular fresh fruit intake referred to those who reported consuming fresh fruit less than 4 days per week. Low physical activity level was defined as <17.8 MET hours per day for men and <12.6 MET hours per day for women.[195] Hypertension was either self-reported or screen-detected based on systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.[217]

To assess the presence of health-related risk factors in participants, a risk factor index was derived by summing the individual scores of these four major risk factors (1=yes, 0=no): current regular smoking, lack of regular fresh fruit intake, low physical activity, and hypertension. Self-reported health status was classified into good (good or excellent) and poor (fair or poor). Prior chronic disease was defined by the self-report of one or more of previously diagnosed major chronic diseases including: diabetes, coronary heart disease, stroke or transient ischaemic attack, cancer, tuberculosis, emphysema or bronchitis, cirrhosis or chronic hepatitis, peptic ulcer, gallstone or gallbladder disease, kidney disease, and rheumatoid arthritis.

5.3.3 Statistical analyses

Given the substantial difference in the prevalence of alcohol drinking, all analyses were conducted separately in men and women.

The prevalence, patterns and temporal trends in alcohol drinking were assessed using cross-sectional data collected at baseline (n=512,891), the first resurvey (n=19,788) and the second resurvey (n=24,996). The crude prevalence of alcohol drinking and mean consumption were calculated at each survey. The temporal trend analyses focused mainly on the changes between the baseline survey and the second resurvey. This is because the first resurvey might be too close to the baseline survey (mean 3 years [SD 0.7] apart from baseline) and might reflect random fluctuation rather than actual behavioural changes, whereas the second resurvey (mean 8 years [SD 0.8] after baseline; 5 years [SD 0.4] after first resurvey) provides a more reasonable time gap for investigating changes in drinking prevalence and patterns at the population level and also at the individual level. For a quality check of the self-reported alcohol intake data,

associations of blood pressure with alcohol drinking categories were assessed using linear regression adjusted for age, study area, education, income, smoking category, physical activity, and month of recruitment. A trend test was performed among current regular drinkers by assessing the effect of an increase in 40g/day of alcohol intake on blood pressure.

Among subgroups defined by socio-demographic factors, major lifestyle and health-related factors, and the risk factor index, the prevalence of alcohol drinking was directly standardised to the age (3 groups) and study area structure (10 groups) of the study population. Similar standardisation approach was also applied to drinking patterns in current regular drinkers. The same analyses were also conducted among subgroups defined by alcohol consumption level (for selected baseline characteristics and drinking characteristics) and major drinking patterns (for drinking characteristics) to compare the characteristics across different types of drinkers. The associations between drinking categories and baseline characteristics were assessed as described in Chapter 4. Due to the small numbers of female current regular drinkers ($n_{baseline}$=6248, $n_{resurvey1}$=226 and $n_{resurvey2}$=292), the main analyses of drinking patterns by subgroups were conducted in male current regular drinkers only ($n_{baseline}$=69,904, $n_{resurvey1}$=2320, and $n_{resurvey2}$=2732), and further analyses among women are presented in Appendix E.

Longitudinal analyses of changes in drinking status were conducted among men who attended both the baseline survey and the second resurvey (n=9569), with analyses among women presented in Appendix E (n=15,427). A similar standardisation approach was applied as above to obtain the prevalence of each status change category standardised to the age and study area structure of the longitudinal subset.

The statistical associations between factors and change in drinking status were tested using logistic regression among baseline non-drinkers and multinomial logistic regression among baseline drinkers. Among men who were current regular drinkers at both baseline and the second resurvey, a dependent sample t-test was used to test for the statistical significance of change in alcohol consumption at the individual level over time. The reasons for stopping regular drinking were assessed among previous regular drinkers (i.e., ex-regular and reduced-intake drinkers combined) in the second resurvey (n=1166). Crude percentages of each of the reasons reported were calculated overall, and by socio-demographic characteristics and health-related factors.

Further temporal trend analyses were performed by using age-at-survey groups instead of birth cohorts to explore any age effects, and by removing hypertension, which may be caused by high alcohol consumption,[24] from the composition of the risk factor index. Further analyses were also done by using baseline health-related characteristics in the individual-level analyses, in order to explore whether the change in drinking status over time was influenced by baseline health or change in health over the study period.

The degree of within-person variation of alcohol consumption over the study period was measured by the regression dilution approach using baseline measure of alcohol consumption and repeat measures at resurveys.[184] Among the subset of participants who were involved in the baseline survey as well as the two resurveys, participants were divided into baseline-defined groups according to their baseline alcohol consumption, separately by men and women. Assuming abstainers and ex-regular drinkers (i.e., past-year non-drinkers) had an alcohol intake level at 0g/week, and

occasional and reduced-intake drinkers (i.e., past-year occasional drinkers) had an alcohol intake level at 5g/week at the time of the survey, the mean consumption levels of the baseline-defined groups were calculated at each survey respectively. The "usual" alcohol intake was calculated as the mean of the repeat alcohol measures of the first and second resurveys for individuals in each of the baseline-defined categories.

The regression dilution ratio (RDR) is the ratio of the steepness of the uncorrected association to that of the real association. The RDR was estimated using the assumption-free, non-parametric MacMahon-Peto method by the ratio of the range (i.e., difference in the mean alcohol intake of the top vs. bottom baseline-defined groups) of the "usual" alcohol intake to the range of baseline alcohol intake.[218] It was compared with the RDRs calculated using parametric methods, including the self-correlation method which assumes constant variance and estimates the RDR by the correlation coefficient between baseline and repeat measurements,[184] and the Rosner's regression method which estimates the RDR by the slope of the regression line between baseline and repeat measurements.[219]

Data from the CKB Data Release 10 was used for the analyses presented in this chapter.

5.4 Results

5.4.1 Baseline prevalence and patterns of alcohol consumption

Among 512,891 participants at baseline, 20% of men were classified as abstainers compared with 64% of women (Table 5.2), with a further 9% of men and 1% of women

being previous regular drinkers (ex-regular and reduced-intake drinkers combined). 33% of men but only 2% of women reported drinking alcohol at least weekly (i.e., current regular drinkers) in the past year, whereas a third of men and women drank occasionally.

Among male current regular drinkers, the mean alcohol intake was 286g in a typical drinking week, 50g on the last drinking day, and 147g on special occasions (Table 5.3). Overall, about two-thirds (62%) of male current regular drinkers drank alcohol daily or almost daily and four-fifths (84%) engaged in HED on special occasions, with 37% doing so on a typical drinking day and 30% on the last drinking day. Of male current regular drinkers, 24% reported at least one indicator of problem drinking. Compared with males, female current regular drinkers had lower mean consumption (116g weekly, 23g on last drinking day, 55g on special occasions) and were less likely to report daily drinking (45%), HED (57% on special occasions), or problems related to their drinking (10%).

In both sexes, strong spirits were the most common beverage type consumed across the three drinking scenarios, followed by weak spirits and beer. Only ~1% of men drank grape wine compared with ~10% of women. Most current regular drinkers usually drank alcohol with meals (~86% in both men and women) and about 20% (18% of men and 24% of women) reported experiencing the flushing response after drinking a small amount of alcohol. On average, male current regular drinkers started regular drinking about 10 years younger than their female counterparts (29 vs. 38 years).

5.4.2 Baseline drinking characteristics by consumption level and drinking patterns

Among men, the drinking profiles of current regular drinkers differed across consumption levels. Among male current regular drinkers at baseline, the proportions of daily drinking, HED, and spirits drinking across all drinking scenarios were progressively higher among heavier drinkers (Table 5.4). While the mealtime drinking habits were broadly similar across drinkers with various consumption levels, heavier drinkers were less likely to report having the flushing response (9% vs. 27%, 420+g/week vs. <140g/week) and started drinking at younger age than the lightest drinkers (26 vs. 31 years).

Male daily drinkers were more likely to report HED than those drinking less frequently, and vice versa (Tables 5.5-5.6). Furthermore, men who drank daily or engaged in HED had a lower prevalence of the flushing response than those who did not. Men who usually drank alcohol without meals tended to have a slightly higher prevalence of HED on a typical drinking day and the last drinking day, but not on special occasions, compared with men usually drinking with meals (Table 5.7).

Among men, the prevalence of daily drinking and of HED was highest among strong spirits drinkers compared with other beverage types (Tables 5.8). Men who drank rice wine on a typical drinking day had the second highest prevalence of daily drinking, but together with grape wine drinkers had the lowest prevalence of HED. Among men who reported drinking one beverage type only, spirits-only drinkers (particularly strong spirits) had the highest mean alcohol consumption compared with other beverage type drinkers in all three drinking scenarios (Table 5.9). However, when mixed-type drinkers (i.e., those who reported drinking more than one beverage type) were included,

mixed-type drinkers had around two-fold higher mean consumption than any other single-type drinkers. The reported beverage types and amount consumed on the last drinking day were significantly correlated with those on a typical drinking day (Table 5.10). The amount consumed on the last drinking day and in a typical drinking week was positively associated with higher blood pressure at all surveys (Tables 5.11-5.12). For consistency of methodology (where reporting ≥ one beverage type on a typical drinking day was not allowed at baseline and the first resurvey), data on the last drinking day was used in the main temporal trend analyses presented later in this chapter.

Among female current regular drinkers, though somewhat less extreme, the profiles of drinking behaviours by consumption level and drinking patterns were generally similar to those observed among male drinkers. (Tables E1-E5).

5.4.3 Trends in alcohol consumption across surveys

Among men, the prevalence of current regular drinking was slightly lower at the two resurveys than at baseline (33% vs. 30% vs. 29%, baseline vs. first resurvey vs. second resurvey), while the prevalence of occasional drinking was consistent between baseline and the first resurvey but was lower at the second resurvey (38% vs. 39% vs. 26%) (Table 5.2). Similar differences were also evident in women for occasional drinking (34% vs. 30% vs. 15%).

Among male current regular drinkers, however, the prevalence of daily drinking increased across the three surveys (62% vs. 65% vs. 71%) (Table 5.3). The mean consumption and prevalence of HED were relatively consistent between baseline and

the first resurvey, and were lower at the second resurvey for drinking on special occasions (baseline vs. second resurvey: 147 vs. 116g/occasion; 84% vs. 73%) but higher for the last drinking day (50 vs. 56g/session; 30% vs. 35%). Further individual-level analyses among men who drank regularly at both baseline and the second resurvey showed that the mean consumption on the last drinking day increased by 3.7g/session between these time points (p=0.004) (Table 5.13).

While strong spirits remained the most common beverage type consumed across all three surveys, the proportion of men consuming multiple beverage types on the last drinking day was higher at the second resurvey (8% vs. 16%, baseline vs. second resurvey) (Table 5.3). Mealtime drinking habits and the proportions of drinkers reporting at least one problem drinking indicator were broadly consistent across the three surveys.

Among female current regular drinkers, higher prevalence of daily drinkers (45% vs. 63%, baseline vs. second resurvey) and mixed-type drinkers (3% vs. 9%) was also observed at the second resurvey, but with no obvious increase in the mean consumption or HED prevalence. Similar temporal trends were evident in the longitudinal subset of participants who were involved in all of the three surveys (Tables E6-7).

5.4.4 Patterns and trends of alcohol consumption by population subgroups

5.4.4.1 Birth cohort

Among men, the patterns and temporal trends of alcohol drinking differed by birth cohort (Figure 5.1). At baseline, the prevalence of current regular drinking was highest

in middle-aged men born in the 1950s and 1960s (~37%), and was lowest in the oldest men born before 1940 (24%) and the youngest men born in the 1970s (27%) (Figure 5.1A, Table 5.14). Between baseline and the second resurvey, the prevalence of current regular drinking decreased in most birth cohorts, except for the youngest cohort born in the 1970s who had a slightly higher prevalence of current regular drinking at the second resurvey (27% vs. 32%), which may be due to the effects of age (Figure 5.2A). Among male current regular drinkers at baseline and the second resurvey, drinking frequency was higher among older birth cohorts (Figure 5.1B), but the mean alcohol consumption and the prevalence of HED on the last drinking day were higher among younger birth cohorts and increased over time in these groups (58g/session vs. 77g/session and 41% vs. 47% respectively in men born in the 1970s) (Figure 5.1C-D). Further analyses among the subset of men who drank regularly at both baseline and the second resurvey confirmed these results, with the mean consumption increasing significantly by 18.2g/session (p=0.026) in those born in the 1970s but changing little in those born before 1960 (Table 5.13). Similarly, the prevalence of HED on special occasions was also higher among younger cohorts, among whom the decline in HED prevalence at the second resurvey was less pronounced than among older cohorts (93% vs. 89% in men born in the 1970s; 66% vs. 46% in men born before 1940) (Table 5.15). Younger generations also had a higher tendency to drink beer or multiple beverage types than older drinkers, with a notable rise in the prevalence of mixed-beverage drinkers between baseline and the second resurvey (10% vs. 25% in those born in the 1970s) (Figure 5.3).

5.4.4.2 Study area

At baseline, the prevalence of current regular drinking was generally higher in urban than in rural areas (38% vs. 29%), with substantial variation across the ten study areas (from 8% in Gansu to 51% in Sichuan) (Figure 5.4). Among male current regular drinkers, there were also large variations in the mean consumption on the last drinking day (from 42g/session in Liuzhou and Zhejiang to 62g/session in Gansu) and the prevalence of daily drinking (from 27% in Gansu to 78% in Sichuan and Zhejiang) and HED on the last drinking day (from 22% in Liuzhou to 63% in Sichuan), but no major differences were observed when compared across overall rural and urban level (rural vs. urban: 49g/session vs. 51g/session; 64% vs. 60%, daily drinking; 29% vs. 31%, HED) (Tables 5.14-5.16). Nevertheless, for drinking in a typical week, the mean weekly consumption and the prevalence of HED were higher in rural than in urban areas (Table 5.17). At baseline, there was a higher proportion of male current regular drinkers reporting at least one problem drinking indicator in rural than in urban areas (34% vs. 14%) (Table 5.15). Alcohol was predominantly consumed with meals across most study areas, except for Gansu where ~80% of male drinkers usually drank outside meals (Table 5.16). Beverage types also varied greatly across the ten study areas, with spirits drinking being more prevalent in rural than in urban areas (Figure 5.5).

Between baseline and the second resurvey, there was an increase in the mean consumption of alcohol on the last drinking day among urban male drinkers, with an increase of 5.6g/session among the subset who were current regular drinkers at both time points (p=0.007) (Tables 5.13-5.14). The directions of temporal trends of drinking patterns were consistent between rural and urban areas, except for the proportion of

men reporting problem drinking indicators which increased in urban areas and particularly in younger urban drinkers, but generally declined in rural areas (Table 5.15, Table 5.18).

5.4.4.3 Socio-economic status

At baseline, the proportion of daily drinkers and those reporting problem drinking indicators appeared to be higher in men with lower education and lower household income (Table 5.15), who also had higher weekly alcohol consumption (Table 5.17). However, over time, a significant increase in the mean consumption on the last drinking day was observed among those with higher household income but not in those with lower income (Tables 5.13-5.14).

5.4.4.4 Lifestyle and health factors

There were strong correlations of the prevalence and certain patterns of alcohol consumption (amount, daily drinking, HED) with regular smoking, low fresh fruit intake, and high blood pressure (Tables 5.19-5.21). Furthermore, having multiple major health-related risk factors (i.e., regular smoking, low fresh fruit intake, hypertension, low physical activity) was correlated with alcohol drinking, with current regular drinking prevalence, drinking frequency, mean consumption, and HED prevalence all increasing with the number of risk factors in men at both surveys (Figure 5.6). When hypertension was removed from the risk factor index, as it may be caused by high alcohol consumption, the correlations persisted between unhealthy lifestyles and alcohol drinking (Figure E1).

At baseline, ex-regular drinkers, reduced-intake drinkers, and abstainers were more likely to report poor health and prior chronic disease than occasional and current regular drinkers (Table 5.19), while the mean consumption and drinking patterns (drinking frequency, HED, mealtime drinking habits) did not differ substantially by these health-related factors (Tables 5.20-5.21). Over time, individual-level analysis showed significant increases in the mean consumption on the last drinking day in those who reported good health or were without prior chronic disease at the time of the second resurvey (Table 5.13).

Among women where the prevalence of current regular drinking was consistently low across population subgroups over time, the proportions of abstainers and ex-regular drinkers were higher among older cohorts (Table E8). The prevalence of occasional drinking was higher among younger cohorts, urban residents, and higher socio-economic groups, and decreased consistently at the second resurvey across subgroups.

5.4.5 Factors associated with reducing drinking

Among 9569 men who attended both the baseline survey and the second resurvey, 55% (stable, decreased-intake, and increased-intake drinkers combined) of them continually drank at both time points while 18% were stable non-drinkers (Table 5.22). Between baseline and the second resurvey, 23% stopped drinking and 4% started drinking. Men who were older, lived in rural areas, or had poor self-reported health status at the second resurvey were more likely to remain as non-drinkers or to have stopped drinking since baseline. Men with lower household income were also more likely to remain as non-drinkers, while those with diagnosed chronic disease by the

time of the second resurvey were more likely to have stopped drinking over time. Furthermore, men with multiple risk factors were more likely to remain as stable drinkers over time. The results were consistent though less apparent when analyses used baseline rather than second resurvey characteristics (Table E9), suggesting that changes in health status (e.g., self-reported health, prior chronic disease) between baseline and the second resurvey were correlated with stopping drinking. Among women who were involved in both surveys, those who were older or had lower socio-economic status were more likely to remain non-drinking over time, with no obvious differences seen across health-related factors (Table E10).

Among the 1166 ex-regular or reduced-intake drinkers at the second resurvey, over half of them (52%) reported existing physical illness as their main reason for stopping regular drinking, and this proportion was higher among men and those who were older, had lower socio-economic status, had poor self-reported health, or had prior chronic disease (Table 5.23). Other reported reasons for stopping drinking were money (24%), future health concerns (6%), and "other" reasons not related to financial or health concerns (19%). In men, money was the second most reported reason for stopping regular drinking. In women, "other" was the second most cited reason overall, and was the most cited reason among urban participants and those with higher socio-economic status (Table 5.24).

5.4.6 Regression dilution

A gradual regression to the mean over time was observed for alcohol consumption in the subset of participants involved in all three CKB surveys (Table 5.25). Among men, the weekly consumption level ranged from 78g/week in those drinking <140g/week to

686g/week in those drinking 420+g/week at baseline. At the first resurvey, there was a sharp convergence (mean consumption for baseline-defined drinker groups of <140g/week vs. 420+g/week: 96g/week vs. 441g/week), followed by a relatively more modest further convergence at the second resurvey (119g/week vs. 436g/week). Consequently, the RDRs became progressively more extreme over time (0.57 vs. 0.52, first resurvey vs. second resurvey, men). With respect to baseline and "usual" alcohol consumption (i.e., average of the first and second resurveys), the RDR calculated from the MacMahon-Peto method was 0.54, broadly similar to the estimates obtained from self-correlation (0.52-0.55) and the Rosner's regression method (0.55). In women, the RDR based on the MacMahon-Peto method (0.55) was similar to that in men, with slightly greater variation from the RDR calculated from the Rosner's regression method (0.69). Among men, the estimated RDRs ranged between 0.4 and 0.6 across subgroups defined by age, study area, income, smoking, fresh fruit intake, physical activity, and BMI, based on small numbers of participants (Table E11).

5.5 Discussion

5.5.1 Summary of findings

This chapter examined the recent patterns and trends of alcohol drinking and factors associated with stopping drinking in ten study areas across China. Overall, one-third of men but only 2% of women were current regular drinkers at baseline. There were huge variations in the prevalence and patterns of alcohol drinking across study areas, and to a lesser extent, birth cohorts. Among current regular drinkers, alcohol was consumed more often and in higher quantities in men than in women, predominantly in the form of spirits and was usually consumed with meals. Among men, heavy total alcohol

consumption was correlated with daily drinking and HED, and was higher among spirits-only and multiple beverage type drinkers. There was a modest decline in past-year regular drinking prevalence between 2004 and 2014 as the study population aged, but modest increases in the mean consumption level, drinking frequency, and HED prevalence among men who drank alcohol regularly. Younger age and having multiple health-related risk factors were important correlates of heavy drinking patterns in male drinkers. In particular, the mean consumption level and the prevalence of HED, and of drinking multiple beverage types, increased over time in the youngest male birth cohort. Furthermore, an increase in the prevalence of reporting problem drinking indicators was observed among male urban younger drinkers. On the other hand, older and less healthy men were more likely to stop drinking, suggesting that illness was a major reason for stopping drinking in this Chinese population.

5.5.2 Comparison with previous studies in China and elsewhere

The findings on drinking prevalence in the CKB are broadly consistent with previous nationwide cross-sectional surveys at particular time points in China during 2002-2011.[3,4,209] A study involving 160,000 participants aged 15+years from the China National Nutrition and Health Survey found a similar weekly drinking prevalence of 39.6% in men and 4.5% in women in 2002.[3] The baseline past-year drinking prevalence in the CKB (76% men, 36% women), particularly among women, is lower than that in Western populations in a similar period (e.g., United Kingdom in 2000: 91% men, 86% women),[220] probably mainly reflecting differences in cultural and genetic factors (e.g., ALDH2-deficiency).[7,23,24]

Several studies have previously reported on the temporal trends of alcohol consumption in the general population, mainly based on the small China Health and Nutrition Survey (CHNS; ~10,000 participants).[8,212] According to the CHNS, during 1997 and 2000, the level of alcohol intake and the prevalence of daily drinking in men increased but then remained steady until 2006.[8] The latest CHNS in 2011 reported a prevalence of past-year ever drinking of 59% in men, which is comparable to that in the CKB second resurvey in 2013-2014.[209] More recently, a study based on the CHNS data showed a rise in beer and wine drinking among male drinkers between 2004 and 2011, but did not report on changes in drinking frequency or other drinking patterns.[212] Since 2011, there have been no reported nationwide studies in the general population in China, except for a recent study focusing on elderly population aged 60+ years which reported increasing trends of alcohol use from 2000 to 2014 using data from the Chinese Longitudinal Healthy Longevity Survey.[221] With detailed information on drinking patterns approximately 8 years apart between baseline and the second resurvey, the CKB study shows a modest decrease in current regular drinking prevalence over time since 2004, similar to findings observed in a previous study of US men and women aged 45-64 years, sampled 6 years apart.[213] The modest decrease in alcohol drinking prevalence may be due to ageing of the study population and the "sick-quitter" effect,[182] as suggested by the associations of older age and poor health with stopping drinking in the CKB. The findings that men with poorer baseline health and lower income were more likely to remain non-drinking over time may also indicate the "sick non-starter" effect, whereby non-drinkers might have abstained from initiating drinking due to pre-existing poor health or social disadvantages.[183] Both of

these effects have implications for the assessment of the associations between alcohol drinking patterns and health (see Section 5.5.4).

Despite the decreased drinking prevalence over time, there were modest increases in the mean consumption and the prevalence of daily drinking and HED among male current regular drinkers in the CKB, which are consistent with the increasing per-capita alcohol consumption in China shown in the WHO report.[1] This is in contrast to patterns observed in many Western populations, for example, the decreasing trends in alcohol consumption levels during the 1990s-2010s among adults aged 18-85 years in Switzerland[222] and in other southern, central-western, and western European countries,[223] and a reduction in frequent drinking (i.e., 5+ days in the previous week) among adults aged 16+ years during 2005-2017 in the UK.[30]

In the CKB, heavier drinkers were more likely than lighter drinkers to exhibit certain drinking patterns, such as drinking daily, HED, and drinking spirits. All these drinking patterns were associated with a lower prevalence of the alcohol flushing response, reflecting the influence of alcohol tolerance in drinking behaviours in individuals. The highest mean consumption observed among those drinking multiple beverage types compared with all other single-beverage type drinkers might reflect the actual heavy consumption in these drinkers, or could also be due to reporting bias, e.g., over-reporting when participants reported their consumption of multiple beverage types.

Previous studies in China conducted in the 2000s reported that harmful drinking patterns peaked between the ages of 30-60 years in men.[4,6] These studies, however, used different and somewhat low thresholds to define harmful drinking behaviours (e.g., >50g/day for binge drinking or >25g/day for excessive drinking in men). Based on

the WHO recommended threshold for high-risk drinking episodes (>60g/session in men),[28] the present study shows that younger men are more likely to report HED, and among them an increase in the prevalence of HED during the study period has been observed. While the Chinese custom of spirits drinking and drinking with meals remained relatively steady throughout the study period, the present study reveals a rise in drinking mixed beverage types, particularly in younger men. This shift is likely the result of the exposure to a wider availability of alcoholic beverages and the influence of Western drinking cultures brought by the rapid economic development and westernisation in modern China.[7,206] Importantly, a rise in drinking multiple beverage types among young Chinese men is of public health concern, since these drinkers seem to drink more in each session when they consume multiple beverage types.

The huge variations of drinking prevalence and patterns across the ten study areas in the CKB reflect the unique local characteristics (e.g., determinants of drinking, drinking culture, locally produced beverage types) across the diverse geographical regions.[224] The significant increase in the mean consumption among men who lived in urban areas or had higher household income in the CKB, together with the increasing reports of problem drinking indicators among urban young drinkers despite a general decline in rural areas, might reflect the social and economic changes happening particularly in urban China. Apart from the expected wider availability of alcohol and more Westernised lifestyles in urban than in rural areas, the increasing use of alcohol in business activities and work-related stress may also potentially contribute to increased

alcohol-related problems among urban working men in China. Further investigations on the associations of problem drinking with mental health are described in Chapter 6.

As in the present study, previous studies in England and Hong Kong have also reported the clustering of heavy drinking with smoking, low fruit and vegetables intake, and lack of exercise, in settings where the lifestyle and behavioural patterns differ from those in mainland China.[225,226] Such clustering of risk factors requires public health and clinical attention as previous studies have shown that people with multiple risk factors, combined with heavy drinking, have higher risks for adverse health outcomes.[227-229] Though the prevalence of smoking may have slightly decreased in China in the last decade, overall cigarette consumption has increased over time,[230,231] as has tobacco-attributed mortality among men.[232] Given the growing tobacco-attributed burden and alcohol epidemic, particularly among men, and the shift to sedentary lifestyles in China which is accelerated by urbanisation, the consequences of these rapid lifestyle transitions may emerge in an increased chronic disease burden.[233]

Finally, findings in the present study that existing illness was the most reported reason for stopping regular drinking are generally consistent with a study of 14,000 participants in China in the 1990s.[210] However, concerns about future health were not a common reason to stop drinking in the CKB, which may indicate a lack of health knowledge about alcohol drinking in China as suggested in a previous study.[234]

5.5.3 Strengths and limitations

Although not designed to be nationally representative, the diverse geographical areas, the large sample size, the repeated detailed assessments of alcohol drinking patterns,

and the extensive data collection of other lifestyle risk factors in the CKB present a good source of data to assess recent alcohol consumption trends among Chinese adults born in the 1920s-1970s. Furthermore, to our best knowledge, it is the first study to explore longitudinal changes in alcohol drinking among Chinese adults. Also, the response rates during the resurveys were very high (~80%), which should help minimise systematic bias. However, the study has limitations. First, although the expected associations between alcohol intake and blood pressure observed in this study have provided support for the data quality, potential reporting bias of the self-reported alcohol intake data may still exist. The design of the CKB baseline questionnaire with only one beverage type allowed to be reported for "a typical drinking day" might lead to the under-reporting of alcohol consumption level, particularly for drinkers who consumed multiple beverage types, and underestimation of HED prevalence in a typical drinking week at baseline. Nevertheless, this should not affect the findings on temporal trends, which were based on consumption on "the last drinking day" assessed with consistent methodology across surveys. Second, although the resurvey response rates were high and highly consistent across baseline alcohol drinking groups, the results may still be partially influenced by the "sick-quitter" effect, with disproportional effects at different age groups and across different drinking categories. Thirdly, the measure of alcohol use based on "the last drinking day" may be subject to time variation and may not always represent typical drinking patterns.[235-237] Nevertheless, the use of "the last drinking day" as a measure of alcohol intake has been supported by findings from the data quality analyses in this chapter as well as previous studies.[236,238-240] Finally, the CKB was designed to investigate the causes of chronic diseases and did not include younger participants below the age of 30 years at

baseline, who may have very different drinking prevalence and patterns than the CKB study population as suggested by the variations observed for different birth cohorts in the present study.

5.5.4 Research implications

The findings in this chapter have important implications for the subsequent analyses in this thesis. Given the large differences between men and women in alcohol drinking in the CKB, subsequent analyses in this thesis are conducted separately by sex, focusing mainly on men among whom drinking is a more noticeable problem as analyses among women are likely to be underpowered.

The “sick-quitter” and “sick non-starter” effects among non-drinkers shown in this chapter could lead to reverse causation and residual confounding, as increased disease risks observed among them may be due to their existing ill health, social disadvantages, or other unknown or unmeasured factors rather than the absence of alcohol intake. Hence, the disease risks in non-drinkers may be overestimated and the disease risks in drinkers may be underestimated, as a result of factors other than alcohol consumption. Also, detailed information on the amount of alcohol consumed and drinking patterns were recorded among current regular drinkers only. Therefore, the main analyses relating to consumption levels and drinking patterns in this thesis are conducted among current regular drinkers only, with non-drinkers included in sensitivity analyses as appropriate.

Although data on consumption on the last drinking day was used in this chapter for temporal trend analyses for reasons of methodological consistency, total alcohol

consumption per week remains a more comprehensive and composite measure in relation to the development of chronic diseases and are used as the main alcohol exposure measure in subsequent chapters. Furthermore, analyses on the effects of drinking patterns and the flushing response on disease risks should take account of the total alcohol consumption level, given the strong correlations between these drinking parameters. Moreover, the correlates of alcohol consumption identified in this chapter, complemented by the established relationships of these correlates with alcohol consumption and disease risks in existing literature, inform the covariates selection in analytical models in subsequent chapters.

Finally, the range of mean alcohol consumption levels across baseline-defined categories attenuated progressively from baseline to the second resurvey in the CKB. This evidence indicates the need to estimate the "usual" alcohol intake using data from all three surveys in order to take account of the within-person variation throughout the long follow-up period. Although the estimated RDRs appeared to vary somewhat slightly across certain population subgroups in men, these subgroup-specific RDR estimates are based on small numbers of participants and may be affected by the specific categorisation of baseline-defined groups,[241] and thus may not be reliable. Therefore, the sex-specific RDRs estimated by the MacMahon-Peto method (0.54 for men, 0.55 for women), which are based on larger numbers of participants and are consistent across different estimation methods, are applied in the prospective analyses analysing alcohol consumption as a continuous trait at both overall level and across subgroups throughout this thesis. Nevertheless, for prospective analyses involving alcohol consumption level as a categorical exposure, the subgroup-specific "usual"

means are used in figure plotting where appropriate. Further details of the application of “usual” alcohol intake and RDRs in the prospective analyses are described in Chapters 7-8.

5.5.5 Conclusions

In summary, alcohol consumption remains predominantly a male phenomenon in China. Among men who drank regularly, the proportion engaging in harmful drinking behaviours has increased in China over the past decade, particularly among younger men, and heavy intake was associated with having other unhealthy lifestyles and health-related risk factors. The exploratory findings on the correlates (e.g., socio-demographic characteristics, lifestyles, health-related factors) and within-person variation of alcohol consumption, as well as reasons for stopping drinking, provide insights into the study design and the analytic methods used in the subsequent chapters of this thesis.

Table 5.1. Definitions of changes in drinking status between baseline and the second resurvey

Categories	Description
Stable non-drinkers	Past-year non-drinkers at both surveys
Starters	Past year non-drinkers at baseline who became past-year drinkers at the second resurvey
Stable drinkers	Past-year drinkers with the same drinking frequency at both surveys (e.g., all-time occasional or all-time current regular drinkers)
Stoppers	Past-year drinkers at baseline who became past-year non-drinkers at the second resurvey
Decreased-intake drinkers	Past-year drinkers at both surveys, but with decreased drinking frequency at the second resurvey (e.g., changed from current regular drinkers at baseline to occasional drinkers at the second resurvey)
Increased-intake drinkers	Past-year drinkers at both surveys, but with increased drinking frequency at the second resurvey (e.g., changed from occasional drinkers at baseline to current regular drinkers at the second resurvey)

Past year non-drinkers included abstainers and ex-regular drinkers; past-year drinkers included reduced-intake drinkers, occasional drinkers, and current regular drinkers.

Table 5.2. Prevalence of alcohol consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014), by sex

	Men			Women		
	Baseline	1st Resurvey	2nd Resurvey	Baseline	1st Resurvey	2nd Resurvey
Number of participants	210259	7770	9569	302632	12018	15427
Drinking categories, %						
Abstainer	20.4	22.9	34.9	63.6	66.9	82.0
Ex-regular drinkers	3.8	4.2	6.3	0.4	0.4	0.7
Reduced-intake drinkers	4.9	4.1	3.8	0.4	0.4	0.5
Occasional drinkers	37.7	38.9	26.4	33.5	30.5	14.9
Current regular drinkers	33.2	29.9	28.6	2.1	1.9	1.9

Table 5.3. Patterns of alcohol consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014) among current regular drinkers, by sex

	Men			Women		
	Baseline	1st Resurvey	2nd Resurvey	Baseline	1st Resurvey	2nd Resurvey
Number of participants	69904	2320	2732	6248	226	292
Number of drinking days per week, %						
1-2	19.9	18.3	14.9	33.1	29.2	21.9
3-5	18.0	16.7	14.0	21.6	13.7	15.4
6-7	62.1	65.0	71.1	45.2	57.1	62.7
Types consumed on typical day, %						
Strong spirits only	46.8	48.1	37.3	49.1	57.1	36.0
Weak spirits only	22.8	16.7	15.6	12.7	6.2	10.6
Beer only	18.2	22.2	8.2	22.2	23.0	10.6
Rice wine only	11.3	12.0	9.3	6.2	4.0	10.6
Grape wine only	0.9	1.0	1.7	9.8	9.7	15.8
Mixed	--	--	28.0	--	--	16.4
Mean intake, g/typical week	285.7	278.8	352.2	115.6	139.5	130.2
Consumption level in g/week, %						
<140	35.9	37.5	26.8	77.0	72.1	72.3
140-279	27.1	26.6	27.4	15.9	19.9	17.8
280-419	18.4	17.5	19.7	4.7	3.5	5.5
420+	18.7	18.4	26.1	2.4	4.4	4.5
Types consumed on last drinking day, %						
Strong spirits only	41.5	38.3	41.8	47.6	55.8	39.4
Weak spirits only	19.8	12.4	16.0	11.4	5.8	12.0
Beer only	20.1	31.5	13.5	22.6	26.1	12.3
Rice wine only	9.8	8.5	2.5	5.9	3.5	16.1
Grape wine only	1.2	1.5	9.8	9.8	8.4	11.0
Mixed	7.7	7.8	16.3	2.7	0.4	9.2
Mean intake, g/last drinking day	49.9	47.9	55.6	22.7	22.4	24.1
Types consumed on special occasions, %						
Strong spirits only	35.7	36.3	35.8	41.4	48.2	33.9
Weak spirits only	16.3	12.1	14.7	9.9	5.8	10.6
Beer only	10.9	15.6	8.4	16.7	20.8	11.0
Rice wine only	6.1	7.5	7.7	5.2	4.0	8.9
Grape wine only	0.5	0.8	1.6	7.1	7.1	16.8
Mixed	30.5	27.8	31.8	19.6	14.2	18.8
Mean intake, g/special occasion	147.4	141.4	116.3	55.1	49.6	41.3
Drinking patterns, %						
HED on a typical drinking day*	37.2	36.1	45.5	26.5	31.0	24.7
HED on the last drinking day*	29.8	28.6	34.7	18.2	16.8	17.8
HED on special occasions*	83.6	82.3	72.9	57.1	56.2	43.8
Problem drinking†	23.9	18.8	23.8	9.8	8.8	9.2
Drinking outside meals	14.1	11.9	17.6	13.8	5.8	20.9
Flushing response after drinking, %	17.9	14.1	15.5	23.6	23.5	13.7
Mean duration of drinking, years	22.5	24.7	28.7	14.9	17.1	19.2
Mean age started drinking, years	28.7	28.8	29.3	37.7	37.2	40.4
Self-reported change in consumption compared with some years ago, %						
Increased	6.1	3.6	4.9	7.3	5.8	5.8
Decreased	31.3	26.0	38.0	16.5	14.6	17.1
Same	62.6	70.4	57.1	76.2	79.6	77.1

HED, heavy episodic drinking.

*HED is defined as drinking >60g of pure alcohol in one session for men and >40g for women.

†Reporting one or more of the following indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 5.4. Baseline drinking characteristics of male current regular drinkers by level of alcohol drinking

		Alcohol consumption per week			
	All current regular	**<140g/week**	**140-279g/week**	**280-419g/week**	**420+g/week**
Number of participants	69904	25096	18910	12830	13068
Mean alcohol consumption					
Typical drinking week, g/week (SD)	285.7 (245.3)	80.8 (38.9)	221.8 (44.9)	371.5 (47.1)	687.2 (237.1)
Last drinking day, g/session (SD)	49.9 (39.3)	32.6 (30.9)	46.7 (33.8)	59.1 (38.6)	78.7 (47.2)
Special occasions, g/occasion (SD)	147.4 (109.0)	107.3 (91.5)	142.8 (100.1)	166.7 (106.7)	212.1 (125.6)
Daily drinkers, %	62.1	31.4	65.2	82.1	94.6
HED, %					
Typical drinking day	37.2	9.9	14.4	63.3	100.0
Last drinking day	29.8	14.9	23.0	41.5	62.3
Special occasions	83.6	68.3	85.3	93.5	97.3
Drinking spirits, %					
Typical drinking day	69.6	53.6	71.0	82.4	87.4
Last drinking day	52.3	43.6	52.4	58.4	62.6
Special occasions	61.4	50.2	62.0	69.8	74.2
Drinking outside meals, %	14.1	13.7	13.5	14.0	16.7
Flushing response after drinking, %	17.9	26.7	17.5	14.5	9.2
Mean duration of regular drinking, year (SD)	22.5 (12.4)	20.4 (12.7)	22.5 (12.3)	23.8 (11.7)	25.1 (11.4)
Mean age started regular drinking, year (SD)	28.7 (11.0)	30.7 (12.2)	28.7 (10.6)	27.3 (9.7)	26.0 (9.0)

SD, standard deviation; HED, heavy episodic drinking.
Prevalences and means are adjusted for age and study area as appropriate.
Associations between level of alcohol consumption and the above drinking parameters: $p<0.01$ for all variables.

Table 5.5. Baseline drinking characteristics of male current regular drinkers by frequency of drinking

	All current regular	1-5 days/week	6-7 days/week
Number of participants	69904	26528	43376
Mean alcohol consumption			
Typical drinking week, g/week (SD)	285.7 (245.3)	133.4 (117.0)	378.8 (254.2)
Last drinking day, g/session (SD)	49.9 (39.3)	45.6 (40.8)	52.5 (38.4)
Special occasions, g/occasion (SD)	147.4 (109.0)	134.2 (109.5)	155.5 (108.7)
HED, %			
Typical drinking day	37.2	25.4	41.2
Last drinking day	29.8	24.3	31.9
Special occasions	83.6	77.2	85.6
Drinking spirits, %			
Typical drinking day	69.6	62.6	73.8
Last drinking day	52.3	47.7	54.8
Special occasions	61.4	54.7	64.9
Drinking outside meals, %	14.1	13.5	14.5
Flushing response after drinking, %	17.9	22.4	15.5
Mean duration of regular drinking, year (SD)	22.5 (12.4)	21.6 (11.4)	23.0 (12.4)
Mean age started regular drinking, year (SD)	28.7 (11.0)	29.2 (10.4)	28.3 (11.4)

SD, standard deviation; HED, heavy episodic drinking.
Prevalences and means are adjusted for age and study area as appropriate.
Associations between drinking frequency and the above drinking parameters: $p<0.01$ for all variables.

Table 5.6. Baseline drinking characteristics of male current regular drinkers by heavy episodic drinking status

		Typical drinking day		Last drinking day	
	All current regular	≤60g/day	>60g/day (i.e., HED)	≤60g/day	>60g/day (i.e., HED)
Number of participants	69904	43890	26014	49039	20865
Mean alcohol consumption					
Typical drinking week, g/week (SD)	285.7 (245.3)	164.1 (103.9)	490.7 (273.8)	227.2 (198.4)	423.1 (296.2)
Last drinking day, g/session (SD)	49.9 (39.3)	37.1 (29.0)	71.4 (45.0)	30.7 (13.5)	94.9 (42.4)
Special occasions, g/occasion (SD)	147.4 (109.0)	119.5 (91.3)	194.4 (118.4)	126.4 (95.1)	196.8 (119.3)
Daily drinkers, %	62.1	56.7	69.8	60.1	67.9
HED, %					
Typical drinking day	37.2	--	--	23.4	71.6
Last drinking day	29.8	14.2	57.6	--	--
Special occasions	83.6	76.8	97.5	79.1	98.3
Drinking spirits, %					
Typical drinking day	69.6	62.6	85.5	66.2	80.0
Last drinking day	52.3	48.8	61.1	51.4	56.3
Special occasions	61.4	57.0	71.6	59.8	68.1
Drinking outside meals, %	14.1	13.5	15.1	13.7	14.8
Flushing response after drinking, %	17.9	22.3	11.6	20.4	12.2
Mean duration of regular drinking, year (SD)	22.5 (12.4)	21.4 (12.9)	24.3 (11.5)	21.8 (12.9)	24.0 (11.0)
Mean age started regular drinking, year (SD)	28.7 (11.0)	29.8 (11.8)	26.7 (8.9)	29.4 (11.7)	26.9 (8.7)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between HED and the above drinking parameters: $p<0.01$ for all variables.

Table 5.7. Baseline drinking characteristics of male current regular drinkers by mealtime drinking habits

	All current regular	Drinking with meals	Drinking without meals
Number of participants	69904	60041	9863
Mean alcohol consumption			
Typical drinking week, g/week (SD)	285.7 (245.3)	282.2 (244.3)	306.8 (250.2)
Last drinking day, g/session (SD)	49.9 (39.3)	49.5 (38.3)	52.2 (44.7)
Special occasions, g/occasion (SD)	147.4 (109.0)	147.6 (108.4)	146.3 (112.4)
Daily drinkers, %	62.1	61.7	63.7
HED, %			
Typical drinking day	37.2	36.7	40.2
Last drinking day	29.8	29.5	34.0
Special occasions	83.6	83.6	83.0
Drinking spirits, %			
Typical drinking day	69.6	69.6	69.4
Last drinking day	52.3	52.1	49.5
Special occasions	61.4	61.4	59.8
Flushing response after drinking, %	17.9	17.9	18.4
Mean duration of regular drinking, year (SD)	22.5 (12.4)	22.3 (12.4)	23.4 (12.7)
Mean age started regular drinking, year (SD)	28.7 (11.0)	28.8 (10.9)	27.7 (11.8)

SD, standard deviation; HED, heavy episodic drinking.
Prevalences and means are adjusted for age and study area as appropriate.
Associations between mealtime drinking habits and the above drinking parameters: $p<0.01$ for most variables, except for flushing response, and mean consumption, spirits drinking, and HED on special occasions (all $p>0.05$).

Table 5.8. Baseline drinking characteristics of male current regular drinkers by beverage type

	All current regular	Beer	Rice wine	Grape wine	Strong spirits	Weak spirits	Mixed
Typical drinking week							
Number of participants	69904	12725	7882	623	32727	15947	--
Daily drinkers, %	62.1	43.3	67.1	51.8	67.3	62.3	--
HED, %							
Typical drinking day	37.2	11.9	4.2	2.0	58.1	22.6	--
Last drinking day	29.8	17.5	12.9	13.6	42.2	24.6	--
Special occasions	83.6	73.0	55.5	57.9	91.9	80.2	--
Drinking outside meals, %	14.1	12.2	14.2	12.6	14.2	13.2	--
Flushing response after drinking, %	17.9	22.9	15.5	20.0	17.0	17.7	--
Mean duration of regular drinking, year (SD)	22.5 (12.4)	21.5 (10.1)	22.3 (13.2)	16.4 (14.4)	22.8 (12.4)	22.8 (12.6)	--
Mean age started regular drinking, year (SD)	28.7 (11.0)	29.1 (9.3)	29.0 (12.2)	35.1 (16.4)	28.4 (10.8)	28.4 (11.6)	--
Last drinking day							
Number of participants	69904	14025	6848	847	29003	13821	5360
Daily drinkers, %	62.1	48.0	60.1	47.9	67.0	63.3	64.9
HED, %							
Typical drinking day	37.2	25.3	14.4	15.9	52.8	29.4	43.6
Last drinking day	29.8	13.6	2.4	2.4	44.2	17.9	70.8
Special occasions	83.6	78.2	62.5	72.9	91.1	79.0	91.6
Drinking outside meals, %	14.1	12.4	15.7	12.9	14.2	14.0	17.0
Flushing response after drinking, %	17.9	20.0	22.4	20.5	17.0	18.9	16.3
Mean duration of regular drinking, year (SD)	22.5 (12.4)	21.7 (10.4)	22.4 (13.3)	18.6 (13.9)	22.6 (12.6)	22.8 (12.9)	23.4 (10.9)
Mean age started regular drinking, year (SD)	28.7 (11.0)	29.0 (9.6)	28.9 (12.4)	32.9 (15.2)	28.7 (11.0)	28.3 (11.7)	27.5 (9.2)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between beverage type and the above drinking parameters: $p<0.01$ for all variables.

Table 5.9. Mean alcohol consumption among male current regular drinkers at baseline (2004-2008) and the two resurveys (2008, 2013-2014), by beverage type

	Baseline						1st Resurvey						2nd Resurvey					
	Typical drinking day		Last drinking day		Special occasions		Typical drinking day		Last drinking day		Special occasions		Typical drinking day		Last drinking day		Special occasions	
	N	Mean, g/day (SD)	N	Mean, g/session (SD)	N	Mean, g/occasion (SD)	N	Mean, g/day (SD)	N	Mean, g/session (SD)	N	Mean, g/occasion (SD)	N	Mean, g/day (SD)	N	Mean, g/session (SD)	N	Mean, g/occasion (SD)
Overall	69904	54.3 (0.14)	69904	49.9 (0.15)	69904	147.4 (0.41)	2320	52.6 (0.73)	2320	47.9 (0.78)	2320	141.4 (2.19)	2732	65.6 (1.01)	2732	55.6 (0.92)	2732	116.3 (1.76)
All drinkers																		
Non-mixed	69904	54.3 (0.14)	64544	45.7 (33.91)	48584	125.9 (87.65)	2320	52.6 (0.73)	2139	44.2 (33.25)	1676	120.8 (81.86)	1968	52.6 (37.84)	2286	47.0 (34.71)	1864	95.1 (66.63)
Mixed	--	--	5360	99.9 (59.12)	21320	196.4 (133.98)	--	--	181	91.8 (53.43)	644	194.9 (134.35)	764	99.0 (67.36)	446	99.6 (72.89)	868	161.8 (113.19)
One-type drinkers																		
Beer only	12725	40.1 (25.55)	14025	34.2 (32.33)	7617	99.3 (65.62)	515	38.3 (23.50)	731	31.7 (30.23)	363	89.2 (61.66)	223	36.8 (28.08)	369	39.6 (40.70)	230	75.6 (58.46)
Rice wine only	7882	33.2 (26.68)	6848	29.9 (21.85)	4270	72.0 (47.77)	278	35.6 (25.30)	197	36.0 (20.33)	174	76.4 (52.43)	253	31.6 (28.51)	269	14.5 (24.73)	209	58.3 (40.97)
Grape wine only	623	16.9 (13.13)	847	16.5 (15.30)	364	51.7 (43.38)	24	16.8 (10.58)	35	16.7 (8.34)	18	44.0 (21.41)	46	18.6 (8.36)	68	24.3 (10.14)	45	39.6 (25.85)
Strong spirits only	32727	67.2 (40.11)	29003	57.0 (36.77)	24924	157.3 (96.98)	1116	65.2 (37.66)	888	55.2 (34.85)	841	148.5 (89.89)	1019	64.4 (40.33)	1142	58.2 (34.40)	979	114.5 (72.35)
Weak spirits only	15947	51.0 (34.33)	13821	44.1 (29.72)	11409	100.2 (67.43)	387	49.6 (35.06)	288	52.1 (36.04)	280	110.3 (64.80)	427	47.8 (34.23)	438	43.0 (31.67)	401	81.5 (48.82)

SD, standard deviation.
Means are adjusted for age and study area as appropriate.

Table 5.10. Cross-tabulation of types of beverage reported on a typical drinking day and on the last drinking day among male current regular drinkers at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Beverage type consumed on a typical drinking day															
	Baseline					1st Resurvey					2nd Resurvey					
Beverage type consumed on the last drinking day (%)	Beer only	Rice wine only	Grape wine only	Strong spirits only	Weak spirits only	Beer only	Rice wine only	Grape wine only	Strong spirits only	Weak spirits only	Beer only	Rice wine only	Grape wine only	Strong spirits only	Weak spirits only	Mixed
Beer only	75.3	8.8	9.3	6.4	10.0	86.0	25.2	8.3	12.1	20.9	83.0	8.7	2.8	3.9	1.6	16.5
Rice wine only	1.6	70.7	6.9	0.9	4.5	0.4	60.4	0.0	1.3	3.4	2.2	76.1	0.8	1.2	0.9	1.3
Grape wine only	0.9	1.2	65.7	0.4	0.6	0.8	0.4	91.7	0.4	1.0	0.9	4.3	81.8	1.0	2.3	5.0
Strong spirits only	7.5	1.8	5.6	83.4	3.7	3.5	0.7	0.0	76.4	3.9	6.3	4.3	7.1	89.2	1.2	25.4
Weak spirits only	4.7	8.0	6.1	1.9	74.8	1.4	5.0	0.0	1.6	64.3	0.9	4.3	3.6	0.4	91.6	3.9
Mixed	9.9	9.5	6.4	6.9	6.5	8.0	8.3	0.0	8.2	6.5	6.7	2.2	4.0	4.3	2.3	47.9

P for chi-squared test and Mantel-Haenszel test are <0.001.

In continuous analyses of intake data reported on the last drinking and on a typical drinking day, Pearson correlation coefficients are 0.487 (p<0.001) at baseline, 0.518 (p<0.001) at the 1st resurvey, and 0.649 (p<0.001) at the 2nd resurvey.

Table 5.11. Associations of blood pressure with alcohol consumption in a typical drinking week

					Current regular drinkers by consumption (g) per week					
	Abstainers	Ex-regular drinkers	Reduced-intake drinkers	Occasional drinkers	(Men) <140 / (Women) <70	(Men) 140-279/ (Women) 70+	(Men) 280-419	(Men) 420+	p_{trend} *	p_{het} †
Men										
Mean systolic blood pressure, mmHg (SE)										
Baseline	131.6 (0.10)	133.5 (0.23)	133.0 (0.19)	130.7 (0.07)	132.0 (0.12)	134.6 (0.14)	136.2 (0.17)	137.3 (0.17)	*<0.0001*	*<0.0001*
1st Resurvey	126.4 (0.46)	128.5 (1.07)	125.7 (1.04)	125.5 (0.34)	127.3 (0.63)	130.4 (0.72)	131.0 (0.89)	132.1 (0.88)	*<0.0001*	*<0.0001*
2nd Resurvey	134.8 (0.34)	135.9 (0.85)	137.1 (1.01)	134.8 (0.38)	136.3 (0.70)	138.6 (0.68)	140.5 (0.80)	141.6 (0.70)	*<0.0001*	*<0.0001*
Mean diastolic blood pressure, mmHg (SE)										
Baseline	78.2 (0.06)	79.5 (0.14)	79.6 (0.11)	77.9 (0.04)	79.2 (0.07)	80.7 (0.08)	81.9 (0.10)	82.6 (0.10)	*<0.0001*	*<0.0001*
1st Resurvey	75.7 (0.27)	77.1 (0.63)	76.4 (0.62)	75.7 (0.20)	76.5 (0.37)	78.3 (0.43)	78.4 (0.52)	80.3 (0.52)	*<0.0001*	*<0.0001*
2nd Resurvey	78.2 (0.20)	79.3 (0.50)	80.1 (0.60)	78.8 (0.23)	80.1 (0.41)	81.1 (0.40)	82.1 (0.47)	82.9 (0.42)	*<0.0001*	*<0.0001*
Women										
Mean systolic blood pressure, mmHg (SE)										
Baseline	130.2 (0.05)	130.9 (0.55)	129.0 (0.54)	128.0 (0.07)	127.5 (0.35)	129.3 (0.49)			*<0.0001*	*<0.0001*
1st Resurvey	125.6 (0.23)	131.9 (3.03)	128.8 (2.75)	124.2 (0.36)	122.1 (1.88)	122.0 (2.44)			*0.4475*	*0.0020*
2nd Resurvey	135.9 (0.18)	136.4 (1.90)	132.7 (2.28)	133.7 (0.43)	134.0 (1.79)	136.1 (2.23)			*0.0002*	*0.0001*
Mean diastolic blood pressure, mmHg (SE)										
Baseline	76.9 (0.03)	77.9 (0.30)	77.3 (0.30)	76.1 (0.04)	76.4 (0.19)	77.7 (0.27)			*<0.0001*	*<0.0001*
1st Resurvey	74.5 (0.12)	78.6 (1.64)	78.0 (1.48)	74.3 (0.19)	73.9 (1.01)	73.9 (1.31)			*0.0654*	*0.0097*
2nd Resurvey	77.4 (0.10)	78.8 (1.07)	78.9 (1.28)	76.9 (0.24)	76.7 (1.00)	77.2 (1.25)			*<0.0001*	*0.0064*

SE, standard error.

Means are adjusted for age group, study area, education level, income level, smoking, physical activity, and seasonality using linear regression model.

Participants with prior coronary heart disease, stroke, or transient ischaemic attack were excluded.

**P* for trend by amount consumed among current regular drinkers.

†*P* for heterogeneity across all drinking categories.

Table 5.12. Associations of blood pressure with alcohol consumption on the last drinking day

					Current regular drinkers by consumption (g) on the last drinking day					
	Abstainers	Ex-regular drinkers	Reduced-intake drinkers	Occasional drinkers	(Men) <21 / (Women) <10	(Men) 21-41/ (Women) 10+	(Men) 42-62	(Men) 63+	p_{trend}*	p_{het}†
Men										
Mean systolic blood pressure, mmHg (SE)										
Baseline	131.5 (0.10)	133.2 (0.23)	133.0 (0.19)	130.8 (0.07)	132.1 (0.13)	134.0 (0.13)	135.6 (0.16)	137.4 (0.16)	*<0.0001*	*<0.0001*
1st Resurvey	126.3 (0.46)	128.2 (1.07)	125.7 (1.04)	125.6 (0.34)	128.7 (0.65)	128.2 (0.67)	131.5 (0.96)	132.2 (0.84)	*<0.0001*	*<0.0001*
2nd Resurvey	134.7 (0.34)	135.8 (0.85)	137.1 (1.01)	134.9 (0.38)	137.2 (0.70)	138.7 (0.66)	139.3 (0.81)	141.6 (0.73)	*<0.0001*	*<0.0001*
Mean diastolic blood pressure, mmHg (SE)										
Baseline	78.2 (0.06)	79.4 (0.14)	79.6 (0.11)	78.0 (0.04)	79.0 (0.08)	80.5 (0.08)	81.5 (0.10)	82.9 (0.09)	*<0.0001*	*<0.0001*
1st Resurvey	75.7 (0.27)	76.9 (0.63)	76.4 (0.62)	75.7 (0.20)	76.9 (0.38)	77.7 (0.40)	79.0 (0.57)	79.7 (0.50)	*<0.0001*	*<0.0001*
2nd Resurvey	78.2 (0.20)	79.3 (0.50)	80.1 (0.60)	78.9 (0.23)	80.3 (0.41)	81.2 (0.39)	81.3 (0.48)	83.3 (0.43)	*<0.0001*	*<0.0001*
Women										
Mean systolic blood pressure, mmHg (SE)										
Baseline	130.2 (0.05)	130.8 (0.55)	128.9 (0.54)	128.0 (0.07)	127.3 (0.52)	129.4 (0.29)			*<0.0001*	*<0.0001*
1st Resurvey	125.6 (0.23)	131.9 (3.03)	128.8 (2.75)	124.2 (0.36)	121.3 (2.90)	123.4 (1.42)			*0.9967*	*0.0014*
2nd Resurvey	135.9 (0.18)	136.4 (1.90)	132.7 (2.28)	133.7 (0.43)	132.3 (2.25)	137.4 (1.39)			*0.2888*	*<0.0001*
Mean diastolic blood pressure, mmHg (SE)										
Baseline	76.9 (0.03)	77.9 (0.30)	77.3 (0.30)	76.1 (0.04)	76.3 (0.28)	77.6 (0.16)			*<0.0001*	*<0.0001*
1st Resurvey	74.5 (0.12)	78.6 (1.64)	78.0 (1.48)	74.3 (0.19)	74.0 (1.57)	74.9 (0.77)			*0.1965*	*0.0245*
2nd Resurvey	77.4 (0.10)	78.7 (1.07)	78.9 (1.28)	76.9 (0.24)	75.9 (1.27)	79.0 (0.78)			*0.0237*	*0.0248*

SE, standard error.

Means are adjusted for age, study area, education level, income level, smoking, physical activity, and seasonality using linear regression model.

Participants with prior coronary heart disease, stroke, or transient ischaemic attack were excluded.

**P* for trend by amount consumed among current regular drinkers.

†*P* for heterogeneity across all drinking categories.

Table 5.13. Changes in alcohol consumption between baseline and the second resurvey at the individual level among men who were current regular drinkers at both time points

	N	Mean difference between 2nd Resurvey and Baseline, g/session (95% CI)	*p*-value
Overall	2042	3.7 (1.2 - 6.1)	*0.004*
Birth cohort			
<1940	148	1.3 (-4.2 - 6.9)	*0.632*
1940-1949	420	1.3 (-3.0 - 5.7)	*0.542*
1950-1959	784	2.3 (-1.5 - 6.1)	*0.238*
1960-1969	610	5.7 (0.3 - 11.0)	*0.040*
1970s	80	18.2 (2.3 - 34.2)	*0.026*
Area			
Rural	1034	1.8 (-1.0 - 4.6)	*0.210*
Urban	1008	5.6 (1.5 - 9.6)	*0.007*
Highest education			
Primary or below	846	1.6 (-1.6 - 4.8)	*0.335*
Middle or above	1196	5.1 (1.6 - 8.6)	*0.004*
Household income (yuan/year)			
<20,000	1115	2.1 (-0.8 - 5.0)	*0.147*
20,000+	927	5.5 (1.3 - 9.6)	*0.010*
Self-reported health*			
Good	1186	4.7 (1.3 - 8.0)	*0.006*
Poor	856	2.2 (-1.4 - 5.8)	*0.222*
Prior chronic disease†			
No	1688	3.7 (1.0 - 6.4)	*0.008*
Yes	354	3.5 (-2.4 - 9.4)	*0.243*

CI, confidence interval.

Significance for change in alcohol consumption over time was tested using dependent sample t-test.

*Poor self-reported health included those who reported fair or poor self-rated health; good self-reported health included those who reported good or excellent self-rated health.

†Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table 5.14. Prevalence and mean levels of alcohol consumption among men at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics

	Baseline							2nd Resurvey						
						Current regular							Current regular	
	N	Abstainer %	Ex-regular %	Reduced-intake %	Occasional %	%	Mean*, g/session (SE)	N	Abstainer %	Ex-regular %	Reduced-intake %	Occasional %	%	Mean*, g/session (SE)
Birth cohort														
<1940	29036	32.3	7.8	5.7	29.8	24.4	34 (0.3)	1106	53.1	10.4	2.7	15.4	18.4	36 (2.1)
1940-1949	47200	24.4	5.7	6.5	33.5	30.0	42 (0.3)	2311	41.0	10.4	4.7	19.9	24.0	45 (1.8)
1950-1959	64939	18.1	3.0	5.2	37.3	36.4	51 (0.3)	3149	32.8	5.6	4.4	25.9	31.3	54 (1.4)
1960-1969	58690	14.6	1.5	3.5	43.7	36.7	57 (0.3)	2632	26.8	2.6	2.8	35.7	32.2	66 (1.9)
1970s	10394	17.3	0.7	2.7	52.3	27.0	58 (0.8)	371	23.1	1.2	4.2	40.1	31.5	77 (7.0)
Area														
Rural	118903	24.2	4.3	4.6	37.5	29.3	49 (0.2)	5433	39.2	7.2	3.3	24.5	25.9	51 (1.0)
Urban	91356	15.3	3.1	5.3	37.9	38.3	51 (0.2)	4136	29.4	5.2	4.5	28.9	32.0	60 (1.5)
Highest education														
Primary or below	88788	22.8	4.5	4.9	34.6	33.2	49 (0.7)	4076	37.6	6.6	3.2	23.9	28.7	56 (2.0)
Middle or above	121471	19.0	3.2	5.2	39.9	32.6	50 (0.2)	5493	33.5	5.7	4.1	28.2	28.4	54 (1.2)
Household income (yuan/year)														
<20,000	114313	21.9	4.3	4.6	36.8	32.3	49 (0.3)	1858	39.5	7.6	3.9	22.9	26.0	48 (2.4)
20,000+	95946	18.5	3.3	5.5	37.9	34.8	52 (0.3)	7711	34.3	5.8	3.9	26.9	29.0	56 (1.0)

SE, standard error.

Prevalences and means are adjusted for age and study area as appropriate.

*Mean consumption of pure alcohol in grams per session among current regular drinker, based on alcohol intake data reported on the last time the participants drank.

Table 5.15. Drinking patterns among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics

	Baseline						2nd Resurvey					
	N	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions† %	Problem drinking‡ %	N	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions† %	Problem drinking‡ %
Birth cohort												
<1940	7109	77.3	15.3	12.4	65.6	23.5	204	87.5	13.2	15.0	45.9	12.6
1940-1949	14047	72.8	14.0	20.5	77.5	25.2	565	78.9	16.1	23.9	62.2	23.5
1950-1959	23987	64.9	14.3	31.3	86.2	25.3	999	75.0	20.0	34.3	75.4	26.0
1960-1969	21622	50.1	13.6	37.5	89.6	21.7	845	59.3	16.9	44.1	82.3	23.7
1970s	3139	36.3	14.8	40.8	93.4	17.5	119	45.0	18.8	47.3	88.5	22.0
Area												
Rural	34881	64.2	17.3	28.6	85.7	33.9	1408	72.6	19.1	33.3	79.0	26.3
Urban	35023	60.1	10.9	30.9	81.1	13.9	1324	69.0	15.9	36.2	66.5	21.3
Highest education												
Primary or below	27770	69.5	14.6	29.2	81.0	28.1	1118	75.2	19.2	33.9	71.3	25.2
Middle or above	42134	59.5	13.8	29.9	84.0	21.7	1614	70.0	17.3	33.4	75.1	21.1
Household income (yuan/year)												
<20,000	33899	64.9	14.7	28.9	81.5	25.9	462	74.2	17.2	27.8	70.0	22.0
20,000+	36005	59.4	13.2	32.5	85.4	21.3	2270	71.1	17.7	35.2	73.1	23.7

HED, heavy episodic drinking.

Prevalences are adjusted for age and study area as appropriate.

*Based on alcohol intake data reported on the last time the participants drank.

†HED is defined as drinking >60g of pure alcohol in one session.

‡Reporting one or more of the following problem drinking indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 5.16. Drinking patterns among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas

	Baseline							2nd Resurvey						
	N	Mean*, g/session (SE)	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions† %	Problem drinking‡ %	N	Mean*, g/session (SE)	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions† %	Problem drinking‡ %
Urban														
Qingdao	7501	54(0.5)	67.4	19.8	34.6	89.3	8.2	230	52(3.2)	72.2	7.8	31.8	78.2	9.1
Harbin	11506	52(0.3)	48.5	12.6	28.0	86.0	22.0	323	65(2.6)	64.2	10.9	47.4	76.9	23.2
Haikou	1703	43(1.0)	57.1	15.8	22.9	56.0	28.5	134	47(5.5)	53.9	17.2	31.5	55.6	32.0
Suzhou	9103	53(0.5)	71.6	1.4	27.4	83.3	5.2	421	70(3.2)	81.4	18.8	36.6	58.7	17.9
Liuzhou	5210	42(0.6)	54.4	9.5	22.3	66.6	14.9	216	54(4.0)	60.4	26	42.5	61.9	30.9
Rural														
Sichuan	10739	47(0.3)	78.3	1.1	62.5	90.6	37.4	457	47(1.5)	85.1	1.4	54.3	81.6	16.0
Gansu	1475	62(1.4)	27.4	80.7	46.9	89.2	28.2	85	64(6.0)	51.2	78.9	53.7	70.4	32.7
Henan	7092	52(0.5)	39.8	30.7	39.5	90.8	24.3	374	59(2.1)	54.3	30.1	64.8	90.5	17.6
Zhejiang	9174	42(0.3)	78.1	1.6	32.0	71.7	35.7	288	44(2.0)	83.2	2.8	29.4	60.6	39.5
Hunan	6401	52(0.5)	56.6	36.8	40.2	89.8	35.2	204	46(2.2)	69.7	38.9	46.5	82.3	42.6

SE, standard error; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

*Based on alcohol intake data reported on the last time the participants drank.

†HED is defined as drinking >60g of pure alcohol in one session.

‡Reporting one or more of the following problem drinking indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 5.17. Drinking patterns in a typical drinking week among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics

	Baseline			2nd Resurvey		
	N	Mean, g/week* (SE)	Regular HED*† %	N	Mean, g/week* (SE)	Regular HED*† %
Birth cohort						
<1940	7109	250 (2.5)	21.9	204	257 (15.6)	22.9
1940-1949	14047	287 (1.9)	31.1	565	311 (10.6)	34.7
1950-1959	23987	303 (1.5)	38.6	999	367 (10.1)	46.3
1960-1969	21622	275 (1.6)	41.8	845	370 (11.9)	54.4
1970s	3139	237 (4.3)	44.0	119	395 (34.0)	58.2
Area						
Rural	34881	333 (1.5)	46.0	1408	377 (7.8)	51.5
Urban	35023	238 (1.1)	28.3	1324	325 (8.9)	39.3
Highest education						
Primary or below	27770	313 (4.2)	38.4	1118	372 (11.8)	44.5
Middle or above	42134	268 (1.5)	35.5	1614	345 (8.5)	45.8
Income (yuan/year)						
<20,000	33899	293 (1.6)	37.0	462	325 (14.8)	40.3
20,000+	36005	280 (1.8)	37.7	2270	355 (6.4)	46.2
Study area						
Qingdao (Urban)	7501	269 (2.5)	34.6	230	274 (17.1)	31.8
Harbin (Urban)	11506	194 (1.4)	28.0	323	292 (12.1)	47.4
Haikou (Urban)	1703	214 (5.7)	22.9	134	282 (32.6)	31.5
Suzhou (Urban)	9103	293 (2.4)	27.4	421	393 (19.9)	36.6
Liuzhou (Urban)	5210	197 (3.0)	22.3	216	337 (26.9)	42.5
Sichuan (Rural)	10739	422 (2.7)	62.5	457	401 (11.5)	54.3
Gansu (Rural)	1475	197 (5.4)	46.9	85	385 (49.6)	53.7
Henan (Rural)	7092	239 (2.6)	39.5	374	385 (15.5)	64.8
Zhejiang (Rural)	9174	348 (2.9)	32.0	288	323 (15.9)	29.4
Hunan (Rural)	6401	279 (3.4)	40.2	204	335 (17.5)	46.5

SE, standard error; HED, heavy episodic drinking.
Prevalences and means are adjusted for age and study area as appropriate.
*Based on alcohol intake data reported on a typical drinking day.
†HED is defined as drinking >60g of pure alcohol in one session.

Table 5.18. Prevalence of problem drinking among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort and study area

	Baseline		2nd Resurvey	
		Problem drinking*		Problem drinking*
	N	%	N	%
Rural				
<1950	11300	36.1	396	25.0
1950-1959	11528	35.9	470	29.6
≥1960	12053	30.1	542	24.0
Urban				
<1950	9856	15.2	373	17.2
1950-1959	12459	14.3	529	22.3
≥1960	12708	12.4	422	23.5

*Reporting one or more of the following problem drinking indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 5.19. Correlates of alcohol consumption among men at baseline

						Current regular				
	Overall	Abstainers	Ex-regular	Reduced-intake	Occasional	All current regular	<140 g/week	140-279 g/week	280-419 g/week	420+ g/week
No of participants	210259	42789	7923	10371	79272	69904	25096	18910	12830	13068
Socio-demographic characteristics										
Mean age, years (SD)	52.4 (10.9)	55.9 (11.1)	58.9 (9.9)	54.6 (10.3)	50.7 (10.8)	51.0 (10.2)	51.2 (10.9)	51.4 (10.2)	50.7 (9.6)	50.9 (9.5)
Urban area, %	43.4	31.2	34.0	46.0	44.1	50.0	58.6	52.7	48.5	31.2
Education >6 years, %	57.8	54.5	53.5	58.9	60.5	57.6	63.9	60.1	59.6	55.6
Income >20000 yuan/year, %	45.6	42.0	38.9	47.9	46.7	46.8	53.1	51.3	49.6	50.4
Married, %	92.9	91.4	92.4	94.1	93.3	93.3	94.6	93.8	93.7	92.1
Lifestyle factors										
Regular smoking, %	61.1	52.3	53.6	64.7	56.9	71.7	64.5	72.0	76.1	79.6
Non-regular fresh fruit intake, %	77.0	75.1	74.7	74.2	74.8	78.9	72.0	78.0	81.1	83.6
Physical activity, mean MET-h/d (SD)	22.0 (15.3)	21.1 (15.1)	19.5 (14.2)	20.8 (14.7)	22.6 (15.6)	22.4 (15.0)	22.7 (14.5)	23.1 (14.9)	23.2 (15.4)	22.7 (15.2)
Daily tea drinking, %	40.8	36.0	37.7	41.7	37.3	48.5	44.6	47.4	48.8	52.3
Physical measurements, mean (SD)										
SBP, mmHg	132.8 (20.0)	132.3 (21.5)	135.0 (22.8)	133.7 (20.3)	131.0 (18.8)	134.8 (19.8)	131.6 (18.9)	134.3 (19.8)	136.0 (19.9)	137.4 (20.7)
DBP, mmHg	79.2 (11.4)	78.6 (11.5)	80.2 (12.2)	79.7 (11.3)	78.1 (10.9)	80.6 (11.5)	79.5 (11.1)	81.0 (11.5)	82.2 (11.6)	82.9 (11.7)
BMI, kg/m^2	23.4 (3.2)	23.3 (3.2)	23.7 (3.4)	24.1 (3.4)	23.4 (3.2)	23.4 (3.2)	23.7 (3.2)	23.7 (3.2)	23.7 (3.2)	23.7 (3.2)
Standing height, cm	165.2 (6.5)	164.7 (6.3)	165.2 (6.3)	165.6 (6.5)	165.3 (6.3)	165.5 (6.7)	165.7 (6.6)	165.8 (6.8)	165.8 (6.8)	166.0 (6.8)
Health and medical history*										
Poor health	8.9	12.8	23.5	14.0	7.7	5.9	6.5	6.4	6.1	7.1
Any chronic disease	22.6	27.2	46.0	33.5	21.2	17.9	19.8	18.0	17.3	17.5
Coronary heart disease	2.7	3.3	5.8	4.7	2.3	2.0	2.1	1.8	1.6	1.7
Stroke or TIA	2.3	3.6	9.4	4.1	1.6	1.3	1.4	1.3	1.1	1.3
Cancer	0.5	0.9	1.8	0.8	0.3	0.3	0.3	0.2	0.2	0.2
Cirrhosis or chronic hepatitis	1.7	2.7	6.0	2.6	1.6	1.2	1.2	1.2	1.2	1.6
Emphysema or bronchitis	3.1	3.9	5.0	4.4	2.7	2.5	2.5	2.5	2.2	2.4
Diabetes	5.6	6.7	9.8	8.2	5.0	4.7	5.0	4.7	5.3	5.9
Psychiatric disorder	0.3	0.6	0.4	0.2	0.2	0.2	0.2	0.1	0.2	0.2

SD, standard deviation; MET-h/d, metabolic equivalents of task per hours per day; S/DBP, systolic/diastolic blood pressure; BMI, body mass index; TIA, transient ischaemic attack.

Prevalences and means are adjusted for age and study area as appropriate. Characteristics across weekly consumption categories are adjusted using current regular drinkers as the standard population.

P for trend by amount drunk category among current regular drinkers are $p<0.01$ for most variables except for BMI, poor self-reported health, and prior stroke or TIA, cirrhosis/hepatitis, emphysema/bronchitis, and psychiatric disorders ($p>0.05$). *P* for heterogeneity for all variables across all drinking categories are $p<0.01$.

*All self-reported except for diabetes which included both self-reported and screen-detected cases. Prior chronic diseases included self-reported coronary heart disease, stroke or TIA, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, and kidney disease.

Table 5.20. Prevalence and mean levels of alcohol consumption among male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health and lifestyle risk factors

	Baseline							2nd Resurvey						
						Current regular							Current regular	
	N	Abstainer %	Ex-regular %	Reduced-intake %	Occasional %	%	Mean*, g/session (SE)	N	Abstainer %	Ex-regular %	Reduced-intake %	Occasional %	%	Mean*, g/session (SE)
Lifestyle and risk factors														
Regular smoking														
No	81864	24.5	4.7	4.6	41.4	24.8	45 (0.3)	4690	40.0	6.8	3.6	28.1	21.5	51 (1.8)
Yes	128395	17.6	3.1	5.2	35.2	38.9	52 (0.2)	4879	30.0	5.9	4.3	24.5	35.3	58 (1.2)
Fresh fruit consumption														
Regular	48419	20.4	4.3	5.8	38.6	30.8	47 (0.4)	3732	36.7	6.3	4.1	28.4	24.6	53 (1.5)
Non-regular	161840	20.1	3.7	4.8	36.5	34.8	51 (0.2)	5837	33.5	6.3	3.8	24.6	31.9	57 (1.1)
Hypertension														
No	133832	20.4	3.2	4.5	40.0	31.9	48 (0.2)	4776	35.7	5.6	3.4	29.2	26.1	53 (1.4)
Yes	76427	20.2	4.5	5.6	33.1	36.6	54 (0.3)	4793	34.0	6.6	4.3	23.4	31.7	59 (1.3)
Low physical activity														
No	110026	18.6	2.8	4.5	39.5	34.6	50 (0.2)	4442	30.9	5.6	3.7	29.4	30.5	57 (1.3)
Yes	100233	21.5	4.5	5.4	35.8	32.9	51 (0.3)	5127	36.9	6.5	3.7	24.6	28.3	56 (1.5)
Health and medical history														
Self-reported health†														
Good	103521	18.1	2.5	4.2	38.4	36.8	51 (0.2)	4498	32.0	4.7	3.7	28.1	31.5	57 (1.5)
Poor	106738	22.3	5.0	5.7	37.2	29.8	49 (0.2)	5071	37.9	7.5	4.0	25.0	25.5	55 (1.3)
Prior chronic disease‡														
No	162844	19.3	2.7	4.2	38.5	35.3	50 (0.2)	6533	33.6	4.7	3.3	27.6	30.8	55 (1.0)
Yes	47415	24.1	7.1	7.3	35.0	26.5	49 (0.4)	3036	38.4	9.5	5.1	23.3	23.7	58 (2.1)

SE, standard error.

Prevalences and means are adjusted for age and study area as appropriate.

*Mean consumption of pure alcohol in grams per session among current regular drinker, based on alcohol intake data reported on the last time the participants drank.

†Poor self-reported health included those who reported fair or poor self-rated health; good self-reported health included those who reported good or excellent self-rated health.

‡Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table 5.21. Drinking patterns among male current regular drinkers at baseline (2004-2008) and second resurvey (2013-2014), by health and lifestyle risk factors

	Baseline						2nd Resurvey					
	N	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions† %	Problem drinking‡ %	N	Daily drinking %	Drinking outside meals %	HED*† %	HED on special occasions* %	Problem drinking‡ %
Lifestyle and risk factors												
Regular smoking												
No	20070	57.8	13.9	30.4	80.3	19.5	1001	68.5	17.1	38.3	67.3	17.6
Yes	49834	63.9	14.1	39.8	85.2	25.8	1731	72.4	18.5	49.5	75.9	27.5
Fresh fruit consumption												
Regular	15939	57.9	12.4	32.0	81.8	19.9	967	68.6	17.1	39.2	73.3	19.2
Non-regular	53965	63.9	14.1	39.0	84.3	25.1	1765	73.1	17.9	49.1	73.1	26.4
Hypertension												
No	42833	60.5	14.2	34.8	82.5	23.1	1299	68.3	16.1	42.8	71.7	21.6
Yes	27071	64.2	13.9	41.7	85.3	25.3	1433	73.3	18.8	48.0	73.8	25.9
Low physical activity												
No	38413	62.1	14.2	37.1	84.3	24.2	1401	70.3	18.7	47.2	75.8	24.7
Yes	31491	61.2	14.0	38.3	84.0	23.0	1331	71.8	16.0	47.8	74.0	24.2
Health and medical history												
Self-reported health§												
Good	38845	62.7	14.6	37.9	84.6	22.6	1472	71.1	16.9	47.2	71.9	22.6
Poor	31059	61.0	13.3	36.4	82.5	25.4	1260	71.3	19.4	44.2	73.9	25.0
Prior chronic disease¶												
No	57166	62.5	14.0	37.5	83.7	23.8	2031	71.2	17.6	46.2	73.9	23.5
Yes	12738	60.3	14.2	36.5	83.0	24.5	701	71.1	17.9	44.8	71.3	24.0

HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

*Based on alcohol intake data reported on the last time the participants drank.

†HED is defined as drinking >60g of pure alcohol in one session.

‡Reporting one or more of the following problem drinking indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

§Poor self-reported health included those who reported fair or poor self-rated health; good self-reported health included those who reported good or excellent self-rated health.

¶Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table 5.22. Changes in drinking status among men from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and health factors

		Baseline non-drinkers[†]		Baseline drinkers[‡]			
Characteristics[*]	N	Stable non-drinkers %	Starters %	Stable drinkers %	Stoppers %	Decreased-intake drinkers %	Increased-intake drinkers %
All men	9569	18.3	4.2	40.0	22.9	8.2	6.3
Socio-demographic characteristics							
Birth cohort							
<1940	1106	33.0	4.3	24.0	30.6	3.9	4.3
1940-1949	2311	23.1	4.3	32.4	28.3	6.9	5.2
1950-1959	3149	16.3	3.8	43.7	22.1	8.2	6.0
1960-1969	2632	11.3	4.6	47.3	18.1	10.7	8.0
1970s	371	8.3	3.7	50.3	16.0	11.7	10.0
Area							
Rural	5433	21.9	4.3	36.3	24.5	6.9	6.1
Urban	4136	13.6	4.1	44.8	20.9	10.0	6.6
Highest education							
Primary or below	4076	20.1	4.2	36.9	24.1	8.6	6.1
Middle or above	5493	16.7	3.9	42.1	22.5	8.4	6.4
Household income (yuan/year)							
<35,000	3573	21.5	3.9	37.0	23.9	6.8	7.0
35,000+	5996	16.8	4.4	40.8	22.9	8.9	6.2
Health-related factors							
Self-reported health status[§]							
Good	4498	16.7	4.4	43.2	20.0	8.4	7.3
Poor	5071	19.9	4.0	37.0	25.6	8.1	5.4
Prior chronic disease[¶]							
No	6533	17.0	3.9	42.6	21.3	8.5	6.7
Yes	3036	21.4	5.1	34.3	26.4	7.6	5.1
Risk factor index[#]							
0	469	18.1	5.4	36.7	25.5	7.9	6.3
1	1962	18.3	4.6	36.8	24.9	9.6	5.8
2	3559	18.4	4.7	40.1	23.0	7.4	6.4
3+	3579	17.4	3.5	43.1	21.1	8.2	6.7

Prevalences at subgroup levels are adjusted for age and study area as appropriate.

[*]Except for age and study area, characteristics are based on the characteristics of the participants collected at the second resurvey.

[†]Among baseline non-drinkers, associations between change in drinking status and factors: $p<0.001$ for trend across birth cohorts and $p<0.02$ for heterogeneity across study areas, income levels, and self-reported health status.

[‡]Among baseline drinkers, associations between change in drinking status and factors: $p<0.02$ across all variables except education.

[§]Poor self-reported health status included those who reported fair or poor self-rated health; good self-reported health status included those who reported good or excellent self-rated health.

[¶]Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

[#]Derived by summing the individual scores of each of the four risk factors (0 if no, 1 if yes): regular smoking, lack of regular fruit intake, hypertension, low physical activity.

Table 5.23. Reasons for stopping drinking among previous regular drinkers at the second resurvey (2013-2014), by socio-demographic characteristics and health factors

		Reasons			
Characteristics*	**N**	**Existing illness (%)**	**Money (%)**	**Future health† (%)**	**Other‡ (%)**
Overall	1166	51.9	23.6	5.8	18.7
Socio-demographic characteristics					
Sex					
Men	970	53.1	24.3	6.3	16.3
Women	196	45.9	19.9	3.6	30.6
Birth cohort					
<1940	174	56.9	17.8	5.7	19.5
1940-1949	408	57.4	21.1	5.4	16.2
1950-1959	381	47.2	27.3	7.1	18.4
≥1960	203	45.3	26.6	4.4	23.6
Area					
Rural	687	60.3	21.5	6.3	11.9
Urban	479	39.9	26.5	5.2	28.4
Highest education					
Primary or below	589	60.1	20.4	7.0	12.6
Middle or above	577	43.5	26.9	4.7	25.0
Household income (yuan/year)					
<35,000	487	58.5	23.2	5.3	12.9
35,000+	679	47.1	23.9	6.2	22.8
Health-related factors					
Self-reported health status§					
Good	408	42.9	26.0	7.1	24.0
Poor	758	56.7	22.3	5.1	15.8
Prior chronic disease¶					
No	618	44.8	27.0	6.5	21.7
Yes	548	59.9	19.7	5.1	15.3

*Except for age and study area, characteristics are based on the characteristics of the participants collected at the resurvey.
†Included health concerns about future illness and doctor's advice.
‡Included family disapproval and other reasons apart from health and financial concern.
§Poor self-reported health status included those who reported fair or poor self-rated health; good self-reported health status included those who reported good or excellent self-rated health.
¶Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table 5.24. Reasons for stopping drinking among previous regular drinkers at the second resurvey (2013-2014) in men and women, by socio-demographic characteristics and health factors

	Men					Women				
Characteristics*	**N**	**Existing illness (%)**	**Money (%)**	**Future health† (%)**	**Other‡ (%)**	**N**	**Existing illness (%)**	**Money (%)**	**Future health† (%)**	**Other‡ (%)**
Overall	970	53.1	24.3	6.3	16.3	196	45.9	19.9	3.6	30.6
Socio-demographic characteristics										
Birth cohort										
<1940	148	56.1	18.2	6.1	19.6	26	61.5	15.4	3.8	19.2
1940-1949	349	58.2	20.9	5.7	15.2	59	52.5	22.0	3.4	22.0
1950-1959	309	49.8	28.2	8.1	13.9	72	36.1	23.6	2.8	37.5
≥1960	164	45.7	29.9	4.3	20.1	39	43.6	12.8	5.1	38.5
Area										
Rural	567	60.1	22.8	6.9	10.2	120	60.8	15.8	3.3	20.0
Urban	403	43.2	26.6	5.5	24.8	76	22.4	26.3	3.9	47.4
Highest education										
Primary or below	465	61.3	20.6	7.7	10.3	124	55.6	19.4	4.0	21.0
Middle or above	505	45.5	27.7	5.0	21.8	72	29.2	20.8	2.8	47.2
Household income (yuan/year)										
<35,000	402	59.2	23.4	6.0	11.4	85	55.3	22.4	2.4	20.0
35,000+	568	48.8	25.0	6.5	19.7	111	38.7	18.0	4.5	38.7
Health-related factors										
Self-reported health status§										
Good	339	42.8	28.0	8.0	21.2	69	43.5	15.9	2.9	37.7
Poor	631	58.6	22.3	5.4	13.6	127	47.2	22.0	3.9	26.8
Prior chronic disease¶										
No	511	44.8	29.0	7.0	19.2	107	44.9	17.8	3.7	33.6
Yes	459	62.3	19.2	5.4	13.1	89	47.2	22.5	3.4	27.0

*Except for age and study area, characteristics are based on the characteristics of the participants collected at the resurvey.

†Included health concerns about future illness and doctor's advice.

‡Included family disapproval and other reasons apart from health and financial concern.

§Poor self-reported health status included those who reported fair or poor self-rated health; good self-reported health status included those who reported good or excellent self-rated health.

¶Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table 5.25. Estimated regression dilution ratios of alcohol intake among subset of participants involved in all three surveys

		Mean consumption, g/week				Regression dilution ratio[†]			
Baseline-defined groups	N	Baseline	1st Resurvey	2nd Resurvey	Usual[*]	MacMahon-Peto method[‡]	Pearson's correlation[§]	Spearman's correlation[§]	Rosner's regression method[¶]
Men									
Abstainers & ex-regular	1254	0.0	8.3	13.2	10.8				
Occasional	2462	5.0	23.0	39.4	31.2				
Current regular						0.54	0.52	0.55	0.55
<140g/week	694	77.8	96.3	118.8	107.6				
140-279g/week	486	223.9	187.7	241.2	214.5				
280-419g/week	335	367.5	295.7	306.2	301.0				
420+g/week	380	686.1	440.9	435.5	438.2				
Women									
Abstainers & ex-regular	5889	0.0	0.9	0.8	0.9				
Occasional	3093	5.0	4.5	3.8	4.2				
Current regular						0.55	0.59	0.49	0.69
<70g/week	88	33.4	28.7	19.9	24.3				
70-139g/week	58	115.0	93.6	54.7	74.1				
140+g/week	60	319.8	198.6	164.9	181.8				

Participants with prior cancer were excluded.

[*]Usual consumption is the average of the consumption levels at the 1st and 2nd resurveys.

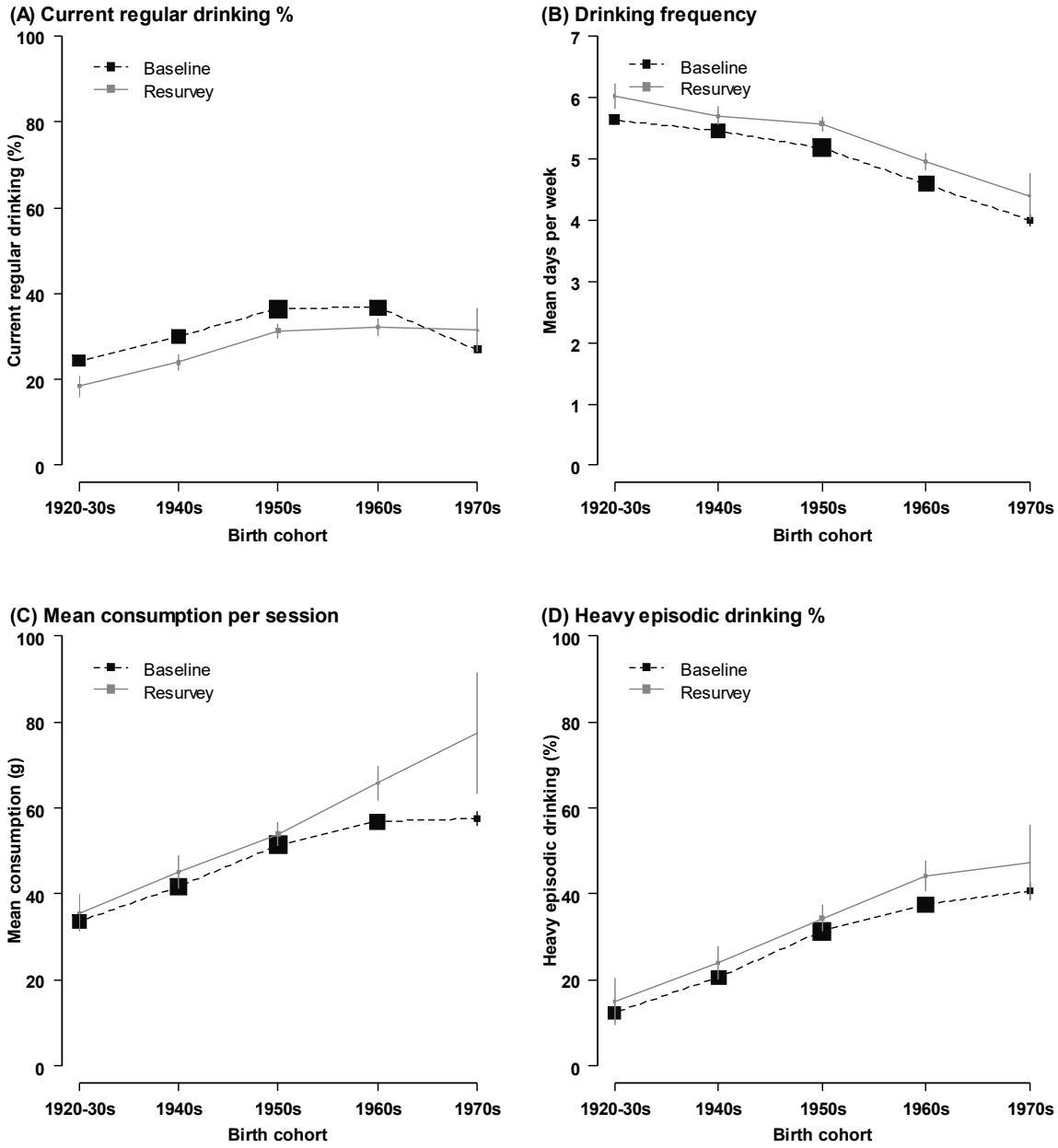
[†]Regression dilution ratio (RDR) is estimated among baseline current regular drinkers using their baseline alcohol intake and usual alcohol intakes. The RDRs calculated using the MacMahon-Peto method based on the baseline survey and the first resurvey are 0.57 for men and 0.59 for women, and those based on the baseline survey and the second resurvey are 0.52 for men and 0.51 for women.

[‡]MacMahon-Peto method estimates RDR with the ratio of the range (i.e., difference between the means of the top vs. bottom baseline-defined groups) of usual alcohol intake to the range of baseline alcohol intake.[218]

[§]Self-correlation method estimates RDR with the correlation coefficient between baseline alcohol intake and usual alcohol intake by Pearson or Spearman correlation.[184]

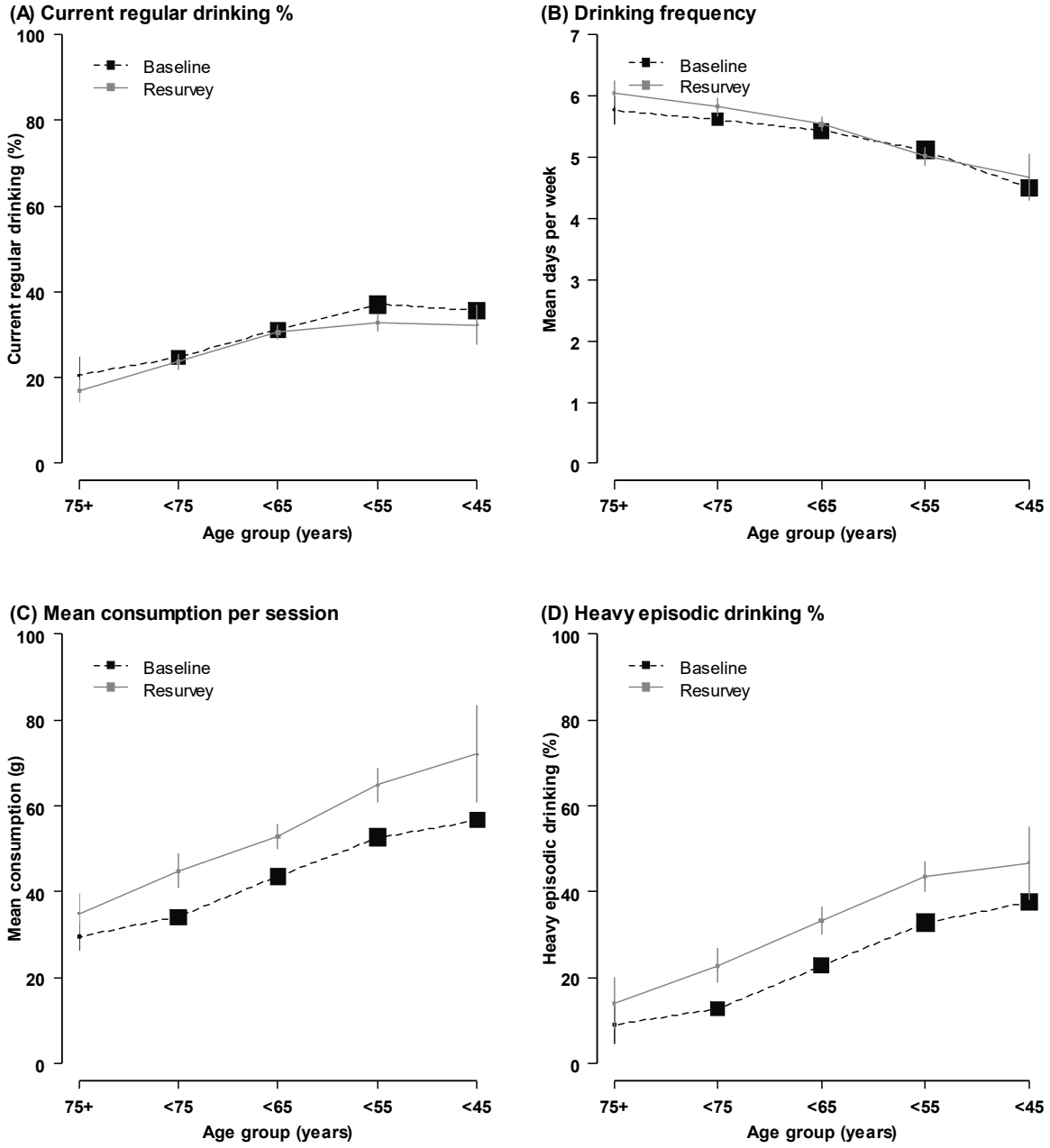
[¶]Rosner's regression method estimates RDR by the slope of the regression line (i.e., regression coefficient) between baseline alcohol intake and usual alcohol intake.[219]

Figure 5.1. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort



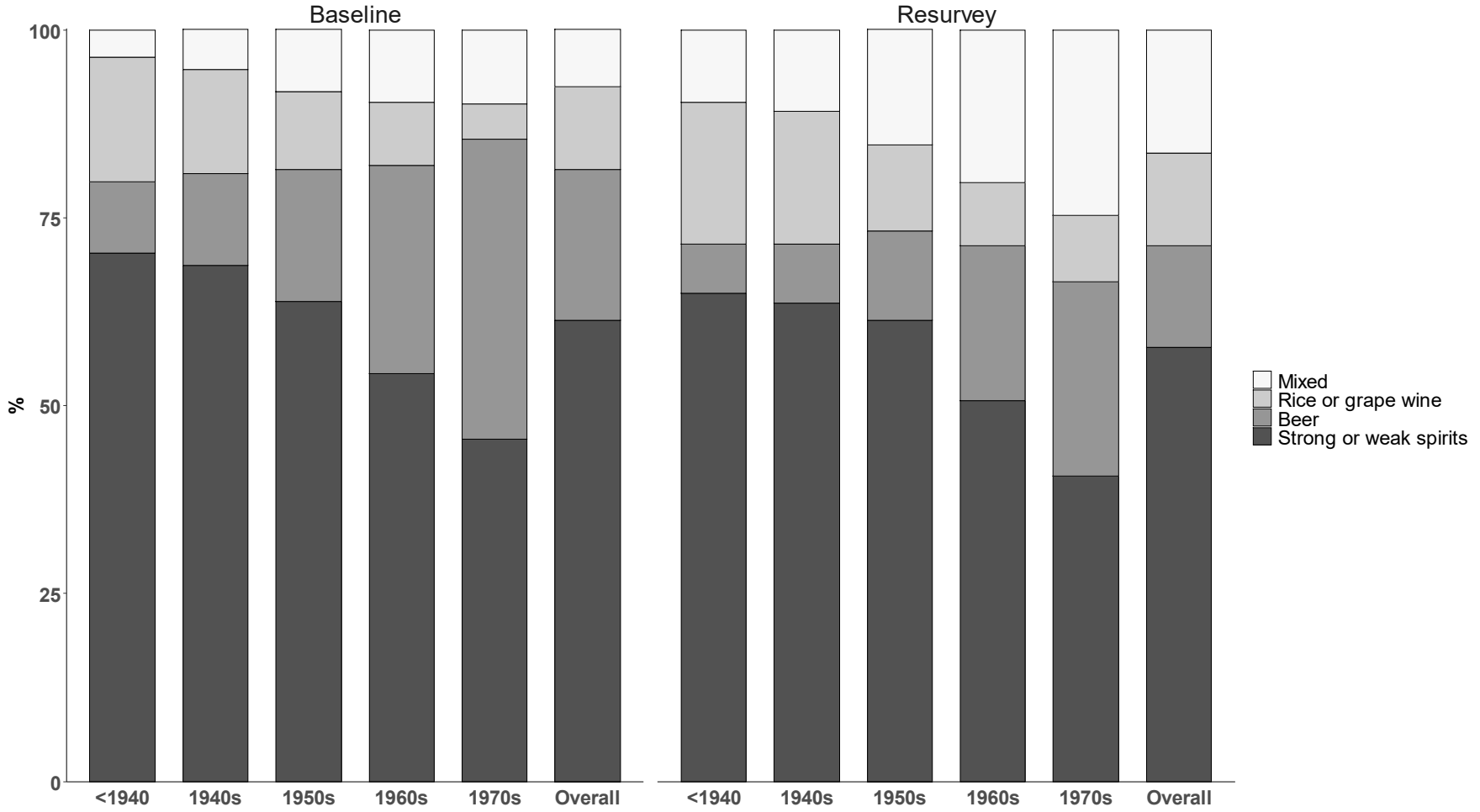
Prevalences and means are adjusted for study area. Size of boxes is proportional to the sample size of each birth cohort. Error bars are 95% confidence intervals. Mean consumption per session (g/session) and heavy episodic drinking status are based on alcohol intake data reported on the last time the participants drank. Heavy episodic drinking is defined as drinking >60g of pure alcohol in one session. All men at baseline (n=210,259) and the second resurvey (n=9569) were included in (A). All male current regular drinkers at baseline (n=69,904) and the second resurvey (n=2732) were included in (B)-(D).

Figure 5.2. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by age group*



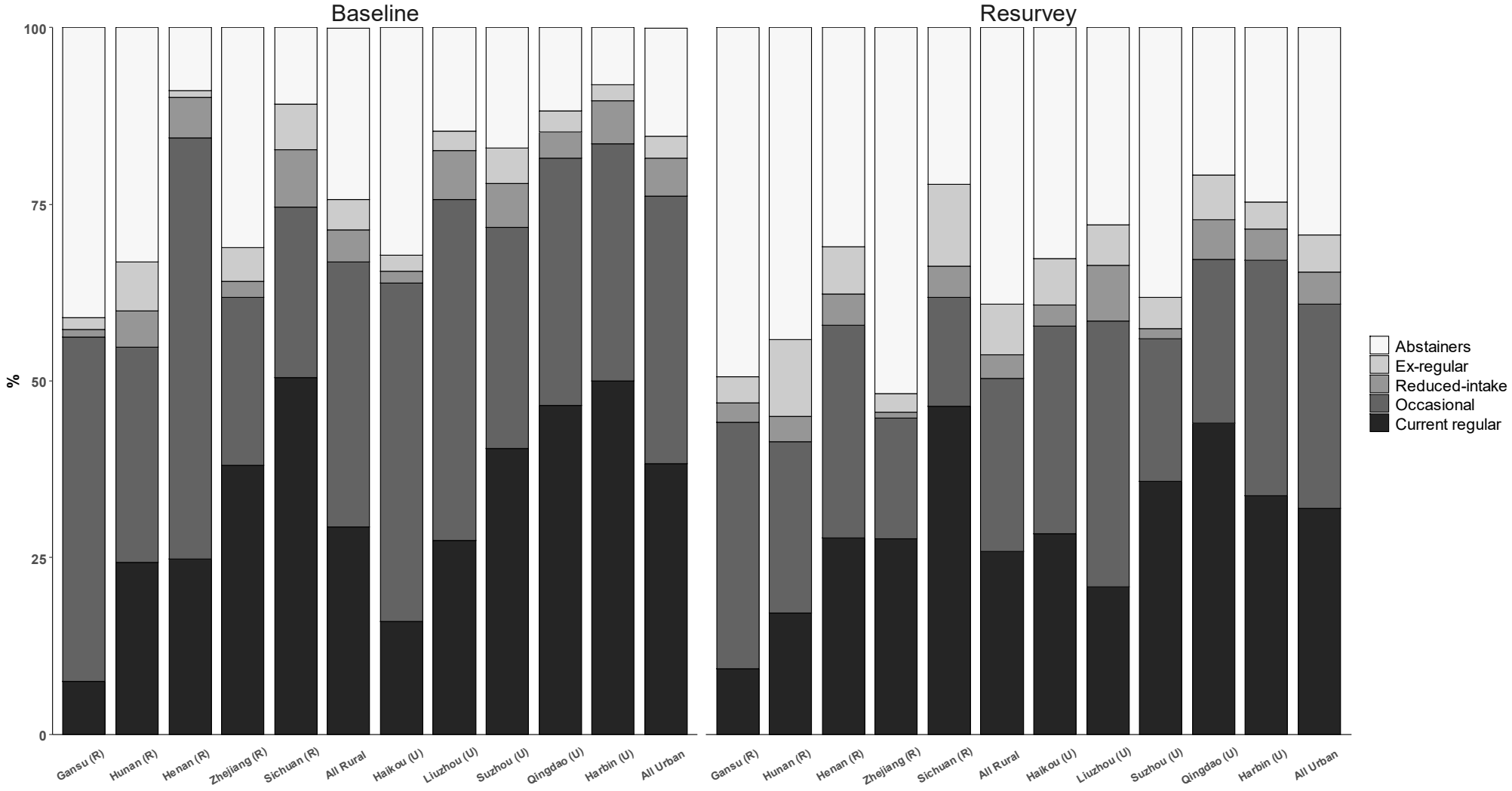
Prevalences and means are adjusted for study area. Size of boxes is proportional to the sample size of each age group. Error bars are 95% confidence intervals. Mean consumption per session (g/session) and heavy episodic drinking status are based on alcohol intake data reported on the last time the participants drank. Heavy episodic drinking is defined as drinking >60g of pure alcohol in one session. All men at baseline (n=210,259) and the second resurvey (n=9569) were included in (A). All male current regular drinkers at baseline (n=69,904) and the second resurvey (n=2732) were included in (B)-(D). *Age at the time of the survey.

Figure 5.3. Proportions of types of alcohol consumed in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by birth cohort



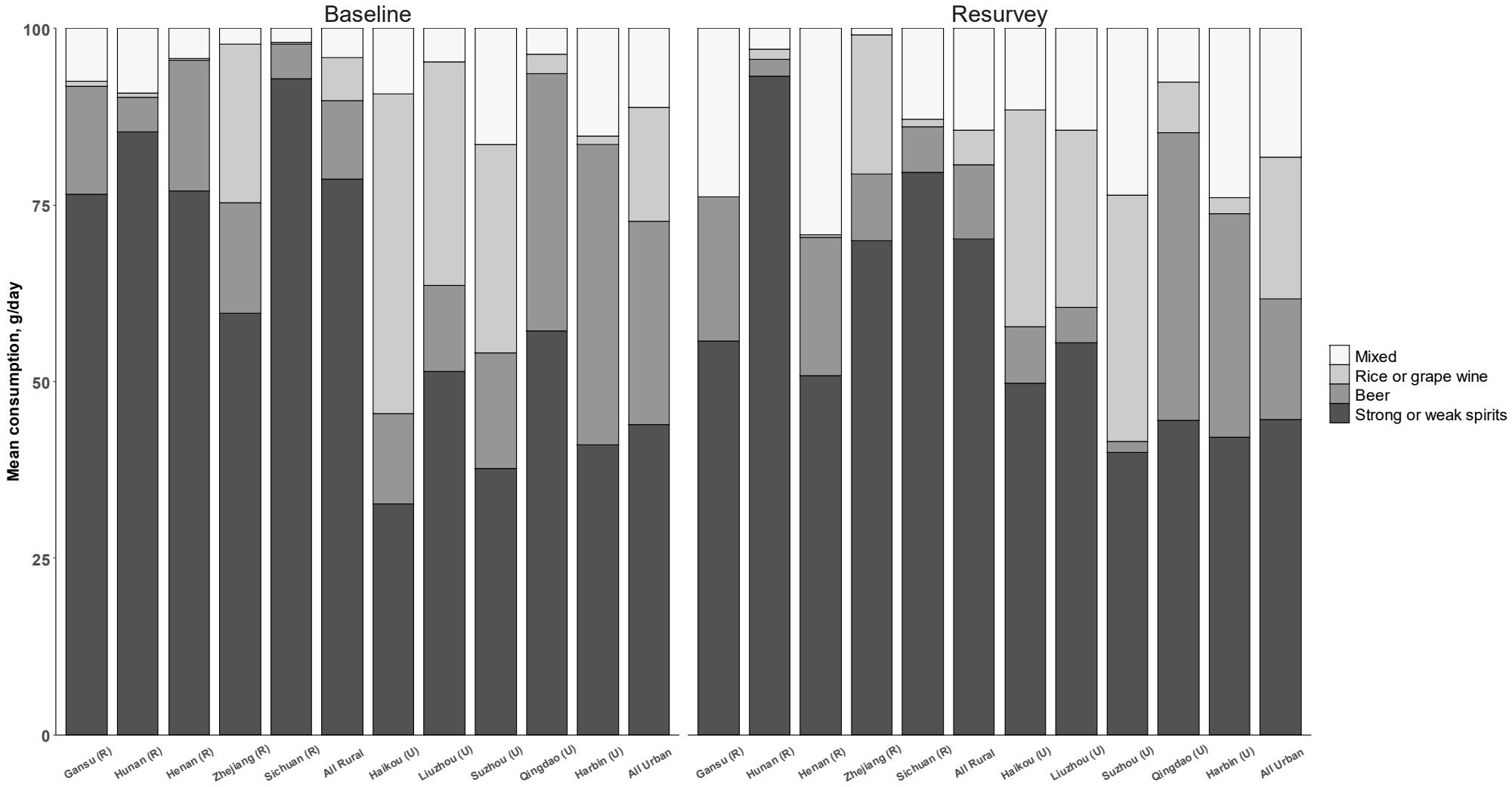
Percentages are adjusted for study area.
Data are based on alcohol intake data reported on the last time the participants drank.

Figure 5.4. Prevalence of alcohol consumption in men at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas



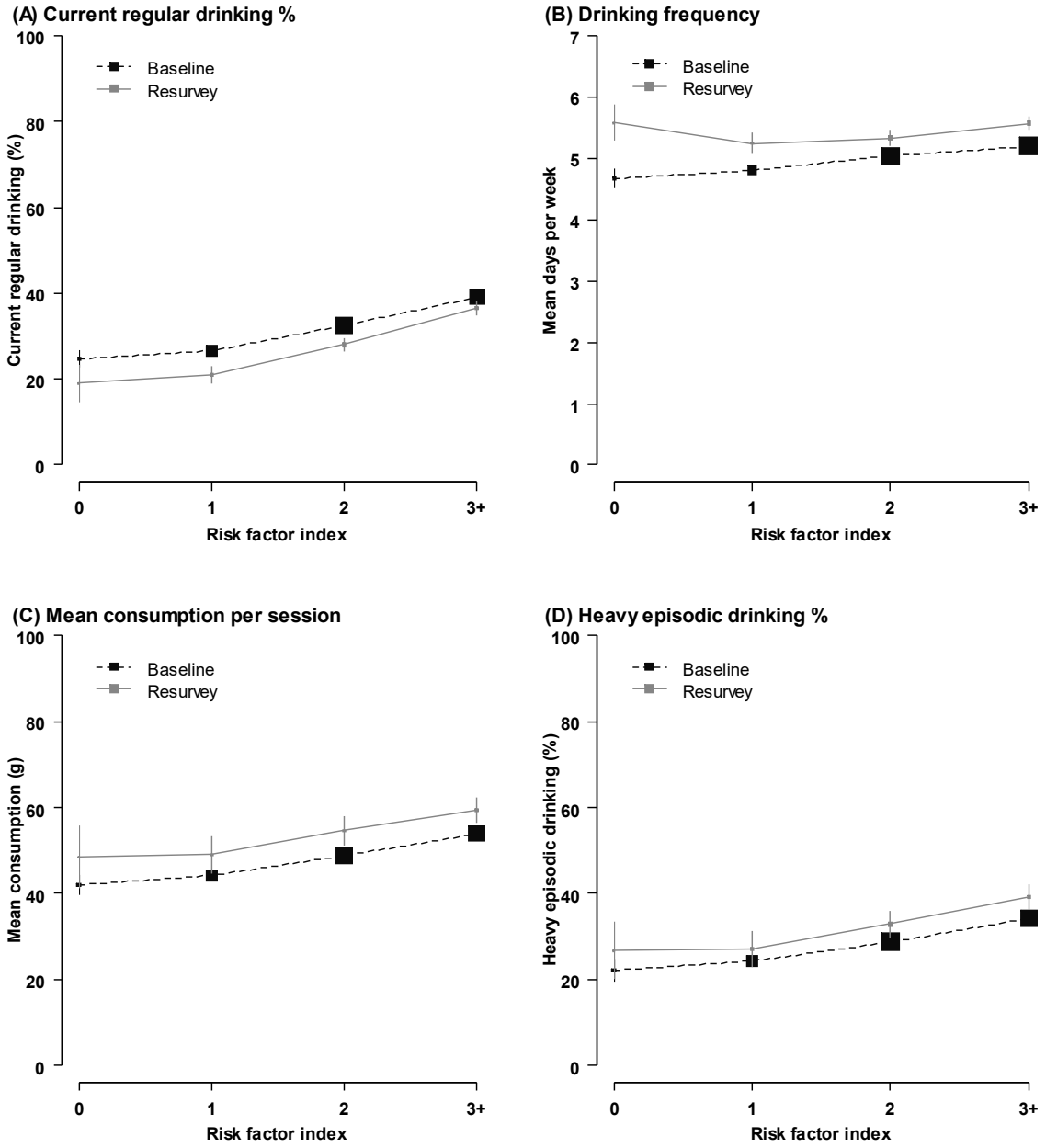
Percentages are adjusted for birth cohort.

Figure 5.5. Proportions of types of alcohol consumed in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by ten study areas



Percentages are adjusted for birth cohort.
Data are based on alcohol intake data reported on the last time the participants drank.

Figure 5.6. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health-related risk factor index



Prevalences and means are adjusted for age group and study area. Size of boxes is proportional to the sample size of each risk factor index group. Error bars are 95% confidence intervals. Mean consumption per session (g/session) and heavy episodic drinking status are based on alcohol intake data reported on the last time the participants drank. Heavy episodic drinking is defined as drinking >60g of pure alcohol in one session. The risk factor index is derived by summing the individual scores of each of the four risk factors (0 if no, 1 if yes): regular smoking, lack of regular fruit intake, hypertension, low physical activity. All men at baseline (n=210,259) and the second resurvey (n=9569) were included in (A). All male current regular drinkers at baseline (n=69,904) and the second resurvey (n=2732) were included in (B)-(D).

Chapter 6. Problem drinking, mental health and mortality risk

6.1 Introduction

Among regular heavy drinkers, a proportion may develop "problem drinking", which is a maladaptive pattern of alcohol use causing problems such as impairment and distress, and may lead to AUD.[242,243] Previous studies in Western populations have shown that problem drinking, using various definitions including heavy drinking, AUD, and the experience of alcohol-related problems, is associated with depression and anxiety,[78-83] sleep problems,[244,245] lower life satisfaction,[246-249] and higher risks of mortality and suicide.[250,251] Also, it has been reported that stressful life events are associated with alcohol craving, HED, and problem drinking.[252-254]

In China, the prevalence of alcohol dependence increased from 0.016% to 0.68% between the 1980s-1990s,[7] along with a sharp rise in per-capita alcohol consumption from 2.5L in 1978 to 7.2L in 2016.[1,207] The burden of problem drinking and its relationship with mental health in China have emerged as important social and public health concerns, as comorbid AUD and mental health disorders have been associated with higher risks of suicide attempts in Western populations.[255,256] Despite this, large-scale epidemiological evidence on problem drinking from Chinese populations, whose drinking cultures differ from those in the West, is limited, with previous studies constrained by small sample size,[257] crude measurement of alcohol drinking (i.e., users vs. non-users),[258,259] and limited data on other health outcomes (e.g., all-cause mortality, injuries).[260,261] Assessment of the relationships between problem drinking

and mental and physical health in Chinese populations is needed to inform treatment and prevention strategies.

6.2 Aims and objectives

Using data from the CKB, this chapter aims to:

1. Examine the prevalence and correlates of problem drinking;
2. Assess the cross-sectional relationships of problem drinking with experience of stressful life events, wellbeing and mental health;
3. Assess the prospective associations of problem drinking with all-cause mortality, any hospitalisation, and fatal and non-fatal events due to external causes.

Although analyses were conducted in both genders, as few women (~2%) drank alcohol regularly and reported problem drinking indicators (~0.2% of all women) in the CKB,[87] this chapter focuses on men.

6.3 Methods

6.3.1 Assessment of problem drinking patterns

Self-reported alcohol drinking patterns and indicators of problem drinking at baseline were recorded by questionnaire, with details described in previous publications and in Chapters 4-5.[87,262,263]

Among current regular drinkers, problem drinking was defined by the report of one or more of the following indicators related to alcohol use in the past month: drinking in the morning; being unable to work or to do anything due to drinking; feeling

depressed, irritated or losing control after drinking (i.e., negative emotions); being unable to keep away from drinking; and having shakes when stopping drinking. Problem drinkers were further categorised into those reporting "one" or "two or more" of the above indicators. Those who did not report any problem drinking indicators (i.e., non-problem drinkers) were further classified based on their weekly alcohol consumption level and HED status (i.e., >60g per session in men and >40g in women) reported on a typical drinking day. Broadly following the US dietary guidelines defining low-risk and at-risk drinking levels for developing AUD,[29] male current regular drinkers who did not report problem drinking were categorised as: (1) low-risk drinkers (i.e., drank alcohol <200g/week and no HED) or (2) high-risk drinkers (i.e., drank alcohol ≥200g/week or HED) (see Figure 6.1 for flow-chart).

6.3.2 Assessment of stressful life events, wellbeing and mental health

Experience of stressful life events in the past two years, wellbeing and mental health (i.e., self-reported health, life satisfaction, sleep problems, depression, anxiety, panic attack, phobia) were assessed by baseline questionnaire (see Appendix C, CKB baseline questionnaire). The ten major stressful life events measured in the CKB are common stressors often examined in epidemiological research[253] and were related to divorce, family conflict, death of spouse, death or major illness of a family member, job loss or retirement, bankruptcy, loss of income or debt, violence, major injury or traffic accident, and natural disaster. For this chapter, self-reported poor health was defined by the report of self-rated health as "poor" (versus "fair", "good", or "excellent"). Life dissatisfaction was defined by the report of "being unsatisfied" or "very unsatisfied" with life (versus "neither satisfied nor dissatisfied", "satisfied", or "very satisfied").

Comparable to the standardised criteria for insomnia used in International Classification of Sleep Disorders,[264] sleep problems were defined by the report of one or more of the following symptoms in at least three days or more in a week during the last month: difficulty in initiating or maintaining sleep; early-morning awakenings; difficulty in staying alert during daytime; and use of sleep aid medications (at least once a week). Major depressive episode (MDE) and general anxiety disorder (GAD) were assessed using the modified Chinese version of the WHO 12-month Composite International Diagnostic Interview - Short Form (CIDI-SF), triggered by positive responses to the screening questions of symptoms of depression and anxiety, respectively.[265] Participants were asked if they had experienced any of the following symptoms of depression for more than two weeks in the past year: feeling sad or depressed; loss of interest; loss of appetite; and feeling worthless. Participants who reported one or more of these depression symptoms were further assessed for MDE using the CIDI-SF (A). Participants who reported continuous anxiety lasting at least one month in the past year were further assessed for GAD using the CIDI-SF (B). Those who responded positively to the screening questions but did not meet the CIDI-SF diagnostic criteria of MDE or GAD were classified as having "depressive symptoms" or "anxiety symptom", respectively. Participants were also asked if they had experienced symptoms of panic attack and phobia (including claustrophobia and agoraphobia) in the past year.

6.3.3 Prospective outcome definitions

Cause-specific mortality and hospitalised events were collected through linkage to death registries and national health insurance systems with annual active

confirmation, with detailed information described in Chapter 4. Outcomes investigated in this chapter were all-cause mortality, any hospitalisation, and any fatal or non-fatal event due to all external causes (ICD-10: V01-Y98), including intentional self-harm (ICD-10: X60-X84) and transport accidents (ICD-10: V01-V99).

6.3.4 Statistical analyses

Across problem drinking categories, means and percentages of selected baseline characteristics were adjusted for age group and study area where appropriate by direct standardisation to the age and study area structure of the study population. Associations between problem drinking categories and baseline characteristics were assessed as described in Chapter 4. For cross-sectional analyses, logistic regression was used to calculate ORs of problem drinking associated with exposure of stressful life events, and ORs of measures of poor wellbeing and mental health associated with exposure to problem drinking and individual problem drinking indicators among male current regular drinkers, adjusted for age group (in 5-year groups), study area (ten areas), education (no formal education, primary school, middle or high school, technical school/college or above), household income (<10,000, 10,000-19,999, 20,000-34,999, 35,000+ yuan/year), and smoking status (never, occasional, ex-regular, current regular smoker). For analyses of problem drinking with wellbeing and mental health, marital status (married, widowed, separated/divorced, never married), prior chronic disease (yes/no), and BMI (<22, 22-24.9, 25-26.9, 27+ kg/m^2) were additionally adjusted for (see Table F1 for details of analytic models).

For prospective analyses, men with major prior chronic disease (as defined in Chapter 5) at baseline were excluded. Cox proportional hazards regression models, with time since entry into the study as the underlying time scale and stratified by age-at-risk (5-year intervals) and ten study areas, and adjusted for education (four groups), income (four groups), smoking status (four groups), fresh fruit intake (regular vs. non-regular), physical activity (<17.8, 17.8-28.7, 28.8+ MET hours per day), and BMI (four groups), were used to estimate HRs for all-cause mortality, any hospitalisation, and events due to external causes associated with problem drinking and individual problem drinking indicators. The proportional hazards assumption was checked using scaled Schoenfeld residuals and by examining the HRs for the first 4 years and for subsequent years of follow-up.[266]

The use of floating SEs for exposure variables involving more than two exposure categories[203,204] and the chi-squared test for heterogeneity across problem drinking categories were described in Chapter 4. The number of problem drinking indicators was fitted as a continuous variable to assess trends within problem drinkers. The cross-sectional and prospective associations were also examined across subgroups defined by study area (rural vs. urban) and household income level (<20,000 vs. ≥20,000 yuan/year).

Sensitivity analyses used different categorisations of non-problem drinkers based on either HED (no [i.e., low-risk] vs. yes) or heavy drinking (<200g/week [i.e., low-risk] vs. 200+g/week). Further analyses explored the associations of problem drinking with depression and anxiety after removing the “negative emotions” indicator from the definition of problem drinking. Further adjustments for potential confounding factors,

e.g., prior chronic disease for stressful life events, physical activity for wellbeing and mental health, and prior psychiatric disorder for all analyses, were performed. Further analyses were done for individual sleep problems, but not for individual depression symptoms due to the small numbers of events. Further sensitivity analyses included all men.

Analyses in this chapter used CKB release 12, with follow-up to 1 January 2016.

6.4 Results

6.4.1 Prevalence and determinants of problem drinking

Among all 210,259 men at baseline, 33% were current regular drinkers (n=69,904). The prevalence of men reporting at least one indicator of problem drinking (i.e., problem drinkers) was 8% among all men and 24% among male current regular drinkers. Compared with low-risk drinkers, problem drinkers tended to have less education and lower household income, and were more likely to smoke regularly (Table 6.1). The prevalence of problem drinking was generally similar across age groups (Figure 6.2A, Figure 6.3). Problem drinkers reported the following indicators: morning drinking (55%) and being unable to stop drinking (47%), which increased with age (p<0.05); and being unable to work due to drinking (15%), having negative emotions after drinking (7%), and having shakes when stopping drinking (2%), which decreased with age (all p<0.05) (Figure 6.3). Among all men, the prevalence of problem drinking varied from 2% in Suzhou to 19% in Sichuan (Figure 6.2B), while among current regular drinkers it varied from 5% in Suzhou to 37% in Sichuan (Figure 6.4). Despite the lower prevalence of current regular drinking, the prevalence of problem drinking was higher in rural than

in urban areas (10% vs. 5% in all men, 34% vs 14% among male current regular drinkers) (Figure 6.2C, Figure 6.5). This was driven mainly by the higher prevalence of morning drinking in rural areas (61% vs 39% among problem drinkers), whereas other problem drinking indicators such as being unable to stop drinking (45% vs. 51%), unable to work due to drinking (13% vs. 19%), and having negative emotions after drinking (6% vs. 9%) were slightly more frequently reported by urban drinkers (Figure 6.5).

6.4.2 Drinking characteristics of problem drinkers

Problem drinkers had significantly different drinking patterns from low-risk drinkers. The proportions of men who reported having drunk alcohol on the day of the survey ranged from 11% in low-risk drinkers to 34% in men with two or more problem drinking indicators (Table 6.2). Compared with low-risk drinkers, problem drinkers consumed on average more than three times as much alcohol each week (>383g/week vs. 109g/week) and were more likely to drink daily (>77% vs. 36%) and to engage in HED on special occasions (>89% vs. 69%) or on the last drinking day (>38% vs. 11%), but were less likely to report a flushing response after drinking (<16% vs. 26%) and started regular drinking at a younger age (<28 years vs. 31 years). High-risk drinkers had a similar mean weekly consumption (378g/week vs. 383g/week) and prevalence of daily drinking (75% vs. 77%) as problem drinkers with one indicator, and similar prevalence of HED (~61% on a typical drinking day) as problem drinkers with two or more indicators. Among problem drinkers, those reporting two or more indicators had higher mean alcohol intake (507g/week vs. 383g/week) and higher prevalence of daily drinking (84% vs. 77%) and HED (61% vs. 48% on a typical drinking day) compared with

those reporting only one indicator. Similar distributions of drinking characteristics across problem drinking status were seen in both rural and urban areas, with higher mean weekly intake and prevalence of men having drunk on the survey day and HED on a typical drinking day in rural than in urban areas (Table 6.3).

For individual problem drinking indicators, the highest mean weekly consumption was observed in problem drinkers reporting having shakes when stopping drinking (500g/week), followed by morning drinking, having negative emotions after drinking, and being unable to stop drinking (430-440g/week), with the lowest consumption observed for being unable to work due to drinking (382g/week) (Table 6.4). The prevalence of HED was similar for each problem drinking indicator, while the prevalence of daily drinking was highest in those reporting being unable to stop drinking (87% vs. 66-81% for other indicators). Men who reported having shakes when stopping drinking (82%) or negative emotions after drinking (73%) were most likely to report more than one drinking problem, followed by those who reported being unable to work due to drinking (47%), being unable to stop drinking (37%), and morning drinking (27%).

6.4.3 Cross-sectional associations of stressful life events and problem drinking

Experience of any stressful life events in the past two years was associated with an adjusted OR of 1.24 (95% CI: 1.16-1.33) for past-month problem drinking compared with those who had not experienced stressful life events (Table 6.5). Of the ten stressful life events surveyed, loss of income or debt (OR=1.86 [1.45-2.39]) and experience of violence (1.68 [1.11-2.56]) had the strongest associations with problem

drinking. Family conflict (OR=1.50 [1.22-1.84]), death or major illness of a family member (1.20 [1.10-1.30]), job loss or retirement (1.45 [1.09-1.91]), and bankruptcy (1.48 [1.11-1.96]) were also significantly associated with problem drinking. Other stressful life events such as divorce or separation, death of spouse, major injury or traffic accident, and natural disaster were directionally consistent but were not significantly associated with problem drinking.

6.4.4 Cross-sectional associations of problem drinking with wellbeing and mental health

There were positive associations between the number of problem drinking indicators and poor wellbeing and mental health (Figure 6.6). Compared with low-risk drinkers, current regular drinkers with one problem drinking indicator had 10%-30% higher risks and those with two or more indicators had 40%-60% higher risks for poor self-reported health, life dissatisfaction, and sleep problems. There were about 50%-66% higher risks of having symptoms of depression or anxiety for those with one problem drinking indicator and ~130% higher risks for those with two or more indicators. The associations of problem drinking with MDE and GAD were similar to those with symptoms of depression and anxiety respectively, albeit the ORs were less extreme for MDE. Almost 2-fold higher risk for panic attacks was associated with those reporting two or more problem drinking indicators compared with low-risk drinkers, while no clear associations were observed for phobia. Among problem drinkers, there were significant dose-response relationships of poor wellbeing and mental health with the number of indicators reported (p<0.05 for all except GAD and phobia, Table F2). High-risk drinking was not associated with most measures of wellbeing and mental health

when compared with low-risk drinking, except for a higher likelihood of sleep problems, particularly early-morning awakening (Table F3). Each individual problem drinking indicator was associated with poor wellbeing and mental health when compared with low-risk drinking, with the strongest associations generally observed for having negative emotions due to drinking and having shakes after stopping drinking, each associated with a 3-4 fold higher risk of depression symptoms and an approximately 4-6 fold higher risk of anxiety symptom (Table 6.6). After removing the negative emotions indicator from the definition of problem drinking, the associations between problem drinking and symptoms of depression and anxiety were attenuated but remained significant (Figure F1).

6.4.5 Problem drinking and risks of all-cause mortality and hospitalisations

All-cause mortality was associated with problem drinking, with adjusted HRs of 1.00 (95% CI: 0.94-1.06) for low-risk drinkers, 1.28 (1.21-1.35) for high-risk drinkers, and 1.37 (1.28-1.46) and 1.91 (1.71-2.13) for drinkers with one and with two or more problem drinking indicators, respectively (Figure 6.7). The patterns of associations of problem drinking with incident events due to external causes were broadly similar to those with all-cause mortality. Compared with low-risk drinkers, there was also slightly increased risk for any hospitalisation among high-risk (HR=1.09 [1.06-1.12]) and problem drinkers (1 indicator: 1.07 [1.04-1.11]; 2+ indicators: 1.15 [1.09-1.22]). The risks of all-cause mortality, any hospitalisation, and events due to all external causes increased progressively with the number of problem drinking indicators reported (all $p<0.01$, Table F4). The number of cases of intentional self-harm was small (n=44) but there was a tendency for problem drinking to increase the risk, whereas there was a

non-significant higher risk of transport accidents associated with having two or more problem drinking indicators (Figure 6.8). Among individual problem drinking indicators, the strongest associations were observed for having shakes when stopping drinking, which was associated with 3- to 3.5-fold higher risks of all-cause mortality and events due to external causes compared with low-risk drinkers, followed by 60%-96% higher risks associated with morning drinking and having negative emotions after drinking (Table 6.7).

6.4.6 Subgroup analyses

Divorce was associated with problem drinking among urban but not rural drinkers, while the associations of finance-related events and violence with problem drinking were significant among rural drinkers only (Table 6.8). Across levels of household income, divorce as well as job loss or retirement were significantly associated with problem drinking among men with higher household income, whereas experience of bankruptcy, loss of income or debt, violence, or major injuries were significantly associated with problem drinking among those with lower household income only (Table 6.9).

The associations between problem drinking and poor wellbeing and mental health were consistent in direction across urban and rural areas but were stronger among urban than rural drinkers, except for MDE and anxiety for which the numbers of cases were small among urban drinkers (Figure 6.9). The associations were generally consistent by level of household income, though the association between problem drinking and poor self-reported health appeared to be stronger among those with

higher household income, whereas the association with life dissatisfaction appeared stronger among those with lower household income (Figure 6.10).

The associations between problem drinking and prospective health outcomes were consistent in direction and shape across subgroups defined by study area and household income level, with a slightly stronger relationship among urban drinkers than in rural drinkers especially for any hospitalisation (Figures 6.11-6.12).

6.4.7 Sensitivity analyses

The associations of problem drinking with wellbeing and mental health and prospective health outcomes persisted in sensitivity analyses which defined low-risk and high-risk drinkers based solely on HED (no/yes) or on heavy weekly consumption (< or ≥200g/week) (Figures F2-F3). Among men without any problem drinking indicator, the ORs for depression and anxiety associated with high-risk drinking defined by HED tended to be slightly higher than the ORs associated with high-risk drinking defined by heavy weekly consumption, indicating that HED might potentially be a more harmful drinking pattern than heavy overall consumption in relation to mental health.

The main results from the cross-sectional and prospective analyses persisted after further adjustments for other relevant covariates such as prior chronic disease, physical activity, and prior psychiatric disorder (Tables F5-F7). Sensitivity analyses including all men showed higher risks of poor wellbeing and mental health as well as mortality and hospitalisation among abstainers and ex-regular drinkers (Figures F4-F5), who were older and had higher prevalence of prior chronic disease and psychiatric disorder at baseline (Table F8), compared with low-risk drinkers.

In women where the prevalence of current regular drinking (2%) and problem drinking (0.2% in all women, 10% in current regular drinkers) was much lower than in men, similar correlations of problem drinking with rural residence, lower socio-economic status, and regular smoking were observed as in men (Tables F9-10). Further analyses among female current regular drinkers were limited by small numbers of cases, but statistically significant positive associations were observed between problem drinking and the experience of finance-related events (driven by bankruptcy) and major injury or traffic accidents, as well as life dissatisfaction (Tables F11-F13).

6.5 Discussion

6.5.1 Summary of findings

In this large study of Chinese adults, one in four men who drank alcohol regularly experienced at least one indicator of problem drinking, equating to one in twelve men in the whole CKB study population. Problem drinking was a much more prominent phenomenon in men than in women, due to the low prevalence of female regular drinking. Among male current regular drinkers, problem drinking was more prevalent among those living in rural areas and those with lower socioeconomic status. The prevalence of particular problem drinking indicators varied across age groups and study areas, e.g., morning drinking was more prevalent among older and rural men, whereas being unable to work due to drinking was more common among younger and urban men. The most harmful drinking patterns (highest mean consumption and prevalence of daily drinking and HED) were observed among problem drinkers with two or more indicators. Experience of stressful life events in the past two years,

especially loss of income, was associated with a higher risk of problem drinking, with divorce being associated with problem drinking in urban and higher-income drinkers only and finance-related events and violence being associated with problem drinking in rural and lower-income drinkers only. Problem drinking was associated with increased risks of poor wellbeing and mental health, all-cause mortality, and incident events due to external causes compared with low-risk drinking, and the associations were stronger among urban than rural drinkers. Negative emotions due to drinking and having shakes after stopping drinking had the strongest associations with poor mental health.

6.5.2 Comparison with previous studies

The extremely low prevalence of regular drinking (2%) and problem drinking (0.2%) in women in the CKB suggests that the burden of harmful alcohol use is likely to be highly skewed towards Chinese men. The overall prevalence of problem drinking in men (8%) in the present study is broadly consistent with a previous meta-analysis of 38 cross-sectional studies (most of which focused on a single geographical region) including 1,304,354 individuals conducted during 1987-2013 in China (sample size ranging from 300 to 340,000, aged 15+ years), which reported a prevalence of AUD of 10% in men and 0.1% in women.[267] Furthermore, the prevalence of problem drinking varied greatly across CKB study areas, with a generally higher prevalence in rural than in urban areas, as shown in the previous meta-analysis in China (overall AUD prevalence: 6.1% in rural vs. 5.2% in urban).[267] The rural-urban divide observed in the CKB may have been due to the heavier weekly alcohol consumption in rural drinkers compared with urban drinkers,[87] and was largely driven by the high frequency of morning drinkers (who also tended to drink more than men reporting other problem drinking indicators) in rural

areas. In addition, negative emotions and being unable to work due to drinking were more prevalent in urban and younger men, among whom an increase in the prevalence of problem drinking between baseline and the second resurvey has been reported in Chapter 5.[262] These findings reflect the different contexts of problem drinking across study areas and generations in China, which may be further widened along with the rapid social and economic development in urban Chinese cities. In line with studies in Western countries,[82,83] the prevalence of problem drinking tended to be higher among those with lower socio-economic status in the CKB, while previous evidence from China is inconsistent and the associations vary greatly across different study areas.[257,268-270]

Previous studies of mostly Western populations have reported the associations of stressful life events, particularly financial-related events, e.g., job loss, with alcohol craving and problem drinking.[253,254,271,272] Two studies on the changes in alcohol use patterns during the 2008 economic crisis in European Union countries[273] and in a US sample of 2 million adults[274] showed that the economic crisis was linked with increased rates of alcohol misuse and alcohol-related mortality and hospitalisation, particularly among the unemployed. The present study provides clear evidence that the experience of stressful life events over the past two years, particularly financial stress, is associated with increased likelihood of past-month problem drinking in Chinese men, although these findings are cross-sectional and the directionality of the associations is still unknown.

Although the evidence is rather limited in Chinese populations, previous studies mostly from Western populations have reported the associations of problem drinking with

various measures of poor wellbeing and mental health, including lower life satisfaction, sleep problems, depression, and anxiety.[78-83,245-249,275-277] A previous study of 16,255 adults aged >65 years in China found that poor life satisfaction was related to a higher likelihood of alcohol drinking ($OR_{\text{better vs. poor life satisfaction}}$=0.91 [95% CI: 0.85-0.97] in men), but there was no further investigation into alcohol consumption level or problem drinking.[259] In the present study, among Chinese men, drinking problems were associated with life dissatisfaction as well as other indicators of poor wellbeing and mental health including poor self-rated health, sleep problems, depression, and anxiety. Interestingly, no significant associations with poor wellbeing and mental health were observed for high-risk drinkers without problem drinking indicators, who had similar a mean consumption to those reporting one problem drinking indicator. This could be due to reverse causation or report bias (e.g., those who had poor mental health might have attributed social or mood problems to alcohol consumption) because of the cross-sectional nature of the analyses. However, it should not be the main cause driving the null associations for high-risk drinkers, as sensitivity analyses have shown persistent associations after removing the negative emotions indicator from the definition of problem drinking. An alternative possibility is that problem drinkers may be more likely to underreport alcohol consumption than other drinkers.[278] Hence, it is possible that the higher ORs of poor mental health in men reporting one problem drinking indicator than the ORs in high-risk drinkers might partly be related to the potentially underreported alcohol consumption and harmful drinking patterns of the former. Nevertheless, the results in the CKB are in line with a recent study in the Netherlands on 6,705 adults, in which lower life satisfaction was associated with alcohol-related problems but not amount of alcohol consumed,

particularly in men.[249] A large genome-wide association analyses meta-analysis of Alcohol Use Disorder Identification Test (AUDIT) score using the UKB cohort (n=121,604) and 23andMe cohort (n=20,328) of European ancestry has also shown that alcohol dependence and major depression are significantly genetically correlated with AUDIT-P score which is related to the problematic consequences of drinking, but are only modestly (for alcohol dependence) and negatively (for major depression) correlated with AUDIT-C score which is related to the amount of alcohol consumption.[279] Therefore, the present study suggests that the relationships between problem drinking and poor wellbeing and mental health may not be due solely to the total amount of alcohol consumed per se, but to the negative consequences (e.g., feeling of guilt, interference with personal social life and health due to alcohol drinking) of, or the genetic predisposition to, problem drinking and potentially HED patterns.[249,279] One exception may be sleep problems, for which evidence from clinical studies suggest that the quantity of alcohol consumption may have a direct physiological role on underlying sleep quality and disturbed sleep.[245] In line with clinical studies, the present study shows an increased likelihood of early-morning awakening in high-risk drinkers compared with low-risk drinkers.

The associations between problem drinking and depression and anxiety disorders have been established previously among Western populations, in both cross-sectional and prospective studies,[78-83,280-282] while in China the evidence is still limited. Previous meta-analyses involving mostly Western populations reported an OR of 2.00 (1.19-3.35) for depression associated with AUD based on both cross-sectional and longitudinal data (15 studies),[78] and an RR of 1.57 (1.41-1.76) for subsequent

depressive symptoms associated with AUD based on cohort studies only (42 studies, 338,426 participants).[282] Regarding alcohol intake, however, there were no clear associations between heavy drinking and depression after adjusting for potential confounders.[282] Epidemiological surveys in Western populations also reported increased ORs between 1.3-2.6 for any anxiety disorder (including GAD and panic disorders but with mixed evidence for phobia) associated with AUD.[79,80,82,83] In China, a recent study of 74,752 men combining surveys from five provinces reported inverse associations of current AUD with mood disorders (OR=0.6 [0.4-0.8]) and anxiety disorders (0.5 [0.3-1.0]), but with limited adjustment for age only.[260] In contrast, the present study covering ten diverse study areas provides strong evidence of the associations between problem drinking and higher risks of depression and anxiety among Chinese male regular drinkers. Apart from the differences in study areas and covariate adjustments, the contrasting results between these two existing largest Chinese studies may be explained by methodological issues. First, the exclusion of substance-induced mental disorder events in the previous study might have attenuated the cross-sectional relationships between problem drinking and mental disorders. Furthermore, unlike the previous study, the present study excluded non-drinkers, some of whom may be “sick-quitters” or “sick non-starters” and thus may have poorer mental health due to reverse causation and residual confounding, as suggested in the sensitivity analyses and a previous study.[283] A cross-sectional study of 38,930 participants in Norway reported U-shaped associations between alcohol consumption and risks of anxiety and depression, noting that the increased risks in self-labelled abstainers may be explained partly by somatic illness, social marginalisation, and sick-quitting.[283] Another study of 15,628 participants in China

reported an inverse association between baseline alcohol drinking (current vs. never) and subsequent depression symptoms (OR=0.6 [0.5-0.7]).[261] However, with further investigation among drinkers, there was a suggestive increased risk of persistent depressive symptoms associated with alcohol withdrawal (2.2 [0.9-5.5]). This suggests that the relationships between problem drinking and mental health problems might only become apparent when investigated among regular drinkers, where potential reverse causation and residual confounding by "sick-quitters/sick non-starters" is avoided.

In addition, the present study also shows that negative emotions after drinking and having shakes when stopping drinking are most strongly associated with poor mental health, which may be due to the higher severity of problem drinking (e.g., number of other problem drinking indicators, having shakes as a withdrawal symptom for alcohol dependence) involved, as well as the direct impact on mental health and personal life due to the severity and nature of these indicators (e.g., negative emotions due to drinking).

For long-term health outcomes, findings in the present study are generally similar to those from previous studies worldwide,[250,251,284-286] mostly based on Western populations. A meta-analysis of 81 observational studies with 221,683 deaths reported an RR for all-cause mortality of 1.91 (95% CI: 1.51-2.42) comparing men with and without AUD,[250] while another meta-analysis of 31 studies (9 cohort studies, 10 case-control studies, 12 cross-sectional studies) reported 2 to 3-fold higher risks for suicidal ideation, suicide attempts, and completed suicide associated with AUD.[251] As well as having shakes when stopping drinking and negative emotions after drinking, morning

drinking was also strongly associated with all-cause mortality in the present study, which was likely due to the high levels of alcohol consumption among morning drinkers. In this study, the excess risk of any hospitalisation associated with problem drinking was modest, possibly diluted by non-alcohol-related conditions.

The present study also suggests that the associations of problem drinking with the experience of stressful life events and poor mental health might vary by rural-urban areas and socio-economic status, although statistical power to assess subgroups is limited. The regional differences observed in the CKB suggest that there may be contextual factors influencing the relationships between stress and problem drinking. For example, the relationships between divorce and problem drinking were more apparent in urban and higher-income drinkers, among whom divorce was more common than in rural contexts, while the links between problem drinking and financial stress and major injuries among rural and low-income drinkers might be related to the lack of financial, social, healthcare, and post-trauma support in these more deprived groups. The present study also suggests that the associations of problem drinking with poor wellbeing and mental health are more pronounced among urban problem drinkers. These findings might be due to the specific problem drinking indicators more commonly experienced by urban problem drinkers (e.g., “negative emotions after drinking” which is a severe indicator, “being unable to work due to drinking” which might be particularly relatable to urban working population) and the potential exacerbation by the stressful environment in urban settings.

6.5.3 Mechanisms

Several primary possible mechanisms have been proposed to explain the direction and pathways linking problem drinking and poor mental health, including: (1) the self-medication theory that people use alcohol to cope with mental health problems (i.e., mental illness causes problem drinking); (2) the substance-induced pathway that problem drinking leads to mental illness via neurophysiological and/or psychosocial impacts; (3) a reciprocal causal relationship that problem drinking and mental illness increases the risk of the other simultaneously; or (4) causation by a common factor that the co-occurrence of problem drinking and mental illness is explained by a third factor, such as genetic factors, personality traits (e.g., anxiety sensitivity), and social and environmental factors.[78,280] Similarly, for sleep problems, as low-dose alcohol consumption may at first help sleep initiation, alcohol may be used by insomniacs as a self-medication. In the long term, however, tolerance develops rapidly along with prolonged use, and high alcohol consumption disturbs sleep.[245] For health outcomes, the excess overall mortality risk may arise from the direct effects of alcohol misuse (e.g., high levels of intake, frequency of intoxication) and possible genetic predisposition to both problem drinking and adverse health outcomes (e.g., impulsive personality).[285]

6.5.4 Strengths and limitations

The chief strengths of the CKB study (large and diverse study population, detailed data collection) have been described in Chapter 5. Nevertheless, the present study has several limitations. First, the CKB was not designed to be nationally representative and,

given the overall response rate of ~30%, the present study may have underestimated the prevalence of problem drinking as individuals with severe problem drinking may have been less likely to participate. However, the associations of problem drinking with stressful life events, wellbeing and mental health, and risks of mortality and hospitalisations are likely to be generalisable to the general population given the large size and diversity of the CKB. Second, the low prevalence of regular drinking and problem drinking among women precluded reliable exploration of associations in women. Third, full clinical diagnostic standard assessment for AUD (i.e., Diagnostic and Statistical Manual of Mental Disorder, 5th Edition) was not used. Nevertheless, the construct of alcohol-related problems used in the assessment in this study was comparable to the major domains of AUD diagnostic criteria (Table F14). Also, the heavy drinking patterns of problem drinkers and the similar prevalence of problem drinking reported here as in previous meta-analysis on AUD prevalence in China[267] suggests that the problem drinking assessment in this study is of good quality. Fourth, the temporal order and causal relationships between problem drinking, stressful life events and mental health could not be established due to the cross-sectional nature of these analyses, and detailed exploration of this is beyond the scope of this study. Lastly, although careful adjustment was made for potential confounders, uncontrolled residual confounding (e.g., parental history of alcohol misuse) might remain.

6.6 Conclusions

In summary, problem drinking was common among Chinese adult men, especially those with lower socio-economic status, with different prevalence and types of alcohol-use problems exhibited across geographical areas. Problem drinking was

associated with stressful life events, particularly financial-related events, poor mental health, and excess risks of overall mortality and hospitalisations, particularly events due to external causes including accidents, injury, and violence.

Table 6.1. Baseline characteristics of male current regular drinkers by problem drinking status

	All current regular	Non-problem drinkers		Problem drinkers	
		Low-risk	High-risk	1 indicator	2+ indicators
Number of men (%)	69904	25958 (37.1)	27254 (39.0)	13271 (19.0)	3421 (4.9)
Socio-demographic characteristics					
Mean age, years (SD)	51.1 (10.2)	51.7 (10.7)	50.2 (9.8)	51.8 (10.1)	50.9 (9.8)
Age group, years %					
<40	14.1	14.7	15.4	12.4	14.7
40-49	32.4	31.2	35.2	31.2	33.2
50-59	31.6	29.8	31.4	33.0	34.6
60-69	16.3	17.6	14.0	17.6	14.2
70+	5.5	6.8	4.0	5.7	3.2
Urban area, %	50.1	61.3	51.9	30.5	24.0
Highest education, %					
Primary or below	39.7	36.9	40.0	42.3	42.5
Middle or high school	52.2	53.6	51.9	51.8	53.4
Technical school, college/university	8.1	9.5	8.1	5.9	4.1
Household income, yuan/year %					
<20,000	48.5	47.3	47.2	52.5	53.2
20,000-34,999	28.0	28.0	28.1	26.8	28.1
35,000+	23.5	24.6	24.7	20.6	18.7
Married, %	93.8	94.8	93.9	92.6	91.1
Lifestyle & physical measurements					
Regular smoking, %	71.3	64.9	74.1	76.2	79.0
Mean physical activity, MET-h/d (SD)	22.9 (15.0)	22.9 (14.8)	22.8 (14.9)	23.1 (15.2)	23.4 (15.7)
Mean SBP, mmHg (SD)	134.2 (19.8)	131.8 (19.1)	135.7 (19.7)	135.3 (20.6)	136.7 (20.9)
Mean BMI, kg/m^2 (SD)	23.7 (3.2)	23.6 (3.2)	23.9 (3.3)	23.5 (3.2)	23.3 (3.1)
Self-reported medical history, %					
Coronary heart disease	1.9	2.0	1.7	1.9	3.0
Stroke or TIA	1.3	1.3	1.2	1.4	2.4
Cancer	0.2	0.3	0.2	0.2	0.2
Cirrhosis or chronic hepatitis	1.2	1.2	1.1	1.4	1.4
Diabetes	2.0	2.1	2.0	1.8	2.5
Psychiatric disorder	0.2	0.1	0.1	0.2	0.4

SD, standard deviation; MET-h/d, metabolic equivalent of task per hour per day; SBP, systolic blood pressure; BMI, body mass index; TIA, transient ischaemic attack; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between problem drinking and baseline characteristics: $p<0.05$ for most variables except prior stroke or TIA ($p=0.06$), cancer, diabetes, and psychiatric disorder (all $p>0.15$).

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

Table 6.2. Drinking characteristics of male current regular drinkers by problem drinking status

	Low-risk drinkers	High-risk drinkers	Problem drinkers with 1 indicator	Problem drinkers with 2+ indicators
Number of men	25958	27254	13271	3421
Drinking characteristics				
Drank alcohol on the day of survey, %	10.7	17.5	28.5	33.7
Daily drinking, %	35.9	74.5	76.8	83.7
Age started regular drinking, mean (SD)	30.8 (12.2)	27.5 (9.5)	27.5 (10.7)	26.1 (9.4)
Drinking outside meals, %	13.0	13.6	15.0	16.5
Flushing response, %	25.5	13.8	15.6	13.8
Typical drinking week				
Mean consumption, g/week (SD)	109.2 (56.5)	378.4 (209.1)	383.4 (277.6)	506.5 (344.4)
HED, %	0.0	60.8	48.4	61.0
Heavy drinking (200+g/week), %	0.0	88.0	69.8	80.7
HED and heavy drinking, %	0.0	48.8	45.3	58.4
Beverage types consumed, %				
Strong spirits (≥40% alcohol) only	34.8	56.4	51.8	55.7
Weak spirits (<40% alcohol) only	21.1	24.1	24.0	23.8
Beer only	27.2	12.3	12.6	10.6
Rice wine or grape wine only	16.8	7.1	11.5	9.9
Special occasions				
Mean consumption, g/occasion (SD)	106.4 (86.3)	169.2 (111.0)	168.3 (112.0)	203.5 (134.4)
HED, %	69.4	93.5	89.2	94.2
Last drinking day				
Mean consumption, g/session (SD)	32.0 (26.7)	61.0 (41.8)	57.6 (40.1)	67.0 (47.5)
HED, %	11.4	41.3	38.4	46.0

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area.

Associations between problem drinking and drinking characteristics: $p<0.001$ for all variables.

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

Table 6.3. Drinking characteristics of male current regular drinkers by problem drinking status, in rural and urban areas

	Rural				Urban			
	Low-risk drinkers	High-risk drinkers	Problem drinkers with 1 indicator	Problem drinkers with 2+ indicators	Low-risk drinkers	High-risk drinkers	Problem drinkers with 1 indicator	Problem drinkers with 2+ indicators
Number of men	10023	13019	9239	2600	15935	14235	4032	821
Drinking characteristics								
Drank alcohol on the day of survey, %	15.0	24.7	37.9	45.1	6.5	11.6	19.3	25.7
Daily drinking, %	32.5	75.5	78.1	84.3	39.3	76.1	75.8	83.9
Age started regular drinking, mean (SD)	30.7 (12.4)	27.0 (10.1)	26.4 (10.5)	25.2 (9.4)	31.7 (12.0)	27.4 (8.9)	28.9 (10.8)	27.1 (9.0)
Drinking outside meals, %	19.0	14.4	18.7	19.3	10.1	11.6	11.3	12.7
Flushing response, %	26.6	17.2	16.2	15.7	21.0	12.1	13.1	12.9
Typical drinking week								
Mean consumption, g/week (SD)	99.1 (56.6)	402.1 (218.5)	426.8 (288.8)	558.7 (348.6)	98.7 (56.4)	367.2 (198.6)	303.0 (227.4)	394.9 (298.8)
HED, %	0.0	66.9	57.7	72.6	0.0	56.1	36.1	51.1
Heavy drinking (200+g/week), %	0.0	88.2	74.9	86.4	0.0	89.2	63.1	75.7
HED and heavy drinking, %	0.0	55.2	54.3	69.4	0.0	45.3	33.8	49.6
Beverage types consumed, %								
Strong spirits (≥40% alcohol) only	45.2	70.6	64.8	68.6	17.3	44.6	42.9	52.1
Weak spirits (<40% alcohol) only	28.4	23.6	25.8	23.9	19.2	22.3	15.6	14.1
Beer only	15.4	2.3	3.4	2.3	39.4	21.3	25.2	22.7
Rice wine or grape wine only	11.0	3.5	6.0	5.2	24.0	11.8	16.2	11.1
Special occasions								
Mean intake, g/occasion (SD)	108.4 (90.4)	169.0 (113.4)	166.0 (113.2)	202.9 (136.3)	107.2 (83.5)	173.1 (108.7)	155.7 (109.0)	190.9 (127.8)
HED, %	67.9	93.6	90.6	94.5	70.2	93.8	85.4	92.2
Last drinking day								
Mean intake, g/session (SD)	30.6 (22.1)	55.6 (35.6)	54.5 (37.7)	62.2 (44.3)	34.6 (29.1)	66.4 (46.1)	58.2 (45.1)	72.3 (55.9)
HED, %	8.5	36.6	34.3	41.3	14.5	45.9	40.8	51.7

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age.

Associations between problem drinking categories and drinking characteristic variables: $p<0.0001$ across all variables.

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

Table 6.4. Drinking characteristics of male problem drinkers reporting specific problem drinking indicators

	Unable to work	Negative emotions	Unable to stop	Had shakes	Morning drinking
Number of men	2428	1102	7796	281	9171
Drinking characteristics					
Drank alcohol on the day of survey, %	22.5	28.0	26.3	32.7	41.2
Daily drinking, %	66.1	71.9	86.6	78.4	81.4
Age started regular drinking, mean (SD)	27.2 (9.4)	26.6 (9.0)	26.7 (9.5)	27.3 (10.4)	27.3 (11.2)
Drinking outside meals, %	14.6	14.9	14.1	17.8	19.9
Flushing response, %	16.4	17.9	14.9	14.7	14.4
Reporting 2+ problem drinking indicators, %	47.1	73.2	36.8	81.9	26.8
Typical drinking week					
Mean consumption, g/week (SD)	381.6 (304.7)	437.7 (345.8)	428.2 (285.1)	499.8 (411.8)	440.9 (334.7)
HED, %	52.4	56.1	53.7	54.8	55.4
Heavy drinking (200+g/week), %	65.2	72.2	79.1	70.9	74.8
HED and heavy drinking, %	46.5	52.5	52.5	52.7	53.3
Beverage types consumed, %					
Strong spirits (≥40% alcohol) only	49.3	50.6	56.3	53.9	55.6
Weak spirits (<40% alcohol) only	23.0	23.8	23.1	20.1	24.6
Beer only	15.3	15.4	11.0	13.0	8.9
Rice wine or grape wine only	12.4	10.1	9.6	13.0	11.0
Special occasion					
Mean consumption, g/occasion (SD)	200.8 (141.5)	212.1 (146.9)	180.4 (117.6)	198.9 (135.7)	171.9 (111.7)
HED, %	91.6	92.2	93.0	88.1	88.8
Last drinking day					
Mean consumption, g/session (SD)	70.1 (54.0)	72.9 (56.6)	59.4 (39.1)	69.1 (53.5)	58.0 (40.5)
HED, %	45.0	47.0	41.3	47.9	41.4

SD, standard deviation; HED, heavy episodic drinking.
Prevalences and means are adjusted for age and study area.
The problem drinking indicators are not mutually exclusive.

Table 6.5. Cross-sectional associations of stressful life events with problem drinking, in male current regular drinkers

	Total regular drinkers N	Problem drinkers* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value
Family-related events				
Divorce or separation				
No	69701	16639 (23.9%)	1.00	
Yes	203	53 (26.1%)	1.32 (0.95-1.83)	*0.1027*
Family conflict				
No	69417	16540 (23.8%)	1.00	
Yes	487	152 (31.2%)	1.50 (1.22-1.84)	*0.0001*
Death of spouse				
No	69550	16596 (23.9%)	1.00	
Yes	354	96 (27.1%)	1.07 (0.83-1.36)	*0.6133*
Death or major illness of other family member				
No	66680	15871 (23.8%)	1.00	
Yes	3224	821 (25.5%)	1.20 (1.10-1.30)	*<0.0001*
Any family-related event				
No	65748	15606 (23.7%)	1.00	
Yes	4156	1086 (26.1%)	1.21 (1.13-1.31)	*<0.0001*
Finance-related events				
Job loss or retirement				
No	69587	16622 (23.8%)	1.00	
Yes	317	70 (22.1%)	1.45 (1.09-1.91)	*0.0102*
Bankruptcy				
No	69683	16608 (23.8%)	1.00	
Yes	221	84 (38.0%)	1.48 (1.11-1.96)	*0.0068*
Loss of income or debt				
No	69592	16577 (23.8%)	1.00	
Yes	312	115 (36.9%)	1.86 (1.45-2.39)	*<0.0001*
Any finance-related event				
No	69099	16441 (23.8%)	1.00	
Yes	805	251 (31.1%)	1.57 (1.34-1.84)	*<0.0001*
Injury-related events				
Violence				
No	69796	16653 (23.9%)	1.00	
Yes	108	39 (36.1%)	1.68 (1.11-2.56)	*0.0149*
Major injury or traffic accident				
No	69403	16566 (23.9%)	1.00	
Yes	501	126 (25.1%)	1.15 (0.93-1.43)	*0.1929*
Natural disaster				
No	69848	16679 (23.9%)	1.00	
Yes	56	13 (23.2%)	1.05 (0.54-2.02)	*0.8869*
Any injury or disaster event				
No	69244	16516 (23.9%)	1.00	
Yes	660	176 (26.7%)	1.22 (1.01-1.47)	*0.0347*
Any major stressful life event				
No	64509	15266 (23.7%)	1.00	
Yes	5395	1426 (26.4%)	1.24 (1.16-1.33)	*<0.0001*

OR, odds ratio; CI, confidence interval.

ORs are adjusted for age group, study area, education, income, and smoking.

*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 6.6. Cross-sectional associations of problem drinking indicators with poor wellbeing and mental health, in male current regular drinkers

	Morning drinking			Unable to stop			Unable to work			Negative emotions			Having shakes		
	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)
Poor self-reported health															
Low-risk drinkers	24478	1480	1.00 (0.94-1.06)	24478	1480	1.00 (0.94-1.06)	24478	1480	1.00 (0.94-1.06)	24478	1480	1.00 (0.94-1.06)	24478	1480	1.00 (0.94-1.06)
High-risk drinkers	25651	1603	0.97 (0.92-1.02)	25651	1603	0.97 (0.92-1.02)	25651	1603	0.97 (0.92-1.02)	25651	1603	0.97 (0.92-1.02)	25651	1603	0.97 (0.92-1.02)
Specified indicator*	8540	631	1.14 (1.05-1.25)	7085	711	1.21 (1.11-1.31)	2173	255	1.63 (1.42-1.86)	965	137	1.78 (1.47-2.14)	247	34	1.87 (1.29-2.71)
Other indicator(s)†	6839	682	1.22 (1.12-1.33)	8294	602	1.16 (1.06-1.27)	13206	1058	1.10 (1.03-1.18)	14414	1176	1.14 (1.06-1.21)	15132	1279	1.17 (1.10-1.25)
			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001
Life dissatisfaction															
Low-risk drinkers	24821	1137	1.00 (0.94-1.07)	24821	1137	1.00 (0.94-1.07)	24821	1137	1.00 (0.94-1.06)	24821	1137	1.00 (0.94-1.07)	24821	1137	1.00 (0.94-1.06)
High-risk drinkers	26118	1136	1.00 (0.94-1.07)	26118	1136	1.00 (0.94-1.07)	26118	1136	1.00 (0.94-1.06)	26118	1136	1.00 (0.94-1.07)	26118	1136	1.00 (0.94-1.07)
Specified indicator*	8827	344	1.24 (1.10-1.40)	7446	350	1.30 (1.15-1.46)	2248	180	1.54 (1.31-1.82)	1002	100	1.85 (1.49-2.30)	256	25	2.20 (1.42-3.42)
Other indicator(s)†	7117	404	1.34 (1.20-1.49)	8498	398	1.29 (1.16-1.44)	13696	568	1.23 (1.12-1.35)	14942	648	1.23 (1.13-1.35)	15688	723	1.28 (1.17-1.38)
			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001
Sleep problems‡															
Low-risk drinkers	22803	3155	1.00 (0.96-1.04)	22803	3155	1.00 (0.96-1.04)	22803	3155	1.00 (0.96-1.04)	22803	3155	1.00 (0.96-1.04)	22803	3155	1.00 (0.96-1.04)
High-risk drinkers	23751	3503	1.08 (1.04-1.12)	23751	3503	1.08 (1.04-1.12)	23751	3503	1.08 (1.04-1.12)	23751	3503	1.08 (1.04-1.12)	23751	3503	1.08 (1.04-1.12)
Specified indicator*	7594	1577	1.24 (1.17-1.32)	6409	1387	1.31 (1.23-1.39)	1942	486	1.67 (1.51-1.85)	849	253	1.98 (1.72-2.29)	215	66	1.96 (1.48-2.60)
Other indicator(s)†	6133	1388	1.44 (1.36-1.53)	7318	1578	1.36 (1.28-1.44)	11785	2479	1.27 (1.22-1.34)	12878	2712	1.29 (1.23-1.35)	13512	2899	1.32 (1.27-1.38)
			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001
Depression symptoms§															
Low-risk drinkers	25496	462	1.00 (0.91-1.10)	25496	462	1.00 (0.91-1.10)	25496	462	1.00 (0.91-1.10)	25496	462	1.00 (0.91-1.10)	25496	462	1.00 (0.91-1.10)
High-risk drinkers	26774	480	0.95 (0.87-1.04)	26774	480	0.95 (0.87-1.04)	26774	480	0.95 (0.87-1.04)	26774	480	0.95 (0.87-1.04)	26774	480	0.95 (0.87-1.04)
Specified indicator*	8899	272	1.43 (1.25-1.63)	7527	269	1.73 (1.52-1.97)	2289	139	2.38 (1.99-2.84)	1003	99	3.74 (3.01-4.63)	261	20	3.24 (2.04-5.16)
Other indicator(s)†	7222	299	1.91 (1.69-2.15)	8594	302	1.60 (1.42-1.81)	13832	432	1.49 (1.35-1.66)	15118	472	1.47 (1.33-1.62)	15860	551	1.63 (1.49-1.79)
			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001			p_{het} <0.0001
Major depressive episode¶															
Low-risk drinkers	25865	93	1.00 (0.81-1.24)	25865	93	1.00 (0.81-1.24)	25865	93	1.00 (0.81-1.24)	25865	93	1.00 (0.81-1.24)	25865	93	1.00 (0.81-1.24)
High-risk drinkers	27165	89	0.90 (0.73-1.10)	27165	89	0.90 (0.73-1.11)	27165	89	0.90 (0.73-1.10)	27165	89	0.89 (0.73-1.10)	27165	89	0.90 (0.73-1.11)
Specified indicator*	9123	48	1.18 (0.86-1.61)	7754	42	1.31 (0.95-1.81)	2409	19	1.52 (0.95-2.41)	1084	18	3.05 (1.88-4.93)	279	2	1.41 (0.35-5.71)
Other indicator(s)†	7478	43	1.32 (0.97-1.80)	8847	49	1.19 (0.89-1.60)	14192	72	1.18 (0.92-1.52)	15517	73	1.07 (0.84-1.37)	16322	89	1.24 (1.00-1.55)
			p_{het} = 0.1778			p_{het} = 0.1797			p_{het} = 0.1302			p_{het} <0.0001			p_{het} = 0.1943

	Morning drinking			Unable to stop			Unable to work			Negative emotions			Having shakes		
	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)	Non-cases N	Cases N	OR (95% CI)
Anxiety symptom															
Low-risk drinkers	25883	75	1.00 (0.79-1.27)	25883	75	1.00 (0.79-1.27)	25883	75	1.00 (0.79-1.27)	25883	75	1.00 (0.79-1.27)	25883	75	1.00 (0.79-1.27)
High-risk drinkers	27156	98	0.99 (0.81-1.21)	27156	98	0.99 (0.81-1.21)	27156	98	0.99 (0.81-1.20)	27156	98	0.98 (0.81-1.20)	27156	98	0.99 (0.81-1.20)
Specified indicator*	9123	48	1.75 (1.29-2.38)	7742	54	1.72 (1.29-2.29)	2402	26	2.01 (1.35-3.00)	1079	23	3.83 (2.50-5.87)	274	7	5.98 (2.79-12.82)
Other indicator(s)†	7458	63	1.88 (1.45-2.43)	8839	57	1.92 (1.46-2.53)	14179	85	1.77 (1.39-2.24)	15502	88	1.58 (1.26-1.98)	16307	104	1.74 (1.41-2.14)
			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*
General anxiety disorder#															
Low-risk drinkers	25931	27	1.00 (0.67-1.48)	25931	27	1.00 (0.67-1.48)	25931	27	1.00 (0.67-1.48)	25931	27	1.00 (0.67-1.48)	25931	27	1.00 (0.67-1.48)
High-risk drinkers	27220	34	0.96 (0.69-1.35)	27220	34	0.96 (0.68-1.34)	27220	34	0.96 (0.69-1.34)	27220	34	0.96 (0.68-1.34)	27220	34	0.96 (0.69-1.34)
Specified indicator*	9149	22	1.83 (1.16-2.88)	7774	22	1.73 (1.11-2.70)	2416	12	2.60 (1.45-4.67)	1093	9	4.03 (2.05-7.92)	279	2	3.99 (0.98-16.29)
Other indicator(s)†	7494	27	2.11 (1.42-3.12)	8869	27	2.22 (1.49-3.30)	14227	37	1.81 (1.27-2.58)	15550	40	1.75 (1.25-2.44)	16364	47	1.94 (1.42-2.64)
			p_{het} *= 0.0052*			p_{het} *= 0.0040*			p_{het} *= 0.0034*			p_{het} *= 0.0003*			p_{het} *= 0.0035*
Panic attacks															
Low-risk drinkers	25805	153	1.00 (0.84-1.18)	25805	153	1.00 (0.84-1.18)	25805	153	1.00 (0.85-1.18)	25805	153	1.00 (0.85-1.18)	25805	153	1.00 (0.85-1.18)
High-risk drinkers	27038	216	1.02 (0.89-1.17)	27038	216	1.02 (0.89-1.16)	27038	216	1.01 (0.89-1.16)	27038	216	1.01 (0.89-1.16)	27038	216	1.02 (0.89-1.16)
Specified indicator*	9109	62	1.11 (0.86-1.44)	7710	86	1.13 (0.90-1.41)	2381	47	1.90 (1.41-2.56)	1065	37	3.17 (2.26-4.45)	267	14	5.90 (3.38-10.28)
Other indicator(s)†	7417	104	1.36 (1.12-1.66)	8816	80	1.42 (1.13-1.78)	14145	119	1.09 (0.90-1.32)	15461	129	1.05 (0.88-1.27)	16259	152	1.17 (0.99-1.39)
			p_{het} *= 0.0804*			p_{het} *= 0.0604*			p_{het} *= 0.0015*			p_{het} *<0.0001*			p_{het} *<0.0001*
Phobia															
Low-risk drinkers	25875	83	1.00 (0.80-1.26)	25875	83	1.00 (0.80-1.26)	25875	83	1.00 (0.80-1.25)	25875	83	1.00 (0.80-1.26)	25875	83	1.00 (0.80-1.26)
High-risk drinkers	27159	95	0.95 (0.77-1.16)	27159	95	0.94 (0.77-1.15)	27159	95	0.94 (0.77-1.15)	27159	95	0.95 (0.77-1.16)	27159	95	0.95 (0.77-1.16)
Specified indicator*	9139	32	1.09 (0.76-1.56)	7760	36	0.93 (0.67-1.31)	2402	26	1.79 (1.20-2.67)	1089	13	1.88 (1.08-3.29)	279	2	1.54 (0.38-6.26)
Other indicator(s)†	7467	54	1.34 (1.02-1.77)	8846	50	1.58 (1.19-2.10)	14204	60	1.07 (0.82-1.41)	15517	73	1.16 (0.91-1.48)	16327	84	1.23 (0.99-1.54)
			p_{het} *= 0.2299*			p_{het} *= 0.0225*			p_{het} *= 0.0409*			p_{het} *= 0.1073*			p_{het} *= 0.3284*

OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking; CIDI-SF, composite international diagnostic interview - short form.

ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index.

P_{het} for heterogeneity across the four problem drinking categories.

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported.

*Reporting the problem drinking indicator specified in the column heading.

†Reporting any problem drinking indicator(s) except the indicator specified in the column heading.

‡Reporting one or more of the following for ≥3 days each week in the past month: delayed or fitful sleep; waking up too early; needing medicine to help sleep; having difficulty staying alert during daytime.

§Reporting one or more of the following for ≥2 weeks in the past 12 months: feeling sad or depressed; loss of interest; loss of appetite; feeling worthless.

¶Assessed by the CIDI-SF (A).

#Assessed by the CIDI-SF (B).

Table 6.7. Prospective associations of problem drinking indicators with all-cause mortality, any hospitalisation and events due to external causes, in male current regular drinkers

	Morning drinking			Unable to stop			Unable to work			Negative emotions			Having shakes		
	Non-cases N	Cases N	HR (95% CI)	Non-cases N	Cases N	HR (95% CI)	Non-cases N	Cases N	HR (95% CI)	Non-cases N	Cases N	HR (95% CI)	Non-cases N	Cases N	HR (95% CI)
All-cause mortality															
Low-risk drinkers	19368	1277	1.00 (0.94-1.06)	19368	1277	1.00 (0.94-1.06)	19368	1277	1.00 (0.94-1.06)	19368	1277	1.00 (0.94-1.06)	19368	1277	1.00 (0.94-1.06)
High-risk drinkers	21262	1610	1.26 (1.20-1.33)	21262	1610	1.27 (1.21-1.34)	21262	1610	1.27 (1.21-1.34)	21262	1610	1.27 (1.21-1.34)	21262	1610	1.27 (1.21-1.34)
Specified indicator*	6642	986	1.68 (1.57-1.80)	5635	622	1.42 (1.31-1.55)	1880	122	1.41 (1.18-1.69)	806	60	1.59 (1.23-2.05)	187	41	3.17 (2.33-4.31)
Other indicator(s)†	5606	415	1.13 (1.02-1.24)	6613	779	1.50 (1.39-1.61)	10368	1279	1.47 (1.39-1.56)	11442	1341	1.46 (1.38-1.54)	12061	1360	1.44 (1.36-1.52)
			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*
Any hospitalisation															
Low-risk drinkers	10664	9981	1.00 (0.98-1.02)	10664	9981	1.00 (0.98-1.02)	10664	9981	1.00 (0.98-1.02)	10664	9981	1.00 (0.98-1.02)	10664	9981	1.00 (0.98-1.02)
High-risk drinkers	11566	11306	1.09 (1.07-1.11)	11566	11306	1.09 (1.07-1.11)	11566	11306	1.09 (1.07-1.11)	11566	11306	1.09 (1.07-1.11)	11566	11306	1.09 (1.07-1.11)
Specified indicator*	2717	4911	1.09 (1.06-1.12)	2635	3622	1.12 (1.08-1.16)	1081	921	1.11 (1.04-1.19)	475	391	1.03 (0.93-1.14)	99	129	1.29 (1.08-1.53)
Other indicator(s)†	2915	3106	1.08 (1.05-1.12)	2997	4395	1.06 (1.03-1.10)	4551	7096	1.08 (1.06-1.11)	5157	7626	1.09 (1.06-1.12)	5533	7888	1.08 (1.06-1.11)
			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*			p_{het} *<0.0001*
External causes (ICD -10: V01-Y98)‡															
Low-risk drinkers	20530	115	1.00 (0.83-1.21)	20530	115	1.00 (0.83-1.21)	20530	115	1.00 (0.83-1.21)	20530	115	1.00 (0.83-1.21)	20530	115	1.00 (0.83-1.21)
High-risk drinkers	22708	164	1.15 (0.98-1.34)	22708	164	1.16 (0.99-1.36)	22708	164	1.16 (0.99-1.35)	22708	164	1.16 (0.99-1.35)	22708	164	1.16 (0.99-1.35)
Specified indicator*	7518	110	1.63 (1.33-2.00)	6184	73	1.50 (1.18-1.91)	1988	14	0.97 (0.57-1.66)	854	12	1.96 (1.10-3.47)	222	6	3.52 (1.57-7.87)
Other indicator(s)†	5978	43	0.97 (0.71-1.32)	7312	80	1.27 (1.01-1.59)	11508	139	1.43 (1.20-1.71)	12642	141	1.33 (1.11-1.58)	13274	147	1.33 (1.12-1.57)
			p_{het} *= 0.0024*			p_{het} *= 0.0710*			p_{het} *= 0.0476*			p_{het} *= 0.0537*			p_{het} *= 0.0077*

HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake and body mass index.

P_{het} for heterogeneity across the four problem drinking categories.

Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses.

Low-risk drinkers were regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported.

*Reporting the problem drinking indicator specified in the column heading.

†Reporting any problem drinking indicator(s) except the indicator specified in the column heading.

‡Deaths and hospitalisations combined.

Table 6.8. Cross-sectional associations of stressful life events with problem drinking, by rural and urban areas in male current regular drinkers

	Rural				Urban			
	Total regular drinkers N	Problem drinkers* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value	Total regular drinker N	Problem drinkers* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value
Family-related events								
Divorce or separation								
No	34818	11820 (33.9%)	1.00		34883	4819 (13.8%)	1.00	
Yes	63	19 (30.2%)	0.85 (0.49-1.46)	*0.5544*	140	34 (24.3%)	1.65 (1.10-2.48)	*0.0163*
Family conflict								
No	34628	11739 (33.9%)	1.00		34789	4801 (13.8%)	1.00	
Yes	253	100 (39.5%)	1.32 (1.02-1.71)	*0.0320*	234	52 (22.2%)	1.86 (1.34-2.59)	*0.0002*
Death of spouse								
No	34690	11768 (33.9%)	1.00		34860	4828 (13.8%)	1.00	
Yes	191	71 (37.2%)	1.10 (0.82-1.49)	*0.5143*	163	25 (15.3%)	0.94 (0.60-1.46)	*0.7746*
Death or major illness of other family member								
No	33447	11276 (33.7%)	1.00		33233	4595 (13.8%)	1.00	
Yes	1434	563 (39.3%)	1.23 (1.10-1.37)	*0.0002*	1790	258 (14.4%)	1.15 (1.00-1.33)	*0.0511*
Any family-related event								
No	32992	11110 (33.7%)	1.00		32756	4496 (13.7%)	1.00	
Yes	1889	729 (38.6%)	1.21 (1.09-1.33)	*0.0002*	2267	357 (15.7%)	1.23 (1.09-1.39)	*0.0010*
Finance-related events								
Job loss or retirement								
No	34847	11825 (33.9%)	1.00		34740	4797 (13.8%)	1.00	
Yes	34	14 (41.2%)	1.63 (0.81-3.26)	*0.1684*	283	56 (19.8%)	1.30 (0.95-1.78)	*0.0968*
Bankruptcy								
No	34697	11760 (33.9%)	1.00		34986	4848 (13.9%)	1.00	
Yes	184	79 (42.9%)	1.53 (1.14-2.07)	*0.0050*	37	5 (13.5%)	1.05 (0.39-2.77)	*0.9287*
Loss of income or debt								
No	34724	11756 (33.9%)	1.00		34868	4821 (13.8%)	1.00	
Yes	157	83 (52.9%)	2.13 (1.55-2.93)	*<0.0001*	155	32 (20.6%)	1.37 (0.90-2.09)	*0.1383*
Any finance-related event								
No	34521	11671 (33.8%)	1.00		34578	4770 (13.8%)	1.00	
Yes	360	168 (46.7%)	1.76 (1.42-2.18)	*<0.0001*	445	83 (18.7%)	1.24 (0.96-1.61)	*0.0952*
Injury-related events								
Violence								
No	34807	11803 (33.9%)	1.00		34989	4850 (13.9%)	1.00	
Yes	74	36 (48.6%)	1.93 (1.22-3.07)	*0.0053*	34	3 (8.8%)	0.78 (0.23-2.68)	*0.6948*
Major injury or traffic accident								
No	34595	11732 (33.9%)	1.00		34808	4834 (13.9%)	1.00	
Yes	286	107 (37.4%)	1.23 (0.96-1.56)	*0.1023*	215	19 (8.8%)	0.92 (0.56-1.49)	*0.7286*
Natural disaster								
No	34848	11826 (33.9%)	1.00		35000	4853 (13.9%)	1.00	
Yes	33	13 (39.4%)	1.48 (0.73-3.01)	*0.2786*	23	0 (0.0%)	--	--
Any injury or disaster event								
No	34490	11685 (33.9%)	1.00		34754	4831 (13.9%)	1.00	
Yes	391	154 (39.4%)	1.35 (1.10-1.66)	*0.0047*	269	22 (8.2%)	0.80 (0.51-1.26)	*0.3383*
Any major stressful life event								
No	32363	10855 (33.5%)	1.00		32146	4411 (13.7%)	1.00	
Yes	2518	984 (39.1%)	1.26 (1.16-1.38)	*<0.0001*	2877	442 (15.4%)	1.19 (1.07-1.33)	*0.0019*

OR, odds ratio; CI, confidence interval.

ORs are adjusted for age group, study area, education, income, and smoking.

*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table 6.9. Cross-sectional associations of stressful life events with problem drinking, by household income level in male current regular drinkers

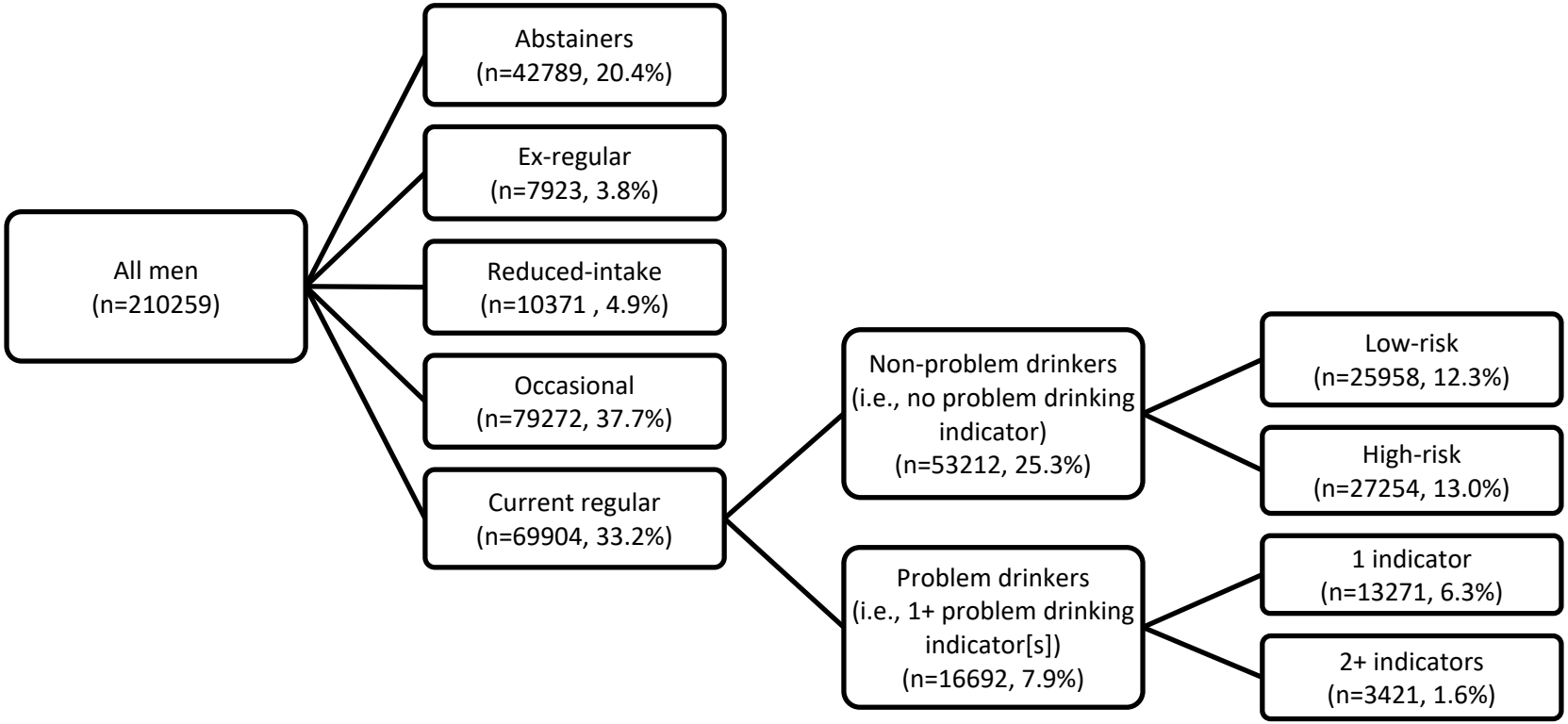
	<20,000 yuan/year				20,000+ yuan/year			
	Total regular drinkers N	Problem drinkers* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value	Total regular drinker N	Problem drinkers* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value
Family-related events								
Divorce or separation								
No	33761	9672 (28.6%)	1.00		35940	6967 (19.4%)	1.00	
Yes	138	37 (26.8%)	1.07 (0.73-1.59)	*0.7238*	65	16 (24.6%)	2.13 (1.17-3.88)	*0.0134*
Family conflict								
No	33609	9612 (28.6%)	1.00		35808	6928 (19.3%)	1.00	
Yes	290	97 (33.4%)	1.31 (1.01-1.69)	*0.0395*	197	55 (27.9%)	1.95 (1.39-2.72)	*0.0001*
Death of spouse								
No	33660	9643 (28.6%)	1.00		35890	6953 (19.4%)	1.00	
Yes	239	66 (27.6%)	1.02 (0.76-1.37)	*0.9189*	115	30 (26.1%)	1.18 (0.76-1.85)	*0.4554*
Death or major illness of other family member								
No	32230	9173 (28.5%)	1.00		34450	6698 (19.4%)	1.00	
Yes	1669	536 (32.1%)	1.23 (1.10-1.37)	*0.0003*	1555	285 (18.3%)	1.17 (1.02-1.34)	*0.0286*
Any family-related event								
No	31635	9000 (28.4%)	1.00		34113	6606 (19.4%)	1.00	
Yes	2264	709 (31.3%)	1.19 (1.08-1.31)	*0.0003*	1892	377 (19.9%)	1.27 (1.12-1.44)	*0.0002*
Finance-related events								
Job loss or retirement								
No	33678	9656 (28.7%)	1.00		35909	6966 (19.4%)	1.00	
Yes	221	53 (24.0%)	1.25 (0.91-1.74)	*0.1708*	96	17 (17.7%)	2.07 (1.19-3.59)	*0.0098*
Bankruptcy								
No	33724	9633 (28.6%)	1.00		35959	6975 (19.4%)	1.00	
Yes	175	76 (43.4%)	1.68 (1.23-2.29)	*0.0010*	46	8 (17.4%)	0.79 (0.36-1.74)	*0.5562*
Loss of income or debt								
No	33660	9605 (28.5%)	1.00		35932	6972 (19.4%)	1.00	
Yes	239	104 (43.5%)	2.07 (1.57-2.72)	*<0.0001*	73	11 (15.1%)	1.06 (0.53-2.12)	*0.8586*
Any finance-related event								
No	33302	9494 (28.5%)	1.00		35797	6947 (19.4%)	1.00	
Yes	597	215 (36.0%)	1.61 (1.34-1.92)	*<0.0001*	208	36 (17.3%)	1.37 (0.93-2.01)	*0.1128*
Injury-related events								
Violence								
No	33830	9676 (28.6%)	1.00		35966	6977 (19.4%)	1.00	
Yes	69	33 (47.8%)	2.24 (1.37-3.68)	*0.0013*	39	6 (15.4%)	0.75 (0.30-1.89)	*0.5464*
Major injury or traffic accident								
No	33637	9620 (28.6%)	1.00		35766	6946 (19.4%)	1.00	
Yes	262	89 (34.0%)	1.32 (1.01-1.73)	*0.0405*	239	37 (15.5%)	0.91 (0.62-1.32)	*0.6156*
Natural disaster								
No	33862	9699 (28.6%)	1.00		35986	6980 (19.4%)	1.00	
Yes	37	10 (27.0%)	0.94 (0.44-1.99)	*0.8666*	19	3 (15.8%)	1.39 (0.37-5.26)	*0.6305*
Any injury or disaster event								
No	33533	9579 (28.6%)	1.00		35711	6937 (19.4%)	1.00	
Yes	366	130 (35.5%)	1.41 (1.13-1.77)	*0.0028*	294	46 (15.6%)	0.91 (0.65-1.27)	*0.5815*
Any major stressful life event								
No	30840	8728 (28.3%)	1.00		33669	6538 (19.4%)	1.00	
Yes	3059	981 (32.1%)	1.26 (1.16-1.37)	*<0.0001*	2336	445 (19.0%)	1.22 (1.09-1.36)	*0.0008*

OR, odds ratio; CI, confidence interval.

ORs are adjusted for age group, study area, education, income, and smoking.

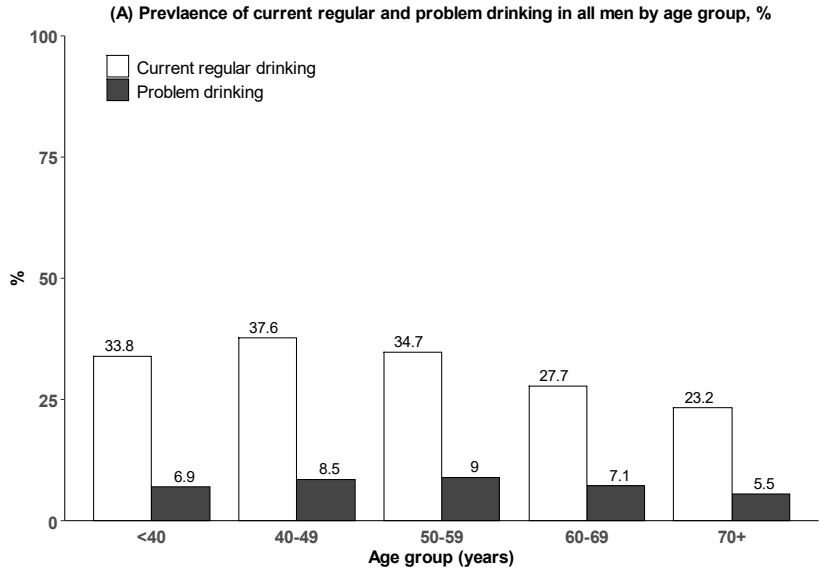
*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

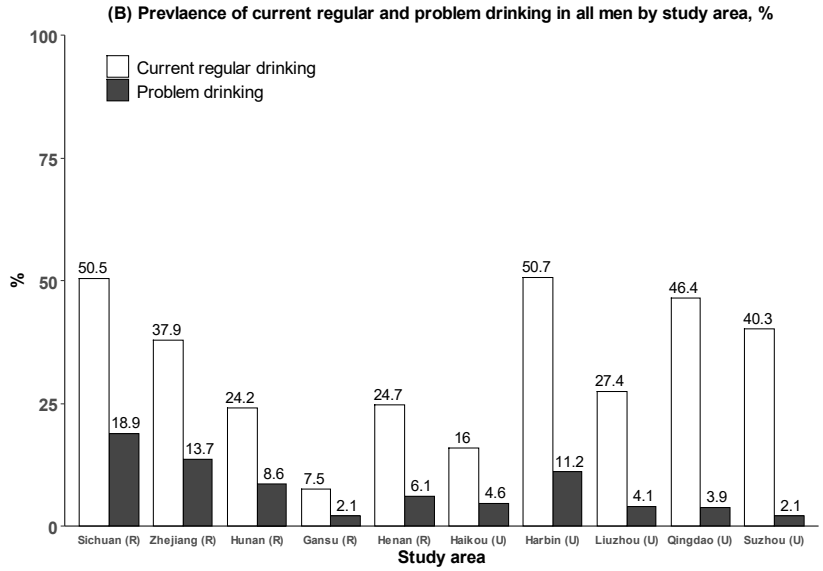
Figure 6.1. Alcohol drinking status and problem drinking categorisation among men in the China Kadoorie Biobank

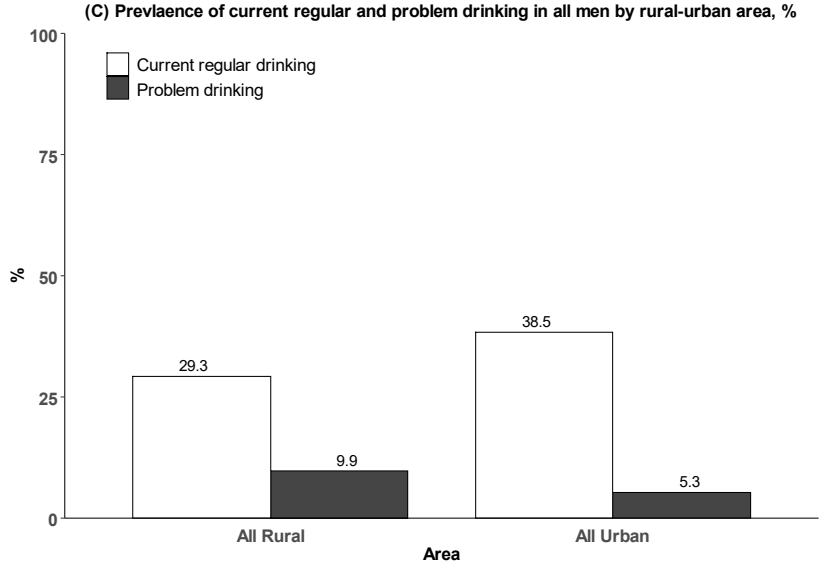


Percentages represent proportions of the entire study sample of all men. Abstainers were men who had not drunk alcohol in the past year and had not drunk ≥weekly previously; ex-regular drinkers were men who had drunk alcohol ≥weekly previously but had not drunk in the past year; reduced-intake drinkers were men who had drunk alcohol ≥weekly previously but had drunk less than weekly in the past year; occasional drinkers were men who reported drinking alcohol less than weekly in the past year and had not drunk alcohol ≥weekly previously; current regular drinkers were men who had drunk alcohol ≥weekly in the past year. Low-risk drinkers were current regular drinkers who drank <200g/week, with no heavy episodic drinking (HED) in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

Figure 6.2. Prevalence of current regular drinking and problem drinking among all men

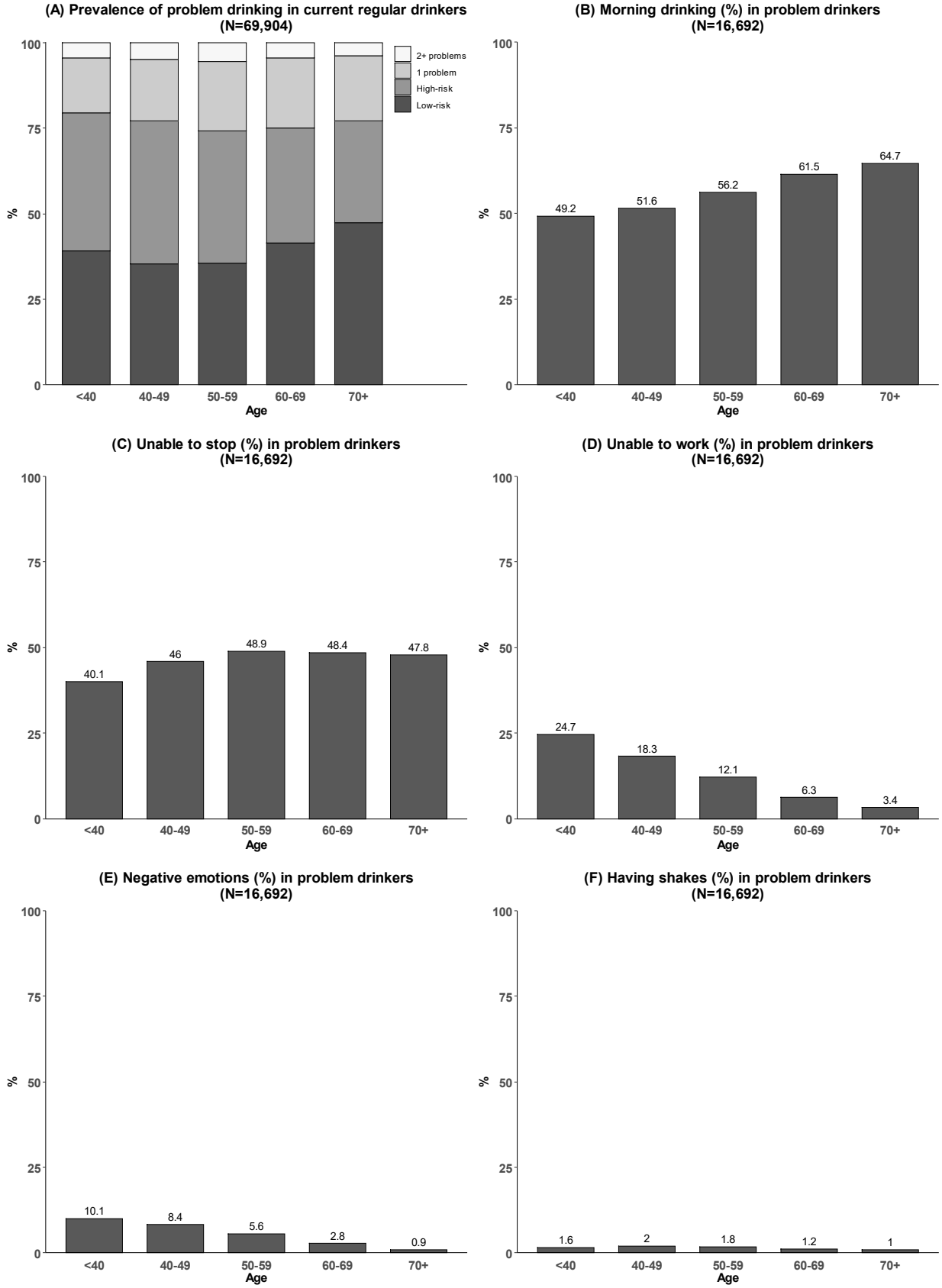






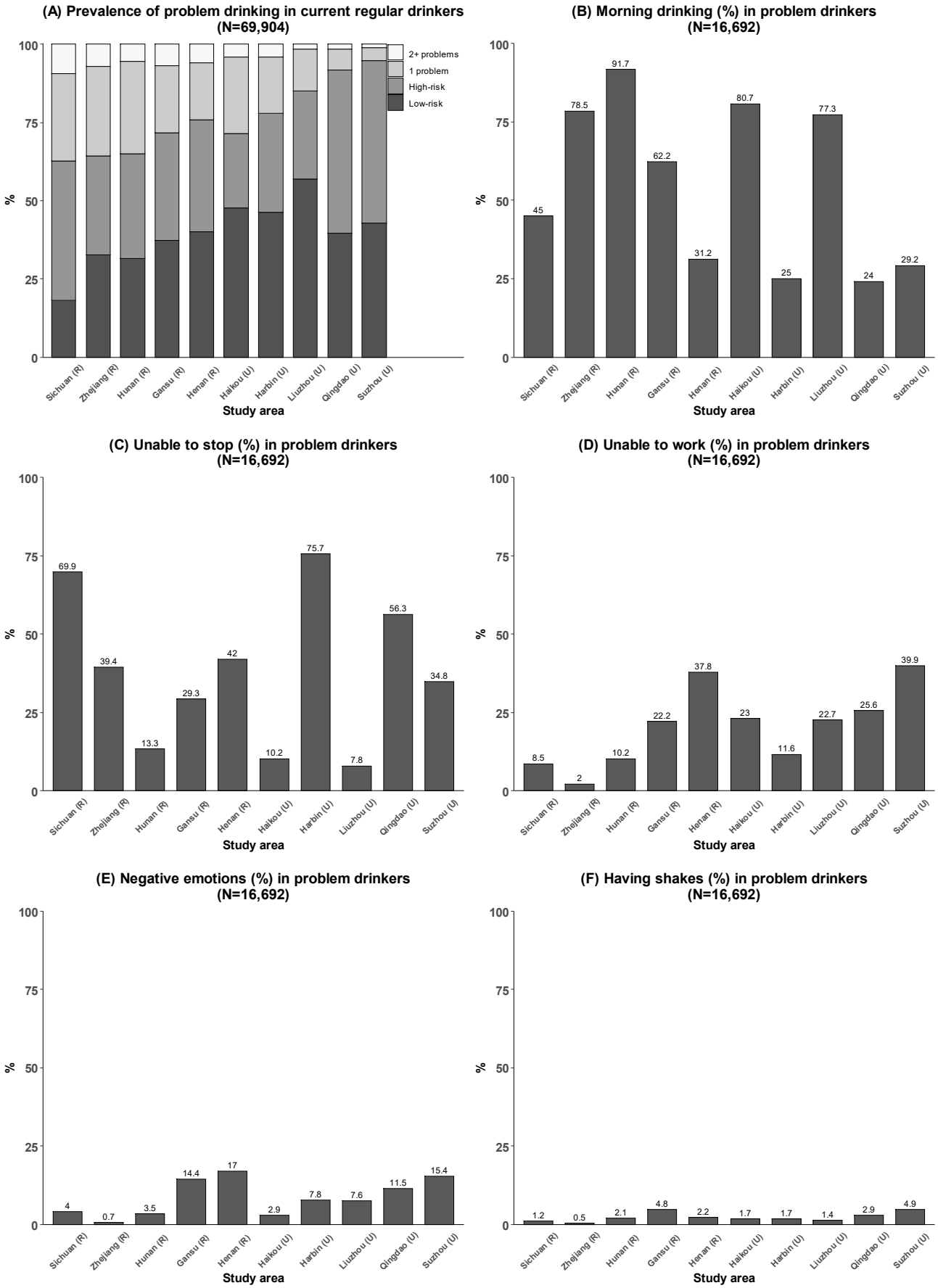
Prevalences are adjusted for study area in (A) and age in (B-C).

Figure 6.3. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by age group in men



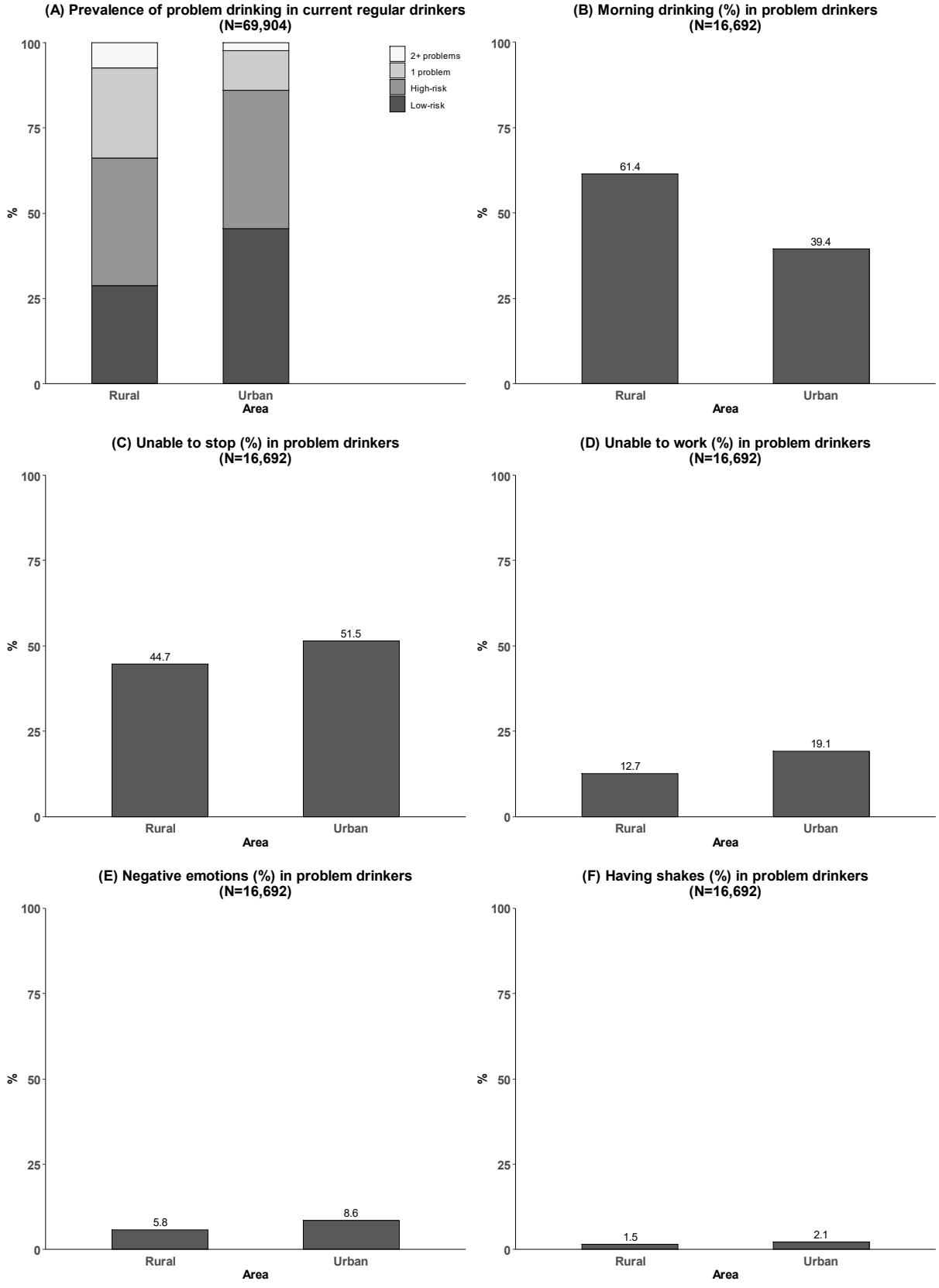
Prevalences are adjusted for study area. *P* for trend <0.05 across age groups for all problem drinking indicators.

Figure 6.4. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by ten study areas in men



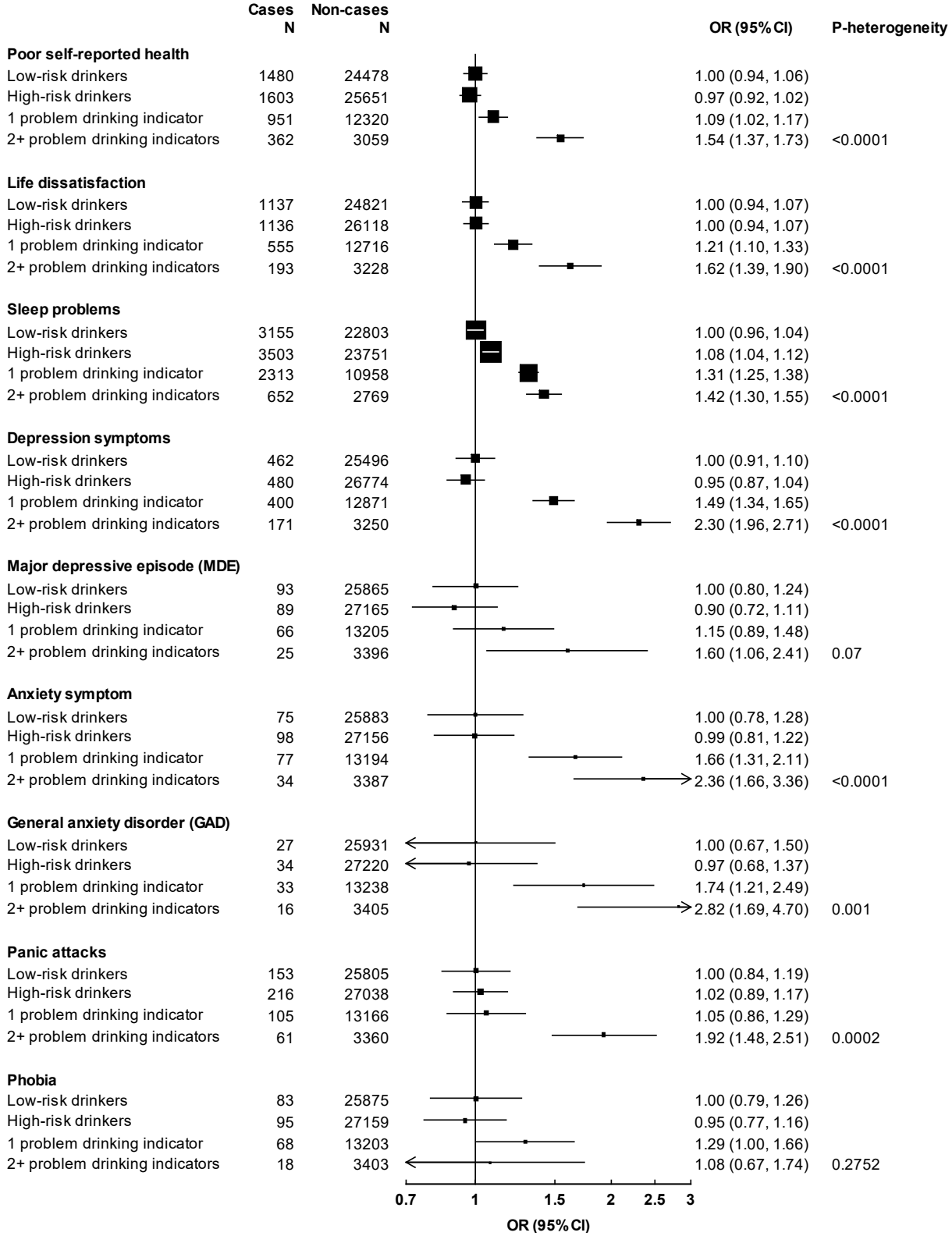
Prevalences are adjusted for age. *P* for heterogeneity across study areas <0.001 for all problem drinking indicators.

Figure 6.5. Prevalence of problem drinking among current regular drinkers and of specific problem drinking indicators among problem drinkers, by rural and urban areas in men



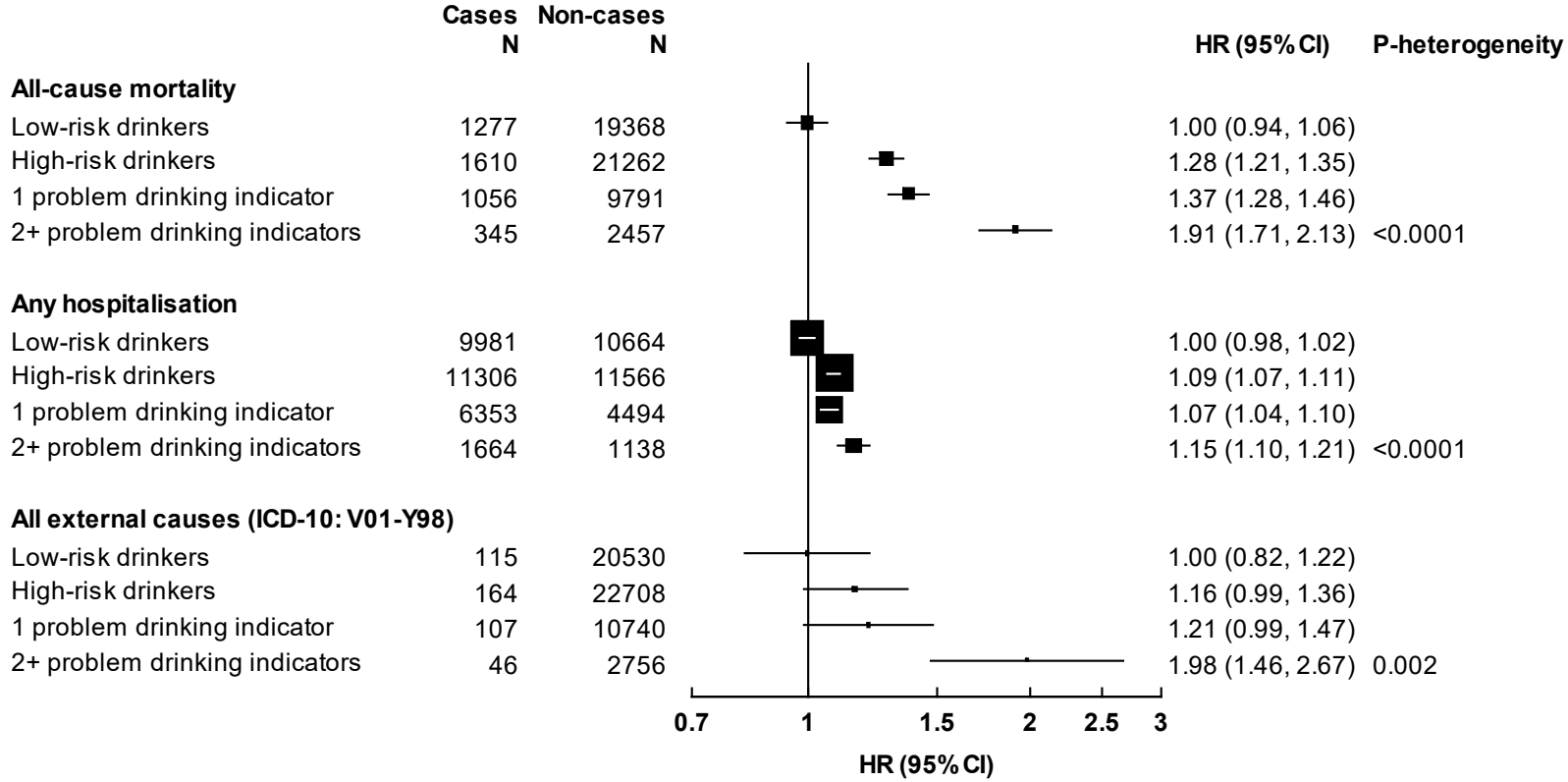
Prevalences are adjusted for age. *P* for heterogeneity across rural-urban areas <0.05 for all problem drinking indicators.

Figure 6.6. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in male current regular drinkers



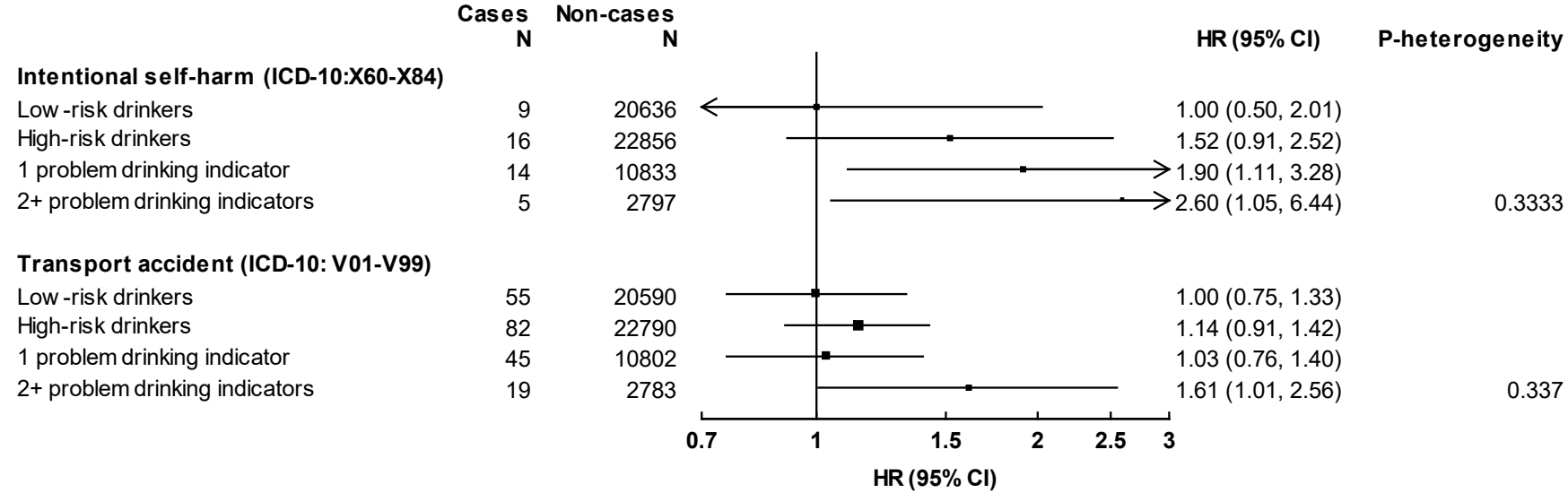
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure 6.7. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, in male current regular drinkers



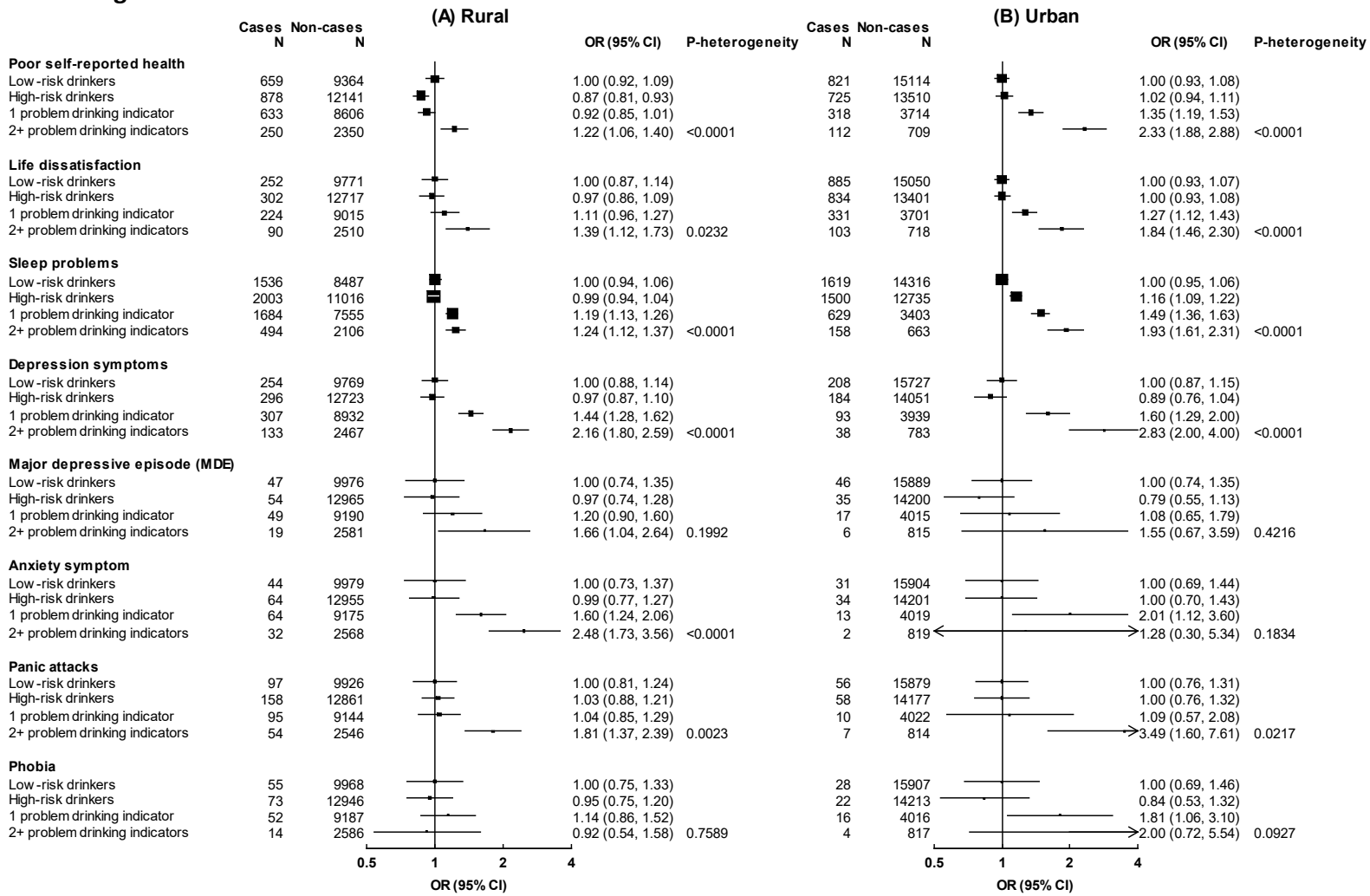
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analysis. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Figure 6.8. Prospective associations of problem drinking with events due to interntional self-harm and transport accidents, in male current regular drinkers



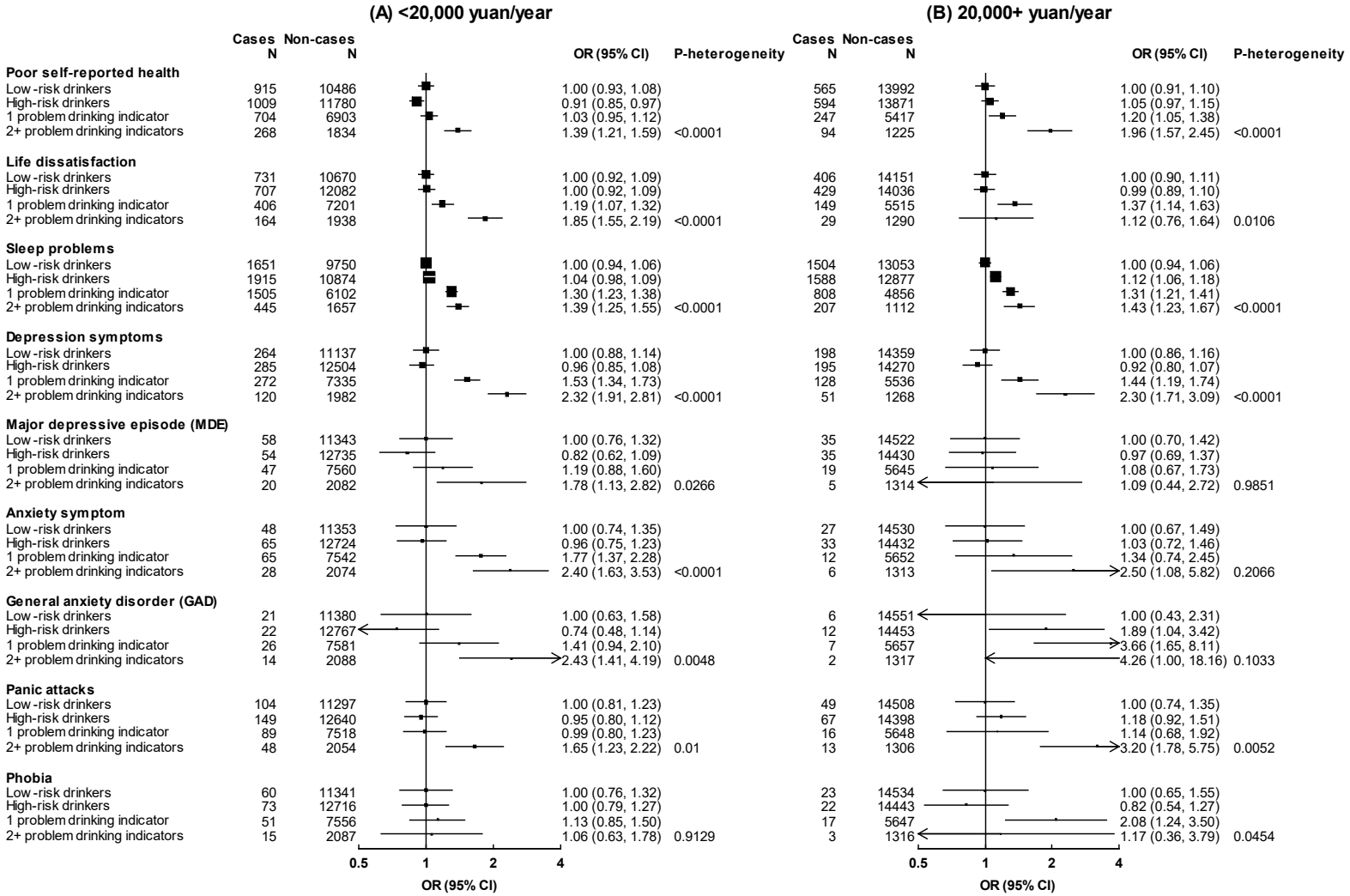
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Figure 6.9. Cross-sectional associations of problem drinking with poor wellbeing and mental health, by rural and urban areas in male current regular drinkers



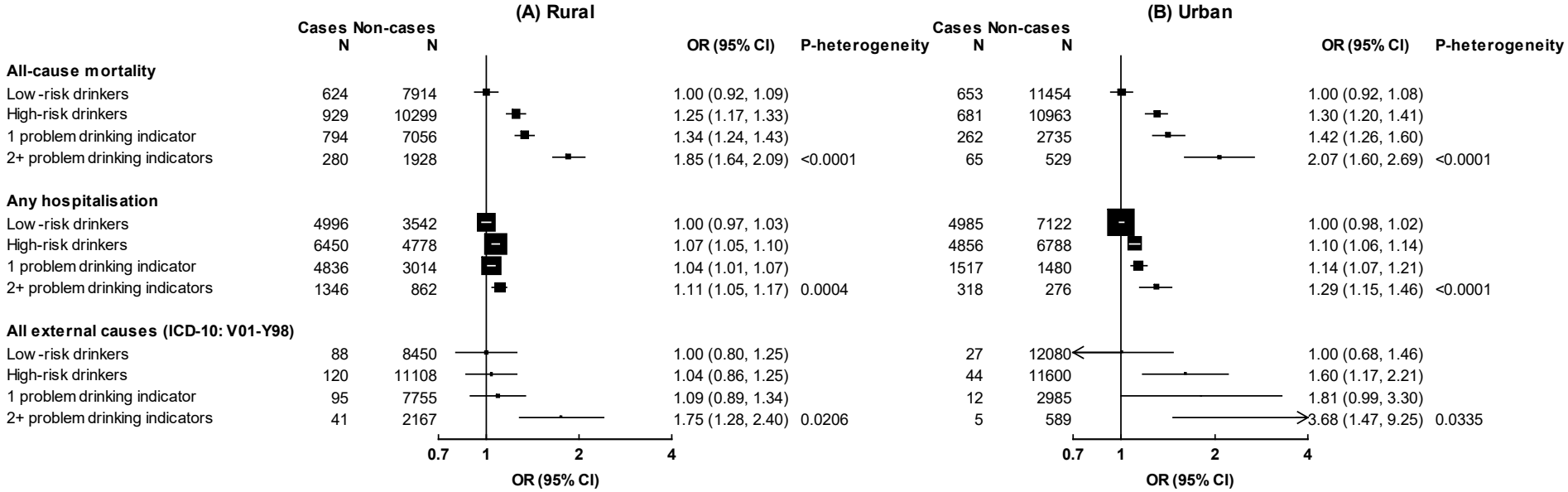
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure 6.10. Cross-sectional associations of problem drinking with poor wellbeing and mental health, by household income level in male current regular drinkers



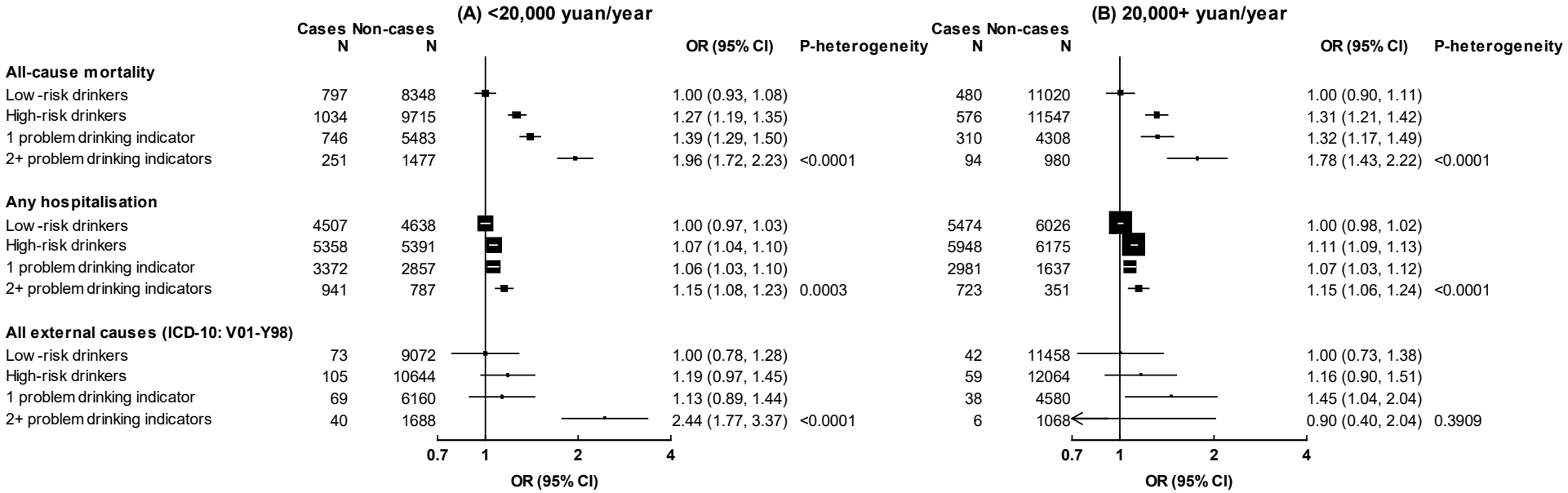
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure 6.11. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, by rural and urban areas in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Figure 6.12. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, by household income level in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Chapter 7. Alcohol consumption and risks of cancers

7.1 Introduction

Of an estimated 3 million annual deaths attributable to alcohol in 2016, ~75% occurred in men and ~20% of the alcohol-attributable burden among men at age 50+ years was from cancer.[1,86] The IARC have concluded, based mainly on evidence from Western populations, that alcohol consumption is causally related to cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colon and rectum, and female breast.[19,20] However, existing evidence is still inconclusive for several other common cancer sites (e.g., lung, stomach, prostate).[19,41,100] Moreover, the effects of different drinking patterns on risks of site-specific cancers have not been extensively explored.[287,288]

In China, the number of cancer deaths increased by about 75% between 2000 and 2011, and the rising trend is likely to continue, mostly due to an ageing and growing population as well as increasingly unhealthy lifestyles.[39] Many epidemiological studies in China have previously examined the relationships between alcohol and cancers, but they are constrained by small sample size and single study region,[72,104,108,109,114,117,131] covering a period in the distant past,[72,73,108,109,114,117,131] and lack of detailed data on drinking patterns.[72,73,104,108,109,114,117,131] Moreover, many people in China and other East Asian countries cannot metabolise alcohol effectively due to an *ALDH2*-rs671 genetic variant, which leads to an accumulation of acetaldehyde in the circulation and the flushing response after alcohol intake, and may alter susceptibility to the carcinogenic effects of alcohol.[25,163] An *ADH1B*-rs1229984 genetic variant, which accelerates the conversion of alcohol into acetaldehyde, is also highly prevalent in East

Asian populations.[22,26] Appropriate and comprehensive assessment of the role of alcohol in cancer aetiology is therefore particularly needed in China where alcohol tolerance, patterns of drinking (e.g., drinking spirits, drinking with meals), and cancer rates and types (e.g., high incidence of liver cancer and oesophageal cancer) differ importantly from the West.[32,40,87,205,289,290]

7.2 Aims and Objectives

Using data of 0.5 million participants from the CKB, this chapter aims to:

(1) Assess the associations of alcohol consumption and drinking patterns with incident site-specific cancers;
(2) Examine the associations of alcohol with cancer risks in population subgroups defined by socio-demographic characteristics, smoking status, physical activity, fresh fruit intake, BMI, and the alcohol flushing response;
(3) Explore the effects of genotypes of two alcohol metabolism genes (*ALDH2*-rs671, *ADH1B*-rs1229984) and potential gene-alcohol interactions on cancer risks, in a subset of genotyped participants.

7.3 Methods

7.3.1 Assessment of alcohol consumption

Detailed information on questionnaire assessment of alcohol consumption and drinking patterns in the CKB study has been described previously and in Chapters 4-6).[87,262] The main parameters of alcohol consumption analysed in this chapter were

drinking status, amount, major drinking patterns (daily drinking, HED, mealtime drinking, beverage types), duration of regular drinking, and the flushing response.

7.3.2 Assessment of cancer outcomes

Detailed information about the data collection of incident cancer cases and cancer deaths through national death and cancer registries and the nationwide health insurance claim system has been described in Chapter 4. The full list of site-specific cancer and aggregate cancer outcomes studied is shown in Table 7.1. "IARC alcohol-related cancers" have been defined in Chapter 2 and referred to cancers concluded to have convincing causal relevance with alcohol by IARC,[19,20] including cancers of the mouth and throat (ICD-10: C00-C14, C32), oesophagus (C15), colon and rectum (C18-C20), liver (C22), and female breast (C50). Other cancers, except ill-defined neoplasms, were classified as "other cancers of known sites". "Major cancers" included site-specific IARC alcohol-related cancers and also common (i.e., lung [C33-C34], stomach [C16]) and deadly (i.e., pancreas [C25]) cancers with probable positive associations with alcohol as indicated by WCRF.[41]

7.3.3 Genotyping data

The two alcohol metabolism genetic variants, *ALDH2*-rs671 and *ADH1B*-rs1229984, were genotyped in 167,924 participants using the Affymetrix Axiom® 800K-SNP array (n=100,408) or 384-SNP Illumina® GoldenGate array (n=92,987). The genotyped population included 151,164 randomly selected participants and an additional 16,760 participants who had been selected as part of nested case-control studies of stroke, coronary heart disease, and COPD. Among 25,471 participants genotyped with both

arrays, the concordance of genotypes was previously reported to be 99.97% for *ALDH2*-rs671 and 99.94% for *ADH1B*-rs1229984.[24] Where discordant, genotypes obtained from the Affymetrix Axiom® 800K-SNP array were used. Each variant has three possible genotypes, AA, AG, and GG, where the A allele is the variant allele.

7.3.4 Statistical analyses

Participants with a self-reported history of cancer at baseline (n=2578) were excluded from the present study, leaving 510,137 participants (209,237 men and 300,900 women) for the main analyses. Participants with a self-reported history of liver cirrhosis or chronic hepatitis (n=6139) were further excluded from the analyses of liver cancer, while those with a history of self-reported bronchitis or emphysema (n=13,231), tuberculosis (a further n=7019), or COPD (a further n=22,945 including self-reported and screen-detected cases from spirometry) were excluded from the analyses of lung cancer. All analyses were conducted separately in men and women. Given very few women drank alcohol regularly (n=6219, 2%), the main analyses focused on men and the analyses among women are presented in Appendix G.

Means and percentages of baseline characteristics by incident cancer outcome were adjusted for age group and study area by direct standardisation. Incidence rates of site-specific cancers, overall and by study area and alcohol drinking status, were calculated with direct standardisation to the age and study area structure of the CKB study population where appropriate.

Cox proportional hazards regression models were used to estimate adjusted HRs of incident site-specific cancers associated with alcohol drinking status (reference group:

abstainers) in all participants, and among current regular drinkers with amount of alcohol consumption in categories (reference group: <140g/week for men; <70g/week for women) and as a continuous variable (per 280g/week), and with drinking patterns. The models were stratified by age-at-risk (5-year groups) and study area (ten areas), and were adjusted for education (four groups), household income (four groups), smoking (five groups in men: never, occasional, ever regular <15, ever regular 15-24, ever regular 25+ cigarettes equivalent/day; four groups in women: never, occasional, ex-regular, current), physical activity (three groups), regular fresh fruit intake (yes/no), BMI (four groups), and family history of cancer (yes/no), with time since entry into the study as the underlying time scale. The analyses were repeated with cancer mortality for comparison. To examine the associations of drinking patterns for risks of major cancer sites and composite endpoints (i.e., IARC alcohol-related cancers, other cancers of known sites, all cancers), each drinking pattern (i.e., daily drinking, HED, mealtime habits, spirit drinking, duration of regular drinking) was modelled individually as an exposure variable, with the total alcohol consumption (in g/week) additionally entered into the models as a continuous variable as well as other covariates (i.e., education, income, smoking, physical activity, fresh fruit intake, BMI, and family history of cancer) and strata (age-at-risk and study area). For analyses of duration of regular drinking, the baseline age was further included in the models as a continuous variable. For daily drinking and HED which were highly correlated with the total amount of alcohol consumption, further analyses were conducted to examine the effects across subgroups defined by total weekly intake (cut-off at 280g/week). Floating SEs were used for exposure variables involving more than two exposure categories as described in Chapter 4.[203,204]

Within-person variation of self-reported alcohol intake was addressed using the regression dilution approach[184] as described in Chapter 5. Among current regular drinkers, the HRs of baseline consumption categories were plotted against their mean usual alcohol intake. Log HR estimates and corresponding SEs for baseline alcohol intake, modelled as a continuous variable, were divided by the RDR calculated using the McMahon-Peto method[218] (0.54 for men, 0.55 for women; see Chapter 5) to obtain estimated HRs per 280g/week higher usual alcohol intake. For major cancers and composite endpoints, the HRs per 280g/week higher usual alcohol intake were also examined across subgroups defined by socio-demographic characteristics, smoking status, BMI, physical activity, fresh fruit intake, HBsAg seropositivity (for liver cancer), high-risk areas (for oesophageal cancer), beverage type, and the flushing response. Heterogeneity across strata was assessed with a chi-squared test. The joint effects of alcohol and smoking on cancer risks were assessed by creating a composite exposure based on combinations of alcohol intake levels and smoking status, and the HRs for each group were estimated. Similar methods were used to assess the joint effects of alcohol with BMI and with the flushing response.

Sensitivity analyses included further exclusions of participants with any prior major chronic disease (as defined in Chapter 5) and/or poor self-reported baseline health, and/or the first three years of follow-up.

Genetic epidemiological analyses were used to explore the cumulative lifetime effect of alcohol consumption predicted by randomly allocated genetic variants of *ALDH2*-rs671 and *ADH1B*-rs1229984 on risks of major cancers and composite endpoints, and to assess the potential *ALDH2*-rs671 gene-alcohol interactions. After excluding

participants with prior cancer, 167,157 participants remained in the genotyped dataset and were used in all genetic analyses (69,235 men; 97,922 women). Cox proportional hazards regression models related major cancers and composite endpoints to the genotypes of *ALDH2*-rs671 and *ADH1B*-rs1228894, separately, stratified by age-at-risk and study area. Sensitivity analyses were conducted using the same model specification as in the conventional epidemiological analyses and with further adjustment for total alcohol intake as a continuous variable. To observe potential effect modification by *ALDH2*-rs671 genotype, the risk estimates of *ALDH2*-rs671 genotype were examined across strata by never and current regular drinkers, and was repeated for *ADH1B*-rs1229984 for comparison. The HRs associated with weekly consumption categories and per 280g/week higher usual alcohol intake were further examined across *ALDH2*-rs671 genotypes among current regular drinkers.

The population attributable fraction (PAF), i.e., the proportion of cancer incidence that was attributed to ever regular drinking in the CKB population, was calculated with the equation PAF=P x (HR-1)/HR, where P was the prevalence of ever regular drinking among participants who developed the relevant cancer in the CKB.[291]

Analyses in this chapter used CKB release 14 with follow-up to 1 January 2017.

7.4 Results

7.4.1 Incidence rates and correlates of cancers

During approximately 5 million person-years of follow-up (median 10.1 years [interquartile range, 9.2-11.1 years]), 26,961 individuals (13,342 men and 13,619 women) developed cancer. The overall cancer incidence rates were 661.5 per 100,000

persons-years among men and 455.7 per 100,000 person-years among women. Those who developed cancer during follow-up tended to be older and to smoke regularly at baseline, especially among men, and had higher prevalence of prior chronic disease and family history of cancer, compared with those who did not develop cancer (Table 7.2).

In men, the ten most common site specific cancers were cancers of the lung (incidence rate per 100,000 person-years=169.8), stomach (109.0), liver (92.2), oesophagus (78.8), colon and rectum (74.9), mouth and throat (26.5), pancreas (19.8), lymphoma (19.7), prostate (19.7), and bladder (17.4) (Figure 7.1A). Among women, the ten most common cancers were cancers of the lung, breast, colon and rectum, stomach, cervix, liver, oesophagus, corpus uteri, thyroid, and ovary (Figure 7.1B). The age-standardised incidence rates of site-specific cancers varied across the ten study areas (Tables G1-G2). The age-standardised incidence rate of overall cancer was higher in urban than in rural areas among both men (678.2 vs. 646.9 per 100,000 person-years, urban vs. rural) and women (502.6 vs. 418.1 per 100,000 person-years). This pattern was also seen for most site-specific cancers, except for oesophageal cancer (which was driven by the high incidence rates in Henan, and to a lesser extent in Sichuan among men), liver cancer, and cervical cancer which were more common in rural than in urban areas (Figure 7.2). In both men and women, the incidence rate of overall cancer appeared higher in ex-regular and current regular drinkers than in abstainers and occasional drinkers (Tables G3-G4).

7.4.2 Alcohol drinking status and risks of cancers

In men, the risks of total and, with a few exceptions, site-specific cancers tended to be higher among current and ex-regular drinkers, and lower among occasional drinkers, than abstainers (Table 7.3). Compared with abstainers, current regular drinkers had 73% (HR=1.73 [95% CI: 1.34-2.24]) higher risk for mouth and throat cancer, 80% (1.80 [1.54-2.11]) higher risk for oesophageal cancer, and 20% (1.20 [1.04-1.39]) higher risk for colorectal cancer, which was higher for rectal cancer (1.26 [1.04-1.52]) than colon cancer (1.11 [0.91-1.35]). Overall, current regular drinkers had 26% (HR=1.26 [1.16-1.36]) higher risk for IARC alcohol-related cancers and 7% (1.07 [1.02-1.12]) higher risk for all cancers combined, with similar findings for cancer mortality (Table G5).

In women, a significantly lower risk of lung cancer was associated with current regular drinkers versus abstainers (Table G6) but not with ever regular drinkers versus never regular drinkers (Table G7). Occasional drinkers had significantly higher risk of breast cancer than abstainers (HR=1.12 [1.02-1.24]), but no significant associations were observed between regular drinking and risks of other site-specific cancers.

7.4.3 Amount of alcohol consumption and risks of cancers

Among male current regular drinkers, alcohol intake was positively associated with risks of cancer at multiple sites, including the mouth and throat (HR=1.74 [1.48-2.05] per 280g/week higher usual alcohol intake), oesophagus (1.98 [1.79-2.18]), colon and rectum (1.19 [1.00-1.43]) with the HR higher for rectum (1.29 [1.04-1.58]) than colon (1.13 [0.87-1.45]), liver (1.52 [1.31-1.76]), and lung (1.25 [1.10-1.42]), but not stomach (1.11 [0.94-1.30]) (Figures 7.3-7.4).

Alcohol intake also showed a significant dose-response relationship with risk of gallbladder and biliary tract cancer (HR=1.60 [1.16-2.22] per 280g/week) (Figure 7.5B). Risks of several less common cancers including prostate cancer, kidney cancer, myeloma, and brain cancer tended to increase with alcohol intake, but with small numbers of events collected the associations were non-significant (Figures 7.5-7.6). No clear dose-response relationships were observed between alcohol intake and risk of pancreatic cancer among male current regular drinkers, but there was a significantly increased risk among men drinking 420+g/week compared with abstainers (Table G8). No apparent associations were observed for other minor cancer sites including bladder, lymphoma, leukaemia, thyroid, and skin.

Overall, the HRs per 280g/week higher usual intake were 1.65 (1.53-1.77) for IARC alcohol-related cancers, 1.17 (1.09-1.27) for other cancers of known sites, and 1.37 (1.30-1.45) for all cancers combined (Figures 7.7-7.8). The associations were broadly similar for cancer mortality (Tables G9-G10).

While the HRs per 280g/week higher usual alcohol intake were examined with sequential covariate adjustments in the Cox regression model, the HRs for most major cancers were consistently attenuated with adjustment for smoking (Table G11). The HRs were also slightly attenuated with adjustment for fruit intake for colorectal cancer and gallbladder cancer and increased slightly with adjustment for BMI for oesophageal cancer, but no obvious changes to the associations were observed with adjustments for physical activity, family history of cancer, meat intake, or preserved vegetable intake.

Among female current regular drinkers, there were no clear associations of alcohol drinking with IARC alcohol-related or other cancers (Table G12, Figure G1), but the numbers of cases were extremely small.

7.4.4 Subgroup analyses

Among men, the risk estimates per 280g/week higher usual alcohol intake for overall cancer, IARC alcohol-related cancers, and other cancers of known sites were similar among never regular and ever regular smokers (Figures 7.7-7.8) and across several other subgroups defined by age, study area, education, BMI, physical activity, and fresh fruit intake (Figure 7.9). The risk estimates for lung cancer were also similar among never regular (HR=1.50 [0.81-2.76] per 280g/week) and ever regular smokers (1.25 [1.10-1.43]) (Figure 7.10). For major cancer sites, there were no significant differences in the associations across different subgroups (Figures 7.11-7.12). The risk estimates were similar across HBsAg test results for liver cancer ($p_{heterogeneity}$=0.24) and all other major cancers (Figure 7.13), and differed little between high-risk (Henan and Sichuan) and other areas for oesophageal cancer ($p_{heterogeneity}$=0.52) (Figure 7.14).

Further examination of the joint effects of alcohol and smoking showed consistently higher risks for most major cancer sites in ever regular smokers than never regular smokers at each level of alcohol consumption (Figures G2-G3). For oesophageal cancer, the absolute increase in incidence rates with increasing alcohol intake appeared substantially greater among ever regular smokers than never regular smokers (Table G13). Consistently higher risks were also observed in men with lower BMI for cancers of the mouth and throat, oesophagus, and lung across all levels of

alcohol consumption, whereas the opposite was observed for colorectal cancer (Figures G4-G5).

7.4.5 Drinking patterns and risks of cancers

In men, daily drinking (i.e., 6-7 days/week) and HED (i.e., drinking >60g/session) tended to increase the risks of most major cancers, while drinking without meals was associated with increased liver cancer risk and drinking spirits was associated with increased oesophageal cancer risk, compared with those who did not report these drinking patterns (Figures 7.15-7.16). Most of the associations between drinking patterns and risks of cancers were attenuated to the null after adjusting for total weekly intake. However, given amount consumed, the increased risks associated with daily drinking persisted for oesophageal cancer (HR=1.74 [1.38-2.20]) and colorectal cancer (1.25 [1.01-1.56]), as did the increased risk associated with HED for oesophageal cancer (1.38 [1.13-1.68]) and the increased risk associated with drinking outside meals for liver cancer (1.31 [1.02-1.68]) (Figure 7.15). Across subgroups defined by weekly alcohol intake, the increased risks of oesophageal cancer, IARC alcohol-related cancers, and overall cancer associated with daily drinking remained significant among those drinking <280g/week, while the association of HED with oesophageal cancer was attenuated to the null (Tables G14-G15, Figures G6-G7). The HRs per 280g/week higher usual alcohol intake did not substantially differ across subgroups defined by beverage type for most major cancers, but appeared statistically stronger among beer drinkers than wine and spirit drinkers for overall cancer and other cancers of known sites, especially for lung cancer ($p_{heterogeneity}$<0.01) (Figure 7.17). Furthermore, the risks of IARC alcohol-related cancers as well as other cancers

of known sites tended to increase with longer duration of regular drinking, but no clear associations were observed at certain cancer sites including colon and rectum, liver, and lung (Figure 7.18).

The risk estimates for IARC alcohol-related cancers, other cancers, and all cancers combined tended to be greater among those who reported flushing after drinking than not, especially for oesophageal cancer (HR=2.75 [2.01-3.76] vs. 1.99 [1.79-2.22] per 280g/week) and lung cancer (2.04 [1.48-2.82] vs. 1.17 [1.02-1.35]), but not for other major cancer sites (Figures 7.19-7.20, Figures G8-G10).

7.4.6 Sensitivity analyses

Sensitivity analyses which excluded the first three years of follow-up and participants with poor self-reported health or prior chronic disease tended to increase cancer risks in current regular drinkers compared with abstainers, particularly for IARC alcohol-related cancers, but did not alter materially the dose-response associations among current regular drinkers (Tables G16-G17).

7.4.7 Genetic analyses

Among the 167,157 participants genotyped, the overall A-allele frequency was 0.21 for *ALDH2*-rs671 and 0.69 for *ADH1B*-rs1229984, with the frequency generally higher in southern than in northern study areas (Table 7.4). For *ALDH2*-rs671, the prevalence of current regular drinking (45% vs. 16% vs. 1%, GG vs. AG vs. AA genotype) and mean alcohol intake (304 vs. 203 vs. 138g/week) in men were progressively lower with an increasing number of A alleles, whereas the prevalence of the flushing response was progressively higher (12% vs. 55% vs. 62%) (Table 7.5). For *ADH1B*-rs1229984, the

prevalence of current regular drinking (43% vs. 33% vs. 32%, GG vs. AG vs. AA genotype) and mean alcohol intake (334 vs. 288 vs. 278 g/week) were higher and the prevalence of flushing response (14% vs. 18% vs. 20%) was lower for men with the GG genotype than those with the AG genotype, but these drinking parameters were broadly similar between those with the AA genotype and those with the AG genotype. Similar patterns of associations across genotypes of these two genetic variants were observed among women, although drinking prevalence and mean alcohol consumption levels were much lower.

Among all men, the *ALDH2*-rs671 AA genotype was associated with significantly decreased risk of IARC alcohol-related cancers (HR=0.65 [0.49-0.85]) compared with the GG genotype, but was not with associated with other cancers (0.99 [0.83-1.18]) or all cancers combined (0.87 [0.75-1.01]) (Table 7.6). For most major cancer sites, the risks associated with the *ALDH2*-rs671 AA genotype were generally lower than those for the GG genotype, but the results were not significant and the numbers of cases were low as only a subset of the cohort was genotyped. While men with the *ALDH2*-rs671 AG genotype had generally similar cancer risks as those with the GG genotype, further subgroup analyses by drinking status showed diverging results. Among male never regular drinkers, the risks of overall and IARC alcohol-related cancers associated with the *ALDH2*-rs671 AG genotype were similar to that for the GG genotype, whereas among current regular drinkers the AG genotype was associated with significantly higher risks of overall cancer (HR=1.14 [1.00-1.31]) and IARC alcohol-related cancers (1.34 [1.10-1.63]), with approximately two-fold higher risks for cancers of the mouth and throat (1.88 [1.11-3.18]) and oesophagus (2.21 [1.63-3.02]), compared with the

GG genotype (Table 7.7). For other cancer sites, an excess risk of lung cancer was associated with the *ALDH2*-rs671 AG versus the GG genotype among never regular drinkers. Adjustments for socio-economic and lifestyle factors (smoking, BMI, physical activity, fruit intake, family history of cancer) attenuated the association between *ALDH2*-rs671 AG genotype and lung cancer among never regular drinkers to the null, but otherwise had little impact on other risk estimates (Tables G18-G19). Further adjustment for total alcohol consumption resulted in more extreme HRs associated with the *ALDH2*-rs671 AG versus the GG genotype for mouth and throat cancer, oesophageal cancer, IARC alcohol-related cancers, and overall cancer, especially among current regular drinkers.

Among male current regular drinkers, there were significant interactions between alcohol intake and *ALDH2*-rs671 genotype for IARC alcohol-related cancers, particularly cancers in the UADT (i.e., mouth and throat, oesophagus) and lung, as well as other cancers combined and overall cancer (all $p_{interaction}$ <0.01), where increasing alcohol consumption was associated with greater HRs in men with the AG genotype compared with men with the GG genotype (Figures 7.21-7.23, Table G20). No clear interactions were observed for cancers of the colon and rectum, liver, or stomach (Figure 7.24).

For *ADH1B*-rs1229984, among men, both AG and AA genotypes were associated with 40%-50% lower risks of cancers of the mouth and throat and oesophagus, and 15-30% lower risks of IARC alcohol-related cancers and overall cancer, compared with the GG genotype (Table 7.8). The associations for theses cancers attenuated slightly with further adjustment for total alcohol intake (Table G21) and were similar in direction

among never and current regular drinkers, though were slightly more apparent among current regular drinkers (Table 7.9).

Among women, no significant associations were observed between *ALDH2*-rs671 or *ADH1B*-rs1229984 and IARC alcohol-related cancers (Tables G22-G23). For specific cancer sites, the *ALDH2*-rs671 AG genotype was associated with significantly reduced risk of oesophageal cancer but higher risks of stomach cancer and lung cancer, and the AA genotype was associated with higher risks of liver cancer and stomach cancer, compared with the GG genotype. For *ADH1B*-rs1229984, the AG genotype was associated with significantly higher risk of mouth and throat cancer, and the AA genotype was associated with higher risk of breast cancer, compared with the GG genotype. The associations changed little with further adjustment for lifestyle factors and total alcohol intake.

7.4.8 Population attributable fraction

If the observed associations between alcohol consumption and cancers are largely causal, 7.2% and 12.4% of overall and IARC alcohol-related cancer cases among men, respectively, in the present study could be attributed to ever regular drinking (Table 7.10). Ever regular alcohol consumption was estimated to attribute to almost 20% of UADT cancers, around 10% of colorectal cancer and liver cancer, and 5% of lung cancer cases among men in this study.

7.5 Discussion

7.5.1 Summary of findings

Among male current regular drinkers, there were significant dose-response relationships of alcohol intake with increased risks of several cancers, not only those previously considered to be alcohol-related cancers (i.e., oesophagus, mouth and throat, liver, colon and rectum) but also certain other cancers such as lung cancer and gallbladder cancer. Smoking was a major confounding factor for these associations, but the associations persisted when restricting analyses to never regular smokers, or excluding early follow-up to account for reverse causation. For lung cancer and oesophageal cancer, the excess risks appeared somewhat greater among male drinkers reporting flushing after drinking, in consistent with results from the genetic epidemiological analyses using *ALDH2*-rs671 genotype. Moreover, for a given amount of alcohol consumed, daily drinkers had higher risk, particularly for oesophageal cancer, compared with non-daily drinkers. As very few women in the study drank alcohol regularly, the associations with cancer could not be evaluated effectively.

7.5.2 Overall cancer

Most previous studies were based mainly on Western or high-income populations and included cancer mortality rather than incidence (where mortality might be biased by other factors, e.g., treatment, comorbidity), and the information on alcohol consumption tended to be relatively crude, e.g., with no information on within-person variation and drinking patterns.[102,288,292-294] Overall, many previous studies have reported J-shaped relationships between alcohol consumption and overall cancer

when considering drinkers and non-drinkers at the same time.[104,288,292,293] However, the shape of the associations may be affected unduly by residual confounding and/or reverse causation (e.g., "sick-quitters" or "sick non-starters"), hence underestimating the hazards of alcohol drinking.[24,182,183] The previous CPSS of 220,000 men with ~5000 cancer deaths in China reported an adjusted HR of 1.06 (1.00-1.13) for total cancer mortality in drinkers compared with non-drinkers,[73] similar in magnitude to findings in the present study. To minimise any biases from reverse causation, the present study further restricted the main analyses to current drinkers only and reports a steeper dose-response relationship among male current drinkers compared with previous Chinese studies.[72,73] The alcohol-attributable cancer burden estimated in the present study (7.2%) is somewhat higher than that previously estimated in the WHO report (4.4%) and a previous study based mainly on meta-analyses of case-control studies from China (5.9%).[1,295] This may be due to the differences in the risk estimates (derived from mainly Western[1] vs. Chinese population, case-control[295] vs. cohort studies) and the data on alcohol drinking prevalence related to the age range of study populations (15+ years[295] vs. 30-79 years), definitions of alcohol drinking (≥monthly drinking in the past year[295] vs. ever regular drinking), and time period (1991[295] vs. 2004-08) between studies.

7.5.3 IARC alcohol-related cancers

Previous studies from different populations have consistently shown strong positive associations between alcohol intake and cancers of the mouth and throat and oesophagus, particularly ESCC which is highly prevalent in China but not EAC which is common in Western countries.[19,20,94,96,100,296] The WCRF meta-analyses of prospective

cohort studies reported a 9-19% higher risk for mouth and throat cancer and a 25% higher risk for ESCC per 10g/day increase in ethanol intake.[94,96] In China, previous prospective studies including the CPSS, the SCS, and a study of elderly population in Hong Kong have demonstrated strong positive associations of alcohol consumption with risks of oesophageal cancer, but not with risks of mouth and throat cancer, possibly due to the small numbers of cancer deaths included.[73,104,109] The present study demonstrates clear associations of alcohol not only with oesophageal cancer but also with mouth and throat cancer, which are the strongest among all site-specific cancers observed and are broadly similar to the risk estimates from WCRF.[94,96]

The incidence rate of colorectal cancer has increased steadily in recent decades in China.[39] In contrast with clear positive findings in cohort studies from Western countries and South Korea,[98,106,110-113] previous cohort studies in China, most of which were done during 1980-1990s and included only mortality, have not produced consistent significant results linking alcohol consumption with colorectal cancer mortality.[72,73,104,114] With more incident colorectal cancer cases than all previous Chinese studies combined, the present study shows that the risk of colorectal cancer increases with the amount of alcohol intake in Chinese men, with the risk estimate (HR=1.04 per 10g/day) broadly consistent with those from high-income populations (HRs around 1.02-1.08 per 10g/day).[98,110-112] Whether the associations between alcohol and colorectal cancer differ by colon and rectal anatomical subsites is uncertain. The WCRF meta-analysis reported similar associations of alcohol intake with colon cancer (RR=1.07 [1.05-1.09] per 10g/day) and with rectal cancer (1.08 [1.07-1.10]),[98] whereas some Western cohort studies have reported stronger associations of

alcohol intake with rectal cancer than with colon cancer.[110,112] In the CKB, the results also demonstrate a slightly stronger, but not statistically significant, association with rectal cancer than with colon cancer.

Previous studies in Western and other East Asian populations have reported dose-response associations between alcohol consumption and liver cancer,[19,20,88,100] with an RR of 1.04 (1.02-1.06) per 10g/day reported by WCRF.[88] Existing evidence from China is limited. A meta-analysis of 18 Chinese case-control studies with 3812 hepatocellular carcinoma cases reported a significant pooled OR of 1.56 (1.16-2.09) in drinkers versus non-drinkers.[101] The CPSS reported non-significant increased liver cancer mortality in drinkers compared with non-drinkers (1.12 [0.98-1.28]; 1115 deaths) and a weak positive association with amount of alcohol intake,[73] but no clear dose-response relationships were reported in other prospective studies in China.[72,104,117] These previous cohort studies had mortality data only and most of them were conducted almost three decades ago, when other major risk factors for liver cancer (e.g., HBV infection, aflatoxin) were more prevalent and alcohol consumption was lower in the population.[39,59,207] In the present study, there were strong significant dose-response relationships between alcohol intake and both liver cancer incidence and mortality in male drinkers, largely independent of HBV infection status.

Epidemiological studies, mainly from Western populations, have shown linear positive associations of alcohol intake with risks of breast cancer and IARC alcohol-related cancers among women.[19,20,97,100] However, there is lack of evidence of clear associations in Asian populations in previous studies,[97,100] and a previous meta-analysis of four case-control studies (1655 female breast cases) in China reported a significantly

reduced OR of 0.76 (0.60-0.97) for drinkers versus non-drinkers,[101] contrasting with findings in Western populations. In the present study where regular alcohol consumption was rare among women, the risk of breast cancer was higher among female occasional drinkers compared with abstainers, but there were no clear associations with regular drinkers or amount of alcohol consumption given the limited number of events.

7.5.4 Lung cancer

For lung cancer, previous studies from different populations tended to show J-shaped associations with excess risks observed only among heavy drinkers when compared with non-drinkers.[73,92,100,104] Given the strong correlation between heavy drinking and smoking, restricting analyses to non-smokers would provide insight on the independent effect of alcohol on lung cancer. There is evidence mainly from Western and Japanese populations that the associations between alcohol and lung cancer differed by smoking status, with strong positive associations among current or heavier smokers,[126,297] while pooled studies and meta-analyses among never smokers generally showed no significant associations with total alcohol intake.[122-124] In China, the CPSS and the study of elderly population in Hong Kong reported a significantly increased mortality risk of lung cancer in heavy drinkers compared with never drinkers after adjusting for smoking, but did not further investigate separately the associations by smoking status.[73,104] In the present study, there were significant dose-response relationships between alcohol consumption and incident lung cancer among male smokers and also never regular smokers. The findings among never regular smokers in the CKB, though with limited power (n=71 cases), are similar to that reported in a

pooled analysis of 7 Western cohorts which involved 74 events.[125] Future studies with much larger number of lung cancers are needed to confirm (or refute) such findings linking alcohol drinking and lung cancer among never smokers.

7.5.5 Other cancers

For stomach cancer, previous studies have suggested weak positive associations with alcohol consumption, with the WCRF meta-analysis reporting a marginally significant 2% higher risk per 10g/day increase in alcohol intake and a probable excess risk among heavy drinkers only.[95,100,127-129] In China, the SCS reported an increased stomach cancer risk in men consuming 4+ drinks/day only compared with non-drinkers,[131] while a weak dose-response relationship among drinkers was reported in the CPSS.[73] In the present study, there were no apparent dose-response relationships between alcohol consumption and stomach cancer. Previous studies have suggested potential antimicrobial effects of alcohol consumption on *H. pylori* infection,[298,299] which is common in China.[300] Furthermore, a case-cohort study involving 949 participants in South Korea reported significantly higher risks of gastric cancer associated with heavy drinking and binge drinking versus non-drinkers only among *H. pylori* non-infected subjects but not those infected.[301] Future studies with *H. pylori* infection data will allow more thorough investigation into the relationships between alcohol and stomach cancer in China.

There has been accumulating evidence mainly from Western populations that heavy alcohol consumption (~ >45g/day) is associated with increased risks of pancreatic cancer.[19,99,100,132,133] In the present study, no apparent linear associations were observed among male current regular drinkers, although the heaviest drinking group

was associated with a significantly increased risk of pancreatic cancer compared with abstainers, as has been reported previously by Pang et al[56] based on the CKB.

Previous studies have suggested possible links between alcohol consumption and several other cancers (e.g., gallbladder cancer, prostate cancer, kidney cancer, non-Hodgkin lymphoma), but there is little prospective evidence from Chinese populations. The meta-analysis by Bagnardi et al (880 cases; 4 cohorts and 4 case-control studies, mostly from Japan and South Korea) reported a 2.6-fold higher gallbladder cancer risk only in heavy but not moderate drinkers compared with non-drinkers.[100] Similarly, the present study observed a significant dose-response relationship between alcohol intake and gallbladder cancer among Chinese men. A weak positive link between alcohol consumption and prostate cancer has also been reported by Bagnardi et al (49,898 cases; 16 cohorts and 11 case-control studies, mostly from Western countries), with a 4-9% higher risk observed in drinkers versus non-drinkers.[100] Likewise, the present study suggests a weak link between increasing alcohol intake and prostate cancer, rates of which have increased in China during the recent decades.[39] However, contrary to previous evidence mostly from Western populations which suggested inverse associations of alcohol consumption with kidney cancer[91,100,137,138] and non-Hodgkin lymphoma,[100,139,140] the present study did not observe any similar inverse associations for kidney cancer and lymphoma. The null findings might be due to limited statistical power and the combination of Hodgkin and non-Hodgkin lymphoma, which might have different associations with alcohol. Existing evidence on alcohol drinking and brain cancer risk is limited. A meta-analysis involving 6 cohorts and 13 case-control studies (4271 cases) reported no overall associations between alcohol drinking and

adult brain cancer, but suggested a potential modest harm among those drinking ≥25g/day based on limited data (3 cohorts and 1 case-control study).[302] In the present study, the risk of brain cancer appeared to increase with higher alcohol consumption, but longer follow-up is needed to accumulate more cases for more reliable assessment of the relationships of alcohol consumption with risks of brain and other less common cancers.

7.5.6 Effect modification by other factors

Overall the present study did not find significant effect modification on the associations between alcohol and cancer risks by other factors, including smoking status and BMI, which may be partly constrained by limited statistical power. Among men, there was substantial excess risk of oesophageal cancer among those who were both heavy drinkers and smokers, which has important implications for alcohol and tobacco control (see further discussion in Chapter 9). The joint effects of alcohol with BMI varied by cancer sites, with the highest risks observed in lean heavy drinkers for UADT and lung cancers but in obese heavy drinkers for colorectal cancer. The findings largely reflect the different associations of BMI with different cancer sites.[303,304] In the CKB, the findings of the highest UADT cancer risk among heavy drinkers with lower BMI are broadly consistent with previous cohort studies in South Korea,[103,107] which may be partly due to reverse causation (e.g., weight loss in early-stage cancer) and residual confounding by amount of smoking, but may also involve poor nutrition as a potential underlying mechanism. Similarly, reverse causation and residual confounding by amount of smoking may also affect the associations between alcohol consumption and cancer risks observed at overall level. In the present study, the associations were

not materially altered after excluding the first three years of follow-up or restricting analyses to never regular smokers, but given the small numbers of cases involved the power to more completely control such biases, especially in analyses of effect modification by other factors, is limited.

7.5.7 Drinking patterns

Existing evidence on the relationships between different drinking patterns and risks of site-specific cancers is limited. A study of health professionals in the United States showed that the risks of alcohol-related cancers increased with drinking frequency in men (p_{trend}=0.03, 1167 cases), after adjusting for total alcohol intake.[287] Likewise, given amount consumed, a Japanese study reported a 25-29% significantly lower total cancer mortality for drinking 5-6 days/week versus drinking daily in men (3050 deaths among male drinkers).[288] Although a few small studies have reported positive associations of frequency and duration of alcohol drinking with oesophageal cancer and colorectal cancer, no adjustments for total alcohol intake were made in those studies, and there were no investigations on the effects of other drinking patterns (e.g., HED, drinking with meals) or for other major cancer sites.[107,109,113] The present study is the first one to systematically investigate the effects of several drinking patterns on a range of site-specific cancers in Chinese population. While residual confounding by amount might remain even after adjustment, the persistent increased cancer risks associated with daily drinking in adjusted and subgroup analyses suggest the detrimental effects of frequent exposure to alcohol on cancer development, especially in the oesophagus. Furthermore, the increased risks of aggregate IARC alcohol-related cancers and other cancers with prolonged duration of regular drinking

observed in the present study, which are broadly consistent with previous findings on oesophageal cancer from the SCS,[109] suggest a potential detrimental role of cumulative exposure to alcohol over years in cancer development.

Consistent with previous studies on liver cirrhosis and ALD,[75,156,158] the present study shows that drinking without meals is associated with greater excess risk of liver cancer, which might be related to the faster absorption of alcohol in the intestine in the absence of food, thus elevated blood alcohol concentrations and transport of alcohol to liver.[305] The effects of mealtime drinking habits as well as other drinking patterns on risks of other major chronic liver diseases are described in Chapter 8.

Although the associations between alcohol consumption and IARC alcohol-related cancers did not significantly differ across beverage types, the association for lung cancer appeared somewhat stronger for beer drinkers than for spirit and wine drinkers. The finding is unlikely to be due to residual confounding by smoking, as beer drinkers had lower smoking prevalence than other drinkers in the CKB. While the finding might still be prone to chance finding given the relatively small number of events among beer drinkers, it has been previously suggested that the concentrations of some chemicals with carcinogenic potential (e.g., nitrosamines) are higher in beer than other alcohol types and might play a role in lung carcinogenesis.[306] On the other hand, as beverage type consumed is closely related to study areas, which differ substantially for environmental exposures, personal lifestyles (e.g., diet), and occupational exposures, the finding might be due to residual confounding by other measured or unmeasured factors.

7.5.8 Gene-alcohol interactions and potential mechanisms

The biological mechanisms underlying the associations between alcohol and cancer risks are still not fully understood and may vary across cancer sites. One of the main pathways proposed is via the metabolism of ethanol into its carcinogenic metabolite acetaldehyde, which disrupts DNA synthesis and repair, particularly in cells of the upper and lower gastrointestinal tract.[20] This potential pathway may be explored using genetic variants in alcohol metabolism genes, particularly *ALDH2*-rs671 which affects acetaldehyde clearance substantially. Previous studies have shown that for oesophageal cancer, individuals with the *ALDH2*-rs671 AA genotype have significantly lower risks compared with those with the GG genotype, while those with the AG genotype have higher risks than those with the GG genotype among alcohol drinkers and particularly among heavy drinkers.[25,162-164,307,308] Consistent with these findings, the present study also reports similar associations between *ALDH2*-rs671 and risks of UADT cancers as well as IARC alcohol-related cancers and overall cancer in men. For *ADH1B*-rs1229984, which also reduces alcohol intake and influences acetaldehyde levels but has less impact per allele than *ALDH2*-rs671, the risks of cancers of the UADT, IARC alcohol-related sites, and all sites combined were reduced in both AA and AG carriers compared with GG carriers in all men and among current drinkers.

These genetic findings complement observational evidence in several important ways. First, alcohol intake increases the risks of UADT cancers. This is demonstrated by the findings that low genotype-predicted alcohol consumption[24] (i.e., *ALDH2*-rs671 AA, *ADH1B*-rs1229984 AA and AG genotypes) was associated with decreased UADT cancer risks compared with high genotype-predicted alcohol intake (GG genotype). The similar

HRs associated with *ADH1B*-rs1229984 AA and AG genotypes reflect the similar genotype-predicted alcohol consumption level for these two genotypes. Second, acetaldehyde is involved in the mechanistic pathway through which alcohol consumption increases the risks of UADT cancers, and can modify the risks by alcohol consumption. This is supported by the increased UADT cancer risks only among *ALDH2*-rs671 AG regular drinkers (who will experience markedly increased acetaldehyde exposure when consuming alcohol) but not among *ALDH2*-rs671 AG never regular drinkers (no exposure to acetaldehyde given the absence of alcohol intake), compared with those with the GG genotype. The supporting evidence is enhanced by the further increased HRs for the *ALDH2*-rs671 AG versus the GG genotype in drinkers after controlling for total alcohol intake and the significant interaction between alcohol amount and the flushing response (which is determined by *ALDH2*-rs671). These findings mean that given the same amount of alcohol consumed, those who experienced a markedly increased acetaldehyde exposure have higher risks of developing UADT cancers, suggesting that alcohol affects development of cancer at these sites through exposure to acetaldehyde.

An interaction between alcohol consumption and *ALDH2*-rs671/flushing response for lung cancer has also been observed in the present study which, although possible, should be interpreted with caution. First, no clear associations were observed with *ALDH2*-rs671 or *ADH1B*-rs1229984 genotypes (i.e., genotype-predicted alcohol consumption) alone, although it might be related to the crude genotype categories which limited investigations of more refined alcohol consumption levels. Second, it is also possible that acetaldehyde exposure might also be derived from tobacco smoking

in alcohol drinkers,[309] potentially exaggerating the apparent gene-alcohol interaction, although the joint effect analyses have been adjusted for smoking. Similarly, there is a possibility that the increased risks associated with the *ALDH2*-rs671 AA and AG versus the GG genotype for some cancers among women in the CKB (who rarely consumed alcohol and, if so, only at low intake levels) might be related to acetaldehyde exposure from other sources (e.g., air pollution, cooking oil fumes, passive smoking) or endogenous exposure,[20,310] while the possibility of chance finding cannot be ruled out. Further research is needed to clarify the causal role of alcohol in lung cancer and the mechanistic role of alcohol in other IARC alcohol-related cancers.

Other than acetaldehyde, other plausible mechanisms through which alcohol may act on cancer development have been described in Chapter 2 and briefly include: the induction of CYP2E1 and associated oxidative stress, particularly for liver cancer;[20,172] the solvent role for tobacco carcinogens for cancers of the upper digestive and respiratory tract;[173] alterations of hormones and related signalling pathways for breast cancer and possibly prostate cancer;[173] liver cirrhosis and pancreatitis as precursors of liver cancer and pancreatic cancer, respectively;[172,173] and changes in folate metabolism particularly for colorectal cancer.[20]

7.5.9 Strengths and Limitations

As already described in Chapter 5, the main strengths of the CKB study include the large and diverse study population, and the repeated and detailed measurement of alcohol drinking patterns and potential covariates. In addition, the completeness of follow-up, the large number of incidents for a wide range of cancer sites traced via comprehensive follow-up systems, the stringent exclusions of prior diseases and early

follow-up in main and sensitivity analyses to reduce reverse causation, and the adjustment for regression dilution bias further added values to the present study. Moreover, ongoing cancer outcome adjudication via review of medical notes showed a ~90% diagnosis reporting accuracy for most cancers studied in this chapter, suggesting good quality of cancer outcome data. However, the present study also has limitations (as mentioned in Chapter 6), of which many are common to observational studies, including potential self-reported bias on alcohol intake and residual confounding, e.g., *H. pylori* and folate intake. Moreover, the statistical power was limited for non-common cancer sites and among women, and the present study lacked sufficient information for investigation across cancer subtypes. As smoking status was self-reported and never regular smokers included those who smoked occasionally (detailed definition in Chapter 4), there may be potential residual confounding in never regular smokers. Nevertheless, the self-reported smoking data has been validated using COex test, which showed a much higher mean COex level in current regular smokers than in participants in other smoking categories (among whom the COex level was similar),[199] and this should help reduce residual confounding due to underreported smoking among never regular smokers.

7.6 Conclusions

In summary, in this large prospective study of Chinese men, alcohol consumption was positively associated with risks of several site-specific cancers, some known (e.g., cancers of mouth and throat, oesophagus, liver, colon and rectum) while others less clearly established (e.g., lung, gallbladder) to be alcohol-related from previous studies in Western and other high-income populations. As well as total amount consumed,

certain drinking patterns (e.g., daily drinking and drinking without meals) and reduced alcohol tolerance may further exacerbate the risks for certain cancers. Given the substantial cancer burden attributed to alcohol consumption, effective public health measures are needed to limit the adverse consequences of alcohol consumption in China.

Table 7.1. Number of incident cancer cases reported in men and women in the CKB

Cancer site (ICD-10 code)	No of cases in men	No of cases in women
Mouth and throat (C00-C14, C32)	541	312
Oesophagus (C15)	1608	740
Colon and rectum (C18-C20)	1527	1529
Colon (C18)	856	901
Rectum (C19-C20)	946	883
Liver (C22)[*]	1651	975
Female breast (C50)	--	2289
Stomach (C16)	2221	1123
Pancreas (C25)	405	399
Lung (including trachea) (C33-C34)[†]	2741	2020
Gallbladder, other and unspecified parts of biliary tract (C23-C24)	279	356
Skin (C43-C44)	137	130
Cervix uteri (C53)	--	1054
Corpus uteri (C54)	--	492
Endometrium (C54.1)	--	410
Uterus (C55)	--	333
Ovary (C56)	--	433
Prostate (C61)	402	--
Kidney (C64)	219	204
Bladder (C67)	356	164
Brain (C71)	227	270
Thyroid (C73)	84	461
Lymphoma (C81-C85)	402	421
Multiple myeloma and malignant plasma cell neoplasms (C90)	137	114
Leukaemia (C91-C95)	287	321
Other less common cancers of known sites	935	925
IARC alcohol-related cancers (C00-C15, C32, C18-C20, C22, C50)	5403	5754
Other cancers of known sites (Non-IARC alcohol-related)	8730	8318
All cancers[‡]	13342	13619

ICD-10, international classification of diseases, 10th revision; IARC, international agency for research on cancer.
Participants with prior cancer were excluded.
[*]Further excluded participants with prior cirrhosis or chronic hepatitis.
[†]Further excluded participants with prior tuberculosis, emphysema or bronchitis, or chronic obstructive pulmonary disease (both self-reported and screen-detected).
[‡]All cancers included ill-defined neoplasm and are patient-based.

Table 7.2. Baseline characteristics of participants by incident cancer outcome, in men and women

	Men			Women		
	All	No cancer	Developed cancer	All	No cancer	Developed cancer
Number of participants	209237	195895	13342	300900	287281	13619
Socio-demographic characteristics						
Mean age, years (SD)	52.8 (10.9)	52.3 (10.8)	60.0 (9.7)	51.4 (10.5)	51.2 (10.4)	55.9 (10.5)
Urban area, %	43.4	43.3	44.1	44.5	44.3	49.7
Educational attainment >6 years, %	57.8	58.0	54.3	43.3	43.3	42.9
Household income ≥20000 yuan/year, %	45.7	45.8	43.1	40.7	40.7	40.8
Married, %	92.9	92.9	92.7	89.0	89.0	89.0
Lifestyle factors						
Regular smoking, %	61.2	60.8	66.8	2.4	2.3	2.9
Non-regular fresh fruit intake, %	77.0	76.9	78.3	68.3	68.3	68.0
Physical activity, mean MET-h/d (SD)	22.1 (15.3)	22.1 (15.3)	21.4 (14.6)	20.5 (12.8)	20.5 (12.8)	20.0 (11.8)
Daily tea drinking, %	40.9	40.7	42.7	15.9	15.9	16.2
Physical measurements, mean (SD)						
Standing height, cm	165.2 (6.5)	165.2 (6.5)	165.4 (6.4)	154.1 (6.0)	154.1 (6.0)	154.4 (6.1)
BMI, kg/m^2	23.4 (3.2)	23.5 (3.2)	23.2 (3.3)	23.8 (3.5)	23.8 (3.4)	23.9 (3.6)
SBP, mmHg	132.8 (20.0)	132.9 (19.9)	132.4 (21.4)	129.9 (22.0)	129.9 (21.9)	129.9 (22.7)
DBP, mmHg	79.2 (11.4)	79.2 (11.4)	78.9 (11.6)	76.8 (10.9)	76.8 (10.9)	76.7 (11.0)
Health and medical history[*], %						
Poor health	8.8	8.7	10.5	11.3	11.2	12.7
Any chronic disease[†]	22.2	22.1	25.3	21.7	21.6	24.2
Coronary heart disease	2.7	2.7	2.6	3.2	3.2	3.6
Stroke or TIA	2.3	2.4	2.1	1.3	1.3	1.4
Cirrhosis or chronic hepatitis	1.7	1.6	3.6	0.8	0.8	1.0
Emphysema or bronchitis	3.1	3.1	3.4	2.2	2.2	2.7
COPD	8.8	8.7	9.9	6.2	6.1	6.7
Diabetes	5.5	5.5	6.2	6.1	6.1	6.8
Family history of cancer	16.5	16.3	19.0	16.3	16.2	18.2

SD, standard deviation; MET-h/d, metabolic equivalents of task per hours per day; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease.

Prevalences and means are adjusted for age and study area as appropriate.

Participants with prior cancer were excluded.

[*]All self-reported except for diabetes and COPD which included both self-reported and screen-detected events.

[†]Chronic diseases included self-reported coronary heart diseases, stroke or TIA, diabetes, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, and kidney disease.

Table 7.3. Adjusted HRs for incident cancers associated with alcohol drinking status, in men

		Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Mouth and throat	541	90	1.00 (0.81-1.24)	61	1.46 (1.13-1.88)	154	1.22 (1.03-1.44)	236	1.73 (1.51-1.99)	*<0.0001*
Oesophagus	1608	243	1.00 (0.88-1.14)	152	1.23 (1.05-1.44)	558	1.05 (0.96-1.15)	655	1.80 (1.66-1.96)	*<0.0001*
Colon and rectum	1527	306	1.00 (0.89-1.13)	203	1.27 (1.10-1.46)	443	0.95 (0.86-1.05)	575	1.20 (1.10-1.31)	*0.0155*
Colon	856	180	1.00 (0.86-1.17)	118	1.28 (1.06-1.53)	255	0.93 (0.81-1.05)	303	1.11 (0.98-1.25)	*0.3064*
Rectum	946	185	1.00 (0.86-1.16)	122	1.22 (1.02-1.46)	261	0.93 (0.82-1.06)	378	1.26 (1.13-1.40)	*0.0170*
Liver	1651	378	1.00 (0.90-1.11)	208	1.23 (1.07-1.41)	492	0.83 (0.76-0.92)	573	1.06 (0.97-1.16)	*0.3866*
Stomach	2221	520	1.00 (0.91-1.10)	242	1.00 (0.88-1.13)	702	0.87 (0.81-0.95)	757	1.02 (0.94-1.10)	*0.7721*
Pancreas	405	89	1.00 (0.80-1.25)	40	0.96 (0.70-1.32)	111	0.97 (0.80-1.18)	165	1.26 (1.07-1.49)	*0.0951*
Lung	2741	660	1.00 (0.92-1.08)	344	1.07 (0.97-1.20)	720	0.80 (0.74-0.86)	1017	0.96 (0.90-1.03)	*0.4755*
Gallbladder	279	54	1.00 (0.76-1.32)	29	1.02 (0.71-1.48)	89	1.31 (1.05-1.64)	107	1.33 (1.09-1.62)	*0.1101*
Skin	137	41	1.00 (0.72-1.39)	17	1.00 (0.61-1.62)	44	0.83 (0.61-1.14)	35	0.65 (0.46-0.92)	*0.0799*
Prostate	402	110	1.00 (0.82-1.22)	64	1.25 (0.97-1.60)	120	1.00 (0.83-1.21)	108	0.89 (0.73-1.08)	*0.4066*
Kidney	219	34	1.00 (0.70-1.43)	28	1.52 (1.04-2.21)	73	1.15 (0.91-1.47)	84	1.27 (1.01-1.60)	*0.2647*
Bladder	356	89	1.00 (0.80-1.25)	57	1.14 (0.88-1.49)	96	0.73 (0.60-0.91)	114	0.75 (0.61-0.90)	*0.0527*
Brain	227	48	1.00 (0.74-1.35)	29	1.12 (0.77-1.62)	80	0.92 (0.73-1.16)	70	0.82 (0.64-1.04)	*0.3141*
Thyroid	84	12	1.00 (0.55-1.82)	10	1.66 (0.88-3.13)	27	0.96 (0.65-1.43)	35	1.18 (0.83-1.68)	*0.6349*
Lymphoma	402	104	1.00 (0.82-1.23)	49	1.02 (0.77-1.36)	115	0.88 (0.73-1.07)	134	0.92 (0.77-1.10)	*0.5567*
Multiple myeloma	137	34	1.00 (0.70-1.43)	10	0.62 (0.33-1.16)	44	0.89 (0.65-1.21)	49	1.01 (0.75-1.36)	*0.9599*
Leukaemia	287	63	1.00 (0.77-1.30)	31	1.15 (0.80-1.64)	86	0.87 (0.70-1.09)	107	1.14 (0.94-1.40)	*0.4267*
Other less common cancers of known sites	935	208	1.00 (0.87-1.15)	122	1.21 (1.01-1.45)	280	0.94 (0.83-1.06)	325	1.05 (0.94-1.18)	*0.5965*
IARC alcohol-related cancers	5403	1056	1.00 (0.94-1.07)	673	1.30 (1.20-1.40)	1669	0.92 (0.88-0.97)	2005	1.26 (1.20-1.32)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	8730	2085	1.00 (0.96-1.05)	1076	1.07 (1.00-1.13)	2523	0.87 (0.83-0.90)	3046	0.99 (0.95-1.03)	*0.7579*
All cancers†	13342	2991	1.00 (0.96-1.04)	1647	1.14 (1.08-1.20)	3947	0.88 (0.85-0.91)	4757	1.07 (1.04-1.10)	*0.0064*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for association comparing current regular drinkers vs. abstainers.

†All cancers included ill-defined neoplasm and are patient-based.

Table 7.4. *ALDH2*-rs671 and *ADH1B*-rs1229984 genotype and allele frequencies across the ten study areas in the CKB

	ALDH2-rs671					*ADH1B*-rs1229984				
		Genotype frequency, %					Genotype frequency, %			
	N	GG	AG	AA	A-allele frequency	N	GG	AG	AA	A-allele frequency
Study area										
Harbin (Urban)	19586	69.9	27.3	2.7	0.16	19571	10.8	44.6	44.5	0.67
Qingdao (Urban)	12314	66.6	30.3	3.1	0.18	12304	9.8	42.9	47.1	0.69
Suzhou (Urban)	15791	59.5	35.4	5.1	0.23	15789	8.6	41.0	50.3	0.71
Liuzhou (Urban)	15132	57.5	36.3	6.2	0.24	15124	8.8	41.7	49.4	0.70
Haikou (Urban)	8299	49.9	41.2	8.8	0.29	8297	6.9	38.4	54.6	0.74
Gansu (Rural)	18560	73.8	24.2	2.0	0.14	18552	13.1	46.4	40.5	0.64
Henan (Rural)	19732	75.5	22.8	1.7	0.13	19716	11.5	44.7	43.6	0.66
Sichuan (Rural)	18306	65.4	31.1	3.5	0.19	18296	10.2	43.3	46.4	0.68
Zhejiang (Rural)	19665	52.4	39.7	7.9	0.28	19660	8.0	40.7	51.3	0.72
Hunan (Rural)	19724	53.9	39.4	6.8	0.26	19706	7.7	39.5	52.7	0.73
Urban	71122	62.0	33.2	4.7	0.21	71085	9.3	42.2	48.5	0.70
Rural	95987	64.1	31.5	4.4	0.20	95930	10.1	42.9	47.0	0.68
All areas	167109	63.2	32.2	4.6	0.21	167015	9.7	42.6	47.6	0.69

Within rural and urban level, the study areas are ordered from North to South.
Participants with prior cancer were excluded.

Table 7.5. Prevlanece and patterns of alcohol drinking by *ALDH2*-rs671 and by *ADH1B*-rs1229984 genotype, in men and women

	ALDH2-rs671			*ADH1B*-rs1229984		
	GG	**AG**	**AA**	**GG**	**AG**	**AA**
Men						
Number of men	43621	22460	3131	6564	29549	33046
Abstainers, %	10.3	32.7	72.1	16.4	21.3	21.8
Ex-regular drinkers, %	11.3	6.1	1.4	9.4	8.7	9.1
Occasional drinkers, %	33.1	45.3	25.4	31.6	36.8	37.4
Current regular drinkers, %	45.3	15.9	1.1	42.6	33.2	31.7
Mean alcohol consumption, g/week (SD)	304.8 (254.7)	203.4 (202.8)	138.2 (194.1)	333.5 (291.9)	287.9 (242.2)	278.3 (244.3)
Daily drinking, %	64.0	55.3	62.1	67.8	63.0	60.7
HED*, %	40.6	21.3	4.8	42.0	37.8	36.4
Drinking outside meals, %	14.6	15.7	11.4	15.4	14.7	14.8
Flushing response, %	11.5	55.4	61.9	14.0	18.1	19.5
Age started regular drinking, year (SD)	28.0 (11.0)	32.2 (11.6)	37.8 (15.3)	28.4 (10.8)	28.8 (11.2)	28.7 (11.2)
Spirits drinking*, %	71.8	64.1	37.0	69.1	71.0	70.5
Women						
Number of women	62022	31399	4476	9698	41622	46536
Abstainers, %	59.5	71.1	87.1	61.0	64.1	65.1
Ex-regular drinkers, %	1.2	0.4	0.1	1.0	1.0	0.8
Occasional drinkers, %	36.4	27.7	12.5	34.7	32.9	32.1
Current regular drinkers, %	2.9	0.8	0.2	3.3	2.1	1.9
Mean alcohol consumption, g/week (SD)	119.3 (126.3)	84.4 (79.2)	--	131.4 (160.8)	113.5 (116.6)	111.3
Daily drinking, %	46.0	48.3	--	49.4	46.3	44.9
HED*, %	28.5	11.7	--	30.6	27.3	25.1
Drinking outside meals, %	13.0	15.3	--	14.7	14.0	13.5
Flushing response, %	17.9	60.0	--	17.5	23.2	24.2
Age started regular drinking, year (SD)	37.0 (13.5)	42.2 (13.7)	--	37.8 (13.1)	37.8 (13.8)	37.3 (13.8)
Spirits drinking*, %	62.2	56.4	--	62.8	60.8	61.0

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Participants with prior cancer were excluded.

*Based on a typical drinking day.

Table 7.6. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, in men

		GG		AG			AA		
Cancer site	**All N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***	**N**	**HR (95% CI)**	***p*-value***
Mouth and throat	181	108	1.00 (0.82-1.22)	69	1.08 (0.86-1.36)	*0.6213*	4	0.41 (0.15-1.08)	*0.0778*
Oesophagus	537	373	1.00 (0.89-1.12)	153	1.00 (0.86-1.17)	*0.9826*	11	0.69 (0.38-1.25)	*0.2275*
Colon and rectum	540	356	1.00 (0.90-1.12)	166	0.84 (0.73-0.98)	*0.0752*	18	0.64 (0.40-1.01)	*0.0638*
Liver	569	372	1.00 (0.90-1.12)	176	0.88 (0.76-1.02)	*0.1714*	21	0.73 (0.47-1.12)	*0.1612*
Stomach	722	485	1.00 (0.91-1.10)	215	0.93 (0.82-1.06)	*0.3776*	22	0.76 (0.50-1.16)	*0.2202*
Pancreas	111	76	1.00 (0.79-1.27)	33	0.79 (0.56-1.10)	*0.2514*	2	0.33 (0.08-1.34)	*0.1265*
Lung	916	545	1.00 (0.91-1.09)	327	1.06 (0.96-1.18)	*0.3748*	44	0.93 (0.69-1.25)	*0.6492*
IARC alcohol-related cancers	1853	1220	1.00 (0.94-1.06)	579	0.94 (0.87-1.02)	*0.2209*	54	0.65 (0.49-0.85)	*0.0019*
Other cancers of known sites (Non-IARC alcohol-related)	2938	1806	1.00 (0.95-1.05)	994	1.02 (0.96-1.08)	*0.6782*	138	0.99 (0.84-1.17)	*0.8997*
All cancers[†]	4537	2850	1.00 (0.96-1.04)	1502	1.00 (0.95-1.05)	*0.9066*	185	0.87 (0.75-1.01)	*0.0712*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

[*] *P* for association comparing the AA or the AG genotype with the GG genotype.

[†] All cancers included ill-defined neoplasm and are patient-based.

Table 7.7. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, by drinking status in men

			GG		AG			AA		
Cancer site	**Drinking status**	**All N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***	**N**	**HR (95% CI)**	***p*-value***
Mouth and throat	Never regular drinkers	85	36	1.00 (0.70-1.43)	45	1.10 (0.83-1.46)	*0.6838*	4	0.49 (0.18-1.31)	*0.1817*
	Current regular drinkers	72	53	1.00 (0.76-1.32)	19	1.88 (1.20-2.94)	*0.0192*	0	--	--
Oesophagus	Never regular drinkers	264	170	1.00 (0.83-1.21)	83	0.92 (0.76-1.13)	*0.5686*	11	1.07 (0.58-1.96)	*0.8374*
	Current regular drinkers	229	174	1.00 (0.84-1.19)	55	2.21 (1.71-2.86)	*<0.0001*	0	--	--
Colon and rectum	Never regular drinkers	265	127	1.00 (0.83-1.21)	122	0.90 (0.75-1.07)	*0.4018*	16	0.63 (0.39-1.04)	*0.0919*
	Current regular drinkers	206	180	1.00 (0.86-1.16)	26	0.80 (0.54-1.18)	*0.2895*	0	--	--
Liver	Never regular drinkers	295	140	1.00 (0.83-1.21)	134	1.01 (0.86-1.19)	*0.9326*	21	0.88 (0.57-1.35)	*0.5918*
	Current regular drinkers	201	173	1.00 (0.86-1.17)	28	0.95 (0.65-1.37)	*0.7847*	0	--	--
Stomach	Never regular drinkers	393	214	1.00 (0.85-1.18)	157	0.91 (0.79-1.06)	*0.4233*	22	0.86 (0.56-1.32)	*0.5211*
	Current regular drinkers	240	199	1.00 (0.86-1.16)	41	1.25 (0.92-1.70)	*0.1920*	0	--	--
Pancreas	Never regular drinkers	52	24	1.00 (0.64-1.57)	26	0.90 (0.63-1.31)	*0.7362*	2	0.37 (0.09-1.51)	*0.1895*
	Current regular drinkers	38	34	1.00 (0.71-1.41)	4	0.69 (0.26-1.85)	*0.4913*	0	--	--
Lung	Never regular drinkers	449	168	1.00 (0.85-1.18)	238	1.29 (1.14-1.45)	*0.0174*	43	1.17 (0.87-1.59)	*0.3620*
	Current regular drinkers	347	295	1.00 (0.89-1.12)	51	0.95 (0.72-1.25)	*0.7411*	1	2.00 (0.28-14.28)	*0.4911*
IARC alcohol-related cancers	Never regular drinkers	933	481	1.00 (0.90-1.11)	400	0.98 (0.89-1.07)	*0.7684*	52	0.75 (0.57-0.98)	*0.0506*
	Current regular drinkers	700	573	1.00 (0.92-1.09)	127	1.34 (1.13-1.59)	*0.0033*	0	--	--
Other cancers of known sites (Non-IARC alcohol-related)	Never regular drinkers	1546	661	1.00 (0.92-1.09)	753	1.12 (1.04-1.20)	*0.0486*	132	1.10 (0.92-1.30)	*0.3522*
	Current regular drinkers	999	853	1.00 (0.93-1.07)	145	1.00 (0.85-1.17)	*0.9724*	1	0.91 (0.13-6.44)	*0.9232*
All cancers†	Never regular drinkers	2342	1063	1.00 (0.93-1.07)	1101	1.09 (1.03-1.15)	*0.0557*	178	1.00 (0.86-1.16)	*0.9683*
	Current regular drinkers	1609	1347	1.00 (0.94-1.06)	261	1.14 (1.01-1.29)	*0.0489*	1	0.61 (0.09-4.31)	*0.6204*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area.

Ex-regular drinkers and participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for association comparing the AA or the AG genotype with the GG genotype.

†All cancers included ill-defined neoplasm and are patient-based.

Table 7.8. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in men

		GG		AG			AA		
Cancer site	**All N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***	**N**	**HR (95% CI)**	***p*-value***
Mouth and throat	180	26	1.00 (0.68-1.47)	74	0.58 (0.46-0.73)	*0.0181*	80	0.53 (0.43-0.66)	*0.0053*
Oesophagus	538	84	1.00 (0.81-1.24)	242	0.64 (0.56-0.73)	*0.0004*	212	0.54 (0.47-0.62)	*<0.0001*
Colon and rectum	540	43	1.00 (0.74-1.35)	238	1.14 (1.01-1.30)	*0.4191*	259	1.09 (0.97-1.24)	*0.5915*
Liver	569	63	1.00 (0.78-1.28)	226	0.77 (0.67-0.87)	*0.0644*	280	0.85 (0.76-0.96)	*0.2537*
Stomach	722	71	1.00 (0.79-1.26)	319	0.98 (0.88-1.10)	*0.8994*	332	0.95 (0.86-1.06)	*0.7225*
Pancreas	111	14	1.00 (0.59-1.69)	44	0.64 (0.48-0.86)	*0.1441*	53	0.70 (0.53-0.92)	*0.2360*
Lung	916	77	1.00 (0.80-1.25)	396	1.06 (0.96-1.17)	*0.6336*	443	1.03 (0.94-1.13)	*0.7938*
IARC alcohol-related cancers	1853	220	1.00 (0.88-1.14)	795	0.77 (0.72-0.83)	*0.0006*	838	0.73 (0.69-0.79)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	2939	270	1.00 (0.89-1.13)	1250	0.96 (0.91-1.02)	*0.5721*	1419	0.97 (0.92-1.02)	*0.6480*
All cancers†	4537	471	1.00 (0.91-1.09)	1938	0.86 (0.83-0.90)	*0.0042*	2128	0.85 (0.81-0.88)	*0.0010*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for association comparing the AA or the AG genotype with the GG genotype.

†All cancers included ill-defined neoplasm and are patient-based.

Table 7.9. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, by drinking status in men

			GG		AG			AA		
Cancer site	**Drinking status**	**All N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***	**N**	**HR (95% CI)**	***p*-value***
Mouth and throat	Never regular drinkers	84	8	1.00 (0.50-2.01)	38	0.77 (0.56-1.06)	*0.5023*	38	0.64 (0.46-0.88)	*0.2514*
	Current regular drinkers	72	14	1.00 (0.59-1.69)	25	0.48 (0.33-0.72)	*0.0304*	33	0.56 (0.40-0.79)	*0.0737*
Oesophagus	Never regular drinkers	264	37	1.00 (0.72-1.38)	126	0.71 (0.60-0.85)	*0.0712*	101	0.58 (0.48-0.71)	*0.0049*
	Current regular drinkers	230	43	1.00 (0.74-1.35)	93	0.58 (0.47-0.71)	*0.0035*	94	0.57 (0.46-0.70)	*0.0022*
Colon and rectum	Never regular drinkers	265	21	1.00 (0.65-1.54)	118	0.96 (0.80-1.14)	*0.8522*	126	0.87 (0.73-1.04)	*0.5608*
	Current regular drinkers	206	19	1.00 (0.64-1.57)	92	1.31 (1.07-1.61)	*0.2849*	95	1.26 (1.03-1.54)	*0.3671*
Liver	Never regular drinkers	295	27	1.00 (0.68-1.46)	113	0.76 (0.63-0.91)	*0.1943*	155	0.93 (0.79-1.09)	*0.7171*
	Current regular drinkers	201	30	1.00 (0.70-1.43)	82	0.72 (0.58-0.90)	*0.1256*	89	0.73 (0.59-0.90)	*0.1384*
Stomach	Never regular drinkers	393	37	1.00 (0.72-1.38)	173	0.91 (0.78-1.06)	*0.6061*	183	0.92 (0.79-1.06)	*0.6431*
	Current regular drinkers	240	27	1.00 (0.68-1.46)	109	1.09 (0.90-1.32)	*0.6893*	104	0.97 (0.80-1.18)	*0.8906*
Pancreas	Never regular drinkers	52	5	1.00 (0.41-2.42)	21	0.72 (0.47-1.10)	*0.5055*	26	0.77 (0.52-1.14)	*0.6042*
	Current regular drinkers	38	7	1.00 (0.47-2.11)	15	0.51 (0.31-0.86)	*0.1488*	16	0.52 (0.32-0.86)	*0.1555*
Lung	Never regular drinkers	449	20	1.00 (0.64-1.55)	190	1.66 (1.44-1.92)	*0.0306*	239	1.76 (1.55-2.00)	*0.0155*
	Current regular drinkers	347	38	1.00 (0.73-1.38)	166	1.13 (0.97-1.32)	*0.4973*	143	0.90 (0.76-1.06)	*0.5565*
IARC alcohol-related cancers	Never regular drinkers	932	93	1.00 (0.81-1.23)	413	0.82 (0.74-0.90)	*0.0827*	426	0.77 (0.69-0.84)	*0.0203*
	Current regular drinkers	701	108	1.00 (0.83-1.21)	286	0.71 (0.63-0.80)	*0.0028*	307	0.71 (0.64-0.80)	*0.0028*
Other cancers of known sites (Non-IARC alcohol-related)	Never regular drinkers	1546	114	1.00 (0.83-1.20)	660	1.01 (0.94-1.09)	*0.8934*	772	1.04 (0.97-1.12)	*0.6749*
	Current regular drinkers	1000	118	1.00 (0.83-1.20)	444	1.00 (0.91-1.10)	*0.9922*	438	0.91 (0.82-1.00)	*0.3419*
All cancers†	Never regular drinkers	2341	196	1.00 (0.87-1.15)	1019	0.93 (0.87-0.98)	*0.3218*	1126	0.90 (0.85-0.96)	*0.1981*
	Current regular drinkers	1610	218	1.00 (0.88-1.14)	687	0.84 (0.78-0.91)	*0.0253*	705	0.80 (0.74-0.86)	*0.0035*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area.

Ex-regular drinkers and participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for association comparing the AA or the AG genotype with the GG genotype.

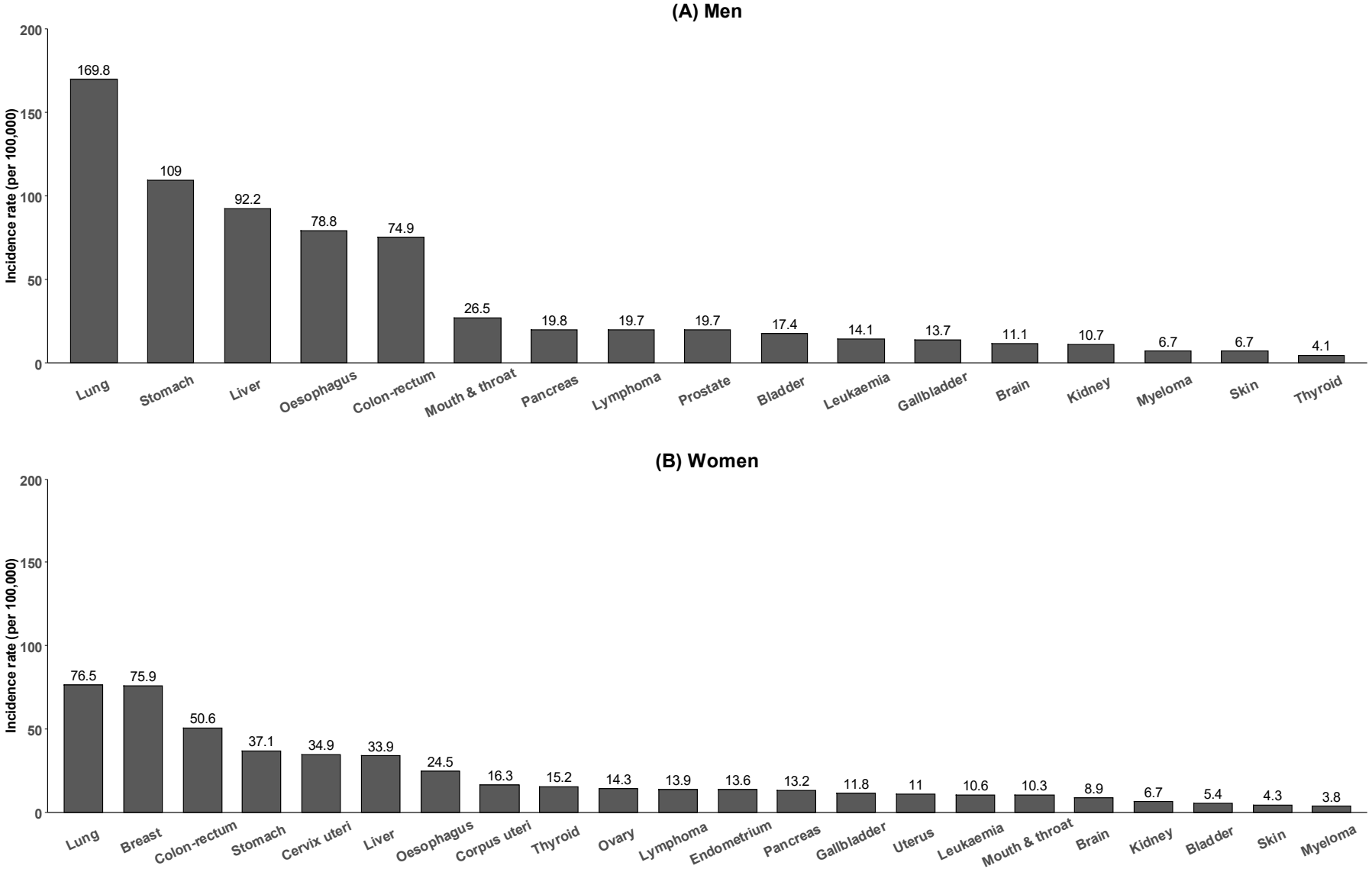
†All cancers included ill-defined neoplasm and are patient-based.

Table 7.10. Population attributable fraction of ever regular drinking on cancers in men in the CKB

Cancer site	N	HR (95% CI)	P	PAF, %
Mouth and throat	541	1.48 (1.23-1.77)	*0.55*	17.7
Oesophagus	1608	1.60 (1.43-1.78)	*0.50*	18.8
Colon and rectum	1527	1.26 (1.13-1.40)	*0.51*	10.4
Colon	856	1.21 (1.05-1.39)	*0.49*	8.5
Rectum	946	1.30 (1.14-1.49)	*0.53*	12.3
Liver	1651	1.23 (1.11-1.37)	*0.47*	8.9
Stomach	2221	1.10 (1.00-1.20)	*0.45*	4.0
Pancreas	405	1.21 (0.98-1.49)	*0.51*	8.7
Lung	2741	1.12 (1.04-1.22)	*0.50*	5.4
IARC alcohol-related cancers	5403	1.33 (1.26-1.41)	*0.50*	12.4
Other cancers of known sites (Non-IARC alcohol-related)	8730	1.10 (1.05-1.15)	*0.47*	4.2
All cancers[†]	13342	1.18 (1.13-1.22)	*0.48*	7.2

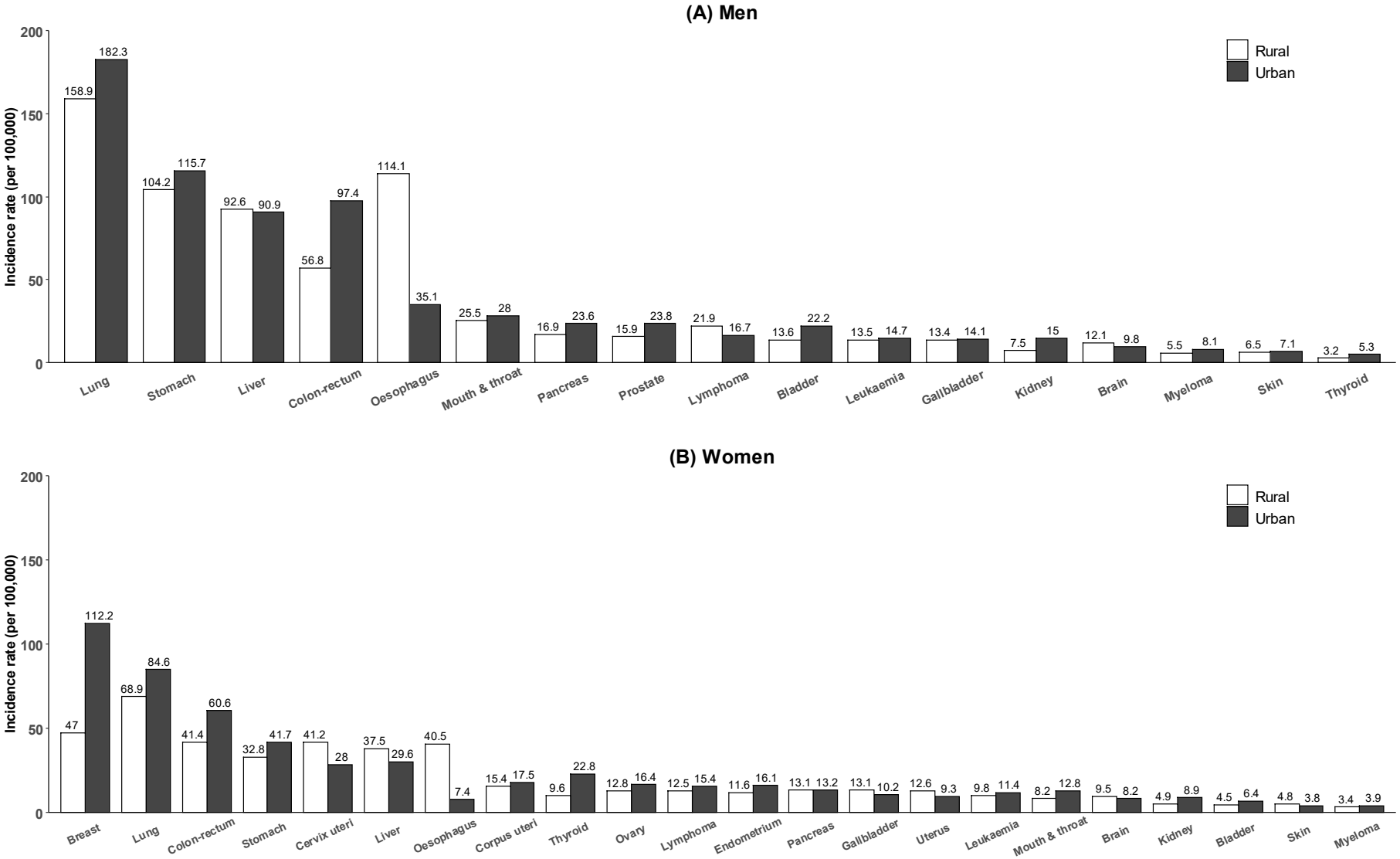
HR, hazard ratio; CI, confidence interval; P, prevalence of ever regular drinking; PAF, population attributable fraction.
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.
Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.
PAF is calculated as P x (HR-1)/HR, where P is the prevalence of ever regular alcohol consumption (i.e., current and ex-regular drinking) among CKB male participants who developed the relevant cancer during follow-up.
[†]All cancers included ill-defined neoplasm and are patient-based.

Figure 7.1. Incidence rates (per 100,000 person-years) of site-specific cancers, in men and women



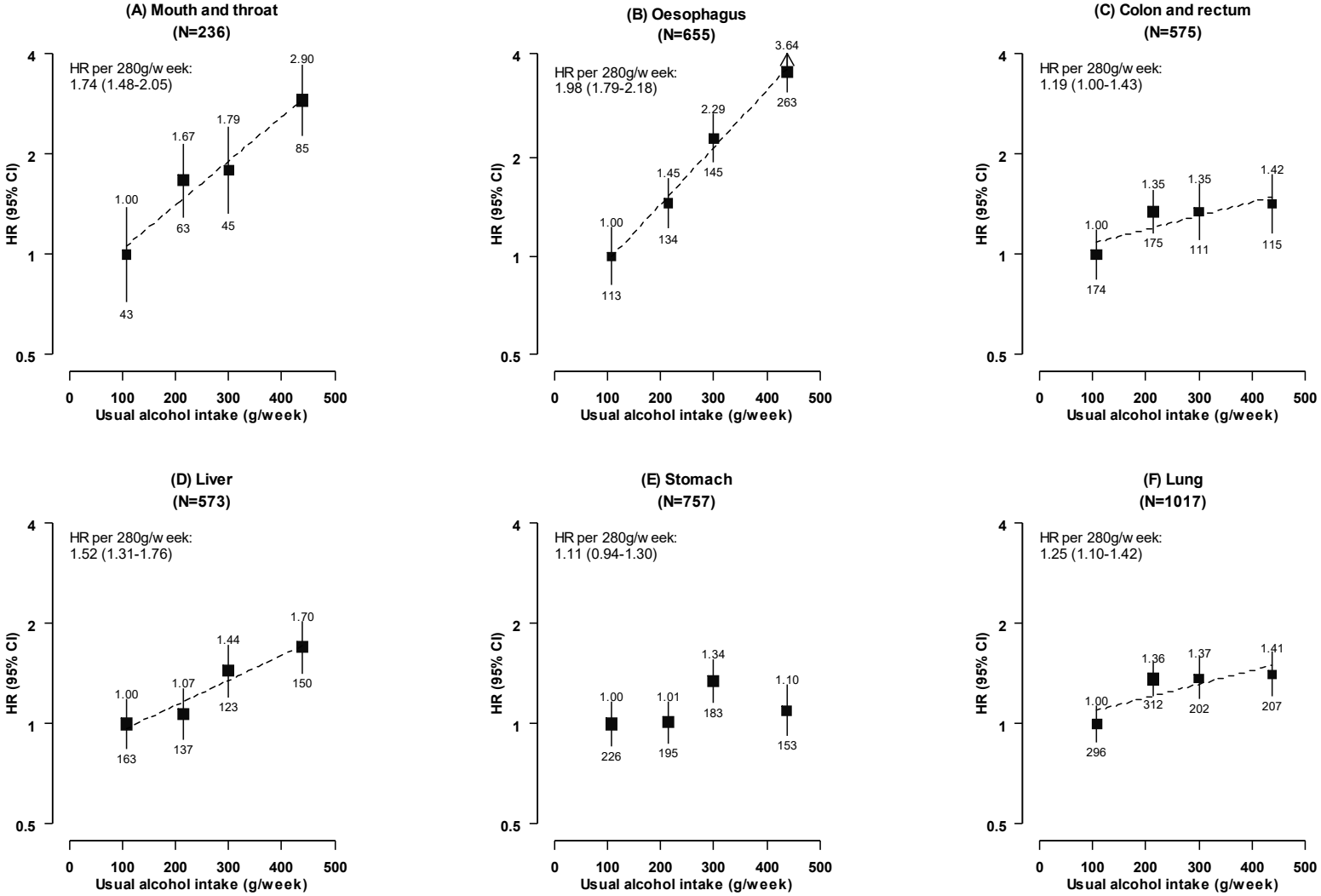
Participants with prior cancer were excluded.

Figure 7.2. Age-standardised incidence rates (per 100,000 person years) of site-specific cancers, by rural and urban areas



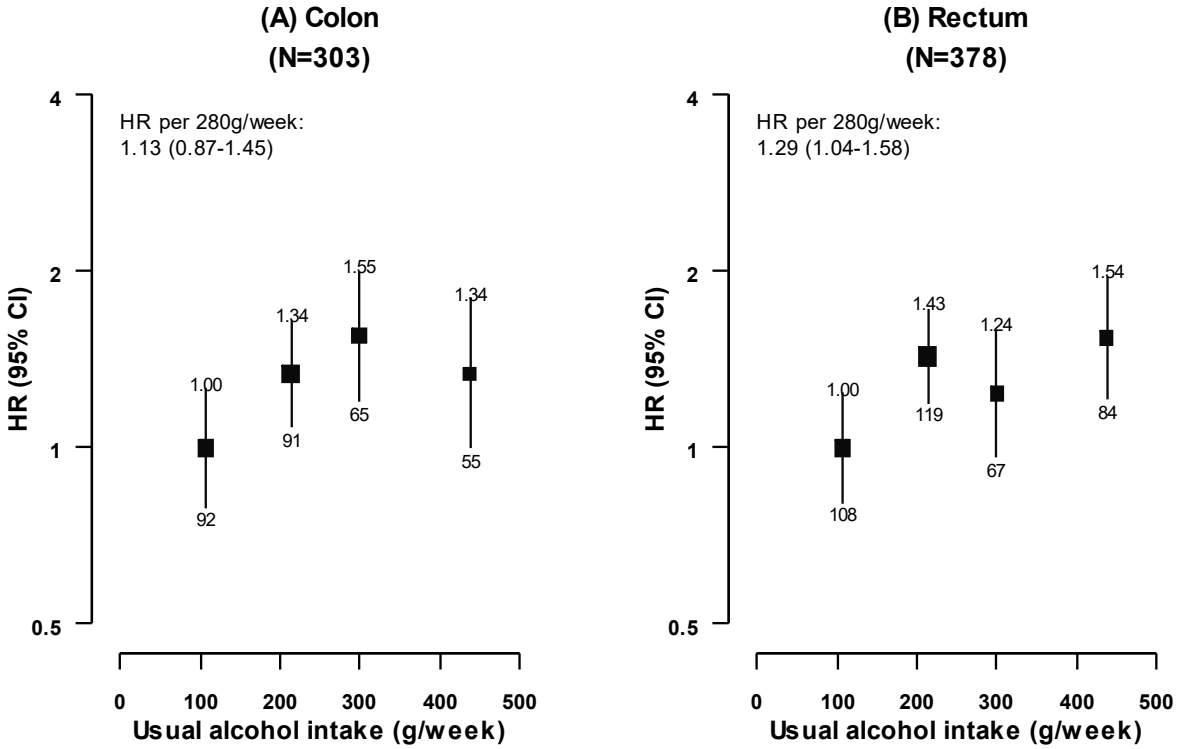
Incidence rates are standardised to the age (10-year intervals) structure of the China Kadoorie Biobank study population in men and women separately. Participants with prior cancer were excluded.

Figure 7.3. Associations of alcohol consumption with common cancers, in male current regular drinkers



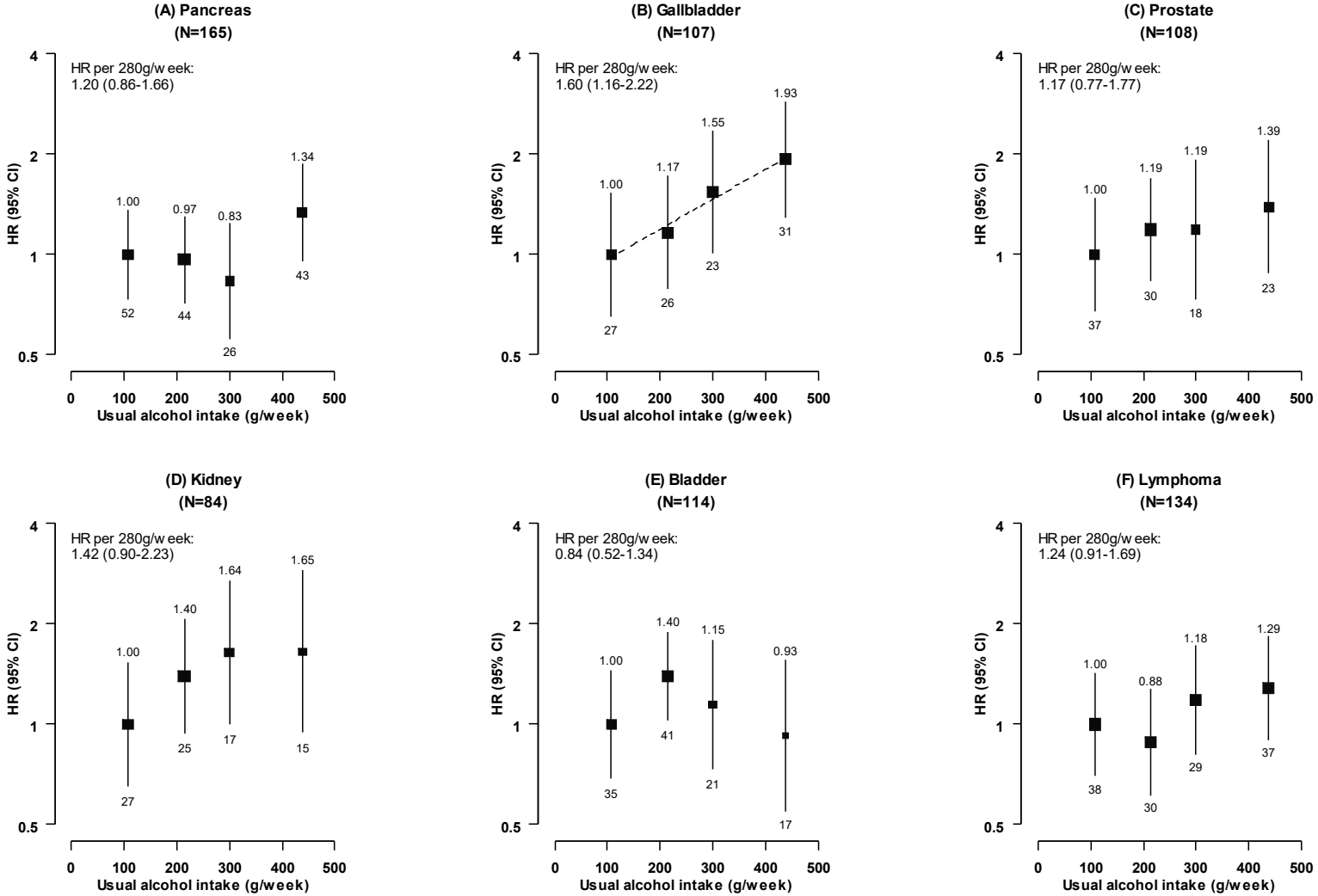
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Figures 7.3A-7.3D are IARC alcohol-related cancers. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. A regression line is fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group, when an approximately linear trend is observed and the HR per 280g/week increment is significant. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure 7.4. Associations of alcohol consumption with colon cancer and rectal cancer, in male current regular drinkers



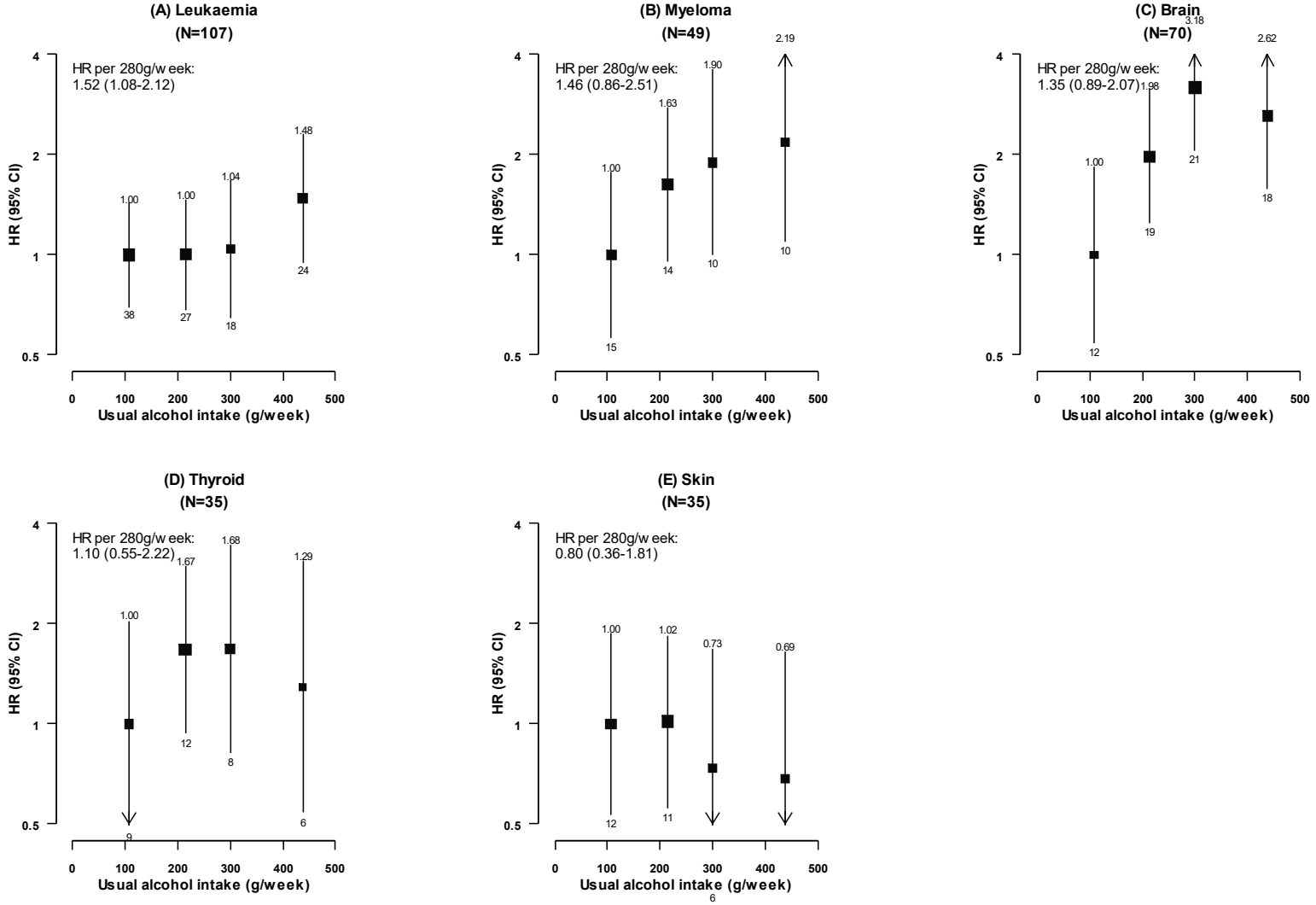
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure 7.5. Associations of alcohol consumption with less common cancers, in male current regular drinkers



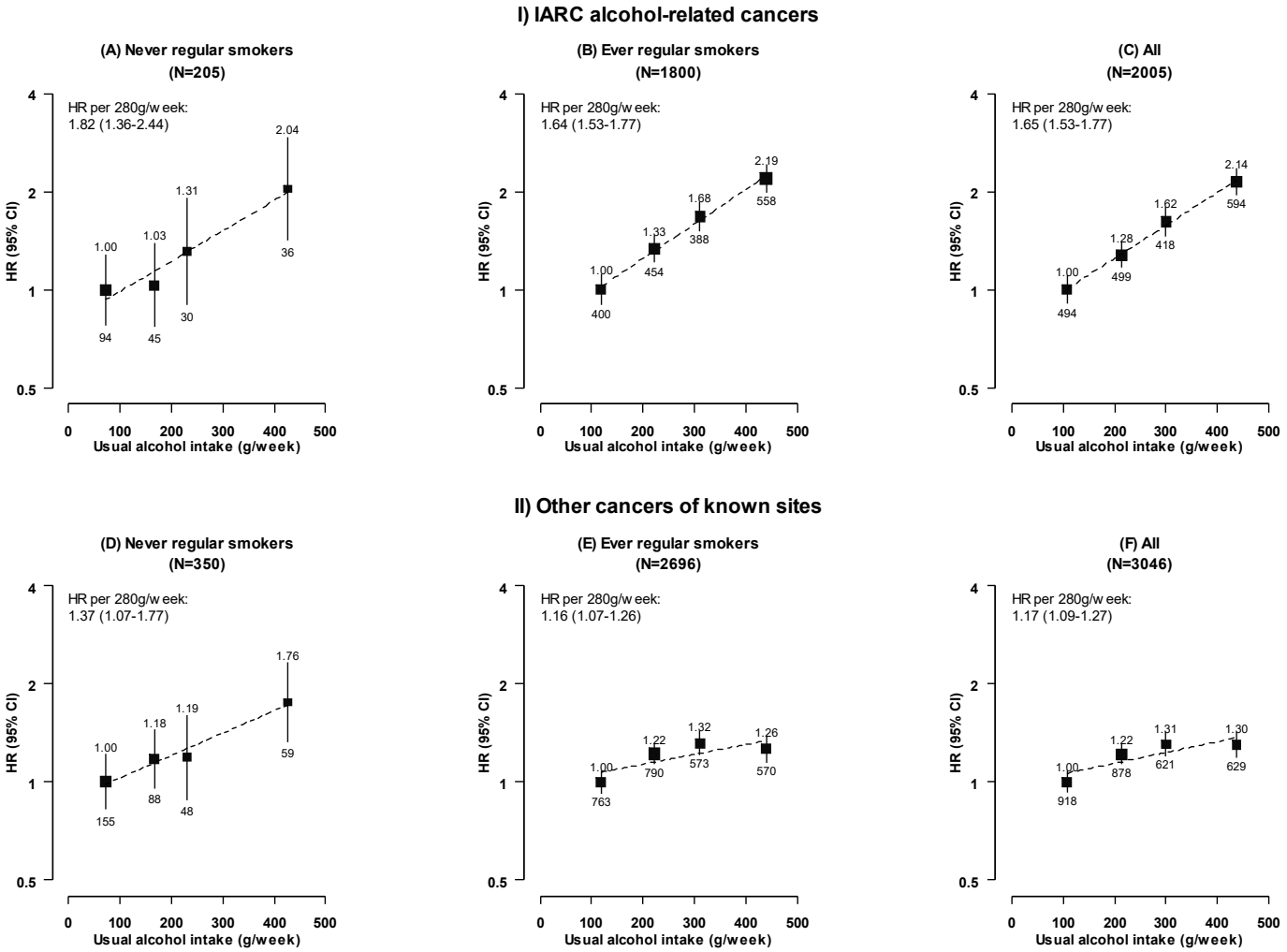
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. A regression line is fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group, when an approximately linear trend is observed and the HR per 280g/week increment is significant. HR, hazard ratio; CI, confidence interval.

Figure 7.6. Associations of alcohol consumption with other less common cancers, in male current regular drinkers



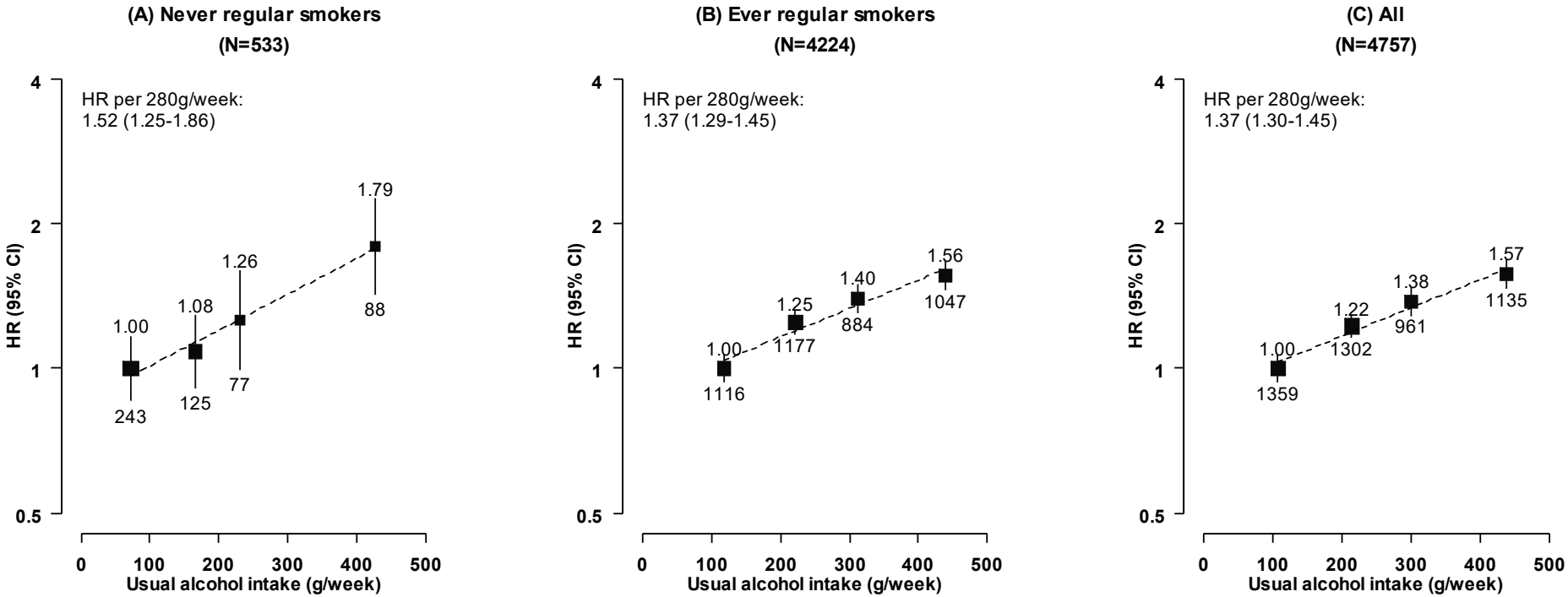
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure 7.7. Associations of alcohol consumption with IARC alcohol-related cancers and other cancers, by smoking status in male current regular drinkers



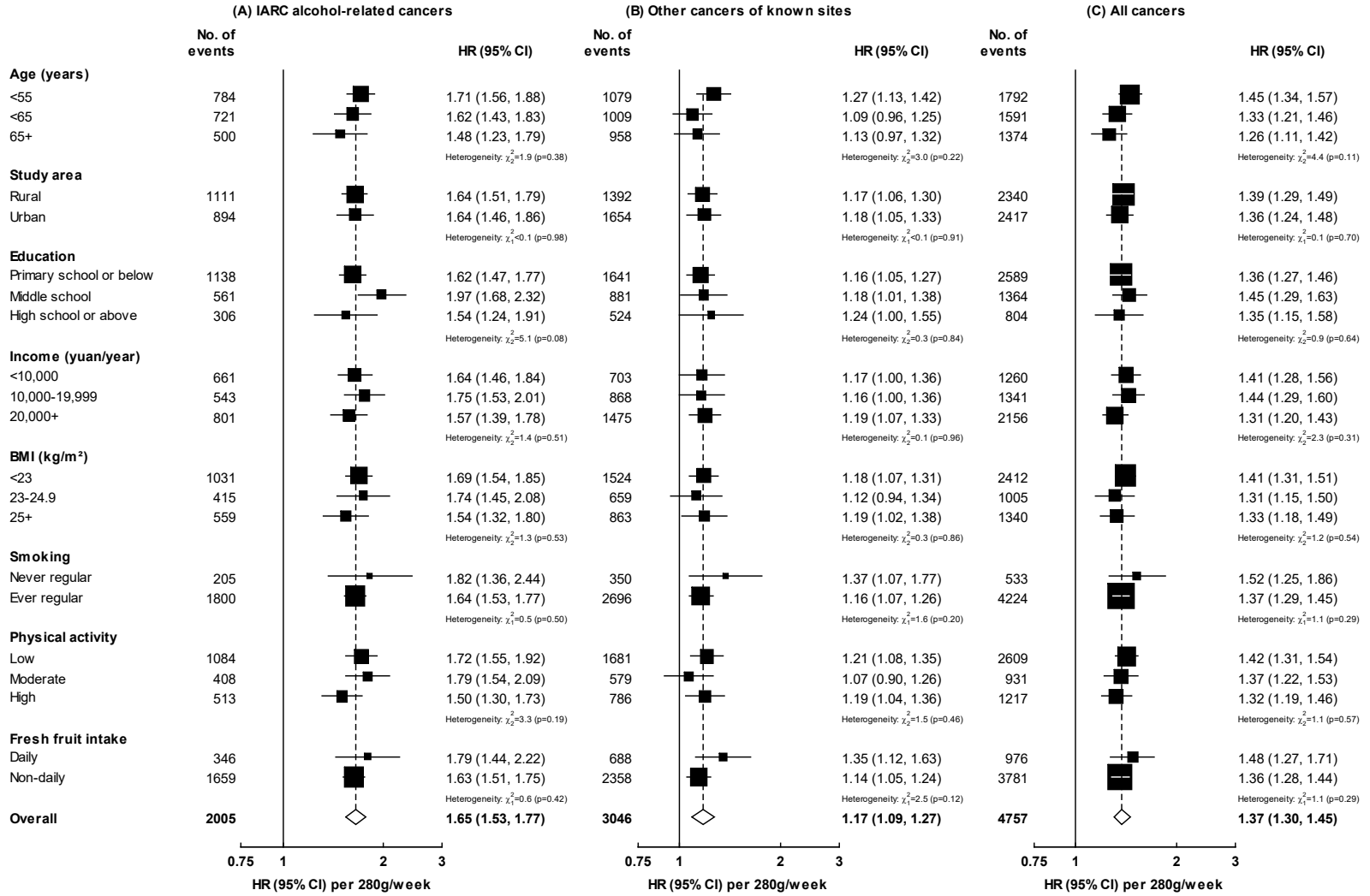
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The regression lines are fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure 7.8. Associations of alcohol consumption with overall cancer, by smoking status in male current regular drinkers



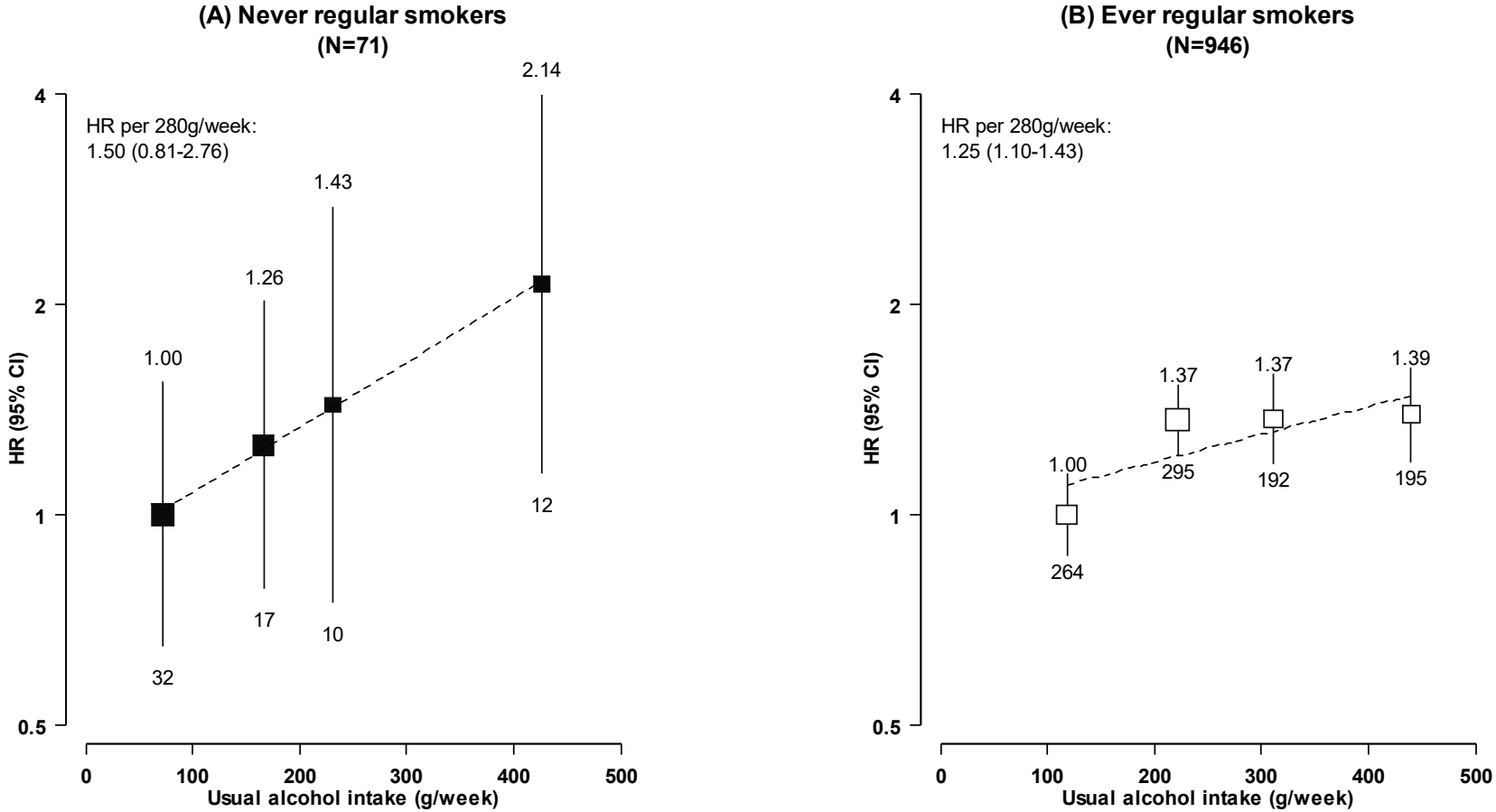
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The regression lines are fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group. HR, hazard ratio; CI, confidence interval.

Figure 7.9. Adjusted HRs per 280g/week higher usual alcohol intake for IARC alcohol-related cancers, other cancers and overall cancer, by population subgroups in male current regular drinkers



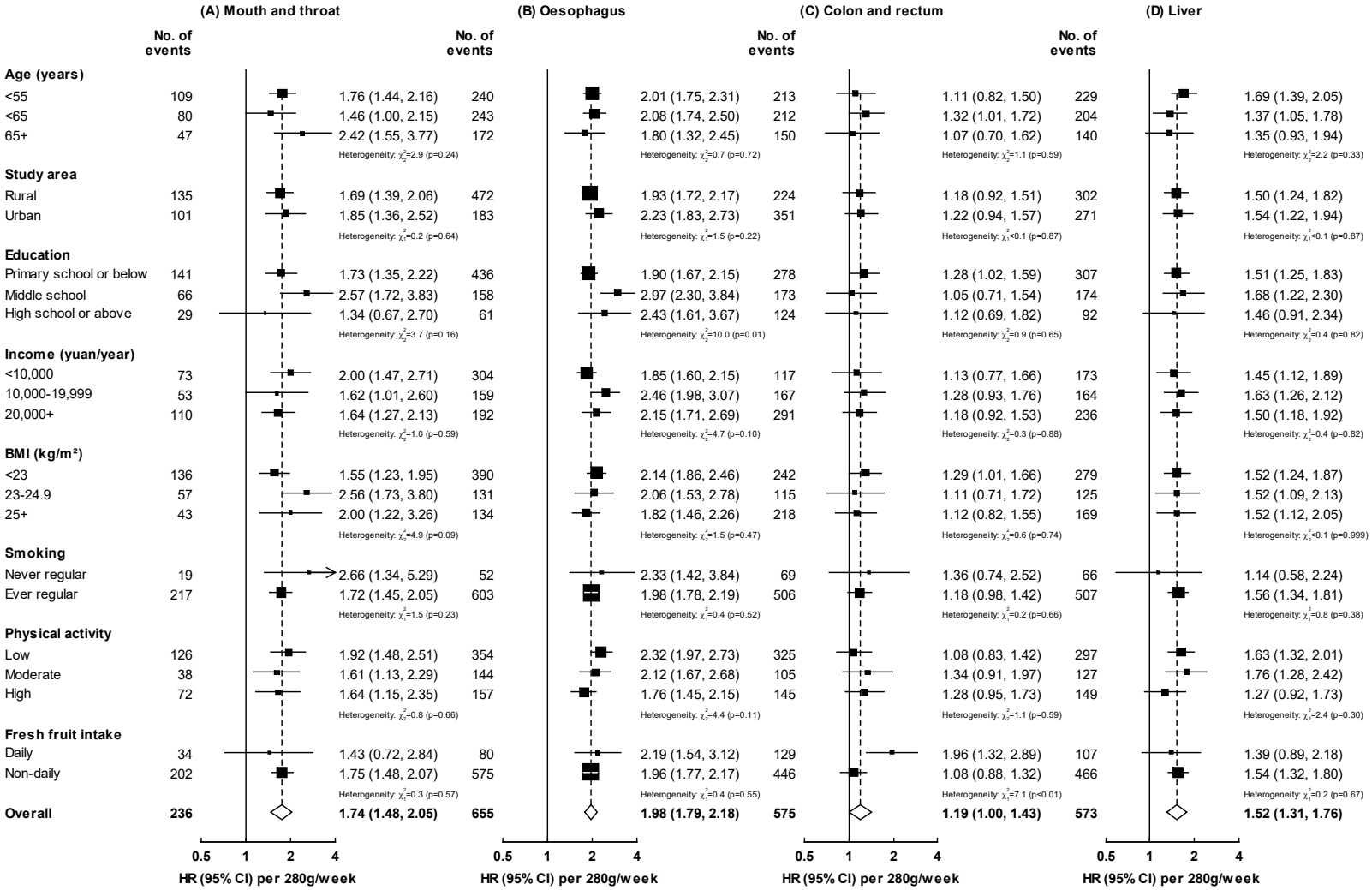
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer, where appropriate. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure 7.10. Associations of alcohol consumption with lung cancer, by smoking status in male current regular drinkers



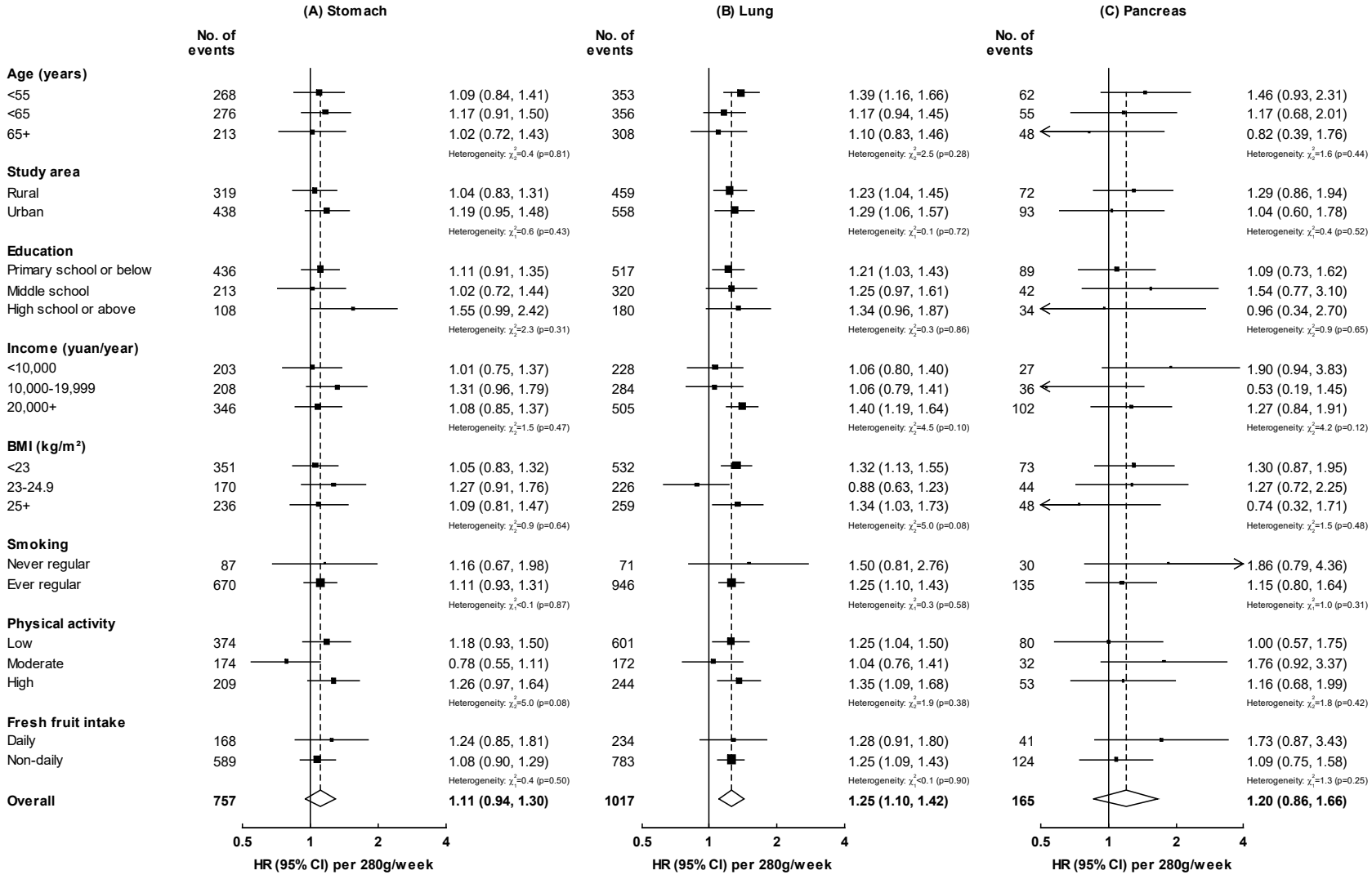
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer, tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The regression lines are fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group. HR, hazard ratio; CI, confidence interval.

Figure 7.11. Adjusted HRs per 280g/week higher usual alcohol intake for site-specific IARC alcohol-related cancers, by population subgroups in male current regular drinkers



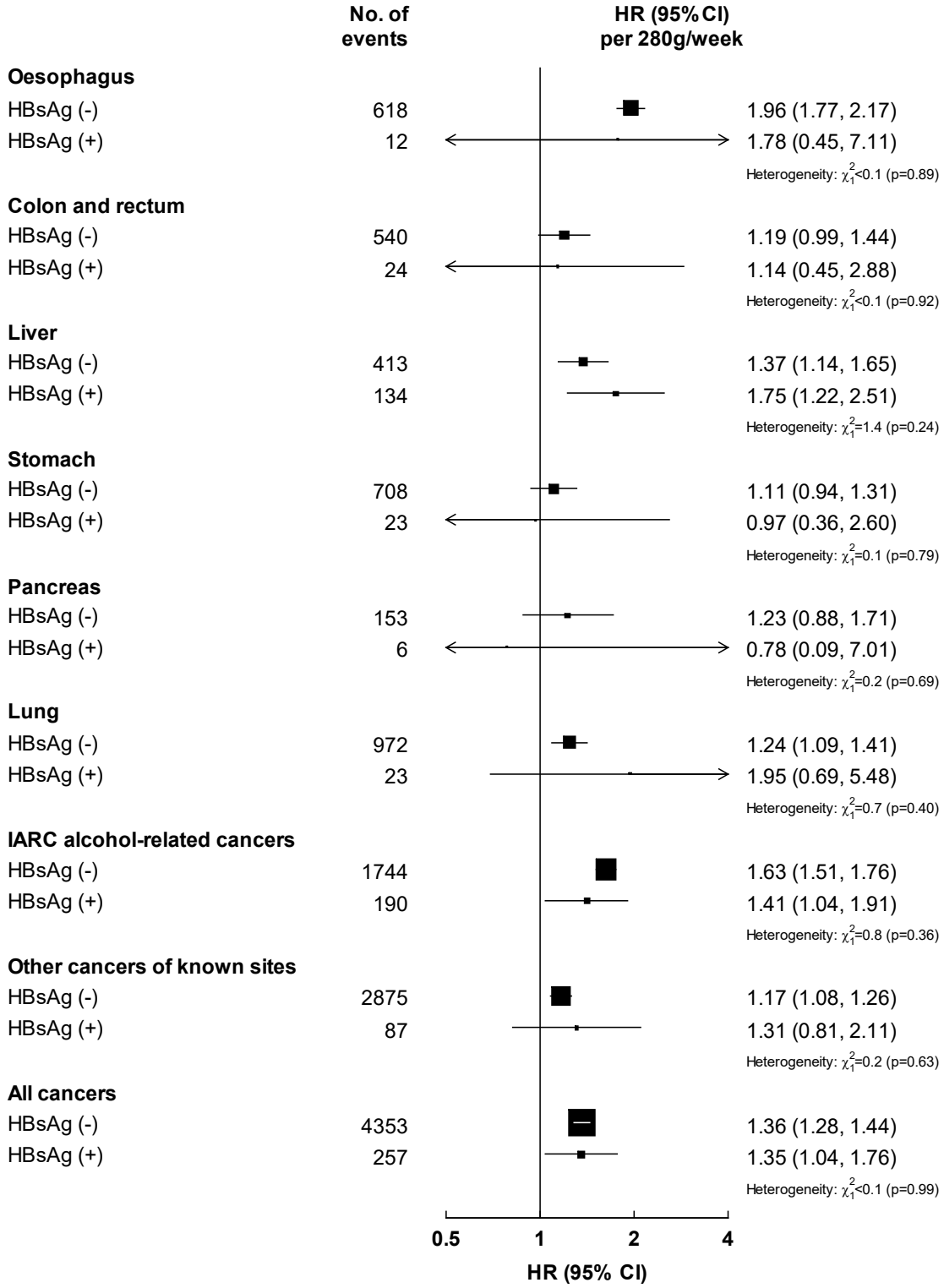
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer, where appropriate. Participants with prior cancer were excluded from all analyses. Participants with prior self-reported chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval.

Figure 7.12. Adjusted HRs per 280g/week higher usual alcohol intake for stomach cancer, lung cancer and pancreatic cancer, by population subgroups in male current regular drinkers



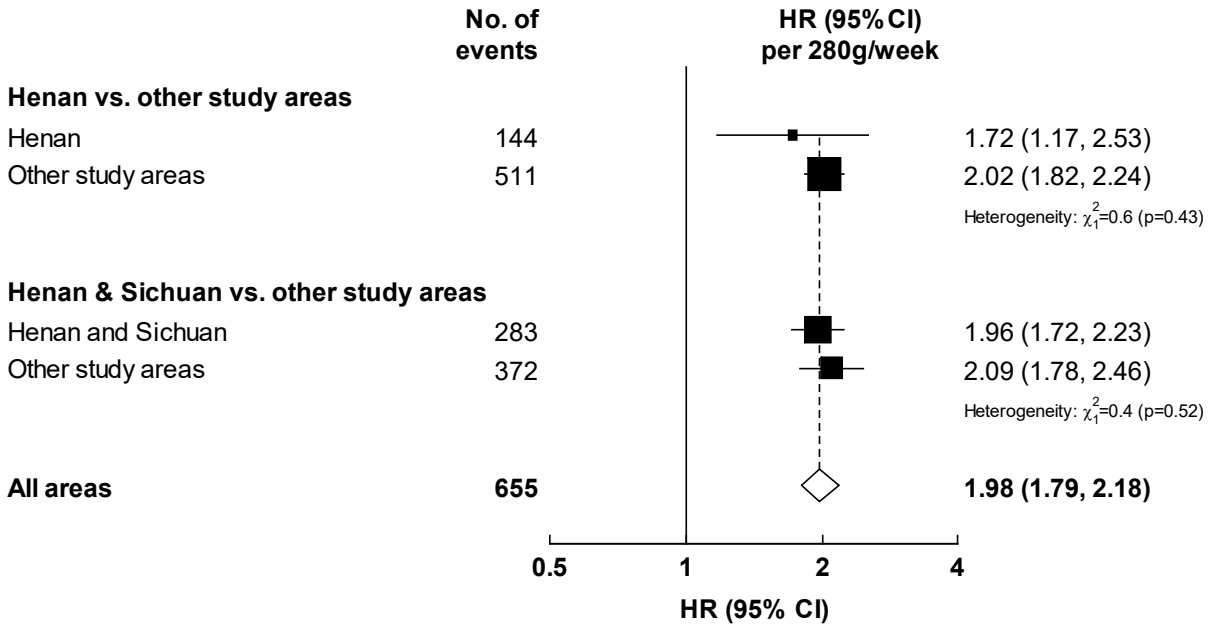
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer, where appropriate. Participants with prior cancer were excluded from all analyses. Participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval.

Figure 7.13. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by HBsAg seroprevalence in male current regular drinkers



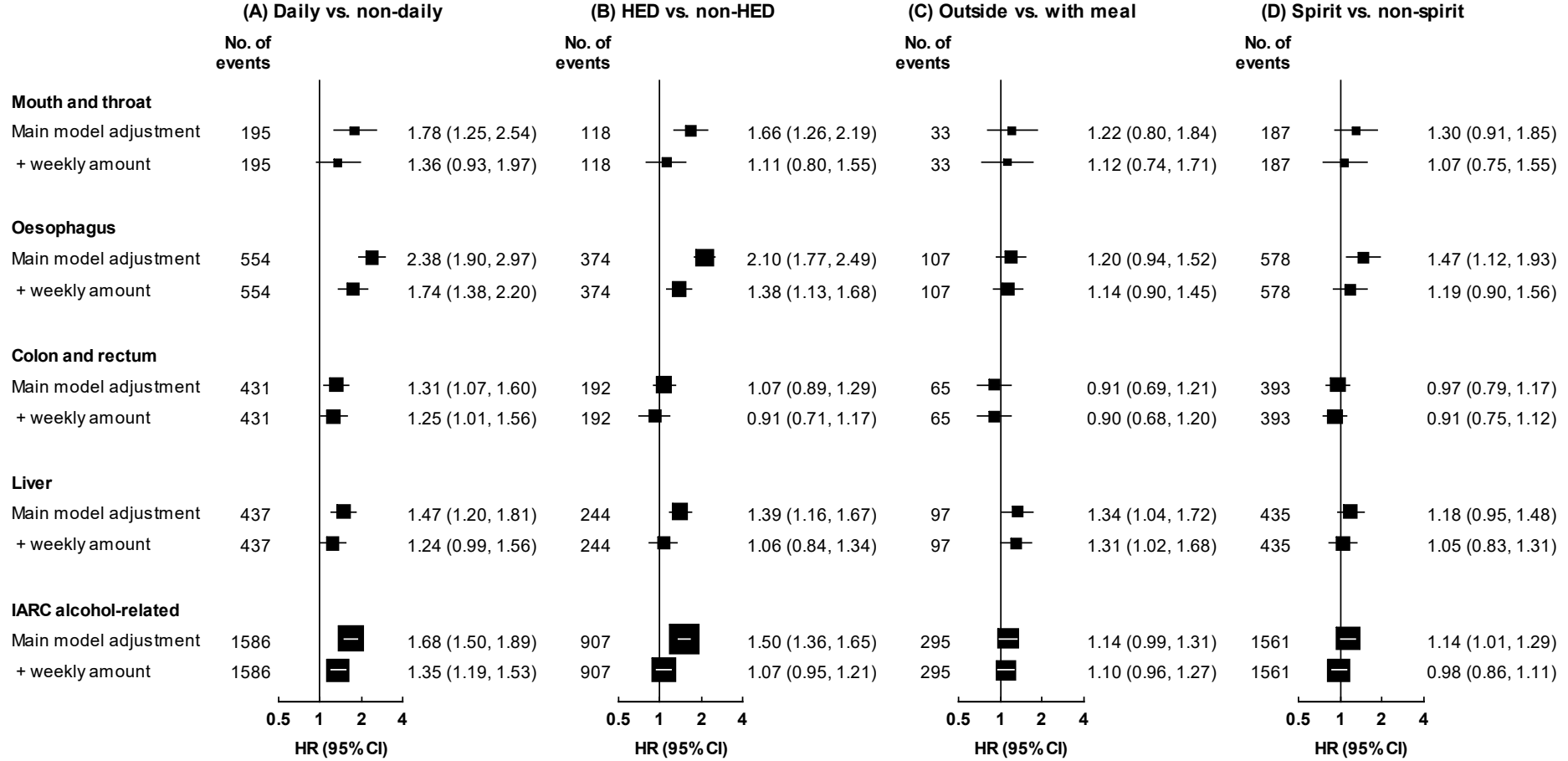
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.14. Adjusted HRs per 280g/week higher usual alcohol intake for oesophageal cancer, by high-risk and other study areas in male current regular drinkers



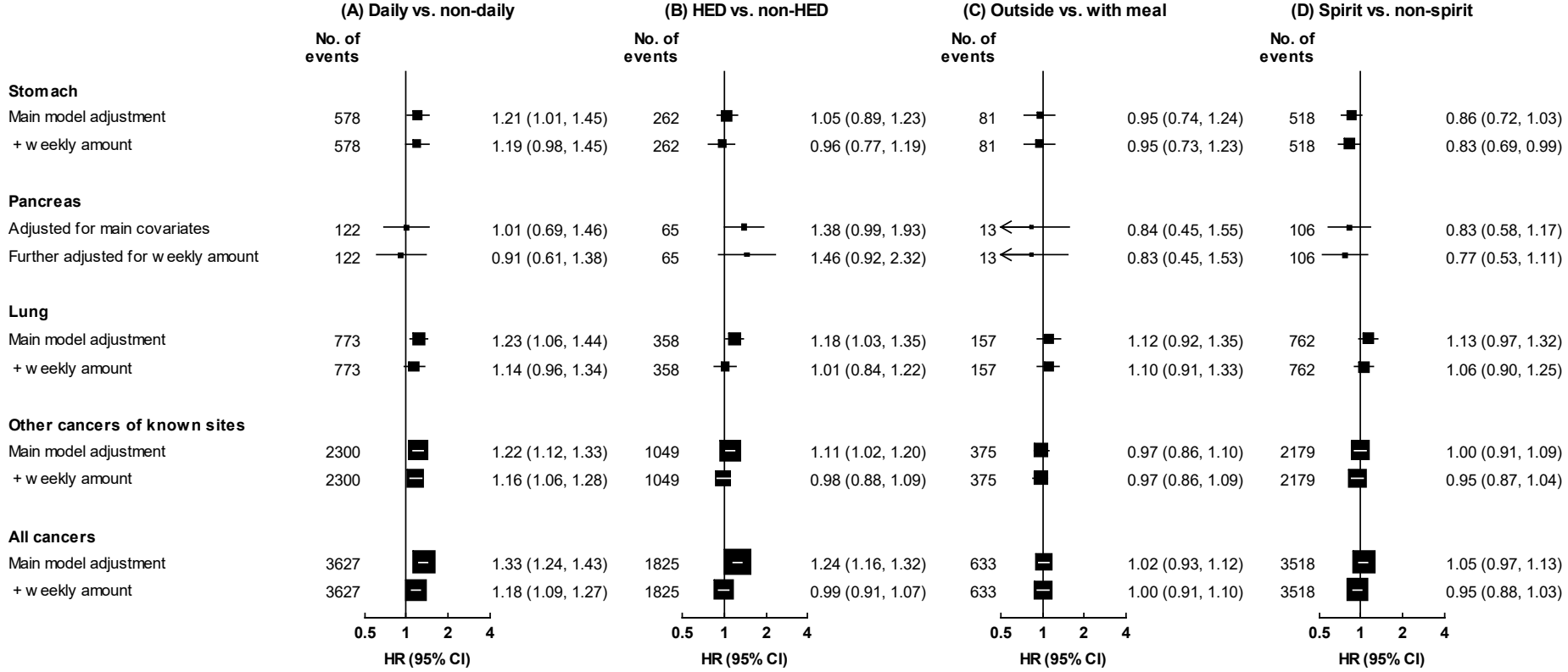
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval.

Figure 7.15. Adjusted HRs for site-specific IARC alcohol-related cancers associated with drinking patterns, in male current regular drinkers



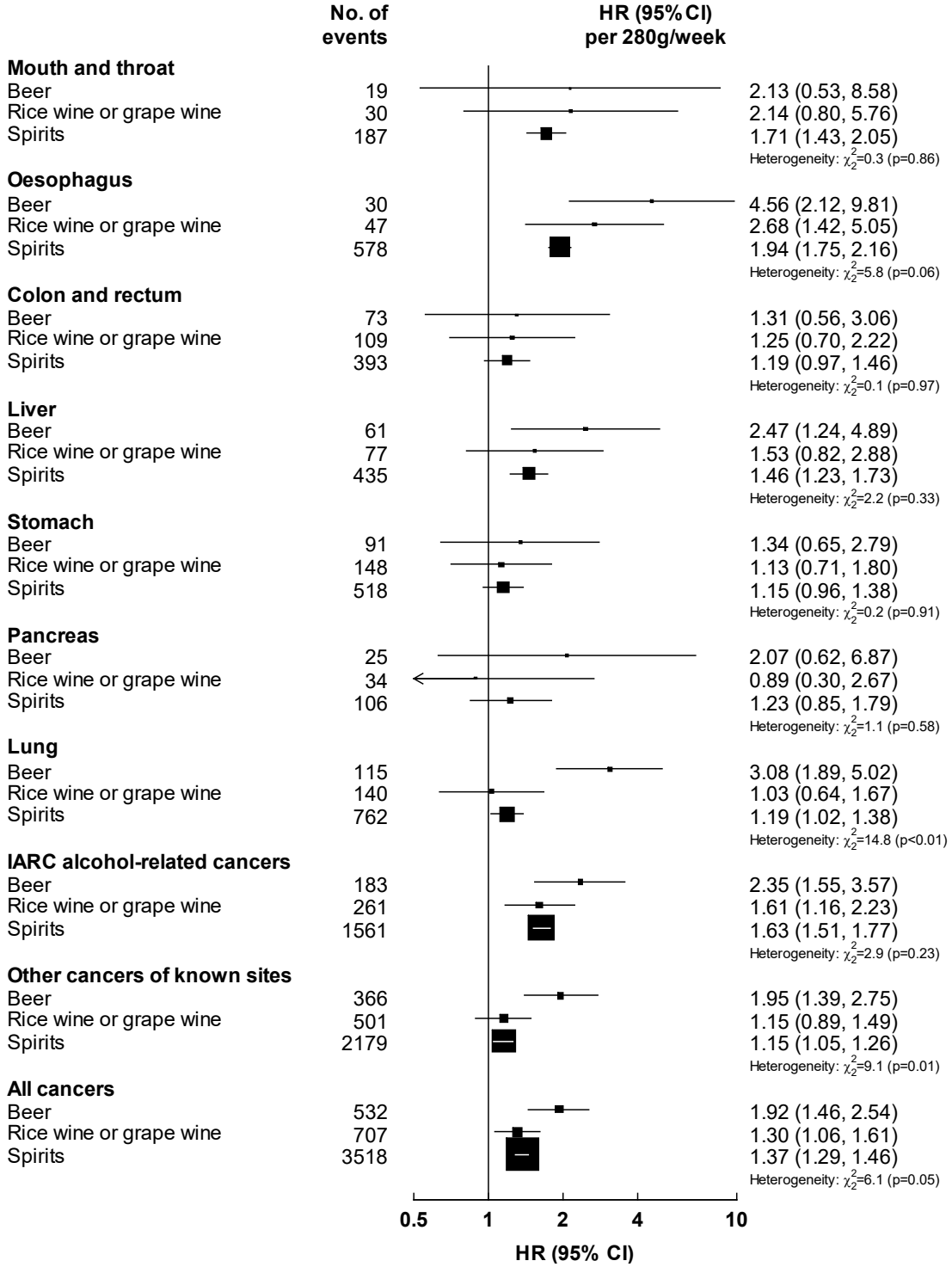
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer, and total weekly alcohol intake where indicated. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HED is defined as drinking >60g/session. HED, heavy episodic drinking; HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.16. Adjusted HRs for other cancers and overall cancer associated with drinking patterns, in male current regular drinkers



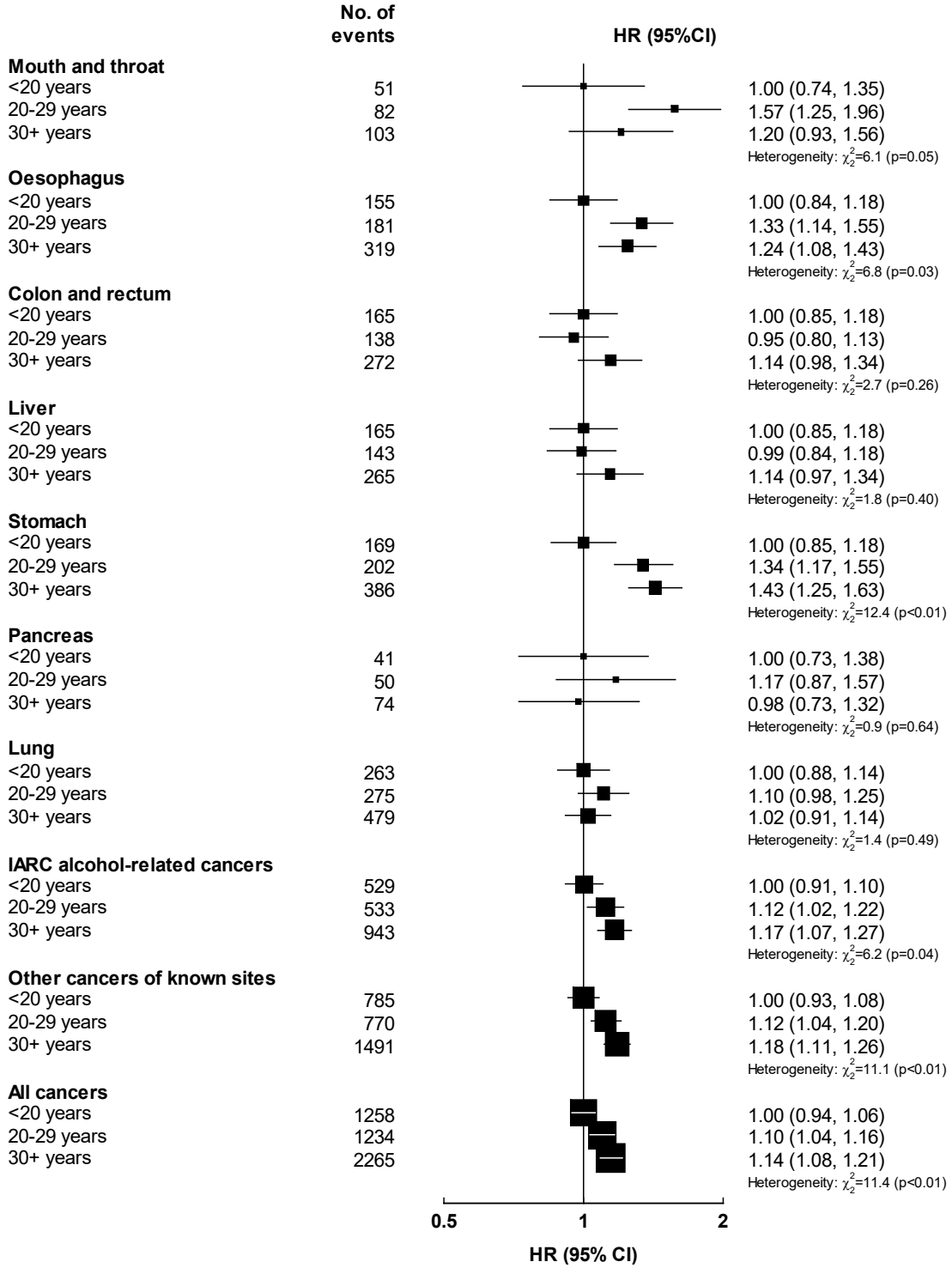
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer, and total weekly alcohol intake where indicated. Participants with prior cancer were excluded from all analyses. Participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HED is defined as drinking >60g/session. HED, heavy episodic drinking; HR, hazard ratio; CI, confidence interval.

Figure 7.17. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by beverage type in male current regular drinkers



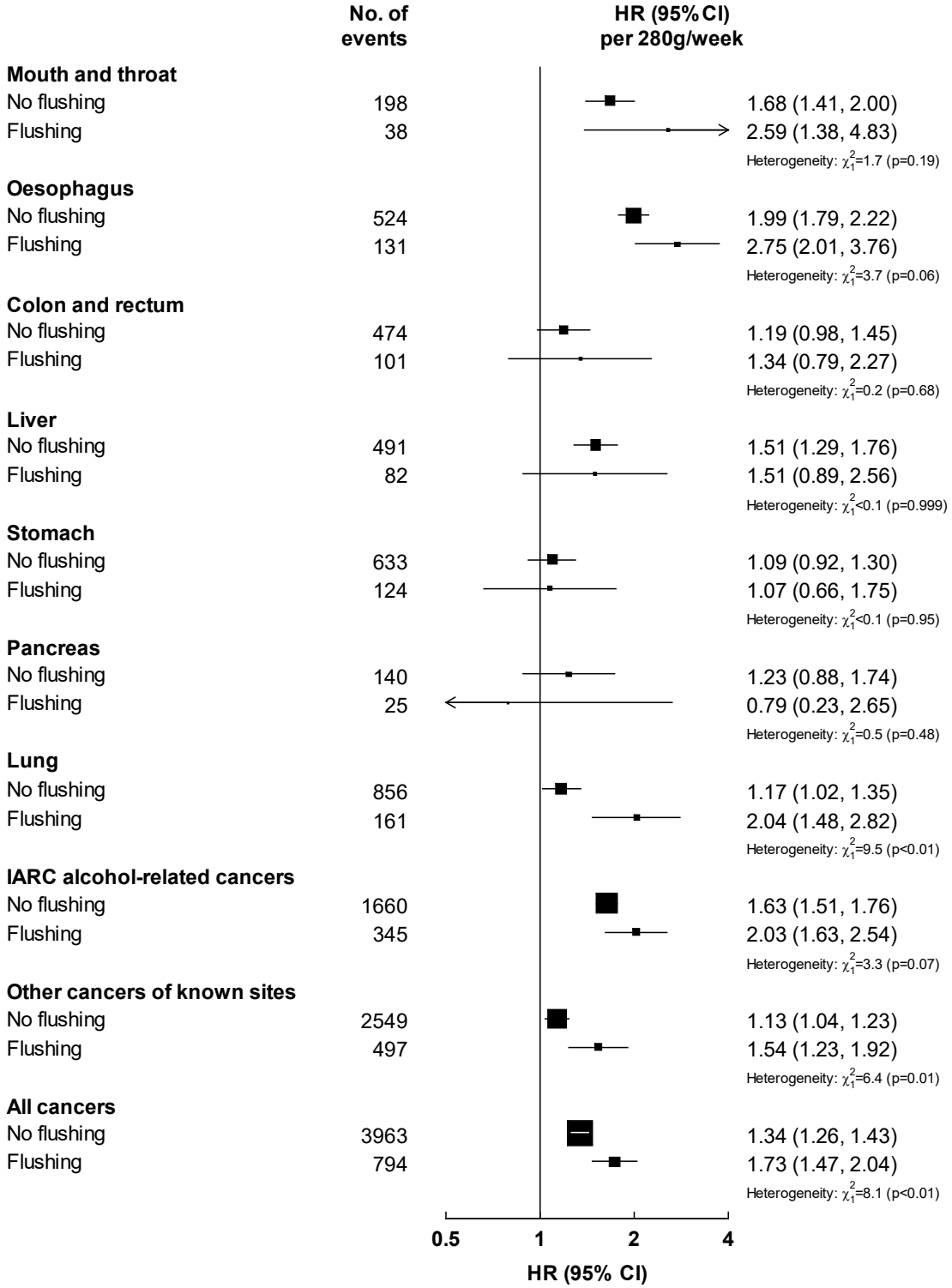
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.18. Adjusted HRs for major cancers associated with duration of regular drinking, in male current regular drinkers



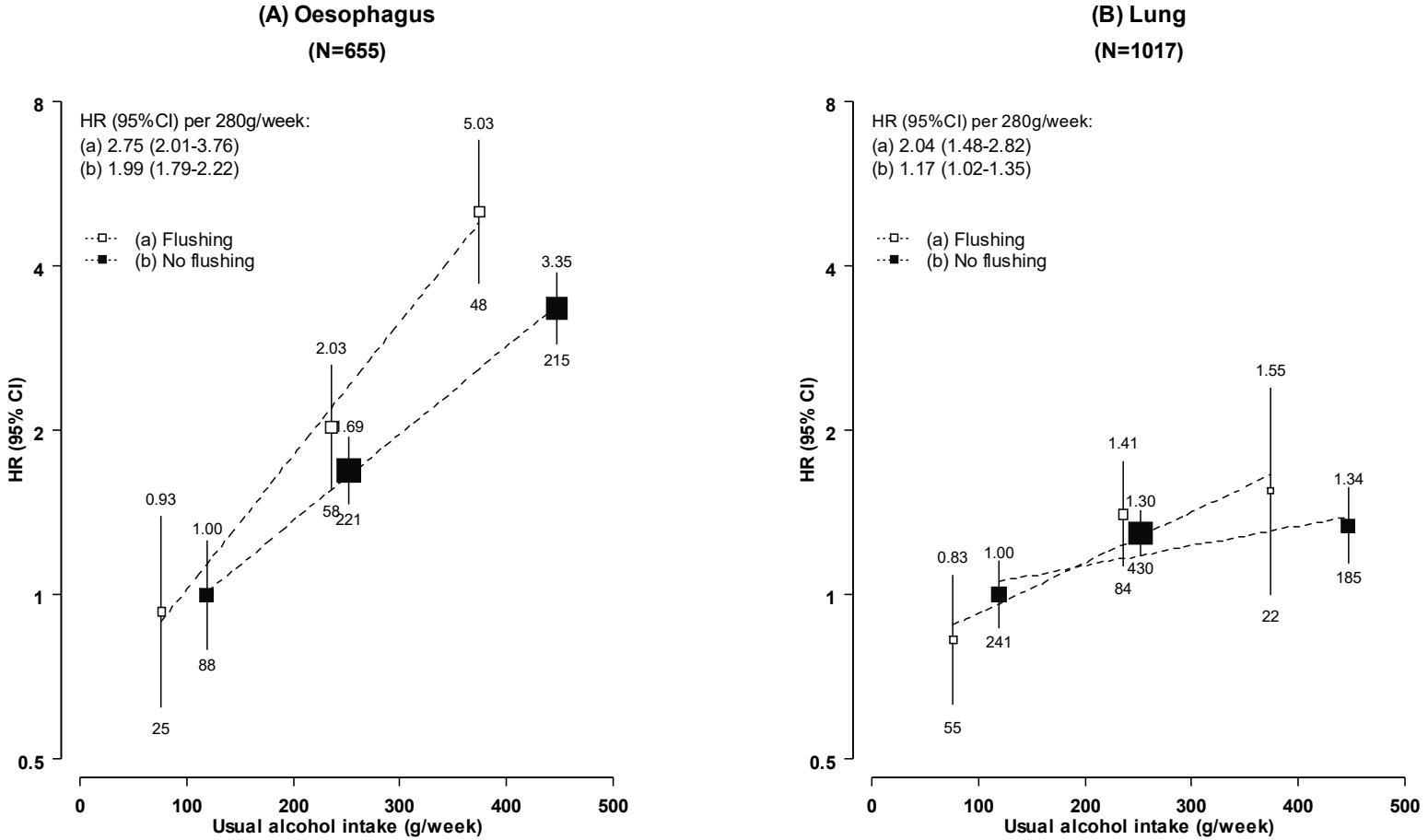
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, family history of cancer, total weekly alcohol intake, and baseline age. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.19. Adjusted HRs per 280g/week usual alcohol intake for major cancers, by flushing status in male current regular drinkers



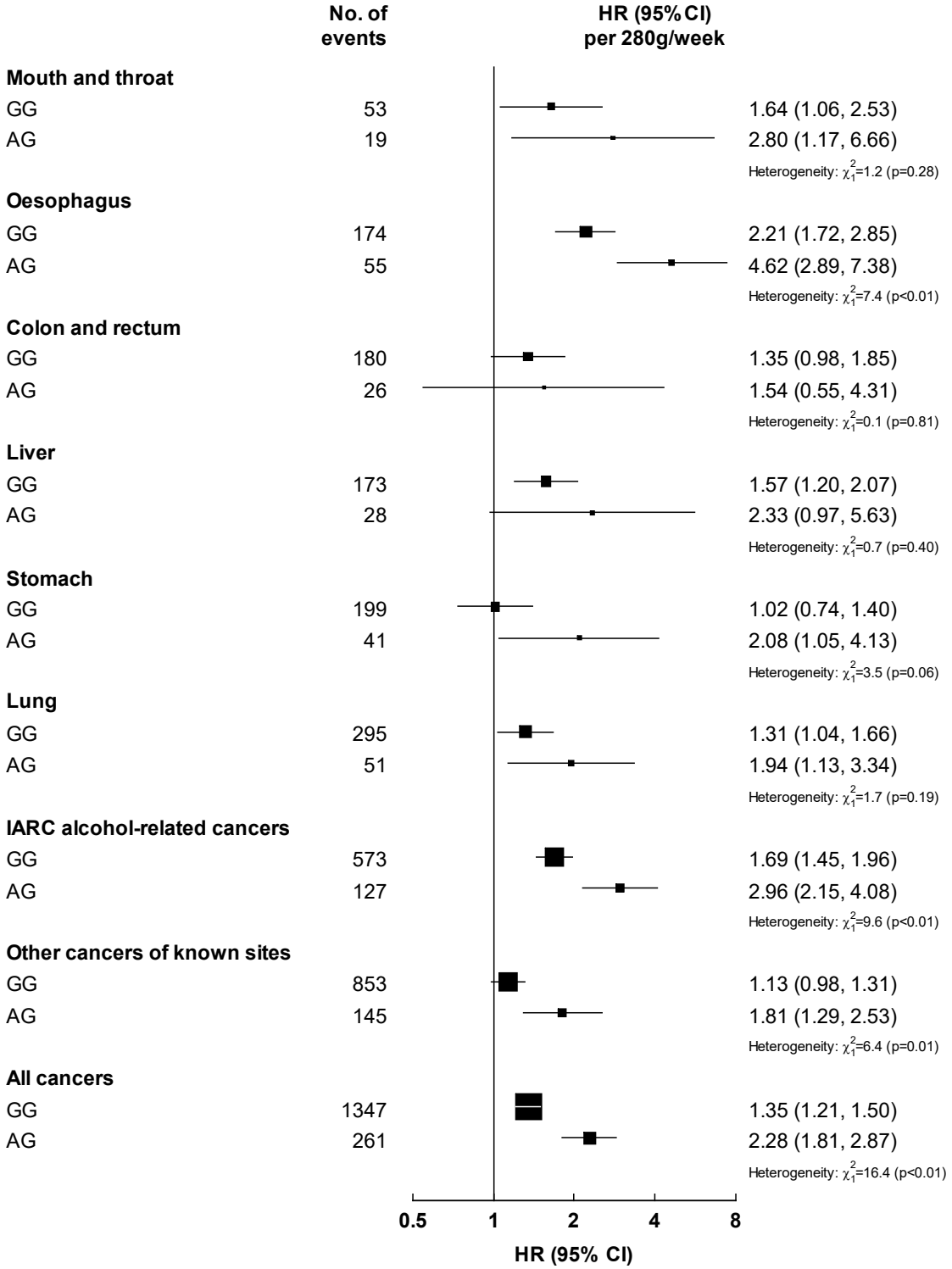
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.20. Associaton of alcohol consumption with oesophageal cancer and lung cancer, by flushing status in male current regular drinkers



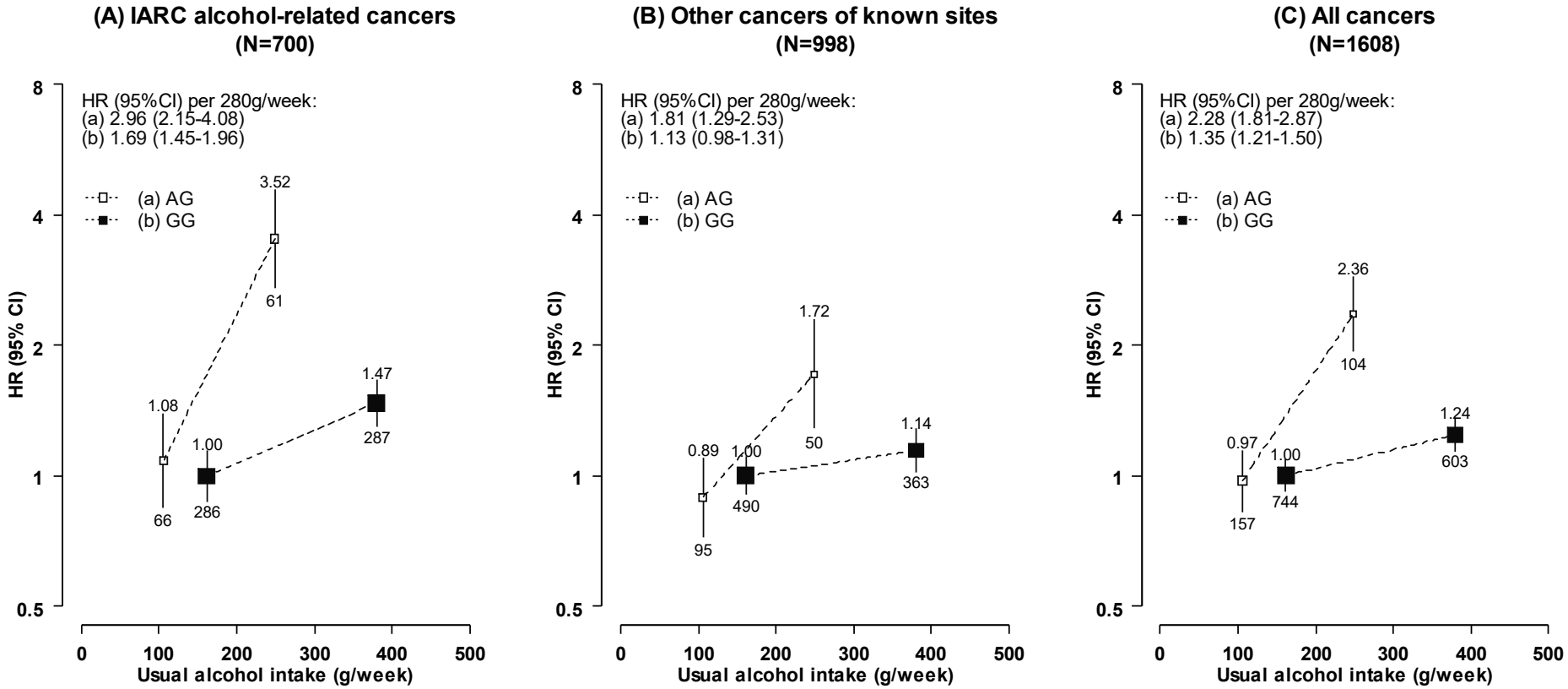
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The regression lines are fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group within strata of flushing status. HR, hazard ratio; CI, confidence interval.

Figure 7.21. Adjusted HRs per 280g/week higher usual alcohol intake for major cancers, by *ALDH2*-rs671 genotype in male current regular drinkers



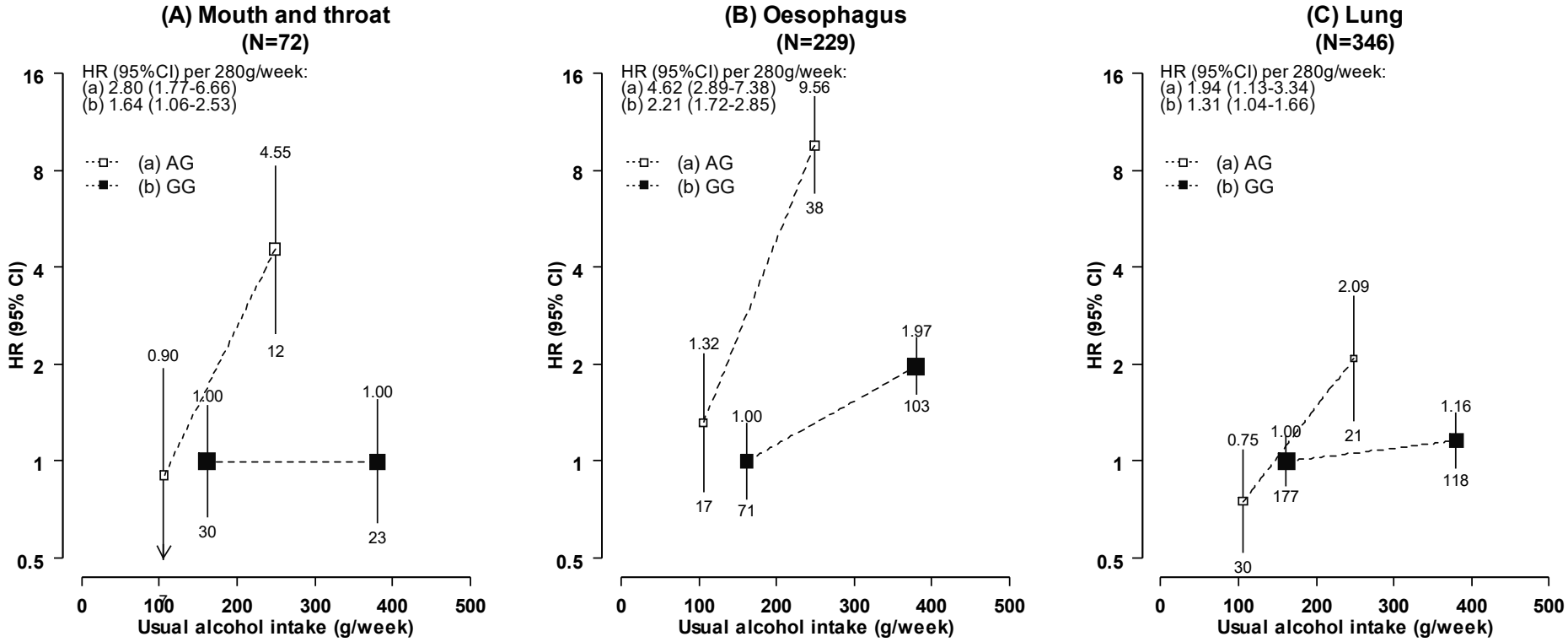
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. Associations among those with the *ALDH2*-rs671 AA genotype were not analysed due to the low prevalence of current regular drinking in this subgroup. Pancreatic cancer is not shown here due to the small number of events. HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure 7.22. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancers by *ALDH2*-rs671 genotype in male current regular drinkers



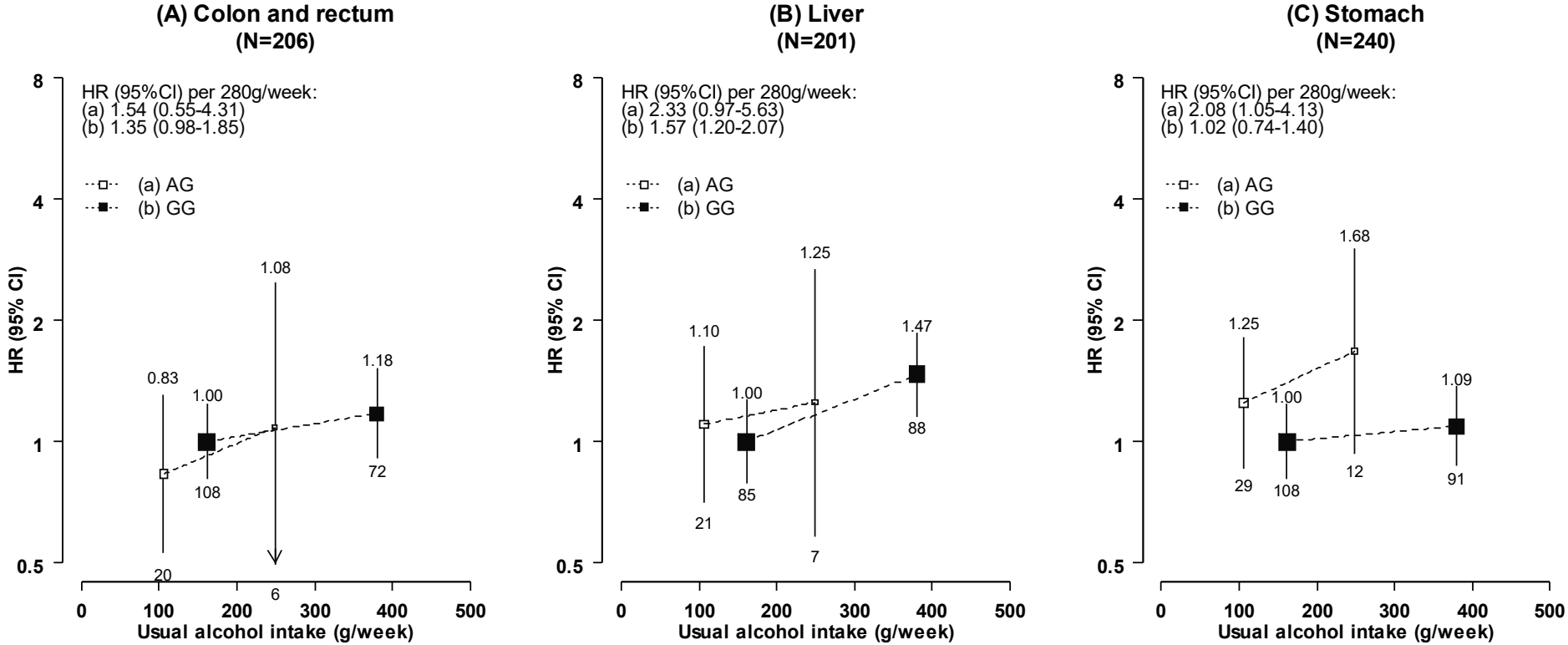
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: GG drinkers drinking <280g/week at baseline (reference group); GG drinkers drinking ≥280g/week at baseline; AG drinkers drinking <280 g/week at baseline; and AG drinkers drinking ≥280g/week at baseline. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure 7.23. Associations of alcohol consumption with mouth and throat cancer, oesophageal cancer and lung cancer, by *ALDH2*-rs671 genotype in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: GG drinkers drinking <280g/week at baseline (reference group); GG drinkers drinking ≥280g/week at baseline; AG drinkers drinking <280 g/week at baseline; and AG drinkers drinking ≥280g/week at baseline. HR, hazard ratio; CI, confidence interval.

Figure 7.24. Associations of alcohol consumption with colorectal cancer, liver cancer and stomach cancer, by *ALDH2*-rs671 genotype in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: GG drinkers drinking <280g/week at baseline (reference group); GG drinkers drinking ≥280g/week at baseline; AG drinkers drinking <280 g/week at baseline; and AG drinkers drinking ≥280g/week at baseline. HR, hazard ratio; CI, confidence interval.

Chapter 8. Alcohol consumption and risks of liver diseases

8.1 Introduction

Liver disease is a major public health problem worldwide and caused 2.3 million deaths in 2017, including 1.3 million from liver cirrhosis and a further 1 million from viral hepatitis and liver cancer.[33] China is a major contributor to the global liver disease burden particularly for liver cancer and chronic HBV infection.[38,59] Although a comprehensive immunization programme for HBV and mandatory HCV screening for blood transfusion during the early 1990s have greatly reduced new HBV and HCV infections in China, both ALD and NAFLD are emerging as leading causes of major chronic liver diseases, possibly due to changes in lifestyles along with rapid economic growth.[59]

Alcohol consumption has been established as a major risk factor for ALD and liver cirrhosis in Western countries and is estimated to cause almost 50% of liver cirrhosis deaths globally.[1] However, little prospective evidence exists on the relationships between alcohol consumption and risks of liver diseases in China, where the primary causes of liver cirrhosis and liver cancer (primarily HBV infection), drinking patterns, and alcohol tolerance differ importantly from the West.[7,60,87,163] Previous studies in China are constrained by one study region,[72,104] limited exploration of drinking patterns,[72,73,104] single baseline measure of alcohol exposure,[72,73,104] studying mortality data only,[72,73,104] and covering a period in the distant past (e.g., in 1980-1990s),[72,73] whereas since then alcohol consumption has increased in China. Recent studies from Western populations have shown that drinking alcohol outside meals and drinking

daily are associated with increased risks of liver cirrhosis and ALD, but the effects of other drinking patterns (e.g., HED, beverage type) remain uncertain.[74,75] There is limited reliable prospective evidence on whether and how the associations between alcohol consumption and risks of liver diseases may be modified by other factors (e.g., HBV infection, BMI, and alcohol tolerance). Appropriate assessment of the relationships between alcohol drinking and liver diseases in Chinese populations is needed to inform public health prevention strategies and to improve understanding of the role of alcohol in the aetiology of liver diseases.

8.2 Aims and Objectives

Using data from the CKB study, this chapter aims to:

(1) Assess the associations of alcohol consumption and drinking patterns with incidence of overall and major chronic liver diseases;
(2) Examine the associations of alcohol on risks of liver diseases in subgroups defined by HBsAg seroprevalence, smoking status, BMI, socio-demographic characteristics, physical activity, diabetes, and the alcohol flushing response;
(3) Explore the effects of genetic variants in two alcohol metabolism genes (*ALDH2*-rs671, *ADH1B*-rs1229984*)* to assess causality and potential gene-alcohol interactions on liver disease risks, in a subset of genotyped participants.

8.3 Methods

8.3.1 Assessment of HBsAg, alcohol consumption and genotypes

Baseline assessment of HBsAg, which can be detected in high levels in serum during acute or chronic HBV infection, has been described in Chapter 4. Detailed information on questionnaire assessment and classifications of alcohol consumption and drinking patterns in the CKB study has been described previously and in Chapters 4-7,[87,262] and genotype measurements for *ALDH2*-rs671 and *ADH1B*-rs1229984 have been described in Chapter 7.

8.3.2 Assessment of liver disease outcomes

Detailed information of the data collection of disease incidence and mortality through national death and cancer registries and the nationwide health insurance claim system has been described in Chapter 4. The incident liver diseases analysed in this chapter were total liver disease (ICD-10: C22, K70-K77, B18-B19, Z22.5, B94.2) and major chronic liver diseases, including ALD (K70), liver cirrhosis (K74), NAFLD (K76.0), and chronic viral hepatitis (B18-B19, Z22.5, B94.2). Although described in details in the previous chapter, liver cancer (C22), as a major end-stage liver disease and a component of total liver disease, was also analysed under the specified statistical models in this chapter for comprehensiveness and comparison with the aforementioned major chronic liver diseases.

8.3.3 Statistical analyses

Participants with a self-reported history of cancer, liver cirrhosis, or chronic hepatitis at baseline were excluded from the current study (n=8717), leaving 503,998 participants (205,628 men and 298,370 women) in the main analyses. Given very few women drank alcohol regularly (n=6169), analyses among current regular drinkers focused on men.

Means and percentages of baseline characteristics by incident total liver disease outcome and incidence rates of liver diseases were adjusted for age and study area, where appropriate, using direct standardisation (see Chapter 7 Methods). Cox proportional hazards regression models were used to estimate adjusted HRs for incident liver diseases associated with alcohol drinking status in all participants, and among current regular drinkers with amount consumed (in categories and per 280g/week) and drinking patterns, with time since entry into the study as the underlying time scale. Models were stratified by age-at-risk (5-year groups), study area (ten areas), and HBsAg seropositivity (negative/unclear/missing vs. positive), and were adjusted for education (four groups), household income (four groups), smoking (five groups in men, four groups in women), physical activity (three groups), and BMI (four groups).

Subgroup analyses were undertaken to examine the HRs per 280g/week higher usual alcohol intake across strata defined by socio-demographic characteristics, smoking status, BMI, physical activity, HBsAg seropositivity, pre-existing diabetes (self-reported or screen-detected at baseline), and the flushing response.

Repeated analyses on liver disease mortality, further covariate adjustments (by additionally including total weekly alcohol intake as a continuous variable in the models) for analyses of drinking patterns, the use of floating SEs for exposure variables involving more than two exposure categories,[203,204] the adjustment of within-person variation using the regression dilution approach,[184] and the chi-squared test for heterogeneity across strata were adopted as described in Chapter 4 and Chapter 7.

In the main analyses, participants with negative, unclear, or missing HBsAg test results were grouped together, given their broadly similar risks of developing liver diseases during follow-up compared with participants who tested HBsAg positive at baseline (Table H1). In sensitivity analysis, participants with unclear or missing HBsAg test results were excluded. Additional sensitivity analyses further excluded participants with any prior major chronic disease and/or poor self-reported baseline health, and/or the first three years of follow-up.

Genetic epidemiological analyses were conducted among 165,135 participants (68,046 men, 97,089 women) without prior self-reported cancer, liver cirrhosis, or chronic hepatitis. Genotypes of *ALDH2*-rs671 and *ADH1B*-rs1229984, which predict alcohol consumption and are randomly allocated at conception (as reported previously[24] and in Chapter 7), were used to explore the cumulative lifetime effect of alcohol consumption on risks of liver diseases. Cox proportional hazards regression models related total and major chronic liver diseases to the genotypes of *ALDH2*-rs671 and *ADH1B*-rs1229984, separately, stratified by age-at-risk, study area, and HBsAg. Sensitivity analyses were performed with additional covariate adjustments (using the same model specification as in the conventional epidemiological analyses and with

total weekly alcohol intake included as a continuous variable) and, given the possible involvement of acetaldehyde in liver damage, subgroup analyses were conducted to explore potential effect modification of alcohol intake by *ALDH2*-rs671 genotype as described in Chapter 7.

PAF was used to estimate the proportion of liver disease incidence attributable to ever regular drinking in the CKB population (see Chapter 7).[291]

Analyses in this chapter used CKB release 14 with follow-up to 1 January 2017.

8.4 Results

8.4.1 Incidence rates and correlates of liver diseases

During approximately 5 million person-years of follow-up (median 10.1 years [interquartile range, 9.2-11.1 years]), 9529 individuals developed liver diseases (4830 men and 4699 women), for which the incidence rates were 242.3 and 157.5 per 100,000 person-years for men and women, respectively. Compared with participants who did not develop any liver disease during follow-up, participants who developed liver diseases were older and were more likely to be rural residents, to have poor baseline health, and to have tested positive for HBsAg at baseline (which was more common in urban than in rural areas; Table H2) (Table 8.1).

Overall, there were 2626 incident cases of liver cancer (incidence rate per 100,000 person-years: 82.3 vs. 32.5, men vs. women), 2116 liver cirrhosis (57.2 vs. 32.3), 1514 chronic viral hepatitis (39.8 vs. 23.9), 1333 NAFLD (23.0 vs. 29.1), and 274 ALD (12.6 vs. 0.7). With the exception of NAFLD, most liver diseases were more common in men

than in women, especially ALD for which the incidence rate was ~18 times higher in men (Figure 8.1). Liver diseases also tended to be more common in rural than in urban areas, particularly for NAFLD in women where the incidence rate was ~4 times higher in rural than in urban areas (Figure 8.2). The age-standardised incidence rates of ALD and NAFLD varied by ~20 to 70 times between certain high-risk areas (i.e., Sichuan and Hunan for ALD; Sichuan, Zhejiang, and Harbin for NAFLD) and low-risk areas (e.g., Gansu for ALD; Henan for NAFLD) (Table H3), which may be related to the differences in lifestyles, socio-economic development, and access to healthcare across study areas. The incidence rate of overall liver disease was highest among ex-regular drinkers and lowest among occasional drinkers across different drinking categories, but the distributions varied by specific liver diseases, especially ALD for which the incidence rate was markedly higher for male current regular drinkers than men in other drinking categories (Table H4).

8.4.2 Alcohol drinking status and risks of liver diseases

Among men, the risks for total and most major chronic liver diseases were highest among ex-regular drinkers across different drinking categories (Table 8.2). The risks also tended to be lower among occasional drinkers and were broadly similar among current regular drinkers compared with abstainers, except for ALD. Compared with abstainers, current regular drinkers had approximately 13-fold higher risk of incident ALD (HR=13.06 [95% CI: 7.03-24.27]) and 6-fold higher risk of ALD mortality (6.01 [2.48-14.60]), while the risks of ALD were similar among occasional drinkers (Table 8.2, Table H5). Among women, current regular drinkers were also associated with significantly higher risk of ALD (HR=7.61 [1.95-29.72]) compared with abstainers, but

no significant associations were observed between drinking status and other liver diseases (Tables H6-H7).

8.4.3 Amount of alcohol consumption and risks of liver diseases

Among male current regular drinkers, alcohol intake was positively associated with risk of total liver disease (HR=1.53 [1.42-1.66] per 280g/week higher usual alcohol intake) (Figure 8.3). There were strong dose-response relationships between usual alcohol intake and risks of ALD (HR=2.02 [1.79-2.28] per 280g/week), liver cirrhosis (1.87 [1.65-2.12]), and NAFLD (1.78 [1.42-2.22]), but not for chronic viral hepatitis (1.25 [0.97-1.62]). For liver cirrhosis and total liver disease, the risk estimates appeared slightly higher for mortality than for incidence (Table H8). Among women, with few current regular drinkers, no significant associations were observed between drinking amount and risks of liver diseases (Figure H1, Table H9).

8.4.4 Subgroup analyses

Among male current regular drinkers, the associations of alcohol intake with total liver disease, liver cirrhosis, and NAFLD were broadly consistent across subgroups defined by education, income, smoking status, BMI, physical activity, and pre-existing diabetes (Figure 8.4; Figure 8.5A, C, D). For ALD, the HRs per 280g/week increase in usual alcohol intake were higher among men who never smoked regularly, or with higher BMI, but the differences were less apparent when examined in alcohol consumption categories (Figure 8.5B, Figures H2-H3). Examination of the joint effects of alcohol and BMI showed that men with higher BMI had consistently higher risks of NAFLD at each level of alcohol consumption, with an 8-fold higher risk observed in men who drank

560+g/week and had a BMI of ≥25 kg/m^2 compared with those who drank <280g/week and had a BMI of <25 kg/m^2 (Figure H4).

The associations of alcohol intake with liver cancer, ALD, liver cirrhosis, and total liver disease were consistent among men who tested HBsAg positive at baseline and those not (Figure 8.6), although those who tested HBsAg positive had substantially higher liver disease risks at all levels of alcohol consumption (Figure H5). The associations of alcohol intake with total and major chronic liver diseases did not differ between study areas of particularly high risk (i.e., Zhejiang, Sichuan, and Harbin for NAFLD; Sichuan and Hunan for ALD) and other study areas (Figure H6).

8.4.5 Drinking patterns and risks of liver diseases

Among male current regular drinkers, drinking daily (i.e., 6-7 days/week), HED (i.e., drinking >60g/session), and drinking spirits were each associated with increased risks of total and most major chronic liver diseases compared with those who did not report these drinking patterns. However, most of the associations were greatly attenuated after taking account of total alcohol consumption (Figure 8.7A, B, D). After adjusting for total alcohol intake, the excess risks associated with daily drinking remained significant for ALD (HR=2.22 [1.45-3.40]) and total liver disease (1.15 [1.01-1.30]), so did the increased risk of ALD associated with HED (1.72 [1.22-2.41]). When further examined across strata of weekly intake level, drinking daily remained associated with higher risks for ALD and total liver disease, and the associations were directionally consistent although non-significant after further adjustment for total weekly alcohol intake within the specified strata of weekly intake level (Table H10, Figure H7). There

were no clear associations between ALD and HED when examined across subgroups of total weekly intake level (Table H11, Figure H8).

Drinking without meals was associated with significantly higher risks of liver cancer, liver cirrhosis, ALD, and total liver disease than drinking with meals, and the associations persisted after further adjustment for total weekly alcohol intake (Figure 8.7C). The risks for ALD, liver cirrhosis, and total liver disease were consistently higher among men who usually drank without meals than those usually drinking with meals at each level of alcohol consumption, especially at higher intake levels (Figure 8.8). The associations between alcohol intake and risks of total and major chronic liver diseases were similar across beer, wine, and spirit drinkers (Figure H9). After adjusting for total weekly alcohol intake and baseline age, longer duration of regular drinking was associated with progressively higher risks of ALD and total liver disease (Figure 8.9).

For total and most major chronic liver diseases, the risk estimates per 280g/week higher usual alcohol intake were similar among those who reported having the flushing response and those without (Figure 8.10). Although the risk estimate for ALD appeared higher among those who reported flushing after drinking than not, no clear heterogeneity was observed when further examining the dose-response relationships in alcohol consumption categories (Figure H10).

8.4.6 Sensitivity analyses

Excluding participants with unclear or missing HBsAg test results slightly attenuated the dose-response associations for liver cancer and liver cirrhosis among HBsAg negative participants in the subgroup analyses, but otherwise did not materially alter

the main results (Figure H11, Tables H12-H13). Further adjustments for family history of cancer and prior diabetes also did not alter the dose-response relationships between alcohol intake and risks of liver diseases (Table H14). In sensitivity analyses with abstainers as the reference group, there were J-shaped associations between alcohol intake and risks of total and most chronic liver diseases except ALD (Table H15). Excluding participants with poor self-reported health or prior major chronic disease, and especially the first three years of follow-up, tended to increase the HRs associated with current regular drinking and to attenuate the lower HRs associated with occasional drinking and light drinking level (<140g/week) as compared with abstinence (Tables H15-H16), but did not alter substantially the dose-response relationships among male current regular drinkers (Table H17).

8.4.7 Genetic analyses

Among men, the *ALDH2*-rs671 AA and AG genotypes were associated with 86% (HR=0.14 [0.02-1.02]) and 83% (0.17 [0.08-0.35]) lower risk of ALD, respectively, compared with the GG genotype (Table 8.3). The association between *ALDH2*-rs671 genotype and total liver disease was directionally consistent, albeit the HRs were less extreme, with that for ALD, whereas no significant associations were observed for other major chronic liver diseases. For *ADH1B*-rs1229984, both AA and AG genotypes were associated with significantly reduced risks of ALD and total liver disease, and the AG genotype was associated with reduced risk of liver cancer, compared with the GG genotype (Table 8.4). The associations of *ALDH2*-rs671 and *ADH1B*-rs1229984 with risks of liver diseases were not affected by adjustments for socio-economic and lifestyle factors (smoking status, physical activity, BMI) but were attenuated with

further adjustment for alcohol consumption, indicating that the observed genetic associations were largely due to alcohol consumption (Tables H18-H19). Across strata by never and current regular drinkers, the significant negative associations of these two genetic variants with ALD and total liver disease persisted among current regular drinkers (Tables 8.5-8.6). Among male current regular drinkers, the *ADH1B*-rs1229984 AG and AG genotypes were also associated with significantly decreased risk of liver cirrhosis compared with the GG genotype.

Among male current regular drinkers, the HR per 280g/week higher usual alcohol intake tended to be higher among men with the *ALDH2*-rs671 AG genotype than men with the GG genotype for total liver disease, but no significant heterogeneity across *ALDH2*-rs671 genotypes was observed (Figure 8.11, Figure H12).

Among women, no significant associations were observed between *ALDH2*-rs671 or *ADH1B*-rs1229984 with risks of total or major non-neoplastic liver diseases (Tables H20-H21).

8.4.8 Population attributable fraction

If the observed associations between alcohol consumption and risks of liver diseases are largely causal, then 9% of all incident liver diseases, including 8% of liver cancer and liver cirrhosis and 12% of NAFLD cases, in the CKB male population could be attributed to ever regular alcohol drinking (Table 8.7).

8.5 Discussion

8.5.1 Summary of findings

In this large prospective study, drinking alcohol in most weeks significantly increased the risk of ALD by 13 times in Chinese men, compared with abstaining. Among male current regular drinkers, there were significant dose-response relationships between alcohol consumption and risks of total and major chronic liver diseases, particularly liver cancer, ALD, liver cirrhosis, and NAFLD. The associations between alcohol consumption and most major liver diseases were consistent across subgroups defined by other risk factors (e.g., smoking status, BMI, HBsAg, prior diabetes), although there was a suggestion of stronger associations for ALD among those who had higher BMI, or had the alcohol flushing response. Furthermore, after adjusting for the total amount of alcohol consumed, drinking daily and longer duration of regular drinking were associated with higher risks of ALD and total liver disease, while drinking without meals was consistently associated with higher risks of liver cancer, liver cirrhosis, ALD, and total liver disease. The AA and AG genotypes of *ALDH2*-rs671 and *ADH1B*-rs1229984, which predicted lower alcohol consumption than the GG genotype, were associated with lower risks of ALD and total liver disease. With few female current regular drinkers, the associations among women could not be assessed reliably.

8.5.2 Total liver disease

Numerous previous studies have reported increased risks of liver diseases among current non-drinkers or ex-drinkers compared with occasional or light drinkers.[71,74,143,144,146,147,150] This phenomenon is likely due to the “sick-quitter/sick non-

starter effects", as former heavy drinkers might have stopped drinking and some people might have abstained from drinking because of pre-existing poor health or social disadvantages, causing reverse causation and residual confounding to the observed associations.[24,182,183] This is supported by the findings in the present study that abstainers and ex-regular drinkers tended to be older and had poorer baseline health (see Chapter 5), and that removing early follow-up years and participants with poor baseline health attenuated the apparently "protective" associations of occasional and light drinking but increased the risks associated with current regular drinking compared with abstainers.

A number of prospective studies have demonstrated strong dose-response relationships between amount of alcohol intake and overall liver disease, but these are mostly based on Western populations and mortality data.[103,145-147] Two prospective studies reported approximately 5-7 fold higher risks of liver disease mortality in the highest versus lowest drinking category based on US ($HR_{>3\ drinks/day\ vs.\ <1\ drink/day}$=5.84 [95%CI: 4.81-7.10]; 789 deaths)[146] and Finnish ($HR_{>20g/day\ vs.\ <5g/day}$=6.68 [4.16-10.71]; 213 deaths)[145] populations, whereas a somewhat weaker association was reported in a South Korean population ($HR_{\geq 28\ drinks/week\ vs.\ <1\ drink/week}$=2.92 [2.12-4.02]; 338 deaths).[103] Consistent with previous studies, the present study reports significant dose-response associations between alcohol consumption and risks of total liver disease incidence and also mortality in Chinese men. The magnitude of the mortality risk estimates in the CKB is broadly similar to that in the South Korean study but is somewhat lower than that in the Western studies, which might be related to the differences in methodology (e.g., different comparison groups) and other underlying factors that may affect liver

disease mortality (e.g., disease severity, treatment, co-existing health conditions) between study populations. Furthermore, the differences in the major cause of liver diseases (e.g., alcohol consumption in European countries vs. chronic HBV infection in China),[60] alcohol consumption level (e.g., higher consumption in Western populations),[1] and drinking patterns (e.g., high prevalence of mealtime drinking in China, see Section 8.5.6) between study populations may also contribute to different association magnitude.

8.5.3 Liver cirrhosis and ALD

Alcohol intake has been consistently shown to be associated with liver cirrhosis and ALD in dose-response relationships in previous meta-analyses and large prospective studies in Western and high-income Asian populations.[71,74,75,103,151,153] A meta-analysis by Rehm et al of 14 cohorts and 3 case-control studies with 3384 liver cirrhosis and ALD cases reported a strong dose-response association of alcohol with liver cirrhosis and ALD mortality ($RR_{60+g/day\ vs.\ 0g/day}$ =14 [11.7-16.7]), and a comparatively weaker association for morbidity ($RR_{60+g/day\ vs.\ 0g/day}$ =5.0 [3.9-6.4]).[71] In China, existing prospective studies including the CPSS ($HR_{\geq 700\ g/week\ vs.\ non\text{-}drinkers}$ =1.74 [1.22-2.48]; 418 deaths)[73] and the SCS ($RR_{\geq 29\ drinks/week\ vs.\ non\text{-}drinkers}$ =2.99; 35 deaths)[72] have also reported links between heavy drinking and liver cirrhosis mortality in men. However, no relevant prospective evidence for ALD or liver cirrhosis incidence, which is more informative than mortality in terms of understanding the role of alcohol in liver disease development and public health prevention (previously discussed in Chapter 2), is available from China. With comprehensive linkage to national health insurance records and the availability of incidence data, the present study demonstrates clear dose-

response relationships between alcohol intake and risks of incident liver cirrhosis and also ALD in Chinese men. In the CKB, the marked regional differences in ALD incidence observed are highly correspondent to the regional alcohol drinking prevalence and consumption level. For example, ALD was common in Sichuan (2nd highest ALD incidence rate in the CKB) where the regular drinking prevalence and total alcohol consumption were the highest in the CKB, whereas the lowest ALD incidence was observed in Gansu where the drinking prevalence was the lowest in the CKB.[87] Other factors may also contribute to the huge regional variation on ALD incidence, such as socio-economic development, drinking patterns, and potentially *ALDH2*-rs671 polymorphism (see Sections 8.5.6-8.5.7).

8.5.4 NAFLD

The distinction between "alcoholic" and "non-alcoholic" fatty liver diseases has recently been questioned,[63,144,159] partly due to the similar histopathological patterns between these two conditions and the underreporting of alcohol consumption at clinical practice, and importantly the uncertainty about the relationship between amount of alcohol intake and fatty liver disease. Two meta-analyses, each with 18 and 16 studies respectively, reported 15-25% significantly lower risks of fatty liver disease associated with low alcohol consumption (i.e., <20g/day) compared with not drinking.[143,144] However, these findings are prone to reverse causation as they are based on almost exclusively cross-sectional studies where ex-drinkers (who were likely "sick-quitters") were not separated from never drinkers. Furthermore, the "protective" associations were largely observed in Japanese studies only, whereas studies conducted in high-income Western populations suggested different findings.[143,144,160]

Focusing on long-term drinking exposure with 30 years of follow-up, the Whitehall II Study of 5407 British civil servants showed that sustained heavy drinking was associated with two-fold higher risk of fatty liver disease compared with stable low-risk drinking (i.e., 8-168g/week for men, 8-112g/week for women), whereas no protective effects from stable low-risk drinking were observed compared with stable non-drinkers.[160] A cross-sectional, regional study of 9432 elderly Chinese men who did not drink excessively (i.e., <210g/week) has also reported positive associations of NAFLD with alcohol consumption and drinking duration,[161] but no prospective evidence is available from China. With a much larger study population than previous studies and a prospective study design, the present study adds to existing evidence by demonstrating a significant dose-response relationship between increasing alcohol intake and risk of NAFLD in Chinese male drinkers. Furthermore, the attenuation of the seemingly lower risks in occasional and light drinkers versus abstainers after exclusions of early follow-up years and "sick-quitters/sick non-starters" indicates that the protective effects from previous studies are likely due to reverse causation and/or residual confounding. Nevertheless, it is also possible that the observed associations with NAFLD might partly be due to some of the reported NAFLD cases being ALD, with the patient's alcohol intake either overlooked or not stated in clinical notes. While the dramatic regional differences in NAFLD incidence rates may partially be due to the regional variations in socio-economic development and lifestyle behaviours linked to increased obesity, it is also possible that NAFLD diagnoses may be affected by differential access to and use of ultrasound or computed tomography in hospitals across CKB study areas, leading to regional variation in the completeness of ascertainment of NAFLD. This may also be relevant for other liver disease endpoints.

Moreover, NAFLD may be diagnosed via health checks which may happen more often in urban areas, or via outpatient department which may not be captured by the health insurance system. Nevertheless, the significant associations of alcohol with NAFLD (and other liver disease endpoints) were similarly observed in areas with high reporting of NAFLD and other study areas in this thesis.

8.5.5 Effect modification by other factors

It has been suggested that HBV infection,[181] smoking,[150] obesity,[120,148] and diabetes[115,116,311] may synergistically interact with alcohol consumption to increase the risks of advanced liver diseases, but existing epidemiological findings are inconsistent.[103,115-120,147,148,150,152,181] In the present study, the associations of usual alcohol intake with risks of liver cancer, liver cirrhosis, and total liver disease did not appear to differ across baseline HBV infection status, smoking status, BMI, and pre-existing diabetes in Chinese men. Although the associations for ALD appeared to be stronger among never smokers, and those with higher BMI, these findings should be interpreted with caution as they may represent chance findings due to the limited number of ALD events. Nevertheless, it has been suggested that obesity and alcohol may synergistically worsen hepatic insulin resistance and necroinflammation and thus lead to progressive liver injury.[312] Furthermore, the exceptional high risk of NAFLD among heavy drinkers with high BMI, and the even more extreme liver cirrhosis risk among heavy drinkers who tested HBsAg positive, warrants clinical and public health attention.

8.5.6 Drinking patterns

This is the first prospective study to report on the associations between alcohol drinking patterns and risks of major chronic liver diseases in a Chinese population. The present study is consistent with findings from the recent MWS which reported a significantly lower risk of liver cirrhosis and ALD associated with usually drinking alcohol with meals than not (RR=0.69 [0.62-0.77]; 1560 cases),[75] as well as two smaller cross-sectional studies conducted in Italy (92 alcohol-induced liver damage cases)[156] and Xi'an city in China (83 ALD cases).[158] One possible mechanism underlying the detrimental effect of drinking in the absence of food might involve the faster gastric emptying and faster absorption of alcohol into the bloodstream from the intestine to the liver, and thus higher blood alcohol concentrations, compared with drinking with food.[305]

Findings from previous studies regarding the type of alcohol consumed are inconsistent. Although previous studies in Danish populations have reported less detrimental effects of grape wine drinking on risks of alcoholic cirrhosis compared with other beverage types,[74,157] it remains unclear whether it is due to the particular composition of wine or residual confounding by other personal and lifestyle characteristics, e.g., diet. In contrast, the MWS reported similar associations in wine-only drinkers and drinkers consuming multiple beverage types.[75] Similar to the MWS, the associations between alcohol consumption and liver diseases did not appear to differ across spirits, beer, or wine (rice wine and grape wine combined) drinkers in the CKB.

There has been controversy in existing literature regarding the impacts between HED and daily drinking on risks of liver diseases. Previous prospective studies from Western populations including the MWS and the DCHS of 55,917 participants (257 alcoholic cirrhosis cases in men, 85 in women) have shown that drinking daily is associated with increased risks of liver cirrhosis and ALD, given amount consumed.[74,75] In contrast, two small prospective studies in Finland (84 decompensated liver disease cases) and the US (~130 liver disease cases) have reported positive associations between HED frequency and risks of liver diseases, but the findings are prone to residual confounding by the total volume and frequency of alcohol consumption (previously discussed in Chapter 2).[154,155] The present study findings, with proper adjustment for total alcohol intake, seem to support the more adverse effects of daily drinking on ALD and total liver disease. The detrimental effects of daily drinking may be explained by the increased hepatic damage with consistent exposure to alcohol, compared with taking breaks from drinking (i.e., "liver holidays") which allows recuperation of the normal metabolic function of the liver.[288] This might be especially relevant for those with low total consumption or occasional drinkers, as the liver damage induced by a single heavy drinking episode may recover during abstinence, particularly at early stage (i.e., fatty liver).[313,314] However, HED should not be taken as a safe drinking pattern. Chronic persistent HED may be particularly harmful, as animal studies have shown that HED may induce and promote liver damage which is exacerbated by repeated heavy drinking episodes.[315,316] The positive associations between longer duration of regular drinking and risks of ALD and total liver disease in the CKB also appear to concur with previous studies on fatty liver disease[161] and liver cancer.[118] Taken together, the

present study suggests that sustained exposure to drinking, in terms of daily and also long-term drinking, is particularly detrimental to liver health.

8.5.7 Causal inference and potential gene-alcohol interactions

In addition to environmental factors (e.g., drinking patterns, obesity, viral hepatitis), genetic factors may also affect individual susceptibility to both alcohol abuse and development of ALD.[177,313,314] *ALDH2*-rs671, which substantially affects acetaldehyde metabolism, may play a particular role among East Asians. It has been suggested that the alcohol-reducing *ALDH2*-rs671 A allele may protect its carriers against alcohol abuse in the first stance due to the unpleasant flushing response after drinking, and thus protect against the development of ALD. Previous meta-analyses of case-control studies in Asian populations have shown that the *ALDH2*-rs671 A allele is associated with substantially lower risks of alcohol dependence and abuse (OR=0.23 [0.20-0.28]; 49 studies) and alcohol-induced diseases (including ALD, liver cirrhosis, or pancreatitis) (OR=0.23 [0.18-0.30]; 7 studies) compared with the G allele,[317] and that the *ALDH2*-rs671 AG genotype was associated with decreased risk of alcoholic cirrhosis (OR=0.78 [0.61-0.99]; 12 studies) compared with the GG genotype.[168] The results in the present study are generally consistent with these meta-analyses. The lower risks of ALD and total liver disease associated with the *ALDH2*-rs671 AA and AG (which predict abstinence [AA] and occasional/lower alcohol consumption [AG]) as well as *ADH1B*-rs1229984 AA and AG (which predict lower alcohol consumption) genotypes, compared with the GG genotype, provide evidence to support the causal role of alcohol intake in development of these liver diseases.

Among those who drink alcohol regularly, the role of *ALDH2*-rs671 becomes more complicated. It has been suggested that drinkers who carry the *ALDH2*-rs671 A allele may be more susceptible to liver damage due to the increased acetaldehyde exposure after drinking than drinkers with the GG genotype, but relevant direct investigation from epidemiological studies is scarce. A case-control study in China showed that among ALD patients (n=281), those with the *ALDH2*-rs671 AG genotype had shorter duration and lower quantity of alcohol consumption than those with the GG genotype, suggesting that the acetaldehyde accumulation among ALDH2 deficient drinkers may increase their susceptibility to ALD.[169] In the present study, the apparently stronger association for ALD among men who reported having the flushing response and the suggestive stronger association for total liver disease among men with the *ALDH2*-rs671 AG genotype broadly support these views. However, the limited number of ALD events (n=5 in male drinkers with the *ALDH2*-rs671 AG genotype) in the current CKB dataset precluded further investigation using *ALDH2*-rs671 and any firm conclusion to be drawn.

8.5.8 Potential mechanisms

Detailed discussion of the mechanisms on how alcohol may affect liver disease risk is described elsewhere (see Chapter 2).[61,177,318] In brief, alcohol use, particularly heavy consumption, can stimulate changes in lipid metabolism via acetaldehyde or regulation of multiple factors, which results in the accumulation of lipids in hepatocytes (i.e., fatty liver). Alcohol use can also cause an inflammatory response leading to alcoholic hepatitis, or steatohepatitis if accompanied by hepatic lipid deposition. The inflammatory response may be induced via the acetaldehyde-induced toxic effects, the

generation of reactive oxygen species and the resulting lipid peroxidation, increased intestinal permeability, and synthesis of pro-inflammatory cytokines. If alcoholic hepatitis and steatohepatitis are persistent and severe, they may eventually lead to fibrosis and sclerotic changes in the liver resulting in liver cirrhosis and liver failure, and ultimately liver cancer.

8.5.9 Strengths and limitations

The chief strengths (large size, comprehensive adjustment and follow-up, prospective study design, stringent exclusions) and limitations (self-report bias, residual confounding, limited statistical power for women) of the CKB study have been discussed in previous chapters (see Chapters 5-7). For this study, the HBsAg test used in the CKB has relatively low sensitivity for lower serum HBsAg levels,[200,319] and participants may have developed HBV infection during follow-up, which might have affected the risk estimates. However, the impact is likely to be minimal, as the results were largely unchanged after further exclusions of participants with unclear and missing HBsAg test results in the sensitivity analyses. Furthermore, this study lacked sufficient statistical power to assess reliably the impact of alcohol consumption on ALD across subgroups, especially of BMI, the flushing response, and *ALDH2*-rs671 genotype, and the associations for grape wine drinking (which was rare in the CKB) versus other beverage types.

8.6 Conclusions

In summary, among Chinese men, alcohol consumption was positively associated with risks of major chronic liver diseases, including liver cancer, ALD, liver cirrhosis, and also

NAFLD. As well as total amount consumed, certain drinking patterns especially drinking without meals, drinking daily, and longer duration of regular drinking might be particularly harmful. In addition to HBV infections, the emerging role of alcohol consumption as a major risk factor for liver diseases among Chinese men warrants public health attention.

Table 8.1. Baseline characteristics of participants by incident liver disease outcome, in men and women

	Men			Women		
	All	No liver disease	Developed liver disease	All	No liver disease	Developed liver disease
Number of participants	205628	200798	4830	298370	293671	4699
Socio-demographic characteristics						
Mean age, years (SD)	52.8 (10.9)	52.8 (10.9)	55.3 (10.7)	51.4 (10.5)	51.4 (10.5)	54.5 (10.0)
Urban area, %	43.5	43.6	36.7	44.5	44.7	29.8
Educational attainment >6 years, %	57.8	57.8	56.7	43.2	43.3	42.5
Income ≥20,000 yuan/year, %	45.6	45.6	44.2	40.6	40.6	39.9
Married, %	92.9	92.9	92.6	89.0	89.0	89.3
Lifestyle factors						
Regular smoking, %	61.3	61.3	63.8	2.4	2.4	2.5
Non-regular fresh fruit intake, %	77.1	77.1	77.7	68.3	68.3	67.9
Physical activity, mean MET-h/d (SD)	22.1 (15.3)	22.1 (15.3)	21.7 (15.0)	20.5 (12.8)	20.5 (12.8)	19.8 (12.8)
Daily tea drinking, %	40.9	40.9	41.1	15.9	15.9	16.2
Physical measurements, mean (SD)						
Standing height, cm	165.2 (6.5)	165.2 (6.5)	165.2 (6.8)	154.1 (6.0)	154.1 (6.0)	154.2 (6.1)
BMI, kg/m^2	23.4 (3.2)	23.4 (3.2)	23.5 (3.4)	23.8 (3.5)	23.8 (3.5)	24.2 (3.6)
SBP, mmHg	132.9 (20.0)	132.9 (20.0)	133.3 (20.8)	129.9 (22.0)	129.9 (22.0)	130.5 (22.2)
DBP, mmHg	79.2 (11.4)	79.2 (11.4)	79.4 (11.5)	76.8 (10.9)	76.8 (10.9)	77.1 (11.0)
Health and medical history[*], %						
Poor health	8.6	8.6	11.2	11.2	11.1	14.4
Any chronic disease[†]	20.8	20.7	24.3	21.0	20.9	27.1
Coronary heart disease	2.7	2.7	2.5	3.2	3.2	3.5
Stroke or TIA	2.3	2.3	2.1	1.3	1.3	1.0
Emphysema or bronchitis	3.1	3.1	3.4	2.2	2.2	2.4
Diabetes	5.5	5.5	8.4	6.1	6.1	7.6
Family history of cancer	16.4	16.4	17.9	16.3	16.3	17.0
Family history of diabetes	6.5	6.5	6.6	7.1	7.1	7.5
HBsAg test positive	3.0	2.6	22.3	2.6	2.4	16.0

SD, standard deviation; MET-h/d, metabolic equivalents of task per hours per day; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischaemic attack; HBsAg, hepatitis B surface antigen.

Prevalences and means are adjusted for age group and study area as appropriate.

Participants with prior cancer or cirrhosis/chronic hepatitis were excluded.

[*]All self-reported except diabetes (included both self-reported and screen-detected cases).

[†]Chronic diseases included self-reported coronary heart disease, stroke or TIA, diabetes, tuberculosis, rheumatoid arthritis, peptic ulcer, emphysema/chronic bronchitis, gallstone/gallbladder disease, and kidney disease.

Table 8.2. Adjusted HRs for incident liver diseases associated with alcohol drinking status, in men

		Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
	All N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Liver cancer	1651	378	1.00 (0.90-1.11)	208	1.22 (1.06-1.40)	492	0.85 (0.78-0.94)	573	1.07 (0.98-1.17)	*0.3508*
Alcoholic liver disease	252	11	1.00 (0.55-1.82)	15	3.31 (1.99-5.50)	15	1.08 (0.65-1.80)	211	13.06 (11.22-15.22)	*<0.0001*
Liver cirrhosis	1147	302	1.00 (0.88-1.13)	118	0.99 (0.82-1.19)	319	0.69 (0.61-0.77)	408	0.97 (0.88-1.09)	*0.7658*
Non-alcoholic fatty liver disease	461	68	1.00 (0.78-1.29)	70	1.63 (1.28-2.08)	115	0.88 (0.73-1.06)	208	1.04 (0.90-1.19)	*0.8157*
Chronic viral hepatitis	798	165	1.00 (0.85-1.18)	85	1.31 (1.05-1.63)	313	1.00 (0.89-1.12)	235	0.87 (0.76-1.00)	*0.2222*
All liver diseases	4830	1064	1.00 (0.94-1.07)	537	1.15 (1.06-1.26)	1368	0.82 (0.78-0.87)	1861	1.06 (1.01-1.12)	*0.1483*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.
**P* for association comparing current regular drinkers vs. abstainers.

Table 8.3. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in men

	All	GG		AG			AA		
	N	N	HR (95% CI)	N	HR (95% CI)	*p*-value*	N	HR (95% CI)	*p*-value*
Liver cancer	569	372	1.00 (0.89-1.12)	176	0.92 (0.79-1.06)	*0.3490*	21	0.74 (0.48-1.14)	*0.1859*
Alcoholic liver disease	90	81	1.00 (0.79-1.26)	8	0.17 (0.08-0.34)	*<0.0001*	1	0.14 (0.02-1.00)	*0.0521*
Liver cirrhosis	386	266	1.00 (0.88-1.14)	101	0.79 (0.65-0.96)	*0.0510*	19	1.08 (0.69-1.71)	*0.7420*
Non-alcoholic fatty liver disease	147	91	1.00 (0.80-1.24)	53	1.15 (0.88-1.49)	*0.4340*	3	0.47 (0.15-1.48)	*0.2061*
Chronic viral hepatitis	267	172	1.00 (0.85-1.18)	83	1.03 (0.83-1.28)	*0.8131*	12	1.11 (0.63-1.98)	*0.7259*
All liver diseases	1623	1066	1.00 (0.94-1.07)	492	0.88 (0.80-0.96)	*0.0178*	65	0.79 (0.62-1.01)	*0.0733*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg.
**P* for association comparing the AA or the AG genotype with the GG genotype.

Table 8.4. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in men

	All	GG		AG			AA		
	N	N	HR (95% CI)	N	HR (95% CI)	p-value*	N	HR (95% CI)	*p*-value*
Liver cancer	569	63	1.00 (0.78-1.28)	226	0.72 (0.63-0.82)	*0.0224*	280	0.82 (0.73-0.93)	*0.1697*
Alcoholic liver disease	90	20	1.00 (0.64-1.56)	34	0.35 (0.25-0.50)	*0.0003*	36	0.32 (0.23-0.45)	*<0.0001*
Liver cirrhosis	386	40	1.00 (0.73-1.37)	165	0.84 (0.72-0.98)	*0.3271*	181	0.87 (0.75-1.01)	*0.4410*
Non-alcoholic fatty liver disease	147	16	1.00 (0.61-1.63)	57	0.76 (0.59-0.99)	*0.3429*	74	0.92 (0.73-1.16)	*0.7686*
Chronic viral hepatitis	267	31	1.00 (0.70-1.43)	113	0.76 (0.63-0.92)	*0.1830*	123	0.78 (0.65-0.93)	*0.2168*
All liver diseases	1622	176	1.00 (0.86-1.16)	685	0.80 (0.74-0.86)	*0.0095*	761	0.81 (0.75-0.87)	*0.0108*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg.
**P* for association comparing the AA or the AG genotype with the GG genotype.

Table 8.5. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, by drinking status in men

			GG		AG			AA		
		All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value*	N	HR (95% CI)	*p*-value*
Liver cancer	Never regular drinkers	295	140	1.00 (0.82-1.22)	134	1.06 (0.90-1.25)	*0.6682*	21	0.89 (0.57-1.37)	*0.6254*
	Current regular drinkers	201	173	1.00 (0.85-1.17)	28	0.97 (0.66-1.42)	*0.8782*	0	--	--
Alcoholic liver disease	Never regular drinkers	9	6	1.00 (0.42-2.36)	2	0.23 (0.06-0.91)	*0.0760*	1	0.55 (0.08-3.95)	*0.5873*
	Current regular drinkers	76	71	1.00 (0.78-1.28)	5	0.34 (0.14-0.81)	*0.0185*	0	--	--
Liver cirrhosis	Never regular drinkers	216	119	1.00 (0.80-1.25)	78	0.90 (0.72-1.11)	*0.4829*	19	1.28 (0.80-2.03)	*0.3476*
	Current regular drinkers	134	119	1.00 (0.82-1.21)	15	0.67 (0.40-1.12)	*0.1522*	0	--	--
Non-alcoholic fatty liver disease	Never regular drinkers	58	19	1.00 (0.62-1.62)	36	1.45 (1.06-1.99)	*0.2089*	3	0.62 (0.20-1.93)	*0.4482*
	Current regular drinkers	67	55	1.00 (0.76-1.31)	12	1.19 (0.67-2.09)	*0.5908*	0	--	--
Chronic viral hepatitis	Never regular drinkers	156	82	1.00 (0.77-1.30)	62	1.11 (0.87-1.42)	*0.5568*	12	1.24 (0.69-2.22)	*0.5088*
	Current regular drinkers	81	70	1.00 (0.77-1.30)	11	0.84 (0.46-1.53)	*0.6078*	0	--	--
All liver diseases	Never regular drinkers	834	385	1.00 (0.89-1.12)	385	1.01 (0.92-1.12)	*0.8558*	64	0.90 (0.70-1.15)	*0.4371*
	Current regular drinkers	609	540	1.00 (0.91-1.09)	69	0.71 (0.56-0.90)	*0.0079*	0	--	--

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Ex-regular drinkers and participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg.
**P* for association comparing the AA or the AG genotype with the GG genotype.

Table 8.6. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, by drinking status in men

			GG		AG			AA		
		All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value*	N	HR (95% CI)	*p*-value*
Liver cancer	Never regular drinkers	295	27	1.00 (0.68-1.47)	113	0.77 (0.64-0.92)	*0.2248*	155	0.94 (0.80-1.11)	*0.7894*
	Current regular drinkers	201	30	1.00 (0.69-1.45)	82	0.70 (0.56-0.88)	*0.1106*	89	0.73 (0.59-0.91)	*0.1499*
Alcoholic liver disease	Never regular drinkers	9	1	1.00 (0.14-7.12)	4	0.63 (0.23-1.68)	*0.6759*	4	0.51 (0.19-1.36)	*0.5478*
	Current regular drinkers	76	17	1.00 (0.62-1.62)	30	0.45 (0.32-0.65)	*0.0098*	29	0.41 (0.28-0.59)	*0.0035*
Liver cirrhosis	Never regular drinkers	216	14	1.00 (0.59-1.70)	98	1.28 (1.05-1.56)	*0.3965*	104	1.29 (1.05-1.58)	*0.3806*
	Current regular drinkers	134	23	1.00 (0.66-1.52)	54	0.59 (0.45-0.77)	*0.0377*	57	0.59 (0.45-0.77)	*0.0376*
Non-alcoholic fatty liver disease	Never regular drinkers	58	4	1.00 (0.37-2.68)	18	0.71 (0.45-1.12)	*0.5336*	36	1.25 (0.90-1.74)	*0.6709*
	Current regular drinkers	67	9	1.00 (0.52-1.93)	32	0.98 (0.70-1.39)	*0.9649*	26	0.78 (0.53-1.15)	*0.5189*
Chronic viral hepatitis	Never regular drinkers	156	15	1.00 (0.59-1.69)	62	0.81 (0.63-1.04)	*0.4675*	79	0.96 (0.76-1.21)	*0.8932*
	Current regular drinkers	81	14	1.00 (0.58-1.72)	37	0.71 (0.51-0.98)	*0.2832*	30	0.54 (0.37-0.78)	*0.0632*
All liver diseases	Never regular drinkers	833	72	1.00 (0.79-1.27)	344	0.83 (0.75-0.93)	*0.1688*	417	0.90 (0.82-0.99)	*0.4242*
	Current regular drinkers	609	90	1.00 (0.81-1.23)	262	0.76 (0.67-0.86)	*0.0262*	257	0.70 (0.62-0.79)	*0.0040*

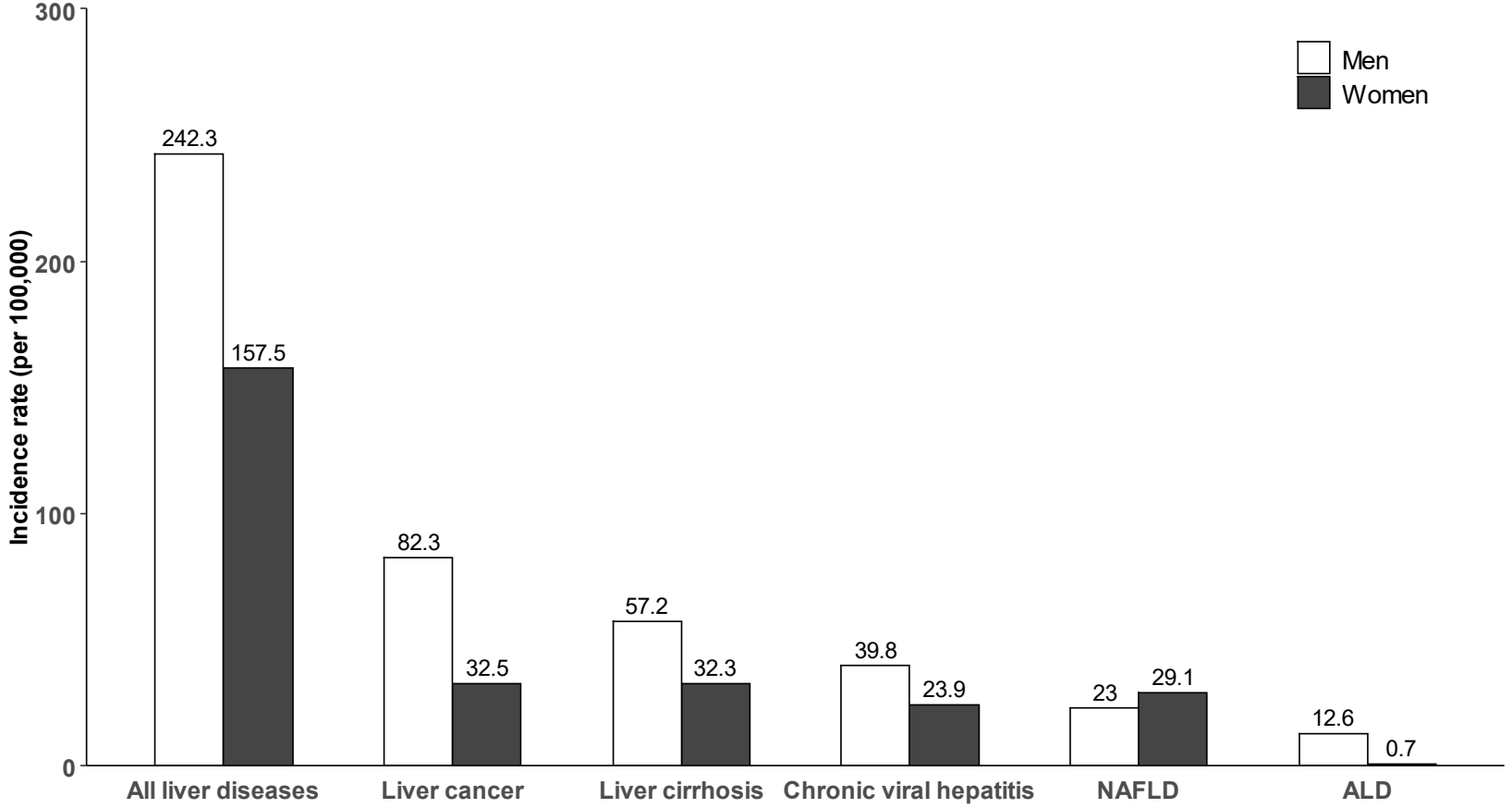
HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Ex-regular drinkers and participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg.
*P for association comparing the AA or the AG genotype with the GG genotype.

Table 8.7. Population attributable fraction of ever regular drinking on liver diseases in men

	N	HR (95% CI)	P	PAF, %
Liver cancer	1651	1.22 (1.09-1.35)	*0.47*	*8.4*
Liver cirrhosis	1147	1.22 (1.07-1.38)	*0.46*	*8.2*
Non-alcoholic fatty liver disease	461	1.24 (1.02-1.51)	*0.60*	*11.7*
All liver diseases	4830	1.22 (1.14-1.29)	*0.50*	*8.8*

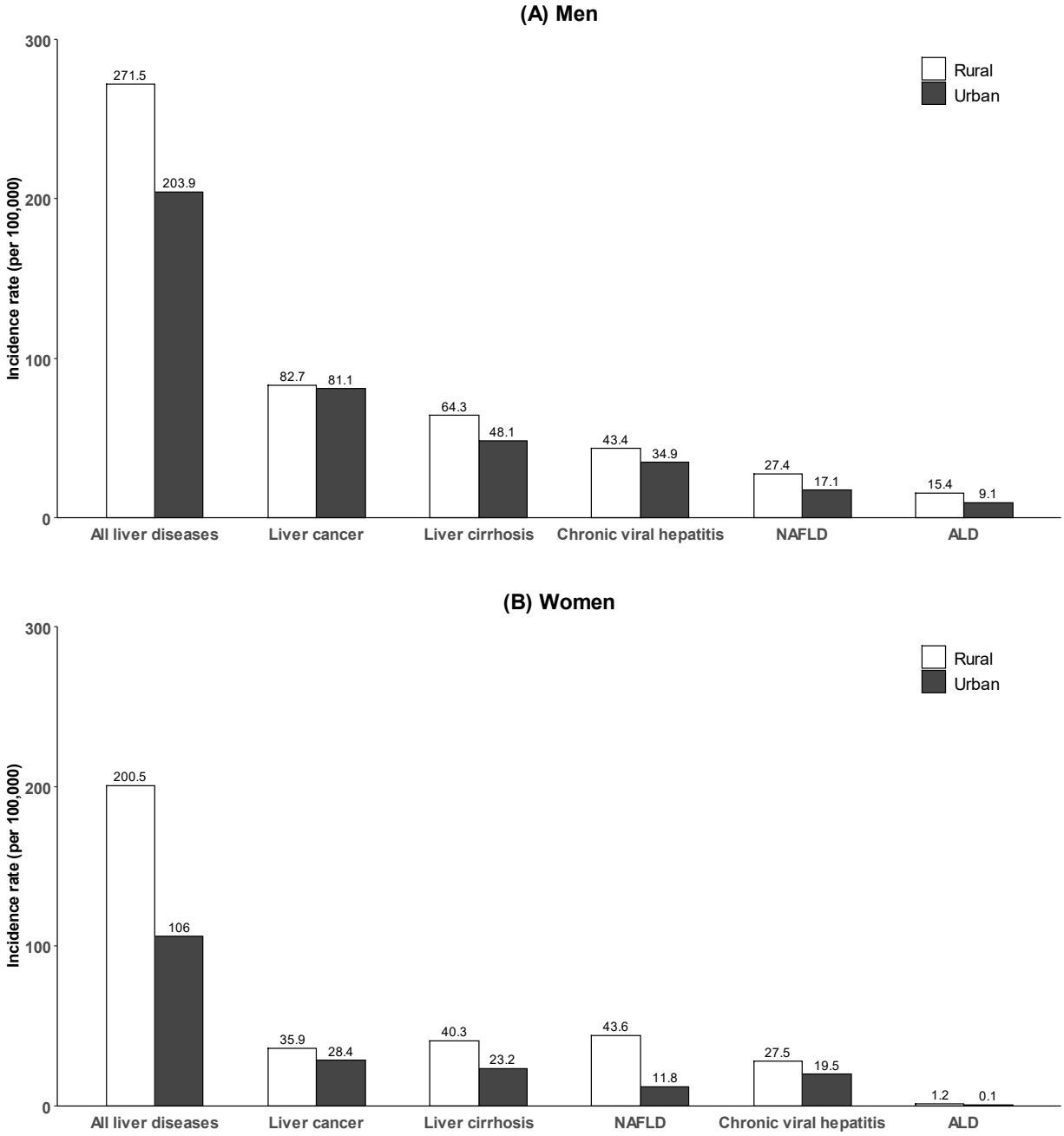
HR, hazard ratio; CI, confidence interval; P, prevalence of ever regular drinking; PAF, population attributable fraction.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index.
PAF is calculated as P x (HR-1)/HR, where P is the prevalence of ever regular alcohol consumption (i.e., current and ex-regular drinking) among those who developed the relevant liver disease during follow-up.

Figure 8.1. Incidence rates (per 100,000 person-years) of liver diseases, in men and women



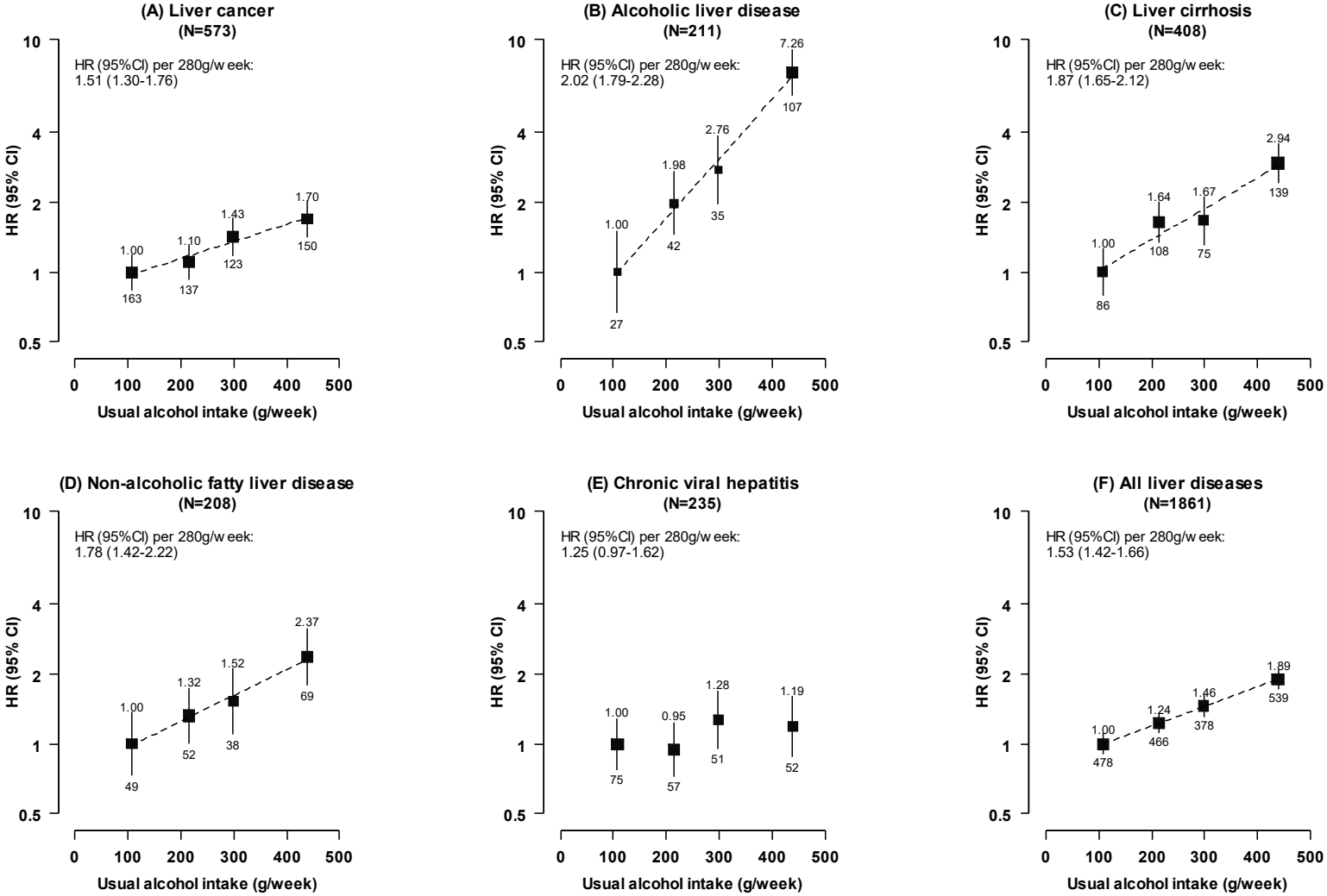
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease.

Figure 8.2. Incidence rates (per 100,000 person-years) of liver diseases, by rural and urban areas



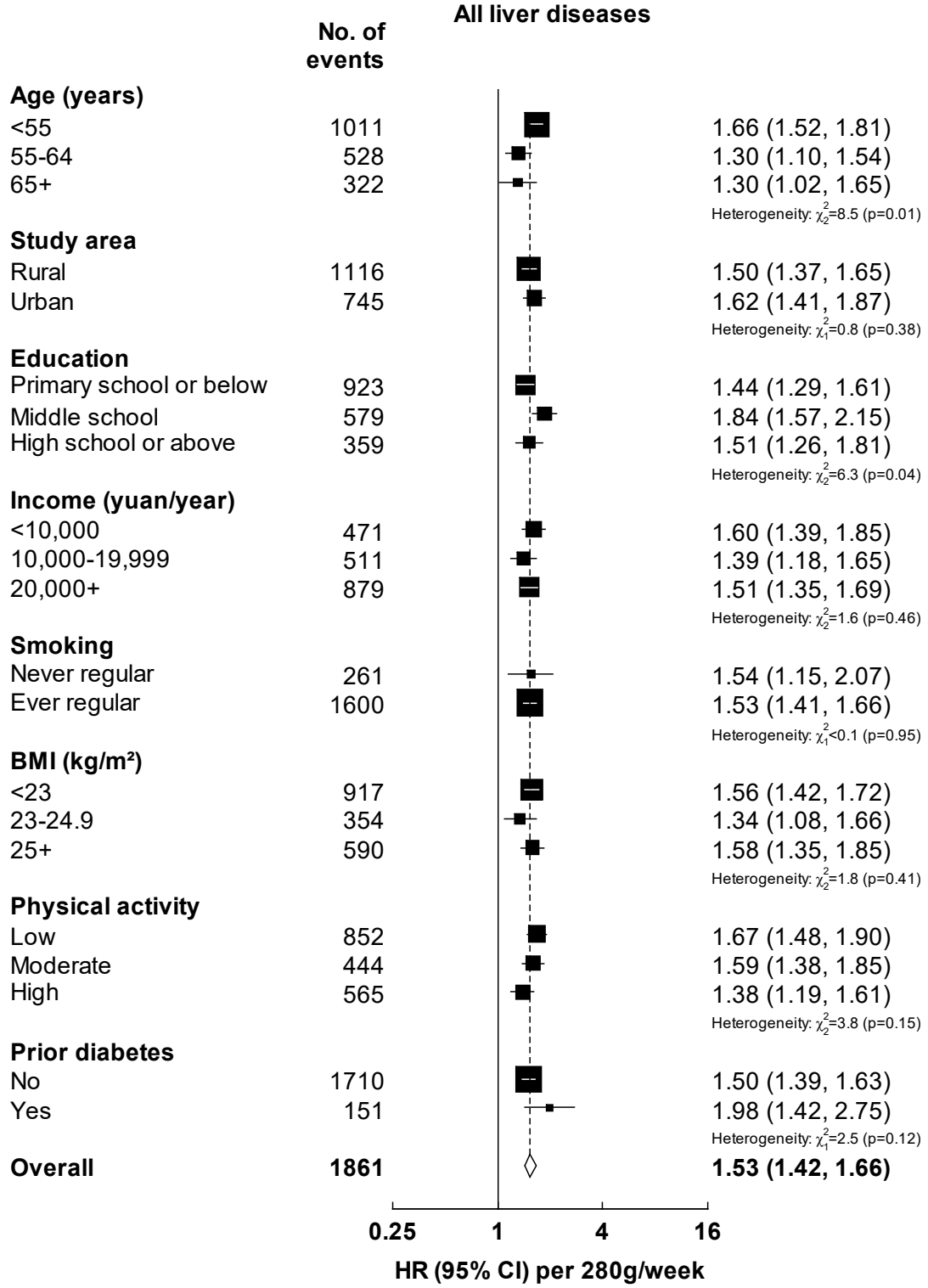
Incidence rates are standardised to the age (10-year intervals) structure of the China Kadoorie Biobank study population in men and women separately. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease.

Figure 8.3. Associations of alcohol consumption with liver diseases, in male current regular drinkers



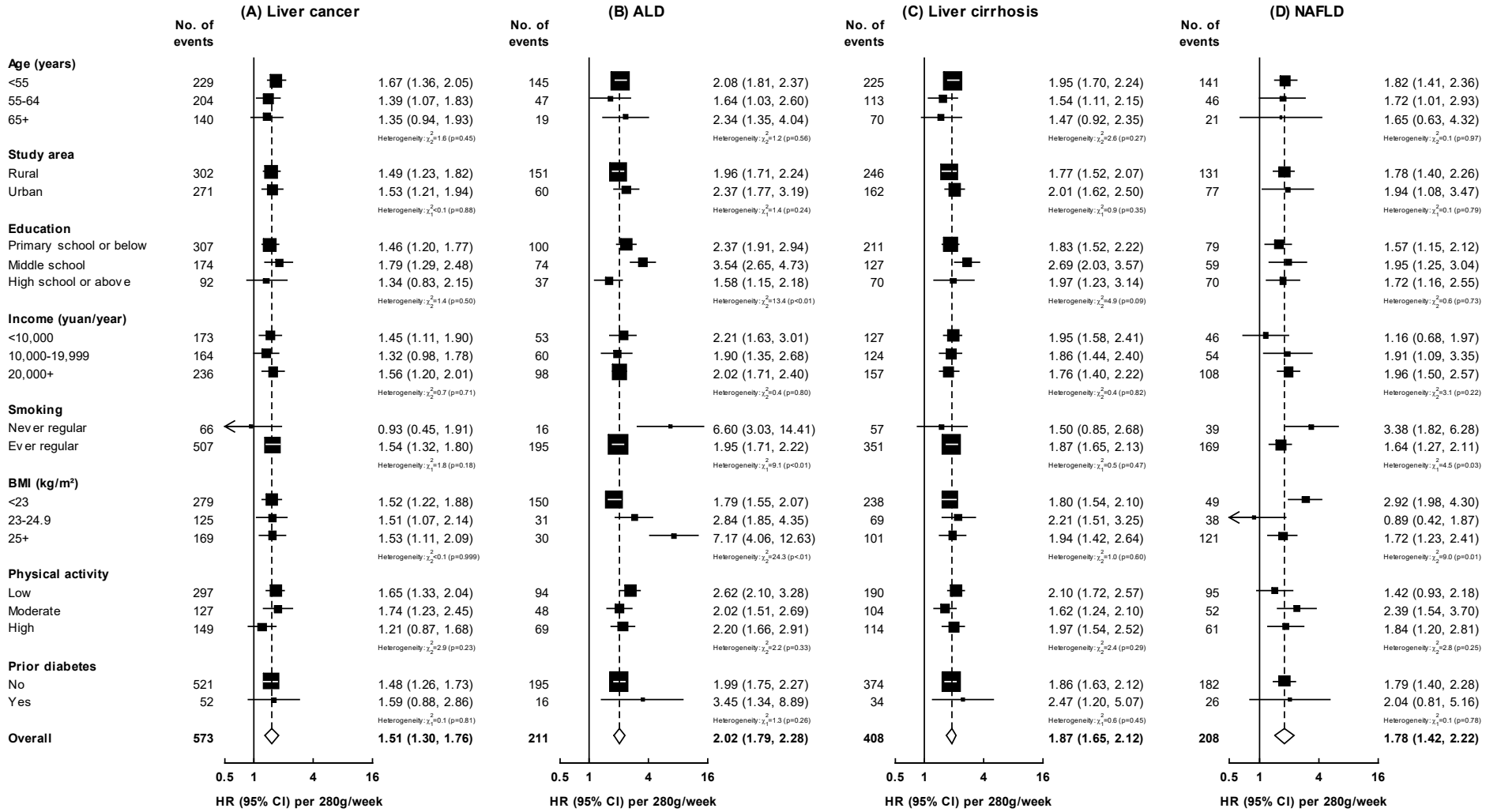
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. A regression line is fitted through the HRs (95%CIs) of alcohol consumption categories plotted at the usual alcohol intake of each group, when an approximately linear trend is observed and the HR per 280g/week increment is significant. HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Figure 8.4. Adjusted HRs per 280g/week higher usual alcohol intake for total liver disease, by population subgroups in male current regular drinkers



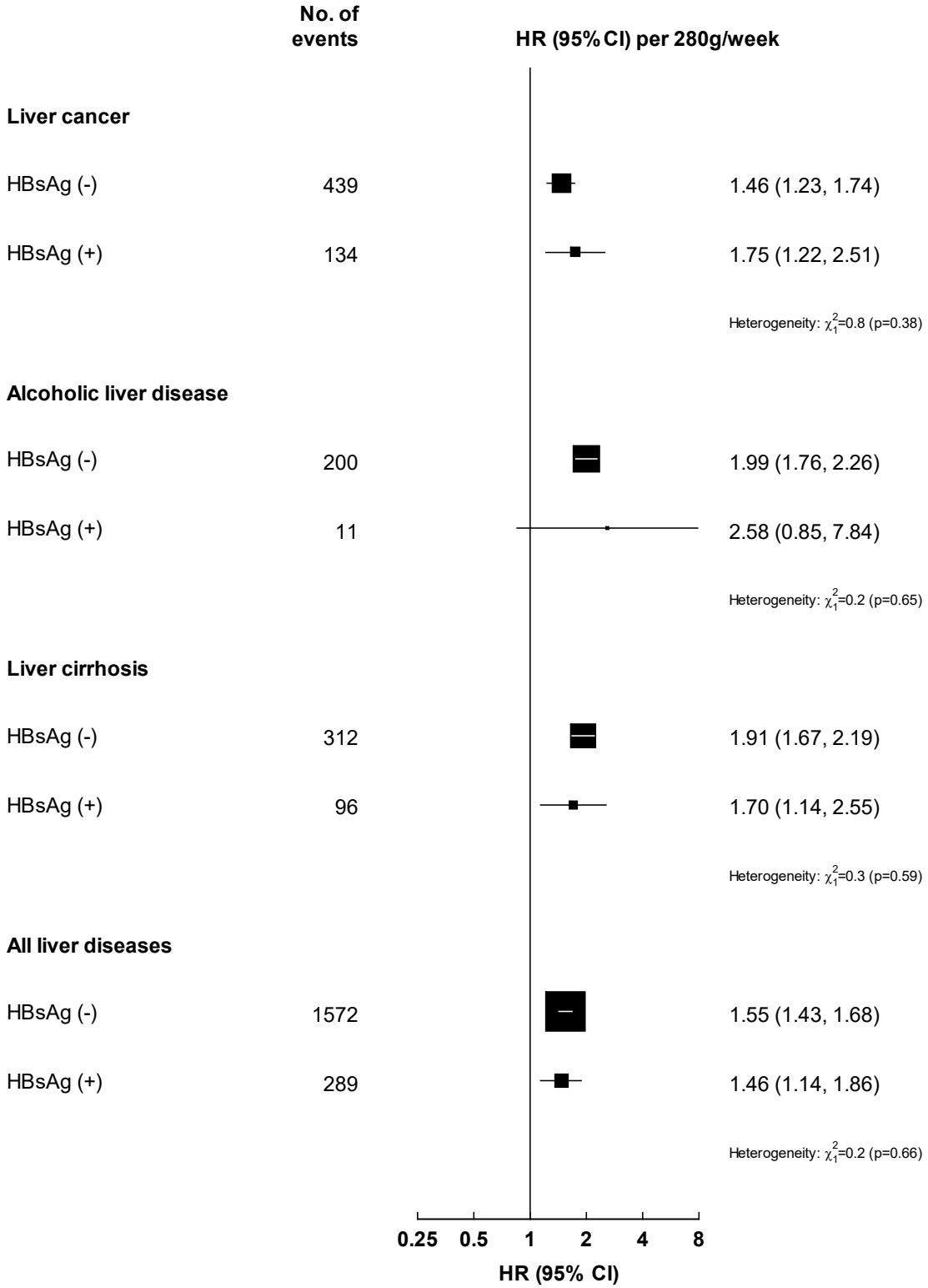
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index, where appropriate. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.5. Adjusted HRs per 280g/week higher usual alcohol intake for major chronic liver diseases, by population subgroups in male current regular drinkers



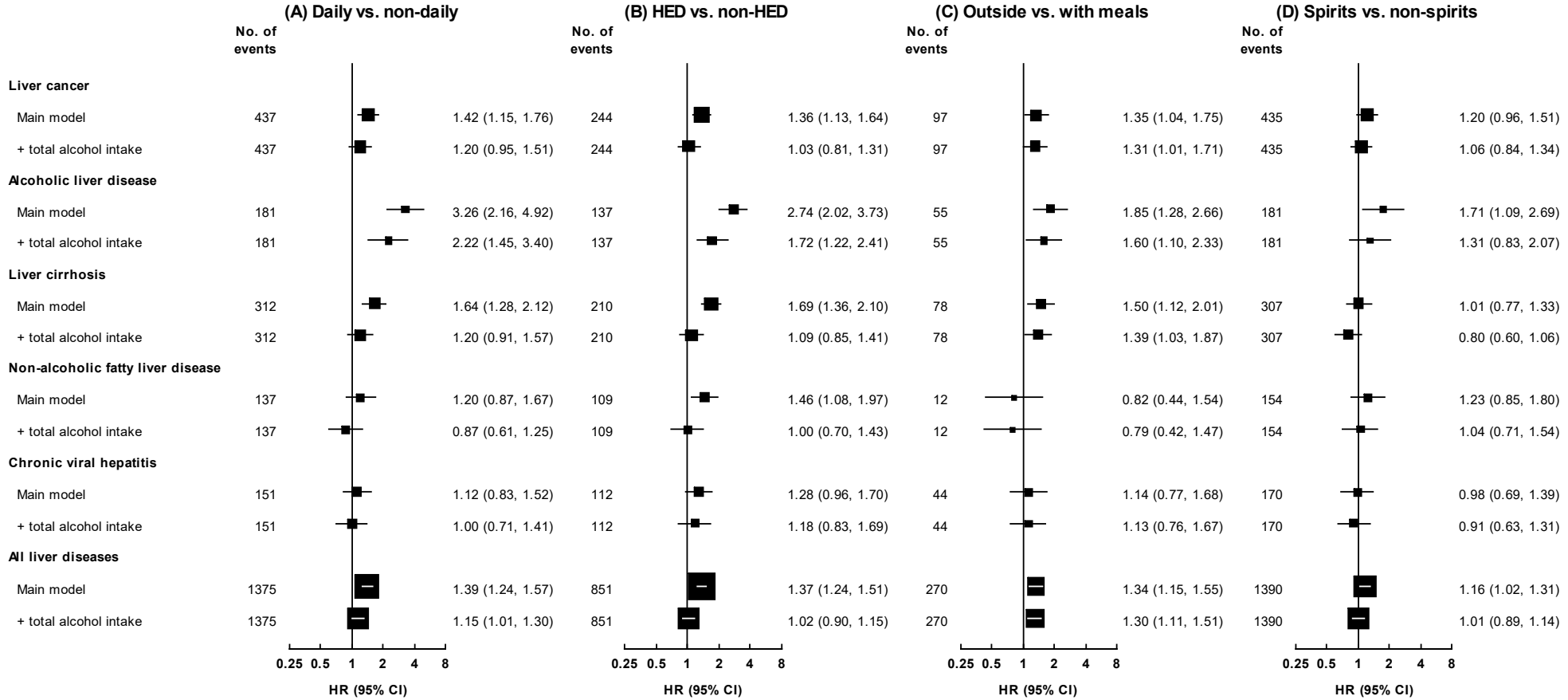
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index, where appropriate. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.6. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by HBsAg seroprevalence in male current regular drinkers



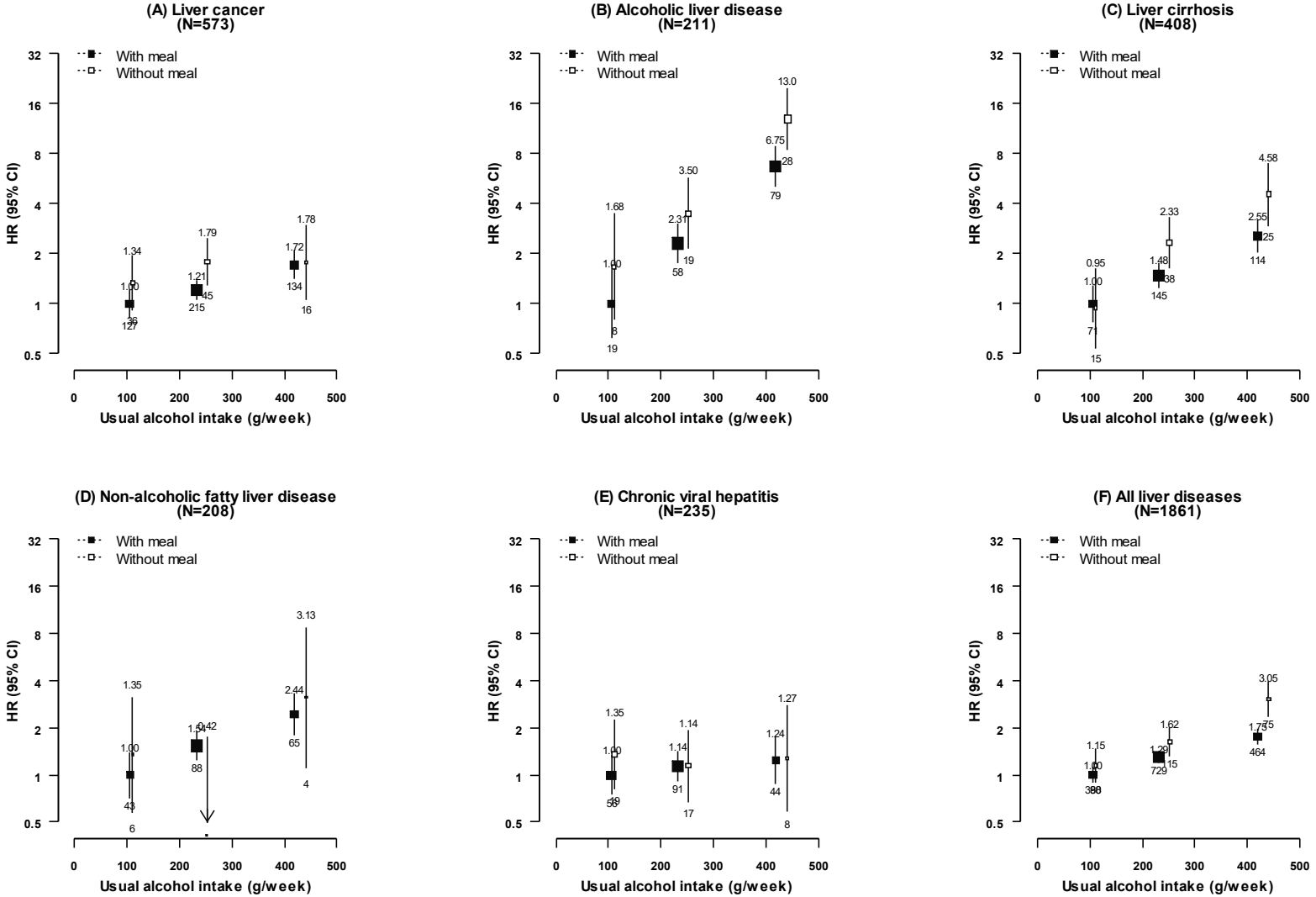
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HBsAg (-) included negative, unclear, or missing test results. Non-alcoholic fatty liver disease is not shown here due to the low number of events in HBsAg positive participants (n=4). HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Figure 8.7. Adjusted HRs for liver diseases associated with drinking patterns, in male current regular drinkers



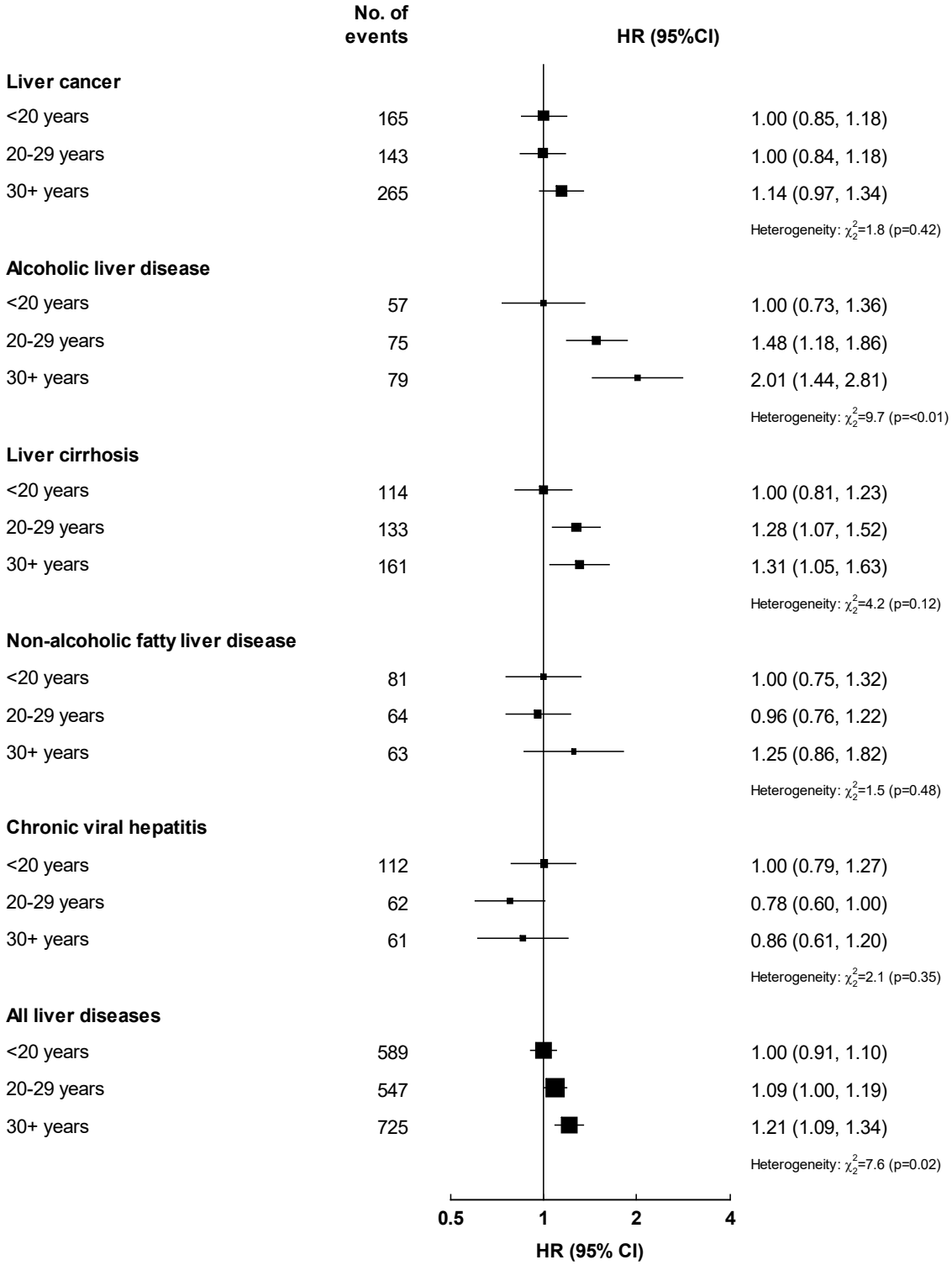
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index, and total weekly alcohol intake where indicated. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HED is defined as drinking >60g/session. HED, heavy episodic drinking; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.8. Associations of alcohol consumption with liver diseases, by mealtime drinking habits in male current regular drinkers



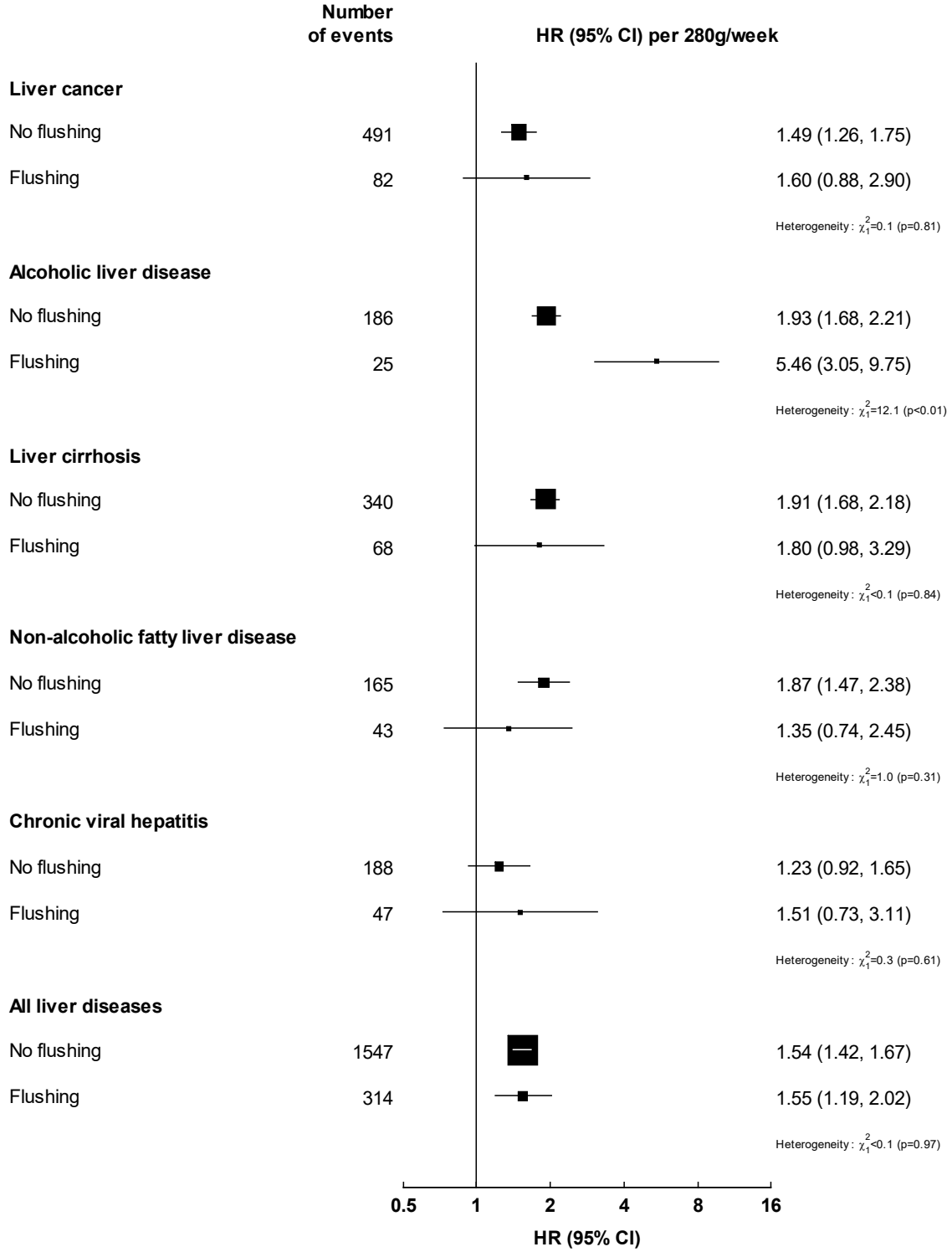
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.9. Adjusted HRs for liver diseases associated with duration of drinking, in male current regular drinkers



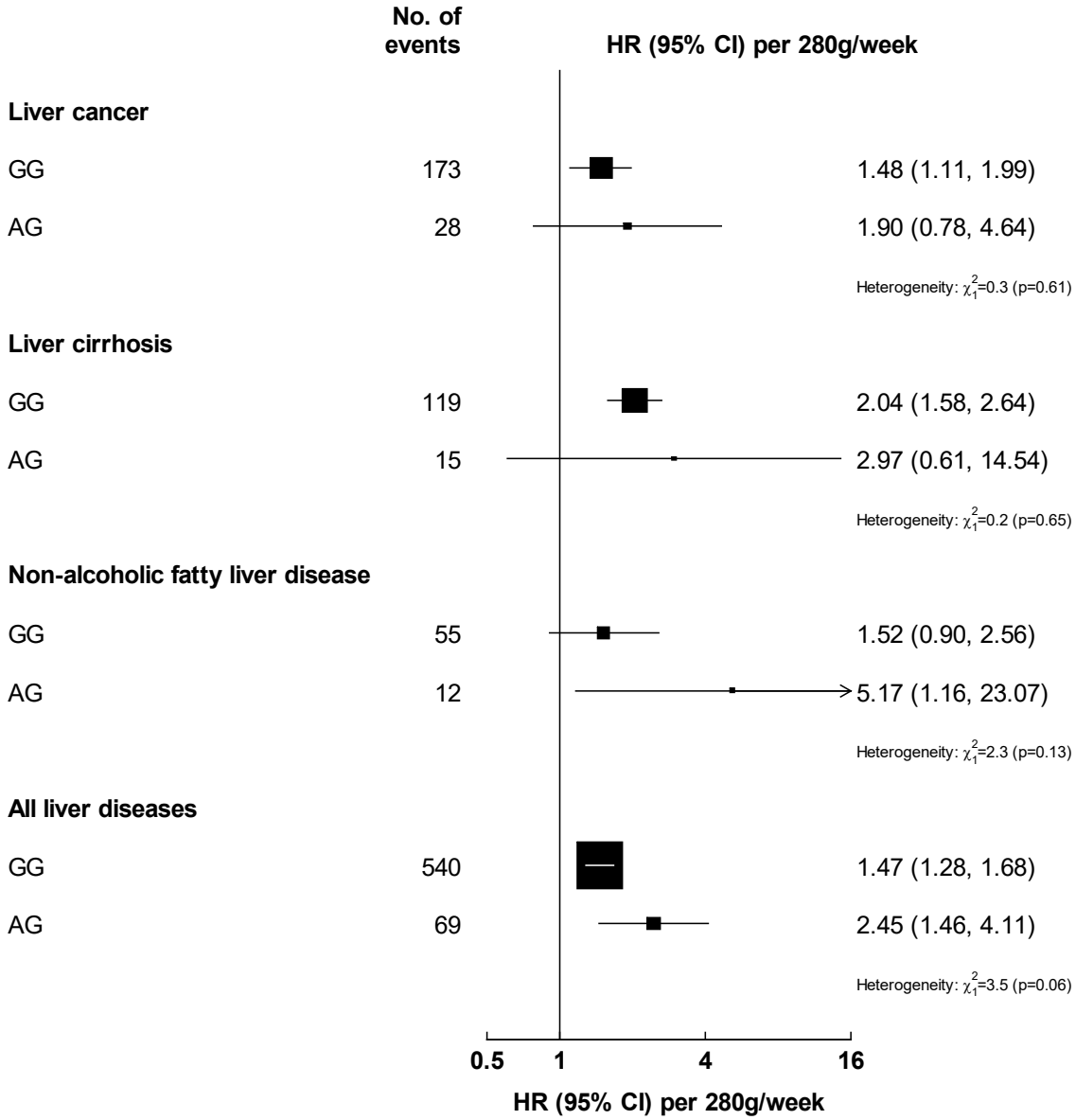
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, body mass index, total weekly alcohol intake, and baseline age. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.10. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by flushing status in male current regular drinkers



Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure 8.11. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by *ALDH2*-rs671 genotype in male current regular drinkers



Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. Alcoholic liver disease (n=5) and chronic viral hepatitis (n=11) are not shown here due to the limited numbers of events in drinkers with the AG genotype. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Chapter 9. General Discussion

Using data of 0.5 million Chinese adults from the CKB prospective cohort, this thesis assessed the recent trends in the prevalence and patterns of alcohol consumption and investigated the relationships between alcohol consumption and health in the Chinese population. This chapter summarises and discusses the main findings in the context of existing literature and the overall thesis. This chapter also discusses the strengths and methodological limitations of the analyses, followed by discussions of future research opportunities and implications for public health and clinical practice.

9.1 Summary of findings

In China, alcohol consumption is primarily a male phenomenon. In the CKB, one-third of men drank alcohol in most weeks (i.e., current regular drinkers), among whom alcohol was mostly consumed daily, in the form of spirits and usually with meals. Between baseline and the second resurvey, there were increases in alcohol consumption level and prevalence of HED (i.e., >60g/session), especially among younger men born in the 1970s, in line with other national survey data. Among male current regular drinkers at baseline, 24% reported experiencing at least one alcohol-related problem (i.e., problem drinkers), which was positively associated with stressful life events, poor wellbeing and mental health (e.g., sleep problem, life dissatisfaction, depression, anxiety), and increased risks of premature mortality and hospitalisations. There were positive dose-response associations of alcohol consumption with risks of several site-specific cancers (including cancers of the mouth and throat, oesophagus, colon and rectum, liver, lung, and gallbladder) and major chronic liver diseases

(including liver cirrhosis, ALD, and NAFLD). Most of the associations did not differ across population subgroups defined by socio-demographics, smoking status, HBsAg status, and BMI, although the associations for ALD appeared to be stronger among men with higher BMI. Furthermore, men with low alcohol tolerance (defined by self-reported flushing response, or *ALDH2*-rs671 AG genotype) had higher risks of oesophageal cancer and lung cancer for a given amount of alcohol consumed. After adjusting for total weekly intake, daily drinkers had increased risks of overall cancer and overall liver disease (mainly driven by oesophageal cancer and ALD), and men who usually drank without meals had increased risks of total and most chronic liver diseases (liver cancer, liver cirrhosis, ALD), compared with their counterparts. Among women, very few (~2%) drank alcohol regularly and with limited statistical power the relationships between alcohol intake and disease risks could not be evaluated effectively.

With the largest sample size and the most comprehensive linkage to follow-up outcomes in a single study from China, this thesis provides robust new evidence and contributes substantially to knowledge in the field of alcohol and health (see Table 9.1 for summary of scientific contributions to existing knowledge). This is the largest study in a Chinese population that supports the detrimental cross-sectional relationships between problem drinking and mental health previously reported in Western populations, and the dose-response relationships between alcohol consumption and certain cancers (mouth and throat, oesophagus, liver, colon and rectum) and ALD previously established to be causally related to alcohol in non-Chinese populations. Moreover, it adds new evidence for disease endpoints for which the existing evidence

is limited and insufficient for causal inference – including lung cancer for which this thesis suggests a dose-response effect among never smokers, gallbladder cancer, and NAFLD. For the first time in a Chinese population this thesis corroborates the harmful effects of daily drinking (particularly for ALD) and drinking without meals on liver diseases previously reported in Western populations, and adds new knowledge about the potential harmful role of daily drinking in cancer development particularly in the oesophagus. As well as confirming the *ALDH2* genotype-alcohol interaction for oesophageal cancer risk previously reported in East Asian populations, this thesis adds new information by suggesting similar interactions for risk of lung cancer and potentially ALD which warrants further investigation for these and other alcohol-related diseases.

9.2 Findings in the context of existing literature and the thesis

9.2.1 Patterns and trends of alcohol consumption

The prevalence of alcohol drinking and the different drinking behaviours between men and women in this thesis are broadly consistent with several national representative surveys in China in the same period.[3,4,209] In the CKB, between 2004 and 2014, there was a modest decrease in regular drinking prevalence. This may partly be due to the "sick-quitter" effect of the ageing study population, as has been previously observed in Western populations[213] and supported by analyses at the individual level, as well as other reasons for stopping drinking such as money. On the other hand, the increases in the amount of alcohol consumption and the prevalence of HED over time, particularly among younger men, are consistent with the WHO Global Status Report on Alcohol and Health 2018 that also provided separate data on China.[1] In addition, this thesis

provides further information on the trends of other more detailed drinking patterns and the scale of problem drinking by socio-demographic characteristics. In particular, there was an increase in the proportion of drinkers consuming multiple beverage types (who were the heaviest drinkers) among younger men, and an increase in the prevalence of problem drinking particularly among younger, urban male drinkers. These findings demonstrate a rising trend of harmful alcohol use in China, especially in certain high-risk groups (i.e., young, urban men) who have had higher exposure to the wider alcohol availability brought about by Westernisation and rapid economic development during the past decades.[7,206,207] The rise in heavy and problematic alcohol use may lead to adverse impacts on both short-term and long-term health, such as poor mental health and increased risks of cancers, liver diseases, and premature mortality as investigated in this thesis.

9.2.2 Problem drinking, mental health and mortality risk

In this Chinese population, 8% of men reported at least one indicator of problem drinking in the past month, which is broadly consistent with a previous meta-analysis on the prevalence of AUD in China.[267] Among men who drank alcohol regularly in the CKB, problem drinking was fairly common, affecting one in four men with higher prevalence in rural areas and in lower socio-economic groups. Among male current regular drinkers, the positive associations of problem drinking with the experience of stressful life events, especially financial stress, and with various measures of poor wellbeing and mental health including poor self-reported health, life dissatisfaction, sleep problems, depression, and anxiety are consistent with previous findings in Western populations.[78-83,244-249,252-254] The findings are in contrast to the inverse

relationships between AUD or alcohol use with mental health observed in previous studies in China, which are likely due to “sick-quitter” and “sick non-starter” bias, or confounding or other biases, as non-drinkers comprised the reference group in those studies.[260,261] The CKB study further shows that the indicator of problem drinking (morning drinking in rural vs. other indicators in urban drinkers), the type of stressful life events related to problem drinking (divorce in urban drinkers vs. financial stress and major injuries in rural drinkers), and the strength of associations between problem drinking and poor mental health (stronger in urban drinkers) appear to differ between rural and urban areas, suggesting the importance of cultural and contextual factors in the relationships between problem drinking and mental health in China. Consistent with previous studies of mostly Western populations,[250,251,284-286] high-risk drinking (i.e., reported either drinking ≥200g/week or HED, but no problem drinking indicator) and problem drinking were associated with increased risks of all-cause mortality, hospitalisations, and events due to external causes in the CKB.

9.2.3 Alcohol consumption and risks of cancers and liver diseases

This thesis demonstrates that alcohol consumption is a strong risk factor for cancers and liver diseases in Chinese men. However, the relationships between alcohol intake and disease risks among Chinese women could not be assessed reliably due to their low drinking prevalence. Among male current regular drinkers, there were significant dose-response relationships between alcohol intake and risks of cancers of mouth and throat, oesophagus, liver, and colon and rectum. These cancers have been considered to be alcohol-related based mostly on evidence from Western and other East Asian populations,[19,20,41] but with relatively weak prospective evidence from China apart

from oesophageal cancer.[72,73,104,108,109,114,117,131] For lung cancer, there was also a significant dose-response relationship with alcohol in the CKB, which was consistent in both ever regular smokers and never regular smokers. Previous evidence on the independent associations between alcohol and lung cancer has been inconclusive due to possible residual confounding by smoking, while studies focusing on never smokers were either limited by statistical power or showed no associations.[19,20,92,122-125] The findings on lung cancer in the CKB therefore contribute importantly to the current evidence base. In addition, there was also a significant association for gallbladder cancer in the CKB, which is consistent with previous meta-analysis.[100] While previous studies have suggested weak associations between heavy alcohol intake and stomach cancer,[95,100,127-129] no clear dose-response associations were observed in the CKB (see Section 9.4.1 for future research incorporating infection data). In contrast to previous findings in Western populations,[91,100,137-140] no inverse associations were observed for kidney cancer and lymphoma based on a limited number of events in the CKB.

For liver diseases, the positive associations between alcohol intake and risks of ALD and liver cirrhosis among male current regular drinkers in the CKB are consistent with existing literature.[71,74,75,103,151,153] In addition, there was a significant dose-response association between alcohol intake and NAFLD. This finding is broadly consistent with the Whitehall II study[160] and challenges previous findings of protective effects of low to moderate drinking on fatty liver disease, which might be due to reverse causation or residual confounding.[143,144] There was no evidence of effect modification of the associations between alcohol consumption and liver diseases by HBV infection status as previously suggested,[181] which may be due to a number of other factors such as

limited statistical power and/or low sensitivity of the HBsAg test (as discussed in Chapter 8). However, there was suggestion of a stronger effect of alcohol consumption among those with higher BMI for ALD, as previously reported in several Western studies.[120,148] Nonetheless, further replication of findings with higher statistical power is needed before any firm conclusion to be made.

This thesis is the largest prospective study to systematically investigate the associations of drinking patterns and risks of site-specific cancers and major chronic liver diseases in China. In the CKB, the adverse effects of several drinking patterns (daily drinking, HED, drinking without meals, drinking spirits) on risks of cancers and liver diseases were largely confounded by the total amount of alcohol consumed. Nevertheless, drinking daily (for overall cancer and total liver disease, mainly driven by oesophageal cancer and ALD), longer duration of drinking (for both IARC alcohol-related cancers and other cancers, ALD, and total liver disease), and drinking without meals (for liver cancer, liver cirrhosis, ALD, and total liver disease) remained detrimental even after controlling for total alcohol intake, which are largely consistent with cohort studies in Western and Japanese populations.[74,75,287,288] These findings offer insights into the potential mechanisms of how the context and patterns of alcohol drinking may increase risks of cancers and liver diseases, e.g., via persistent exposure to alcohol and/or acetaldehyde in the context of daily drinking (and cumulative exposure in the context of longer duration of drinking), and via faster absorption of alcohol into the blood for transport to liver in the absence of food. Although daily drinking appeared to be more detrimental to risks of cancers and liver diseases after rigorous adjustments of total amount consumed in the regression

models and by subgroup, the findings should not be taken to dispute the potential harmful effects of HED. HED is still an important harmful drinking pattern as it results in a high amount consumed, particularly if repeated. Also, single-session HED might relate to other short-term consequences, e.g., intoxication, accidents, and injuries.[31]

9.2.4 Causal relevance of alcohol and gene-alcohol interactions on risks of cancers and liver diseases

Using genetic variants in two alcohol metabolism genes which substantially affect alcohol intake and are common in East Asians (*ALDH2*-rs671, *ADH1B*-rs1229984), this thesis demonstrates significantly reduced risks of UADT cancers, IARC alcohol-related cancers, ALD, and total liver disease associated with genotypes which predict lower alcohol intake in men, suggesting a causal role of alcohol for these diseases. The lack of similar associations for these outcomes among women (who rarely consumed alcohol in the CKB) suggests that the strong associations observed among men are due chiefly to alcohol intake rather than pleiotropy (i.e., effects of the genotype that are independent of alcohol drinking), as has been shown in a previous study which explored the causal relationships between alcohol and cardiovascular diseases in the CKB.[24] Among male current regular drinkers, the risks of oesophageal cancer and lung cancer associated with alcohol intake were higher among those who had the alcohol flushing response than those who did not, and similarly among those who had the *ALDH2*-rs671 AG genotype compared with those who had the GG genotype. These findings provide support for a causal role of acetaldehyde, which has already been identified as Group I carcinogen by IARC,[19,20] in cancer development. Furthermore, these findings also suggest that the associations between alcohol consumption and

these cancers may be modified by the inherited ability to metabolise acetaldehyde. The potential *ALDH2*-rs671 gene-alcohol interaction on oesophageal cancer has been reported in previous studies,[25,163,164,308] and the novel findings on lung cancer suggest further investigation into other major alcohol-related cancers is warranted. In the CKB, there was also indication of a gene-alcohol interaction for ALD based on the self-reported flushing response, which is biologically plausible given the role of acetaldehyde in liver damage.[167] However, genetic analyses were underpowered and did not confirm this.

9.3 Strengths and limitations

The major strengths of this thesis are the large population recruited from ten diverse areas and the large numbers of incident cancer and liver disease cases in the CKB, which enabled adequate study power for the main analyses among men. Moreover, the CKB study has comprehensive and complete follow-up systems via electronic linkage to health insurance records on top of death and disease registries and the active follow-up approach, which provided a wide range of disease outcomes including less common cancer sites and non-fatal liver diseases (e.g., NAFLD). The extensive data on various aspects of alcohol consumption also allowed thorough investigation on how problem drinking, drinking patterns, and the flushing response are related to mental health and disease risks. Furthermore, the distinction of ex-regular drinkers from never regular drinkers with available information on past drinking, and the exclusions of prior diseases and the first few years of follow-up greatly reduced reverse causation. Importantly, the repeat measures from the two resurveys enabled assessment and adjustment of regression dilution bias in the prospective associations between alcohol

consumption and disease risks. Moreover, the extensive assessments of a range of risk factors and medical history allowed for comprehensive adjustments for potential confounders in the analyses and examination of the associations across important population subgroups. Finally, the availability of genetic data allowed exploration of causality and investigation of gene-alcohol interactions.

Despite the strengths of this thesis, there are several methodological limitations to consider in the interpretation of the results.

9.3.1 Representativeness

The CKB was not designed to be nationally representative and did not enrol participants outside the age range of 30-79 years at baseline, but the large and diverse study population provides reliable and detailed information on the drinking habits among Chinese adults born in the 1920s-1970s. Although the overall response rate (~30%) was relatively low,[190] it is comparable with those of other large nationwide prospective studies.[320] However, it is possible that the estimates of alcohol consumption levels and prevalence of alcohol drinking and problem drinking reported in this thesis may be underestimated due to the "healthy worker effect" often described in occupational epidemiology,[321] i.e., heavy drinkers and persons with severe mental or alcohol use problems are less likely to present themselves for employment (in this case, to visit the local assessment centres in the CKB). Nevertheless, the main aim of this thesis is to investigate the prospective associations between alcohol consumption and chronic health, which the CKB study is well-designed for (through collection of diverse exposure and outcomes, and limited loss to follow-up). Thus, the relationships between alcohol consumption and health outcomes are likely to be

generalisable to Chinese adults overall given the large size and diversity of the CKB study population. Since the prevalence of ever regular drinking used in the PAF calculation was obtained within the male population in the CKB study (i.e., middle to older-aged male group), the alcohol-attributable fraction of cancers and liver diseases estimated in this thesis may not be generalisable to China. If the associations of alcohol consumption with cancers and liver diseases were stronger in younger Chinese men born after 1978 given the observed rising trends of alcohol drinking level and HED among younger Chinese men, the PAF estimated in the present study would probably be underestimated for the overall Chinese population. Nevertheless, the CKB data is one of the best current sources of evidence on relative risks that can be used for national estimates of disease burden in China. Further estimation using nationwide representative drinking prevalence data would provide useful information on alcohol-related disease burden in China (see Section 9.4.4).

9.3.2 Reverse causation

Reverse causation is a major issue particularly in epidemiological research on the associations between alcohol consumption and health. This is because people may have reduced or stopped drinking in response to early symptoms of diseases, or may abstain from starting drinking due to poor general health or social disadvantages, as discussed regarding the effects of "sick-quitter" and "sick non-starter" groups throughout this thesis.[24,182,183] The restriction of the main analyses to current regular drinkers without self-reported cancer or liver disease history, plus further exclusions of early follow-up years and more general poor health conditions in sensitivity analyses, should have substantially reduced reverse causation in the prospective associations

observed. However, given the long latency period for cancer, there may still be reverse causation in the analyses that may not be fully accounted for.

9.3.3 Measurement errors

In the CKB, although the positive correlations of self-reported alcohol intake with blood pressure and gamma-glutamyl transferase suggest good quality of the alcohol data,[24] self-report bias and random measurement errors in alcohol intake are inevitable as in other observational studies. The CKB baseline questionnaire design allowed only one beverage type to be reported for a typical drinking session, and this might have resulted in under-reporting of typical alcohol consumption levels and HED at baseline. It is possible that under-detection of HED among male drinkers might have led to an underestimation of the effects of HED on disease risks. To account for measurement errors of alcohol intake level, repeat measurements of alcohol intake were used to estimate the "usual" alcohol intake over time and to correct for regression dilution bias in analyses relating amount of alcohol consumption to disease risks. In this thesis, the overall RDR was applied to the HR estimates per 280g/week increase in alcohol intake across population subgroups. It is possible that changes and measurement errors in alcohol intake might vary across specific population subgroups (e.g., those with the flushing response vs. without). However, given the limited number of male current regular drinkers involved in the resurvey population, the subgroup-specific RDRs estimated are unlikely to be as robust and reliable as the overall RDR (see Chapter 5). Furthermore, the application of group-specific RDRs in subgroup analyses is unlikely to make substantial changes to the conclusions, at least for the case of ALD (see Table H22).

Although self-reported smoking status has been validated with COex which suggests reliable data quality, there may still be measurement errors in smoking and other major covariates (e.g., self-reported fruit intake, physical activity, undetected HBV infections), resulting in inadequate adjustment for covariates which might introduce residual confounding and could somewhat bias the associations between alcohol intake and disease risks. Similarly, measurement errors in baseline alcohol intake level (especially given only one beverage type was reported at baseline) may result in inadequate adjustment for alcohol intake level which could lead to residual confounding in the estimation of the effects of drinking patterns on disease risks.

9.3.4 Residual confounding

As in all observational studies, residual confounding may still persist in spite of the careful covariate adjustments in the analyses in this thesis. This may include unmeasured factors such as specific family medical history (e.g., on site-specific cancers, AUD) and infections (e.g., *H. pylori*), crudely measured and/or categorised covariates (e.g., socio-economic status), and other unknown factors. In particular, previous studies have shown potential inverse relationships between alcohol consumption and *H. pylori* infection, which is prevalent in China.[298-300] Further investigations including data on *H. pylori* infection (which have recently become available in the CKB) may offer the opportunity to elucidate the relationships between alcohol consumption, *H. pylori* infection, and stomach cancer in China.

Furthermore, the effects of residual confounding cannot be ruled out even though the relevant factors have been adjusted for in the regression models, particularly in the cases of drinking patterns (daily drinking, HED) and smoking which are strongly

associated with amount of alcohol consumption. Where possible, subgroup analyses were performed to examine potential effect modification and to further avoid residual confounding. However, as trade-off it may result in limited statistical power within strata (more in the next section). Nevertheless, for aggregate outcome levels (e.g., overall cancer, IARC alcohol-related cancers, total liver disease), most of the associations presented in this thesis were robust and consistent across major population subgroups.

9.3.5 Statistical power

Although the main prospective analyses presented in this thesis included more participants than previously published studies in Chinese populations, the statistical power was still limited for less common cancers, e.g., kidney cancer, lymphoma, prostate cancer. Statistical power was also limited for subgroup analyses of common cancers, making it difficult to rule out chance finding for the significant heterogeneity observed across subgroups (e.g., associations for ALD across strata of BMI or flushing) and to confirm truly significant associations in women and some population subgroups (e.g., association for lung cancer among never regular smokers). For less common cancer endpoints and lung cancer among never smokers, future studies will need to accumulate enough cases to achieve adequate statistical power, for example, ~120-140 cases among male current regular drinkers may be needed to detect a RR of 2.00 for heavy drinkers versus light drinkers (i.e., 420+g/week vs. <140g/week) at $p<0.05$ with 80% power, ~360-450 cases to detect a RR of 1.50, and ~1210-1570 cases to detect a RR of 1.25 (Table 9.2). Larger numbers of ALD events are also needed to be accumulated in future studies to achieve adequate statistical power to detect

significant multiplicative interaction effects between alcohol intake level and flushing status (e.g., ~540 cases among male current regular drinkers to detect an interaction effect of 2 at $p<0.05$ with 80% power) and BMI (e.g., ~330 cases) (Table 9.3). Furthermore, information on cancer histological subtype is currently available only in a subset of cancer cases as systematic outcome adjudication through review of original medical notes is still on-going in the CKB. Thus, the present thesis lacked sufficient data for exploration across cancer subtypes.

9.4 Future research

9.4.1 Further analyses including other risk factors and cancer subtypes

Longer follow-up with further accumulation of less-common cancer and liver disease events will allow for more reliable assessment of these associations. In this thesis, the relative risk estimates relating alcohol consumption to disease endpoints were assessed across the CKB using Cox regression models stratified by study areas to account for possible regional variation in the associations. For oesophageal cancer, ALD, and NAFLD, which clustered in certain high-risk areas, the associations were further examined separately in high-risk areas and other areas. Given the variation between study areas in alcohol intake, in the prevalence of other disease risk factors (i.e., potential confounders), and in the completeness of endpoint data, it may be informative to also examine the heterogeneity in associations for each disease by each study area in future research. Also, further analyses of cancers and liver diseases may include other newly available information in the CKB. For example, the recently completed assays on multiple infections (e.g., *H. pylori*, HBV, HCV, Epstein-Barr virus, etc.) and the ongoing outcome adjudication will offer the opportunity to assess the

associations of alcohol with major cancer histological subtypes, and to explore the potential interactions between alcohol consumption and infections in relation to major cancers and liver diseases.

9.4.2 Multi-omics biomarkers

Although alcohol consumption has been associated with several cancers and liver diseases in previous epidemiological studies and in this thesis,[71,100,322] substantial uncertainty persists about the causal relevance for cancers with limited existing evidence on their relations to alcohol consumption, such as lung cancer and gallbladder cancer, and the likely mechanisms involved in these associations. On top of conventional blood biomarkers, novel multi-omic approaches such as metabolomics and proteomics offer opportunities to identify novel biomarkers associated with both alcohol intake and disease risks, which could serve as molecular intermediates in alcohol-disease biological pathways.[323] Identifying these biomarkers and exploring their potential roles in the aetiology of chronic diseases will provide novel insights into the mechanisms through which alcohol may influence risks of diseases. In the CKB, conventional and novel blood biomarkers (clinical biochemistry, nuclear magnetic resonance-based metabolomics, and proteomics) have been measured in subsets of stored baseline samples, with further sample analysis underway. This will allow a multi-omics approach to understand the role of alcohol consumption in cancer and liver disease aetiology. Genetic variants can further be used to assess causal associations of alcohol with alcohol-related biomarkers using a Mendelian Randomization (MR) approach (see next section).

9.4.3 Mendelian randomisation

Conventional epidemiological analyses are often limited by reverse causation and residual confounding, especially in the case of alcohol consumption. In contrast, MR studies are not affected by reverse causation and confounding, since genetic markers of alcohol consumption are allocated at random at conception and therefore should not be associated with confounders. The present study in China offers an unique opportunity for MR studies on alcohol consumption and disease risks because of the high frequency of two common genetic variants (*ALDH2*-rs671 and *ADH1B*-rs1229984) in Chinese (and other East Asians), which jointly predict large absolute differences in mean alcohol intake. A recent report based on the CKB using this MR approach has demonstrated reliably that the previous protective effects of moderate drinking on stroke risks observed in conventional epidemiological analyses are non-causal, and are likely due to residual confounding and reverse causation.[24] A similar MR approach will help to assess the causal associations of alcohol intake with risks of cancers and liver diseases, and with novel biomarkers which may provide insights on the biological pathways of how alcohol may influence the development of these diseases. However, extra attention should be paid when interpreting the results from MR analyses of alcohol and cancers (and possibly ALD), given the *ALDH2*-rs671 gene-alcohol interactions (i.e., the *ALDH2*-rs671 AG genotype is associated with both lower alcohol consumption but elevated acetaldehyde level and cancer risks given the same amount of alcohol consumed compared with the GG genotype) shown in this thesis. In other words, for MR studies of alcohol and diseases for which acetaldehyde is a causal factor, the interactions between *ALDH2*-rs671 and alcohol intake need to be

considered. Development of appropriate genetic instruments relevant to investigations of the causal relationships between alcohol and cancers and liver diseases will improve future MR studies.

9.4.4 Burden of alcohol-related diseases in China

The current estimates of alcohol-attributable disease burden from the GBD study for China are based mainly on relative risks derived from prospective studies in Western countries and focus primarily on mortality rather than incidence,[1,86,324] which may not be directly applicable to Chinese populations (discussed in Chapter 1). Future studies in the CKB may expand the investigation in this thesis to assess the risks of a phenome-wide range of disease outcomes associated with alcohol use, which will provide country-specific relative risk estimates in China. Future investigations combining these China-specific risk estimates and nationally representative data on alcohol drinking prevalence will contribute to reliable estimates of the disease burden attributed to alcohol drinking in China, which is important to inform public health policy and disease prevention strategies.

9.5 Public health and clinical implications

The rising level of alcohol consumption and the fairly common occurrence of problem drinking among Chinese men, which are associated with adverse impacts on mental health and risks of cancers and liver diseases, indicate that reducing alcohol consumption will have substantial health benefits to the general populations in China. This thesis shows that while there are several different reasons for stopping drinking alcohol among Chinese men, the most frequently reported reason was existing illness

rather than for future health precautions. Given this and the rising trends of alcohol consumption in young and middle-aged men, actions on alcohol control should be taken immediately and should focus on primary prevention. Policy measures may aim to increase public awareness of the harms of alcohol drinking to cancer and liver diseases as well as other health outcomes to encourage a reduction in alcohol consumption at the population level for disease prevention. In the CKB, money was the second most reported reason for stopping drinking. The findings suggest that interventions involving the increase in pricing and taxation of alcohol, which have been identified as one of the "best buys" alcohol policies by WHO,[1] may be worth exploring in China.

Although the present study findings suggest that certain drinking patterns may be less harmful than others given the same total amount of alcohol consumed (e.g., drinking less than daily, drinking with meals), it should be noted that the amount of alcohol consumed remains the most important risk factor for cancers and liver diseases. Public health messages should primarily focus on reducing the amount of alcohol consumption rather than changing drinking patterns, in order to achieve the greatest impact on cancer and liver disease prevention. The findings on the stronger alcohol-associated harms for cancers among individuals with the flushing response (and potentially high BMI for ALD, once confirmed by further reliable evidence) may also be taken into account for strategies for tailored personal advice and individual risk assessment in clinical settings.

This thesis has shown that heavy drinking is often clustered with other major risk factors (e.g., smoking), and problem drinking with poor mental health. Therefore,

screening and offering support and treatment for people with these risk factors and/or conditions on top of heavy drinking in clinical and community settings may facilitate early prevention and detection of diseases (e.g., undiagnosed depression, chronic diseases for which both smoking and alcohol are risk factors), which will help to substantially reduce the chronic disease burden. Finally, the huge differences in drinking prevalence, alcohol consumption level, and prevalence and presentation of problem drinking across study areas and age groups reported in this thesis offer important information on resource allocation for alcohol policy making.

9.6 Conclusions

By providing large-scale epidemiological evidence on the prevalence and patterns of alcohol consumption and problem drinking, and their relation to mental health and cancers and liver diseases, this thesis adds the best current evidence to date to the field of research on alcohol consumption and health in the Chinese population. The findings show that alcohol consumption has increased among younger men and is related to poor mental health and risks of cancers (including cancers of the upper-aerodigestive tract, colon and rectum, liver, lung, and gallbladder) and liver diseases (including liver cirrhosis, ALD, and NAFLD). In the CKB, 7% of all cancers and 9% of all liver diseases in men are attributable to ever regular drinking, with daily drinking and drinking without meals being particularly harmful. Male drinkers who have the alcohol flushing response may have particularly higher risks of oesophageal cancer (and to a lesser extent lung cancer), and potentially ALD, given the same amount consumed. The findings reinforce the need for public health strategies to curb the rising levels of alcohol consumption in China. This thesis also paves the way for future research

opportunities with the use of genetic data to elucidate the underlying mechanisms linking alcohol and major diseases, and contributes to the reliable estimation of the alcohol-related disease burden in China.

Table 9.1. Summary of existing evidence and CKB findings on associations of alcohol drinking and health outcomes

Heath outcome	Global expert reports/meta-analyses	Asian/Chinese studies	CKB findings
Cross-sectional associations			
Mental health (direction of association not established – could be either way or bi-directional)			
Depression	Detrimental OR=2.00 (1.19-3.35) for AUD vs. no AUD[78]	Limited evidence - inverse association for AUD in Chinese studies	Detrimental OR=1.49 (1.34-1.65) to 2.30 (1.96-2.71) for 1 and 2+ problem drinking indicators vs. low-risk drinking
Anxiety	Detrimental OR=2.11 (2.03-2.19) for AUD vs. no AUD[325]	Limited evidence - inverse association for AUD in Chinese studies	Detrimental OR=1.66 (1.31-2.11) to 2.36 (1.66-3.36) for 1 and 2+ problem drinking indicators vs. low-risk drinking
Prospective associations			
All-cause mortality	Detrimental RR=1.91 (1.51-2.42) for AUD vs. no AUD[250]	Limited evidence*	Detrimental HR=1.37 (1.28-1.46) to 1.91 (1.71-2.13) for 1 and 2+ problem drinking indicators vs. low-risk drinking
Events due to external cause including suicides	Detrimental RR for completed suicides=1.74 (1.26-2.21) for AUD vs. no AUD[251]	Limited evidence*	Detrimental HR=1.21 (0.99-1.47) to 1.98 (1.46-2.67) for 1 and 2+ problem drinking indicators vs. low-risk drinking
Cancers with sufficient evidence for causality with alcohol			
Mouth and throat	Detrimental RR per 10g/day=1.19 (1.10-1.30) for oral cavity and pharynx[96] RR per 10g/day=1.09 (1.05-1.13) for larynx[96]	Detrimental (amount, *ALDH2*-alcohol interaction)	Detrimental (amount, *ALDH2*-alcohol interaction) HR per 40g/day=1.74 (1.48-2.05)
Oesophagus	Detrimental for ESCC, no association for EAC RR per 10g/day=1.25 (1.12-1.41) for ESCC[94]	Detrimental (amount, *ALDH2*-alcohol interaction)	Detrimental (amount, daily drinking, *ALDH2*-alcohol interaction) HR per 40g/day=1.98 (1.79-2.18)
Colon and rectum	Detrimental (>30g/day) RR per 10g/day=1.07 (1.05-1.09)[98]	Detrimental (men) - but no association in Chinese studies	Detrimental HR per 40g/day=1.19 (1.00-1.43)
Liver	Detrimental (>45g/day) RR per 10g/day=1.04 (1.02-1.06)[88]	Detrimental - but limited evidence (no/weak detrimental effects) in Chinese studies	Detrimental (amount, drinking without meals) HR per 40g/day=1.52 (1.31-1.76)
Female breast	Detrimental RR per 10g/day=1.07 (1.05-1.10)[97]	Limited evidence* – mainly no/weak association	No clear association, possibly due to low prevalence and level of drinking in women HR=0.68 (0.36-1.30) for 70+ vs. <70g/week

Heath outcome	Global expert reports/meta-analyses	Asian/Chinese studies	CKB findings
Cancers for which causality with alcohol not established			
Lung	Suggestive - weak detrimental effects (>40g/day), but limited evidence (mainly no association) in never smokers. RR per 10g/day=1.03 (1.01-1.05)[92]	Limited evidence - weak detrimental effects but no investigation in never smokers in Chinese studies	Detrimental (suggestive detrimental effects in never smokers, *ALDH2*-alcohol interaction) HR per 40g/day=1.25 (1.10-1.42)
Stomach	Probable - detrimental (>45g/day) RR per 10g/day=1.02 (1.00-1.04)[95]	Detrimental - but limited evidence (mainly no/weak detrimental effects in heavy drinkers) in Chinese studies	No clear association HR per 40g/day=1.11 (0.94-1.30)
Pancreas	Suggestive - detrimental >45g/day only RR per 10g/day=1.00 (0.99-1.01)[99]	Limited evidence - mainly no association	Potentially detrimental in the heaviest drinkers but no clear association overall. HR per 40g/day=1.20 (0.86-1.66)
Gallbladder	Limited evidence - mainly no association/detrimental effects (driven by high-income East Asian studies) RR per 10g/day=1.07 (0.98-1.17)[93]	Limited evidence* – potentially detrimental	Detrimental HR per 40g/day=1.60 (1.16-2.22)
Kidney	Lack of carcinogenicity/probable inverse association (<30g/day) RR per 10g/day=0.92 (0.86-0.97)[91]	Limited evidence* - mainly no/inverse association	No clear association HR per 40g/day=1.42 (0.90-2.23)
Non-Hodgkin lymphoma	Lack of carcinogenicity/inverse association RR=0.88 (0.80-0.97) to 0.75 (0.64-0.88) for light to heavy drinking vs. non-drinking[100]	Limited evidence* - inverse association	No clear association for lymphoma HR per 40g/day=1.24 (0.91-1.69)
Prostate	Limited evidence - mainly no association/weak detrimental effects RR per drink/day=1.01 (0.99-1.02)[90]	Limited evidence – mainly no association/detrimental effects for advanced prostate cancer	No clear association HR per 40g/day=1.17 (0.77-1.77)
Liver diseases			
Alcoholic liver disease	Detrimental (amount, potentially daily drinking and drinking without meals) RR=1.40 (1.00-1.97) to 10.70 (2.95-38.78) for 1 to 7+ drinks/day vs. long-term abstainers[153]	Detrimental*	Detrimental (amount, daily drinking, drinking without meals, potentially flushing-alcohol interaction) HR per 40g/day=2.02 (1.79-2.28)
Liver cirrhosis	Refer to alcoholic liver disease	Detrimental	Detrimental (amount, drinking without meals) HR per 40g/day=1.87 (1.65-2.12)
Non-alcoholic fatty liver disease	Limited evidence - inverse association for moderate drinking overall (RR=0.85 [0.75-0.96],[144] mainly driven by Japanese studies), but detrimental in heavy drinkers in a limited number of Western studies	Limited evidence* - inverse association in Japanese studies (mainly cross-sectional studies)	Detrimental HR per 40g/day=1.78 (1.42-2.22)

AUD, alcohol use disorder; CKB, china kadoorie biobank; EAC, oesophageal adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; OR, odds ratio; RR, relative risk; HR, hazard ratio.
Global expert reports included the International Agency for Research on Cancer Monographs in 2010 and 2012, and the World Cancer Research Fund Continuous Update Project Expert Report 2018.
RRs (95% confidence intervals) displayed in the Global evidence column are obtained from the most complete meta-analyses, where available.
*No previous Chinese cohort studies were available.

Table 9.2. Estimated numbers of incident cancer cases at p<0.05 for the effects of heavy drinking in male current regular drinkers

	Statistical power		
Relative risk: Heavy vs. light drinkers (420+ vs. <140g/week)	60%	70%	80%
Less common cancers[*] (e.g., prostate, lymphoma)			
1.25	729	925	1214
1.50	219	280	360
2.00	73	94	122
Lung cancer in never regular smokers[†]			
1.25	953	1218	1569
1.50	265	342	445
2.00	79	104	138

CKB, China Kadoorie Biobank.

[*]Estimated numbers of cancer cases needed among all male current regular drinkers in the CKB, based on the proportions of drinkers of different intake levels among them.

[†]Estimated numbers of lung cancer cases needed among male current regular drinkers who were never regular smokers in the CKB, based on the proportions of drinkers of different intake levels among them.

Table 9.3. Estimated numbers of alcoholic liver disease events at p<0.05 for the interaction effects of alcohol intake level and flushing status and BMI in male current regular drinkers

	Statistical power		
Interaction effect size*	60%	70%	80%
Alcohol (<280 vs. 280+g/week) and flushing status (no/yes)†			
1.25	3229	4068	5173
1.50	978	1232	1567
2.00	335	422	536
3.00	133	168	213
Alcohol (<280 vs. 280+g/week) and BMI (<25 vs. 25+kg/m^2)‡			
1.25	1960	2469	3140
1.50	594	748	951
2.00	203	256	325
3.00	81	102	130

BMI, body mass index; CKB, China Kadoorie Biobank.

*Hazard ratio of the multiplicative interaction term in the Cox model (see Schmoor et al 2000[326] for details on method).

†Estimated numbers of alcoholic liver disease events needed among male current regular drinkers, based on the proportions of each category of the combinations of alcohol intake level and flushing status (<280g/week without flushing, 280+g/week without flushing, <280g/week with flushing, 280+g/week with flushing) in the CKB.

‡Estimated numbers of alcoholic liver disease events needed among male current regular drinkers, based on the proportions of each category of the combinations of alcohol intake level and BMI (<280g/week and <25kg/m^2, 280+g/week and <25kg/m^2, <280g/week and 25+kg/m^2, 280+g/week and 25+kg/m^2) in the CKB.

References

1. World Health Organization. *Global status report on alcohol and health 2018.* Geneva: World Health Organization; 2018.

2. Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *Lancet.* 2019;393(10190):2493-2502.

3. Ma GS, Xhu DH, Hu XQ, Luan DC, Kong LZ, Yang XQ. The drinking practice of people in China. *Acta Nutrimenta Sinica.* 2005;27(5):362-365.

4. Li Y, Jiang Y, Zhang M, Yin P, Wu F, Zhao W. Drinking behaviour among men and women in China: the 2007 China Chronic Disease and Risk Factor Surveillance. *Addiction.* 2011;106(11):1946-1956.

5. Li R, Wang D, Chen J, Chai J, Tang M. Regional differences in smoking, drinking, and physical activities of Chinese residents. *Asia Pac J Public Health.* 2015;27(2):NP230-239.

6. Ma GS, Du SM, Hao LN, Li YP, Hu XQ, Kong LZ. The prevalence of heavy drinking among adults in China. *Acta Nutrimenta Sinica.* 2009;31(3):213-217.

7. Cochrane J, Chen H, Conigrave KM, Hao W. Alcohol use in China. *Alcohol Alcohol.* 2003;38(6):537-542.

8. Ma YX, Zhang B, Wang HJ, Du WW, Su C, Zhai FY. Status and trend of alcohol consumption among adults in nine provinces (antonomous region) of China from 1993 to 2006. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2011;45(4):323-329.

9. Guo X, Huang YG. The development of alcohol policy in contemporary China. *J Food Drug Anal.* 2015;23(1):19-29.

10. Ji CY, Hu PJ, Song Y. The epidemiology of alcohol consumption and misuse among Chinese college students. *Alcohol Alcohol.* 2012;47(4):464-472.

11. Hingson RW, Heeren T, Winter MR. Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Arch Pediatr Adolesc Med.* 2006;160(7):739-746.

12. DeWit DJ, Adlaf EM, Offord DR, Ogborne AC. Age at first alcohol use: a risk factor for the development of alcohol disorders. *Am J Psychiatry.* 2000;157(5):745-750.

13. Liang W, Chikritzhs T. Age at first use of alcohol and risk of heavy alcohol use: a population-based study. *Biomed Res Int.* 2013;2013:721761.

14. Healey C, Rahman A, Faizal M, Kinderman P. Underage drinking in the UK: changing trends, impact and interventions. A rapid evidence synthesis. *Int J Drug Policy.* 2014;25(1):124-132.

15. Feng Y, Newman IM. Estimate of adolescent alcohol use in China: a meta-analysis. *Arch Public Health.* 2016;74:45.

16. Oldham M, Holmes J, Whitaker V, Fairbrother H, Curtis P. *Youth Drinking in Decline*; 2018.

17. Lu S, Du S, Hu X, Zou S, Liu W, Ba L, et al. Drinking patterns and the association between socio-demographic factors and adolescents' alcohol use in three metropolises in China. *Int J Environ Res Public Health.* 2015;12(2):2037-2053.

18. Shell DF, Newman IM, Xiaoyi F. The influence of cultural orientation, alcohol expectancies and self-efficacy on adolescent drinking behavior in Beijing. *Addiction.* 2010;105(9):1608-1615.

19. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. In: *IARC monographs on the evaluation of carcinogenic risks to humans.* Vol 100E. Lyon, France: International Agency for Research on Cancer; 2012.

20. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. In: *IARC monographs on the evaluation of carcinogenic risks to humans.* Vol 96. Lyon, France: International Agency for Research on Cancer; 2010.

21. Setshedi M, Wands JR, Monte SM. Acetaldehyde adducts in alcoholic liver disease. *Oxid Med Cell Longev.* 2010;3(3):178-185.

22. Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. *Alcohol Res Health.* 2007;30(1):22-27.

23. Li H, Borinskaya S, Yoshimura K, Kal'ina N, Marusin A, Stepanov VA, et al. Refined geographic distribution of the oriental ALDH2*504Lys (nee 487Lys) variant. *Ann Hum Genet.* 2009;73(Pt 3):335-345.

24. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, Bian Z, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet.* 2019;393(10183):1831-1842.

25. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. *PLoS Med.* 2009;6(3):e50.

26. Li H, Mukherjee N, Soundararajan U, Tarnok Z, Barta C, Khaliq S, et al. Geographically separate increases in the frequency of the derived

ADH1B*47His allele in eastern and western Asia. *Am J Hum Genet.* 2007;81(4):842-846.

27. Lai CL, Yao CT, Chau GY, Yang LF, Kuo TY, Chiang CP, et al. Dominance of the inactive Asian variant over activity and protein contents of mitochondrial aldehyde dehydrogenase 2 in human liver. *Alcohol Clin Exp Res.* 2014;38(1):44-50.

28. World Health Organization. *International Guide for Monitoring Alcohol Consumption and Related Harm.* Geneva: World Health Organization; 2000.

29. US Department of Health and Human Services, US Department of Agriculture. *Dietary Guidelines for Americans 2015-2020*. 8th edition. 2015.

30. Office for National Statistics. *Adult drinking habits in Great Britain: 2017*; 2018.

31. Alcohol and Public Policy Group. Alcohol: no ordinary commodity - a summary of the second edition. *Addiction.* 2010;105(5):769-779.

32. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1736-1788.

33. Institute for Health Metrics and Evaluation. GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington; 2018. Available from: https://vizhub.healthdata.org/gbd-compare/. Accessed 9th November, 2019.

34. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1211-1259.

35. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;394(10204):1145-1158.

36. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2018;4(11):1553-1568.

37. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.

38. International Agency for Research on Cancer. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2018. Available from: https://gco.iarc.fr/today/home. Accessed 9th November, 2019.

39. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.

40. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, et al. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res.* 2018;30(1):1-12.

41. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Alcoholic drinks and the risk of cancer*; 2018.

42. Zhang SW, Zheng RS, Yang ZX, Zeng HM, Sun KX, Gu XY, et al. Trend analysis on incidence and age at diagnosis for lung cancer in cancer registration areas of China, 2000-2014. *Zhonghua Yu Fang Yi Xue Za Zhi.* 2018;52(6):579-585.

43. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and lung cancer*; 2018.

44. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer*; 2018.

45. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-691.

46. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer*; 2018.

47. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and stomach cancer*; 2018.

48. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and liver cancer*; 2018.

49. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology.* 2015;62(4):1190-1200.

50. Kew MC. Hepatocellular carcinoma: epidemiology and risk factors. *J Hepatocell Carcinoma.* 2014;1:115-125.

51. Lin Y, Totsuka Y, Shan B, Wang C, Wei W, Qiao Y, et al. Esophageal cancer in high-risk areas of China: research progress and challenges. *Ann Epidemiol.* 2017;27(3):215-221.

52. Abbas G, Krasna M. Overview of esophageal cancer. *Ann Cardiothorac Surg.* 2017;6(2):131-136.

53. Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. *Cancer Biol Med.* 2017;14(1):33-41.

54. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and oesophageal cancer*; 2018.

55. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and prostate cancer*; 2018.

56. Pang Y, Holmes MV, Guo Y, Yang L, Bian Z, Chen Y, et al. Smoking, alcohol, and diet in relation to risk of pancreatic cancer in China: a prospective study of 0.5 million people. *Cancer Med.* 2018;7(1):229-239.

57. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer*; 2018.

58. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx*; 2018.

59. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. *Hepatology.* 2014;60(6):2099-2108.

60. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol.* 2019;70(1):151-171.

61. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol.* 2013;59(1):160-168.

62. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64(1):73-84.

63. Nascimbeni F, Pais R, Bellentani S, Day CP, Ratziu V, Loria P, et al. From NAFLD in clinical practice to answers from guidelines. *J Hepatol.* 2013;59(4):859-871.

64. Wong MCS, Huang JLW, George J, Huang J, Leung C, Eslam M, et al. The changing epidemiology of liver diseases in the Asia-Pacific region. *Nat Rev Gastroenterol Hepatol.* 2019;16(1):57-73.

65. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. *Vaccine.* 2009;27(47):6550-6557.

66. Wang WJ, Xiao P, Xu HQ, Niu JQ, Gao YH. Growing burden of alcoholic liver disease in China: A review. *World J Gastroenterol.* 2019;25(12):1445-1456.

67. Bao XY, Xu BB, Fang K, Li Y, Hu YH, Yu GP. Changing trends of hospitalisation of liver cirrhosis in Beijing, China. *BMJ Open Gastroenterol.* 2015;2(1):e000051.

68. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol.* 2018;15(1):11-20.

69. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol.* 2017;67(4):862-873.

70. Li Z, Xue J, Chen P, Chen L, Yan S, Liu L. Prevalence of nonalcoholic fatty liver disease in mainland of China: a meta-analysis of published studies. *J Gastroenterol Hepatol.* 2014;29(1):42-51.

71. Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev.* 2010;29(4):437-445.

72. Yuan JM, Ross RK, Gao YT, Henderson BE, Yu MC. Follow up study of moderate alcohol intake and mortality among middle aged men in Shanghai, China. *BMJ.* 1997;314(7073):18-23.

73. Yang L, Zhou M, Sherliker P, Cai Y, Peto R, Wang L, et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. *Int J Epidemiol.* 2012;41(4):1101-1113.

74. Askgaard G, Gronbaek M, Kjaer MS, Tjonneland A, Tolstrup JS. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. *J Hepatol.* 2015;62(5):1061-1067.

75. Simpson RF, Hermon C, Liu B, Green J, Reeves GK, Beral V, et al. Alcohol drinking patterns and liver cirrhosis risk: analysis of the prospective UK Million Women Study. *Lancet Public Health.* 2019;4(1):e41-e48.

76. Chang Y, Cho YK, Kim Y, Sung E, Ahn J, Jung HS, et al. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: a cohort study. *Hepatology.* 2019;69(1):64-75.

77. Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. *Curr Psychiatry Rep.* 2019;21(2):10.

78. Boden JM, Fergusson DM. Alcohol and depression. *Addiction.* 2011;106(5):906-914.

79. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry.* 2004;61(8):807-816.

80. Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, et al. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addict Behav.* 1998;23(6):893-907.

81. McCaul ME, Hutton HE, Stephens MA, Xu X, Wand GS. Anxiety, anxiety sensitivity, and perceived stress as predictors of recent drinking, alcohol craving, and social stress response in heavy drinkers. *Alcohol Clin Exp Res.* 2017;41(4):836-845.

82. Teesson M, Hall W, Slade T, Mills K, Grove R, Mewton L, et al. Prevalence and correlates of DSM-IV alcohol abuse and dependence in Australia: findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction.* 2010;105(12):2085-2094.

83. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry.* 2015;72(8):757-766.

84. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry.* 2016;3(2):171-178.

85. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1923-1994.

86. Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2018;392(10152):1015-1035.

87. Millwood IY, Li L, Smith M, Guo Y, Yang L, Bian Z, et al. Alcohol consumption in 0.5 million people from 10 diverse regions of China: prevalence, patterns and socio-demographic and health-related correlates. *Int J Epidemiol.* 2013;42(3):816-827.

88. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The*

Associations between Food, Nutrition and Physical Activity and the Risk of Liver Cancer; 2014.

89. World Cancer Research Fund/American Institute for Cancer Research. *WCRF/AICR Systematic Literature Review Continuous Update Project Report. The Associations between Food, Nutrition and Physical Activity and the Risk of Bladder Cancer*; 2014.

90. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Prostate Cancer*; 2014.

91. World Cancer Research Fund/American Institute for Cancer Research. *WCRF/AICR Systematic Literature Review Continuous Update Project. The Associations between Diet, Nutrition and Physical Activity and the Risk of Kidney Cancer*; 2015.

92. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Lung Cancer*; 2015.

93. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Gallbladder Cancer*; 2015.

94. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Oesophageal Cancer*; 2015.

95. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Stomach Cancer*; 2015.

96. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Mouth, Pharynx and Larynx cancer*; 2016.

97. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer*; 2017.

98. World Cancer Research Fund/American Institute for Cancer Research. *World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer*; 2016.

99. World Cancer Research Fund/American Institute for Cancer Research. *WCRF/AICR Systematic Literature Review Continuous Update Project Report. The Associations between Food, Nutrition and Physical Activity and the Risk of Pancreatic Cancer*; 2011.

100. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer.* 2015;112(3):580-593.

101. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population—a systematic review and meta-analysis. *PLoS One.* 2011;6(4):e18776.

102. Klatsky AL, Li Y, Nicole Tran H, Baer D, Udaltsova N, Armstrong MA, et al. Alcohol intake, beverage choice, and cancer: a cohort study in a large kaiser permanente population. *Perm J.* 2015;19(2):28-34.

103. Yi SW, Hong JS, Yi JJ, Ohrr H. Impact of alcohol consumption and body mass index on mortality from nonneoplastic liver diseases, upper aerodigestive tract cancers, and alcohol use disorders in Korean older middle-aged men: Prospective cohort study. *Medicine (Baltimore).* 2016;95(39):e4876.

104. Shen C, Schooling CM, Chan WM, Xu L, Lee SY, Lam TH. Alcohol intake and death from cancer in a prospective Chinese elderly cohort study in Hong Kong. *J Epidemiol Community Health.* 2013;67(10):813-820.

105. Jayasekara H, MacInnis RJ, Room R, English DR. Long-term alcohol consumption and breast, upper aero-digestive tract and colorectal cancer risk: a systematic review and meta-Analysis. *Alcohol Alcohol.* 2016;51(3):315-330.

106. Choi YJ, Lee DH, Han KD, Kim HS, Yoon H, Shin CM, et al. The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: A nationwide population-based cohort study of South Korea. *PLoS One.* 2017;12(10):e0185778.

107. Choi YJ, Lee DH, Han K, Yoon H, Shin CM, Park YS, et al. Joint effects of low body mass index and alcohol consumption on developing esophageal squamous cell cancer: a Korean nationwide population-based cohort study. *Asian Pac J Cancer Prev.* 2017;18(7):1881-1887.

108. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer.* 2005;113(3):456-463.

109. Fan Y, Yuan JM, Wang R, Gao YT, Yu MC. Alcohol, tobacco, and diet in relation to esophageal cancer: the Shanghai Cohort Study. *Nutr Cancer.* 2008;60(3):354-363.

110. Jayasekara H, MacInnis RJ, Williamson EJ, Hodge AM, Clendenning M, Rosty C, et al. Lifetime alcohol intake is associated with an increased risk of KRAS+ and BRAF-/KRAS- but not BRAF+ colorectal cancer. *Int J Cancer.* 2017;140(7):1485-1493.

111. Park SY, Wilkens LR, Setiawan VW, Monroe KR, Haiman CA, Le Marchand L. Alcohol intake and colorectal cancer risk in the Multiethnic Cohort Study. *Am J Epidemiol.* 2019;188(1):67-76.

112. Bradbury KE, Murphy N, Key TJ. Diet and colorectal cancer in UK Biobank: a prospective study. *Int J Epidemiol.* 2019.

113. Cho S, Shin A, Park SK, Shin HR, Chang SH, Yoo KY. Alcohol drinking, cigarette smoking and risk of colorectal cancer in the Korean Multi-center Cancer Cohort. *J Cancer Prev.* 2015;20(2):147-152.

114. Chen K, Jiang Q, Ma X, Li Q, Yao K, Yu W, et al. Alcohol drinking and colorectal cancer: a population-based prospective cohort study in China. *Eur J Epidemiol.* 2005;20(2):149-154.

115. Chuang SC, Lee YC, Wu GJ, Straif K, Hashibe M. Alcohol consumption and liver cancer risk: a meta-analysis. *Cancer Causes Control.* 2015;26(9):1205-1231.

116. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the Liver Cancer Pooling Project. *Br J Cancer.* 2018;118(7):1005-1012.

117. Evans AA, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. *Cancer Epidemiol Biomarkers Prev.* 2002;11(4):369-376.

118. Wang LY, You SL, Lu SN, Ho HC, Wu MH, Sun CA, et al. Risk of hepatocellular carcinoma and habits of alcohol drinking, betel quid chewing and cigarette smoking: a cohort of 2416 HBsAg-seropositive and 9421 HBsAg-seronegative male residents in Taiwan. *Cancer Causes Control.* 2003;14(3):241-250.

119. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst.* 2004;96(24):1851-1856.

120. Loomba R, Yang HI, Su J, Brenner D, Barrett-Connor E, Iloeje U, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol.* 2013;177(4):333-342.

121. Key TJ, Balkwill A, Bradbury KE, Reeves GK, Kuan AS, Simpson RF, et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. *Int J Epidemiol.* 2019;48(2):489-500.

122. Fehringer G, Brenner DR, Zhang ZF, Lee YA, Matsuo K, Ito H, et al. Alcohol and lung cancer risk among never smokers: a pooled analysis from the international lung cancer consortium and the SYNERGY study. *Int J Cancer.* 2017;140(9):1976-1984.

123. Garcia Lavandeira JA, Ruano-Ravina A, Kelsey KT, Torres-Duran M, Parente-Lamelas I, Leiro-Fernandez V, et al. Alcohol consumption and lung cancer risk in never smokers: a pooled analysis of case-control studies. *Eur J Public Health.* 2018;28(3):521-527.

124. Bagnardi V, Rota M, Botteri E, Scotti L, Jenab M, Bellocco R, et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. *Ann Oncol.* 2011;22(12):2631-2639.

125. Freudenheim JL, Ritz J, Smith-Warner SA, Albanes D, Bandera EV, van den Brandt PA, et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr.* 2005;82(3):657-667.

126. Brenner DR, Fehringer G, Zhang ZF, Lee YA, Meyers T, Matsuo K, et al. Alcohol consumption and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium and the SYNERGY study. *Cancer Epidemiol.* 2019;58:25-32.

127. Rota M, Pelucchi C, Bertuccio P, Matsuo K, Zhang ZF, Ito H, et al. Alcohol consumption and gastric cancer risk-A pooled analysis within the StoP project consortium. *Int J Cancer.* 2017;141(10):1950-1962.

128. He Z, Zhao TT, Xu HM, Wang ZN, Xu YY, Song YX, et al. Association between alcohol consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. *Oncotarget.* 2017;8(48):84459-84472.

129. Wang PL, Xiao FT, Gong BC, Liu FN. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. *Oncotarget.* 2017;8(58):99013-99023.

130. Wang S, Freedman ND, Loftfield E, Hua X, Abnet CC. Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: A 16-year prospective analysis from the NIH-AARP diet and health cohort. *Int J Cancer.* 2018;143(11):2749-2757.

131. Moy KA, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. *Cancer Epidemiol Biomarkers Prev.* 2010;19(9):2287-2297.

132. Wang YT, Gou YW, Jin WW, Xiao M, Fang HY. Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. *BMC Cancer.* 2016;16:212.

133. Naudin S, Li K, Jaouen T, Assi N, Kyro C, Tjonneland A, et al. Lifetime and baseline alcohol intakes and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer.* 2018;143(4):801-812.

134. Jayasekara H, English DR, Hodge AM, Room R, Hopper JL, Milne RL, et al. Lifetime alcohol intake and pancreatic cancer incidence and survival: findings from the Melbourne Collaborative Cohort Study. *Cancer Causes Control.* 2019;30(4):323-331.

135. Zhao J, Stockwell T, Roemer A, Chikritzhs T. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. *BMC Cancer.* 2016;16(1):845.

136. Fowke JH, McLerran DF, Gupta PC, He J, Shu XO, Ramadas K, et al. Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. *Am J Epidemiol.* 2015;182(5):381-389.

137. Xu X, Zhu Y, Zheng X, Xie L. Does beer, wine or liquor consumption correlate with the risk of renal cell carcinoma? A dose-response meta-analysis of prospective cohort studies. *Oncotarget.* 2015;6(15):13347-13358.

138. Wozniak MB, Brennan P, Brenner DR, Overvad K, Olsen A, Tjonneland A, et al. Alcohol consumption and the risk of renal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer.* 2015;137(8):1953-1966.

139. Psaltopoulou T, Sergentanis TN, Ntanasis-Stathopoulos I, Tzanninis IG, Tsilimigras DI, Dimopoulos MA. Alcohol consumption and risk of hematological malignancies: a meta-analysis of prospective studies. *Int J Cancer.* 2018;143(3):486-495.

140. Jayasekara H, Juneja S, Hodge AM, Room R, Milne RL, Hopper JL, et al. Lifetime alcohol intake and risk of non-Hodgkin lymphoma: findings from the Melbourne Collaborative Cohort Study. *Int J Cancer.* 2018;142(5):919-926.

141. Botteri E, Ferrari P, Roswall N, Tjonneland A, Hjartaker A, Huerta JM, et al. Alcohol consumption and risk of urothelial cell bladder cancer in the European prospective investigation into cancer and nutrition cohort. *Int J Cancer.* 2017;141(10):1963-1970.

142. Masaoka H, Matsuo K, Sawada N, Yamaji T, Goto A, Shimazu T, et al. Alcohol consumption and bladder cancer risk with or without the flushing response: The Japan Public Health Center-based Prospective Study. *Int J Cancer.* 2017;141(12):2480-2488.

143. Cao G, Yi T, Liu Q, Wang M, Tang S. Alcohol consumption and risk of fatty liver disease: a meta-analysis. *PeerJ.* 2016;4:e2633.

144. Roerecke M, Nanau R, Rehm J, Neuman M. Ethnicity matters: a systematic review and meta-analysis of the non-linear relationship between alcohol consumption and prevalence and incidence of hepatic steatosis. *EBioMedicine.* 2016;8:317-330.

145. Schwartz LM, Persson EC, Weinstein SJ, Graubard BI, Freedman ND, Mannisto S, et al. Alcohol consumption, one-carbon metabolites, liver cancer and liver disease mortality. *PLoS One.* 2013;8(10):e78156.

146. Persson EC, Schwartz LM, Park Y, Trabert B, Hollenbeck AR, Graubard BI, et al. Alcohol consumption, folate intake, hepatocellular carcinoma, and liver disease mortality. *Cancer Epidemiol Biomarkers Prev.* 2013;22(3):415-421.

147. Trembling PM, Apostolidou S, Gentry-Maharaj A, Parkes J, Ryan A, Tanwar S, et al. Risk of chronic liver disease in post-menopausal women due to body mass index, alcohol and their interaction: a prospective nested cohort study within the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *BMC Public Health.* 2017;17(1):603.

148. Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ.* 2010;340:c1240.

149. Curcic IB, Berkovic MC, Kuna L, Roguljic H, Smolic R, Varzic SC, et al. Obesity paradox in chronic liver diseases: product of bias or a real thing? *Journal of clinical and translational hepatology.* 2019;7(3):275-279.

150. Liu B, Balkwill A, Roddam A, Brown A, Beral V. Separate and joint effects of alcohol and smoking on the risks of cirrhosis and gallbladder disease in middle-aged women. *Am J Epidemiol.* 2009;169(2):153-160.

151. Goh GB, Chow WC, Wang R, Yuan JM, Koh WP. Coffee, alcohol and other beverages in relation to cirrhosis mortality: the Singapore Chinese Health Study. *Hepatology.* 2014;60(2):661-669.

152. Liu B, Balkwill A, Reeves G, Beral V. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ.* 2010;340:c912.

153. Roerecke M, Vafaei A, Hasan OSM, Chrystoja BR, Cruz M, Lee R, et al. Alcohol consumption and risk of liver cirrhosis: a systematic review and meta-analysis. *Am J Gastroenterol.* 2019;114(10):1574-1586.

154. Aberg F, Helenius-Hietala J, Puukka P, Jula A. Binge drinking and the risk of liver events: a population-based cohort study. *Liver Int.* 2017;37(9):1373-1381.

155. Dawson DA, Li TK, Grant BF. A prospective study of risk drinking: at risk for what? *Drug Alcohol Depend.* 2008;95(1-2):62-72.

156. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. *Gut.* 1997;41(6):845-850.

157. Gronbaek M, Jensen MK, Johansen D, Sorensen TI, Becker U. Intake of beer, wine and spirits and risk of heavy drinking and alcoholic cirrhosis. *Biol Res.* 2004;37(2):195-200.

158. Lu XL, Luo JY, Tao M, Gen Y, Zhao P, Zhao HL, et al. Risk factors for alcoholic liver disease in China. *World J Gastroenterol.* 2004;10(16):2423-2426.

159. Volzke H. Multicausality in fatty liver disease: is there a rationale to distinguish between alcoholic and non-alcoholic origin? *World J Gastroenterol.* 2012;18(27):3492-3501.

160. Britton A, Mehta G, O'Neill D, Bell S. Association of thirty-year alcohol consumption typologies and fatty liver: findings from a large population cohort study. *Drug Alcohol Depend.* 2019;194:225-229.

161. Liu P, Xu Y, Tang Y, Du M, Yu X, Sun J, et al. Independent and joint effects of moderate alcohol consumption and smoking on the risks of non-alcoholic fatty liver disease in elderly Chinese men. *PLoS One.* 2017;12(7):e0181497.

162. Zuo W, Zhan Z, Ma L, Bai W, Zeng S. Effect of ALDH2 polymorphism on cancer risk in Asians: a meta-analysis. *Medicine (Baltimore).* 2019;98(13):e14855.

163. Chang JS, Hsiao JR, Chen CH. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. *J Biomed Sci.* 2017;24(1):19.

164. Yu C, Guo Y, Bian Z, Yang L, Millwood IY, Walters RG, et al. Association of low-activity ALDH2 and alcohol consumption with risk of esophageal cancer in Chinese adults: a population-based cohort study. *Int J Cancer.* 2018;143(7):1652-1661.

165. Matsuo K, Oze I, Hosono S, Ito H, Watanabe M, Ishioka K, et al. The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. *Carcinogenesis.* 2013;34(7):1510-1515.

166. Zakhari S. Overview: how is alcohol metabolized by the body? *Alcohol Res Health.* 2006;29(4):245-254.

167. Kwon HJ, Won YS, Park O, Chang B, Duryee MJ, Thiele GE, et al. Aldehyde dehydrogenase 2 deficiency ameliorates alcoholic fatty liver but worsens liver inflammation and fibrosis in mice. *Hepatology.* 2014;60(1):146-157.

168. He L, Deng T, Luo H. Aldehyde dehydrogenase 2 (ALDH2) polymorphism and the risk of alcoholic liver cirrhosis among East Asians: a meta-analysis. *Yonsei Med J.* 2016;57(4):879-884.

169. Chang B, Hao S, Zhang L, Gao M, Sun Y, Huang A, et al. Association Between Aldehyde Dehydrogenase 2 Glu504Lys Polymorphism and Alcoholic Liver Disease. *Am J Med Sci.* 2018;356(1):10-14.

170. Yokoyama A, Taniki N, Hara S, Haysashi E, Nakamoto N, Mizukami T, et al. Slow-metabolizing ADH1B and inactive heterozygous ALDH2 increase vulnerability to fatty liver in Japanese men with alcohol dependence. *J Gastroenterol.* 2018;53(5):660-669.

171. Oniki K, Morita K, Watanabe T, Kajiwara A, Otake K, Nakagawa K, et al. The longitudinal effect of the aldehyde dehydrogenase 2*2 allele on the risk for nonalcoholic fatty liver disease. *Nutr Diabetes.* 2016;6:e210.

172. Ratna A, Mandrekar P. Alcohol and cancer: mechanisms and therapies. *Biomolecules.* 2017;7(3).

173. Rehm J, Gmel GE, Sr., Gmel G, Hasan OSM, Imtiaz S, Popova S, et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. *Addiction.* 2017;112(6):968-1001.

174. Kim YI. Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? *Cancer Epidemiol Biomarkers Prev.* 2004;13(4):511-519.

175. World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and kidney cancer*; 2018.

176. Solarek W, Czarnecka AM, Escudier B, Bielecka ZF, Lian F, Szczylik C. Insulin and IGFs in renal cancer risk and progression. 2015;22(5):R253.

177. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology.* 2011;141(5):1572-1585.

178. Louvet A, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol.* 2015;12(4):231-242.

179. Engen PA, Green SJ, Voigt RM, Forsyth CB, Keshavarzian A. The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota. *Alcohol Res.* 2015;37(2):223-236.

180. Osna NA, Donohue TM, Jr., Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. *Alcohol Res.* 2017;38(2):147-161.

181. Iida-Ueno A, Enomoto M, Tamori A, Kawada N. Hepatitis B virus infection and alcohol consumption. *World J Gastroenterol.* 2017;23(15):2651-2659.

182. Emberson JR, Bennett DA. Effect of alcohol on risk of coronary heart disease and stroke: causality, bias, or a bit of both? *Vasc Health Risk Manag.* 2006;2(3):239-249.

183. Ng Fat L, Cable N, Shelton N. Worsening of health and a cessation or reduction in alcohol consumption to special occasion drinking across three decades of the life course. *Alcohol Clin Exp Res.* 2015;39(1):166-174.

184. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol.* 1999;150(4):341-353.

185. Turati F, Galeone C, Rota M, Pelucchi C, Negri E, Bagnardi V, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol.* 2014;25(8):1526-1535.

186. Kim HJ, Jung S, Eliassen AH, Chen WY, Willett WC, Cho E. Alcohol consumption and breast cancer risk in younger women according to family history of breast cancer and folate intake. *Am J Epidemiol.* 2017;186(5):524-531.

187. White AJ, DeRoo LA, Weinberg CR, Sandler DP. Lifetime alcohol intake, binge drinking behaviors, and breast cancer risk. *Am J Epidemiol.* 2017;186(5):541-549.

188. Williams LA, Olshan AF, Hong CC, Bandera EV, Rosenberg L, Cheng TD, et al. Alcohol intake and breast cancer risk in African American women from the AMBER Consortium. *Cancer Epidemiol Biomarkers Prev.* 2017;26(5):787-794.

189. Dickerman BA, Markt SC, Koskenvuo M, Pukkala E, Mucci LA, Kaprio J. Alcohol intake, drinking patterns, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control.* 2016;27(9):1049-1058.

190. Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol.* 2011;40(6):1652-1666.

191. Chen Z, Lee L, Chen J, Collins R, Wu F, Guo Y, et al. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol.* 2005;34(6):1243-1249.

192. Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. *Int J Epidemiol.* 2002;31(1):168-174.

193. Matthews CE, Shu XO, Yang G, Jin F, Ainsworth BE, Liu D, et al. Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. *Am J Epidemiol.* 2003;158(11):1114-1122.

194. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc.* 2011;43(8):1575-1581.

195. Du H, Bennett D, Li L, Whitlock G, Guo Y, Collins R, et al. Physical activity and sedentary leisure time and their associations with BMI, waist circumference, and percentage body fat in 0.5 million adults: the China Kadoorie Biobank study. *Am J Clin Nutr.* 2013;97(3):487-496.

196. Yang L, Li L, Millwood IY, Lewington S, Guo Y, Sherliker P, et al. Adiposity in relation to age at menarche and other reproductive factors among 300 000 Chinese women: findings from China Kadoorie Biobank study. *Int J Epidemiol.* 2017;46(2):502-512.

197. Lacey B, Lewington S, Clarke R, Kong XL, Chen Y, Guo Y, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0.5 million adults in China: a prospective cohort study. *Lancet Glob Health.* 2018;6(6):e641-e649.

198. Smith M, Li L, Augustyn M, Kurmi O, Chen J, Collins R, et al. Prevalence and correlates of airflow obstruction in approximately 317,000 never-smokers in China. *Eur Respir J.* 2014;44(1):66-77.

199. Zhang Q, Li L, Smith M, Guo Y, Whitlock G, Bian Z, et al. Exhaled carbon monoxide and its associations with smoking, indoor household air pollution and chronic respiratory diseases among 512,000 Chinese adults. *Int J Epidemiol.* 2013;42(5):1464-1475.

200. Song C, Lv J, Liu Y, Chen JG, Ge Z, Zhu J, et al. Associations between hepatitis B virus infection and risk of all cancer types. *JAMA Netw Open.* 2019;2(6):e195718.

201. Bragg F, Holmes MV, Iona A, Guo Y, Du H, Chen Y, et al. Association between diabetes and cause-specific mortality in rural and urban areas of China. *JAMA.* 2017;317(3):280-289.

202. Pan R, Zhu M, Yu C, Lv J, Guo Y, Bian Z, et al. Cancer incidence and mortality: A cohort study in China, 2008-2013. *Int J Cancer.* 2017;141(7):1315-1323.

203. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med.* 1991;10(7):1025-1035.

204. Firth D. Quasi-variances. *Biometrika.* 2004;91(1):65-80.

205. Hao W, Chen H, Su Z. China: alcohol today. *Addiction.* 2005;100(6):737-741.

206. Tang YL, Xiang XJ, Wang XY, Cubells JF, Babor TF, Hao W. Alcohol and alcohol-related harm in China: policy changes needed. *Bull World Health Organ.* 2013;91(4):270-276.

207. Jiang H, Room R, Hao W. Alcohol and related health issues in China: action needed. *Lancet Glob Health.* 2015;3(4):e190-191.

208. Hao W, Su Z, Liu B, Zhang K, Yang H, Chen S, et al. Drinking and drinking patterns and health status in the general population of five areas of China. *Alcohol Alcohol.* 2004;39(1):43-52.

209. Lee YH, Wang Z, Chiang TC, Liu CT. Beverage intake, smoking behavior, and alcohol consumption in contemporary China-a cross-sectional analysis from the 2011 China Health and Nutrition Survey. *Int J Environ Res Public Health.* 2017;14(5).

210. Hao W, Young D, Li L, Xiao S. Psychoactive substance use in three sites in China: gender differences and related factors. *Psychiatry Clin Neurosci.* 1998;52 Suppl:S324-328.

211. Wei H, Derson Y, Xiao S, Li L, Zhang Y. Alcohol consumption and alcohol-related problems: Chinese experience from six area samples, 1994. *Addiction.* 1999;94(10):1467-1476.

212. Liu R, Chen L, Zhang F, Zhu R, Lin X, Meng X, et al. Trends in alcohol intake and the association between socio-demographic factors and volume of alcohol intake amongst adult male drinkers in China. *Int J Environ Res Public Health.* 2019;16(4).

213. Eigenbrodt ML, Mosley TH, Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: a cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. *Am J Epidemiol.* 2001;153(11):1102-1111.

214. Britton A, Ben-Shlomo Y, Benzeval M, Kuh D, Bell S. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. *BMC Med.* 2015;13:47.

215. Knott CS, Bell S, Britton A. The stability of baseline-defined categories of alcohol consumption during the adult life-course: a 28-year prospective cohort study. *Addiction.* 2018;113(1):34-43.

216. Rehm J, Patra J, Popova S. Alcohol drinking cessation and its effect on esophageal and head and neck cancers: a pooled analysis. *Int J Cancer.* 2007;121(5):1132-1137.

217. Chen Z, Iona A, Parish S, Chen Y, Guo Y, Bragg F, et al. Adiposity and risk of ischaemic and haemorrhagic stroke in 0.5 million Chinese men and women: a prospective cohort study. *Lancet Glob Health.* 2018;6(6):e630-e640.

218. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335(8692):765-774.

219. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med.* 1989;8(9):1051-1069; discussion 1071-1053.

220. World Health Organization. *Global status report on alcohol 2004.* Geneva: World Health Organization; 2004.

221. Lee YH, Chang YC, Liu CT, Shelley M. Correlates of alcohol consumption and alcohol dependence among older adults in contemporary China: Results from the Chinese Longitudinal Healthy Longevity Survey. *J Ethn Subst Abuse.* 2018:1-16.

222. Dumont S, Marques-Vidal P, Favrod-Coune T, Theler JM, Gaspoz JM, Broers B, et al. Alcohol policy changes and 22-year trends in individual alcohol consumption in a Swiss adult population: a 1993-2014 cross-sectional population-based study. *BMJ Open.* 2017;7(3):e014828.

223. World Health Organization. *Status report on alcohol and health in 35 European countries 2013.* Copenhagen, Denmark: World Health Organization; 2013.

224. Zhou L, Conner KR, Caine ED, Xiao S, Xu L, Gong Y, et al. Epidemiology of alcohol use in rural men in two provinces of China. *J Stud Alcohol Drugs.* 2011;72(2):333-340.

225. Poortinga W. The prevalence and clustering of four major lifestyle risk factors in an English adult population. *Prev Med.* 2007;44(2):124-128.

226. Chou KL. The prevalence and clustering of four major lifestyle risk factors in Hong Kong Chinese older adults. *J Aging Health.* 2008;20(7):788-803.

227. Hart CL, Davey Smith G, Gruer L, Watt GC. The combined effect of smoking tobacco and drinking alcohol on cause-specific mortality: a 30 year cohort study. *BMC Public Health.* 2010;10(1):789.

228. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med.* 2010;170(8):711-718.

229. Lv J, Yu C, Guo Y, Bian Z, Yang L, Chen Y, et al. Adherence to Healthy Lifestyle and Cardiovascular Diseases in the Chinese Population. *J Am Coll Cardiol.* 2017;69(9):1116-1125.

230. Liu S, Zhang M, Yang L, Li Y, Wang L, Huang Z, et al. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health.* 2017;71(2):154-161.

231. Li S, Meng L, Chiolero A, Ma C, Xi B. Trends in smoking prevalence and attributable mortality in China, 1991-2011. *Prev Med.* 2016;93:82-87.

232. Chen Z, Peto R, Zhou M, Iona A, Smith M, Yang L, et al. Contrasting male and female trends in tobacco-attributed mortality in China: evidence from successive nationwide prospective cohort studies. *Lancet.* 2015;386(10002):1447-1456.

233. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet.* 2013;381(9882):1987-2015.

234. Yin Z, Geng G, Lan X, Zhang L, Wang S, Zang Y, et al. Status and determinants of health behavior knowledge among the elderly in China: a community-based cross-sectional study. *BMC Public Health.* 2013;13(1):710.

235. Rehm J, Greenfield TK, Walsh G, Xie X, Robson L, Single E. Assessment methods for alcohol consumption, prevalence of high risk drinking and harm: a sensitivity analysis. *Int J Epidemiol.* 1999;28(2):219-224.

236. Kesmodel U, Olsen SF. Self reported alcohol intake in pregnancy: comparison between four methods. *J Epidemiol Community Health.* 2001;55(10):738-745.

237. Dawson DA. Methodological issues in measuring alcohol use. *Alcohol Res Health.* 2003;27(1):18-29.

238. Ekholm O, Strandberg-Larsen K, Christensen K, Gronbaek M. Comparison of assessment methods for self-reported alcohol consumption in health interview surveys. *Eur J Clin Nutr.* 2008;62(2):286-291.

239. Stockwell T, Donath S, Cooper-Stanbury M, Chikritzhs T, Catalano P, Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. *Addiction.* 2004;99(8):1024-1033.

240. Knibbe RA, Bloomfield K. Alcohol consumption estimates in surveys in Europe: comparability and sensitivity for gender differences. *Subst Abus.* 2001;22(1):23-38.

241. Frost C, Thompson SG. Correcting for regression dilution bias: comparison of methods for a single predictor variable. *Journal of the Royal Statistical Society Series A (Statistics in Society).* 2000;163(2):173-189.

242. National Institute on Alcohol Abuse and Alcoholism. Alcohol Use Disorder. National Institute on Alcohol Abuse and Alcoholism. Available from: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-use-disorders. Accessed 9th November, 2019.

243. Rehm J. How should prevalence of alcohol use disorders be assessed globally? *Int J Methods Psychiatr Res.* 2016;25(2):79-85.

244. Chakravorty S, Jackson N, Chaudhary N, Kozak PJ, Perlis ML, Shue HR, et al. Daytime sleepiness: associations with alcohol use and sleep duration in americans. *Sleep Disord.* 2014;2014:959152.

245. Roehrs T, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. *Sleep Med Rev.* 2001;5(4):287-297.

246. Geiger BB, MacKerron G. Can alcohol make you happy? A subjective wellbeing approach. *Soc Sci Med.* 2016;156:184-191.

247. Koivumaa-Honkanen H, Kaprio J, Korhonen T, Honkanen RJ, Heikkila K, Koskenvuo M. Self-reported life satisfaction and alcohol use: a 15-year follow-up of healthy adult twins. *Alcohol Alcohol.* 2012;47(2):160-168.

248. Massin S, Kopp P. Is life satisfaction hump-shaped with alcohol consumption? Evidence from Russian panel data. *Addict Behav.* 2014;39(4):803-810.

249. Mies GW, Verweij KJH, Treur JL, Ligthart L, Fedko IO, Hottenga JJ, et al. Polygenic risk for alcohol consumption and its association with alcohol-related phenotypes: Do stress and life satisfaction moderate these relationships? *Drug Alcohol Depend.* 2018;183:7-12.

250. Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction.* 2013;108(9):1562-1578.

251. Darvishi N, Farhadi M, Haghtalab T, Poorolajal J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. *PLoS One.* 2015;10(5):e0126870.

252. Kachadourian LK, Pilver CE, Potenza MN. Trauma, PTSD, and binge and hazardous drinking among women and men: findings from a national study. *J Psychiatr Res.* 2014;55:35-43.

253. Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. *Psychopharmacology (Berl).* 2011;218(1):1-17.

254. Kim JH, Martins SS, Shmulewitz D, Santaella J, Wall MM, Keyes KM, et al. Childhood maltreatment, stressful life events, and alcohol craving in adult drinkers. *Alcohol Clin Exp Res.* 2014;38(7):2048-2055.

255. Dhossche DM, Meloukheia AM, Chakravorty S. The association of suicide attempts and comorbid depression and substance abuse in psychiatric consultation patients. *Gen Hosp Psychiatry.* 2000;22(4):281-288.

256. Cornelius JR, Salloum IM, Mezzich J, Cornelius MD, Fabrega H, Jr., Ehler JG, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. *Am J Psychiatry.* 1995;152(3):358-364.

257. Xiang YT, Ma X, Lu JY, Cai ZJ, Li SR, Xiang YQ, et al. Alcohol-related disorders in Beijing, China: prevalence, socio-demographic correlates, and unmet need for treatment. *Alcohol Clin Exp Res.* 2009;33(6):1111-1118.

258. Tang J, Liao Y, He H, Deng Q, Zhang G, Qi C, et al. Sleeping problems in Chinese illicit drug dependent subjects. *BMC Psychiatry.* 2015;15(1):28.

259. Li J, Wu B, Selbaek G, Krokstad S, Helvik AS. Factors associated with consumption of alcohol in older adults - a comparison between two cultures, China and Norway: the CLHLS and the HUNT-study. *BMC Geriatr.* 2017;17(1):172.

260. Cheng HG, Phillips MR, Li X, Zhang J, Shi Q, Xu G, et al. Co-occurrence of DSM-IV mental disorders and alcohol use disorder among adult Chinese males. *Psychol Med.* 2017;47(16):2811-2822.

261. Cheng HG, Chen S, McBride O, Phillips MR. Prospective relationship of depressive symptoms, drinking, and tobacco smoking among middle-aged and elderly community-dwelling adults: Results from the China Health and Retirement Longitudinal Study (CHARLS). *J Affect Disord.* 2016;195:136-143.

262. Im PK, Millwood IY, Guo Y, Du H, Chen Y, Bian Z, et al. Patterns and trends of alcohol consumption in rural and urban areas of China: findings from the China Kadoorie Biobank. *BMC Public Health.* 2019;19(1):217.

263. Im PK, Millwood IY, Chen Y, Guo Y, Du H, Kartsonaki C, et al. Problem drinking, wellbeing and mortality risk in Chinese men: findings from the China Kadoorie Biobank. *Addiction.* 2020;115(5):850-862.

264. Thorpy MJ. Classification of sleep disorders. *Neurotherapeutics.* 2012;9(4):687-701.

265. Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen HU. The World Health Organization composite international diagnostic interview short-form (CIDI-SF). *Int J Methods Psychiatr Res.* 1998;7(4):171-185.

266. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515-526.

267. Cheng HG, Deng F, Xiong W, Phillips MR. Prevalence of alcohol use disorders in mainland China: a systematic review. *Addiction.* 2015;110(5):761-774.

268. Kim JH, Lee S, Chow J, Lau J, Tsang A, Choi J, et al. Prevalence and the factors associated with binge drinking, alcohol abuse, and alcohol dependence: a population-based study of Chinese adults in Hong Kong. *Alcohol Alcohol.* 2008;43(3):360-370.

269. Zhou L, Conner KR, Phillips MR, Caine ED, Xiao S, Zhang R, et al. Epidemiology of alcohol abuse and dependence in rural chinese men. *Alcohol Clin Exp Res.* 2009;33(10):1770-1776.

270. Phillips MR, Cheng HG, Li X, Zhang J, Shi Q, Xu G, et al. Prevalence, correlates, comorbidity, and age of onset of alcohol use disorders in adult males from five provinces in China. *Drug Alcohol Depend.* 2017;173:170-177.

271. Popovici I, French MT. Does unemployment lead to greater alcohol consumption? *Ind Relat (Berkeley).* 2013;52(2):444-466.

272. Mulia N, Zemore SE, Murphy R, Liu H, Catalano R. Economic loss and alcohol consumption and problems during the 2008 to 2009 U.S. recession. *Alcohol Clin Exp Res.* 2014;38(4):1026-1034.

273. Dom G, Samochowiec J, Evans-Lacko S, Wahlbeck K, Van Hal G, McDaid D. The impact of the 2008 economic crisis on substance use patterns in the countries of the European Union. *Int J Environ Res Public Health.* 2016;13(1).

274. Bor J, Basu S, Coutts A, McKee M, Stuckler D. Alcohol use during the great recession of 2008-2009. *Alcohol Alcohol.* 2013;48(3):343-348.

275. Wong WS, Fielding R. Prevalence of insomnia among Chinese adults in Hong Kong: a population-based study. *J Sleep Res.* 2011;20(1 Pt 1):117-126.

276. Ohayon MM, Bader G. Prevalence and correlates of insomnia in the Swedish population aged 19-75 years. *Sleep Med.* 2010;11(10):980-986.

277. Ohayon MM, Hong SC. Prevalence of insomnia and associated factors in South Korea. *J Psychosom Res.* 2002;53(1):593-600.

278. Heeb JL, Gmel G. Measuring alcohol consumption: a comparison of graduated frequency, quantity frequency, and weekly recall diary methods in a general population survey. *Addict Behav.* 2005;30(3):403-413.

279. Sanchez-Roige S, Palmer AA, Fontanillas P, Elson SL, Adams MJ, Howard DM, et al. Genome-wide association study meta-analysis of the Alcohol Use Disorders

Identification Test (AUDIT) in two population-based cohorts. *Am J Psychiatry.* 2018;176(2):107-118.

280. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. *Alcohol Res.* 2012;34(4):414-431.

281. Kuria MW, Ndetei DM, Obot IS, Khasakhala LI, Bagaka BM, Mbugua MN, et al. The association between alcohol dependence and depression before and after treatment for alcohol dependence. *ISRN Psychiatry.* 2012;2012:482802.

282. Li J, Wang H, Li M, Shen Q, Li X, Zhang Y, et al. Effect of alcohol use disorders and alcohol intake on the risk of subsequent depressive symptoms: a systematic review and meta-analysis of cohort studies. *Addiction.* 2020;115(7):1224-1243.

283. Skogen JC, Harvey SB, Henderson M, Stordal E, Mykletun A. Anxiety and depression among abstainers and low-level alcohol consumers. The Nord-Trondelag Health Study. *Addiction.* 2009;104(9):1519-1529.

284. Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. *Int J Epidemiol.* 2014;43(3):906-919.

285. Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Alcohol use disorder and mortality across the lifespan: a longitudinal cohort and co-relative analysis. *JAMA Psychiatry.* 2016;73(6):575-581.

286. Westman J, Wahlbeck K, Laursen TM, Gissler M, Nordentoft M, Hallgren J, et al. Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. *Acta Psychiatr Scand.* 2015;131(4):297-306.

287. Cao Y, Willett WC, Rimm EB, Stampfer MJ, Giovannucci EL. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. *BMJ.* 2015;351:h4238.

288. Saito E, Inoue M, Sawada N, Charvat H, Shimazu T, Yamaji T, et al. Impact of alcohol intake and drinking patterns on mortality from all causes and major causes of death in a Japanese population. *J Epidemiol.* 2018;28(3):140-148.

289. Hao W, Young D. Drinking patterns and problems in China. *J Subst Use.* 2000;5(1):71-78.

290. Wang YC, Wei LJ, Liu JT, Li SX, Wang QS. Comparison of Cancer Incidence between China and the USA. *Cancer Biol Med.* 2012;9(2):128-132.

291. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health.* 1998;88(1):15-19.

292. Jin M, Cai S, Guo J, Zhu Y, Li M, Yu Y, et al. Alcohol drinking and all cancer mortality: a meta-analysis. *Ann Oncol.* 2013;24(3):807-816.

293. Jung EJ, Shin A, Park SK, Ma SH, Cho IS, Park B, et al. Alcohol consumption and mortality in the Korean Multi-Center Cancer Cohort Study. *J Prev Med Public Health.* 2012;45(5):301-308.

294. Kunzmann AT, Coleman HG, Huang WY, Berndt SI. The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. *PLoS Med.* 2018;15(6):e1002585.

295. Liang H, Wang J, Xiao H, Wang D, Wei W, Qiao Y, et al. Estimation of cancer incidence and mortality attributable to alcohol drinking in China. *BMC Public Health.* 2010;10(1):730.

296. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer.* 2012;31(6):281-286.

297. Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Yamaji T, et al. Alcohol and risk of lung cancer among Japanese men: data from a large-scale population-based cohort study, the JPHC study. *Cancer Causes Control.* 2008;19(10):1095-1102.

298. Brenner H, Rothenbacher D, Bode G, Adler G. Relation of smoking and alcohol and coffee consumption to active Helicobacter pylori infection: cross sectional study. *BMJ.* 1997;315(7121):1489-1492.

299. Liu SY, Han XC, Sun J, Chen GX, Zhou XY, Zhang GX. Alcohol intake and Helicobacter pylori infection: a dose-response meta-analysis of observational studies. *Infect Dis (Lond).* 2016;48(4):303-309.

300. Xie C, Lu NH. Review: clinical management of Helicobacter pylori infection in China. *Helicobacter.* 2015;20(1):1-10.

301. Ma SH, Jung W, Weiderpass E, Jang J, Hwang Y, Ahn C, et al. Impact of alcohol drinking on gastric cancer development according to Helicobacter pylori infection status. *Br J Cancer.* 2015;113(9):1381-1388.

302. Galeone C, Malerba S, Rota M, Bagnardi V, Negri E, Scotti L, et al. A meta-analysis of alcohol consumption and the risk of brain tumours. *Ann Oncol.* 2013;24(2):514-523.

303. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet.* 2014;384(9945):755-765.

304. Wang L, Jin G, Yu C, Lv J, Guo Y, Bian Z, et al. Cancer incidence in relation to body fatness among 0.5 million men and women: findings from the China Kadoorie Biobank. *Int J Cancer.* 2020;146(4):987-998.

305. Gentry RT. Effect of food on the pharmacokinetics of alcohol absorption. *Alcohol Clin Exp Res.* 2000;24(4):403-404.

306. Bandera EV, Freudenheim JL, Vena JE. Alcohol consumption and lung cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev.* 2001;10(8):813-821.

307. Matejcic M, Gunter MJ, Ferrari P. Alcohol metabolism and oesophageal cancer: a systematic review of the evidence. *Carcinogenesis.* 2017;38(9):859-872.

308. Lewis SJ, Smith GD. Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev.* 2005;14(8):1967-1971.

309. Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. *Eur Neuropsychopharmacol.* 2007;17(10):627-636.

310. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. In: *IARC monographs on the evaluation of carcinogenic risks to humans.* Vol 71. Lyon, France: International Agency for Research on Cancer; 1999.

311. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. *Am J Med.* 2007;120(10):829-834.

312. Diehl AM. Obesity and alcoholic liver disease. *Alcohol.* 2004;34(1):81-87.

313. Liangpunsakul S, Haber P, McCaughan GW. Alcoholic liver disease in Asia, Europe, and North America. *Gastroenterology.* 2016;150(8):1786-1797.

314. O'Shea RS, Dasarathy S, McCullough AJ, Practice Guideline Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology.* 2010;51(1):307-328.

315. Mathurin P, Deltenre P. Effect of binge drinking on the liver: an alarming public health issue? *Gut.* 2009;58(5):613-617.

316. Llerena S, Arias-Loste MT, Puente A, Cabezas J, Crespo J, Fabrega E. Binge drinking: burden of liver disease and beyond. *World J Hepatol.* 2015;7(27):2703-2715.

317. Li D, Zhao H, Gelernter J. Strong protective effect of the aldehyde dehydrogenase gene (ALDH2) 504lys (*2) allele against alcoholism and alcohol-induced medical diseases in Asians. *Hum Genet.* 2012;131(5):725-737.

318. European Association for the Study of the Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol.* 2012;57(2):399-420.

319. Scheiblauer H, El-Nageh M, Diaz S, Nick S, Zeichhardt H, Grunert HP, et al. Performance evaluation of 70 hepatitis B virus (HBV) surface antigen (HBsAg) assays from around the world by a geographically diverse panel with an array of HBV genotypes and HBsAg subtypes. *Vox Sang.* 2010;98(3 Pt 2):403-414.

320. Allen N, Sudlow C, Downey P, Peakman T, Danesh J, Elliott P, et al. UK Biobank: Current status and what it means for epidemiology. *Health Policy and Technology.* 2012;1(3):123-126.

321. Shah D. Healthy worker effect phenomenon. *Indian J Occup Environ Med.* 2009;13(2):77-79.

322. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med.* 2004;38(5):613-619.

323. Sundkvist A, Myte R, Boden S, Enroth S, Gyllensten U, Harlid S, et al. Targeted plasma proteomics identifies a novel, robust association between cornulin and Swedish moist snuff. *Sci Rep.* 2018;8(1):2320.

324. Rehm J, Imtiaz S. A narrative review of alcohol consumption as a risk factor for global burden of disease. *Subst Abuse Treat Prev Policy.* 2016;11(1):37.

325. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug Alcohol Depend.* 2015;154:1-13.

326. Schmoor C, Sauerbrei W, Schumacher M. Sample size considerations for the evaluation of prognostic factors in survival analysis. *Stat Med.* 2000;19(4):441-452.

A. List of publications, presentations and awards

Published manuscripts

Im PK, Millwood IY, Chen Y, Guo Y, Du H, Kartsonaki C, Bian Z, Tan Y, Su J, Li Y, Yu C, Lv J, Li L, Yang L, Chen: Problem drinking, wellbeing and mortality risk in Chinese men: findings from the China Kadoorie Biobank. *Addiction* 2020; 115(5): 850-62.

Im PK, Millwood IY, Guo Y, Du H, Chen Y, Bian Z, Tan Y, Guo Z, Wu S, Hua Y, Li L, Yang L, Chen Z: Patterns and trends of alcohol consumption in rural and urban areas of China: findings from the China Kadoorie Biobank. *BMC Public Health* 2019; 19(1):217.

Submitted and working papers

Im PK, Millwood IY, Chen Y, Guo Y, Du H, Kartsonaki C, Bian Z, Tan Y, Walters RG, Yu C, Lv J, Li L, Yang L, Chen: Alcohol drinking and risk of cancer: findings from the China Kadoorie Biobank. *Lancet Global Health* 2019. Under review.

Im PK, Millwood IY, Kartsonaki C, Turnbull I, Chen Y, Guo Y, Du H, Bian Z, Tan Y, Yu C, Lv J, Li L, Yang L, Chen: Alcohol drinking and risk of liver diseases: findings from the China Kadoorie Biobank. In preparation.

Oral presentations

IM PK, Millwood IY, Kartsonaki C, Turnbull I, Chen Y, Guo Y, Du H, Bian Z, Tan Y, Yu C, Lv J, Li L, Yang L & Chen Z: Alcohol drinking and risk of liver diseases: findings from the China Kadoorie Biobank. *45th Annual Alcohol Epidemiology Symposium of the Kettil Bruun Society (KBS) 2019, Utrecht*, June 2019

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol and cancer in Chinese adults: findings from the China Kadoorie Biobank. *Nuffield Department of Population Health Symposium, Oxford*, March 2019

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and risk of cancers: findings from the China Kadoorie Biobank. *CKB Research Seminar, Oxford*, March 2019

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and risk of cancers: findings from the China Kadoorie Biobank. *CKB Annual Research Day, Oxford*, November 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and risk of cancers: findings from the China Kadoorie Biobank. *19th World Congress of International Society for Biomedical Research on Alcoholism (ISBRA), Kyoto*, September 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Patterns and trends of alcohol consumption in rural and urban areas of China: findings from the China Kadoorie Biobank. *Global Health Symposium, Belfast*, April 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Patterns and trends of alcohol drinking, and problem drinking in relation to wellbeing. *CKB Research Seminar, Oxford*, April 2018

Poster presentations

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and risk of cancer: findings from the China Kadoorie Biobank. *CRUK Symposium, Oxford*, June 2019

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Problem drinking and well-being: findings from the China Kadoorie Biobank. *CKB Annual Research Day, University of Oxford*, *Oxford*, November 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and liver cirrhosis: findings from the China Kadoorie Biobank. *Nuffield Department of Population Health DPhil Poster Competition, University of Oxford*, October 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Alcohol drinking and liver cirrhosis: findings from the China Kadoorie Biobank. *13th International Symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis (ISALPD/C), Kyoto*, September 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Problem drinking and well-being: findings from the China Kadoorie Biobank. *Global Health Symposium, Belfast*, April 2018

Im PK, Yang L, Millwood IY, Guo Y, Bian Z, Li L, Chen Z: Patterns and trends of alcohol consumption in rural and urban areas of China: findings from the China Kadoorie Biobank. *Global Health Symposium, Belfast*, April 2018

Awards received

Ole-Jørgen Skog Award for best paper presented by an early career researcher at the *45th Annual Alcohol Epidemiology Symposium of the Kettil Bruun Society (KBS), Utrecht,* June 2019

ISBRA-WHO Travel Award for the *19th World Congress of International Society for Biomedical Research on Alcoholism (ISBRA), Kyoto,* September 2018

Young Investigator Travel Award for the *13th International Symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis (ISALPD/C), Kyoto,* September 2018

B. Supplementary methods on literature review

For cancers, the IARC Monographs (2010 and 2012), the most recent WCRF SLRs for 12 site-specific cancers, and a comprehensive dose-response meta-analysis of 23 site-specific cancers published in 2015 by Bagnardi et al[1] were reviewed as the starting point. A literature search on PubMed was conducted to search for meta-analyses and prospective cohort studies in human participants using the search strategy below:

(alcohol or "Alcohol Drinking"[Mesh] or "alcohol intake"[title] or "alcohol consumption"[title] or "drinking pattern"[title]) AND (risk[title] or mortality[title] or longitudinal[title] or prospective[title] or cohort[title] or meta-analysis[title]) AND ("Neoplasms"[Mesh] or cancer).

Meta-analyses published after the Bagnardi et al meta-analysis or the latest WCRF SLR report relevant to the site-specific cancer, whichever is more recent, and large-scale prospective cohort studies published since the most recent meta-analyses identified were included in the review if they (i) were human studies; (ii) were written in English; (iii) reported risk estimates (HRs, RRs, ORs) and confidence intervals/or p-values; (iv) did not restrict analyses to a single type of beverage only; and (v) had sample size of n>10,000 for prospective studies. An updated literature search using the same search strategy was conducted on 14 April 2019 to identify any newly published studies for inclusion. Meta-analyses and prospective studies conducted in China, though already included in the meta-analyses reviewed, were also identified through review of

[1]Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580-593.

reference lists and were included as individual studies to summarise existing evidence and to identify evidence gap in China.

For literature of liver diseases, similar review methodology was used as for cancers by reviewing the most recent meta-analyses plus subsequently published large-scale prospective cohort studies. The following search strategy was searched for articles reporting human studies on PubMed:

(alcohol[title] or ethanol[title] "Alcohol Drinking"[Mesh] or "alcohol intake"[title] or "alcohol consumption"[title] or "heavy drinking"[title] or "drinking pattern"[title]) AND (risk[title] or incidence[title] or mortality[title] or longitudinal[title] or prospective[title] or cohort[title] or meta-analysis[title]) AND ("Liver diseases"[Mesh] or "Non-alcoholic Fatty Liver Disease"[Mesh] or "Liver Cirrhosis"[Mesh] or "Liver Cirrhosis"[Mesh] or "liver disease"[title] or "liver cirrhosis"[title] or “liver neoplasm”[MESH] or “liver cancer”[title]).

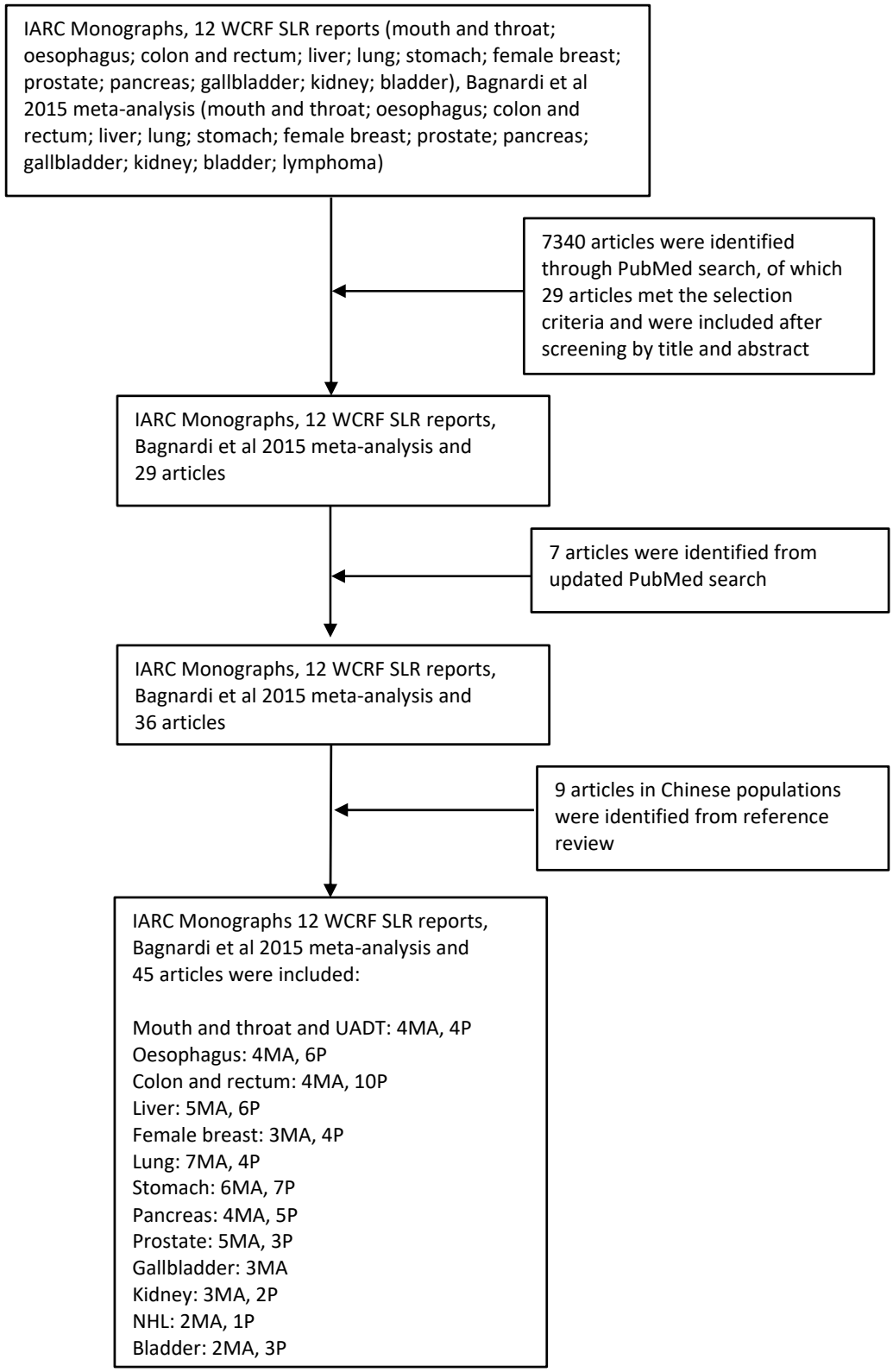
The same inclusion criteria as for cancers was used in selecting articles published within the recent 10 years. An updated literature search and review of reference lists was then conducted to identify any newly published studies for inclusion. Due to the lack of reliable, large prospective studies on alcohol consumption and NAFLD, the recent prospective Whitehall II study by Britton et al[2] (although with small sample size n=5407) with 30 years of follow-up added important information to the existing evidence and was therefore included in the literature review. Meta-analyses and

[2]Britton A, Mehta G, O'Neill D, Bell S. Association of thirty-year alcohol consumption typologies and fatty liver: findings from a large population cohort study. *Drug Alcohol Depend*. 2019;194:225-229.

prospective studies conducted in China, though already included in the meta-analyses reviewed, were also identified through review of reference lists and were included in the review. As liver cancer had been included in the earlier review of cancers, this review on liver diseases did not include liver cancer.

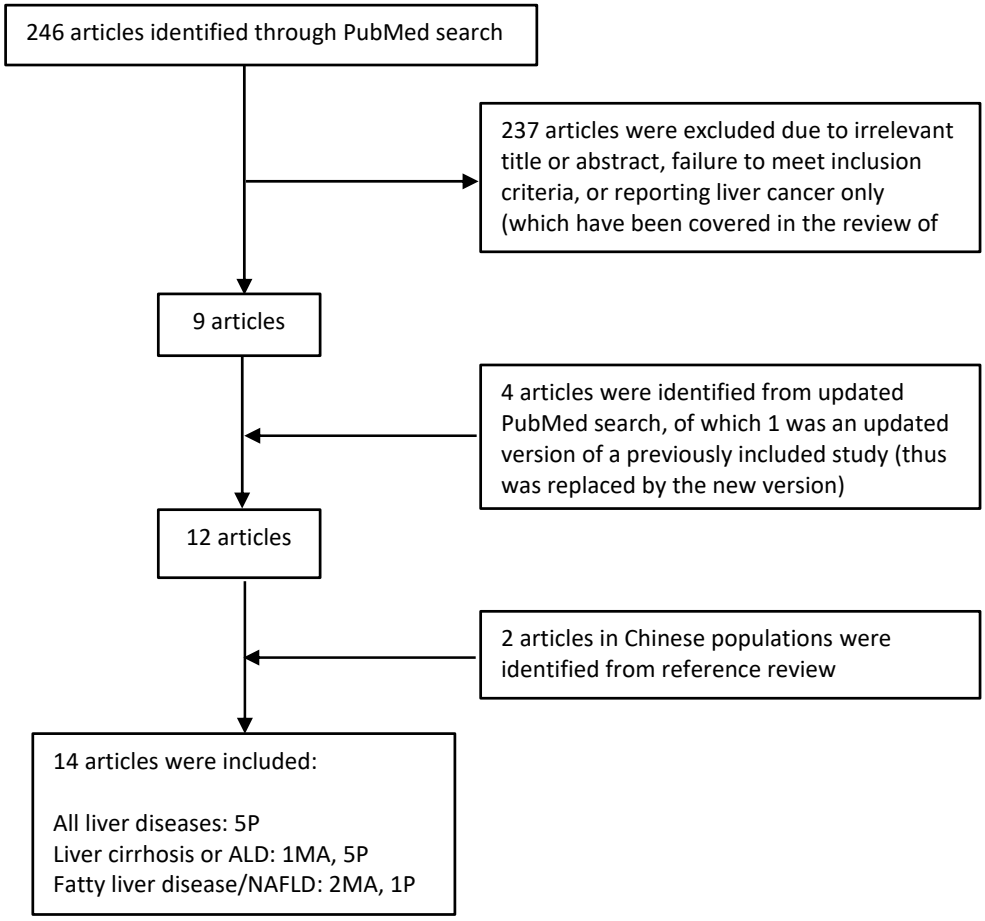
Flow diagrams for the literature review process are shown in Figure B1 and Figure B2.

Figure B 1. Flow diagram for the literature review on alcohol consumption and site-specific cancers



IARC, International Agency for Research on Cancer; WCRF SLR, World Cancer Research Fund Systematic Literature Review; MA, meta-analysis; P, prospective study; NHL, non-Hodgkin lymphoma.

Figure B 2. Flow diagram for the literature review on alcohol consumption and liver diseases



MA, meta-analysis; P, prospective cohort study; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease.

C. CKB Baseline questionnaire

June 10, 2004

Kadoorie Study of Chronic Disease in China

【Questionnaire】

Clinical Trial Service Unit & Epidemiological Studies Unit,
Nuffield Department of Clinical Medicine, University of Oxford, UK
&
Chinese Centre for Disease Control and Prevention, Beijing, P. R. China

Section 1: Background information

1.1 **Study ID:** ☐☐☐☐☐☐☐☐☐☐ *(The date & time of interview will be recorded by computer)*

1.2 **Name**_____, **Sex** : Male ☐ Female ☐ , **Name of spouse**_____

1.3 **Date of birth:** ☐☐☐☐ Year ☐☐ Month ☐☐ Day

1.4 **National ID number (if no, put #)** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.5 **Home address** : _____Province _____City_____ District/County _____Street/Village

Home telephone: Not available ☐ , Yes: ☐☐☐-☐☐☐☐☐☐☐☐

1.6 **What is the highest level of school education you ever received?**

- ☐ No formal school
- ☐ Primary School
- ☐ Middle School
- ☐ High School
- ☐ Technical school / college
- ☐ University

1.7 **What is your current occupation?**

- ☐ Agriculture & related workers
- ☐ Factory worker
- ☐ Administrator / manager
- ☐ Professional / technical
- ☐ Sales & service workers
- ☐ Retired
- ☐ House wife / husband
- ☐ Self-employed
- ☐ Unemployed
- ☐ Other or not stated

1.8 **How many people living together in the household?** ☐☐ persons

1.9 **What is your current marital status?**

- ☐ Married
- ☐ Widowed
- ☐ Separated / divorced
- ☐ Never married

1.10 **What is the total income last year in your household?**

- ☐ <2,500 yuan
- ☐ 2,500-4,999 yuan
- ☐ 5,000-9,999 yuan
- ☐ 10,000-19,999 yuan
- ☐ 20,000-34,999 yuan
- ☐ ≥35,000 yuan

1.11 **Do you have any health care cover and following items in your household?**

Yes	No	
☐	☐	Health care cover
☐	☐	Own house / apartment
☐	☐	Toilet for private use
☐	☐	Telephone or mobile phone
☐	☐	Motor vehicle (e.g. car or motorbike)
☐	☐	Holiday during last five years

Section 2: Tea drinking

2.1 During the past 12 months, how often did you drink any tea?

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → *Go to Q2.3* (were2.2)

2.2(were 2.1a) In the past, did you ever have a period of at least 1 year during which you usually drank tea at least once a week?

- ☐ Yes, → (were 2.1b) if so, how long ago did it end? ☐☐ Years } *Go to section 3*
- ☐ No

2.3(were 2.2) During the past 12 months, on how many days did you drink tea in a typical week?

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

2.4(were2.3)At about what age did you start drinking tea in most weeks? ····· ☐☐ Years

---

2.5(were2.4)On days when you drink tea, how many cups do you usually drink? (choose one only)

Green /Jasmine tea ·····	☐☐	cups/day
Oolong tea ·····	☐☐	cups/day
Black tea ·····	☐☐	cups/day
Other tea ·····	☐☐	cups/day

2.6(were2.5) How often do you change tea leaves during a day? ····· ☐☐ times

---

2.7(were2.6) About how much tea leaves do you usually add each time? ☐☐ Grams

---

2.8(were2.7) What strength of tea do you usually prefer to drink?

- ☐ Weak
- ☐ Moderate
- ☐ Strong

2.9(were2.8) At about what temperature do you usually drink your tea?

- ☐ Room temperature / warm
- ☐ Hot
- ☐ Burning hot

2.10(were2.9)Has your tea consumption changed significantly compared with that some years ago? ☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 3: Alcohol consumption

3.1(were3.0) **Have you drunk any alcohol today?** ☐ Yes , ☐ No

3.2(were3.1)**During the past 12 months, how often did you drink any alcohol?**

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → *Go to Q3.4* (wereQ3.2)

3.3(were3.1a)**In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?**

- ☐ Yes, →(were 3.1b) If so, how long ago did it e ☐☐ Years } *Go to section 4*
- ☐ No

3.4(were3.2)**During the past 12 months, on how many days did you drink alcohol in a typical week?**

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

3.5(were3.3)**At about what age did you start drinking some alcohol in most weeks?** ☐☐ Years

---

3.6(were3.4) **On days when you drink, how much alcohol do you usually drink in a day?**
(Can choose up to 3 types of alcohol for special occasions; for beer, 1 large bottle=2 small ones)

Alcohol type	On a typical day (choose one)		On a special day when you drink a lot		Last time when you drank	
Beer (large)	☐☐	Bottle	☐☐	Bottle	☐☐	Bottle
Rice Wine	☐☐	liang	☐☐	liang	☐☐	liang
Wine	☐☐	liang	☐☐	liang	☐☐	liang
Spirit (≥50% alcohol)	☐☐	liang	☐☐	liang	☐☐	liang
Spirit (<50% alcohol)	☐☐	liang	☐☐	liang	☐☐	liang

3.7(were3.5)**On a typical day when you drink alcohol, when do you usually take the drink?**

- ☐ Usually drink with the meal
- ☐ Usually drink between or after the meals
- ☐ No regular pattern

3.8(were3.6)**After drinking alcohol, do you usually experience hot flushes or dizziness?**

- ☐ Yes, soon after first mouthful
- ☐ Yes, after drinking small amount of alcohol
- ☐ Yes, but only after drinking large amount of alcohol
- ☐ No

3.9(were3.7)During the past month, how often have you drunk alcohol in the morning?

- ☐ Never
- ☐ <1 day/week
- ☐ A few days a week
- ☐ Daily or almost daily

3.10(were3.8)During the past month, have you ever had the following experiences?

Yes	No	
☐	☐	Unable to work or to do anything because of drinking
☐	☐	Felt depressed, irritated or couldn't control yourself after drinking
☐	☐	Could not keep away from drinking
☐	☐	Had shakes when you stopped drinking

3.11(were3.9) Has your alcohol consumption changed significantly compared with that some years ago?

- ☐ About the same as before
- ☐ Has increased a lot
- ☐ Has decreased a lot

Section 4: Smoking history

4.1(were4.0) **Have you smoked any tobacco today?** ☐ Yes , ☐ No, →if yes, how many: __ total, __in last hour

4.2(were4.1)**How often do you smoke tobacco now?**

- ☐ Do not smoke now
- ☐ Only occasionally
- ☐ Yes, on most days
- ☐ Yes, daily or almost every day

→ *Go to Q4.7* (were Q4.5)

4.3(were4.2)**In the past, how frequently did you smoke?**

- ☐ Did not smoke
- ☐ Smoked only occasionally
- ☐ Smoked on most days
- ☐ Smoked daily or almost every day

→ *Go to Q 4.5* (were Q4.3)

4.4(were4.2a)**In your life time, have you smoked a total of at least 100 cigarettes or equivalent?**

- ☐ Yes
- ☐ No

➔ *Please go to section 5*

4.5(were4.3)**How many years ago did you last stop smoking regularly?** ☐☐ Years

4.6(were4.4)**What was your main reason for stopping?**

- ☐ Physical illness that you already had
- ☐ Money
- ☐ Health concerns (about future illness)
- ☐ Family against
- ☐ Other

4.7(were4.5)**At about what age did you first start smoking on most days?** ☐☐ Years

4.8(were4.6)**What tobacco did you use when you first started smoking on most days?**

Mainly cigarette ☐, Mainly non-cigarette ☐, Mixed types ☐

↳ (4.6a) If so, have you always smoked some cigarettes on most days, never having a month or more without them? Yes ☐, No ☐

4.9(were4.7)**How much tobacco do you usually smoke (or did you smoke before giving up)?**

Filter cigarettes (factory) ·····	☐☐	number/day
Non-filter cigarettes (factory)·····	☐☐	number/day
Hand-rolled cigarettes ····· ····· ·····	☐☐	liang/month
Pipe or water pipe ·····	☐☐	liang/month
Cigars ·····	☐☐	number/day

4.10(were4.9) **How deeply do you usually inhale the smoke?**

- ☐ Mouth only
- ☐ Throat
- ☐ Lung ➔ 4.9a Have you always inhaled the smoke into your lung when smoking? Yes ☐, No ☐

4.11(were4.10)**Has your tobacco consumption changed significantly compared with that some years ago?**

☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 5: Diet

5.1(were5.2)During the past 12 months, about how often did you eat the following foods?

	Daily	4-6 days per week	1-3 days per week	Monthly	Never/rarely
Rice	☐	☐	☐	☐	☐
Wheat	☐	☐	☐	☐	☐
Other staple food (corn, millet etc.)	☐	☐	☐	☐	☐
Meat	☐	☐	☐	☐	☐
Poultry	☐	☐	☐	☐	☐
Fish/sea food	☐	☐	☐	☐	☐
Fresh eggs	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐
Soybean products	☐	☐	☐	☐	☐
Preserved vegetables	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐
Dairy products (milk, yogurt)	☐	☐	☐	☐	☐

5.2(were5.3)During the past 12 months, have you taken the following supplements regularly?

Yes	No	
☐	☐	Fish oil/cod liver oil
☐	☐	Vitamins
☐	☐	Calcium/iron/zinc
☐	☐	Ginshen (at least 5 or more times during a year)
☐	☐	Other herbal products

5.3(were5.3a)Have you ever experienced any severe food shortage? ☐Yes, ☐ No → *Go to Q5.6(were Q5.3c)*

5.4(were5.3a1)What year was the worst food shortage you experienced? _____ **years**

5.5(were5.3b)During the most severe food shortage you experienced:

5.5.1– did you lose weight? ☐ Yes, ☐ No, → If yes, about how much? _____ *jin*,

5.5.2– did you develop any specific disease related to food shortage? ☐ Yes, ☐ No

5.6(were5.3c)How many years have you had a refrigerator in your home? ☐☐ Years

5.7(were5.4) During the past month, about how often did you eat hot spicy food?

☐ Never or almost never
☐ Only occasionally } → *Go to section 6*
☐ 1-2 days/week
☐ 3-5 days/week
☐ Daily or almost every day

5.8(were5.5)At what age did you start to eat spicy food at least once a week? ☐☐ Years

5.9(were5.6)What strength of spicy food do you usually prefer to eat?

☐ Weak, ☐ Moderate, ☐ Strong

5.10(were5.7)On day when you eat spicy food, what are the main sources of spice usually used?

Yes	No	
☐	☐	Chili sauce
☐	☐	Chili oil
☐	☐	Dried chili pepper
☐	☐	Fresh chili pepper
☐	☐	Other or don't know

Section 6: Passive smoking & indoor air pollution

6.1 Have you ever lived with smoker in the same house for at least 6 months?

- ☐ Never
- ☐ Yes, but not now
- ☐ Yes, at present

→ *If yes, duration of living together* ☐☐ years

6.2 How frequently are you exposed to other people's tobacco smoke either at home, workplace or in public places? *(i.e. a minimum of 5 consecutive minutes each time)*

- ☐ Never or almost never
- ☐ Occasionally (<1 time/week)

→ *Go to Q6.4*

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

6.3 What is the usual duration of your exposure per week? ☐☐ Hours

---

6.4 During past year, how long did you store pesticides at home? ☐☐ Months

---

6.5(were6.4a)Please tell us the duration you lived in 3 most recent houses (each for at least 1 year)?

Present house	☐☐	years
Previous house	☐☐	years
The house before previous	☐☐	years

6.6(were6.5) In your present & two previous houses, how often did you cook at home?

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Never/Rarely → *Go to Q6.10* (wereQ6.8)
- ☐ No cooking facility → *Go to Q6.11* (wereQ6.11)

6.7(were6.6)In your present & two previous houses, what was the main cooking fuel used?

- ☐ Gas
- ☐ Coal
- ☐ Wood
- ☐ Eletricity
- ☐ Other

6.8(were6.7)In your present & two previous houses, what was the main cooking oil used?

- ☐ Rapeseed
- ☐ Peanut
- ☐ Soybean
- ☐ Lard
- ☐ Other

6.9(were6.7a)How much time have you spent on cooking so far today? ☐☐ minutes

---

6.10(were6.8)In your present & two previous houses, did your stove(s) all have a chimney / extractor?

☐ Yes ☐ Not all stoves ☐ No

6.11(were6.9)In your present & two previous houses, was your stove always kept under slow burning throughout the day?

☐ Yes, always ☐ Yes, sometimes ☐ No → if ticked, *Go to Q6.14*

6.12(were 6.9a) If yes , types of the fuel most commonly used?

☐ Smokeless coal ☐ Coal brick / Coalite

☐ Smoky coal ☐ Other

6.13(were 6.9b) And , the place where stove was usually kept?

☐ Inside the house ☐ Outside the house

6.14(were6.11)In winter, did you normally heat your house?

☐ Yes, ☐ No

6.15 If yes, what was the main heating fuel used?

☐ Central heating ☐ Wood

☐ Gas ☐ Electricity

☐ Coal ☐ Other

6.16(were6.12)From what year did the inside of your house tend to be coal-smoky in winter?

☐ Never → if ticked, *Go to section 7*

☐ Ever since childhood

☐ Since the year: _____ year

6.17(were6.13)In what year did the inside of your house stop being really coal-smoky in winter?

☐ In the year: _____ year

☐ Still is

Section 7: Personal & family medical history

7.1 How is your current general health status?

7.1.1 Self-rated health status?

- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor

7.1.2. Compared to someone of your own age?

- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Don't know

7.2 If you were walking on level ground with other healthy people of the same age, would you usually:

7.2.1 Become short of breath? ☐ Yes ☐ No ☐ Disabled

7.2.2 Slow down due to chest discomfort? ☐ Yes ☐ No ☐ Disabled

---

7.3 During the past 12 months, have you usually had the following symptoms?

7.3.1 Cough frequently?

- ☐ No
- ☐ Yes, for <3 months
- ☐ Yes, for ≥3months

7.3.2 Cough up sputum after getting up in the morning?

- ☐☐ No
- ☐☐ Yes, for <3 months
- ☐☐ Yes, for ≥3 months

7.4 Has a doctor EVER told you that you had had the following disease?

	Diagnosed disease? Yes	Diagnosed disease? No	Age at first diagnosis	Still on treatment? Yes	Still on treatment? No
Diabetes	☐	☐	_____	☐	☐
CHD	☐	☐	_____	☐	☐
Stroke or TIA	☐	☐	_____	☐	☐
Hypertension	☐	☐	_____	☐	☐
Rheumatic heart dis.	☐	☐	_____	☐	☐
TB	☐	☐	_____	☐	☐
Emphysema/bronchitis	☐	☐	_____	☐	☐
Asthma	☐	☐	_____	☐	☐
Cirrhosis/chronic hepatitis	☐	☐	_____	☐	☐
Peptic ulcer	☐	☐	_____	☐	☐
Gallstone/gallbladder dis.	☐	☐	_____	☐	☐
Kidney disease	☐	☐	_____	☐	☐
Fracture	☐	☐	_____	☐	☐
Rheumatoid arthritis	☐	☐	_____	☐	☐
Psychiatric disorders	☐	☐	_____	☐	☐
Neurasthenia	☐	☐	_____	☐	☐
Head injury	☐	☐	_____	☐	☐
Cancer*	☐	☐	_____	☐	☐

For CHD, stroke, and hypertension what is the current medication:

1. Aspirin
2. ACE-I
3. Beta-blocker
4. Statins
5. Diuretics
6. Ca^{++} antagonist

& for diabetes, the above list plus

7. Chlorpropamide or metformin
8. Insulin

***If yes, please indicate the site of cancer** ☐ *(If more than one, choose the one that occurred first)*

0. Lung 1. Esophagus 2. Stomach 3. Liver 4. Intestine 5. Breast 6. Prostate 7. Cervix 8. Other

7.5 **Have many blood transfusions have you ever received?** *(If none, put 0)* ☐☐ times

7.6(were7.5a)**How many times have you ever donated blood for financial payment?**

(If none, put 0) ☐☐ times

7.7(were7.6)**About how often do you have bowel movements each week?**

- ☐ More than once on most days
- ☐ About daily
- ☐ Once every 2-3 days
- ☐ Less than 3 times a week

7.8(were7.7)**How often do your gums bleed when you brush your teeth?**

- ☐ Occasionally, rarely or never
- ☐ Sometimes
- ☐ Always
- ☐ Brush teeth rarely or never

7.9(were7.8)**How many brothers & sisters do you have?** *(Including half siblings. If unknown, put#)* ☐☐

7.10(were7.9)**How many children do you have?** *(Including only biological ones)* ☐☐

7.11(were7.9a)**Is your mother still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.12(were7.9b)**Is your father still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.13(were7.10) **Did any of your parents, siblings or children have following diseases?** *(For sibling and children, please record the number with disease)*

	Stroke	Heart attack	Diabetes	Mental disorder	Cancer
Mother *(tick box)*	☐	☐	☐	☐	☐
Father *(tick box)*	☐	☐	☐	☐	☐
Siblings *(inclu. half)*	☐	☐	☐	☐	☐
Children	☐	☐	☐	☐	☐

Section 8U: Physical activities (Urban)

8.1 During the past 12 months, how active were you at work?

- ☐ Mainly sedentary (e.g. office worker)
- ☐ Standing occupation (e.g. guard, shop assistant)
- ☐ Manual work (e.g. plumber, carpenter)
- ☐ Heavy manual work (e.g. miner, construction worker)
- ☐ Retired or housewife/husband or unemployed or disabled → ***If ticked, please go to Q8.8***

8.2(were8.1a) In a typical week, about how many hours did you usually work? _____ hours

8.3(were8.2) During the past 12 months, how did you usually get to work?

- ☐ Mainly walk
- ☐ By motorbike
- ☐ By bicycle
- ☐ By bus/car/ferry/train
- ☐ Mainly stay at home or work near home

↳***If ticked, please go to Q8.8***

8.4(were8.3) How much time did you spend each day on journey to & from work? ____minutes

Section 8F: Physical activities (New section for rural farmers)

8.1 During the past 12 months, did your farming work change seasonally?

- ☐ No → *go to Q8.3*
- ☐ Yes

8.2 During the farming season in the last 12 months:

8.2.1 How many months did it usually last? ☐☐ month

8.2.2 What types of work did it usually involve?

☐ manual ☐ Semi-mechanized ☐ Fully mechanized

8.2.3 How many hours did you usually work each day? ☐☐ hours

8.2.4 Of which , how many hours did you sweat or have a much faster heartbeat? ☐☐ hours

8.3 In a typical week, how many hours did you usually work in the field? ☐☐ hours

8.4 Apart from agriculture work, did you have any other job?

- ☐ No → ***go to Q8.7***
- ☐ Yes

8.5 How active were you at work with other job?

- ☐ Mainly sedentary
- ☐ Mainly standing
- ☐ Mainly general manual work
- ☐ Mainly heavy manual work

8.6 In a typical week, about how many hours did you work at other job? ☐☐ hours

8.7 In a typical day how much time did you usually spend on the journey to and from work on foot or by bicycle? ☐☐☐ minutes

Section 8C: Physical activities (Common to both rural farmers and urban)

8.8 During the past 12 months, how often did you do exercise in your leisure time?

- ☐ Never or almost never } → *If ticked, please go to Q8.11*
- ☐ 1-3 times/month }
- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.9 What is your main type of exercise? *(tick one box only)*

- ☐ Taichi / Qigong
- ☐ Jogging/aerobic exercise
- ☐ Ball games (basketball, table tennis, etc)
- ☐ Walking
- ☐ Swimming
- ☐ Other (eg. mountain climbing)

8.10 About how many hours per week did you do such exercise in leisure time? ___ hours

---

8.11 In a typical week during the past 12 months, how often did you sweat or have a much faster heartbeat because of heavy physical activities/exercise?

- ☐ Never or almost never } → *If ticked, please go to Q8.13*
- ☐ <1 time / week }
- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.12 About how many hours per week did you do such activities? _____ hours

---

8.13 About how many hours per week did you do house work? _____ hours

8.14 About how many hours per week did you watch TV or read? _____ hours

---

8.15 During the past 12 months, has your weight changed significantly?

☐ About the same as before ☐ Yes, gained ≥2.5 kg ☐ Yes, lost ≥2.5 kg

---

8.16 Have you tried to reduce weight in the past 12 months? No ☐, Yes ☐

8.17 How much did you weigh when you were at age 25? (If unknown put #) ☐☐☐ jin

---

Section 9: Reproductive history (for women)

9.1 How old were you when you had your first menstrual period? ☐☐ Year

---

9.2 Have you had your menopause?

- ☐ No
- ☐ Yes, currently
- ☐ Yes, had menopause → If so, age of completion of menopause: ☐☐ Year

---

9.3 How many times have you ever been pregnant? (if none, put 0. Go to Q9.6) ☐☐ imes

— Of which,

Live birth ☐☐ times → If none, Go to Q9.5 (wereQ9.6)

Still birth ☐☐ times, Spontaneous abortion ☐☐ times, Induced abortion ☐☐ times

---

9.4 Age and length of breastfeeding at each live birth (twins=one birth)?

Live Birth	Age at end of pregnancy	Months of breastfeeding
1st	☐☐	☐☐
2nd	☐☐	☐☐
3rd	☐☐	☐☐
4th	☐☐	☐☐
5th	☐☐	☐☐

9.5(were9.6)Have you ever used oral contraceptive pills?

- ☐ Never → *If ticked, please go to Q9.8* (were Q9.9)
- ☐ Past use → **if ticked,** age when you last stopped the pill: ☐☐ Year
- ☐ Current use

9.6(were9.7)How old were you when you first used oral contraceptives? ☐☐ Year

9.7(were9.8)For how long altogether have you used oral contraceptives? ☐☐ Year

---

9.8(were9.9)Have you had a hysterectomy?

☐ No, ☐ Yes → If yes, age when you had the operation ☐☐ Year

9.9(were9.10)Have you had one or both ovaries removed?

☐ No, ☐ Yes → If yes, age when you had the most recent operation ☐☐ Year

---

9.10(were9.11) Have you ever had surgery to remove a breast lump?

☐ No, ☐ Yes → If yes, age when you most recently had the operation ☐☐ Year

---

Section 10: Sleeping, mood & mental situation

10.1 In general, how satisfied are you with your life?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Unsatisfied
- ☐ Very unsatisfied

10.2 Over the past two years have you had any of the following major events in your life?

Yes	No		Yes	No	
☐	☐	Marital separation/divorce	☐	☐	Major injury or traffic accident
☐	☐	Loss of job/retirement	☐	☐	Death /major illness of spouse
☐	☐	Business bankrupt	☐	☐	Death/major illness of other close family member
☐	☐	Violence	☐	☐	Major natural disaster (e.g. flood & drought)
☐	☐	Major conflict within family	☐	☐	Loss of income / living on debt

---

10.3 During the past month, did you have any of the following for ≥3 days each week?

Yes	No	
☐	☐	Taking >30 minutes to fall asleep after going to bed or waking up in the middle of the night
☐	☐	Waking up early and not being able to go back to sleep
☐	☐	Needing to take medicine (including herbal or sleeping pills) at least once a week to help sleep
☐	☐	Having difficulty staying alert while at work, eating or meeting people during daytime

---

10.4 Do you usually take a daytime nap? ☐ Yes usually, ☐ Yes ,but only in summer , ☐ No

10.5(were10.4a) Do you snore during sleep? ☐ Yes, Frequently, ☐ Yes, Sometimes, ☐ No / Don't know

10.6(were10.5)How many hours do you typically sleep per day (incl. naps)? ☐☐ Hours

---

10.7(were10.6)During the past 12 months, have you had following situations for 2 or more weeks?
(If answer yes to any of the questions, complete CIDI-A)

Yes	No	
☐	☐	Feeling much more sad, or depressed than usual
☐	☐	Loss of interest in most things like hobbies or activities that usually give you pleasure
☐	☐	Felt so hopeless that you had no appetite to eat even your favourite food
☐	☐	Feeling worthless and useless, everything went wrong was your fault and life is very difficult that there was no way out

---

10.8(were10.7) During the past 12 months, have you experienced the following situations?

Yes	No	
☐	☐	Having a period lasting one month or longer when most of time you felt worried, tense, or anxious and it interfered your life *(if yes, complete CIDI-B)*
☐	☐	Having a pain or discomfort in your body lasting ≥3 months that interfered with your life
☐	☐	Having had a spell or an attack when all of sudden felt frightened, anxious, or very uneasy
☐	☐	Having had inexplicable strong fear in situations such as closed space (cave, elevator, airplane etc), in the crowds or public such that you would avoid such situations

---

Section 11: Physical examination

11.1 **Standing height** (without shoes) ..... ☐☐☐.☐ m

11.2 **Sitting height** ..... ☐☐☐.☐ cm

11.3 **Waist** ..... ☐☐☐.☐ cm

11.4 **Hip** ..... ☐☐☐.☐ cm

11.5 **Weight** (without shoes, but in light clothing) ..... ☐☐☐.☐ Kg

11.6 **BMI** ..... ☐☐.☐ Kg/m^2

11.7 **Impedance** ..... ☐☐☐ Ω

Staff code ☐☐☐

11.8 **Fat %** (with one decimal point) ..... ☐☐.☐

11.9 **Did you take any drugs to lower blood pressure in the last 2 days?** ☐ Yes ☐ No

11.10 **Blood pressure & heart rate** (to be measured after 5 minutes in the seated position)

	First	Second	
SBP	☐☐☐	☐☐☐	mmHg
DBP	☐☐☐	☐☐☐	mmHg
Heart rate	☐☐☐	☐☐☐	bpm

11.11(were11.10a)**Hours since last ate anything (ignore any drinks)?** _____ **hours** *Staff code* ☐☐☐

11.12(were11.11)**Blood sample collected:** Yes (, Failed (

11.13 (were11. 12) **Lung function & CO levels:**

	First	Second	
CO	☐☐☐	☐☐☐	
%COHB	☐☐.☐☐	☐☐.☐☐	%
FEV1	☐.☐☐	☐.☐☐	Liter
FVC	☐.☐☐	☐.☐☐	Liter

Staff code ☐☐☐

11.14(were11.13)**Assessment of subject's cooperation and the reliability of data collected?**

Assessment of subject's cooperation?

☐ Good
☐ Fair
☐ Poor

11.15 Assessment of the reliability of the information collected?

☐ Good
☐ Fair
☐ Poor

Date of interview _____Year_____Month___Day, **Signature of interviewer**_____

D. Additional information on CKB cancer endpoint data and resurvey subsets

Table D 1. Distribution of cancer incidents in the CKB by reporting source

	Cancer registries	
	No	Yes
Death certificates		
No	7687 (28.5%)	5507 (20.4%)
Yes	7005 (26.0%)	6762 (25.1%)
Health insurance		
No	3654 (13.6%)	3872 (14.4%)
Yes	11038 (40.9%)	8397 (31.1%)

Participants with prior cancer were excluded.

Table D 2. Baseline socio-demographic characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Overall			Men			Women		
Characteristics	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**
Number of participants	512891	19788	24996	210259	7770	9569	302632	12018	15427
Mean age, years	51.5	51.5	51.0	52.4	52.3	51.8	51.0	51.0	50.5
Birth cohort, %									
1940-1949	21.3	22.8	23.0	22.4	23.6	24.2	20.6	22.3	22.2
1950-1959	31.6	32.2	33.8	30.9	30.2	32.9	32.2	33.5	34.4
1960-1969	29.9	28.5	29.3	27.9	27.0	27.5	31.3	29.5	30.5
1970s	5.4	4.0	4.2	4.9	4.0	3.9	5.7	4.0	4.3
Rural area, %	55.9	58.8	56.9	56.6	60.5	56.8	55.4	57.7	57.1
Highest education, %									
No formal education	18.6	19.9	18.7	8.9	9.7	8.0	25.3	26.5	25.4
Primary school	32.2	32.8	34.0	33.3	34.5	35.1	31.4	31.7	33.3
Middle/high school	43.4	40.9	41.9	49.9	47.1	49.3	38.8	36.9	37.4
≥Technical school/college	5.9	6.3	5.4	7.9	8.6	7.6	4.4	4.9	3.9
Household income (yuan/year), %									
<10,000	28.2	32.5	31.6	26.0	30.1	28.3	29.8	34.0	33.7
10,000-19,999	29.1	30.4	30.8	28.3	29.9	30.6	29.6	30.8	31.0
20,000-34,999	24.7	22.1	22.3	25.4	22.2	22.3	24.2	22.1	22.3
35,000+	18.0	14.9	15.2	20.2	17.8	18.8	16.5	13.1	13.0
Married, %	90.6	91.3	92.2	92.9	93.6	94.7	89.0	89.7	90.6

Characteristics are based on the characteristics of the participants collected at baseline.

Table D 3. Baseline lifestyles and health-related characteristics of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Overall			Men			Women		
Characteristics	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Baseline**	**1st Resurvey**	**2nd Resurvey**
Number of participants	512891	19788	24996	210259	7770	9569	302632	12018	15427
Lifestyle factors									
Regular smoking, %	26.4	25.2	24.8	61.1	60.3	61.4	2.4	2.5	2.1
Regular fruit intake, %	28.2	27.5	27.1	23.0	22.1	21.8	31.8	31.0	30.4
Physical activity, mean MET hours/day	21.1	20.7	21.4	22.0	21.8	22.7	20.4	20.0	20.6
Daily tea drinking, %	26.1	25.4	24.6	40.8	39.5	40.0	15.9	16.2	15.0
Physical measurements									
Mean SBP, mmHg	131.1	132.2	131.0	132.8	133.7	132.4	129.9	131.3	130.1
Mean DBP, mmHg	77.8	77.9	77.6	79.2	79.0	78.8	76.8	77.2	76.9
Mean heart rate, beats/minute	78.9	79.1	79.0	77.7	77.9	77.6	79.7	79.9	79.8
Mean BMI, kg/m^2	23.7	23.7	23.7	23.4	23.5	23.5	23.8	23.9	23.9
Mean WHR	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Mean standing height, cm	158.7	158.5	158.3	165.2	165.2	165.1	154.1	154.2	154.0
Self-reported wellbeing, health and medical history									
Satisfied with life*, %	68.5	68.6	66.3	69.7	70.6	68.2	67.7	67.3	65.2
Self-reported good health†, %	45.8	46.5	47.5	49.2	49.1	51.2	43.3	44.9	45.2
Prior chronic disease‡, %	22.3	22.0	20.8	22.6	23.0	21.1	22.1	21.3	20.6
Prior coronary heart disease, %	3.0	3.4	2.8	2.7	3.1	2.6	3.2	3.6	3.0
Prior stroke or TIA, %	1.7	1.6	1.0	2.3	2.3	1.4	1.3	1.1	0.8
Prior cancer, %	0.5	0.6	0.4	0.5	0.5	0.4	0.5	0.6	0.5
Prior cirrhosis or chronic hepatitis, %	1.2	1.1	1.0	1.7	1.5	1.3	0.8	0.8	0.8
Prior emphysema or bronchitis, %	2.6	2.7	2.4	3.1	3.4	2.8	2.2	2.3	2.2
Prior diabetes, %	3.2	3.1	2.6	2.9	3.1	2.4	3.3	3.2	2.7
Prior psychiatric disorder, %	0.4	0.4	0.4	0.3	0.3	0.3	0.4	0.4	0.5

MET, metabolic equivalent task; S/DBP, systolic/diastolic blood pressure; BMI, body mass index; WHR, waist-hip ratio; TIA, transient ischaemic attack.
Characteristics are based on the characteristics of the participants collected at baseline.
*Reporting being satisfied or very satisfied with life.
†Reporting good or excellent self-rated health.
‡Diagnosed with one or more of: coronary heart disease, stroke or TIA, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table D 4. Baseline drinking patterns of study participants at baseline (2004-2008) and the two resurveys (2008, 2013-2014)

	Men			Women		
	Baseline	1st Resurvey	2nd Resurvey	Baseline	1st Resurvey	2nd Resurvey
Number of participants	210259	7770	9569	302632	12018	15427
Drinking categories, %						
Abstainers	20.4	19.9	19.3	63.6	63.3	64.6
Ex-regular drinkers	3.8	3.6	3.3	0.4	0.5	0.5
Reduced-intake drinkers	4.9	4.8	4.7	0.4	0.4	0.4
Occasional drinkers	37.7	38.1	38.2	33.5	33.6	32.2
Current regular drinkers	33.2	33.6	34.5	2.1	2.2	2.3
Number of current regular drinkers	69904	2611	3301	6248	264	347
Number of drinking days per week, %						
1-2	19.9	22.4	20.6	33.1	27.3	26.5
3-5	18.0	18.5	19.0	21.6	20.8	20.5
6-7	62.1	59.2	60.4	45.2	51.9	53.0
Types consumed on typical day, %						
Strong spirits only	46.8	44.8	45.5	49.1	59.1	59.4
Weak spirits only	22.8	23.2	24.5	12.7	10.6	10.4
Beer only	18.2	18.0	16.7	22.2	15.2	14.1
Rice wine only	11.3	13.1	12.6	6.2	5.7	5.8
Grape wine only	0.9	1.0	0.7	9.8	9.5	10.4
Mean intake, g/typical week	285.7	283.7	282.9	115.6	131.5	129.2
Consumption level in g/week, %						
<140	35.9	37.8	36.3	77.0	73.1	72.9
140-279	27.1	25.2	26.8	15.9	17.8	17.6
280-419	18.4	17.7	17.8	4.7	6.1	6.9
420+	18.7	19.3	19.2	2.4	3.0	2.6
Types consumed on last drinking day, %						
Strong spirits only	41.5	39.4	39.4	47.6	57.6	57.1
Weak spirits only	19.8	20.7	20.7	11.4	6.1	7.8
Beer only	20.1	20.1	19.0	22.6	21.6	18.4
Rice wine only	9.8	10.0	10.1	5.9	4.2	5.2
Grape wine only	1.2	1.2	1.2	9.8	8.7	9.8
Mixed	7.7	8.7	9.7	2.7	1.9	1.7
Mean intake, g/last drinking day	49.9	50.5	51.8	22.7	21.5	21.5
Types consumed on special occasions, %						
Strong spirits only	35.7	34.0	34.0	41.4	48.5	51.0
Weak spirits only	16.3	15.2	16.2	9.9	5.7	6.3
Beer only	10.9	10.2	9.2	16.7	11.7	9.2
Rice wine only	6.1	6.2	5.7	5.2	4.9	5.2
Grape wine only	0.5	0.5	0.4	7.1	7.2	7.8
Mixed	30.5	34.0	34.5	19.6	22.0	20.5
Mean intake, g/special occasion	147.4	144.5	147.6	55.1	53.3	55.2
Drinking patterns, %						
HED on a typical drinking day*	37.2	38.6	38.1	26.5	28.4	28.2
HED on the last drinking day*	29.8	30.3	31.0	18.2	15.5	15.0
HED on special occasions*	83.6	83.2	84.5	57.1	56.4	57.1
Problem drinking†	23.9	26.7	26.0	9.8	10.6	13.8
Drinking outside meals	14.1	16.1	15.9	13.8	13.3	13.5
Flushing response after drinking, %	17.9	18.4	19.7	23.6	23.1	23.3
Mean duration of drinking, years	22.5	21.9	21.8	14.9	15.1	14.8
Mean age started drinking, years	28.7	29.0	28.8	37.7	37.6	37.5
Self-reported change in consumption compared with some years ago, %						
Increased	6.1	7.1	7.1	7.3	8.3	8.4
Decreased	31.3	34.3	33.9	16.5	19.0	17.3
Same	62.6	58.6	59.0	76.2	72.7	74.3

HED, heavy episodic drinking.

Drinking characteristics are based on information collected at baseline.

*HED is defined as drinking >60g of pure alcohol in one session for men and >40g for women.

†Reporting one or more of the following indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

E. Additional results on alcohol drinking patterns and trends

Table E 1. Baseline drinking characteristics of female current regular drinkers by level of alcohol drinking

		Alcohol consumption per week		
	All current regular	<70g/week	70-139g/week	140+g/week
Number of participants	6248	3226	1587	1435
Mean alcohol consumption				
Typical drinking week, g/week (SD)	115.6 (127.4)	39.0 (19.1)	109.3 (23.8)	295.1 (138.9)
Last drinking day, g/session (SD)	22.7 (20.6)	14.9 (15.7)	24.6 (18.8)	38.5 (24.9)
Special occasions, g/occasion (SD)	55.1 (52.2)	36.6 (40.8)	58.5 (51.7)	92.8 (60.8)
Daily drinkers, %	45.2	22.3	60.0	70.3
HED, %				
Typical drinking day	26.5	9.7	9.8	79.9
Last drinking day	18.2	9.4	13.7	45.6
Special occasions	57.1	39.2	60.1	91.7
Drinking spirits, %				
Typical drinking day	61.8	56.4	66.4	81.9
Last drinking day	51.4	47.8	55.4	62.3
Special occasions	59.1	54.8	63.0	74.8
Drinking outside meals, %	13.8	13.5	14.7	11.8
Flushing response after drinking, %	23.6	26.7	22.8	19.8
Mean duration of regular drinking, year (SD)	14.9 (12.9)	13.1 (11.7)	15.6 (12.6)	18.5 (13.0)
Mean age started regular drinking, year (SD)	37.7 (13.6)	39.6 (13.6)	37.2 (13.1)	34.1 (12.0)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between level of alcohol consumption and the above drinking parameters: $p<0.01$ for all variables except mealtime drinking habits ($p=0.19$).

Table E 2. Baseline drinking characteristics of female current regular drinkers by frequency of drinking

	All current regular	1-5 days/week	6-7 days/week
Number of participants	6248	3421	2827
Mean alcohol consumption			
Typical drinking week, g/week (SD)	115.6 (127.4)	65.5 (61.1)	176.3 (150.1)
Last drinking day, g/session (SD)	22.7 (20.6)	22.2 (22.1)	23.4 (18.7)
Special occasion, g/occasion (SD)	55.1 (52.2)	53.5 (53.0)	57.0 (51.0)
HED, %			
Typical drinking day	26.5	20.2	27.1
Last drinking day	18.2	16.0	17.1
Special occasions	57.1	53.1	57.9
Drinking spirits, %			
Typical drinking day	61.8	59.3	65.1
Last drinking day	51.4	49.7	54.5
Special occasions	59.1	56.9	62.2
Drinking outside meals, %	13.8	12.3	15.5
Flushing response after drinking, %	23.6	23.8	23.5
Mean duration of regular drinking, year (SD)	14.9 (12.9)	14.9 (11.6)	15.0 (13.8)
Mean age started regular drinking, year (SD)	37.7 (13.6)	37.6 (12.3)	37.9 (14.9)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between drinking frequency and the above drinking parameters: $p<0.01$ for most variables, except for flushing response, HED on the last drinking day, duration of regular drinking, and age started regular drinking (all $p>0.05$).

Table E 3. Baseline drinking characteristics of female current regular drinkers by heavy episodic drinking status

		Typical drinking day		Last drinking day	
	All current regular	≤40g/day	>40g/day (i.e., HED)	≤40 g/day	>40g/day (i.e., HED)
Number of participants	6248	4593	1655	5108	1140
Mean alcohol consumption					
Typical drinking week, g/week (SD)	115.6 (127.4)	68.3 (52.2)	247.0 (165.0)	92.7 (99.7)	218.4 (182.3)
Last drinking day, g/session (SD)	22.7 (20.6)	16.5 (13.0)	40.0 (26.4)	15.4 (7.9)	55.5 (25.7)
Special occasions, g/occasion (SD)	55.1 (52.2)	40.8 (40.0)	94.8 (59.6)	45.3 (42.4)	98.8 (62.3)
Daily drinkers, %	45.2	42.2	51.7	44.8	51.6
HED, %					
Typical drinking day	26.5	--	--	15.5	78.3
Last drinking day	18.2	5.8	54.9	--	--
Special occasions	57.1	45.2	97.3	50.2	97.9
Drinking spirits, %					
Typical drinking day	61.8	59.2	77.8	60.1	73.4
Last drinking day	51.4	50.7	58.3	50.6	56.6
Special occasions	59.1	57.7	69.8	57.8	69.4
Drinking outside meals, %	13.8	13.6	12.1	13.8	12.9
Flushing response after drinking, %	23.6	26.0	17.6	25.0	16.1
Mean duration of regular drinking, year (SD)	14.9 (12.9)	13.9 (12.7)	18.0 (12.5)	14.4 (13.0)	17.4 (11.9)
Mean age started regular drinking, year (SD)	37.7 (13.6)	38.9 (13.8)	34.5 (10.7)	38.3 (13.9)	35.0 (10.1)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between HED on a typical drinking day and the above drinking parameters: $p<0.02$ for all variables except mealtime drinking habits ($p=0.94$). Associations between HED on the last drinking day and the above drinking parameters: $p<0.01$ for all variables, except drinking daily and mealtime drinking habits ($p>0.05$).

Table E 4. Baseline drinking characteristics of female current regular drinkers by mealtime drinking habits

	All current regular	Drinking with meals	Drinking without meals
Number of participants	6248	5387	861
Mean alcohol consumption			
Typical drinking week, g/week (SD)	115.6 (127.4)	115.9 (132.4)	113.8 (81.2)
Last drinking day, g/session (SD)	22.7 (20.6)	22.9 (20.7)	21.9 (20.2)
Special occasions, g/occasion (SD)	55.1 (52.2)	56.1 (52.2)	48.5 (51.3)
Daily drinkers, %	45.2	44.1	43.9
HED, %			
Typical drinking day	26.5	26.6	22.6
Last drinking day	18.2	18.5	16.1
Special occasions	57.1	58.2	48.4
Drinking spirits, %			
Typical drinking day	61.8	61.6	62.3
Last drinking day	51.4	50.8	56.6
Special occasions	59.1	58.6	61.4
Flushing response after drinking, %	23.6	23.3	27.0
Mean duration of regular drinking, year (SD)	14.9 (12.9)	15.3 (12.9)	12.7 (11.4)
Mean age started regular drinking, year (SD)	37.7 (13.6)	37.3 (13.2)	40.0 (14.2)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between mealtime drinking habits and the above drinking parameters: $p<0.05$ for drinking daily, HED on special occasions, spirits drinking on the last drinking day, mean consumption on special occasions, duration of regular drinking, and age started regular drinking.

Table E 5. Baseline drinking characteristics of female current regular drinkers by beverage type

	All current regular	Beer	Rice wine	Grape wine	Strong spirits	Weak spirits	Mixed
Typical drinking week							
Number of participants	6248	1388	390	611	3067	792	--
Daily drinkers, %	45.2	22.3	48.8	38.9	49.3	30.6	--
HED, %							
Typical drinking day	26.5	11.5	2.5	0.4	39.3	13.1	--
Last drinking day	18.2	16.4	2.7	5.1	24.5	15.1	--
Special occasions	57.1	54.9	22.6	17.4	66.6	43.3	--
Drinking outside meals, %	13.8	7.4	25.9	13.7	15.2	10.3	--
Flushing response after drinking, %	23.6	26.7	18.0	26.2	23.2	28.7	--
Mean duration of regular drinking, year (SD)	14.9 (12.9)	16.0 (8.5)	16.8 (14.6)	9.3 (9.4)	15.2 (13.5)	15.4 (12.7)	--
Mean age started regular drinking, year (SD)	37.7 (13.6)	36.1 (10.0)	36.2 (15.0)	43.4 (13.5)	37.6 (13.5)	37.4 (13.8)	--
Last drinking day							
Number of participants	6248	1412	367	615	2974	713	167
Daily drinkers, %	45.2	36.9	42.6	34.6	50.1	47.9	45.3
HED, %							
Typical drinking day	26.5	23.4	3.8	11.1	33.8	15.4	39.3
Last drinking day	18.2	13.3	3.0	1.7	25.5	11.6	49.6
Special occasions	57.1	58.8	21.2	27.9	67.6	59.4	74.3
Drinking outside meals, %	13.8	6.9	16.0	14.5	15.1	10.0	19.2
Flushing response after drinking, %	23.6	24.2	18.4	28.5	25.1	18.5	21.3
Mean duration of regular drinking, year (SD)	14.9 (12.9)	16.5 (9.2)	15.5 (14.6)	10.0 (9.8)	15.1 (13.6)	14.7 (12.6)	17.2 (10.8)
Mean age started regular drinking, year (SD)	37.7 (13.6)	35.8 (10.3)	37.6 (15.3)	42.7 (13.8)	37.7 (13.5)	38.2 (13.8)	35.0 (10.9)

SD, standard deviation; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Associations between beverage type and the above drinking parameters: $p<0.01$ for all variables except flushing response.

Table E 6. Prevalence of alcohol consumption of the subset of participants involved in all three surveys, by sex

	Men			Women		
	Baseline	1st Resurvey	2nd Resurvey	Baseline	1st Resurvey	2nd Resurvey
Number of participants	5630	5630	5630	9233	9233	9233
Drinking categories, %						
Abstainer drinkers	19.1	21.8	35.3	63.5	66.6	82.4
Ex-regular drinkers	3.3	3.7	6.1	0.6	0.4	0.8
Reduced-intake drinkers	4.6	3.9	3.7	0.4	0.4	0.5
Occasional drinkers	39.2	40.6	26.1	33.3	30.8	14.3
Current regular drinkers	33.8	30.0	28.9	2.2	1.9	2.0

Table E 7. Patterns of alcohol consumption of the subset of participants involved in all three surveys, by sex

	Men			Women		
	Baseline	1st Resurvey	2nd Resurvey	Baseline	1st Resurvey	2nd Resurvey
Number of participants	1900	1119	1624	206	172	182
Number of drinking days per week, %						
1-2	22.0	17.6	15.0	26.2	26.1	23.6
3-5	18.1	16.0	13.7	21.4	14.0	14.3
6-7	59.9	66.5	71.3	52.4	60.0	62.1
Types consumed on typical day, %						
Strong spirits only	45.9	48.6	36.6	62.1	59.9	41.8
Weak spirits only	24.2	17.9	14.0	10.7	7.0	9.3
Beer only	16.6	20.8	7.8	13.6	20.4	8.2
Rice wine only	12.6	12.0	8.7	5.8	3.5	11.5
Wine only	0.7	0.7	1.8	7.8	9.3	11.5
Mixed	--	--	31.1	--	--	17.6
Mean intake, g/typical week	288.4	284.6	353.8	139.8	144.5	135.2
Consumption level in g/week, %						
<140	36.6	36.2	26.1	70.9	69.2	71.4
140-279	25.7	26.9	28.6	18.9	22.1	17.6
280-419	17.6	17.5	19.0	6.8	4.7	7.1
420+	20.1	19.4	26.3	3.4	4.1	3.9
Types consumed on last drinking day, %						
Strong spirits only	40.2	39.1	41.8	59.7	58.7	45.1
Weak spirits only	21.3	13.2	14.5	6.8	5.8	11.5
Beer only	19.4	30.1	14.1	20.4	23.3	8.8
Rice wine only	9.4	8.6	9.4	4.9	2.9	12.1
Wine only	1.0	1.1	2.9	6.8	8.7	11.5
Mixed	8.7	8.0	17.4	1.5	0.6	11.0
Mean intake, g/last drinking day	51.1	48.1	56.0	21.9	22.3	26.0
Types consumed on special occasions, %						
Strong spirits only	34.9	35.8	35.1	51.9	49.4	39.0
Weak spirits only	15.8	12.3	13.2	5.8	5.8	9.3
Beer only	9.6	14.8	7.9	10.7	18.0	9.3
Rice wine only	6.1	7.5	7.3	5.3	3.5	9.9
Wine only	0.3	0.6	1.7	6.3	7.6	13.2
Mixed	33.3	28.9	34.9	19.9	15.7	19.2
Mean intake, g/special occasion	145.2	140.8	119.5	55.8	48.6	42.1
Drinking patterns, %						
HED on a typical drinking day*	38.9	36.4	46.4	30.6	30.8	26.4
HED on the last drinking day*	31.2	28.2	35.0	14.1	16.3	18.7
HED on special occasions*	83.9	82.4	73.3	59.2	51.7	44.5
Problem drinking†	27.4	19.9	24.6	12.6	8.8	9.3
Drinking outside meals	16.1	12.0	19.1	11.6	6.4	23.1
Flushing response after drinking, %	19.0	15.3	15.3	23.8	23.3	13.7
Mean age started drinking, years	28.9	28.5	29.7	36.7	36.8	39.0
Self-reported change in consumption compared with some years ago, %						
Increased	7.5	3.5	4.9	9.7	6.4	4.4
Decreased	33.8	26.3	38.0	20.9	14.5	17.0
Same	58.7	70.2	57.1	69.4	79.1	78.6

HED, heavy episodic drinking.

*HED is defined as drinking >60g of pure alcohol in one session for men and >40g for women.

†Reporting one or more of the following indicators in the past month: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table E 8. Prevalence and mean levels of alcohol consumption among women at baseline (2004-2008) and the second resurvey (2013-2014), by socio-demographic characteristics

	Baseline							2nd resurvey						
						Current regular							Current regular	
	N	Abstainer %	Ex-regular %	Reduced -intake %	Occasional %	%	Mean consumption* (SE)	N	Abstainer %	Ex-regular %	Reduced -intake %	Occasional %	%	Mean consumption* (SE)
Birth cohort														
<1940	31109	72.9	1.1	0.6	22.7	2.7	16 (3.9)	1320	87.9	1.6	0.4	7.2	3.0	18 (15.5)
1940-1949	62246	69.1	0.8	0.6	27.4	2.2	17 (2.7)	3431	86.5	1.3	0.5	9.9	1.8	26 (16.4)
1950-1959	97344	63.0	0.4	0.5	33.9	2.2	23 (2.8)	5303	83.0	0.7	0.7	13.8	1.9	22 (12.1)
1960-1969	94772	58.0	0.1	0.3	39.8	1.8	27 (3.0)	4702	76.1	0.4	0.4	21.5	1.7	24 (15.6)
1970s	17161	54.3	0.0	0.1	43.0	2.6	25 (9.3)	671	71.3	0.1	0.5	26.1	2.1	35 (7.8)
Area														
Rural	167802	65.4	0.7	0.6	31.3	2.1	23 (2.4)	8802	85.5	1.0	0.4	11.1	2.0	25 (10.0)
Urban	134830	60.9	0.2	0.3	36.4	2.1	21 (1.5)	6625	76.7	0.5	0.7	20.3	1.8	24 (11.5)
Highest education														
Primary or below	171649	68.8	0.5	0.5	28.4	1.9	25 (4.5)	9016	84.1	0.7	0.5	13.0	1.7	22 (7.8)
Middle or above	130983	59.7	0.4	0.5	37.4	2.1	22 (3.4)	6411	79.5	0.5	0.7	17.3	2.0	21 (11.6)
Household income (yuan/year)														
<20,000	179532	65.9	0.4	0.4	31.4	1.9	22 (2.3)	3390	84.3	0.5	1.0	12.4	1.8	19 (10.8)
20,000+	123100	59.7	0.4	0.5	37.2	2.2	23 (4.9)	12037	81.4	0.8	0.4	15.5	1.8	22 (8.4)

SE, standard error.

Prevalences and means are adjusted for age and study area as appropriate.

*Mean consumption of pure alcohol in grams per session among current regular drinkers, based on alcohol intake data reported on the last time the participants drank.

Table E 9. Changes in drinking status among men from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and baseline health factors (based on baseline information)

		Baseline non-drinkers[†]		Baseline drinkers[‡]			
Characteristics[*]	N	Stable non-drinkers %	Starters %	Stable drinkers %	Stoppers %	Decreased-intake drinkers %	Increased-intake drinkers %
All men	9569	18.3	4.2	40.0	22.9	8.2	6.3
Socio-demographic characteristics							
Birth cohort							
<1940	1106	33.0	4.3	24.0	30.6	3.9	4.3
1940-1949	2311	23.1	4.3	32.4	28.3	6.9	5.2
1950-1959	3149	16.3	3.8	43.7	22.1	8.2	6.0
1960-1969	2632	11.3	4.6	47.3	18.1	10.7	8.0
1970s	371	8.3	3.7	50.3	16.0	11.7	10.0
Area							
Rural	5433	21.9	4.3	36.3	24.5	6.9	6.1
Urban	4136	13.6	4.1	44.8	20.9	10.0	6.6
Highest education level							
Primary or below	4121	20.4	4.0	38.9	23.7	6.8	6.3
Middle or above	5448	16.6	4.0	42.1	22.6	8.4	6.3
Income level (yuan/year)							
<20,000	5639	19.1	4.5	39.2	22.9	7.4	6.8
20,000+	3930	17.0	3.2	43.2	19.5	10.6	6.5
Health-related factors							
Self-reported health[§]							
Good	4898	15.9	3.3	42.8	22.4	9.2	6.3
Poor	4671	21.1	5.0	36.6	23.5	7.5	6.3
Prior chronic disease[¶]							
No	7550	17.0	4.0	41.2	22.7	8.8	6.3
Yes	2019	23.0	5.6	36.1	23.1	6.2	6.0
Risk factor index[#]							
0	3911	17.7	4.5	39.3	23.6	8.5	6.3
1	3619	17.7	3.4	42.4	21.9	8.7	6.0
2	285	16.3	4.0	36.2	25.3	6.1	11.9
3+	1754	20.1	5.1	38.3	22.2	7.7	6.5

Prevalences at subgroup levels are adjusted for age group and study area as appropriate.

[*]Characteristics are based on the characteristics of the participants collected at the baseline.

[†]Among baseline non-drinkers, associations between change in drinking status and factors: $p<0.001$ for significant trend across birth cohorts and heterogeneity across study area.

[‡]Among baseline drinkers, associations between change in drinking status and factors: $p<0.02$ across all variables except education.

[§]Poor self-reported health status included those who reported fair or poor self-rated health; good self-reported health status included those who reported good or excellent self-rated health.

[¶]Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

[#]Derived by summing the individual scores of each of the four risk factors (0 if no, 1 if yes): regular smoking, lack of regular fruit intake, hypertension, low physical activity.

Table E 10. Changes in drinking status among women from baseline (2004-2008) to the second resurvey (2013-2014), by socio-demographic characteristics and health factors

		Non-drinkers at baseline[†]		Drinkers at baseline[‡]			
Characteristics[*]	N	Stable non-drinkers %	Starters %	Stable drinkers %	Stoppers %	Decreased-intake drinkers %	Increased-intake drinkers %
All women	15427	59.9	5.3	10.4	22.9	0.8	0.8
Socio-demographic characteristics							
Birth cohort							
<1950	4751	67.6	3.8	6.4	20.7	0.7	0.8
1950-1959	5303	60.1	5.0	9.7	23.6	0.9	0.7
≥1960	5373	52.4	7.1	15.0	23.9	0.8	0.9
Area							
Rural	8802	61.0	4.2	7.8	25.5	0.8	0.7
Urban	6625	58.2	6.9	14.1	19.0	0.9	1.0
Highest education level							
Primary or below	9054	64.6	4.6	7.2	21.9	1.1	0.5
Middle or above	6373	54.2	6.2	12.2	25.5	0.9	1.0
Income level (yuan/year)							
<20,000	9974	61.3	5.6	9.5	22.2	0.7	0.7
20,000+	5453	53.9	5.2	12.1	26.9	1.0	1.1
Health-related factors							
Self-reported health[§]							
Poor	8981	61.3	4.9	9.8	22.5	0.8	0.7
Good	6446	57.1	5.9	11.5	23.5	0.9	1.0
Prior chronic disease[¶]							
No	9169	59.0	5.5	10.7	23.2	0.8	0.8
Yes	6258	61.1	5.0	9.6	22.5	1.0	0.9

Prevalences at subgroup levels are adjusted for age and study area as appropriate.

[*]Except for age and study area, characteristics are based on the characteristics of the participants collected at the second resurvey.

[†]Among baseline non-drinkers, associations between change in drinking status and factors: $p<0.001$ for trend across birth cohorts and $p<0.05$ for heterogeneity across all other variables.

[‡]Among baseline drinkers, associations between change in drinking status and factors: $p<0.01$ across birth cohorts, study areas, and income levels.

[§]Poor self-reported health status included those who reported fair or poor self-rated health; good self-reported health status included those who reported good or excellent self-rated health.

[¶]Diagnosed with one or more of: coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease.

Table E 11. Estimated regression dilution ratios of alcohol intake among the subset of participants involved in all three surveys, by selected population subgroups

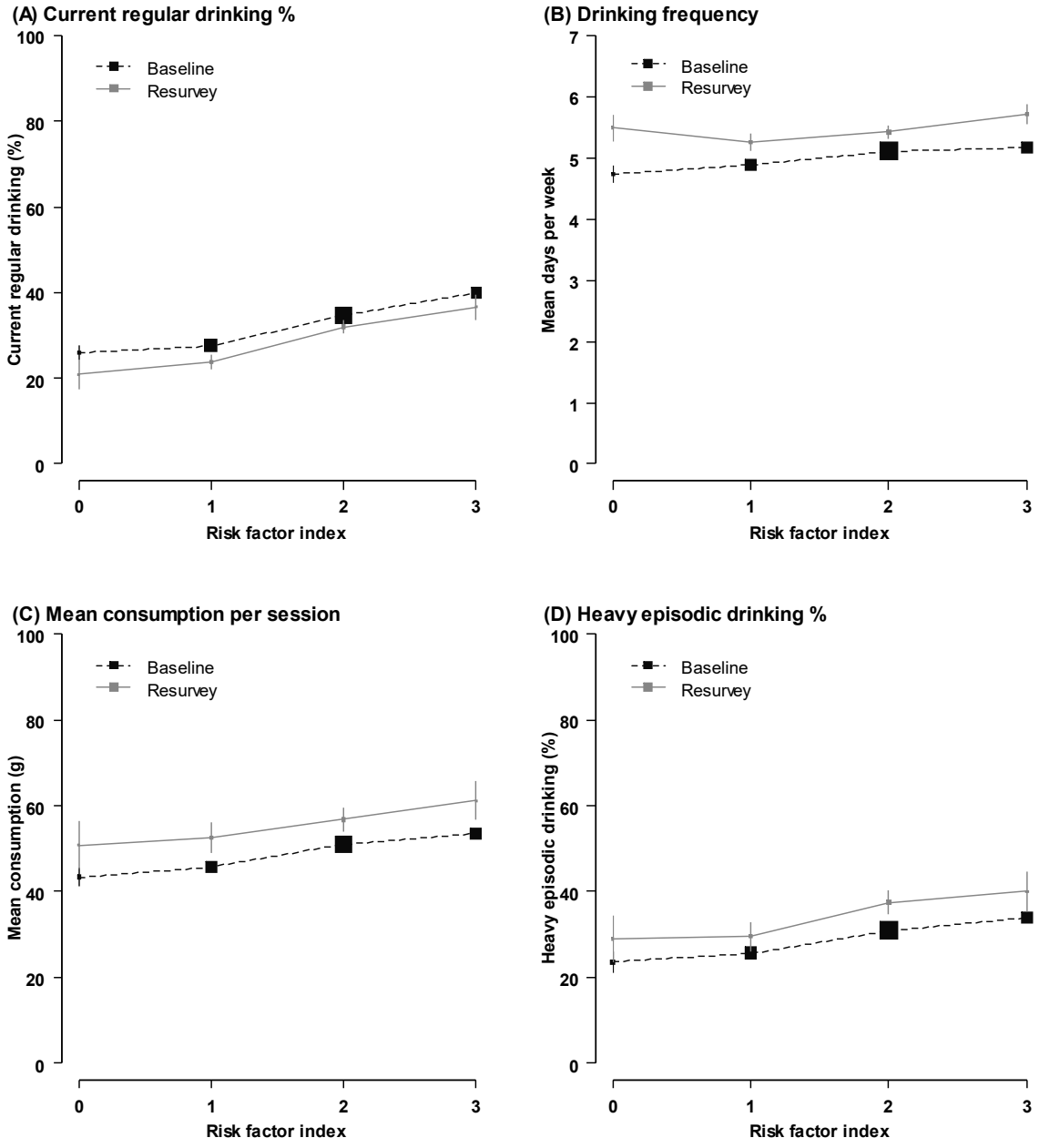
			Mean intake, g/week		Estimated RDRs[†]			
	Baseline-defined groups	N	Baseline	Usual[*]	MMP[‡]	Pearson[§]	Spearman[§]	Rosner[¶]
Baseline age group (years)								
<55	<140g/week	459	77	116				
	140-279g/week	302	221	229				
	280-419g/week	233	367	310				
	420+g/week	240	693	455				
	Current regular	1234	--	--	0.55	0.50	0.55	0.51
55-65	<140g/week	168	82	93				
	140-279g/week	129	225	198				
	280-419g/week	70	368	288				
	420+g/week	103	677	435				
	Current regular	470	--	--	0.58	0.58	0.59	0.64
65+	<140g/week	58	75	92				
	140-279g/week	50	241	168				
	280-419g/week	28	376	269				
	420+g/week	26	679	338				
	Current regular	162	--	--	0.41	0.56	0.49	0.67
Area								
Rural	<140g/week	317	78	104				
	140-279g/week	299	223	215				
	280-419g/week	201	371	314				
	420+g/week	277	684	441				
	Current regular	1094	--	--	0.55	0.51	0.55	0.53
Urban	<140g/week	377	77	110				
	140-279g/week	187	226	213				
	280-419g/week	134	362	282				
	420+g/week	103	691	432				
	Current regular	801	--	--	0.52	0.52	0.55	0.55
Highest education								
Primary school or below	<140g/week	212	81	111				
	140-279g/week	239	224	205				
	280-419g/week	154	362	302				
	420+g/week	211	681	429				
	Current regular	816	--	--	0.53	0.49	0.52	0.49
Middle school	<140g/week	222	79	114				
	140-279g/week	142	225	233				
	280-419g/week	113	376	307				
	420+g/week	121	689	453				
	Current regular	598	--	--	0.56	0.52	0.55	0.56
High school or above	<140g/week	260	74	99				
	140-279g/week	105	223	209				
	280-419g/week	68	366	289				
	420+g/week	48	700	439				
	Current regular	481	--	--	0.54	0.55	0.60	0.59

	Baseline-defined groups	N	Mean intake, g/week		Estimated RDRs[†]			
			Baseline	Usual[*]	MMP[‡]	Pearson[§]	Spearman[§]	Rosner[¶]
Household income (yuan/year)								
<10,000	<140g/week	133	82	91				
	140-279g/week	120	230	198				
	280-419g/week	94	377	339				
	420+g/week	130	679	449				
	Current regular	477	--	--	0.60	0.57	0.59	0.57
10,000-19,999	<140g/week	193	75	111				
	140-279g/week	159	226	217				
	280-419g/week	92	375	272				
	420+g/week	108	671	386				
	Current regular	552	--	--	0.46	0.47	0.51	0.55
20,000+	<140g/week	368	78	112				
	140-279g/week	207	219	222				
	280-419g/week	149	357	295				
	420+g/week	142	704	467				
	Current regular	866	--	--	0.57	0.52	0.56	0.52
Smoking status								
Never regular smokers	<140g/week	163	70	72				
	140-279g/week	64	223	166				
	280-419g/week	46	376	230				
	420+g/week	40	668	426				
	Current regular	313	--	--	0.59	0.61	0.56	0.68
Ever regular smokers	<140g/week	531	80	118				
	140-279g/week	422	224	222				
	280-419g/week	289	366	312				
	420+g/week	340	688	440				
	Current regular	1582	--	--	0.53	0.50	0.54	0.52
Physical activity								
Low	<140g/week	334	77	92				
	140-279g/week	232	231	211				
	280-419g/week	137	366	314				
	420+g/week	161	681	413				
	Current regular	864	--	--	0.53	0.52	0.57	0.55
Moderate	<140g/week	142	82	117				
	140-279g/week	91	216	226				
	280-419g/week	77	375	301				
	420+g/week	84	670	494				
	Current regular	394	--	--	0.64	0.57	0.60	0.56
High	<140g/week	218	76	125				
	140-279g/week	163	218	213				
	280-419g/week	121	365	287				
	420+g/week	135	703	433				
	Current regular	637	--	--	0.49	0.49	0.49	0.54

	Baseline-defined groups	N	Mean intake, g/week		Estimated RDRs[†]			
			Baseline	Usual[*]	MMP[‡]	Pearson[§]	Spearman[§]	Rosner[¶]
Body mass index (kg/m^2)								
<23	<140g/week	261	79	106				
	140-279g/week	227	226	219				
	280-419g/week	164	370	288				
	420+g/week	174	678	437				
	Current regular	826	--	--	0.55	0.56	0.55	0.61
23-24.9	<140g/week	165	76	119				
	140-279g/week	111	221	225				
	280-419g/week	79	358	325				
	420+g/week	93	699	419				
	Current regular	448	--	--	0.48	0.50	0.57	0.59
25+	<140g/week	268	78	103				
	140-279g/week	148	224	200				
	280-419g/week	92	371	304				
	420+g/week	113	687	456				
	Current regular	621	--	--	0.58	0.49	0.53	0.46
Fresh fruit intake								
Regular	<140g/week	190	74	88				
	140-279g/week	105	230	214				
	280-419g/week	58	362	305				
	420+g/week	50	683	455				
	Current regular	403	--	--	0.60	0.57	0.61	0.56
Non-regular	<140g/week	504	79	115				
	140-279g/week	381	222	215				
	280-419g/week	277	369	300				
	420+g/week	330	687	436				
	Current regular	1492	--	--	0.53	0.50	0.53	0.54
Flushing response								
No	<140g/week	511	79	119				
	140-279g/week	402	223	217				
	280-419g/week	286	368	300				
	420+g/week	336	693	447				
	Current regular	1535	--	--	0.53	0.51	0.54	0.54
Yes	<140g/week	183	75	75				
	140-279g/week	84	226	203				
	280-419g/week	49	367	307				
	420+g/week	44	630	369				
	Current regular	360	--	--	0.53	0.55	0.57	0.55

RDR, regression dilution ratio; MMP, MacMahon-Peto.
Participants with prior cancer were excluded.
[*]Usual consumption is the average of the consumption levels at the 1st and 2nd resurveys.
[†]RDR is estimated among baseline current regular drinkers using their baseline alcohol intake and usual alcohol intake.
[‡]MacMahon-Peto method estimates RDR with the ratio of the range (i.e., difference between the means of the top vs. bottom baseline-defined groups) of usual alcohol intake to the range of baseline alcohol intake.
[§]Self-correlation method estimates RDR with the correlation coefficient between baseline alcohol intake and usual alcohol intake by Pearson or Spearman correlation.
[¶]Rosner's regression method estimates RDR by the slope of the regression line (i.e., regression coefficient) between baseline alcohol intake and usual alcohol intake.

Figure E 1. Alcohol drinking characteristics in male current regular drinkers at baseline (2004-2008) and the second resurvey (2013-2014), by health-related risk factor index (hypertension removed)



Percentages are adjusted for age and study area. Size of boxes is proportional to the sample size of each risk factor index group. Error bars are 95% confidence intervals. Mean consumption per session (g/session) and heavy episodic drinking status are based on alcohol intake data reported on the last time the participants drank. Heavy episodic drinking is defined as drinking >60g of pure alcohol in one session. Risk factor index is derived by summing the individual scores of each of the three lifestyle risk factors (0 if no, 1 if yes): regular smoking, lack of regular fruit intake, low physical activity. All men at baseline (n=210,259) and the second resurvey (n=9,569) were included in (A). All male current regular drinkers at baseline (n=69,904) and the second resurvey (n=2,732) were included in (B)-(D).

F. Additional results on problem drinking, mental health and mortality risk

Table F 1. Details of main analytic models

Exposure	Outcome	Analytic model and adjustment	Study participants
Experience of stressful life events [reference group: no experience of the specified stressful life event]	Problem drinking, i.e., reporting at least 1 problem drinking indicator(s)	Logistic regression adjusted for age (in 5-year groups), study area (10 study areas), highest education (4 groups: no formal education, primary school, middle or high school, technical school/college or above), household income (4 groups: <10,000, 10,000-19,999, 20,000-34,999, 35,000+ yuan/year), and smoking (4 groups: never, occasional, ex-regular, current regular smokers)	Current regular drinkers
Problem drinking categories [reference group: low-risk drinkers]	Measures of poor wellbeing and mental health: • Poor self-rated heath • Life dissatisfaction • Sleep problems • Depression symptoms • MDE • Anxiety symptom • GAD • Panic attacks • Phobia	Logistic regression adjusted for age (in 5-year groups), study area (10 study areas), highest education (4 groups: no formal education, primary school, middle or high school, technical school/college or above), household income (4 groups: <10,000, 10,000-19,999, 20,000-34,999, 35,000+ yuan/year), smoking (4 groups: never, occasional, ex-regular, current regular smokers), marital status (4 groups: married, widowed, separated/divorced, never married), prior chronic diseases (yes vs.no), and BMI (4 groups: <22, 22-24.9, 25-26.9, 27+ kg/m^2)	Current regular drinkers
Problem drinking categories [reference group: low-risk drinkers]	Prospective outcomes: • All-cause mortality • Any hospitalisation • Fatal or non-fatal incidents due to external causes (ICD-10: V01-Y98) • Transport accidents (ICD-10: V01-V99) • International self-harm (ICD-10: X60-X84)	Cox regression, stratified by age-at-risk (5-year intervals) and 10 study areas, and adjusted for highest education (4 groups: no formal education, primary school, middle or high school, technical school/college or above), household income (4 groups: <10,000, 10,000-19,999, 20,000-34,999, 35,000+ yuan/year), smoking (4 groups: never, occasional, ex-regular, current regular smokers), fresh fruit intake (regular vs. non-regular), physical activity (3 groups: <17.8, 17.8-28.7, 28.8+ MET-h/d), and BMI (4 groups: <22, 22-24.9, 25-26.9, 27+ kg/m^2)	Current regular drinkers without prior chronic disease (coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, cirrhosis/chronic hepatitis, tuberculosis, emphysema/bronchitis, peptic ulcer, kidney disease, gallstone/gallbladder disease, rheumatoid arthritis)

MDE, major depressive episode; GAD, general anxiety disorder; ICD-10; international classification of diseases, 10th revision; MET-h/d, metabolic equivalent of task per hour per day; BMI, body mass index.

Table F 2. Adjusted odds ratios (ORs) for poor wellbeing and mental health associated with per increase in the number of problem drinking indicators, in male problem drinkers

	Cases N	Non-cases N	Adjusted OR (95% CI)	*p*-value
Poor self-reported health	1313	15379	1.28 (1.17-1.40)	*<0.0001*
Life dissatisfaction	748	15944	1.22 (1.08-1.38)	*0.0011*
Sleep problems[*]	2965	13727	1.08 (1.01-1.16)	*0.0333*
Depression symptoms[†]	571	16121	1.40 (1.24-1.58)	*<0.0001*
Major depressive episode[‡]	91	16601	1.45 (1.11-1.91)	*0.0073*
Anxiety symptom	111	16581	1.39 (1.07-1.80)	*0.0126*
General anxiety disorder[§]	49	16643	1.24 (0.82-1.89)	*0.3077*
Panic attacks	166	16526	1.53 (1.25-1.88)	*<0.0001*
Phobia	86	16606	0.99 (0.67-1.45)	*0.9434*

OR, odds ratio; CI, confidence interval; CIDI-SF, composite international diagnostic interview - short form.
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index.
[*]Reporting one or more of the following for ≥3 days each week in the past month: delayed or fitful sleep; waking up too early; needing medicine to help sleep; having difficulty staying alert during daytime.
[†]Reporting one or more of the following for ≥2 weeks in the past 12 months: feeling sad or depressed; loss of interest; loss of appetite; feeling worthless.
[‡]Assessed by the CIDI-SF (A).
[§]Assessed by the CIDI-SF (B).

Table F 3. Cross-sectional associations of problem drinking with sleep problems, in male current regular drinkers

	Cases N	Non-cases N	Adjusted OR (95% CI)	p_{het}*
Delayed/fitful sleep				
Low-risk drinkers	2082	23876	1.00 (0.95-1.05)	
High-risk drinkers	2221	25033	1.04 (1.00-1.09)	
1 problem drinking indicator	1469	11802	1.28 (1.21-1.35)	
2+ problem drinking indicators	426	2995	1.39 (1.25-1.54)	*<0.0001*
Early-morning awakening				
Low-risk drinkers	1925	24033	1.00 (0.95-1.05)	
High-risk drinkers	2221	25033	1.14 (1.09-1.20)	
1 problem drinking indicator	1517	11754	1.41 (1.33-1.49)	
2+ problem drinking indicators	439	2982	1.60 (1.45-1.78)	*<0.0001*
Sleep medication				
Low-risk drinkers	161	25797	1.00 (0.85-1.18)	
High-risk drinkers	124	27130	0.89 (0.75-1.07)	
1 problem drinking indicator	92	13179	1.38 (1.12-1.71)	
2+ problem drinking indicators	33	3388	1.87 (1.32-2.66)	*0.0002*
Difficulty in staying alert during daytime				
Low-risk drinkers	303	25655	1.00 (0.89-1.13)	
High-risk drinkers	357	26897	1.07 (0.96-1.19)	
1 problem drinking indicator	246	13025	1.56 (1.37-1.78)	
2+ problem drinking indicators	95	3326	2.02 (1.64-2.49)	*<0.0001*

OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.
**P* for heterogeneity across the four problem drinking categories.

Table F 4. Adjusted hazard ratios (HRs) for prospective outcomes associated with per increase in the number of problem drinking indicators, in male problem drinkers

	Cases N	Non-cases N	Adjusted HR (95% CI)	*p*-value
All-cause mortality	1401	12248	1.31 (1.20-1.43)	*<0.0001*
Any hospitalisation	8017	5632	1.06 (1.01-1.10)	*0.0087*
External causes (ICD-10:V01-Y98)*	153	13496	1.43 (1.15-1.78)	*0.0013*
Intentional self-harm (ICD-10: X60-X84)*	19	13630	1.04 (0.46-2.36)	*0.9201*
Transport accident (ICD-10: V01-V99)*	64	13585	1.27 (0.88-1.82)	*0.2058*

HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision.
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index.
Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses.
*Deaths and hospitalisations combined.

Table F 5. Cross-sectional associations of stressful life events with problem drinking, in male current regular drinkers - in sequentially adjusted models

			Age group & study area		+Education & income		Main model (+smoking)		+Prior chronic disease		+Prior psychiatric disorder	
	Total regular drinkers, N	Problem drinkers*, N (%)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Family-related events												
Divorce or separation												
No	69701	16639 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	203	53 (26.1%)	1.45 (1.04-2.01)	*0.0274*	1.38 (0.99-1.92)	*0.0558*	1.32 (0.95-1.83)	*0.1027*	1.31 (0.94-1.83)	*0.1059*	1.31 (0.94-1.82)	*0.1088*
Family conflict												
No	69417	16540 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	487	152 (31.2%)	1.52 (1.24-1.87)	*<0.0001*	1.51 (1.23-1.86)	*<0.0001*	1.50 (1.22-1.84)	*0.0001*	1.49 (1.21-1.83)	*0.0001*	1.49 (1.21-1.82)	*0.0002*
Death of spouse												
No	69550	16596 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	354	96 (27.1%)	1.11 (0.87-1.42)	*0.3881*	1.07 (0.83-1.36)	*0.6033*	1.07 (0.83-1.36)	*0.6133*	1.07 (0.83-1.36)	*0.6169*	1.06 (0.83-1.36)	*0.6202*
Death or major illness of other family member												
No	66680	15871 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	3224	821 (25.5%)	1.22 (1.12-1.33)	*<0.0001*	1.20 (1.10-1.31)	*<0.0001*	1.20 (1.10-1.30)	*<0.0001*	1.19 (1.09-1.30)	*<0.0001*	1.19 (1.09-1.30)	*<0.0001*
Any family-related event												
No	65748	15606 (23.7%)	1.00		1.00		1.00		1.00		1.00	
Yes	4156	1086 (26.1%)	1.24 (1.15-1.34)	*<0.0001*	1.22 (1.13-1.32)	*<0.0001*	1.21 (1.13-1.31)	*<0.0001*	1.21 (1.12-1.31)	*<0.0001*	1.21 (1.12-1.31)	*<0.0001*
Finance-related events												
Job loss or retirement												
No	69587	16622 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	317	70 (22.1%)	1.59 (1.20-2.10)	*0.0012*	1.44 (1.08-1.90)	*0.0115*	1.45 (1.09-1.91)	*0.0102*	1.44 (1.09-1.91)	*0.0110*	1.44 (1.09-1.90)	*0.0113*
Bankruptcy												
No	69683	16608 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	221	84 (38.0%)	1.51 (1.14-2.00)	*0.0041*	1.47 (1.10-1.94)	*0.0080*	1.48 (1.11-1.96)	*0.0068*	1.47 (1.11-1.96)	*0.0075*	1.47 (1.11-1.96)	*0.0074*
Loss of income or debt												
No	69592	16577 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	312	115 (36.9%)	2.10 (1.63-2.69)	*<0.0001*	1.85 (1.44-2.37)	*<0.0001*	1.86 (1.45-2.39)	*<0.0001*	1.85 (1.44-2.38)	*<0.0001*	1.85 (1.44-2.37)	*<0.0001*
Any finance-related event												
No	69099	16441 (23.8%)	1.00		1.00		1.00		1.00		1.00	
Yes	805	251 (31.1%)	1.69 (1.44-1.99)	*<0.0001*	1.56 (1.33-1.83)	*<0.0001*	1.57 (1.34-1.84)	*<0.0001*	1.56 (1.33-1.84)	*<0.0001*	1.56 (1.33-1.83)	*<0.0001*

	Total regular drinkers, N	Problem drinkers*, N (%)	Age group & study area		+Education & income		Main model (+smoking)		+Prior chronic disease		+Prior psychiatric disorder	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Injury-related events												
Violence												
No	69796	16653 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	108	39 (36.1%)	1.68 (1.11-2.55)	*0.0143*	1.67 (1.10-2.54)	*0.0155*	1.68 (1.11-2.56)	*0.0149*	1.68 (1.10-2.55)	*0.0156*	1.67 (1.10-2.54)	*0.0161*
Major injury or traffic accident												
No	69403	16566 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	501	126 (25.1%)	1.18 (0.95-1.46)	*0.1355*	1.16 (0.94-1.44)	*0.1663*	1.15 (0.93-1.43)	*0.1929*	1.15 (0.93-1.43)	*0.2001*	1.15 (0.93-1.43)	*0.2040*
Natural disaster												
No	69848	16679 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	56	13 (23.2%)	1.09 (0.56-2.09)	*0.8057*	1.05 (0.54-2.02)	*0.8862*	1.05 (0.54-2.02)	*0.8869*	1.05 (0.54-2.03)	*0.8819*	1.05 (0.54-2.03)	*0.8803*
Any injury or disaster event												
No	69244	16516 (23.9%)	1.00		1.00		1.00		1.00		1.00	
Yes	660	176 (26.7%)	1.24 (1.03-1.49)	*0.0210*	1.23 (1.02-1.48)	*0.0297*	1.22 (1.01-1.47)	*0.0347*	1.22 (1.01-1.47)	*0.0367*	1.22 (1.01-1.46)	*0.0380*
Any major stressful life event												
No	64509	15266 (23.7%)	1.00		1.00		1.00		1.00		1.00	
Yes	5395	1426 (26.4%)	1.28 (1.20-1.37)	*<0.0001*	1.25 (1.17-1.33)	*<0.0001*	1.24 (1.16-1.33)	*<0.0001*	1.24 (1.16-1.33)	*<0.0001*	1.24 (1.16-1.33)	*<0.0001*

OR, odds ratio; CI, confidence interval.

*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table F 6. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in male current regular drinkers - in sequentially adjusted models

			Age group & study area		+Education & income		Main model (+marital status, prior chronic disease, smoking, BMI)		+Prior psychiatric disorder		+Physical activity	
	Cases N	Non-cases N	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*
Poor self-reported health												
Low-risk drinkers	1480	24478	1.00 (0.95-1.06)		1.00 (0.95-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)	
High-risk drinkers	1603	25651	0.99 (0.94-1.04)		0.97 (0.92-1.02)		0.97 (0.92-1.02)		0.97 (0.92-1.02)		0.97 (0.92-1.02)	
1 problem drinking indicator	951	12320	1.18 (1.10-1.26)		1.12 (1.04-1.20)		1.09 (1.02-1.17)		1.09 (1.02-1.17)		1.09 (1.02-1.17)	
2+ problem drinking indicators	362	3059	1.70 (1.52-1.91)	*<0.0001*	1.60 (1.43-1.79)	*<0.0001*	1.54 (1.37-1.73)	*<0.0001*	1.54 (1.37-1.73)	*<0.0001*	1.54 (1.37-1.72)	*<0.0001*
Life dissatisfaction												
Low-risk drinkers	1137	24821	1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.07)		1.00 (0.94-1.07)		1.00 (0.94-1.07)	
High-risk drinkers	1136	26118	1.04 (0.98-1.10)		1.02 (0.96-1.08)		1.00 (0.94-1.07)		1.00 (0.94-1.07)		1.00 (0.94-1.07)	
1 problem drinking indicator	555	12716	1.40 (1.28-1.53)		1.24 (1.14-1.36)		1.21 (1.11-1.33)		1.21 (1.11-1.33)		1.21 (1.10-1.33)	
2+ problem drinking indicators	193	3228	1.99 (1.71-2.31)	*<0.0001*	1.70 (1.45-1.98)	*<0.0001*	1.62 (1.39-1.89)	*<0.0001*	1.62 (1.39-1.89)	*<0.0001*	1.62 (1.39-1.89)	*<0.0001*
Sleep problems†												
Low-risk drinkers	3155	22803	1.00 (0.96-1.04)		1.00 (0.96-1.04)		1.00 (0.96-1.04)		1.00 (0.96-1.04)		1.00 (0.96-1.04)	
High-risk drinkers	3503	23751	1.07 (1.03-1.11)		1.06 (1.02-1.10)		1.08 (1.04-1.12)		1.08 (1.04-1.12)		1.08 (1.04-1.12)	
1 problem drinking indicator	2313	10958	1.34 (1.28-1.41)		1.31 (1.25-1.37)		1.31 (1.25-1.37)		1.31 (1.25-1.37)		1.31 (1.25-1.37)	
2+ problem drinking indicators	652	2769	1.48 (1.36-1.61)	*<0.0001*	1.43 (1.31-1.56)	*<0.0001*	1.42 (1.30-1.55)	*<0.0001*	1.42 (1.30-1.55)	*<0.0001*	1.42 (1.30-1.55)	*<0.0001*
Depression symptoms‡												
Low-risk drinkers	462	25496	1.00 (0.91-1.10)		1.00 (0.91-1.10)		1.00 (0.91-1.10)		1.00 (0.91-1.10)		1.00 (0.91-1.10)	
High-risk drinkers	480	26774	0.95 (0.87-1.04)		0.96 (0.87-1.05)		0.95 (0.87-1.04)		0.95 (0.87-1.04)		0.95 (0.86-1.04)	
1 problem drinking indicator	400	12871	1.57 (1.42-1.75)		1.54 (1.39-1.70)		1.49 (1.34-1.65)		1.48 (1.34-1.64)		1.48 (1.33-1.64)	
2+ problem drinking indicators	171	3250	2.53 (2.16-2.96)	*<0.0001*	2.45 (2.10-2.87)	*<0.0001*	2.30 (1.97-2.70)	*<0.0001*	2.29 (1.96-2.69)	*<0.0001*	2.29 (1.95-2.68)	*<0.0001*
Major depressive episode§												
Low-risk drinkers	93	25865	1.00 (0.81-1.23)		1.00 (0.81-1.23)		1.00 (0.81-1.24)		1.00 (0.81-1.24)		1.00 (0.81-1.24)	
High-risk drinkers	89	27165	0.91 (0.74-1.13)		0.91 (0.74-1.12)		0.90 (0.73-1.11)		0.90 (0.72-1.11)		0.89 (0.72-1.10)	
1 problem drinking indicator	66	13205	1.26 (0.99-1.62)		1.20 (0.93-1.54)		1.15 (0.90-1.48)		1.13 (0.88-1.45)		1.12 (0.87-1.44)	
2+ problem drinking indicators	25	3396	1.83 (1.23-2.72)	*0.0104*	1.72 (1.16-2.57)	*0.0296*	1.60 (1.07-2.39)	*0.0700*	1.55 (1.04-2.32)	*0.1015*	1.54 (1.03-2.31)	*0.1023*

	Cases N	Non-cases N	Age group & study area		+Education & income		Main model (+marital status, prior chronic disease, smoking, BMI)		+Prior psychiatric disorder		+Physical activity	
			OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*	OR (95% CI)	p_{het}*
Anxiety symptom												
Low-risk drinkers	75	25883	1.00 (0.79-1.27)		1.00 (0.79-1.27)		1.00 (0.79-1.27)		1.00 (0.79-1.27)		1.00 (0.79-1.27)	
High-risk drinkers	98	27156	0.99 (0.81-1.21)		0.99 (0.81-1.21)		0.99 (0.81-1.21)		0.99 (0.81-1.21)		0.99 (0.81-1.21)	
1 problem drinking indicator	77	13194	1.74 (1.38-2.19)		1.69 (1.34-2.13)		1.66 (1.32-2.10)		1.65 (1.31-2.08)		1.65 (1.30-2.08)	
2+ problem drinking indicators	34	3387	2.48 (1.76-3.50)	*<0.0001*	2.42 (1.71-3.41)	*<0.0001*	2.36 (1.67-3.34)	*<0.0001*	2.34 (1.66-3.31)	*<0.0001*	2.33 (1.65-3.29)	*<0.0001*
General anxiety disorder¶												
Low-risk drinkers	27	25931	1.00 (0.67-1.48)		1.00 (0.67-1.48)		1.00 (0.67-1.49)		1.00 (0.67-1.49)		1.00 (0.67-1.49)	
High-risk drinkers	34	27220	0.94 (0.67-1.32)		0.96 (0.68-1.35)		0.97 (0.69-1.36)		0.96 (0.68-1.35)		0.96 (0.68-1.35)	
1 problem drinking indicator	33	13238	1.81 (1.27-2.57)		1.78 (1.25-2.53)		1.74 (1.22-2.47)		1.72 (1.21-2.45)		1.72 (1.21-2.45)	
2+ problem drinking indicators	16	3405	2.86 (1.74-4.71)	*0.0005*	2.85 (1.73-4.69)	*0.0007*	2.82 (1.71-4.66)	*0.0010*	2.79 (1.69-4.61)	*0.0012*	2.79 (1.69-4.61)	*0.0012*
Panic attacks												
Low-risk drinkers	153	25805	1.00 (0.85-1.18)		1.00 (0.85-1.18)		1.00 (0.84-1.18)		1.00 (0.84-1.18)		1.00 (0.84-1.18)	
High-risk drinkers	216	27038	0.99 (0.87-1.13)		1.00 (0.87-1.14)		1.02 (0.90-1.17)		1.02 (0.89-1.17)		1.02 (0.89-1.16)	
1 problem drinking indicator	105	13166	1.04 (0.85-1.26)		1.03 (0.84-1.26)		1.05 (0.87-1.29)		1.05 (0.86-1.28)		1.05 (0.86-1.28)	
2+ problem drinking indicators	61	3360	1.86 (1.44-2.41)	*0.0002*	1.85 (1.42-2.39)	*0.0003*	1.92 (1.48-2.50)	*0.0002*	1.92 (1.48-2.50)	*0.0001*	1.92 (1.48-2.49)	*0.0002*
Phobia												
Low-risk drinkers	83	25875	1.00 (0.80-1.25)		1.00 (0.80-1.25)		1.00 (0.80-1.26)		1.00 (0.80-1.26)		1.00 (0.80-1.26)	
High-risk drinkers	95	27159	0.91 (0.75-1.12)		0.91 (0.74-1.11)		0.95 (0.77-1.16)		0.94 (0.77-1.15)		0.94 (0.77-1.16)	
1 problem drinking indicator	68	13203	1.31 (1.03-1.67)		1.26 (0.99-1.61)		1.29 (1.01-1.65)		1.28 (1.00-1.63)		1.28 (1.00-1.64)	
2+ problem drinking indicators	18	3403	1.10 (0.69-1.75)	*0.1618*	1.05 (0.66-1.68)	*0.2438*	1.08 (0.68-1.72)	*0.2752*	1.07 (0.67-1.71)	*0.2914*	1.08 (0.68-1.72)	*0.2846*

OR, odds ratio; CI, confidence interval; BMI, body mass index; CIDI-SF, composite international diagnostic interview - short form; HED, heavy episodic drinking.

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

**P* for heterogeneity across the four problem drinking categories.

†Reporting one or more of the following for ≥3 days each week in the past month: delayed or fitful sleep; waking up too early; needing medicine to help sleep; having difficulty staying alert during daytime.

‡Reporting one or more of the following for ≥2 weeks in the past 12 months: feeling sad or depressed; loss of interest; loss of appetite; feeling worthless.

§Assessed by the CIDI-SF (A).

¶Assessed by the CIDI-SF (B).

Table F 7. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to external causes, in male current regular drinkers - in sequentially adjusted models

			Age group & study area		+Education & income		+Smoking status		+BMI		Main model (+fruit intake & physical activity)		+Prior psychiatric disease	
	Non-cases N	Cases N	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*
All-cause mortality														
Low-risk drinkers	19368	1277	1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)		1.00 (0.94-1.06)	
High-risk drinkers	21262	1610	1.33 (1.27-1.40)		1.31 (1.25-1.38)		1.28 (1.22-1.35)		1.29 (1.22-1.35)		1.28 (1.22-1.34)		1.28 (1.22-1.34)	
1 problem drinking indicator	9791	1056	1.47 (1.38-1.56)		1.42 (1.34-1.51)		1.38 (1.30-1.47)		1.37 (1.29-1.46)		1.37 (1.29-1.46)		1.37 (1.28-1.46)	
2+ problem drinking indicators	2457	345	2.10 (1.88-2.33)	*<0.0001*	2.01 (1.80-2.24)	*<0.0001*	1.93 (1.73-2.15)	*<0.0001*	1.92 (1.72-2.13)	*<0.0001*	1.91 (1.71-2.12)	*<0.0001*	1.91 (1.71-2.12)	*<0.0001*
Any hospitalisation														
Low-risk drinkers	10664	9981	1.00 (0.98-1.02)		1.00 (0.98-1.02)		1.00 (0.98-1.02)		1.00 (0.98-1.02)		1.00 (0.98-1.02)		1.00 (0.98-1.02)	
High-risk drinkers	11566	11306	1.11 (1.09-1.13)		1.11 (1.09-1.13)		1.10 (1.08-1.12)		1.10 (1.08-1.12)		1.09 (1.07-1.11)		1.09 (1.07-1.11)	
1 problem drinking indicator	4494	6353	1.09 (1.06-1.12)		1.09 (1.06-1.12)		1.08 (1.05-1.11)		1.08 (1.05-1.11)		1.07 (1.04-1.10)		1.07 (1.04-1.10)	
2+ problem drinking indicators	1138	1664	1.17 (1.12-1.23)	*<0.0001*	1.17 (1.12-1.23)	*<0.0001*	1.16 (1.11-1.22)	*<0.0001*	1.16 (1.11-1.22)	*<0.0001*	1.15 (1.10-1.21)	*<0.0001*	1.15 (1.10-1.21)	*<0.0001*
External causes (ICD-10: V01-Y98)†														
Low-risk drinkers	20530	115	1.00 (0.83-1.21)		1.00 (0.83-1.21)		1.00 (0.83-1.21)		1.00 (0.83-1.21)		1.00 (0.83-1.21)		1.00 (0.83-1.21)	
High-risk drinkers	22708	164	1.19 (1.02-1.39)		1.17 (1.00-1.37)		1.16 (0.99-1.35)		1.16 (0.99-1.36)		1.16 (0.99-1.36)		1.16 (0.99-1.36)	
1 problem drinking indicator	10740	107	1.29 (1.06-1.56)		1.23 (1.01-1.49)		1.21 (1.00-1.47)		1.21 (0.99-1.46)		1.21 (1.00-1.47)		1.21 (0.99-1.47)	
2+ problem drinking indicators	2756	46	2.13 (1.59-2.86)	*0.0003*	2.02 (1.51-2.71)	*0.0012*	1.98 (1.47-2.65)	*0.0020*	1.97 (1.47-2.64)	*0.0022*	1.98 (1.47-2.65)	*0.0020*	1.97 (1.47-2.64)	*0.0022*

	Non-cases N	Cases N	Age group & study area		+Education & income		+Smoking status		+BMI		Main model (+fruit intake & physical activity)		+Prior psychiatric disease	
			HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*	HR (95% CI)	p_{het}*
Intentional self-harm (ICD-10: X60-X84)†														
Low-risk drinkers	20636	9	1.00 (0.51-1.97)		1.00 (0.51-1.97)		1.00 (0.51-1.98)		1.00 (0.50-1.99)		1.00 (0.50-1.99)		1.00 (0.49-2.03)	
High-risk drinkers	22856	16	1.53 (0.93-2.50)		1.49 (0.90-2.44)		1.52 (0.92-2.49)		1.56 (0.95-2.56)		1.52 (0.92-2.49)		1.60 (0.97-2.64)	
1 problem drinking indicator	10833	14	2.01 (1.18-3.43)		1.83 (1.07-3.13)		1.88 (1.10-3.20)		1.90 (1.12-3.25)		1.90 (1.12-3.25)		2.04 (1.19-3.50)	
2+ problem drinking indicators	2797	5	2.87 (1.19-6.96)	*0.2372*	2.47 (1.02-5.98)	*0.3831*	2.56 (1.05-6.22)	*0.3502*	2.57 (1.06-6.24)	*0.3471*	2.60 (1.07-6.32)	*0.3333*	2.77 (1.14-6.78)	*0.2804*
Transport accident (ICD-10: V01-V99)†														
Low-risk drinkers	20590	55	1.00 (0.76-1.31)		1.00 (0.76-1.32)		1.00 (0.76-1.32)		1.00 (0.76-1.32)		1.00 (0.76-1.32)		1.00 (0.76-1.32)	
High-risk drinkers	22790	82	1.16 (0.93-1.44)		1.14 (0.91-1.42)		1.13 (0.91-1.41)		1.13 (0.91-1.41)		1.14 (0.91-1.42)		1.14 (0.91-1.42)	
1 problem drinking indicator	10802	45	1.07 (0.79-1.44)		1.03 (0.76-1.39)		1.02 (0.76-1.38)		1.02 (0.76-1.38)		1.03 (0.76-1.39)		1.03 (0.76-1.39)	
2+ problem drinking indicators	2783	19	1.67 (1.06-2.63)	*0.2826*	1.60 (1.02-2.53)	*0.3371*	1.59 (1.01-2.50)	*0.3553*	1.59 (1.01-2.51)	*0.3491*	1.61 (1.02-2.54)	*0.3370*	1.61 (1.02-2.54)	*0.3370*

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses.

Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

*P for heterogeneity across the four problem drinking categories.

†Deaths and hospitalisations combined.

Table F 8. Baseline characteristics of men by alcohol drinking and problem drinking status

					Current regular drinkers				
						Non-problem drinkers		Problem drinkers	
	All men	Abstainers	Ex-regular drinkers	Occasional drinkers	All current regular	Low-risk	High-risk	1 indicator	2+ indicators
Number of men (%)	210259	42789 (20.4)	18294 (8.7)	79272 (37.7)	69904 (33.2)	25958 (12.3)	27254 (13.0)	13271 (6.3)	3421 (1.6)
Socio-demographic characteristics									
Mean age, years (SD)	52.4 (10.9)	55.8 (11.1)	56.4 (10.3)	50.7 (10.8)	51.0 (10.2)	51.7 (10.7)	50.2 (9.8)	51.8 (10.1)	50.9 (9.8)
Age group, years %									
30-39	14.1	8.8	6.9	18.3	15.1	14.7	15.4	12.4	14.7
40-49	28.2	19.4	19.5	31.1	31.8	31.2	35.2	31.2	33.2
50-59	30.3	29.0	32.9	28.5	31.2	29.8	31.4	33.0	34.6
60-69	19.7	28.2	28.9	15.9	16.4	17.6	14.0	17.6	14.2
70+	7.8	14.7	11.7	6.0	5.5	6.8	4.0	5.7	3.2
Urban area, %	43.4	31.2	41.1	44.1	50.0	61.3	51.9	30.5	24.0
Educational attainment >6 years, %	57.8	54.5	56.7	60.5	57.6	63.1	60.0	57.7	57.5
Income >20000 yuan/year, %	45.6	42.0	44.9	46.7	46.8	52.7	52.8	47.5	46.8
Married, %	92.9	91.4	93.4	93.3	93.3	94.8	93.9	92.6	91.1
Lifestyle & physical measurements									
Regular smoking, %	61.1	52.3	60.4	56.9	71.7	64.9	74.1	76.2	79.0
Mean physical activity, MET-h/d (SD)	22.0 (15.3)	21.1 (15.1)	20.2 (14.5)	22.6 (15.6)	22.4 (15.0)	22.9 (14.8)	22.8 (14.9)	23.1 (15.2)	23.4 (15.7)
Mean SBP, mmHg (SD)	132.8 (20.0)	132.3 (21.5)	134.3 (21.5)	131.0 (18.8)	134.8 (19.8)	131.8 (19.1)	135.7 (19.7)	135.3 (20.6)	136.7 (20.9)
Mean BMI, kg/m^2 (SD)	23.4 (3.2)	23.3 (3.2)	23.9 (3.4)	23.4 (3.2)	23.4 (3.2)	23.6 (3.2)	23.9 (3.3)	23.5 (3.2)	23.3 (3.1)
Self-reported medical history, %									
Coronary heart disease	2.7	3.3	5.2	2.3	2.0	2.0	1.7	1.9	3.0
Stroke or TIA	2.3	3.6	6.0	1.6	1.3	1.3	1.2	1.4	2.4
Cancer	0.5	0.9	1.1	0.3	0.3	0.3	0.2	0.2	0.2
Chronic hepatitis or cirrhosis	1.7	2.7	3.8	1.6	1.2	1.2	1.1	1.4	1.4
Diabetes	2.9	3.8	6.1	2.6	1.9	2.1	2.0	1.8	2.5
Psychiatric disorder	0.3	0.6	0.3	0.2	0.2	0.1	0.1	0.2	0.4

SD, standard deviation; MET-h/d, metabolic equivalent of task per hour per day; SBP, systolic blood pressure; BMI, body mass index; TIA, transient ischaemic attack; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate by direct standardisation to the age group and study area structure of all men for drinking categories (abstainers, ex-regular drinkers, occasional drinkers, current regular drinkers), and of current regular drinkers for problem drinking status (low-risk, high-risk, 1 indicator, 2+ indicators). Associations between drinking categories and baseline characteristic variables: $p<0.001$ across all variables.

Abstainers were men who had not drunk alcohol in the past year and had not drunk ≥weekly previously; ex-regular drinkers were men who had drunk alcohol ≥weekly previously but stopped so in the past year; occasional drinkers were men who reported drinking alcohol less than weekly in the past year and had not drunk alcohol ≥weekly previously; low-risk drinkers were current regular drinkers (i.e., drank ≥weekly in the past year) who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported.

Table F 9. Prevalence of current regular drinking and problem drinking in women

	All women			Female current regular drinkers	
	N	Current regular drinking %	Problem drinking* %	N	Problem drinking* %
Overall	302632	2.1	0.2	6248	9.8
Age group, years					
30-39	48203	1.5	0.1	648	6.2
40-49	93508	2.1	0.2	1908	8.9
50-59	93831	2.1	0.2	2048	9.4
60-69	50434	2.4	0.3	1221	11.6
70-79	16656	2.6	0.4	423	12.8
Area					
Rural	167802	2.1	0.3	3428	12.6
Urban	134830	2.1	0.1	2820	6.1
Study area					
Gansu (Rural)	30696	0.1	0.0	43	13.7
Hunan (Rural)	33541	1.2	0.2	394	15.2
Henan (Rural)	35516	1.0	0.1	355	9.2
Zhejiang (Rural)	33677	1.4	0.1	493	4.4
Sichuan (Rural)	34372	6.4	1.0	2143	14.4
Haikou (Urban)	18897	0.4	0.0	75	8.7
Liuzhou (Urban)	30851	2.2	0.1	706	4.9
Suzhou (Urban)	30898	0.6	0.0	186	3.2
Qingdao (Urban)	19883	1.5	0.1	299	5.5
Harbin (Urban)	34301	4.7	0.3	1554	6.9

Prevalences are adjusted for age and study area as appropriate.

*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table F 10. Baseline characteristics of female current regular drinkers by problem drinking status

	All regular drinkers	Non-problem drinkers		Problem drinkers
		Low-risk drinkers	High-risk drinkers	
Number of women (%)	6248	3316 (53.1)	2318 (37.1)	614 (9.8)
Socio-demographic characteristics				
Mean age, years (SD)	52.7 (10.3)	53.2 (10.6)	51.5 (9.8)	54.2 (10.2)
Age group, years %				
<40	10.4	11.1	11.1	8.4
40-49	30.5	28.7	37.9	27.8
50-59	32.8	32.5	30.6	31.0
60-69	19.5	20.3	15.8	22.9
70+	6.8	7.5	4.6	9.9
Urban area, %	45.1	57.1	31.6	29.7
Highest education, %				
Primary or below	52.4	50.7	54.1	58.1
Middle or high school	39.5	40.5	39.2	34.9
Technical school, college or university	8.1	8.9	6.7	7.0
Household income, yuan/year %				
<20,000	60.6	59.5	61.7	67.1
20,000-34,999	21.5	21.7	20.9	19.9
35,000+	17.9	18.8	17.4	13.0
Married, %	85.2	86.3	82.1	85.5
Lifestyle & physical measurements				
Regular smoking, %	15.7	9.6	20.8	22.7
Mean physical activity, MET-h/d (SD)	20.0 (11.6)	20.1 (11.7)	19.8 (11.5)	19.9 (11.3)
Mean SBP, mmHg (SD)	128.2 (21.6)	127.5 (21.0)	129.2 (22.1)	128.7 (22.7)
Mean BMI, kg/m^2 (SD)	23.7 (3.4)	23.7 (3.4)	23.7 (3.3)	23.3 (3.6)
Self-reported medical history, %				
Coronary heart disease	2.7	3.0	1.7	2.6
Stroke or TIA	0.9	0.8	1.1	1.5
Cancer	0.4	0.4	0.3	1.0
Chronic hepatitis or cirrhosis	0.8	1.2	0.8	0.5
Diabetes	1.3	1.3	1.1	0.6
Psychiatric disorder	0.2	0.3	0.1	0.1

SD, standard deviation; MET-h/d, metabolic equivalent of task per hour per day; SBP, systolic blood pressure; BMI, body mass index; TIA, transient ischaemic attack; HED, heavy episodic drinking.

Prevalences and means are adjusted for age and study area as appropriate.

Low-risk drinkers were current regular drinkers who drank <100g/week, with no HED (defined as drinking >40g per drinking session) in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥100g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator.

Table F 11. Cross-sectional associations of stressful life events with problem drinking, in female current regular drinkers

	Total regular drinkers N	Problem drinker* N (%)	Adjusted OR (95% CI) for problem drinking	*p*-value
Family-related events				
Divorce or separation				
No	6224	612 (9.8%)	1.00	
Yes	24	2 (8.3%)	0.96 (0.22-4.22)	*0.9577*
Family conflict				
No	6172	604 (9.8%)	1.00	
Yes	76	10 (13.2%)	1.40 (0.70-2.78)	*0.3367*
Death of spouse				
No	6177	609 (9.9%)	1.00	
Yes	71	5 (7.0%)	0.57 (0.23-1.45)	*0.2383*
Death or major illness of other family member				
No	5916	587 (9.9%)	1.00	
Yes	332	27 (8.1%)	0.86 (0.57-1.29)	*0.4646*
Any family-related event				
No	5759	571 (9.9%)	1.00	
Yes	489	43 (8.8%)	0.90 (0.64-1.25)	*0.5133*
Finance-related events				
Job loss or retirement				
No	6229	612 (9.8%)	1.00	
Yes	19	2 (10.5%)	1.97 (0.44-8.78)	*0.3745*
Bankruptcy				
No	6212	602 (9.7%)	1.00	
Yes	36	12 (33.3%)	4.02 (1.94-8.33)	*0.0002*
Loss of income or debt				
No	6230	611 (9.8%)	1.00	
Yes	18	3 (16.7%)	1.31 (0.36-4.76)	*0.6774*
Any finance-related event				
No	6177	597 (9.7%)	1.00	
Yes	71	17 (23.9%)	2.85 (1.59-5.09)	*0.0004*
Injury-related events				
Violence				
No	6235	613 (9.8%)	1.00	
Yes	13	1 (7.7%)	0.77 (0.10-6.01)	*0.8006*
Major injury or traffic accident				
No	6216	605 (9.7%)	1.00	
Yes	32	9 (28.1%)	4.00 (1.74-9.19)	*0.0011*
Natural disaster				
No	6244	613 (9.8%)	1.00	
Yes	4	1 (25.0%)	3.82 (0.39-37.55)	*0.2511*
Any injury or disaster event				
No	6199	603 (9.7%)	1.00	
Yes	49	11 (22.4%)	2.87 (1.41-5.82)	*0.0035*
Any major stressful life event				
No	5665	548 (9.7%)	1.00	
Yes	583	66 (11.3%)	1.22 (0.92-1.61)	*0.1663*

OR, odds ratio; CI, confidence interval.

ORs are adjusted for age group, study area, education, income, and smoking.

*Reporting one or more in the past month of: drinking in the morning; being unable to work or do anything due to drinking; feeling depressed, irritated or losing control due to drinking; being unable to stop drinking; having shakes when stopping drinking.

Table F 12. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in female current regular drinkers

	Non-cases N	Cases N	Adjusted OR (95% CI)	p_{het}*
Poor self-reported health				
Low-risk drinkers	3012	304	1.00 (0.86-1.16)	
High-risk drinkers	2078	240	0.89 (0.77-1.02)	
Problem drinkers	523	91	1.21 (0.96-1.52)	*0.0819*
Life dissatisfaction				
Low-risk drinkers	3202	114	1.00 (0.80-1.25)	
High-risk drinkers	2250	68	1.05 (0.82-1.36)	
Problem drinkers	584	30	1.92 (1.30-2.83)	*0.0132*
Sleep problems†				
Low-risk drinkers	2612	704	1.00 (0.90-1.11)	
High-risk drinkers	1762	556	0.97 (0.88-1.08)	
Problem drinkers	444	170	1.05 (0.87-1.25)	*0.7894*
Depression symptoms‡				
Low-risk drinkers	3221	95	1.00 (0.79-1.26)	
High-risk drinkers	2231	87	1.28 (1.02-1.59)	
Problem drinkers	585	29	1.48 (1.00-2.19)	*0.1616*
Major depressive episode§				
Low-risk drinkers	3288	28	1.00 (0.64-1.56)	
High-risk drinkers	2296	22	0.97 (0.64-1.49)	
Problem drinkers	608	6	0.95 (0.41-2.19)	*0.9924*
Anxiety symptom				
Low-risk drinkers	3294	22	1.00 (0.62-1.62)	
High-risk drinkers	2296	22	0.80 (0.53-1.22)	
Problem drinkers	601	13	1.80 (1.01-3.22)	*0.0843*
General anxiety disorder¶				
Low-risk drinkers	3306	10	1.00 (0.49-2.03)	
High-risk drinkers	2309	9	0.86 (0.44-1.66)	
Problem drinkers	608	6	2.18 (0.94-5.04)	*0.2073*
Panic attacks				
Low-risk drinkers	3260	56	1.00 (0.73-1.36)	
High-risk drinkers	2265	53	0.78 (0.59-1.03)	
Problem drinkers	599	15	0.83 (0.49-1.42)	*0.4999*
Phobia				
Low-risk drinkers	3292	24	1.00 (0.61-1.63)	
High-risk drinkers	2293	25	0.88 (0.60-1.31)	
Problem drinkers	612	2	0.24 (0.06-0.99)	*0.1747*

OR, odds ratio; CI, confidence interval; CIDI-SF, composite international diagnostic interview - short form; HED, heavy episodic drinking.

ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Low-risk drinkers were current regular drinkers who drank <100g/week, with no HED (defined as drinking >40g per drinking session) in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥100g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator.

*P for heterogeneity across the three problem drinking categories.

†Reporting one or more of the following for ≥3 days each week in the past month: delayed or fitful sleep; waking up too early; needing medicine to help sleep; having difficulty staying alert during daytime.

‡Reporting one or more of the following for ≥2 weeks in the past 12 months: feeling sad or depressed; loss of interest; loss of appetite; feeling worthless.

§Assessed by the CIDI-SF (A).

¶Assessed by the CIDI-SF (B).

Table F 13. Prospective associations of problem drinking indicators with all-cause mortality, any hospitalisation and events due to external causes, in female current regular drinkers

	Non-cases N	Cases N	Adjusted HR (95% CI)	p_{het}*
All-cause mortality				
Low-risk drinkers	2420	104	1.00 (0.79-1.26)	
High-risk drinkers	1747	113	1.10 (0.90-1.33)	
Problem drinkers	436	40	1.17 (0.86-1.60)	*0.7045*
Any hospitalisations				
Low-risk drinkers	1055	1469	1.00 (0.94-1.07)	
High-risk drinkers	812	1048	0.92 (0.87-0.98)	
Problem drinkers	202	274	0.94 (0.83-1.06)	*0.1934*
External causes (ICD-10: V01-Y98)†				
Low-risk drinkers	2517	7	1.00 (0.44-2.29)	
High-risk drinkers	1853	7	0.94 (0.43-2.06)	
Problem drinkers	472	4	2.17 (0.75-6.33)	*0.4211*

HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index.
Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses.
Low-risk drinkers were current regular drinkers who drank <100g/week, with no HED (defined as drinking >40g per drinking session) in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥100g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator.
*P for heterogeneity across the three problem drinking categories.
†Deaths and hospitalisations combined.

Table F 14. Comparison of problem drinking and AUD definitions in the CKB and commonly used screening tests and diagnostic criteria

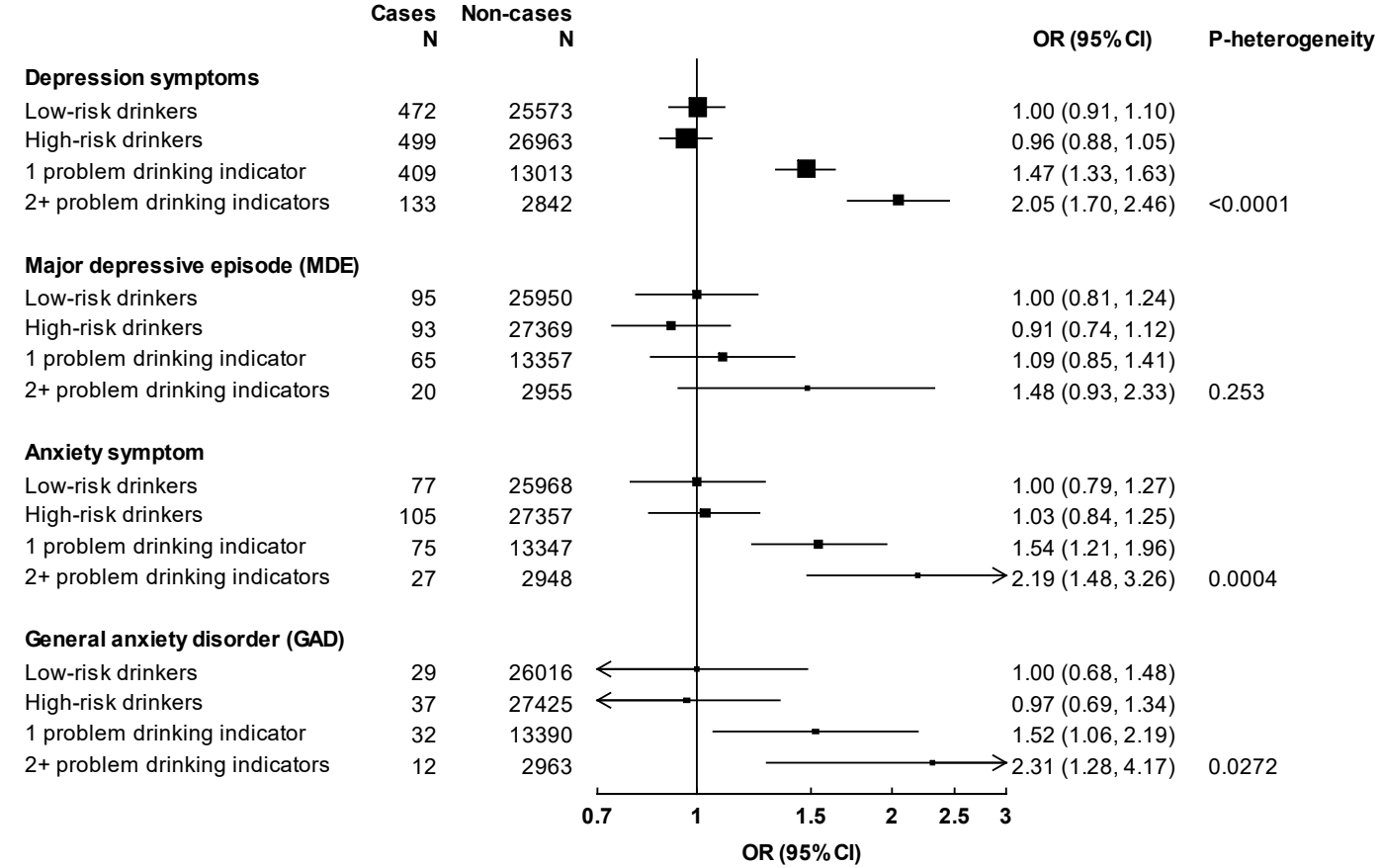
	DSM-5	CKB	CAGE	AUDIT*
Definition	**AUD (in the past year):** - Mild (2-3 items) - Moderate (4-5 items) - Severe (≥6 items)	**Problem drinking (in the past month):** ≥1 problem drinking indicator(s)	**Problem drinking (lifetime):** ≥2 ”yes” responses	**Hazardous or harmful alcohol consumption:** score ≥8 (men) or ≥7 (women) **Alcohol dependence (in the past year):** score ≥20
Indicators related to amount				- How often did you have a drink containing alcohol in the past year? - How many drinks containing alcohol did you have on a typical day when you were drinking in the past year? - How often did you have 6 or more drinks on one occasion in the past year?
Indicators related to alcohol dependence and problems		- Ever drinking in the morning	- Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?	- How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
	- Experienced craving — a strong need, or urge, to drink?			
	- Had times when you ended up drinking more, or longer than you intended?	- Being unable to keep away from drinking		- How often during the last year have you found that you were not able to stop drinking once you had started?
	- More than once wanted to cut down or stop drinking, or tried to, but couldn’t?		- Have you ever felt you needed to **C**ut down on your drinking?	
	- Spent a lot of time drinking? Or being sick or getting over the after effects?			
	- Had withdrawal symptoms e.g., trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or	- Having shakes when stopping drinking		

DSM-5	CKB	CAGE	AUDIT*
sweating? Or sensed things that were not there?			
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?			
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	- Negative emotions after drinking		- How often during the last year have you been unable to remember what happened the night before because you had been drinking?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?			
- Found that drinking - or being sick from drinking - often interfered with taking care of your home or family? Or caused job troubles? Or school problems?	- Being unable to work or to do anything because of drinking		- How often during the last year have you failed to do what was normally expected from you because of drinking?
		- Have you ever felt **G**uilty about drinking?	- How often during the last year have you had a feeling of guilt or remorse after drinking?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (e.g., driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?			- Have you or someone else been injured as a result of your drinking?
- Continued to drink even though it was causing trouble with your family or friends?		- Have people **A**nnoyed you by criticizing your drinking?	- Has a relative or friend or doctor or other health care worker been concerned about your drinking or suggested you cut down?

AUD, alcohol use disorder; DSM-5, diagnostic and statistical manual of mental disorders, 5th edition; CKB, China Kadoorie Biobank; CAGE, cut down, annoyed, guilty, eye-opener; AUDIT, alcohol use disorder identification test.

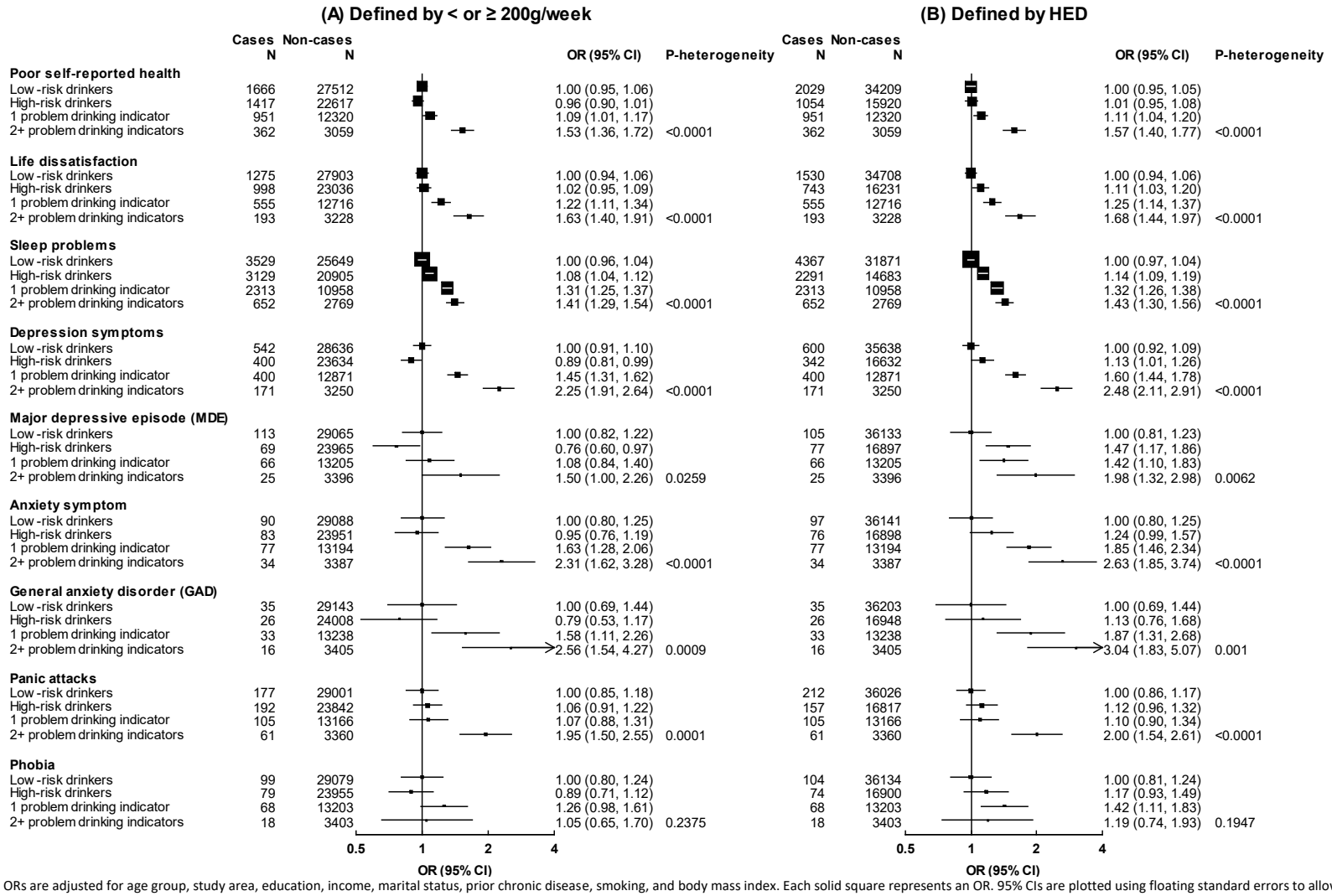
*AUDIT scoring system: each question is based on a 0-4 point scale (0="Never", 1="Less than monthly", 2="Monthly", 3="Weekly", 4="Daily/almost daily").

Figure F 1. Cross-sectional associations of problem drinking (excluding negative emotions indicator from the definition of problem drinking) with depression and anxiety, in male current regular drinkers



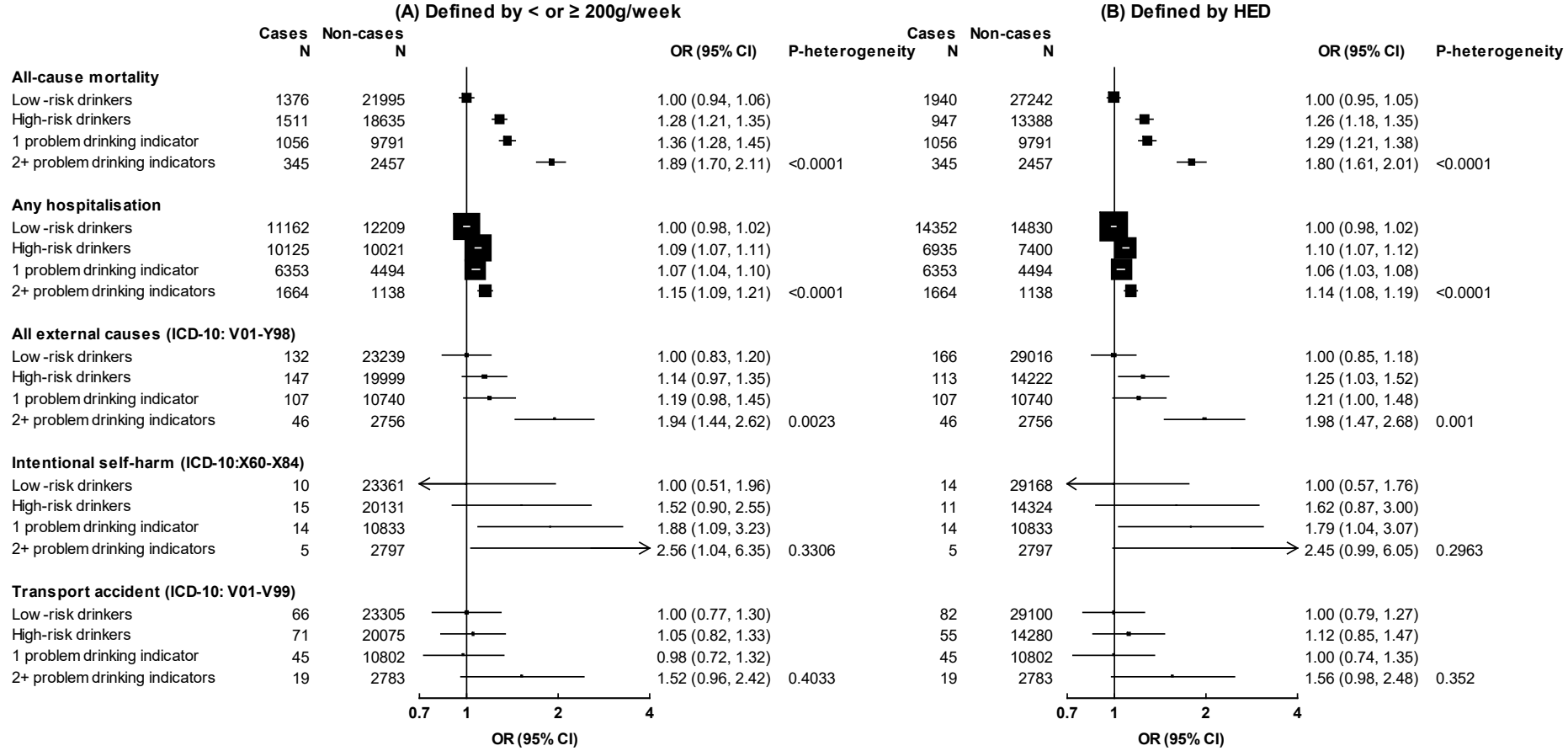
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Problem drinking indicators included: drinking in the morning; being unable to work or do anything due to drinking; being unable to stop drinking; having shakes when stopping drinking. Low-risk drinkers were current regular drinkers who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure F 2. Cross-sectional associations of problem drinking (with different definitions of low-risk and high-risk drinkers) with poor wellbeing and mental health, in male current regular drinkers



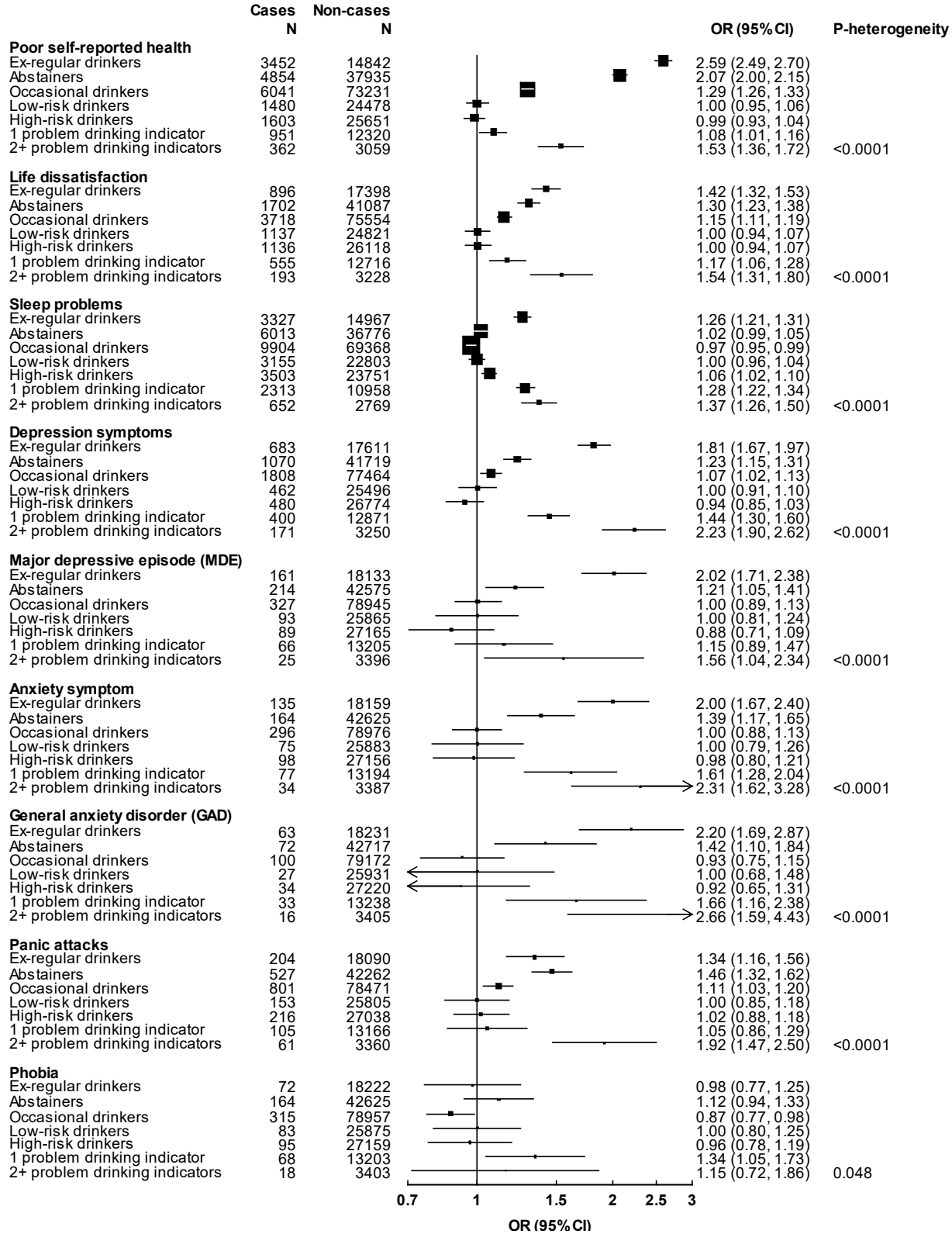
ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers with no problem drinking indicator reported, and drank <200g/week in (A) or did not engage in HED in a typical drinking week in (B); high-risk drinkers were current regular drinkers with no problem drinking indicator reported, and drank ≥200g/week in (A) or engaged in HED in a typical drinking week in (B); problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure F 3. Prospective associations of problem drinking (with different definitions of low-risk and high-risk drinkers) with all-cause mortality, any hospitalisation and events due to all external causes, in male current regular drinkers



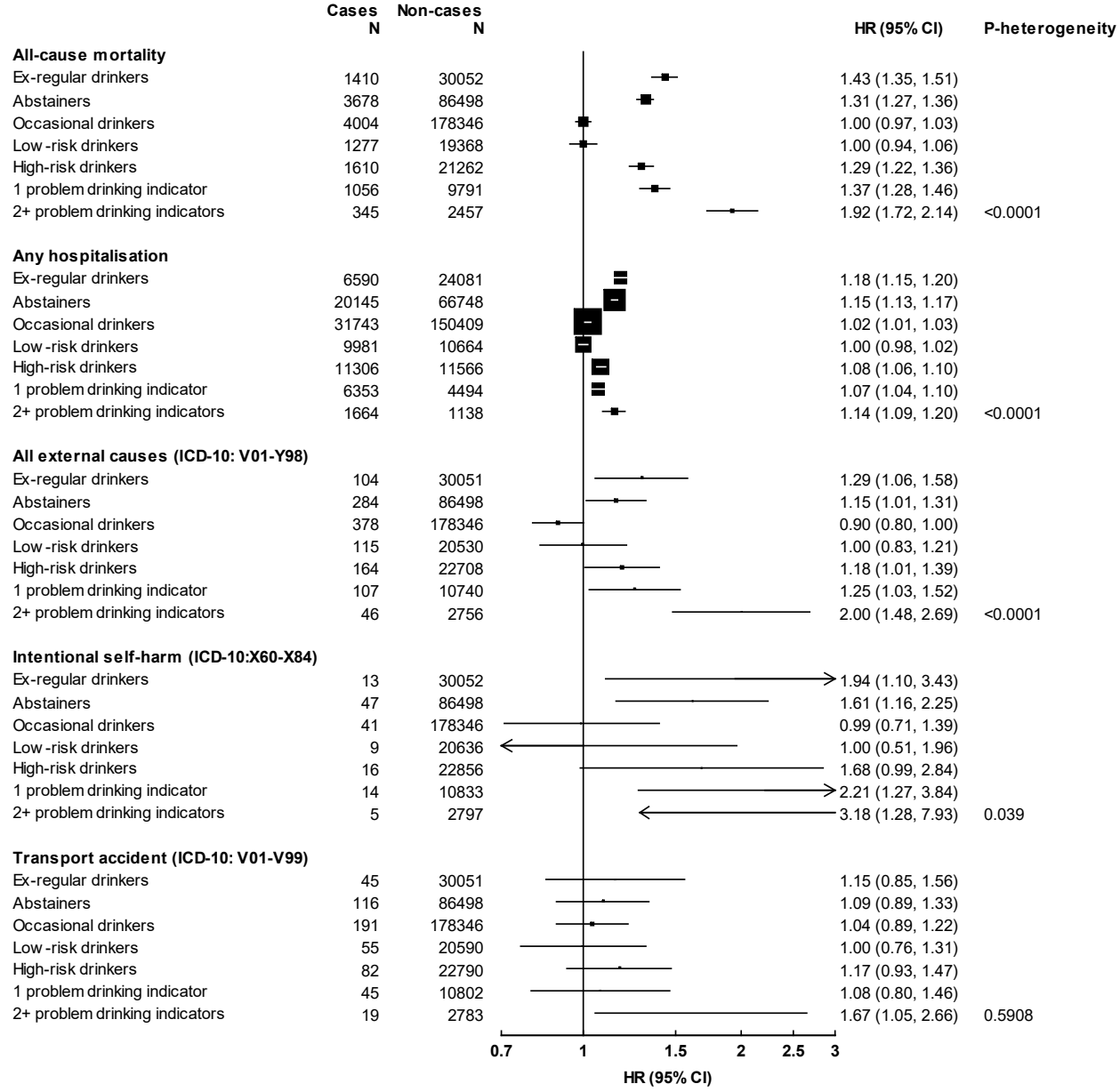
Models are stratified by age-at-risk and study area, further adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Low-risk drinkers were current regular drinkers with no problem drinking indicator reported, and drank <200g/week in (A) or did not engage in HED in a typical drinking week in (B); high-risk drinkers were current regular drinkers with no problem drinking indicator reported, and drank ≥200g/week reported in (A) or engaged in HED in a typical drinking week in (B); problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

Figure F 4. Cross-sectional associations of problem drinking with poor wellbeing and mental health, in men



ORs are adjusted for age group, study area, education, income, marital status, prior chronic disease, smoking, and body mass index. Each solid square represents an OR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log OR in each group and the error bars indicate the group-specific 95% CI. Ex-regular drinkers (including reduced-intake drinkers) were men who had drunk alcohol ≥weekly previously but stopped so in the past year; abstainers were men who had not drunk alcohol in the past year and had not drunk ≥weekly previously; occasional drinkers were men who reported drinking alcohol less than weekly in the past year and had not drunk alcohol ≥weekly previously; low-risk drinkers were current regular drinkers (i.e., drank ≥weekly in the past year) who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. OR, odds ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure F 5. Prospective associations of problem drinking with all-cause mortality, any hospitalisation and events due to all external causes, in men



Models are stratified by age-at-risk and study area, further adjusted for education, income, smoking, physical activity, fresh fruit intake, and body mass index. Participants with prior coronary heart disease, stroke or transient ischaemic attack, diabetes, cancer, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, or kidney disease were excluded from the analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. Ex-regular drinkers (including reduced-intake drinkers) were men who had drunk alcohol ≥weekly previously but stopped so in the past year; abstainers were men who had not drunk alcohol in the past year and had not drunk ≥weekly previously; occasional drinkers were men who reported drinking alcohol less than weekly in the past year and had not drunk alcohol ≥weekly previously; low-risk drinkers were current regular drinkers (i.e., drank ≥weekly in the past year) who drank <200g/week, with no HED in a typical drinking week or problem drinking indicator reported; high-risk drinkers were current regular drinkers who either drank ≥200g/week or engaged in HED in a typical drinking week, but with no problem drinking indicator reported; problem drinkers were current regular drinkers who reported at least one problem drinking indicator, and were further classified into "1 problem drinking indicator" and "2+ problem drinking indicators" according to the number of problem drinking indicators reported. HR, hazard ratio; CI, confidence interval; ICD-10, international classification of diseases, 10th revision; HED, heavy episodic drinking.

G. Additional results on alcohol consumption and risks of cancers

Table G 1. Age-standardised incidence rates (per 100,000 person-years) of major cancers, by ten study areas in men

	Rural										Urban									
	Henan		Sichuan		Zhejiang		Hunan		Gansu		Qingdao		Suzhou		Harbin		Liuzhou		Haikou	
Cancer site	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*
Mouth and throat	28	11.1	88	42.5	73	29.3	87	33.6	16	9.5	35	27.1	49	22.8	38	16.7	85	44.1	42	40.7
Oesophagus	694	289.0	307	147.9	98	39.2	89	33.9	104	63.2	75	59.3	142	67.1	49	22.4	35	16.7	15	13.9
Colon and rectum	110	43.8	161	77.1	180	72.1	146	55.3	50	28.7	167	132.1	194	91.5	227	96.4	211	100.4	81	71.4
Liver	274	106.5	224	109.0	196	78.5	216	82.5	152	88.9	143	106.7	196	92.2	189	82.5	182	92.0	109	95.0
Stomach	374	153.4	263	127.7	213	85.8	47	18.0	284	168.4	213	165.6	443	221.1	203	88.1	111	54.3	70	59.0
Pancreas	29	12.1	31	15.1	81	32.5	27	10.1	24	13.8	34	27.5	82	38.1	68	28.7	19	9.2	10	8.0
Lung	238	95.3	283	138.0	561	225.4	566	213.5	154	93.1	291	242.6	370	176.4	515	215.3	335	155.9	148	128.6
IARC alcohol-related cancers	1084	443.6	756	366.3	532	213.9	525	200.7	317	187.0	406	316.5	560	264.3	490	212.7	494	244.9	239	214.8
Other cancers of known sites (Non-IARC alcohol-related)	877	355.8	846	412.9	1256	511.2	1002	382.9	578	343.9	785	637.8	1204	579.3	1144	482.3	723	341.4	315	275.5
All cancers†	1783	730.6	1482	723.3	1692	690.4	1486	569.8	844	501.4	1124	909.2	1621	781.9	1608	687.7	1170	564.9	532	471.6

SIR, standardised incidence rate; IARC, international agency for research on cancer.

Participants with prior cancer were excluded.

*Incidence rates (per 100,000 person-years) are standardised to the age structure of the China Kadoorie Biobank male population.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 2. Age-standardised incidence rates (per 100,000 person-years) of major cancers, by ten study areas in women

	Rural										Urban									
	Henan		Sichuan		Zhejiang		Hunan		Gansu		Qingdao		Suzhou		Harbin		Liuzhou		Haikou	
Cancer site	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*
Mouth and throat	19	5.6	33	9.6	39	10.6	36	10.8	8	2.9	14	7.1	49	15.6	19	5.2	50	16.0	45	24.5
Oesophagus	494	157.8	60	19.7	19	4.9	18	5.4	39	16.8	12	5.9	58	17.8	10	2.7	17	4.8	13	5.9
Colon and rectum	111	32.8	153	47.2	196	53.9	137	41.7	62	25.3	160	80.4	185	57.6	236	61.4	215	63.5	74	38.7
Liver	108	32.7	144	44.7	106	30.0	122	37.0	116	47.2	56	28.1	94	28.9	104	27.0	91	26.8	84	43.1
Female breast	203	56.9	130	37.7	255	71.1	147	43.6	61	20.5		132.1	189	60.8	491	144.7	371	124.8	182	103.3
Stomach	142	45.0	128	39.1	100	27.0	28	8.7	123	50.1	109	54.8	232	71.8	103	26.8	72	21.7	86	43.3
Pancreas	28	9.3	62	19.4	71	19.3	16	4.9	26	10.3	34	17.1	55	16.9	68	16.9	30	8.6	9	4.3
Lung	164	50.7	281	87.5	269	73.9	258	80.5	109	45.0	212	107.1	231	71.7	418	105.8	275	81.2	96	47.2
IARC alcohol-related cancers	910	279.5	503	153.9	608	169.1	452	136.5	281	110.5	490	249.1	563	177.6	850	239.1	717	228.8	380	206.2
Other cancers of known sites (Non-IARC alcohol-related)	714	217.1	859	265.0	1038	287.8	973	298.1	600	228.0	771	392.6	968	304.8	1189	320.3	780	237.9	426	223.0
All cancers†	1548	475.7	1285	396.6	1567	438.0	1417	434.5	865	332.5	1214	624.2	1477	468.5	2035	565.4	1437	452.1	774	414.4

SIR, age-standardised incidence rate; IARC, international agency for research on cancer.

Participants with prior cancer were excluded.

*Incidence rates (per 100,000 person-years) are standardised to the age structure of the China Kadoorie Biobank female population.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 3. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol drinking categories in men

	Abstainers			Ex-regular drinkers			Occasional drinkers			Current regular drinkers		
Cancer site	**N**	**Crude IR**	**SIR***	**N**	**Crude IR**	**SIR***	**N**	**Crude IR**	**SIR***	**N**	**Crude IR**	**SIR***
Mouth and throat	90	22.3	19.3	61	36.1	30.7	154	19.8	20.5	236	34.2	32.6
Oesophagus	243	60.3	64.1	152	90.0	75.3	558	71.7	57.4	655	95.0	103.3
Colon and rectum	306	76.1	67.9	203	120.4	90.6	443	56.9	65.1	575	83.5	84.8
Liver	445	110.5	102.2	271	160.5	161.3	550	70.6	73.7	615	89.2	96.1
Stomach	520	129.3	115.1	242	143.5	124.6	702	90.2	96.8	757	109.9	113.2
Pancreas	89	22.1	18.7	40	23.7	20.1	111	14.2	16.7	165	23.9	21.7
Lung	885	220.1	184.7	460	272.9	207.7	866	111.3	133.7	1250	181.5	192.5
IARC alcohol-related cancers	1056	263.2	246.2	673	400.8	351.5	1669	215.0	212.5	2005	292.0	307.4
Other cancers of known sites (Non-IARC alcohol-related)	2085	521.7	453.4	1076	643.6	512.6	2523	325.6	372.9	3046	444.8	459.2
All cancers†	2991	751.8	671.3	1647	992.0	826.7	3947	511.5	555.6	4757	698.3	727.2

IR, incidence rate; SIR, standardised incidence rate; IARC, international agency for research on cancer.

Participants with prior cancer were excluded.

*Incidence rates (per 100,000 person-years) are standardised to the age and study area structure of the China Kadoorie Biobank male population.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 4. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol drinking categories in women

	Never regular drinkers			Ever regular drinkers		
Cancer site	**N**	**Crude IR**	**SIR***	**N**	**Crude IR**	**SIR***
Mouth and throat	303	10.3	10.3	9	10.1	9.7
Oesophagus	717	24.4	24.3	23	25.9	29.0
Colon and rectum	1471	50.2	50.5	58	65.4	58.0
Liver	987	33.6	33.9	38	42.8	62.0
Female breast	2214	75.6	75.6	75	84.7	87.2
Stomach	1092	37.2	37.3	31	34.9	26.9
Pancreas	382	13.0	13.2	17	19.1	10.5
Lung	2231	76.1	76.8	82	92.4	70.9
IARC alcohol-related cancers	5556	190.3	190.8	198	224.1	243.3
Other cancers of known sites (Non-IARC alcohol-related)	8042	275.7	277.0	276	312.5	306.4
All cancers†	13163	453.9	455.5	456	519.3	516.9

IR, incidence rate; SIR, standardised incidence rate; IARC, international agency for research on cancer.

Participants with prior cancer were excluded.

Categories are presented as never regular drinkers versus ever regular drinkers due to the small numbers of cancer events among ex-regular drinkers and current regular drinkers respectively.

*Incidence rates (per 100,000 person-years) are standardised to the age and study area structure of the China Kadoorie Biobank female population.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 5. Adjusted HRs for cancer mortality associated with alcohol drinking status, in men

		Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Mouth and throat	200	38	1.00 (0.72-1.40)	24	1.31 (0.87-1.96)	46	0.98 (0.72-1.33)	92	1.76 (1.41-2.20)	*0.0059*
Oesophagus	966	150	1.00 (0.84-1.18)	102	1.38 (1.13-1.67)	297	1.00 (0.88-1.13)	417	1.95 (1.76-2.17)	*<0.0001*
Colon and rectum	499	102	1.00 (0.81-1.23)	77	1.46 (1.16-1.83)	148	1.03 (0.86-1.22)	172	1.16 (0.99-1.35)	*0.2762*
Colon	199	40	1.00 (0.72-1.39)	32	1.71 (1.20-2.43)	59	1.04 (0.79-1.37)	68	1.27 (0.99-1.63)	*0.2510*
Rectum	300	62	1.00 (0.77-1.30)	45	1.31 (0.97-1.76)	89	1.01 (0.81-1.26)	104	1.08 (0.88-1.33)	*0.6388*
Liver	1208	279	1.00 (0.88-1.14)	154	1.27 (1.08-1.49)	368	0.85 (0.77-0.95)	407	1.07 (0.96-1.19)	*0.4211*
Stomach	1227	338	1.00 (0.89-1.12)	141	0.96 (0.81-1.14)	381	0.80 (0.72-0.89)	367	0.89 (0.80-0.99)	*0.1592*
Pancreas	285	61	1.00 (0.77-1.30)	28	0.96 (0.66-1.40)	79	1.01 (0.80-1.27)	117	1.27 (1.05-1.55)	*0.1505*
Lung	1768	442	1.00 (0.91-1.10)	224	1.03 (0.90-1.17)	444	0.77 (0.70-0.85)	658	0.97 (0.89-1.05)	*0.6046*
Gallbladder	102	13	1.00 (0.57-1.76)	14	1.92 (1.13-3.27)	32	1.90 (1.30-2.78)	43	2.05 (1.50-2.80)	*0.0304*
Skin	29	7	1.00 (0.45-2.21)	1	0.33 (0.05-2.35)	14	2.04 (1.17-3.55)	7	0.85 (0.40-1.84)	*0.7803*
Prostate	131	36	1.00 (0.71-1.42)	27	1.71 (1.16-2.52)	38	1.00 (0.71-1.39)	30	0.83 (0.57-1.19)	*0.4651*
Kidney	37	9	1.00 (0.49-2.05)	6	1.46 (0.65-3.30)	11	0.64 (0.34-1.19)	11	0.83 (0.44-1.56)	*0.7011*
Bladder	91	25	1.00 (0.65-1.53)	16	1.13 (0.69-1.86)	25	0.82 (0.54-1.24)	25	0.73 (0.49-1.11)	*0.3107*
Brain	126	25	1.00 (0.66-1.51)	15	1.23 (0.73-2.05)	46	1.07 (0.78-1.46)	40	1.07 (0.77-1.49)	*0.7991*
Thyroid	12	1	1.00 (0.14-7.35)	3	6.55 (2.02-21.22)	2	1.39 (0.32-6.01)	6	4.45 (1.95-10.15)	*0.1759*
Lymphoma	76	18	1.00 (0.62-1.63)	11	1.29 (0.71-2.36)	18	0.76 (0.47-1.24)	29	1.10 (0.75-1.61)	*0.7657*
Multiple myeloma	65	19	1.00 (0.62-1.61)	4	0.46 (0.17-1.22)	18	0.74 (0.46-1.20)	24	0.88 (0.58-1.34)	*0.6993*
Leukaemia	145	38	1.00 (0.71-1.40)	15	0.86 (0.51-1.43)	41	0.75 (0.54-1.04)	51	0.95 (0.71-1.27)	*0.8228*
Other less common cancers of known sites	281	68	1.00 (0.78-1.29)	37	0.98 (0.71-1.36)	70	0.69 (0.54-0.88)	106	1.04 (0.85-1.27)	*0.8346*
IARC alcohol-related cancers	3044	617	1.00 (0.92-1.09)	401	1.36 (1.23-1.50)	904	0.89 (0.83-0.95)	1122	1.27 (1.19-1.35)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	4899	1261	1.00 (0.94-1.06)	627	1.03 (0.95-1.12)	1321	0.81 (0.76-0.86)	1690	0.98 (0.93-1.03)	*0.5592*
All cancers†	8016	1895	1.00 (0.95-1.05)	1033	1.13 (1.06-1.20)	2250	0.83 (0.79-0.87)	2838	1.07 (1.03-1.11)	*0.0381*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P*-value for association comparing current regular drinkers vs. abstainers.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 6. Adjusted HRs for incident cancers associated with alcohol drinking status, in women

		Abstainers		Ex-regular		Occasional		Current regular		
	All women									
Cancer site	**N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***
Mouth and throat	312	214	1.00 (0.83-1.20)	4	1.23 (0.45-3.33)	89	1.11 (0.89-1.38)	5	0.73 (0.30-1.78)	*0.5166*
Oesophagus	740	340	1.00 (0.89-1.13)	8	1.17 (0.57-2.41)	377	0.99 (0.88-1.12)	15	1.23 (0.73-2.06)	*0.4823*
Colon and rectum	1529	1018	1.00 (0.92-1.08)	17	0.92 (0.57-1.50)	453	0.96 (0.87-1.06)	41	1.10 (0.81-1.51)	*0.5813*
Colon	901	600	1.00 (0.90-1.11)	8	0.70 (0.35-1.42)	265	0.93 (0.82-1.05)	28	1.21 (0.83-1.76)	*0.3645*
Rectum	883	587	1.00 (0.90-1.11)	11	0.96 (0.53-1.76)	265	1.02 (0.90-1.16)	20	0.95 (0.61-1.48)	*0.8032*
Liver	975	702	1.00 (0.91-1.10)	16	1.17 (0.71-1.94)	236	0.78 (0.68-0.89)	21	0.81 (0.52-1.25)	*0.3451*
Breast	2289	1280	1.00 (0.93-1.08)	19	1.24 (0.79-1.95)	934	1.12 (1.05-1.20)	56	1.16 (0.89-1.52)	*0.2834*
Stomach	1123	788	1.00 (0.91-1.10)	7	0.61 (0.29-1.30)	304	0.96 (0.85-1.08)	24	0.99 (0.66-1.49)	*0.9607*
Pancreas	399	274	1.00 (0.86-1.17)	5	0.94 (0.38-2.29)	108	0.96 (0.79-1.17)	12	1.10 (0.62-1.97)	*0.7473*
Lung	2020	1344	1.00 (0.93-1.07)	26	1.05 (0.71-1.55)	610	0.96 (0.89-1.05)	40	0.67 (0.49-0.92)	*0.0170*
Gallbladder	356	261	1.00 (0.85-1.18)	2	0.41 (0.10-1.64)	82	0.98 (0.78-1.24)	11	1.30 (0.71-2.38)	*0.4260*
Skin	130	87	1.00 (0.75-1.33)	1	0.63 (0.09-4.61)	40	1.58 (1.14-2.21)	2	0.71 (0.17-2.88)	*0.6453*
Cervix uteri	1054	719	1.00 (0.91-1.10)	14	1.61 (0.94-2.74)	303	0.99 (0.87-1.11)	18	0.98 (0.62-1.57)	*0.9070*
Corpus uteri	492	324	1.00 (0.87-1.16)	3	0.67 (0.21-2.09)	158	0.86 (0.73-1.01)	7	0.63 (0.30-1.33)	*0.2429*
Endometrium	410	258	1.00 (0.85-1.17)	3	0.85 (0.27-2.66)	143	0.89 (0.75-1.06)	6	0.62 (0.28-1.40)	*0.2785*
Uterus	333	220	1.00 (0.84-1.19)	4	1.22 (0.45-3.29)	102	0.93 (0.75-1.15)	7	0.99 (0.47-2.10)	*0.9969*
Ovary	433	282	1.00 (0.86-1.17)	4	1.03 (0.38-2.79)	139	0.86 (0.72-1.03)	8	0.82 (0.41-1.65)	*0.5835*
Kidney	204	125	1.00 (0.79-1.26)	3	1.80 (0.56-5.72)	72	1.10 (0.86-1.40)	4	0.83 (0.31-2.23)	*0.7053*
Bladder	164	106	1.00 (0.79-1.27)	4	2.31 (0.84-6.36)	52	1.28 (0.96-1.72)	2	0.55 (0.14-2.22)	*0.3948*
Brain	270	194	1.00 (0.82-1.21)	2	0.63 (0.16-2.56)	66	0.73 (0.56-0.94)	8	1.08 (0.53-2.20)	*0.7936*
Thyroid	461	271	1.00 (0.85-1.18)	6	1.82 (0.81-4.11)	172	0.93 (0.79-1.09)	12	1.01 (0.57-1.79)	*0.9958*
Lymphoma	421	297	1.00 (0.86-1.17)	6	1.22 (0.54-2.77)	112	1.01 (0.83-1.24)	6	0.68 (0.30-1.52)	*0.3529*
Multiple myeloma	114	76	1.00 (0.76-1.32)	2	1.32 (0.32-5.47)	35	1.11 (0.78-1.57)	1	0.41 (0.06-2.94)	*0.3519*

	All women	Abstainers		Ex-regular		Occasional		Current regular		
Cancer site	**N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value***
Leukaemia	321	226	1.00 (0.84-1.19)	2	0.58 (0.14-2.33)	84	0.83 (0.66-1.04)	9	1.22 (0.63-2.38)	*0.5642*
Other less common cancers of known sites	925	644	1.00 (0.90-1.11)	10	0.94 (0.50-1.76)	250	0.92 (0.81-1.05)	21	0.98 (0.64-1.52)	*0.8977*
IARC alcohol-related cancers	5754	3502	1.00 (0.96-1.04)	63	1.14 (0.88-1.46)	2054	1.01 (0.96-1.06)	135	1.05 (0.89-1.25)	*0.5939*
Other cancers of known sites (Non-IARC alcohol-related)	8318	5625	1.00 (0.97-1.04)	96	0.98 (0.80-1.20)	2417	0.94 (0.90-0.98)	180	0.85 (0.74-0.99)	*0.0419*
All cancers†	13619	8829	1.00 (0.97-1.03)	155	1.05 (0.90-1.24)	4334	0.97 (0.94-1.00)	301	0.92 (0.82-1.03)	*0.1356*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P*-values for association comparing current regular drinkers vs. abstainers.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 7. Adjusted HRs for incident cancers associated with ever regular drinking status, in women

		Never regular drinkers		Ever regular drinkers		
Cancer site	**All women N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value**
Mouth and throat	312	303	1.00 (Ref)	9	0.86 (0.43-1.72)	*0.6771*
Oesophagus	740	717	1.00 (Ref)	23	1.23 (0.79-1.91)	*0.3514*
Colon and rectum	1529	1471	1.00 (Ref)	58	1.06 (0.81-1.39)	*0.6811*
Colon	901	865	1.00 (Ref)	36	1.08 (0.77-1.53)	*0.6482*
Rectum	883	852	1.00 (Ref)	31	0.95 (0.65-1.37)	*0.7677*
Liver	975	938	1.00 (Ref)	37	1.01 (0.72-1.43)	*0.9349*
Breast	2289	2214	1.00 (Ref)	75	1.11 (0.88-1.41)	*0.3758*
Stomach	1123	1092	1.00 (Ref)	31	0.89 (0.61-1.29)	*0.5463*
Pancreas	399	382	1.00 (Ref)	17	1.07 (0.65-1.78)	*0.7862*
Lung	2020	1954	1.00 (Ref)	66	0.79 (0.61-1.01)	*0.0646*
Gallbladder	356	343	1.00 (Ref)	13	0.99 (0.56-1.77)	*0.9795*
Skin	130	127	1.00 (Ref)	3	0.58 (0.18-1.89)	*0.3680*
Cervix uteri	1054	1022	1.00 (Ref)	32	1.18 (0.82-1.69)	*0.3777*
Corpus uteri	492	482	1.00 (Ref)	10	0.69 (0.36-1.31)	*0.2543*
Endometrium	410	401	1.00 (Ref)	9	0.72 (0.37-1.42)	*0.3493*
Uterus	333	322	1.00 (Ref)	11	1.07 (0.58-1.99)	*0.8280*
Ovary	433	421	1.00 (Ref)	12	0.95 (0.53-1.70)	*0.8572*
Kidney	204	197	1.00 (Ref)	7	1.01 (0.47-2.20)	*0.9741*
Bladder	164	158	1.00 (Ref)	6	0.97 (0.42-2.27)	*0.9479*
Brain	270	260	1.00 (Ref)	10	1.06 (0.55-2.06)	*0.8597*
Thyroid	461	443	1.00 (Ref)	18	1.22 (0.75-1.97)	*0.4311*
Lymphoma	421	409	1.00 (Ref)	12	0.87 (0.48-1.57)	*0.6451*
Multiple myeloma	114	111	1.00 (Ref)	3	0.73 (0.23-2.36)	*0.6037*
Leukaemia	321	310	1.00 (Ref)	11	1.09 (0.58-2.02)	*0.7946*
Other less common cancers of known sites	925	894	1.00 (Ref)	31	1.00 (0.69-1.45)	*0.9898*
IARC alcohol-related cancers	5754	5556	1.00 (Ref)	198	1.07 (0.93-1.24)	*0.3387*
Other cancers of known sites (Non-IARC alcohol-related)	8318	8042	1.00 (Ref)	276	0.92 (0.81-1.04)	*0.1650*
All cancers*	13619	13163	1.00 (Ref)	456	0.97 (0.88-1.07)	*0.5463*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.
Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.
*All cancers included ill-defined neoplasm and are patient-based.

Table G 8. Adjusted HRs for incident cancers associated with drinking status and amount, in men

								Current regular drinkers								
		Abstainers		Ex-regular drinkers		Occasional drinkers		<140g/week		140-279g/week		280-419g/week		420+g/week		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{het}*
Mouth and throat	541	90	1.00 (0.80-1.24)	61	1.48 (1.15-1.91)	154	1.19 (1.01-1.42)	43	0.97 (0.72-1.31)	63	1.76 (1.37-2.26)	45	1.83 (1.36-2.47)	85	3.00 (2.38-3.78)	*<0.0001*
Oesophagus	1608	243	1.00 (0.87-1.14)	152	1.28 (1.09-1.50)	558	1.02 (0.93-1.12)	113	0.99 (0.82-1.19)	134	1.45 (1.22-1.72)	145	2.21 (1.87-2.61)	263	3.66 (3.19-4.20)	*<0.0001*
Colon and rectum	1527	306	1.00 (0.89-1.13)	203	1.27 (1.11-1.47)	443	0.94 (0.86-1.04)	174	0.98 (0.84-1.14)	175	1.32 (1.14-1.54)	111	1.33 (1.10-1.61)	115	1.38 (1.14-1.67)	*<0.0001*
Colon	856	180	1.00 (0.86-1.17)	118	1.28 (1.07-1.54)	255	0.92 (0.81-1.05)	92	0.89 (0.73-1.10)	91	1.21 (0.99-1.50)	65	1.38 (1.08-1.77)	55	1.17 (0.89-1.54)	*0.0057*
Rectum	946	185	1.00 (0.86-1.17)	122	1.22 (1.02-1.46)	261	0.92 (0.81-1.05)	108	1.00 (0.83-1.21)	119	1.43 (1.19-1.72)	67	1.26 (0.99-1.61)	84	1.54 (1.23-1.93)	*<0.0001*
Liver	1651	378	1.00 (0.90-1.12)	208	1.24 (1.08-1.42)	492	0.83 (0.75-0.91)	163	0.86 (0.74-1.00)	137	0.94 (0.79-1.11)	123	1.27 (1.06-1.52)	150	1.49 (1.25-1.76)	*<0.0001*
Stomach	2221	520	1.00 (0.91-1.10)	242	1.00 (0.88-1.14)	702	0.87 (0.80-0.94)	226	0.93 (0.82-1.06)	195	0.95 (0.82-1.10)	183	1.26 (1.09-1.46)	153	1.03 (0.87-1.22)	*0.0023*
Pancreas	405	89	1.00 (0.80-1.25)	40	0.96 (0.70-1.31)	111	0.96 (0.79-1.17)	52	1.18 (0.89-1.55)	44	1.19 (0.88-1.60)	26	1.05 (0.71-1.55)	43	1.75 (1.27-2.40)	*0.0655*
Lung	2741	660	1.00 (0.92-1.09)	344	1.07 (0.97-1.20)	720	0.79 (0.73-0.86)	296	0.80 (0.72-0.90)	312	1.06 (0.94-1.18)	202	1.06 (0.92-1.21)	207	1.05 (0.91-1.21)	*<0.0001*
Gallbladder	279	54	1.00 (0.75-1.33)	29	1.02 (0.71-1.48)	89	1.29 (1.03-1.62)	27	1.02 (0.69-1.49)	26	1.15 (0.78-1.70)	23	1.52 (1.01-2.30)	31	1.93 (1.33-2.81)	*0.0912*
Skin	137	41	1.00 (0.72-1.39)	17	1.00 (0.61-1.62)	44	0.83 (0.61-1.14)	12	0.65 (0.36-1.14)	11	0.75 (0.41-1.37)	6	0.59 (0.26-1.33)	6	0.57 (0.25-1.29)	*0.6670*
Prostate	402	110	1.00 (0.82-1.22)	64	1.25 (0.97-1.60)	120	1.00 (0.82-1.20)	37	0.80 (0.58-1.11)	30	0.92 (0.64-1.31)	18	0.88 (0.55-1.40)	23	1.05 (0.69-1.61)	*0.4945*
Kidney	219	34	1.00 (0.70-1.43)	28	1.52 (1.04-2.22)	73	1.14 (0.90-1.46)	27	1.02 (0.70-1.50)	25	1.34 (0.90-2.00)	17	1.53 (0.94-2.48)	15	1.57 (0.93-2.66)	*0.4775*
Bladder	356	89	1.00 (0.80-1.25)	57	1.14 (0.88-1.49)	96	0.74 (0.60-0.91)	35	0.64 (0.46-0.90)	41	0.95 (0.70-1.30)	21	0.78 (0.51-1.21)	17	0.60 (0.37-0.99)	*0.0313*
Brain	227	48	1.00 (0.74-1.35)	29	1.13 (0.78-1.64)	80	0.91 (0.72-1.15)	12	0.41 (0.23-0.73)	19	0.84 (0.53-1.32)	21	1.33 (0.86-2.05)	18	1.06 (0.65-1.72)	*0.0603*
Thyroid	84	12	1.00 (0.55-1.82)	10	1.65 (0.88-3.12)	27	0.95 (0.63-1.42)	9	0.78 (0.40-1.51)	12	1.44 (0.81-2.56)	8	1.53 (0.76-3.09)	6	1.31 (0.58-2.97)	*0.5400*
Lymphoma	402	104	1.00 (0.82-1.23)	49	1.02 (0.77-1.36)	115	0.88 (0.72-1.06)	38	0.81 (0.59-1.11)	30	0.76 (0.53-1.09)	29	1.05 (0.73-1.52)	37	1.21 (0.87-1.70)	*0.4312*
Multiple myeloma	137	34	1.00 (0.70-1.43)	10	0.62 (0.33-1.16)	44	0.88 (0.64-1.20)	15	0.80 (0.48-1.33)	14	1.10 (0.64-1.86)	10	1.21 (0.64-2.26)	10	1.20 (0.63-2.30)	*0.6942*

								Current regular drinkers								
		Abstainers		Ex-regular drinkers		Occasional drinkers		<140g/week		140-279g/week		280-419g/week		420+g/week		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{het}*
Leukaemia	287	63	1.00 (0.77-1.30)	31	1.15 (0.80-1.64)	86	0.87 (0.69-1.09)	38	1.11 (0.81-1.54)	27	1.06 (0.72-1.55)	18	1.05 (0.66-1.68)	24	1.43 (0.94-2.17)	*0.5189*
Other less common cancers of known sites	935	208	1.00 (0.87-1.16)	122	1.21 (1.01-1.45)	280	0.93 (0.82-1.06)	103	0.95 (0.78-1.15)	98	1.14 (0.93-1.39)	57	1.02 (0.78-1.33)	67	1.15 (0.90-1.48)	*0.2277*
IARC alcohol-related cancers	5403	1056	1.00 (0.94-1.07)	673	1.31 (1.22-1.42)	1669	0.91 (0.86-0.96)	494	0.89 (0.82-0.98)	499	1.17 (1.07-1.28)	418	1.46 (1.33-1.61)	594	1.96 (1.80-2.14)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	8730	2085	1.00 (0.95-1.05)	1076	1.07 (1.01-1.14)	2523	0.86 (0.83-0.90)	918	0.86 (0.80-0.92)	878	1.03 (0.97-1.10)	621	1.11 (1.02-1.20)	629	1.08 (0.99-1.17)	*<0.0001*
All cancers†	13342	2991	1.00 (0.96-1.04)	1647	1.14 (1.09-1.20)	3947	0.87 (0.84-0.90)	1359	0.87 (0.83-0.92)	1302	1.07 (1.01-1.13)	961	1.20 (1.12-1.28)	1135	1.35 (1.27-1.44)	*<0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*P for heterogeneity across the seven drinking categories.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 9. Adjusted HRs for cancer mortality associated with amount of alcohol consumption, in male current regular drinkers

		<140g/week		140-279g/week		280-419g/week		420+g/week		Per 280g/week usual intake		
Cancer site	All N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{trend}
Mouth and throat	92	13	1.00 (0.56-1.77)	27	2.27 (1.56-3.32)	17	2.27 (1.41-3.64)	35	3.83 (2.65-5.54)	92	1.68 (1.29-2.19)	*0.0001*
Oesophagus	417	64	1.00 (0.77-1.30)	90	1.67 (1.36-2.05)	81	2.19 (1.77-2.72)	182	4.21 (3.55-5.00)	417	2.04 (1.81-2.29)	*<0.0001*
Colon and rectum	172	54	1.00 (0.75-1.34)	49	1.18 (0.89-1.55)	32	1.19 (0.84-1.69)	37	1.30 (0.92-1.85)	172	1.38 (1.03-1.86)	*0.0320*
Colon	68	27	1.00 (0.65-1.54)	16	0.81 (0.50-1.32)	15	1.26 (0.75-2.10)	10	0.85 (0.44-1.65)	68	1.11 (0.63-1.93)	*0.7217*
Rectum	104	27	1.00 (0.67-1.50)	33	1.53 (1.09-2.14)	17	1.16 (0.72-1.87)	27	1.68 (1.11-2.54)	104	1.53 (1.08-2.16)	*0.0154*
Liver	407	108	1.00 (0.81-1.23)	97	1.16 (0.95-1.41)	90	1.62 (1.32-1.99)	112	1.93 (1.57-2.36)	407	1.58 (1.34-1.87)	*<0.0001*
Stomach	367	121	1.00 (0.82-1.22)	85	0.83 (0.68-1.03)	83	1.19 (0.96-1.48)	78	1.04 (0.82-1.32)	367	1.14 (0.91-1.43)	*0.2535*
Pancreas	117	37	1.00 (0.70-1.44)	30	0.91 (0.64-1.29)	20	0.90 (0.58-1.41)	30	1.31 (0.89-1.94)	117	1.18 (0.79-1.77)	*0.4090*
Lung	658	210	1.00 (0.86-1.16)	174	1.09 (0.94-1.26)	138	1.41 (1.19-1.67)	136	1.38 (1.15-1.66)	658	1.29 (1.10-1.51)	*0.0015*
Gallbladder	43	15	1.00 (0.56-1.80)	10	0.80 (0.43-1.47)	9	1.13 (0.58-2.18)	9	0.94 (0.46-1.92)	43	0.93 (0.45-1.90)	*0.8392*
Prostate	30	10	1.00 (0.49-2.05)	11	2.08 (1.17-3.69)	4	1.35 (0.50-3.67)	5	1.56 (0.61-4.03)	30	1.22 (0.56-2.68)	*0.6170*
Kidney	11	5	1.00 (0.35-2.84)	2	0.78 (0.20-3.09)	3	2.31 (0.71-7.51)	1	0.90 (0.12-6.86)	11	1.25 (0.30-5.20)	*0.7573*
Bladder	25	9	1.00 (0.48-2.10)	7	0.83 (0.41-1.71)	2	0.31 (0.08-1.23)	7	0.88 (0.38-2.08)	25	0.74 (0.28-2.00)	*0.5555*
Brain	40	8	1.00 (0.48-2.07)	14	2.14 (1.27-3.61)	11	2.51 (1.38-4.56)	7	1.57 (0.73-3.38)	40	1.14 (0.58-2.23)	*0.6964*
Lymphoma	29	7	1.00 (0.45-2.23)	7	1.10 (0.53-2.28)	4	0.77 (0.29-2.05)	11	1.83 (0.95-3.52)	29	1.58 (0.86-2.93)	*0.1416*
Myeloma	24	9	1.00 (0.47-2.11)	7	1.29 (0.63-2.66)	3	0.85 (0.27-2.65)	5	1.42 (0.54-3.73)	24	1.10 (0.43-2.78)	*0.8445*
Leukaemia	51	19	1.00 (0.60-1.67)	13	0.99 (0.58-1.69)	10	1.21 (0.65-2.27)	9	1.11 (0.55-2.22)	51	1.41 (0.88-2.24)	*0.1529*
Other less common cancers of known sites	106	34	1.00 (0.69-1.46)	31	1.25 (0.89-1.77)	20	1.37 (0.88-2.13)	21	1.49 (0.94-2.38)	106	1.24 (0.81-1.90)	*0.3125*
IARC alcohol-related cancers	1122	252	1.00 (0.87-1.14)	270	1.33 (1.18-1.50)	227	1.68 (1.48-1.91)	373	2.48 (2.21-2.78)	1122	1.76 (1.61-1.91)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	1690	552	1.00 (0.91-1.10)	439	1.02 (0.93-1.12)	343	1.24 (1.12-1.38)	356	1.23 (1.10-1.38)	1690	1.20 (1.08-1.32)	*0.0007*
All cancers*	2838	811	1.00 (0.93-1.08)	713	1.11 (1.04-1.20)	576	1.39 (1.28-1.51)	738	1.65 (1.52-1.79)	2838	1.46 (1.36-1.56)	*<0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*All cancers included ill-defined neoplasm and are patient-based.

Table G 10. Adjusted HRs for cancer mortality associated with drinking status and amount, in men

								Current regular drinkers								
		Abstainers		Ex-regular drinkers		Occasional drinkers		<140g/week		140-279g/week		280-419g/week		420+g/week		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{het}*
Mouth and throat	200	38	1.00 (0.71-1.40)	24	1.34 (0.89-2.01)	46	0.96 (0.70-1.31)	13	0.78 (0.45-1.35)	27	1.95 (1.33-2.85)	17	1.89 (1.17-3.05)	35	3.21 (2.23-4.61)	*<0.0001*
Oesophagus	966	150	1.00 (0.84-1.19)	102	1.45 (1.19-1.76)	297	0.96 (0.85-1.10)	64	0.98 (0.77-1.26)	90	1.68 (1.37-2.07)	81	2.14 (1.72-2.67)	182	4.16 (3.52-4.93)	*<0.0001*
Colon and rectum	499	102	1.00 (0.81-1.23)	77	1.46 (1.16-1.83)	148	1.02 (0.86-1.21)	54	0.99 (0.76-1.30)	49	1.19 (0.90-1.58)	32	1.26 (0.89-1.79)	37	1.37 (0.98-1.93)	*0.1166*
Colon	199	40	1.00 (0.72-1.39)	32	1.71 (1.20-2.43)	59	1.04 (0.79-1.37)	27	1.30 (0.88-1.90)	16	1.10 (0.67-1.80)	15	1.66 (0.99-2.78)	10	1.12 (0.59-2.12)	*0.2478*
Rectum	300	62	1.00 (0.77-1.31)	45	1.32 (0.98-1.78)	89	1.01 (0.81-1.26)	27	0.80 (0.55-1.18)	33	1.24 (0.87-1.75)	17	1.03 (0.64-1.67)	27	1.48 (1.00-2.21)	*0.2556*
Liver	1208	279	1.00 (0.88-1.14)	154	1.28 (1.09-1.51)	368	0.85 (0.76-0.95)	108	0.81 (0.67-0.98)	97	0.95 (0.78-1.16)	90	1.34 (1.08-1.65)	112	1.57 (1.29-1.91)	*<0.0001*
Stomach	1227	338	1.00 (0.89-1.12)	141	0.96 (0.81-1.14)	381	0.80 (0.72-0.89)	121	0.88 (0.74-1.06)	85	0.75 (0.60-0.93)	83	1.06 (0.85-1.32)	78	0.94 (0.74-1.19)	*0.0369*
Pancreas	285	61	1.00 (0.77-1.31)	28	0.96 (0.66-1.39)	79	1.00 (0.79-1.26)	37	1.18 (0.85-1.64)	30	1.14 (0.80-1.64)	20	1.16 (0.74-1.80)	30	1.75 (1.20-2.55)	*0.2594*
Lung	1768	442	1.00 (0.91-1.10)	224	1.03 (0.90-1.17)	444	0.77 (0.70-0.85)	210	0.87 (0.76-0.99)	174	0.90 (0.78-1.05)	138	1.16 (0.98-1.37)	136	1.08 (0.91-1.29)	*<0.0001*
Gallbladder	102	13	1.00 (0.57-1.76)	14	1.92 (1.13-3.27)	32	1.90 (1.30-2.78)	15	2.17 (1.29-3.63)	10	1.67 (0.89-3.11)	9	2.30 (1.18-4.46)	9	2.14 (1.08-4.26)	*0.4684*
Prostate	131	36	1.00 (0.70-1.42)	27	1.71 (1.16-2.53)	38	1.00 (0.71-1.40)	10	0.71 (0.38-1.33)	11	1.14 (0.63-2.07)	4	0.68 (0.25-1.84)	5	0.76 (0.31-1.87)	*0.1736*
Bladder	91	25	1.00 (0.65-1.53)	16	1.13 (0.69-1.87)	25	0.82 (0.54-1.24)	9	0.77 (0.40-1.49)	7	0.74 (0.35-1.56)	2	0.34 (0.08-1.37)	7	1.02 (0.46-2.24)	*0.7150*
Brain	126	25	1.00 (0.66-1.52)	15	1.24 (0.74-2.07)	46	1.06 (0.78-1.46)	8	0.60 (0.30-1.20)	14	1.42 (0.83-2.41)	11	1.71 (0.94-3.14)	7	0.98 (0.45-2.11)	*0.3803*
Lymphoma	76	18	1.00 (0.61-1.63)	11	1.30 (0.72-2.38)	18	0.75 (0.46-1.23)	7	0.79 (0.37-1.67)	7	1.05 (0.50-2.21)	4	0.84 (0.31-2.26)	11	1.97 (1.04-3.73)	*0.3401*
Multiple myeloma	65	19	1.00 (0.62-1.62)	4	0.46 (0.17-1.22)	18	0.75 (0.46-1.21)	9	0.94 (0.48-1.83)	7	0.96 (0.45-2.04)	3	0.61 (0.19-1.92)	5	0.91 (0.36-2.29)	*0.8377*
Leukaemia	145	38	1.00 (0.71-1.41)	15	0.85 (0.51-1.43)	41	0.75 (0.54-1.04)	19	0.99 (0.63-1.57)	13	0.88 (0.51-1.53)	10	1.03 (0.55-1.93)	9	0.89 (0.45-1.75)	*0.9273*
Other less common cancers	281	68	1.00 (0.77-1.29)	37	0.99 (0.71-1.37)	70	0.68 (0.53-0.88)	34	0.89 (0.63-1.25)	31	1.09 (0.76-1.56)	20	1.15 (0.74-1.79)	21	1.18 (0.75-1.84)	*0.1715*
IARC alcohol-related cancers	3044	617	1.00 (0.92-1.09)	401	1.38 (1.25-1.52)	904	0.87 (0.81-0.94)	252	0.84 (0.74-0.95)	270	1.15 (1.02-1.30)	227	1.46 (1.28-1.66)	373	2.16 (1.94-2.42)	*<0.0001*

								Current regular drinkers								
		Abstainers		Ex-regular drinkers		Occasional drinkers		<140g/week		140-279g/week		280-419g/week		420+g/week		
Cancer site	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{het}*
Other cancers of known sites (Non-IARC alcohol-related)	4899	1261	1.00 (0.94-1.06)	627	1.03 (0.95-1.12)	1321	0.80 (0.76-0.85)	552	0.91 (0.84-0.99)	439	0.91 (0.83-1.00)	343	1.11 (0.99-1.23)	356	1.07 (0.96-1.20)	*<0.0001*
All cancers†	8016	1895	1.00 (0.95-1.05)	1033	1.14 (1.07-1.21)	2250	0.82 (0.79-0.86)	811	0.88 (0.82-0.95)	713	0.98 (0.91-1.06)	576	1.22 (1.12-1.32)	738	1.44 (1.33-1.55)	*<0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for heterogeneity across the seven drinking categories.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 11. Adjusted HRs per 280g/week higher usual alcohol intake for incident cancers, in male current regular drinkers – in sequentially adjusted models

	Mouth and throat HR (95% CI)	Oesophagus HR (95% CI)	Colon and rectum HR (95% CI)	Liver HR (95% CI)	Stomach HR (95% CI)	Pancreas HR (95% CI)	Lung HR (95% CI)	Gallbladder HR (95% CI)	IARC alcohol-related cancers HR (95% CI)	Other cancers of known sites HR (95% CI)	All cancers* HR (95% CI)
Stratified by age-at-risk & study area	1.80 (1.56-2.08)	2.11 (1.93-2.31)	1.26 (1.06-1.49)	1.57 (1.37-1.81)	1.18 (1.01-1.37)	1.19 (0.87-1.63)	1.42 (1.27-1.60)	1.63 (1.19-2.23)	1.74 (1.63-1.85)	1.26 (1.17-1.35)	1.46 (1.39-1.54)
Further adjusted for											
+ Education	1.80 (1.55-2.09)	2.08 (1.90-2.27)	1.25 (1.05-1.49)	1.57 (1.36-1.81)	1.14 (0.98-1.33)	1.19 (0.86-1.64)	1.40 (1.25-1.58)	1.66 (1.21-2.27)	1.72 (1.61-1.84)	1.24 (1.15-1.33)	1.45 (1.37-1.52)
+ Income	1.80 (1.55-2.09)	2.06 (1.89-2.26)	1.25 (1.05-1.49)	1.57 (1.36-1.80)	1.14 (0.98-1.33)	1.20 (0.87-1.64)	1.40 (1.24-1.58)	1.65 (1.20-2.25)	1.72 (1.61-1.84)	1.24 (1.15-1.33)	1.45 (1.37-1.52)
+ Smoking	1.73 (1.48-2.03)	1.96 (1.78-2.15)	1.22 (1.02-1.45)	1.53 (1.32-1.77)	1.11 (0.95-1.30)	1.20 (0.87-1.66)	1.26 (1.11-1.43)	1.62 (1.18-2.23)	1.66 (1.55-1.78)	1.18 (1.09-1.27)	1.38 (1.31-1.46)
+ Physical activity	1.75 (1.49-2.06)	1.97 (1.79-2.17)	1.22 (1.02-1.45)	1.53 (1.32-1.77)	1.11 (0.95-1.30)	1.20 (0.87-1.66)	1.26 (1.11-1.43)	1.63 (1.18-2.25)	1.66 (1.55-1.78)	1.18 (1.09-1.27)	1.38 (1.31-1.46)
+ Fruit intake	1.74 (1.48-2.05)	1.96 (1.78-2.16)	1.20 (1.01-1.44)	1.52 (1.31-1.77)	1.11 (0.94-1.30)	1.20 (0.87-1.66)	1.26 (1.11-1.43)	1.61 (1.16-2.22)	1.65 (1.54-1.77)	1.18 (1.09-1.27)	1.38 (1.30-1.45)
+ BMI	1.74 (1.48-2.05)	2.00 (1.81-2.21)	1.20 (1.00-1.43)	1.52 (1.31-1.77)	1.11 (0.94-1.30)	1.20 (0.86-1.66)	1.25 (1.10-1.42)	1.60 (1.16-2.22)	1.65 (1.54-1.77)	1.17 (1.09-1.27)	1.38 (1.30-1.45)
+ Family history of cancer (Main Model)	**1.74 (1.48-2.05)**	**1.98 (1.79-2.18)**	**1.19 (1.00-1.43)**	**1.52 (1.31-1.76)**	**1.11 (0.94-1.30)**	**1.20 (0.86-1.66)**	**1.25 (1.10-1.42)**	**1.60 (1.16-2.22)**	**1.65 (1.53-1.77)**	**1.17 (1.09-1.27)**	**1.37 (1.30-1.45)**
+ Meat intake	1.74 (1.47-2.05)	1.98 (1.79-2.18)	1.20 (1.00-1.43)	1.52 (1.31-1.76)	1.11 (0.95-1.30)	1.19 (0.86-1.65)	1.25 (1.10-1.42)	1.60 (1.16-2.22)	1.65 (1.53-1.77)	1.17 (1.09-1.27)	1.37 (1.30-1.45)
+ Preserved vegetable intake	1.73 (1.47-2.05)	1.99 (1.80-2.20)	1.20 (1.00-1.43)	1.52 (1.31-1.76)	1.11 (0.94-1.30)	1.19 (0.86-1.65)	1.25 (1.10-1.42)	1.61 (1.17-2.22)	1.64 (1.53-1.76)	1.18 (1.09-1.27)	1.37 (1.30-1.45)

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer; BMI, body mass index.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*All cancers included ill-defined neoplasm and are patient-based.

Table G 12. Adjusted HRs for incident cancers associated with amount of alcohol consumption, in female current regular drinkers

		<70g/week		70+g/week		
Cancer site	**All current regular N**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	***p*-value**
Mouth and throat	5	3	1.00 (Ref)	2	0.72 (0.04-13.23)	*0.8273*
Oesophagus	15	6	1.00 (Ref)	9	1.65 (0.48-5.71)	*0.4278*
Colon and rectum	41	22	1.00 (Ref)	19	1.25 (0.60-2.63)	*0.5525*
Colon	28	15	1.00 (Ref)	13	1.04 (0.42-2.59)	*0.9354*
Rectum	20	10	1.00 (Ref)	10	1.86 (0.61-5.66)	*0.2735*
Liver	21	8	1.00 (Ref)	13	1.39 (0.48-3.97)	*0.5439*
Breast	56	40	1.00 (Ref)	16	0.68 (0.36-1.30)	*0.2436*
Stomach	24	7	1.00 (Ref)	17	2.67 (0.96-7.46)	*0.0606*
Pancreas	12	6	1.00 (Ref)	6	0.78 (0.22-2.80)	*0.6994*
Lung	40	20	1.00 (Ref)	20	0.91 (0.44-1.87)	*0.7980*
Gallbladder	11	5	1.00 (Ref)	6	0.73 (0.19-2.72)	*0.6371*
Cervix uteri	18	11	1.00 (Ref)	7	0.65 (0.22-1.94)	*0.4425*
Kidney	4	3	1.00 (Ref)	1	0.09 (0.00-3.97)	*0.2101*
Thyroid	12	8	1.00 (Ref)	4	1.27 (0.35-4.56)	*0.7137*
Lymphoma	6	3	1.00 (Ref)	3	5.43 (0.19-153.87)	*0.3211*
Leukaemia	9	5	1.00 (Ref)	4	1.05 (0.23-4.86)	*0.9527*
Other less common cancers of known sites	21	11	1.00 (Ref)	10	0.74 (0.26-2.10)	*0.5661*
IARC alcohol-related cancers	135	77	1.00 (Ref)	58	1.00 (0.67-1.49)	*0.9948*
Other cancers of known sites (Non-IARC alcohol-related)	180	89	1.00 (Ref)	91	1.05 (0.75-1.46)	*0.7926*
All cancers*	301	162	1.00 (Ref)	139	0.99 (0.76-1.29)	*0.9428*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.
Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.
*All cancers included ill-defined neoplasm and are patient-based.

Table G 13. Crude and standardised incidence rates (per 100,000 person-years) of major cancers, by alcohol consumption and smoking status in male current regular drinkers

	Never regular smokers									Ever regular smokers								
	<140g/week			140-419g/week			420+g/week			<140g/week			140-419g/week			420+g/week		
		Crude			Crude			Crude			Crude			Crude			Crude	
Cancer site	N	IR	SIR*	N	IR	SIR*	N	IR	SIR*	N	IR	SIR*	N	IR	SIR*	N	IR	SIR*
Oesophagus	19	33.9	35.5	19	43.8	45.3	14	116.3	99.8	94	49.0	46.2	260	96.3	95.8	249	214.6	183.9
Colon-rectum	35	62.4	46.5	26	59.9	63.3	8	66.5	99.9	139	72.6	70.8	260	96.5	98.1	107	92.1	87.4
Liver	38	67.7	68.5	22	50.7	51.3	10	83.1	95.1	140	73.0	71.6	258	95.5	96.9	147	126.5	123.3
Stomach	40	71.3	91.9	33	76.1	82.2	14	116.3	91.0	186	97.1	100.8	345	128.0	120.8	139	119.7	120.3
Lung	41	73.1	68.0	30	69.1	71.3	19	158.0	166.6	333	173.9	157.3	592	219.7	222.0	235	202.3	222.4
IARC alcohol-related	94	167.9	155.5	75	173.1	180.3	36	300.3	337.2	400	209.3	201.0	842	313.4	316.0	558	483.2	435.4
Other cancers of known sites (Non-IARC alcohol-related)	115	277.3	270.2	136	315.0	336.0	59	494.0	455.7	763	400.4	384.4	1363	509.2	501.9	570	493.5	506.8
All cancers	243	436.1	413.6	202	469.4	495.2	88	740.3	749.7	1116	588.1	562.3	2061	774.3	770.2	1047	913.5	890.4

IR, incidence rate; SIR, standardised incidence rate; IARC, international agency for research on cancer.

Participants with prior cancer were excluded. Mouth and throat cancer and pancreatic cancer are not shown due to the small number of cases (n<5 in at least one category).

*Incidence rates (per 100,000 person-years) are standardised to the age (10-year intervals) and study area (10 areas) structure of the China Kadoorie Biobank male population.

Table G 14. Adjusted HRs for major cancers associated with daily drinking, by weekly alcohol intake level in male current regular drinkers

			1-5 days/week		6-7 days/week				
					Full model*			Further adjusted for total alcohol intake	
Cancer site		All current regular N	N	HR (95% CI)	N	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Mouth and throat	<280g/week	106	36	1.00 (Ref)	70	1.48 (0.97-2.26)	*0.0698*	1.06 (0.63-1.76)	*0.8317*
	≥280g/week	130	5	1.00 (Ref)	125	1.40 (0.56-3.53)	*0.4718*	1.18 (0.47-2.99)	*0.7263*
Oesophagus	<280g/week	247	86	1.00 (Ref)	161	1.77 (1.33-2.34)	*<0.0001*	1.51 (1.08-2.12)	*0.0155*
	≥280g/week	408	15	1.00 (Ref)	393	1.72 (1.01-2.95)	*0.0467*	1.47 (0.86-2.52)	*0.1630*
Colon and rectum	<280g/week	349	131	1.00 (Ref)	218	1.33 (1.05-1.68)	*0.0161*	1.26 (0.95-1.66)	*0.1090*
	≥280g/week	226	13	1.00 (Ref)	213	0.99 (0.54-1.83)	*0.9827*	0.99 (0.53-1.83)	*0.9628*
Liver	<280g/week	300	122	1.00 (Ref)	178	1.28 (1.00-1.65)	*0.0511*	1.23 (0.91-1.65)	*0.1852*
	≥280g/week	273	14	1.00 (Ref)	259	1.30 (0.74-2.30)	*0.3651*	1.19 (0.67-2.12)	*0.5551*
Stomach	<280g/week	421	166	1.00 (Ref)	255	1.12 (0.91-1.38)	*0.2936*	1.12 (0.87-1.44)	*0.3736*
	≥280g/week	336	13	1.00 (Ref)	323	1.15 (0.65-2.06)	*0.6303*	1.20 (0.67-2.15)	*0.5390*
Lung	<280g/week	608	224	1.00 (Ref)	384	1.18 (0.99-1.41)	*0.0616*	1.04 (0.84-1.28)	*0.7442*
	≥280g/week	409	20	1.00 (Ref)	389	1.13 (0.70-1.81)	*0.6137*	1.08 (0.67-1.74)	*0.7437*
IARC alcohol-related cancers	<280g/week	993	370	1.00 (Ref)	623	1.44 (1.26-1.66)	*<0.0001*	1.32 (1.12-1.56)	*0.0011*
	≥280g/week	1012	49	1.00 (Ref)	963	1.29 (0.96-1.75)	*0.0960*	1.15 (0.85-1.56)	*0.3670*
Other cancers of known sites (Non-IARC alcohol-related)	<280g/week	1796	689	1.00 (Ref)	1107	1.16 (1.05-1.29)	*0.0035*	1.06 (0.94-1.20)	*0.3382*
	≥280g/week	1250	57	1.00 (Ref)	1193	1.16 (0.88-1.53)	*0.2977*	1.16 (0.88-1.54)	*0.2981*
All cancers†	<280g/week	2661	1027	1.00 (Ref)	1634	1.23 (1.13-1.34)	*<0.0001*	1.14 (1.03-1.26)	*0.0129*
	≥280g/week	2096	103	1.00 (Ref)	1993	1.16 (0.94-1.43)	*0.1554*	1.09 (0.88-1.35)	*0.4157*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 15. Adjusted HRs for major cancers associated with heavy episodic drinking, by weekly alcohol intake level in male current regular drinkers

			≤60g/session		>60g/session (i.e., HED)				
						Full model*		Further adjusted for total alcohol intake	
Cancer site		All current regular N	N	HR (95% CI)	N	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Mouth and throat	<280g/week	106	96	1.00 (Ref)	10	1.31 (0.66-2.60)	*0.4482*	1.23 (0.62-2.45)	*0.5577*
	≥280g/week	130	22	1.00 (Ref)	108	1.06 (0.63-1.80)	*0.8183*	0.81 (0.47-1.40)	*0.4530*
Oesophagus	<280g/week	247	231	1.00 (Ref)	16	0.81 (0.48-1.37)	*0.4282*	0.75 (0.44-1.27)	*0.2794*
	≥280g/week	408	50	1.00 (Ref)	358	1.33 (0.95-1.86)	*0.0949*	1.02 (0.72-1.44)	*0.9114*
Colon and rectum	<280g/week	349	324	1.00 (Ref)	25	0.93 (0.61-1.44)	*0.7536*	0.90 (0.59-1.39)	*0.6474*
	≥280g/week	226	59	1.00 (Ref)	167	0.87 (0.62-1.22)	*0.4328*	0.83 (0.56-1.21)	*0.3256*
Liver	<280g/week	300	273	1.00 (Ref)	27	1.02 (0.67-1.56)	*0.9310*	0.99 (0.64-1.52)	*0.9551*
	≥280g/week	273	56	1.00 (Ref)	217	1.15 (0.82-1.60)	*0.4162*	0.96 (0.67-1.38)	*0.8169*
Stomach	<280g/week	421	393	1.00 (Ref)	28	0.97 (0.65-1.46)	*0.8985*	0.97 (0.64-1.45)	*0.8652*
	≥280g/week	336	102	1.00 (Ref)	234	0.80 (0.62-1.05)	*0.1060*	0.82 (0.61-1.12)	*0.2149*
Lung	<280g/week	608	562	1.00 (Ref)	46	1.20 (0.87-1.65)	*0.2558*	1.17 (0.85-1.61)	*0.3337*
	≥280g/week	409	97	1.00 (Ref)	312	1.01 (0.78-1.31)	*0.9252*	0.92 (0.69-1.22)	*0.5474*
IARC alcohol-related cancers	<280g/week	993	917	1.00 (Ref)	76	0.94 (0.73-1.21)	*0.6273*	0.90 (0.70-1.15)	*0.3955*
	≥280g/week	1012	181	1.00 (Ref)	831	1.12 (0.93-1.34)	*0.2440*	0.90 (0.74-1.09)	*0.2652*
Other cancers of known sites (Non-IARC alcohol-related)	<280g/week	1796	1675	1.00 (Ref)	121	1.01 (0.83-1.23)	*0.9346*	0.98 (0.81-1.20)	*0.8697*
	≥280g/week	1250	322	1.00 (Ref)	928	0.92 (0.80-1.07)	*0.2830*	0.90 (0.77-1.06)	*0.2081*
All cancers†	<280g/week	2661	2471	1.00 (Ref)	190	0.98 (0.84-1.14)	*0.7778*	0.95 (0.81-1.11)	*0.5197*
	≥280g/week	2096	461	1.00 (Ref)	1635	1.01 (0.90-1.14)	*0.8483*	0.88 (0.77-1.00)	*0.0500*

HED, heavy episodic drinking; HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 16. Adjusted HRs for IARC alcohol-related cancers, other cancers and overall cancer associated with alcohol drinking status after various exclusions of participants, in men

	All men	Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
	N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Excluding the first three years of follow-up										
IARC alcohol-related cancers	3977	735	1.00 (0.93-1.08)	464	1.27 (1.16-1.40)	1252	0.97 (0.92-1.03)	1526	1.33 (1.26-1.41)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	6642	1519	1.00 (0.95-1.06)	767	1.04 (0.97-1.12)	1966	0.90 (0.86-0.94)	2390	1.04 (0.99-1.08)	*0.3230*
All cancers†	9952	2137	1.00 (0.96-1.05)	1155	1.11 (1.05-1.18)	3008	0.92 (0.88-0.95)	3652	1.12 (1.08-1.16)	*0.0001*
Excluding those with poor self-reported health status at baseline										
IARC alcohol-related cancers	4780	900	1.00 (0.93-1.07)	524	1.28 (1.18-1.40)	1509	0.95 (0.90-1.00)	1847	1.29 (1.23-1.36)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	7809	1819	1.00 (0.95-1.05)	863	1.05 (0.98-1.13)	2295	0.87 (0.84-0.91)	2832	1.00 (0.96-1.04)	*0.9997*
All cancers†	11873	2588	1.00 (0.96-1.04)	1298	1.12 (1.06-1.18)	3585	0.89 (0.86-0.92)	4402	1.09 (1.05-1.12)	*0.0015*
Excluding those with prior chronic disease‡ at baseline										
IARC alcohol-related cancers	3815	668	1.00 (0.92-1.08)	342	1.25 (1.12-1.39)	1240	1.00 (0.94-1.06)	1565	1.40 (1.33-1.48)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	6188	1408	1.00 (0.95-1.06)	597	1.08 (0.99-1.17)	1855	0.88 (0.84-0.93)	2328	1.01 (0.97-1.06)	*0.7666*
All cancers†	9423	1979	1.00 (0.95-1.05)	892	1.14 (1.06-1.21)	2900	0.91 (0.88-0.95)	3652	1.12 (1.08-1.16)	*0.0001*
Excluding all of above										
IARC alcohol-related cancers	2676	443	1.00 (0.91-1.10)	218	1.24 (1.08-1.41)	886	1.05 (0.98-1.13)	1129	1.44 (1.35-1.53)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	4443	969	1.00 (0.94-1.07)	374	1.01 (0.91-1.12)	1372	0.92 (0.87-0.97)	1728	1.04 (0.99-1.10)	*0.3146*
All cancers†	6655	1342	1.00 (0.94-1.06)	564	1.10 (1.01-1.19)	2096	0.95 (0.91-0.99)	2653	1.15 (1.10-1.20)	*0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses.

**P* for association comparing current regular drinking vs. abstainers.

†All cancers included ill-defined neoplasm and are patient-based.

‡Prior chronic diseases included self-reported coronary heart diseases, stroke or transient ischaemic attack, diabetes, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, and kidney disease.

Table G 17. Adjusted HRs for IARC alcohol-related cancers, other cancers and overall cancer associated with amount of alcohol consumption after various exclusions of participants, in male current regular drinkers

		<140g/week		140-279g/week		280-419g/week		420+g/week		By 280g/week usual intake		
	All current regular N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{trend}
Excluding the first three years of follow-up												
IARC alcohol-related cancers	1526	372	1.00 (0.90-1.12)	384	1.31 (1.18-1.44)	317	1.61 (1.44-1.80)	453	2.15 (1.94-2.39)	1526	1.66 (1.53-1.80)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	2390	714	1.00 (0.92-1.08)	682	1.22 (1.13-1.31)	498	1.34 (1.23-1.46)	496	1.32 (1.20-1.45)	2390	1.19 (1.09-1.30)	*<0.0001*
All cancers*	3652	1041	1.00 (0.94-1.07)	994	1.22 (1.15-1.30)	745	1.38 (1.29-1.49)	872	1.57 (1.46-1.68)	3652	1.38 (1.30-1.47)	*<0.0001*
Excluding those with poor self-reported health status at baseline												
IARC alcohol-related cancers	1847	467	1.00 (0.91-1.10)	453	1.23 (1.12-1.35)	385	1.57 (1.42-1.73)	542	2.09 (1.91-2.30)	1847	1.66 (1.54-1.79)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	2832	844	1.00 (0.93-1.08)	822	1.24 (1.16-1.32)	578	1.30 (1.20-1.42)	588	1.31 (1.20-1.43)	2832	1.18 (1.09-1.28)	*<0.0001*
All cancers*	4402	1261	1.00 (0.94-1.06)	1204	1.22 (1.15-1.29)	886	1.35 (1.27-1.45)	1051	1.56 (1.46-1.67)	4402	1.38 (1.30-1.46)	*<0.0001*
Excluding those with prior chronic disease† at baseline												
IARC alcohol-related cancers	1565	359	1.00 (0.89-1.12)	376	1.27 (1.15-1.40)	333	1.65 (1.48-1.83)	497	2.28 (2.07-2.51)	1565	1.74 (1.60-1.89)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	2328	645	1.00 (0.92-1.09)	674	1.23 (1.14-1.33)	504	1.34 (1.23-1.46)	505	1.29 (1.17-1.41)	2328	1.17 (1.07-1.27)	*0.0005*
All cancers*	3652	965	1.00 (0.93-1.07)	989	1.22 (1.15-1.30)	772	1.41 (1.31-1.51)	926	1.59 (1.49-1.71)	3652	1.39 (1.31-1.49)	*<0.0001*
Excluding all of above												
IARC alcohol-related cancers	1129	270	1.00 (0.88-1.14)	267	1.21 (1.08-1.37)	237	1.56 (1.38-1.77)	355	2.16 (1.92-2.42)	1129	1.70 (1.54-1.88)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)	1728	480	1.00 (0.91-1.10)	501	1.23 (1.13-1.34)	372	1.32 (1.19-1.46)	375	1.29 (1.15-1.43)	1728	1.17 (1.06-1.30)	*0.0018*
All cancers*	2653	716	1.00 (0.92-1.08)	714	1.19 (1.11-1.28)	555	1.35 (1.24-1.47)	668	1.54 (1.42-1.68)	2653	1.37 (1.27-1.48)	*<0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses.

*All cancers included ill-defined neoplasm and are patient-based.

†Prior chronic diseases included self-reported coronary heart diseases, stroke or transient ischaemic attack, diabetes, tuberculosis, chronic hepatitis/cirrhosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, and kidney disease.

Table G 18. Adjusted HRs for major cancers associated with *ALDH2-rs671* genotype, in men – in sequentially adjusted models

		Full adjustment as in conventional epidemiological analyses*								Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA			GG	AG		AA	
Cancer site	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Mouth and throat	181	108	1.00 (0.82-1.22)	69	1.07 (0.84-1.35)	*0.6819*	4	0.40 (0.15-1.06)	*0.0721*	1.00 (0.80-1.25)	1.23 (0.98-1.55)	*0.1966*	0.48 (0.18-1.29)	*0.1546*
Oesophagus	537	373	1.00 (0.89-1.12)	153	1.00 (0.85-1.16)	*0.9619*	11	0.68 (0.38-1.24)	*0.2188*	1.00 (0.88-1.14)	1.29 (1.11-1.50)	*0.0132*	0.99 (0.54-1.79)	*0.9623*
Colorectal	540	356	1.00 (0.90-1.12)	166	0.86 (0.74-0.99)	*0.1026*	18	0.66 (0.41-1.04)	*0.0842*	1.00 (0.88-1.13)	0.91 (0.78-1.05)	*0.3222*	0.71 (0.44-1.12)	*0.1571*
Liver	569	372	1.00 (0.90-1.12)	176	0.87 (0.76-1.01)	*0.1437*	21	0.72 (0.47-1.11)	*0.1511*	1.00 (0.88-1.13)	0.96 (0.83-1.10)	*0.6435*	0.81 (0.53-1.25)	*0.3622*
Stomach	722	485	1.00 (0.91-1.10)	215	0.93 (0.82-1.06)	*0.4034*	22	0.77 (0.51-1.17)	*0.2345*	1.00 (0.89-1.12)	0.95 (0.84-1.08)	*0.5796*	0.79 (0.52-1.21)	*0.2942*
Pancreas	111	76	1.00 (0.78-1.27)	33	0.80 (0.57-1.12)	*0.2897*	2	0.34 (0.09-1.37)	*0.1353*	1.00 (0.75-1.33)	0.78 (0.56-1.08)	*0.2598*	0.33 (0.08-1.33)	*0.1263*
Lung	916	545	1.00 (0.91-1.09)	327	1.05 (0.95-1.17)	*0.4604*	44	0.94 (0.70-1.27)	*0.7039*	1.00 (0.90-1.11)	1.11 (1.00-1.23)	*0.1770*	1.00 (0.74-1.35)	*0.9855*
IARC alcohol-related cancers	1853	1220	1.00 (0.94-1.06)	579	0.94 (0.86-1.01)	*0.1984*	54	0.65 (0.49-0.85)	*0.0019*	1.00 (0.93-1.07)	1.07 (0.99-1.15)	*0.2246*	0.77 (0.59-1.00)	*0.0618*
Other cancers of known sites (Non-IARC alcohol-related)	2938	1806	1.00 (0.95-1.05)	994	1.01 (0.95-1.08)	*0.7558*	138	1.00 (0.84-1.18)	*0.9875*	1.00 (0.94-1.06)	1.04 (0.98-1.10)	*0.3939*	1.03 (0.87-1.22)	*0.7543*
All cancers‡	4537	2850	1.00 (0.96-1.04)	1502	0.99 (0.94-1.04)	*0.8236*	185	0.88 (0.76-1.01)	*0.0879*	1.00 (0.96-1.05)	1.06 (1.01-1.12)	*0.0653*	0.96 (0.83-1.11)	*0.5950*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk and study area, and adjusted for education, income, smoking, body mass index, physical activity, fresh fruit intake, and family history of cancer.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

‡All cancers included ill-defined neoplasm and are patient-based.

Table G 19. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, by drinking status in men – in sequentially adjusted models

		Full adjustment as in conventional epidemiological analyses*							Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA		GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Mouth and throat														
Never regular	85	36	1.00 (0.70-1.43)	45	1.08 (0.81-1.44)	*0.7342*	4	0.47 (0.17-1.25)	*0.1564*	1.00 (0.68-1.48)	1.11 (0.86-1.44)	*0.6624*	0.50 (0.18-1.36)	*0.2059*
Current regular	72	53	1.00 (0.74-1.36)	19	1.83 (1.18-2.83)	*0.0261*	0	--	--	1.00 (0.72-1.38)	2.02 (1.31-3.11)	*0.0108*	--	--
Oesophagus														
Never regular	264	170	1.00 (0.82-1.22)	83	0.90 (0.73-1.09)	*0.4380*	11	1.04 (0.57-1.91)	*0.8935*	1.00 (0.81-1.24)	0.91 (0.76-1.09)	*0.5111*	1.10 (0.59-2.04)	*0.7822*
Current regular	229	174	1.00 (0.83-1.21)	55	2.25 (1.76-2.88)	*<0.0001*	0	--	--	1.00 (0.81-1.24)	2.94 (2.31-3.73)	*<0.0001*	--	--
Colon and rectum														
Never regular	265	127	1.00 (0.82-1.21)	122	0.90 (0.75-1.07)	*0.4185*	16	0.65 (0.39-1.06)	*0.1064*	1.00 (0.81-1.24)	0.86 (0.73-1.01)	*0.2730*	0.58 (0.35-0.97)	*0.0549*
Current regular	206	180	1.00 (0.85-1.17)	26	0.83 (0.56-1.21)	*0.3671*	0	--	--	1.00 (0.85-1.18)	0.88 (0.60-1.30)	*0.5477*	--	--
Liver														
Never regular	295	140	1.00 (0.82-1.21)	134	0.99 (0.84-1.16)	*0.9339*	21	0.85 (0.55-1.31)	*0.4970*	1.00 (0.81-1.24)	0.99 (0.85-1.14)	*0.9153*	0.84 (0.54-1.31)	*0.4931*
Current regular	201	173	1.00 (0.85-1.18)	28	0.95 (0.66-1.38)	*0.8167*	0	--	--	1.00 (0.84-1.19)	1.05 (0.72-1.52)	*0.8128*	--	--
Stomach														
Never regular	393	214	1.00 (0.84-1.18)	157	0.88 (0.76-1.02)	*0.2706*	22	0.83 (0.54-1.27)	*0.4163*	1.00 (0.83-1.20)	0.88 (0.77-1.01)	*0.2703*	0.82 (0.53-1.27)	*0.4141*
Current regular	240	199	1.00 (0.85-1.17)	41	1.30 (0.96-1.75)	*0.1350*	0	--	--	1.00 (0.84-1.19)	1.34 (0.99-1.81)	*0.0986*	--	--
Pancreas														
Never regular	52	24	1.00 (0.63-1.58)	26	0.91 (0.63-1.31)	*0.7469*	2	0.38 (0.09-1.53)	*0.1968*	1.00 (0.60-1.66)	0.89 (0.63-1.24)	*0.7000*	0.36 (0.09-1.49)	*0.1849*
Current regular	38	34	1.00 (0.72-1.39)	4	0.67 (0.25-1.82)	*0.4596*	0	--	--	1.00 (0.66-1.51)	0.67 (0.25-1.78)	*0.4622*	--	--
Lung														
Never regular	449	168	1.00 (0.84-1.19)	238	1.13 (1.00-1.27)	*0.2725*	43	1.02 (0.75-1.38)	*0.9304*	1.00 (0.83-1.21)	1.10 (0.99-1.23)	*0.3681*	0.97 (0.71-1.33)	*0.8872*
Current regular	347	295	1.00 (0.88-1.14)	51	0.96 (0.73-1.26)	*0.7862*	1	2.84 (0.39-20.49)	*0.3012*	1.00 (0.87-1.15)	1.02 (0.78-1.34)	*0.8845*	3.16 (0.44-22.82)	*0.2551*
IARC alcohol-related cancers														
Never regular	933	481	1.00 (0.90-1.11)	400	0.96 (0.87-1.05)	*0.5364*	52	0.73 (0.55-0.96)	*0.0334*	1.00 (0.89-1.12)	0.94 (0.86-1.02)	*0.4125*	0.70 (0.53-0.92)	*0.0206*
Current regular	700	573	1.00 (0.91-1.10)	127	1.36 (1.15-1.62)	*0.0020*	0	--	--	1.00 (0.90-1.11)	1.56 (1.31-1.85)	*<0.0001*	--	--

		Full adjustment as in conventional epidemiological analyses*								Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Other cancers of known sites (Non-IARC alcohol-related)														
Never regular	1546	661	1.00 (0.92-1.09)	753	1.05 (0.98-1.13)	*0.3656*	132	1.03 (0.87-1.23)	*0.7406*	1.00 (0.91-1.10)	1.04 (0.97-1.10)	*0.5416*	1.00 (0.83-1.19)	*0.9750*
Current regular	999	853	1.00 (0.93-1.08)	145	1.01 (0.86-1.19)	*0.8982*	1	1.12 (0.16-7.97)	*0.9132*	1.00 (0.92-1.08)	1.05 (0.89-1.23)	*0.5949*	1.16 (0.16-8.29)	*0.8814*
All cancers‡														
Never regular	2342	1063	1.00 (0.93-1.07)	1101	1.04 (0.99-1.10)	*0.3671*	178	0.95 (0.82-1.10)	*0.5510*	1.00 (0.93-1.08)	1.02 (0.97-1.07)	*0.6747*	0.90 (0.78-1.05)	*0.2483*
Current regular	1609	1347	1.00 (0.94-1.06)	261	1.16 (1.03-1.31)	*0.0302*	1	0.75 (0.11-5.37)	*0.7780*	1.00 (0.94-1.07)	1.25 (1.11-1.41)	*0.0012*	0.82 (0.12-5.87)	*0.8469*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Ex-regular drinkers and participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk and study area, and adjusted for education, income, smoking, body mass index, physical activity, fresh fruit intake, and family history of cancer.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

‡All cancers included ill-defined neoplasm and are patient-based.

Table G 20. Adjusted HRs for major cancers associated with the joint effects of *ALDH2*-rs671 genotype and alcohol consumption, in male current regular drinkers

		<280g/week		280+g/week		
	All current regular N	N	HR (95% CI)	N	HR (95% CI)	$p_{interaction}$ *
UADT						
GG	223	99	1.00 (0.80-1.25)	124	1.69 (1.41-2.03)	
AG	70	23	1.18 (0.78-1.78)	47	7.54 (5.60-10.16)	*<0.0001*
Mouth and throat						
GG	53	30	1.00 (0.68-1.48)	23	1.00 (0.65-1.53)	
AG	19	7	0.90 (0.43-1.90)	12	4.55 (2.53-8.16)	*0.0031*
Oesophagus						
GG	174	71	1.00 (0.77-1.30)	103	1.97 (1.63-2.39)	
AG	55	17	1.32 (0.81-2.13)	38	9.56 (6.84-13.37)	*<0.0001*
Colon and rectum						
GG	180	108	1.00 (0.81-1.23)	72	1.18 (0.91-1.51)	
AG	26	20	0.83 (0.54-1.29)	6	1.08 (0.48-2.42)	*0.8369*
Liver						
GG	173	85	1.00 (0.79-1.26)	88	1.47 (1.16-1.85)	
AG	28	21	1.10 (0.72-1.70)	7	1.25 (0.59-2.64)	*0.5757*
Stomach						
GG	199	108	1.00 (0.81-1.23)	91	1.09 (0.88-1.36)	
AG	41	29	1.25 (0.86-1.80)	12	1.68 (0.95-2.97)	*0.5844*
Pancreas						
GG	34	16	1.00 (0.58-1.72)	18	1.66 (0.99-2.79)	
AG	4	3	0.83 (0.27-2.61)	1	0.94 (0.13-6.80)	*0.7469*
Lung						
GG	295	177	1.00 (0.85-1.18)	118	1.16 (0.96-1.40)	
AG	51	30	0.75 (0.52-1.07)	21	2.09 (1.35-3.23)	*0.0058*
IARC alcohol-related cancers						
GG	573	286	1.00 (0.88-1.14)	287	1.47 (1.30-1.66)	
AG	127	66	1.08 (0.85-1.38)	61	3.52 (2.73-4.55)	*<0.0001*
Other cancers of known sites (Non-IARC alcohol-related)						
GG	853	490	1.00 (0.91-1.10)	363	1.14 (1.02-1.28)	
AG	145	95	0.89 (0.73-1.09)	50	1.72 (1.30-2.27)	*0.0071*
All cancers†						
GG	1347	744	1.00 (0.92-1.08)	603	1.24 (1.14-1.36)	
AG	261	157	0.97 (0.83-1.14)	104	2.36 (1.94-2.87)	*<0.0001*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Cox models are stratified by age-at-risk and study area; adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

**P* for interaction was assessed using the likelihood ratio test, with inclusion of an interaction term in the model.

†All cancers included ill-defined neoplasm and are patient-based.

Table G 21. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in men – in sequentially adjusted models

		Full adjustment as in conventional epidemiological analyses*								Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Mouth and throat	180	26	1.00 (0.68-1.47)	74	0.58 (0.46-0.73)	*0.0183*	80	0.53 (0.43-0.66)	*0.0053*	1.00 (0.68-1.48)	0.62 (0.49-0.78)	*0.0382*	0.57 (0.46-0.71)	*0.0143*
Oesophagus	538	84	1.00 (0.81-1.24)	242	0.62 (0.55-0.70)	*0.0002*	212	0.52 (0.45-0.59)	*<0.0001*	1.00 (0.80-1.24)	0.68 (0.60-0.77)	*0.0025*	0.58 (0.50-0.66)	*<0.0001*
Colon and rectum	540	43	1.00 (0.74-1.35)	238	1.15 (1.02-1.31)	*0.3874*	259	1.10 (0.97-1.25)	*0.5589*	1.00 (0.74-1.35)	1.19 (1.05-1.35)	*0.3025*	1.14 (1.01-1.29)	*0.4350*
Liver	569	63	1.00 (0.78-1.28)	226	0.77 (0.67-0.87)	*0.0647*	280	0.85 (0.76-0.96)	*0.2507*	1.00 (0.78-1.28)	0.79 (0.70-0.91)	*0.1090*	0.88 (0.79-1.00)	*0.3832*
Stomach	722	71	1.00 (0.79-1.26)	319	0.98 (0.88-1.10)	*0.8934*	332	0.95 (0.85-1.06)	*0.7023*	1.00 (0.79-1.26)	0.99 (0.89-1.11)	*0.9463*	0.96 (0.86-1.07)	*0.7639*
Pancreas	111	14	1.00 (0.59-1.69)	44	0.64 (0.48-0.86)	*0.1527*	53	0.70 (0.53-0.92)	*0.2363*	1.00 (0.59-1.70)	0.64 (0.48-0.87)	*0.1548*	0.70 (0.53-0.92)	*0.2396*
Lung	916	77	1.00 (0.80-1.25)	396	1.05 (0.95-1.16)	*0.6873*	443	1.02 (0.93-1.12)	*0.8921*	1.00 (0.80-1.25)	1.07 (0.97-1.18)	*0.6126*	1.03 (0.94-1.14)	*0.7919*
IARC alcohol-related cancers	1853	220	1.00 (0.88-1.14)	795	0.77 (0.72-0.82)	*0.0006*	838	0.73 (0.68-0.78)	*<0.0001*	1.00 (0.88-1.14)	0.81 (0.75-0.86)	*0.0051*	0.77 (0.72-0.83)	*0.0007*
Other cancers of known sites (Non-IARC alcohol-related)	2939	270	1.00 (0.89-1.13)	1250	0.96 (0.91-1.01)	*0.5436*	1419	0.96 (0.91-1.02)	*0.5744*	1.00 (0.89-1.13)	0.97 (0.91-1.02)	*0.6130*	0.97 (0.92-1.02)	*0.6594*
All cancers‡	4537	471	1.00 (0.91-1.09)	1938	0.86 (0.82-0.90)	*0.0035*	2128	0.84 (0.80-0.88)	*0.0006*	1.00 (0.91-1.10)	0.88 (0.84-0.92)	*0.0137*	0.86 (0.83-0.90)	*0.0038*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk and study area, and adjusted for education, income, smoking, body mass index, physical activity, fresh fruit intake, and family history of cancer.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

‡All cancers included ill-defined neoplasm and are patient-based.

Table G 22. Adjusted HRs for major cancers associated with *ALDH2*-rs671 genotype, in women – in sequentially adjusted models

		Model stratified by age-at-risk and study area								Full adjustment plus alcohol consumption*			
		GG		AG			AA			AG		AA	
Cancer site	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Mouth and throat	111	65	1.00 (Ref)	36	0.93 (0.62-1.41)	*0.7382*	10	1.62 (0.83-3.17)	*0.1608*	0.92 (0.61-1.40)	*0.7080*	1.59 (0.81-3.12)	*0.1771*
Oesophagus	233	184	1.00 (Ref)	42	0.61 (0.43-0.85)	*0.0038*	7	0.96 (0.45-2.06)	*0.9192*	0.61 (0.44-0.86)	*0.0044*	0.98 (0.46-2.09)	*0.9527*
Colon and rectum	541	324	1.00 (Ref)	198	1.15 (0.96-1.38)	*0.1211*	19	0.75 (0.47-1.19)	*0.2202*	1.15 (0.96-1.38)	*0.1248*	0.75 (0.47-1.19)	*0.2178*
Liver	321	189	1.00 (Ref)	109	1.12 (0.88-1.42)	*0.3620*	23	1.62 (1.04-2.51)	*0.0318*	1.12 (0.88-1.42)	*0.3515*	1.61 (1.04-2.49)	*0.0345*
Female breast	780	482	1.00 (Ref)	253	1.04 (0.89-1.21)	*0.6480*	45	1.29 (0.95-1.76)	*0.1057*	1.04 (0.89-1.21)	*0.6467*	1.29 (0.95-1.76)	*0.1078*
Stomach	382	217	1.00 (Ref)	141	1.33 (1.07-1.65)	*0.0090*	24	1.65 (1.07-2.52)	*0.0219*	1.35 (1.09-1.67)	*0.0066*	1.67 (1.09-2.56)	*0.0192*
Pancreas	130	86	1.00 (Ref)	40	0.88 (0.60-1.29)	*0.5148*	4	0.59 (0.22-1.63)	*0.3114*	0.88 (0.60-1.29)	*0.5159*	0.60 (0.22-1.65)	*0.3264*
Lung	696	404	1.00 (Ref)	261	1.25 (1.07-1.47)	*0.0047*	31	1.07 (0.74-1.54)	*0.7271*	1.25 (1.07-1.47)	*0.0053*	1.06 (0.74-1.54)	*0.7452*
IARC alcohol-related cancers	1952	1228	1.00 (Ref)	622	1.01 (0.92-1.11)	*0.8231*	102	1.17 (0.95-1.43)	*0.1409*	1.01 (0.92-1.12)	*0.8040*	1.17 (0.95-1.43)	*0.1359*
Other cancers of known sites (Non-IARC alcohol-related)	2834	1684	1.00 (Ref)	1008	1.17 (1.08-1.26)	*0.0001*	142	1.14 (0.96-1.36)	*0.1281*	1.17 (1.08-1.26)	*0.0001*	1.14 (0.96-1.36)	*0.1385*
All cancers†	4630	2835	1.00 (Ref)	1557	1.08 (1.02-1.15)	*0.0117*	238	1.16 (1.01-1.33)	*0.0297*	1.08 (1.02-1.15)	*0.0116*	1.16 (1.01-1.32)	*0.0310*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, body mass index, physical activity, fresh fruit intake, family history of cancer, and total alcohol intake.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

‡All cancers included ill-defined neoplasm and are patient-based.

Table G 23. Adjusted HRs for major cancers associated with *ADH1B*-rs1229984 genotype, in women – in sequentially adjusted models

		Model stratified by age-at-risk and study area								Full adjustment plus alcohol consumption*			
		GG		AG			AA			AG		AA	
Cancer site	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Mouth and throat	111	4	1.00 (Ref)	53	2.92 (1.06-8.06)	*0.0390*	54	2.48 (0.90-6.85)	*0.0800*	2.92 (1.06-8.09)	*0.0386*	2.49 (0.90-6.87)	*0.0793*
Oesophagus	233	33	1.00 (Ref)	89	0.71 (0.47-1.06)	*0.0912*	111	0.85 (0.58-1.26)	*0.4304*	0.72 (0.48-1.08)	*0.1106*	0.86 (0.58-1.27)	*0.4523*
Colon and rectum	541	51	1.00 (Ref)	235	1.04 (0.77-1.41)	*0.7805*	255	1.00 (0.74-1.35)	*0.9913*	1.04 (0.77-1.41)	*0.7878*	1.00 (0.74-1.35)	*0.9938*
Liver	321	36	1.00 (Ref)	146	0.94 (0.65-1.36)	*0.7424*	139	0.80 (0.55-1.15)	*0.2219*	0.95 (0.66-1.37)	*0.7720*	0.80 (0.56-1.16)	*0.2411*
Female breast	780	60	1.00 (Ref)	333	1.28 (0.97-1.69)	*0.0753*	387	1.33 (1.01-1.74)	*0.0417*	1.28 (0.97-1.69)	*0.0779*	1.32 (1.01-1.74)	*0.0447*
Stomach	382	36	1.00 (Ref)	159	1.05 (0.73-1.51)	*0.7940*	187	1.13 (0.79-1.61)	*0.5097*	1.06 (0.74-1.52)	*0.7597*	1.14 (0.80-1.63)	*0.4791*
Pancreas	130	17	1.00 (Ref)	57	0.77 (0.45-1.32)	*0.3398*	56	0.68 (0.39-1.17)	*0.1647*	0.78 (0.45-1.34)	*0.3715*	0.69 (0.40-1.19)	*0.1828*
Lung	696	54	1.00 (Ref)	313	1.32 (0.99-1.77)	*0.0566*	329	1.24 (0.93-1.66)	*0.1392*	1.33 (0.99-1.77)	*0.0561*	1.24 (0.93-1.65)	*0.1484*
IARC alcohol-related cancers	1952	185	1.00 (Ref)	845	1.07 (0.91-1.25)	*0.4213*	922	1.04 (0.89-1.22)	*0.6251*	1.07 (0.91-1.25)	*0.4177*	1.04 (0.89-1.22)	*0.6268*
Other cancers of known sites (Non-IARC alcohol-related)	2834	271	1.00 (Ref)	1185	1.01 (0.88-1.15)	*0.8850*	1378	1.05 (0.92-1.19)	*0.4830*	1.01 (0.88-1.15)	*0.8913*	1.05 (0.92-1.19)	*0.4940*
All cancers‡	4631	444	1.00 (Ref)	1954	1.02 (0.92-1.13)	*0.6793*	2233	1.04 (0.94-1.16)	*0.4125*	1.02 (0.92-1.13)	*0.6744*	1.04 (0.94-1.16)	*0.4159*

HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

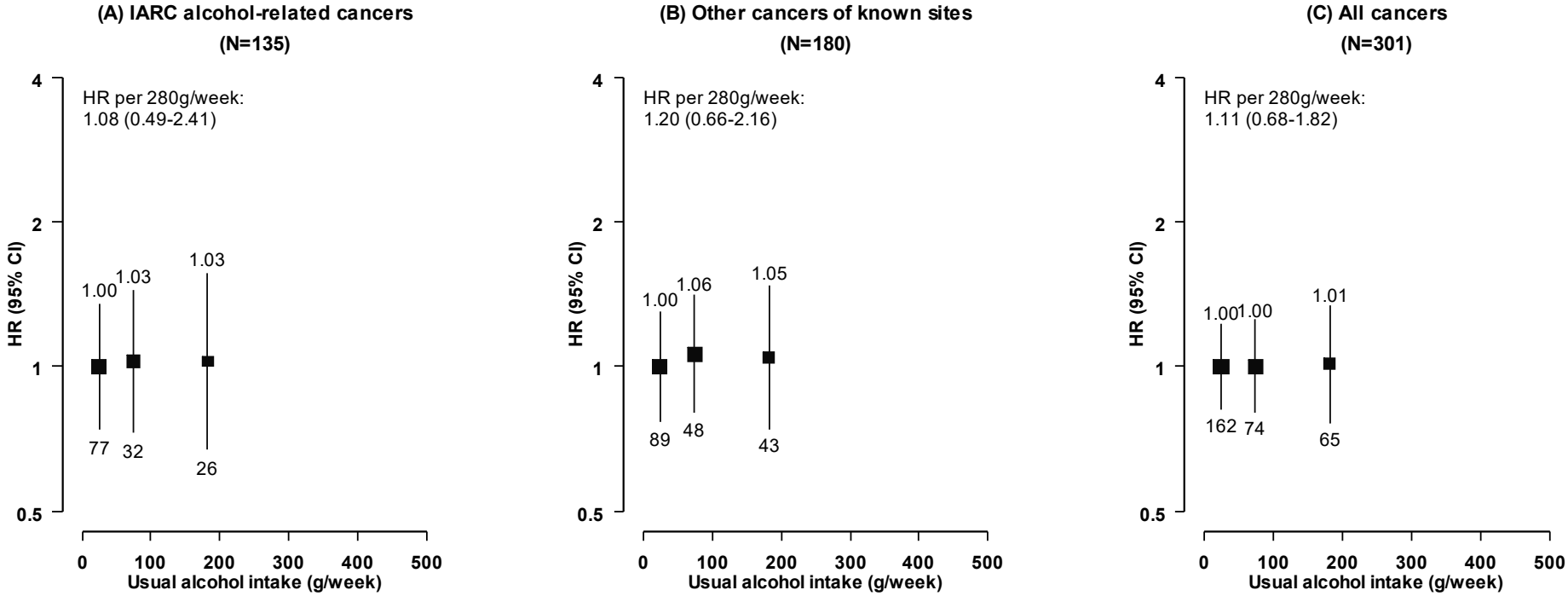
Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer.

*Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, body mass index, physical activity, fresh fruit intake, family history of cancer, and total alcohol intake.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

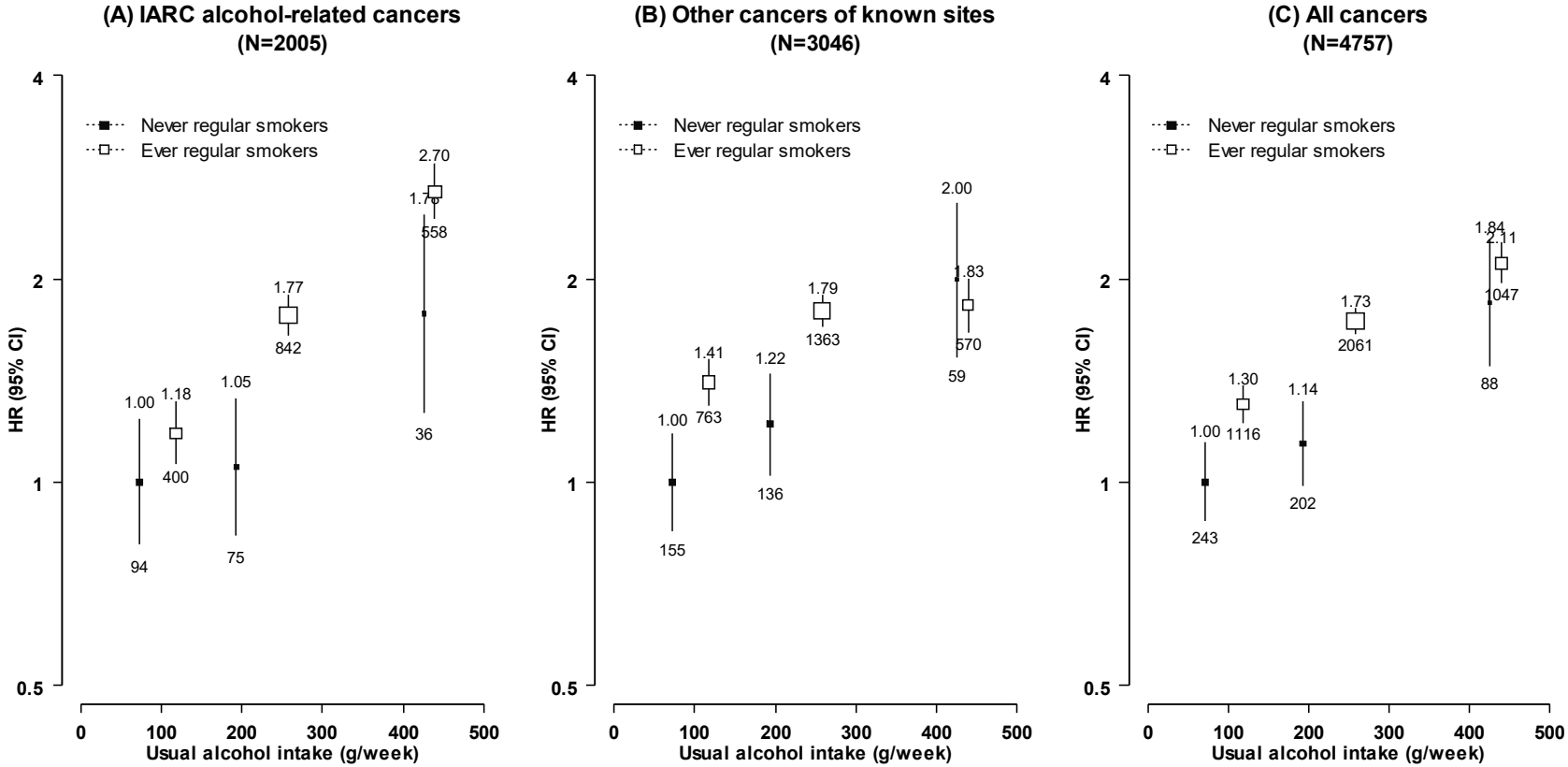
‡All cancers included ill-defined neoplasm and are patient-based.

Figure G 1. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancer, in female current regular drinkers



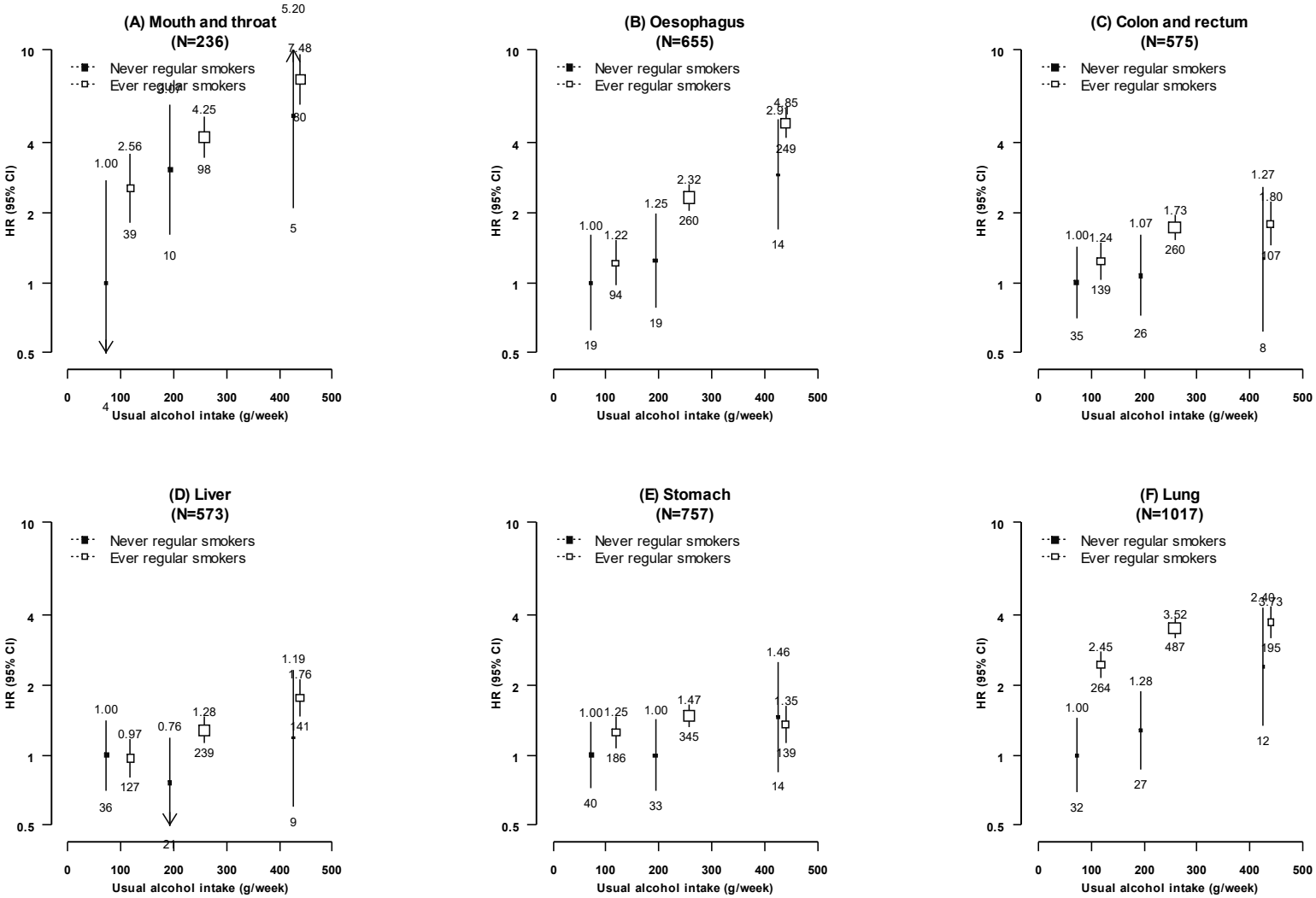
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; IARC, international agency for research on cancer.

Figure G 2. Associations of the joint effects of alcohol consumption and smoking with IARC alcohol-related cancers, other cancers and overall cancer, in male current regular drinkers



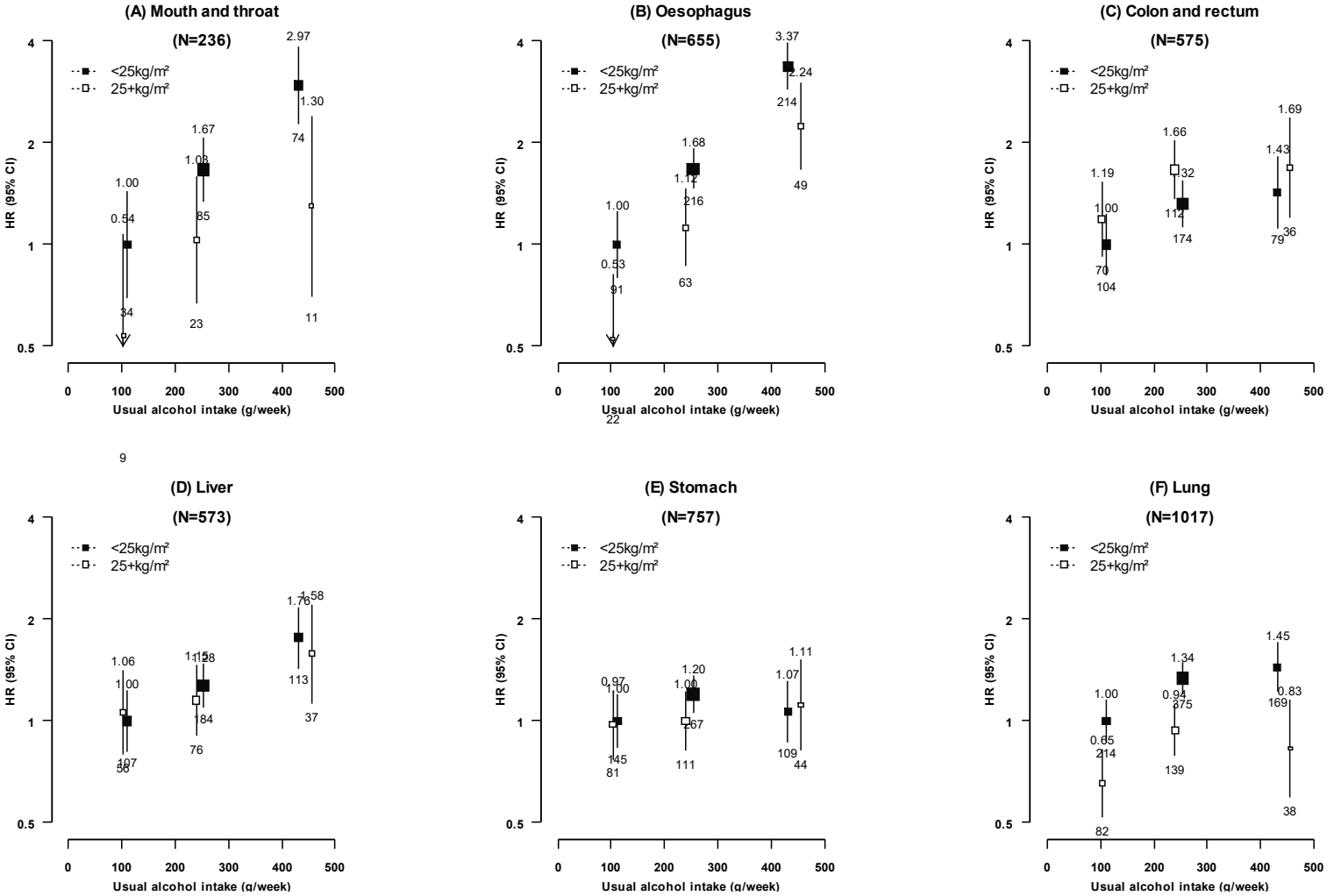
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure G 3. Associations of the joint effects of alcohol consumption and smoking with major cancers, in male current regular drinkers



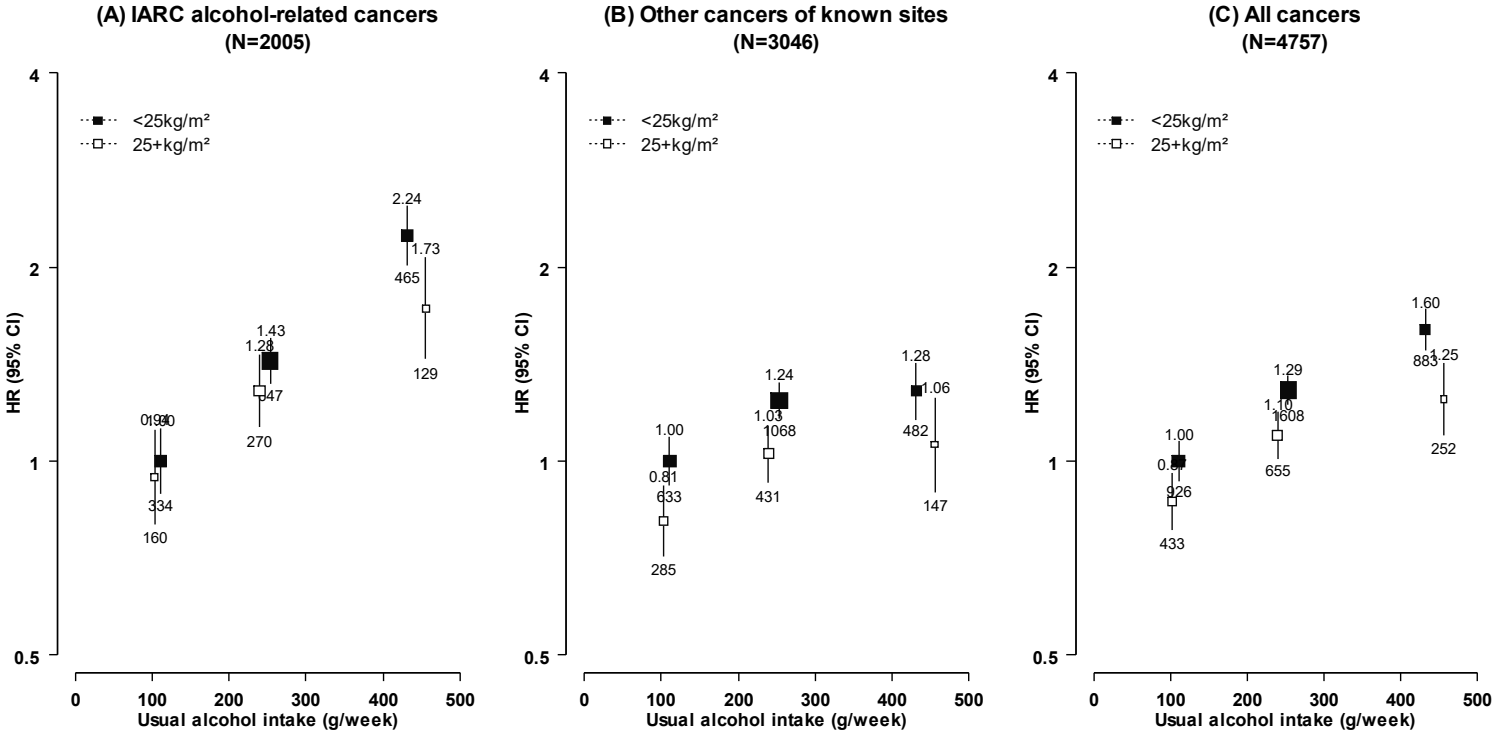
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure G 4. Associations of the joint effects of alcohol consumption and body mass index with major cancers, in male current regular drinkers



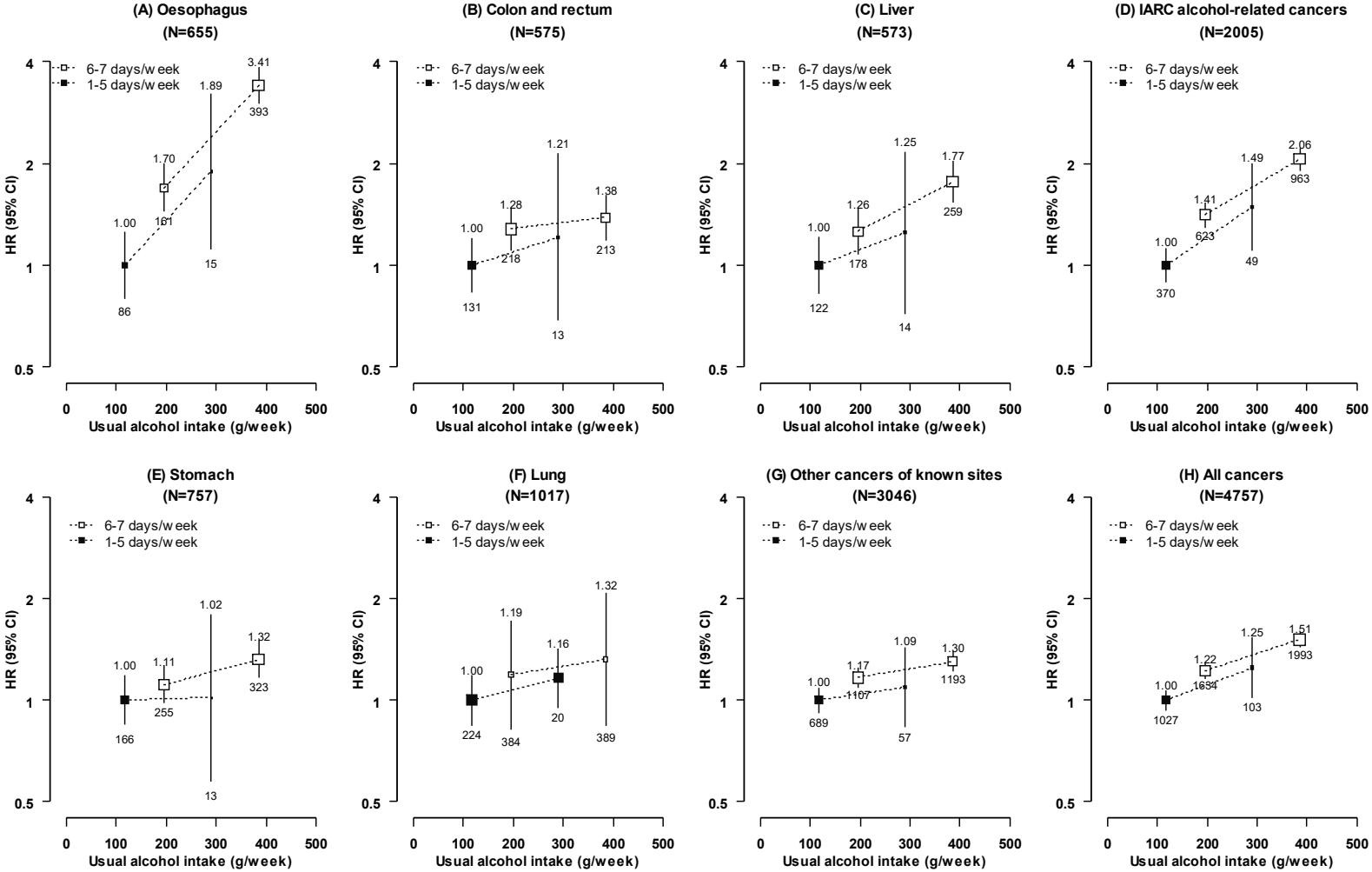
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure G 5. Associations of the joint effects of alcohol consumption and body mass index with IARC alcohol-related cancers, other cancers and overall cancer, in male current regular drinkers



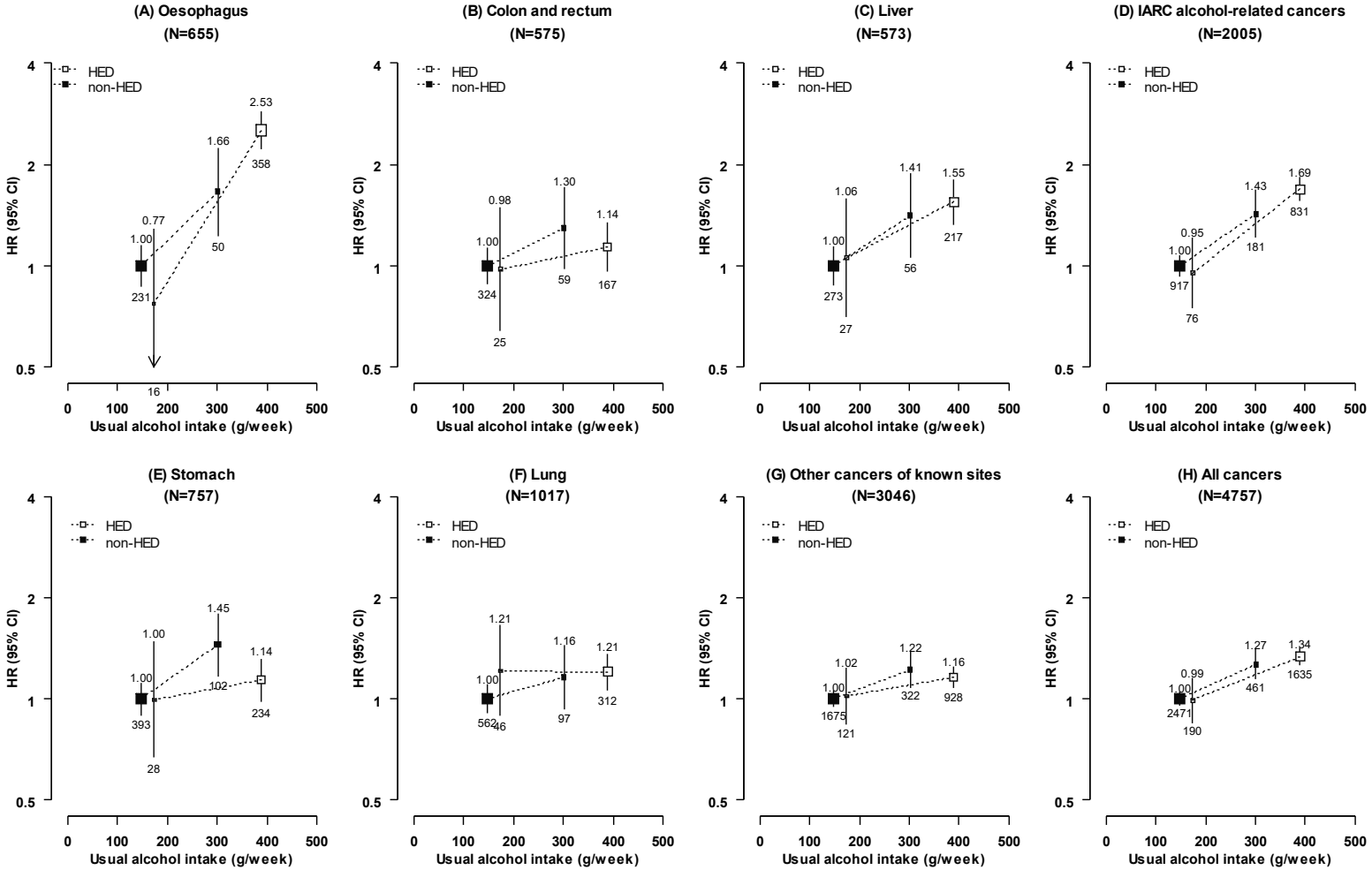
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure G 6. Associations of alcohol consumption with major cancers, by drinking frequency in male current regular drinkers



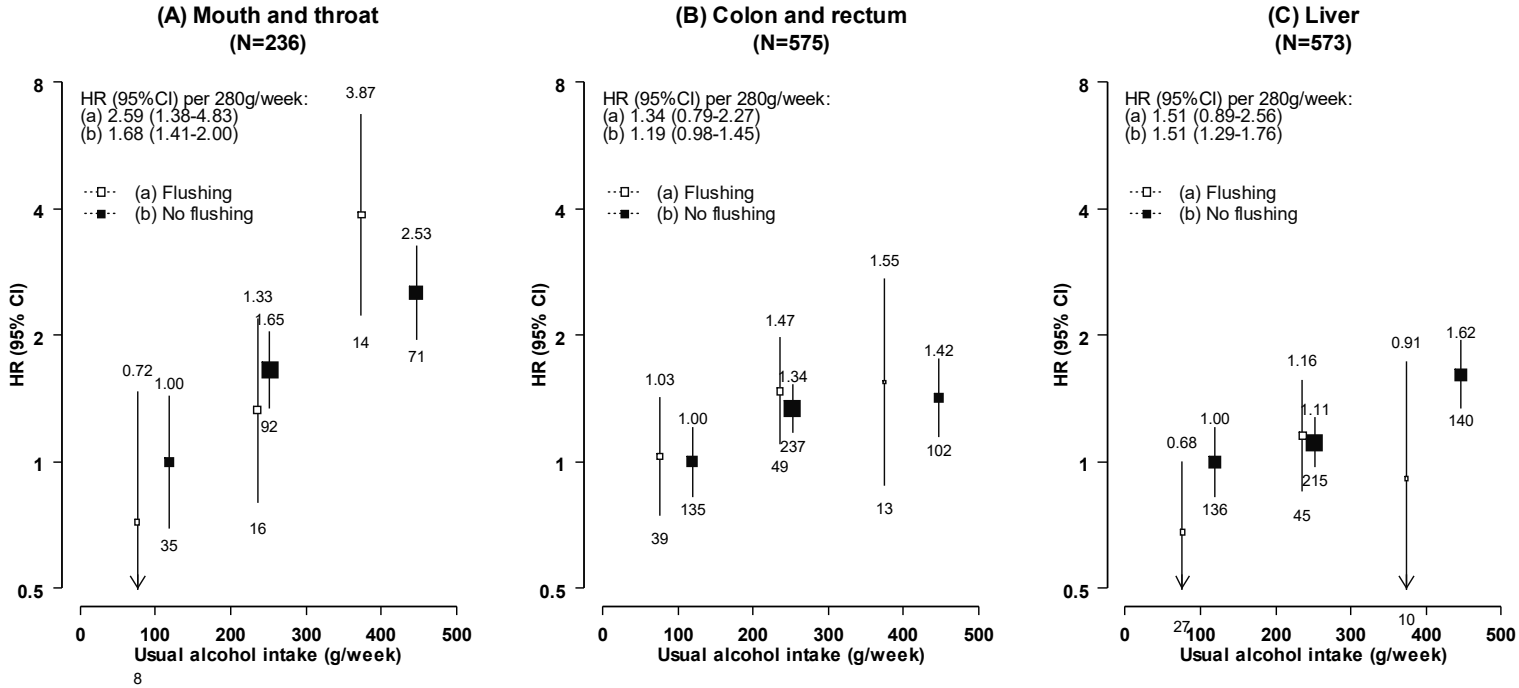
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. Mouth and throat cancer is not shown here due to the limited number of events. The four exposure categories refer to: non-daily drinkers drinking <280g/week at baseline (reference group); non-daily drinkers drinking ≥280g/week at baseline; daily drinkers drinking <280 g/week at baseline; and daily drinkers drinking ≥280g/week at baseline. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

Figure G 7. Associations of alcohol consumption with major cancers, by heavy episodic drinking status in male current regular drinkers



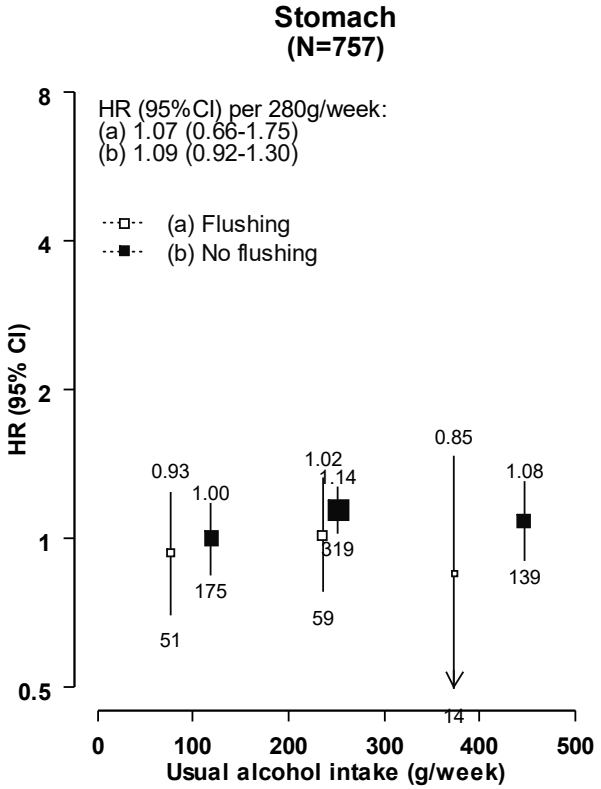
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer, and participants with prior tuberculosis, emphysema/bronchitis, or chronic obstructive pulmonary disease were further excluded from the analysis of lung cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. Mouth and throat cancer is not shown here due to the limited number of events. The four exposure categories refer to: non-HED (i.e., ≤60g/session) drinkers drinking <280g/week at baseline (reference group); non-HED drinkers drinking ≥280g/week at baseline; HED (i.e., >60g/session) drinkers drinking <280 g/week at baseline; and HED drinkers drinking ≥280g/week at baseline. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval; HED, heavy episodic drinking.

Figure G 8. Associations of alcohol consumption with mouth and throat cancer, colorectal cancer and liver cancer, by flushing status in male current regular drinkers



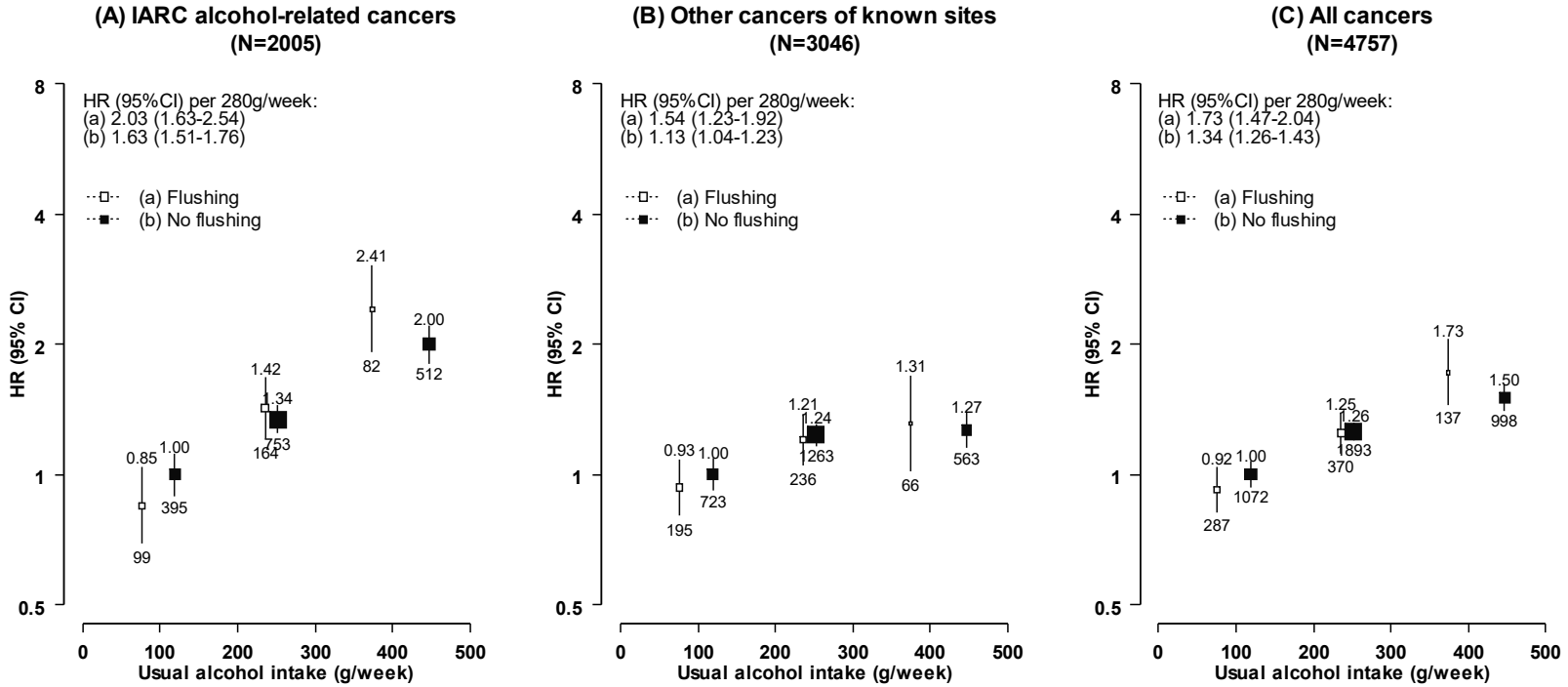
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Participants with prior chronic hepatitis/cirrhosis were further excluded from the analysis of liver cancer. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure G 9. Association of alcohol consumption with stomach cancer, by flushing status in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval.

Figure G 10. Associations of alcohol consumption with IARC alcohol-related cancers, other cancers and overall cancer, by flushing status in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, fresh fruit intake, body mass index, and family history of cancer. Participants with prior cancer were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. IARC, international agency for research on cancer; HR, hazard ratio; CI, confidence interval.

H. Additional results on alcohol and risks of liver diseases

Table H 1. Proportions of participants who developed incident liver diseases during follow-up, by baseline HBsAg test results

	Overall		Men		Women	
HBsAg test result	Total N	Developed liver disease, %	Total N	Developed liver disease, %	Total N	Developed liver disease, %
Positive	13723	10.93	6104	14.86	7619	7.78
Negative/unclear/missing	490275	1.64	199524	1.97	290751	1.41
Negative	478920	1.60	194935	1.92	283985	1.38
Unclear	3409	3.02	1376	4.00	2033	2.36
Missing	7946	3.61	3213	4.17	4733	3.23

HBsAg, Hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

Table H 2. Baseline prevalence of HBsAg seropositivity in the CKB

	Overall		Men		Women	
	Total N	HBsAg positive, %	Total N	HBsAg positive, %	Total N	HBsAg positive, %
Study areas						
Harbin (Urban)	56162	1.54	22619	1.70	33543	1.43
Qingdao (Urban)	35153	2.75	15437	2.96	19716	2.58
Suzhou (Urban)	52482	4.00	21922	4.42	30560	3.69
Liuzhou (Urban)	49412	3.71	18968	3.87	30444	3.60
Haikou (Urban)	28893	4.31	10401	4.79	18492	4.04
Gansu (Rural)	49518	1.70	19117	1.69	30401	1.70
Henan (Rural)	62458	3.24	27362	3.69	35096	2.89
Sichuan (Rural)	54626	1.55	20695	1.50	33931	1.57
Zhejiang (Rural)	56357	2.81	23257	2.80	33100	2.82
Hunan (Rural)	58937	2.42	25850	2.95	33087	2.00
Urban	222102	3.15	89347	3.41	132755	2.98
Rural	281896	2.38	116281	2.63	165615	2.21
Overall	503998	2.72	205628	2.97	298370	2.55

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

Table H 3. Age-standardised incidence rates (per 100,000 person-years) of liver diseases, by ten study areas in men and women

	Rural										Urban									
	Zhejiang		Sichuan		Gansu		Hunan		Henan		Qingdao		Harbin		Liuzhou		Haikou		Suzhou	
	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*	N	SIR*
Men																				
Liver cancer	163	67.1	189	94.0	140	83.3	201	78.0	239	94.4	134	101.0	148	65.1	161	81.9	96	85.4	180	85.9
ALD	34	13.9	53	26.4	1	0.7	82	32.6	4	1.4	27	17.3	17	8.1	23	12.3	7	7.3	4	1.8
Liver cirrhosis	128	54.0	168	83.3	161	94.7	137	53.7	131	49.8	106	68.1	98	45.9	93	48.6	66	60.6	59	28.5
NAFLD	136	65.4	149	74.1	8	4.3	11	4.7	8	2.9	5	3.5	126	58.2	10	5.6	3	3.3	5	2.3
Chronic viral hepatitis	76	34.3	93	46.3	118	67.2	90	35.7	118	43.1	106	63.1	50	22.6	86	47.0	32	28.9	29	13.7
All liver diseases	962	438.7	775	389.8	353	203.1	479	188.9	478	183.9	362	244.8	524	241.9	383	200.9	194	178.2	320	152.5
Women																				
Liver cancer	96	27.7	137	42.9	113	46.4	119	36.4	101	30.8	53	26.7	97	25.6	89	26.4	77	39.8	93	28.8
ALD	1	0.3	3	1.0	0	--	16	4.9	0	--	0	--	0	--	2	0.6	0	--	0	--
Liver cirrhosis	143	40.8	122	38.1	178	70.0	107	32.7	93	27.2	61	31.2	109	29.9	61	18.4	32	18.0	63	19.2
NAFLD	235	69.9	440	135.3	12	4.3	16	4.8	7	1.9	7	3.6	128	37.1	9	2.6	9	4.7	9	2.9
Chronic viral hepatitis	83	23.3	95	28.1	108	39.1	82	24.7	89	24.8	84	42.5	51	15.0	79	25.1	28	16.1	17	5.4
All liver diseases	1105	327.6	1099	342.1	366	138.7	376	114.4	290	84.2	253	128.7	500	141.1	311	95.8	167	90.5	232	72.3

SIR, standardised incidence rate; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
*Incidence rates (per 100,000 person-years) are standardised to the age structure of the China Kadoorie Biobank study population in men and women separately.

Table H 4. Crude and standardised incidence rates (per 100,000 person-years) of liver diseases, by alcohol drinking categories

	Abstainers			Ex-regular drinkers			Occasional drinkers			Current regular drinkers		
	N	Crude IR	SIR*	N	Crude IR	SIR*	N	Crude IR	SIR*	N	Crude IR	SIR*
Men												
Liver cancer	378	96.0	83.2	208	127.3	126.0	492	64.1	67.2	573	84.1	91.3
ALD	11	2.8	1.5	15	9.2	7.9	15	2.0	2.8	211	31.0	31.7
Liver cirrhosis	302	76.7	72.7	118	72.2	71.0	319	41.6	42.3	408	59.9	63.1
NAFLD	68	17.3	15.8	70	42.9	41.7	115	15.0	19.1	208	30.5	23.3
Chronic viral hepatitis	165	41.9	41.6	85	52.1	63.1	313	40.8	39.7	235	34.5	36.6
All liver diseases	1064	272.2	251.3	537	331.1	325.3	1368	179.1	198.1	1861	275.2	268.1

	Never regular drinkers			Ever regular drinkers		
Women†						
Liver cancer	938	32.2	32.5	37	42.1	62.2
ALD	18	0.6	0.6	4	4.6	4.2
Liver cirrhosis	931	32.0	32.1	38	43.3	45.3
NAFLD	799	27.5	29.0	73	83.2	30.3
Chronic viral hepatitis	688	23.7	23.7	28	31.9	43.1
All liver diseases	4481	154.8	157.7	218	249.4	181.0

IR, incidence rate; SIR, standardised incidence rate; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

*Incidence rates (per 100,000 person-years) are standardised to the age and study area structure of the study population in men and women separately.

†Women are categorised into never regular drinkers versus ever regular drinkers due to the small numbers of events in ex-regular drinkers and current regular drinkers respectively.

Table H 5. Adjusted HRs for liver disease mortality associated with drinking status, in men

		Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
	All N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Liver cancer	1208	279	1.00 (0.88-1.14)	154	1.25 (1.07-1.47)	368	0.88 (0.79-0.98)	407	1.07 (0.97-1.19)	*0.4056*
Alcoholic liver disease	60	6	1.00 (0.44-2.27)	3	1.35 (0.43-4.22)	6	0.99 (0.44-2.24)	45	6.01 (4.33-8.36)	*<0.0001*
Liver cirrhosis	148	34	1.00 (0.69-1.45)	21	0.97 (0.62-1.52)	40	0.69 (0.50-0.96)	53	0.82 (0.61-1.11)	*0.4325*
Chronic viral hepatitis	129	40	1.00 (0.71-1.40)	9	0.79 (0.41-1.55)	43	0.83 (0.61-1.12)	37	1.08 (0.75-1.55)	*0.7591*
All liver diseases	1577	370	1.00 (0.90-1.12)	193	1.21 (1.04-1.39)	466	0.85 (0.78-0.94)	548	1.11 (1.01-1.21)	*0.1606*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.
No deaths from non-alcoholic fatty liver disease as underlying cause were recorded.
**P* for association comparing current regular drinkers vs. abstainers.

Table H 6. Adjusted HRs for incident liver diseases associated with drinking status, in women

		Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
	All N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Liver cancer	975	702	1.00 (0.91-1.10)	16	1.17 (0.71-1.94)	236	0.79 (0.69-0.91)	21	0.82 (0.53-1.27)	*0.3933*
Alcoholic liver disease	22	16	1.00 (0.54-1.87)	1	3.35 (0.46-24.44)	2	0.51 (0.13-2.06)	3	7.61 (2.28-25.44)	*0.0035*
Liver cirrhosis	969	683	1.00 (0.90-1.11)	18	1.44 (0.89-2.34)	248	0.83 (0.73-0.95)	20	0.81 (0.52-1.27)	*0.3754*
Non-alcoholic fatty liver disease	872	517	1.00 (0.90-1.11)	24	0.89 (0.59-1.34)	282	0.99 (0.88-1.12)	49	1.07 (0.81-1.43)	*0.6542*
Chronic viral hepatitis	716	439	1.00 (0.88-1.13)	13	1.89 (1.08-3.32)	249	1.07 (0.94-1.23)	15	0.98 (0.59-1.65)	*0.9501*
All liver diseases	4699	3172	1.00 (0.95-1.05)	86	1.06 (0.85-1.32)	1309	0.91 (0.86-0.97)	132	0.84 (0.70-1.00)	*0.0565*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

**P* for association comparing current regular drinkers vs. abstainers.

Table H 7. Adjusted HRs for incident liver diseases associated with regular drinking status, in women

		Never regular drinkers		Ever regular drinkers		
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value
Liver cancer	975	938	1.00 (Ref)	37	1.03 (0.73-1.45)	*0.8852*
Alcoholic liver disease	22	18	1.00 (Ref)	4	6.53 (1.99-21.42)	*0.0020*
Liver cirrhosis	969	931	1.00 (Ref)	38	1.09 (0.78-1.54)	*0.6093*
Non-alcoholic fatty liver disease	872	799	1.00 (Ref)	73	1.01 (0.79-1.30)	*0.9402*
Chronic viral hepatitis	716	688	1.00 (Ref)	28	1.22 (0.82-1.82)	*0.3259*
All liver diseases	4699	4481	1.00 (Ref)	218	0.95 (0.82-1.09)	*0.4639*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

Table H 8. Adjusted HRs for liver disease mortality associated with amount of alcohol consumption, in male current regular drinkers

		<140g/week		140-279g/week		280-419g/week		420+g/week		Per 280g/week usual intake		
	All current regular N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{trend}
Liver cancer	407	108	1.00 (0.81-1.23)	97	1.20 (0.98-1.46)	90	1.58 (1.28-1.94)	112	1.93 (1.57-2.36)	407	1.57 (1.32-1.87)	*<0.0001*
Alcoholic liver disease	45	6	1.00 (0.43-2.34)	10	2.04 (1.08-3.83)	8	2.56 (1.29-5.08)	21	5.26 (3.24-8.56)	45	1.99 (1.53-2.59)	*<0.0001*
Liver cirrhosis	53	9	1.00 (0.50-2.00)	15	2.09 (1.23-3.54)	11	2.43 (1.35-4.38)	18	3.42 (2.01-5.82)	53	2.07 (1.53-2.79)	*<0.0001*
Chronic viral hepatitis	37	9	1.00 (0.48-2.06)	10	1.62 (0.87-3.03)	9	2.12 (1.09-4.13)	9	1.78 (0.90-3.53)	37	1.70 (0.96-3.01)	*0.0662*
All liver diseases	548	132	1.00 (0.83-1.21)	134	1.35 (1.14-1.60)	119	1.71 (1.43-2.05)	163	2.22 (1.88-2.64)	548	1.74 (1.53-1.97)	*<0.0001*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

No deaths from non-alcoholic fatty liver disease as underlying cause were recorded.

Table H 9. Adjusted HRs for incident liver diseases associated with amount of alcohol consumption, in female current regular drinkers

	All current regular	<70g/week		70+g/week		
	N	N	HR (95% CI)	N	HR (95% CI)	*p*-value
Liver cancer	21	8	1.00 (Ref)	13	1.29 (0.43-3.92)	*0.6499*
Liver cirrhosis	20	11	1.00 (Ref)	9	0.59 (0.21-1.67)	*0.3214*
Non-alcoholic fatty liver disease	49	16	1.00 (Ref)	33	0.96 (0.49-1.88)	*0.9131*
All liver diseases	132	51	1.00 (Ref)	81	0.92 (0.62-1.36)	*0.6756*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.
Alcoholic liver disease (n=3) and chronic viral hepatitis (n=15) are not shown due to the extremely small numbers of events.

Table H 10. Adjusted HRs for liver diseases associated with daily drinking, by weekly alcohol intake level in male current regular drinkers

			1-5 days/week		6-7 days/week				
					Full model*			Further adjusted for total alcohol intake	
		All current regular N	N	HR (95% CI)	N	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Liver cancer	<280g/week	300	122	1.00 (Ref)	178	1.22 (0.95-1.57)	*0.1190*	1.16 (0.86-1.57)	*0.3287*
	≥280g/week	273	14	1.00 (Ref)	259	1.24 (0.70-2.22)	*0.4618*	1.13 (0.63-2.04)	*0.6723*
Alcoholic liver disease	<280g/week	69	24	1.00 (Ref)	45	1.91 (1.13-3.25)	*0.0163*	1.39 (0.73-2.63)	*0.3115*
	≥280g/week	142	6	1.00 (Ref)	136	2.11 (0.91-4.90)	*0.0836*	1.66 (0.71-3.89)	*0.2442*
Liver cirrhosis	<280g/week	194	81	1.00 (Ref)	113	1.35 (0.99-1.84)	*0.0604*	0.99 (0.68-1.45)	*0.9629*
	≥280g/week	214	15	1.00 (Ref)	199	1.36 (0.74-2.49)	*0.3213*	1.11 (0.60-2.05)	*0.7407*
Non-alcoholic fatty liver disease	<280g/week	101	64	1.00 (Ref)	37	0.74 (0.48-1.14)	*0.1730*	0.58 (0.34-0.97)	*0.0391*
	≥280g/week	107	7	1.00 (Ref)	100	1.90 (0.83-4.36)	*0.1289*	1.61 (0.70-3.73)	*0.2650*
Chronic viral hepatitis	<280g/week	132	69	1.00 (Ref)	63	1.17 (0.80-1.71)	*0.4235*	1.34 (0.85-2.12)	*0.2132*
	≥280g/week	103	15	1.00 (Ref)	88	0.68 (0.36-1.29)	*0.2385*	0.64 (0.33-1.22)	*0.1768*
All liver diseases	<280g/week	944	431	1.00 (Ref)	513	1.13 (0.98-1.30)	*0.0917*	1.01 (0.86-1.20)	*0.8907*
	≥280g/week	917	55	1.00 (Ref)	862	1.38 (1.03-1.86)	*0.0312*	1.24 (0.92-1.68)	*0.1550*

HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

*Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

Table H 11. Adjusted HRs for liver diseases associated with heavy episodic drinking, by weekly alcohol intake level in male current regular drinkers

			≤60g/session		>60g/session (i.e., HED)				
					Full model*			Further adjusted for total alcohol intake	
		All current regular N	N	HR (95% CI)	N	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Liver cancer	<280g/week	300	273	1.00 (Ref)	27	1.00 (0.65-1.54)	*0.9829*	0.98 (0.64-1.51)	*0.9351*
	≥280g/week	273	56	1.00 (Ref)	217	1.10 (0.78-1.55)	*0.5790*	0.91 (0.63-1.33)	*0.6373*
Alcoholic liver disease	<280g/week	69	63	1.00 (Ref)	6	0.80 (0.33-1.92)	*0.6218*	0.73 (0.30-1.77)	*0.4898*
	≥280g/week	142	11	1.00 (Ref)	131	1.69 (0.86-3.35)	*0.1306*	1.21 (0.61-2.42)	*0.5827*
Liver cirrhosis	<280g/week	194	172	1.00 (Ref)	22	1.12 (0.70-1.81)	*0.6369*	1.06 (0.66-1.71)	*0.8145*
	≥280g/week	214	26	1.00 (Ref)	188	1.52 (0.94-2.45)	*0.0893*	1.06 (0.65-1.73)	*0.8278*
Non-alcoholic fatty liver disease	<280g/week	101	84	1.00 (Ref)	17	1.16 (0.67-2.03)	*0.5961*	1.14 (0.65-2.00)	*0.6546*
	≥280g/week	107	15	1.00 (Ref)	92	0.99 (0.52-1.88)	*0.9847*	0.67 (0.34-1.31)	*0.2370*
Chronic viral hepatitis	<280g/week	132	108	1.00 (Ref)	24	1.24 (0.76-2.01)	*0.3952*	1.25 (0.77-2.04)	*0.3699*
	≥280g/week	103	15	1.00 (Ref)	88	1.27 (0.67-2.41)	*0.4630*	1.21 (0.61-2.37)	*0.5872*
All liver diseases	<280g/week	944	838	1.00 (Ref)	106	1.10 (0.88-1.36)	*0.4079*	1.06 (0.85-1.33)	*0.5768*
	≥280g/week	917	172	1.00 (Ref)	745	1.07 (0.89-1.30)	*0.4631*	0.86 (0.70-1.05)	*0.1428*

HED, heavy episodic drinking; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

*Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

Table H 12. Adjusted HRs for liver diseases associated with drinking status (after exclusion of unclear or missing HBsAg test results), in men

	All men	Abstainers		Ex-regular drinkers		Occasional drinkers		Current regular drinkers		
	N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Liver cancer	1592	365	1.00 (0.90-1.12)	203	1.24 (1.08-1.43)	477	0.86 (0.78-0.94)	547	1.07 (0.98-1.17)	*0.3640*
Alcoholic liver disease	239	10	1.00 (0.53-1.87)	15	3.72 (2.24-6.20)	14	1.11 (0.65-1.88)	200	14.03 (12.00-16.41)	*<0.0001*
Liver cirrhosis	1098	291	1.00 (0.88-1.14)	112	0.97 (0.81-1.18)	307	0.68 (0.60-0.76)	388	0.96 (0.86-1.07)	*0.6447*
Non-alcoholic fatty liver disease	440	64	1.00 (0.77-1.30)	67	1.73 (1.35-2.22)	111	0.91 (0.75-1.10)	198	1.07 (0.93-1.24)	*0.6453*
Chronic viral hepatitis	778	162	1.00 (0.85-1.18)	82	1.30 (1.04-1.62)	308	1.00 (0.89-1.13)	226	0.86 (0.75-0.99)	*0.1956*
All liver diseases	4641	1021	1.00 (0.94-1.07)	513	1.16 (1.06-1.27)	1332	0.83 (0.79-0.88)	1775	1.07 (1.01-1.12)	*0.1363*

HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Participants with prior self-reported cancer, liver cirrhosis or chronic hepatitis, or with unclear or missing HBsAg test results were excluded.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

**P* for association comparing current regular drinkers vs. abstainers.

Table H 13. Adjusted HRs for liver diseases associated with amount of alcohol consumption (after exclusion of unclear or missing HBsAg test results), in male current regular drinkers

		<140g/week		140-279g/week		280-419g/week		420+g/week		Per 280g/week usual intake		
	All current regular N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{trend}
Liver cancer	547	159	1.00 (0.84-1.19)	129	1.07 (0.90-1.27)	121	1.45 (1.21-1.73)	138	1.64 (1.37-1.97)	547	1.44 (1.23-1.69)	*<0.0001*
Alcoholic liver disease	200	26	1.00 (0.67-1.49)	41	2.04 (1.50-2.78)	35	2.92 (2.10-4.05)	98	7.24 (5.80-9.04)	200	2.01 (1.77-2.28)	*<0.0001*
Liver cirrhosis	388	84	1.00 (0.80-1.26)	106	1.68 (1.38-2.03)	72	1.66 (1.31-2.09)	126	2.79 (2.30-3.40)	388	1.83 (1.60-2.09)	*<0.0001*
Non-alcoholic fatty liver disease	198	48	1.00 (0.73-1.36)	49	1.28 (0.97-1.69)	36	1.49 (1.08-2.06)	65	2.37 (1.79-3.13)	198	1.71 (1.35-2.16)	*<0.0001*
Chronic viral hepatitis	226	74	1.00 (0.78-1.28)	55	0.94 (0.72-1.22)	48	1.23 (0.92-1.64)	49	1.18 (0.87-1.59)	226	1.23 (0.94-1.60)	*0.1347*
All liver diseases	1775	460	1.00 (0.91-1.10)	445	1.24 (1.13-1.36)	368	1.49 (1.34-1.65)	502	1.89 (1.72-2.08)	1775	1.52 (1.40-1.64)	*<0.0001*

HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Participants with prior self-reported cancer, liver cirrhosis or chronic hepatitis, or with unclear or missing HBsAg test results were excluded.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

Table H 14. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, in male current regular drinkers – in sequentially adjusted models

		Basic model			Main model				Further adjustment	
		Age, study area	+ Education	+ Income	+ HBsAg	+ Smoking	+ BMI	+ Physical activity	+ Family history of cancer	+ Prior diabetes
	N	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Liver cancer	573	1.57 (1.37-1.81)	1.57 (1.36-1.81)	1.57 (1.36-1.80)	1.55 (1.34-1.79)	1.51 (1.30-1.76)	1.51 (1.30-1.76)	1.51 (1.30-1.76)	1.51 (1.30-1.76)	1.51 (1.29-1.75)
Alcoholic liver disease	211	2.00 (1.79-2.23)	1.98 (1.77-2.21)	2.02 (1.80-2.26)	2.03 (1.81-2.27)	1.98 (1.76-2.23)	2.02 (1.79-2.27)	2.02 (1.79-2.28)	2.02 (1.79-2.28)	2.02 (1.79-2.28)
Liver cirrhosis	408	1.87 (1.66-2.10)	1.85 (1.64-2.08)	1.85 (1.64-2.08)	1.84 (1.63-2.09)	1.87 (1.65-2.12)	1.87 (1.65-2.13)	1.87 (1.65-2.12)	1.87 (1.65-2.13)	1.88 (1.65-2.13)
Non-alcoholic fatty liver disease	208	1.75 (1.41-2.16)	1.82 (1.47-2.26)	1.82 (1.47-2.26)	1.82 (1.47-2.25)	1.78 (1.43-2.22)	1.78 (1.42-2.22)	1.78 (1.42-2.22)	1.78 (1.42-2.22)	1.77 (1.42-2.22)
Chronic viral hepatitis	235	1.32 (1.03-1.68)	1.30 (1.01-1.66)	1.30 (1.01-1.66)	1.26 (0.98-1.62)	1.26 (0.97-1.63)	1.26 (0.97-1.63)	1.25 (0.97-1.62)	1.25 (0.97-1.62)	1.25 (0.97-1.62)
All liver diseases	1861	1.56 (1.45-1.68)	1.56 (1.45-1.67)	1.56 (1.44-1.67)	1.54 (1.43-1.66)	1.53 (1.42-1.66)	1.54 (1.42-1.66)	1.53 (1.42-1.66)	1.53 (1.42-1.66)	1.53 (1.42-1.65)

HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.
Participants with prior self-reported cancer, liver cirrhosis, or chronic hepatitis were excluded.

Table H 15. Adjusted HRs for liver diseases associated with drinking status and amount, in men

								Current regular drinkers								
		Abstainers		Ex-regular drinkers		Occasional drinkers		<140g/week		140-279g/week		280-419g/week		420+g/week		
	All men N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value *
Same exclusion (i.e., participants with prior cancer, liver cirrhosis, or chronic hepatitis) as in main analyses																
Liver cancer	1651	378	1.00 (0.90-1.12)	208	1.22 (1.07-1.41)	492	0.85 (0.77-0.93)	163	0.87 (0.75-1.02)	137	0.96 (0.81-1.13)	123	1.24 (1.04-1.49)	150	1.47 (1.24-1.74)	*0.0002*
ALD	252	11	1.00 (0.55-1.83)	15	3.44 (2.06-5.75)	15	1.04 (0.62-1.75)	27	5.13 (3.49-7.54)	42	10.02 (7.40-13.57)	35	13.69 (9.84-19.06)	107	36.32 (29.32-45.00)	*<0.0001*
Liver cirrhosis	1147	302	1.00 (0.88-1.14)	118	1.00 (0.83-1.21)	319	0.68 (0.60-0.76)	86	0.61 (0.49-0.76)	108	0.96 (0.79-1.17)	75	0.98 (0.78-1.23)	139	1.70 (1.42-2.04)	*<0.0001*
NAFLD	461	68	1.00 (0.78-1.29)	70	1.64 (1.29-2.09)	115	0.86 (0.71-1.04)	49	0.75 (0.56-0.99)	52	0.94 (0.71-1.24)	38	1.05 (0.76-1.44)	69	1.52 (1.18-1.95)	*0.0200*
Chronic viral hepatitis	798	165	1.00 (0.85-1.18)	85	1.31 (1.06-1.63)	313	0.99 (0.88-1.12)	75	0.80 (0.63-1.00)	57	0.80 (0.61-1.04)	51	1.04 (0.78-1.37)	52	0.97 (0.73-1.29)	*0.8622*
All liver diseases	4830	1064	1.00 (0.94-1.07)	537	1.16 (1.06-1.26)	1368	0.81 (0.77-0.86)	478	0.83 (0.75-0.91)	466	1.00 (0.91-1.10)	378	1.15 (1.04-1.28)	539	1.45 (1.33-1.59)	*<0.0001*
Further excluded first three years of follow-up and participants with poor self-reported health or prior chronic disease†																
Liver cancer	817	166	1.00 (0.85-1.18)	72	1.18 (0.93-1.49)	264	0.91 (0.80-1.04)	90	0.98 (0.79-1.20)	72	0.96 (0.76-1.22)	68	1.28 (1.00-1.63)	85	1.58 (1.26-1.99)	*0.0015*
ALD	150	4	1.00 (0.37-2.70)	5	3.75 (1.55-9.10)	10	1.78 (0.94-3.37)	15	7.12 (4.25-11.94)	26	15.20 (10.33-22.36)	22	20.69 (13.63-31.39)	68	56.35 (43.16-73.57)	*<0.0001*
Liver cirrhosis	593	126	1.00 (0.82-1.21)	45	1.17 (0.87-1.58)	184	0.80 (0.68-0.93)	49	0.75 (0.56-0.99)	68	1.31 (1.03-1.67)	44	1.24 (0.92-1.68)	77	2.17 (1.70-2.76)	*<0.0001*
NAFLD	186	16	1.00 (0.60-1.67)	28	2.43 (1.65-3.58)	49	1.11 (0.83-1.50)	21	0.96 (0.62-1.50)	23	1.14 (0.75-1.72)	17	1.33 (0.82-2.14)	32	1.85 (1.27-2.69)	*0.0576*
Chronic viral hepatitis	412	61	1.00 (0.76-1.31)	32	1.88 (1.32-2.67)	178	1.42 (1.21-1.67)	43	1.30 (0.96-1.76)	38	1.49 (1.08-2.06)	32	1.84 (1.29-2.62)	28	1.44 (0.98-2.13)	*0.1356*
All liver diseases	2281	396	1.00 (0.90-1.11)	187	1.29 (1.11-1.49)	714	0.95 (0.88-1.03)	249	1.01 (0.89-1.15)	260	1.28 (1.13-1.44)	188	1.34 (1.16-1.55)	287	1.84 (1.63-2.09)	*<0.0001*

HR, hazard ratio; CI, confidence interval; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

**P* for association comparing current regular drinkers consuming 420+g/week with abstainers.

†Chronic diseases included self-reported coronary heart disease, stroke or TIA, diabetes, tuberculosis, rheumatoid arthritis, peptic ulcer, emphysema/chronic bronchitis, gallstone/gallbladder disease, and kidney disease

Table H 16. Adjusted HRs for liver diseases associated with alcohol drinking status after various exclusions of participants, in men

	All men	Abstainers		Ex-regular		Occasional		Current regular		
	N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	*p*-value*
Liver cancer										
Excluded first three years of follow-up	1200	252	1.00 (0.88-1.14)	141	1.23 (1.04-1.45)	373	0.94 (0.84-1.05)	434	1.20 (1.08-1.32)	*0.0381*
Excluded poor self-reported health	1464	320	1.00 (0.89-1.13)	164	1.23 (1.05-1.44)	453	0.90 (0.81-0.99)	527	1.10 (1.00-1.21)	*0.2185*
Excluded prior chronic disease†	1128	245	1.00 (0.87-1.15)	115	1.23 (1.02-1.48)	349	0.85 (0.76-0.95)	419	1.08 (0.97-1.20)	*0.3768*
Excluded all of above	781	154	1.00 (0.84-1.19)	72	1.26 (1.00-1.60)	256	0.95 (0.84-1.09)	299	1.16 (1.03-1.31)	*0.1649*
Alcoholic liver disease										
Excluded first three years of follow-up	203	8	1.00 (0.50-2.02)	11	3.44 (1.90-6.24)	15	1.54 (0.93-2.57)	169	14.73 (12.42-17.47)	*<0.0001*
Excluded poor self-reported health	216	9	1.00 (0.52-1.94)	12	3.54 (2.00-6.26)	13	1.11 (0.64-1.92)	182	13.58 (11.52-16.01)	*<0.0001*
Excluded prior chronic disease†	190	7	1.00 (0.47-2.12)	9	3.57 (1.85-6.88)	8	0.85 (0.42-1.71)	166	14.81 (12.47-17.60)	*<0.0001*
Excluded all of above	136	3	1.00 (0.32-3.13)	4	3.94 (1.47-10.54)	8	2.03 (1.01-4.09)	121	25.44 (20.80-31.12)	*<0.0001*
Liver cirrhosis										
Excluded first three years of follow-up	853	201	1.00 (0.86-1.16)	82	1.07 (0.86-1.34)	255	0.81 (0.71-0.92)	315	1.18 (1.04-1.33)	*0.1070*
Excluded poor self-reported health	1007	251	1.00 (0.87-1.15)	94	1.05 (0.85-1.29)	299	0.75 (0.67-0.85)	363	1.00 (0.90-1.13)	*0.9696*
Excluded prior chronic disease†	785	179	1.00 (0.85-1.17)	67	1.11 (0.87-1.42)	231	0.75 (0.65-0.86)	308	1.11 (0.98-1.26)	*0.3169*
Excluded all of above	556	115	1.00 (0.82-1.22)	42	1.17 (0.86-1.60)	176	0.84 (0.72-0.98)	223	1.27 (1.09-1.47)	*0.0638*
Non-alcoholic fatty liver disease										
Excluded first three years of follow-up	312	30	1.00 (0.69-1.45)	60	2.12 (1.63-2.76)	73	0.92 (0.72-1.16)	149	1.16 (0.98-1.37)	*0.4898*
Excluded poor self-reported health	408	59	1.00 (0.76-1.31)	54	1.64 (1.25-2.16)	109	0.97 (0.80-1.17)	186	1.07 (0.92-1.24)	*0.6709*
Excluded prior chronic disease†	297	43	1.00 (0.73-1.37)	41	2.00 (1.45-2.75)	77	0.97 (0.77-1.22)	136	1.12 (0.94-1.33)	*0.5462*
Excluded all of above	177	16	1.00 (0.60-1.67)	28	2.42 (1.64-3.57)	46	1.10 (0.81-1.48)	87	1.27 (1.02-1.58)	*0.4065*
Chronic viral hepatitis										
Excluded first three years of follow-up	596	105	1.00 (0.81-1.23)	59	1.47 (1.13-1.91)	241	1.17 (1.03-1.34)	191	1.16 (0.99-1.35)	*0.2723*
Excluded poor self-reported health	708	139	1.00 (0.84-1.20)	67	1.38 (1.08-1.77)	280	1.04 (0.92-1.17)	222	0.96 (0.83-1.11)	*0.7463*
Excluded prior chronic disease†	584	102	1.00 (0.81-1.23)	56	1.67 (1.27-2.18)	253	1.22 (1.07-1.39)	173	0.99 (0.84-1.16)	*0.9260*
Excluded all of above	395	54	1.00 (0.75-1.33)	32	2.15 (1.51-3.06)	175	1.57 (1.35-1.84)	134	1.59 (1.32-1.91)	*0.0081*
All liver diseases										
Excluded first three years of follow-up	3349	636	1.00 (0.92-1.09)	368	1.23 (1.11-1.36)	1005	0.92 (0.86-0.98)	1340	1.22 (1.15-1.29)	*0.0002*
Excluded poor self-reported health	4258	912	1.00 (0.93-1.07)	418	1.16 (1.05-1.28)	1248	0.86 (0.81-0.91)	1680	1.08 (1.03-1.14)	*0.0721*
Excluded prior chronic disease†	3399	690	1.00 (0.92-1.08)	313	1.25 (1.12-1.40)	1007	0.87 (0.82-0.93)	1389	1.13 (1.07-1.20)	*0.0143*
Excluded all of above	2177	375	1.00 (0.90-1.11)	181	1.30 (1.12-1.51)	690	0.98 (0.91-1.06)	931	1.32 (1.22-1.41)	*<0.0001*

HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Participants with prior self-reported cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

**P* for association comparing current regular drinkers vs. abstainers.

†Prior chronic diseases included self-reported coronary heart diseases, stroke or transient ischaemic attack, tuberculosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease, and diabetes (both self-reported and screen-detected).

Table H 17. Adjusted HRs for liver disease associated with amount of alcohol consumption after various exclusions of participants, in male current regular drinkers

	All current regular	<140g/week		140-279g/week		280-419g/week		420+g/week		Per 280 g/week usual intake		
	N	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p_{trend}
Liver cancer												
Excluded first three years of follow-up	434	129	1.00 (0.83-1.21)	101	1.04 (0.86-1.27)	93	1.41 (1.15-1.73)	111	1.66 (1.35-2.03)	434	1.58 (1.32-1.90)	*<0.0001*
Excluded poor self-reported health	527	154	1.00 (0.84-1.19)	121	1.03 (0.87-1.24)	111	1.36 (1.13-1.64)	141	1.71 (1.43-2.06)	527	1.55 (1.32-1.83)	*<0.0001*
Excluded prior chronic disease[†]	419	109	1.00 (0.81-1.23)	99	1.12 (0.92-1.36)	97	1.55 (1.27-1.89)	114	1.78 (1.45-2.17)	419	1.53 (1.27-1.85)	*<0.0001*
Excluded all of above	299	84	1.00 (0.79-1.27)	70	1.03 (0.82-1.31)	66	1.41 (1.11-1.80)	79	1.62 (1.27-2.06)	299	1.50 (1.19-1.89)	*0.0005*
Alcoholic liver disease												
Excluded first three years of follow-up	169	19	1.00 (0.63-1.59)	34	2.26 (1.61-3.18)	29	3.12 (2.17-4.47)	87	8.16 (6.44-10.33)	169	2.05 (1.77-2.37)	*<0.0001*
Excluded poor self-reported health	182	23	1.00 (0.65-1.53)	35	1.92 (1.38-2.69)	30	2.79 (1.96-3.98)	94	7.47 (5.94-9.38)	182	2.08 (1.82-2.38)	*<0.0001*
Excluded prior chronic disease[†]	166	22	1.00 (0.65-1.54)	31	1.74 (1.22-2.47)	26	2.34 (1.60-3.43)	87	6.56 (5.18-8.30)	166	2.05 (1.76-2.38)	*<0.0001*
Excluded all of above	121	14	1.00 (0.58-1.72)	24	2.12 (1.42-3.17)	20	2.78 (1.80-4.30)	63	7.59 (5.76-10.00)	121	2.21 (1.80-2.71)	*<0.0001*
Liver cirrhosis												
Excluded first three years of follow-up	315	65	1.00 (0.77-1.30)	87	1.77 (1.43-2.19)	57	1.72 (1.32-2.24)	106	3.18 (2.57-3.94)	315	1.91 (1.64-2.23)	*<0.0001*
Excluded poor self-reported health	363	80	1.00 (0.79-1.27)	96	1.60 (1.31-1.96)	68	1.68 (1.32-2.13)	119	2.80 (2.29-3.42)	363	1.92 (1.66-2.21)	*<0.0001*
Excluded prior chronic disease[†]	308	61	1.00 (0.76-1.31)	81	1.72 (1.38-2.15)	62	1.94 (1.51-2.49)	104	3.03 (2.45-3.75)	308	1.85 (1.59-2.15)	*<0.0001*
Excluded all of above	223	47	1.00 (0.74-1.36)	63	1.80 (1.40-2.31)	43	1.91 (1.41-2.58)	70	2.97 (2.29-3.85)	223	1.90 (1.57-2.29)	*<0.0001*
Non-alcoholic fatty liver disease												
Excluded first three years of follow-up	149	40	1.00 (0.71-1.41)	36	1.07 (0.77-1.47)	24	1.18 (0.79-1.75)	49	1.98 (1.42-2.75)	149	1.78 (1.31-2.43)	*<0.0001*
Excluded poor self-reported health	186	43	1.00 (0.72-1.39)	46	1.37 (1.03-1.83)	36	1.70 (1.23-2.35)	61	2.56 (1.91-3.42)	186	1.80 (1.38-2.35)	*<0.0001*
Excluded prior chronic disease[†]	136	29	1.00 (0.67-1.48)	33	1.36 (0.97-1.91)	27	1.66 (1.14-2.42)	47	2.28 (1.65-3.15)	136	1.55 (1.13-2.14)	*0.0072*
Excluded all of above	87	20	1.00 (0.62-1.62)	21	1.19 (0.78-1.83)	16	1.42 (0.88-2.31)	30	2.03 (1.33-3.09)	87	1.45 (0.93-2.24)	*0.0976*
Chronic viral hepatitis												
Excluded first three years of follow-up	191	60	1.00 (0.76-1.32)	49	1.03 (0.78-1.37)	44	1.41 (1.04-1.91)	38	1.12 (0.80-1.58)	191	1.08 (0.78-1.51)	*0.1546*
Excluded poor self-reported health	222	71	1.00 (0.78-1.29)	53	0.93 (0.71-1.22)	49	1.32 (0.99-1.75)	49	1.20 (0.88-1.62)	222	1.27 (0.97-1.66)	*0.0781*
Excluded prior chronic disease[†]	173	52	1.00 (0.74-1.34)	45	1.02 (0.76-1.37)	39	1.32 (0.96-1.82)	37	1.10 (0.78-1.55)	173	1.15 (0.83-1.60)	*0.3900*
Excluded all of above	134	43	1.00 (0.72-1.38)	35	0.98 (0.70-1.38)	31	1.36 (0.95-1.95)	25	0.98 (0.65-1.49)	134	1.11 (0.75-1.63)	*0.6036*
All liver diseases												
Excluded first three years of follow-up	1340	359	1.00 (0.89-1.12)	345	1.22 (1.10-1.36)	256	1.35 (1.20-1.53)	380	1.85 (1.65-2.07)	1340	1.53 (1.39-1.69)	*<0.0001*
Excluded poor self-reported health	1680	439	1.00 (0.90-1.11)	415	1.21 (1.10-1.33)	344	1.46 (1.31-1.62)	482	1.89 (1.72-2.09)	1680	1.56 (1.44-1.70)	*<0.0001*
Excluded prior chronic disease[†]	1389	333	1.00 (0.89-1.12)	341	1.24 (1.11-1.38)	292	1.50 (1.34-1.69)	423	1.96 (1.77-2.18)	1389	1.55 (1.34-1.80)	*<0.0001*
Excluded all of above	931	242	1.00 (0.87-1.15)	243	1.22 (1.07-1.38)	178	1.32 (1.14-1.53)	268	1.79 (1.57-2.05)	931	1.51 (1.35-1.70)	*<0.0001*

HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Participants with prior self-reported cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.

Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

[†]Prior chronic diseases included self-reported coronary heart diseases, stroke or transient ischaemic attack, tuberculosis, rheumatoid arthritis, peptic ulcer, emphysema/bronchitis, gallstone/gallbladder disease, kidney disease, and diabetes (both self-reported and screen-detected).

Table H 18. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in men – in sequentially adjusted models

		Full adjustment as in conventional epidemiological analyses*								Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Liver cancer	569	372	1.00 (0.89-1.12)	176	0.91 (0.79-1.06)	*0.3413*	21	0.74 (0.48-1.14)	*0.1861*	1.00 (0.88-1.14)	1.00 (0.86-1.15)	*0.9699*	0.83 (0.54-1.27)	*0.4086*
ALD	90	81	1.00 (0.79-1.26)	8	0.16 (0.08-0.32)	*<0.0001*	1	0.14 (0.02-0.99)	*0.0502*	1.00 (0.76-1.31)	0.23 (0.11-0.45)	*<0.0001*	0.21 (0.03-1.51)	*0.1243*
Liver cirrhosis	386	266	1.00 (0.88-1.14)	101	0.77 (0.64-0.94)	*0.0303*	19	1.05 (0.67-1.66)	*0.8381*	1.00 (0.86-1.16)	0.88 (0.73-1.07)	*0.3195*	1.25 (0.79-1.97)	*0.3697*
NAFLD	147	91	1.00 (0.80-1.25)	53	1.23 (0.95-1.60)	*0.2359*	3	0.52 (0.17-1.62)	*0.2667*	1.00 (0.76-1.31)	1.38 (1.07-1.78)	*0.0896*	0.60 (0.19-1.87)	*0.3892*
Chronic viral hepatitis	267	172	1.00 (0.85-1.18)	83	1.04 (0.84-1.29)	*0.7684*	12	1.14 (0.64-2.04)	*0.6581*	1.00 (0.83-1.21)	1.05 (0.85-1.29)	*0.7507*	1.15 (0.65-2.05)	*0.6475*
All liver diseases	1623	1066	1.00 (0.94-1.07)	492	0.87 (0.80-0.95)	*0.0164*	65	0.80 (0.62-1.02)	*0.0771*	1.00 (0.93-1.08)	0.95 (0.87-1.04)	*0.4014*	0.89 (0.69-1.13)	*0.3583*

HR, hazard ratio; CI, confidence interval; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.

*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

Table H 19. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in men – in sequentially adjusted models

		Full adjustment as in conventional epidemiological analyses*								Full adjustment* plus further adjustment for alcohol consumption				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Liver cancer	569	63	1.00 (0.78-1.28)	226	0.72 (0.63-0.83)	*0.0244*	280	0.82 (0.73-0.93)	*0.1713*	1.00 (0.78-1.28)	0.74 (0.65-0.85)	*0.0414*	0.85 (0.76-0.96)	*0.2591*
ALD	90	20	1.00 (0.64-1.56)	34	0.34 (0.25-0.48)	*0.0002*	36	0.31 (0.22-0.43)	*<0.0001*	1.00 (0.61-1.63)	0.45 (0.32-0.64)	*0.0089*	0.41 (0.30-0.57)	*0.0032*
Liver cirrhosis	386	40	1.00 (0.73-1.37)	165	0.84 (0.72-0.98)	*0.3281*	181	0.88 (0.76-1.02)	*0.4576*	1.00 (0.73-1.37)	0.88 (0.75-1.03)	*0.4731*	0.93 (0.80-1.08)	*0.6876*
NAFLD	147	16	1.00 (0.61-1.64)	57	0.81 (0.63-1.05)	*0.4593*	74	0.99 (0.79-1.25)	*0.9759*	1.00 (0.61-1.64)	0.83 (0.64-1.08)	*0.5250*	1.02 (0.81-1.29)	*0.9302*
Chronic viral hepatitis	267	31	1.00 (0.70-1.43)	113	0.76 (0.63-0.92)	*0.1909*	123	0.77 (0.64-0.92)	*0.1996*	1.00 (0.70-1.43)	0.76 (0.63-0.92)	*0.1901*	0.77 (0.64-0.92)	*0.1987*
All liver diseases	1622	176	1.00 (0.86-1.16)	685	0.80 (0.75-0.87)	*0.0109*	761	0.81 (0.75-0.87)	*0.0122*	1.00 (0.86-1.16)	0.83 (0.77-0.89)	*0.0281*	0.84 (0.78-0.90)	*0.0362*

HR, hazard ratio; CI, confidence interval; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HBsAg, hepatitis B surface antigen.

Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.

*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.

†*P* for association comparing the AA or the AG genotype with the GG genotype.

Table H 20. Adjusted HRs for liver diseases associated with *ALDH2*-rs671 genotype, in women – in sequentially adjusted models

		Model stratified by age-at-risk, study area, and HBsAg								Full adjustment plus alcohol consumption*				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Liver cancer	321	189	1.00 (0.86-1.16)	109	1.13 (0.94-1.35)	*0.3332*	23	1.59 (1.05-2.40)	*0.0404*	1.00 (0.86-1.17)	1.13 (0.94-1.36)	*0.3215*	1.58 (1.04-2.39)	*0.0441*
ALD	8	6	1.00 (0.44-2.27)	2	0.54 (0.14-2.16)	*0.4581*	0	--	--	1.00 (0.39-2.55)	0.72 (0.18-2.91)	*0.6987*	--	--
Liver cirrhosis	303	191	1.00 (0.86-1.17)	100	1.08 (0.89-1.31)	*0.5594*	12	0.99 (0.56-1.75)	*0.9692*	1.00 (0.86-1.17)	1.05 (0.87-1.28)	*0.6899*	0.98 (0.55-1.74)	*0.9514*
NAFLD	295	180	1.00 (0.86-1.16)	101	1.06 (0.88-1.29)	*0.6202*	14	1.03 (0.61-1.75)	*0.9097*	1.00 (0.86-1.17)	1.07 (0.89-1.30)	*0.5698*	1.01 (0.60-1.71)	*0.9700*
Chronic viral hepatitis	240	154	1.00 (0.84-1.18)	78	1.03 (0.83-1.29)	*0.8107*	8	0.76 (0.38-1.52)	*0.4462*	1.00 (0.84-1.19)	1.03 (0.83-1.29)	*0.8300*	0.77 (0.38-1.54)	*0.4678*
All liver diseases	1584	971	1.00 (0.94-1.07)	537	1.03 (0.95-1.12)	*0.5393*	76	0.98 (0.78-1.23)	*0.8733*	1.00 (0.94-1.07)	1.03 (0.95-1.12)	*0.5994*	0.97 (0.78-1.22)	*0.8299*

HBsAg, hepatitis B surface antigen HR, hazard ratio; CI, confidence interval; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.
*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.
†*P* for association comparing the AA or the AG genotype with the GG genotype.

Table H 21. Adjusted HRs for liver diseases associated with *ADH1B*-rs1229984 genotype, in women – in sequentially adjusted models

		Model stratified by age-at-risk, study area, and HBsAg								Full adjustment plus alcohol consumption*				
		GG		AG			AA			GG	AG		AA	
	All N	N	HR (95% CI)	N	HR (95% CI)	*p*-value†	N	HR (95% CI)	*p*-value†	HR (95% CI)	HR (95% CI)	*p*-value†	HR (95% CI)	*p*-value†
Liver cancer	321	36	1.00 (0.72-1.39)	146	0.93 (0.79-1.10)	*0.7055*	139	0.79 (0.67-0.94)	*0.2168*	1.00 (0.72-1.39)	0.93 (0.79-1.10)	*0.7189*	0.80 (0.68-0.95)	*0.2363*
ALD	8	2	1.00 (0.25-4.03)	4	0.46 (0.17-1.23)	*0.3738*	2	0.19 (0.05-0.75)	*0.0941*	1.00 (0.24-4.19)	0.45 (0.17-1.23)	*0.3728*	0.15 (0.03-0.66)	*0.0702*
Liver cirrhosis	303	31	1.00 (0.70-1.43)	134	1.01 (0.85-1.20)	*0.9487*	138	0.93 (0.79-1.11)	*0.7367*	1.00 (0.70-1.43)	1.00 (0.84-1.18)	*0.9839*	0.92 (0.77-1.09)	*0.6702*
NAFLD	295	28	1.00 (0.69-1.45)	140	1.15 (0.97-1.36)	*0.5021*	127	0.95 (0.80-1.13)	*0.8052*	1.00 (0.69-1.45)	1.15 (0.98-1.36)	*0.4975*	0.97 (0.81-1.15)	*0.8694*
Chronic viral hepatitis	240	29	1.00 (0.69-1.45)	109	0.85 (0.70-1.02)	*0.4288*	102	0.69 (0.57-0.85)	*0.0874*	1.00 (0.69-1.45)	0.86 (0.71-1.04)	*0.4692*	0.70 (0.57-0.85)	*0.0969*
All liver diseases	1584	150	1.00 (0.85-1.17)	711	1.07 (1.00-1.16)	*0.4278*	723	0.96 (0.90-1.04)	*0.6848*	1.00 (0.85-1.17)	1.07 (1.00-1.15)	*0.4398*	0.96 (0.89-1.04)	*0.6737*

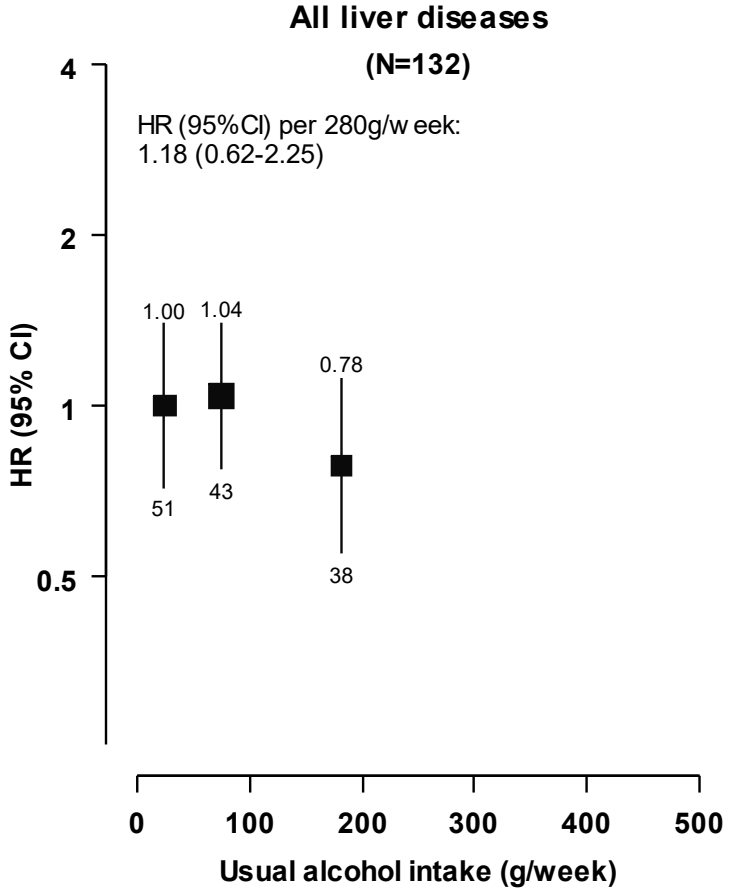
HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.
*Cox models have the same model specification as in the conventional epidemiological analyses, i.e., stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, body mass index, and physical activity.
†*P* for association comparing the AA or the AG genotype with the GG genotype.

Table H 22. Adjusted HRs for alcoholic liver disease per 280g/week higher alcohol intake by flushing status and body mass index in male current regular drinkers, with application of overall and group-specific regression dilution ratios

	No RDR applied	Overall RDR (0.54)	Group-specific RDR							
	Baseline	MacMahon-Peto*	MacMahon-Peto*		Pearson's correlation†		Spearman's correlation†		Rosner's regression‡	
	HR (95% CI)	HR (95% CI)	RDR	HR (95% CI)	RDR	HR (95% CI)	RDR	HR (95% CI)	RDR	HR (95% CI)
Flushing response										
No flushing	1.43 (1.33-1.53)	1.93 (1.69-2.20)	0.53	1.95 (1.71-2.24)	0.51	2.01 (1.74-2.31)	0.54	1.93 (1.69-2.20)	0.54	1.93 (1.69-2.20)
Flushing	2.50 (1.84-3.40)	5.46 (3.09-9.64)	0.53	5.63 (3.15-10.06)	0.55	5.29 (3.02-9.25)	0.57	4.99 (2.91-8.56)	0.55	5.29 (3.02-9.25)
p_{het}§	*0.0005*	*0.0005*		*0.0005*		*0.0010*		*0.0008*		*0.0007*
Body mass index										
<23 kg/m^2	1.37 (1.26-1.48)	1.79 (1.55-2.07)	0.55	1.77 (1.53-2.04)	0.56	1.75 (1.52-2.02)	0.55	1.77 (1.53-2.04)	0.61	1.67 (1.47-1.90)
23-24.9 kg/m^2	1.76 (1.40-2.21)	2.84 (1.85-4.35)	0.48	3.24 (2.00-5.23)	0.50	3.09 (1.95-4.90)	0.57	2.69 (1.79-4.03)	0.59	2.60 (1.76-3.84)
<25+ kg/m^2	2.90 (2.13-3.93)	7.17 (4.06-12.63)	0.58	6.26 (3.69-10.60)	0.49	8.76 (4.69-16.36)	0.53	7.44 (4.17-13.25)	0.46	10.09 (5.19-19.63)
p_{het}§	*<0.0001*	*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*

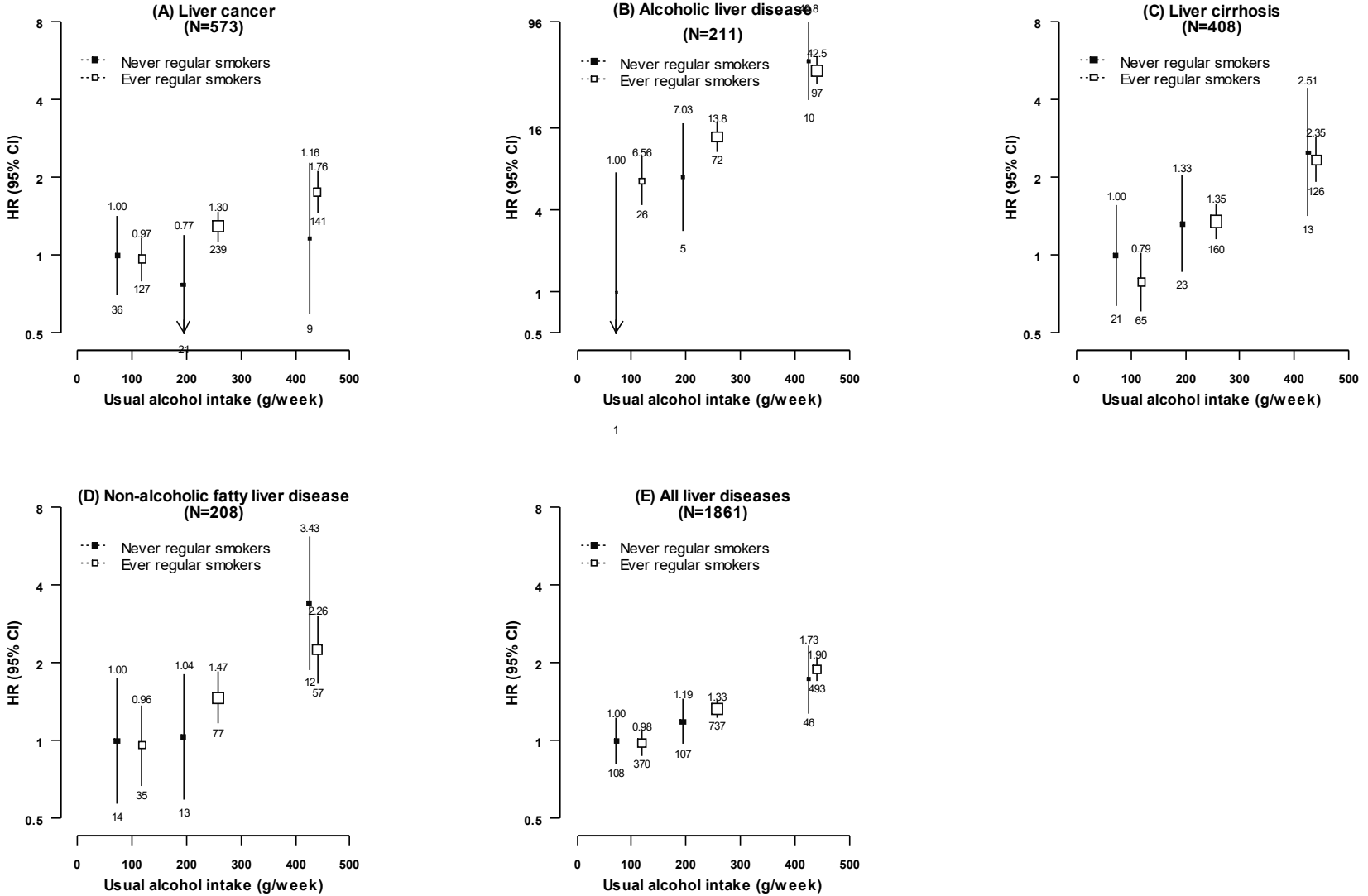
RDR, regression dilution ratio; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.
Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses.
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index (for analyses of flushing response).
Usual consumption is the average of the consumption levels at the 1st and 2nd resurveys.
*MacMahon-Peto method estimates RDR with the ratio of the range (i.e., difference between the means of the top vs. bottom baseline-defined groups) of usual alcohol intake to the range of baseline alcohol intake.
†Self-correlation method estimates RDR with the correlation coefficient between baseline alcohol intake and usual alcohol intake by Pearson or Spearman correlation.
‡Rosner's regression method estimates RDR by the slope of the regression line (i.e., regression coefficient) between baseline alcohol intake and usual alcohol intake.
§*P* for heterogeneity across strata of flushing response or body mass index.

Figure H 1. Association of alcohol consumption with total liver disease, in female current regular drinkers



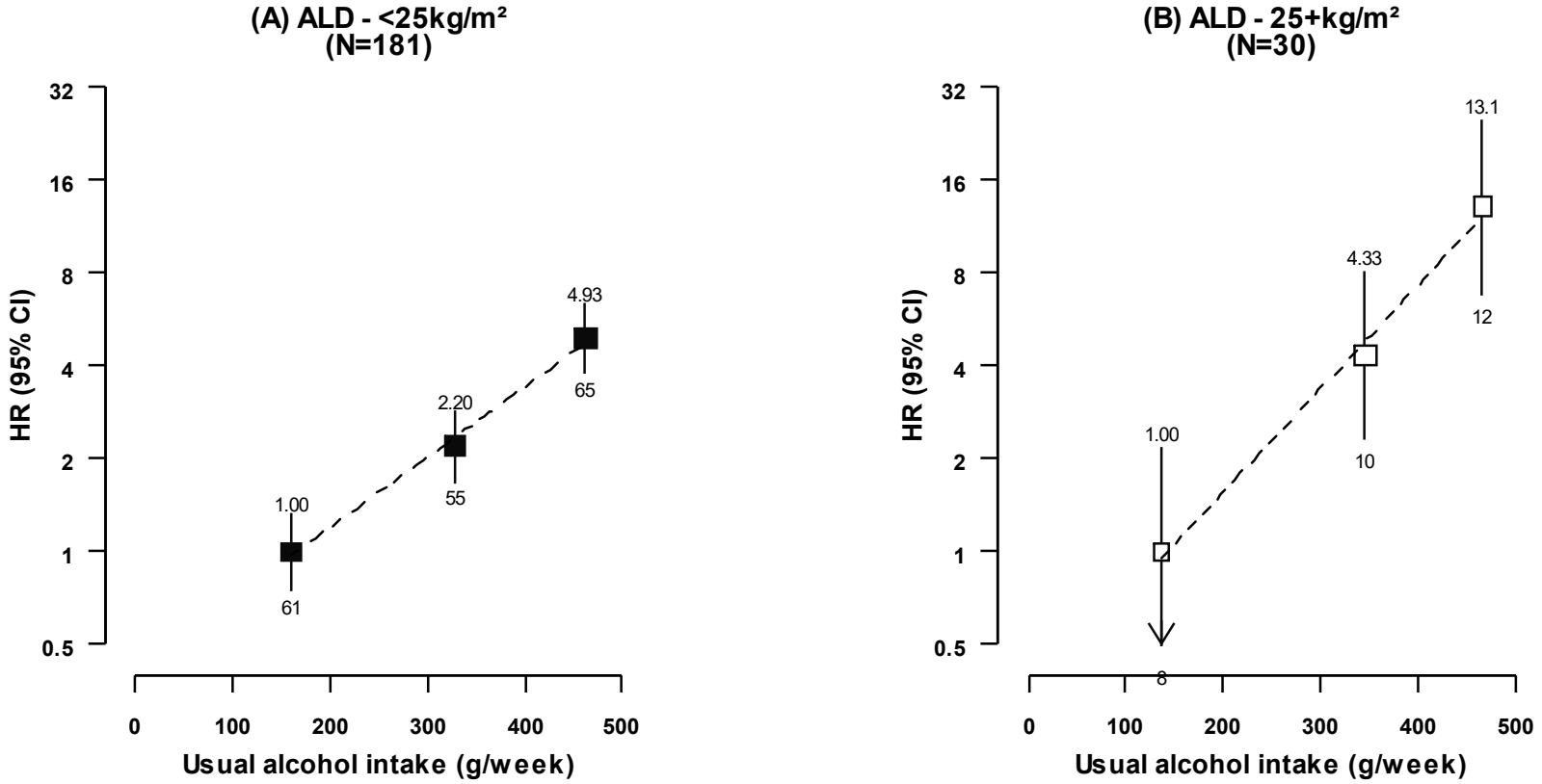
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 2. Associations of the joint effects of alcohol consumption and smoking with liver diseases, in male current regular drinkers



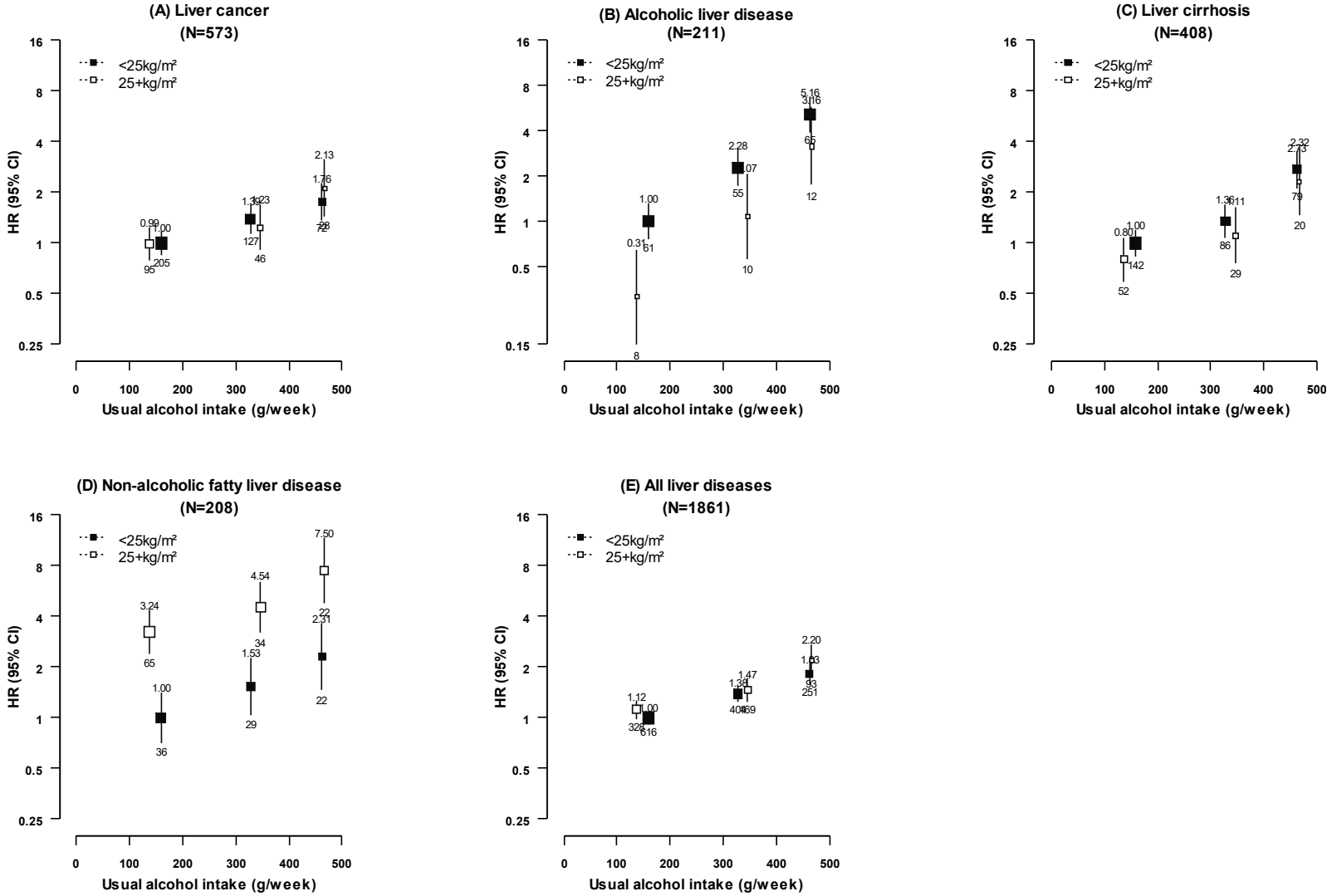
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 3. Associations of alcohol consumption with alcoholic liver disease, by body mass index in male current regular drinkers



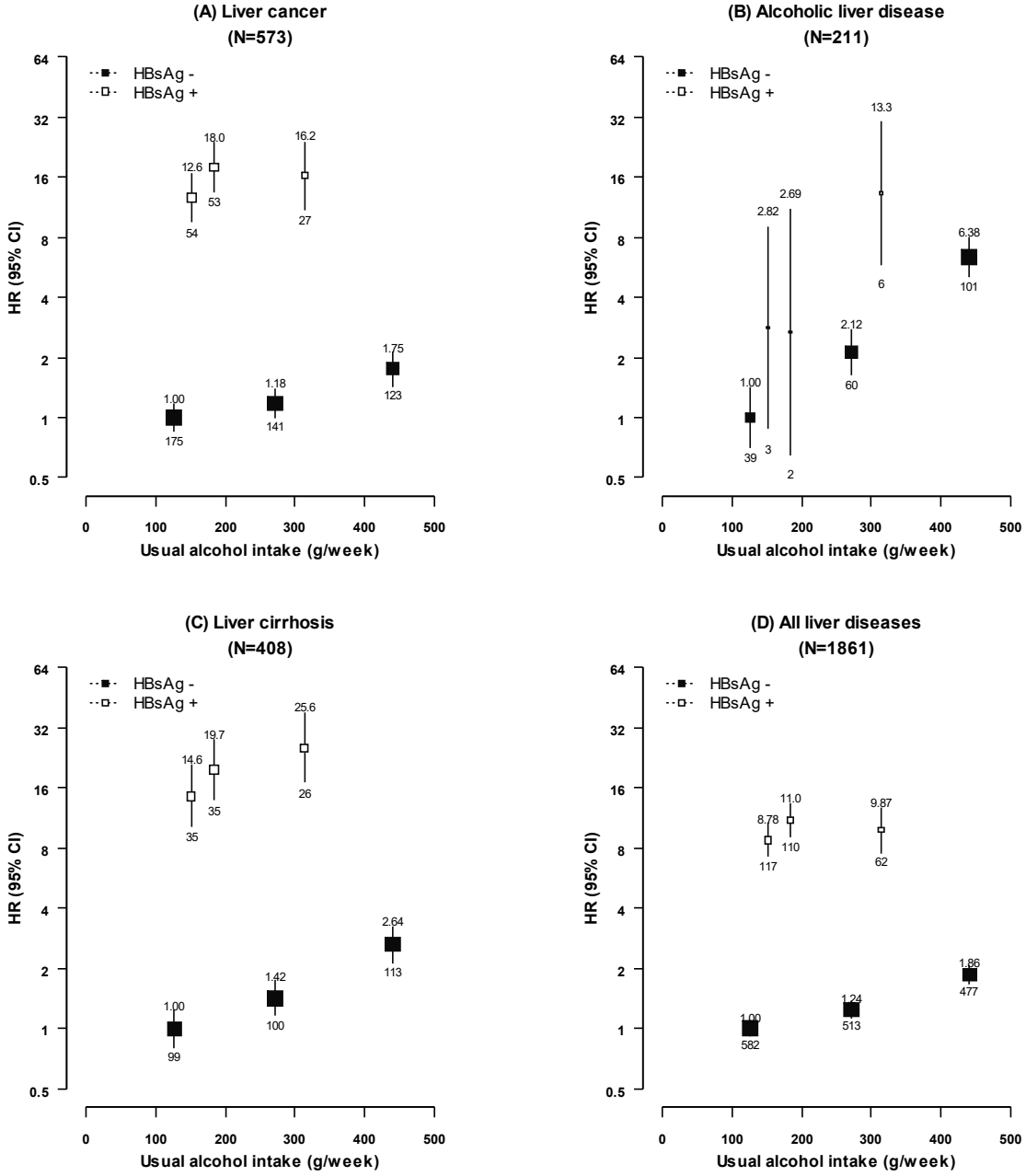
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, and physical activity. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 4. Associations of the joint effects of alcohol consumption and body mass index with liver diseases, in male current regular drinkers



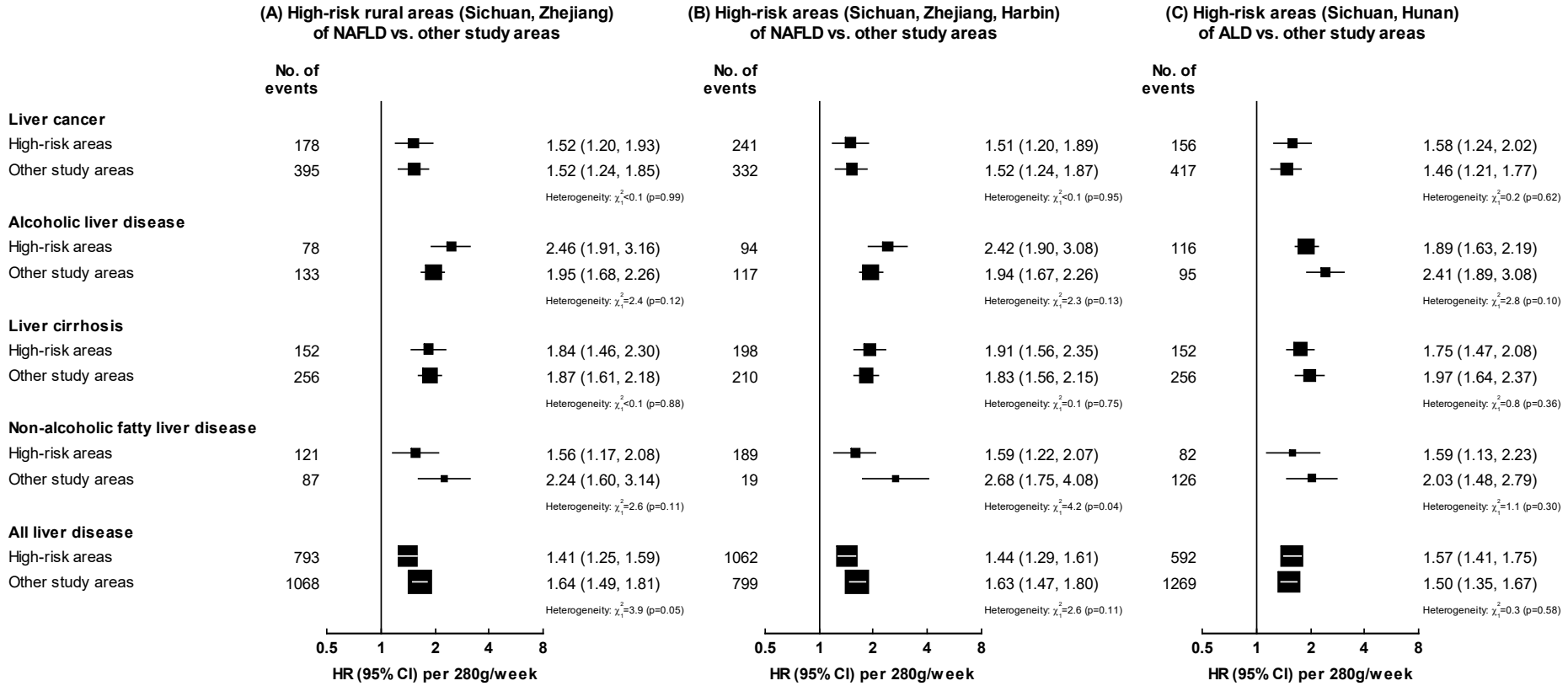
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, and physical activity. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 5. Associations of the joint effects of alcohol consumption and HBsAg seropositivity with liver diseases, in male current regular drinkers



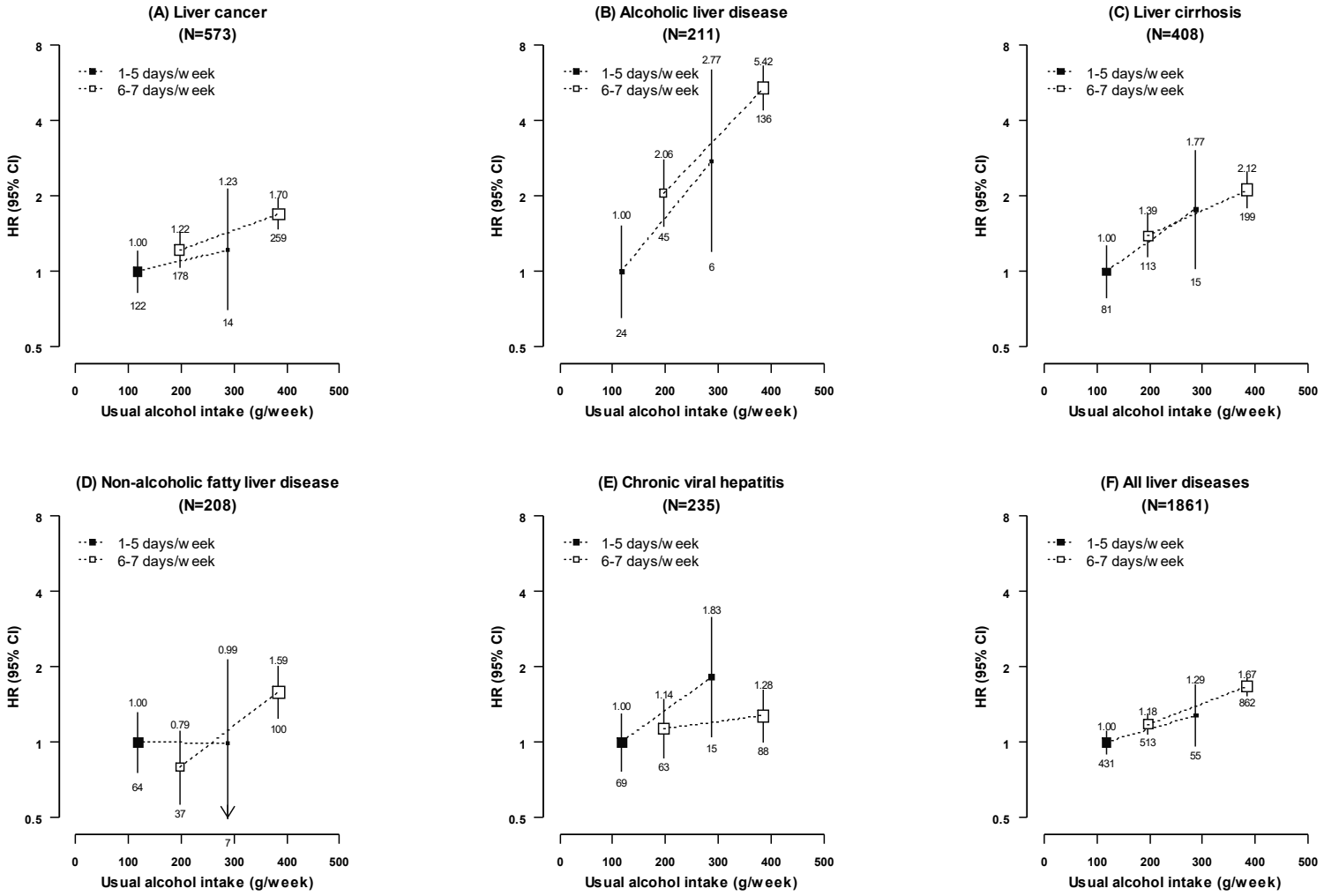
Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HBsAg (-) included negative, unclear, or missing test results. Non-alcoholic fatty liver disease is not shown here due to low number of events in HBsAg positive participants (n=4). HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Figure H 6. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by high-risk and other study areas in male current regular drinkers



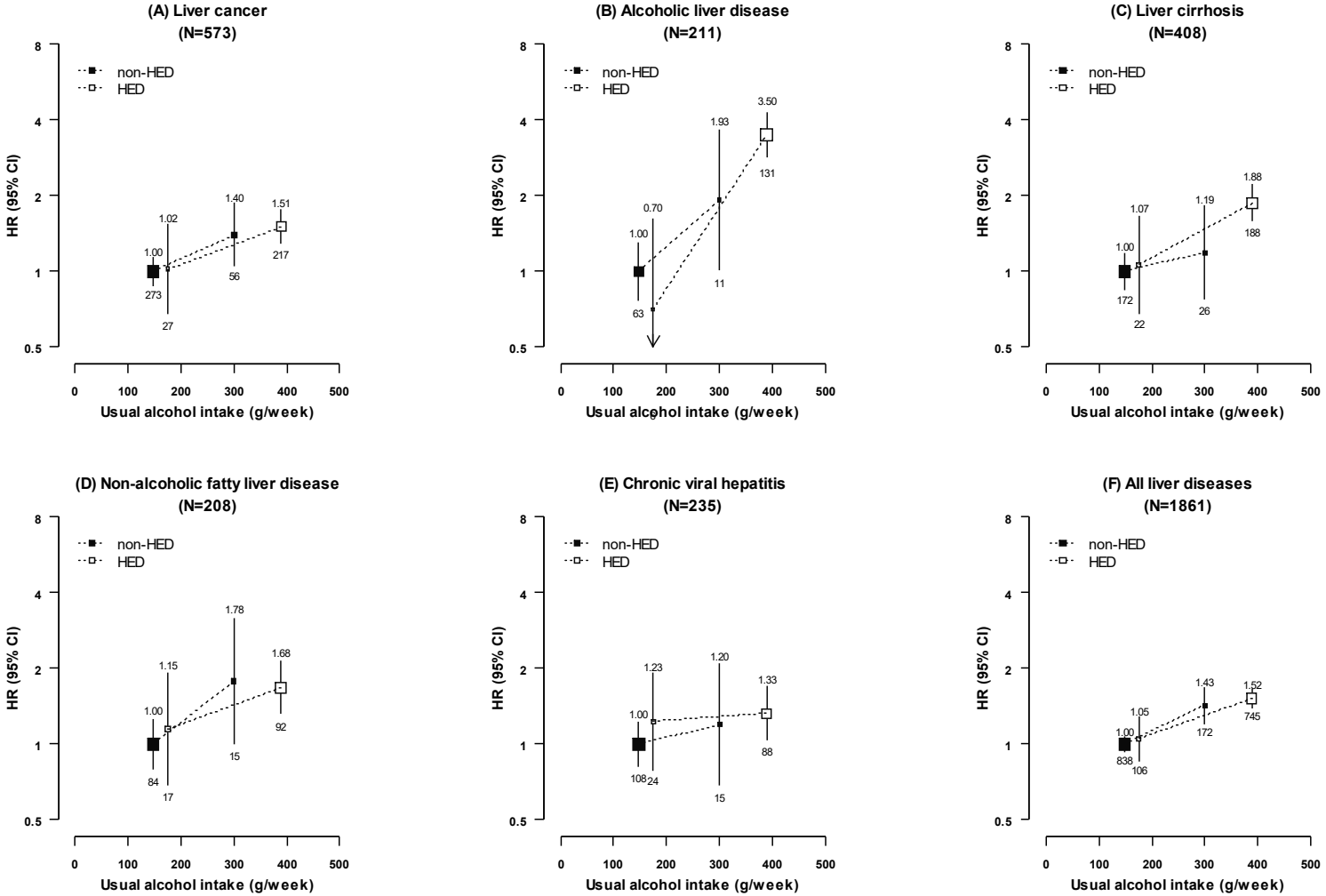
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 7. Associations of alcohol consumption with liver diseases, by drinking frequency in male current regular drinkers



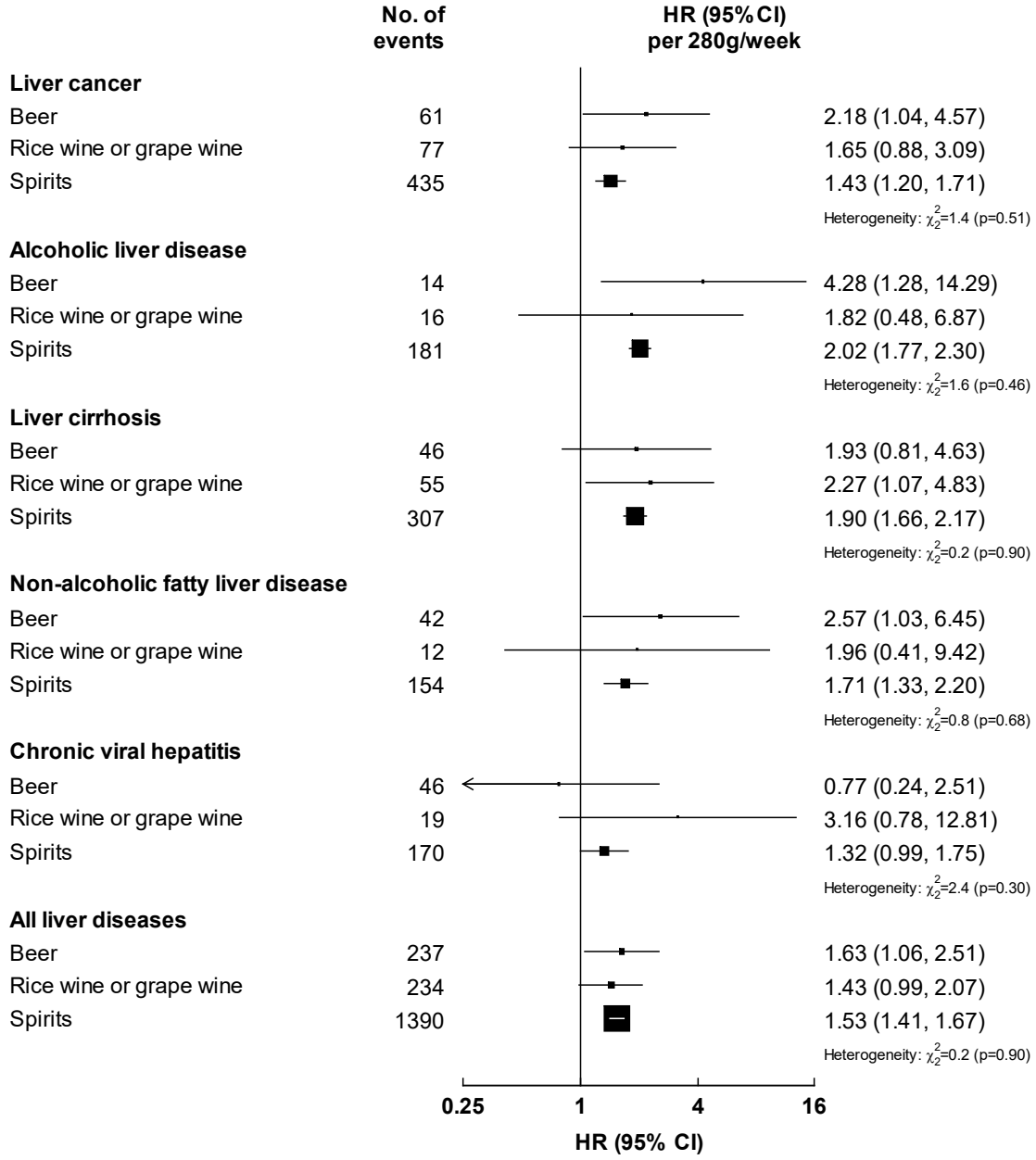
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: non-daily drinkers drinking <280g/week at baseline (reference group); non-daily drinkers drinking ≥280g/week at baseline; daily drinkers drinking <280 g/week at baseline; and daily drinkers drinking ≥280g/week at baseline. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 8. Associations of alcohol consumption with liver diseases, by heavy episodic drinking status in male current regular drinkers



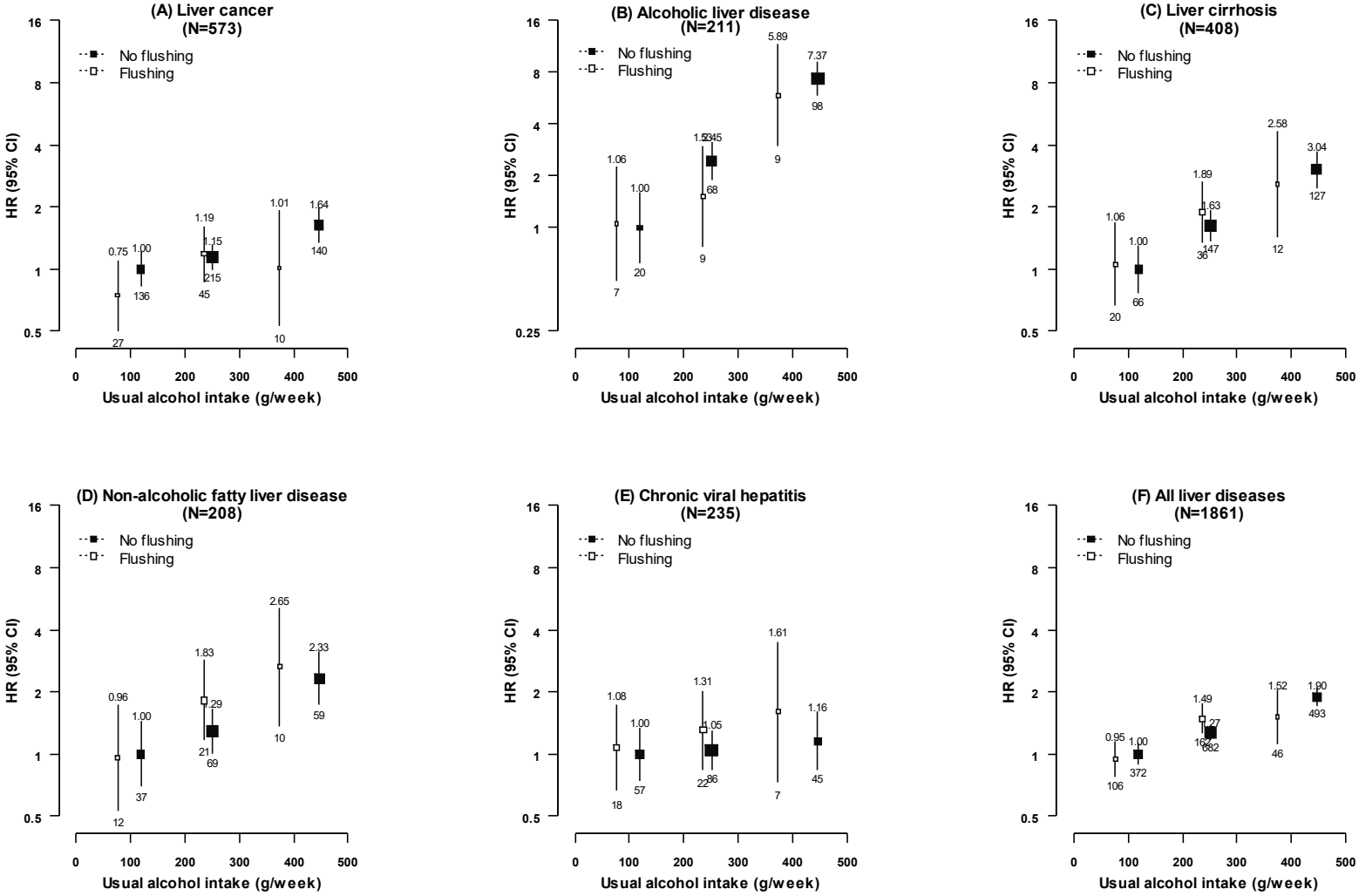
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: non-HED (i.e., ≤60g/session) drinkers drinking <280g/week at baseline (reference group); non-HED drinkers drinking ≥280g/week at baseline; HED (i.e., >60g/session) drinkers drinking <280 g/week at baseline; and HED drinkers drinking ≥280g/week at baseline. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; HED, heavy episodic drinking.

Figure H 9. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases, by beverage type in male current regular drinkers



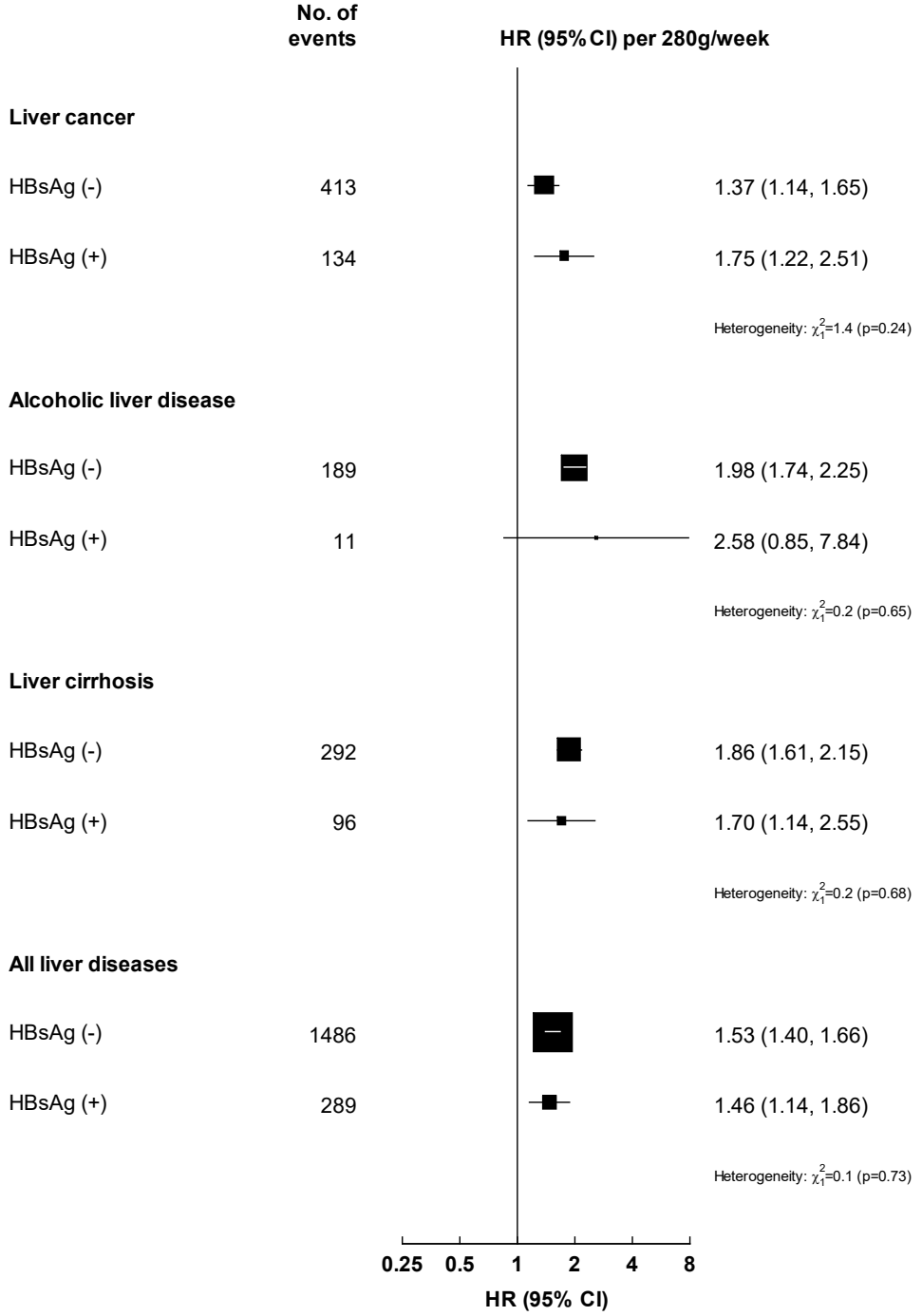
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 10. Associations of alcohol consumption with liver diseases, by flushing status in male current regular drinkers



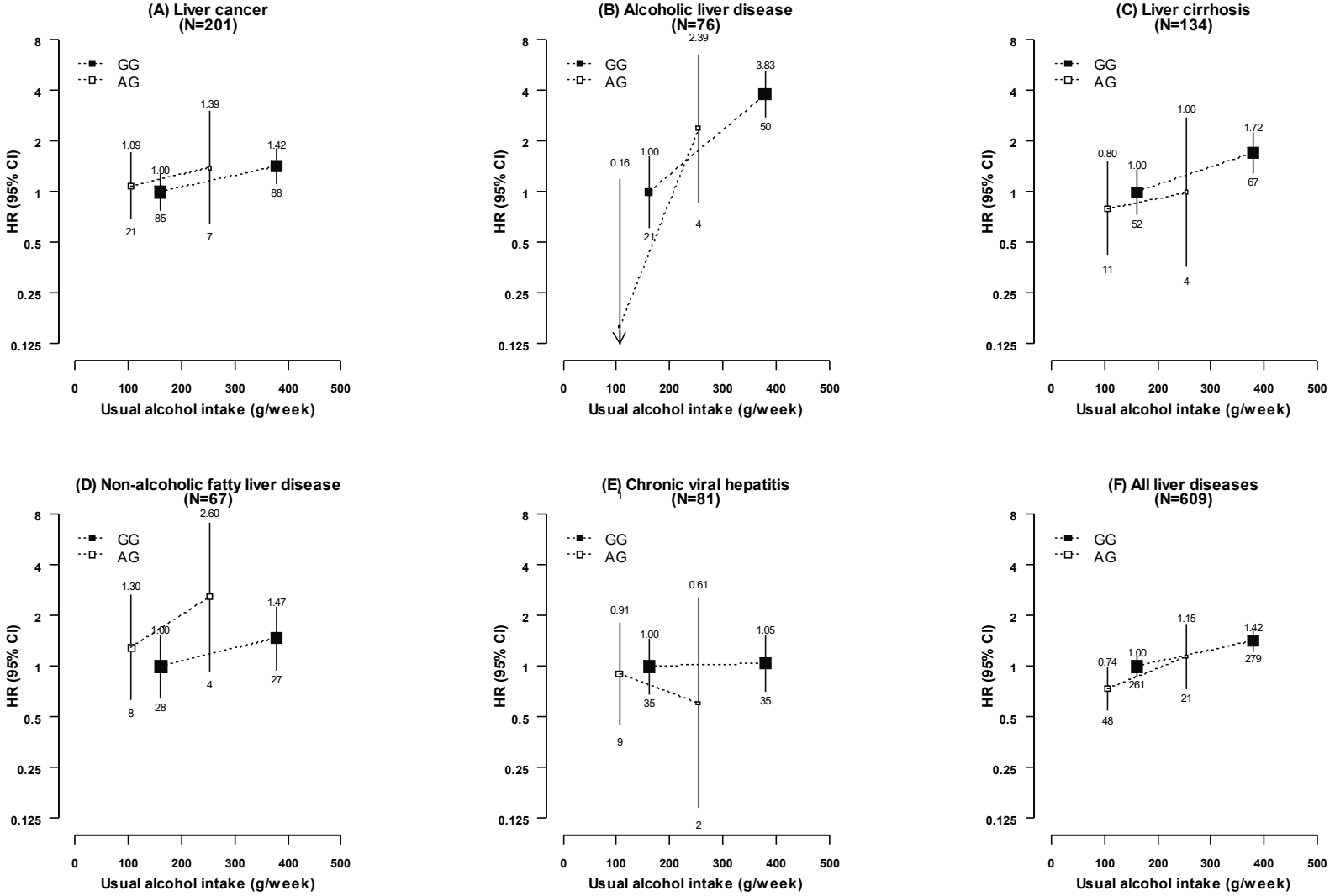
Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval.

Figure H 11. Adjusted HRs per 280g/week higher usual alcohol intake for liver diseases by HBsAg seroprevalence (after exclusion of unclear or missing HBsAg test results), in male current regular drinkers



Cox models are stratified by age-at-risk and study area, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis or chronic hepatitis, or with unclear or missing HBsAg test results were excluded. Each solid square represents an HR. The size of each box is inversely proportional to the variance of the log HR in each group and the error bars indicate the 95% CI. Non-alcoholic fatty liver disease is not shown here due to the low number of events in HBsAg positive participants (n=4). HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

Figure H 12. Associations of alcohol consumption with liver diseases, by *ALDH2*-rs671 genotype in male current regular drinkers



Cox models are stratified by age-at-risk, study area, and HBsAg, and adjusted for education, income, smoking, physical activity, and body mass index. Participants with prior cancer, liver cirrhosis, or chronic hepatitis were excluded from all analyses. Each solid square represents an HR. 95% CIs are plotted using floating standard errors to allow for comparison between any two categories. The size of each box is inversely proportional to the "floated" variance of the log HR in each group and the error bars indicate the group-specific 95% CI. The numbers above the error bars are point estimates for HRs, and the numbers below are number of events. Usual alcohol intake is calculated by the average of the self-reported alcohol intakes at two resurveys in each group. The four exposure categories refer to: *ALDH2*-rs671 GG drinkers drinking <280g/week at baseline (reference group); GG drinkers drinking ≥280g/week at baseline; AG drinkers drinking <280 g/week at baseline; and AG drinkers drinking ≥280g/week at baseline. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.