Lifestyle and cardiometabolic risk factors of cataract in Chinese adults

Mingshu Yan

Linacre College, University of Oxford

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Abstract

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Mingshu Yan, Linacre College, University of Oxford, DPhil, Michaelmas Term 2024

Background: Cataract is a common eye disease among older adults and is a major cause of global vision impairment and blindness, with high prevalence in low- and middle-income countries. Previous epidemiological studies on cataract risk factors were limited, had inconsistent findings, and were mainly based on Western populations.

Methods: This thesis used data from the China Kadoorie Biobank (CKB), a prospective cohort study of 512 726 adults (41% men) aged 30-79 years from ten regions in China followed for 11 years, to comprehensively assess the associations of major modifiable lifestyle and cardiometabolic factors (including smoking, alcohol drinking, physical activity, diet, adiposity, blood glucose, and diabetes) with age-related cataract incidence. Cox regression yielded hazard ratios (HRs) adjusted for confounders relating each of the risk factors to cataract risk. A health index (*Cataract Health Index*) that combines all the identified risk factors was created to assess its association with cataract risk, and to provide an estimation of the impact of controlling modifiable risk factors for cataract prevention.

Results: In CKB, 16 518 (3.2%) participants developed age-related cataract, with an incidence rate of 293 per 100 000 person years. There was higher cataract incidence in women and rural residents than their counterparts. Current smokers had 13% higher risk of cataract than never smokers. Ex-drinkers and current drinkers with consumption level higher than 420 g/week had 14% and 24% higher risk respectively than current drinkers in the lowest drinking category (i.e., consumed <140 g/week). Physical activity was associated with lower risk of cataract in a dose-response manner in women (HR per 10 MET-h/d: 0.89) but not in men. Among the 12 major food groups in China, there was an inverse association between fresh fruit (HR per 100 daily gram: 0.83) and risk of cataract in a dose-response manner. Waist-to-hip ratio (a measure of central

adiposity) was positively (HR per 1 SD: 1.05 in both sexes) associated with risk of cataract, but no clear association was observed for other adiposity measures. Participants with diabetes identified at baseline study and self-reported diabetes had respectively 35% and 80% higher risk of cataract than those without prevalent diabetes. Each 1 mmol/L usual random blood glucose was associated with 6% and 3% higher risk of cataract among participants with and without prevalent diabetes, respectively. The *Cataract Health Index*, which combines six major lifestyle and cardiometabolic factors (defined as number of unhealthy factors), was positively (HR per 1 unit: 1.13) associated with risk of cataract. Assuming these associations are causal, about 16.9 million cataract cases could potentially be prevented if all these unhealthy factors could be eliminated from the Chinese population.

Conclusions: This DPhil project found smoking, alcohol consumption, physical inactivity, low consumption of fresh fruit, high level of waist-to-hip ratio, diabetes, and high level of blood glucose were associated with higher risk of cataract. Individuals with a higher number of unhealthy lifestyle and cardiometabolic factors were more likely to have a higher risk of cataract than their counterparts. The current study findings could help to promote healthy lifestyle and manage key cardiometabolic indicators for effective cataract prevention purposes.

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Lastly, I would like to express my deepest gratitude to my parents, for their unwavering love, encouragement, and support during my DPhil.

Statement of contribution to the original work

This thesis is my own work, and I have acknowledged and cited all sources used. The idea to study the association between lifestyle and cardiometabolic factors with risk of cataract was conceived by my supervisors (Associate Professor Huaidong Du, Associate Professor Iona Millwood, Associate Professor Derrick Bennett, and Professor Zhengming Chen). I led the research presented in this thesis. I performed all aspects of the literature reviews and planned and designed the study. I conducted all statistical analyses (some analyses used statistical programmes developed within the Clinical Trial Service Unit and Epidemiological Studies Unit of the Nuffield Department of Population Health). I produced all the tables and figures presented. I interpreted the findings and wrote all aspects of the study in this thesis, under the supervision of my supervisors.

Table of Contents

Abstract ..... **i**
Acknowledgements iii
Statement of contribution to the original work iv
Table of Contents v
List of Tables ix
List of Figures xii
List of Abbreviations xvi
1 Introduction **1**
1.1 Formation of cataract 1
1.2 Burden of cataract 5
1.2.1 Global burden 5
1.2.2 Cataract burden in China 7
1.3 Risk factors for cataract 7
1.4 Aim and objectives of the thesis 8
2 Literature review of lifestyle and cardiometabolic risk factors for cataract **10**
2.1 Introduction 10
2.2 Aim and objectives 10
2.3 Methods 11
2.4 Results 14
2.4.1 Lifestyle factors in relation to risk of cataract 16
2.4.2 Cardiometabolic factors in relation to risk of cataract 22
2.5 Summary of the current evidence and implications for future research 26
2.6 Strengths and limitations of the literature review 27
2.7 Summary 28
3 Study population and statistical methods **29**
3.1 The China Kadoorie Biobank 29
3.1.1 Study design 29
3.1.2 Baseline survey 31
3.1.3 Resurveys 34
3.1.4 Participant follow-up 35
3.1.5 Outcome definition 36
3.2 Statistical methods 37

3.2.1 Correcting for confounding by age-at-risk 38
3.2.2 Floating absolute risk 38
3.2.3 Correcting for regression dilution bias 39
3.3 Summary 40
4 Patterns and correlates of cataract incidence in China 41
4.1 Introduction 41
4.2 Study population and methods 42
4.3 Results 43
4.3.1 Baseline characteristics of study population 43
4.3.2 Patterns of cataract incidence 45
4.3.3 Socio-demographic correlates of cataract incidence 49
4.4 Discussion 58
4.4.1 Summary of findings 58
4.4.2 Patterns and correlates of cataract incidence 58
4.5 Summary 63
5 Associations of smoking and alcohol drinking with risk of cataract 64
5.1 Introduction 64
5.2 Methods 65
5.2.1 Assessment of smoking 66
5.2.2 Assessment of alcohol consumption 67
5.2.3 Statistical analyses 68
5.3 Results 72
5.3.1 Baseline characteristics of participants by smoking or alcohol status 72
5.3.2 Smoking and risk of cataract 74
5.3.3 Alcohol consumption and risk of cataract 82
5.4 Discussion 89
5.4.1 Summary of findings 89
5.4.2 Smoking and risk of cataract 89
5.4.3 Alcohol consumption and risk of cataract 91
5.4.4 Strengths and limitations 93
5.5 Summary 95
6 Associations of physical activity and diet with risk of cataract 96
6.1 Introduction 96
6.2 Methods 97
6.2.1 Assessment of physical activity 98

6.2.2 Assessment of dietary factors ... 99
6.2.3 Statistical analyses ... 100
6.3 Results ... 106
6.3.1 Baseline characteristics of participants by physical activity ... 106
6.3.2 Baseline characteristics of participants by dietary factors ... 106
6.3.3 Physical activity and risk of cataract ... 112
6.3.4 Diet and risk of cataract ... 119
6.4 Discussion ... 128
6.4.1 Summary of findings ... 128
6.4.2 Physical activity and risk of cataract ... 128
6.4.3 Dietary factors and risk of cataract ... 130
6.4.4 Strengths and limitations ... 134
6.5 Summary ... 135
7 Associations of adiposity, diabetes, and glucose with risk of cataract ... 136
7.1 Introduction ... 136
7.2 Methods ... 137
7.2.1 Assessment of adiposity factors ... 137
7.2.2 Assessment of diabetes and blood glucose ... 139
7.2.3 Statistical analyses ... 140
7.3 Results ... 145
7.3.1 Baseline characteristics of participants by adiposity factors ... 145
7.3.2 Baseline characteristics of participants by diabetes and glucose status ... 147
7.3.3 Adiposity factors and risk of cataract ... 152
7.3.4 Diabetes and blood glucose with risk of cataract ... 161
7.4 Discussion ... 172
7.4.1 Summary of findings ... 172
7.4.2 Adiposity factors and risk of cataract ... 172
7.4.3 Diabetes and blood glucose with risk of cataract ... 177
7.4.4 Strengths and limitations ... 179
7.5 Summary ... 180
8 The combined association of cataract risk factors ... 181
8.1 Introduction ... 181
8.2 Methods ... 183
8.2.1 Definition of *Cataract Health Index* ... 184
8.2.2 Statistical analyses ... 188

8.3 Results 189
8.3.1 Patterns of *Cataract Health Index* 189
8.3.2 *Cataract Health Index* and risk of cataract 198
8.3.3 Population attributable fraction of *Cataract Health Index* 203
8.4 Discussion 204
8.4.1 Summary of findings 204
8.4.2 *Cataract Health Index* and risk of cataract 205
8.4.3 Strategies for cataract prevention 206
8.4.4 Strength and limitations 208
8.5 Summary 209
9 Summary of thesis and discussion 210
9.1 Cataract burden and risk factors 210
9.2 Key findings and comparison with other studies 211
9.2.1 Patterns and correlations of cataract incidence 211
9.2.2 Lifestyle factors and risk of cataract 212
9.2.3 Cardiometabolic factors and risk of cataract 215
9.2.4 The combined association of cataract risk factors 216
9.3 Public health implications 217
9.4 Future research 219
9.5 Conclusion 220
Appendix A. Introduction of the thesis 222
Appendix B. Literature review of lifestyle and cardiometabolic risk factors for cataract 225
Appendix C. Additional results: Patterns and correlates of cataract incidence in CKB 245
Appendix D. Additional results: Associations of smoking and alcohol with risk of cataract 247
Appendix E. Additional results: Associations of physical activity and diet with risk of cataract 252
Appendix F. Additional results: Associations of adiposity and diabetes with risk of cataract ... 266
Appendix G. Additional results: The combined association of cataract risk factors 271
References 281

List of Tables

Table 1.1 International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for cataract 3

Table 2.1 Summary of risk of bias assessment 15

Table 2.2 Summary of risk factors assessed in studies included in the literature review 15

Table 3.1 Reported cataract events among CKB study participants 36

Table 4.1 Baseline characteristics of the study population 44

Table 4.2 Baseline characteristics of the study population with and without cataract reported 48

Table 4.3 Sex-specific mean age at cataract incidence by socio-demographic characteristics of study population with cataract 50

Table 4.4 Cataract incidence rates by socio-demographic status and self-assessed health 56

Table 4.5 Cataract incidence rate by socio-demographic status and self-assessed health in men and women 57

Table 4.6 Incidence rates of age-related cataract and cataract surgery in prospective studies 59

Table 5.1 Baseline characteristics of CKB men by smoking and alcohol consumption status 73

Table 5.2 Hazard ratios for cataract by smoking in men - results of sensitivity analysis 81

Table 5.3 Hazard ratios for cataract by alcohol consumption in men - results of sensitivity analysis 87

Table 6.1 Calculation of usual fresh fruit consumption 104

Table 6.2 Baseline characteristics of CKB participants by level of baseline total physical activity 107

Table 6.3 Baseline characteristics of CKB participants by baseline fresh fruit consumption status 109

Table 6.4 Average daily consumption of food groups by sex, region, education, and household income in CKB participants 111

Table 6.5 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract - results of sensitivity analysis 118

Table 6.6 Adjusted HRs per one daily portion of fresh fruit for cataract 124

Table 7.1 Baseline characteristics of CKB participants by level of baseline body mass index 146

Table 7.2 Baseline characteristics of CKB participants by diabetes status 149

Table 7.3 Baseline characteristics of CKB participants by level of baseline random blood glucose in those without prevalent diabetes 151

Table 7.4 Adjusted HRs per 1SD higher of usual waist-to-hip ratio for cataract - results of sensitivity analysis..... 161

Table 7.5 Adjusted HRs for cataract by prevalent diabetes - results of sensitivity analysis .. 170

Table 7.6 Adjusted HRs per 1 mmol/L higher usual random blood glucose for cataract in participants without prevalent diabetes - results of sensitivity analysis 171

Table 8.1 Components of *Cataract Health Index* in CKB 187

Table 8.2 Baseline characteristics of CKB participants by category of the *Cataract Health Index* 191

Table 8.3 *Cataract Health Index* by age at baseline..... 193

Table 8.4 *Cataract Health Index* by study region. 194

Table 8.5 *Cataract Health Index* by education status. 195

Table 8.6 *Cataract Health Index* by household income. 196

Table 8.7 Adjusted HRs per 1 unit of *CHI* with cataract risk - results of sensitivity analysis .. 202

Table B.1 Systematic literature review search terms with MEDLINE (Ovid) database 225

Table B.2 Systematic literature review search terms with EMBASE (Ovid) database..... 226

Table B.3 Bias domains included in the ROBINS-I tool for follow-up studies, with a summary of the issues addressed..... 227

Table B.4 Prospective cohort studies evaluating the association between smoking and cataract 228

Table B.5 Prospective cohort studies evaluating the association between alcohol consumption and cataract 232

Table B.6 Prospective cohort studies evaluating the association between physical activity and cataract 234

Table B.7 Prospective cohort studies evaluating the association between dietary factors and cataract 235

Table B.8 Prospective cohort studies evaluating the association between adiposity factors and cataract 238

Table B.9 Prospective cohort study evaluating the association between diabetes, blood glucose, and cataract 242

Table D.1 Baseline characteristics of CKB women by smoking and alcohol consumption status 247

Table D.2 Estimated regression dilution ratios for alcohol consumption in current drinkers in men 248

Table D.3 Adjusted HRs for cataract by smoking status 249

Table D.4 Adjusted HRs for cataract by alcohol consumption 250

Table E.1 Physical activity types, MET values, codes and intensity categories 252

Table E.2 Estimated regression dilution ratios for physical activity 253

Table E.3 Prevalence of fresh fruit consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014). 254

Table E.4 Baseline fresh fruit consumption status by age at baseline. 255

Table E.5 Baseline fresh fruit consumption status by study region. 256

Table E.6 Cross tabulation of baseline consumption frequency of 11 food groups and baseline fresh fruit consumption status in CKB 257

Table E.7 Average daily consumption of 12 food groups by region in CKB participants..... 259

Table E.8 Adjusted HRs for cataract by physical activity 260

Table E.9 Adjusted HRs for cataract by frequency of dietary intake (1 of 2) 261

Table E.10 Adjusted HRs for cataract by frequency of dietary intake (2 of 2) 262

Table F.1 Estimated regression dilution ratios for body mass index in men..... 266

Table F.2 Adjusted HRs for cataract by adiposity factors (1 of 3) 267

Table F.3 Adjusted HRs for cataract by adiposity factors (2 of 3) 268

Table F.4 Adjusted HRs for cataract by adiposity factors (3 of 3) 269

Table F.5 Adjusted HRs for cataract by diabetes status and random blood glucose 270

Table G.1 Baseline characteristics of CKB participants by quintiles of the weighted *Cataract Health Index* 274

Table G.2 Adjusted HRs per 1 SD of $CHI_{weighted}$ with risk of cataract - results of sensitivity analysis 279

Table G.3 Adjusted HRs for cataract by *Cataract Health Index* 280

List of Figures

Figure 1.1 Normal eye and eye with cataract 1

Figure 1.2 Types of cataract 4

Figure 1.3 Relative contribution of each cause to crude prevalence of vision impairment and blindness globally in 2020 by age groups 6

Figure 3.1 Map of ten China Kadoorie Biobank study regions 30

Figure 4.1 Number of incident cataract cases by year of follow-up (2004-2017) 46

Figure 4.2 Number of first event cataract cases by year of follow-up (2004-2017) in ten study regions 47

Figure 4.3 Histogram of age at cataract incidence 49

Figure 4.4 Region-standardised cataract incidence rates by baseline age group in men and women ... 51

Figure 4.5 Cataract incidence rates by baseline age group and region in men and women 52

Figure 4.6 Cataract incidence rates by baseline age group in men and women in ten study regions..... 54

Figure 4.7 Age-standardised cataract incidence rates in men and women in ten study regions 55

Figure 5.1 Adjusted HRs for cataract by smoking in men 75

Figure 5.2 Adjusted HRs of smoking patterns with cataract in current versus never smokers in men 76

Figure 5.3 Adjusted HRs of cataract by reasons for, and years after, smoking cessation in ex-smokers versus never smokers in men. 78

Figure 5.4 Adjusted HRs of cataract associated with current smoking by selected population characteristics in men 79

Figure 5.5 Adjusted HRs of cataract associated with current smoking by region in men 80

Figure 5.6 Adjusted HRs for cataract by alcohol consumption in men 82

Figure 5.7 Adjusted HRs for cataract by alcohol drinking patterns in male current drinkers .. 84

Figure 5.8 Adjusted HRs per 280g/week higher usual alcohol consumption for cataract by selected population characteristics in male current drinkers 85

Figure 5.9 Adjusted HRs per 280g/week higher usual alcohol consumption for cataract by region in male current drinkers 86

Figure 5.10 Adjusted HRs for cataract for the joint associations of smoking and alcohol consumption in men 88

Figure 6.1 Adjusted HRs for cataract by quintiles of total physical activity 112

Figure 6.2 Adjusted HRs for cataract by quintiles of total physical activity, by sex and by region 113

Figure 6.3 Adjusted HRs for cataract by vigorous physical activity and sedentary leisure time 114

Figure 6.4 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by selected population characteristics 116

Figure 6.5 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by region 117

Figure 6.6 Adjusted HRs for cataract by fresh fruit consumption 119

Figure 6.7 Adjusted HRs for cataract by fresh fruit consumption, stratified by sex or region121

Figure 6.8 Adjusted HRs per one daily portion of fresh fruit for cataract by selected population characteristics among the >10 portions/month consumption groups..... 122

Figure 6.9 Adjusted HRs per one daily portion of fresh fruit for cataract by region among the >10 portions/month consumption groups..... 123

Figure 6.10 Adjusted HRs for cataract by red meat and preserved vegetable consumption 125

Figure 6.11 Adjusted HRs for cataract by rice, wheat, other staple food, and dairy products consumption 126

Figure 6.12 Adjusted HRs for cataract by poultry, fish/seafood, eggs, and soybean products consumption 127

Figure 7.1 Correlation coefficients between adiposity measures in men and women..... 148

Figure 7.2 Adjusted HRs for cataract by BMI at age 25 years in men and women 152

Figure 7.3 Adjusted HRs for cataract by BMI and body fat percentage in men and women. 153

Figure 7.4 Adjusted HRs for cataract by fat mass and fat mass index in men and women ... 154

Figure 7.5 Adjusted HRs for cataract by usual levels of central and general adiposity measures 155

Figure 7.6 Adjusted HRs for cataract by waist circumference and waist-to-hip ratio in men and women 157

Figure 7.7 Adjusted HRs for cataract by waist-to-height ratio in men and women..... 158

Figure 7.8 Adjusted HRs per 1SD higher of usual waist-to-hip ratio for cataract by selected population characteristics 159

Figure 7.9 Adjusted HRs per 1SD higher of usual waist-to-hip ratio for cataract by region .. 160

Figure 7.10 Adjusted HRs for cataract by diabetes status and random blood glucose..... 162

Figure 7.11 Adjusted HRs for cataract by duration of diabetes and age at diabetes diagnosis in participants with prevalent diabetes..... 163

Figure 7.12 Adjusted HRs of cataract associated with prevalent diabetes by selected population characteristics 165

Figure 7.13 Adjusted HRs of cataract associated with prevalent diabetes by region..... 166

Figure 7.14 Adjusted HRs per 1mmol/L higher of usual random blood glucose for cataract by selected population characteristics in participants without prevalent diabetes..... 168

Figure 7.15 Adjusted HRs per 1mmol/L higher of usual random blood glucose for cataract by region in participants without prevalent diabetes..... 169

Figure 8.1 Distribution of the *Cataract Health Index* 190

Figure 8.2 Proportion of incident cataract by category of *CHI*..... 197

Figure 8.3 Adjusted HRs for cataract by *CHI*..... 198

Figure 8.4 Adjusted HRs per 1 unit of *CHI* for cataract by population characteristics..... 200

Figure 8.5 Adjusted HRs per 1 unit of *CHI* for cataract by region..... 201

Figure A.1 Age-standardised global prevalence of blindness in adults aged 50 years and older from 1990 to 2020 222

Figure A.2 Age-standardised global prevalence of moderate to severe vision impairment in adults aged 50 years and older from 1990 to 2020..... 223

Figure A.3 Global and regional prevalence of cataract, based on pooled estimates from a systematic review conducted in 2019 224

Figure C.1 Cataract incidence rates by baseline age group in men and women with different levels of highest education received 245

Figure C.2 Cataract incidence rates by baseline age group in men and women with different household income (yuan) levels 246

Figure D.1 Adjusted HRs for cataract by usual level of smoking and alcohol consumption in women 251

Figure E.1 Adjusted HRs for cataract by vigorous physical activity and sedentary leisure time in men and women 263

Figure E.2 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by selected population characteristics in men and women 264

Figure E.3 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by region in men and women 265

Figure G.1 Distribution of the weighted *Cataract Health Index* 273

List of Abbreviations

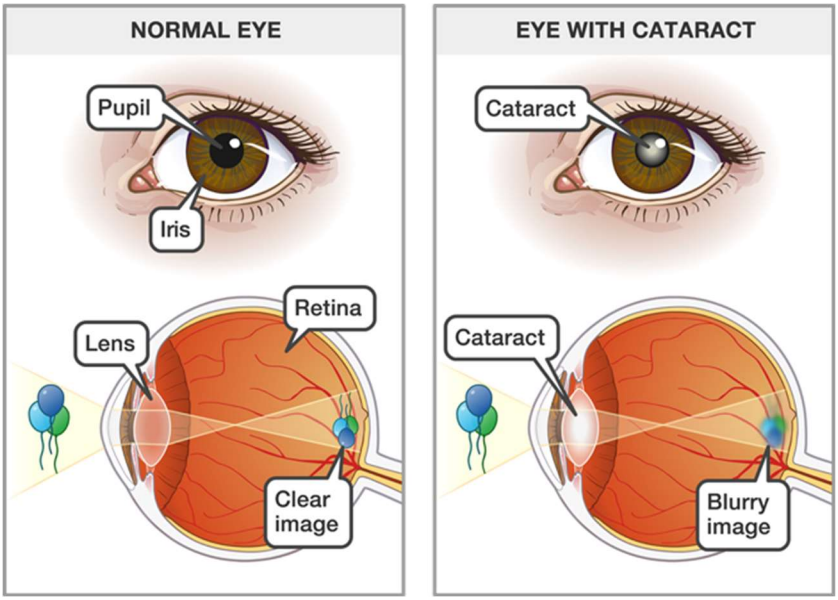
BMI	body mass index
CDC	Centre for Disease Control and Prevention
CHD	coronary heart disease
CVD	cardiovascular disease
CI	confidence interval
CKB	China Kadoorie Biobank
CHI	Cataract Health Index
DBP	diastolic blood pressure
EPIC	European Prospective Investigation into Cancer and Nutrition
HR	hazard ratio
MET	metabolic equivalent of task
SBP	systolic blood pressure
SD	standard deviation
TIA	transient ischemic attack
WHO	World Health Organisation
WHR	waist-to-hip ratio

1 Introduction

1.1 Formation of cataract

Cataract is a cloudiness in the eye lens which causes blurred vision. The lens is a transparent disc located behind the pupil and the iris, with no blood circulation and relatively low levels of cellular metabolism[1]. The lens functions to refract and focus light onto the retina, which is located at the back of the eye (**Figure 1.1**). The light signals are transformed into nerve signals in the retina and then transmitted to the brain to generate visual images[1]. Crystallins are the predominant structural proteins in the lens, and are responsible for the refractive function of the lens[2,3]. The formation of cataract is due to the denaturation and degradation of crystallins, in which process their native folds are lost, high molecular weight complexes are aggregated, and crystallins are converted from water-soluble proteins into water-insoluble proteins[4,5,6]. Therefore, light passing through a lens with a cataract is not clearly focused on the retina, leading to blurred images received in the brain (**Figure 1.1**).

Figure 1.1 Normal eye and eye with cataract (From AboutKidsHealth 2021[7]).



The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) specifies cataract subtypes according to its main causes leading to cataract formation (**Table 1.1**). A person can develop cataract before childhood (i.e., congenital cataract), or acquire it during adulthood mainly due to ageing (i.e., age-related cataract or senile cataract), direct injury to the head or eye (i.e., traumatic cataract), side effect of pharmacological therapy (i.e., drug-induced cataract), certain diseases such as diabetes (i.e., diabetic cataract), or other ocular disorders (e.g., myopic refractive error)[8,9,10]. Among all these subtypes, age-related cataract is the most common type[11] and often starts developing in a person's 40-50s, although people do not usually experience impaired vision until their 60s or later[9]. The global prevalence of cataract for those aged 20-39, 40-59, and 60+ years in 2019 was 3.0%, 17.0%, and 54.4%, respectively[12].

Depending on the location of opacification within the lens, cataract can also be classified as nuclear cataract, cortical cataract, and posterior subcapsular cataract (**Figure 1.2**). Nuclear cataract (the most common subtype) is defined by cloudiness starting from the centre of the lens, while cortical cataract is normally wedge-shaped, with cloudiness starting from the cortex and extending to the centre of the lens. Posterior subcapsular cataract has a plaque-like opacity in the axial posterior cortical layer. The three types of cataract can present separately or in combination[10]. The estimated global age-standardised prevalence of cataract among adults was 17.2% in 2019, and the prevalence for nuclear, cortical, and posterior subcapsular cataract subtypes was 8.2%, 8.1%, and 2.2%, respectively[12].

Table 1.1 International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for cataract (Version 2019, from WHO, 2019[13])

(H00-H59) Diseases of the eye and adnexa
(H25 to H28) Disorders of lens

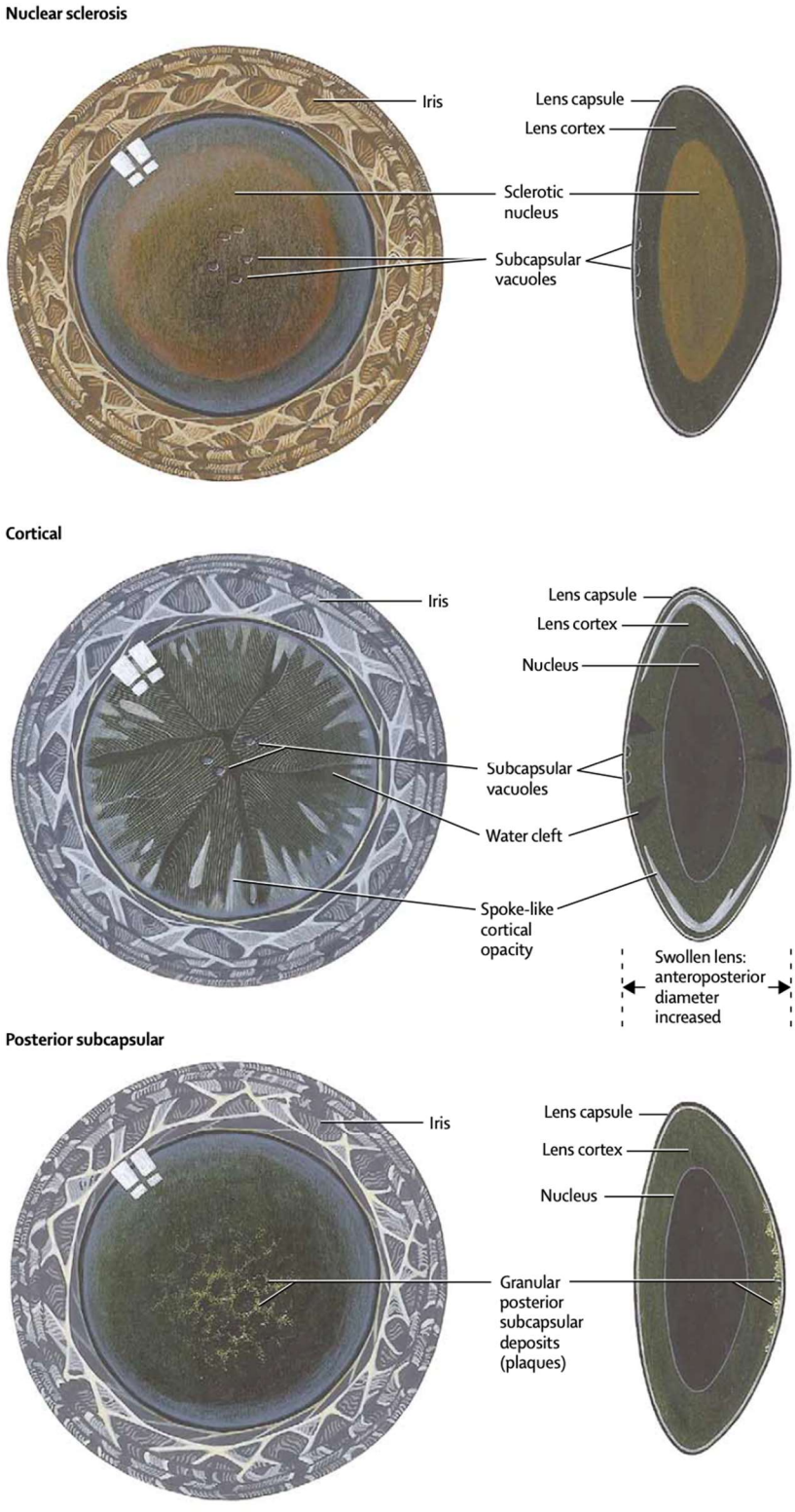
(H25) Senile cataract
Excl.: capsular glaucoma with pseudoexfoliation of lens (H40.1)
(H25.0) Senile incipient cataract
Senile cataract: coronary, cortical, punctate
Subcapsular polar senile cataract (anterior)(posterior)
Water clefts
(H25.1) Senile nuclear cataract
Cataract brunescens
Nuclear sclerosis cataract
(H25.2) Senile cataract, morgagnian type
Senile hypermature cataract
(H25.8) Other senile cataract
Combined forms of senile cataract
(H25.9) Senile cataract, unspecified

(H26) Other cataract
Excl.: congenital cataract (Q12.0)
(H26.0) Infantile, juvenile and presenile cataract
(H26.1) Traumatic cataract
(H26.2) Complicated cataract
Cataract in chronic iridocyclitis
Cataract secondary to ocular disorders
Glaucomatous flecks (subcapsular)
(H26.3) Drug-induced cataract
(H26.4) After-cataract
Secondary cataract
Soemmerring ring
(H26.8) Other specified cataract
(H26.9) Cataract, unspecified

(H27) Other disorders of lens
Excl.: congenital lens malformations (Q12)
mechanical complications of intraocular lens (T85.2)
pseudophakia (Z96.1)
(H27.0) Aphakia
(H27.1) Dislocation of lens
(H27.8) Other specified disorders of lens
(H27.9) Disorder of lens, unspecified

(H28) Cataract and other disorders of lens in diseases classified elsewhere
(H28.0) Diabetic cataract
(H28.1) Cataract in other endocrine, nutritional and metabolic diseases
Cataract in hypoparathyroidism (E20)
Malnutrition-dehydration cataract (E40-E46)
(H28.2) Cataract in other diseases classified elsewhere
Myotonic cataract (G71.1)
(H28.8) Other disorders of lens in diseases classified elsewhere

Figure 1.2 Types of cataract (From Asbell et al. 2005[10]).



Symptoms of cataract, which can vary depending on the subtypes of cataract, include blurred vision, glare, poor night vision, loss of contrast sensitivity, loss of ability to discern colours, and increasing near-sightedness[14,15]. Nuclear cataract impairs far vision more than near vision, whereas the opposite is true for posterior subcapsular cataract[9]. Cataract often develops slowly without clear symptoms, and may not be diagnosed until discovered incidentally or when vision is significantly impaired. At a late stage, cataract can cause severe vision impairment or even blindness[16]. Thus far, there is no pharmaceutical treatment which can reverse the development of cataract and surgery is the only treatment to restore cataract-related vision impairment. During the surgery, the opaque lens is removed and replaced with an artificial intraocular lens[17].

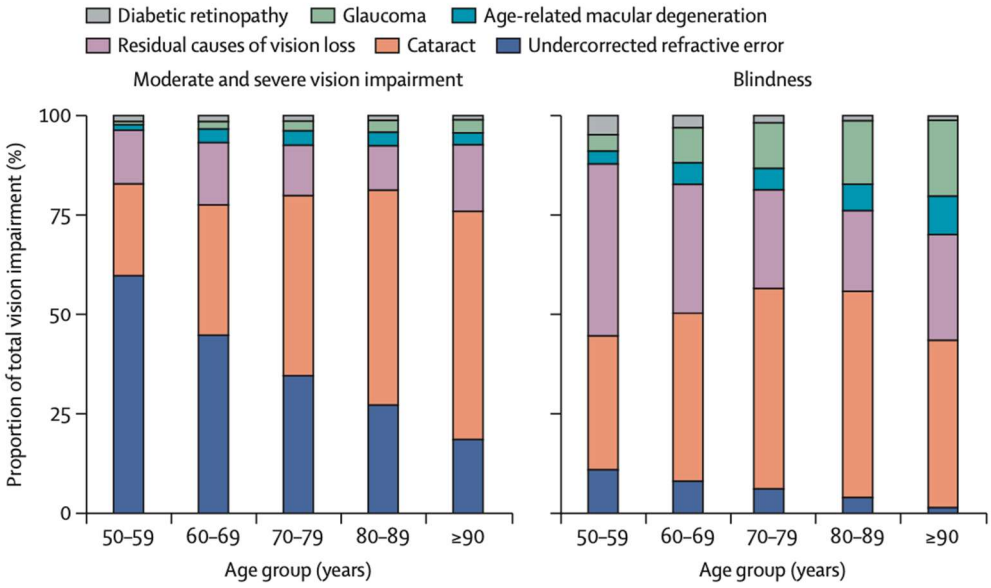
1.2 Burden of cataract

1.2.1 Global burden

Globally, around 43 million people were blind and 295 million were visually impaired in 2020, with half of the blindness (i.e., visual acuity <3/60 in the better eye, according to the World Health Organisation [WHO] definition) and one third of the visual impairment (i.e., visual acuity <6/12 in the better eye) caused by cataract[18,19]. The contribution of cataract to vision impairment and blindness increases with age, and it is the leading cause of moderate/severe vision impairment and blindness among adults aged 70 years and older (**Figure 1.3**).

The relative contribution of cataract to blindness and vision impairment had notable regional variability, with significantly higher proportions in low- and middle-income countries including south and southeast Asia, sub-Saharan Africa, and Oceania (>43% for blindness and >32% for

Figure 1.3 Relative contribution of each cause to crude prevalence of vision impairment and blindness globally in 2020 by age groups (From Steinmetz et al. 2021[19]).



vision impairment) than in Europe, America, and high-income Asia Pacific (<28% for blindness and <17% for vision impairment) in 1990-2020 (**Supplementary Figure A.1** & **Supplementary Figure A.2** in **Appendix A**)[20]. Across the six WHO regions, the prevalence of cataract ranged from 9% in American regions to 36% in both south-eastern Asia and western Pacific regions (**Supplementary Figure A.3**).

There has been great improvement in the treatment of cataract related blindness, however the growing and ageing population globally introduces new challenges. Barriers exist in many countries that prevent access to cataract surgery[21,22], including treatment cost, gender inequality, poor patient education, and social/cultural norms[23]. Compared to the general population, people with cataract are more likely to have reduced quality of life[24,25] and increased risk of falls and depression[26,27].

1.2.2 Cataract burden in China

China had the largest number of blindness and vision impairment cases in the world in 2019, accounting for one fifth and one sixth of the global cases, respectively[18,28]. Among the 9 million people with blindness and 50 million people with vision impairment in China in 2019, one third of both conditions were caused by cataract[28]. In 2020, the estimated prevalence of cataract in Chinese adults aged 50 years and older was 27.5%, with slightly higher prevalence in rural (28.8%) than in urban regions (26.7%)[29]. With the increase of age from 50-59 to 80+ years, the estimated prevalence increased dramatically from 7.9% to 78.4%.

Regional variations of cataract prevalence in China is poorly studied, and the most recent estimates were obtained in 2010. By then, the prevalence was higher in northeast China (24.6%) and south central China (28.5%) than in north, east, southwest and northwest parts of China (range from 15.0% to 21.7%)[30]. This pattern might be due to the combined effects of differences in socio-economic status, health behaviors, health services quality, and environmental factors (e.g., altitude)[31,32].

1.3 Risk factors for cataract

The exact causes of cataract are largely unknown, although previous epidemiological studies (mainly from western high-income countries) have provided some evidence on factors which may have an impact on cataract etiology[33,34]. Apart from advanced age, which is the most important factor associated with cataract[35,36], several socio-demographic factors (including female sex, low socio-economic status[37,38]) and lifestyle factors (including smoking, inadequate vegetable

intake[33,39]) have been found having a relation with cataract formation. In addition, the process of cataract development could also be affected by a range of cardiometabolic factors (including high body mass index [BMI], high blood pressure[40,41]), disease and medication (including ocular disorders [e.g., myopic refractive error], diabetes mellitus, metabolic syndrome, steroid use, aspirin use[42,43]), environmental factors (including ultraviolet radiation exposure, air pollution[44,45]), and genetic factors[10,46]. However, previous findings are largely inconsistent and relationships of lifestyle and cardiometabolic factors with cataract risk are inconclusive.

Despite China having the world's largest number of blindness and vision impairment cases, with one third of both conditions caused by cataract[18,28], epidemiological evidence of cataract risk factors in Chinese population is highly limited. Few such studies have been constrained by small sample size[47,48] or short duration of follow-up[49].

1.4 Aim and objectives of the thesis

The primary aim of this DPhil project is to investigate the associations of major modifiable lifestyle and cardiometabolic factors, including smoking, alcohol drinking, physical activity, diet, adiposity, blood glucose, and diabetes, with risk of age-related cataract in a large prospective cohort study among Chinese adults. Such knowledge gained could help to further understand the aetiology of age-related cataract, to identify high risk populations, and to guide public health strategies for age-related cataract prevention. The specific objectives of this thesis include:

1) To conduct a literature review to identify evidence gaps on the relationships between lifestyle and cardiometabolic risk factors with risk of age-related cataract;

2) To describe incidence patterns of age-related cataract by age, sex, and other socio-demographic factors;
3) To investigate the associations of the above-mentioned modifiable risk factors individually, with risk of age-related cataract;
4) To create a cataract index, using information from important modifiable risk factors, to examine the combined associations of these factors with risk of age-related cataract.

2 Literature review of lifestyle and cardiometabolic risk factors for cataract

2.1 Introduction

Lifestyle and cardiometabolic factors (e.g., smoking, diet, adiposity) are related to ageing, and healthier lifestyles could postpone and shorten the duration of disability and age-related diseases[50,51]. As a major type of age-related diseases, incidence of age-related cataract may be related to these ageing-related factors[33,39,40]. To confirm or refute this, a thorough understanding of existing evidence is warranted. A systematic review can be used to identify and evaluate major lifestyle and cardiometabolic risk factors for age-related cataract, and therefore help to identify research gaps, determine key research questions, and inform data analysis strategies (e.g., consideration of potential confounding variables when investigating the prospective associations of major lifestyle and cardiometabolic factors with cataract risk).

2.2 Aim and objectives

This literature review aims to systematically summarise existing evidence from large prospective studies on the associations of lifestyle and cardiometabolic factors with age-related cataract risk. The two main objectives of this literature review are:

(1) To evaluate the existing evidence on major lifestyle and cardiometabolic risk factors (including smoking, alcohol drinking, physical activity, diet, adiposity, diabetes, and blood glucose) for age-related cataract;

(2) To provide a descriptive summary of all other risk factors for age-related cataract.

2.3 Methods

This literature review was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[52,53]. MEDLINE (Ovid) and EMBASE (Ovid) databases were searched for publications from database inception to 14 December 2023, and were limited to English language articles. Similar search terms were used for both databases. Scottish Intercollegiate Guidelines Network (SIGN) filters[54] were used in the search strategy to identify prospective studies. To capture diverse risk factors, a broad search term (i.e., "risk"), instead of specific risk factor terms (e.g., "smoking", "adiposity", etc.), was used. Key search terms included "cataract", "risk", and "epidemiologic studies", with full lists of search terms and relevant search results provided in **Supplementary Table B.1** & **Supplementary Table B.2** in **Appendix B**. Based on the adaptation of the PICOS (population, interventions, comparisons, outcomes, and study design) framework[55,56], the inclusion and exclusion criteria of this review were as follows:

Population/participants:

- Inclusion criteria:
    - Human participants with no restriction to age, sex, ancestry group, and geographic location.
- Exclusion criteria:
    - Studies include only participants with certain type(s) of disease(s) (e.g., metabolic syndrome) rather than the general population as their study population.
    - Animal studies.

Interventions/exposure:

- Inclusion criteria:
    - Studies with lifestyle and/or cardiometabolic factors as exposures.

Outcomes:

- Inclusion criteria:
    - Cataract cases identified through self-reporting, clinical diagnosis, government disease registry, or health insurance reimbursement.
    - Cataract in one eye or both eyes.
    - Nuclear, cortical, or posterior subscapular cataract.
- Exclusion criteria:
    - Congenital or infantile cataract.
    - Traumatic cataract.

Study design:

- Inclusion criteria:
    - Cohort studies (with follow-up period ≥3 years and number of cataract cases ≥100).
    - No restriction on number of study participants.
- Exclusion criteria:
    - Cross-sectional studies, case-control studies, nested case-control studies, case series studies, case reports studies, cohort studies with follow-up period <3 years or number of cataract cases <100, or narrative reviews.

Type of publication:

- Inclusion criteria:

    - Publications by 14 December 2023.
    - Publications in English with full-text access.
- Exclusion criteria:
    - Conference abstracts, poster presentations, or editorials.

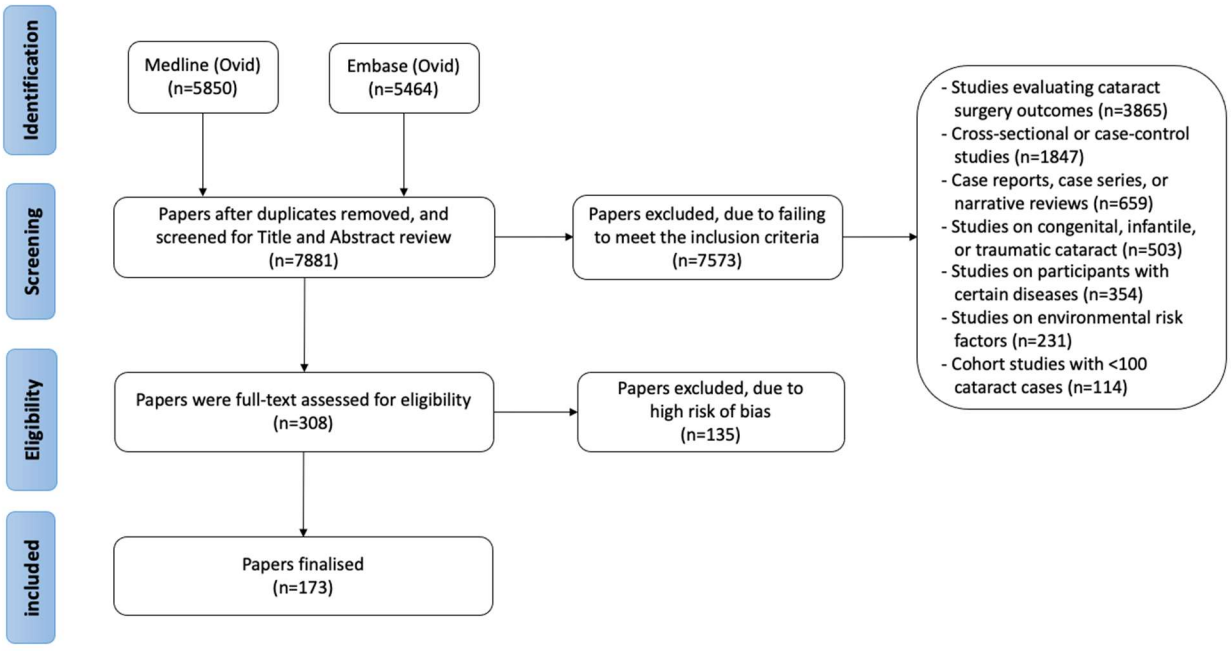
The initial selection of studies was performed based on "Title and abstract". Then, full-text review of eligible publications was conducted. Extracted information included: study methodology (e.g., design, length of follow-up); study population (e.g., population demographics, baseline characteristics); exposure(s) and outcome(s) [e.g., definition, measurement, quality control]; descriptive results (e.g., number of participants, number of cases); effect estimates (e.g., adjusted and unadjusted, 95% confidence intervals [CIs]); and risk of bias (e.g., level of adjustment, missing data). The ROBINS (Risk of Bias In Non-randomised Studies) tool[57] for follow-up studies was adopted to assess the risk of bias for the shortlisted studies, with a summary of the tool provided in **Supplementary Table B.3**. To evaluate the risk of bias, the quality of included publications was categorised into five levels of risk (i.e., low, moderate, serious, critical, or no information), based on the seven domain of risks: (1) bias due to confounding (i.e., level of adjustment); (2) bias in selection of participants; (3) bias in classification of exposures; (4) bias due to missing data; (5) bias in measurement of outcomes; (6) bias in selection of the reported results; (7) other bias not specified above. The final list of included publications was categorised based on type(s) of risk factor analysed. Since major modifiable lifestyle and cardiometabolic risk factors (i.e., smoking, alcohol drinking, physical activity, diet, adiposity, diabetes, and blood glucose) were the focus of this review, relevant publications including these factors were

summarised and compared. As a secondary objective of this review, descriptive summaries were provided for other risk factors identified.

2.4 Results

In total, 5850 and 5464 publications were identified from MEDLINE and EMBASE, respectively. The PRISMA four-stage flow diagram was used to show the screening process (**Figure 2.1**).

Figure 2.1 Overview of study selection process for the literature review.



After eliminating duplicates, 7881 publications were available for title and abstract review, with 7573 excluded (mainly due to failing to meet the inclusion criteria of study design, exposure definition, and outcome definition), leaving 308 publications for full-text review (**Figure 2.1**). In total, 173 of the 308 publications had low or moderate levels of potential bias were included for the final review (**Table 2.1**).

Table 2.1 Summary of risk of bias assessment

Domain of bias	Number of publications based on risk of bias assessment (N=308)			
	Low risk	Moderate risk	Serious risk	Critical risk
1. Bias due to confounding (level of adjustment)	218	53	18	19
2. Bias in selection of participants	237	36	23	12
3. Bias in classification of exposures	207	41	44	16
4. Bias due to missing data	217	49	34	8
5. Bias in measurement of outcomes	177	81	36	14
6. Bias in selection of the reported results	201	47	42	18
Overall	**173**		**135**	

The 173 publications included in this literature review have a sample size ranging from 500 to 1.3 million and a follow-up period from 3 years to 20 years. Most of the studies were conducted among Western populations, with risk factors from smoking, alcohol consumption, physical activity, dietary factors, adiposity, blood pressure, and plasma glucose to female reproductive factors, prior disease history (e.g., diabetes, metabolic syndrome), and medication history (e.g., statin, postmenopausal hormone) (**Table 2.2**).

Table 2.2 Summary of risk factors assessed in studies included in the literature review

	Risk factor	Number of publications*
Lifestyle factors	Smoking	15
	Alcohol consumption	10
	Physical activity	4
	Dietary factors (food groups: grains, vegetables, etc.)	13
	Dietary factors (micronutrient intake, supplements)	35
Cardiometabolic factors and medication history	Adiposity	19
	Blood pressure	2
	Plasma glucose	2
	Female reproductive factors	6
	Prior disease history (exclude diabetes)	41
	Diabetes	18
	Medication history	44
Overall		**173**

*Some publications involved more than one risk factor, so subcategories in this table do not sum to the total.

2.4.1 Lifestyle factors in relation to risk of cataract

2.4.1.1 Smoking and risk of cataract

As shown in the detailed summary of results (**Supplementary Table B.4** in **Appendix B**), smoking was largely consistently associated with a higher risk of age-related cataract. Of the 15 studies reviewed, all of them were conducted among Western populations. The sample size of the 15 studies ranged from 660 to over 1 million, with 9 of them involving more than 10 thousand participants. The follow-up period ranged from 5 to 20 years and smoking status was assessed though self-reported questionnaire at baseline in all studies. Seven studies used cataract diagnosis, 6 studies used cataract surgery, and 2 studies used either diagnosis or surgery to define the study outcome. Fourteen of the 15 studies suggested current smoking was associated with higher risk of cataract, and the relative risk ranged from 1.12 (95% CI: 1.09-1.14) to 2.84 (1.46-5.51) compared with never smoking, except for the 45 and Up Study[58] which found no clear association between smoking and cataract surgery performed before age 65 years. The hazard ratio (HR) for smoking 15 or more cigarettes per day ranged from 1.26 (1.23-1.30)[59] to 1.53 (1.39-1.69)[60] compared to never smoking, whereas the HR of current smoking of 20 or more cigarettes per day ranged from 1.68 (1.04-2.27)[61] to 2.05 (1.38-3.05)[62] compared to never smoking. Higher smoking amount was also positively associated with cataract risk. Compared with never smokers, ever smokers who had smoked at least 25 pack-years had 33% (15%-53%)[63] higher risk of developing cataract, those who had smoked for 36 or more pack-years had 46% (2%-108%)[64] higher risk, and those who had smoked 65 or more pack-years had HRs that ranged from 1.58 (1.13-2.19)[61] to 1.78 (1.58-2.00)[60].

The association between smoking cessation and cataract risk was assessed in 5 studies (**Supplementary Table B.4**). Four of these suggested an inverse association between cessation length and risk of cataract among smokers[60,65,66,67]. For example, in the Cohort of Swedish Men Study, former smokers with years since quitting of <10, 10-20, and >20 years had HRs of 1.27 (1.15-1.41), 1.22 (1.12-1.32), and 1.13 (1.04-1.22), respectively, compared with never smokers[65]. Findings from the Nurses' Health Study and the Health Professionals Follow-up Study with participants aged 45 years and older also suggested former smokers with years since quitting of 15-24.9 and ≥25 years had 16% (0.84, 0.74-0.95) and 20% (0.80, 0.71-0.91) lower risk of cataract, respectively, compared with current smokers, though no difference in risk was seen for those who had quit smoking for less than 15 years[60]. However, in the Blue Mountain Study with 2406 participants aged 49 years and older, longer smoking cessation time was not significantly associated with a lower risk of nuclear cataract compared with non-smokers, probability due to shorter follow-up period (10 years) than the four studies mentioned above[68].

2.4.1.2 Alcohol consumption and risk of cataract

The existing body of literature is inconsistent regarding the association between alcohol consumption and age-related cataract risk, and a detailed summary of previous studies is provided in **Supplementary Table B.5**. Of the 10 studies on this topic, 8 were conducted among Western populations, one from Asia, and one from Africa. Three studies included women only. Sample sizes ranged from nearly 1800 to over 1 million, with 7 studies having a sample size greater than 10 thousand. The follow-up period ranged from 5 to 20 years and alcohol consumption status was assessed though self-reported questionnaire at baseline in all 10 studies.

Five studies used cataract diagnosis to define the study outcome, 4 studies used cataract surgery and 1 study used both cataract diagnosis and surgery.

Two studies found a J-shaped association between alcohol consumption and cataract risk, two studies found an inverse association, one study found an inverted J-shaped association, two study found a positive association, despite no clear association was found in three studies. Drinkers consuming ≤4.9, 5.0-14.9, 15.0-24.9, and ≥25.0 grams of alcohol per day had HRs of 0.84 (0.73-0.96), 0.83 (0.71-0.97), 1.08 (0.87-1.33) and 1.10 (0.90-1.35), respectively, compared with never drinkers in the Nurses' Health Study[69]. In the Blue Mountains Eye Study followed-up participants for 10 years, never drinkers, drinkers consuming less than one drink per day, and drinkers consuming more than two drinks per day had odds ratios of 2.36 (1.25-4.46), 1.77 (0.90-3.48), and 2.10 (1.16-3.81) when compared to drinkers consuming 1-2 drinks per day[70]. However, findings from the UK Million Women Study suggested that higher alcohol consumption was associated with lower risk of cataract, with respective HRs of 0.93 (0.91-0.94) and 0.92 (0.89-0.96) for drinkers consuming 2-14 and ≥15 units (1 unit ~10g) of alcohol per week compared with drinkers consuming <2 units of alcohol per week, which might be explained by the lower risk of moderate drinking (than heavy drinking)[59]. The European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study also found an inverse association between higher alcohol consumption and cataract risk, with participants in the 2nd to 4th quartile of weekly alcohol consumption level having HRs of 0.92 (0.84-1.01), 0.86 (0.79-0.95), and 0.82 (0.74-0.90), respectively, compared with those in the 1st (lowest) quartile[71]. The Swedish Mammography Cohort Study found an inverted J-shaped association, with current drinkers consuming <6, 6-13,

14-20, 21-30, and >30 grams of alcohol per day having HRs of 1.11 (1.02-1.22), 1.14 (1.01-1.29), 1.24 (1.03-1.49), 1.29 (0.99-1.68) and 0.84 (0.53-1.33), respectively, compared with never drinkers[72]. The Nakuru Eye Disease Cohort Study conducted on African population found a positive association, with risk ratio of 1.4 (1.1-1.8) for current drinkers when compared with never drinkers[73]. The China Kadoorie Biobank study conducted on Asian population also found a positive association, with HR per 280 g/week of alcohol consumption among current drinkers being 1.21 (1.09-1.33)[74]. The exact causes for the inconsistent findings of the association between alcohol consumption and risk of cataract remain unknown.

2.4.1.3 Physical activity and risk of cataract

Existing evidence generally suggests that a higher level of physical activity is inversely associated with age-related cataract in a dose-response manner (**Supplementary Table B.6**). All the 4 included studies were conducted among Western populations. Their sample sizes ranged from nearly 1600 to over 50 thousand, with the follow-up period ranging from 6 to 12 years. They all used questionnaires to collect self-reported physical activity status at baseline. Three of them used cataract diagnosis as the study outcome and one used cataract surgery. Three of the 4 studies suggested that a higher level of physical activity was associated with lower risk of cataract incidence, despite the combined Women's Health Initiative Observational Study and Age-Related Eye Disease Study[75] followed-up 1577 U.S. women aged 50-79 years for 6 years found no clear association. Two of the 3 studies (with inverse association findings) used metabolic equivalent of task hours per day (MET-h/d) to measure physical activity. For instance, in the combined Swedish Mammography Cohort and Cohort of Swedish Men Study of 11 thousand participants from

Sweden, compared with participants in the lowest quartile (<38.4 MET-h/d), those in the 2nd to 4th quartiles had HRs of 0.94 (0.89-0.99), 0.91 (0.86-0.96) and 0.87 (0.82-0.92), respectively[76]. Each 4 MET-h/d increment of physical activity was associated with 5% (4%-7%) lower risk of cataract. A similar inverse association was identified in a study with combined data from the National Runners' Health Study II and the National Walkers' Health Study[77], with HR of 0.58 (0.43-0.80) comparing the top (≥9 MET-h/d) vs bottom (<1.8 MET-h/d) category of physical activity, and HR of 0.95 (0.93-0.97) per 1 MET-h/d of physical activity increment. However, in the National Runners' Health Study[78], a significant association was only found in men but not in women, with relative risk of 0.72 (0.60-0.87) and 0.71 (0.47-1.06), respectively, for an increment of 1 unit for 10km performance times. This study focused on leisure time physical exercise only instead of total physical activity, which might explain the different findings observed compared with other three studies.

2.4.1.4 Dietary factors and risk of cataract

Several dietary factors (e.g., fresh vegetables, fruits, vitamins and minerals) were found to be inversely associated with age-related cataract risk[79,39,80]. Of the 13 studies on dietary groups (e.g., grains, vegetables, etc.) included in this review, 10 were conducted among Western populations and 3 were among Asian populations (**Supplementary Table B.7**). The study sample sizes ranged from nearly 2000 to over 70 thousand. The follow-up period ranged from 3 to 16 years, with 10 studies using cataract diagnosis and 3 studies using cataract surgery as the study outcome. Dietary intake of food groups was assessed using self-reported questionnaires at baseline in all studies, with 2 studies assessing multiple food groups, 6 studies on fruit and vegetables intake, 2

on fat intake, one on dairy intake, one on wholegrain and legume intake, and one on tea intake. Dietary scores or dietary patterns were assessed in 2 studies[81,82]. The Blue Mountains Eye Study found that the Australian Healthy Eating Index was not associated with cataract risk[81], but the EPIC-Oxford Study found that meat eaters with <50 gram/day meat consumption, fish eaters, vegetarians, and vegans had 15% (0.85, 0.72-0.99), 21% (0.79, 0.65-0.97), 30% (0.70, 0.58-0.84) and 40% (0.60, 0.38-0.96) lower risk of cataract, respectively, compared with meat eaters consuming ≥100 gram/day meat[82]. Studies focusing on individual food items mainly assessed fruit and vegetables. Of the 6 such studies, 3 found no significant associations[83,84,85]. However, findings from the Nurses' Health Study[86] and the UK Biobank[74] suggested that a higher intake of some fruits and vegetables (including apple, pear, spinach, and winter squash), but not all (e.g., broccoli, carrots, sweet potatoes, tomatoes, berry, etc.) was associated with a lower risk of cataract. The Tzu Chi Health Study also found that vegetarians had a 20% (0.80, 0.65-0.99) lower risk of cataract compared with non-vegetarians[47]. No clear association of fat[87,88], dairy[89], wholegrain[47], and legume[47] intake with risk of cataract was identified. The study on tea intake found tea drinkers had 15% (0.85, 0.75-0.96) lower risk of cataract than non-tea drinkers[49].

In terms of the relevance of vitamin/mineral intake on age-related cataract development, existing evidence supports a potential benefit of multivitamin/mineral supplement intake. For instance, a pooled analysis of data from 12 prospective studies found that multivitamin/mineral supplement intake was associated with lower risk of cataract (0.66, 0.39-0.93)[80]. The association varied across different subtypes of cataract, with inverse associations for nuclear cataract (0.73, 0.64-0.82) and cortical cataract (0.81, 0.68-0.94), but no association for posterior capsular

cataract (0.96, 0.72-1.20). Intakes of omega-3 fatty acids, multivitamins (vitamin A, vitamin C, vitamin E), and carotenoids (β-carotene, lutein, and zeaxanthin) supplements were also found to be inversely associated with risk of cataract, with consumers having a relative risk between 0.80 and 0.90 compared with non-consumers[90,91].

2.4.2 Cardiometabolic factors in relation to risk of cataract

2.4.2.1 Adiposity and risk of cataract

The most studied cardiometabolic factor, for its association with risk of age-related cataract, is adiposity. Thus far, the research evidence is inconsistent for the association between the two (**Supplementary Table B.8**). Of the 19 included studies, 15 were conducted among Western populations and 4 from Asia; 6 studies included either men or women only; and one was conducted among athletes. Sample sizes ranged from 500 to 1.3 million, with 12 of the studies involving more than 10 thousand people. The follow-up period ranged from 5 to 18 years, with 13 studies using cataract diagnosis and the other 6 using cataract surgery as the study outcome. Fourteen studies investigated the association between BMI (kg/m^2) and cataract risk, with 6 finding a positive association and 8 finding no clear association. Among the 6 studies suggesting a positive association, HRs for those with BMI ≥30 kg/m^2 ranged from 1.10 (1.06-1.15) to 1.44 (1.21-1.72) compared with those in the lowest BMI categories (either <20, <23, <25, or <30kg/m^2)[92,78,93,94,95,96]. Three of the 6 studies examined the linear associations between BMI and cataract risk, creating inconsistent results. For instance, in the Physicians' Health Study, each increment of 2 kg/m^2 of BMI was associated with 12% (1.12, 1.05-1.19) higher risk in men[94]. In the National Runners' Health Study, each 1 kg/m^2 higher of BMI was associated with 4% (1.04,

1.01-1.07) higher risk of cataract in men but not in women (HR=0.97, 0.91-1.03)[78]. However, in the Nurses' Health Study, each increment of 5 kg/m^2 of BMI was associated with 12% (1.12, 1.07-1.17) higher risk of cataract in women, but no association was found in men (HR = 1.03, 0.93-1.15)[97].

In addition to BMI, waist circumference (4 studies), waist-to-hip ratio (WHR, 3 studies), weight change (2 studies), and body fat percentage (one study) were examined for their associations with risk of cataract. Both the Cohort of Swedish Men Study[98] and Swedish Mammography Cohort Study[99] found no association between waist circumference and cataract risk. However, findings from the UK Biobank Study suggested higher waist circumference (≥102cm in men and ≥88cm in women) and higher WHR (≥1.00 in men and ≥0.85 in women) was associated with 9% (1.09, 1.06-1.13) and 14% (1.14, 1.09-1.19), respectively, higher risk of cataract than those with lower central adiposity (<102cm in men and <88cm in women for waist, and <1.00 in men and <0.85 in women for WHR)[96]. This was in line with the results from the National Runners' Health Study, where an increment of 1cm waist circumference was associated with 2% (1.02, 1.00-1.03) higher risk in men and 4% (1.04, 1.01-1.06) higher risk in women[78], and the results from the Physicians' Health Study, where a higher WHR was associated with higher cataract risk, with male physicians in the highest WHR (>0.985) group had more than 30% (1.31, 1.02-1.67) higher risk of cataract compared with those with the lowest WHR (<0.897)[100]. In addition, the combined Nurses' Health Study and Health Professionals' Follow-up Study found that greater weight gain from early to middle adulthood was associated with higher risk of cataract in both men and women[101]. Similar findings were observed in the Age-related Eye Diseases Study, where participants in the

top quintiles of weight change having 35% (1.35, 1.09-1.67) higher risk of cortical cataract and 48% (1.48, 1.10-1.97) higher risk of posterior subcapsular cataract than those in the lowest quintile[102]. However, no clear differences of cataract risk between participants with high (≥25% in men and ≥35% in women) and low (<25% in men and <35% in women) level of body fat percentage in the UK Biobank[96], and no association between WHR and cataract risk in the Shihpai Eye Study[48] was found.

2.4.2.2 Diabetes, blood glucose, and risk of cataract

Diabetes is an important risk factor for age-related cataract development[103,95]. Evidence on this is generally consistent (**Supplementary Table B.9**). Of the 18 studies included in the review, 11 were conducted among Western populations, 3 among African, 3 from Asia, and one from Latin America. Four studies included either men or women, while the rest included both genders. Sample sizes ranged from nearly 500 to 1.1 million, with 5 of the studies having a sample size greater than 10 thousand. The follow-up period ranged from 4 to 25 years; with 12 studies using cataract diagnosis, 5 using cataract surgery, and one study using both cataract diagnosis and surgery as study outcome.

Seventeen of the 18 studies have examined the association between diabetes status and cataract risk, with 14 studies finding a positive association, and the rest 3 finding no clear association (**Supplementary Table B.9**). Among the studies suggesting a positive association, the relative risk ranged from 1.43 (1.10-1.86)[99] to 4.10 (3.24-5.20)[63] comparing participants with and without diabetes. Two of the 18 studies, both used data from the Blue Mountains Eye Study to examine

the association between blood glucose levels and cataract risk, found a positive association, i.e., an increment of 1 standard deviation (SD) or 1 mmol/L of fasting blood glucose was associated with 13% (1.13, 1.01-1.27)[104] higher risk with 5 years of follow-up and 23% (1.23, 1.01-1.48)[105] higher odds after 10 years of follow-up, respectively, of cortical cataract and any cataract.

2.4.2.3 Other risk factors for cataract

This section provides a descriptive summary of other major risk factors for age-related cataract. With the inclusion of evidence from published systematic reviews, the following summary is not limited to original studies identified in the literature review I performed. Several studies assessed the associations of other cardiometabolic factors, including blood pressure[106], metabolic syndrome[42,99], medication history (e.g., statin use)[43], and female reproductive factors[107] with age-related cataract incidence. Although no clear association between blood pressure (either systolic or diastolic) and risk of cataract was found[41], a systematic review of 9 cohort studies conducted in western high-income countries, involving 0.3 million people, found that hypertension status was associated with higher risk of cataract (1.08, 1.05-1.12). Subgroup analysis found hypertension was associated with higher risk of posterior capsular cataract (1.22, 1.03-1.46), but not nuclear cataract (1.07, 0.95-1.20) or cortical cataract (1.02, 0.88-1.19)[106].

Metabolic syndrome (i.e., cluster of metabolic abnormalities) has been consistently associated with cataract risk[42,99]. A systematic review conducted in 2016 including 6 observational studies (2 of them were prospective cohort studies involving 37K participants in total)[42] concluded that metabolic syndrome was associated with higher risk of cataract, and relative risk of the 2

prospective cohort studies was 1.68 (1.40-2.02) and 1.49 (1.14-1.95), respectively, comparing participants with and without metabolic syndrome[42].

It has been suggested that certain treatments and medications, including statins and female hormones, are associated with risk of cataract[43,108,109,110]. A systematic review of 6 cohort studies (313K participants) concluded that statin use was associated with higher risk of cataract (1.13, 1.01-1.25), and the association was more pronounced among participants aged ≤60 years (1.28, 1.19-1.38)[43]. A systematic review of 4 cohort studies (3300 participants) on postmenopausal hormone use and cataract risk found no clear difference of cataract risk in past and current postmenopausal hormone users when compared with never users[110]. No clear associations between female reproductive factors (including age at menarche, age at menopause, year of menses, type of menopause, and number of live births) and risk of cataract were found[111,107], though oral contraceptive pill use was also found to be inversely associated with risk of cortical cataract (0.70, 0.50-0.98)[107]. In addition, cataract could also occur due to intraocular surgery for other eye conditions including glaucoma filtration surgery and vitrectomy[2].

2.5 Summary of the current evidence and implications for future research

This literature review demonstrates considerable gaps in understanding of the associations of major lifestyle and cardiometabolic factors with risk of age-related cataract. The evidence for smoking and diabetes with risk of cataract is mainly based on Western populations, with limited evidence from low-and-middle income countries, although a large proportion of current smokers[112] and global diabetes prevalence[113] are actually in those countries. The associations

between physical activity (4 studies) and fruit/vegetables consumption (6 studies) with risk of cataract is poorly studied, and existing evidence is limited to Western populations, despite different patterns in physical activity[114] and diet[115] between Western and non-Western populations. The evidence is inconsistent or unclear for alcohol consumption and adiposity in relation to cataract risk. Future prospective studies, especially studies on non-Western populations, with high quality-data could help to fill the research gaps.

2.6 Strengths and limitations of the literature review

The strengths of this literature review include the coverage of diverse lifestyle and cardiometabolic risk factors for cataract, the comprehensive assessment of potential bias in the shortlisted studies to ensure quality of evidence, and a detailed summary of the finalised studies. However, this review also has limitations. During the scoping review stage, I found the inclusion of publications in other languages, publications without full text accessibility, and unpublished evidence (e.g., conference abstracts, poster presentations, grey literature) would lead to an extremely large number of studies to be included (many of which may be of poor quality), which went beyond the capacity of this review. With the priority to include a wide range of lifestyle and cardiometabolic risk factors for cataract, this review focused on publications in English with accessibility to the full text, aiming to capture a large majority of the evidence on this topic. These restrictions may have introduced language bias and publication bias, potentially omitting some important evidence published in other languages (e.g. Chinese) or without full text access. Consequently, this review may not fully represent the global body of evidence on this topic.

2.7 Summary

Existing evidence on lifestyle and cardiometabolic risk factors for age-related cataract was mainly from Western populations, with very limited high-quality data from East Asian countries which account for the majority of the global cataract burden. The few studies in Asian populations had relatively small sample sizes or short follow-up periods. Due to limitations of study design, some of the previous studies failed to collect information on key confounding variables, which weakened their findings. Prospective studies in a large East Asian population with detailed information on lifestyles, physical measurements, medical history, and a range of potential confounding variables could help to confirm or refute previous findings on these factors in relation to cataract risk. This is particularly important for the Chinese population where one third of the global cataract burden occurs.

3 Study population and statistical methods

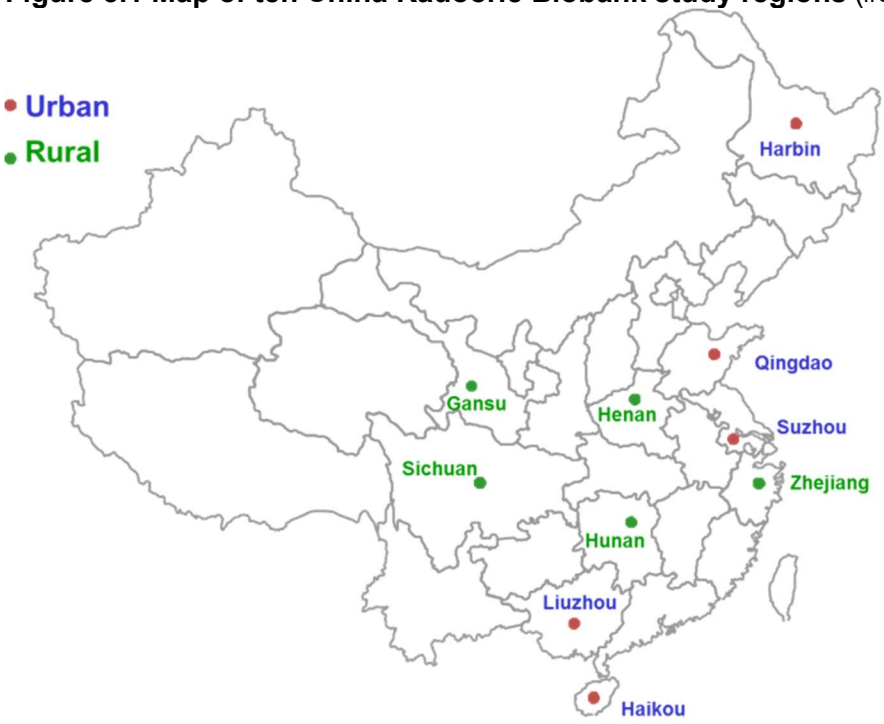
3.1 The China Kadoorie Biobank

The China Kadoorie Biobank (CKB) study is a prospective cohort study involving over 0.5 million adults from 10 regions in China. It has collected information on a wide range of socio-economic, lifestyle, cardiometabolic, and environmental factors which have relevance for the incidence and mortality of many chronic diseases. The long-term follow-up of CKB participants has recorded a large number of different disease events (including cataract), enabling prospective evaluation of associations between exposures and outcomes. Therefore, CKB represents a valuable resource to advance our understanding on lifestyle and cardiometabolic factors in relation to age-related cataract incidence in a Chinese population.

3.1.1 Study design

The CKB is a large prospective cohort study on risk factors of common chronic diseases[116,117]. The study was established by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) of the University of Oxford and the China Centre for Disease Control and Prevention (CDC) in 2004. The aim is to assess the relevance of both established and emerging risk factors for morbidity and mortality rates of a wide range of diseases. It recruited 0.5 million middle-aged adults from 10 diverse regions (5 urban and 5 rural) in China between 2004 and 2008, which were chosen from China's nationally representative Disease Surveillance Points and based on local disease patterns, risk exposures, population stability, quality of death and disease registries, and local capacity and commitment (**Figure 3.1**). As shown in the map, the five urban regions are: Qingdao, Harbin, Haikou, Suzhou, and Liuzhou, and the five rural regions are: Sichuan, Gansu, Henan, Zhejiang, and Hunan. Even though CKB is not designed to be representative of the general

Figure 3.1 Map of ten China Kadoorie Biobank study regions (from Chen et.al, 2011[117])



Chinese population in terms of the selection of 10 study regions, participants within each study region were relatively unselected[118].

Ethical approval for the study was obtained from the ethics committees of the University of Oxford, China national CDC, Chinese Academy of Medical Sciences, and institutional research boards at the Chinese local CDCs in the 10 study regions. Written informed consent for study participation, access to their medical records, and long-term storage of blood for anonymised and non-specific medical research purposes was obtained from all participants before the baseline survey.

For the baseline survey, a regional coordination centre including about 15 full-time staff with medical qualifications and fieldwork experience was established in each of the 10 study regions[116,117]. In these selected regions, permanent residents aged 35-74 years without major

disability identified through official residential records were invited to participate in the study. 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 only slightly outside the original target age range (i.e., aged 30-34 or 75-79 years) were not turned away (n~10 000). The overall response rate was about 30%, with 26%-38% in rural regions and 16%-50% in urban regions. In total, 512 726 (*data release version 17.02*) adults aged 30-79 years were included in the CKB study.

3.1.2 Baseline survey

The baseline survey took place at local assessment centres between June 25, 2004 and July 15, 2008, with data collection methods including questionnaire survey, physical measurements, and collection of blood samples[116,117]. Participants' eligibility was first confirmed on arrival using national identification card before signing the informed consent. During the survey, participants moved through 10 stations in the assessment centre, and spent ~60-75 minutes to complete the whole process. Each participant was interviewed by a study staff (a trained health worker) using an interviewer-administered laptop-based electronic questionnaire specially developed for the CKB study. Computer software was adopted during the interview to help to prevent missing data and implausible values (i.e., extreme values, logic errors, and inconsistent answers). Information on age, sex, and region was obtained automatically from participants' national identity card. The questionnaire covers 10 major areas related to general demographic and socio-economic status (including highest education achieved, total annual household income, occupation, and marital status, etc.), a range of lifestyle habits, mental status and life satisfaction (depression, anxiety, and self-rated health status), female reproductive history (menopausal status, age at menarche,

history of pregnancy, child birth, and breast feeding), exposure to passive smoking and domestic air pollution, and medication history (physician-diagnosed common diseases including cardiovascular, respiratory, malignant and other diseases, and relevant treatment). Lifestyle information included smoking (frequency, amount, type of tobacco smoked, age started smoking regularly and stopped smoking, and the main reason for smoking cessation), alcohol consumption (frequency, amount, drinking time of day, alcohol type, and age started drinking regularly), physical activity (usual type and duration of physical activities related to occupation, commuting, housework, and leisure-time exercise), dietary habits (consumption frequency of rice, wheat, other staple food, red meat, poultry, fish, eggs, dairy products, fresh vegetables, fresh fruit, preserved vegetables, and soybean), and sleep quality (duration, snoring behaviour, number of disturbances). Participants who reported prior diagnosed diseases were also asked to provide addition information about age at diagnosis and current medication use.

A range of physical measurements including height, weight, body fat percentage, waist and hip circumference, blood pressure, and pulse rate were taken using standard instruments and protocols[116,117].

Anthropometric measurements

All anthropometric measurements were conducted while participants were wearing light clothes and no shoes. Standing and sitting height were measured to the nearest 0.1 cm using a portable stadiometer. Weight and body fat percentage were measured using a body composition analyser (TANITA-TBF-300GS; Tanita Inc., Tokyo, Japan), with estimated weight of clothing subtracted (0.5 kg in summer; 1.0 kg in spring/autumn; 2.0 kg in winter). Waist circumference and hip circumference were measured to the nearest 0.1 cm, using a non-stretchable tape. Waist

circumference was measured at midway between the lowest rib and the iliac crest. Hip circumference was measured around the maximum circumference of the buttocks.

Blood pressure

Blood pressure was measured using a UA-779 digital sphygmomanometer (A&D Instruments; Abingdon, UK) after the participants taking at least five minutes of rest in a seating position. For most participants, two measurements were collected and recorded. For those with two systolic blood pressure (SBP) measurements differed by more than 10mmHg, a third measurement was taken and the last two measurements were recorded. Mean values of the two recordings for SBP and diastolic blood pressure (DBP) were used in analyses.

Blood glucose

A 10 ml non-fasting venous blood samples was collected for onsite spot blood tests of glucose level (using the SureStep Plus System [Johnson and Johnson, USA]) and for long-term storage (DNA and plasma). Those participants who did not report a diabetes history but had non-fasting blood glucose level between 7.8-11.0 mmol/L were invited to return to the survey site for a fasting blood glucose test (a finger-prick test using the same SureStep Plus System) the following day in order to detect undiagnosed prevalent diabetes.

Storage of blood samples

All venous blood samples were kept in portable 0-4°C fridge for a few hours before being taken to a local study laboratory, centrifuged and aliquoted into four cryovials. Ice packs were used during sample transfer from assessment clinics to local labs, where the cryovials were stored in

a -40°C freezer for 3-4 months, before being transported to the central blood repository in Beijing for long-term storage at -80°C. Every 6 months, two frozen aliquots of plasma were transported to Oxford for long-term storage in liquid nitrogen tanks.

3.1.3 Resurveys

After the baseline survey, periodic resurveys were conducted every 5-6 years among a randomly-selected approximately 5% of surviving participants, with local administrative units (i.e., rural village or urban residential committee) in the 10 regions as the basic sampling unit[116,117]. Thus far, three resurveys have been conducted, including the first resurvey conducted from May to October in 2008 (n=19 788, response rate ~80%), shortly after the completion of baseline survey, the second resurvey conducted from August 2013 to September 2014 (n=25 176, response rate ~75%), and the third resurvey conducted between August 2020 and December 2021 (n=25 238, response rate ~47%).

The main purpose of conducting resurveys is to collect information for the same exposures assessed at baseline in order to understand their long-term variation, which will be used to correct for "regression dilution bias"[119] in prospective analyses. Single measurement of a specific exposure factor at baseline may not reflect the true or "usual" level of the exposure, leading to underestimation of the true association between the exposure and a disease outcome[119]. Repeated measurements of the same exposure factor every 5-10 years can be used to correct for such bias. The second purpose of conducting resurveys is to collect new data (i.e., enhancements). For instance, through three resurveys CKB has collected a wide range of new data including more detailed dietary information and bone mineral density, collected since the 2nd resurvey, and liver

scan (fibrosis and steatosis), intraocular pressure, and retinal images, collected in the 3rd resurvey.

3.1.4 Participant follow-up

CKB participants are continuously followed-up for cause-specific morbidity and mortality[116,117]. Their vital status was monitored through China's Disease Surveillance Points (DSP) system via review of official residential records and death certificates. Information on non-fatal events was collected through linkages with disease registries (four major diseases including ischemic heart disease, stroke, cancer, and diabetes) and the nationwide health insurance reimbursement databases using participant's National ID as a unique personal identifier. The health insurance databases covered more than 98% of CKB participants across the 10 study regions.

Death and disease events in CKB were standardised (through review of original diagnosis description) and coded using the 10th version of the *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* by trained staff "blinded" to participants' baseline information. Losses to follow-up in this study refer to: (1) participants permanently moved out of study region; (2) participants could not be contacted after at least three reasonable attempts within one year. To minimise loss to follow-up and ensure reporting quality, annual active follow-up through visiting to local communities and checking residential, medical, and health insurance records was conducted. By the global censoring date of 1 January 2018 (median 10.8 years of follow-up, interquartile range 9.8-12.0 years), for the current release of CKB data (*release version 17.02*), 49 376 (9.6%) participants had died and 5317 (1.0%) were loss to follow-up.

3.1.5 Outcome definition

Since there is no nationwide cataract registry in China, CKB obtained information on incidence (hospitalization) of age-related cataract from health insurance records (including both inpatients and outpatients data) used for reimbursement purposes. It was defined as events *ICD-10* coded as H25 (senile cataract) or H26.9 (cataract unspecified), and included only the first reported cataract events (**Table 3.1**). In total, 6155 cases of H25 (senile cataract) and 11 192 cases of H26.9 (cataract unspecified) were recorded among 16 552 participants. The current analysis further excluded few dozen cataract cases (34 cases) occurring before participants reached age 40 years given it is rare that age-related cataract develops among people younger than 40 years[1,46]. The final analysis included 16 518 first-event cataract cases which occurred after age 40 years.

Table 3.1 Reported cataract events among CKB study participants

ICD-10 code and description	Number of cases
(H25 to H28) Disorders of lens	16,845
(H25) Senile cataract	6155
(H25.0) Senile incipient cataract	58
(H25.1) Senile nuclear cataract	10
(H25.2) Senile cataract, morgagnian type	4
(H25.8) Other senile cataract	2
(H25.9) Senile cataract, unspecified	6092
(H26) Other cataract	11,465
(H26.0) Infantile, juvenile and presenile cataract	16
(H26.1) Traumatic cataract	19
(H26.2) Complicated cataract	277
(H26.3) Drug-induced cataract	0
(H26.4) After-cataract	0
(H26.8) Other specified cataract	13
(H26.9) Cataract, unspecified	11,192
(H28) Cataract and other disorders of lens in diseases classified elsewhere	38
(H28.0) Diabetic cataract	38
(H28.1) Cataract in other endocrine, nutritional, and metabolic diseases	0
(H28.2) Cataract in other diseases classified elsewhere	0
(H28.8) Other disorders of lens in diseases classified elsewhere	0

Cataract event was recorded as the first event for each cataract sub-type (for example, H25.0), therefore subcategories in this table may sum to greater than the total due to potential multiple records across subcategories for one participant.

3.2 Statistical methods

Follow-up duration was defined as the time from the date of study entry or, for those who were younger than 40 years old at baseline, the date when they reached age 40 years, to the date of the first event of cataract hospitalization (H25 [senile cataract] or H26.9 [cataract unspecified]) or loss to follow-up, death, or the global censoring date (1 January 2018), whichever came first.

Age-related cataract is the focus of this thesis, which is hereinafter referred to as cataract. Cox proportional hazards models adjusted for confounders were used to estimate the HRs and 95% CIs for risk factors in association with cataract incidence. The Cox models were developed based on a combination of information from the literature and statistical criteria (likelihood ratio statistic)[120]. To be specific, a variable (e.g., household air pollution) would be selected as a candidate covariate for the Cox model if existing literature suggests a potential confounding role for the association under examination. The basic Cox model was stratified by age-at-risk (5-year groups) and study region (ten regions), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), smoking status (four groups), alcohol consumption status (four groups), and total physical activity (as continuous), as appropriate. A likelihood ratio test was conducted to compare the basic model and the basic model with additional adjustment for the candidate covariate, with a p-value <0.05 as the indicator to include this candidate covariate in the final Cox model.

To explore potential effect modification of the main association analysis, subgroup analyses were conducted by selected baseline population characteristics (e.g., age-at-risk, region, smoking status, etc.). To address multiple testing in the subgroup analyses of the associations between

selected lifestyle and cardiometabolic factors with risk of cataract, two-sided p-values were used (without correction for multiple testing made differently for each of the selected risk factors) with multiple comparisons made by using 99% confidence intervals (i.e., a more stringent threshold than the 95% CIs) for each component of the subgroup, and the overall result was still presented as 95% CI[121,122]. The threshold for significance in each individual test of the subgroup analyses was set as 0.01. In this part of the chapter, I will provide some detailed explanation on specific methods used in the Cox analysis.

3.2.1 Correcting for confounding by age-at-risk

As a common confounder for the association between a risk factor and disease outcome in population studies, age recorded at study entry (i.e., age at baseline) is normally adjusted for in the Cox model. However, age "acquired" during study follow-up (i.e., age-at-risk) rather than baseline age is more appropriate to determine current risk. In this study, Lexis expansion was used to facilitate the adjustment of age-at-risk in Cox model by expanding the observation of each participant into several observations of different 5-year age-at-risk bands[123]. Age-at-risk is a time-varying covariate whereby as an individual gets older they may contribute to more than one 5-year age-at-risk group, which is equivalent to using age as the timescale in a Cox regression analysis model[123,124,125].

3.2.2 Floating absolute risk

Floating absolute risk is an alternative statistical approach to present relative risk estimates for exposure variables with more than two categories[126]. Instead of choosing one category of the exposure as a reference, every category is assigned a 'floated' variance to describe its uncertainty

in risk estimates, which allows comparison of risk estimates between any two categories of exposure (not just with the reference category). The group specific variances are calculated so that each category of the exposure (including the reference) has a 95% CI derived from the variance of the log risk for that category[126,127].

3.2.3 Correcting for regression dilution bias

Due to the combined effects of random measurement errors and within-person biological variation (including both short-term and longer-term fluctuation), one single measurement of an exposure at baseline may not reflect the true exposure level (also called the "usual" level of exposure). Association analyses in prospective studies which rely on a single exposure measurement at baseline could underestimate the true association between the exposure and disease outcomes[119]. Repeated measurements of exposures on a representative subsample of the total study population can be used to calculate the "usual" exposure levels, and therefore help to correct the regression dilution bias. To be specific, in CKB the "usual" level of a continuous exposure variable (for example, the amount of weekly alcohol consumption) was calculated as the mean of the repeated exposure variable measures of the first and second resurveys for participants in each of the baseline-defined categories. Then, the regression dilution ratio, which describes the ratio of the steepness of the uncorrected association to that of the real association, were calculated to correct for regression dilution bias[128]. In data analyses, the MacMahon-Peto method, which requires no assumption about constant variances of the recorded exposure variable at baseline and remeasurement (i.e., assume the distribution are the same at both time points), was used to calculate the regression dilution ratio[119,128,129]. With this method, the ratio of the ranges (i.e., difference in the mean exposure variable of the top vs bottom baseline-

defined groups) for the repeat measurements and the baseline measurements was calculated and used as regression dilution ratio[119]. For comparison purposes, self-correlation methods (which assume similar variances of the recorded exposure variable at baseline and remeasurement), including Pearson's method (for normal distribution) and Spearman's method (for skewed distribution), were used to calculate the regression dilution ratio[128,129]. It is worth mentioning that, even though the risk estimates for exposure factors in this study were corrected for regression dilution bias, errors/biological variation in confounders could not be corrected simultaneously due to the complexity and potential inappropriateness of available statistical methods[130,131].

3.3 Summary

The CKB is a prospective cohort study of 0.5 million adults aged 30-79 years from 10 regions in China. A wide range of socio-economic, lifestyle, and cardiometabolic factors were collected at the baseline survey and subsequent resurveys. Study participants were followed-up for a median of 11 years for cause-specific mortality and morbidity outcomes (including cataract) through linkages with disease and mortality registries as well as nation-wide health insurance databases in China. The definition of age-related cataract in this study refers to first cataract event occurred after age 40 years, with *ICD-10* coded as H25 (senile cataract) or H26.9 (cataract unspecified). In this thesis, Cox proportional hazards models were used to estimate the adjusted HRs for selected lifestyle and cardiometabolic factors in association with cataract risk.

4 Patterns and correlates of cataract incidence in China

4.1 Introduction

Cataract is a common eye disease among older adults and is a major cause of global vision impairment and blindness. As an age-related disorder caused by the degradation of lens protein, cataract usually occurs in people older than 50 years, with age as the most important determinant[132]. Previous studies conducted in Western, African, Latin American, and Asian populations have reported a more than ten times higher incidence rate in those aged 70 and older than in the 50-54 age group[37,133,134]. Apart from age, other socio-demographic factors may be related to cataract incidence. For instance, previous studies, mainly in Western populations, reported that cataract incidence rate was ~10-20% higher in women than in men[37,135]. Limited evidence from a few small studies conducted in major cities in China (e.g., Beijing and Guangzhou) reported a broadly similar sex difference[134,136]. In terms of socio-economic status (e.g., education, income, and occupation), although it has been frequently associated with risks of cardiometabolic diseases in different populations[137], no reliable information is available on its relationship with cataract incidence, probably due to the small sample size (less than 5000) of previous studies[38,138]. Similarly, self-rated health and levels of life satisfaction are two subjective assessments of health and well-being, and have been repeatedly found as strong independent predictors of subsequent incidence of major diseases and mortality in population-based studies[139,140]. However, to the best of my knowledge, cataract incidence patterns by these two factors have never been investigated in large scale studies.

Investigating the variation in cataract incidence across various subgroups of the CKB could improve understanding of cataract disease patterns, and provide valuable information to inform

subsequent prospective association analyses. Therefore, this chapter aims to examine patterns and correlates of cataract incidence among 0.5 million participants in CKB, with the following specific objectives: (1) to determine the age- and sex-related patterns of incident cataract in rural and urban regions; (2) to describe incident cataract patterns by socio-economic status (i.e., education, income, marital status, and occupation) and self-assessed health and wellbeing (i.e., self-rated health and life satisfaction level).

4.2 Study population and methods

Details of study population and the CKB study design have been described in the Chapter 3. In brief, the CKB is a large on-going prospective cohort study including 512 726 men and women recruited from 10 regions in China, with the collection of a wide range of socio-economic, lifestyle, and cardiometabolic factors at the baseline survey and subsequent resurveys. Participants were followed-up through linkages with death and disease registries as well as nationwide health insurance databases in China. Age-related cataract was defined as first cataract event occurred after age 40 years, with *ICD-10* code of H25 (senile cataract) or H26.9 (cataract unspecified). Follow-up duration was defined as the time from the date of study entry or, for those who were younger than 40 years old at baseline, the date when participants reached age 40 years, to the date of cataract onset or loss to follow-up, death, or the global censoring date (1 January 2018), whichever came first.

The present analysis excluded individuals with incident cataract before age 40 years (n=34), leaving 512 692 participants (210 187 men and 302 505 women) for the main analyses. Prevalence and mean values of baseline characteristics were calculated separately in men and

women; and among those with/without incident cataract. Cataract incidence rates per 100 000 person years were calculated by baseline age groups, sex, study regions (ten regions and rural/urban residence), education level, annual household income, occupation, marital status, self-rated health status and life satisfaction level. Where appropriate, adjustments were made for baseline age (5-year age groups), sex, and study region (ten regions) by direct standardisation to the baseline CKB population[141]. The variance of the standardised incidence rates was calculated by assuming that the number of events in each strata followed a Poisson distribution[142]. All statistical analyses were performed in R (version 4.0.3).

4.3 Results

4.3.1 Baseline characteristics of study population

Among the 512 692 study participants, the mean age at baseline was 52.5 (SD 10.1) years, and 59% were women and 56% were from rural regions (**Table 4.1**). About half of them received middle/high school education or above. More than 40% of the participants were agricultural or related workers. More than 90% of participants were in marriage. Compared with women, men on average were more likely to have formal education (91.1% in men vs 74.7% in women), had slightly higher household income (79.8% vs 83.5% with annual income ≥35K Chinese Yuan), and were more likely to be in marriage (92.9 % vs 89.0%).

There were substantial differences in smoking and alcohol drinking patterns between CKB men and women. Two thirds of men were current smokers and one third regularly drank alcohol, while the corresponding proportions were only 2.4% and 2.1% in women. Men had higher mean value of total physical activity than women (22.0 vs 20.4 MET-hours/day), while their fresh fruit

Table 4.1 Baseline characteristics of the study population

	Men (N=210,187)	Women (N=302,505)	Overall (N=512,692)
Mean (SD) age, years	53.2 (10.4)	51.9 (9.9)	52.5 (10.1)
Socio-demographic factors			
Rural, %	56.5	55.4	55.9
Education, %			
No formal school	8.9	25.3	18.6
Primary school	33.4	31.4	32.2
Middle/high school	49.9	38.8	43.4
College/university	7.9	4.4	5.8
Income (yuan), %			
<10,000	26.0	29.8	28.2
10,000-19,999	28.3	29.6	29.1
20,000-34,999	25.4	24.2	24.7
≥35,000	20.2	16.5	18.0
Occupation[a], %			
Agricultural	43.4	40.5	41.7
Factory	19.1	10.6	14.1
Professional/sales	12.0	8.9	10.2
Retired	14.7	17.9	16.6
Other	10.8	22.0	17.4
Not in marriage[b], %	7.1	11.0	9.4
Lifestyle factors			
Current smoker, %	61.1	2.4	26.4
Current regular drinkers, %	33.3	2.1	14.9
Physical activity, mean (SD) MET-hours/day	22.0 (15.2)	20.4 (12.8)	21.1 (13.9)
Daily fresh vegetables consumption, %	94.9	94.7	94.8
Daily fresh fruit consumption, %	14.5	21.8	18.8
Cardiometabolic factors, mean (SD)			
BMI, kg/m^2	23.4 (3.3)	23.8 (3.5)	23.7 (3.4)
WHR	0.90 (0.07)	0.87 (0.07)	0.88 (0.07)
SBP, mmHg	132.8 (20.0)	129.9 (22.0)	131.1 (21.3)
DBP, mmHg	79.2 (11.4)	76.8 (10.9)	77.8 (11.2)
Random blood glucose, mmol/L	6.0 (2.3)	6.1 (2.3)	6.1 (2.3)
Prior disease history, %			
Hypertension	11.3	11.9	11.6
Stroke or TIA	2.3	1.3	1.7
CHD	2.7	3.2	3.0
Cancer	0.5	0.5	0.5
Diabetes	2.9	3.3	3.2
Self-rated health, %			
Poor	8.9	11.4	10.4
Fair	41.9	45.3	43.9
Good	29.2	27.4	28.1
Excellent	20.0	16.0	17.6
Self-rated life satisfaction, %			
Unsatisfied	4.4	4.0	4.2
Neither satisfied nor dissatisfied	25.9	28.3	27.3
Satisfied	69.7	67.7	68.5

SD standard deviation, MET metabolic equivalent of task, BMI body mass index, WHR waist-to-hip ratio, SBP systolic blood pressure, DBP diastolic blood pressure, TIA transient ischaemic attack, CHD coronary heart disease.

[a] Agricultural: agricultural & related workers; Factory: factory workers; Professional/sales: administrator/manager, professional/technical, sales or service workers; Retired: retired; Other: house wife/husband, self-employed, unemployed, other, or not stated.

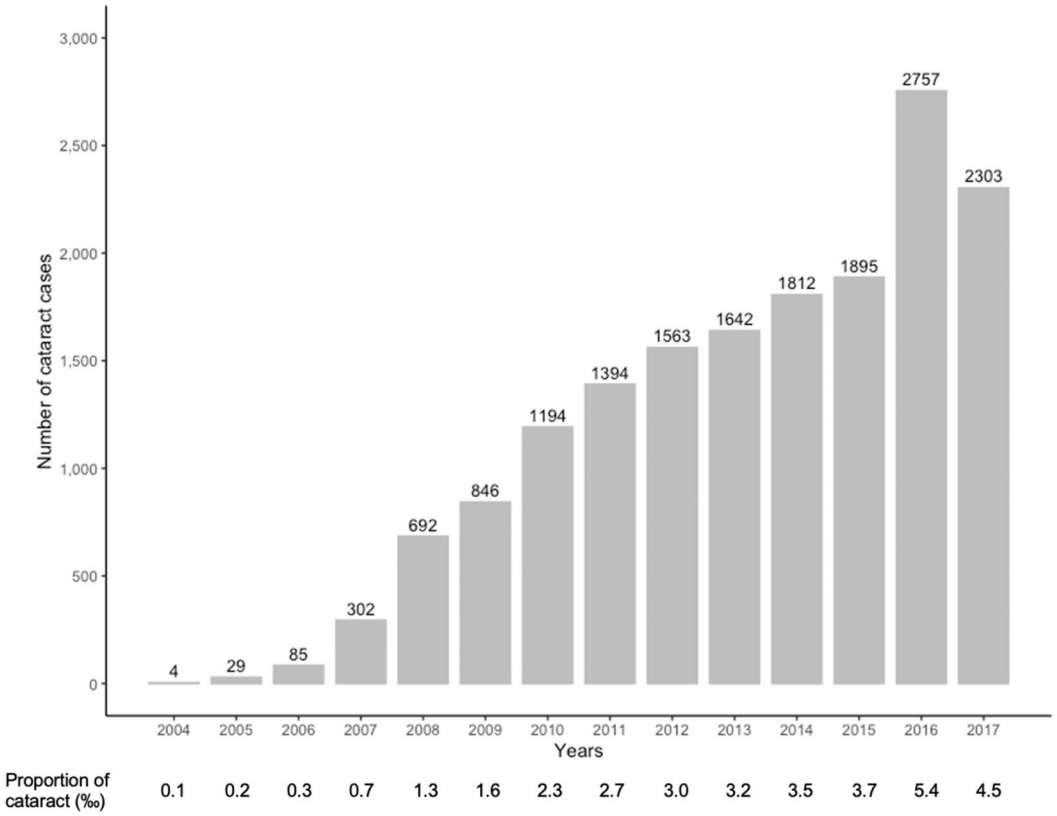
[b] Include separated/divorced, widowed, and never married.

consumption level was lower (14.5% vs 21.8% daily consumers). Interestingly, men had a slightly lower mean BMI (23.4 vs 23.8 kg/m^2) but higher WHR (0.90 vs 0.87) than women. In addition, men had slightly higher mean SBP (132.8 vs 129.9 mmHg) and DBP (79.2 vs 76.8 mmHg) than women, whereas both sexes had similar mean random blood glucose level (6.0 vs 6.1 mmol/L). Overall, at baseline, 11.6% of participants reported hypertension (men 11.3%; women 11.9%), 1.7% reported a prior diagnosis of stroke or transient ischaemic attack (TIA) (men 2.3%; women 1.3%), 3.0% reported coronary heart disease (CHD) (men 2.7%; women 3.2%), 0.5% reported cancer (0.5% in both men and women), and 3.2% reported diabetes (men 2.9%; women 3.3%). Men reported poor self-rated health less frequently than women (8.9% vs 11.4%), though both sexes had similar self-rated life satisfaction (4.4% men and 4.0% women reported unsatisfied).

4.3.2 Patterns of cataract incidence

After a median of 11 years of follow-up, 16 518 (3.2%) participants (5939 men and 10 579 women) had a cataract event. The annual number of reported cataract cases increased steadily from 2004 (4 cases reported) to 2017 (2303 cases), reflecting the ageing nature of the cohort and the slightly improved health insurance coverage among CKB participants, though the number of new cases was slightly higher in 2016 (2757 cases) than in 2017 (2303 cases) (**Figure 4.1**). The trend of annual number of reported cases from 2004 to 2017 differed across the 10 CKB regions (**Figure 4.2**). In general, although varied largely across 10 regions, an increasing time trend of cataract events was observed in each region except for in Gansu and Hunan. Gansu reported a higher number of cataract cases in 2012 than in other years, and similar fluctuations were reported in Hunan, though in different years.

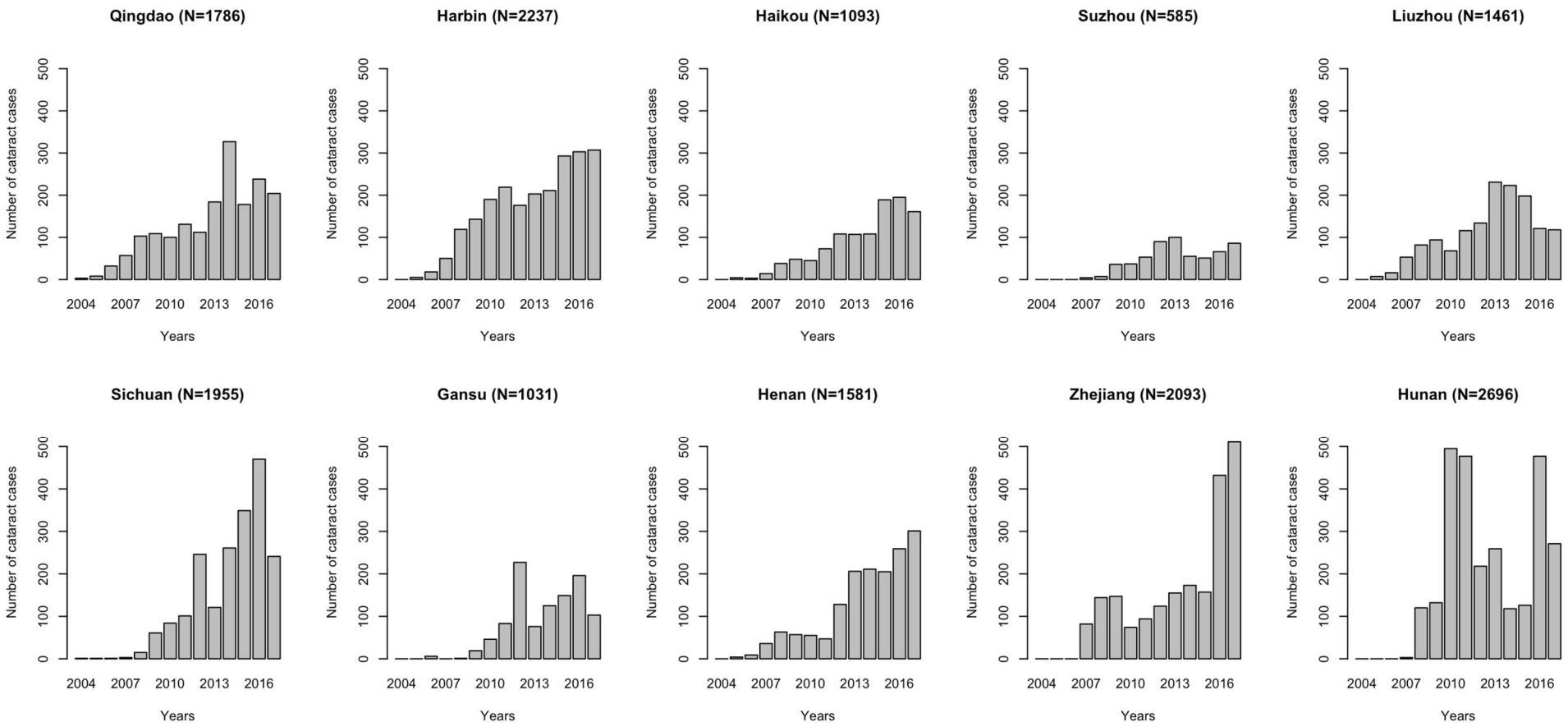
Figure 4.1 Number of incident cataract cases by year of follow-up (2004-2017)



The numbers above the bar represent the number of cataract cases in corresponding years.
The numbers below the x-axis represent incidence proportion in corresponding years.

The mean baseline age of participants who developed cataract during follow-up was 10 years older than those who did not have incident cataract (62.2 vs 51.7 years) (**Table 4.2**). Compared with participants who did not have a cataract reported during follow-up, those who developed cataract had lower education (28.3% vs 18.2% without formal schooling), lower household income (33.0% vs 28.1% with income less than 10K Chinese Yuan/year), and less likely to be in marriage (83.1% vs 90.8%). They also reported poor self-rated health more frequently (13.1% vs 10.3%), though the self-rated life satisfaction (2.9% vs 4.2% as unsatisfied) was roughly similar in both groups.

Figure 4.2 Number of first event cataract cases by year of follow-up (2004-2017) in ten study regions



The five regions on top are urban regions, and the five at the bottom are rural regions.

Table 4.2 Baseline characteristics of the study population with and without cataract reported

	Without cataract reported during follow-up (N=496,174)	With incident cataract reported during follow-up (N=16,518)	Overall (N=512,692)
Mean (SD) age, years	51.7 (10.6)	62.2 (8.3)	52.5 (10.1)
Socio-demographic factors			
Rural, %	55.9	56.6	55.9
Education			
No formal school	18.2	28.3	18.6
Primary school	31.9	40.3	32.2
Middle/high school	43.9	26.7	43.4
College/university	5.9	4.7	5.8
Income (yuan), %			
<10,000	28.1	33.0	28.2
10,000-19,999	29.0	29.8	29.1
20,000-34,999	24.8	22.9	24.7
≥35,000	18.1	14.3	18.0
Occupation[a], %			
Agricultural	41.8	38.5	41.7
Factory	14.5	4.2	14.1
Professional/sales	10.4	3.6	10.2
Retired	16.1	32.1	16.6
Other	17.3	21.6	17.4
Not in marriage[b], %	9.2	16.9	9.4
Lifestyle factors			
Current regular smoker, %	26.6	22.8	26.4
Current regular drinkers, %	14.9	12.6	14.9
Physical activity, mean (SD) MET-h/d	21.3 (13.9)	15.3 (11.3)	21.1 (13.9)
Cardiometabolic factors, mean (SD)			
BMI, kg/m^2	23.7 (3.4)	23.8 (3.7)	23.7 (3.4)
WHR	0.88 (0.07)	0.89 (0.07)	0.88 (0.07)
SBP, mmHg	130.9 (21.2)	137.8 (22.1)	131.1 (21.3)
Random blood glucose, mmol/L	6.1 (2.3)	6.8 (3.4)	6.1 (2.3)
Prior disease history, %			
Diabetes	3.0	8.7	3.2
CHD	2.9	7.2	3.0
Cancer	0.5	0.5	0.5
Self-rated health, %			
Poor	10.3	13.1	10.4
Fair	43.7	50.2	43.9
Good	28.3	23.7	28.1
Excellent	17.8	12.9	17.6
Self-rated life satisfaction, %			
Unsatisfied	4.2	2.9	4.2
Neither satisfied nor dissatisfied	27.3	27.6	27.3
Satisfied	68.5	69.5	68.5

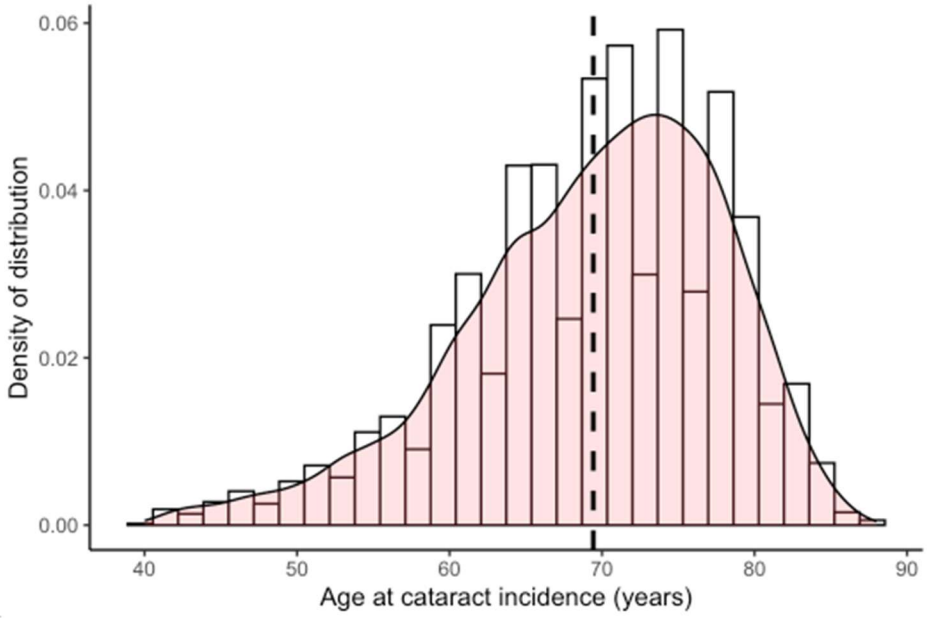
SD standard deviation, MET metabolic equivalent of task, SBP systolic blood pressure, BMI body mass index, WHR waist-to-hip ratio, CHD coronary heart disease.

[a] Agricultural: agricultural & related workers; Factory: factory workers; Professional/sales: administrator/manager, professional/technical, sales or service workers; Retired: retired; Other: house wife/husband, self-employed, unemployed, other, or not stated.

[b] Include separated/divorced, widowed, and never married.

The distribution of age at cataract incidence was left-skewed, with the mean at 69.4 years (**Figure 4.3**). This was similar for men (mean 69.8 years) and women (69.2 years), in urban (69.2 years) and rural (69.6 years) areas, among the ten study regions (mean ranging from 68.8 to 70.1 years), and by education, household income, occupation, and marital status (**Table 4.3**).

Figure 4.3 Histogram of age at cataract incidence.



*The dotted line represents mean value

4.3.3 Socio-demographic correlates of cataract incidence

The overall incidence rate of cataract was 293 (288-298) per 100 000 person years. With the increase of baseline age, incidence rates became substantially higher, particularly after 55 years old, where the rates increased about 4 times for both men and women. As shown in **Figure 4.4**, the incidence rate was 155 (142-168) and 220 (208-232) respectively in men and women aged 50-54 years, and 758 (717-799) and 1088 (1043-1133) respectively in those aged 65-69 years. The trend plateaued at 70-74 years of age and there was a modest decrease thereafter. Similar

Table 4.3 Sex-specific mean age at cataract incidence by socio-demographic characteristics of study population with cataract

Characteristics	Men (N=5,939)		Women (N=10,579)		Overall (N=16,518)	
	Mean age at baseline (SD), years	Mean age[a] at cataract incidence (95% CI), years	Mean age at baseline (SD), years	Mean age[a] at cataract incidence (95% CI), years	Mean age at baseline (SD), years	Mean age[a] at cataract incidence (95% CI), years
Overall	53.2 (10.4)	69.8 (69.7, 69.9)	51.9 (9.9)	69.2 (69.2, 69.3)	52.5 (10.1)	69.4 (69.4, 69.5)
Residence						
Urban	53.5 (10.6)	69.5 (69.4, 69.7)	53.0 (10.2)	69.0 (68.9, 69.1)	53.2 (10.3)	69.2 (69.1, 69.3)
Rural	53.0 (10.2)	70.0 (69.9, 70.1)	51.0 (9.6)	69.4 (69.3, 69.5)	51.9 (9.9)	69.6 (69.5, 69.7)
Region (U: urban; R: rural)						
Qingdao (U)	50.4 (9.4)	69.4 (69.2, 69.7)	51.9 (9.8)	68.9 (68.7, 69.1)	51.2 (9.6)	69.1 (68.9, 69.2)
Harbin (U)	54.3 (11.2)	69.5 (69.2, 69.7)	53.5 (10.5)	69.0 (68.8, 69.2)	53.8 (10.8)	69.2 (69.0, 69.3)
Haikou (U)	54.7 (11.2)	69.8 (69.5, 70.2)	53.0 (10.9)	69.7 (69.4, 69.9)	53.6 (11.0)	69.7 (69.6, 69.9)
Suzhou (U)	52.9 (9.8)	70.2 (69.8, 70.5)	52.2 (9.8)	69.3 (69.0, 69.6)	52.5 (9.8)	69.7 (69.4, 69.9)
Liuzhou (U)	55.3 (10.5)	69.2 (69.0, 69.5)	53.9 (9.8)	68.6 (68.4, 68.8)	54.5 (10.1)	68.9 (68.7, 69.0)
Sichuan (R)	53.3 (10.2)	70.5 (70.3, 70.8)	51.3 (9.6)	69.8 (69.7, 70.0)	52.0 (9.9)	70.1 (70.0, 70.2)
Gansu (R)	51.9 (10.0)	70.0 (69.7, 70.4)	49.2 (9.4)	69.4 (69.2, 69.7)	50.2 (9.7)	69.6 (69.4, 69.8)
Henan (R)	52.2 (10.3)	70.1 (69.8, 70.4)	50.8 (9.4)	69.5 (69.3, 69.7)	51.4 (9.8)	69.7 (69.6, 69.9)
Zhejiang (R)	53.8 (10.0)	70.6 (70.3, 70.8)	52.4 (9.4)	69.7 (69.5, 69.9)	53.0 (9.7)	70.0 (69.8, 70.1)
Hunan (R)	53.9 (10.3)	69.1 (68.9, 69.3)	51.3 (9.7)	68.6 (68.5, 68.8)	52.4 (10.1)	68.8 (68.7, 68.9)
Highest education level						
No formal school	60.9 (9.6)	70.5 (70.2, 70.8)	57.6 (9.8)	69.5 (69.4, 69.6)	58.2 (9.8)	69.8 (69.7, 69.9)
Primary school	56.7 (9.7)	69.8 (69.7, 69.9)	52.8 (9.6)	69.1 (69.0, 69.2)	54.5 (9.8)	69.4 (69.3, 69.4)
Middle/high school	49.8 (9.2)	69.5 (69.4, 69.7)	47.9 (8.1)	69.0 (68.8, 69.1)	48.8 (8.7)	69.2 (69.1, 69.3)
College/university	52.1 (11.4)	69.5 (69.2, 69.9)	48.2 (9.4)	68.8 (68.4, 69.2)	50.3 (10.8)	69.2 (68.9, 69.4)
Annual household income, yuan						
< 10,000	55.2 (10.8)	70.2 (70.0, 70.3)	53.2 (10.7)	69.6 (69.5, 69.7)	54.0 (10.8)	69.8 (69.7, 69.9)
10,000-19,999	53.2 (10.3)	69.6 (69.5, 69.8)	51.6 (9.8)	69.2 (69.1, 69.3)	52.3 (10.0)	69.4 (69.3, 69.5)
20,000-34,999	52.4 (10.0)	69.5 (69.3, 69.6)	51.1 (9.3)	68.9 (68.8, 69.1)	51.7 (9.6)	69.1 (69.0, 69.2)
≥ 35,000	51.9 (9.9)	69.8 (69.6, 70.1)	51.2 (9.2)	68.9 (68.7, 69.0)	51.5 (9.5)	69.2 (69.1, 69.4)
Occupation[b]						
Agricultural	53.2 (10.0)	70.0 (69.9, 70.2)	50.2 (8.9)	69.5 (69.4, 69.7)	51.5 (9.5)	69.7 (69.6, 69.8)
Factory	47.4 (6.7)	70.0 (69.5, 70.5)	44.1 (5.1)	68.3 (67.6, 69.0)	45.9 (6.3)	69.7 (69.3, 70.1)
Professional/sales	48.6 (7.8)	69.6 (69.2, 70.0)	45.9 (6.1)	67.4 (66.7, 68.1)	47.2 (7.1)	69.2 (68.9, 69.6)
Retired	65.0 (6.4)	67.2 (66.8, 67.5)	59.8 (7.6)	68.5 (68.4, 68.6)	61.7 (7.6)	68.7 (68.6, 68.8)
Other	53.0 (10.6)	69.6 (69.3, 69.8)	54.9 (10.8)	69.1 (69.0, 69.2)	54.4 (10.8)	69.3 (69.2, 69.4)
Marital status						
Not in marriage[c]	58.0 (11.4)	69.6 (69.3, 69.9)	60.7 (10.3)	69.4 (69.2, 69.6)	59.8 (10.7)	69.5 (69.4, 69.6)
In marriage	52.9 (10.2)	69.8 (69.7, 69.9)	50.8 (9.3)	69.2 (69.1, 69.3)	51.7 (9.7)	69.4 (69.3, 69.5)

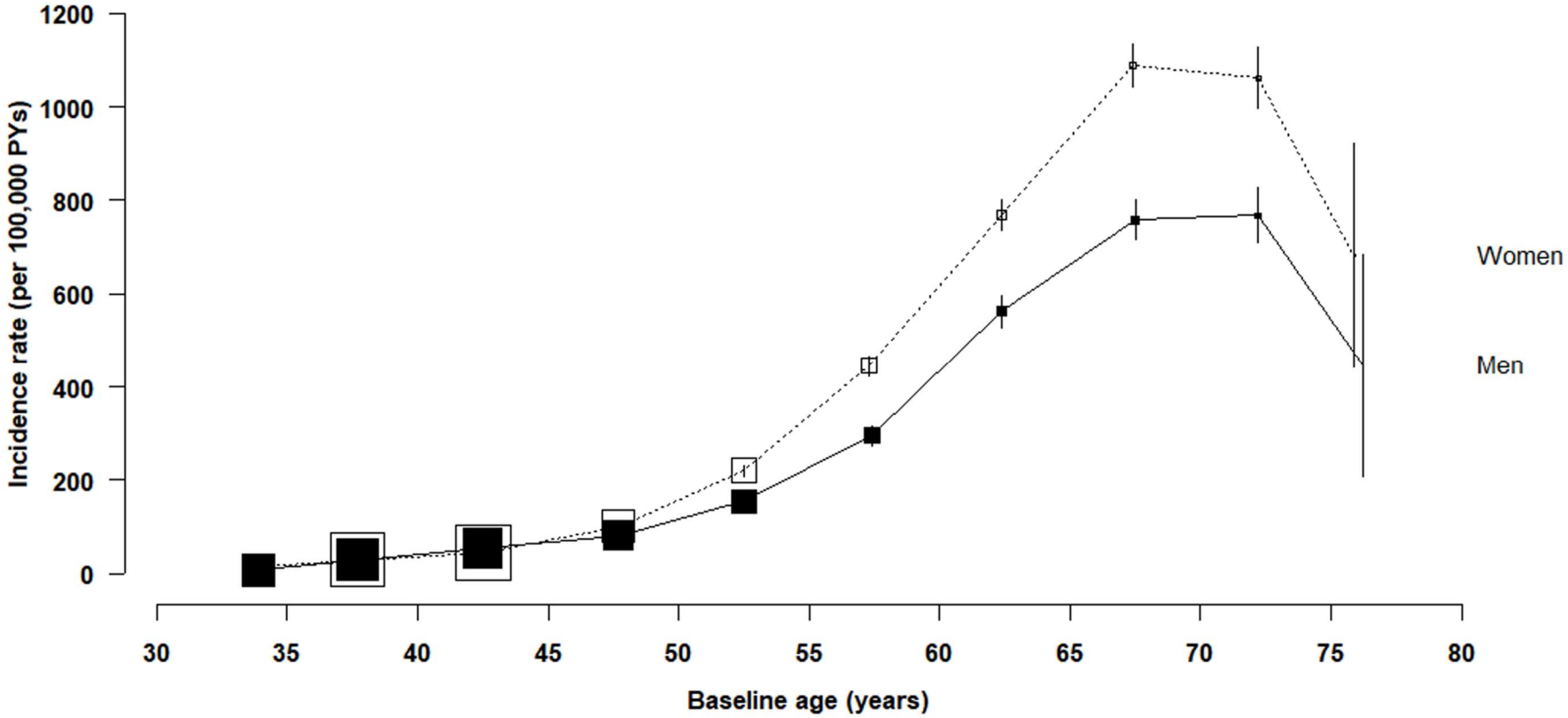
95% CI 95% confidence interval.

[a] The mean age at cataract incidence was adjusted for 5-year age group at study enrollment.

[b] Agricultural: agricultural & related workers; Factory: factory workers; Professional/sales: administrator/manager, professional/technical, sales or service workers; Retired: retired; Other: house wife/husband, self-employed, unemployed, other, or not stated.

[c] Include separated/divorced, widowed, and never married.

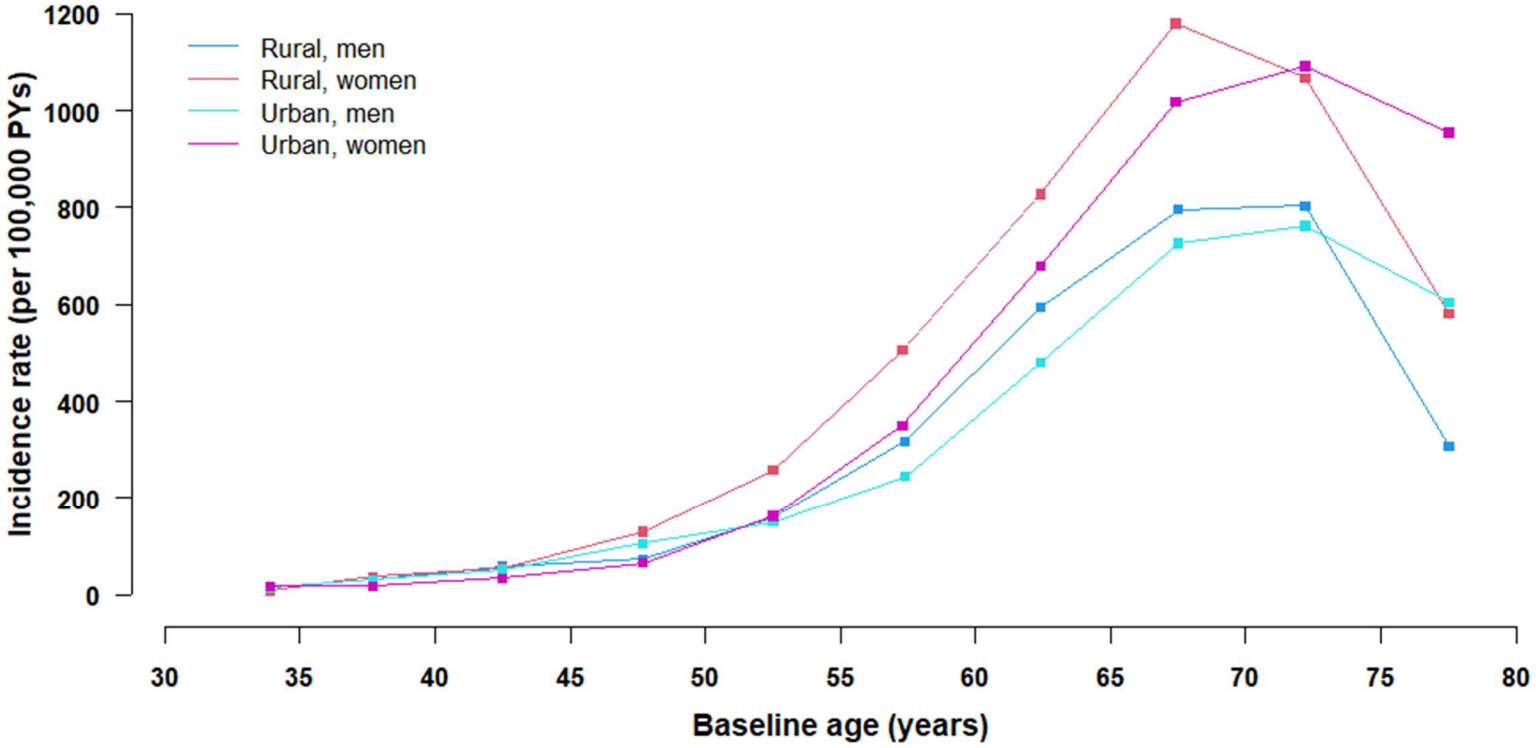
Figure 4.4 Region-standardised cataract incidence rates by baseline age group in men and women



	Number of participants	3570	25,979	31,990	27,228	34,878	28,873	21,977	19,363	14,556	1773
Men	Number of cases	3	71	197	265	587	876	1209	1429	1172	130
	Incidence Rate (95% CI)	8(1,18)	30(23,37)	55(47,62)	83(72,93)	155(142,168)	295(275,315)	562(530,594)	758(717,799)	768(711,825)	446(213,679)
	Number of participants	6238	41,802	52,150	41,401	52,684	41,181	27,920	22,493	14,939	1697
Women	Number of cases	4	114	273	466	1259	1938	2204	2437	1697	187
	Incidence Rate (95% CI)	15(2,34)	30(24,35)	46(41,52)	102(93,111)	220(208,232)	445(425,465)	769(737,801)	1088(1043,1133)	1062(997,1127)	682(447,917)

95% CI 95% confidence interval.
The incidence rates were adjusted for 10 regions. The squares represent incidence rate, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the incidence rate. The numbers in the table below the figure represent corresponding age groups in figure.

Figure 4.5 Cataract incidence rates by baseline age group and region in men and women

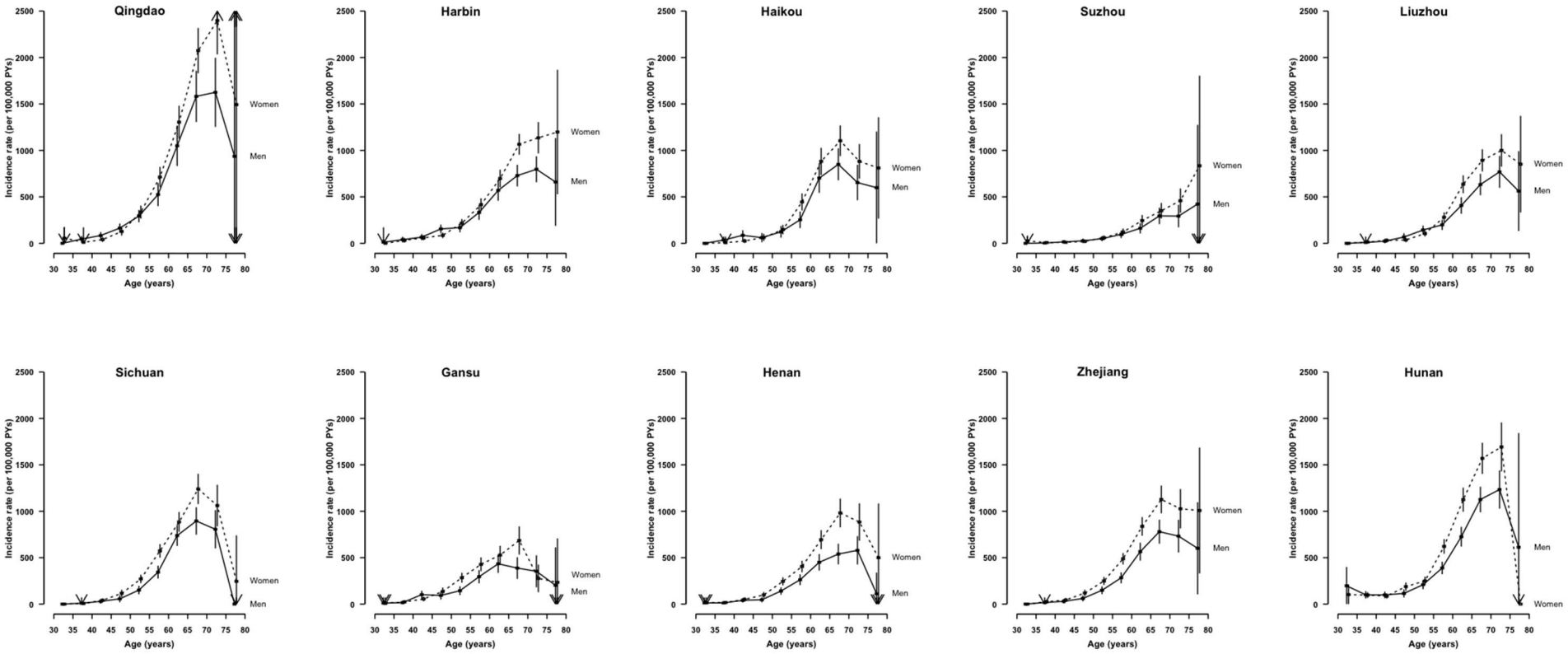


patterns (i.e., increased cataract incidence rates with baseline age until the incidence rate reached its highest in those aged 65-75 years, followed by a modest decrease in the incidence rate thereafter) were observed in rural and urban regions among men and women (**Figure 4.5**), in each of the ten CKB regions (**Figure 4.6**), and among participants with different education and income levels (**Supplementary Figure C.1** & **Supplementary Figure C.2** in **Appendix C**).

Women had a 28% higher cataract incidence rate than men (333 [326-340] vs 241 [234-248]). This sex-difference was rather consistent across different age groups (**Figure 4.4**), and in all ten regions (**Figure 4.6**), despite a slightly larger sex-difference in rural (32% higher in women than men, 369 [359-379] vs 252 [243-261]) than in urban (22% higher in women than men, 288 [279-297] vs 226 [217-235]) regions (**Figure 4.7**). A dramatically large regional difference was observed in cataract incidence rate across 10 regions, i.e., more than five times higher in urban Qingdao (466 [427-505] in men and 584 [549-619] in women) than in another urban area Suzhou (81 [70-93] in men and 106 [95-117] in women). Overall, rural residents had a higher incidence than urban residents (319 [312-326] vs 260 [254-266]) (**Table 4.4**).

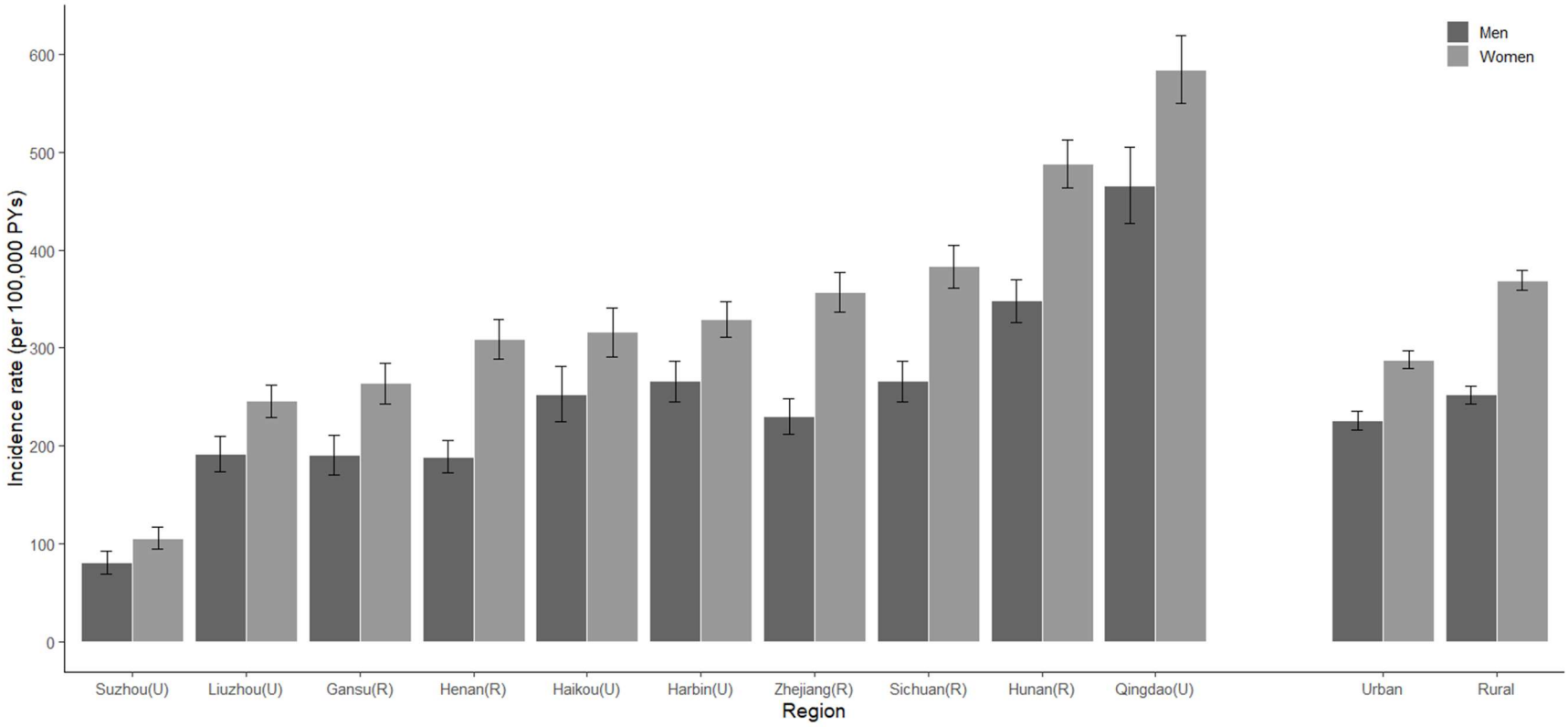
There was no clear trend for cataract incidence in relation to social economic status defined by levels of education. However, men with lower household income had higher cataract incidence. Among the 5 occupation categories, factory workers had the lowest cataract incidence rate (187 [155-219]), and participants in the other category, including housewife, self-employed, unemployed and unspecified occupation, had the highest (295 [282, 308]), similarly for both men and women (**Table 4.4** & **Table 4.5**). Compared to their counterparts, married men had a 7%

Figure 4.6 Cataract incidence rates by baseline age group in men and women in ten study regions



The squares represent incidence rate, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of incidence rate. The five regions on top are urban regions, and the five at the bottom are rural regions.

Figure 4.7 Age-standardised cataract incidence rates in men and women in ten study regions



	Number of participants	22,366	19,321	19,298	27,841	10,794	23,251	24,026	21,314	26,353	15,623	91,355	118,832
Men	Number of cases	205	530	370	546	363	814	722	677	1090	622	2534	3405
	Incidence Rate (95% CI)	81(70,93)	192(174,210)	191(171,211)	189(172,206)	253(225,281)	266(245,287)	230(212,248)	266(245,287)	348(326,370)	466(427,505)	226(217,235)	252(243,261)
	Number of participants	30,902	30,853	30,589	35,513	18,892	34,304	33,677	34,371	33,520	19,884	134,835	167,670
Women	Number of cases	380	931	661	1035	730	1423	1371	1278	1606	1164	4628	5951
	Incidence Rate (95% CI)	106(95,117)	246(229,263)	264(243,285)	309(289,329)	316(291,341)	329(311,347)	357(337,377)	383(361,405)	488(464,513)	584(549,619)	288(279,297)	369(359,379)

95% CI 95% confidence interval, U urban, R rural.
The incidence rates were per 100 000 person years, adjusted for 5-year age group at baseline study. The bars represent incidence rate, and the vertical lines on top of the bar represent 95% CIs. The numbers in the table below the figure represent corresponding regions in figure.

Table 4.4 Cataract incidence rates by socio-demographic status and self-assessed health

	Number of participants (N=512,692)	Number of cases (N=16,518)	Standardised incidence rate (95% CI)[a]
Sex			
Men	210,187	5939	241 (234, 248)
Women	302,505	10,579	333 (326, 340)
Region			
Urban	226,190	7162	260 (254, 266)
Rural	286,502	9356	319 (312, 326)
Education			
No formal school	95,179	4671	288 (269, 307)
Primary school	165,175	6657	311 (300, 322)
Middle/high school	222,364	4416	271 (257, 285)
College/university	29,974	774	271 (174, 368)
Annual household income, yuan			
< 10,000	144,733	5449	300 (288, 312)
10,000-19,999	148,943	4924	292 (283, 301)
20,000-34,999	126,698	3780	295 (277, 313)
≥ 35,000	92,318	2365	259 (241, 277)
Occupation[b]			
Agricultural	213,906	6359	259 (246, 272)
Factory	72,390	689	187 (155, 219)
Professional/sales	52,181	596	286 (242, 330)
Retired	84,944	5299	270 (251, 289)
Other	89,271	3575	295 (282, 308)
Marital status			
Not in marriage[c]	48,250	2784	294 (278, 310)
In marriage	464,442	13,734	294 (289, 299)
Self-rated health			
Poor	53,088	2171	348 (331, 365)
Fair	225,011	8297	301 (294, 308)
Good	144,198	3913	269 (260, 278)
Excellent	90,395	2137	259 (246, 272)
Self-rated life satisfaction			
Unsatisfied	21,332	481	339 (297, 381)
Neither satisfied nor dissatisfied	139,982	4557	301 (290, 312)
Satisfied	351,378	11,480	289 (283, 295)

95% CI 95% confidence interval.

[a] The incidence rates were numbers per 100,000 person years, adjusted for 5-year age group at study enrolment, sex and 10 regions (2 region for occupation), as appropriate.

[b] Agricultural: agricultural & related workers; Factory: factory workers; Professional/sales: administrator/manager, professional/technical, sales or service workers; Retired: retired; Other: house wife/husband, self-employed, unemployed, other, or not stated.

[c] Include separated/divorced, widowed, and never married.

Table 4.5 Cataract incidence rate by socio-demographic status and self-assessed health in men and women

	Men		Women	
	Number of cases	Standardised incidence rate (95% CI)[a]	Number of cases	Standardised incidence rate (95% CI)[a]
Overall	5939	241 (234, 248)	10,579	333 (326, 340)
Education				
No formal school	759	209 (174, 244)	3912	346 (324, 368)
Primary school	2580	254 (238, 270)	4077	356 (341, 371)
Middle/high school	2096	232 (220, 244)	2320	302 (277, 327)
College/university	504	229 (174, 284)	270	302 (127, 477)
Income, yuan				
< 10,000	1781	253 (233, 273)	3668	336 (321, 351)
10,000-19,999	1770	248 (235, 261)	3154	327 (314, 340)
20,000-34,999	1435	230 (212, 248)	2345	347 (318, 376)
≥ 35,000	953	205 (185, 225)	1412	299 (271, 327)
Occupation[b]				
Agricultural	2640	224 (202, 246)	3719	287 (270, 304)
Factory	474	177 (151, 203)	215	197 (142, 252)
Professional/sales	362	237 (203, 271)	234	327 (247, 407)
Retired	1920	232 (209, 255)	3379	296 (267, 325)
Other	543	247 (223, 271)	3032	337 (324, 350)
Marital status				
Not in marriage[c]	624	258 (231, 285)	2160	320 (300, 340)
In marriage	5315	239 (232, 246)	8419	337 (329, 345)
Self-rated health				
Poor	606	280 (254, 306)	1565	400 (376, 424)
Fair	2901	251 (241, 261)	5396	340 (330, 350)
Good	1529	224 (212, 236)	2384	303 (289, 317)
Excellent	903	217 (200, 234)	1234	292 (272, 312)
Self-rated life satisfaction				
Unsatisfied	170	264 (210, 318)	311	398 (336, 460)
Neither satisfied nor dissatisfied	1563	254 (238, 270)	2994	338 (323, 353)
Satisfied	4206	237 (229, 245)	7274	330 (322, 338)

95% CI 95% confidence interval.

[a] The incidence rates were numbers per 100,000 person years, adjusted for 5-year age group at study enrolment and 10 regions (2 region for occupation).

[b] Agricultural: agricultural & related workers; Factory: factory workers; Professional/sales: administrator/manager, professional/technical, sales or service workers; Retired: retired; Other: house wife/husband, self-employed, unemployed, other, or not stated.

[c] Include separated/divorced, widowed, and never married.

lower cataract incidence rate but married women had a 5% higher incidence rate. Men and women with higher levels of self-rated health and life satisfaction had lower cataract incidence rates than their counterparts.

4.4 Discussion

4.4.1 Summary of findings

In this large-scale prospective study among Chinese adults, as expected, a very strong positive trend for cataract incidence with age was observed. In addition, the incidence of cataract was 28% higher in women than in men overall, and this difference was larger in rural regions than in urban regions, despite the substantial variation across individual regions. No clear trends for cataract incidence were found in relation to education and marital status, but men with lower household income seemed to have a higher cataract incidence. Participants with better subjective assessments of health and well-being (i.e., self-rated heath status and levels of life satisfaction) had lower rates of cataract incidence.

4.4.2 Patterns and correlates of cataract incidence

Similar age- and sex-related patterns of cataract incidence have been observed in previous studies, among Western[135,37,143], African[144,133], Latin American[145] and Asian[134,136,146,147] populations (**Table 4.6**). As an age-related disorder usually occurring in people older than 50 years[148], the observed increase in cataract incidence rates between 50-70 years was expected. However, it is still unclear what might be the main driving force for the overall higher cataract incidence rate in women[149]. It has been speculated that hormonal factors (e.g., decrease in

Table 4.6 Incidence rates of age-related cataract and cataract surgery in prospective studies

Study name	Study location	Study population	Sample size	Baseline examination	Age at baseline (years)	Follow-up years	Measurement of cataract	Incidence rate of cataract		
								Total	By sex	By age-group (years)
Singapore Epidemiology of Eye Disease Study[147]	Singapore	Malays, Indians, Chinese	6762	2004-2011	≥40	6	slit lamp examination using Wisconsin Cataract Grading system	cataract surgery: 11.0% (10.2%-11.8%)	Men: 10.9% Women: 10.7%	40-49: 2.1% 50-59: 5.8% 60-69: 20.1% ≥70: 36.5%
Liwan Eye Study[136]	Guangzhou, China	Chinese	778	2003	≥50	10	detailed eye care questionnaire	cataract surgery: 9.4% (7.4%-11.7%)	Men: 8.7% (5.9%-12.3%) Women: 9.9% (7.3%-13.0%)	50-54: 1.5% 55-64: 3.5% 65-74: 17.4% ≥75: 23.2%
Beijing Eye Study[134]	Beijing, China	Chinese	3251	2001	≥40	5	slit lamp examination using AREDS grading system	any cataract: 16.8% (16.8%-16.9%); cataract surgery: 2.0% (2.0%-2.0%)	Any cataract: men: 13.8% (13.7%-13.8%) women: 20.7% (20.6%-20.7%) Cataract surgery: men: 1.8% (1.8%-1.8%) women: 2.4% (2.3%-2.4%)	Any cataract: 40-54: 3.8% (2.8%-4.8%) 55-64: 20.8% (18.0%-23.7%) 65-74: 44.2% (38.6%-49.7%) ≥75: 56.3% (31.9%-80.6%) Cataract surgery: 40-54: 0.7% (0.3%-1.2%) 55-64: 0.7% (0.2%-1.3%) 65-74: 5.4% (3.5%-7.3%) ≥75: 9.5% (3.3%-15.8%)
Los Angeles Latino Eye Study[145]	Los Angeles, U.S.	Latin American	4658	2000-2003	≥40	4	slit lamp examination using LOCS II system	any cataract: 14.2% (13.1%-15.3%)	N.A.	40-49: 3.4% (2.5%-4.3%) 50-59: 11.9% (10.1%-13.7%) 60-69: 36.0% (32.2%-39.8%) ≥70: 63.5% (55.8%-71.2%)
Shihpai Eye Study[146]	Taiwan region	Chinese	460	1999-2000	≥65	7	slit lamp examination using LOCS III system	Nuclear cataract: 29.4% Cortical cataract: 49.1% Posterior subcapsular cataract: 8.1%	Nuclear cataract: men: 29.6% women: 29.2% Cortical cataract: men: 39.8% women: 49.7% Posterior subcapsular cataract: men: 7.9% women: 8.3%	N.A.
Age-Related Eye Disease Study[144]	11 clinical centers in U.S.	Western and African	4757	1992-1998	55-80	10	slit lamp examination using AREDS grading system	Any cataract: 43.6% (41.8%-45.4%); Cataract surgery: 26.8% (25.5%-28.2%)	Any cataract: men: 40.9% (38.3%-43.6%) women: 45.9% (43.4%-48.4%) Cataract surgery: men: 24.7% (22.7%-26.6%) women: 28.5% (26.7%-30.3%)	Any cataract: 55-64: 29.4% (26.2%-32.6%) 65-69: 42.2% (39.2%-45.2%) ≥70: 56.2% (53.1%-59.3%) Cataract surgery: 55-64: 12.2% (10.1%-14.3%) 65-69: 15.6% (23.3%-27.8%) ≥70: 35.3% (33.1%-37.5%)

AREDES Age-related Eye Disease Study system, LOCS Lens Opacity Classification system. (cont.)

Table 4.6 Incidence rates of age-related cataract and cataract surgery in prospective studies (cont.)

Study name	Study location	Study population	Sample size	Baseline examination	Age at baseline (years)	Follow-up years	Measurement of cataract	Incidence rate of cataract		
								Total	By sex	By age-group (years)
Melbourne Visual Impairment Project[143]	Melbourne, Australia	Western	2594	1992-1994	≥40	5	slit lamp examination using Wilmer system	Nuclear cataract: 16.4% (12.1%-20.8%) Cortical cataract: 7.7% (5.8%-9.5%) Posterior subcapsular cataract: 7.0% (5.3%-8.7%) Cataract surgery: 5.1% (3.9%-6.2%)	Nuclear cataract: men: 17.0% (13.0%-20.9%) women: 15.9% (10.6%-21.4%) Cortical cataract: men: 5.7% (3.6%-7.8%) women: 9.4% (7.5%-11.2%) Posterior subcapsular cataract: men: 7.0% (4.4%-9.5%) women: 7.0% (5.7%-8.4%)	Cataract incidence for participants aged 40-49, 50-59, 60-69, 70-79 and ≥80 at baseline were provided for nuclear, cortical, and posterior subcapsular cataract separately.
Blue Mountain Eye Study[135]	Sydney, Australia	Western	1952	1992-1994	≥49	10	slit lamp examination using Wisconsin Cataract Grading system	Any cataract: 53.7%; Cataract surgery: 17.8%	Any cataract: men: 47.3% women: 59.1% Cataract surgery: men: 14.4% women: 20.2%	Any cataract: 49-54: 24.0% 55-64: 47.7% 65-74: 77.0% ≥75: 87.3% Cataract surgery: 49-54: 3.6% 55-64: 9.1% 65-74: 28.0% ≥75: 45.4%
Beaver Dam Eye Study[37]	Wisconsin, U.S.	Western	2764	1988-1990	43-86	15	slit lamp examination using Wisconsin Cataract Grading system	Any cataract: 38.0% (35.9%-40.1%); Cataract surgery: 13.0% (11.7%-14.2%)	Any cataract: men: 35.3% (32.3%-38.3%) women: 40.4% (37.5%-43.2%) Cataract surgery: men: 10.0% (8.3%-11.7%) women: 15.2% (13.5%-16.9%)	Any cataract: 43-54: 16.4% (14.1%-18.7%) 55-64: 46.8% (42.9%-50.7%) 65-74: 75.1% (70.4%-79.8%) ≥75: 87.7% (77.4%-98.1%) Cataract surgery: 43-54: 2.7% (1.7%-3.6%) 55-64: 11.2% (9.1%-13.3%) 65-74: 26.4% (23.1%-29.7%) ≥75: 29.8% (23.4%-36.2%)
Barbados Eye Study[133]	Barbados	African	2793	1987-1992	40-84	9	slit lamp examination using LOCS II system	Any cataract: 46.0% (43.8%-48.3%); Cataract surgery: 4.2% (3.5%-5.0%)	Any cataract: men: 44.5% women: 47.2% Cataract surgery: men: 4.4% (3.2%-5.6%) women: 4.1% (3.2%-5.1%)	Any cataract: 40-49: 22.3% 50-59: 59.5% 60-69: 86.1% ≥70: 83.6% Cataract surgery: 40-49: 0.4% (0.0%-0.8%) 50-59: 2.6% (1.4%-3.7%) 60-69: 5.7% (3.8%-7.5%) ≥70: 14.4% (10.9%-17.9%)

LOCS Lens Opacity Classification system.

estrogen at menopause) might contribute[150], but previous evidence has been inconsistent about the association between postmenopausal hormone use and cataract risk[150,151,152]. It might also be related to the major role of women in domestic cooking and exposure to indoor air pollution, especially for those living in rural regions[45]. Previous work within the CKB has shown that air pollution was a significant risk factor for cataract in women but not in men[153]. In the current study, larger sex-differences were observed in cataract incidence in rural regions than in urban regions, supporting the potential impact of indoor air pollution resulting from inefficient burning of coal and biomass for cooking or heating[154,155]. However, a post hoc analysis with additional adjustment for household air pollution level and female reproductive factors did not eliminate the sex-difference in cataract incidence.

The higher cataract incidence among rural residents compared to urban residents may also be related to indoor air pollution, while this is consistent with the socio-economic patterns observed in previous studies in several regions in China[134,156,157]. In this study, lower household income was related to a higher cataract incidence only in men, not in women. This suggests that improving living conditions in rural areas might have larger potential to facilitate cataract prevention in China, in contrast to enhancement of education and income levels, particularly for women.

This study found that factory workers had lower incidence of cataract than other occupations, in contrast to no clear patterns in relation to occupation reported in previous western studies (e.g., the Beaver Dam Eye Study)[38,138]. Similar to the occupation classification used in the current study, occupation was classified as white collar, blue collar, and farm worker in the Beaver Dam Eye

Study[38]. Future studies using clearly described occupation categories (i.e. specific occupations included each of the occupation category) could help to clarify patterns of cataract incidence in relation to occupation, i.e. whether specific work-related exposure is involved in the aetiology of cataract. For the first time, this study found contrasting patterns of cataract incidence in relation to marital status between men and women (married men had a lower but married women had a higher incidence of cataract than their not-married counterparts), which might be potentially due to marriage benefitting men more than women. Marriage might encourage healthier lifestyle choices in men (e.g., improved diet, reduced smoking, less cooking task which is related to indoor air pollution), but married women might experience an increased level of stress or have reduced healthy behaviours due their caregiving responsibilities[158].

No previous studies have evaluated cataract patterns in relation to self-rated health and life satisfaction, despite a body of literature on their associations with health and mortality[139,159,140,160]. It has been suggested that self-rated health is a comprehensive health indicator reflecting determinants of well-being including symptoms of disease not yet diagnosed in preclinical stages, family history of diseases, behaviors that subsequently affect health status, and within-person resources[159]. This study found that participants with better self-rated heath status and life satisfaction had lower rates of cataract incidence, suggesting the potential predictive value of these two easily assessed factors for cataract incidence (e.g., facilitating the identification of high-risk groups for clinical screening).

4.5 Summary

In addition to advanced age, female gender and rural residency, lower income (at least in men), and lower self-rated heath status and life satisfaction level were also related to a higher cataract incidence in China. Policy makers should take these messages into account when developing public health strategies for cataract prevention and allocation of cataract treatment facilities. Findings from this chapter informed the selection of confounding factors in the subsequent association analysis for lifestyle and cardiometabolic factors.

5 Associations of smoking and alcohol drinking with risk of cataract

5.1 Introduction

Smoking and alcohol drinking are important lifestyle risk factors relating to a wide range of age-related diseases including cardiovascular diseases and cancer[161,162,163]. Smoking was the leading risk factor for global cancer burden in both sexes in 2019, accounting for 33.9% and 10.7% disability-adjusted life-years (DALYs) in men and women, respectively[161]. Alcohol use was the next greatest risk factor in men, attributing to 7.4% cancer DALYs in 2019[161]. Age-related cataract is an age-related disease with a substantial global burden, responsible for half of the 43 million global blindness cases and one third of the 295 million global visual impairment cases in 2020[18,19]. Understanding the associations between smoking and alcohol consumption with risk of cataract could help to identify high risk population subgroups as the principle target for cataract prevention measures and provide evidence for policies to control smoking and alcohol use.

Previous studies have found consistent evidence associating smoking with a higher risk of cataract, with the relative risk of current smoking ranging from 1.12 (1.09-1.14) to 2.84 (1.46-5.51) when compared with never smoking[95,164]. Higher smoking amount (assessed as cigarettes per day or pack-years) was associated with higher risk of cataract[61,63], and longer duration of smoking cessation was inversely associated with risk of cataract[66,67]. However, existing evidence on smoking mainly comes from Western populations, with very limited high-quality evidence from Asian countries which account for majority of the global cataract burden and have higher smoking levels than other parts of the world[12,165].

In contrast to the consistent positive association observed between smoking and cataract risk, evidence on alcohol consumption has been less consistent. For instance, findings from both the Nurses' Health Study[69] and the Blue Mountains Eye Study[70] suggest a J-shaped association between alcohol consumption and cataract risk (i.e., lowest cataract incidence among moderate alcohol drinkers), while the Swedish Mammography Cohort Study[72] found current drinkers consuming 21-30 grams/day had higher risk of cataract than others with either lower or higher alcohol intake. The UK Million Women Study suggested an inverse association between alcohol consumption and risk of cataract[59], but no clear associations were found in three studies[166,167,168]. In addition, only one study have assessed the joint associations of smoking and alcohol consumption on cataract risk[169].

A better understanding of the associations between smoking and alcohol drinking with cataract risk, especially among Asian populations, could help to facilitate cataract prevention strategies. To fill the gap in knowledge, this chapter aims to use data from 0.5 million participants in CKB to investigate the independent associations of smoking and alcohol drinking patterns with risk of cataract. In addition, the joint associations of smoking and alcohol drinking patterns with risk of cataract will be explored.

5.2 Methods

Detailed information about the study design and data collection in CKB has been described in chapter 3. In brief, the CKB is a prospective cohort study involving 0.5 million adults aged 30-79 years from 10 regions in China, with the collection of information on a wide range of socio-

economic, lifestyle, and cardiometabolic factors at the baseline survey and subsequent resurveys, and extended follow-up for a median of 11 years. In this study, age-related cataract was defined as the first cataract event occurring after age 40 years, with an *ICD-10* code of H25 (senile cataract) or H26.9 (cataract unspecified).

5.2.1 Assessment of smoking

Information on smoking was self-reported by participants at baseline (and resurveys) using an interviewer-administered laptop-based electronic questionnaire. Participants were asked to report how often they smoke currently and in the past (for occasional smokers)[170,165]. Among current and ex-regular smokers, additional information was collected on daily smoking amount and types of tobacco smoked; age and types of tobacco when first started smoking on most days; depth of inhalation; and change of smoking behaviour compared with some years ago. Among participants who had stopped smoking regularly by baseline survey, the main reason for smoking cessation was collected. Smoking equivalents per day was calculated in gram/day, assuming 1g of tobacco per factory cigarette, 2g per cigar, and actual amount in pipes and hand-rolled cigarettes as reported. Smoking duration was derived from the age started smoking regularly to age at baseline for current smokers or to age quitted smoking for ex-smokers. Smoking status was classified as never smokers (including those who had smoked <100 cigarettes in lifetime), ex-regular smokers (who had smoked ≥100 cigarettes or equivalent but had quit smoking at least six months before baseline by choice), occasional smokers (who did not meet the criteria for never or ex-regular smokers, and had not stopped smoking completely for at least six months before baseline), and current smokers (who ever smoked ≥1 cigarettes or equivalent daily for at least six

months). To avoid bias, smokers who had smoked ≥100 cigarettes or equivalent but had quit smoking at least six months before baseline due to ill health were also counted as current smokers in the main analyses[165]. Current smokers were further categorised into three groups: <15; 15 to <25; ≥25 smoking equivalents per day.

5.2.2 Assessment of alcohol consumption

During the questionnaire survey, participants were asked to choose from the following categories about the frequency of alcohol drinking during the past 12 months: never or almost never; only occasionally; only at certain seasons; every month but less than weekly; usually at least once a week[171,170]. Except for regular alcohol drinkers (i.e., drinking alcohol at least weekly in the past 12 months), all other participants were asked to answer a follow-up question about whether in the past they had drunk alcohol at least once a week. Regular drinkers were further asked to report 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 [<40% alcohol content], and strong spirits [≥40% alcohol content]) and amount consumed (reported as number of small [250 ml] or large [640 ml] bottles for beer, and number of liang (50g) for wines and spirits) on a typical drinking day, on special occasions, and at the last time of drinking; time of drinking in relation to meals (with meal versus not with meal); age started drinking in most weeks; and whether their alcohol consumption had changed significantly in the past few years.

In this thesis, participants were classified into four main drinking categories[124]: (1) non-drinkers (i.e., who had never or almost never drank alcohol in the past 12 months and had not drunk in

most weeks in any past year); (2) occasional drinkers (who drank alcohol in the past 12 months only occasionally, at certain seasons, or monthly, and not in most weeks, and had not drunk alcohol in most weeks in any past year); (3) ex-drinkers (who did not drink alcohol in most weeks in the past 12 months but did so in some of the past year(s)); (4) current drinkers (who drank alcohol usually at least once a week during the past 12 months). Current drinkers were further categorised into groups based on weekly drinking amount: for men <140, 140 to <280, 280 to <420, or ≥420 g alcohol/week, and for women <70 or ≥70 g/week. These drinking categories were selected to provide a reasonable estimate of drinking behaviours, for example, for men ranging from moderate drinking (<140g/week or about 1-2 drinks/day on average, assuming 1 drink=10g of alcohol) to heavy drinking (≥420 g/week or over 6 drinks/day on average).

Smoking and alcohol consumption were re-assessed in the same way among subsets of study participants at resurveys in 2008 (n=19 788) and 2013-2014 (n=25 176). The resurvey data were used to estimate the "usual" level (i.e., the habitual level) of smoking (in current smokers) and alcohol consumption (in current drinkers) in each baseline category.

5.2.3 Statistical analyses

The present analysis excluded individuals with incident cataract before age 40 years (n=34) and individuals with missing data on BMI (n=2), leaving 512 690 participants (210 186 men and 302 504 women) for the main analyses. Baseline characteristics of CKB participants by category of smoking and alcohol consumption status were calculated separately in men and women, with direct standardisation to age groups (in 5 year intervals) and study region (ten regions)[141]. Given

very few women smoked or drank regularly (2.8% and 2.1%, respectively) (**Supplementary Table D.1** in **Appendix D**), the main analyses focused on men, and the results for women are presented in **Supplementary Figure D.1**.

In the Cox proportional hazards regression models investigating the association of smoking with cataract risk, smoking status was assessed as a categorical variable (six groups: never smokers, ex-regular smokers [quit smoking by choice], occasional smokers, and current smokers [include current smokers and ex-smokers quit smoking due to illness] with <15, 15 to <25, or ≥25 smoking equivalent per day). To account for measurement error and within person variability (i.e., regression dilution bias), the usual level of smoking in current smokers was estimated with the MacMahon-Peto method by taking the mean smoking amount at resurveys 1 and 2 for each baseline smoking category as previously described (see Chapter 3.2.3), and the log HRs were plotted against usual level of smoking. In addition to smoking status, age started smoking, duration of smoking, depth of inhalation, and types of tobacco were also assessed for their associations with incident cataract risk. Among ex-smokers, duration since and reason for smoking cessation (i.e., quit by choice for <5 years, quit by choice for 5 to <15 years, quit by choice for ≥15 years, quit due to illness for <5 years, quit due to illness for 5 to <15 years, and quit due to illness for ≥15 years) were also analysed (with never smokers as reference category) to estimate their associations with cataract risk.

For alcohol consumption, drinking status was assessed as a categorical variable (including non-drinkers, occasional drinkers, ex-drinkers, and current drinkers with drinking amount of <140,

140 to <280, 280 to <420, or ≥420 g/week in men and <70 or ≥70 g/week in women). Similar to the method used for smoking, the usual level of alcohol consumption in current drinkers was estimated and the log HRs were plotted against usual level of drinking. As an example, the calculation of usual level of alcohol consumption among the baseline defined drinking groups (i.e., <140, 140 to <280, 280 to <420, or ≥420 g alcohol/week in men) in current drinkers is presented in **Supplementary Table D.2**. In addition, to obtain the per unit effect of alcohol intake, the drinking status was assessed as a continuous variable among current drinkers (per 280 g/week, which is the mean drinking amount among current drinkers, and it is equivalent to about 4 drinks per day), and the per unit effect was adjusted by the regression dilution ratio. As well as the main analysis on alcohol drinking status, the relevance of drinking time (i.e., with meal; not with meal; no pattern), types of beverage, and age started drinking were also assessed.

The Cox regression models were stratified by age-at-risk (5-year groups) and study region (ten regions), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), total physical activity (continuous), BMI (continuous), fresh fruit consumption (four groups), prevalent diabetes (dichotomous), self-rated health (four groups), and mutually adjusted for alcohol consumption status (four groups) and smoking status (four groups). Floating absolute risk method[126,127] was used for exposure variables with more than two categories as previously described (Chapter 3.2.2). The proportional hazards assumption was assessed with scaled Schoenfeld residuals[172], with no violations found.

To explore potential effect modification by other population characteristics, subgroup analyses were conducted by region, age-at-risk, education, household income, alcohol consumption or smoking where appropriate, physical activity, fresh fruit consumption, BMI, and prevalent diabetes. The Chi-square tests for trend and heterogeneity across strata were applied to the log HRs and their SEs. The joint associations of smoking and alcohol drinking were assessed by comparing the risk of cataract across nine exposure groups: i.e., never smokers and non-drinkers, never smokers and occasional drinkers, never smokers and ever regular drinkers, occasional smokers (include ex-smokers quit by choice) and non-drinkers, occasional smokers and occasional drinkers, occasional smokers and ever regular drinkers, current smokers (include ex-smokers quit due to illness) and non-drinkers, current smokers and occasional drinkers, and current smokers and ever regular drinkers.

Several sensitivity analyses were conducted to assess the robustness of the results, including: 1) additionally adjusting for potential confounding factors including household air pollution from cooking (assessed as type of cooking fuel use [five groups: always clean fuel, changed from solid to clean fuel, always solid fuel, never-regular cook, and other]), SBP, waist circumference, waist-to-hip ratio, fat percentage, and blood glucose separately; 2) excluding the first 3 years of follow-up, to assess the impact of reverse causation since cataract that occurs soon after the exposure might have influenced participant's lifestyle behaviour rather than the other way around. The first 3 years of follow-up is a pragmatic choice of period to exclude, given the median follow up period of 11 years in CKB; 3) excluding participants aged ≥70 years at baseline, to assess the impact of potential inclusion of participants who had already had cataract (i.e., some of the

participants may had their lens removed before baseline, therefore no longer being at risk of cataract) prior to the baseline study; 4) excluding participants with poor self-rated health, prevalent cancer, cardiovascular diseases, or diabetes, to assess the potential impact of reverse causation since participants with these pre-existing health conditions might have changed their lifestyle behaviours due to those conditions; 5) excluding participants with incident diabetes during follow-up, because those cataract events might be diabetic cataract instead of age-related cataract. All statistical analyses were performed in R (version 4.0.3).

5.3 Results

5.3.1 Baseline characteristics of participants by smoking or alcohol consumption status

Among the 210 186 male participants, 67.7 % were current smokers and 33.3% were current drinkers (**Table 5.1**). In contrast, among the 302 504 female participants, only 2.8% were current smokers and 2.1% were current drinkers (**Supplementary Table D.1**). In men, compared with never smokers, current smokers were more likely to be younger (52.4 vs 54.2 years), be rural residents (60.3% vs 45.1%), and have less formal education (43.9% vs 38.7% below high school) and lower income (55.5% vs 53.0% with household income <20K yuan/year). They also consumed more frequently red meat (33.7% vs 30.9% as daily eaters) and fish/seafood (3.5% vs 2.3% as daily eaters), but less frequently fresh fruit (13.0% vs 18.2% as daily eaters). Their mean values of systolic/diastolic blood pressure (132.5/78.9 vs 133.6/79.7 mmHg), BMI (23.2 vs 23.8 kg/m^2), and waist circumference (81.7 vs 82.4 cm) were also lower. The prevalence rates of prior diseases were lower in current smokers than in never smokers (2.8% vs 3.2% for diabetes, 10.8% vs 12.7%

Table 5.1 Baseline characteristics of CKB men by smoking and alcohol consumption status

	Smoking				Alcohol consumption				All men (N=210,186)
	Never smokers (N=30,299)	Occasional smokers (N=23,612)	Ex-regular smokers (N=14,079)	Current smokers* (N=142,196)	Non-drinkers (N=42,775)	Ex-drinkers (N=18,295)	Occasional drinkers (N=79,221)	Current drinkers (N=69,895)	
Mean age (SD), years	54.2 (12.4)	50.8 (11.4)	56.1 (11.2)	52.4 (10.6)	57.0 (12.9)	56.8 (11.5)	51.0 (11.1)	51.5 (12.0)	52.9 (10.9)
Socio-demographic factors									
Rural, %	45.1	55.5	48.6	60.3	68.8	59.0	55.9	50.1	56.5
Education below high school, %	38.7	38.5	39.7	43.9	45.2	42.9	39.7	42.5	42.2
Household income <20 000 yuan/year, %	53.0	52.9	52.3	55.5	57.9	54.9	53.3	53.2	54.3
Lifestyle factors									
Physical activity, MET-hours/day, mean (SD)	21.8 (15.4)	22.6 (13.7)	21.8 (14.9)	21.9 (13.1)	21.2 (19.3)	20.4 (16.9)	22.5 (13.9)	22.2 (15.6)	22.0 (15.3)
Daily intake of dietary factors, %									
Red meat	30.9	30.6	33.7	33.7	28.6	33.5	31.1	36.9	32.9
Fish/seafood	2.3	2.9	3.3	3.5	2.5	3.7	2.5	4.1	3.2
Fresh vegetables	94.9	94.9	96.0	94.8	94.3	96.1	95.2	95.5	94.9
Fresh fruit	18.2	16.1	18.1	13.0	16.0	16.9	15.8	13.6	14.5
Cardiometabolic factors, mean (SD)									
SBP, mmHg	133.6 (20.5)	133.1 (20.7)	134.6 (20.1)	132.5 (19.7)	131.9 (23.9)	134.0 (23.7)	131.1 (20.3)	134.3 (23.2)	132.8 (20.0)
DBP, mmHg	79.7 (12.1)	79.5 (11.9)	80.5 (12.2)	78.9 (11.3)	78.3 (14.7)	79.8 (14.4)	78.2 (11.7)	80.3 (13.4)	79.2 (11.4)
BMI, kg/m^2	23.8 (3.4)	23.8 (3.2)	24.2 (3.4)	23.2 (3.1)	23.3 (4.4)	23.9 (4.1)	23.4 (3.3)	23.5 (3.6)	23.4 (3.3)
Waist circumference, cm	82.4 (10.2)	82.7 (9.6)	84.3 (10.1)	81.7 (9.3)	81.2 (12.9)	83.5 (11.9)	81.8 (9.8)	82.5 (10.8)	82.0 (9.8)
Waist-to-hip ratio	0.90 (0.07)	0.91 (0.07)	0.92 (0.07)	0.90 (0.06)	0.90 (0.08)	0.91 (0.08)	0.90 (0.07)	0.91 (0.07)	0.91 (0.07)
Random blood glucose, mmol/L	6.0 (2.5)	6.0 (2.5)	6.1 (2.6)	5.9 (2.4)	6.0 (3.1)	6.1 (3.0)	5.9 (2.4)	5.9 (2.6)	6.0 (2.3)
Prior disease history, %									
Diabetes	3.2	3.0	3.3	2.8	3.8	6.0	2.7	1.9	2.9
CHD	2.8	2.6	2.6	2.8	3.2	5.2	2.3	2.0	2.7
Stroke or TIA	2.2	1.9	1.8	2.6	3.5	5.9	1.6	1.4	2.3
Cancer	0.5	0.4	0.4	0.5	0.8	1.1	0.3	0.3	0.5
Hypertension	12.7	12.1	12.2	10.8	12.5	20.6	9.4	9.3	11.3
Poor self-rated health	8.5	8.2	6.5	9.5	12.7	17.1	7.7	5.9	8.9

SD standard deviation, MET metabolic equivalent of task hours/day, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, CHD coronary heart disease, TIA transient ischemic attack.

The results were standardised by age at baseline (5-year age group) and 10 study regions, as appropriate.

*Current smokers included current smokers and ex-regular smokers stopped due to illness.

for hypertension). Current smokers reported poor self-rated health more frequently than never smokers (9.5% vs 8.5%).

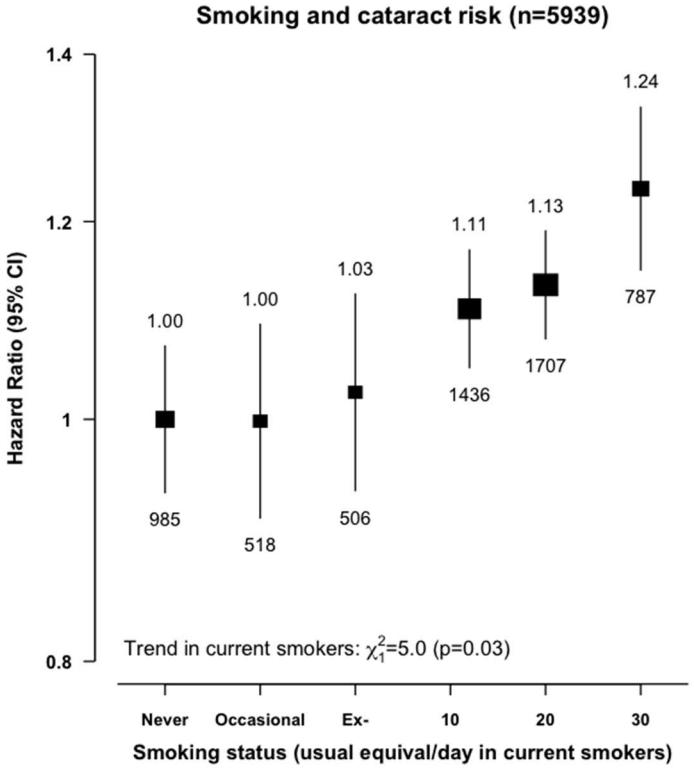
Similar socio-demographic patterns were observed for alcohol drinking. When compared with non-drinkers, current drinkers were more likely to be younger (51.5 vs 57.0 years), be urban residents (49.9% vs 31.2%), with higher education (42.5% vs 45.2% below high school) and higher household income (53.2% vs 57.9% with household income <20K yuan/year), and be more active (22.2 vs 21.2 MET-hours/day of mean physical activity). Current drinkers also included more daily eaters of red meat (36.9% vs 28.6%) and fish/seafood (4.1% vs 2.5%), but few daily eaters of fresh fruit (13.6% vs 16.0%) than never drinkers. Compared to the latter group, current drinkers had higher systolic/diastolic blood pressure (134.3/80.3 vs 131.9/78.3 mmHg) and higher waist circumference (82.5 vs 81.2 cm), but included few participants with prior diseases (1.9% vs 3.8% for diabetes, 2.0% vs 3.2% for CHD, 1.4% vs 3.5% for stroke or TIA, 0.3% vs 0.8% for cancer, and 9.3% vs 12.5% for hypertension). Current drinkers reported poor self-rated health less frequently than non-drinkers (5.9% vs 12.7%).

5.3.2 Smoking and risk of cataract

Smoking was associated with a higher risk of cataract in men. Male current smokers had 13% (1.13, 1.05-1.22) higher risk of cataract than never smokers, and there is a linear association (P_{trend}=0.03) between smoking amount and risk of cataract among current smokers. Compared with never smokers (1.00, 0.94-1.07), current smokers with <15, 15 to <25, and ≥25 cigarette-equivalents per day had 11% (1.11, 1.05-1.17), 13% (1.13, 1.08-1.19), and 24% (1.24, 1.15-1.33)

higher risk of cataract, respectively (**Figure 5.1** & **Supplementary Table D.3**). No clear association between smoking and risk of cataract was observed in women (**Supplementary Figure D.1** & **Supplementary Table D.3**).

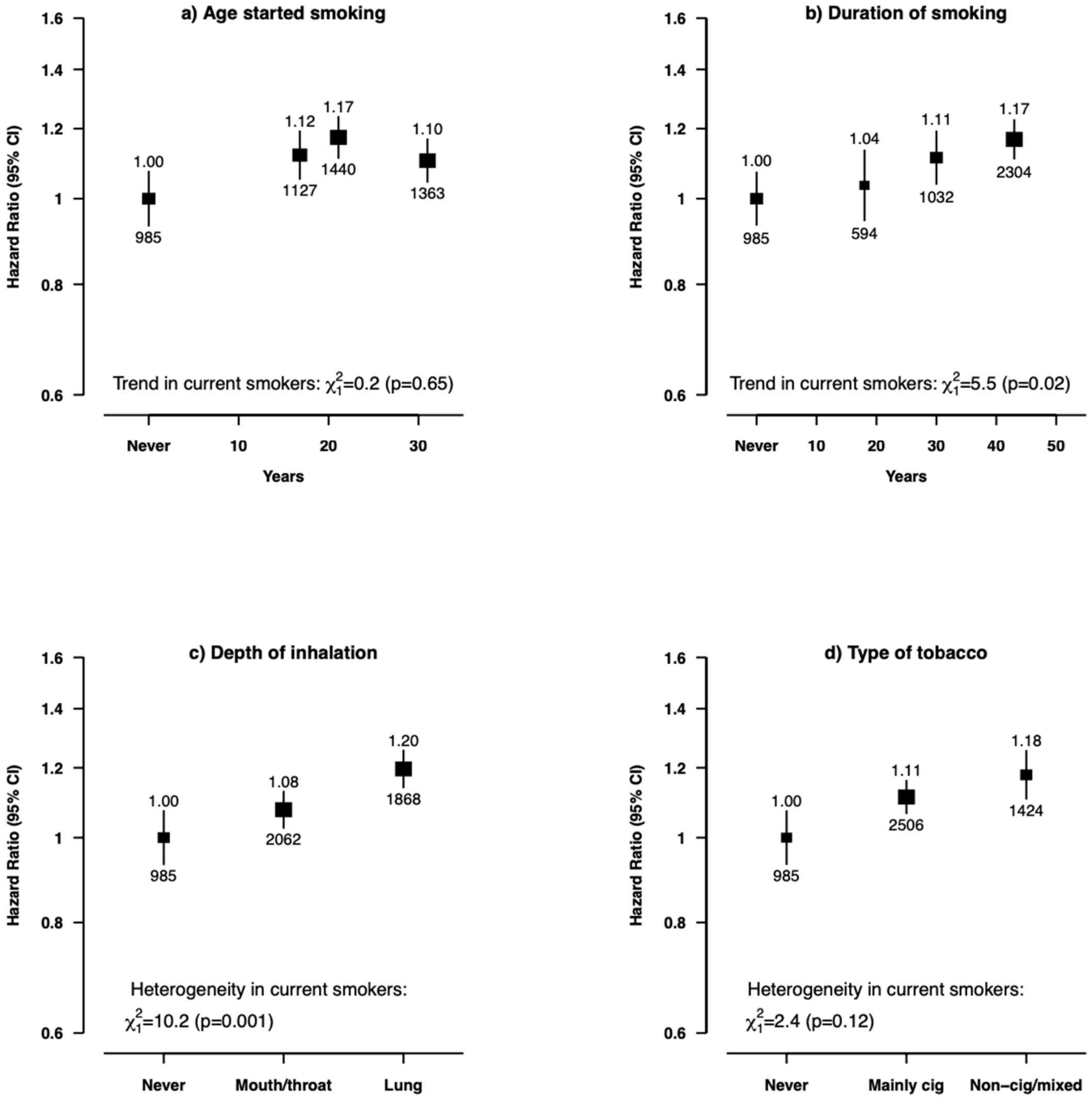
Figure 5.1 Adjusted HRs for cataract by smoking in men.



N stands for number of cases.
Ex-smokers included ex-smokers stopped by choice.
Current smokers included current smokers and ex-smokers stopped due to illness.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

There were no clear patterns between age started smoking and risk of cataract in men (**Figure 5.2a** & **Supplementary Table D.3**)**.** Compared with never smokers (1.00, 0.93-1.07), current smokers who started to smoke at <20, 20 to <25, and ≥25 years had 12% (1.12, 1.05-1.19), 17% (1.17, 1.11-1.24), and 10% (1.10, 1.05-1.17) higher risk of cataract. However, there was a clear positive linear trend between smoking duration and cataract risk, with current smokers who had smoked for <25, 25 to <35, and ≥35 years having 4% (1.04, 0.95-1.13), 11% (1.11, 1.04-1.19), and

Figure 5.2 Adjusted HRs of smoking patterns with cataract in current versus never smokers in men (number of cases=4915).



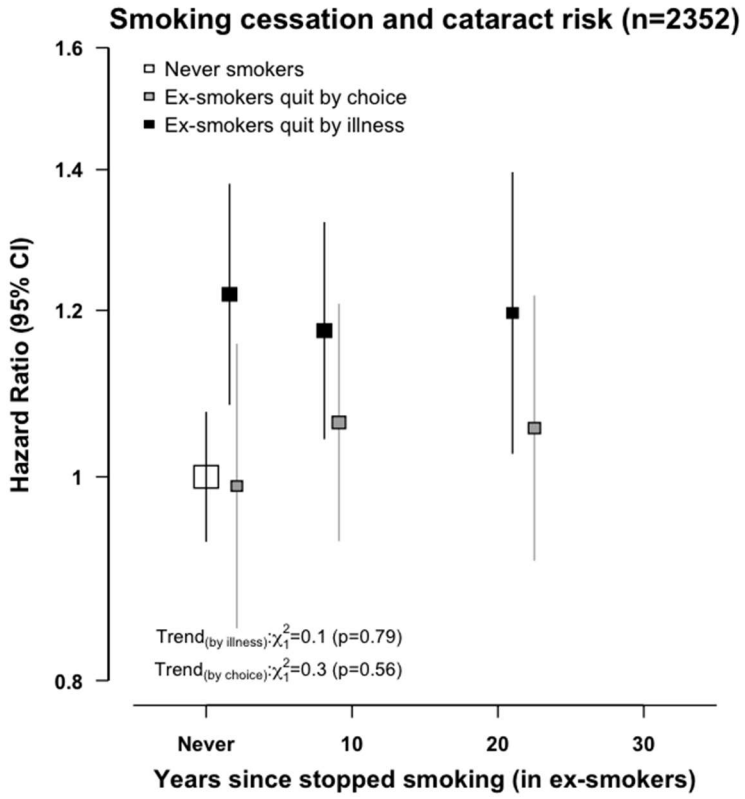
Current smokers included current smokers and ex-smokers stopped due to illness.
Duration of smoking (in Figure b) was derived from age started smoking regularly to age at study baseline.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

17% (1.17, 1.11-1.23) higher risks of cataract than never smokers (1.00, 0.93-1.07) (**Figure 5.2b** & **Supplementary Table D.3**).

Current smokers who inhaled to the lungs had higher risk of cataract than those inhaled to the mouth/throat, with the HRs being 1.20 (1.14-1.25) and 1.08 (1.03-1.13) respectively in comparison with never smokers (1.00, 0.93-1.07) (**Figure 5.2c** & **Supplementary Table D.3**). Those who smoked non-cigarette or mixed types of tobacco had about 7% higher risk of cataract than those smoked mainly cigarettes (HR 1.18 [1.11-1.25] vs 1.11 [1.07-1.16] in contrast to never smokers (1.00, 0.93-1.07), **Figure 5.2d** & **Supplementary Table D.3**).

Overall, smoking cessation by choice (1.04, 0.96-1.13) was associated with a lower risk of cataract than cessation due to illness (1.20, 1.11-1.29), in comparison with never smokers (1.00, 0.93-1.07). However, time since cessation was not associated with cataract risk in either group (**Figure 5.3** & **Supplementary Table D.3**).

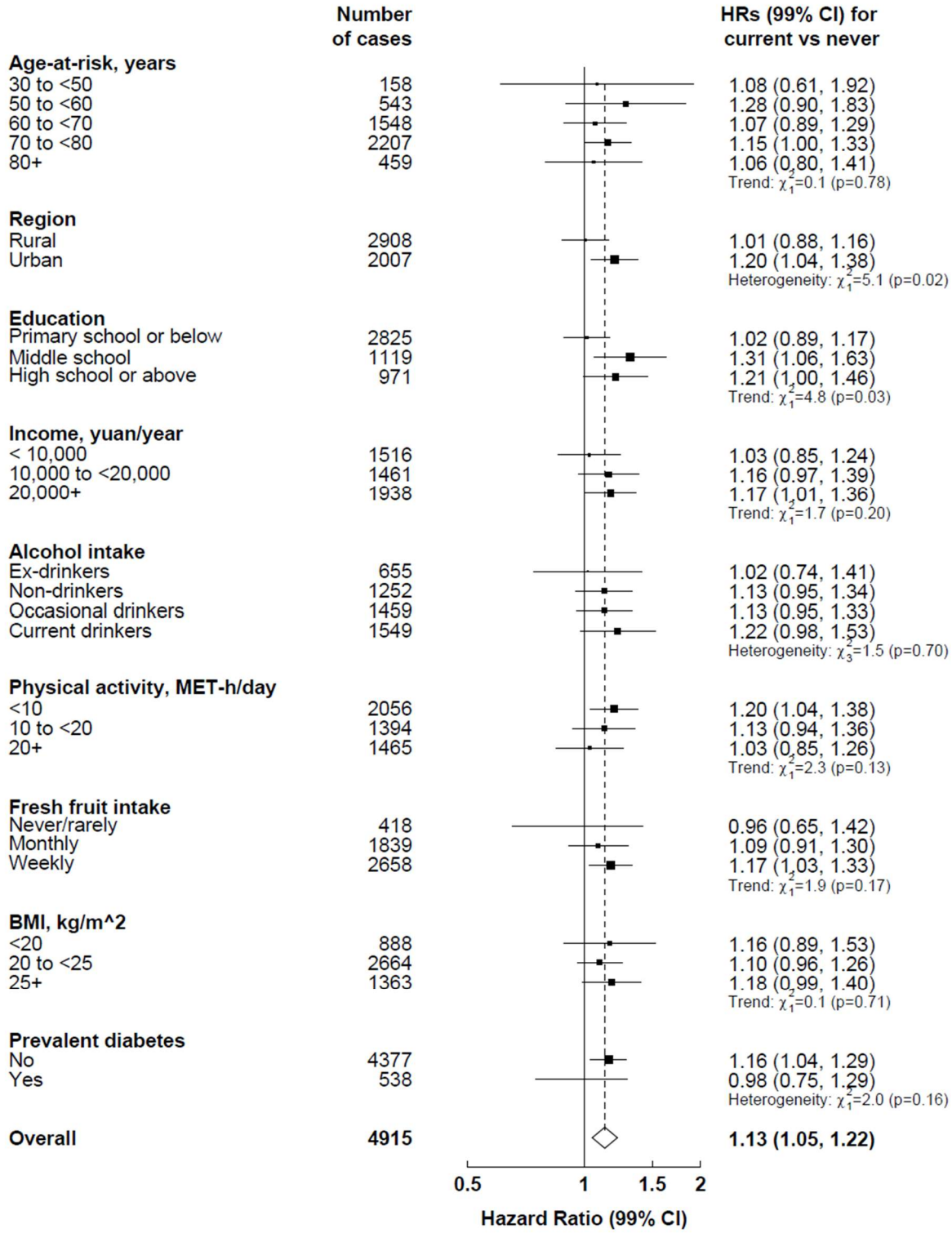
Figure 5.3 Adjusted HRs of cataract by reasons for, and years after, smoking cessation in ex-smokers versus never smokers in men.



N stands for number of cases.
Years since stopped smoking was derived from age stopped smoking to age at study baseline.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR.

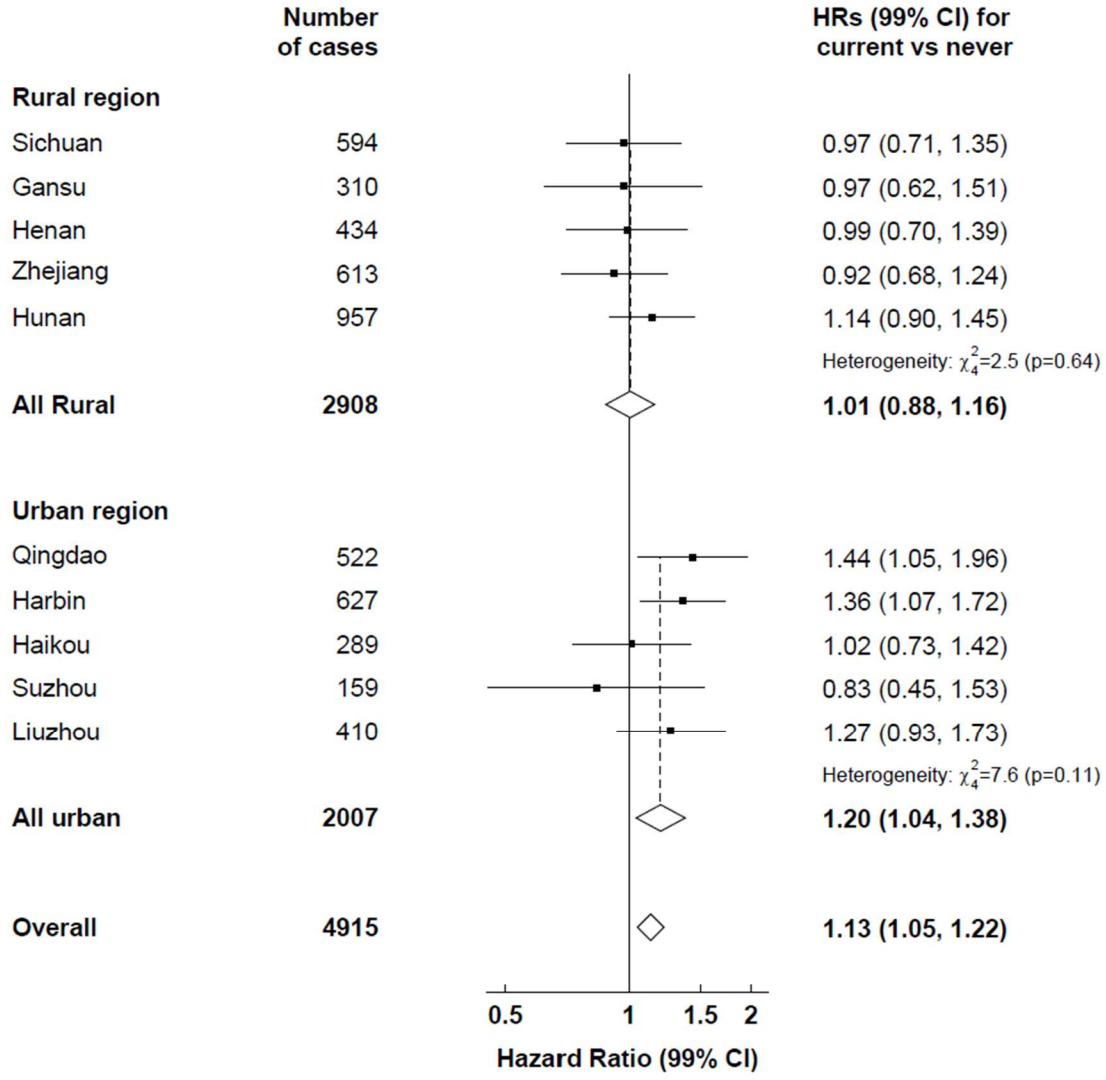
The association between current smoking and cataract risk was largely consistent across several subgroups defined by age, region, education, income, alcohol consumption, physical activity, fresh fruit consumption, BMI, and prevalent diabetes status (**Figure 5.4** & **Figure 5.5**). All observed associations remained essentially unchanged in sensitivity analyses with additional adjustments, excluding participants with poor self-rated health, prevalent diseases, and incidence diabetes during follow-up, or excluding the first 3 years of follow-up (**Table 5.2**).

Figure 5.4 Adjusted HRs of cataract associated with current smoking by selected population characteristics in men.



Current smokers included current smokers and ex-smokers stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status, as appropriate.

Figure 5.5 Adjusted HRs of cataract associated with current smoking by region in men.



Current smokers included current smokers and ex-smokers stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.

Table 5.2 Hazard ratios for cataract by smoking in men - results of sensitivity analysis.

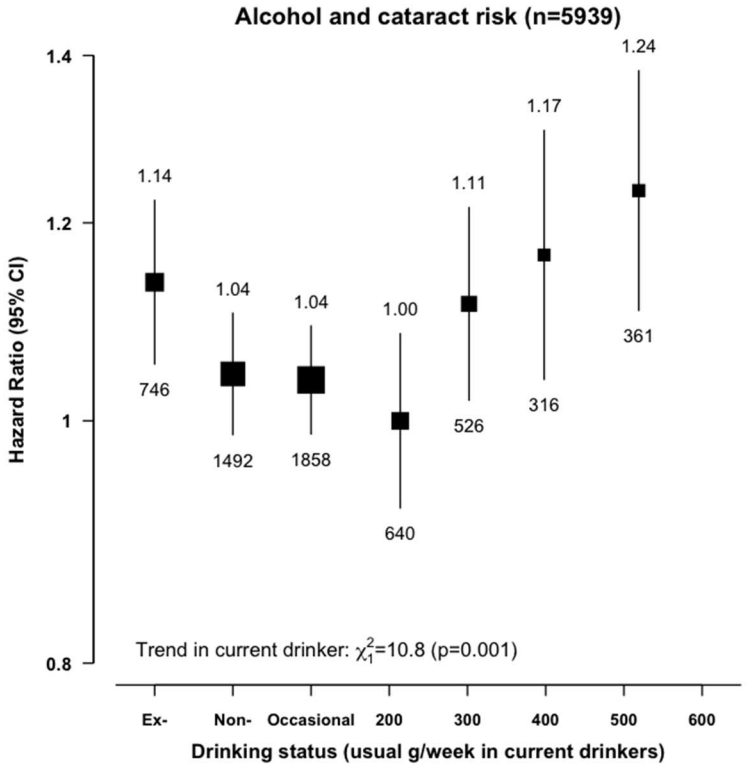
	Current vs never smokers	
	Number of cases	HR (95%CI)
Primary analysis* (n=210,186)	4915	1.13 (1.05-1.22)
Exclude those aged ≥70 years at study entry (n=193,874)	3883	1.17 (1.07-1.27)
Exclude those with poor self-rated health (n=191,462)	4399	1.17 (1.08-1.26)
Exclude those with cancer or CVD at baseline (n=199,239)	4448	1.12 (1.03-1.21)
Exclude those with cancer, CVD, or diabetes at baseline (n=189,099)	3988	1.14 (1.05-1.24)
Exclude those with cancer, CVD, or diabetes at baseline, or incident diabetes during study follow-up (n=181,391)	3701	1.14 (1.05-1.25)
Exclude first 3 years of follow-up (n=210,186)	4915	1.14 (1.05-1.22)
Additional adjustment (primary analysis + household air pollution)	4915	1.13 (1.05-1.22)
Additional adjustment (primary analysis + SBP)	4915	1.13 (1.05-1.22)
Additional adjustment (primary analysis + waist circumference)	4915	1.13 (1.05-1.22)
Additional adjustment (primary analysis + waist-to-hip ratio)	4915	1.13 (1.04-1.21)
Additional adjustment (primary analysis + fat percentage)	4915	1.13 (1.04-1.21)
Additional adjustment (primary analysis + blood glucose)	4915	1.13 (1.05-1.22)

Current smokers included current smokers and ex-smokers stopped due to illness.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age (continuous), education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.

5.3.3 Alcohol consumption and risk of cataract

In men, there was a J-shaped association between alcohol consumption and cataract risk. As shown in **Figure 5.6** & **Supplementary Table D.4**, the risk of cataract tended to be higher among current drinkers who consumed more than 140 g/week (i.e., about 1-2 drinks/day on average) of alcohol as well as ex-drinkers in comparison with those as non-drinkers, occasional drinkers, and current drinkers who had drinking level of <140 g/week. Compared to the latter group which was considered as reference category (HR=1.00, 0.92-1.08), both non-drinkers and occasional drinkers had a non-significant HR of 1.04, while ex-drinkers and those current drinkers who had higher levels of consumption had 14% (1.14, 1.06-1.22), 11% (1.11, 1.02-1.22), 17% (1.17, 1.04-1.31), and 24% (1.24, 1.11-1.38) higher risk of cataract, respectively. However, evidence from the

Figure 5.6 Adjusted HRs for cataract by alcohol consumption in men.



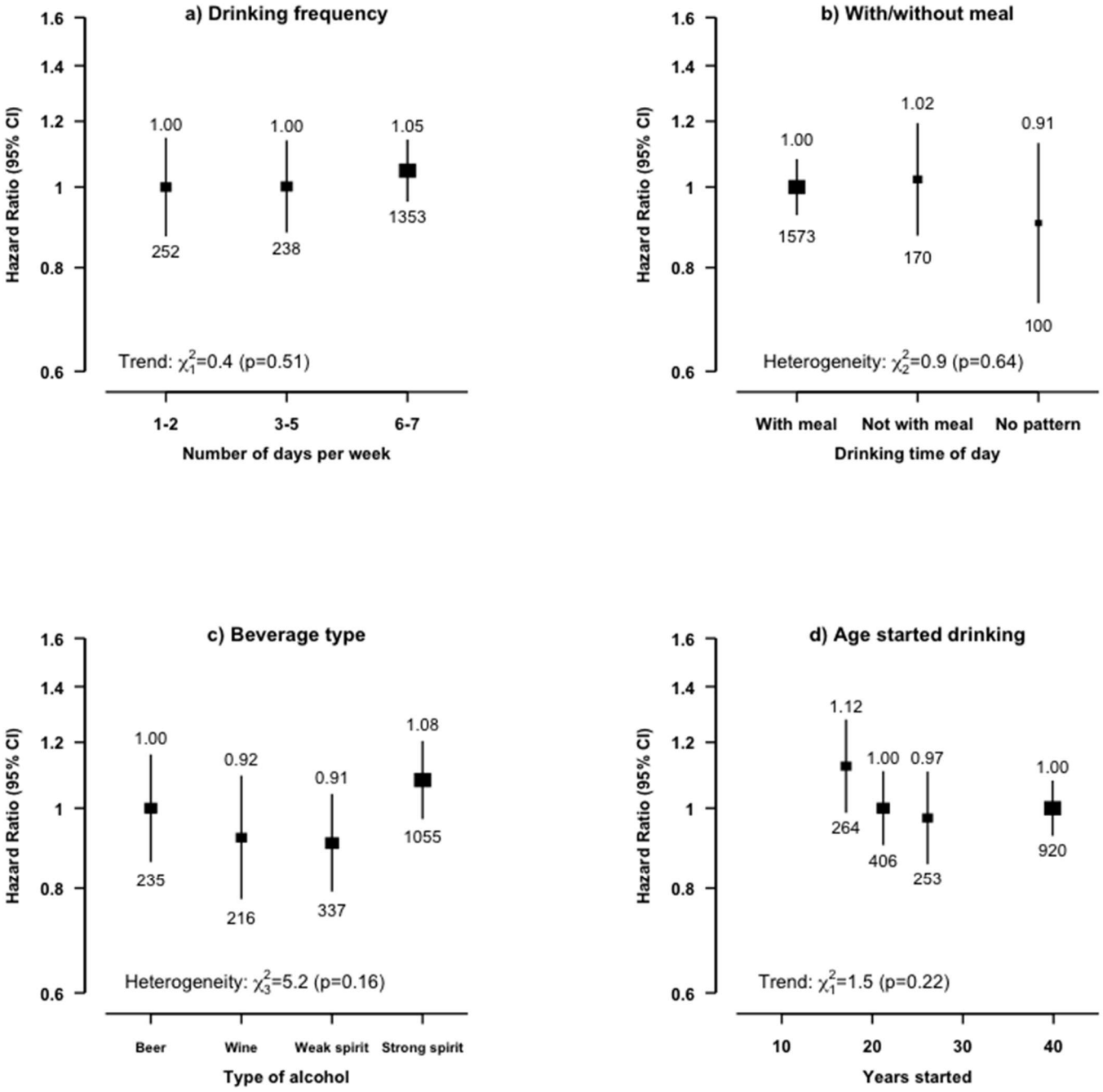
N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

few female drinkers in CKB seemed to suggest an inverse association between alcohol drinking and cataract risk (**Supplementary Figure D.1** & **Supplementary Table D.4**). Female current drinkers with intake of ≥70 g/week, which is the heavy drinking category, had 20% (0.80, 0.67-0.97) lower risk of cataract when compared with non-drinkers (1.00, 0.97-1.03).

No clear differences in cataract risk were observed among male current drinkers with different drinking frequencies, drinking time (whether drink with meal), beverage types, and ages started drinking (**Figure 5.7** & **Supplementary Table D.4**). Although not statistically significant, men who started drinking before age 20 years had 12% (1.12, 0.99-1.27) higher risk of cataract than those started drinking after age 30 years (1.00, 0.93-1.08) (**Figure 5.7d** & **Supplementary Table D.4**).

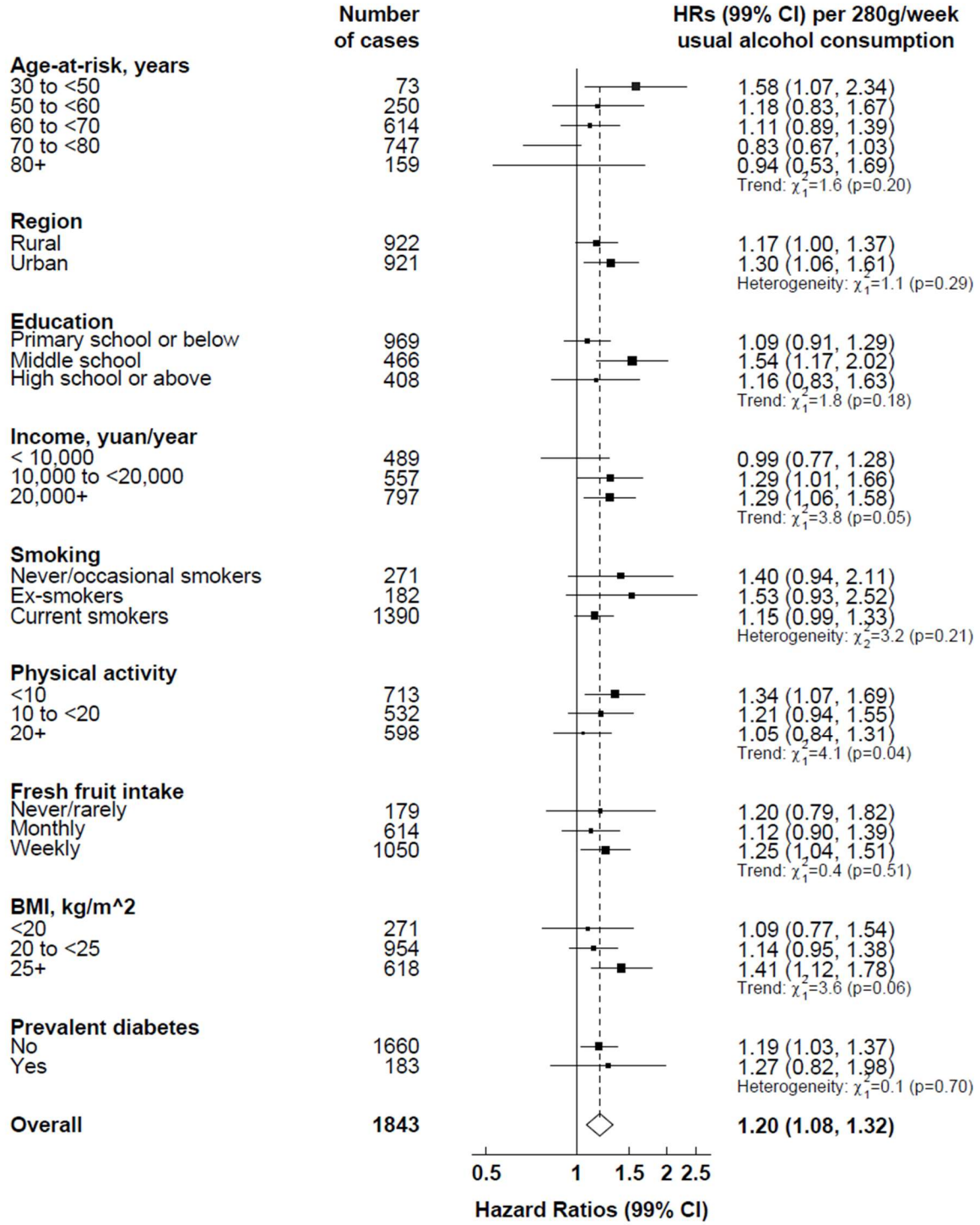
Among current alcohol drinkers, the amount of alcohol consumed was positively associated with risk of cataract, with HR per 280g/week (i.e., the mean drinking amount among current drinkers, equivalent to about 4 drinks per day) higher usual alcohol consumption being 1.20 (1.08-1.32). This association was similar across subgroups defined by age, region, education, income, smoking, physical activity, fresh fruit consumption, BMI, and prevalent diabetes status (**Figure 5.8** & **Figure 5.9**). Similar to the results on smoking, the associations of alcohol consumption with cataract risk remained largely unchanged in all the sensitivity analyses (**Table 5.3**).

Figure 5.7 Adjusted HRs for cataract by alcohol drinking patterns in male current drinkers (number of cases = 1843).



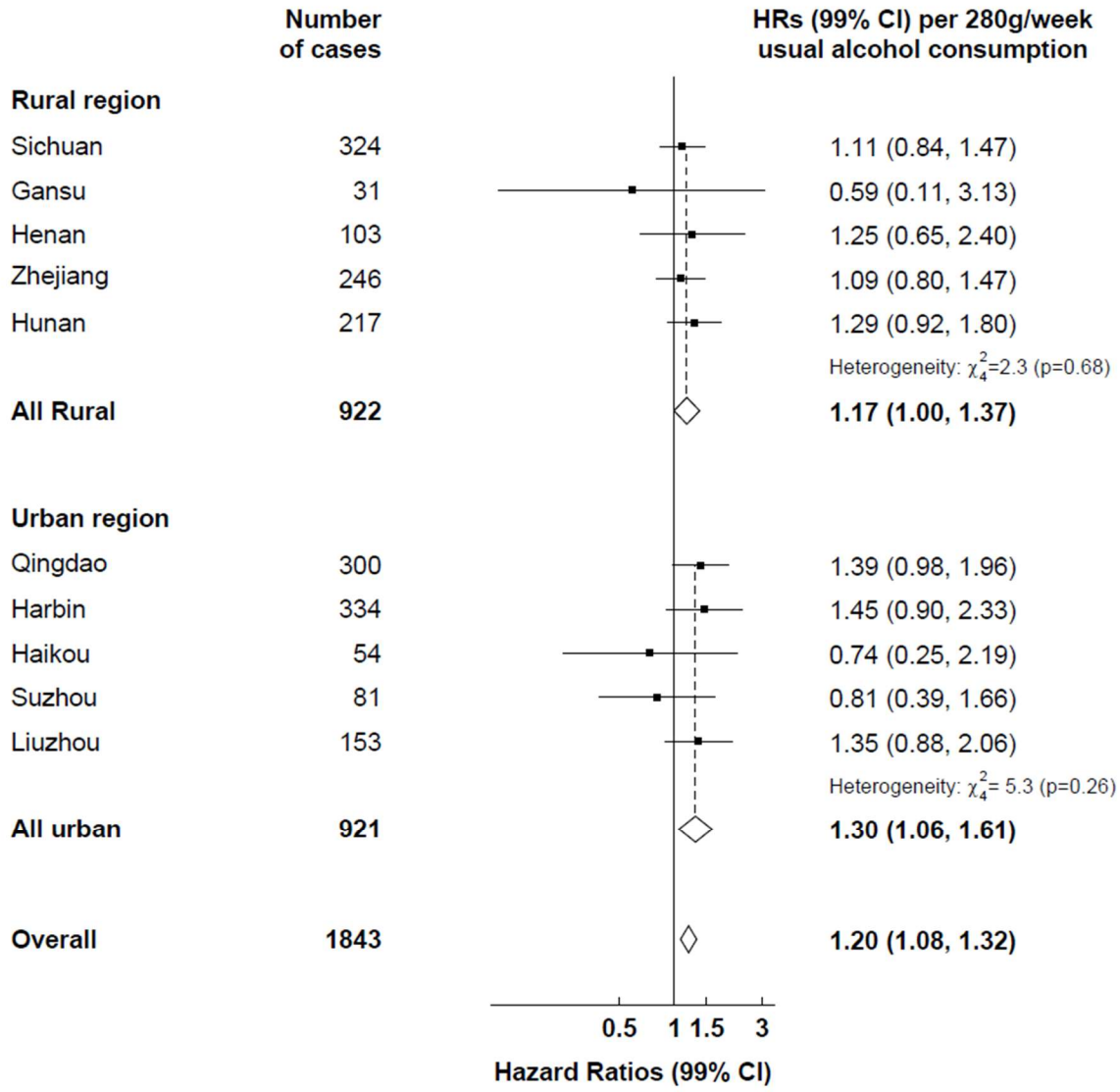
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases

Figure 5.8 Adjusted HRs per 280g/week higher usual alcohol consumption for cataract by selected population characteristics in male current drinkers.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status, as appropriate.
HRs were calculated for per "usual" level of 280/g/week alcohol consumption by treating it as a continuous variable and then apply the regression dilution ratio.

Figure 5.9 Adjusted HRs per 280g/week higher usual alcohol consumption for cataract by region in male current drinkers.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), and adjusted for baseline age, education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
HRs were calculated for per “usual” level of 280/g/week alcohol consumption by treating it as a continuous variable and then apply the regression dilution ratio.

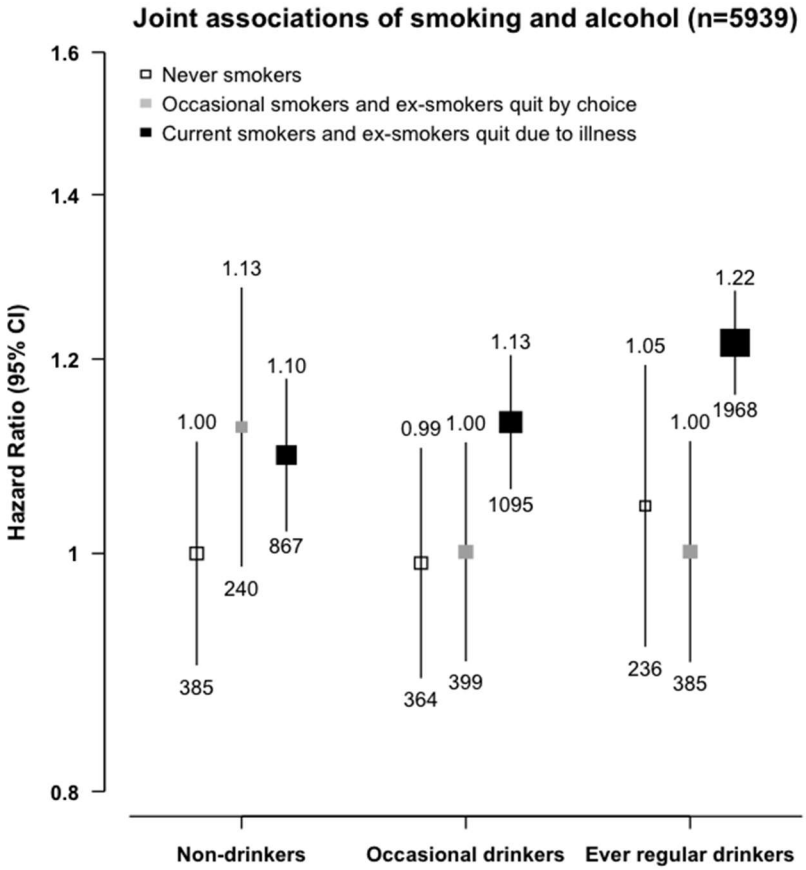
Table 5.3 Hazard ratios for cataract by alcohol consumption in men - results of sensitivity analysis.

	Ever vs never regular drinkers	
	Number of cases	**HR (95%CI)**
Primary analysis* (n=210,186)	5939	1.06 (1.01-1.12)
Exclude those aged ≥70 years at study entry (n=193,874)	4637	1.09 (1.02-1.16)
Exclude those with poor self-rated health (n=191,462)	5333	1.03 (0.98-1.10)
Exclude those with cancer or CVD at baseline (n=199,239)	5376	1.06 (1.00-1.13)
Exclude those with cancer, CVD, or diabetes at baseline (n=189,099)	4811	1.06 (1.00-1.13)
Exclude those with cancer, CVD, or diabetes at baseline, or incident diabetes during study follow-up (n=181,391)	4473	1.05 (0.98-1.12)
Exclude first 3 years of follow-up (n=210,186)	5939	1.06 (1.00-1.12)
Additional adjustment (primary analysis + household air pollution)	5939	1.06 (1.01-1.12)
Additional adjustment (primary analysis + SBP)	5939	1.07 (1.01-1.13)
Additional adjustment (primary analysis + waist circumference)	5939	1.06 (1.00-1.12)
Additional adjustment (primary analysis + waist-to-hip ratio)	5939	1.06 (1.00-1.12)
Additional adjustment (primary analysis + fat percentage)	5939	1.06 (1.00-1.12)
Additional adjustment (primary analysis + blood glucose)	5939	1.07 (1.01-1.13)

Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age (continuous), education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.

Cataract risk was highest among men who both smoke and drink alcohol, compared with other men (**Figure 5.10** & **Supplementary Table D.4**). "Current smokers (include ex-smokers stopped due to illness) and ever regular drinkers" had 22% (1.22, 1.16-1.28) higher risk of cataract than "never smokers and non-drinkers" (1.00, 0.90-1.11), though no statistically significant difference of HRs were found for the other seven groups defined jointly by smoking and alcohol drinking status. In addition, there was a trend towards higher risk of cataract with alcohol drinking among current smokers (including ex-smokers stopped due to illness), but not among never smokers nor occasional smokers (including ex-smokers stopped by choice).

Figure 5.10 Adjusted HRs for cataract for the joint associations of smoking and alcohol consumption in men.



N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

5.4 Discussion

5.4.1 Summary of findings

In this large prospective cohort study, smoking was associated with higher risk of cataract in men. Among male current smokers, those who had longer smoking duration, inhaled to the lung, or smoked mixed tobacco types had higher cataract risk than their counterparts. Male ex-smokers who stopped smoking by choice had a lower risk of cataract than those who stopped due to illness.

Alcohol consumption had a J-shaped association with cataract risk, with non-drinkers, occasional drinkers, and current drinkers consumed <140 g/week having a lower risk than other groups. Among male current drinkers, there was a significant positive dose-response relationship of alcohol consumption and risk of cataract. In addition, cataract risk was highest among men who both smoked and drank alcohol, compared with other men.

5.4.2 Smoking and risk of cataract

Most previous studies of the association between smoking and cataract risk were based on Western high-income countries, with consistent evidence from prospective studies suggesting smoking was associated with higher risk of cataract (**Supplementary Table B.4**). The relative risk of cataract from previous evidence ranged from 1.12 (1.09-1.14) to 2.84 (1.46-5.51) when comparing current smokers with never smokers[95,164]. Similar to previous studies, the analysis in CKB men also found current smokers had 13% (1.13, 1.05-1.22) higher risk of cataract than never smokers. The exact mechanisms linking smoking and cataract development are not fully

understood, but it has been speculated that the oxidative stress introduced through smoking might contribute to lens protein damage[173]. Smoking induces oxidative stress through generating free radicals and reducing plasma concentration of several antioxidants[174,175]. In this process, the activity of proteolytic enzymes and their function to remove damaged lens proteins is impaired[176]. Exposure to oxidative stress leads to accumulation of damaged lens proteins, which in the long-term results in blurred vision and cataract formation. Cigarette smoke contains toxic heavy metals (e.g., cadmium, lead, and copper), which may also affect the function of antioxidative lens enzymes[174,177].

Previous evidence on the association between length of smoking cessation and risk of cataract was less consistent, with some studies[65,66,67] suggesting an inverse association, while the Blue Mountain Study[68] found no clear association (**Supplementary Table B.4**). With comprehensive baseline information about reasons for quitting smoking and years since quitting, the current study results suggested ex-smokers who stopped smoking by choice had a consistently lower risk of cataract than those who quit due illness, but found no clear differences in cataract risk with different cessation length among those quitting by choice or due to illness. The Cohort of Swedish Men Study followed-up more than 44K men aged 45-79 years for 12 years found past smokers with years since quitting of <10, 10-20, and >20 years had HRs of 1.27 (1.15-1.41), 1.22 (1.12-1.32), and 1.13 (1.04-1.22) compared with never smokers, respectively[65]. This suggested that the lens might potentially have some capacity to recover once the oxidative stress from smoking has been removed. However, this study also acknowledged that the risk of cataract remained 13% (1.13, 1.04-1.22) after more than 20 years of quitting when compared with non-smokers, which

suggests that any recovery of the lens transparency will only be partial. Other previous studies with long follow-up periods (13.6 and 20 years) also found inverse associations between years of smoking cessation and cataract risk[66,67]. This is in contrast to the CKB and the Blue Mountain study[68] (with ~10 years follow-up), which did not find a clear lens recovery potential after smoking cessation related oxidative stress removal. It is worth mentioning that, in CKB and all the four previous studies mentioned above, length of smoking and smoking cessation were derived from age started/stopped smoking to age at study baseline, without including the follow-up period after baseline. This potential measurement error may lead to exposure misclassification, which could bias the association between length of smoking and smoking cessation with risk of cataract towards null[178].

5.4.3 Alcohol consumption and risk of cataract

Previous findings on association between alcohol consumption and cataract risk are largely inconsistent, with some suggesting a J-shaped[69,70] or inverted J-shaped association[72], while others supporting an inverse[59] or no association[166,167,168] (**Supplementary Table B.5**). The J-shaped association from the present study is similar to findings from the Nurses' Health Study[69] and the Blue Mountains Eye Study[70], but different from the significant inverse association observed in 1.3 million UK women (aged 50-64 years followed up for 11 years)[59]. In the UK Million Women Study, a higher level of alcohol consumption was associated with lower risk of cataract, with HRs of 0.93 (0.91-0.94) and 0.92 (0.89-0.96) for drinkers consuming 2-14 and ≥15 units of alcohol consumption per week compared with drinkers with <2 units of alcohol consumption per week[59]. In CKB women, a similar non-statistically significant inverse association was observed,

due to the very few numbers of current drinkers in the study. The inverse association observed in women in the UK Million Women Study and the present study might be due to a lower risk of moderate drinking and the absence of excessive alcohol consumption group in women. However, the Swedish Mammography Cohort Study, which followed up 34K women aged 49-83 for 7 years, found an inverted J-shaped association, and current drinkers consuming <6, 6-13, 14-20, 21-30, and >30 grams of alcohol per day had HRs of 1.11 (1.02-1.22), 1.14 (1.01-1.29), 1.24 (1.03-1.49), 1.29 (0.99-1.68), and 0.84 (0.53-1.33) compared with never drinkers[72]. Except for the relatively low (but not significant) HR for those in the highest level of drinking (i.e., HR = 0.84 for those with >30 grams of alcohol per day), the Swedish Mammography Cohort Study suggested a positive association between alcohol consumption and risk of cataract, with no evidence of a lower risk related to moderate drinking. The lowest drinking group (<6 g/day) in the Swedish Mammography Cohort Study had much higher drinking amount than the lowest group (<2 unit/week, which is equivalent to <2.3 g/day) in the UK Million Women Study, which might explain the differences in findings from these two studies.

Apparent lower risk of major chronic diseases (including stroke and myocardial infarction) due to moderate drinking have been observed in many prospective studies[179,180]. However, it is suspected that this may be largely due to reverse causality (e.g., early stages of cataract affects drinking behavior) or residual confounding[181]. Similarly, the J-shaped association, suggesting a moderate alcohol consumption is associated with lower incidence of cataract, observed in this study using conventional epidemiological methods might be due to reverse causality. A recent CKB study with genetic epidemiological methods found the lower risk of cataract due to

moderate drinking is unlikely to be causal[74].

Existing evidence on the joint effect of smoking and alcohol consumption on risk of cataract is limited. The Blue Mountains Eye Study found participants who smoked and drank heavily had an higher prevalence of nuclear cataract than those who had never drank or smoked[169]. Similarly, the current study suggested cataract risk associated with smoking was higher among alcohol drinkers. Alcohol drinking might further enhance the oxidative stress introduced through smoking, and therefore strengthen the association between smoking and cataract formation.

5.4.4 Strengths and limitations

The strengths of this study include the large sample size (over half million) with participants from 10 different regions in China, the detailed assessment of smoking and drinking patterns at baseline and resurveys, the assessment of diverse socio-economic, lifestyle, and cardiometabolic factors, and the long-term follow-up with a large number of cataract cases identified through linkage to electronic health records.

This study also has several limitations. Firstly, participants' prior history of cataract was not collected at baseline in CKB. Therefore, this study could not exclude prevalent cataract cases from the analyses. In addition, without information on prior cataract history, the CKB might have recruited participants who had cataract surgery (i.e., had lens removed and replaced by an artificial lens) prior to the baseline study. However, considering the much higher likelihood of prior cataract in older participants than in younger participants, and the consistent findings in

sensitivity analyses removing the first 3 years of follow-up (a reasonably long period to capture cases with delayed cataract diagnosis) or participants aged ≥70 years (those with higher likelihood of prior cataract than participants aged <70 years) at study entry, I believe the influence of lacking data on prior cataract history on current study findings should be minimal. Secondly, there was no nationwide cataract registry in China when the CKB study was conducted and the cataract incidence data in CKB were obtained from health insurance records used for hospitalization reimbursement purposes. Considering the large number of participants in CKB, it was not plausible to conduct regular ocular examinations for the whole cohort during study follow-up. The current analyses may therefore underestimate the true incidence of cataract due to an inability to capture early cataract cases (i.e., those not hospitalized would not be recorded in the CKB database). Thirdly, detailed information on subtypes of cataracts was not available in CKB, eliminating the possibility of performing separate analysis on subtypes (i.e., nuclear, cortical, and posterior subcapsular cataract). Fourthly, the selection of the 10 study regions in CKB was not designed to be representative of the general Chinese population, which may lead to selection bias. However, the association analyses findings of particular risk factors with disease outcomes from a prospective study of a non-representative cohort but including a sufficiently large number of individuals with heterogeneity in risk exposures like the CKB can still provide reliable and generalizable epidemiological evidence[182]. Even though non-representative sampling may lead to selection bias (due to impact on study participation from disease prognosis), its level of bias is expected to be small compared with other systematic errors (e.g., loss during follow-up) or random errors (e.g., lack of sufficient number of outcome events due to small sample size or short term of follow-up) which may occur[182]. Fifthly, even though the risk estimates for smoking

and alcohol consumption in the current study were corrected for regression dilution bias, I was unable to correct for measurement errors in covariates, which might lead to potential residual confounding. Lastly, like all other epidemiological studies, the current study could be biased due to residual confounding, and the causality of the observed associations could not be assessed using the conventional epidemiology methods presented.

5.5 Summary

In Chinese men, smoking has a positive association with risk of cataract while the relationship between alcohol drinking and cataract risk is J-shaped. In addition, among current users of tobacco, higher intake of alcohol might strengthen the potential impacts of tobacco on cataract development. The present findings from a large Chinese population lend additional evidence supporting the control of smoking and alcohol consumption for a better health.

6 Associations of physical activity and diet with risk of cataract

6.1 Introduction

Physical inactivity accounted for 7.2% of all-cause mortality and 8% of non-communicable disease burden globally in 2016[183]. Unhealthy diet was found to be attributable for 11 million deaths and 255 million disability-adjusted life-years (DALYs) globally in 2017, with leading dietary risk factors including high intake of sodium and low intake of whole grains and fruits[184]. Lack of physical activity and unhealthy diet are the major global risks for poor health, though their associations with cataract, the leading cause of global blindness and visual impairment, are poorly studied.

Limited prospective evidence generally supports an inverse linear association between physical activity and risk of cataract. For instance, 1 MET (metabolic equivalent of tasks)-hour/day of physical activity higher was associated with 5% lower risk of cataract among 47K U.S. adults (mean age 50 years, with 6 years of follow-up)[77] and 4 MET-hours/day higher physical activity was associated with 5% lower risk of cataract among 52K Swedish adults (aged 45-83 years, with 12 years of follow-up)[76]. However, no association was observed in the study followed-up 1600 U.S. women for 6 years, which also used MET-hour/day to measure physical activity[75]. To date, there is a lack of evidence from non-Western populations.

A wide range of dietary food groups (including vegetables, fruit, dairy, wholegrain, and legume) have been assessed for their associations with cataract in previous prospective studies. Vegetable consumption was found to be inversely associated with risk of cataract, and vegetarians had 20%[47] to 30%[82] lower risk of cataract when compared with non-vegetarians (in the Tzu Chi Health

Study, which followed-up 4400 Chinese aged ≥40 years for 6 years) or meat eaters (in the EPIC-Oxford Study, which followed-up 27 000 U.K. participants aged ≥40 years for 13 years), respectively. However, studies on fruit[83,84,85], dairy[89], wholegrain[47], and legume[47] consumption found no clear association with risk of cataract. All the aforementioned studies were conducted in Western populations, except for one study[47] on vegetarian diet (conducted in Taiwan) and another study[85] on fruit and vegetables consumption (conducted in Japan).

Asian populations account for the majority of the global cataract burden but there is a lack of prospective evidence on its associations with physical activity and dietary factors (which are the major modifiable lifestyle factors). Therefore, it is particularly important to conduct such studies to improve our understanding of these risk factors, as well as to provide epidemiological evidence to support cataract prevention strategies in Asia. The main objectives of the current chapter are: (1) Investigate the association between physical activity and risk of cataract; (2) Investigate the associations between 12 major dietary factors in China and risk of cataract.

6.2 Methods

The study design and data collection method of CKB study have been described in detail previously in chapter 3. In brief, the CKB is a prospective cohort study involving 512 726 adults aged 30-79 years from 10 regions in China, followed-up for 11 years. Information on a wide range of socio-economic, lifestyle, and cardiometabolic factors was collected at the baseline survey and subsequent resurveys.

6.2.1 Assessment of physical activity

Information on physical activity and sedentary leisure time was self-reported by participants at the baseline survey and subsequent resurveys. The questions were adapted from questionnaires used in several other studies on Western and Chinese populations (e.g., the EPIC Study[185] and the Shanghai Women's Health Study[186]) and modified for the CKB study[187,131]. Participants were asked to report their usual type, frequency, intensity, and duration for each of the four domains of physical activities during the past 12 months. This included information on occupational tasks (i.e., paid employment), commuting (i.e., the journeys between home and work, excluding transportation for other purposes), household chores, and leisure-time activities (i.e., sports, television watching, reading, playing cards or mahjong, and using a computer outside of work). Due to different types of occupational and commuting related activities between farmers and non-farmers, two sets of occupation- and commuting-related questions were designed in the questionnaire for farmers and non-farmers, respectively. Non-farmers were asked to report the intensity level of their occupational activity, hours spent on that activity per week, usual method of commuting between home and work place, and time spent on the journey each day. Farmers were asked about some key features of their farming work including the length of farming season, mechanical level of farming work, hours spent on farming each day, intensity and hours spent per week for jobs other than agriculture work, and time spent on commuting each day. All the study participants were also asked to report frequency of vigorous physical activity from any domain per day.

The 2011 version of METs for major compendium of physical activities (hereinafter referred as

Compendium) was used to quantify the total amount of physical activity in CKB[188]. The MET value represents the ratio of energy expended for a particular type of physical activity per kilogram of body weight per hour to the energy expended when sitting quietly. One MET stands for sitting quietly for 1 hour. An average MET score for the activities reported by study participants was derived according to the detailed activity type and MET values listed in the Compendium. Physical activity listed in the compendium but not widely performed in China (e.g., paddleball) was excluded from MET calculation. To avoid overrepresentation of physical activities with multiple entries, mean MET scores were weighted by the number of entries representing the same activity. The derived mean MET score for different types of activities were presented in **Supplementary Table E.1**[131] in **Appendix E**. Each of these mean MET scores was multiplied by the number of hours spent per day on that specific activity to derive the MET-hour/day for that activity. The total daily amount of physical activity (in MET-h/d) was calculated by summing the MET-hours of occupational, commuting, household chores, and leisure-time activities. Sedentary leisure time was not included in the physical activity calculation, and was quantified as hours per day. A similar physical activity questionnaire was used among subsets of study participants at resurveys in 2008 (the 1st resurvey, n=19 788) and 2013-2014 (the 2nd resurvey, n=25 176). The resurvey data were used to estimate the long-term "usual" level of total daily amount of physical activity in each baseline category.

6.2.2 Assessment of dietary factors

Dietary information was self-reported by participants at the baseline survey and subsequent resurveys, and covered 12 major food groups widely consumed by adults in China (including rice,

wheat products, other staple foods [corn, millet, etc.], red meat, poultry, fish/seafood, eggs, dairy products, fresh vegetables, preserved vegetables, fresh fruit, and soybean products). Participants were asked about their consumption frequency (five categories to choose from: daily, 4 to 6 days per week, 1 to 3 days per week, monthly, or never/rarely) during the past 12 months.

At the 2nd resurvey, in addition to consumption frequency, participants were also asked to report the daily consumption portion (measured as liang [equal to 50 gram], ml [for milk, juice, etc.], or number [for eggs]) of each food group. This information was used to estimate average consumption amount for each baseline category of the food group and to correct for regression dilution bias.

6.2.3 Statistical analyses

The analysis for physical activity excluded individuals with incident cataract before age 40 years (n=34), individuals with missing data on BMI (n=2), those who had both physical activity and sedentary leisure time equal to zero (n = 81), and those who reported spending more than 20 hours daily on all waking activities (including all physical activities and sitting activities) (n = 814), leaving 511 796 participants (include 209 726 men and 302 070 women) for the main analyses. Baseline characteristics of CKB participants by quintile of total physical activity and five groups of fresh fruit consumption frequency (as an example of the analyses for 12 food groups) were calculated, with direct standardisation to baseline age groups (in 5 year intervals), sex, and study region (ten regions) of the baseline CKB population[141]. Cross tabulation of consumption frequency (five groups) of the 11 food groups with fresh fruit consumption frequency (five groups)

was calculated to describe baseline consumption frequency of CKB participants. In addition, the "usual" daily amounts consumed of the 12 food groups were assessed by sex, region (2 groups: rural/urban; and 10 groups: the 10 study regions), education level (2 groups: below high school, above high school), and annual household income (2 groups: <20 000 yuan, ≥20 000 yuan).

Cox proportional hazards regression models were used to estimate adjusted HRs and 95% Cls of physical activity and consumption of the 12 food groups with incident cataract. For physical activity, the Cox model was stratified by age-at-risk (5-year groups), sex, and study region (10 areas), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), smoking status (four groups), alcohol consumption status (four groups), sedentary leisure time (continuous), fresh fruit consumption (5 categories), household air pollution (assessed as five groups of cooking fuel used: always clean fuel, changed from solid to clean fuel, always solid fuel, non-regular cook, and others), BMI (continuous), prevalent cardiovascular diseases (dichotomous, including CHD and stroke/TIA), prevalent diabetes (dichotomous), and self-rated health (four groups). To account for measurement errors and within person variability (i.e., regression dilution bias), the "usual" physical activity was estimated with the MacMahon-Peto method by taking the mean physical activity at resurveys 1 and 2 for each baseline physical activity category (**Supplementary Table E.2**, with method explained in detail in Chapter 3.2.3), and the log HRs were plotted against usual level of physical activity. Total physical activity was assessed as a categorical variable (the five quintiles) and as a continuous variable (per 10 MET-h/d, and adjusted by the regression dilution ratio). Considering that total physical activity was a composite of different types of activities in

men and women (i.e., more household activities in women and more heavy occupational activities in men), and between rural and urban participants (i.e., more sedentary types of occupational activity in urban participants while more farming activities in rural participants), the analyses on total physical activity were performed overall, and separately by sex and study region. In addition to total physical activity amount, frequency of vigorous physical activity and sedentary leisure time were also assessed for their associations with cataract risk.

The analysis for diet excluded individuals with incident cataract before age 40 years (n=34) and individuals with missing data on BMI (n=2), leaving 512 690 participants (210 186 men and 302 504 women) for the main analyses. Among the 12 food groups, 11 of them (except for fresh vegetables) were analysed with daily portion from the 2nd resurvey as a proxy measure to estimate the average daily consumption amount for each of the five consumption frequency category at baseline[125]. The calculation included three steps: (1) The mean daily portions for the five consumption frequency groups were computed using data collected from the 2nd resurvey, which was then multiplied with mean number of days per month of consumption to calculate the mean portions per month; (2) Assuming the daily portion of consumption didn't vary from baseline to the 2nd resurvey (i.e., participants may change their consumption frequency, but daily consumption amount remains roughly similar), the daily portion multiplied by baseline consumption frequency could be used as a proxy of "*baseline consumption amount"* of that food group; (3) Consumption frequency from the 1st resurvey was used to assess food consumption variation from the baseline. The average "*usual consumption amount*" for the five baseline consumption frequency groups was calculated as the summation of the products of multiplying

the "*baseline consumption amount"* for each group with percentage of participants in each of the consumption frequency group at the 1st resurvey. This "*usual consumption amount*" was assigned to each individual participant to generate number of daily portions of consumption (1 daily portion = 100 gram/day). The "*usual consumption amount*" was also used to calculate the regression dilution ratio, to account for regression dilution bias. The average "*usual consumption amount*" was used to plot against the HRs computed via Cox regression analyses with baseline consumption as a categorical variable. As an example, the calculation of usual fresh fruit consumption was presented in **Table 6.1**. Given most participants (94.8%) consumed fresh vegetables daily, cataract risk assessment was compared between daily and less than daily eaters.

For the 12 food groups, Cox models were stratified by age-at-risk (5-year groups), sex, and study region (10 regions), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), smoking status (four groups), alcohol consumption status (four groups), physical activity (continuous), BMI (continuous), prevalent cardiovascular diseases (dichotomous, including CHD and stroke/TIA), prevalent diabetes (dichotomous), self-rated health (four groups), and where appropriate, fresh fruit, meat, or fish/seafood consumption. The proportional hazards assumption was assessed using scaled Schoenfeld residuals method[172] and no violation was found. A Bonferroni correction was conducted to address multiple testing of the 12 food groups, with the threshold for significance in each individual test set as 0.004 (i.e., 0.05/12)[189]. Considering the differences (both levels and types) in fresh fruit consumption between men and women[190], and between rural and urban participants in China[191], separate analyses were also performed by sex and study region. This

Table 6.1 Calculation of usual fresh fruit consumption (based on 19,785 participants who attended the 1st resurvey).

Baseline	1st resurvey (mean 2.6 years later)					Consumption frequency (days/month)	Mean daily portion*	Baseline consumption (portions/month)	Usual consumption (portions/month)†
	Never/rarely	Monthly	1-3 days/week	4-6 days/week	Daily				
Never/rarely	17.86% (244)	55.71% (761)	18.01% (246)	4.25% (58)	4.17% (57)	0	-	B_1=0	U_1=7.85
Monthly	7.36% (495)	52.09% (3504)	29.02% (1952)	6.84% (460)	4.70% (316)	2.5	1.45	B_2=3.6 (2.5*1.45)	U_2=10.25
1-3 days/week	4.00% (250)	31.70% (1981)	37.43% (2339)	11.67% (729)	15.20% (950)	8.6	1.48	B_3=12.7 (8.6*1.48)	U_3=17.58
4-6 days/week	1.59% (29)	20.12% (368)	35.05% (641)	15.04% (275)	28.21% (516)	21.5	1.55	B_4=33.3 (21.5*1.55)	U_4=24.66
Daily	1.25% (45)	6.81% (246)	18.32% (662)	13.17% (476)	60.46% (2185)	30.0	1.71	B_5=51.3 (30.0*1.71)	U_5=37.97
Difference between the 5th vs 1st group								51.3	30.13
MacMahon-Peto regression dilution ratio									0.59

*The mean daily portion number came from the 2nd resurvey data, used as a proxy of baseline mean daily portion.

†Usual intake amount for each group was estimated by taking into account changes in consumption frequency between baseline and 1st resurvey using this formula Un = $\sum_{i=1}^{3}(\mathrm{Fni} \times \mathrm{Bi})$; F is the percentage in each cell, B is the baseline proportion per month for each baseline category, U is the usual proportion per month for each baseline category. This method for correcting for regression dilution bias is equivalent to the MacMahon-Peto method, described in detail by Frost C and Thompson SG. In "*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]. For example, U_2= 7.36%*0+52.09%*3.6+29.02%*12.7+6.84%*33.3+4.70%*51.3= 10.25.

subgroup analysis could help to assess whether the observed association between fresh fruit and cataract risk is influenced by residual confounding of socio-economic status and smoking/alcohol habits, as such factors differ greatly between rural and urban regions (i.e., socio-economic status) and between men and women (i.e., smoking and alcohol consumption). To explore the potential effect modification by population characteristics, subgroup analyses for physical activity and diet food groups were conducted by age-at-risk, sex, region, occupation (for the analysis of physical activity only), smoking, alcohol consumption, fresh fruit consumption or physical activity where appropriate, household air pollution, BMI, and prevalent diabetes.

Several sensitivity analyses were conducted to assess the robustness of the results, including: 1) additionally adjusting for potential confounding factors including sleep duration (for the analysis of physical activity only), household air pollution, life satisfaction level, SBP, waist circumference, waist-to-hip ratio, body fat percentage, and baseline blood glucose separately; 2) excluding the first 3 years of follow-up; 3) excluding participants aged ≥70 years at baseline; 4) excluding participants with poor self-rated health, prevalent cancer, cardiovascular diseases, or diabetes. All these three approaches were applied to assess the potential impact of reverse causation. 5) excluding participants with incident diabetes during follow-up because those cataract events might be diabetic cataract instead of age-related cataract. All statistical analyses were performed in R (version 4.0.3).

6.3 Results

6.3.1 Baseline characteristics of participants by physical activity

Of the 511 796 participants included in the analyses, mean baseline age was 52.5 (SD 10.1) years, 59.0% were women, and 55.9% resided in rural regions (**Table 6.2**). Participants with higher levels of physical activity were more likely to be younger (highest vs lowest quintile: 46.9 vs 58.9 years) and live in rural regions (69.6 vs 47.9%) than those with lower levels of physical activity. Women with higher levels of physical activity were more likely to drink alcohol regularly (highest vs lowest quintile: 2.7% vs 1.9% as current drinkers). Participants with higher levels of physical activity had lower mean values of sedentary leisure time (highest vs lowest quintile: 2.5 vs 3.6 hours/day), systolic/diastolic blood pressure (128.8/76.4 vs 131.5/78.4 mmHg), BMI (23.2 vs 23.9 kg/m^2), waist circumference (78.5 vs 81.2 cm), and random blood glucose (5.9 vs 6.2 mmol/L) than their counterparts. Their prevalence rates of prior diseases (including diabetes [1.7% vs 4.6%], CHD [1.7% vs 3.7%], stroke or TIA [1.0% vs 3.1%], cancer [0.3% vs 1.0%], and hypertension [8.6% vs 14.0%]) were lower, and they reported poor self-rated health less frequently (7.8% vs 16.2%).

6.3.2 Baseline characteristics of participants by dietary factors

Participants reported consuming fresh fruit more frequently at the 2nd resurvey than at the baseline survey, with fewer monthly eaters (13.2% at the 2nd resurvey vs 34.0% at the baseline survey) and more daily eaters (34.4% vs 18.8%) (**Supplementary Table E.3**). Women reported consuming fresh fruit more frequently than men at both the baseline survey (21.8% daily eaters in women vs 14.5% in men) and the 2nd resurvey (37.8% vs 28.9% daily eaters). Participants with older age were more likely to report as never/rare fruit eaters (10.2% in the 70-79 age group vs

Table 6.2 Baseline characteristics of CKB participants by level of baseline total physical activity

Characteristic	Physical activity (MET-h/d)					Overall
	Quintile 1 (<8.7)	Quintile 2 (8.7 to <14.2)	Quintile 3 (14.2 to <21.8)	Quintile 4 (21.8 to <33.2)	Quintile 5 (≥33.2)	
No. of participants	101,836	102,828	102,887	102,183	102,062	511,796
Mean physical activity (SD), MET-h/d	5.8 (3.5)	11.7 (2.0)	17.7 (2.3)	26.9 (5.1)	41.5 (17.5)	21.0 (13.8)
Socio-demographic factors						
Mean age (SD), years	58.9 (11.8)	55.6 (12.0)	51.3 (9.9)	48.8 (8.4)	46.9 (7.9)	52.5 (10.1)
Women, %	59.6	67.0	60.8	55.1	44.5	59.0
Rural, %	47.9	53.1	53.5	65.5	69.6	55.9
Education below high school, %	50.2	48.2	48.0	50.4	51.8	50.8
Household income <20K, yuan/year, %	63.2	55.6	53.7	56.0	58.5	57.2
Lifestyle factors						
Current smokers*, % of men	69.4	67.8	65.6	66.8	67.4	67.6
Current smokers*, % of women	3.6	2.8	2.6	2.6	2.8	2.8
Current drinkers, % of men	30.2	34.6	34.1	34.5	34.0	33.3
Current drinkers, % of women	1.9	2.0	2.2	2.5	2.7	2.1
Daily intake of dietary factors, %						
Red meat	30.6	31.0	29.8	28.6	28.0	29.3
Fish/seafood	2.7	3.1	3.1	2.8	2.5	2.8
Fresh vegetables	95.1	96.2	95.4	93.0	94.2	94.8
Fresh fruit	18.5	21.1	21.4	19.1	17.2	18.8
Sedentary leisure time, h/d, mean (SD)	3.6 (2.7)	3.3 (1.9)	3.0 (1.5)	2.7 (2.0)	2.5 (3.1)	3.0 (1.5)
Cardiometabolic factors, mean (SD)						
SBP, mmHg	131.5 (29.1)	131.1 (24.6)	130.7 (22.0)	130.4 (33.0)	128.8 (53.8)	131.1 (21.3)
DBP, mmHg	78.4 (17.6)	78.0 (14.2)	77.7 (12.1)	77.4 (17.1)	76.4 (28.1)	77.8 (11.2)
BMI, kg/m^2	23.9 (5.3)	23.9 (4.2)	23.7 (3.5)	23.5 (5.4)	23.2 (8.2)	23.7 (3.4)
Waist circumference, cm	81.2 (14.4)	81.0 (11.9)	80.3 (10.1)	79.6 (15.2)	78.5 (25.6)	80.3 (9.8)
Waist-to-hip ratio	0.89 (0.10)	0.89 (0.09)	0.88 (0.07)	0.88 (0.11)	0.87 (0.18)	0.88 (0.07)
Random blood glucose, mmol/L	6.2 (4.3)	6.1 (2.8)	6.0 (2.5)	6.0 (4.3)	5.9 (5.9)	6.1 (2.3)
Prior disease history, %						
Diabetes	4.6	3.6	2.9	2.2	1.7	3.2
CHD	3.7	3.3	2.8	2.4	1.7	3.0
Stroke or TIA	3.1	1.6	1.2	1.1	1.0	1.7
Cancer	1.0	0.6	0.4	0.3	0.3	0.5
Hypertension	14.0	13.0	11.1	10.0	8.6	11.6
Poor self-rated health, %	16.2	10.8	8.9	8.6	7.8	10.3

SD standard deviation, MET metabolic equivalent of task hours per day, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex and region, as appropriate.
*Current smokers included current smokers and ex-smokers stopped due to illness.

4.4% in the 30-39 age group), and this pattern was consistent in men and women separately (**Supplementary Table E.4**). The proportion of daily fruit eaters had a U-shaped pattern with age, with participants aged 50-59 years (17.5%) having a lower proportion than other age groups (ranged 18.5%-20.2%). Urban residents reported consuming fresh fruit more frequently than rural residents, with the proportion of daily eaters more than five times higher in urban (35.8%) than in rural (5.5%) regions (**Supplementary Table E.5**). Regional variation of fresh fruit consumption was observed among the five urban and five rural regions, with the proportion of daily eaters ranging between 9.3%-54.2% and 2.6%-11.5% in urban and rural regions, respectively.

Participants who consumed fresh fruit more frequently were more likely to be younger (highest vs lowest consumption group: 50.7 vs 55.8 years), be women (64.9% vs 46.4%), have higher level of education (61.6% vs 40.4% above high school) and household income (53.1% vs 31.3% with annual income >20K yuan), and were less likely to smoke regularly (61.3% vs 77.6% in men, and 2.4% vs 4.7% in women) (**Table 6.3**). Their mean values of systolic/diastolic blood pressure (top vs lowest consumption group: 130.0/77.6 vs 133.0/78.4 mmHg) and random blood glucose (6.0 vs 6.6 mmol/L) were lower, though they had higher mean values of BMI (24.1 vs 23.4 kg/m^2) and waist circumference (81.3 vs 79.9 cm), and had higher prevalence of cancer (0.7% vs 0.4%). As for the consumption frequency of the rest 11 food groups, more than half of the participants at least weekly consumed rice (87.4%), wheat (70.6%), red meat (82.7%), eggs (71.1%), fresh vegetables (99.7%), preserved vegetables (50.7%), and soybean products (60.1%), while less than half of the participants consumed other staple food (26.8%), poultry (28.1%), fish/seafood (46.7%), and dairy products (20.5%) on a weekly basis (**Supplementary Table E.6**).

Table 6.3 Baseline characteristics of CKB participants by baseline fresh fruit consumption status

Characteristic	Fresh fruit consumption frequency					Overall
	Never/rarely	Monthly	1-3 days/week	4-6 days/week	Daily	
No. of participants	32,762	174,107	161,277	47,957	96,587	512,690
Socio-demographic factors						
Mean age (SD), years	55.8 (12.6)	53.5 (13.6)	51.9 (10.2)	50.9 (11.4)	50.7 (16.1)	52.0 (10.7)
Women, %	46.4	53.0	56.2	61.1	64.9	59.0
Rural, %	68.3	77.6	56.8	45.3	16.4	55.9
Education below high school, %	59.6	56.7	50.5	44.9	38.4	50.8
Household income <20K yuan/year, %	68.7	64.0	58.7	51.5	46.9	57.3
Lifestyle factors						
Current smokers*, % of men	77.6	72.7	66.4	62.1	61.3	67.7
Current smokers*, % of women	4.7	4.1	3.0	2.6	2.4	2.8
Current drinkers, % of men	43.1	36.5	32.8	30.3	31.7	33.3
Current drinkers, % of women	2.4	2.1	2.0	2.0	2.7	2.1
Physical activity, MET-hours/day, mean (SD)	20.5 (21.7)	21.4 (15.6)	21.2 (12.2)	20.7 (15.0)	19.6 (21.4)	21.1 (13.9)
Daily intake of dietary factors, %						
Red meat	27.9	25.3	27.9	30.1	45.1	29.3
Fish/seafood	2.3	2.9	2.1	2.3	5.0	2.8
Fresh vegetables	93.4	92.2	95.9	97.2	98.7	94.8
Cardiometabolic factors, mean (SD)						
SBP, mmHg	133.0 (28.9)	131.7 (27.3)	131.2 (20.6)	130.7 (24.7)	130.0 (35.9)	131.1 (21.3)
DBP, mmHg	78.4 (16.9)	77.9 (15.5)	77.8 (11.4)	77.7 (13.8)	77.6 (20.3)	77.8 (11.2)
BMI, kg/m^2	23.4 (4.9)	23.5 (4.7)	23.7 (3.4)	23.9 (4.4)	24.1 (5.8)	23.7 (3.4)
Waist circumference, cm	79.9 (15.6)	80.0 (12.9)	80.4 (9.6)	80.8 (12.4)	81.3 (16.7)	80.3 (9.8)
Waist-to-hip ratio	0.89 (0.12)	0.88 (0.09)	0.88 (0.07)	0.88 (0.09)	0.88 (0.12)	0.88 (0.07)
Random blood glucose, mmol/L	6.6 (5.0)	6.2 (3.7)	6.0 (2.4)	6.0 (2.9)	6.0 (4.1)	6.1 (2.3)
Prior disease history, %						
Diabetes	11.1	4.2	2.9	2.4	2.9	3.3
CHD	3.4	3.0	2.9	3.3	3.6	3.0
Stroke or TIA	2.0	2.0	1.7	1.5	1.9	1.7
Cancer	0.4	0.5	0.5	0.5	0.7	0.5
Hypertension	12.8	10.9	11.8	12.7	14.4	11.6
Poor self-rated health, %	19.1	12.0	9.3	9.0	9.1	10.4

SD standard deviation, MET metabolic equivalent of task hours per day, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex and region, as appropriate.
*Current smokers included current smokers and ex-smokers stopped due to illness.

Cross tabulation of baseline consumption frequency of the 11 food groups in CKB with baseline fresh fruit consumption status found varying patterns. The majority (69.7%) of participants consumed rice every day, among whom 65.4% consumed fresh fruit at least weekly. As for wheat, only 40.0% of participants were daily eaters, and 54.2% of them consumed fresh fruit every week. More than a quarter (29.3%) of participants were daily red meat eaters, and 78.2% of them consumed fresh fruits at least weekly. Most (94.8%) participants consumed fresh vegetables every day, and 60.9% of them were weekly fresh fruit eaters.

Compared with men, women reported consuming lower amounts of wheat products (103.4 vs 109.5 g) and red meat (40.8 vs 44.3 g) per day, but greater amounts of fresh fruit (64.9 vs 58.6 g) (**Table 6.4**). Participants from urban regions reported consuming fewer staple foods other than rice (103.6 vs 107.0 g for wheat products, 20.6 vs 43.5 g for staple foods e.g., corn, millets), but consumed more animal-sourced foods (50.6 vs 35.7 g for red meat, 18.9 vs 11.7 g for poultry, 30.0 vs 13.7 g for fish/seafood, 34.4 vs 18.4 g for dairy products) and plant-sourced foods (78.9 vs 49.3 g for fresh fruit, 15.0 vs 13.4 g for soybean products) on a daily basis, compared with rural participants. Regional variations in the daily amounts consumed for the 12 food groups were also observed among the 10 CKB regions (**Supplementary Table E.7**). The mean consumption of staple foods, animal-sourced foods, and plant-sourced foods (except for preserved vegetables) was higher in participants with higher education levels and household income than their counterparts (**Table 6.4**).

Table 6.4 Average daily consumption of food groups by sex, region, education, and household income in CKB participants.

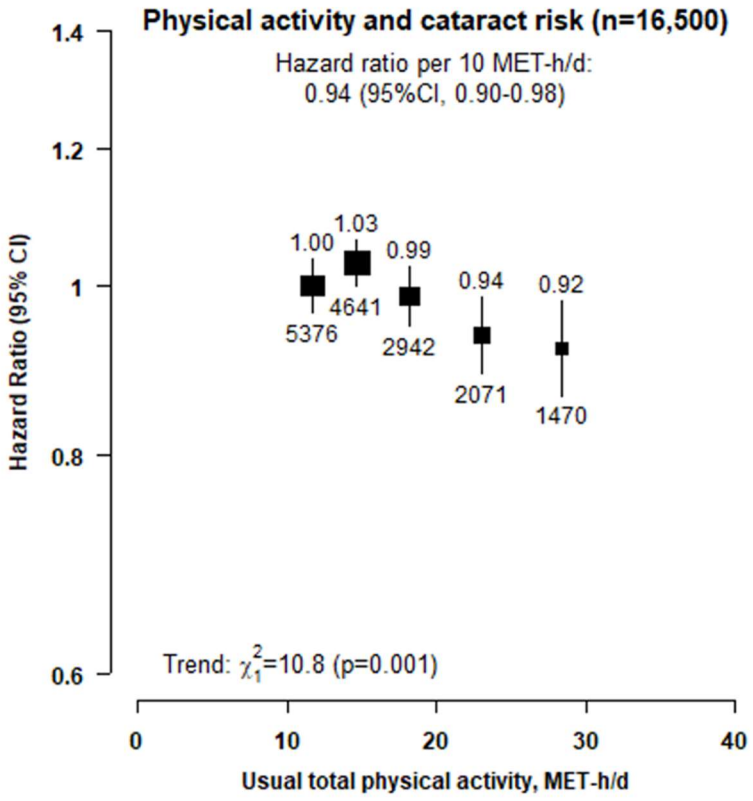
Characteristics	Sex		Region		Education		Annual household income		Overall
	Men	Women	Rural	Urban	Below high school	Above high school	<20,000 yuan	≥20,000 yuan	
No. of participants	210,186	302,504	286,500	226,190	260,353	252,337	293,676	219,014	512,690
Staple foods, g/day									
Rice	195.5	197.1	174.9	224.4	194.3	197.7	195.0	199.0	196.4
Wheat products	109.5	103.4	107.0	103.6	103.2	111.3	103.5	110.0	105.9
Other staple foods (corn, millet, etc.)	32.8	33.9	43.5	20.6	32.9	34.2	33.0	34.1	33.5
Animal-sourced foods, g/day									
Red meat	44.3	40.8	35.7	50.6	40.9	43.6	40.7	45.5	42.2
Poultry	15.7	14.3	11.7	18.9	13.8	15.7	13.9	16.7	14.8
Fish/seafood	21.7	20.3	13.7	30.0	19.7	22.1	19.8	23.0	20.9
Eggs	24.3	23.8	23.1	25.2	23.3	24.9	23.6	25.2	24.1
Dairy products	24.8	25.9	18.4	34.4	21.6	29.2	23.2	29.8	25.5
Plant-sourced foods, g/day									
Fresh vegetables	231.2	231.2	231.0	231.5	231.1	231.3	231.1	231.6	231.2
Preserved vegetables	7.0	7.0	6.6	7.4	7.1	6.9	7.0	6.9	7.0
Fresh fruit	58.6	64.9	49.3	78.9	56.9	68.8	58.7	69.7	62.4
Soybean products	14.4	14.0	13.4	15.0	13.7	14.7	13.9	14.9	14.1

The results were standardised by age at baseline (5-year age group), sex, and region, as appropriate.

6.3.3 Physical activity and risk of cataract

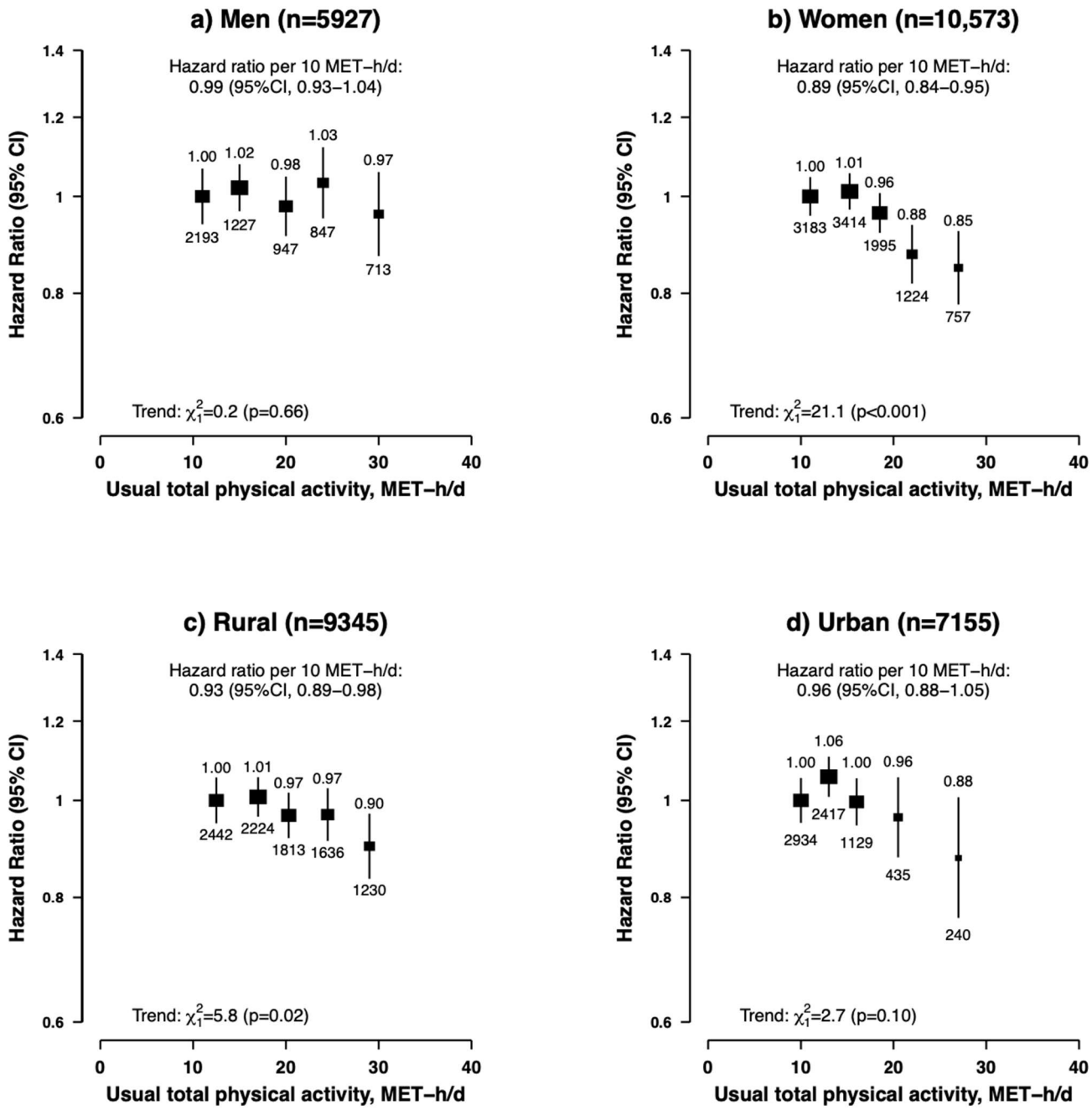
There was an overall clear inverse linear association (P_{trend}=0.001) between the level of total physical activity and risk of cataract, with HR of 0.94 (0.90-0.98) per 10 MET-h/d of usual total physical activity (**Figure 6.1** & **Supplementary Table E.8**). Compared with those in the lowest physical activity quintile (1.00, 0.97-1.04), the HR for cataract incidence was 1.03 (95%CI: 1.00-1.06), 0.99 (0.95-1.03), 0.94 (0.89-0.99), and 0.92 (0.87-0.98) respectively in the 2nd to 5th quintile. When men and women were analysed separately ($P_{heterogeneity}$=0.02), a clear inverse association was observed in women (HR per 10 MET-h/d: 0.89 [0.84-0.95]), not in men (0.99 [0.93-1.04]) (**Figure 6.2** & **Supplementary Table E.8**).

Figure 6.1 Adjusted HRs for cataract by quintiles of total physical activity.



N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including coronary heart disease, stroke, and transient ischemic attack), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend was related to all five groups.

Figure 6.2 Adjusted HRs for cataract by quintiles of total physical activity, by sex and by region.

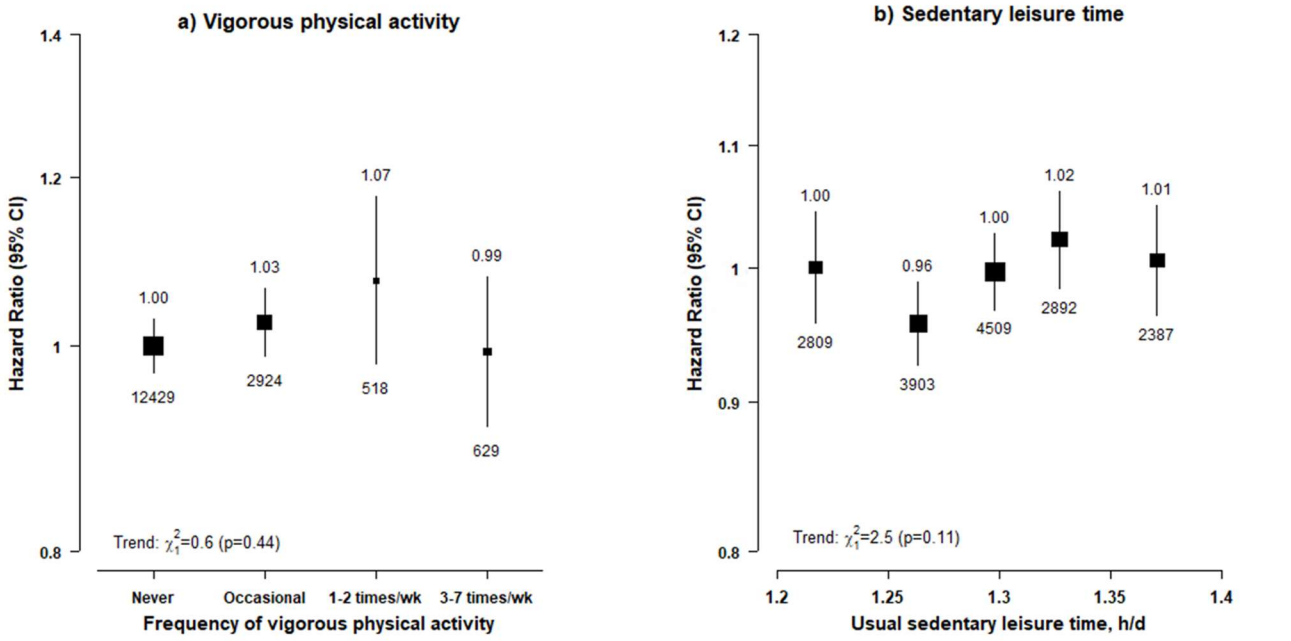


N stands for number of cases.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status, as appropriate.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend was related to all five groups.

In women, those in the 4th and 5th physical activity quintile had 12% (0.88, 0.82-0.93) and 15% (0.85, 0.78-0.92) lower risk of cataract than those in the lowest quintile (1.00 [0.96-1.04], P_{trend}<0.001) (**Figure 6.2b** & **Supplementary Table E.8**). The association was not significantly different ($P_{heterogeneity}$=0.52) between rural and urban residents, with HRs per 10 MET-h/d being 0.93 (0.89-0.98) and 0.96 (0.88-1.05), respectively, and HRs in top vs bottom quintiles being 0.90 (0.84-0.97) and 0.88 (0.77-1.00), respectively (**Figure 6.2** & **Supplementary Table E.8**).

No clear differences in cataract risk were observed among participants with different level of vigorous physical activity or sedentary leisure time either overall (**Figure 6.3** & **Supplementary Table E.8**), or in men and women separately (**Supplementary Figure E.1**).

Figure 6.3 Adjusted HRs for cataract by vigorous physical activity and sedentary leisure time (number of cases=16,500).

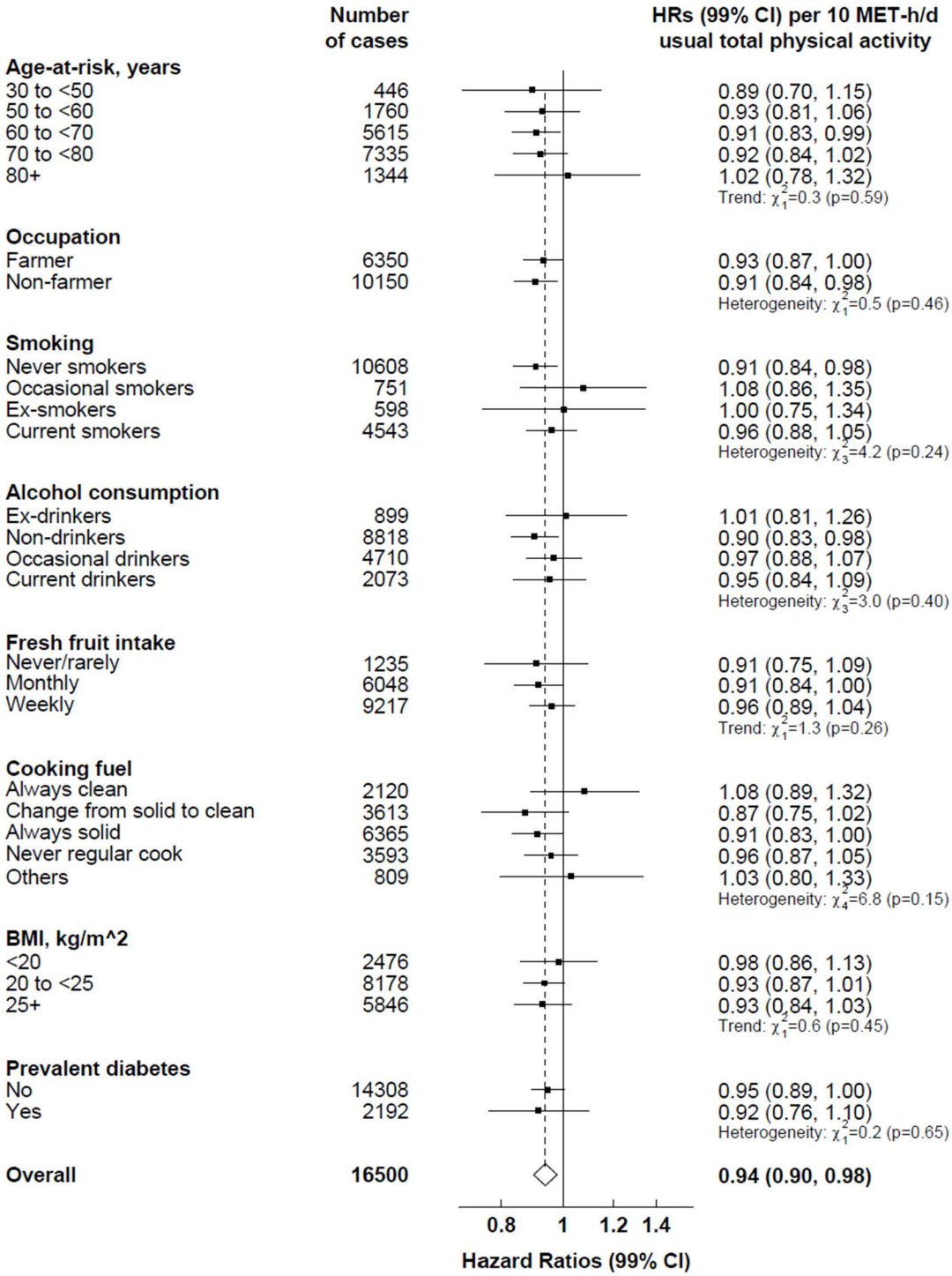


Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, total physical activity (for the analysis of sedentary leisure time), fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

The inverse association between total physical activity and cataract risk was similar across subgroups defined by age, occupation (farmer or non-farmer), smoking, alcohol consumption, fresh fruit consumption, household air pollution, BMI, and prevalent diabetes status (**Figure 6.4** & **Figure 6.5**). Additional analysis of HRs per 10 MET-h/d higher usual total physical activity conducted in men and women separately found consistent results across selected subgroups (**Supplementary Figure E.2** & **Supplementary Figure E.3**).

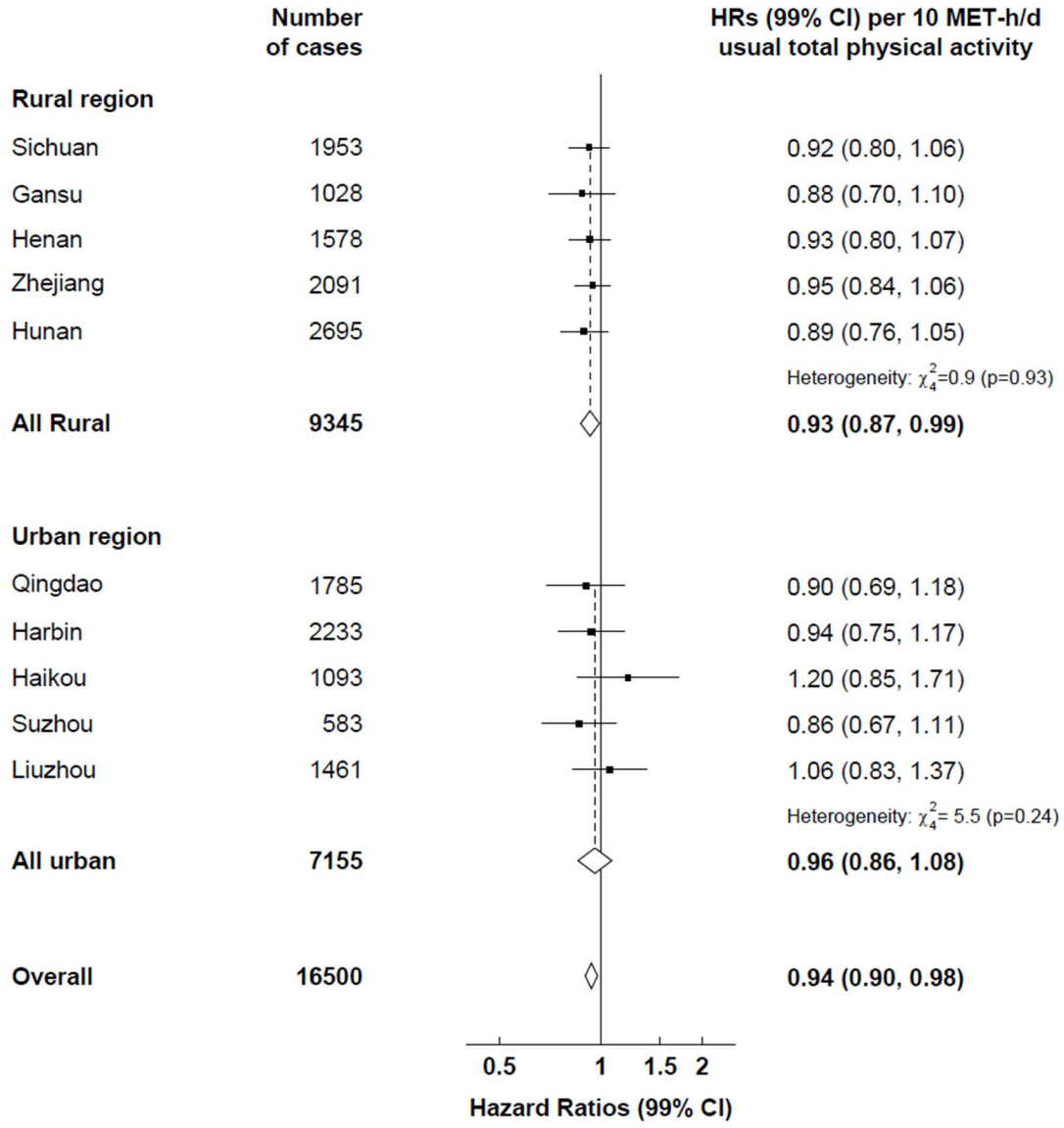
The overall associations remained essentially unchanged in sensitivity analyses with additional adjustments, excluding the first 3 years of follow-up, or excluding participants aged 70 years and older, with poor self-rated health, prevalent diseases, and incident diabetes during follow-up (**Table 6.5**).

Figure 6.4 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by selected population characteristics.



Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution (i.e., cooking fuel), BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status, as appropriate.

Figure 6.5 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by region.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and sex, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.

Table 6.5 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract - results of sensitivity analysis.

	Per 10 MET-h/d higher total usual physical activity	
	Number of cases	**HRs (95%CI)**
Primary analysis* (n=511,796)	16,500	0.94 (0.90-0.98)
Exclude first 3 years of follow-up (n=511,796)	16,500	0.94 (0.91-0.98)
Exclude those aged ≥70 years at study entry (n=478,908)	13,317	0.93 (0.89-0.97)
Exclude those with poor self-rated health (n=458,861)	14,332	0.93 (0.88-0.97)
Exclude those with cancer or CVD at baseline (n=486,345)	14,888	0.93 (0.89-0.97)
Exclude those with cancer, CVD, or diabetes at baseline (n=460,209)	13,063	0.94 (0.90-0.98)
Exclude those with cancer, CVD, or diabetes at baseline, and incident diabetes during study follow-up (n=440,319)	12,000	0.94 (0.89-0.98)
Additional adjustment (primary analysis + sleep duration)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + life satisfaction)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + systolic blood pressure)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + waist circumference)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + waist-to-hip ratio)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + fat percentage)	16,500	0.94 (0.90-0.98)
Additional adjustment (primary analysis + blood glucose)	16,500	0.94 (0.90-0.98)

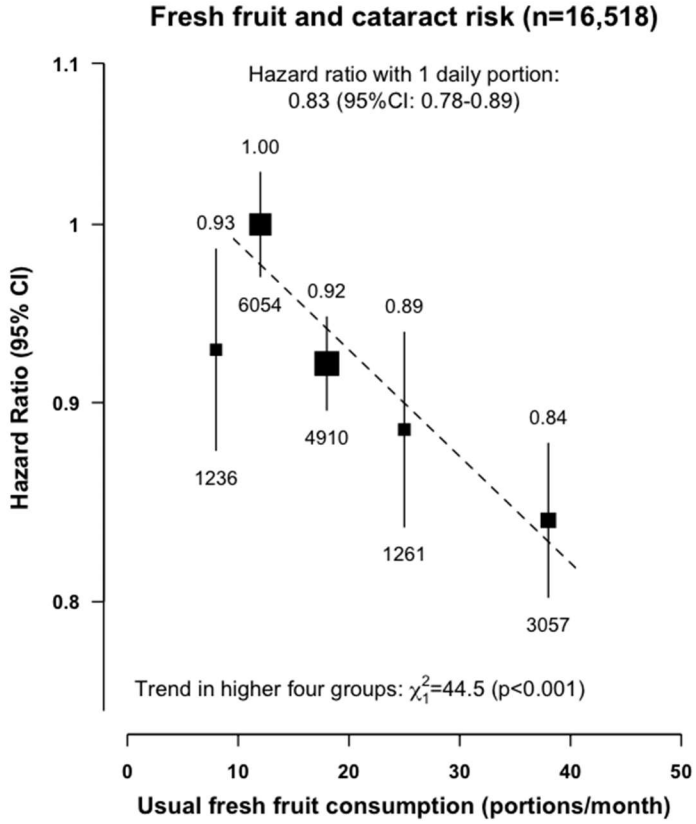
MET metabolic equivalent of task hours per day, CVD cardiovascular disease (including coronary heart disease, stroke, and transient ischemic attack).
*Hazard Ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.

6.3.4 Diet and risk of cataract

6.3.4.1 Fresh fruit and risk of cataract

There was a largely linear inverse association between fresh fruit consumption and cataract risk. As shown in **Figure 6.6** & **Supplementary Table E.9**, the risk of cataract tended to be lower with the increase of fruit consumption from the monthly to daily consumption group. Compared with those who reported monthly consuming fresh fruit at baseline (HR=1.00, 0.97-1.03), participants with consumption frequency of 1 to 3 days per week, 4 to 6 days per week, and daily had HRs of 0.92 (0.90-0.95), 0.89 (0.84-0.94), and 0.84 (0.80-0.88), respectively (**Figure 6.6** & **Supplementary Table E.9**). However, for those never/rarely consuming fruit, their risk for cataract was 7% (0.93, 0.88-0.98) lower than monthly consumers, instead of higher.

Figure 6.6 Adjusted HRs for cataract by fresh fruit consumption.

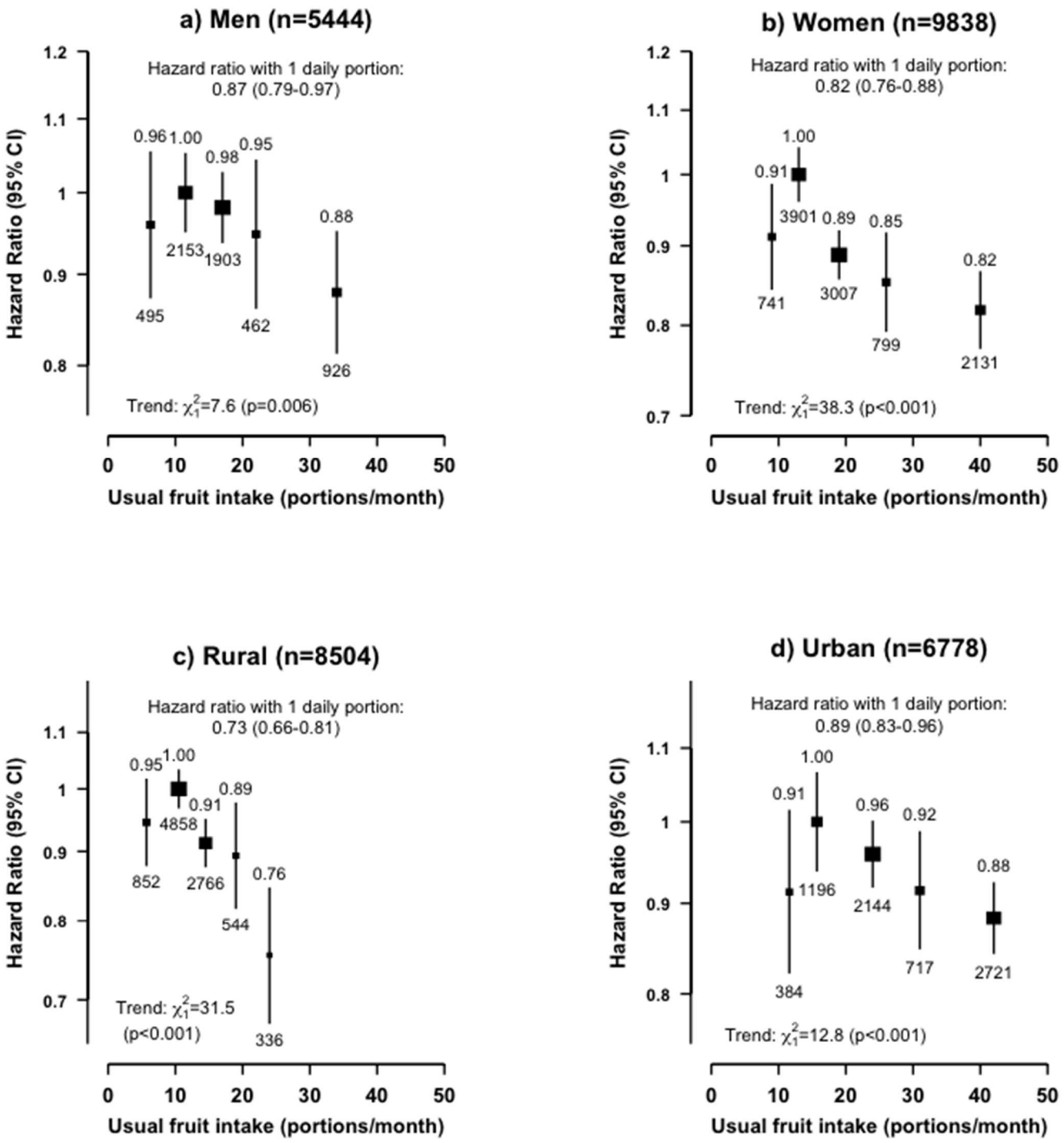


N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including coronary heart disease, stroke, and transient ischemic attack), prevalent diabetes, self-rated health status, and consumption of meat and fish/seafood.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
The dotted line presents best fitting line for the >10 portions/month consumption groups.
Hazard ratio per one daily portion was calculated among the >10 portions/month consumption groups.

There is an inverse linear association (P_{trend}<0.001) between fresh fruit consumption and risk of cataract among the >10 portions/month consumption groups, with a HR per 1 daily portion (i.e., 100 g/day) of fresh fruit consumption of 0.83 (0.78-0.89). Inverse associations were also observed in men and women, and in rural and urban residents separately (**Figure 6.7** & **Supplementary Table E.9**). The associations were not significantly different ($P_{heterogeneity}$=0.31) between men and women, with HRs per 1 daily portion of fresh fruit consumption among the >10 portions/month consumption groups being respectively 0.87 (0.79-0.97) and 0.82 (0.76-0.88), and daily vs monthly fresh fruit consumption groups being 0.88 (0.82-0.95) and 0.82 (0.78-0.87), respectively (**Figure 6.7a**, **Figure 6.7b** & **Supplementary Table E.9**). However, the inverse associations were stronger ($P_{heterogeneity}$=0.002) in rural than in urban residents, with HRs per 1 daily portion of fresh fruit consumption among the >10 portions/month consumption groups being respectively 0.73 (0.66-0.81) and 0.89 (0.83-0.96), and daily vs monthly fresh fruit consumption groups being 0.76 (0.68-0.84) and 0.88 (0.84-0.92), respectively (**Figure 6.7c**, **Figure 6.7d** & **Supplementary Table E.9**).

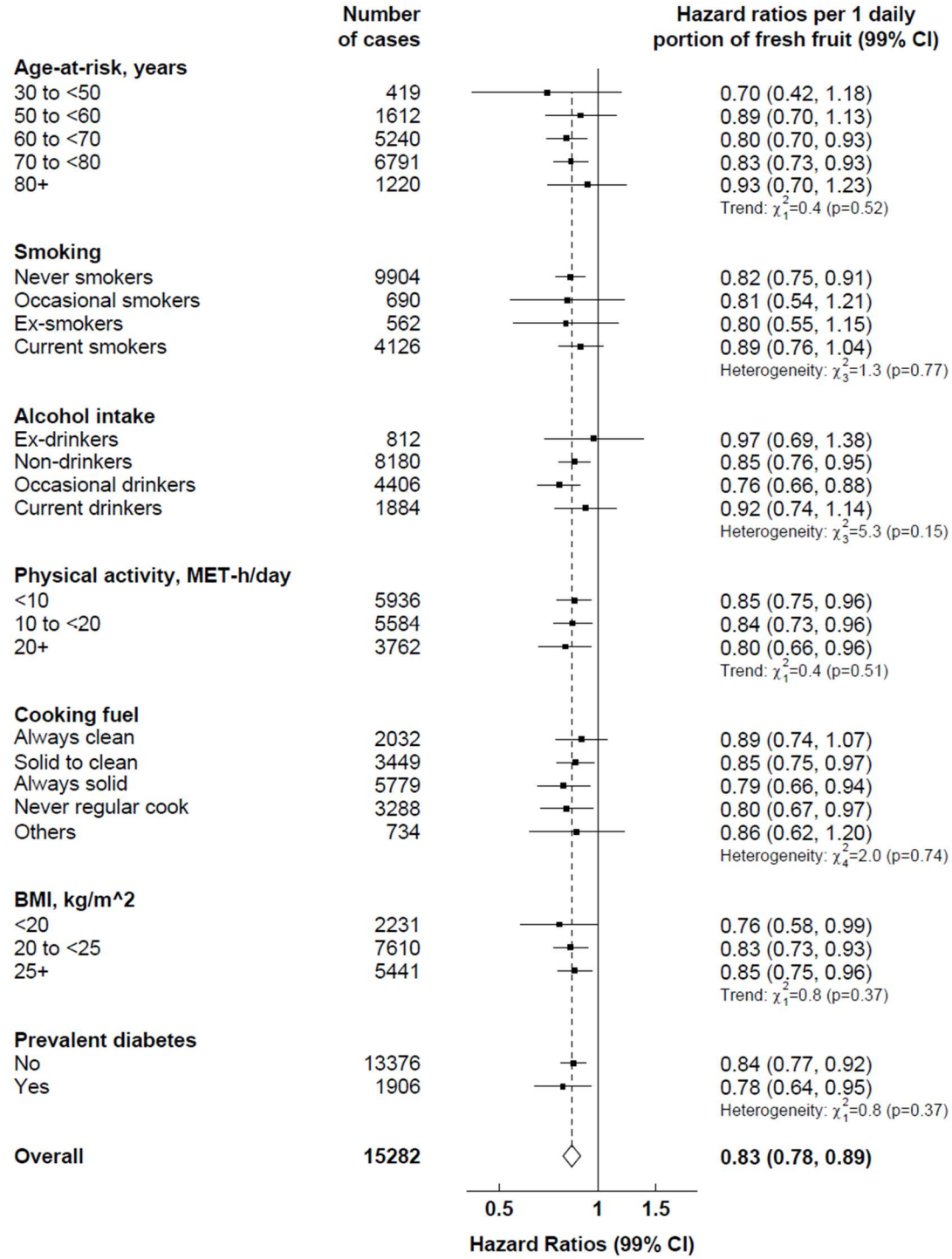
The inverse associations between fresh fruit consumption and risk of cataract among the >10 portions/month consumption groups were similar across subgroups defined by age, smoking, alcohol consumption, physical activity, indoor air pollution (assessed as type of cooking fuel used), BMI, and prevalent diabetes status (**Figure 6.8** & **Figure 6.9**). The associations remained essentially unchanged in sensitivity analyses (**Table 6.6**).

Figure 6.7 Adjusted HRs for cataract by fresh fruit consumption, stratified by sex or region.



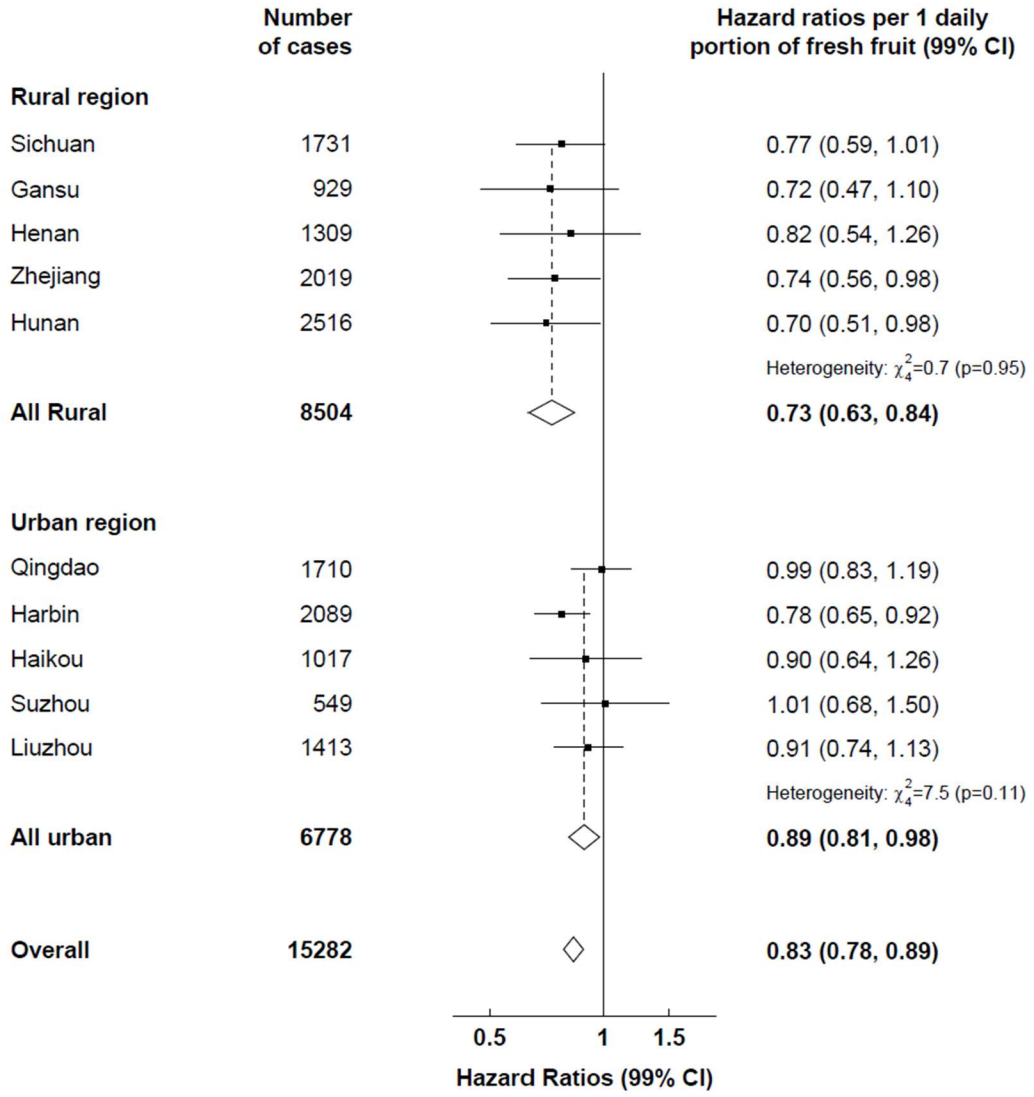
N stands for number of cases.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, self-rated health status, and consumption of meat and fish/seafood, as appropriate.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
Hazard ratio per 1 daily portion relates to >10 portions/month consumption groups.
P-value for trend is based on the >10 portions/month consumption groups.

Figure 6.8 Adjusted HRs per one daily portion of fresh fruit for cataract by selected population characteristics among the >10 portions/month consumption groups (i.e., excluding those who never/rarely consumed fresh fruit).



Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, self-rated health status, and consumption of meat and fish/seafood, as appropriate.

Figure 6.9 Adjusted HRs per one daily portion of fresh fruit for cataract by region among the >10 portions/month consumption groups (i.e., excluding those who never/rarely consumed fresh fruit).



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and sex, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, self-rated health status, and consumption of meat and fish/seafood.

Table 6.6 Adjusted HRs per one daily portion of fresh fruit for cataract among the >10 portions/month consumption groups (i.e., excluding those who never/rarely consumed fresh fruit) - results of sensitivity analysis.

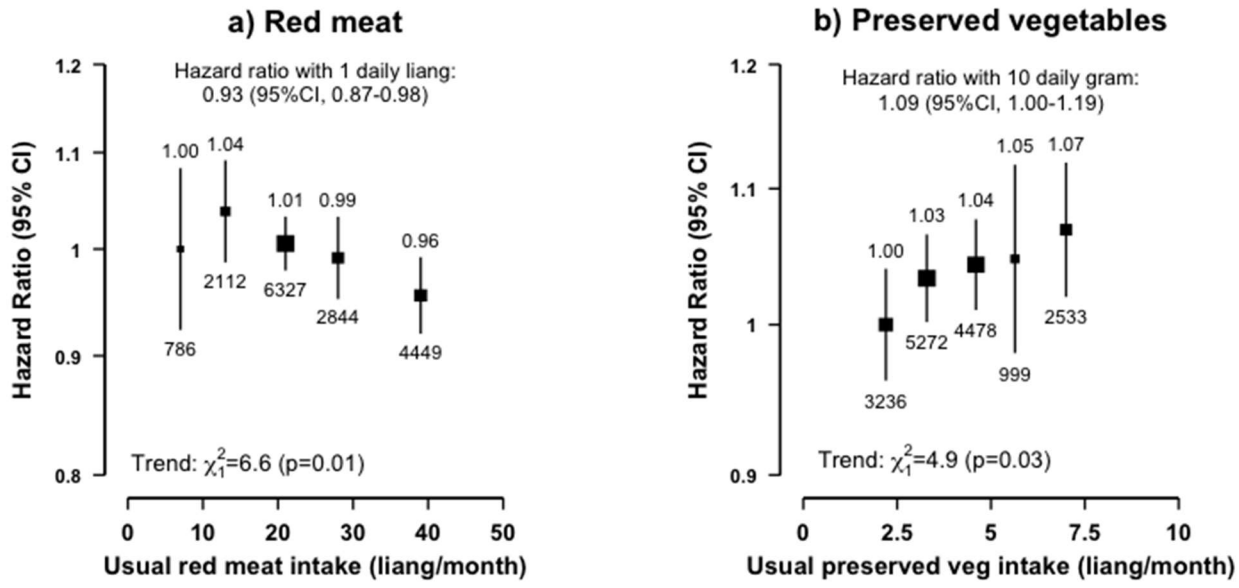
	Per 1 daily portion of fresh fruit	
	Number of cases	**HR (95%CI)**
Primary analysis* (n=479,928)	16,282	0.83 (0.79-0.89)
Exclude first 3 years of follow-up (n=479,928)	16,282	0.83 (0.90-0.89)
Exclude those aged ≥70 years at study entry (n=450,341)	12,371	0.83 (0.77-0.89)
Exclude those with poor self-rated health (n=433,418)	13,411	0.83 (0.78-0.89)
Exclude those with cancer or CVD at baseline (n=456,477)	13,783	0.81 (0.76-0.86)
Exclude those with cancer, CVD, or diabetes at baseline (n=433,584)	12,198	0.82 (0.76-0.88)
Exclude those with cancer, CVD, or diabetes at baseline, and incident diabetes during study follow-up (n=414,697)	11,194	0.81 (0.75-0.87)
Additional adjustment (primary analysis + household air pollution)	16,282	0.84 (0.79-0.89)
Additional adjustment (primary analysis + life satisfaction)	16,282	0.83 (0.78-0.89)
Additional adjustment (primary analysis + systolic blood pressure)	16,282	0.83 (0.78-0.88)
Additional adjustment (primary analysis + waist circumference)	16,282	0.83 (0.79-0.89)
Additional adjustment (primary analysis + waist-to-hip ratio)	16,282	0.84 (0.79-0.89)
Additional adjustment (primary analysis + fat percentage)	16,282	0.83 (0.78-0.89)
Additional adjustment (primary analysis + blood glucose)	16,282	0.83 (0.78-0.89)
Additional adjustment (primary analysis + preserved vegetables)	16,282	0.83 (0.78-0.89)

CVD cardiovascular disease (including coronary heart disease, stroke, and transient ischemic attack).
*Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, self-rated health status, and consumption of meat and fish/seafood.

6.3.4.2 Eleven food groups and risk of cataract

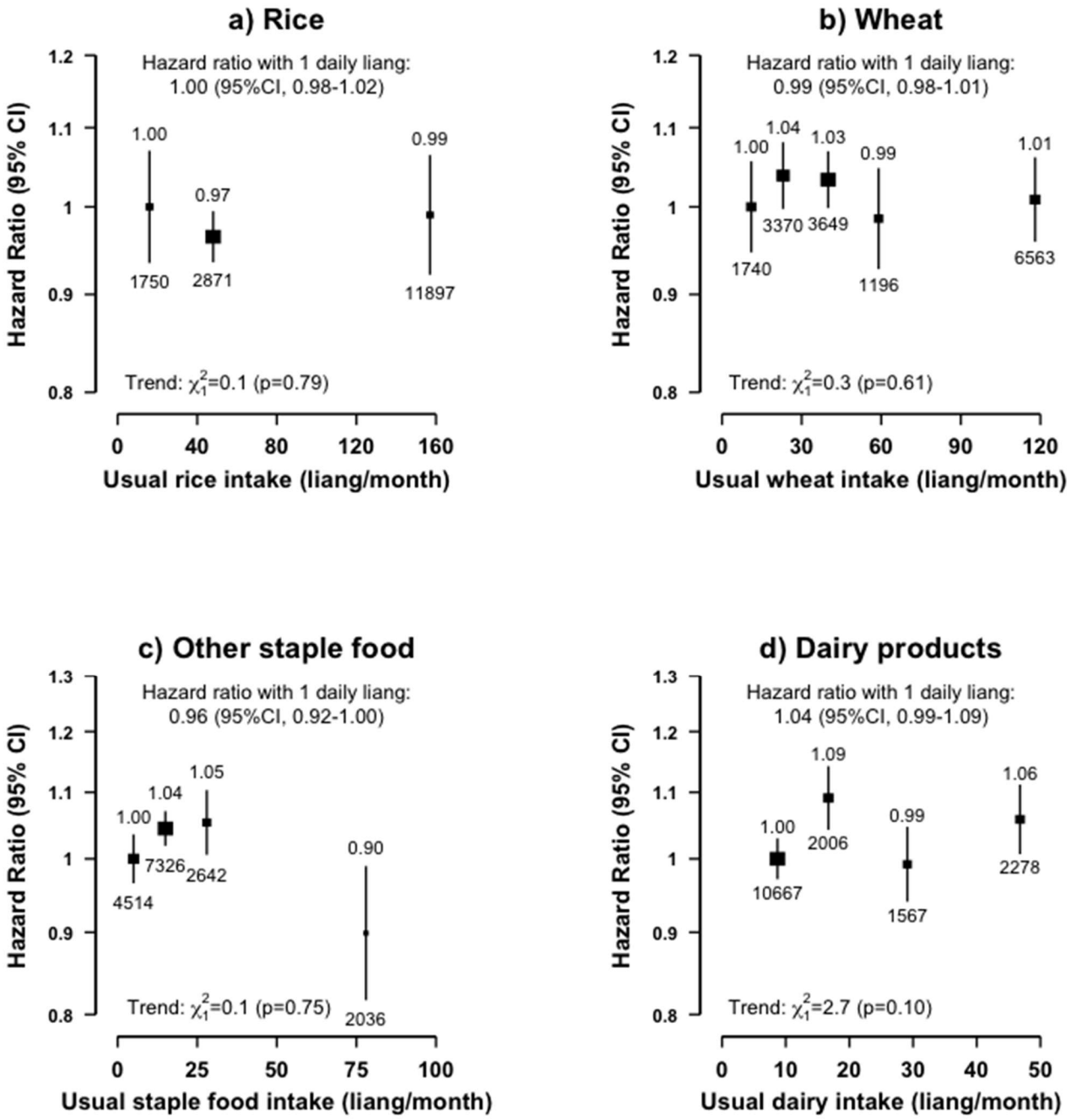
No clear differences in cataract risk were observed among participants with different usual consumption levels of red meat, preserved vegetables, rice, wheat, other staple food (corn, millet, etc.), dairy products, poultry, fish/seafood, eggs, soybean products, (**Figure 6.10-6.12** & **Supplementary Table E.9-E.10**). No difference in cataract risk was found between less frequent than daily (HR= 1.01, 0.94-1.09) and daily consumers of fresh vegetables.

Figure 6.10 Adjusted HRs for cataract by red meat and preserved vegetable consumption (number of cases =16,518).



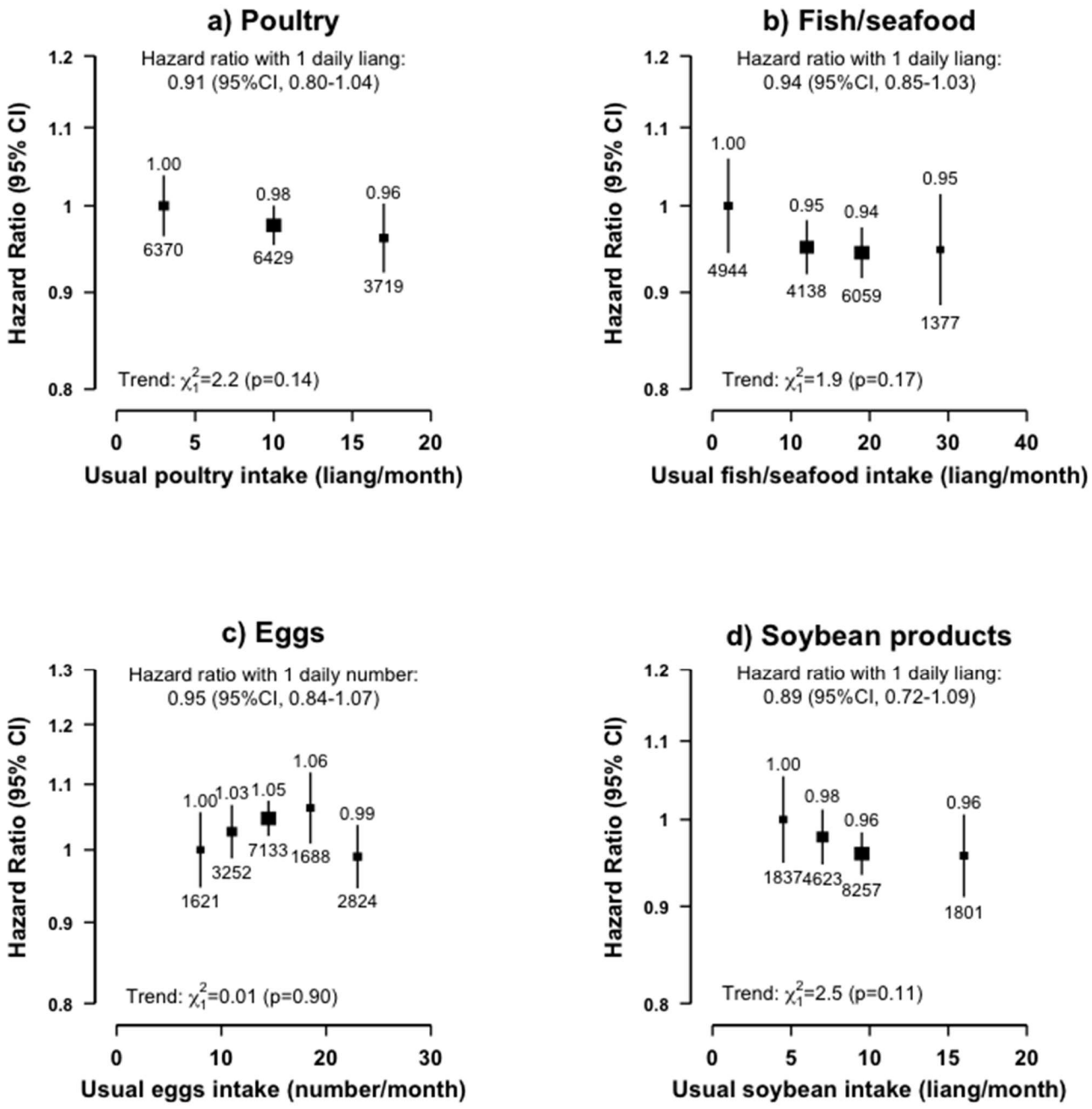
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, fresh fruit consumption, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.
1 liang =50 gram.

Figure 6.11 Adjusted HRs for cataract by rice, wheat, other staple food, and dairy products consumption (number of cases =16,518).



Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, fresh fruit consumption, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.
1 liang =50 gram.

Figure 6.12 Adjusted HRs for cataract by poultry, fish/seafood, eggs, and soybean products consumption (number of cases =16,518).



Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, fresh fruit consumption, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.
1 liang =50 gram.

6.4 Discussion

6.4.1 Summary of findings

In this analysis, physical activity was associated with a lower risk of cataract in a dose-response manner, particularly in women. Each 10 MET-h/d higher usual total physical activity was associated with 11% lower risk of cataract in women, though no clear association was observed in men.

Among the 12 major food groups in China, there was an inverse association for fresh fruit with risk of cataract in a dose-response manner, but no clear association was found for the other 11 food groups. Each 100 gram/day of fresh fruit consumption was associated with 17% lower risk of cataract among the >10 portions/month consumption groups, with stronger estimates in rural than in urban regions.

6.4.2 Physical activity and risk of cataract

There is limited prospective evidence on the association between physical activity and risk of cataract. In brief, 4 previous studies conducted among Western populations have assessed the association between physical activity and risk of cataract (**Supplementary Table B.6**). The inverse association between physical activity and risk of cataract observed in the current study is consistent with the findings from two[76,77], but not with the other two[75,78], previous studies. Two studies used MET-h/d to measure physical activity, and both reported an inverse linear association between physical activity and risk of cataract in men and women. The study followed-up 47K U.S. adults (with mean age of 50 years) for 6 years found each increment of 1 MET-h/d of

physical activity was associated with 4% (2%-5%) and 7% (5%-10%] lower risk of cataract in men and women, respectively[77]. Similarly, the study followed-up 52K Swedish adults aged 45-83 years for 12 years suggested each increment of 4 MET-h/d of physical activity was associated with 6% (3-8%) and 4% (2%-6%) lower risk of cataract in men and women, respectively[77]. Liked these two studies, the current study with 0.5 million Chinese also found an inverse linear association between physical activity and risk of cataract, though only statistically significant in women. Physical activity have different domain specific patterns in men and women in China[192]. For men, those with higher levels of physical activity were mainly participants with occupations that involve a large amount of outdoor activity, especially in rural regions. UV exposure, which has been linked to cataract development in previous studies[44,193], might have diluted the potential beneficial effects of physical activity. In CKB, the stratified analysis results by region also support this speculation because the association between physical activity and cataract risk in men was in strong positive direction in Haikou and Liuzhou (**Supplementary Figure E.3**), which are the two CKB regions closer to the equator (therefore with stronger UV exposure) than other regions. For women in CKB, they performed more household activities and spent more time indoors than men[192]. However, further research is needed to understand the different risk estimates of the association between physical activity and cataract incidence observed between Chinese men and women.

The third study, followed-up 1600 U.S. women aged 50-79 years for 6 years, which also used MET to measure physical activity, found no clear association with risk of nuclear cataract[75]. This finding seemed to suggest the inverse association between physical activity and risk of cataract was more

pronounced for cortical cataract and posterior subcapsular cataract than nuclear cataract. The forth study (the National Runner's eHealth Study), followed-up 40K U.S. athletes aged 39-44 years for 7 years, used running distance and cardio-respiratory fitness to measure physical activity, found per 1 unit higher of 10km performance times was associated with 28% (0.72, 0.60-0.87) lower risk of cataract in men, but no clear association was found in women[78]. This study focused on leisure time physical exercise only instead of total physical activity, which might explain the different findings observed compared with the CKB.

Several mechanisms may explain the inverse association between physical activity and cataract risk[76,78,77]. Higher levels of physical activity were found to be associated with lower levels of oxidative damage and higher antioxidant capacity in adults, which leads to a lower rate of lens protein damage[194]. Physical activity may also reduce the concentration of circulating C-reactive protein, which is a marker of systemic inflammation and has been associated with higher risk of cataract[195,196]. In addition, physical activity could contribute to lower risk of cataract through improved insulin sensitivity[197,198]. Physical activity was also found to be associated with elevated high-density lipoprotein (HDL) cholesterol concentration and lower level of plasma triglyceride, which have been inversely associated with cataract formation[199,200,201].

6.4.3 Dietary factors and risk of cataract

There is limited prospective evidence (2 studies in Western populations and 1 in Japanese) on the association between fruit consumption and risk of cataract, but none of them have observed a clear association[83,84,85]. In the CKB, fresh fruit consumption was inversely and linearly associated

with risk of cataract. Several factors may account for the different results observed in CKB compared with previous findings. Firstly, unlike previous studies, CKB assessed fresh fruit consumption (which is a common way of fruit consumption in China). Perhaps the potential association of fruit consumption with risk of cataract is stronger when consumed fresh/raw. Secondly, fresh fruit consumption amount is much lower in Chinese than in Western populations. For example, the average daily consumption of fresh fruit was less than half in CKB than in the UK Biobank (a prospective cohort study including half million middle-aged adults living in UK)[202]. It is possible that the log linear association means the association would be stronger in groups with lower consumption level[203].

In this study, participants who never/rarely consumed fresh fruit had lower risk of cataract than those with a monthly consumption, despite a clear inverse association among other four consumption groups (i.e., lower risk of cataract with increase of fruit consumption from monthly to daily consumption of fresh fruit). This might be explained that participants in the never/rarely group might have extreme lifestyle habits and poor health[204], therefore they could potentially already have had cataract surgery before the baseline and were unable to develop cataract during the study follow-up. This study also found the inverse association between fresh fruit consumption and risk of cataract was stronger in rural than in urban residents. It is unknown whether this is due to regional differences in fruit consumption patterns, as the relationship between fresh fruit consumption and risk of cataract might be more pronounced for some fruits (e.g., apple, pear) than others (e.g., berry)[74,86]. Some previous studies have suggested a regional variation in the types and amounts of fruits consumed in China[191,205], however information on

types of fruit was not collected in CKB.

Fresh fruit is the most important source of antioxidants which have been found to play a major role in reducing the level of oxidative stress. Oxidative stress is thought to cause damage to lens protein and lipids in the lens epithelium, which leads to lens opacification and the development of cataract[206,173,207]. Antioxidants (e.g., Quercetin[208]) which are found in fruit, could protect the lens against oxidative stress and scavenge free radicals, therefore prevent or delay the development of cataract[209,210].

Existing evidence generally supports an inverse association between vegetable consumption and cataract risk, with 20% (0.80, 0.65-0.99) lower risk of cataract when comparing vegetarians with non-vegetarians in the Tzu Chi Health Study (4400 Taiwanese participants aged 40+ years followed-up for 6 years)[47], and respectively 30% (0.70, 0.58-0.84) and 40% (0.60, 0.38-0.96) lower risk of cataract when comparing vegetarians and vegans with meat eaters who consumed ≥100 gram/day of meat in the EPIC-Oxford Study (27K U.K. participants aged 40+ years followed-up for 13 years)[82]. Findings from the Nurses' Health Study suggested higher intake of some vegetables (including spinach, winter squash), though not all (e.g., broccoli, carrots, sweet potatoes) was associated with lower risk of cataract[86]. However, no clear association between fresh vegetables consumption and cataract risk was observed in CKB. This might be due to the limited power in CKB, since 95% of CKB participants reported as a daily consumer of fresh vegetables (i.e., low variation in levels of exposure).

Previous prospective studies are limited and inconsistent on the association between meat consumption and risk of cataract. The EPIC-Oxford which followed-up 27 670 U.K. non-diabetic participants aged 40 years and older for 13 years, found that in contrast to meat eaters who consumed ≥100 g/day, the HRs for those who consumed 50-99 g/day and <50 g/day were 0.96 (0.84-1.11) and 0.85 (0.72-0.99), respectively[211]. The 45 and UP Study, which followed-up 8752 Australian participants aged 45-65 years with diabetes for 8 years, suggested no clear differences in cataract risk between highest (HR=1.20, 0.95-1.51) and lowest intake quintile of red meat[212]. In CKB, no statistically significant association between red meat consumption and risk of cataract was observed. Red meat cooked at high temperatures was found to be associated with a higher risk of cancer[213,214], though its association with cataract is unclear. It is unknown whether the different findings between the current study and the EPIC-Oxford study is due to different meat-eating culture (e.g., types of animal meat, cooking practice, the proportion of processed meat) in Chinese and Western populations. Further research is needed to validate the associations between red meat consumption and cataract incidence.

Previous studies also investigated the association between fat[87,88], dairy[89], wholegrain[47], and legume[47] consumption with risk of cataract, but found no clear associations with cataract risk. Similarly, the current study findings suggested no clear associations between rice, wheat, other staple food (corn, millet, etc.), and dairy products consumption with risk of cataract (**Figure 6.11**). In addition, the current study on preserved vegetables, poultry, fish/seafood, eggs, and soybean products consumption also found no clear association with cataract risk (**Figure 6.10 and Figure 6.12**).

6.4.4 Strengths and limitations

In addition to the large study population, this study has comprehensive assessment of physical activity patterns, and include 12 major dietary food groups in China. However, there are several limitations of this study. Firstly, in addition to the limitations of cataract data in CKB (i.e., lack of participants' prior cataract surgery history, no cataract registry in China, and subtypes of cataract are unknown), the measurement of physical activity and dietary factors in CKB may introduce some level of bias. The assessment of physical activity in the current study relied on self-reported questionnaire (rather than objective measurement), which may lead to recall bias. Despite comprehensive measurement of the four domains of physical activities (including occupational tasks, commuting, household chores, and leisure-time activities), the current study had no data on cardiorespiratory fitness, which could potentially introduce measurement bias. The assessment of food group consumption at the baseline survey only collected information on consumption frequency, and the exact measurement of consumption amount was estimated indirectly based on data collected from the resurveys. Secondly, even though the current study included 12 major food groups in China, information on specific types of those food groups (e.g., types of fruit) were unknown. Lastly, participant's total energy intake was not available in CKB. Total energy intake can confound the association between dietary factors and risk of disease, since participants with different total energy intake levels might have different dietary patterns which can independently affect disease risk[215,216]. Therefore, residual confounding by total energy intake may exist in this study. However, this study has adjusted for total physical activity and BMI which are the other two components of the energy equation, and this may have mitigated the impact of residual confounding from total energy intake.

6.5 Summary

In CKB, physical activity was inversely associated with risk of cataract in women. Fresh fruit was inversely associated with cataract risk, but there was no clear association for the other 11 major dietary food groups. The previous chapter and current chapter have assessed the association between major lifestyle factors (including smoking, alcohol consumption, physical activity, and dietary factors) and risk of cataract. The following chapter will assess the association between major modifiable cardiometabolic factors (i.e., adiposity, diabetes, and blood glucose) and risk of cataract.

7 Associations of adiposity, diabetes, and glucose with risk of cataract

7.1 Introduction

Obesity is a significant contributor to morbidity in the 21 century and its prevalence is increasing globally[217]. Although the impact of obesity on major chronic diseases, e.g., CVD and certain cancers, has been well established, the potential association of adiposity with cataract is less clear and the mechanisms are largely unknown. Some existing evidence supports a direct link between increased levels of adiposity and certain age-related diseases, via mechanisms of age-related changes in body fat distribution contributing to insulin resistance and metabolic syndrome[218]. However, previous studies of associations between adiposity and risk of cataract mainly used BMI as a measure of adiposity, and had inconsistent findings, especially between Western and Asian populations (detailed literature summary provided in Chapter 2.4.2.1). Very few studies have compared the associations of different adiposity measurements (e.g., body fat percentage [instead of BMI] as an indicator for general adiposity and indicators of central adiposity [e.g., waist circumference]) with risk of cataract.

Diabetes is one of the top ten causes of mortality globally, with more than 1 million deaths per year attributed to diabetes alone[219]. The global incidence and prevalence of diabetes in 2017 was 23 million and 476 million, respectively[220]. Adults with diabetes are more vulnerable to heart attacks, stroke, and blindness[221,19]. In contrast to the inconsistent associations between adiposity and risk of cataract, diabetes has been found to be strongly and positively associated with cataract[103,95]. Despite the consistent evidence among Western populations, studies on Asian populations are limited and inconsistent[222,48,223]. The association between blood glucose and risk

of cataract is poorly studied[105].

Therefore, a prospective study on the associations between different adiposity measurements, diabetes, and blood glucose with risk of cataract conducted in a large Asian population could greatly contribute to global evidence of these important modifiable health conditions on cataract incidence. The current chapter aims to use data from 0.5 million adults in CKB to: (1) Investigate the associations of different adiposity measures with risk of cataract; (2) Investigate the associations between diabetes and blood glucose with risk of cataract.

7.2 Methods

Detailed information about the CKB study design and data collection methods has been described previously (see Chapter 3). In brief, the CKB is a prospective cohort study of 0.5 million adults aged 30-79 years from 10 regions in China. A wide range of socio-economic, lifestyle, and cardiometabolic factors were collected at the baseline survey and subsequent resurveys. Study participants were follow-up for a median of 11 years.

7.2.1 Assessment of adiposity factors

A range of adiposity traits including standing height, weight, body fat percentage, waist circumference, and hip circumference were measured at the baseline survey using standard instruments and protocols[116,117], while participants wore light clothes and no shoes. Standing height was measured to the nearest 0.1 cm using a portable stadiometer. Weight was measured to the nearest 0.1 kg using a body composition analyser (TANITA-TBF-300GS; Tanita Inc., Tokyo,

Japan), with estimated weight of clothing subtracted (0.5 kg in summer; 1.0 kg in spring/autumn; 2.0-2.5 kg in winter). Body fat percentage was measured with the same body composition analyser, using its in-built proprietary algorithm to conduct the foot-to-foot bioelectrical impedance analysis. Waist circumference and hip circumference were measured to the nearest 0.1 cm using a soft non-stretchable tape, and were usually measured over underclothes with 1.0-2.0 cm subtracted from the reading, or over clothes with 1.0-2.5 cm (1.0 cm for skirt and 2.5 cm for trousers) subtracted. Waist circumference was measured at midway between the lowest rib and the iliac crest. Hip circumference was measured around the maximum circumference of the buttocks. In addition, participants were asked to report their recalled weight at around 25 years old (i.e., $weight_{25}$).

BMI (kg/m^2) was calculated as weight (in kilograms) divided by the square of the standing height (in meters). BMI at age 25 years old (i.e., BMI_{25}) was calculated using self-reported $weight_{25}$ and height measured at baseline. Fat mass (kg) was calculated as the product of body fat percentage divided by 100 and weight (in kilograms). Fat mass index (kg/m^2) was calculated as fat mass (in kilograms) divided by the square of standing height (in meters). Waist-to-hip ratio was calculated as the ratio of waist circumference to hip circumference (both in centimetres). Waist-to-height ratio was calculated as the ratio of waist circumference to standing height (both in centimetres).

Adiposity factors were re-measured at the resurveys in 2008 and 2013-2014 with similar methods as conducted in the baseline survey. The resurvey data were used to estimate the “usual” level of adiposity in each baseline category.

7.2.2 Assessment of diabetes and blood glucose

During the baseline survey, participants were asked to report their prior history of physician-diagnosed diabetes (through the question of "Has a doctor ever told you that you had had diabetes?"), and those with self-reported diabetes were asked to provide additional information about age at diagnosis and current medication (i.e., hypoglycaemic medications, like insulin and metformin) use. A 10 ml random (except for Zhejiang region, where participants were asked to fast prior attending the assessment) venous blood sample was collected for onsite testing of random blood glucose level using the SureStep Plus System (Johnson and Johnson, USA) and long-term storage, and the time since last eating was recorded. Fasting was defined as at least 8 hours since the last meal. Participants who did not report a diabetes diagnosis but had non-fasting blood glucose level between 7.8-11.0 mmol/L were invited to return to the survey site for a fasting blood glucose test (a finger-prick test using the same SureStep Plus System) on the following day to detect prevalent diabetes. According to diabetes diagnosis recommendations from the American Diabetes Association[224], screen-detected diabetes was defined as: (1) plasma glucose level ≥7.0 mmol/L if time since last eating ≥8 hours; (2) plasma glucose level ≥11.1 mmol/L if time since last eating <8 hours; (3) finger-prick test of fasting blood glucose level ≥7.0 mmol/L on the subsequent day[225,226]. Prevalent diabetes cases included both self-reported diabetes and screen-detected diabetes. For baseline self-reported diabetes, CKB did not collect information about diabetes subtype. However, based on the age of diagnosis (i.e., diagnosed before 35 years of age) and medication use (i.e., treated with insulin), it should be reasonable to assume that only a very small number of participants having type 1 diabetes (n= 102, <1% of self-reported diabetes cases at baseline).

During the first CKB resurvey conducted in 2008, blood glucose level was measured using the same procedures and the same devices among subsets of study participants (n=19 788) as in the baseline survey. Since the SureStep Plus meter was no longer available in the 2nd resurvey (conducted in 2013-2014, n=25 176), the On Call Advanced blood glucose meter (ACON Laboratories Inc., San Diego, California, USA) was used instead. In addition, participants in Zhejiang were not asked to fast (this was the case at the baseline) prior to attending survey clinics. The resurvey data were used to estimate the "usual" level of blood glucose in each baseline category.

7.2.3 Statistical analyses

7.2.3.1 Adiposity in relation to cataract risk

The analysis excluded individuals with incident cataract before age 40 years (n=34), and individuals with missing data on BMI (n=2) and body fat percentage (n=238), leaving 512 452 participants (210 063 men and 302 389 women) for the main analyses. The analysis for BMI_{25} further excluded individuals with missing data on $weight_{25}$ (n= 82 208). Baseline characteristics of participants across categories of BMI were calculated using direct standardisation to baseline age groups (in 5 year intervals), sex, and study region (ten regions) of the baseline CKB population[141]. Pearson correlation coefficients[227] between different adiposity measures (including BMI, body fat percentage, fat mass, fat mass index, waist circumference, waist-to-hip ratio, and waist-to-height ratio) were calculated to describe baseline adiposity status of CKB participants. The correlation coefficients were calculated separately for men and women due to difference in fat distribution patterns and potentially different impact of general and central

adiposity on cataract risk between men and women.

Cox proportional hazards regression models were used to estimate adjusted HRs and 95% CIs for adiposity factors with incident cataract, with men and women analysed separately. The adiposity factors were assessed as categorical variables. To cover different thresholds to define overweight and obesity in Chinese population and to ensure a reasonable number of participants in each group, participants were classified into groups by different adiposity indices. The categorising criteria included: by BMI (five groups: <18.5, 18.5 to <23.0, 23.0 to <25.0, 25.0 to <28.0, and ≥28.0 kg/m^2); by BMI_{25} (five groups: <18.5, 18.5 to <20.0, 20.0 to <23.0, 23.0 to <25.0, and ≥25.0 kg/m^2); by body fat percentage (five gender-specific quintiles); by fat mass (four groups: in men <10, 10 to <15, 15 to <20, and ≥20 kg; in women <12, 12 to <18, 18 to <24, and ≥24 kg); by fat mass index (five gender-specific quintiles); by waist circumference (five groups: in men <80, 80 to <85, 85 to <90, 90 to <95, and ≥95 cm; in women <75, 75 to <80, 80 to <85, 85 to <90, and ≥90 cm); by waist-to-hip ratio (five groups: in men <0.85, 0.85 to <0.90, 0.90 to <0.95, 0.95 to <1.00, and ≥1.00; in women <0.80, 0.80 to <0.85, 0.85 to <0.90, 0.90 to <0.95, and ≥0.95); and by waist-to-height ratio (five gender-specific quintiles). The Cox models were stratified by age-at-risk (5-year groups) and study region (ten regions), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), smoking status (four groups), alcohol consumption status (four groups), total physical activity (continuous), fresh fruit consumption (four groups), prevalent cardiovascular diseases (dichotomous, including CHD and stroke/TIA), prevalent diabetes (dichotomous), and self-rated health (four groups). Floating absolute risk method[126,127] were used to allow comparison of risk estimates between any two

categories of exposure (not just with the reference category), with the method previously explained in Chapter 3.2.2. The adiposity factors were also assessed as continuous variables (per 1 SD, and adjusted by the regression dilution ratio). To account for regression dilution bias, usual adiposity level was estimated with MacMahon-Peto method by taking the mean adiposity measurements at resurveys 1 and 2 (as explained in Chapter 3.2.3) for each baseline adiposity category (**Supplementary Table F.1** in **Appendix F** illustrates the calculation using BMI as an example)**,** and the log HRs were plotted against usual adiposity level. A Bonferroni correction was applied to address multiple testing of the 8 adiposity factors conducted on men and women separately, with a threshold for significance for each individual test set as 0.003 (i.e., 0.05/[8*2])[228].

To explore potential effect modification by other population characteristics, subgroup analyses were conducted by age-at-risk, region, smoking, alcohol consumption, physical activity, fresh fruit consumption, and prevalent diabetes. Similar as for previous chapters, several sensitivity analyses were also conducted to assess residual confounding as well as reverse causality bias therefore to confirm the robustness of the results, including: 1) additionally adjusting for potential confounding factors including SBP, blood glucose, and life satisfaction level separately; 2) excluding the first 3 years of follow-up; 3) excluding participants aged ≥70 years at baseline; 4) excluding participants with poor self-rated health, prevalent cancer, cardiovascular diseases, or diabetes; 5) excluding participants with incident diabetes during follow-up. All statistical analyses were performed in R (version 4.0.3).

7.2.3.2 Diabetes and random blood glucose in relation to cataract risk

The analysis excluded individuals with incident cataract before age 40 years (n=34), and individuals with missing data on BMI (n=2) and random blood glucose (n=8341), leaving 504 349 participants (206 776 men and 297 573 women) for the main analyses. Baseline characteristics of participants by category of diabetes status (three groups: nondiabetic, screen-detected diabetes, and self-reported diabetes) and, in participants without prevalent diabetes, random blood glucose levels were calculated with direct standardisation to baseline age groups (in 5 year intervals), sex, and study region (ten regions) of the baseline CKB population[141].

Cox proportional hazards regression models were used to estimate adjusted HRs and 95% Cls of incident cataract in participants with different diabetic status and blood glucose levels (seven groups: screen-detected diabetes, prior diabetes history, and among participants without prevalent diabetes, those with blood glucose levels of: <5.2, 5.2 to <5.7, 5.7 to <6.7, 6.7 to <7.7, and ≥7.7 mmol/L). The models were stratified by age-at-risk (5-year groups), sex, and study region (ten regions), and adjusted for baseline age (continuous), education level (four groups), annual household income (four groups), occupation (five groups), smoking status (four groups), alcohol consumption status (four groups), total physical activity (continuous), fresh fruit consumption (four groups), self-rated health (four groups), and fasting hours (continuous). Similar to the method used for adiposity factors, the usual level of random blood glucose in participants without prevalent diabetes was estimated, and the log HRs were plotted against usual level of random blood glucose. In addition, random blood glucose was assessed as a continuous variable among participants without prevalent diabetes (per 1 mmol/L, and adjusted

by the regression dilution ratio). The association between random blood glucose and risk of cataract was also assessed among participants with prevalent diabetes. Among participants with baseline prevalent diabetes, the associations of duration of diagnosed diabetes (i.e., years with diabetes; five groups: 0 [i.e., those with screen-detected diabetes], 0 to <2, 2 to <5, 5 to<10, and ≥10 years), age at diabetes diagnosis (five groups: <40, 40 to <50, 50 to <60, 60 to <70, and ≥70 years), and diabetes medication use, with risk of cataract were also assessed.

To explore the potential effect modification by other population characteristic factors, subgroup analyses were conducted by age-at-risk, sex, region, smoking, alcohol consumption, physical activity, BMI, and fasting hours. Several sensitivity analyses were conducted to assess the robustness of the results, including: 1) additionally adjusting for potential confounding factors including SBP, life satisfaction level, and other adiposity factors (including body fat percentage, waist circumference, and waist-to-hip ratio) separately; 2) excluding the first 3 years of follow-up; 3) excluding participants aged ≥70 years at baseline; 4) excluding participants with poor self-rated health, prevalent cancer, or cardiovascular diseases. All these three approaches were applied to assess the potential impact of reverse causation. 5) excluding participants from Zhejiang where fasting, instead of random, blood glucose was assessed and used in the analyses; 6) excluding participants with possible type 1 diabetes status at baseline, to assess the potentially different impacts of diabetes subtypes. All statistical analyses were performed in R (version 4.0.3).

7.3 Results

7.3.1 Baseline characteristics of participants by adiposity factors

Of the 512 452 participants included in the analyses, mean baseline age was 52.0 (SD 10.7) years, 59.0% were women, 55.9% resided in rural regions, and mean BMI was 23.7 (3.4) kg/m^2 (**Table 7.1**). No clear trends in age and sex across BMI categories were observed. Participants with higher BMI were less likely to be rural residents (top vs lowest BMI group: 43.3% vs 68.4%), likely to smoke regularly (61.2% vs 76.5% male current smokers), and were less active (19.6 vs 20.8 MET-hours/day of mean total physical activity). They were also more likely to consume red meat (31.8% vs 25.7% as daily eaters), fish/seafood (3.2% vs 2.5% as daily eaters), and fresh fruit (20.3% vs 15.1% as daily eaters), more likely to have higher mean values of systolic/diastolic blood pressure (140.6/82.8 vs 121.1/72.9 mmHg), body fat percentage (30.6% vs 12.8% in men, 42.8% vs 19.2% in women), waist circumference (97.8 vs 67.6 cm in men, 92.9 vs 64.3 cm in women), waist-to-hip ratio (0.98 vs 0.83 in men, 0.93 vs 0.79 in women), and random blood glucose (6.5 vs 5.9 mmol/L). Their prevalence of prior diseases (including diabetes [4.6% vs 1.8%], CHD [4.4% vs 2.0%], stroke or TIA [2.4% vs 1.0%], and hypertension [23.2% vs 3.8%]) were also higher.

Table 7.1 Baseline characteristics of CKB participants by level of baseline body mass index

Characteristic	Category of baseline body mass index (kg/m^2)					Overall
	<18.5	18.5 to <23.0	23.0 to <25.0	25.0 to <28.0	≥28.0	
No. of participants	22,332	205,997	115,254	114,549	54,320	512,452
Mean body mass index (SD), kg/m^2	17.6 (1.0)	21.1 (1.2)	23.9 (0.6)	26.3 (0.9)	29.2 (2.0)	23.7 (3.4)
Socio-demographic factors						
Mean age (SD), years	55.1 (14.6)	51.4 (11.1)	51.6 (10.3)	52.0 (10.2)	52.1 (11.3)	52.0 (10.7)
Women, %	59.2	56.7	59.6	59.8	66.1	59.0
Rural, %	68.4	63.2	53.6	48.1	43.3	55.9
Education below high school, %	51.9	50.7	49.7	50.1	51.5	50.8
Household income <20K yuan/year, %	63.4	58.6	56.2	55.2	55.5	57.3
Lifestyle factors						
Current smokers*, % of men	76.5	71.8	65.2	62.5	61.2	67.6
Current smokers*, % of women	4.8	3.1	2.6	2.4	2.7	2.8
Current drinkers, % of men	28.7	33.7	33.6	32.6	32.2	33.3
Current drinkers, % of women	2.1	2.1	2.1	2.0	1.9	2.1
Physical activity, mean (SD) MET-hours/day	20.8 (15.7)	21.7 (11.9)	21.1 (11.7)	20.5 (12.1)	19.6 (13.8)	21.1 (13.9)
Daily intake of dietary factors, %						
Red Meat	25.7	28.2	29.7	30.9	31.8	29.3
Fish/seafood	2.5	2.6	2.7	2.9	3.2	2.8
Fresh vegetables	93.5	94.5	95.0	95.3	95.2	94.8
Fresh fruit	15.1	17.9	19.2	19.8	20.3	18.8
SBP, mmHg	121.1 (25.3)	126.9 (19.7)	131.7 (19.1)	135.5 (20.1)	140.6 (23.6)	131.1 (21.3)
DBP, mmHg	72.9 (14.3)	75.4 (10.9)	78.1 (10.6)	80.3 (11.2)	82.8 (13.2)	77.8 (11.2)
Body fat percentage, % of men	12.8 (4.2)	18.2 (3.9)	23.2 (3.8)	26.6 (4.4)	30.6 (5.9)	22.0 (6.2)
Body fat percentage, % of women	19.2 (3.4)	27.1 (3.7)	32.7 (3.3)	36.9 (4.0)	42.8 (5.8)	32.1 (7.1)
Waist circumference of men, cm	67.6 (6.2)	75.7 (5.7)	83.6 (5.0)	89.7 (5.7)	97.8 (7.8)	82.0 (9.8)
Waist circumference of women, cm	64.3 (6.5)	72.9 (5.7)	79.6 (5.0)	84.9 (5.5)	92.9 (7.8)	79.1 (9.6)
Waist-to-hip ratio in men	0.83 (0.07)	0.87 (0.05)	0.92 (0.05)	0.95 (0.05)	0.98 (0.07)	0.90 (0.07)
Waist-to-hip ratio in women	0.79 (0.08)	0.84 (0.06)	0.87 (0.05)	0.90 (0.06)	0.93 (0.07)	0.87 (0.07)
Random blood glucose, mmol/L	5.9 (3.4)	5.9 (2.4)	6.1 (2.3)	6.2 (2.5)	6.5 (3.1)	6.1 (2.3)
Prior disease history, %						
Diabetes	1.8	2.5	3.4	3.8	4.6	3.3
CHD	2.0	2.2	3.0	3.7	4.4	3.0
Stroke or TIA	1.0	1.4	1.8	2.1	2.4	1.7
Cancer	1.1	0.5	0.5	0.5	0.5	0.5
Hypertension	3.8	7.2	11.8	16.3	23.2	11.6
Poor self-rated health, %	18.0	10.5	9.2	9.6	11.3	10.4

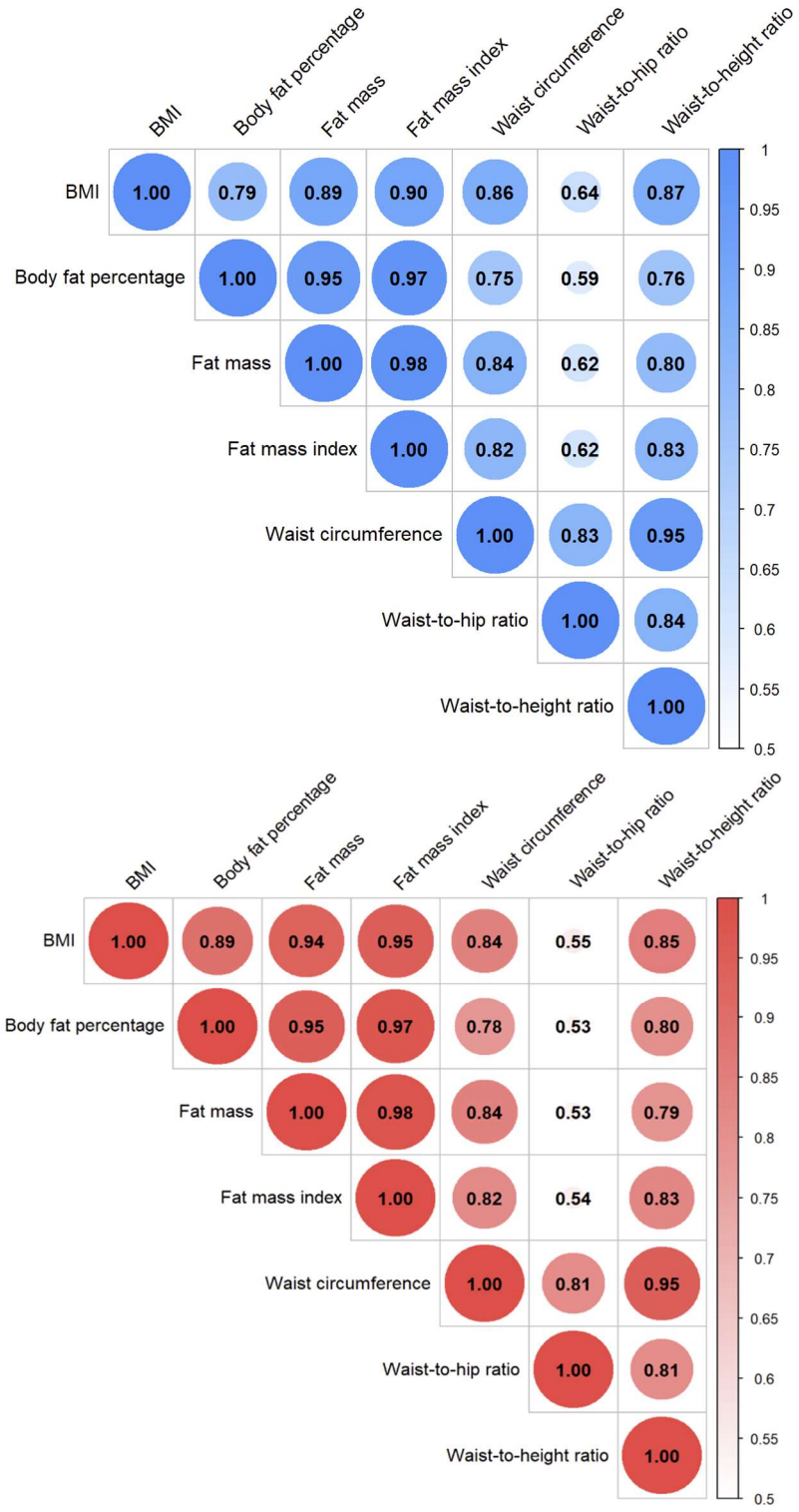
SD standard deviation, MET metabolic equivalent of task hours/day, SBP systolic blood pressure, DBP diastolic blood pressure, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex and region, as appropriate.
*Current smokers included current smokers and ex-smokers stopped due to illness.

Different adiposity measures were positively correlated with each other, with correlation coefficients ranging from 0.59 to 0.98 in men and from 0.53 to 0.98 in women, after adjusting for age at baseline and region (**Figure 7.1**). In both sexes, BMI was strongly correlated with body fat percentage, fat mass, fat mass index, waist circumference, and waist-to-height ratio (with r [Pearson correlation coefficient] ranging from 0.79 to 0.90 in men, and from 0.84 to 0.95 in women), but was modestly correlated with waist-to-hip ratio (r: 0.64 in men; 0.55 in women). Other general and central adiposity measures were strongly correlated with each other in both sexes, except for waist-to-hip ratio. There were modest correlations of waist-to-hip ratio with other adiposity measures, with correlation coefficients ranging from 0.59 to 0.64 in men and from 0.53 to 0.55 in women, apart from waist circumference (r: 0.83 in men and 0.81 in women).

7.3.2 Baseline characteristics of participants by diabetes and glucose status

Of the 504 349 participants included in the analyses, mean baseline age was 52.0 (SD 10.7) years, 59.0% were women, and 55.3% resided in rural regions (**Table 7.2**). Participants with prevalent diabetes were 6 years older on average (57.7 vs 51.7 years) and more likely to live in urban regions (57.4% vs 43.8%), but were less active (18.8 vs 21.1 MET-hours/day of total physical activity), and consumed less fresh fruit (16.3% vs 19.1% daily eaters) than those without prevalent diabetes (**Table 7.2**). They were also more likely to consume red meat (30.1% vs 29.2% daily eaters) and fish/seafood (3.1% vs 2.8% daily eaters), and had higher mean systolic/diastolic blood pressure (138.3/80.4 vs 130.7/77.7 mmHg), BMI (24.9 vs 23.6 kg/m^2), body fat percentage (30.4% vs 27.9%), waist circumference (84.9 vs 80.1 cm), waist-to-hip ratio (0.92 vs 0.88), and random blood glucose (12.6 vs 5.7 mmol/L), and had higher prevalence of prior diseases

Figure 7.1 Correlation coefficients between adiposity measures in men (blue) and women (red).



Pearson correlation coefficients were adjusted for age at baseline (5-year groups) and region.

Table 7.2 Baseline characteristics of CKB participants by diabetes status

	Participants without missing data for baseline random blood glucose				
	Nondiabetic	Prevalent diabetes			Overall
		Screen detected	Self-reported	All diabetes	
No. of participants	474,230	14,138	15,981	30,119	504,349
Socio-demographic factors					
Mean age (SD), years	51.7 (10.5)	56.5 (10.3)	58.9 (10.1)	57.7 (10.3)	52.0 (10.7)
Women, %	58.8	61.0	58.5	60.5	59.0
Rural, %	56.2	45.6	39.2	42.6	55.3
Education below high school, %	50.5	52.2	47.9	50.5	50.5
Household income <20K yuan/year, %	57.3	57.3	55.4	56.7	57.2
Lifestyle factors					
Current smokers*, % of men	67.7	66.8	67.3	64.3	67.6
Current smokers*, % of women	2.7	3.1	2.9	3.0	2.8
Current drinkers, % of men	33.3	35.7	22.1	29.5	33.0
Current drinkers, % of women	2.1	1.8	0.6	1.3	2.0
Physical activity, mean (SD) MET-hours/day	21.1 (11.5)	19.8 (15.2)	17.5 (20.9)	18.8 (17.8)	21.0 (13.8)
Daily intake of dietary factors, %					
Red Meat	29.2	30.1	30.2	30.1	29.3
Fish/seafood	2.8	2.9	3.1	3.1	2.8
Fresh vegetables	94.8	94.6	95.0	94.9	94.8
Fresh fruit	19.1	18.3	13.6	16.3	18.8
Cardiometabolic factors, mean (SD)					
SBP, mmHg	130.7 (19.4)	139.0 (24.3)	136.9 (33.6)	138.3 (27.3)	131.1 (21.3)
DBP, mmHg	77.7 (10.8)	81.0 (14.0)	79.6 (18.1)	80.4 (15.5)	77.8 (11.2)
BMI, kg/m^2	23.6 (3.2)	25.1 (4.4)	24.6 (5.9)	24.9 (5.2)	23.7 (3.4)
Body fat percentage	27.9 (6.4)	31.0 (8.7)	29.5 (11.8)	30.4 (10.1)	28.0 (8.4)
Waist circumference, cm	80.1 (9.0)	85.2 (11.9)	84.3 (15.9)	84.9 (13.9)	80.3 (9.8)
Waist-to-hip ratio	0.88 (0.06)	0.92 (0.09)	0.92 (0.10)	0.92 (0.10)	0.88 (0.07)
Random blood glucose, mmol/L	5.7 (1.1)	13.3 (6.4)	11.8 (11.1)	12.6 (7.9)	6.1 (2.3)
Prior disease history, %					
CHD	2.8	3.2	6.8	5.2	3.0
Stroke or TIA	1.6	2.2	3.9	3.2	1.8
Cancer	0.5	0.7	0.7	0.7	0.5
Hypertension	10.9	17.2	27.4	22.2	11.6
Poor self-rated health, %	9.7	10.9	31.1	20.0	10.3

SD standard deviation, MET metabolic equivalent of task hours/day, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, N/A data not available, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex and region, as appropriate.
*Current smokers included current smokers and ex-smokers stopped due to illness.

(including CHD [5.2% vs 2.8%], stroke or TIA [3.2% vs 1.6%], cancer [0.7% vs 0.5%], and hypertension [22.2% vs 10.9%]), and reported poor self-rated health more frequently (20.0% vs 9.7%) than their counterparts.

Compared with these 504 349 participants who had their random blood glucose measured at study baseline, the 8341 participants with missing data on random blood glucose at baseline (excluded from the subsequent analyses in this chapter) were more likely to be younger (50.9 vs 52.0 years) and live in rural regions (93.1% vs 55.3%), have less formal education (69.1% vs 50.5% below high school) and lower household income (59.5% vs 57.2% with annual income < 20K yuan), and reported poor self-rated health more frequently (13.6% vs 10.3%).

Among the 474 230 participants without prevalent diabetes at baseline, mean random blood glucose was 5.7 (SD 1.1) mmol/L (**Table 7.3**). Participants with higher random blood glucose were more likely to be older (top vs lowest glucose group: 55.5 vs 49.5 years), have less formal education (51.4% vs 49.7% below high school), and were less likely to consume fresh fruit (18.0% vs 18.9% as daily eaters). They also had higher mean SBP (134.0 vs 129.5 mmHg), BMI (24.3 vs 23.3 kg/m^2), body fat percentage (28.8% vs 27.6%), waist circumference (82.2 vs 78.9 cm), waist-to-hip ratio (0.90 vs 0.87), and had higher prevalence of prior diseases (including CHD [3.1% vs 2.5%], stroke or TIA [1.9% vs 1.4%], and hypertension [13.5% vs 9.4%]) than their counterparts.

Table 7.3 Baseline characteristics of CKB participants by level of baseline random blood glucose in those without prevalent diabetes.

	Category of baseline random blood glucose (mmol/L)					Overall
	<5.2	5.2 to <5.7	5.7 to <6.7	6.7 to <7.7	≥7.7	
No. of participants	162,680	102,127	129,409	51,470	28,544	474,230
Mean random blood glucose (SD), mmol/L	4.6 (0.4)	5.4 (0.1)	6.1 (0.3)	7.1 (0.3)	8.6 (1.0)	5.7 (1.1)
Socio-demographic factors						
Mean age (SD), years	49.5 (10.4)	51.2 (10.5)	52.8 (10.6)	54.3 (10.9)	55.5 (11.2)	51.7 (10.6)
Women, %	52.2	60.8	63.8	63.3	59.2	58.9
Rural, %	62.7	53.2	52.4	54.0	53.5	56.3
Education below high school, %	49.7	50.1	50.8	51.2	51.4	50.3
Household income <20K yuan/year, %	58.0	56.9	57.1	57.8	58.4	57.4
Lifestyle factors						
Current smokers*, % of men	69.5	66.8	66.5	67.1	68.3	67.9
Current smokers*, % of women	3.1	2.7	2.5	2.4	2.9	2.7
Current drinkers, % of men	33.0	34.0	33.8	33.3	32.5	33.3
Current drinkers, % of women	2.1	2.2	2.0	1.9	1.7	2.1
Physical activity, mean (SD) MET-hours/day	21.3 (11.7)	21.3 (11.8)	21.3 (12.3)	21.3 (13.7)	21.3 (15.2)	21.3 (13.9)
Daily intake of dietary factors, %						
Red Meat	29.8	28.9	28.3	28.2	29.2	28.9
Fish/seafood	2.8	2.7	2.7	2.8	2.7	2.7
Fresh vegetables	95.0	94.8	94.5	94.4	94.4	94.7
Fresh fruit	18.9	18.8	18.7	18.4	18.0	18.7
Cardiometabolic factors, mean (SD)						
SBP, mmHg	129.5 (20.6)	130.0 (19.5)	130.8 (19.3)	131.7 (20.7)	134.0 (23.1)	130.5 (21.0)
DBP, mmHg	77.7 (11.4)	77.9 (10.9)	77.6 (11.0)	77.2 (11.9)	77.6 (13.0)	77.7 (11.1)
BMI, kg/m^2	23.3 (3.3)	23.5 (3.2)	23.7 (3.2)	24.0 (3.6)	24.3 (4.1)	23.6 (3.4)
Body fat percentage	27.6 (6.8)	27.6 (6.4)	27.8 (6.5)	28.1 (7.1)	28.8 (8.2)	27.8 (8.4)
Waist circumference, cm	78.9 (9.2)	79.8 (9.0)	80.5 (9.2)	81.3 (10.1)	82.2 (11.3)	80.0 (9.6)
Waist-to-hip ratio	0.87 (0.07)	0.88 (0.06)	0.88 (0.06)	0.89 (0.07)	0.90 (0.08)	0.88 (0.07)
Prior disease history, %						
CHD	2.5	2.6	2.6	2.9	3.1	2.7
Stroke or TIA	1.4	1.5	1.6	1.7	1.9	1.5
Cancer	0.5	0.5	0.5	0.5	0.6	0.5
Hypertension	9.4	10.1	11.0	12.0	13.5	10.5
Poor self-rated health, %	9.7	9.3	9.5	9.9	10.5	9.6

RBG random blood glucose, SD standard deviation, MET metabolic equivalent of task hours/day, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, CHD coronary heart disease, TIA transient ischemic attack.

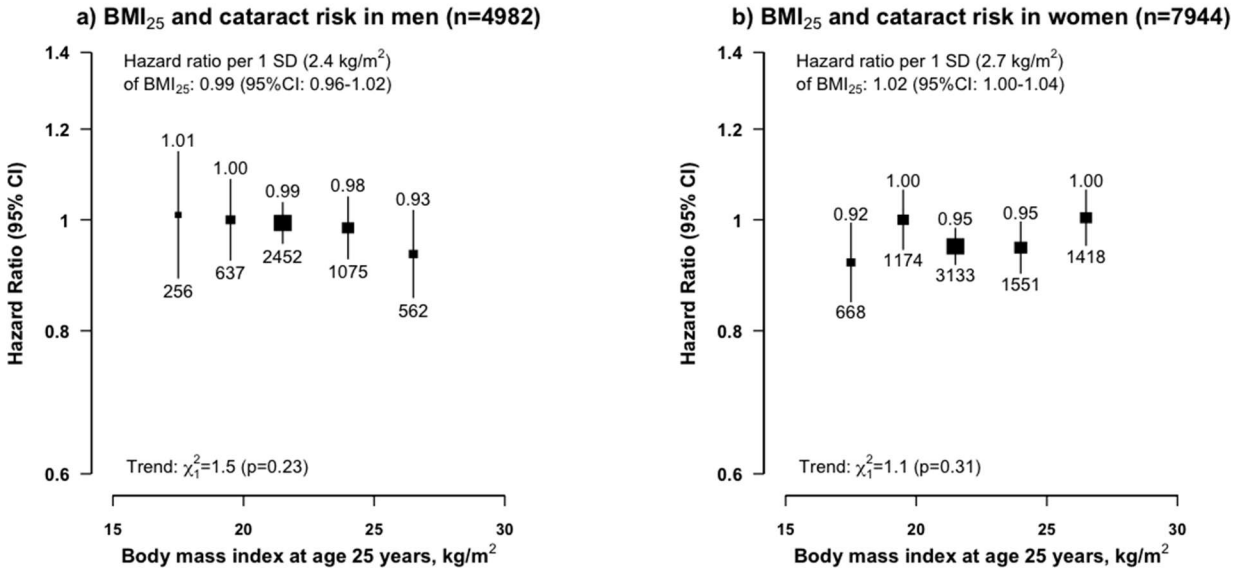
The results were standardised by age at baseline (5-year age group), sex and region, as appropriate.

*Current smokers included current smokers and ex-smokers stopped due to illness.

7.3.3 Adiposity factors and risk of cataract

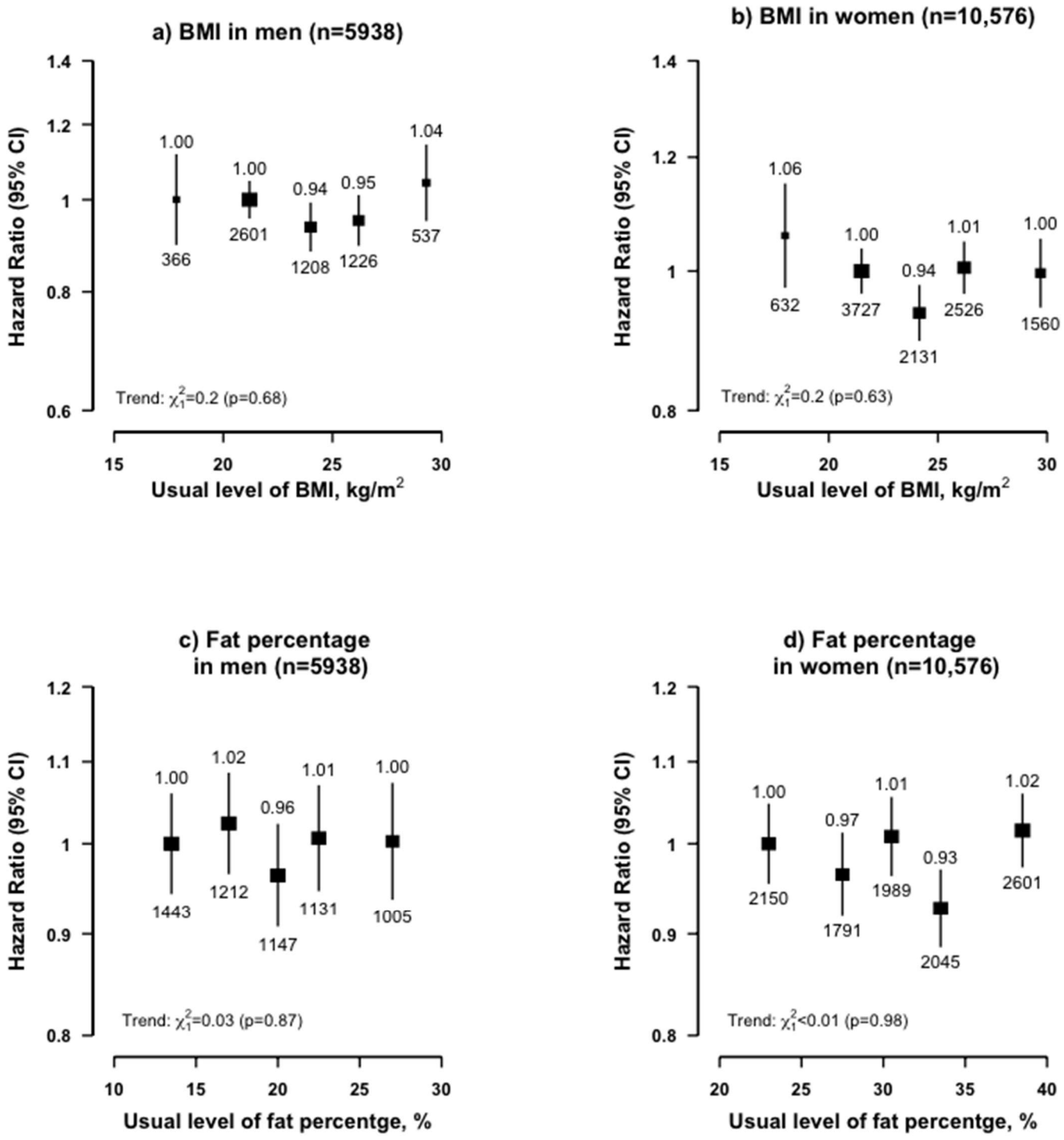
There was no clear association between each of the five general adiposity measurements (including BMI_{25}, BMI, body fat percentage, fat mass, and fat mass index) and risk of cataract (**Figures 7.2**-**7.5** and **Supplementary Table F.2** & **F.3**).

Figure 7.2 Adjusted HRs for cataract by BMI at age 25 years in men and women.



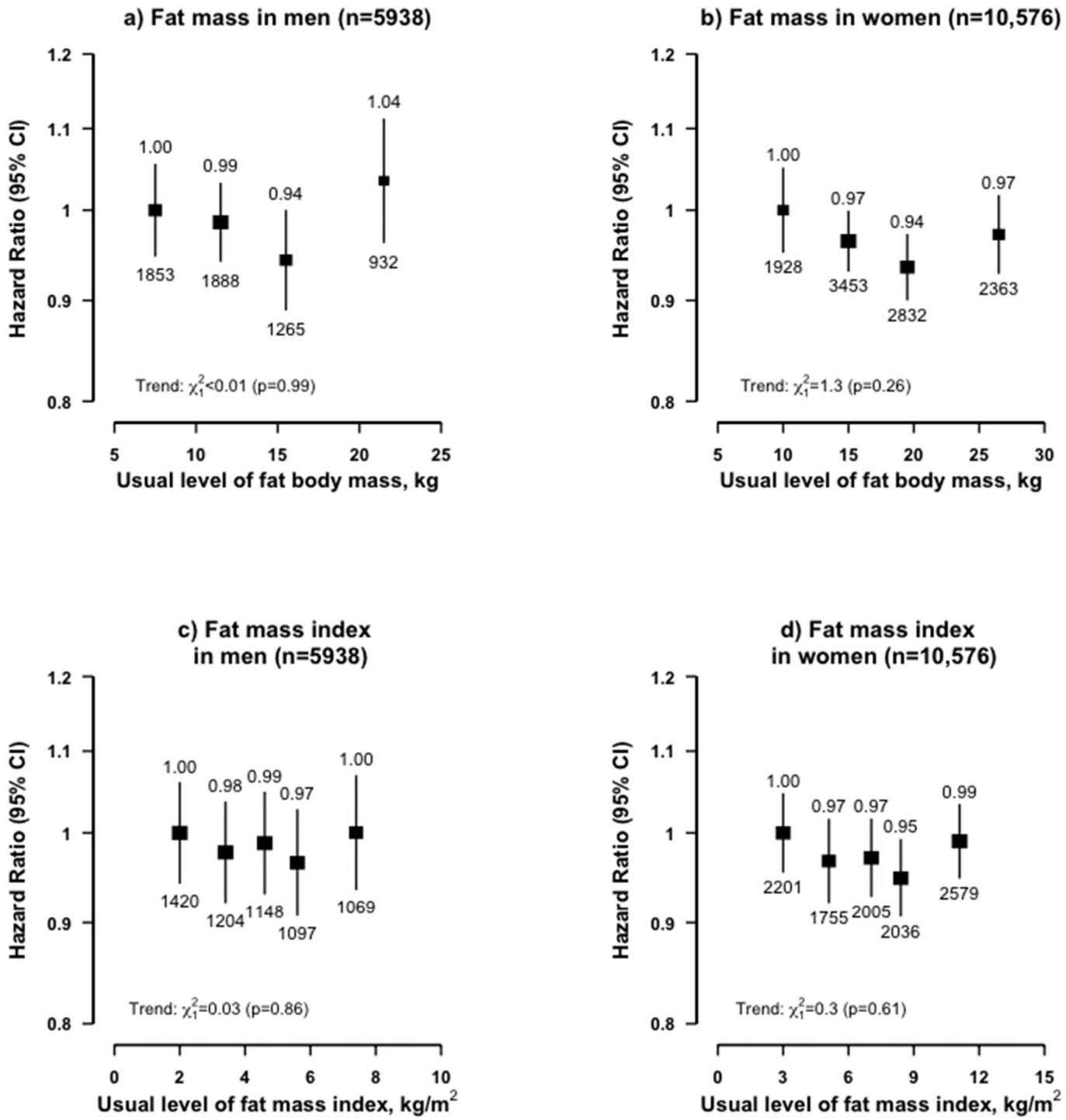
BMI body mass index
N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, baseline BMI, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.

Figure 7.3 Adjusted HRs for cataract by BMI and body fat percentage in men and women.



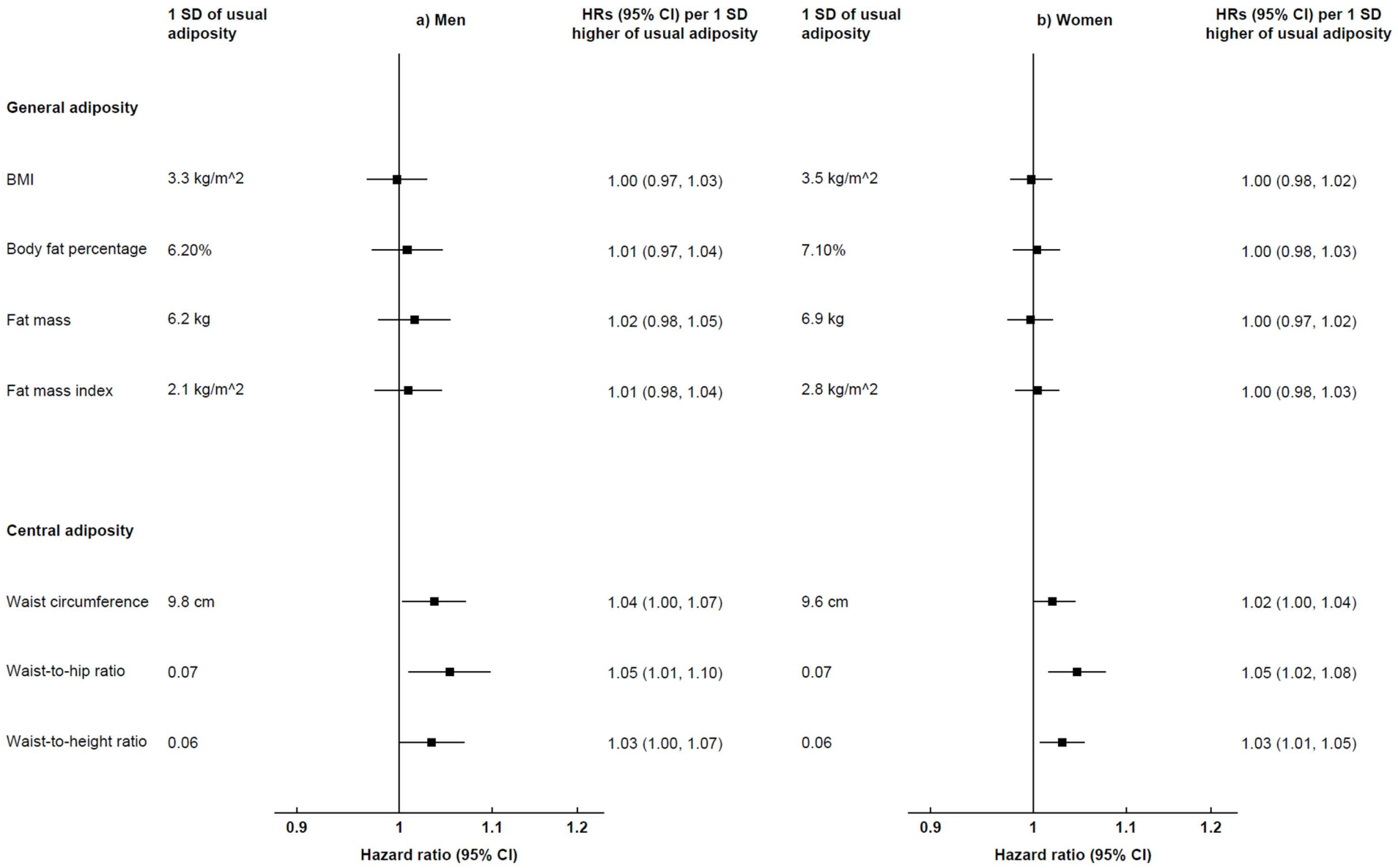
BMI body mass index.
N stands for number of cases.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA; adjusted for the analysis of BMI only), prevalent diabetes, and self-rated health status.
P-value for trend relates to all five groups.

Figure 7.4 Adjusted HRs for cataract by fat mass and fat mass index in men and women.



N stands for number of cases.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status.
P-value for trend relates to all four groups for fat mass and all five groups for fat mass index.

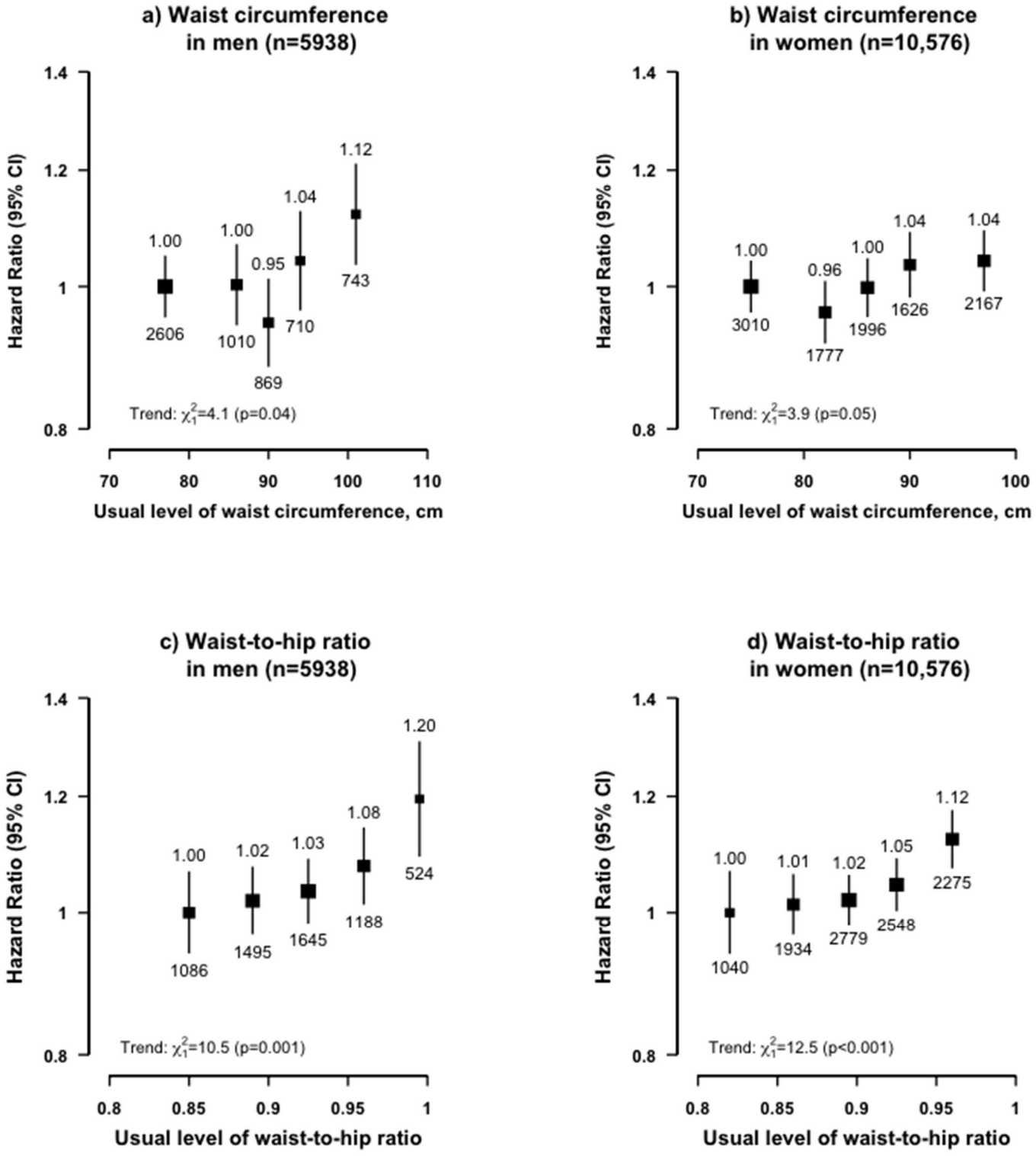
Figure 7.5 Adjusted HRs for cataract by usual levels of central and general adiposity measures.



SD standard deviation, BMI body mass index.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA; adjusted for the analysis of BMI, fat mass, fat mass index, waist-to-hip ratio, and waist-to-height ratio only), prevalent diabetes, and self-rated health status.

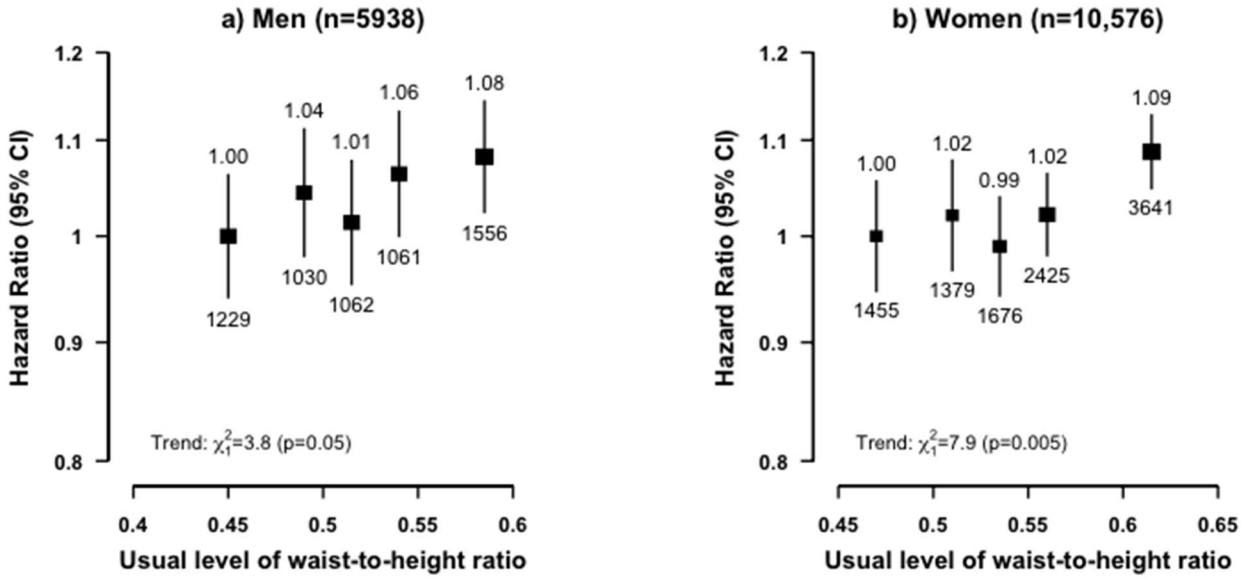
Among the three central adiposity measures, only waist-to-hip ratio was significantly associated with cataract incidence in both men and women, not for waist circumference and waist-to-height ratio (**Figure 7.5**-**7.7** & **Supplementary Table F.4**). There was a clear positive linear association between waist-to-hip ratio and risk of cataract in both men (P_{trend}=0.001 across the five waist-to-hip ratio categories) and women (P_{trend}<0.001), with HRs per 1 SD (0.07 unit in both men and women) of usual waist-to-hip ratio being 1.05 (1.01-1.10) in men and 1.05 (1.02-1.08) in women (**Figure 7.5**-**7.6** & **Supplementary Table F.4**). In men, compared with those in the lowest waist-to-hip ratio category (<0.85, HR=1.00 [95%CI: 0.94-1.06]), the HRs for those with higher waist-to-hip ratio were 1.02 (0.97-1.07), 1.03 (0.99-1.09), 1.08 (1.02-1.14), and 1.10 (1.20-1.30), respectively. The association in women was of similar strength, with HRs in those with higher waist-to-hip ratio being 1.01 (0.97-1.06), 1.02 (0.98-1.06), 1.05 (1.01-1.09), and 1.12 (1.07-1.17), respectively, when compared with women in the lowest waist-to-hip ratio group (<0.80, HR=1.00 [0.94-1.07]).

Figure 7.6 Adjusted HRs for cataract by waist circumference and waist-to-hip ratio in men and women.



N stands for number of cases.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent diabetes, and self-rated health status.
P-value for trend relates to all five groups.

Figure 7.7 Adjusted HRs for cataract by waist-to-height ratio in men and women.

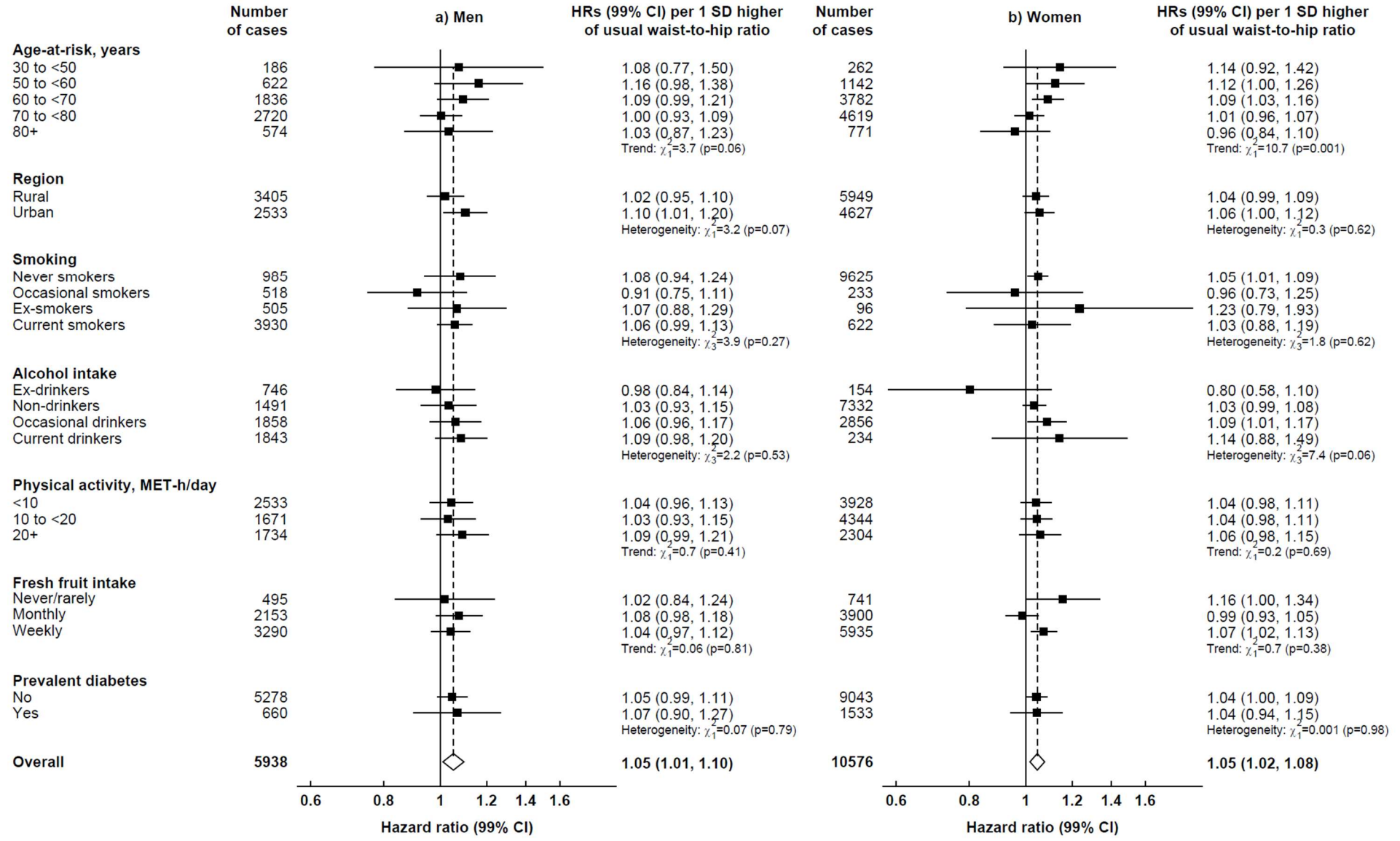


N stands for number of cases.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status.
P-value for trend relates to all five groups.

In men, the positive association between waist-to-hip ratio and risk of cataract was similar across all selected subgroups (**Figure 7.8** and **Figure 7.9**). However, in women the association was significantly stronger in younger age-at-risk groups, and HRs for women with age-at-risk of 30 to <50, 50 to <60, and 60 to<70 years being 1.14 (0.92-1.42), 1.12 (1.00-1.26), and 1.09 (1.03-1.16), respectively (**Figure 7.8**).

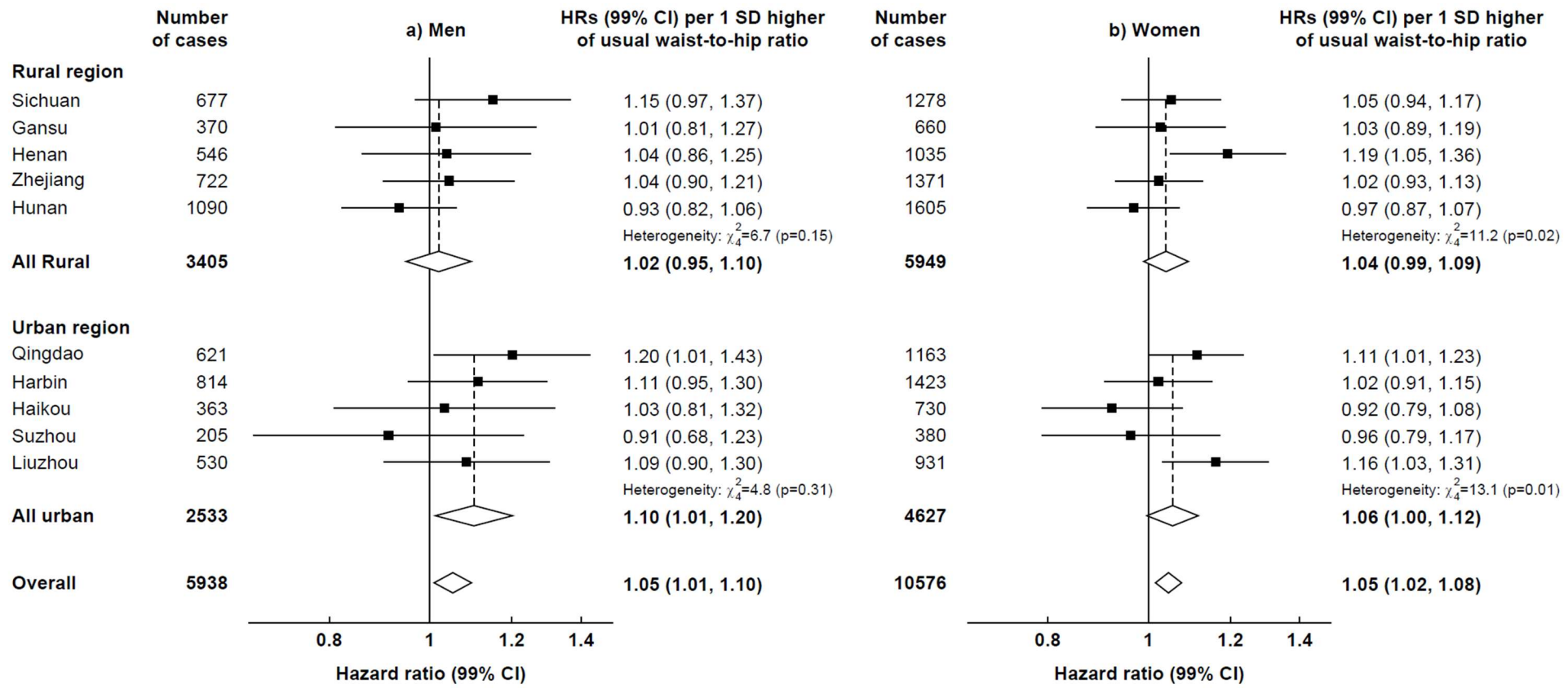
The observed association between waist-to-hip ratio and risk of cataract remained essentially unchanged in sensitivity analyses, except rather large attenuation in HRs (from 1.05 to 1.03 in men and 1.02 in women for 1 SD of waist-to-hip ratio) after excluding participants with prevalent diseases and incident diabetes during study follow-up (**Table 7.4**).

Figure 7.8 Adjusted HRs per 1SD (0.07 unit in both men and women) higher of usual waist-to-hip ratio for cataract by selected population characteristics.



SD standard deviation.
Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status, as appropriate.

Figure 7.9 Adjusted HRs per 1SD (0.07 unit in both men and women) higher of usual waist-to-hip ratio for cataract by region.



SD standard deviation.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status.

Table 7.4 Adjusted HRs per 1SD higher of usual waist-to-hip ratio for cataract - results of sensitivity analysis.

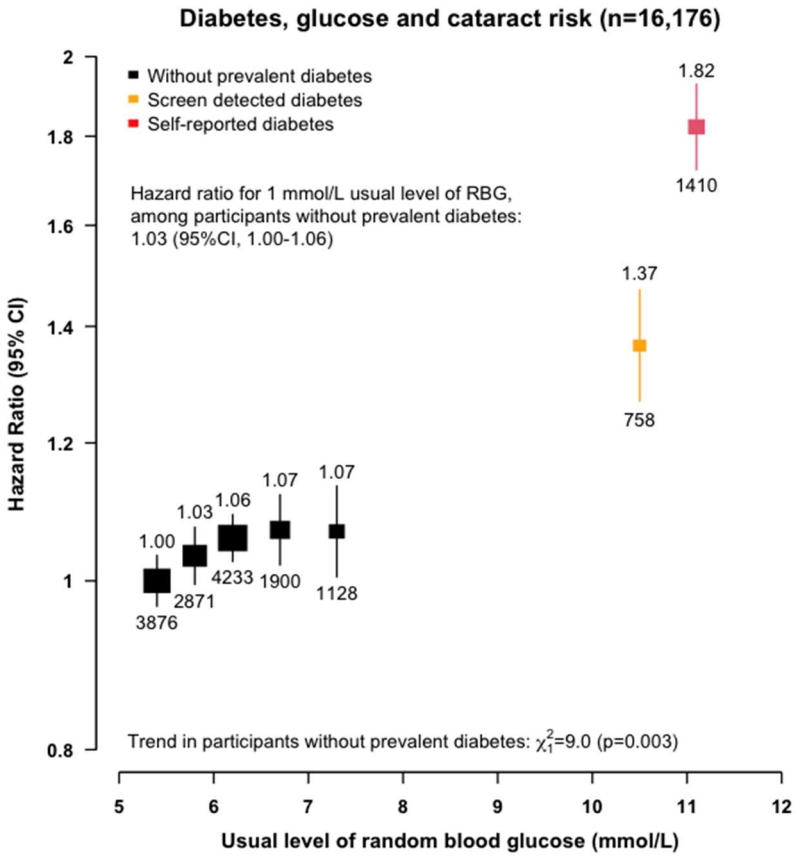
	Per 1SD higher of usual waist-to-hip ratio			
	Per 1SD (0.07 unit) in men		Per 1SD (0.07 unit) in women	
	Number of cases	HRs (95%CI)	Number of cases	HRs (95%CI)
Primary analysis* (n=210,063 in men; 302,389 in women)	**5938**	**1.05 (1.01-1.10)**	**10,576**	**1.05 (1.02-1.08)**
Exclude those aged ≥70 years at study entry (n=193,757 in men; 285,782 in women)	4636	1.06 (1.01-1.11)	8693	1.06 (1.03-1.09)
Exclude those with poor self-rated health (n=191,358 in men; 268,081 in women)	5333	1.05 (1.01-1.10)	9012	1.04 (1.01-1.07)
Exclude those with cancer or CVD at baseline (n=199,123 in men; 287,864 in women)	5376	1.06 (1.01-1.10)	9525	1.04 (1.01-1.07)
Exclude those with cancer, CVD, or diabetes at baseline (n=188,990 in men; 271,844 in women)	4811	1.06 (1.01-1.11)	8264	1.03 (1.00-1.07)
Exclude those with cancer, CVD, or diabetes at baseline, or with incident diabetes during follow-up (n=181,283 in men; 259,634 in women)	4473	1.03 (0.98-1.08)	7538	1.02 (0.98-1.05)
Exclude first 3 years of follow-up (n=210,063 in men; 302,389 in women)	5938	1.06 (1.01-1.10)	10,576	1.04 (1.01-1.07)
Additional adjustment (primary analysis + systolic blood pressure)	5938	1.06 (1.02-1.11)	10,576	1.05 (1.02-1.08)
Additional adjustment (primary analysis + blood glucose)	5938	1.04 (1.00-1.09)	10,576	1.03 (1.00-1.06)
Additional adjustment (primary analysis + life satisfaction)	5938	1.05 (1.01-1.10)	10,576	1.05 (1.02-1.08)

SD standard deviation, CVD cardiovascular disease (including coronary heart disease, stroke, and transient ischemic attack)
Hazard Ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD and stroke/TIA), prevalent diabetes, and self-rated health status.

7.3.4 Diabetes and blood glucose with risk of cataract

Prevalent diabetes was related to a higher risk of cataract. Compared with participants without prevalent diabetes, the HR for those with any prevalent diabetes was 1.56 (1.49-1.63). The HRs for participants with screen-detected and self-reported diabetes were respectively 1.35 (1.25-1.45) and 1.80 (1.70-1.90), when compared with those without prevalent diabetes (1.00, 0.98-1.02). As shown in **Figure 7.10** & **Supplementary Table F.5**, among those without diabetes at baseline, random blood glucose was associated with higher risk of cataract, with each 1 mmol/L usual level of random blood glucose being associated with 3% (HR=1.03, 1.00-1.06) higher risk of

Figure 7.10 Adjusted HRs for cataract by diabetes status and random blood glucose.

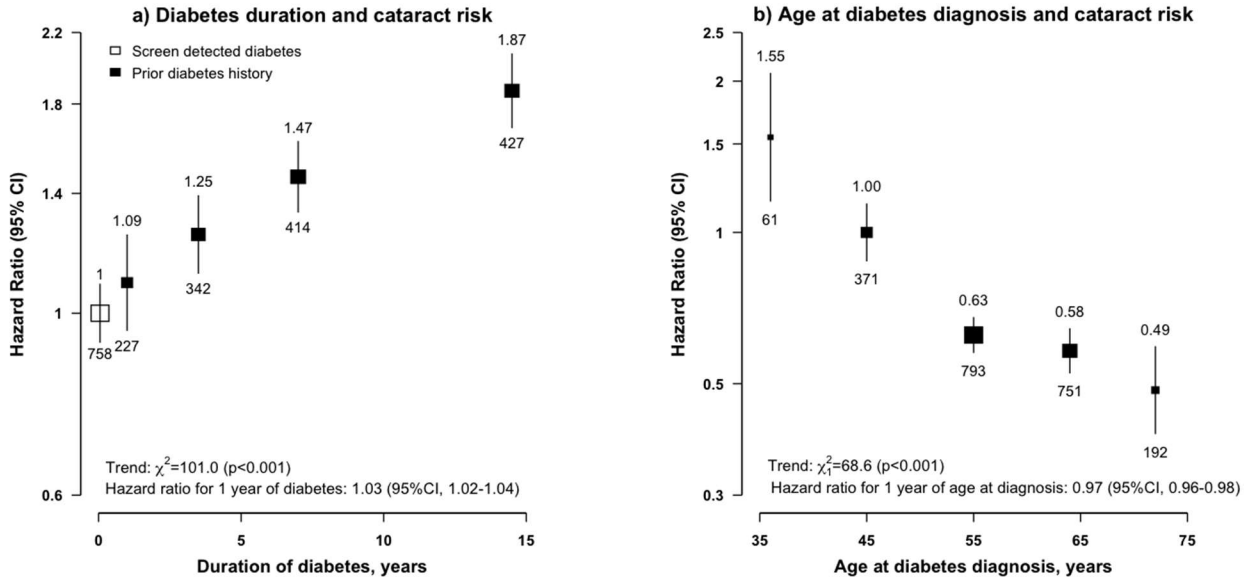


Prevalent diabetes include prior diabetes history and screen detected diabetes.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status and fasting hours.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

cataract (**Figure 7.10** & **Supplementary Table F.5**). Compared to those with baseline random blood glucose level <5.5 mmol/L (HR=1.00, 0.97-1.03), participants with blood glucose levels above 7.0 mmol/L had 7% (1.07, 1.01-1.13) higher risk of cataract. The positive association between random blood glucose and risk of cataract was stronger among those with prevalent diabetes at baseline, with HR of 1.06 (1.05-1.08) per 1 mmol/L usual level of random blood glucose.

There was a clear positive linear association (*P*<0.001) between duration of diagnosed diabetes and risk of cataract among participants with prevalent diabetes, with HR of 1.03 (1.02-1.04) per 1 year of diabetes duration (**Figure 7.11a** & **Supplementary Table F.5**). Compared with those

Figure 7.11 Adjusted HRs for cataract by duration of diabetes and age at diabetes diagnosis in participants with prevalent diabetes (n=2168).

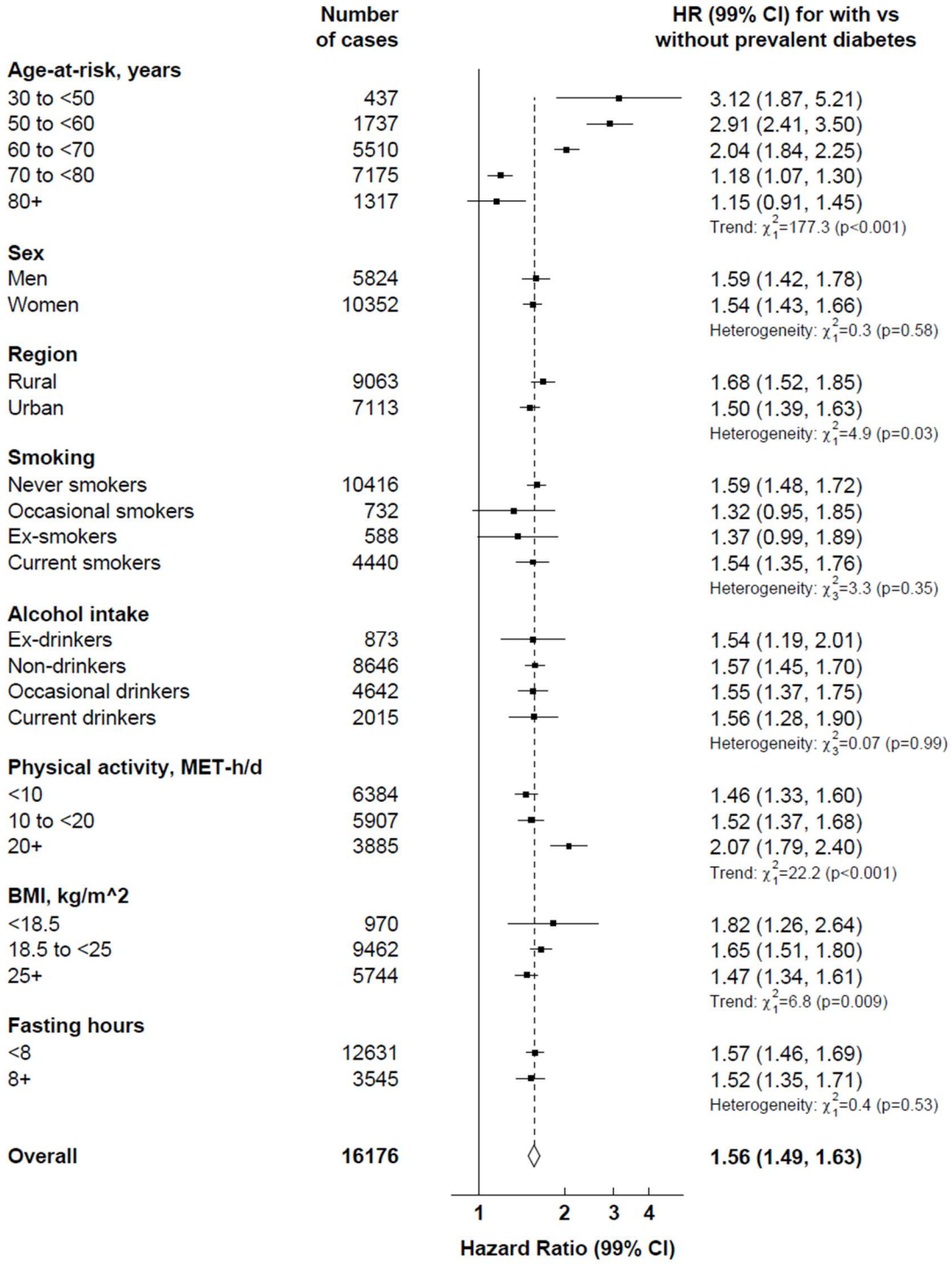


Prevalent diabetes include prior diabetes history and screen detected diabetes.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status, and fasting hours.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.

who had screen-detected diabetes (i.e., diabetes duration imputed as 0, HR=1.00 [0.92-1.08]), participants with self-reported diabetes of 2 to <5, 5 to <10, and ≥10 years had 25% (1.25, 1.12-1.39), 47% (1.47, 1.33-1.62), and 87% (1.87, 1.69-2.07) higher risks of cataract, respectively. In contrast, age at diabetes diagnosis was inversely associated with risk of cataract, with 1 year age later at diabetes diagnosis being associated with 3% (0.97, 0.96-0.98) lower risk of cataract (**Figure 7.11b** & **Supplementary Table F.5**). Compared to participants with diabetes diagnosed at 40 to <50 years (HR=1.00, 0.88-1.14), HRs for those with age at diabetes diagnosis of <40, 50 to <60, 60 to <70, and ≥70 years were 1.55 (1.16-2.06), 0.63 (0.58-0.68), 0.58 (0.53-0.64), and 0.49 (0.40-0.59), respectively. Among participants with self-reported diabetes, taking anti-diabetic medication (i.e., hypoglycaemic medications, like insulin and metformin) was associated with a higher risk of cataract (HR=1.16, 1.00-1.33), compared with not taking medication.

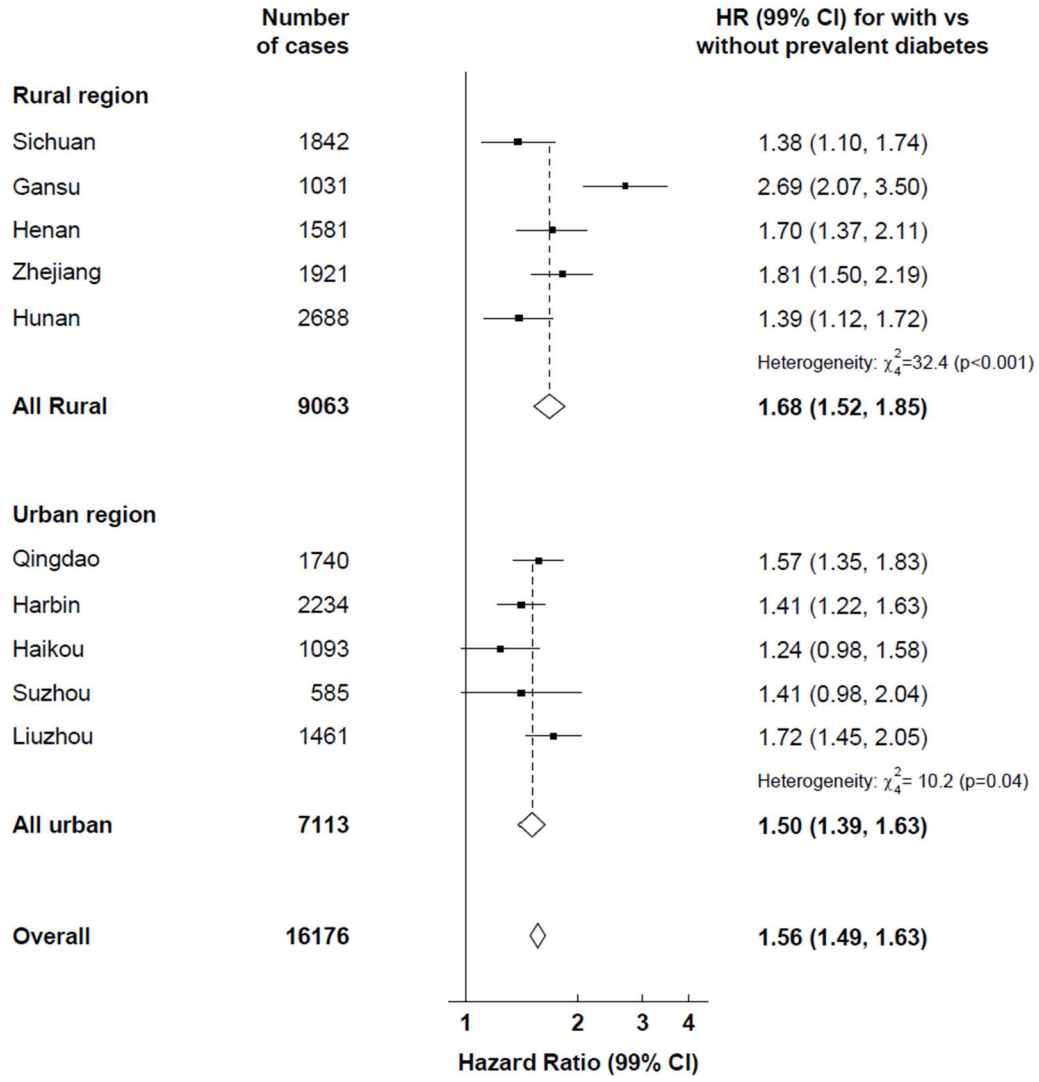
The positive association between prevalent diabetes and risk of cataract was largely consistent across selected subgroups, though the risk estimates were different across subgroups defined by age-at-risk, physical activity, and BMI (**Figure 7.12** & **Figure 7.13**). Diabetes was associated with more than 3 times higher risk of cataract in those with age-at-risk <50 years, but the corresponding risk was only 18% higher in those with age-at-risk of 70 to <80 years. Diabetes was associated with more than 2 times higher risk of cataract in those with more than 20 MET-hours/day of total physical activity, but the corresponding risk was around 1.5 times in those with total physical activity less than 20 MET-hours/day. The HRs for prevalent diabetes were 1.82 (1.26-2.64), 1.65 (1.51-1.80), and 1.47 (1.34-1.61), respectively, among participants with BMI of <18.5, 18.5 to <25.0, and ≥25.0 kg/m^2.

Figure 7.12 Adjusted HRs of cataract associated with prevalent diabetes by selected population characteristics.



Prevalent diabetes include prior diabetes history and screen detected diabetes.
Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status, and fasting hours, as appropriate.

Figure 7.13 Adjusted HRs of cataract associated with prevalent diabetes by region.

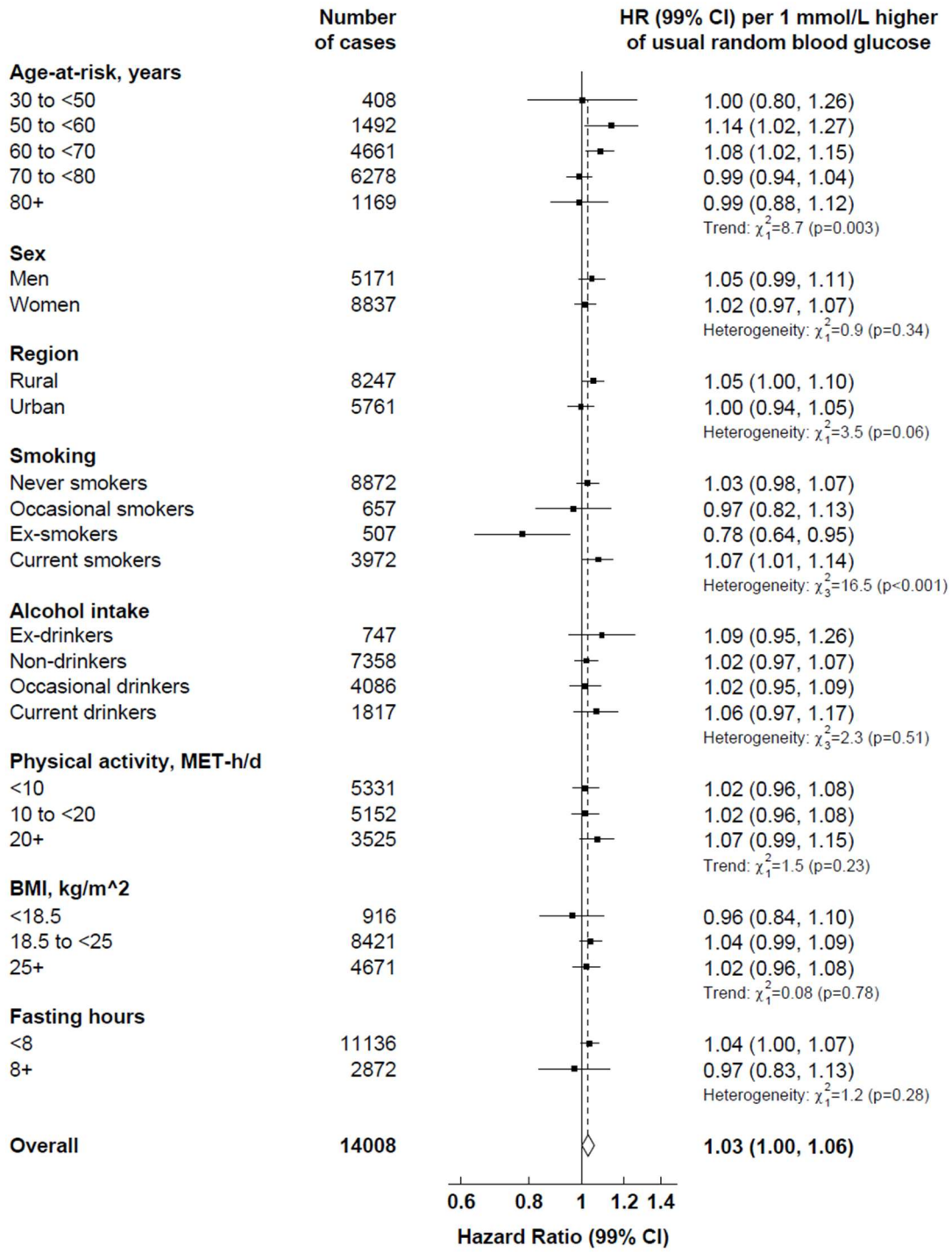


Prevalent diabetes include prior diabetes history and screen detected diabetes.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status, and fasting hours.

The positive association between random blood glucose and risk of cataract in participants without prevalent diabetes was consistent across selected subgroups, though the risk estimates were different across subgroups defined by age-at-risk and smoking (**Figure 7.14** & **Figure 7.15**). Per 1 mmol/L higher usual random blood glucose was associated with 14% and 8% higher risk of cataract among those with age-at-risk of 50 to <60 and 60 to <70 years, respectively, but the associations were not statistically significant among those with age-at-risk of <50 or >70 years. Per 1 mmol/L higher usual random blood glucose was associated with 22% (HR=0.78, 0.64-0.95) lower risk of cataract among ex-smokers (stopped by choice), while the associations among other smoking categories ranged from 0.97 (HR) to 1.07.

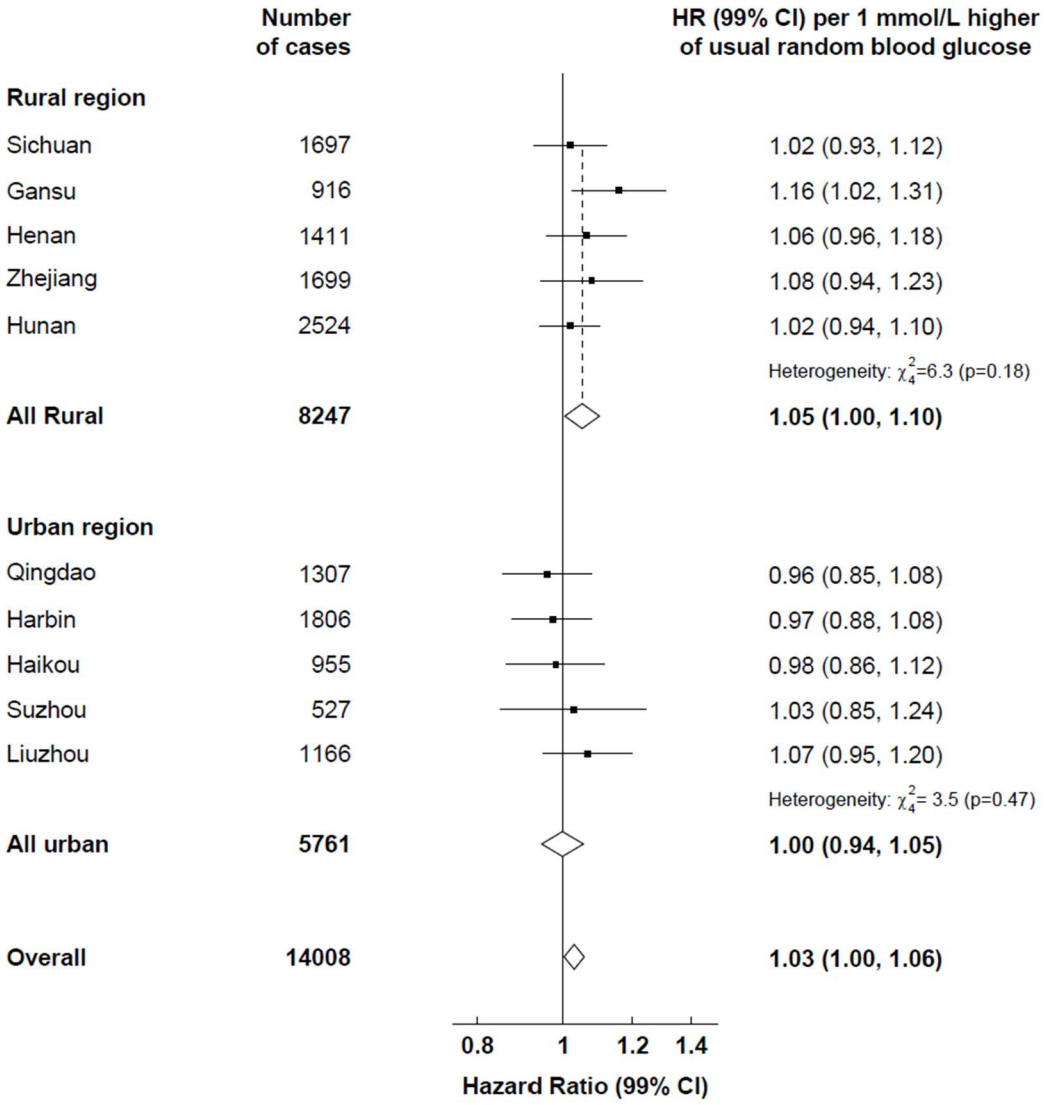
The observed associations between prevalent diabetes and random blood glucose with risk of cataract remained largely unchanged in sensitivity analyses (**Table 7.5** & **Table 7.6**).

Figure 7.14 Adjusted HRs per 1mmol/L higher of usual random blood glucose for cataract by selected population characteristics in participants without prevalent diabetes.



Prevalent diabetes includes prior diabetes history and screen detected diabetes.
Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status, and fasting hours, as appropriate.

Figure 7.15 Adjusted HRs per 1mmol/L higher of usual random blood glucose for cataract by region in participants without prevalent diabetes.



Prevalent diabetes includes prior diabetes history and screen detected diabetes.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status, and fasting hours.

Table 7.5 Adjusted HRs for cataract by prevalent diabetes - results of sensitivity analysis.

	With vs without prevalent diabetes	
	Number of cases	HRs (95%CI)
Primary analysis[2] (n=504,349)	16,176	1.56 (1.49, 1.63)
Exclude those aged ≥70 years at study entry (n=471,798)	13,032	1.71 (1.62, 1.80)
Exclude those with poor self-rated health (n=452,430)	14,069	1.50 (1.42, 1.58)
Exclude those with cancer or CVD at baseline (n=479,091)	14,582	1.60 (1.52, 1.68)
Exclude first 3 years of follow-up (n=504,349)	16,176	1.56 (1.49, 1.64)
Excluding individuals from Zhejiang[3] (n=450,551)	14,255	1.53 (1.46, 1.61)
Exclude those with estimated type 1 diabetes (n=504,281)	16,168	1.56 (1.48, 1.63)
Additional adjustment (primary analysis + systolic blood pressure)	16,176	1.57 (1.49, 1.64)
Additional adjustment (primary analysis + life satisfaction)	16,176	1.56 (1.49, 1.63)
Additional adjustment (primary analysis + body fat percentage)	16,176	1.56 (1.49, 1.63)
Additional adjustment (primary analysis + waist circumference)	16,176	1.54 (1.47, 1.61)
Additional adjustment (primary analysis + waist-to-hip ratio)	16,176	1.54 (1.47, 1.61)

CVD cardiovascular disease (including coronary heart disease, stroke, and transient ischemic attack)
[1]Prevalent diabetes include prior diabetes history and screen detected diabetes.
[2]Hazard ratios were stratified by age-at-risk (5-year groups), sex and 10 study regions, and adjusted for baseline age (continuous), education, income, occupation, smoking, alcohol, physical activity (continuous), fresh fruit, self-rated health status, and fasting hours.
[3]In Zhejiang, 72.5% of participants reported not having consumed food for ≥8 hours before testing.

Table 7.6 Adjusted HRs per 1 mmol/L higher usual random blood glucose for cataract in participants without prevalent diabetes - results of sensitivity analysis.

	Per 1mmol/L higher usual RBG	
	Number of cases	HRs (95%CI)
Primary analysis[2] (n=474,230)	14,008	1.03 (1.00, 1.06)
Exclude those aged ≥70 years at study entry (n=445,424)	11,251	1.04 (1.01, 1.07)
Exclude those with poor self-rated health (n=428,596)	12,401	1.03 (1.00, 1.06)
Exclude those with cancer or CVD at baseline (n=453,086)	12,779	1.03 (1.00, 1.06)
Exclude first 3 years of follow-up (n=474,230)	14,008	1.03 (1.00, 1.06)
Excluding individuals from Zhejiang[3] (n=423,266)	12,309	1.03 (1.00, 1.05)
Additional adjustment (primary analysis + systolic blood pressure)	14,008	1.03 (1.00, 1.06)
Additional adjustment (primary analysis + life satisfaction)	14,008	1.03 (1.00, 1.06)
Additional adjustment (primary analysis + body fat percentage)	14,008	1.03 (1.00, 1.06)
Additional adjustment (primary analysis + waist circumference)	14,008	1.03 (1.00, 1.05)
Additional adjustment (primary analysis + waist-to-hip ratio)	14,008	1.03 (1.00, 1.05)

RBG random blood glucose, CVD cardiovascular disease (including coronary heart disease, stroke, and transient ischemic attack)
[1]Prevalent diabetes include prior diabetes history and screen detected diabetes.
[2]Hazard ratios were stratified by age-at-risk (5-year groups), sex and 10 study regions, and adjusted for baseline age (continuous), education, income, occupation, smoking, alcohol, physical activity (continuous), fresh fruit, self-rated health status, and fasting hours.
[3]In Zhejiang, 72.5% of participants reported not having consumed food for ≥8 hours before testing.

7.4 Discussion

7.4.1 Summary of findings

In this prospective study with a large Asian population, waist-to-hip ratio (a measure of central adiposity) was positively associated with risk of cataract in both men and women, but no clear association was found for other adiposity measures. The HRs per 1 SD of usual waist-to-hip ratio (0.07 unit in both sexes) were 1.05 (1.01-1.10) and 1.05 (1.02-1.08) respectively in men and women, and those in the highest waist-to-hip ratio category had 20% in men and 12% in women higher cataract risk than those in the lowest category. The association in women, but not in men, was slightly stronger in younger age groups.

Diabetes and a higher level of random blood glucose were both associated with a higher cataract risk. Compared with those without prevalent diabetes at baseline, participants with prevalent diabetes at baseline had a 35% and 80% higher risk of cataract for screen-detected and self-reported diabetes respectively. The HRs per 1 mmol/L usual level of random blood glucose were 1.03 (1.00-1.06) and 1.06 (1.05-1.08) respectively among those without and with prevalent diabetes at baseline.

7.4.2 Adiposity factors and risk of cataract

A large number of prospective studies have assessed the association between adiposity and cataract risk, but findings have been inconsistent (**Supplementary Table B.8**). Studies on general adiposity mainly used BMI to measure adiposity, and among the 14 such studies, 6 (all among Western populations) reported a positive association, but 8 (4 among Western populations and

4 among Asian populations) observed no clear association. Among the studies suggesting a positive association, HRs for those with BMI ≥30 kg/m^2 ranged from 1.10 (1.06-1.15) to 1.44 (1.21-1.72) compared with those in the lowest BMI categories (either <20, <23, <25, or <30 kg/m^2)[93,94,95,92,78,96]. Two studies compared the linear association between BMI and cataract risk in men and women separately, but found conflicting results. One study involving 133K U.S. nurses and health professionals aged 45+ followed for 10 years found that each increment of 5 kg/m^2 of BMI was associated with 12% (1.12, 1.07-1.17) higher risk of cataract in women but not in men (1.03, 0.93-1.15)[97]. However, a positive association was found in men but not in women in another study which followed-up 40K U.S. athletes aged 38-44 years for 7 years, with HRs per 1kg/m^2 BMI higher being 1.04 (1.01-1.07) and 0.97 (0.91-1.03) in men and women, respectively[78]. The current study in a general Chinese population found no clear association between BMI and risk of cataract, which is consistent with results from the four previous studies among Asian populations.

Current evidence on the association between central adiposity and risk of cataract included studies on waist circumference and waist-to-hip ratio measures. The four studies on waist circumference were all conducted among Western populations, but had inconsistent findings. Two studies, conducted in the U.S.[78] (40K non-diabetic athletes aged 38-44 years followed-up for 7 years) and the U.K.[96] (153K participants aged 40-70 years for followed-up for 10 years), both found positive associations in men and women, with per increment of 1cm waist circumference associated with respectively 2% (1.02, 1.00-1.03) and 4% (1.04, 1.01-1.06) higher risk of cataract in men and women in the U.S. study, and 9% (1.09, 1.06-1.13) higher risk when comparing

participants with high (≥102cm in men and ≥88cm in women) and low (<102cm in men and <88cm in women) waist circumference measurements in the U.K. study. The other two studies[98,99], conducted among Swedish populations (with sample sizes of 35K and 45K, participants aged 45-79 and 49-83 years, and follow-up periods of 8 and 15 years), found no clear differences of cataract risk between participants with waist circumference of <94/≥94cm in one study in men and <80/≥80cm in another study in women. Like the findings in the Swedish populations, the current study in a Chinese population found no statistically significant association between waist circumference and risk of cataract in both men and women.

The three studies on waist-to-hip ratio and risk of cataract also had inconsistent findings, with two studies (153K participants aged 40-70 years followed-up for 10 years in the U.K.[96], and 17K male physicians aged 40-84 years followed-up for 14 years in the U.S.[100]) in Western populations suggesting a positive association, while the study[48] (460 participants aged 65+ years followed-up for 7 years) in an Asian population found no clear association (probably due to the small sample size). In the U.K. study, participants with a higher level of waist-to-hip ratio (≥1.00 in men and ≥0.85 in women) had a 14% (1.14, 1.09-1.19) higher risk of cataract than those with a lower level of waist-to-hip ratio (<1.00 in men and <0.85 in women)[96]. In the U.S. study, male physicians in the top waist-to-hip ratio group (>0.985) had more than 30% (1.31, 1.02-1.67) higher risk of cataract than those in the lowest waist-to-hip ratio group (<0.897)[100]. Similar to the previous two Western studies with large sample sizes, the current study observed a positive linear association between waist-to-hip ratio and risk of cataract in both men and women.

The association between waist-to-hip ratio and risk of cataract was stronger in women with younger baseline age. Younger women with a higher waist-to-hip ratio might have more severe metabolic issues (e.g., insulin resistance, inflammation), which lead to more pronounced elevation in oxidative stress and potential cataract development[229]. Probably due to a lack of power (as the event size decreased by ~25%), the association between waist-to-hip ratio and risk of cataract became borderline non-significant after excluding participants with prevalent diseases and incident diabetes during study follow-up, but the HR did not essentially change.

Overall, with comprehensive assessment of the associations between five general adiposity and three central adiposity measures with risk of cataract, the current study found central adiposity measure waist-to-hip ratio (rather than general adiposity or other central adiposity measure) is positively associated with risk of cataract in both men and women. BMI is known as a relatively good measurement of general adiposity[230]. However, individuals with the same BMI could have different body composition and fat distribution. Other adiposity measures used in this study could evaluate fat percentage (i.e., body fat percentage) or absolute amount of abdominal fat (i.e., waist circumference), but they were not able to represent fat distribution. Therefore, this study suggested the distribution of body fat is associated with risk of cataract. These findings demonstrated that weight-control based cataract prevention programs should focus on balancing fat distribution (e.g., promote dietary habits that influence fat distribution) instead of general weight loss.

Given that no clear association was found between waist circumference and risk of cataract, it

seemed the positive association between waist-to-hip ratio and risk of cataract might be explained by the protective effect of hip fat on health outcomes (e.g., cardiovascular diseases and diabetes) as observed in other studies[306,307,308]. However, analyses using CKB data found no clear association between hip circumference and risk of cataract. These finding suggests that the elevated risk is not driven by waist fat or hip fat alone, but rather by the relative distribution of fat between the waist and hip (i.e., the relative deficiency of hip fat compared to waist fat).

Several mechanisms could potentially explain the positive association between waist-to-hip ratio and risk of cataract. Firstly, individuals with imbalanced fat distribution are likely to have higher level of leptin[309], which is related to elevated oxidative stress. Leptin is a hormone that helps to reduce food intake and regulate body weight, and is proportional to the amount of body fat[234]. Therefore, individuals with imbalanced fat distribution have high levels of circulating leptin. However, leptin is also related to higher levels of reactive oxygen accumulation, which leads to molecular damage and elevated level of oxidative stress[235,236]. Excessive oxidative stress could lead to damaged lens protein and accelerate cataract formation. Secondly, waist-to-hip ratio reflects the imbalance of abdominal fat, and a higher waist-to-hip ratio indicates more abdominal fat relative to hip fat. Visceral fat (also called intra-abdominal fat) is the belly fat deep within the abdominal cavity. Visceral fat secretes a protein called retinol-binding protein 4 (RBP4), which was found to be associated with higher level of insulin resistance[231,232,233]. Therefore, higher waist-to-hip ratio and accumulation of visceral fat can lead to glucose intolerance and type 2 diabetes, which is associated with cataract formation. Lastly, individuals with obesity and imbalanced fat distribution have elevated levels of C-reactive protein [310], an inflammation marker

suggested to reflect ocular and systematic inflammatory process and associated with a higher risk of cataract[196,235].

7.4.3 Diabetes and blood glucose with risk of cataract

Existing evidence on the association between diabetes and cataract incidence is largely consistent, but mainly based on Western populations. A literature review of prospective studies identified 17 studies, among which 10 were conducted among Western populations, 3 among African populations, 3 among Asian populations, and one in a Latin American population (**Supplementary Table B.9**). Among the 17 studies, 14 studies found a positive association, and 3 found no clear association with cataract risk. Among the studies suggesting a positive association, the relative risk of cataract ranged from 1.43 (1.10-1.86)[99] to 4.10 (3.24-5.20)[63]. Evidence from Asian populations is limited but consistent. Two studies, conducted in Singapore[222] (6000 participants aged 45+ years followed-up for 6 years) and Taiwan[48] (460 participants aged 65+ years followed-up for 7 years), both found a positive association between diabetes and risk of cataract, with HRs of 1.90 (1.54-2.33) and 2.43 (1.02-5.81), respectively. Similar to these two studies, the current study in a large Chinese population found a positive association between diabetes and risk of cataract.

In this study, there was a positive association between duration of diagnosed diabetes, and an inverse association between age at diabetes diagnosis, with risk of cataract among participants with prevalent diabetes, which is consistent with findings from studies conducted in UK[237,238] and Indian[239] populations. However, this study also found that taking anti-diabetic medication was

associated with a higher risk of cataract compared with not taking medication among participants with self-reported diabetes. This may be explained by confounding by indication because those taking medication tend to have more severe diabetes, which could lead to elevated risk of cataract[240].

Evidence on the association between blood glucose and risk of cataract is highly limited, and only one prospective study (with small sample size) was found. The Blue Mountains Eye Study followed-up 2400 Australians aged 49+ years for 10 years found an increment of 1 mmol/L fasting blood glucose was associated with 23% (1.23, 1.01-1.48) higher odds of cataract[105], which is consistent with findings from the current study.

In this study, the positive associations between prevalent diabetes and random blood glucose with risk of cataract was stronger in participants with younger baseline age. This study also found the association between prevalent diabetes and cataract risk was stronger in participants with higher levels of total physical activity and lower levels of BMI. Individuals with higher total physical activity tended to be younger and with lower BMI compared to their counterparts (as shown in Table 6.2 in Chapter 6.3.1), and they may be less likely to adhere to diabetes management recommendations, which could lead to poorer blood glucose control and higher cataract risk[243]. In this study, random blood glucose was inversely associated with cataract risk among ex-smokers who stopped by choice, despite positive associations identified in other smoking categories. This inverse association might be due to reverse causation as ex-smokers stopped by choice might adopt healthier lifestyles (e.g., better dietary habits, regular physical

activity) and better glucose management, which result in a lower observed risk of cataract among ex-smokers stopped by choice.

The associations between diabetes and blood glucose with risk of cataract could be explained by the osmotic stress in eye lens introduced by elevated level of blood glucose. High levels of glucose in the blood are converted to sorbitol (a type of carbohydrate) in the eye, and this process creates osmotic stress[245]. Osmotic stress might be related to cataract formation through two mechanisms. Firstly, osmotic stress in the eye could draw fluid into eye lens to disturb the integrity and structure of lens fibers, which leads to the formation of lens opacities[246]. Secondly, osmotic stress is related to the production of free radicals, impaired antioxidation, and elevated levels of oxidative stress, which could damage lens fibers and accelerate cataract formation[247,248].

7.4.4 Strengths and limitations

The strengths of this study include the large sample size, comprehensive assessment of a range of general adiposity and central adiposity factors at baseline and resurveys, and the detailed assessment of diabetes status. The current study also has several limitations. Firstly, as mentioned previously, there were several limitations of cataract data in CKB (i.e., lack of participants' prior cataract surgery history, no cataract registry in China, subtypes of cataract are unknown). It is important to mention that the subtypes of cataract are not classified in CKB, which limits the current association analysis to cataract instead of the three subtypes (i.e., nuclear, cortical, and posterior subcapsular cataract). Some previous studies have suggested diabetes and blood glucose were only associated with one/two subtype(s) of cataract[249,105]. For example, the

Visual Impairment Project study found a positive association between diabetes and posterior subcapsular cataract, but no associations were observed for cortical and nuclear cataract[249]. The Blue Mountains Eye Study suggested blood glucose was positively associated with cortical and nuclear cataract, but no association was found for posterior subcapsular cataract[105]. Secondly, the random blood glucose data for 8341 participants (1.6% of the total study population) were missing in CKB, which might lead to selection bias due to healthy volunteer effect. Participants with missing data on random blood glucose at baseline had lower socio-economic status (i.e., resided in rural regions, had less formal education and lower household income) than those with random blood glucose measured at baseline study. However, the proportion of missing data on random blood glucose was small (1.6%), so the impact should be minor. Thirdly, due to limitation of data, the current study was only able to explore the association between BMI at age 25 year and risk of cataract. Therefore, it remains unknown whether other adiposity measures at age 25 years are associated with risk of cataract.

7.5 Summary

In this chapter, the associations between major cardiometabolic factors (adiposity, diabetes, and blood glucose) and cataract incidence were assessed. In CKB, waist-to-hip ratio (a measure of central adiposity) was positively linearly associated with risk of cataract. There was a positive association between diabetes and blood glucose with risk of cataract. The current study findings highlight the importance of fat distribution control and maintaining healthy blood glucose level for cataract prevention.

8 The combined association of cataract risk factors

8.1 Introduction

Cataract is a major contributor to global blindness and visual impairment, and it accounted for half of the global blindness and one third of the visual impairment in 2020[18,19]. As presented in the previous chapters (Chapter 5-7) of this thesis, several lifestyle and cardiometabolic factors (e.g., smoking, diabetes) have been associated with cataract risk independently. However, the combined association of those risk factors has not been quantified, and such knowledge is critical for the development of cataract prevention strategies.

Individual-based and population-wide strategies are the two main approaches for disease prevention. The "high-risk" strategy, a typical individual-based approach to disease prevention, focuses on prioritising public health resources to individuals with the highest relative risk in the population and provide targeted individual-level protection[257,258]. It offers a cost-effective solution by using limited resources and producing interventions tailored to individuals[257]. However, it is a temporary solution that focuses on risk reduction among high-risk individuals rather than addressing the underlying causes of the disease in the whole population. Alternatively, the "population-wide" strategy calls for lowering levels of risk in the population as a whole, instead of focusing only on the high-risk individuals[257,258]. This strategy is effective in addressing the underlying causes of the disease in the entire population, though it faces challenges such as small individual benefits and poor motivation among participants[257]. Understanding cataract disease patterns among participants with different numbers of unhealthy behaviours could help in evaluating an appropriate strategy for cataract prevention.

A health index method, which generates a combined lifestyle index based on key health behaviours and health factors, is a reasonable approach to estimate the potential combined impact of multiple lifestyle factors on health and well-being[253,254]. *Life's Essential 8* is a well-known health index developed by the American Heart Association to estimate the combined associations of eight health factors with cardiovascular health (include greater cardiovascular diseases [CVD]-free survival and higher quality of life). The eight health factors include diet, physical activity, nicotine use, sleep quality, body weight, blood lipids, blood glucose, and blood pressure, and the average of these eight single health factors were used to represent the overall health index[250]. *MEDLIFE* is a similar health index used to assess the adherence to a Mediterranean healthy lifestyle, which consist of 28 factors covering health behaviours including Mediterranean dietary habits, alcohol consumption, physical activity, sleep quality, and social engagement, with risks of various chronic diseases (including CVD, certain cancers, and metabolic diseases)[251,252]. One mark is assigned to each of the 28 factors based on risk level and the sum of marks is calculated for each individual as their *MEDLIFE* index. Both the *Life's Essential 8* and *MEDLIFE* developed an index, which was associated with disease-free survival and quality of life and such findings were used to promote healthy lifestyles, reduce disease burden, and improve health outcome of the entire population. Besides the *Life's Essential 8* and *MEDLIFE*, several other similar health indices combining different sets of health factors in relation to various health outcomes have been developed[255,256]. However, this approach has not been used previously to examine the association of multiple health factors with cataract risk. This knowledge might provide valuable insight on population strategies for prevention of cataract, which is a major contributor to the global burden of blindness and visual impairment.

The population attributable fraction (PAF)[259] is a measurement used to assess the proportion of disease cases in a population that can be attributed to a particular risk factor. It helps estimate the potential public health impact if exposure to a certain risk factor were reduced or eliminated. The PAF can be used to estimate the number of cataract cases that could theoretically be prevented if the population were not exposed to a set of established lifestyle and cardiometabolic risk factors.

Based on the six major lifestyle and cardiometabolic risk factors identified in previous chapters, the current chapter aims to use a health index approach to examine the combined association of these lifestyle and cardiometabolic factors with cataract incidence. The specific objectives of this chapter include:

1) To assess the shape and strength of the association of the health index;
2) To investigate the PAF of the health index;
3) To inform public health policy recommendations for cataract prevention.

8.2 Methods

Detailed information about the CKB study design and data collection methods has been provided in Chapter 3. In brief, the CKB is a prospective cohort study involving 512 726 adults aged 30-79 years from 10 regions in China, with extended followed-up for 11 years. Information on a wide range of socio-economic, lifestyle, and cardiometabolic factors was collected at the baseline survey and subsequent resurveys.

8.2.1 Definition of *Cataract Health Index*

Based on findings from Chapters 5-7, six lifestyle and cardiometabolic factors (i.e., smoking, alcohol consumption, physical activity, fresh fruit consumption, adiposity, and diabetes) were selected to construct a *Cataract Health Index* (*CHI*) to investigate the combined associations of lifestyle and cardiometabolic risk factors with cataract incidence. Coding of the components of the *CHI* is presented below.

Coding of smoking:

As shown in Chapter 5, smoking had a positive association with cataract risk in CKB men, i.e., higher risk in current smokers than in never smokers, but no clearly elevated risk was observed in either occasional or ex-regular smokers. However, when ex-regular smokers were further divided into those who had quit smoking by choice and those who had quit due to illness, a higher risk was found in the latter group only, when compared with never smokers. Therefore, to calculate the *CHI*, I created a dichotomous variable (e.g., $Index_{smoking}$) with a value of 1 for current smokers and those ex-smokers who had stopped smoking due to ill health, and a value of 0 for all other men. For female participants in CKB, due to the small proportion of current smokers (2.8%) involved, no reliable analysis on smoking in relation to cataract risk could be conducted. However, no evidence was available in the literature suggesting that smoking could have different health impacts between men and women. Therefore, the same approach was used to define $Index_{smoking}$ in women.

Coding of alcohol consumption:

In CKB men, the risks of cataract tended to be higher among ex- and current drinkers than non- and occasional drinkers, with a J-shaped association (see Chapter 5). Compared to current drinkers consuming <140 g/week, non-drinkers and occasional drinkers had similar risk of cataract, while ex-drinkers and current drinkers with alcohol consumption ≥140 g/week had a higher risk of cataract. Therefore, a dichotomous variable $Index_{alcohol}$ was created with a value of 1 for ex-drinkers and current drinkers consuming ≥140 g/week, and a value of 0 for other men. As with smoking, similar rules were applied in women to assign 1 (ex-drinkers and current drinkers who consumed ≥70 g/week) or 0 (others) to generate the $Index_{alcohol}$.

Coding of physical activity:

As presented in Chapter 6, a higher level of total physical activity was associated with a lower risk of cataract in a dose-response manner, particularly in women. As men on average had higher total physical activity levels than women, a dichotomous variable $Index_{physical_activity}$ was creased based on the sex-specific median of total physical activity. To be specific, men with baseline total physical activity levels <18.7 MET-h/d and women with baseline total physical activity levels <16.8 MET-h/d were assigned a value 1 for the $Index_{physical_activity}$, and others were assigned 0.

Coding of diet:

Among the 12 major food groups analysed, only fresh fruit was significantly (inversely) associated with cataract risk (see Chapter 6). Therefore, a dichotomous variable $Index_{fresh_fruit}$ *was* created, with participants who consumed fresh fruit consumption less frequently than weekly being

assigned a value of 1 for the $Index_{fresh_fruit}$, and others being assigned 0.

Coding of adiposity:

As presented in Chapter 7, waist-to-hip ratio (a measure of central adiposity) was positively associated with risk of cataract in both men and women. Therefore, a dichotomous variable $Index_{adiposity}$ was created based on the sex-specific median of waist-to-hip ratio, with a value of 1 being assigned to men with a waist-to-hip ratio ≥0.95 and women with a waist-to-hip ratio ≥0.90, and 0 being assigned to others.

Coding of diabetes:

As shown in Chapter 7, prevalent diabetes was related to a higher risk of cataract. Therefore, a dichotomous variable $Index_{diabetes}$ was created with a value of 1 for those with prevalent diabetes (including self-reported diabetes and screen-detected diabetes) and 0 for those without prevalent diabetes.

The factors contributing to the *CHI* are summarised in **Table 8.1**. The *CHI* was calculated as the sum of the six high-risk index components, with values ranging from 0 to 6.

Table 8.1 Components of *Cataract Health Index* in CKB

Lifestyle and cardiometabolic factors	High-risk group (1 point)	Low-risk group (0 point)
Smoking	Current smokers Ex-smokers who stop smoking due to illness	Never smokers Occasional smokers Ex-smokers who stop smoking by choice
Alcohol consumption	Ex-drinkers Current drinkers with ≥140 g/week in men and ≥70 g/week in women	Non-drinkers Occasional drinkers Current drinkers with <140 g/week in men and <70 g/week in women
Physical activity	Total physical activity levels below the sex-specific median level (MET: men <18.7 h/d; women <16.8 h/d)	Others
Fresh fruit consumption	Less than weekly consumption (i.e., never/rarely or monthly eaters)	At least weekly consumption (i.e., 1-3 days/week, 4-6 days/week, and daily eaters)
Adiposity	Waist-to-hip ratio ≥0.95 in men and ≥0.90 in women	Others
Diabetes	Self-reported diabetes and screen-detected diabetes	Nondiabetic

8.2.2 Statistical analyses

A similar analytical approach as in previous chapters (5 to 7) was applied to investigate the association of *CHI* with risk of cataract. In brief, the main analyses were conducted among 512 690 participants (210 186 men and 302 504 women), after excluding individuals with incident cataract before age 40 years (n=34) and individuals with missing data on BMI (n=2). Baseline characteristics of CKB participants by categories of *CHI* (five groups: 0, 1, 2, 3, and ≥4 [include 4, 5, and 6]) were calculated with direct standardisation to baseline age groups (in 5-year intervals), sex, and study area (10 regions) of the baseline CKB population[141]. Cox proportional hazards regression models were used to estimate adjusted HRs and 95% CIs of cataract in each category of the *CHI*. Analyses were stratified by age-at-risk (in 5-year groups), sex, and study areas (10 areas), and adjusted for baseline age (continuous), education (four groups), annual household income (four groups), occupation (five groups), prevalent cardiovascular diseases (dichotomous, including CHD and stroke/TIA), and self-rated health status (four groups). The floating absolute risk method[126,127] was used, as previously described (Chapter 3.2.2). In addition, the *CHI* was assessed as a continuous variable to estimate the linear association between one unit of *CHI* with risk of cataract.

To explore the potential effect modification by other population characteristic factors, subgroup analyses were conducted by age-at-risk, sex, region, education, and household income. Several sensitivity analyses were conducted to assess reverse causality bias therefore to confirm the robustness of the results, including: 1) excluding the first 3 years of follow-up; 2) excluding participants aged ≥70 years at baseline; 3) excluding participants with poor self-rated health; 4)

excluding participants with prevalent cancer or cardiovascular diseases.

As a sensitivity analysis of the *CHI*, a weighted *CHI* (i.e., with specific weighting assigned to the six individual component factors) was calculated to assess its association with risk of cataract, with detailed methods presented in **Appendix G.1**.

Assuming the association is causal, the population-attributable fraction (PAF)[259,260] of cataract incidence based on the combined cataract risk factors (i.e., the *CHI*) was estimated. The threshold of *CHI* was selected based on the Comparative Risk Assessment method (to select a minimal risk exposure level)[261], which means having none of the six selected cataract risk factors (i.e., with *CHI* =0) in this study. The PAF of cataract incidence based on the *CHI* was estimated using the formula PAF= p(HR-1)/[p(HR-1)+1], where p is the prevalence of having at least one of the six selected cataract risk factors (i.e., with *CHI* >0) in the population, and HR is the hazard ratio comparing those having *CHI* >0 with those having *CHI* =0[259,260]. All statistical analyses were performed in R (version 4.2.3).

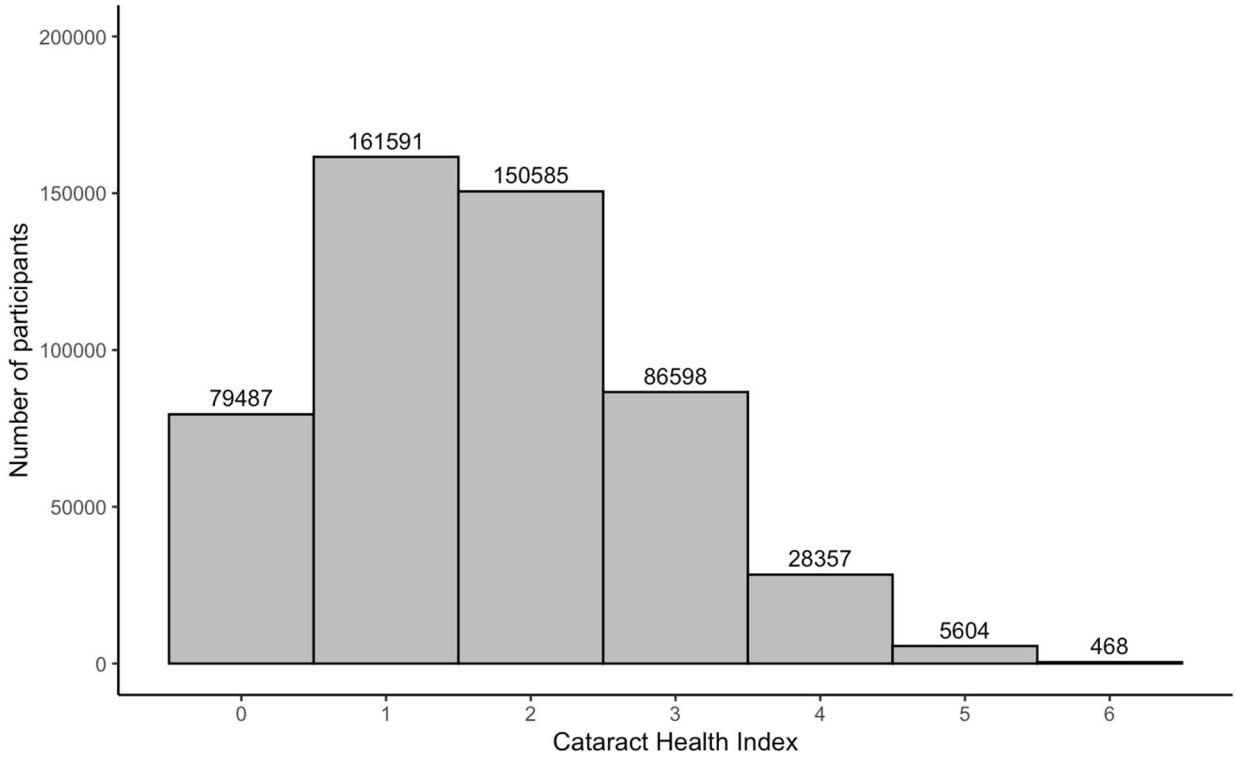
8.3 Results

8.3.1 Patterns of *Cataract Health Index*

The *CHI* had a slightly right-skewed distribution, with the majority of the participants having a value of either 1 (31.5% of participants) or 2 (29.4% of participants) (**Figure 8.1**). Participants with higher *CHI* were more likely to be older (highest vs lowest group: 59.3 vs 46.8 years as mean age), be men (87.2% vs 19.1%), be rural residents (65.1% vs 48.7%), have lower levels of formal

education (55.3% vs 45.8% below high school) and lower household income (67.4% vs 48.9% with household income <20K yuan/year), and were less likely to be married (88.3% vs 91.8%) (**Table 8.2**). They were also more likely to have prior diseases (including CHD [5.1% vs 2.0%], stroke or TIA [3.7% vs 0.8%], cancer [0.7% vs 0.3%] and hypertension [19.8% vs 8.5%]), and had worse self-rated health status (22.3% vs 6.6% as poor) and life satisfaction level (5.5% vs 3.6% not satisfied with life). Similar patterns were observed for the weighted *CHI* (**Appendix G.1.2.1**).

Figure 8.1 Distribution of the *Cataract Health Index*.



The numbers above the bar represent the number of participants in corresponding groups.

Table 8.2 Baseline characteristics of CKB participants by category of the *Cataract Health Index*

	Category of *Cataract Health Index*					Overall
	0	**1**	**2**	**3**	**≥4**	
No. of participants, n (% of total)	79,487 (15.5%)	161,591 (31.5%)	150,585 (29.4%)	86,598 (16.9%)	34,429 (6.7%)	512,690
Socio-demographic factors						
Mean age, years (SD)	46.8 (11.0)	50.9 (10.0)	54.6 (10.0)	57.6 (11.1)	59.3 (14.4)	52.0 (10.7)
Women, %	80.9	70.3	51.5	30.9	12.8	59.0
Rural, %	48.7	50.8	61.9	69.2	65.1	55.9
Education level below high school, %	45.8	47.1	54.2	56.9	55.3	50.8
Annual household income <20K yuan, %	48.9	54.0	62.2	66.8	67.4	57.3
Not in marriage*, %	8.2	8.8	9.2	9.5	11.7	9.4
Prior disease history, %						
CHD	2.0	2.9	3.0	3.4	5.1	3.0
Stroke or TIA	0.8	1.2	1.6	2.4	3.7	1.7
Cancer	0.3	0.5	0.6	0.6	0.7	0.5
Hypertension	8.5	10.0	11.8	14.2	19.8	11.6
Poor self-rated health, %	6.6	8.2	11.0	13.9	22.3	10.4
Self-rated life satisfaction as unsatisfied, %	3.6	4.0	4.3	4.5	5.5	4.2

SD standard deviation, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex, and region, as appropriate.
*Include separated/divorced, widowed, and never married.

Participants with younger age were more likely to have lower *CHI* (28.9% in the 30-39 age group vs 2.0% in the 70-79 age group had a *CHI* of 0), and this pattern was consistent in men and women separately (**Table 8.3**). Women were more likely to have lower *CHI* than men, with 22.5% women vs 5.5% men having a *CHI* of 0 and 38.1% women vs 22.1% men having a *CHI* of 1. Urban residents were more likely to have lower *CHI* than rural residents, with 18.5% urban residents vs 13.2% rural residents having a *CHI* of 0 and 34.4% urban residents vs 29.2% rural residents having a *CHI* of 1 (**Table 8.4**). Regional variation of *CHI* was observed among the five urban and five rural regions, with the proportion of participants having a *CHI* of 0 ranging between 10.7%-21.3% and 3.4%-21.7% in urban and rural regions, respectively. Participants with higher education level were more likely to have lower *CHI*, and the proportions of having a *CHI* of 0 were 24.4% and 18.7%, respectively, among those who had school education until college or university and middle/high school, in contrast to 11.0% and 13.2%, respectively, for those with primary school education and no formal schooling (**Table 8.5**). Women were more likely to have lower *CHI* than men across all education levels, and the proportions of having a *CHI* of 0 were 42.9% vs 9.2% (in women vs in men), 29.4% vs 6.7%, 16.5% vs 3.4%, and 15.6% vs 3.4% for women and men with education levels of college or university, middle/high school, primary school, and no formal schooling, respectively. Similar patterns (as for education) were observed for household income, i.e., lower *CHI* among participants with higher household income, and women were more likely to have lower *CHI* than men across all income groups (**Table 8.6**).

Table 8.3 *Cataract Health Index* by age at baseline.

Age at baseline, years	N	Category of the *Cataract Health Index*				
		0	1	2	3	≥4
Overall, %	**512,690**	**15.5**	**31.5**	**29.4**	**16.9**	**6.7**
30-39	77,588	28.9	36.3	22.4	9.1	3.3
40-49	152,769	22.7	34.3	25.4	12.8	4.8
50-59	157,616	11.0	32.4	31.5	18.1	7.0
60-69	91,753	4.7	25.1	35.2	24.5	10.5
70-79	32,964	2.0	20.8	37.6	27.9	11.7
Men, %	**210,186**	**5.5**	**22.1**	**32.7**	**25.9**	**13.8**
30-39	29,548	10.3	29.4	33.2	18.8	8.3
40-49	59,218	7.1	24.2	33.3	23.7	11.7
50-59	63,751	5.0	20.6	32.8	27.1	14.5
60-69	41,340	2.3	17.8	31.6	30.3	18.0
70-79	16,329	1.1	17.1	32.8	30.9	18.1
Women, %	**302,504**	**22.5**	**38.1**	**27.0**	**10.6**	**1.8**
30-39	48,040	40.4	40.6	15.7	3.2	0.1
40-49	93,551	32.6	40.7	20.4	5.7	0.6
50-59	93,865	15.1	40.3	30.8	11.9	1.9
60-69	50,413	6.7	31.3	38.1	19.6	4.3
70-79	16,635	2.9	24.3	42.3	24.9	5.6

Table 8.4 *Cataract Health Index* by study region.

Region	N	Category of the *Cataract Health Index*				
		0	1	2	3	≥4
Urban, %	**226,190**	**18.5**	**34.4**	**27.0**	**14.1**	**6.0**
Qingdao	35,507	21.3	33.1	26.0	13.5	6.1
Harbin	57,555	19.2	36.2	24.0	13.4	7.2
Haikou	29,686	10.7	36.9	32.1	15.7	4.6
Suzhou	53,268	19.0	31.0	27.9	15.8	6.3
Liuzhou	50,174	19.7	35.7	27.2	12.4	5.0
Rural, %	**286,500**	**13.2**	**29.2**	**31.2**	**19.1**	**7.3**
Sichuan	55,685	16.2	29.3	26.5	17.8	10.2
Gansu	49,887	18.0	39.8	30.2	9.9	2.1
Henan	63,354	3.4	18.2	37.7	30.1	10.6
Zhejiang	57,703	21.7	34.6	26.1	13.2	4.4
Hunan	59,871	8.4	26.7	34.3	22.3	8.3

Table 8.5 *Cataract Health Index* by education status.

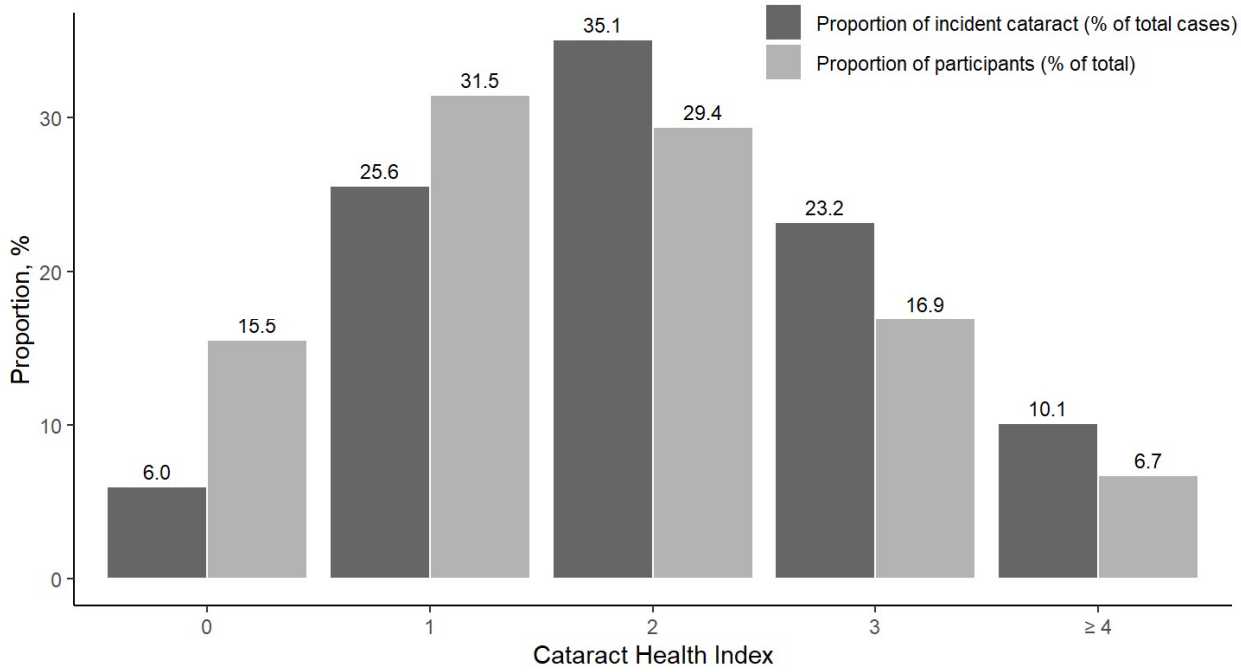
Education level	N	Category of the *Cataract Health Index*				
		0	1	2	3	≥4
Overall, %	**512,690**	**15.5**	**31.5**	**29.4**	**16.9**	**6.7**
No formal school	95,178	13.2	31.9	32.4	17.4	5.1
Primary school	165,175	11.0	28.1	32.2	20.5	8.2
Middle/high school	222,363	18.7	33.1	26.9	14.8	6.5
College/university	29,974	24.4	37.2	22.1	11.1	5.2
Men, %	**210,186**	**5.5**	**22.1**	**32.7**	**25.9**	**13.8**
No formal school	18,661	3.4	20.1	34.7	27.7	14.1
Primary school	70,110	3.4	18.0	32.9	29.7	16.0
Middle/high school	104,880	6.7	23.6	32.5	24.3	12.9
College/university	16,535	9.2	31.6	31.3	18.6	9.3
Women, %	**302,504**	**22.5**	**38.1**	**27.0**	**10.6**	**1.8**
No formal school	76,517	15.6	34.8	31.9	14.8	2.9
Primary school	95,065	16.5	35.6	31.8	13.8	2.3
Middle/high school	117,483	29.4	41.6	21.8	6.3	0.9
College/university	13,439	42.9	44.0	10.9	1.9	0.3

Table 8.6 *Cataract Health Index* by household income.

Household income (yuan)	N	Category of the *Cataract Health Index*				
		0	1	2	3	≥4
Overall, %	**512,690**	**15.5**	**31.5**	**29.4**	**16.9**	**6.7**
<10,000	144,733	11.2	29.2	32.6	19.5	7.5
10,000-19,999	148,943	14.2	30.9	30.1	17.8	7.0
20,000-34,999	126,696	18.9	33.3	27.2	14.8	5.8
≥35,000	92,318	19.6	33.7	26.1	14.2	6.4
Men, %	**210,186**	**5.5**	**22.1**	**32.7**	**25.9**	**13.8**
<10,000	54,722	3.8	18.9	33.9	28.0	15.4
10,000-19,999	59,537	5.4	21.0	32.1	26.9	14.6
20,000-34,999	53,402	6.6	24.2	32.7	24.3	12.2
≥35,000	42,525	6.5	24.8	32.2	23.9	12.6
Women, %	**302,504**	**22.5**	**38.1**	**27.0**	**10.6**	**1.8**
<10,000	90,011	15.7	35.5	31.8	14.4	2.6
10,000-19,999	89,406	20.1	37.5	28.8	11.7	1.9
20,000-34,999	73,294	27.9	39.9	23.2	7.8	1.2
≥35,000	49,793	30.8	41.3	20.8	6.0	1.1

Participants in the highest *CHI* category (i.e., with *CHI* ≥4), whom made up 6.7% of the total participants, accounted for 10.1% of total incident cataract cases in CKB (**Figure 8.2**). Approximately 84% of the incident cataract cases occurred among participants with a *CHI* of 1 (25.6% of total cases), 2 (35.1%), or 3 (23.2%), who comprised about 80% of the total participants (with 6% of cases among the remaining 15.5% of participants with *CHI* =0).

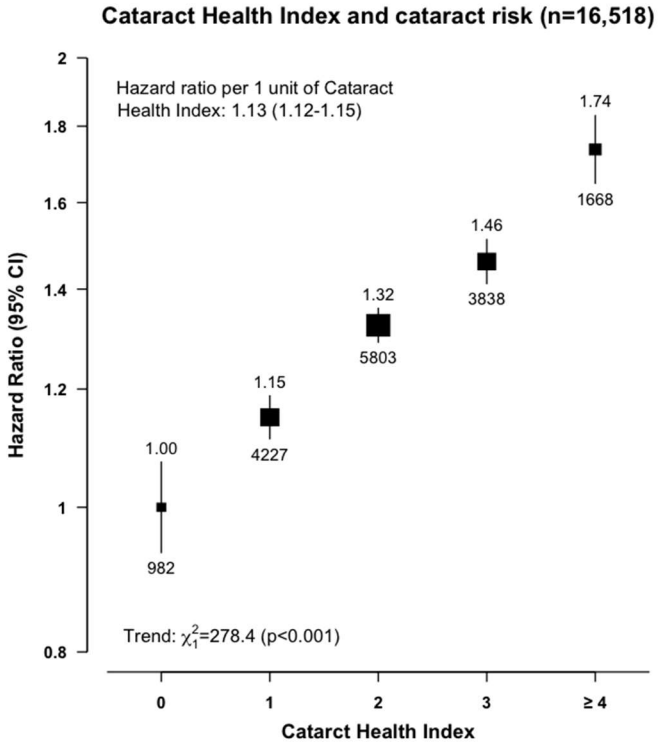
Figure 8.2 Proportion of incident cataract by category of *CHI*



8.3.2 *Cataract Health Index* and risk of cataract

As expected, higher *CHI* was related to a higher risk of cataract. Participants with *CHI* >0 had 26% (HR=1.26, 1.18-1.35) higher risk of cataract than those with a *CHI* of 0, and there was a linear association between *CHI* and risk of cataract (P_{trend} <0.001). Compared to participants with a *CHI* of 0 (HR=1.00, 0.93-1.07), the four groups with *CHI* of 1, 2, 3, and ≥4 had 15% (1.15, 1.11-1.19), 32% (1.32, 1.29-1.36), 46% (1.46, 1.41-1.51), and 74% (1.74, 1.65-1.83) higher risk of cataract, respectively (**Figure 8.3** & **Supplementary Table G.3**). Each *CHI* unit higher was associated with 13% (1.13, 1.12-1.15) higher risk of cataract, and no specific threshold was identified. A similar positive linear association was observed between the weighted *CHI* and risk of cataract (**Appendix G.1.2.2**).

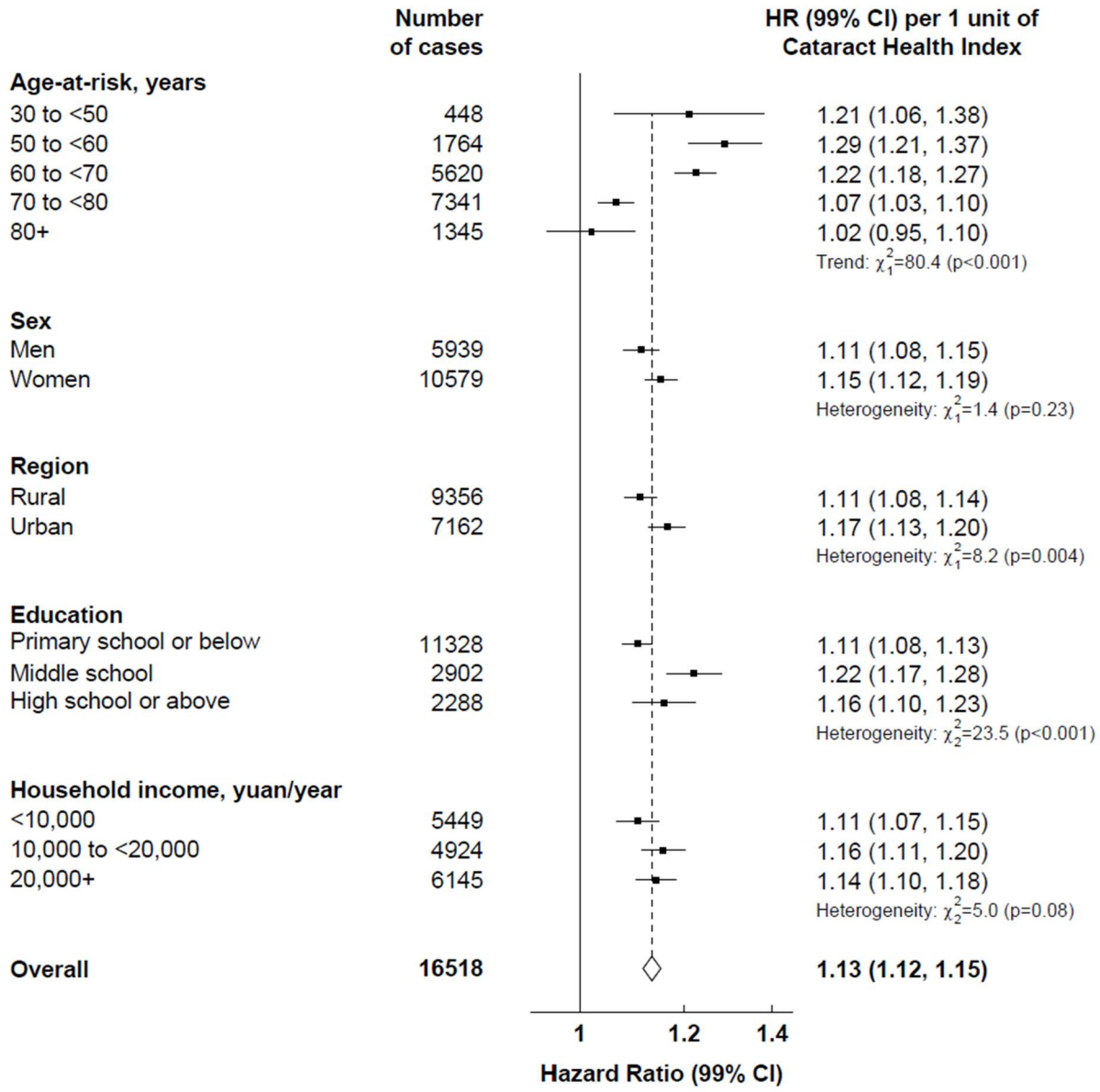
Figure 8.3 Adjusted HRs for cataract by *CHI*



Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD, stroke, and TIA), and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend relates to all five groups.

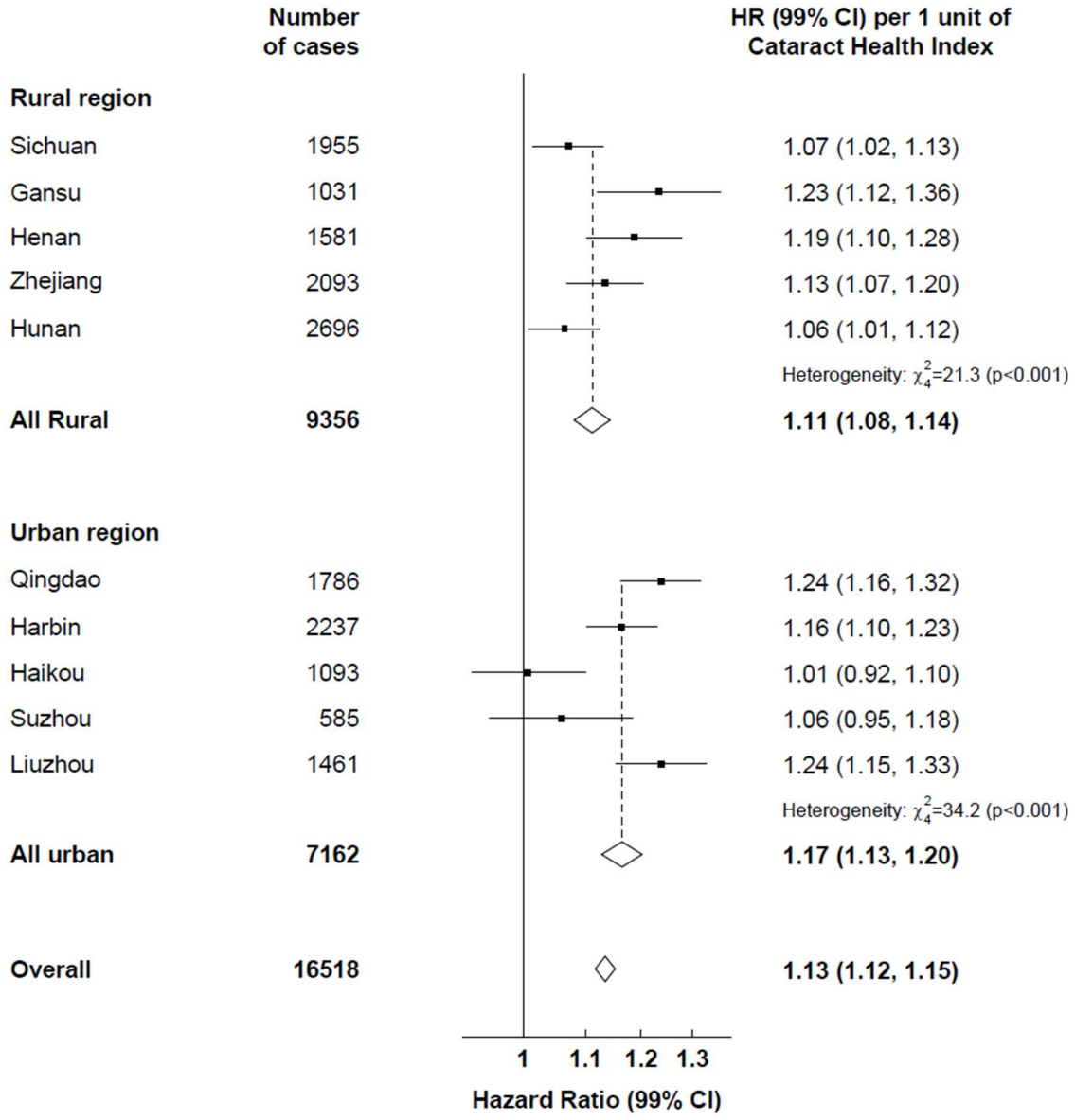
The positive association of *CHI* with risk of cataract differed across subgroups defined by age, region, and education level (**Figure 8.4** & **Figure 8.5**). In line with previous results on associations of each individual risk factor with cataract risk, the associations between *CHI* and risk of cataract were stronger in younger age-at-risk groups (except for those in the youngest group [30 to <50 years], probably due to the small number of cases in this age group). *CHI* was associated with 29% higher risk of cataract in those with age-at-risk of 50 to <60 years, but the corresponding risk was only 7% higher in those with age-at-risk of 70 to <80 years. The association between *CHI* and risk of cataract was stronger in urban (HR=1.17, 1.13-1.20) than in rural (1.11, 1.08-1.14) regions, with HRs ranging 1.06-1.23 and 1.01-1.24 in the five rural and five urban regions, respectively. *CHI* had a slightly stronger association with cataract risk in participants with higher education levels (HR 1.22 [1.17-1.28] and 1.16 [1.10-1.23] respectively for the medium and high education groups) than in those with lower level of education (HR 1.11 [1.08-1.13]). The observed association between *CHI* and risk of cataract remained largely unchanged in sensitivity analyses (**Table 8.7**).

Figure 8.4 Adjusted HRs per 1 unit of *CHI* for cataract by selected population characteristics.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD and stroke and TIA), and self-rated health status, as appropriate.

Figure 8.5 Adjusted HRs per 1 unit of *CHI* for cataract by region.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD and stroke and TIA), and self-rated health status, as appropriate.

Table 8.7 Adjusted HRs per 1 unit of *CHI* with cataract risk - results of sensitivity analysis.

	Number of cases	HRs (95%CI) per 1 unit of *CHI*
Primary analysis (n=512,690)	16,518	1.13 (1.12-1.15)
Exclude first 3 years of follow-up (n=512,690)	16,518	1.13 (1.11-1.15)
Exclude those aged ≥70 years at study entry (n=479,760)	13,332	1.16 (1.14-1.18)
Exclude those with poor self-rated health (n=459,633)	14,347	1.13 (1.11-1.15)
Exclude those with cancer or CVD at baseline (n=487,210)	14,903	1.14 (1.12-1.16)

Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD, stroke, and TIA), and self-rated health status, as appropriate.

8.3.3 Population attributable fraction of *Cataract Health Index*

The hazard ratio for cataract with *CHI* >0 versus *CHI* =0 was 1.26 (1.18-1.35). Since there is no data available on prevalence of the combined unhealthy factors (of the six selected lifestyle and cardiometabolic factors) among the Chinese population, the prevalence in the CKB population was used for the estimation of the population attributable fraction (PAF). In CKB, about 84.5% of participants had *CHI* >0. Therefore, assuming there is a causal association, this study suggested 18.0% (95%CI: 16.9%-19.1%) of age-related cataract is attributable to having at least one of the six cataract risk factors (**Table 8.8**). Applying this proportion to the 94 million age-related cataract cases in China[262], up to 16.9 (15.9-18.0) million cataract cases could potentially be prevented if Chinese people had no exposure to any of the six unhealthy lifestyle and cardiometabolic factors.

Table 8.8 Population attributable fraction of *CHI* on incidence of age-related cataract

	HR (95% CI) of having at least one of the six unhealthy factors (i.e., HR with *CHI* >0 vs *CHI* =0)	Proportion of participants having at least one of the six unhealthy factors, %	Population attributable fraction (95% CI), %
Overall	1.26 (1.18-1.35)	84.5	18.0 (16.9-19.1)
Age at baseline, years			
30 to <40	1.34 (0.91-1.96)	71.1	19.5 (12.9-26.0)
40 to <50	1.32 (1.12-1.57)	77.3	19.8 (16.9-22.8)
50 to <60	1.32 (1.18-1.47)	89.0	22.2 (20.0-24.3)
60 to <80	1.13 (1.02-1.26)	96.0	11.1 (10.0-12.2)
Sex			
Men	1.19 (1.01-1.40)	94.5	15.2 (12.9-17.6)
Women	1.27 (1.18-1.37)	77.5	17.3 (16.1-18.5)
Region			
Urban	1.32 (1.18-1.49)	81.5	20.7 (18.6-22.8)
Rural	1.22 (1.12-1.33)	86.8	16.0 (14.7-17.3)

CHI Cataract Health Index, PAF population attributable fraction

The PAF of *CHI* on age-related cataract was higher in younger age groups, in men, and in urban residents (**Table 8.8**). Participants aged younger than 60 years (PAF ranged 19.5% to 22.2%) had PAF about twice as high as those aged 60 years and older (PAF=11.1%). The PAF was slightly higher in women (17.3%, 16.1%-18.5%) than in men (15.2%, 12.9%-17.6%), and higher in urban (20.7%, 18.6%-22.8%) than in rural residents (16.0%, 14.7%-17.3%).

8.4 Discussion

8.4.1 Summary of findings

In this prospective study with half million Chinese adults, a *CHI* (defined as number of high-risk factors), which is a combined index of six major lifestyle and cardiometabolic factors including smoking, alcohol consumption, physical activity, fresh fruit consumption, adiposity, and diabetes, was significantly associated with risk of cataract. Each *CHI* unit higher was associated with 13% higher risk of cataract, and no specific threshold was identified. In addition, participants with at least four unhealthy factors (among the six lifestyle and cardiometabolic factors) had a 74% higher risk of cataract than those with none of the six unhealthy factors. In sensitivity analysis with weighting assigned to the component factors of the *CHI*, a similar positive linear association with cataract risk was found. Assuming the association between *CHI* and cataract risk is causal, 18.0% (95%CI: 16.9%-19.1%) of age-related cataract in China could be attributed to having a *CHI* >0 (i.e., having at least one of the six unhealthy lifestyle and cardiometabolic factors), and 16.9 (15.9-18.0) million cataract cases could potentially be prevented if all these unhealthy lifestyle and cardiometabolic factors could be eliminated from the Chinese population.

8.4.2 Cataract Health Index and risk of cataract

Although there are some prospective studies on the associations of each of these six lifestyle and cardiometabolic factors with risk of cataract, to the best of my knowledge, the current study is the first prospective study exploring their combined association with cataract risk through a composite index. The *MEDLIFE* used the summed score of 28 single health scores[251,252], while the *Life's Essential 8* used the average score of 8 single health scores[250], both in relation to cardiovascular health (and other chronic health [i.e., greater chronic diseases-free survival and quality of life]). Like the *MEDLIFE*, the *CHI* developed in this study used the sum of 6 selected lifestyle and cardiometabolic factors. Both the *Life's Essential 8* and *MEDLIFE* were generated by assessing the number of healthy behaviours (i.e., lifestyle factors in the low-risk category), and were used to investigate their combined association with cardiovascular health (i.e., to assess the amount of reduction in CVD risk). This study adopted the health index approach to develop a *CHI*, by assessing the number of unhealthy factors (i.e., lifestyle and cardiometabolic factors in the high-risk category), to study their combined association with cataract risk (i.e., to assess the amount of elevated cataract risk). The positive association of *CHI* with risk of cataract observed in this study demonstrated that participants with a higher number of lifestyle and cardiometabolic factors in the high-risk category were more likely to have a higher risk of cataract than their counterparts.

This study found a slightly stronger association between *CHI* and cataract risk in participants with younger age-at-risk. The possible explanation might be participants with older age have other factors (e.g., social participation[263], genetic factors[10,46]) that contribute to their survival, so the

impact of lifestyle and cardiometabolic factors was less obvious. The current study also observed the associations between *CHI* and risk of cataract were stronger in urban than in rural regions, and stronger in participants with higher education levels than in those with lower education status. This quantitative inconsistency might be explained by the interaction between lifestyle factors and other risk factors (e.g., access to health care, level of social support, exposure to environmental hazards, etc.). Rural residents and participants with lower education status are more likely to experience social and environmental disadvantages[264,265], therefore the relative impact of a healthy lifestyle alone on their cataract risk might be slightly diminished.

8.4.3 Strategies for cataract prevention

In this study, participants with *CHI* ≥4 had a significantly (74%) higher risk of cataract than those with *CHI* =0. However, despite the significantly higher risk, participants with *CHI* ≥4 only accounted for 10.1% of total incident cataract cases in CKB. The majority (~84%) of incident cataract cases in CKB were among participants with moderate levels of *CHI* (i.e., as 1, 2, or 3). This suggests that participants with slightly higher numbers of unhealthy factors (among the six lifestyle and cardiometabolic factors) were the main driving force for the cataract burden in CKB, given that few participants (6.7% of total CKB population) had 4 or more unhealthy factors, but majority of the participants (~80%) had 1, 2, or 3 unhealthy factors. These findings provide quantitative evidence on the potential number of cases that could be averted if exposure to those unhealthy factors were reduced.

Given that the burden of cataract in CKB is dominated by individuals with a moderate number of

unhealthy factors (i.e., those with *CHI* of 1, 2, or 3), cataract prevention strategies that include risk reduction among the "moderate-risk'' group (i.e., those with *CHI* of 1, 2, or 3) rather than focusing on the "high-risk'' group (i.e., those with *CHI* ≥4), could potentially be more effective in reducing cataract disease burden in the population. Slightly reducing the risk of the entire population could be more effective in lowering the overall disease burden than greatly reducing the risk of high-risk individuals. This study suggests the "population-wide" strategy, rather than the "high-risk" strategy, could be prioritised to guide cataract prevention policies. In order to achieve the shift of the entire risk distribution to the lower end, the "population-wide" strategy relies on controlling the determinants of unhealthy behaviours at the population-level[257]. Public health policies on cataract prevention could focus on controlling determinants of the six unhealthy lifestyle and cardiometabolic factors including smoking, alcohol consumption, physical inactivity, low consumption of fresh fruit, high level of waist-to-hip ratio, and being diabetic. For example, in the smoking control scenario, the "population-wide" strategy focuses on interventions to change the social environment of smoking (e.g., promote smoking-free area, raise taxes on tobacco, warning graphic labels on cigarette packs, etc.) to make smoking the harder choice (than not smoking) for the entire population. This approach would not only reduce the amount of cigarettes smoked by high-risk smokers, but also protect never smokers and occasional smokers from smoking. Appropriate population-level interventions could be developed and adopted to address all six unhealthy factors.

Existing public health strategies to reduce the cataract burden mainly focused on cataract surgery. In the vision health guideline released in 2022, improving cataract surgery coverage was the

recommended policy by WHO[267]. Similarly, the prioritised strategies in China aim to improve cataract surgery treatment quality and coverage, as mentioned in a recent Chinese national eye health policy released in 2022[268,269]. The current study highlighted the importance of promoting a healthy lifestyle and managing key cardiometabolic indicators to reduce the cataract burden.

8.4.4 Strength and limitations

The strengths of this study include the large sample size, the utilisation of a health index to study the combined associations of six lifestyle and cardiometabolic factors with risk of cataract, and the adoption of a weighted index in sensitivity analyses to test the robustness of the main results. However, this study also has several limitations. Firstly, lifestyle and cardiometabolic risk factors were dichotomised to create the *CHI*, simplifying cataract risk estimates among diverse exposure subgroups, and participants in modest risk groups could easily be misclassified, which may lead to over- or under- estimation of the composite index. Secondly, the *CHI* might be more applicable to men than women. Due to the small proportion of current smokers (2.8%) and current drinkers (2.1%) in CKB women, the associations between smoking and alcohol consumption with risk of cataract were less clear in women. In considering no clear evidence suggesting the mechanisms of smoking and alcohol may affect cataract risk differ between men and women, the coding of smoking and alcohol indices in women were based on associations found in men. Therefore, the *CHI* developed in this study might be more appropriate for men than for women. Thirdly, since there is no data available on the prevalence of unhealthy factors (of the six selected lifestyle and cardiometabolic factors) among the Chinese population, the calculation of the PAF in this study is based on prevalence estimated from the CKB population, which does not represent the

prevalence in China. In considering the large number of participants and the representation of 10 diverse Chinese regions in CKB, the prevalence in CKB might provide a good estimation of the prevalence in the overall Chinese population. Lastly, due to practical reasons, this health index study is conducted in the same population (i.e., the CKB) as the association studies on each of the lifestyle and cardiometabolic factors in previous chapters. Findings from this study might not be fully applicable in other populations. Future studies to evaluate the *CHI* in other populations could help to validate my findings.

8.5 Summary

In this chapter, the association of a composite of six major lifestyle and cardiometabolic factors with cataract incidence was assessed with the development of a *CHI*. Individuals with a higher number of unhealthy lifestyle and cardiometabolic factors were more likely to have a higher risk of cataract than their counterparts. Cataract prevention strategies rely on controlling the determinants of unhealthy lifestyle and cardiometabolic factors at the population-level, rather than focusing on risk reduction among individuals with the highest relative risk in the population, might potentially be more effective in reducing cataract disease burden in the population.

9 Summary of thesis and discussion

9.1 Cataract burden and risk factors

Cataract is the clouding of eye lens which leads to blurred vision and eventually blindness. Age-related cataract is the most common type of cataract, and it was the major cause of blindness and visual impairment, accounting for more than 20 million blindness and about 100 million visual impairment cases globally in 2020[18,19]. The burden of cataract is distributed unevenly around the world, with high prevalence in south-eastern Asia and western Pacific regions[12]. China had the largest number of blindness and vision impairment cases in the world, with cataract accounting for one third of both conditions[270].

The exact causes of cataract are largely unknown, although previous epidemiological studies have provided some largely inconsistent evidence relating advanced age[35,36], and several socio-demographic factors (including female sex, low socio-economic status[37,38]), lifestyle factors (including smoking, inadequate vegetable intake[33,39]), and cardiometabolic factors (including high BMI, high blood pressure[40,41]) with cataract formation. Despite the significant cataract disease burden in Asia, existing evidence on major modifiable lifestyle and cardiometabolic risk factors for cataract is mainly based on Western high-income populations. The few studies on Asian populations had relatively small sample sizes and short follow-up periods, and some studies failed to collect information on key confounding variables.

With data from the CKB study which followed up 0.5 million Chinese adults for more than 10 years, this thesis has provided robust new evidence on cataract disease patterns, as well as major

modifiable lifestyle and cardiometabolic risk factors for cataract.

9.2 Key findings and comparison with other studies

The CKB study has followed-up 512 726 participants aged 30-79 years from 10 regions in China for 11 years, and recorded 16 518 incident cataract cases. This thesis described the incidence patterns and socio-demographic correlates of cataract, and assessed the associations of major modifiable lifestyle (include smoking, alcohol consumption, physical activity, and diet) and cardiometabolic (include adiposity, diabetes, and blood glucose) factors with risk of cataract in CKB.

9.2.1 Patterns and correlations of cataract incidence

The overall incidence rate of cataract was 293 (288-298) per 100 000 person years in CKB. Previous studies (conducted among Western, Asian, Latin American, and African populations) mainly used proportion to describe cataract incidence, with findings ranged from 9.4%[271] to 53.7%[272] (see details in **Table 4.6** in Chapter 4.4.2), which is higher than the proportion (3.2%) found in CKB. There was a strong positive trend for higher cataract incidence with increasing age (particularly between 50 and 70 years of age). Cataract incidence was 28% higher in women (333 [326-340]) than in men (241 [234-248]). Similar age- and sex-patterns have been observed in previous studies, among Western[135,37,143], African[144,133], Latin American[145], and Chinese[134,136,146,147] populations. In the CKB, urban regions (260 [254-266]) tended to have lower cataract incidence rates than rural regions (319 [312-326]), which was in line with the socio-economic patterns observed in previous studies in several regions in China[134,156,157].

Participants with better subjective assessments of health and well-being (i.e., self-rated heath status and levels of life satisfaction) had lower incidence of cataract in CKB. The incidence rate was 348 (331-365) in participants with poor self-rated health, in contrast to 259 (246-272) in those with self-rated excellent health. Those who were self-reported satisfied with life at baseline (289 [283-295]) had lower incidence of cataract than those who were not satisfied (339 [297-381]). These two easily assessed self-rated health factors could contribute to the prediction of cataract incidence and identification of high-risk groups for clinical screening. Except for a body of literature on associations between self-rated health status with well-being and mortality[139,159,140,160], no previous studies have evaluated cataract patterns in relation to self-rated health and life satisfaction.

9.2.2 Lifestyle factors and risk of cataract

9.2.2.1 Smoking and risk of cataract

In CKB, smoking was associated with a higher risk of cataract in men. Current smokers and ex-smokers who stopped smoking due to illness had 13% higher risk of cataract than never smokers. Similarly, previous studies (mainly from Western high-income countries) have consistently associated smoking with a higher risk of cataract, with the relative risk of current vs never smokers ranging from 1.12 to 2.84 [95,164].

Male current smokers who had higher smoking amount, longer smoking duration, inhaled to the lung, or smoked mixed tobacco types had higher cataract risk than their counterparts. Previous studies have also demonstrated higher smoking amount[61,63] and longer smoking duration[63,64,60]

were associated with higher risk of cataract, though evidence on inhalation depth and type of tobacco smoked is highly limited.

In the CKB, ex-smokers who stopped smoking due to illness had a higher risk of cataract than those who stopped by choice, though no clear difference of cataract risk was found among those with different cessation length. Previous studies had inconsistent findings on the association between smoking cessation and risk of cataract, and studies with relatively longer follow-up periods (ranging from 12 to 20 years)[65,66,67] suggested an inverse association, while the Blue Mountains Eye Study[68] with 10 years of follow-up found no clear association. The reasons for the varying results are largely unknown, it is possible that the lens might potentially have some capacity to recover once the impact from smoking has been removed and participants stopped smoking for longer period have a shorter period of exposure to smoking.

9.2.2.2 Alcohol consumption and risk of cataract

There was a J-shaped association between alcohol consumption and risk of cataract, with a higher risk among ex- and current drinkers than non- and occasional drinkers in CKB. Compared to current drinkers with lowest level of alcohol consumption (<140 g/week of alcoholic drinks), ex-drinkers had 14% higher risk of cataract, and current drinkers with higher alcohol intake had 11% to 24% higher risk of cataract, while the risk in non-drinkers and occasional drinkers were not different. In addition, in male current drinkers, the HR per 280g/week higher usual alcohol consumption being 1.20.

The exact causes of this J-shaped association between alcohol consumption and cataract risk is unknown. However, it is possible that reverse causality (e.g., early stages of cataract affects drinking behavior) or residual confounding[181] may play a role. The apparent findings of a lower risk of major chronic diseases due to moderate drinking in previous prospective studies[179,180] may also have resulted from similar biases[181]. A recent CKB study using a genetic epidemiological approach (Mendelian randomization) indicated that the lower risk of cataract due to moderate drinking is unlikely to be causal[74].

9.2.2.3 Physical activity and risk of cataract

Physical activity was associated with lower risk of cataract in a dose-response manner, particularly in women. Each 10 MET-h/d higher of usual total physical activity was associated with 11% lower risk of cataract in women, though no statistically significant association was observed in men (HR=0.99, 0.93-1.04). Although the exact causes of the sex difference needs to be explored further, it might be related to the potential effect of ultraviolet radiation exposure from sunlight. UV exposure has been found to be related to a higher risk of cataract[44,193]. Men with higher levels of physical activity were mainly those workers with manual and heavy manual occupations which involves a large amount of outdoor activities.

9.2.2.4 Diet and risk of cataract

Among the 12 major food groups, there was an inverse association between fresh fruit and cataract risk in a dose-response manner, but no clear associations were found for the other 11 food groups. Each 100 gram/day fresh fruit consumption was associated with 17% lower risk of

cataract among the >10 portions/month consumption groups (i.e., excluding never/rarely consumers). This is the first prospective study reporting a significant relationship between fruit consumption and cataract risk. The difference between the current and previous studies might be explained by the fact that the current study have only included fresh fruits (i.e., consumed raw) in the exposure assessment, which is different from the combination of raw fruits, processed fruits, and juices assessed in previous studies. In addition, the average daily consumption of fresh fruit in CKB was less than half of that in a western population[202]. It is possible that the log linear inverse association might be stronger at the lower end of consumption range, similar to the association between fruit consumption and incidence of CVD[203].

9.2.3 Cardiometabolic factors and risk of cataract

9.2.3.1 Adiposity and risk of cataract

Waist-to-hip ratio (a measure of central adiposity) was positively associated with risk of cataract in both men and women, but no clear association was observed for general adiposity or other central adiposity measures. The HRs per 1 SD of usual waist-to-hip ratio (0.07 unit in both sexes) were 1.05 and 1.05 respectively in men and women, and those in the highest waist-to-hip ratio category had 20% in men and 12% in women higher cataract risk than those in the lowest category.

The finding on waist-to-hip ratio in relation to the cataract risk from the current DPhil research was consistent with some[100,96], but not all[48], previous findings. Compared with other adiposity measures analysed in this DPhil, waist-to-hip ratio could better represent fat distribution. These

findings demonstrated that weight-control based cataract prevention programs should focus on balancing fat distribution instead of general weight loss.

9.2.3.2 Diabetes and blood glucose with risk of cataract

Prevalent diabetes was related to a higher risk of cataract in CKB, and participants with screen-detected and self-reported diabetes had 35% and 80%, respectively, higher risk of cataract than those without prevalent diabetes. Among participants with/without diabetes at baseline, there was a positive linear association between random blood glucose and cataract risk, with each 1 mmol/L usual level of random blood glucose being associated with 6% and 3% higher risk of cataract, respectively. The findings were consistent with published literature[99,63], though the majority of the evidence to date is from Western populations.

9.2.4 The combined association of cataract risk factors

Cataract Health Index (*CHI,* defined as number of high-risk factors), which combines six lifestyle and cardiometabolic factors (including smoking, alcohol consumption, physical activity, fresh fruit consumption, adiposity, and diabetes) was significantly and positively associated with risk of cataract, with HR per one unit of *CHI* (i.e., per one unhealthy factors) being 1.13, and participants with at least four unhealthy factors (among the six lifestyle and cardiometabolic factors) had a 74% higher risk of cataract than those with none of the six unhealthy factors. Assuming the association between *CHI* and cataract risk is causal, 18.0% (95%CI: 16.9%-19.1%) of age-related cataract in China could be attributed to having a *CHI* >0 (i.e., having at least one of the six unhealthy factors), and 16.9 (15.9-18.0) million cataract cases could potentially be

prevented if all these unhealthy lifestyle and cardiometabolic factors could be eliminated from the Chinese population.

9.3 Public health implications

In 2020, around 43 million people were blind and 295 million were visually impaired globally, with half of the blindness and one third of the visual impairment caused by cataract[18,19]. With an ageing population, the global prevalence of cataract is expected to rise. Compared to the general population, people with cataract are more likely to have reduced quality of life (both physically and mentally)[24,25] and increased risk of falls and depression[26,27]. In addition to the personal impact, cataract leads to enormous global financial burden due to productivity loss, contributing to a large share of the estimated US$ 411 billion loss annually caused by vision impairment[273]. Therefore, the identification of key modifiable lifestyle and cardiometabolic risk factors is urgent for cataract prevention.

As demonstrated in this thesis, lifestyle and cardiometabolic factors including smoking, alcohol consumption, physical inactivity, low consumption of fresh fruit, high levels of waist-to-hip ratio and blood glucose, being diabetic were all associated with higher risk of cataract. Previous epidemiological studies on cataract risk factors are mainly based on Western high-income countries, with very limited evidence from Asian populations. Findings from this thesis is based on data from 0.5 million Chinese adults, which could greatly contribute to the evidence of cataract risk factors on Asian population (specifically the Chinese). Given the high cataract disease burden in Chinese population, this thesis has significant public health importance to

inform cataract prevention and treatment strategies in China. In considering the ageing population[274], high prevalence of smoking and alcohol consumption (in men)[274,275,170], and rising prevalence of obesity[273] and diabetes[276,277] in China, public health intervention programs including strategies to reduce smoking and alcohol drinking, promote physical activity and healthy diet, and maintain a healthy fat distribution and blood glucose level are of great importance because of the potential health benefits to delay cataract development.

The combined associations of the above-mentioned lifestyle and cardiometabolic factors with risk of cataract demonstrated that individuals with a higher number of unhealthy lifestyle and cardiometabolic factors were more likely to have a higher risk of cataract than their counterparts. The burden of cataract in CKB is dominated by individuals with moderate number of unhealthy factors (i.e., those with 1, 2, or 3 unhealthy factors among the 6 lifestyle and cardiometabolic factors), therefore this thesis suggests cataract prevention strategies could aim at shifting cataract risk distribution of the entire population to the lower end instead of focusing on reducing the risk of high-risk individuals. Cataract prevention policies could target at controlling the determinants of the six unhealthy lifestyle and cardiometabolic factors at population level. Promoting smoking-free area to change the social environment of smoking (i.e., to make smoking the harder choice [than not smoking] for the entire population) is a good example of such interventions, and appropriate population-level interventions could be developed and adopted to address all six unhealthy factors.

Existing public health strategies to reduce the cataract burden mainly focused on cataract surgery.

As a global effort to address the burden of vision impairment and blindness, the WHO announced guidelines in 2022 to achieve the 2030 global targets for effective coverage of eye care[267]. The WHO recommended policy on cataract was to improve cataract surgery coverage. A recent Chinese national eye health policy, the *14th Five-Year Plan for National Eye Health (2021-2025)* released in 2022, identifies cataract as one of the major eye disease burden in China[268,269]. Similar to the WHO recommendation, cataract control guidelines in China focused on improving cataract surgery treatment quality and coverage. The current study highlighted the importance of promoting a healthy lifestyle and managing key cardiometabolic indicators to reduce the cataract burden.

9.4 Future research

Future research should address several limitations and un-answered questions of the current DPhil research. For large population studies like the CKB, it is important to collect participants' information on prior cataract history to improve the reliability of study findings. This would allow the exclusion of participants no longer at risk of developing cataract (i.e., those with cataract surgery operated before baseline study), therefore improve the accuracy of cataract incidence calculation and the association analyses of risk factors.

The CKB captured a large number of incident cataract cases through linkage with health insurance databases, but subtypes (i.e., nuclear, cortical, and posterior subcapsular cataract) of these cataract cases are unknown. Future research with capacity to classify cataract subtypes (e.g., collection of information on cataract subtypes through clinical diagnosis) could enhance our

understanding on the aetiology of different subtypes, since previous studies suggested some risk factors (e.g., diabetes and blood glucose) were only associated with one/two subtype(s) of cataract[249,105].

Moreover, this thesis focused on conventional epidemiological methods to explore the associations of lifestyle and cardiometabolic factors with risk of cataract, so the findings could be biased due to residual confounding and the causality of the observed associations could not be assessed within the scope of the thesis. Previous studies using a Mendelian Randomisation (MR)[278] approach generally suggested a causal effect of type 2 diabetes on cataract, but the evidence on smoking, blood pressure, and obesity were inconsistent[279,280,281,282]. Future research using genetic data in CKB and other populations such as UK Biobank could use an MR approach to investigate the causal relevance of the risk factor associations identified in this thesis.

9.5 Conclusion

Age-related cataract was the leading cause of blindness and visual impairment globally, with high prevalence in Asia. Previous epidemiological studies on cataract risk factors were mainly based on Western high-income countries, with very limited evidence from Asian populations. The current analyses based on 0.5 million Chinese adults followed-up for 11 years have comprehensively assessed the associations of major modifiable lifestyle and cardiometabolic factors with cataract incidence. Smoking, alcohol consumption, physical inactivity, low consumption of fresh fruit, high level of waist-to-hip ratio, diabetes, and high level of blood glucose were associated with higher risk of cataract. Future research with MR analyses could help

to investigate the causal relevance of these associations. Furthermore, individuals with a higher number of unhealthy lifestyle and cardiometabolic factors were more likely to have a higher risk of cataract than their counterparts. Cataract prevention strategies could aim at shifting cataract risk distribution of the entire population to the lower end instead of focusing on reducing the risk of high-risk individuals. The current study findings could help to promote healthy lifestyles and management of key cardiometabolic indicators for effective cataract prevention purposes.

Appendix A. Introduction of the thesis

Figure A.1 Age-standardised global prevalence of blindness in adults aged 50 years and older from 1990 to 2020 (From Flaxman et al. 2017[20]).

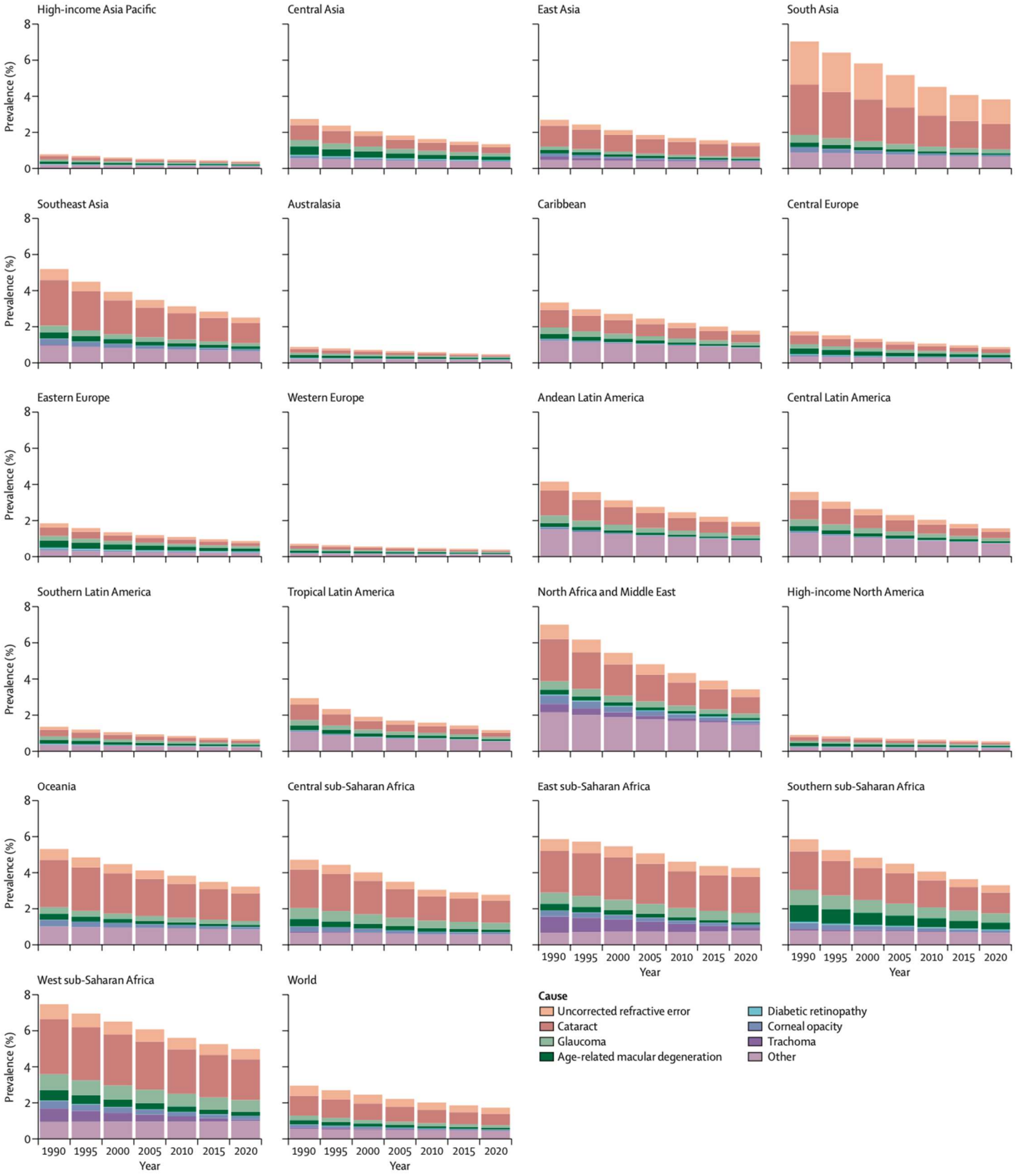


Figure A.2 Age-standardised global prevalence of moderate to severe vision impairment in adults aged 50 years and older from 1990 to 2020 (From Flaxman et al. 2017[20]).

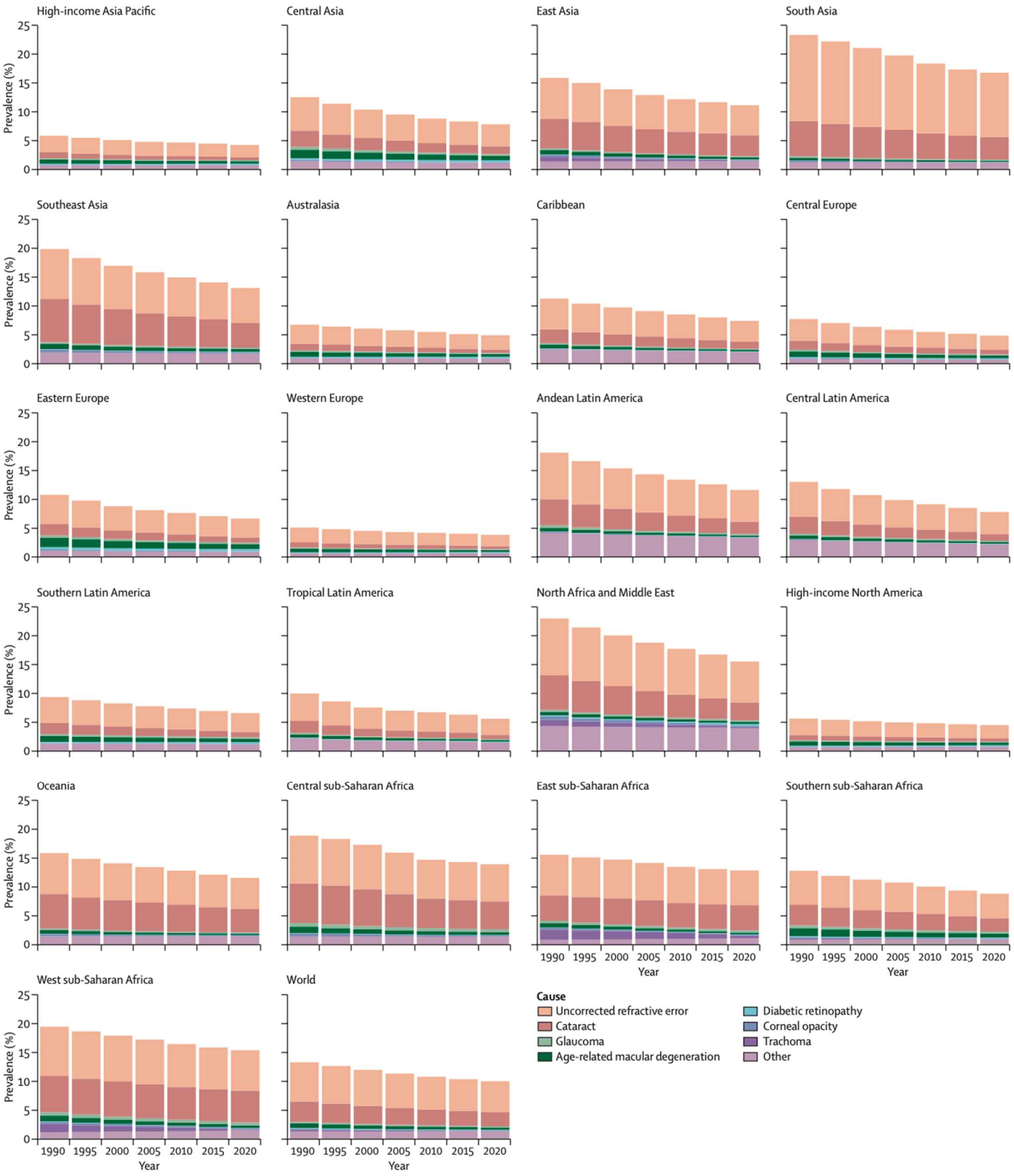
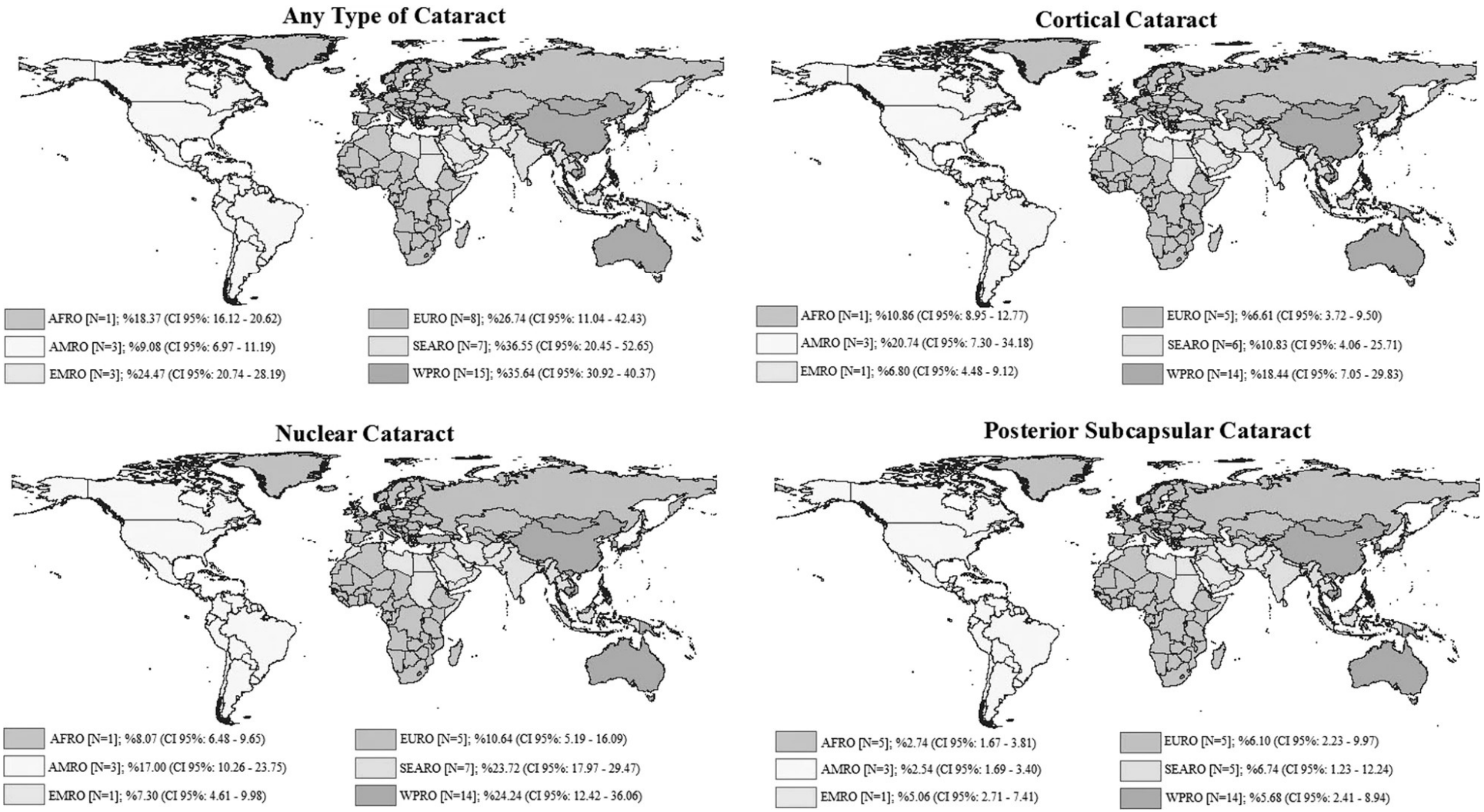


Figure A.3 Global and regional prevalence of cataract, based on pooled estimates from a systematic review conducted in 2019 (From Hashemi et al. 2020[12]).



AFRO (African Region), AMRO (Region of the Americas), EMRO (Eastern Mediterranean Region), EURO (European Region), SEARO (South-Eastern Asian Region), and WPRO (Western Pacific Region) represents six WHO (World Health Organization) regions.
The number of "N" represents number of studies from the systematic review included for the pooled estimates. The percentage estimates represent corresponding cataract prevalence.

Appendix B. Literature review of lifestyle and cardiometabolic risk factors for cataract

Table B.1 Systematic literature review search terms with MEDLINE (Ovid) database.

Steps	Search terms	Search results	
1	exp cataract/	33,219	
2	cataract*.tw.	65,009	
3	1 or 2	72,346	
4	Risk Factors/ or Risk Reduction Behavior/ or Health Risk Behaviors/ or Risk/ or Risk Assessment/	1,309,144	
5	risk*.tw.	2,980,858	
6	4 or 5	3,416,200	
7	3 and 6	9534	
8	exp cataract/ep, et [Epidemiology, Etiology]	9066	
9	7 or 8	16,636	
10	epidemiologic studies/	9443	Apply the Scottish Intercollegiate Guidelines Network (SIGN) filters to select prospective studies in MEDLINE database
11	exp case control studies/	1,465,840	
12	exp cohort studies/	2,550,613	
13	case control.tw.	158,229	
14	(cohort adj (study or studies)).tw.	333,621	
15	cohort analy$.tw.	12,443	
16	(Follow up adj (study or studies)).tw.	57,246	
17	(observational adj (study or studies)).tw.	169,799	
18	Longitudinal.tw.	333,964	
19	Retrospective.tw.	777,946	
20	Cross sectional.tw.	537,588	
21	Cross-sectional studies/	486,266	
22	case report.tw.	411,608	
23	case series.tw.	107,287	
24	or/10-21	3,896,783	
25	or/22-23	516,765	
26	9 and 24	6355	
27	26 not 25	**5850**	

Table B.2 Systematic literature review search terms with EMBASE (Ovid) database.

Steps	Search terms	Search results	
1	exp cataract/	69,719	
2	cataract*.tw.	77,246	
3	radiation cataract/ or subcapsular cataract/ or cataract/ or senile cataract/ or traumatic cataract/ or congenital cataract/	67,259	
4	or/1-3	101,332	
5	risk*.tw.	4,303,089	
6	risk/ or population risk/ or high risk behavior/ or "risk evaluation and mitigation strategy"/ or risk assessment/ or high risk infant/ or high risk population/ or low risk population/ or attributable risk/ or risk management/ or low risk patient/ or high risk patient/ or genetic risk/ or risk factor/ or risk reduction/	2,743,835	
7	5 or 6	4,979,388	
8	4 and 7	15,643	
9	exp cataract/ep, et [Epidemiology, Etiology]	7242	
10	8 or 9	21,428	
11	Clinical study/	164,925	Apply the Scottish Intercollegiate Guidelines Network (SIGN) filters to select prospective studies in EMBASE database
12	Case control study/	210,556	
13	Family study/	25,758	
14	Longitudinal study/	202,340	
15	Retrospective study/	1,533,741	
16	Prospective study/	896,175	
17	Randomized controlled trials/	266,325	
18	16 not 17	885,248	
19	Cohort analysis/	1,088,370	
20	(Cohort adj (study or studies)).mp.	490,843	
21	(Case control adj (study or studies)).tw.	171,375	
22	(follow up adj (study or studies)).tw.	74,755	
23	(observational adj (study or studies)).tw.	263,315	
24	(epidemiologic$ adj (study or studies)).tw.	123,739	
25	(cross sectional adj (study or studies)).tw.	354,842	
26	case report.tw.	551,735	
27	case series.tw.	151,101	
28	or/11-15,18-25	4,051,890	
29	10 and 28	5872	
30	26 or 27	698,810	
31	29 not 30	**5464**	

Table B.3 Bias domains included in the ROBINS-I tool for follow-up studies, with a summary of the issues addressed.

Bias domain	Explanation
Bias due to confounding	Whether: • the review author should consider baseline confounding only, or both baseline confounding and time-varying confounding; • all important confounding domains were controlled for; • the confounding domains were measured validly and reliably by the variables available; and • appropriate analysis methods were used to control for the confounding.
Bias in selection of participants	Whether: • selection of participants into the study (or into the analysis) was based on participant characteristics observed; • (if applicable) these characteristics were associated with exposure and influenced by outcome (or a cause of the outcome); • (if applicable) adjustment techniques were used to correct for the presence of selection biases.
Bias in classification of exposures	Whether: • exposure status was classified correctly for all (or nearly all) participants; • classification of exposure status could have been influenced by knowledge of the outcome or risk of the outcome.
Bias due to missing data	Whether: • the number of participants omitted from the analysis due to missing outcome data was small; • the number of participants omitted from the analysis due to missing data on exposure status was small; • the number of participants omitted from the analysis due to missing data on other variables needed for the analysis was small; • (if applicable) there was evidence that the result was not biased by missing outcome data; and • (if applicable) missingness in the outcome was likely to depend on the true value of the outcome (e.g., because of different proportions of missing outcome data, or different reasons for missing outcome data, between exposure groups).
Bias in measurement of the outcome	Whether: • the method of measuring the outcome was inappropriate; • measurement or ascertainment of the outcome could have differed between exposure groups; • outcome assessors were aware of the exposure received by study participants; and • (if applicable) assessment of the outcome could have been influenced by knowledge of exposure received; and whether this was likely.
Bias in selection of the reported result	Whether: • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple outcome measurements within the outcome domain; • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple analyses of the data; and • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple subgroups of a larger cohort.

Table from Sterne et al. 2016[57,283]

Table B.4 Prospective cohort studies evaluating the association between smoking and cataract.

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Physicians' Health Study[62]	U.S.	557/ 22,071 men	40-84	5	self-reported cataract confirmed by medical records	cataract diagnosis or surgery	age, aspirin and carotene intake, diabetes, hypertension, cholesterol level, BMI, alcohol, physical activity, parental history of myocardial infarction	(1) smoking frequency: (1a) never smoker (1b) past smoker (1c) current smoker, < 20/day (1d) current smoker, ≥20/day	(1) relative risk for cataract diagnosis (1b) vs (1a): 1.12(0.87-1.43) (1c) vs (1a): 0.94(0.48-1.86) (1d) vs (1a): 2.05(1.38-3.05)
Nurses' Health Study[61]	U.S.	493/ 50,828 women	45-67	8	medical records of cataract surgery	cataract surgery	age, dietary antioxidant score, vitamin C supplement, diabetes, hypertension, BMI, and number of physician visits	(1) pack-years (1a) non-smoker (1b) 1-9 (1c) 10-24 (1d) 25-44 (1e) 45-64 (1f) ≥65 (2a-2f) number of cigarettes per day among non-smoker, ex-smoker, and current smokers with 1-14, 15-24, 25-34 and ≥35 cig/day	(1) incidence rate ratio (IRR) for cataract surgery (1b) vs (1a): 0.78(0.54-1.11) (1c) vs (1a): 0.95(0.70-1.28) (1d) vs (1a): 1.10(0.85-1.42) (1e) vs (1a): 1.11(0.82-1.49) (1f) vs (1a): 1.58(1.13-2.19) (2) No association observed for the comparisons.
The Framingham Studies[284]	U.S.	381/ 660	52-80	12.5	slit-lamp eye examination	nuclear and non-nuclear cataract diagnosis	age, gender, education, diabetes	(1) smoking status: (1a) non-smoker (1b) light smoker (1c) heavy smoker (2) smoking amount (2a) never (2b) past smoker (2c) current, <20/day (2d) current, ≥20/day	(1) odds ratio (OR) for nuclear cataract (1b) vs (1a): 1.89(1.15-3.11) (1c) vs (1a): 2.46(1.31-4.60) No association observed for non-nuclear cataract. (2) OR for nuclear (2b) vs (2a): 2.02(1.14-3.57) (2c) vs (2a): 1.65(0.82-3.34) (2d) vs (2a): 2.84 (1.46-5.51) No association observed for non-nuclear cataract.
Swedish Mammography Cohort Study[66]	Sweden	2128/ 34,595 women	49-83	5	cataract surgery medical records	cataract surgery	age, education, diabetes, hypertension, steroid medication use, vitamin supplement, and BMI	(1) smoking intensity for ARC (1a) never smokers (1b1-4) past smokers with 1-5, 6-10, 11-15, >15 cig/day (1c1-4) current smokers with 1-5, 6-10, 11-15, >15 cig/day (2) comparison between categories of smoking intensity (1-5, 6-10, >10 cig/day) and time since quitting (<10,10-20,>20 years) for past smokers	(1) incidence rate ratio (IRR) for ARC surgery (1b3) vs (1a): 1.55(1.25-1.93) No association observed for other comparisons. (2) No clear association observed for 1-5 cig/day. IRR for 6-10 cig/day: <10 years vs non-smokers: 1.52 (1.12-2.06) 10-20 vs non: 1.18 (0.88-1.56) >20 vs non: 0.89 (0.64-1.23) for >10 cig/day: <10 yrs vs non: 1.63 (1.23-2.16) 10-20 vs non: 1.49 (1.12-1.99) >20 vs non: 1.20 (0.81-1.77)

(cont.)

Table B.4 Prospective cohort studies evaluating the association between smoking and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Blue Mountains Eye Study[64]	Australia	429/ 2406	49+	10	slit-lamp lens photograph	cataract diagnosis	age, gender, hypertension, myopia, diabetes, skin damage and steroid use	(1) smoking status (1a) never (1b) ever (1c) past (1d) current (2) pack-years for ever smokers: (2a) none (2b) ≤14 (2c) 14-36 (2d) >36 (3) time since quitting: never, smoker, and tertile of years since quitting for past smoker.	(1) incidence risk ratio (IRR) for nuclear cataract (1b) vs (1a): 1.41(1.09-1.83) (1c) vs (1a): 1.37(1.04-1.81) (1d) vs (1a): 1.57(1.06-2.31) No association observed for cortical nor PS cataract. (2) IRR for nuclear cataract (2b) vs (2a): 1.28(0.90-1.82) (2c) vs (2a): 1.33(0.92-1.92) (2d) vs (2a): 1.46(1.02-2.08) Results for cortical and PS cataract not reported. (3) No association observed for nuclear. Cortical and PS not reported.
Physicians' Health Study[67]	U.S.	2074 diagnosis and 1193 surgery/ 20,907 men	40-84	13.6	self-reported cataract confirmed by medical records	cataract diagnosis or surgery	age, aspirin and carotene intake, diabetes, hypertension, BMI, alcohol, physical activity, parental history of myocardial infarction, multivitamin use, smoking	(1) smoking status: (1a) current smoker (1b) never smoker (1c) past smoker, year since quitting <10 (1d) past smoker, year since quitting 10-19 (1e) past smoker, year since quitting ≥20	(1) incidence rate ratio (IRR) for ARC (1b) vs (1a): 0.64(0.54-0.76) (1c) vs (1a): 0.79(0.64-0.98) (1d) vs (1a): 0.73(0.61-0.88) (1e) vs (1a): 0.74(0.63-0.87) (1) IRR for cataract surgery (1b) vs (1a): 0.65(0.53-0.79) (1c) vs (1a): 0.75(0.57-0.98) (1d) vs (1a): 0.70(0.56-0.88) (1e) vs (1a): 0.69(0.56-0.85)
Nurses' Health Study and Health Professionals Follow-up Study[60]	U.S.	4281/ 117,731	45+	20 for women and 10 for men	self-reported questionnaire with medical records checks of cataract surgery	cataract surgery	age, gender, BMI, diabetes, lutein intake, region, and smoking	(1) smoking status: (1a) never smoker (1b) past smoker, 1-14 cig/day (1c) past smoker, ≥15 cig/day (1d) current smoker, 1-14 cig/day (1e) current smoker, ≥15 cig/day (2) Pack-years (2a) never smoker (2b) <10 (2c) 10-24.9 (2d) 25-44.9 (2e) 45-64.9 (2f) ≥65 (3) time since quitting: (3a) current smoker (3b-e) past smoker with year since quitting <5, 5-14.9, 15-24.9 and ≥25	(1) incidence rate ratio (IRR) for cataract surgery: (1b) vs (1a): 1.13(1.03-1.23) (1c) vs (1a): 1.33(1.24-1.44) (1d) vs (1a): 1.12(0.75-1.68) (1e) vs (1a): 1.53(1.39-1.69) (2) IRR for cataract surgery: (2b) vs (2a): 0.99(0.88-1.11) (2c) vs (2a): 1.18(1.08-1.30) (2d) vs (2a): 1.33(1.22-1.45) (2e) vs (2a): 1.45(1.31-1.60) (2f) vs (2a): 1.78(1.58-2.00) (3) IRR for cataract surgery: (3b) vs (3a): 1.20(0.93-1.55) (3c) vs (3a): 0.96(0.85-1.08) (3d) vs (3a): 0.84(0.74-0.95) (3e) vs (3a): 0.80(0.71-0.91)

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Table B.4 Prospective cohort studies evaluating the association between smoking and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
The Cohort of Swedish Men Study[65]	Sweden	5713/ 44,371 men	45-79	12	Swedish National Day-Surgery Register and local registers of cataract surgery	cataract surgery	age, education, diabetes, hypertension, corticosteroid medication, alcohol, vitamin supplement, and BMI	(1) cigarettes per day (1a) never smoker (1b) 1-5 (1c) 6-10 (1d) 11-15 (1e) >15 (2) pack-years for ever smokers: (2a) never smoker (2b) <10 (2c) 10-24 (2d) 25-44 (2e) >44 (3) time since quitting: (3a) never smoker (3b) year since quitting <10 (3c) year since quitting 10-20 (3d) year since quitting >20	(1) incidence rate ratio (IRR) for cataract surgery (1b) vs (1a): 1.11(1.00-1.24) (1c) vs (1a): 1.14(1.05-1.23) (1d) vs (1a): 1.18(1.08-1.28) (1e) vs (1a): 1.35(1.25-1.46) (2) IRR for cataract surgery (2b) vs (2a): 1.09(1.00-1.81) (2c) vs (2a): 1.16(1.07-1.25) (2d) vs (2a): 1.34(1.24-1.45) (2e) vs (2a): 1.45(1.29-1.63) (3) IRR for cataract surgery (3b) vs (3a): 1.27(1.15-1.41) (3c) vs (3a): 1.22(1.12-1.32) (3d) vs (3a): 1.13(1.04-1.22)
UK Million Women Study[59]	U.K.	89,343/1,312,051 postmenopausal women	50-64	11	UK national health medical records	cataract surgery	age, region, education, BMI, alcohol, physical activity, diabetes, age at menarche, parity, contraceptive use, and hormone therapy use	(1) smoking status: (1a) never smoker (1b) past smoker (1c) current smoker, <15 cig/day (1d) current smoker, 15+ cig/day	(1) relative risk for cataract surgery: (1b) vs (1a): 1.10(1.08-1.12) (1c) vs (1a): 1.12(1.09-1.14) (1d) vs (1a): 1.26(1.23-1.30)
The US Radiological Technologists Study[63]	U.S.	2382/ 35,705	24-44	20	self-reported cataract diagnosis	cataract diagnosis	age, sex, BMI, education, marital status, skin complexion, hair and iris colour, UV radiation exposure, alcohol, vitamin intake, aspirin use, diabetes, hypertension, CVD, and arthritis	(1) pack-years: (1a) never smoker (1b) <5 (1c) 5-<15 (1d) 15-<25 (1e) ≥25	(2) hazard ratio for cataract diagnosis: (1b) vs (1a): 0.98 (0.87-1.11) (1c) vs (1a): 1.11 (0.99-1.25) (1d) vs (1a): 1.25 (1.09-1.43) (1e) vs (1a): 1.33 (1.15-1.53)
Age-Related Eye Disease Study[102]	U.S.	2280/ 4425	55-80	12.2	lens photographs examination	cataract diagnosis	age, sex, race, education, diabetes, weight change, iris colour, refraction error, centrum use	(1) smoking status (1a) non-smoker (1b) former smoker (1c) current smoker	(1) hazard ratio for cortical cataract: (1b) vs (1a): 1.01 (0.88-1.17) (1c) vs (1a): 1.41 (1.09-1.83)
The Visual Impairment Project[249]	Australia	555/ 2392	40+	5	lens photographs examination	cataract diagnosis	age, sex, country of birth, occupation, diabetes, arthritis, vitamin C supplement intake, calcium channel blockers intake	(1) smoking status (1a) never (1b) past smoker (1c) current smoker	(1) relative risk for cortical cataract: (1b) vs (1a): 0.90 (0.59-1.30) (1c) vs (1a): 0.80 (0.49-1.40) (1) relative risk for nuclear cataract: (1b) vs (1a): 0.80 (0.54-1.10) (1c) vs (1a): 2.20 (1.40-3.30) (1) relative risk for PS cataract: (1b) vs (1a): 0.80 (0.54-1.30) (1c) vs (1a): 0.90 (0.55-1.50)

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Table B.4 Prospective cohort studies evaluating the association between smoking and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Oxford arm of the European Prospective Investigation into Cancer and Nutrition[82]	U.K.	1484/ 27,670	40+	13	UK NHS diagnostic records	cataract diagnosis	age, sex, region	(1) smoking status (1a) never (1b) former smoker (1c) current smoker, <15 cig/day (1d) current smoker, ≥15 cig/day	(1) hazard ratio for cataract: (1b) vs (1a): 1.16 (1.04-1.29) (1c) vs (1a): 1.06 (0.81-1.38) (1d) vs (1a): 1.50 (1.12-2.01)
Women's Health Initiative Observational Study and Age-Related Eye Disease Study[285]	U.S.	454/1577 women	50-79	6	slit lamp photographs and self-reported cataract surgery	nuclear cataract diagnosis or surgery	age, iris colour, healthy eating index score, BMI, and pulse pressure	(1) pack-years (1a) 0 (1b) 0 to <7 (1c) ≥7	(1) odds ratio for nuclear cataract (1b) vs (1a): 1.17 (0.89-1.54) (1c) vs (1a): 1.53 (1.15-2.04)
45 and Up Study[286]	Australia	1713/ 70,886	45-55	7	medical records of cataract surgery	cataract surgery performed before age 65 years	age, gender, income, education, BMI, hypertension, cardiovascular disease, family history of diabetes, insulin use, alcohol, and physical activity	(1) smoking frequency: (1a) never (1b) former (1c) current	(1)Hazard ratio for total: (1b) vs (1a): 1.07 (0.96-1.20) (1c) vs (1a): 0.96 (0.79-1.16) For men: (1b) vs (1a): 1.07 (0.90-1.27) (1c) vs (1a): 0.81 (0.59-1.11) For women: (1b) vs (1a): 1.07 (0.93-1.23) (1c) vs (1a): 1.07 (0.84-1.36)

Table B.5 Prospective cohort studies evaluating the association between alcohol consumption and cataract.

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Nurses' Health Study[69]	U.S.	1468/ 77,466 women	45+	12	medical records of cataract surgery and lens opacity confirmed by ophthalmologist	cataract diagnosis or surgery	age, smoking, BMI, region, number of physician visits, aspirin use, calories, physical activity, parental history of myocardial infarction, history elevated cholesterol, hypertension, diabetes	(1) daily intake (g/day) (1a) never (1b) ≤4.9 (1c) 5.0-14.9 (1d)15.0-24.9 (1e) ≥25.0	(1) incidence rate ratio (IRR) for cataract surgery (1b) vs (1a): 0.84(0.73-0.96) (1c) vs (1a): 0.83(0.71-0.97) (1d) vs (1a): 1.08(0.87-1.33) (1e) vs (1a): 1.10(0.90-1.35)
Swedish Mammography Cohort[72]	Sweden	3587/ 34,713 women	49-83	7	register of cataract surgery	cataract surgery	age, education, smoking, diabetes, hypertension, steroid medication use, vitamin supplements, and BMI	(1) drinking frequency (1a) never drinkers (1b) past drinkers (1c) current drinkers (g/day) (1c1) <6 (1c2) 6-13 (1c3) 14-20 (1c4) 21-30 (1c5) >30 (2) each increment of 13g alcohol per day	(1) incidence rate ratio (IRR) for cataract surgery (1b) vs (1a): 1.11(0.95-1.29) (1c1) vs (1a): 1.11(1.02-1.22) (1c2) vs (1a): 1.14(1.01-1.29) (1c3) vs (1a): 1.24(1.03-1.49) (1c4) vs (1a): 1.29(0.99-1.68) (1c5) vs (1a): 0.84(0.53-1.33) (2) IRR 1.07(1.02-1.12)
Blue Mountains Eye Study[70]	Australia	308/ 2564	49+	10	Slit-lamp lens photograph	cataract diagnosis	age, gender, smoking, diabetes, myopia, socioeconomic status, and steroid use	number of drinks per day: (1) total alcohol (1a) 0 (1b) 0-1 (1c) 2 (1d) >2 (2) beer, spirits, red wine, white wine	(1) odds ratio for cataract surgery (1a) vs (1c): 2.36(1.25-4.46) (1b) vs (1c): 1.77(0.90-3.48) (1d) vs (1c): 2.10(1.16-3.81) (2) no association observed.
UK Million Women Study[59]	U.K.	89,343/ 1,312,051 postmenopausal women	50-64	11	UK national health medical records	cataract surgery	age, region, education, smoking, BMI, physical activity, diabetes, age at menarche, parity, contraceptive use, and hormone therapy use	(1) intake amount (unit/week): (1a) <2 (1b) 2-14 (1c) 15+	(1) relative risk for surgery: (1b) vs (1a): 0.93(0.91-0.94) (1c) vs (1a): 0.92(0.89-0.96)

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Table B.5 Prospective cohort studies evaluating the association between alcohol consumption and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
The US Radiological Technologists Study[63]	U.S.	2382/ 35,705	24-44	20	self-reported cataract diagnosis	cataract diagnosis	age, sex, BMI, education, marital status, skin complexion, hair and iris colour, UV radiation exposure, smoking, vitamin intake, aspirin use, diabetes, hypertension, CVD, and arthritis	(1) intake amount (drinks per week) (1a) never (1b) <1 (1c) 1-2 (1d) 3-6 (1e) 7-10 (1f) >10	(1) hazard ratio for cataract diagnosis (1a) vs (1b): 1.05 (0.94-1.17) (1c) vs (1b): 0.84 (0.74-0.96) (1d) vs (1b): 0.88 (0.78-1.00) (1e) vs (1b): 0.84 (0.70-1.01) (1f) vs (1b): 0.92 (0.75-1.13)
EPIC-Oxford (Oxford arm of the European Prospective Investigation into Cancer and Nutrition)[82]	U.K.	1484/ 27,670	40+	13	UK NHS diagnostic records	cataract diagnosis	age, sex, region	(1) daily alcohol intake (g/day) (1a) <1 (1b) 1-7 (1c) 8-15 (1d) ≥16	(1) hazard ratio for cataract diagnosis: (1a) vs (1b): 1.05 (0.92-1.20) (1c) vs (1b): 1.03 (0.90-1.19) (1d) vs (1b): 1.08 (0.92-1.27)
Blue Mountains Eye Study[88]	Australia	520/ 1988	49+	5	slit lamp eye examination	cataract diagnosis	age, sex, diabetes, corticosteroids use, hypertension, BMI, smoking, myopia, iris colour	(1) daily alcohol intake (g/day) (1a) 0 (1b) 0-<5 (1c) 5-<10 (1d) 10-<20 (1e) >20	(1) odds ratio for cataract: No association was identified when comparing (1b), (1c), (1d), (1e) with (1a) for cortical, PS nor nuclear cataracts.
UK Biobank and European Prospective Investigation of Cancer (EPIC)-Norfolk[287]	UK	19,011/ 469,387 and 4573/ 23,162	40-69 and 40-79	8 and 16	UK NHS cataract surgery records	cataract surgery	age, sex, ethnicity, township deprivation index, BMI, smoking, diabetes	(1) quartiles of total weekly alcohol intake in EPIC-Norfolk: (1a) Q1 (lowest); (1b) Q2; (1c) Q3; (1d) Q4 (2) Frequency of alcohol consumption in UK Biobank: (2a) 1-3 times/months or less (2b) 1-2 times/week (2c) 3-4 times/week (2d) daily or almost daily	(1) hazard ratio for cataract: (1b) vs (1a): 0.92 (0.84-1.01) (1c) vs (1a): 0.86 (0.79-0.95) (1d) vs (1a): 0.82 (0.74-0.90) (2b) vs (2a): 0.93 (0.89-0.97) (2c) vs (2a): 0.94 (0.90-0.98) (2d) vs (2a): 0.97 (0.93-1.01)
Nakuru Eye Disease Cohort Study[288]	Kenya	449/ 1799	50+	6	ophthalmic examination	cataract diagnosis	age, sex, region, education, SES, ethnicity, smoking, BMI, diabetes, hypertension	Drinking status: (a) never (b) former (c) current	Risk ratio: (b) vs (a): 1.1 (0.9-1.3) (c) vs (a): 1.4 (1.1-1.8)
China Kadoorie Biobank[74]	China	2028/69,488 men	30-79	12	health insurance records	cataract surgery	age, region, education, smoking	(1) ever-regular vs occasional drinking (2) per 280 g/week among current drinkers	Hazard Ratio for cataract: (1) 1.08 (1.03-1.12) (2) 1.21 (1.09-1.33)

Table B.6 Prospective cohort studies evaluating the association between physical activity and cataract.

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Swedish Mammography Cohort and Cohort of Swedish Men[76]	Sweden	11,580/ 52,660	45-83	12.1	Swedish National Cataract Register of cataract surgery	cataract surgery	age, gender, smoking, waist circumference, hypertension history, corticosteroid use and education	(1) total MET hours/day (1a) quartile 1 (<38.4) (1b) Q2 (38.4-41.6) (1c) Q3 (41.6-45.5) (1d) Q4 (>45.5) (2) per 4 MET increment	(1) hazard ratio (HR) for cataract surgery: (1b) vs (1a): 0.94(0.89-0.99) (1c) vs (1a): 0.91(0.86-0.96) (1d) vs (1a): 0.87(0.82-0.92) (2) HR for total: 0.95 (0.94-0.97) Men: 0.94 (0.92-0.97) Women: 0.96 (0.94-0.98)
The National Runners' Health Study[78]	U.S.	912/ 40,992 non-diabetic runners	38-44	7	self-reported cataract diagnosis	cataract diagnosis	age, intake of meat/fish/fruit, alcohol, BMI	(1) running distance (km per week): <16, 16-32, 32-48, 48-64, ≥64 (2) running distance (km per week): per 1 unit higher (3) cardio-respiratory fitness (10km performance times) [m/s]: <3.25, 3.25-3.75, 3.75-4.25, 4.25-4.75, ≥4.75 (4) cardio-respiratory fitness (10km performance times) [m/s]: per 1 unit higher	Results reported include: (1) higher running distance was associated with lower relative risk of cataract in men. 28% lower risk in the highest than the lowest group. (2) relative risk for cataract diagnosis: men: 0.995 (0.991-0.999) women: 0.998 (0.991-1.006) (3) cardio-respiratory fitness was associated with lower relative risk of cataract in men and women. 43% lower risk in the highest than the lowest group. (4) relative risk for cataract diagnosis: men: 0.72 (0.60-0.87) women: 0.71 (0.47-1.06)
The National Runners' Health Study II and The National Walkers' Health Study[77]	U.S.	1807/ 47,527 runners and walkers (with mixture of races)	not reported (mean age around 50)	6.2	self-reported cataract diagnosis	cataract diagnosis	age, gender, race, education, smoking, intake of meat/fruit, and alcohol	(1) categories of MET hours/day: (1a) <1.8 (1.8 is the guideline level) (1b) 1.8-3.6; (1c) 3.6-5.4 (1d) 5.4-7.2; (1e) 7.2-9.0 (1f) ≥9.0 (2) MET: per 1 unit higher (3) quintiles of cardiorespiratory fitness (10-km performance times) [m/s]: Q1, Q2, Q3, Q4, Q5	HR for cataract diagnosis: (1b) vs (1a): 0.84 (0.75-0.94) (1c) vs (1a): 0.81 (0.70-0.94) (1d) vs (1a): 0.74 (0.61-0.89) (1e) vs (1a): 0.66 (0.49-0.90) (1f) vs (1a): 0.58 (0.43-0.80) (2) overall: 0.95 (0.93-0.97) men: 0.96 (0.95-0.98) women: 0.93 (0.90-0.95) (3) Q2 vs Q1: 0.90 (95%CI not reported) Q3 vs Q1: 0.80 Q4 vs Q1: 0.63 Q5 vs Q1: 0.67
Women's Health Initiative Observational Study and Age-Related Eye Disease Study[75]	U.S.	454/1577 women	50-79	6	slit lamp photographs and self-reported cataract surgery	nuclear cataract diagnosis or surgery	age, iris colour, healthy eating index score, smoking, BMI, and pulse pressure	(1) MET h/d: (1a) <3 (1b) 3 to <10 (1c) 10 to <21 (1d) ≥21	(1) odds ratio for nuclear cataract (1b) vs (1a): 0.84 (0.61-1.16) (1c) vs (1a): 0.87 (0.63-1.20) (1d) vs (1a): 0.89 (0.64-1.23)

Table B.7 Prospective cohort studies evaluating the association between dietary factors and cataract.

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Women's Health Study[83]	U.S.	2031/ 35,551 female health professionals	45+	10	cataract diagnosis confirmed with ophthalmologist	cataract diagnosis	age, smoking, alcohol, BMI, physical activity, postmenopausal hormone use, hypertension, hypercholesterolemia, diabetes, family history of myocardial infarction, history of eye examination	(1) Quintile of intake frequency (1a) Q1 (1b) Q2 (1c) Q3 (1d) Q4 (1e) Q5	(1) relative risk for cataract: fruit intake: (1b) vs (1a): 0.95 (0.82-1.11) (1c) vs (1a): 0.99 (0.85-1.15) (1d) vs (1a): 1.00 (0.87-1.16) (1e) vs (1a): 0.93 (0.80-1.08) vegetables intake: (1b) vs (1a): 0.94 (0.81-1.09) (1c) vs (1a): 0.96 (0.83-1.11) (1d) vs (1a): 0.96 (0.83-1.10) (1e) vs (1a): 0.92 (0.80-1.06)
Nurses' Health Study[289]	U.S.	493/ 50,828 female nurses	45-67	8	self-reported cataract surgery confirmed by medical records	cataract surgery	age, diabetes, smoking, residence	Intake frequency of <1 time/month, 1-3 times/month, 1 time/week, 2-4 times/week and ≥5 times/week	Higher intake frequency of spinach and winter squash was associated with lower risk of cataract. No association identified between broccoli, carrots, sweet potatoes and cataract risk.
Nurses' Health Study[87]	U.S.	4196/ 71,083 female nurses	30-55	16	self-reported cataract surgery confirmed by medical records	cataract surgery	age, smoking, alcohol, physical activity, lutein and zeaxanthin intake, BMI, postmenopausal status and hormone use, hypertension, annual number of physician visits, residency	(1) quintile of total fat intake (1a) Q1 (1b) Q2 (1c) Q3 (1d) Q4 (1e) Q5	(1) relative risk for cataract: (1b) vs (1a): 0.98 (0.89-1.07) (1c) vs (1a): 1.06 (0.96-1.17) (1d) vs (1a): 1.11 (1.01-1.22) (1e) vs (1a): 1.10 (0.99-1.22)
EPIC-Oxford (Oxford arm of the European Prospective Investigation into Cancer and Nutrition)[82]	U.K.	1484/ 27,670	40+	13	UK NHS diagnostic records	cataract diagnosis	age, sex, region, smoking, ethnicity, hypertension	(1) diet group (1a) meat eater, ≥100g/d (1b) meat eater, 50-99g/d (1c) meat eater, <50g/d (1d) fish eater (1e) vegetarian (1f) vegan	(1) hazard ratio for cataract: (1b) vs (1a): 0.96 (0.84-1.11) (1c) vs (1a): 0.85 (0.72-0.99) (1d) vs (1a): 0.79 (0.65-0.97) (1e) vs (1a): 0.70 (0.58-0.84) (1f) vs (1a): 0.60 (0.38-0.96)
UK Biobank[290]	U.K.	5753/72,160	40-69	9	hospital records and self-reported cataract	cataract diagnosis	age, sex, ethnicity, income, education, total energy intake, vitamin supplement, alcohol, physical activity, sleep duration, smoking, BMI, hypertension, depression, medication (for lipids, blood pressure, glucose control)	(1) high (≥6.5 servings/week) vs low (<2) intake of total fruit and vegetables (2) high vs low intake of specific vegetables and fruits: (2a) tomatoes (≥5.2 vs <1.8 serving/week) (2b) apple/pear (>7 vs <3.5) (2c) legumes, cruciferous vegetables, green leafy vegetables, berry, or citrus fruit/melon	Hazard ratio for cataract: (1) 0.82 (0.76-0.89) (2a) 0.94 (0.88-1.00) (2b) 0.89 (0.83-0.94) (2c) No clear association was found.

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Table B.7 Prospective cohort studies evaluating the association between dietary factors and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Blue Mountains Eye Study[81]	Australia	788/ 2173	49+	10	slit lamp eye examination	cataract diagnosis	age, sex, smoking, hypertension, diabetes, education, steroids use and myopia	(1) quartile of total diet score (based on Australian Healthy Eating Index): Q1, Q2, Q3, Q4 (2) per 1 unit higher in total diet score	(1) odds ratio (OR) for cataract: No association was identified when comparing Q2, Q3, Q4, Q5 with Q1 for cortical, PS nor nuclear cataracts. (2) OR for cataract: No association was identified for cortical, PS nor nuclear cataracts.
PREvencion con Dleta MEDiterranea (PREDIMED) Study[89]	Spain	768/ 5680	55-80	5.6	cataract surgery records from GP records	cataract surgery	age, sex, region, education, smoking, alcohol, leisure time activity, diabetes, hypertension, hypercholesterolemia, intake of other dietary factors(including vegetables, fruits, legumes, cereals, meat, fish, olive oil, and nuts)	Tertile of cumulative intake amount (g/day): (a) T1 (lowest intake) (b) T2 (c) T3 for: (1) dairy products (2) milk (3) yogurt (4) cheese	Hazard ratios: (1) dairy products (1b) vs (1a): 0.82 (0.67-1.00) (1c) vs (1a): 0.88 (0.70-1.11) (2) milk (2b) vs (2a): 1.05 (0.86-1.28) (2c) vs (2a): 0.93 (.072-1.21) (3) yogurt (3b) vs (3a): 0.75 (0.62-0.90) (3c) vs (3a): 0.92 (0.77-1.09) (4) cheese (4b) vs (4a): 0.97 (0.81-1.16) (4c) vs (4a): 1.04 (0.87-1.25)
Blue Mountains Eye Study[88]	Australia	520/ 1988	49+	5	slit lamp eye examination	cataract diagnosis	age, sex, diabetes, corticosteroids use, hypertension, BMI, alcohol, smoking, myopia, iris colour	(1) quintile of total fat intake (1a) Q1 (1b) Q2 (1c) Q3 (1d) Q4 (1e) Q5	(1) odds ratio for cataract: No association was identified when comparing Q2, Q3, Q4, Q5 with Q1 for cortical, PS nor nuclear cataracts.
Women's Health Study[84]	U.S.	2067/ 39,876	45+	10	cataract diagnosis confirmed with ophthalmologist	cataract diagnosis	age, smoking, alcohol, diabetes, hypertension, hypercholesterolemia, BMI, physical activity, myocardial infarction, menopause status, hormone use, vitamin supplements intake, total energy intake, history of eye exam	(1) quintile of intake (1a) Q1 (1b) Q2 (1c) Q3 (1d) Q4 (1e) Q5	(1) relative risk for cataract: fruits: (1b) vs (1a): 0.95 (0.80-1.11) (1c) vs (1a): 1.00 (0.85-1.18) (1d) vs (1a): 0.97 (0.83-1.14) (1e) vs (1a): 0.89 (0.75-1.06) vegetables: (1b) vs (1a): 0.94 (0.81-1.10) (1c) vs (1a): 0.96 (0.83-1.12) (1d) vs (1a): 0.94 (0.80-1.10) (1e) vs (1a): 0.88 (0.74-1.04)
Tzu Chi Health Study[47]	Taiwan region	476/ 4436	40+	5.7	cataract diagnostic records from health insurance database	cataract diagnosis	sex, education, smoking, alcohol, physical activity, volunteer status, BMI, hypertension, diabetes, hyperlipidemia, corticosteroid prescription	Dietary status: (a) non-vegetarian diet (b) vegetarian diet	hazard ratio: (b) vs (a): 0.80 (0.65-0.99)

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Table B.7 Prospective cohort studies evaluating the association between dietary factors and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Japan Public Health Center-based Prospective Cohort Study[85]	Japan	1836/ 71,720	45-74	5	self-reported cataract diagnosis confirmed by medical records review	cataract diagnosis	age, region, smoking, alcohol, BMI, fruit intake, vegetable intake, supplement intake, fundus photographic examination	Quartiles of intake, g/day: (a) Q1 (lowest) (b) Q2 (c) Q3 (d) Q4 and per 50g/day increment for: (1) vegetable (2) fruit in men and women	Odds ratios in men: (1b) vs (1a): 0.98 (0.76-1.27) (1c) vs (1a): 0.85 (0.65-1.10) (1d) vs (1a): 0.77 (0.59-1.01) per 50g/day increment: 0.95 (0.91-0.99) (2b) vs (2a): 0.93 (0.71-1.22) (2c) vs (2a): 1.22 (0.94-1.59) (2d) vs (2a): 1.13 (0.85-1.49) per 50g/day increment: 1.02 (0.99-1.05) Odds ratios in women: (1b) vs (1a): 1.13 (0.94-1.36) (1c) vs (1a): 1.15 (0.95-1.38) (1d) vs (1a): 1.28 (1.06-1.53) per 50g/day increment: 1.02 (1.00-1.04) (2b) vs (2a): 0.98 (0.82-1.18) (2c) vs (2a): 1.13 (0.94-1.36) (2d) vs (2a): 1.15 (0.96-1.39) per 50g/day increment: 1.01 (0.99-1.03)
Blue Mountains Eye Study[291]	Australia	301/ 1541	49+	5	slit lamp eye examination	cataract diagnosis	age, sex, education, smoking, vitamin E intake, steroid use and myopia	(1) quintile of wholegrain intake: Q1(lowest), Q2, Q3, Q4, Q5; and per 8g/day increment (2) quintile of legume intake: Q1, Q2, Q3, Q4, Q5; and per 75 g/day increment	(1) odds ratio for cataract: No association was identified when comparing Q2, Q3, Q4, Q5 with Q1, or per 8g/day increment for cortical, PS nor nuclear cataracts. (2) odds ratio for cataract: No association was identified when comparing Q2, Q3, Q4, Q5 with Q1, or per 75g/day increment for cortical nor nuclear cataracts. For PSC cataract: Q2 vs Q1: 0.52 (0.23-1.18) Q3 vs Q1: 0.62 (0.28-1.35) Q4 vs Q1: 0.71 (0.32-1.56) Q5 vs Q1: 0.37 (0.15-0.92) per 75g/day increment: 1.02 (0.59-1.75)
Taiwan Biobank Study[49]	Taiwan	1780/ 12,080	55+	3	self-reported	cataract diagnosis	age, sex, smoking, alcohol, physical activity, education, hypertension, diabetes, dyslipidemia, red blood counts, hemoglobin, albumin, hemoglobin A1c, total cholesterol, serum uric acid	(1) non-tea drinking (2) tea-drinking (3) tea-drinking with ≥2 cups/day	Relative risk for cataract: (2) vs (1): 0.85 (0.75-0.96) (3) vs (1): 0.84 (0.74-0.96)

Table B.8 Prospective cohort studies evaluating the association between adiposity factors and cataract.

Name of study cohort	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Framingham Eye Study[292]	U.S.	444/ 714	52-80	13	slit-lamp examinations	nuclear, cortical, and PS lens opacities	age, sex, education, diabetes, smoking	(1) BMI (kg/m^2) at baseline: (1a) <22.0 (1b) 22.0-27.7 (1c) >27.7 (2) per 1 kg/m^2 higher in BMI	(1) odds ratio (OR) for lens opacities (1b) vs (1a): 1.07(0.63-1.18) (1c) vs (1a): 1.38(0.71-2.67) (2) OR for lens opacities: 1.69 (0.80-3.55)
Nurses' Health Study and Health Professionals' Follow-up Study[97]	U.S.	4430/ 133,231	45+	16 years for women and 10 years for men	medical records of cataract surgery	cataract surgery	age, smoking, lutein intake, diabetes	(1) BMI (kg/m^2) (1a) <23.0 (1b) 23.0-24.9 (1c) 25.0-27.9 (1d) 28.0-29.9 (1e) >29.9 (2) per 5 kg/m^2 higher in BMI	(1) incidence rate ratio (IRR) for cataract surgery men: (1b) vs (1a): 0.90(0.75-1.07) (1c) vs (1a): 1.00(0.85-1.18) (1d) vs (1a): 1.15(0.92-1.43) (1e) vs (1a): 1.22(0.97-1.54) women: (1b) vs (1a): 1.11(1.00-1.22) (1c) vs (1a): 1.15(1.05-1.27) (1d) vs (1a): 1.16(1.02-1.32) (1e) vs (1a): 1.39(1.25-1.54) (2) IRR for cataract surgery men: 1.03(0.93-1.15) women: 1.12(1.07-1.17)
Japan Public Health Center Study[293]	Japan	2811/ 76,190	45-74	10	self-reported cataract diagnosis	cataract diagnosis	age, history of hypertension and diabetes, alcohol, smoking, region	(1) BMI (kg/m^2) (1a) <19.0 (1b) 19.0-20.9 (1c) 21.0-22.9 (1d) 23.0-24.9 (1e) >24.9	(1) odds ratio for cataract diagnosis men: (1a) vs (1c): 1.29(0.93-1.79) (1b) vs (1c): 1.16(0.93-1.44) (1d) vs (1c): 1.02(0.84-1.22) (1e) vs (1c): 1.15(0.96-1.39) women: (1a) vs (1c): 1.23(0.97-1.55) (1b) vs (1c): 1.22(1.03-1.44) (1d) vs (1c): 1.13(0.98-1.30) (1e) vs (1c): 1.19(1.04-1.36)
Nurses' Health Study, and Health Professionals' Follow-up Study[101]	U.S.	41,600/ 118,140	55+	18	self-reported cataract surgery	cataract surgery	age, height, race, smoking, aspirin use, menopause and hormone therapy status, parity, physical activity, alcohol, dietary qualify, family history of respective diseases and weight at age 18.	(1) weight change from early to middle adulthood (1a) loss >2.5kg (1b) loss ≤2.5kg or gain <2.5kg (1c) gain 2.5-9.9 kg (1d) gain 10.0-19.9 kg (1e) gain >19.9kg	(1) incidence rate ratio for cataract surgery men: (1a) vs (1b): 1.09(0.97-1.23) (1c) vs (1b): 1.07(0.98-1.16) (1d) vs (1b): 1.16(1.06-1.27) (1e) vs (1b): 1.21(1.09-1.35) women: (1a) vs (1b): 0.96(0.92-1.00) (1c) vs (1b): 1.01(0.98-1.03) (1d) vs (1b): 1.02(1.00-1.05) (1e) vs (1b): 1.05(1.02-1.08)

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Table B.8 Prospective cohort studies evaluating the association between adiposity factors and cataract (cont.)

Name of study cohort	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Physician's Health Study[294]	U.S.	370/ 17,764 men	40-84	5	self-reported cataract confirmed by medical records	cataract diagnosis	age, diabetes, alcohol, physical activity, hypertension, cholesterol level, smoking, multivitamins use	(1) BMI (kg/m^2) (1a) <22.0 (1b) 22.0-24.9 (1c) 25.0-27.7 (1d) >27.7 (2) per 2 kg/m^2 higher in BMI	(1) incidence rate ratio (IRR) for cataract (1b) vs (1a): 1.54(1.04-2.27) (1c) vs (1a): 1.46(0.98-2.20) (1d) vs (1a): 2.10(1.35-3.25) (2) IRR for cataract: 1.12 (1.05-1.19)
Physician's Health Study[100]	U.S.	1727/ 17,150 men	40-84	14	self-reported cataract confirmed by medical records	cataract diagnosis	age, aspirin and carotene use, smoking, alcohol, physical activity, multivitamin use, (plus BMI and WHR, as appropriate)	(1) BMI (kg/m^2) (1a) <22.0 (1b) 22.0-24.9 (1c) 25.0-27.7 (1d) >27.7 (2) waist-to-hip ratio (2a) <0.897 (2b) 0.897-0.924 (2c) 0.925-0.950 (2d) 0.951-0.985 (2e)>0.985	(1) incidence rate ratio (IRR) for cataract (1b) vs (1a): 1.13(0.96-1.32) (1c) vs (1a): 1.15(0.97-1.36) (1d) vs (1a): 1.25(1.03-1.51) (2) IRR for cataract (2b) vs (2a): 1.16(0.90-1.50) (2c) vs (2a): 1.13(0.89-1.45) (2d) vs (2a): 1.30(1.01-1.66) (2e) vs (2a): 1.31(1.02-1.67)
UK Million Women Study[95]	U.K.	89,343/ 1,312,051 postmenopausal women	50-64	11	UK national health medical records	cataract surgery	age, region, education, smoking, alcohol, physical activity, diabetes, age at menarche, parity, contraceptive use, and hormone therapy use	(1) BMI (kg/m^2): (1a) <25 (1b) 25-<30 (1c) ≥30	(1) relative risk for cataract: (1b) vs (1a): 1.02(1.01-1.04) (1c) vs (1a): 1.12(1.10-1.14)
The National Runners' Health Study[78]	U.S.	912/ 40,992 non-diabetic runners	38-44	7	self-reported cataract diagnosis	cataract diagnosis	age, intake of meat/fish/fruit, alcohol, physical activity	(1) BMI (kb/m^2): <20, 20-22.5, 22.5-25, 25-27.5, ≥27.5 (2) BMI: per 1 unit higher (3) waist circumference (cm): per 1 unit higher	(1) higher BMI was associated with higher relative risk of cataract in men. 88% lower risk in the highest than the lowest group. (2) relative risk (RR) for cataract: men: 1.04 (1.01-1.07) women: 0.97 (0.91-1.03) (3) RR for cataract: men: 1.02 (1.00-1.03) women: 1.04 (1.01-1.06)
Women's Health Initiative Observational Study and Age-Related Eye Disease Study[285]	U.S.	454/1577 women	50-79	6	slit lamp photographs and self-reported cataract surgery	nuclear cataract diagnosis and surgery	age, iris colour, healthy eating index score, smoking, and pulse pressure	(1) BMI (kg/m^2) (1a) <22.5 (1b) 22.5 to <25.0 (1c) 25.0 to <30.0 (1d) 30.0 to <35.0 (1e) ≥35.0	(1) odds ratio for nuclear cataract (1a) vs (1b): 1.29 (0.90-1.85) (1c) vs (1b): 1.34 (0.97-1.84) (1d) vs (1b): 1.24 (0.86-1.80) (1e) vs (1b): 1.61 (1.02-2.53)

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Table B.8 Prospective cohort studies evaluating the association between adiposity factors and cataract (cont.)

Name of study cohort	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Blue Mountains Eye Study[104]	Australia	756 cortical, 530 PS, 130 nuclear/ 2406	49+	5	self-reported cataract confirmed by photograph check	cataract diagnosis	age, gender, smoking, myopia, pulse pressure, hypertension, use of steroids, glucose, diabetes, and sun-related skin damage	(1) BMI (kg/m^2): (1a) <25 (1b) 25-<30 (1c) ≥30 (2) per 1kg/m^2 higher in BMI	(1) incidence rate ratio (IRR) for nuclear surgery: (1b) vs (1a): 0.88 (0.66-1.16) (1c) vs (1a): 1.15 (0.82-1.61) (2) IRR for nuclear surgery: 1.02 (0.89-1.15) [similar results in (1) and (2) for cortical and posterior subcapsular cataracts]
The US Radiological Technologists Study[63]	U.S.	2382/ 35,705	24-44	20	self-reported cataract diagnosis	cataract diagnosis	age, sex, education, marital status, skin complexion, hair and iris colour, UV radiation exposure, alcohol, smoking, vitamin intake, aspirin use, diabetes, hypertension, CVD, and arthritis	(1) BMI (kg/m^2) (1a) <20 (1b) 20-<25 (1c) 25-<30 (1d) ≥30	(1) hazard ratio for cataract (1b) vs (1a): 1.10 (0.97-1.25) (1c) vs (1a): 1.43 (1.24-1.66) (1d) vs (1a): 1.44 (1.21-1.72)
Cohort of Swedish Men[295]	Sweden	7573/ 45,049 men	45-79	15	registry of cataract surgery	cataract surgery	age, smoking, alcohol, steroid medication use, vitamin supplement use, education, physical activity, diabetes, hypertension	(1) waist circumference (cm) (1a) <94 (1b) ≥94	(1) relative risk for cataract: (1b) vs (1a): 1.04 (0.99-1.10)
Swedish Mammography Cohort[99]	Sweden	4508/ 35,369 women	49-83	8.2	registry of cataract surgery	cataract surgery	age, smoking, alcohol, steroid medication use, vitamin supplement use, education	(1) waist circumference (cm) among non-diabetics (1a) <80 (1b) ≥80	(1) relative risk for cataract: (1b) vs (1a): 1.08 (0.99-1.17)
The Shihpai Eye Study[48]	Taiwan region	128/ 460	65+	7	diagnose by ophthalmologist	cataract diagnosis	age, sex, education, diabetes, smoking, alcohol, cardiovascular diseases history	(1) waist-to-hip ratio (1a) not high (<0.92 for men, <0.88 for women) (1b) high (≥0.92 for men, ≥0.88 for women)	(1) relative risk for cortical cataract: (1b) vs (1a): 0.63 (0.37-1.07) Results for nuclear and PS cataract not reported.
Age-Related Eye Disease Study[102]	U.S.	2280/ 4425	55-80	12.2	lens photographs examination	cataract diagnosis	age, sex, race, education, diabetes, smoking, iris colour, refraction error, centrum use	(1) weight change since age 20 (1a) lowest quintile (1b) middle quintile (1c) top quintile	(1) hazard ratio (HR) for cortical cataract: (1b) vs (1a): 1.20 (1.00-1.43) (1c) vs (1a): 1.35 (1.09-1.67) (1) HR for PS cataract: (1b) vs (1a): 1.25 (0.98-1.60) (1c) vs (1a): 1.48 (1.10-1.97) Results for nuclear cataract not reported.
Chennai Eye Disease Incidence Study[223]	India	158/ 2484	40+	6	slit-lamp eye examination	cataract diagnosis	age, sex, region	(1) BMI (kg/m^2) (1a) <18.5 (1b) 18.5-24.9 (1c) 25.0-29.9 (1d) ≥30.0	(1) odds ratio for cataract (1a) vs (1b): 0.89 (0.54-1.47) (1c) vs (1b): 0.86 (0.46-1.61) (1d) vs (1b): 0.34 (0.11-1.06)

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Table B.8 Prospective cohort study evaluating the association between adiposity factors and cataract (cont.)

Name of study cohort	Study location	Study population (cases/ participants)	Baseline age (years)	Follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Singapore Malay Eye Study[296]	Singapore	440/ 1765	40+	6	cataract diagnosis by lens photo from eye examination	cataract diagnosis	age, sex, smoking, diabetes, SES, best-corrected visual acuity, myopia, hypertension, chronic kidney disease, C-reactive protein, cardiovascular disease, total cholesterol	category of BMI (kg/m^2) (a) <25 (b) 25-29.9 (c) ≥30	(1) relative risk for cortical cataract (b) vs (a): 1.01 (0.72-1.43) (c) vs (a): 1.23 (0.84-1.82) (2) relative risk for nuclear cataract (b) vs (a): 0.86 (0.61-1.21) (c) vs (a): 1.03 (0.69-1.53) (3) relative risk for PSC (b) vs (a): 1.05 (0.71-1.55) (c) vs (a): 1.15 (0.71-1.85)
UK Biobank[96]	UK	15,255/ 153,139	40-70	10.9	hospital records and self-reported cataract	cataract diagnosis	age, sex, ethnicity, income, education, height, diet score, alcohol, physical activity, sleep, smoking, hypertension, heart disease, stroke, depression, AMD, glaucoma	Compare between defined groups: (1) BMI: ≥30 vs <30 kg/m^2 (2) waist circumference: ≥102 vs <102cm in men, ≥88 vs <88cm in women (3) waist-to-hip ratio ≥1.00 vs <1.00 in men, ≥0.85 vs <0.85 in women (4) body fat percentage ≥25% vs <25% in men, ≥35% vs <35% in women	Hazard ratio for cataract: (1) 1.10 (1.06-1.15) (2) 1.09 (1.06-1.13) (3) 1.14 (1.09-1.19) (4) 1.00 (0.96-1.05)
45 and Up Study[297]	Australia	1764/ 73,007	45-55	8.8	healthcare records	early onset of cataract surgery (i.e., onset before age 65 years)	age, sex, ethnicity, income, education, smoking, alcohol, physical activity, hypertension, cardiovascular diseases, diabetes	BMI (kg/m^2) category at baseline: 18.5-19.9, 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-50.0	No statistically significant HRs were found when compared with the reference group (with BMI of 20.0-22.4 kg/m^2)

Table B.9 Prospective cohort study evaluating the association between diabetes, blood glucose, and cataract.

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Study follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
Blue Mountains Eye Study[105]	Australia	256 cortical, 365 nuclear, 28 PS/ 2454 non-diabetic participants	49+	10	slit-lamp lens photograph	cataract diagnosis	age, gender, socioeconomic status, smoking, myopia, and steroid use	Per increment of 1 mmol/L fasting blood glucose: (1) Cortical cataract (2) Nuclear cataract (3) PSC (4) Any cataract	odds ratio: (1) 1.14 (1.01-1.27) (2) 1.20 (1.01-1.43) (3) 0.94 (0.60-1.45) (4) 1.23(1.01-1.48)
Blue Mountains Eye Study[298]	Australia	294 cortical, 88 PS, 440 nuclear, 151 extraction/ 2335	49+	5	slit-lamp lens photograph	cataract diagnosis or surgery	age, gender, smoking, alcohol, corticosteroids use, hypertension and education	(1) diabetes status (1a) none (1b) impaired fasting glucose (fasting glucose level at 6-7 mmol/L) (1c) diabetes	(1) odds ratio (OR) for cortical cataract (1b) vs (1a): 2.2 (1.1-4.1) (1c) vs (1a): 1.5 (0.9-2.6) OR for PSC: (1b) vs (1a): 0.3 (0.0-2.2) (1c) vs (1a): 1.4 (0.6-3.3) OR for nuclear cataract (1b) vs (1a): 0.9 (0.4-1.9) (1c) vs (1a): 1.3 (0.7-2.2) OR for cataract surgery (1b) vs (1a): 0.8 (0.3-2.2) (1c) vs (1a): 1.2 (0.6-2.4)
(Not reported)[299]	Canada	5247/ 1,108,541 pregnant women	from <20 to >40	25	medical records	cataract surgery	age, calendar year at recruitment, parity, socioeconomic status, hypertension, dyslipidaemia, obesity, smoking and asthma	(1) with vs without gestational diabetes (2) gestational diabetes and infant birth weight (kg): (2a) no, (2b) yes, <4.0, (2c) yes, 4-4.5, (2d) yes, >4.5 (3) diabetes status (3a) none (3b) type 2 diabetes only (3c) gestational diabetes only (3d) gestational and type 2 diabetes	(1): hazard ratio (HR) for cataract surgery: 1.14 (1.01-1.29) (2) HR for cataract surgery: (2b) vs (2a): 1.14 (1.01-1.30) (2c) vs (2a): 1.11 (0.83-1.48) (2d) vs (2a): 1.36 (0.84-2.22) (3) HR for cataract surgery: (3b) vs (3a): 3.67 (2.78-4.83) (3c) vs (3a): 1.15 (1.01-1.31) (3d) vs (3a): 3.81 (3.10-4.68)
Blue Mountains Eye Study[104]	Australia	756 cortical, 530 PS, 130 nuclear, 429 extraction/ 2406	49+	5	slit-lamp lens photograph	cataract diagnosis	age, gender, smoking, myopia, pulse pressure, hypertension, use of steroids, BMI, and sun-related skin damage	(1) diabetes status (1a) none (1b) impaired fasting glucose (fasting glucose level at 6-7 mmol/L) (1c) diabetes (1d) impaired fasting glucose or diabetes (2) per 1 standard deviation higher in fasting blood glucose (mmol/L)	(1) relative risk for cortical cataract: (1b) vs (1a): 2.01 (1.20-3.36) (1c) vs (1a): 1.33 (0.84-2.10) (1d) vs (1a): 1.57 (1.10-2.24) PSC: (1b) vs (1a): 0.94 (0.37-2.38) (1c) vs (1a): 1.45 (0.75-2.77) (1d) vs (1a): 1.24 (0.71-2.15) nuclear cataract: (1b) vs (1a): 0.85 (0.42-1.74) (1c) vs (1a): 1.64 (1.02-2.64) (1d) vs (1a): 1.33 (0.89-1.98) (2) relative risk Cortical cataract: 1.13 (1.01-1.27) PS cataract: 0.91 (0.70-1.17) Nuclear cataract: 1.05 (0.90-1.22) Any cataract: 1.08 (0.96-1.21)

(cont.)

Table B.9 Prospective cohort study evaluating the association between diabetes, blood glucose, and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Study follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
The Framingham Studies[284]	U.S.	381/ 660	52-80	12.5	slit-lamp examinations	nuclear and non-nuclear lens opacities diagnosis	age, gender, education	(1) diabetes status (1a) without diabetes (1b) with diabetes	(1) odds ratio (OR) for nuclear cataract: (1b) vs (1a): 1.81 (0.49-6.63) (1) OR for non-nuclear cataract: (1b) vs (1a): 3.18 (0.91-11.09)
UK Million Women Study[59]	U.K.	89,343/ 1,312,051 postmenopausal women	50-64	11	UK national health medical records	cataract surgery	age, region, education, smoking, BMI, alcohol, physical activity, age at menarche, parity, contraceptive use, and hormone therapy use	(1) had treatment for diabetes (1a) no (1b) yes	(1) relative risk for cataract: (1b) vs (1a): 2.90 (2.82-2.97)
The US Radiological Technologists Study[63]	U.S.	2382/ 35,705	24-44	20	self-reported cataract diagnosis	cataract diagnosis	age, sex, BMI, education, marital status, skin complexion, hair and iris colour, UV radiation exposure, smoking, vitamin intake, aspirin use, hypertension, CVD, and arthritis	(1) diabetes status (1a) never (1b) yes	(1) relative risk for cataract: (1b) vs (1a): 4.10 (3.24-5.20)
Cohort of Swedish Men[295]	Sweden	7573/ 45,049 men	45-79	15	registry of cataract surgery	cataract surgery	age, smoking, alcohol, steroid medication use, vitamin supplement use, education, physical activity	(1) diabetes status (1a) no (1b) yes	(1) relative risk for cataract: (1b) vs (1a): 1.77 (1.64-1.92)
Nakuru Eye Disease Cohort Study[300]	Kenya	449/ 1799	50+	6	ophthalmic examination	cataract diagnosis	age, sex, region, education, alcohol, BMI, socio-economic status, smoking, hypertension, ethnic group	(1) diabetes status (1a) no (1b) yes	(1) relative risk for cataract: (1b) vs (1a): 1.7 (1.3-2.3)
Swedish Mammography Cohort[99]	Sweden	4508/ 35,369 women	49-83	8	registry of cataract surgery	cataract surgery	age, smoking, alcohol, steroid medication use, vitamin supplement use, education	(1) diabetes status (1a) no (1b) yes	(1) relative risk for cataract: (1b) vs (1a): 1.43 (1.10-1.86)
Singapore Epidemiology of Eye Diseases Study[222]	Singapore	656/ 6083	40+	6	slit-lamp eye examination	cataract surgery	age, sex, smoking, hypertension, socio-economic status	(1) diabetes status (1a) no (1b) yes	(1) odds ratio for cataract: (1b) vs (1a): 1.90 (1.54-2.33)
The Los Angeles Latino Eye Study[301]	U.S.	455/ 4658 Latin Americans	40+	4	slit-lamp eye examination	cataract diagnosis	age, sex, income, acculturation, education, haemoglobin, blood pressure, smoking, intraocular pressure, glaucoma, large drusen	(1) diabetes status (1a) no (1b) yes	(1) odds ratio (OR) for nuclear cataract: (1b) vs (1a): 1.11 (1.01-1.22) (1) OR for cortical cataract: (1b) vs (1a): 2.32 (1.58-3.41)

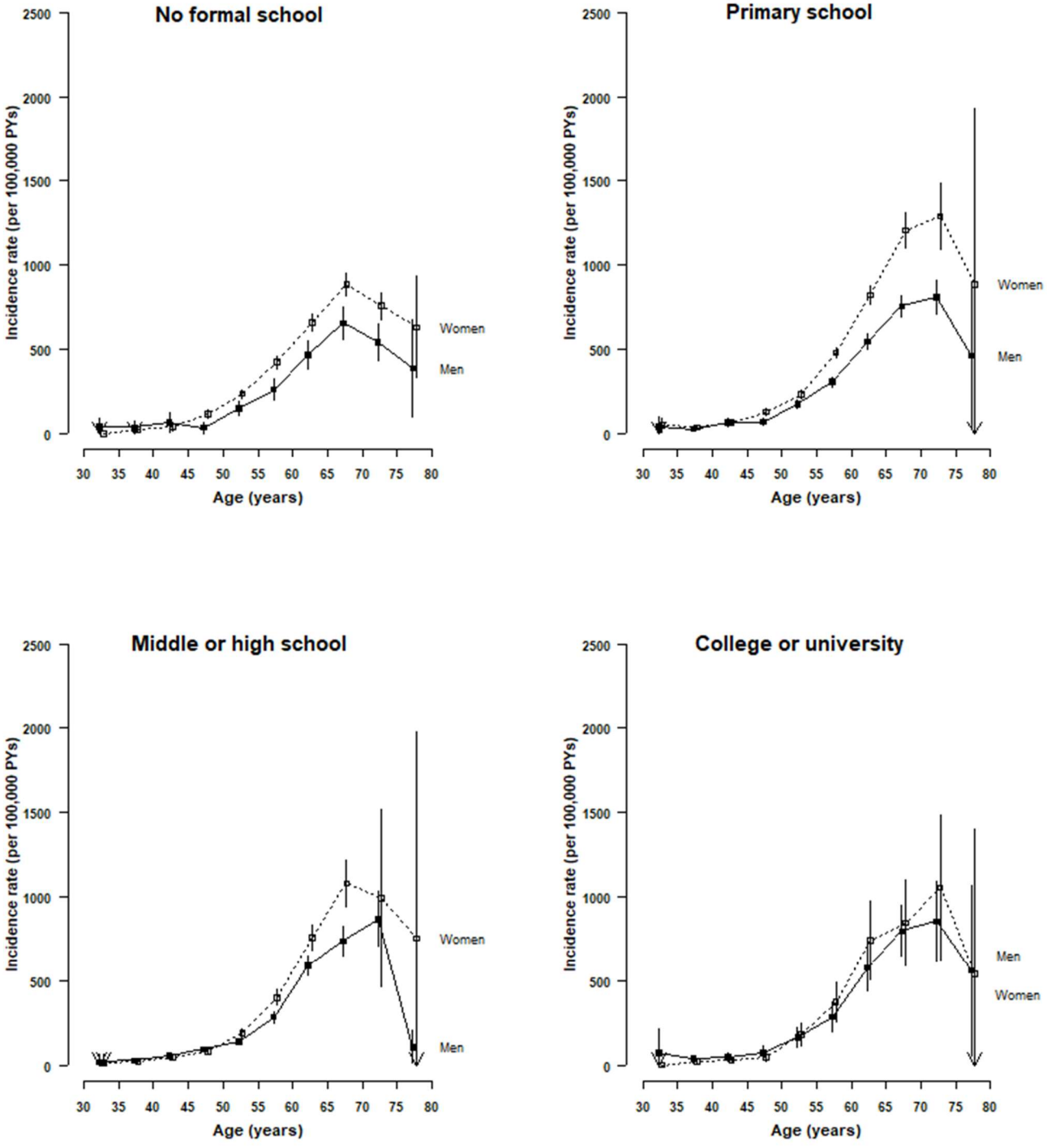
(cont.)

Table B.9 Prospective cohort study evaluating the association between diabetes, blood glucose, and cataract (cont.)

Study name	Study location	Study population (cases/ participants)	Baseline age (years)	Study follow-up (years)	Outcome		Adjustment for covariates	Association estimates	
					Measurement of cataract	Type(s) of cataract		Comparisons	Results
The Shihpai Eye Study[48]	Taiwan region	128/ 460	65+	7	diagnose by ophthalmologist	cataract diagnosis	age, sex, education, BMI, smoking, alcohol, cardiovascular diseases history	(1) diabetes status (1a) no (1b) yes	(1) relative risk for cortical cataract: (1b) vs (1a): 2.43 (1.02-5.81)
Barbados Eye Studies[302]	Barbados	549/ 2954	40-84	4	slit-lamp eye examination	cortical and PS cataract diagnosis	age, sex, socio-economic status, aspirin use, glycosylated haemoglobin level	(1) diabetes status (1a) no (1b) yes	(1) relative risk for cortical cataract: (1b) vs (1a): 2.4 (1.8-3.2) (1) RR for PS cataract: (1b) vs (1a): 2.9 (1.9-4.5)
Age-Related Eye Disease Study[102]	U.S.	2280/ 4425	55-80	12	lens photographs examination	cataract diagnosis	age, sex, race, education, smoking, weight change, iris colour, refraction error, centrum use	(1) diabetes status (1a) no (1b) yes	(1) hazard ratio (HR) for cortical cataract: (1b) vs (1a): 1.31 (1.04-1.66) (1) HR for PS cataract: (1b) vs (1a): 1.71 (1.29-2.27)
The Visual Impairment Project[249]	Australia	555/ 2392	40+	5	lens photographs examination	cataract diagnosis	age, sex, country of birth, occupation, smoking, arthritis, vitamin c supplement intake, calcium channel blockers intake	(1) diabetes status (1a) no (1b) yes	(1) relative risk (RR) for cortical cataract: (1b) vs (1a): 1.40 (0.70-2.80) (1) RR for nuclear cataract: (1b) vs (1a): 1.10 (0.64-2.00) (1) RR for PS cataract: (1b) vs (1a): 2.90 (1.70-5.10)
Barbados Eye Studies[303]	Barbados	241/ 2609	40-84	4	slit-lamp eye examination	nuclear cataract diagnosis	age, sex, BMI, iris colour, myopia, intraocular pressure	(1) diabetes status (1a) no (1b) yes	(1) relative risk for nuclear cataract: 1.60 (1.10-2.40)
Chennai Eye Disease Incidence Study[223]	India	158/ 2484	40+	6	slit-lamp eye examination	cataract diagnosis	age, sex, region	(1) diabetes status (1a) no (1b) yes	(1) odds ratio for cataract: (1b) vs (1a): 1.12 (0.73-1.73)

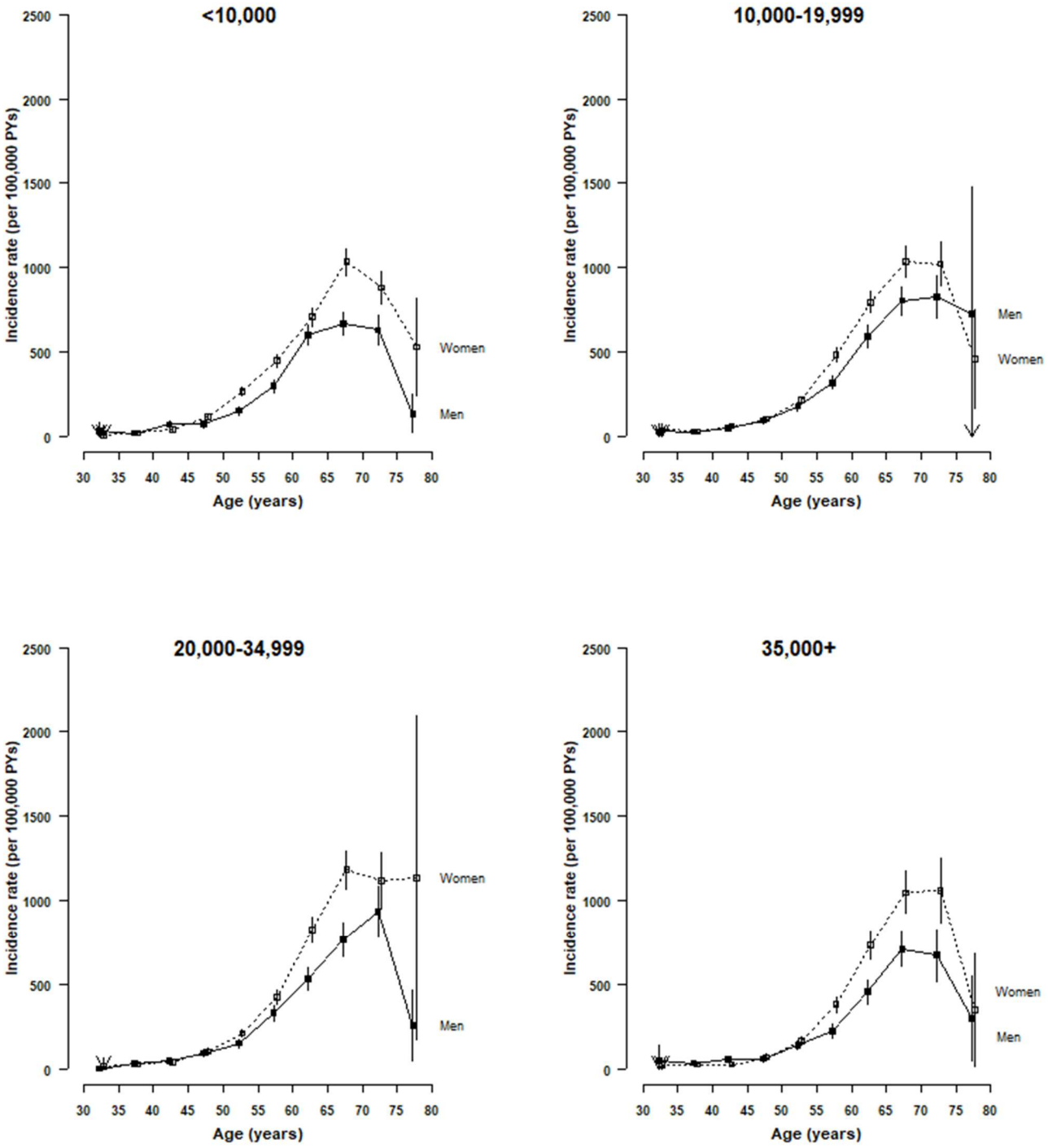
Appendix C. Additional results: Patterns and correlates of cataract incidence in CKB

Figure C.1 Cataract incidence rates by baseline age group in men and women with different levels of highest education received.



The square represents incidence rate, and the vertical lines represents 95% CIs. The size of the square is inversely proportional to the variance of the incidence rate.

Figure C.2 Cataract incidence rates by baseline age group in men and women with different household income (yuan) levels.



The square represents incidence rate, and the vertical lines represents 95% CIs. The size of the square is inversely proportional to the variance of the incidence rate.

Appendix D. Additional results: Associations of smoking and alcohol drinking with risk of cataract

Table D.1 Baseline characteristics of CKB women by smoking and alcohol consumption status.

	Smoking				Alcohol consumption				All women (N=302,504)
	Never smokers (N=287,175)	Occasional smokers (N=5533)	Ex-regular smokers (N=1201)	Current smokers* (N=8595)	Non-drinkers (N=192,322)	Ex-drinkers (N=2657)	Occasional drinkers (N=101,280)	Current drinkers (N=6245)	
Mean age (SD), years	51.1 (10.2)	52.4 (16.1)	61.9 (21.7)	59.5 (21.1)	52.7 (11.5)	55.2 (21.8)	49.3 (12.8)	52.9 (18.9)	51.5 (10.5)
Socio-demographic factors									
Rural, %	55.0	60.3	54.4	60.9	57.3	69.2	51.9	53.5	55.4
Education below high school, %	56.3	54.4	54.6	59.6	58.6	51.9	51.3	51.1	56.7
Household income <20K yuan/year, %	59.0	61.2	57.8	62.6	61.9	52.8	55.9	52.7	59.4
Lifestyle factors									
Physical activity, mean (SD) MET-hours/day	20.5 (10.5)	19.4 (18.2)	15.5 (13.7)	18.1 (36.8)	20.2 (11.8)	19.6 (25.2)	20.5 (14.9)	20.5 (23.7)	20.4 (12.8)
Daily intake of dietary factors, %									
Red meat	26.8	26.1	24.9	30.2	25.7	30.3	28.9	33.7	26.7
Fish/seafood	2.5	2.7	1.3	4.0	2.3	3.6	3.1	4.3	2.5
Fresh vegetables	94.7	92.6	81.9	94.9	94.5	94.7	95.6	96.0	94.7
Fresh fruit	22.1	22.8	17.4	18.3	20.5	29.8	25.4	29.9	21.8
Cardiometabolic factors, mean (SD)									
SBP, mmHg	130.0 (19.9)	127.8 (30.9)	108.3 (21.7)	126.1 (53.2)	130.8 (22.2)	127.1 (28.3)	127.9 (27.2)	127.6 (29.6)	129.9 (22.0)
DBP, mmHg	76.8 (10.7)	76.3 (16.3)	64.9 (12.5)	75.5 (31.1)	77.1 (12.1)	75.3 (15.6)	76.0 (14.1)	76.4 (17.8)	76.8 (10.9)
BMI, kg/m^2	23.8 (3.3)	24.1 (5.6)	21.0 (3.9)	23.9 (10.4)	23.9 (3.8)	23.7 (5.1)	23.8 (4.4)	23.7 (6.1)	23.8 (3.5)
Waist circumference, cm	79.1 (9.0)	80.1 (14.6)	70.4 (10.3)	80.2 (30.8)	79.1 (10.3)	78.5 (13.9)	79.1 (12.1)	79.0 (16.0)	79.1 (9.6)
Waist-to-hip ratio	0.87 (0.07)	0.87 (0.1)	0.76 (0.07)	0.87 (0.2)	0.87 (0.07)	0.85 (0.09)	0.87 (0.09)	0.87 (0.11)	0.87 (0.07)
Random blood glucose, mmol/L	6.1 (2.3)	6.3 (5.0)	5.6 (2.7)	6.3 (9.0)	6.2 (2.7)	6.1 (4.2)	6.0 (2.9)	5.9 (3.2)	6.1 (2.3)
Prior disease history, %									
Diabetes	3.3	3.9	3.0	4.3	4.0	4.9	2.4	1.2	3.3
CHD	3.2	3.7	3.7	3.6	3.5	5.1	2.8	2.6	3.2
Stroke or TIA	1.3	1.1	2.8	2.0	1.6	2.5	1.0	0.7	1.3
Cancer	0.5	0.7	0.3	0.9	0.6	1.4	0.4	0.7	0.5
Hypertension	12.0	11.6	11.7	10.9	13.0	16.9	9.6	8.2	11.9
Poor self-rated health	11.2	13.0	15.4	16.0	12.6	22.2	9.6	8.1	11.4

SD standard deviation, MET metabolic equivalent of task, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group) and 10 study regions, as appropriate.
*Current smokers included current smokers and ex-regular smokers stopped due to illness.

Table D.2 Estimated regression dilution ratios for alcohol consumption in current drinkers in men.

		Mean alcohol consumption, g/week				Regression dilution ratio		
Alcohol consumption in current drinkers, g/week	**N**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Average of 1st and 2nd**	**MacMahon-Peto's method**	**Pearson's method**	**Spearman's method**
<140	640	79.5	169.9	257.7	213.8	0.50	0.49	0.56
140 to <280	526	222.6	255.7	348.7	302.2			
280 to <420	316	370.2	353.3	442.7	398.0			
≥420	361	689.7	509.2	529.0	519.1			
Difference between the 4th vs 1st group		610.2	339.3	271.3	305.3			

Regression dilution ratio with the MacMahon-Peto's method is used for data analysis.

Table D.3 Adjusted HRs for cataract by smoking status.

	Number of cases	Hazard ratio (95% CI)
Smoking status in men		
Never smokers	985	1.00 (0.94-1.07)
Occasional smokers	518	1.00 (0.92-1.09)
Ex-smokers (quit due to choice)	506	1.03 (0.94-1.12)
Current smokers*, smoking equivalents/day		
<15	1436	1.11 (1.05-1.17)
15 to <25	1707	1.13 (1.08-1.19)
≥25	787	1.24 (1.15-1.33)
Smoking status in women		
Never smokers	9628	1.00 (0.96-1.04)
Occasional smokers	233	0.96 (0.84-1.09)
Ex-smokers (quit due to choice)	96	0.98 (0.80-1.20)
Current smokers*, smoking equivalents/day		
<15	495	1.08 (0.99-1.19)
15 to <25	110	0.94 (0.78-1.14)
≥25	17	0.90 (0.56-1.45)
Age started smoking in men		
Never smokers	985	1.00 (0.93-1.07)
<20	1127	1.12 (1.05-1.19)
20 to <25	1440	1.17 (1.11-1.24)
≥25	1363	1.10 (1.05-1.17)
Duration of smoking in men		
Never smokers	985	1.00 (0.94-1.07)
<25	594	1.04 (0.95-1.13)
25 to <35	1032	1.11 (1.04-1.19)
≥35	2304	1.17 (1.11-1.23)
Depth of inhalation in men		
Never smokers	985	1.00 (0.94-1.07)
Mouth/throat	2062	1.08 (1.03-1.13)
Lung	1868	1.20 (1.14-1.25)
Types of tobacco smoked in men		
Never smokers	985	1.00 (0.94-1.07)
Mainly cigarettes	2506	1.11 (1.07-1.16)
Non-cigarette or mixed	1424	1.18 (1.11-1.25)
Smoking cessation in men		
Never smokers	985	1.00 (0.93-1.07)
Quit by choice		
≥15	196	1.06 (0.92-1.22)
5 to <15	243	1.06 (0.94-1.21)
<5	169	0.99 (0.85-1.15)
Quit because of illness		
≥15	173	1.20 (1.03-1.39)
5 to <15	293	1.17 (1.05-1.32)
<5	293	1.22 (1.09-1.37)

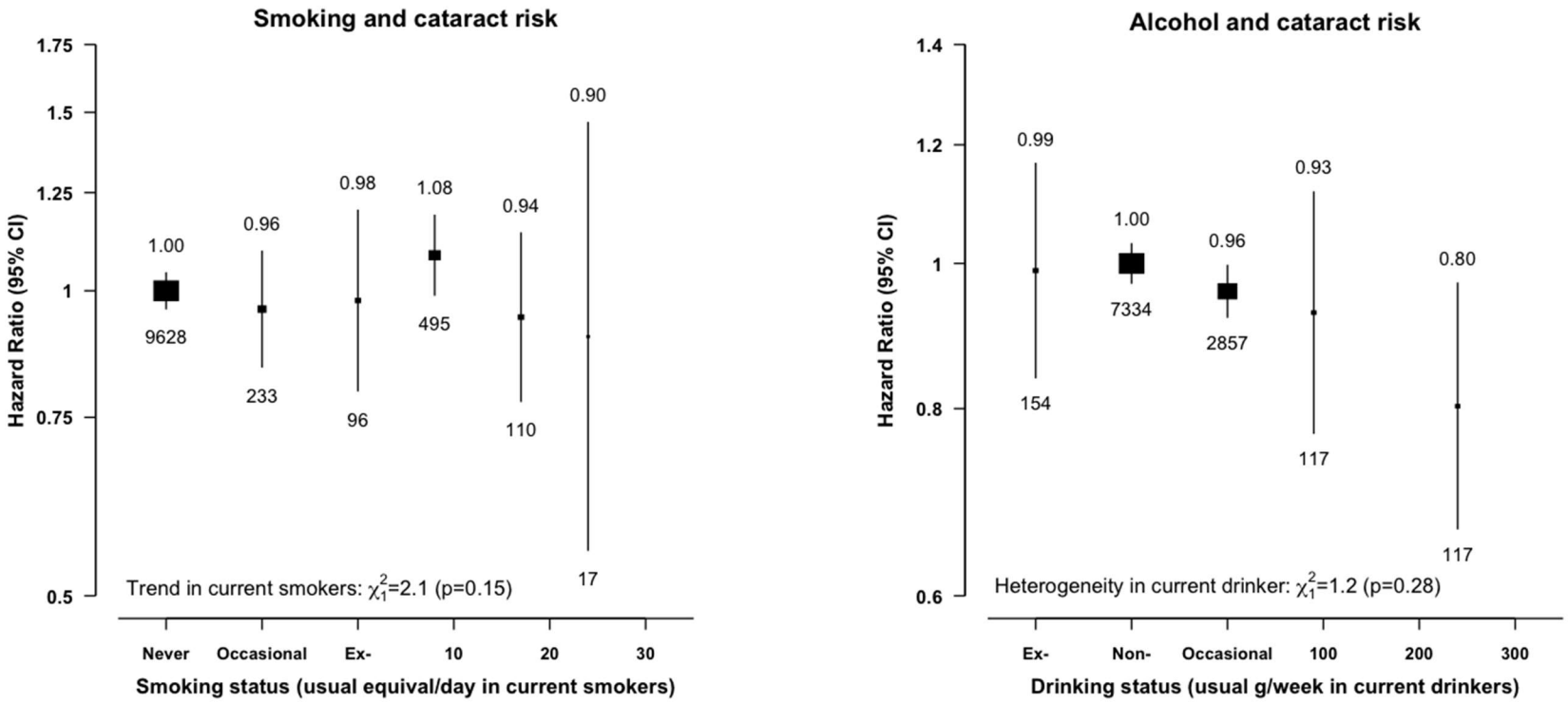
95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status.
*Current smokers included current smokers and ex-smokers stopped due to illness.

Table D.4 Adjusted HRs for cataract by alcohol consumption.

	Number of cases	Hazard ratio (95% CI)
Alcohol consumption in men		
Ex-drinkers	746	1.14 (1.06-1.22)
Non-drinkers	1492	1.04 (0.99-1.10)
Occasional drinkers	1858	1.04 (0.99-1.09)
Current drinkers, g/week		
<140	640	1.00 (0.92-1.08)
140 to <280	526	1.11 (1.02-1.22)
280 to <420	316	1.17 (1.04-1.31)
≥420	361	1.24 (1.11-1.38)
Alcohol consumption in women		
Ex-drinkers	154	0.99 (0.84-1.16)
Non-drinkers	7334	1.00 (0.97-1.03)
Occasional drinkers	2857	0.96 (0.92-1.00)
Current drinkers, g/week		
<70	117	0.93 (0.77-1.11)
≥70	117	0.80 (0.67-0.97)
Drinking frequency in men, days/week		
1-2	252	1.00 (0.88-1.14)
3-5	238	1.00 (0.89-1.13)
6-7	1353	1.05 (0.97-1.14)
Drinking time of day in men		
With meal	1573	1.00 (0.93-1.08)
Between or after meal	170	1.02 (0.88-1.19)
No regular pattern	100	0.91 (0.73-1.12)
Type of alcohol in men		
Beer	235	1.00 (0.87-1.15)
Rice/grape wine	216	0.92 (0.78-1.09)
Weak spirit	337	0.91 (0.80-1.04)
Strong spirit	1055	1.08 (0.98-1.20)
Age started drinking in men		
≥30	920	1.00 (0.93-1.08)
25 to <30	253	0.97 (0.86-1.10)
20 to <25	406	1.00 (0.91-1.10)
<20	264	1.12 (0.99-1.27)
Joint association of smoking and alcohol in men		
Never smokers and non-drinkers	385	1.00 (0.90-1.11)
Never smokers and occasional drinkers	364	0.99 (0.89-1.10)
Never smokers and ever regular drinkers	236	1.05 (0.92-1.19)
Occasional smokers, ex-smokers quit by choice, and non-drinkers	240	1.13 (0.99-1.28)
Occasional smokers, ex-smokers quit by choice, and occasional drinkers	399	1.00 (0.91-1.11)
Occasional smokers, ex-smokers quit by choice, and ever regular drinkers	385	1.00 (0.91-1.11)
Current smokers* and non-drinkers	867	1.10 (1.02-1.18)
Current smokers* and occasional drinkers	1095	1.13 (1.06-1.20)
Current smokers* and ever regular drinkers	1968	1.22 (1.16-1.28)

95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status, as appropriate.
*Current smokers included current smokers and ex-smokers stopped due to illness.

Figure D.1 Adjusted HRs for cataract by usual level of smoking and alcohol consumption in women (number of cases = 10,579).



Ex-smokers included ex-smokers stopped by choice.
Current smokers included current smokers and ex-smokers stopped due to illness.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, BMI, prevalent diabetes, and self-rated health status, as appropriate.
The square represents HRs, and the vertical lines represents 95% CIs. The size of the square is inversely proportional to the variance of the log HRs. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

Appendix E. Additional results: Associations of physical activity and diet with risk of cataract

Table E.1 Physical activity types, MET values, codes and intensity categories*.

Activity type	Intensity	MET	Codes*
Heavy manual work	Vigorous	6.5	11477
Manual work	Moderate	4.5	11476
Standing work	Moderate	3.8	Mean of 11610 and 11630
Sedentary work	Low	1.8	Mean of 11580, 11585, and 11590
Manual work in the farming season	Vigorous	6.3	Mean of 11145 and 11146
Semi-mechanized work in the farming season	Moderate	3.4	Mean of 11146 and 11147
Fully mechanized work in the farming season	Low	2.4	Mean of 11147 and 11170
Work outside the farming season	Low	2	11147
Walking	Moderate	4	17270
Bicycle	Vigorous	6.8	1011
Motorbike	Moderate	3.5	16030
Private or public transportation (such as bus, car, underground, and ferry)	Low	1.7	Mean of 16010, 16015, and 16016
Household activity	Low	2.8	Mean of 05030†, 05040†, 05035, 05055, 05070, 05090†, 05092†, 05184, 05197, and 05200
Tai-Chi/qigong/leisure walking	Moderate	3.3	Mean of 15670 and 17160
Jogging/aerobic exercise	Vigorous	7.4	Mean of 03015, 12020, and 12150
Ball games	Moderate	5.5	Mean of 15020†, 15030†, 15055, 15080, 15090, 15255, 15605†, 15610†, 15652, 15660, 15675, 15710†, and 15711†
Brisk walking/gymnastics/folk dancing	Moderate	4.2	Mean of 03025, 15300, and 17200
Swimming	Vigorous	7.2	Mean of 18230, 18240, and 18310
Other exercise, e.g., mountain walking, home exercise and rope jumping	Moderate	5.9	Mean of 02010, 02064, 04001, 04100, 15110†, 15120†, 15200, 15240, 15310, 15425†, 15430†, 15537, 15550‡, 15551‡, 15552‡, 15580, 15590, 15730, 15732‡, 15733‡, 15734‡, and 19030

MET: Metabolic equivalent of tasks. * Based on the 2011 Compendium of Physical Activities: a second update of codes and MET values. Ainsworth BE, et al. Medicine and Science in Sports and Exercise, 2011;43(8):1575-1581.
† Assigned 1/2 weight in calculating the mean MET value because the connecting two items represent one type of activity.
‡ Assigned 1/3 weight in calculating the mean MET value because the connecting three items represent one type of activity.
Table from Derrick et al. 2017[131].

Table E.2 Estimated regression dilution ratios for physical activity.

		Mean physical activity, MET-h/d				Regression dilution ratio		
Baseline physical activity groups, MET-h/d	**N**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Average of 1st and 2nd**	**MacMahon-Peto's method**	**Pearson's method**	**Spearman's method**
<8.7	5376	5.7	11.5	12.0	11.7			
8.7 to <14.2	4641	11.6	14.7	14.7	14.7			
14.2 to <21.8	2942	17.6	18.8	17.6	18.2	1st: 0.54 2nd: 0.35 Usual: 0.44*	1st: 0.53 2nd: 0.34 Usual: 0.52	1st: 0.57 2nd: 0.36 Usual: 0.55
21.8 to <33.2	2071	27.3	25.0	21.0	23.0			
≥33.2	1470	43.2	31.7	25.0	28.4			
Difference between the 5th vs 1st group		37.5	20.2	13.0	16.6			

Regression dilution ratio with the MacMahon-Peto's method is used for data analysis.

Table E.3 Prevalence of fresh fruit consumption at baseline (2004-2008) and the two resurveys (2008, 2013-2014).

Age at baseline, years	N	Fresh fruit consumption				
		Never/rarely	Monthly	1-3 days/week	4-6 days/week	Daily
Overall, %						
Baseline	512,690	6.4	34.0	31.5	9.4	18.8
1st Resurvey	19,788	5.4	34.7	29.5	10.1	20.3
2nd Resurvey	25,176	9.2	13.2	32.5	10.7	34.4
Men, %						
Baseline	210,186	8.1	35.9	32.9	8.5	14.5
1st Resurvey	7772	7.0	37.7	30.6	9.3	15.4
2nd Resurvey	9694	11.9	14.4	34.7	10.1	28.9
Women, %						
Baseline	302,504	5.2	32.6	30.4	9.9	21.8
1st Resurvey	12,016	4.3	32.8	28.8	10.6	23.5
2nd Resurvey	15,482	7.5	12.5	31.2	11.1	37.8

Table E.4 Baseline fresh fruit consumption status by age at baseline.

Age at baseline, years	N	Fresh fruit consumption				
		Never/rarely	Monthly	1-3 days/week	4-6 days/week	Daily
Overall, %	**512,690**	**6.4**	**34.0**	**31.5**	**9.4**	**18.8**
30-39	77,588	4.4	30.3	33.5	11.6	20.2
40-49	152,769	5.3	33.2	32.2	9.7	19.6
50-59	157,616	6.6	35.3	31.4	9.2	17.5
60-69	91,753	8.1	35.4	29.9	8.0	18.5
70-79	32,964	10.2	35.5	27.5	7.0	19.8
Men, %	**210,186**	**8.1**	**35.9**	**32.9**	**8.5**	**14.5**
30-39	29,548	6.4	32.1	35.2	10.2	16.2
40-49	59,218	7.5	35.5	34.1	8.6	14.3
50-59	63,751	8.6	37.9	33.0	8.2	12.3
60-69	41,340	8.8	36.5	31.4	8.2	15.1
70-79	16,329	10.0	35.0	28.4	7.4	19.3
Women, %	**302,504**	**5.2**	**32.6**	**30.4**	**9.9**	**21.8**
30-39	48,040	3.2	29.3	32.5	12.4	22.6
40-49	93,551	3.9	31.7	31.1	10.4	22.9
50-59	93,865	5.3	33.5	30.3	9.8	21.0
60-69	50,413	7.5	34.6	28.8	7.9	21.3
70-79	16,635	10.5	36.0	26.6	6.6	20.3

Table E.5 Baseline fresh fruit consumption status by study region.

Region	N	Fresh fruit consumption				
		Never/rarely	Monthly	1-3 days/week	4-6 days/week	Daily
Urban, %	**226,190**	**4.7**	**17.4**	**30.7**	**11.4**	**35.8**
Qingdao	35,507	2.6	10.4	24.0	8.8	54.2
Harbin	57,555	6.1	9.5	24.9	7.3	52.1
Haikou	29,686	7.8	30.6	34.0	18.3	9.3
Suzhou	53,268	4.8	31.5	35.0	11.1	17.7
Liuzhou	50,174	2.8	8.8	35.5	14.0	38.8
Rural, %	**286,500**	**7.7**	**47.0**	**32.1**	**7.8**	**5.5**
Sichuan	55,685	7.5	27.9	43.1	10.1	11.5
Gansu	49,887	6.5	48.7	27.9	12.7	4.2
Henan	63,354	15.7	62.1	17.5	1.9	2.8
Zhejiang	57,703	2.1	42.1	38.3	10.8	6.7
Hunan	59,871	5.9	52.1	34.7	4.8	2.6

Table E.6 Cross tabulation of baseline consumption frequency of 11 food groups and baseline fresh fruit consumption status in CKB.

	Fresh fruit consumption frequency					Overall (N=512,690)
	Never/rarely (N=32,762)	Monthly (N=174,107)	1-3 days/week (N=161,277)	4-6 days/week (N=47,957)	Daily (N=96,587)	
Rice, %						
Never/rarely (N=16,616)	0.6	1.4	0.7	0.2	0.2	3.1
Monthly (N=48,540)	0.8	5.0	2.2	0.8	0.7	9.5
1-3 days/week (N=80,213)	1.4	6.6	3.6	0.9	3.2	15.7
4-6 days/week (N=10,458)	0.1	0.4	0.5	0.2	0.8	2.0
Daily (N=356,863)	3.5	20.6	24.5	7.1	14.0	69.7
Wheat, %						
Never/rarely (N=50,736)	0.9	4.1	3.4	0.7	0.8	9.9
Monthly (N=100,742)	0.8	8.2	7.0	1.8	1.8	19.6
1-3 days/week (N=119,038)	0.9	5.1	8.9	2.7	5.6	23.2
4-6 days/week (N=37,380)	0.3	1.7	2.6	1.2	1.6	7.4
Daily (N=204,794)	3.5	14.8	9.6	3.0	9.1	40.0
Staple food, %						
Never/rarely (N=147,207)	2.5	9.5	10.2	2.7	3.7	28.6
Monthly (N=228,037)	1.4	14.8	15.2	4.7	8.3	44.4
1-3 days/week (N=65,717)	0.5	1.9	3.5	1.6	5.4	12.9
4-6 days/week (N=4541)	0.0	0.1	0.2	0.1	0.4	0.8
Daily (N=67,188)	1.9	7.6	2.3	0.3	1.0	13.1
Red meat, %						
Never/rarely (N=24,507)	1.0	2.1	0.8	0.4	0.5	4.8
Monthly (N=64,218)	1.2	7.5	2.5	0.5	0.8	12.5
1-3 days/week (N=182,157)	2.2	13.7	12.4	2.7	4.6	35.6
4-6 days/week (N=91,792)	0.6	5.6	6.6	2.7	2.3	17.8
Daily (N=150,016)	1.4	5.0	9.1	3.1	10.7	29.3
Poultry, %						
Never/rarely (N=188,247)	4.3	16.4	10.0	2.4	3.6	36.7
Monthly (N=179,928)	1.2	13.0	11.6	3.2	6.1	35.1
1-3 days/week (N=137,729)	0.8	4.3	9.5	3.6	8.7	26.9
4-6 days/week (N=4587)	0.0	0.1	0.2	0.2	0.3	0.8
Daily (N=2199)	0.0	0.1	0.1	0.0	0.2	0.4
Fish/seafood, %						
Never/rarely (N=163,925)	3.7	15.3	8.8	2.2	1.9	31.9
Monthly (N=108,702)	1.0	8.1	6.6	1.6	3.8	21.1
1-3 days/week (N=194,508)	1.3	8.3	13.3	4.1	10.8	37.8
4-6 days/week (N=31,400)	0.2	1.5	2.1	1.1	1.3	6.2
Daily (N=14,155)	0.1	0.7	0.7	0.3	0.9	2.7

(cont.)

Table E.6 Cross tabulation of baseline consumption frequency of 11 food groups and baseline fresh fruit consumption status in CKB (cont.)

	Fresh fruit consumption frequency					Overall (N=512,724)
	Never/rarely (N=32,765)	Monthly (N=174,120)	1-3 days/week (N=161,292)	4-6 days/week (N=47,959)	Daily (N=96,588)	
Eggs, %						
Never/rarely (N=46,550)	1.6	3.1	2.5	0.7	1.1	9.0
Monthly (N=101,109)	1.3	9.3	5.9	1.6	1.8	19.9
1-3 days/week (N=239,694)	2.2	15.1	16.5	4.4	8.4	46.6
4-6 days/week (N=54,038)	0.4	3.6	3.3	1.5	1.8	10.6
Daily (N=71,299)	0.9	2.9	3.2	1.1	5.8	13.9
Dairy products, %						
Never/rarely (N=350,605)	5.4	28.0	22.5	5.6	6.9	68.4
Monthly (N=57,058)	0.4	3.8	3.8	1.2	2.0	11.2
1-3 days/week (N=43,988)	0.2	0.9	2.8	1.3	3.4	8.6
4-6 days/week (N=10,601)	0.0	0.2	0.5	0.5	0.8	2.0
Daily (N=50,438)	0.4	1.0	1.9	0.8	5.8	9.9
Fresh vegetables, %						
Never/rarely (N=127)	0.0	0.0	0.0	0.0	0.0	0.0
Monthly (N=1400)	0.0	0.2	0.0	0.0	0.0	0.2
1-3 days/week (N=7189)	0.1	0.8	0.3	0.1	0.1	1.4
4-6 days/week (N=18,060)	0.3	1.9	1.0	0.3	0.1	3.6
Daily (N=485,914)	6.0	31.0	30.1	9.0	18.6	94.7
Preserved vegetables, %						
Never/rarely (N=93,473)	2.6	5.6	4.6	1.5	4.0	18.3
Monthly (N=158,923)	1.3	13.6	9.3	2.6	4.2	31.0
1-3 days/week (N=144,408)	1.0	8.9	10.5	2.9	4.8	28.1
4-6 days/week (N=34,882)	0.4	2.2	2.1	1.1	1.0	6.8
Daily (N=81,004)	1.1	3.8	4.9	1.2	4.8	15.8
Soybean products, %						
Never/rarely (N=56,139)	2.3	4.4	2.6	0.6	1.0	10.9
Monthly (N=148,061)	1.7	13.2	8.6	2.5	2.9	28.9
1-3 days/week (N=257,922)	2.0	13.8	17.6	5.0	11.9	50.3
4-6 days/week (N=31,072)	0.2	1.9	1.8	0.8	1.3	6.0
Daily (N=19,496)	0.2	0.6	1.0	0.3	1.7	3.8

Table E.7 Average daily consumption of 12 food groups by study region in CKB participants.

Characteristics	Rural					Urban					Overall
	Sichuan	Gansu	Henan	Zhejiang	Hunan	Qingdao	Harbin	Haikou	Suzhou	Liuzhou	
No. of participants	55,685	49,887	63,354	57,703	59,871	35,507	57,555	29,686	53,268	50,174	512,690
Staple foods, g/day											
Rice	261.9	28.6	49.2	261.9	262.0	92.9	222.1	258.2	261.9	260.7	196.4
Wheat products	44.6	192.7	192.1	40.7	69.8	178.8	145.1	75.1	48.3	78.4	105.9
Other staple foods (corn, millet, etc.)	13.2	16.9	146.8	13.1	14.2	24.8	28.6	18.1	14.0	17.0	33.5
Animal-sourced foods, g/day											
Red meat	43.3	26.9	24.9	41.8	41.1	52.9	48.9	52.3	43.1	57.6	42.2
Poultry	11.6	6.1	7.1	19.7	13.4	16.3	16.1	19.1	18.7	24.0	14.8
Fish/seafood	8.7	3.4	4.2	24.3	26.7	32.3	23.3	39.4	31.2	29.1	20.9
Eggs	21.8	22.9	24.1	21.8	24.8	31.6	27.0	20.2	23.4	23.6	24.1
Dairy products	18.4	20.4	19.2	16.0	18.7	45.6	41.6	25.8	23.1	35.1	25.5
Plant-sourced foods, g/day											
Fresh vegetables	231.6	227.9	232.0	231.1	231.8	231.8	231.7	229.6	231.9	231.7	231.2
Preserved vegetables	7.8	7.5	5.4	6.6	6.2	7.6	7.8	5.4	9.1	6.1	7.0
Fresh fruit	58.4	49.1	40.0	54.6	46.3	93.8	90.2	58.5	63.4	83.8	62.4
Soybean products	11.8	12.0	11.9	16.6	14.7	15.2	16.3	12.3	14.7	15.5	14.1

The results were standardised by age at baseline (5-year age group) and sex.

Table E.8 Adjusted HRs for cataract by physical activity.

	Number of cases	Hazard ratio (95% CI)
Total physical activity, MET-h/d		
Quintile 1 (<8.7)	5376	1.00 (0.97-1.04)
Quintile 2 (8.7 to <14.2)	4641	1.03 (1.00-1.06)
Quintile 3 (14.2 to <21.8)	2942	0.99 (0.95-1.03)
Quintile 4 (21.8 to <33.2)	2071	0.94 (0.89-0.99)
Quintile 5 (≥33.2)	1470	0.92 (0.87-0.98)
Total physical activity in men, MET-h/d		
Quintile 1 (<8.0)	2193	1.00 (0.94-1.06)
Quintile 2 (8.0 to <15.0)	1227	1.02 (0.97-1.08)
Quintile 3 (15.0 to <24.2)	947	0.98 (0.92-1.04)
Quintile 4 (24.2 to <35.7)	847	1.03 (0.95-1.12)
Quintile 5 (≥35.7)	713	0.97 (0.88-1.06)
Total physical activity in women, MET-h/d		
Quintile 1 (<9.3)	3183	1.00 (0.96-1.04)
Quintile 2 (9.3 to <14.0)	3414	1.01 (0.97-1.05)
Quintile 3 (14.0 to <20.4)	1995	0.96 (0.92-1.01)
Quintile 4 (20.4 to <31.4)	1224	0.88 (0.82-0.93)
Quintile 5 (≥31.4)	757	0.85 (0.78-0.92)
Total physical activity in rural region, MET-h/d		
Quintile 1 (<10.2)	2442	1.00 (0.95-1.05)
Quintile 2 (10.2 to <16.3)	2224	1.01 (0.96-1.04)
Quintile 3 (16.3 to <24.8)	1813	0.97 (0.92-1.02)
Quintile 4 (24.8 to <36.1)	1636	0.97 (0.91-1.03)
Quintile 5 (≥36.1)	1230	0.90 (0.84-0.97)
Total physical activity in urban region, MET-h/d		
Quintile 1 (<8.4)	2934	1.00 (0.95-1.05)
Quintile 2 (8.4 to <12.2)	2417	1.06 (1.01-1.10)
Quintile 3 (12.2 to <17.9)	1129	1.00 (0.95-1.05)
Quintile 4 (17.9 to <29.7)	435	0.96 (0.88-1.05)
Quintile 5 (≥29.7)	240	0.88 (0.77-1.00)
Vigorous physical activity		
Never	12,429	1.00 (0.97-1.03)
Occasionally	2924	1.03 (0.99-1.06)
1-2 times/week	518	1.07 (0.98-1.17)
3-7 times/week	629	0.99 (0.92-1.08)
Sedentary leisure time, hours/day		
<1.5	2809	1.00 (0.96-1.04)
1.5 to <2.5	3903	0.96 (0.93-0.99)
2.5 to <3.5	4509	1.00 (0.97-1.03)
3.5 to <4.5	2892	1.02 (0.99-1.06)
≥4.5	2387	1.01 (0.96-1.05)

95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including coronary heart disease, stroke, and transient ischemic attack), prevalent diabetes, and self-rated health status, as appropriate.

Table E.9 Adjusted HRs for cataract by frequency of dietary intake (1 of 2).

	Number of cases	Hazard ratio (95% CI)
Fresh fruit		
Never/rarely	1236	0.93 (0.88-0.98)
Monthly	6054	1.00 (0.97-1.03)
Weekly (1-3 days/week)	4910	0.92 (0.90-0.95)
Regularly (4-6 days/week)	1261	0.89 (0.84-0.94)
Daily	3057	0.84 (0.80-0.88)
Fresh fruit in men		
Never/rarely	495	0.96 (0.88-1.05)
Monthly	2153	1.00 (0.95-1.05)
Weekly (1-3 days/week)	1903	0.98 (0.94-1.03)
Regularly (4-6 days/week)	462	0.95 (0.86-1.04)
Daily	926	0.88 (0.82-0.95)
Fresh fruit in women		
Never/rarely	741	0.91 (0.85-0.98)
Monthly	3901	1.00 (0.96-1.04)
Weekly (1-3 days/week)	3007	0.89 (0.86-0.92)
Regularly (4-6 days/week)	799	0.85 (0.80-0.92)
Daily	2131	0.82 (0.78-0.87)
Fresh fruit in rural region		
Never/rarely	852	0.95 (0.88-1.01)
Monthly	4858	1.00 (0.97-1.03)
Weekly (1-3 days/week)	2766	0.91 (0.88-0.95)
Regularly (4-6 days/week)	544	0.89 (0.82-0.97)
Daily	336	0.76 (0.68-0.84)
Fresh fruit in urban region		
Never/rarely	384	0.91 (0.82-1.01)
Monthly	1196	1.00 (0.94-1.06)
Weekly (1-3 days/week)	2144	0.96 (0.92-1.00)
Regularly (4-6 days/week)	717	0.92 (0.85-0.99)
Daily	2721	0.88 (0.84-0.92)
Red meat		
Never/rarely	786	1.00 (0.93-1.08)
Monthly	2112	1.04 (0.99-1.09)
Most days (1-3 days/week)	6327	1.01 (0.98-1.03)
Most days (4-6 days/week)	2844	0.99 (0.95-1.03)
Daily	4449	0.96 (0.92-0.99)
Preserved vegetables		
Never/rarely	3236	1.00 (0.96-1.04)
Monthly	5272	1.03 (1.00-1.06)
Weekly (1-3 days/week)	4478	1.04 (1.01-1.08)
Regularly (4-6 days/week)	999	1.05 (0.98-1.12)
Daily	2533	1.07 (1.02-1.12)

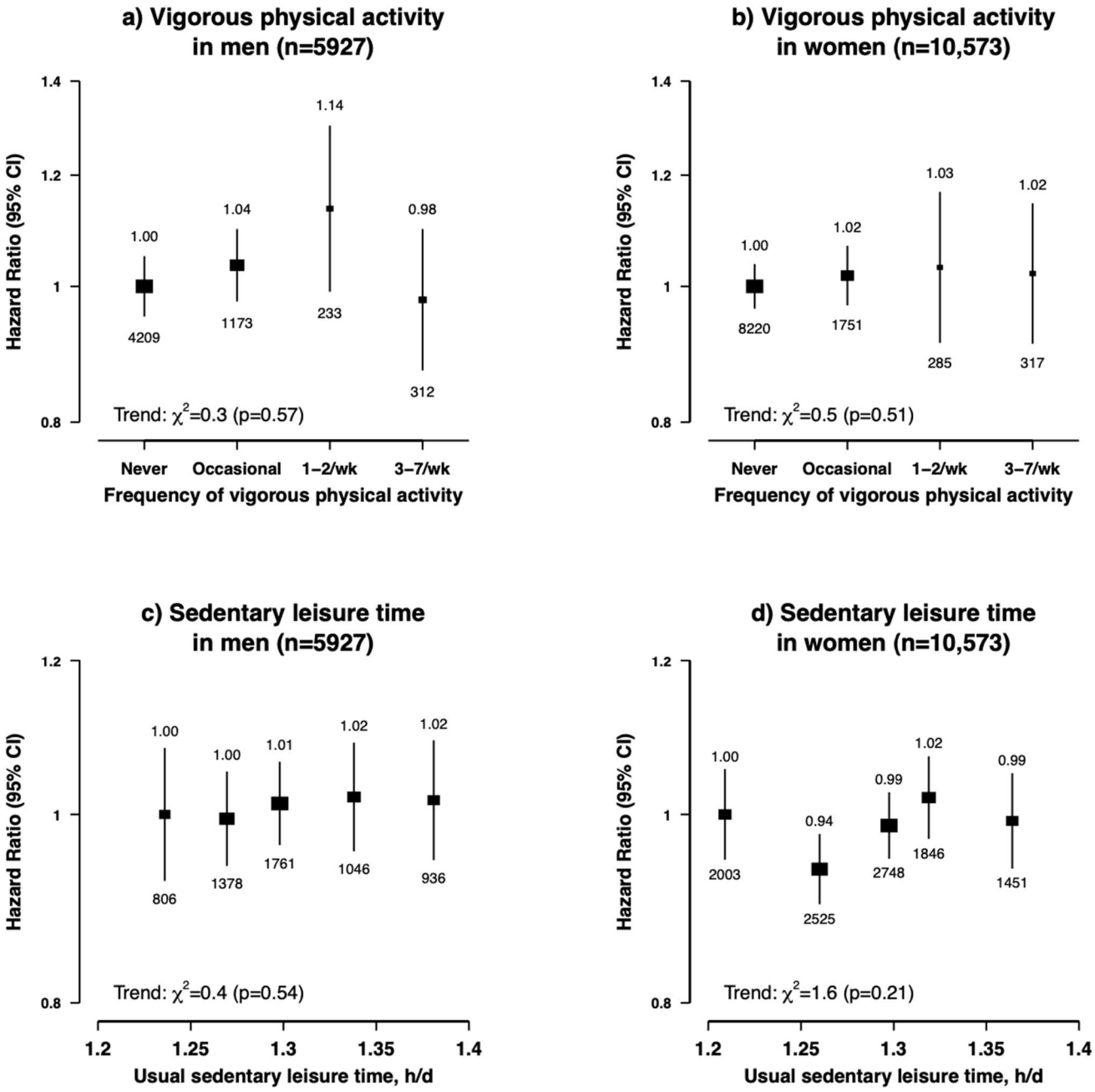
95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, BMI, prevalent cardiovascular diseases (including coronary heart disease, stroke, and transient ischemic attack), prevalent diabetes, self-rated health status, and consumption of fresh fruit, meat, and fish/seafood, as appropriate.

Table E.10 Adjusted HRs for cataract by frequency of dietary intake (2 of 2).

	Number of cases	Hazard ratio (95% CI)
Rice		
Never/rarely or monthly	1750	1.00 (0.94-1.07)
Most days (1-6 days/week)	2871	0.97 (0.94-0.99)
Daily	11,897	0.99 (0.92-1.06)
Wheat		
Never/rarely	1740	1.00 (0.95-1.05)
Monthly	3370	1.04 (1.00-1.08)
Most days (1-3 days/week)	3649	1.03 (1.00-1.07)
Most days (4-6 days/week)	1196	0.99 (0.93-1.05)
Daily	6563	1.01 (0.96-1.06)
Other staple food (corn, millet, etc.)		
Never/rarely	4514	1.00 (0.97-1.03)
Monthly	7326	1.04 (1.02-1.07)
Most days (1-3 days/week)	2642	1.05 (1.01-1.10)
Daily or Most days (4-6 days/week)	2036	0.90 (0.82-0.99)
Dairy products		
Never/rarely	10,667	1.00 (0.97-1.03)
Monthly	2006	1.09 (1.05-1.14)
Weekly (1-6 days/week)	1567	0.99 (0.94-1.04)
Daily	2278	1.06 (1.01-1.11)
Poultry		
Never/rarely	6370	1.00 (0.97-1.04)
Monthly	6429	0.98 (0.96-1.00)
Regularly (1-7 days/week)	3719	0.96 (0.92-1.00)
Fish/seafood		
Never/rarely	4944	1.00 (0.95-1.06)
Monthly	4138	0.95 (0.92-0.98)
Most days (1-3 days/week)	6059	0.94 (0.91-0.97)
Daily or Most days (4-6 days/week)	1377	0.95 (0.89-1.01)
Eggs		
Never/rarely	1621	1.00 (0.95-1.05)
Monthly	3252	1.03 (0.99-1.07)
Most days (1-3 days/week)	7133	1.05 (1.02-1.07)
Most days (4-6 days/week)	1688	1.06 (1.01-1.12)
Daily	2824	0.99 (0.95-1.03)
Soybean products		
Never/rarely	1837	1.00 (0.95-1.05)
Monthly	4623	0.98 (0.95-1.01)
Weekly (1-3 days/week)	8257	0.96 (0.94-0.98)
Daily or Regularly (4-6 days/week)	1801	0.96 (0.91-1.00)

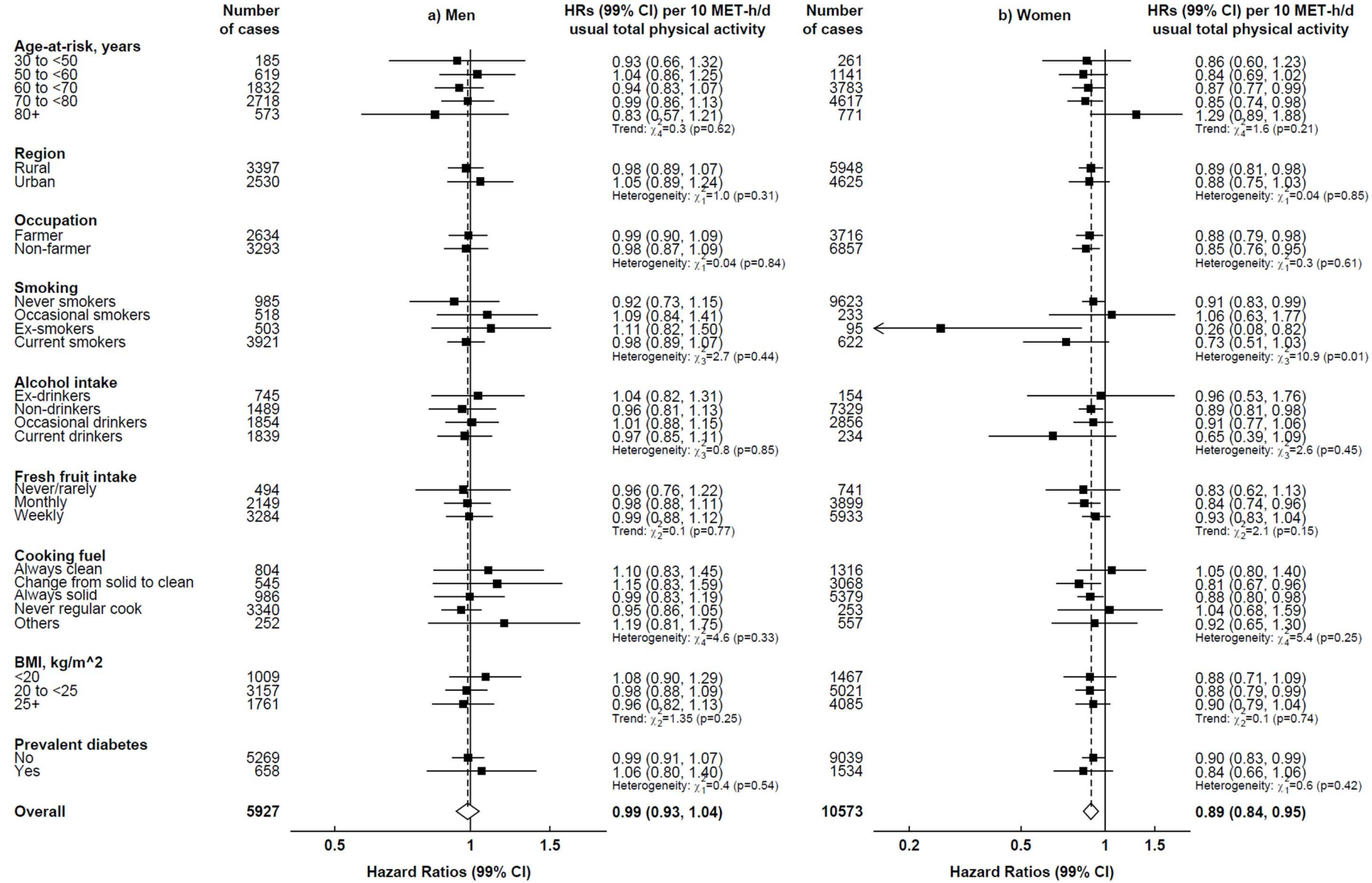
95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, physical activity, fresh fruit consumption, BMI, prevalent cardiovascular diseases (including coronary heart disease, stroke, and transient ischemic attack), prevalent diabetes, and self-rated health status.

Figure E.1 Adjusted HRs for cataract by vigorous physical activity and sedentary leisure time in men and women.



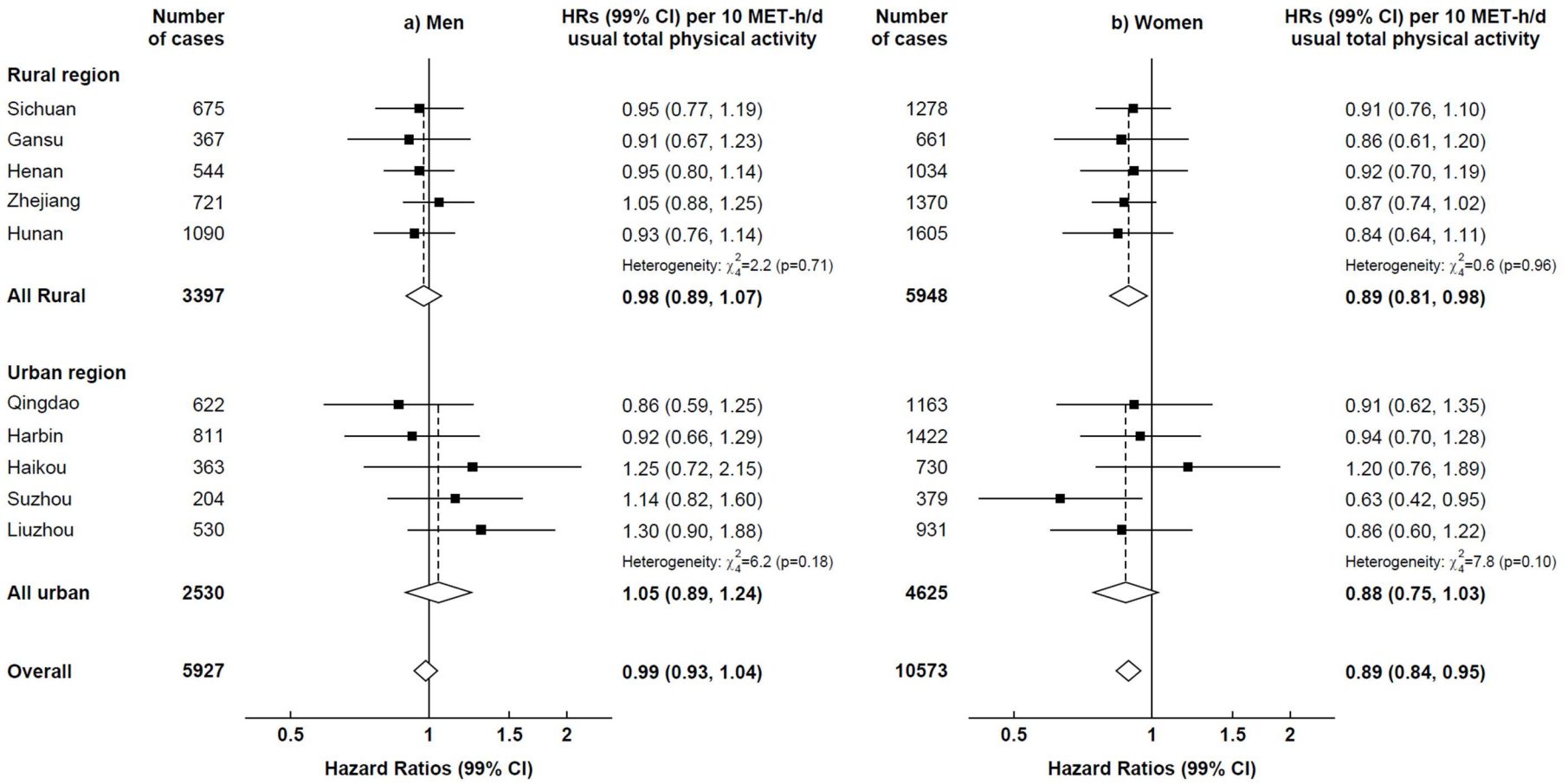
"1-2/week" stands for 1-2 times per week.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, sedentary leisure time, total physical activity (for the analysis of sedentary leisure time), fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.
The square represents HRs, and the vertical lines represents 95% CIs. The size of the square is inversely proportional to the variance of the log HRs. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.

Figure E.2 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by selected population characteristics in men and women.



Ex-smokers includes ex-smokers that stopped by choice. Current smokers includes current smokers and ex-smokers that stopped due to illness.
The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status, as appropriate.

Figure E.3 Adjusted HRs per 10 MET-h/d higher usual total physical activity for cataract by region in men and women.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), and adjusted for baseline age, education, income, occupation, smoking, alcohol consumption, sedentary leisure time, fresh fruit, household air pollution, BMI, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.

Appendix F. Additional results: Associations of adiposity, diabetes, and glucose with risk of cataract

Table F.1 Estimated regression dilution ratios for body mass index in men.

		Body mass index, kg/m^2				Regression dilution ratio		
Baseline BMI groups, kg/m^2	**N**	**Baseline**	**1st Resurvey**	**2nd Resurvey**	**Average of 1st and 2nd**	**MacMahon-Peto's method**	**Pearson's method**	**Spearman's method**
<18.5	366	17.5	17.6	18.3	18.0			
18.5 to <23.0	2601	21.1	21.0	21.8	21.4			
23.0 to <25.0	1208	23.9	23.8	24.4	24.1	1st: 0.95 2nd: 0.92 Average: 0.94*	1st: 0.94 2nd: 0.88 Average: 0.93	1st: 0.93 2nd: 0.87 Average: 0.93
25.0 to <28.0	1226	26.3	25.9	26.4	26.2			
≥28.0	537	30.0	29.5	29.8	29.7			
Difference between the 5th vs 1st groups		12.5	11.9	11.5	11.7			

*Regression dilution ratio with the MacMahon-Peto's method is used for data analysis.

Table F.2 Adjusted HRs for cataract by adiposity factors (1 of 3).

	Number of cases	Hazard ratio (95% CI)
BMI in men, kg/m^2		
<18.5	366	1.00 (0.90-1.11)
18.5 to <23.0	2601	1.00 (0.96-1.04)
23.0 to <25.0	1208	0.94 (0.89-0.99)
25.0 to <28.0	1226	0.95 (0.90-1.01)
≥28.0	537	1.04 (0.95-1.14)
BMI in women, kg/m^2		
<18.5	632	1.06 (0.98-1.15)
18.5 to <23.0	3727	1.00 (0.97-1.03)
23.0 to <25.0	2131	0.94 (0.90-0.98)
25.0 to <28.0	2526	1.01 (0.97-1.05)
≥28.0	1560	1.00 (0.95-1.05)
BMI at age 25 years in men, kg/m^2		
<18.5	256	1.01 (0.89-1.14)
18.5 to <20.0	637	1.00 (0.92-1.08)
20.0 to <23.0	2452	0.99 (0.96-1.03)
23.0 to <25.0	1075	0.98 (0.93-1.04)
≥25.0	562	0.93 (0.86-1.02)
BMI at age 25 years in women, kg/m^2		
<18.5	668	0.92 (0.85-0.99)
18.5 to <20.0	1174	1.00 (0.94-1.06)
20.0 to <23.0	3133	0.95 (0.92-0.98)
23.0 to <25.0	1551	0.95 (0.90-0.99)
≥25.0	1418	1.00 (0.95-1.06)
Fat percentage in men, %		
Quintile 1 (<16.5)	1443	1.00 (0.95-1.06)
Quintile 2 (16.5 to <20.0)	1212	1.02 (0.97-1.08)
Quintile 3 (20.0 to <23.3)	1147	0.96 (0.91-1.02)
Quintile 4 (23.3 to <27.2)	1131	1.01 (0.95-1.07)
Quintile 5 (≥27.2)	1005	1.00 (0.94-1.07)
Fat percentage in women, %		
Quintile 1 (<26.1)	2150	1.00 (0.96-1.05)
Quintile 2 (26.1 to <30.0)	1791	0.97 (0.92-1.01)
Quintile 3 (30.0 to <33.5)	1989	1.01 (0.97-1.05)
Quintile 4 (33.5 to <37.9)	2045	0.93 (0.89-0.97)
Quintile 5 (≥37.9)	2601	1.02 (0.98-1.06)

95% CI 95% confidence interval; n.a. not available.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, baseline BMI (for the analysis of BMI at age 25 years), prevalent cardiovascular diseases (including CHD, stroke, and TIA; adjusted for the analysis of BMI only), prevalent diabetes, and self-rated health status.

Table F.3 Adjusted HRs for cataract by adiposity factors (2 of 3).

	Number of cases	Hazard ratio (95% CI)
Fat mass in men, kg		
<10	1853	1.00 (0.95-1.05)
10 to <15	1888	0.99 (0.94-1.03)
15 to <20	1265	0.94 (0.89-1.00)
≥20	932	1.04 (0.97-1.11)
Fat mass in women, kg		
<12	1928	1.00 (0.95-1.05)
12 to <18	3453	0.97 (0.93-1.00)
18 to <24	2832	0.94 (0.90-0.97)
≥24	2363	0.97 (0.93-1.02)
Fat mass index in men, kg/m^2		
Quintile 1 (<3.4)	1420	1.00 (0.95-1.06)
Quintile 2 (3.4 to <4.5)	1204	0.98 (0.92-1.04)
Quintile 3 (4.5 to <5.6)	1148	0.99 (0.93-1.05)
Quintile 4 (5.6 to <7.0)	1097	0.97 (0.91-1.03)
Quintile 5 (≥7.0)	1069	1.00 (0.94-1.07)
Fat mass index in women, kg/m^2		
Quintile 1 (<5.5)	2201	1.00 (0.96-1.05)
Quintile 2 (5.5 to <6.8)	1755	0.97 (0.92-1.01)
Quintile 3 (6.8 to <8.2)	2005	0.97 (0.93-1.02)
Quintile 4 (8.2 to <10.0)	2036	0.95 (0.91-0.99)
Quintile 5 (≥10.0)	2579	0.99 (0.95-1.03)

95% CI 95% confidence interval.

Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.

Table F.4 Adjusted HRs for cataract by adiposity factors (3 of 3).

	Number of cases	Hazard ratio (95% CI)
Waist circumference in men, cm		
<80	2606	1.00 (0.96-1.05)
80 to <85	1010	1.00 (0.94-1.07)
85 to <90	869	0.95 (0.88-1.01)
90 to <95	710	1.04 (0.97-1.12)
≥95	743	1.12 (1.04-1.21)
Waist circumference in women, cm		
<75	3010	1.00 (0.96-1.04)
75 to <80	1777	0.96 (0.92-1.01)
80 to <85	1996	1.00 (0.96-1.04)
85 to <90	1626	1.04 (0.99-1.09)
≥90	2167	1.04 (1.00-1.09)
Waist-to-hip ratio in men		
<0.85	1086	1.00 (0.94-1.06)
0.85 to <0.90	1495	1.02 (0.97-1.07)
0.90 to <0.95	1645	1.03 (0.99-1.09)
0.95 to <1.00	1188	1.08 (1.02-1.14)
≥1.00	524	1.20 (1.10-1.30)
Waist-to-hip ratio in women		
<0.80	1040	1.00 (0.94-1.07)
0.80 to <0.85	1934	1.01 (0.97-1.06)
0.85 to <0.90	2779	1.02 (0.98-1.06)
0.90 to <0.95	2548	1.05 (1.01-1.09)
≥0.95	2275	1.12 (1.07-1.17)
Waist-to-height ratio in men		
Quintile 1 (<0.45)	1229	1.00 (0.94-1.06)
Quintile 2 (0.45 to <0.48)	1030	1.04 (0.98-1.11)
Quintile 3 (0.48 to <0.51)	1062	1.01 (0.96-1.08)
Quintile 4 (0.51 to <0.54)	1061	1.06 (1.00-1.13)
Quintile 5 (≥0.54)	1556	1.08 (1.03-1.14)
Waist-to-height ratio in women		
Quintile 1 (<0.46)	1455	1.00 (0.95-1.06)
Quintile 2 (0.46 to <0.49)	1379	1.02 (0.97-1.08)
Quintile 3 (0.49 to <0.52)	1676	0.99 (0.94-1.04)
Quintile 4 (0.52 to <0.56)	2425	1.02 (0.98-1.06)
Quintile 5 (≥0.56)	3641	1.09 (1.05-1.13)

95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups) and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, prevalent cardiovascular diseases (including CHD, stroke, and TIA), prevalent diabetes, and self-rated health status.

Table F.5 Adjusted HRs for cataract by diabetes status and random blood glucose.

	Number of cases	Hazard ratio (95% CI)
Diabetes status and random blood glucose, mmol/L		
Without prevalent diabetes*		
<5.2	3876	1.00 (0.97-1.03)
5.2 to <5.7	2871	1.03 (1.00-1.07)
5.7 to <6.7	4233	1.06 (1.03-1.09)
6.7 to <7.7	1900	1.07 (1.02-1.12)
≥7.7	1128	1.07 (1.01-1.13)
Screen detected diabetes	758	1.37 (1.27-1.47)
Prior diabetes history	1410	1.82 (1.73-1.93)
Duration of diabetes, years		
0 (Screen-detected diabetes)	758	1.00 (0.92-1.08)
0 to <2	227	1.09 (0.96-1.24)
2 to <5	342	1.25 (1.12-1.39)
5 to <10	414	1.47 (1.33-1.62)
≥10	427	1.87 (1.69-2.07)
Age at diabetes diagnosis, years		
<40	61	1.55 (1.16-2.06)
40 to <50	371	1.00 (0.88-1.14)
50 to <60	793	0.63 (0.58-0.68)
60 to <70	751	0.58 (0.53-0.64)
≥70	192	0.49 (0.40-0.59)

95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex and region, and adjusted for baseline age, education, income, occupation, smoking, alcohol, physical activity, fresh fruit, self-rated health status and fasting hours.
*Prevalent diabetes include prior diabetes history and screen detected diabetes.

Appendix G. Additional results: The combined association of cataract risk factors

Appendix G.1 The association between weighted *Cataract Health Index* and risk of cataract

G.1.1 Method: Generation of the weighted *Cataract Health Index* and statistical analyses method

A Cox proportional hazards regression model including all six dichotomous variables, with adjustment for potential confounders (age, sex, region, education, income, occupation, prevalent cardiovascular diseases, and self-rated health), was used to obtain β coefficients (i.e., log-HR) for each risk factor[304,305]. For each participant, the weighted *CHI* was calculated as the sum of each dichotomous factor (0 or 1) multiplied by its corresponding β coefficient:

$$CHI_{weighted} = 0.098575*Index_{smoking} + 0.061944*Index_{alcohol} + 0.060861*Index_{physical_activity} + 0.099432*Index_{fresh_fruit} + 0.069396*Index_{adiposity} + 0.434462*Index_{diabetes}$$

The analyses were conducted among 512 690 participants (210 186 men and 302 504 women), after excluding individuals with incident cataract before age 40 years (n=34) and individuals with missing data on BMI (n=2). Baseline characteristics of CKB participants by quintiles of $CHI_{weighted}$ were calculated with direct standardisation to baseline age groups (in 5-year intervals), sex, and study area (10 regions) of the baseline CKB population. Cox proportional hazards regression models were used to estimate adjusted HRs and 95% CIs of cataract in each quintile of $CHI_{weighted}$. Analyses were stratified by age-at-risk (in 5-year groups), sex, and study areas (10 areas), and adjusted for baseline age (continuous), education (four groups), annual household income (four

groups), occupation (five groups), prevalent cardiovascular diseases (dichotomous, including CHD, stroke, and TIA), and self-rated health status (four groups). In addition, the $CHI_{weighted}$ was assessed as a continuous variable to estimate the linear association between 1 SD of $CHI_{weighted}$ with cataract risk.

To explore the potential effect modification by other population characteristic factors, subgroup analyses were conducted by age-at-risk, sex, region, education, and household income. Similar sensitivity analyses (as in the main analyses for *CHI*) were conducted to assess the robustness of the results.

G.1.2 Results

G.1.2.1 Patterns of the weighted *Cataract Health Index*

The distribution of $CHI_{weighted}$ was right-skewed, ranging from 0 to 0.825, with median of 0.130 and mean of 0.154 (SD 0.142) (**Figure G.1**). Participants with higher values were more likely to older (top vs lowest quintile: 57.2 vs 50.1 years as mean age), be men (66.0% vs 18.7%), be rural residents (66.4% vs 36.3%), have less formal education (54.8% vs 44.1% below high school) and lower household income (60.4% vs 53.6% with household income <20K yuan/year), and were less likely to be married (89.7% vs 91.5%) (**Table G.1**). They were also more likely to have prior diseases (include CHD [4.1% vs 2.7%)] stroke or TIA [2.6% vs 1.2%], and hypertension [16.6% vs 9.8%]), and have worse self-rated health status (15.2% vs 8.0% as poor) and life satisfaction level (5.4% vs 3.1% not satisfied with life).

Figure G.1 Distribution of the weighted *Cataract Health Index*.

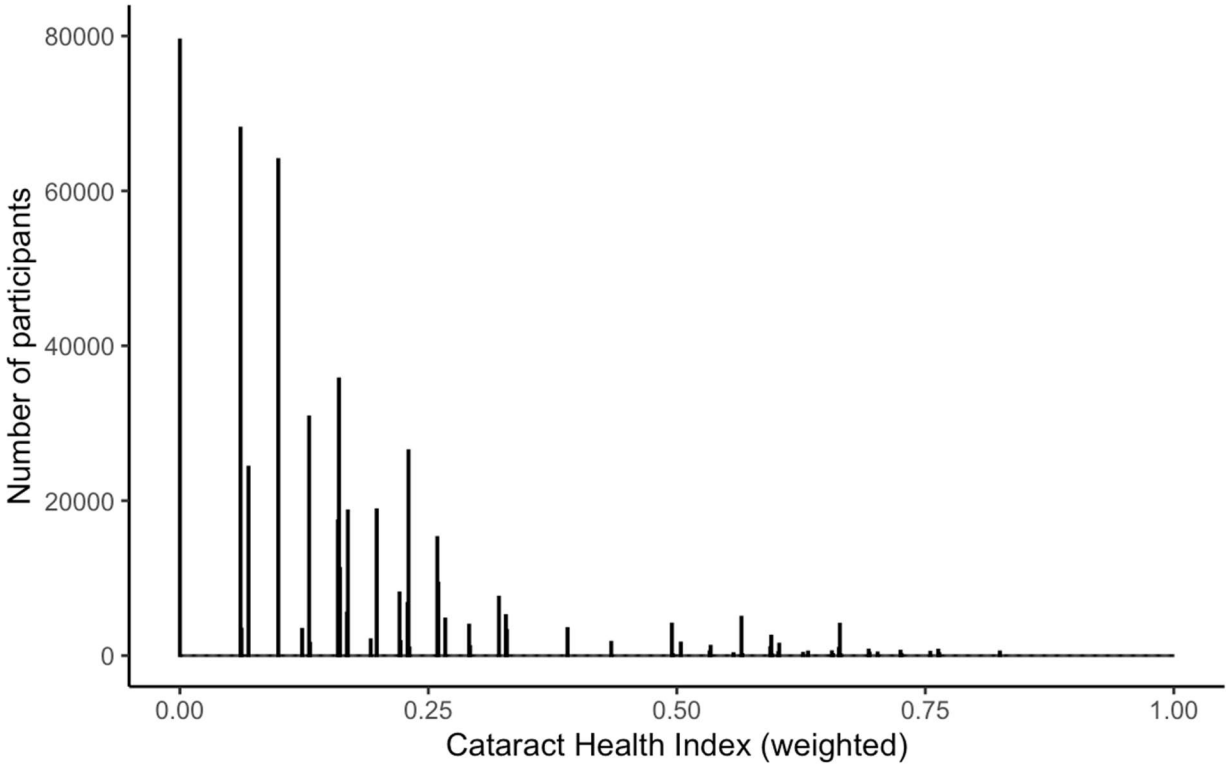


Table G.1 Baseline characteristics of CKB participants by quintiles of the weighted *Cataract Health Index*

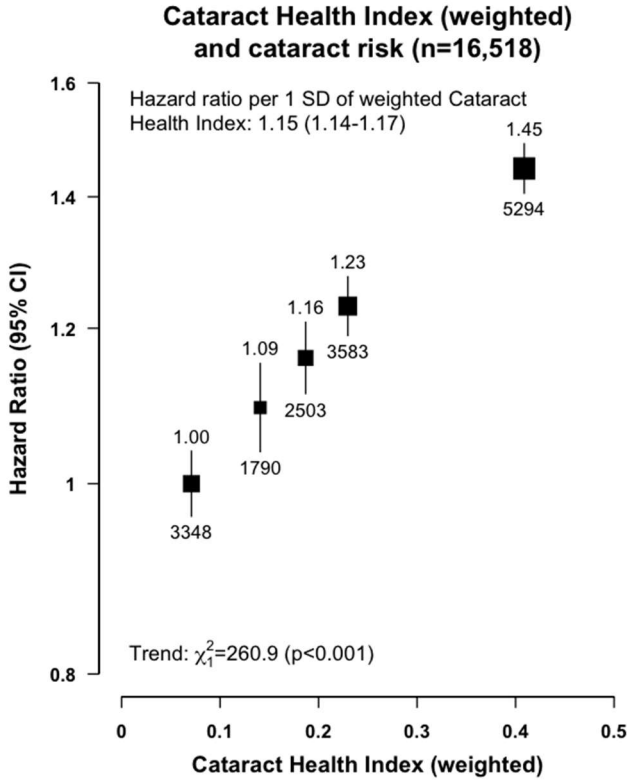
	Quintiles of the weighted *Cataract Health Index*					Overall
	1st (lowest)	2nd	3rd	4th	5th (top)	
No. of participants, n	147,585	91,781	53,171	108,599	111,554	512,690
Cataract Health Index, mean	0.028	0.090	0.139	0.179	0.358	0.154
Socio-demographic factors						
Mean age, years (SD)	50.1 (13.6)	48.9 (9.5)	56.3 (11.3)	53.9 (13.1)	57.2 (10.9)	52.0 (10.7)
Women, %	81.3	61.6	50.9	40.6	34.0	59.0
Rural, %	36.3	69.4	43.3	72.2	66.4	55.9
Education level below high school, %	44.1	52.4	47.7	55.9	54.8	50.8
Annual household income <20K yuan, %	53.6	58.6	55.8	63.1	60.4	57.3
Not in marriage*, %	8.5	8.9	8.7	10.6	10.3	9.4
Prior disease history, %						
CHD	2.7	2.6	3.4	2.8	4.1	3.0
Stroke or TIA	1.2	1.0	1.9	1.9	2.6	1.7
Cancer	0.5	0.3	0.8	0.5	0.6	0.5
Hypertension	9.8	9.0	14.5	10.5	16.6	11.6
Poor self-rated health, %	8.0	8.5	10.4	11.8	15.2	10.4
Self-rated life satisfaction as unsatisfied, %	3.1	4.5	3.4	6.0	5.4	4.2

SD standard deviation, CHD coronary heart disease, TIA transient ischemic attack.
The results were standardised by age at baseline (5-year age group), sex, and region, as appropriate.
*Include separated/divorced, widowed, and never married.

G.1.2.2 *Cataract Health Index* and risk of cataract

A higher $CHI_{weighted}$ was associated with a higher risk of cataract (P_{trend}<0.001), with a HR per 1 SD of $CHI_{weighted}$ of 1.15 (1.14-1.17). As shown in **Figure G.2** & **Table G.3**, compared to participants in the lowest quintile (HR=1.00, 0.96-1.04), the HRs for cataract incidence were 1.09 (1.04-1.15), 1.16 (1.11-1.21), 1.23 (1.19-1.27), and 1.45 (1.41-1.49), respectively, for those in the 2nd to 5th quintiles.

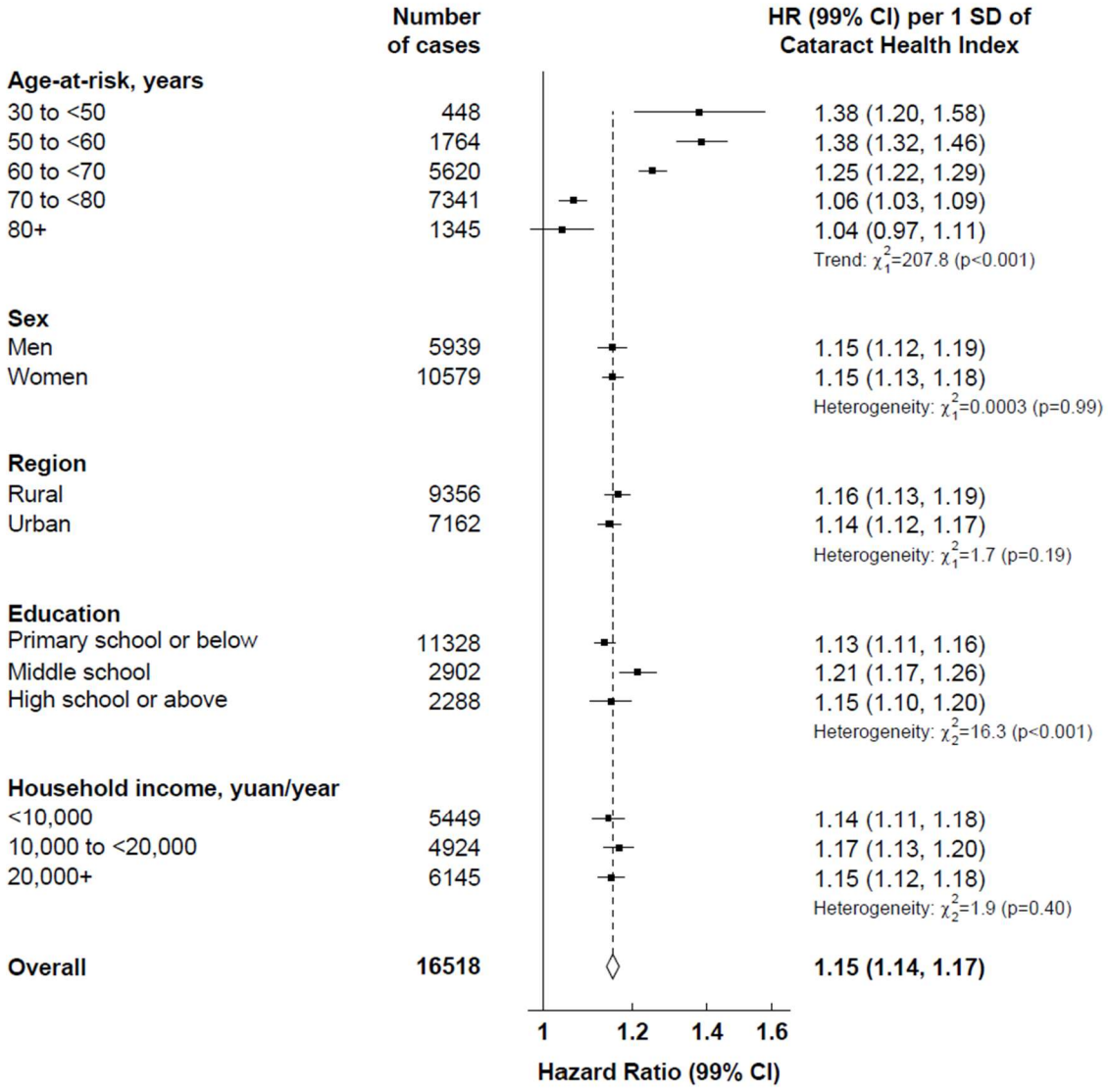
Figure G.2 Adjusted HRs for cataract by $CHI_{weighted}$



Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD, stroke, and TIA), and self-rated health status.
The squares represent HRs, and the vertical lines represent 95% CIs. The size of the square is inversely proportional to the variance of the log HR. Numerical values above the 95% CIs represent the hazard ratios and the values beneath the 95% CIs represent the number of cataract cases.
P-value for trend was related to all five quintiles.

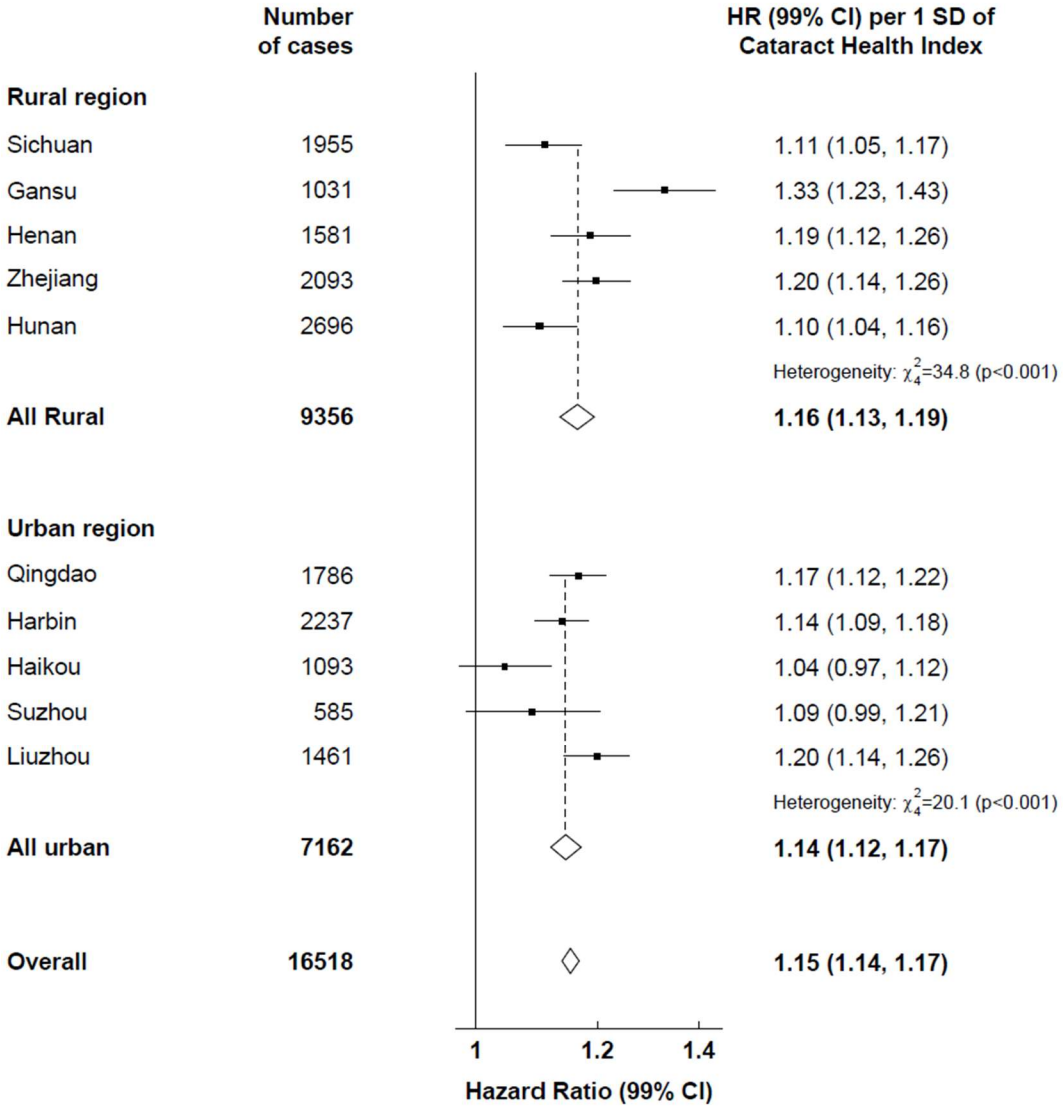
The positive associations of $CHI_{weighted}$ and risk of cataract differed across subgroups defined by age and education level (**Figure G.3** & **Figure G.4**). The associations between $CHI_{weighted}$ and risk of cataract were stronger in younger age-at-risk groups and in participants with an education level of middle school. $CHI_{weighted}$ was associated with 38% higher risk of cataract in those with age-at-risk of 30 to <60 years, but the corresponding risk was only 6% higher in those with age-at-risk of 70 to <80 years. $CHI_{weighted}$ had a slightly stronger association with cataract risk in participants with education level as middle school (HR=1.21, 1.17-1.26) than in those with other levels of education (HR 1.13 [1.11-1.16] and 1.15 [1.10-1.20] respectively for the primary school or below and high school or above education groups). The observed associations between $CHI_{weighted}$ and risk of cataract remained largely unchanged in sensitivity analyses (**Table G.2**).

Figure G.3 Adjusted HRs per 1 SD of *CHI*$_{weighted}$ for cataract by selected population characteristics.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD and stroke and TIA), and self-rated health status, as appropriate.

Figure G.4 Adjusted HRs per 1 SD of *CHI*$_{weighted}$ for cataract by region.



The hazard ratio for the overall estimate was calculated using a 95% CI.
Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD and stroke and TIA), and self-rated health status, as appropriate.

Table G.2 Adjusted HRs per 1 SD of $CHI_{weighted}$ with cataract risk - results of sensitivity analysis.

	Number of cases	HR (95%CI) per 1 SD of $CHI_{weighted}$
Primary analysis (n=512,690)	16,518	1.15 (1.14-1.17)
Exclude first 3 years of follow-up (n=512,690)	16,518	1.15 (1.14-1.16)
Exclude those aged ≥70 years at study entry (n=479,760)	13,332	1.19 (1.17-1.20)
Exclude those with poor self-rated health (n=459,633)	14,347	1.14 (1.13-1.16)
Exclude those with cancer or CVD at baseline (n=487,210)	14,903	1.16 (1.15-1.18)

Hazard ratios were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD, stroke, and TIA), and self-rated health status, as appropriate.

Table G.3 Adjusted HRs for cataract by *Cataract Health Index*.

	Number of cases	Hazard ratio (95% CI)
***Cataract Health Index* (unweighted)**		
0	982	1.00 (0.93-1.07)
1	4227	1.15 (1.11-1.19)
2	5803	1.32 (1.29-1.36)
3	3838	1.46 (1.41-1.51)
4-6	1668	1.74 (1.65-1.83)
***Cataract Health Index* (weighted)**		
Quintile 1	3348	1.00 (0.96-1.04)
Quintile 2	1790	1.09 (1.04-1.15)
Quintile 3	2503	1.16 (1.11-1.21)
Quintile 4	3583	1.23 (1.19-1.27)
Quintile 5	5294	1.45 (1.41-1.49)

95% CI 95% confidence interval.
Hazard ratios (HRs) were stratified by age-at-risk (5-year groups), sex, and region, and adjusted for baseline age, education, income, occupation, prevalent cardiovascular diseases (include CHD, stroke, and TIA), and self-rated health status.

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