ASSESSING THE ASSOCIATIONS OF METABOLIC RISK FACTORS WITH RISK OF CANCER IN CHINESE ADULTS: A PROSPECTIVE STUDY OF 0.5 MILLION PEOPLE

Yuanjie Pang

MBBS, ScM

Green Templeton College, University of Oxford

A thesis submitted for the degree of Doctor of Philosophy

Trinity Term, 2018

Abstract

Assessing the associations of metabolic risk factors with risk of cancer in Chinese adults: a prospective study of 0.5 million people

Yuanjie Pang, Green Templeton College, University of Oxford

A thesis submitted for the degree of Doctor of Philosophy, Trinity Term, 2018

Background: Metabolic risk factors are associated with higher risks of certain cancers in Western populations. Uncertainty remains about the direction, shape, and strength of their associations with specific cancers and their subtypes in China. This thesis aims to investigate the associations of major metabolic risk factors (physical activity [PA], sedentary leisure time [SLT], adiposity, diabetes, and blood glucose) with risks of pancreatic, liver, and colorectal cancer in Chinese adults.

Methods: The prospective China Kadoorie Biobank (CKB) recruited 512,713 adults aged 30-79 years from 10 diverse areas of China during 2004-08. After ~10 years of follow-up, there were 26,594 incident cases of cancer, including 796 pancreatic, 2847 liver, and 3024 colorectal cancer cases among 509,892 participants with no prior history of cancer at baseline. Cox regression was used to estimate adjusted hazard ratios (HRs) of specific cancer associated with PA, SLT, adiposity, diabetes, and, among those without previously diagnosed diabetes, with levels of random plasma glucose (RPG).

Results: At baseline, the mean (SD) age was 52 (10.7) years and 59% were women. The mean (SD) BMI was 23.7 (3.3) kg/m^2, with 33% being overweight (BMI 25-29.9 kg/m^2, 29%) or obese (BMI ≥30 kg/m^2, 4%), and 5.9% had previously diagnosed (3.1%) or screen-detected (2.8%) diabetes. The mean (SD)

total PA and SLT were 21.1 (13.9) metabolic equivalent of tasks (MET)-h/day and 3.0 (1.5) h/day. Total PA was inversely associated with risks of liver and colorectal cancer (HR per 4 MET-h/day: 0.95 [0.93-0.98] and 0.97 [0.94-1.00], respectively) but not with pancreatic cancer, while SLT was positively associated with risk of colorectal cancer (1.13 [1.00-1.26] per 1.5 h/day) but not with pancreatic and liver cancer. For colorectal cancer, the positive association with SLT was stronger for colon than rectal cancer (1.14 [0.98-1.32] vs 1.05 [0.89-1.23]). General (e.g. BMI) and central (e.g. waist circumference [WC]) adiposity measures were positively associated with risk of colorectal cancer (e.g. 1.13 [1.07-1.20] per 5 kg/m^2 BMI and 1.17 [1.11-1.22] per 10 cm WC) but not with pancreatic cancer. The positive associations tended to be stronger for colon than rectal cancer (BMI per 5 kg/m^2 1.18 [1.10-1.27] vs 1.09 [1.01-1.17]; WC per 10 cm 1.23 [1.16-1.30] vs 1.12 [1.06-1.20]). Liver cancer showed no association with BMI (1.01 [0.93-1.10]) but a positive association with WC (1.08 [1.01-1.15]) after excluding the first five years of follow-up. Diabetes (previously diagnosed or screen-detected) was associated with higher risks of all three cancers (pancreatic 1.62 [1.31-2.00], liver 1.43 [1.26-1.62], colorectal 1.16 [1.02-1.31]), and among participants without previously diagnosed diabetes there were also positive associations of RPG with risks of these cancers, even after exclusion of the first five years of follow-up.

Conclusions: In this Chinese population with relatively low levels of adiposity and high levels of physical activity, metabolic risk factors showed different associations with certain common cancers and cancer subtypes, with some consistent with (e.g. diabetes, blood glucose) while others different from (e.g. physical activity, adiposity) previous findings reported in Western populations.

Acknowledgements

First and foremost, I would like to express my gratitude to all my DPhil supervisors, Professor Zhengming Chen, Dr. Christiana Kartsonaki, and Dr. Michael Holmes, for all the enormous support and guidance they gave me during the past three years. Besides my supervisors, I would like to thank all CKB staff, participants, and funders. I am also grateful to the scholarship received through the Nuffield Department of Population Health, University of Oxford to undertake my DPhil. I thank my former advisors in the following institution: Professor Ana Navas-Acien (Columbia University), Dr. Yiyi Zhang (Columbia University), Professor Kunihiro Matsushita (Johns Hopkins University), Professor Zheng Xie (Peking University), and Professor Guang Jia (Peking University). Last but not the least, I am grateful to my friends and family members who have always been supportive over the past five years.

Disclaimer

I declare that this thesis is my own original work and has not been submitted before to any institution for assessment purposes. I have acknowledged all sources used and have cited these in the reference section.

Table of Contents

Abstract i
Table of Contents v
Abbreviations ix
Chapter 1 Introduction 1
1.1 Burden of cancer 1
1.1.1 Overview 1
1.1.2 Pancreatic cancer 5
1.1.3 Liver cancer 11
1.1.4 Colorectal cancer 14
1.2 Metabolic risk factors in relation to cancer 17
1.2.1 Physical activity 17
1.2.2 Obesity 22
1.2.3 Diabetes 26
1.3 Conclusions 30
Chapter 2 Literature review 31
2.1 Physical activity, sedentary behaviours and specific GI cancers 31
2.1.1 Physical activity 31
2.1.2 Sedentary behaviours 37
2.2 Adiposity and specific GI cancers 41
2.2.1 General and central adiposity 43
2.2.2 Other measures of adiposity 51
2.2.3 Mendelian randomisation studies 53
2.3 Diabetes, blood glucose and specific GI cancers 55
2.3.1 Diabetes 55
2.3.2 Blood glucose 65
2.3.3 Mendelian randomisation studies 67
2.4 Mechanisms 68
2.4.1 Physical activity, sedentary behaviours and cancer 68
2.4.2 Adiposity and cancer 69
2.4.3 Diabetes and cancer 72
2.5 Summary of findings and gaps in evidence 73

Chapter 3 Aims and objectives 77
Chapter 4 Methods 79
4.1 China Kadoorie Biobank study population 79
4.2 Exposure assessment 80
4.3 Outcome assessment 86
4.4 Statistical methods 87
Chapter 5 Cancer incidence and mortality 97
5.1 Results 97
5.1.1 Overall incidence and mortality 97
5.1.2 Incidence and mortality by region 100
5.1.3 Incidence and mortality by age and sex 103
5.1.4 Incidence and mortality by SES 106
5.1.5 Subtypes of colorectal cancer 109
5.1.6 Cancer survival 110
5.1.7 Comparison of CKB with national estimates in 2010 111
5.2 Discussion 112
5.2.1 Summary of findings 112
5.2.2 Urban vs rural differences 113
5.2.3 Individual-level SES 117
5.2.4 Sex differences 119
5.2.5 Subtypes of colorectal cancer 120
5.2.6 Cancer survival 121
5.3 Conclusions 123
Chapter 6 PA, SLT, and risk of specific GI cancers 125
6.1 Results 125
6.1.1 Patterns and correlates of PA and SLT 125
6.1.2 Associations of PA and SLT with specific GI cancers 135
6.1.3 Exclusion of early years of follow-up, smokers or drinkers 144
6.1.4 Associations of PA and SLT with specific GI cancers by work activity level 144
6.1.5 Interactions of PA with SLT and of occupational with nonoccupational PA 152
6.1.6 Associations of PA and SLT with HBsAg negative and positive liver cancer 155
6.1.7 Associations of PA and SLT with colon and rectal cancer 158
6.1.8 Subgroup analyses 162

6.1.9 Sensitivity analyses 170
6.2 Discussion 172
6.2.1 Summary of findings 172
6.2.2 PA and pancreatic cancer 172
6.2.3 PA and liver cancer 175
6.2.4 PA and colorectal cancer 177
6.2.5 Sitting time and specific GI cancers 179
6.2.6 Mechanisms 181
6.3 Conclusions 183
Chapter 7 Adiposity and risks of specific GI cancers 185
7.1 Results 185
7.1.1 Patterns and correlates of adiposity 185
7.1.2 Associations of adiposity with pancreatic cancer 195
7.1.3 Associations of adiposity with liver cancer 210
7.1.4 Associations of adiposity with colorectal cancer 232
7.1.5 Comparison across adiposity traits 251
7.1.6 Sensitivity analyses 253
7.1.7 Associations of adiposity-related measures with specific GI cancers 254
7.2 Discussion 256
7.2.1 Adiposity and pancreatic cancer 256
7.2.2 Adiposity and liver cancer 258
7.2.3 Adiposity and colorectal cancer 263
7.2.4 Young adulthood adiposity and specific GI cancers 268
7.2.5 Comparison across adiposity traits 270
7.2.6 Mechanisms 271
7.3 Conclusions 275
Chapter 8 Diabetes and risk of GI cancer 277
8.1 Results 277
8.1.1 Patterns and correlates of diabetes and plasma glucose 277
8.1.2 Associations of diabetes and plasma glucose with specific GI cancers 284
8.1.3 Exclusion of early years of follow-up, smokers or drinkers 299
8.1.4 Subgroup analyses 300
8.1.5 Sensitivity analyses 304

8.2 Discussion 307
8.2.1 Summary of findings 307
8.2.2 Diabetes 308
8.2.3 Duration of diabetes 314
8.2.4 Diabetes medications 317
8.2.5 Type 1 diabetes 320
8.2.6 Plasma glucose 321
8.2.7 Mechanisms 323
8.3 Conclusions 326
Chapter 9 General discussion 329
9.1 Summary of findings 329
9.2 Consistency of CKB findings with literatures 332
9.3 Mechanisms of adiposity and proteomics 336
9.4 Strengths and limitations 336
9.5 Future studies 344
9.6 Implications 347
References 350
Appendix 385

Abbreviations

%BF	Percent body fat
ADA	American Diabetes Association
BMI	Body mass index
BMI25	Body mass index at age 25
CDC	Centre for Disease Control and Prevention
CHD	Coronary heart disease
CI	Confidence interval
CKB	China Kadoorie Biobank
CRP	C-reactive protein
CVD	Cardiovascular disease
DSP	Disease Surveillance Points
EPIC	European Prospective Investigation into Cancer and Nutrition
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
GI	Gastrointestinal
HbA1c	Haemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Hip circumference
HCV	Hepatitis C virus
HOMA	Homeostasis model assessment
HR	Hazard ratio
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
ICC	Intraclass correlation coefficiency
ICD-10	International Classification of Diseases, 10th Revision
IDF	International Diabetes Federation
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IL	Interleukin
IQR	Interquartile range
LOD	Limit of detection
Me-Can	Metabolic syndrome and Cancer project
MET	Metabolic equivalent of task
MIR	Mortality-to-incidence ratio
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCCR	National Central Cancer Registry

NCI	National Cancer Institute
OR	Odds ratio
PA	Physical activity
PAQ	Physical activity questionnaire
QC	Quality control
RCT	Randomised controlled trial
RDR	Regression dilution ratio
RPG	Random plasma glucose
RR	Relative risk
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SLR	Systematic Literature Review
SLT	Sedentary leisure time
SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study
TIA	Transient ischaemic attack
TNF	Tumour necrosis factor
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
WC	Waist circumference
WCRF	World Cancer Research Fund
WHO	World Health Organisation
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

Chapter 1 Introduction

This chapter describes the burden and epidemiology of major cancers and metabolic risk factors (e.g. physical activity, obesity, and diabetes) in different populations. The objectives of this chapter are to set the scene and to describe why it is important to understand metabolic risk factors for cancer in China.

1.1 Burden of cancer

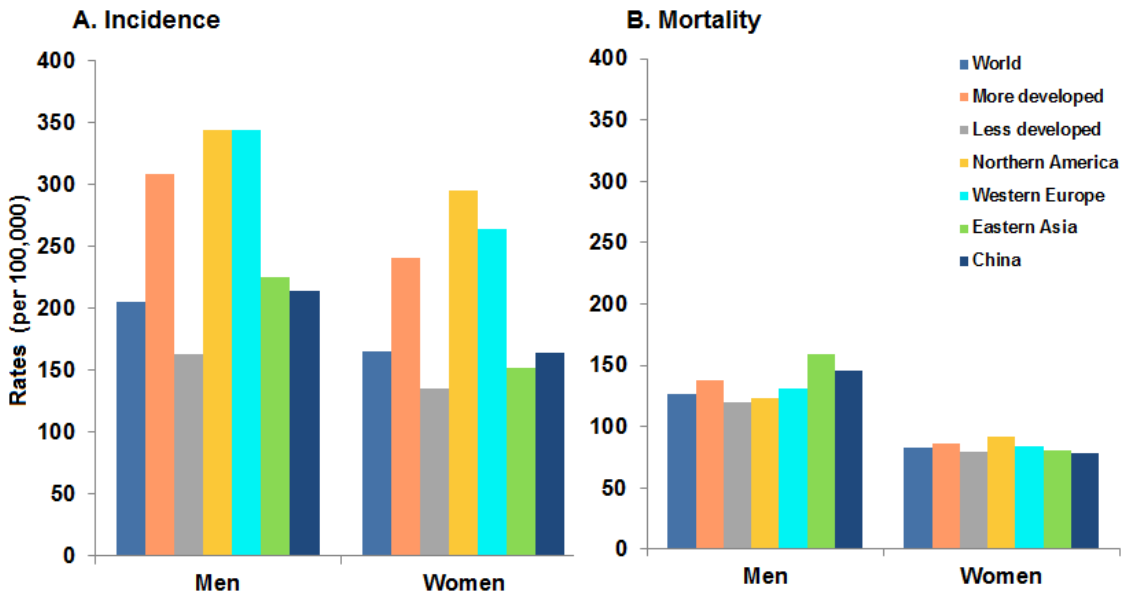
1.1.1 Overview

Cancer is a leading cause of morbidity and mortality worldwide.[1] The Global Burden of Disease 2015 estimated that there were 17.5 million new cancer cases and 8.7 million cancer deaths in 2015,[2] compared with IARC estimates of 14.1 million new cases and 8.2 million deaths in 2012 and 12.7 million new cases and 7.6 million deaths in 2008.[3,4] Despite the increasing numbers of new cases and deaths, age-standardised mortality rates have been decreasing globally over the past three decades.[2] In China, the number of cancer deaths increased from 1.5 million in 1990 to 2.1 million in 2013,[5] while the age-standardised mortality rate decreased from 187.8 to 154.0 per 100,000 persons over the same period.[5] In 2012, the age-standardised incidence rate of cancer in China was lower than that in high-income countries, while the age-standardised mortality rate was comparable (**Figures 1.1**).[4]

The distribution of cancer types differs importantly between China and high-income countries (**Table 1.1**).[2] In 2015, the five most common cancers (excluding nonmelanoma skin cancer) in high-income countries were prostate, breast, colorectal, lung, and stomach cancer.[2] In China, the five most common cancers

were lung cancer, followed by four cancers of the gastrointestinal (GI) system (stomach, oesophageal, liver, and colorectal cancer).[6]

Figure 1.1 Age-standardised incidence and mortality rates of total cancer (per 100,000) worldwide in 2012*



* Estimates were obtained from the GLOBOCAN Project. Estimates in China were obtained from the National Central Cancer Registry (NCCR).
All rates were age-standardised using direct method and the World standard population.
More developed regions included Northern America, Europe, Australia/New Zealand, and Japan. Less developed regions included the remaining regions and countries

Table 1.1 Top 10 cancer by age-standardised incidence rates*

Rank	High-income†	China
1	Prostate cancer	Lung cancer
2	Breast cancer	Stomach cancer
3	Colorectal cancer	Oesophageal cancer
4	Lung cancer	Liver cancer
5	Stomach cancer	Colorectal cancer
6	Non-Hodgkin lymphoma	Breast cancer
7	Kidney cancer	Brain cancer
8	Bladder cancer	Cervix cancer
9	Malignant skin melanoma	Pancreatic cancer
10	Liver cancer	Thyroid cancer

* Estimates were obtained from the Global Burden of Disease Study 2015 and from the National Central Cancer Registry (NCCR) 2015 in China.[2,6]
† High-income countries are defined by the highest quintile of sociodemographic index (SDI).

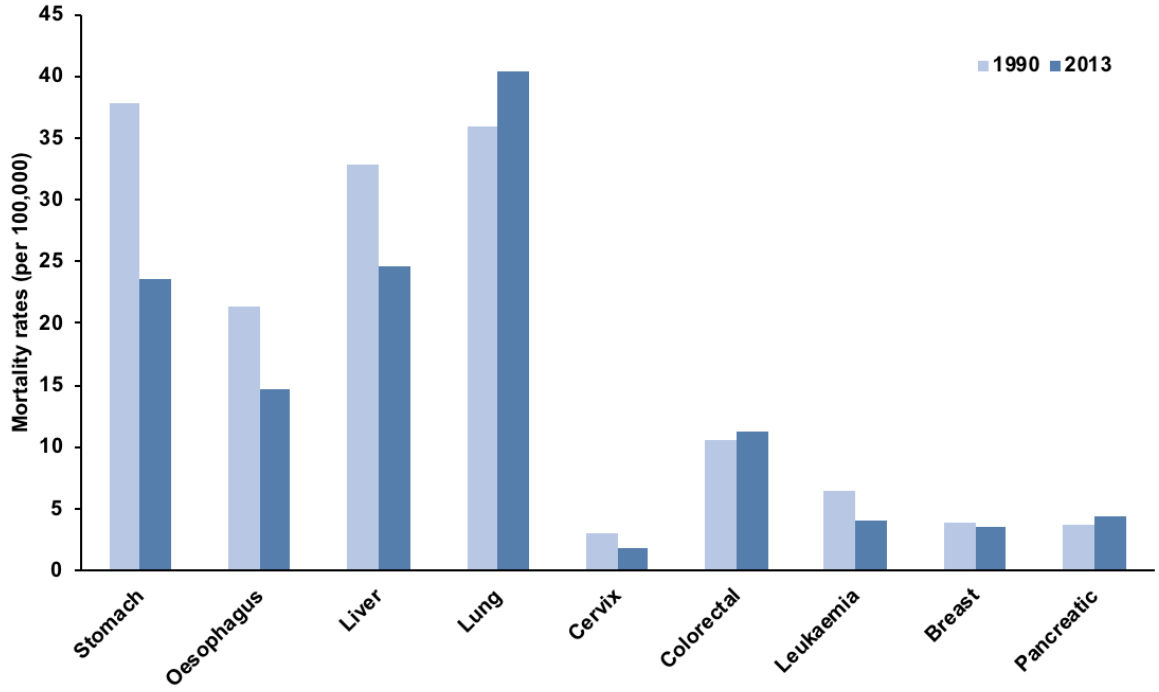
For liver, oesophageal, and stomach cancer, 70-80% of global cases occur in low- and middle-income countries, with about 50% in China.[4] This is probably due to the high prevalence of infectious agents including HBV and *Helicobacter pylori*.[7-9] Although colorectal and pancreatic cancer are mainly diseases of high-income countries, the age-standardised incidence rates have been rising in low- and middle-income countries in recent years possibly due to the increasing prevalence of sedentary lifestyle and changing dietary patterns (i.e. increased consumption of foods of animal origin).[10]

In China, the overall patterns of cancer and age-standardised mortality rates have been changing since the 1990s (**Figure 1.2**).[5,11] For certain cancers (e.g. liver, oesophageal, and stomach cancer), the age-standardised mortality rates have been declining, perhaps due partly to improvements in diet including substantial reduction in aflatoxin contamination of foodstuff. Recent changes in lifestyle and metabolic risk factors (e.g. smoking, dietary patterns, obesity, physical inactivity, and hyperglycaemia) in general populations have been associated with an increase in age-standardised mortality rates of certain other cancers that are more common in Western populations (e.g. pancreatic and colorectal cancer).[5,11-16]

Furthermore, there is substantial variation in cancer rates between urban and rural areas in China.[6,17-23] Age-standardised incidence and mortality rates are higher in urban areas for pancreatic and colorectal cancer, possibly due to the higher prevalence of sedentary lifestyle and consumption of animal origin foods in urban areas. [6,13,15,17-23] In contrast, age-standardised incidence and mortality rates are higher for stomach, oesophageal, and liver cancer in rural areas possibly due to the higher prevalence of *Helicobacter pylori* and HBV. [6-9,17-23] There is also large

and well-documented regional variation in age-standardised cancer rates across China.[5] Assessing the urban-rural differences is important to understand risk factors, to plan for targeted interventions, and to allocate resources for cancer prevention and treatment.

Figure 1.2 Age-standardised mortality rates of cancer (per 100,000) in China*



* The 1990 and 2013 data were obtained from the Global Burden of Disease Study.[5]
All rates were age-standardised using the direct method and the World standard population.

In my thesis, I will focus on three cancers related to the GI system, which are pancreatic, liver, and colorectal cancer. Except for viral-related liver cancer, age-standardised incidence rates of pancreatic, liver, and colorectal cancer are rising in parallel with increasing prevalences of physical inactivity, obesity, and diabetes,[5,14-16] suggesting a role of metabolic risk factors in the aetiology of these cancers. As the proportion of cancer types and patterns of lifestyle and metabolic risk factors differ importantly between China and Western countries, assessing

metabolic risk factors in relation to cancer risk should help understand cancer aetiology and inform cancer prevention in the Chinese population.

1.1.2 Pancreatic cancer

1.1.2.1 Incidence, mortality and trends

Pancreatic cancer ranks the 12th most common cancer worldwide and is the seventh most common cause of death from cancer in both sexes combined, responsible for 331,000 deaths per year.[4] Pancreatic cancer has the highest case fatality of any major cancer.[4] The age-standardised incidence and mortality rates have been rising over the past 50 years.[24] Pancreatic cancer is mainly a disease of high-income countries, where the overall incidence is nearly three times higher than that in low- and middle- income countries (**Figures 1.3**-**1.4**).[3,4] In China, pancreatic cancer is the sixth leading cause of death from cancer and the ninth most common cancer.[6] The age-standardised incidence and mortality rates of pancreatic cancer were rising in China between 2008 and 2012 (**Figures 1.5**-**1.6**), which was consistent with a previous report showing a 1.14-fold increase in age-standardised mortality between 2003 and 2011. In 2014, the age-standardised incidence and mortality rates of pancreatic cancer were 4.3 and 3.7 per 100,000 persons, and both were higher in men and in urban areas.

Figure 1.3 Age-standardised incidence rates of specific GI cancers (per 100,000) worldwide in 2012*

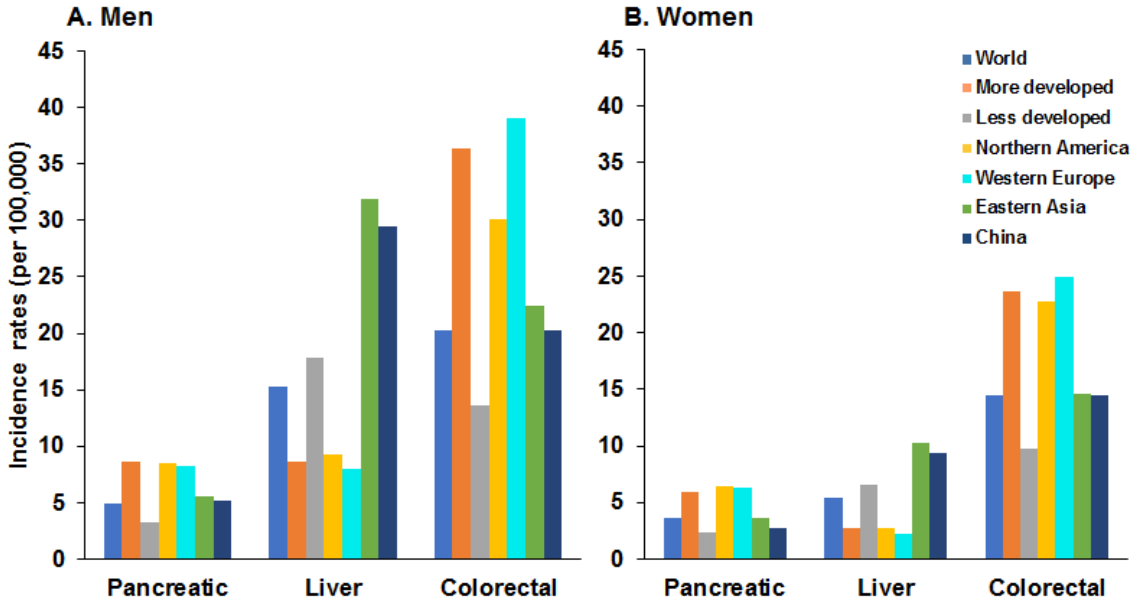
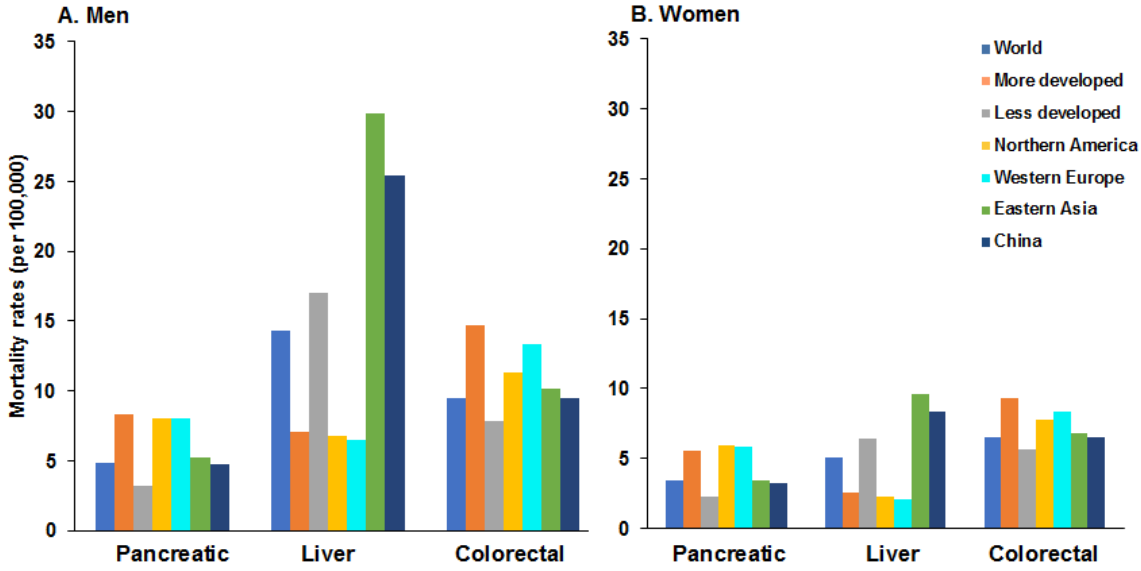
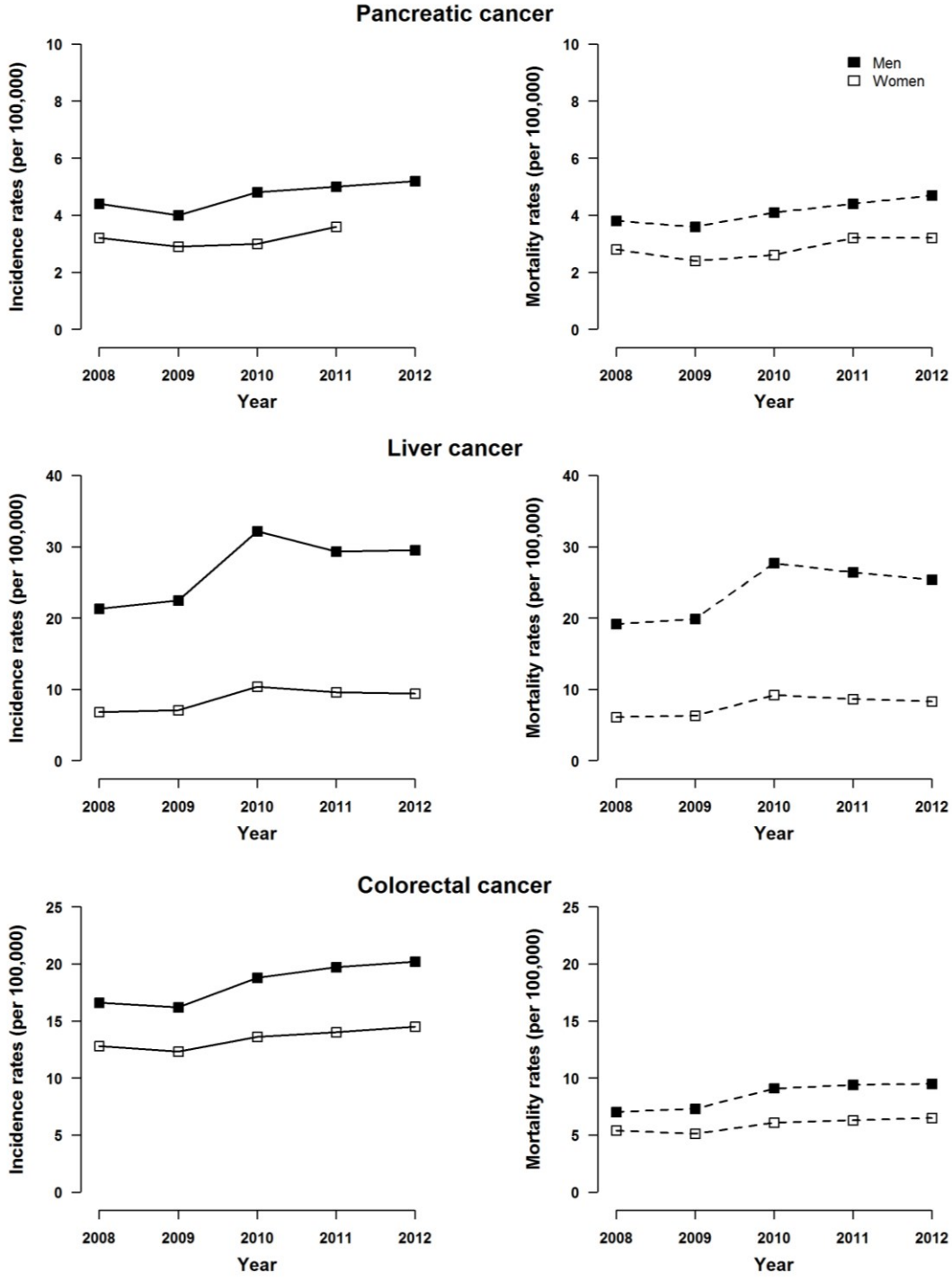


Figure 1.4 Age-standardised mortality rates of specific GI cancers (per 100,000) worldwide in 2012*



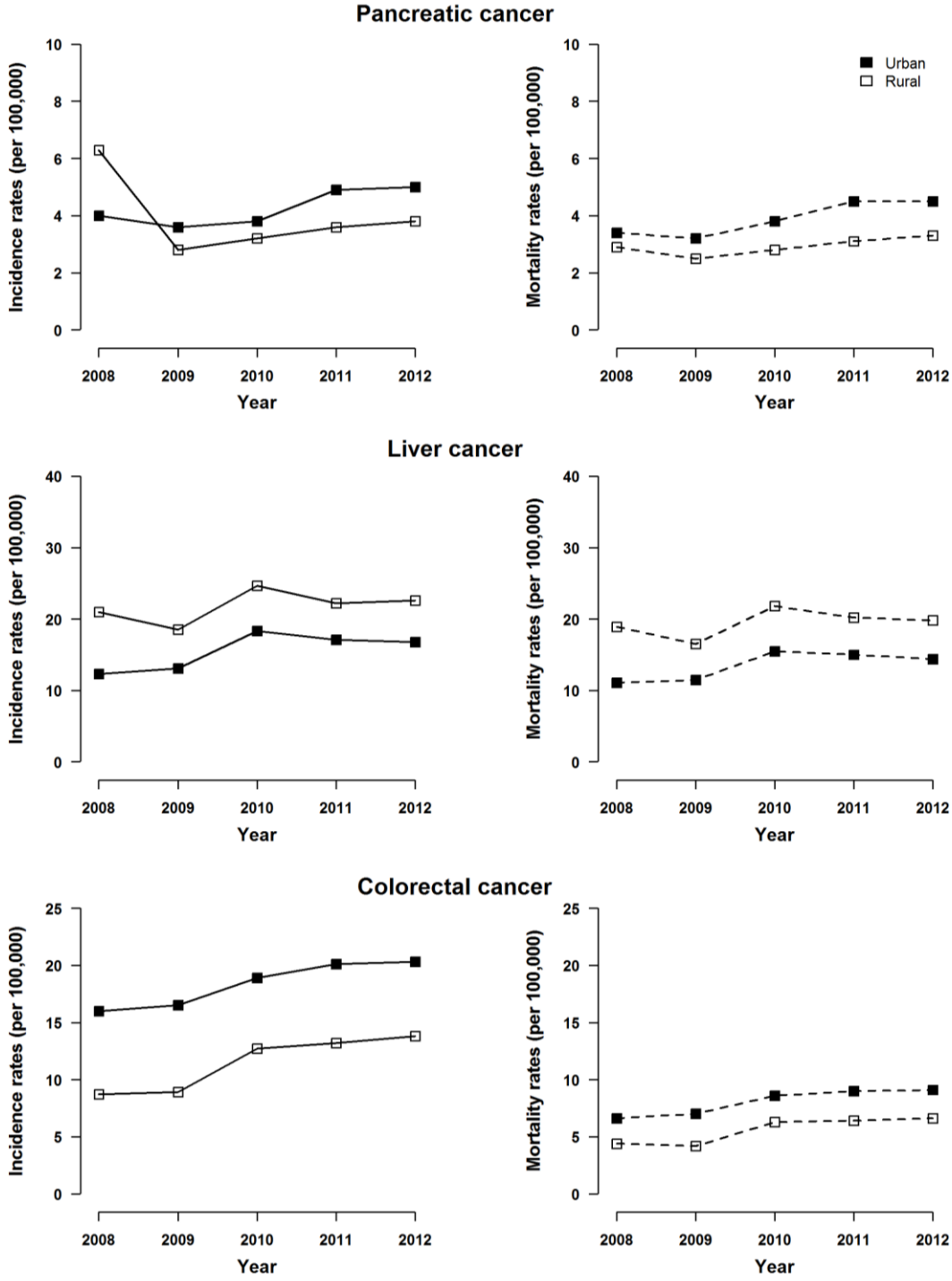
* Estimates were obtained from the GLOBOCAN Project.[4] Estimates in China were obtained from the National Central Cancer Registry (NCCR).[21]
All rates were age-standardised using direct method and the World standard population.
More developed regions included Northern America, Europe, Australia/New Zealand, and Japan. Less developed regions included the remaining regions and countries.

Figure 1.5 Age-standardised incidence and mortality rates of specific GI cancers (per 100,000) in China by sex, 2008-2012*



* Estimates were obtained from the National Central Cancer Registry (NCCR).[17-21] Age-standardised incidence rate of pancreatic cancer in women in 2012 was not available.
All rates were age-standardised using direct method and the World standard population.

Figure 1.6 Age-standardised incidence and mortality rates of specific GI cancers (per 100,000) in China by region, 2008-2012*



* Estimates were obtained from the National Central Cancer Registry (NCCR).[17-21]
All rates were age-standardised using direct method and the World standard population.

1.1.2.2 Subtypes

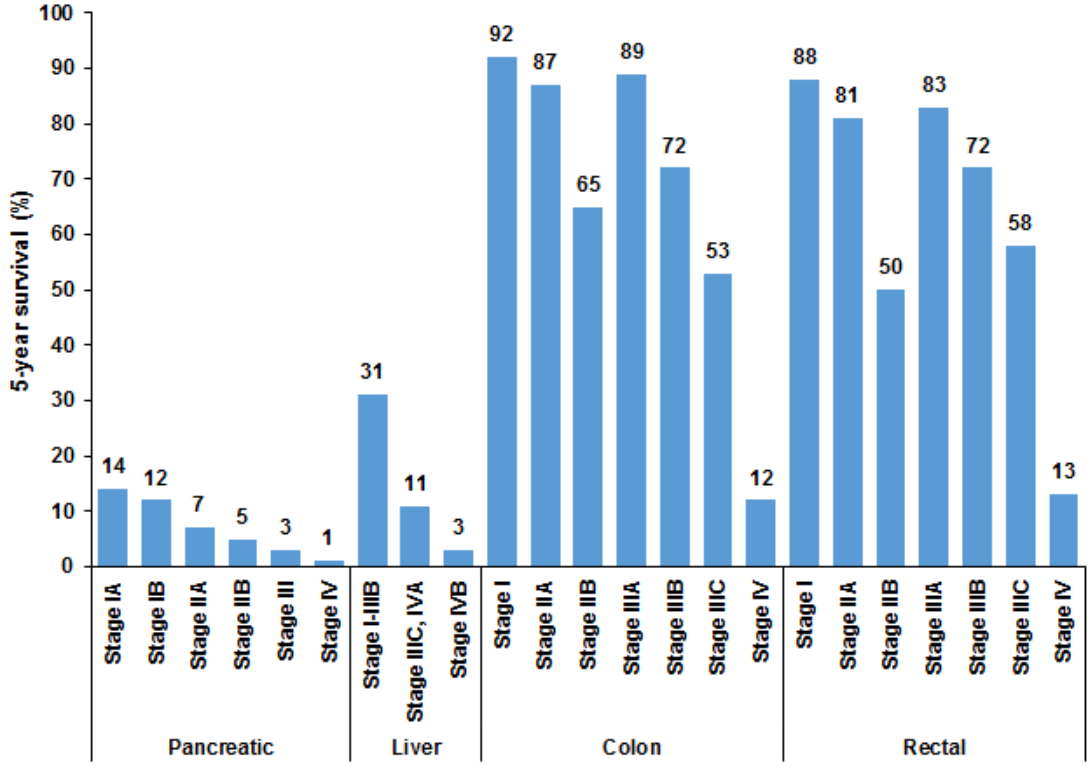
Two main subtypes of pancreatic cancer are exocrine and endocrine tumours.[24,25] Over 95% of pancreatic cancer cases are adenocarcinomas of the exocrine pancreas (i.e. pancreatic ductal adenocarcinoma [PDAC]).[24] PDAC develops from cells of the pancreatic ducts which carry digestive juices and enzymes into the main pancreatic duct and then into the duodenum.[26] There are other rare exocrine tumours such as acinar cell carcinoma and solid pseudopapillary neoplasm.[25] Pancreatic endocrine tumours, also known as neuroendocrine or islet cell tumours, originate from islets of Langerhans which produce hormones (e.g. insulin, glucagon, and gastrin).[25,27] These are rare neoplasms and occur in approximately 1 of 100,000 persons, representing 1-10% of all pancreatic neoplasms.[25,27] Approximately 15% of pancreatic endocrine tumours are benign.[25,27] Pancreatic endocrine tumours can be functioning or nonfunctioning depending on the presence of hormonal hypersecretion symptoms. Functioning tumours such as gastrinomas and insulinomas can produce polypeptide hormones, while nonfunctioning tumours (~30%) produce no clinical syndromes probably because the tumours produce no hormones.[28]

1.1.2.3 Prognosis

Pancreatic cancer has the highest case fatality of any major cancer.[24] Reasons for the poor survival include the insidious and aggressive nature of these tumours, late diagnosis, low rates of resection, and lack of effective therapies.[24,29] The Cancer Research UK data showed 1-year survival of 20%, 5-year survival of 5%, and 10-year survival of 1%, with little improvement since the 1970s.[30] A recent

study of 17 population-based cancer registries in China (number of participants: half urban, half rural) reported slightly higher 5-year survival (7%).[31] The median survival was 6-11 months for stage III (i.e. locally advanced disease) and 2-6 months for stage IVB (i.e. metastatic disease).[32] Similarly, the 5-year survival was lower among patients diagnosed with a more advanced stage (**Figure 1.7**).

Figure 1.7 5-year survival of cancer in the US, 2005-2011*



* Estimates were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and were based on patients who were diagnosed with pancreatic, liver, and colorectal cancer between 2005 and 2011.[32-34]

1.1.2.4 Risk factors

Pancreatic cancer has multi-factorial aetiology.[35] About two-thirds of the major risk factors are potentially modifiable, which affords opportunities for prevention.[35] These include smoking, obesity, diabetes, and history of chronic pancreatitis. Several other possible risk factors are excessive alcohol intake (i.e. more than 3

drinks/day), consumption of red meat and processed meat, *Helicobacter pylori* infection, HBV, and young adulthood obesity (at age ~20).[35,36] Possible protective factors include history of allergy and increasing intake of fruit and folate, although the evidence has been less consistent for history of allergy.[35] **Appendix 1.1** summarises risk factors for pancreatic cancer from published meta-analyses. A previous report in the China Kadoorie Biobank has shown that smoking and heavy alcohol drinking (≥420 g/week) are possible risk factors for pancreatic cancer in men, while lower fresh fruit and higher red meat intake are associated with higher risk of pancreatic cancer.[37]

1.1.3 Liver cancer

1.1.3.1 Incidence, mortality and trends

Liver cancer is the sixth most common cancer worldwide, with 782,000 new cases diagnosed in 2012, and it is the second most common cause of death from cancer.[4] Approximately 80% of global liver cancer cases occur in low- and middle-income countries, with the highest age-standardised incidence rates in Asia and Africa and the lowest in Europe, Latin America, and the Caribbean.[4] In 2012, the age-standardised incidence and mortality rates of liver cancer were almost four times higher in Eastern Asia than Western Europe (**Figures 1.3**-**1.4**).[4] Although the age-standardised incidence rate is increasing in many areas of the world, including North America, Western Europe, and Oceania, it is declining in Asian countries.[38]

Approximately 75% of all liver cancer occurs in Asia, with China accounting for over 50% of the world's burden.[4] In China, liver cancer is the second leading

cause of death from cancer and the fourth most common cancer.[6] The age-standardised mortality rate of liver cancer in China is declining over time,[5] largely attributable to the substantial reduction in aflatoxin contamination of foodstuff and HBV.[7,8] The seroprevalence of HBsAg in individuals aged 20-49 years decreased from 9.8% in 1992 to 6.3% in 2010-2012.[7,8] The age-standardised mortality rate of liver cancer attributable to HBV decreased from 15.6 per 100,000 persons in 1990 to 11.0 per 100,000 persons in 2013 (25% reduction).[5] Despite a rapid decrease in age-standardised mortality rate since the 1970s, there was a moderate increase in age-standardised incidence and mortality rates after 2010 for reasons that are not well understood (**Figures 1.5-1.6**).[5,11] In 2014, the age-standardised incidence and mortality rates were 17.8 and 15.3 per 100,000 persons, and both were higher in men and in rural areas.

1.1.3.2 Subtypes

Globally, hepatocellular carcinoma (HCC) is the dominant histological subtype of liver cancer in most countries accounting for approximately 80% of total liver cancer cases.[39] Intrahepatic cholangiocarcinoma (ICC) which originates from the intrahepatic biliary ducts is the second most common histological subtype, accounting for approximately 15% of total liver cancer cases.[39] Other subtypes of liver cancer include angiosarcoma (originating from the intrahepatic blood vessels), childhood hepatoblastoma, and other sarcoma.[39]

1.1.3.3 Prognosis

Liver cancer has a poor prognosis, with little improvement in 5-year survival over the last few decades.[40] The Cancer Research UK data showed 1-year survival of

36% and 5-year survival of 12%.[40] Similarly, the 5-year survival was 12% in European adults diagnosed with liver cancer between 2000 and 2007,[40] while a recent study of 17 population-based cancer registries in China (half urban, half rural) reported overall 5-year survival of 12%.[31] The American Cancer Society data showed that 5-year survival was highest for patients diagnosed with a localised tumour (stage I, II, and some stage III; 31%) and lowest for those diagnosed with distant tumours (stage IVB; 3%) (**Figure 1.7**).[33]

1.1.3.4 Risk factors

Risk factors for liver cancer generally fall into two broad categories: infection-related and non-infection-related. Their relative importance differs between high-income and low- and middle-income countries.[38] In East Asia and sub-Saharan Africa, the major risk factors are chronic infection with HBV and aflatoxins, where approximately 80% of liver cancer occurs.[38] In contrast, infection with HCV and alcohol drinking are the main risk factors in North America, Europe, and Japan.[38] Major modes of HBV transmission are perinatal transmission from mother to infant, sexual or household contact with an infected person, and injection drug use,[41] while major modes of HCV transmission are injection drug use, unsafe transfusions, therapeutic injections, and other health-care-related procedures.[42] Chronic HBV carriers have a 100-fold higher risk of developing liver cancer than noncarriers.[43] It was estimated that two billion people worldwide were infected with HBV in 2010.[44] In 2010, the estimated seroprevalence of HBV was 3.6% globally, with the highest endemicity in countries of the African region (8.8%) and Western Pacific region (5.3%).[44] In contrast, the global seroprevalence of HCV was 2.8% in 2005, with a higher seroprevalence in Europe (1.5-3.5%) than Asia Pacific and

North America (<1.5%).[45] Despite a decrease in seroprevalence over the past few decades, the Global Burden of Disease 2015 estimates showed that HBV and HCV each accounted for 33% and 21% of liver cancer deaths.[46] The proportions of total liver cancer deaths attributable to HBV and HCV were 18% and 40% in high-income countries and 41% and 9% in East Asia.[46]

Apart from aflatoxins and heavy alcohol intake, non-infection-related risk factors include smoking,[47-49] and possibly, long-term use of oral contraceptives.[50] Drinking coffee is associated with a lower risk, while there is limited evidence of a protective role of physical activity and fish consumption.[38,49] **Appendix 1.2** summarises risk factors for liver cancer from published meta-analyses.

1.1.4 Colorectal cancer

1.1.4.1 Incidence, mortality and trends

Colorectal cancer is the third most common cancer and the fourth most common cause of death from cancer worldwide.[4] Around 1.4 million cases were recorded in 2012, accounting for ~10% of all cancers.[4] Incidence of colorectal cancer is increasing with industrialisation and urbanisation and has at least doubled in high-income countries since the mid-1970s.[10] Colorectal cancer is mainly a disease of high-income countries, where the age-standardised incidence rate is nearly three times higher than that in low- and middle-income countries (**Figures 1.3** and **1.4**).[4] In China, colorectal cancer is the fifth leading cause of death from cancer and ranks the fifth most common cancer.[6] The age-standardise incidence and mortality of colorectal cancer increased from 2008 to 2012 (**Figures 1.5** and **1.6**). In 2014, the age-standardised incidence and mortality rates were 17.5 and 7.9 per 100,000

persons, and both were higher in men and in urban areas.

1.1.4.2 Subtypes

Approximately 95% of colorectal cancers are adenocarcinomas, which originate from epithelial cells of the colorectal mucosa.[51] Other rare subtypes of colorectal cancer are squamous cell tumours, carcinoid tumours, sarcoma, and lymphomas.[51] Colorectal cancer can be classified by anatomical site into colon and rectal cancer, while colon cancer can be further classified into proximal (i.e. splenic flexure, descending colon, and sigmoid colon) and distal colon cancer (i.e. cecum, ascending, and hepatic flexure).[10] In low-risk countries, rectal cancer accounts for the largest proportion of all colorectal cancers.[52] The proportion of rectal cancer among all colorectal cancers is generally less than 40% in Europe and North America, in contrast to 50% or more in Asia.[10,52] According to IARC data, the ratio of age-standardised incidence rates of colon and rectal cancer was higher in the US (2-3.5) and Japan (1.6-2.2) than that in China (1.1-1.8) and Korea (1.0-1.1).[53]

In China, there are no large national data on subtypes of colorectal cancer in the present decade. Anatomical surveys conducted before 2008 showed that the proportion of colon cancer was increasing. The proportion of rectal cancer decreased from 73% in the 1980s to 67% in the 1990s, while the proportion of colon cancer increased from 27% to 33% over the same period. Hospital-based anatomical surveys after 2000 also suggested a decreasing proportion of rectal cancer and an increasing proportion of colon cancer. An anatomical survey of 8172 colorectal cancer patients in Guangdong, an eastern coastal province, reported that the proportion of colon cancer increased from 41% (1989-1991) to

48% (2004-2006). Another report involving 3607 colorectal cancer patients in Heilongjiang, a northeast inland province, reported that the proportion of colon cancer increased from 23% in 1981-1985 to 37% in 2001-2005.

1.1.4.3 Prognosis

The 5-year overall survival ranges from ~60% in North America, Japan, Australia, and Western Europe to 40% or less in Algeria, Brazil, and other European countries.[54,55] The Cancer Research UK data showed 1-year survival of 76%, 5-year survival of 59%, and 10-year survival of 57%, which improved from the 10-year survival of 22% in the 1970s.[56] Similarly, a recent study of 17 population-based cancer registries in China reported overall 5-year survival of 57% for colorectal cancer.[31] That study showed lower 5-year survival in rural than urban areas (52% vs 60%), but did not examine colon and rectal cancer separately. The American Cancer Society data showed that 5-year survival was highest for patients diagnosed at stage I (colon 92%, rectal 88%) and lowest for those diagnosed at stage IV (colon 12%, rectal 13%) (**Figure 1.7**).[34]

1.1.4.4 Risk factors

Several modifiable risk factors have been associated with colorectal cancer.[52] These include smoking, excessive alcohol consumption, high consumption of red and processed meat, body fatness and abdominal fatness, greater adult attained height, diabetes, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and family history of colorectal cancer.[52,57-59] As judged by the World Cancer Research Fund, there is strong evidence that physical activity, taking calcium supplements, and consumption of wholegrains, dairy products, and foods

containing dietary fibre are associated with a lower risk of colorectal cancer.[57] Other factors that may be associated with a lower risk of colorectal cancer risk are use of hormone replacement therapy, aspirin, and statin therapy.[52] Furthermore, emerging evidence suggests that infectious agents including *Helicobacter pylori* and *Fusobacterium* may be associated with a higher risk.[52] **Appendix 1.3** summarises risk factors for colorectal cancer from published meta-analyses. Two prospective cohort studies in urban Chinese (the Shanghai Women's Health Study and the Shanghai Men's Health Study, <1000 cases) have investigated possible risk factors for colorectal cancer. Factors associated with a lower risk of colorectal cancer were dietary fibre and fruit.[60,61] Factors associated with a higher risk were foods of animal origin (red meat, eggs, fish),[62] smoking (for rectal cancer in men),[63] heavy alcohol intake (>560 g/week, for colon cancer in men),[63] and adiposity (for colon cancer in men).[64]

1.2 Metabolic risk factors in relation to cancer

Metabolic risk factors are a range of factors associated with cardiometabolic diseases (e.g. diabetes, CHD, stroke), including physical activity, adiposity, blood glucose, blood pressure, and lipids.[65,66] In recent decades, prospective studies have shown associations of these factors with risks of several cancers.[66] In my thesis, I will focus on three major metabolic risk factors, which are physical activity, adiposity, and diabetes (including blood glucose).

1.2.1 Physical activity

Physical activity, defined as any bodily movement produced by skeletal muscles, can be divided into three categories: sleep, occupation, and leisure-time.[67]

Leisure-time physical activity can be subdivided into exercise, household tasks, and other activities.[67] Epidemiological studies have used different but meaningful categories taking into account the complexity of physical activity. Nationwide surveys in China have categorised physical activity into four domains, including occupational, household, commuting, and leisure-time (mainly exercise).[15] In epidemiological studies, physical activity is often defined based on exercise in leisure-time. For example, the 2010 WHO guidelines recommend ≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity aerobic physical activity per week (equivalent to a minimum of 7.5 MET-h/week).[68]

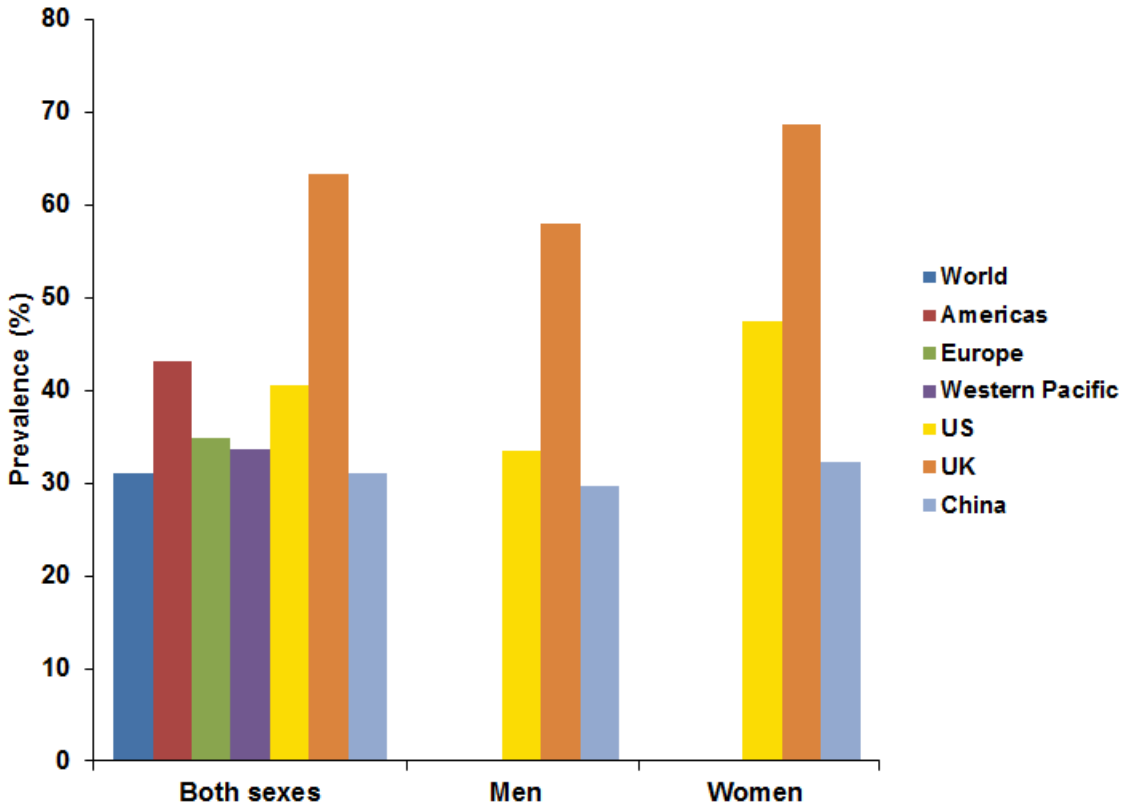
1.2.1.1 High-income countries vs China

Physical inactivity, as well as obesity and diabetes, contributes to the rising burden of noncommunicable diseases worldwide. According to WHO, 31% of adults worldwide are physically inactive (i.e. not attaining recommended physical activity levels).[69] The prevalence of physical inactivity is higher in high-income countries than in low- and middle-income countries, with a prevalence of 63% in the UK, 41% in the US, 60% in Japan, and 31% in China (**Figure 1.8**).[70] Although physical activity has been declining over time mainly due to reduced occupation-related activities, leisure-time physical activity has increased in the past 20-30 years both in high-income countries and in China.[15,70,71] The nature of physical activity is different between China and high-income countries. In high-income countries, leisure-time physical activity is the largest domain, accounting for approximately 70% of total physical activity.[70,72,73] In China, by contrast, occupational physical activity is the largest domain and accounts for approximately 75% and 50% of total physical activity in men and women,[15,74]

respectively, while leisure-time physical activity accounts for about 4% of total physical activity in both sexes.[15,74]

The decline in physical activity has been accompanied by an increase in sedentary time, mainly due to increased TV watching and computer use.[75] Overall, the proportion of adults spending ≥4 h/day sitting was 42% worldwide, 55% in the Americas, 64% in Europe, and 40% in Western Pacific.[70] According to a recent study of 20 countries worldwide, the median sitting time among adults was 300 min/day worldwide and 240 min/day in China.[76]

Figure 1.8 Age-standardised prevalence of physical inactivity among individuals aged ≥15 years*



* Physical inactivity was defined as not meeting any of the following criteria: (a) 5 x 30 minutes of moderate-intensity activity per week; (b) 3 x 20 minutes of vigorous-intensity activity per week; (c) an equivalent combination achieving 600 metabolic equivalent-minute per week. All estimates were adjusted for age and region.

1.2.1.2 China: past vs present

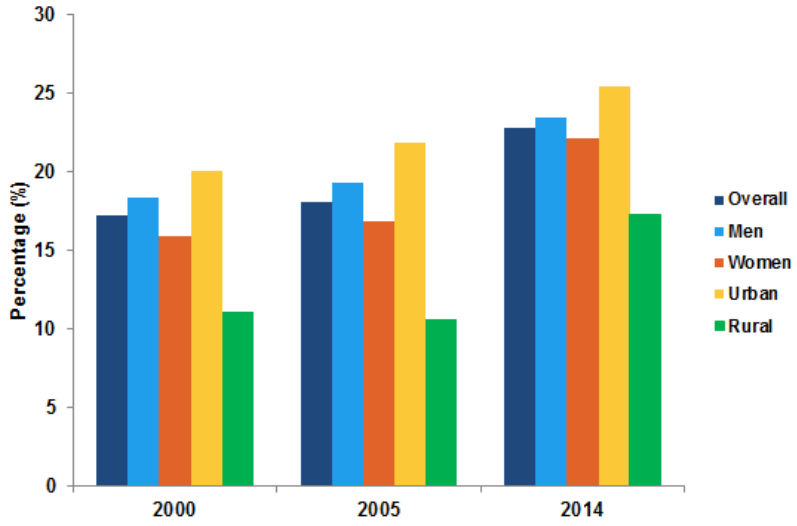
In China, there is a rapid decline in total physical activity in both sexes mainly due to a decline in occupational activity (**Table 1.2**).[15] Among Chinese women, there is a faster decline as both occupational and household activity are decreasing over time. Between 1997 and 2006, total physical activity decreased from 350 to 253 MET-h/week in men and from 390 to 246 MET-h/week in women.[15] Over the same period, leisure-time activity increased from 1.4 to 3.6 MET-h/week in men and from 0.6 to 2.3 MET-h/week in women.[15] Similarly, the proportion of adults meeting the minimum leisure-time physical activity (i.e. 150 min of moderate or 75 min of vigorous exercise per week) increased over time (**Figure 1.9**), from 17.2% in 2000 to 22.8% in 2014.[71] In contrast, a national survey showed that the mean level of sedentary leisure time changed little between 2004 and 2011 (mean ~20 h/week).[74]

Table 1.2 Mean levels of physical activity (MET-h/week) by domain in China, 1991-2006*

	Occupational	Household	Leisure-time	Commuting	Total
Men					
1991	370.6	19.1	–	–	**–**
1997	334.4	11.7	1.4	2.6	**350.0**
2006	241.5	5.6	3.6	1.9	**252.7**
Women					
1991	399.7	61.3	–	–	**–**
1997	340.1	46.8	0.6	2.5	**390.0**
2006	217.1	25.3	2.3	1.3	**246.1**

* Estimates were obtained from the China Health and Nutrition Survey.[15] Data were not available for leisure-time and commuting physical activity in 1991. All estimates were standardised to the age distribution of the China Census population in 2000.

Figure 1.9 Percentage of participants meeting the recommendations for leisure-time physical activity in China, 2000-2014*



* Meeting the recommendations for leisure-time was defined as 150 min of moderate-intensity exercise or 75 min of vigorous-intensity exercise per week to achieve a total energy expenditure of at least 500-1000 MET-min per week.
All estimates were standardised to the age distribution of the China census data from 2000 (for the 2000 survey), 2005 (for the 2005 survey), and 2010 (for the 2010 and 2014 surveys).

1.2.1.3 China: urban vs rural

In China, urban residents have higher levels of leisure-time physical activity, whereas rural residents engage in higher levels of occupational physical activity. Data from the International Collaborative Study of Cardiovascular Disease in Asia showed that 75.8% and 16.5% of residents participated in work-related activity (i.e. ≥30 minutes of moderate or vigorous activity daily) in rural and urban China, respectively.[77] In contrast, the proportion of adults meeting the minimum leisure-time physical activity (i.e. 150 min of moderate or 75 min of vigorous exercise per week) was higher in urban than rural areas (25.4% vs 17.3%) (**Figure 1.9**).[71] Although there were no data on sedentary leisure time comparing urban and rural areas, a national survey showed that the mean level of sedentary leisure time was higher in three megacities compared with nine provinces including urban and rural areas.[74] Between 1991 and 2011, the mean sedentary leisure time was 19 h/week

in men and 17 h/week in women in the nine provinces, and it was 27 h/week in men and 23 h/week in women in the three megacities.

1.2.2 Obesity

Obesity occurs when the body gains weight mainly in the form of fat storage as a result of either excess energy intake or low energy expenditure.[78] BMI is a marker for general adiposity most widely used in population-based studies and surveys to monitor trends of overweight (BMI ≥25 kg/m^2) and obesity (≥30 kg/m^2),[79] while central adiposity (or abdominal adiposity) is often assessed by waist circumference (WC).[78]

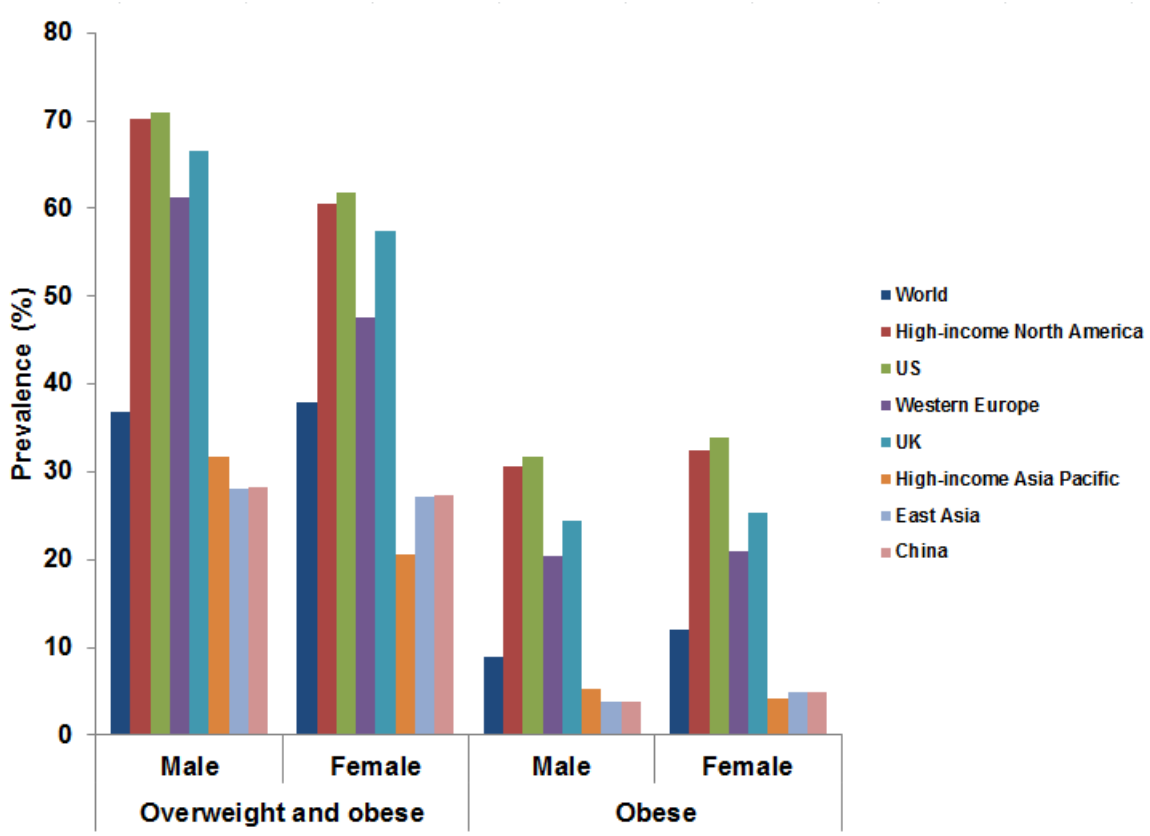
1.2.2.1 High-income countries vs China

In 2016, over 1.9 billion adults worldwide were overweight and more than 650 million were obese, with age-standardised prevalences of 39% for overweight (BMI ≥25 kg/m^2) and 13% for obesity (BMI ≥30 kg/m^2).[80] More than 50% of obese individuals were from 10 countries (ordered by the number of obese individuals): US, China, India, Russia, Brazil, Mexico, Egypt, Germany, Pakistan, and Indonesia.[79] China accounted for 15% of obese individuals worldwide.[79]

The global prevalence of obesity has more than doubled since 1980.[79] According to the Global Burden of Disease Study 2013, the number of overweight and obese individuals (BMI ≥25 kg/m^2) increased from 857 million in 1980 to 2.1 billion in 2013.[79] It is predicted that by 2030 an estimated 38% of the world's adult population will be overweight and another 20% will be obese.[81] Although the prevalence of obesity is increasing over time, the prevalence is relatively low in China. In 2013, 3.8% of men and 5.0% of women in China were obese (**Figure**

1.10).[79] In contrast, the prevalences of obesity in men and women were 31.7% and 33.9% in the US, 20.5% and 21.0% in Western Europe, and 24.5% and 25.4% in the UK (**Figure 1.10**).[79]

Figure 1.10 Age-standardised prevalence of overweight and obesity and obesity alone in men and women aged ≥20 years in 2013*



* Age-standardised prevalence rates were based on the average country-level population distribution by age from the World Population Prospects 2012 revision.
High-income North America included US and Canada. High-income West Pacific included Brunei, Japan, Singapore, and Korea.

1.2.2.2 China: past vs present

In China, there has been a substantial increase in the prevalences of overweight and obesity over the past two decades.[14] From 1991 to 2011, the mean BMI in China increased from 21.7 to 23.4 kg/m^2, while the prevalence of overweight (BMI ≥25 kg/m^2) increased from 11.7% to 29.2%.[14] By the WHO criteria for Chinese, the prevalence of obesity (BMI ≥27.5 kg/m^2) increased from 2.9% to 9.7% in men

and from 5.0% to 7.5% in women between 1993 and 2014.[82]

1.2.2.3 China: urban vs rural

In recent decades, mean BMI levels are higher in urban than rural areas (**Figures 1.11** and **1.12**).[82] While mean BMI levels are increasing in both urban and rural areas, there is a more rapid increase in rural than urban areas, particular between 1990 and 2005.[71] The mean BMI levels in urban and rural areas were 22.1 and 21.7 kg/m^2 in 1993 and 23.2 and 23.1 kg/m^2 in 2006. Similarly, there is a more rapid annual increase in prevalences of overweight and obesity in rural than urban areas.[71] The prevalences of obesity (BMI ≥27.5 kg/m^2) in urban and rural areas were 2.4% and 1.7% in 1989 and 13.7% and 14.5% in 2011.

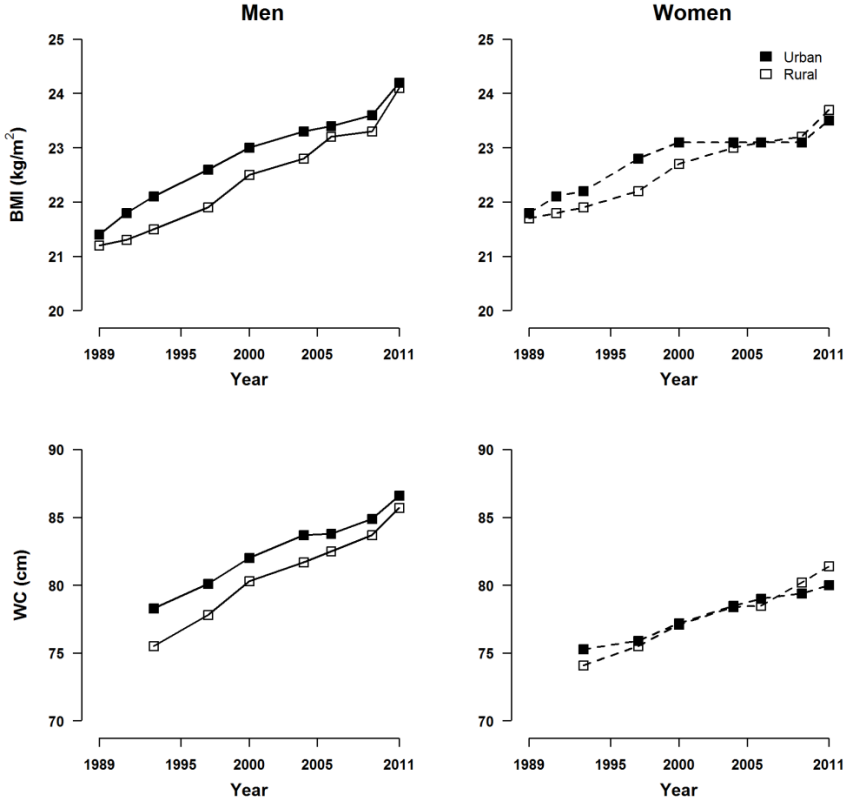
1.2.2.4 Central obesity

Similar to general obesity, the prevalence of central obesity assessed by WC is increasing over time and is higher in high-income countries than in China.[83-85] From 1999 to 2012, the mean WC in the US increased from 99.0 cm to 101.0 cm in men and from 92.2 cm to 96.0 cm in women; the prevalence of central obesity (≥102 cm for men ≥88 cm for women) increased from 46.4% to 54.2%.[85] Likewise, in the UK, the mean WC increased from 93.2 cm to 97.4 cm in men and from 81.7 cm to 88.4 cm in women from 1993 to 2015; the prevalence of central adiposity (≥102cm for men and ≥88cm for women) increased from 20% to 35% in men and from 26% to 47% in women.[86] In China, the mean WC increased from 76.3 cm to 86.0 cm in men and from 74.4 cm to 80.8 cm in women from 1993 to 2011 (**Figure 1.11**). Over the same period, the prevalence of central obesity increased from 16.2 % to 42.9%, according to the WHO criterion for Asians (≥90 cm for men ≥80

cm for women) (**Figure 1.12**).

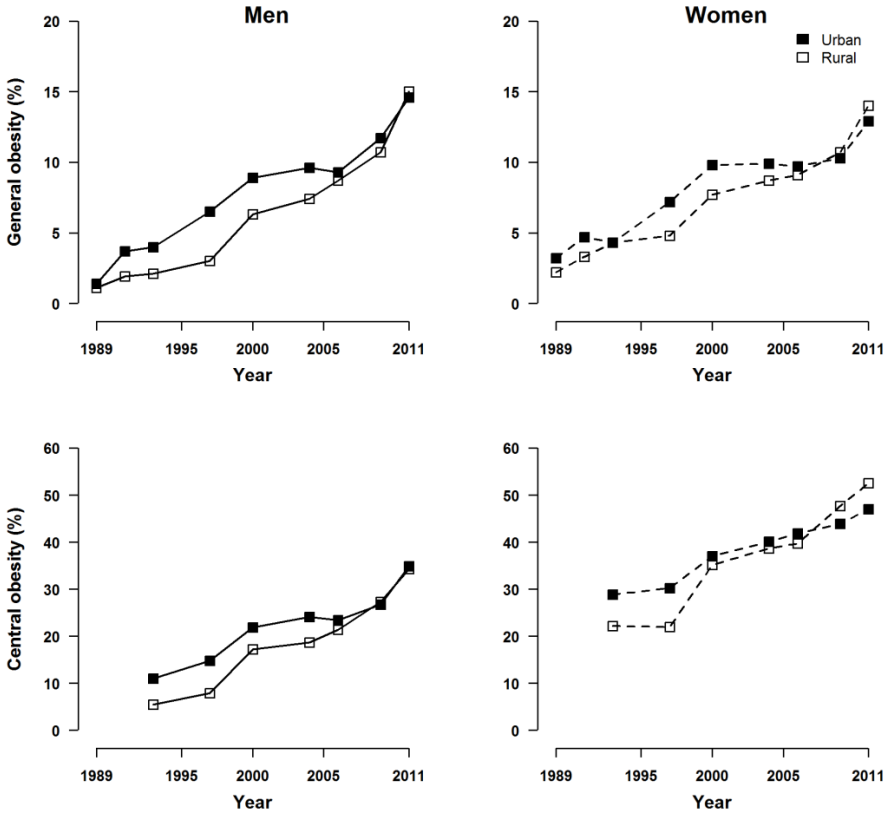
Similar to general obesity, the prevalence of central obesity is increasing in China, with a higher prevalence change per year seen in rural areas.[71] While the prevalence of central obesity (≥90 cm for men ≥85 cm for women) was lower in rural areas before 2005 (urban vs rural: 14.3% vs 13.0% in 2000, 18.3% vs 18.3% in 2005), the prevalence was higher in rural areas after 2005 (urban vs rural: 21.1% vs 24.2% in 2010, 23.9% and 27.0% in 2014). The estimated prevalence change per year was 0.67% in urban and 1.02% in rural areas.[71]

Figure 1.11 Age-standardised mean BMI and WC among Chinese adults, 1989-2011*



* Data were obtained from the China Health and Nutrition Survey.[14] Survey years were 1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, and 2011. WC was not available in 1989 and 1991.
All estimates were standardised to the age distribution of the China Census population in 2000.

Figure 1.12 Age-standardised prevalence of general obesity and central obesity among Chinese adults, 1989-2011*



* Data were obtained from the China Health and Nutrition Survey.[14] Survey years were 1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009, and 2011. WC was not available in 1989 and 1991.
General obesity was defined as BMI ≥27.5 kg/m^2. Central obesity was defined as WC ≥90 cm for men and ≥80 cm for women.
All estimates were standardised to the age distribution of the China Census population in 2000

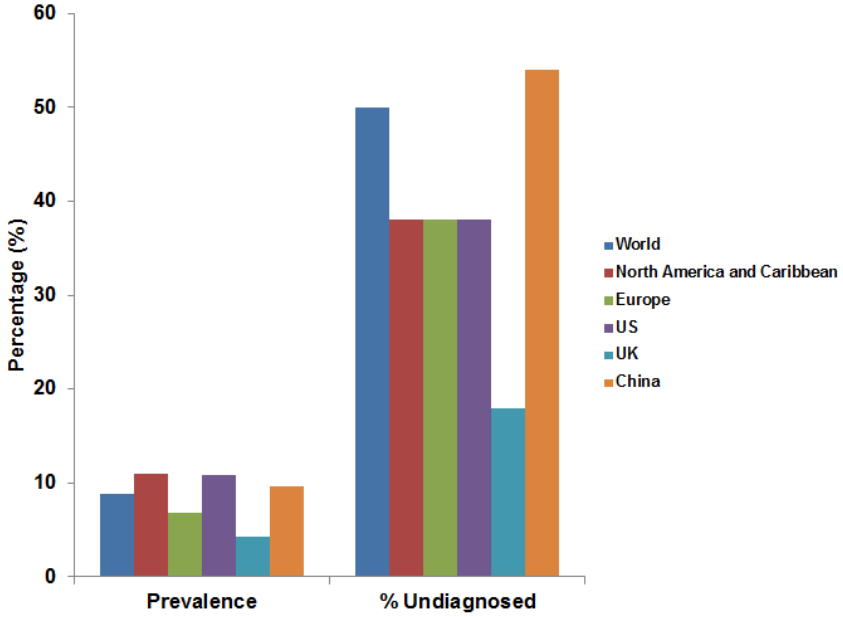
1.2.3 Diabetes

Diabetes is strongly related to obesity and physical inactivity and is considered as a metabolic disease.[87] According to the American Diabetes Association (ADA) 2014 and WHO 2006 criteria,[88-90] diabetes is defined as (1) fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), (2) 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L), (3) HbA1c ≥6.5%, or (4) in a patient with classic symptoms of hyperglycaemia or hyperglycaemia crisis, random plasma glucose ≥200 mg/dL (11.1 mmol/L).

1.2.3.1 High-income countries vs China

In parallel with the global pandemic of obesity, the prevalence of diabetes is increasing rapidly worldwide.[91,92] The global prevalence of diabetes is 8.8% in 2017, representing a total of 425 million people living with diabetes.[92] According to the International Diabetes Federation (IDF) estimation in 2017 (**Figure 1.13**), the prevalence of diabetes was higher in the US than China, while it is lower in Europe, particular in the UK.[92] Although the prevalence of diabetes was lower in China than the US, the percentage of undiagnosed diabetes was much higher in China. The prevalence of diabetes in Asian populations is increasing rapidly in recent decades with a disproportionate burden among young and middle-aged individuals.[93,94] The IDF has projected that the number of people with diabetes in the world will increase from 425 million in 2017 to 592 million by 2035, with 80% of cases occurring in low- and middle-income countries.[95]

Figure 1.13 International Diabetes Federation estimates for 2017 in adults aged 20-79*



* Estimates were obtained from the IDF Diabetes Atlas 8th Edition 2017.[92]
All rates were age-standardised using direct method and the World standard population.

1.2.3.2 China: past vs present

China is now among countries with the highest prevalence of diabetes in Asia and has the largest absolute disease burden in the world.[16,93,95] In 2014, about 114 million Chinese adults had diabetes and 60% were undiagnosed.[92] The prevalence of diabetes has increased significantly in recent decades and is now reaching epidemic proportions in China.[16,96,97] According to periodic national surveys, the prevalence of diabetes was less than 1% in 1980,[98] 2.5% in 1994,[99] 5.5% in 2001, 9.7% in 2007,[96] and 11.6% in 2010.[97] The most recent national survey in 2013 reported a prevalence of 10.9%, with diagnosed diabetes of 4.0% and prediabetes of 35.7%.[16] Although different sampling methods, screening procedures, and diagnostic criteria were used, these data documented a rapid increase in the prevalence of diabetes in the Chinese population.

1.2.3.3 China: urban vs rural

In China, there is large urban-rural variation in the prevalence and control of diabetes.[16,97] Although the prevalence of diabetes was higher in urban than rural areas, the prevalence of prediabetes was higher in rural areas.[16,97] **Appendix 1.4** shows the estimated prevalences of diabetes, prediabetes, and awareness, treatment, and control of diabetes among Chinese adults in 2010 and 2013. In 2013, the prevalences of previously diagnosed diabetes, undiagnosed diabetes, and prediabetes were 5.4%, 7.2%, and 34.3% in urban areas and were 2.8%, 6.7%, 37.0% in rural areas.[16] The proportions of patients who were aware of their diabetes (i.e. awareness) and treated for their diabetes (i.e. treatment) were also lower in rural areas, so was the proportion of patients who controlled their HbA1c levels (i.e. control). The awareness, treatment, and control rates were 43.1%,

38.4%, and 53.3% in urban areas and were 29.1%, 25.2%, and 42.3% in rural areas.[16]

1.2.3.4 Type 1 diabetes

Type 1 diabetes is an immune-mediated or idiopathic condition in which pancreatic β-cell destruction leads to absolute insulin deficiency.[89] A clinical diagnosis is often made based on age of onset (<30, mostly in children and adolescents) and the presence of diabetic ketoacidosis.[89] In immune-mediated diabetes, autoantibodies (e.g. to insulin, glutamic acid decarboxylase [GAD]) are present in 85-90% of patients.[89] In epidemiological studies, type 1 diabetes is often defined based on age of diagnosis (mostly <30) and current insulin use.[100-102] Previous national and international surveys have focussed on the prevalence of diabetes regardless of its subtypes. It has been estimated that 87-91% of adults with diabetes in high-income countries have type 2 diabetes, 7-12% have type 1 diabetes, and 1-3% have other subtypes (e.g. maturity-onset diabetes of the young [MODY], diseases of the exocrine pancreas, drug induced).[92] Among populations aged under 15 years, there is substantial variation in the incidence rates in different populations, with the lowest incidence in China (0.1 per 100,000) and highest in Finland, Sweden, and Norway (57.6, 43.1, 32.8 per 100,000).[103] The incidence rate is also high in the US and the UK (28.2 and 23.7 per 100,000).[103] According to the IDF estimates, the prevalent cases per year for type 1 diabetes among children aged under 15 years in 2013 were (in 1000) 85.6 in the US, 19.2 in the UK, and 7.7 in China.[103] The prevalence estimates indicated that there were almost 500,000 children aged under 15 years with type 1 diabetes worldwide, with the largest numbers in Europe (129,000) and North America

(108,700).[103]

1.3 Conclusions

Although age-standardised incidence rates of pancreatic and colorectal cancer are higher in high-income countries, there has been a rapid increase in China in recent decades, both in urban and rural areas, which is chiefly due to changes in lifestyle. While incidence of liver cancer is still high in China, there has been a decreasing trend. Except for viral-related liver cancer, age-standardised incidence rates of pancreatic, liver, and colorectal cancer are increasing in parallel with increasing prevalences of physical inactivity, obesity, and diabetes, suggesting a role of metabolic risk factors in the aetiology of these cancers. Understanding metabolic risk factors for these cancers in diverse populations with different lifestyle and disease patterns may provide valuable insights into cancer aetiology and inform cancer prevention.

Chapter 2 Literature review

This chapter provides a narrative review of published literature from previous prospective studies on metabolic risk factors and risks of three GI cancers (namely pancreatic, liver, and colorectal cancer), with due emphasis on relevant studies in China. The search strategies and a flow diagram are shown in **Appendix 2.1**. Where possible, it also compares not only the strengths but also the shape of the associations between different studies and between different populations. Moreover, it discusses possible mechanisms linking certain specific metabolic factors (e.g. adiposity, diabetes) with cancer and evidence gap.

2.1 Physical activity, sedentary behaviours and specific GI cancers

2.1.1 Physical activity

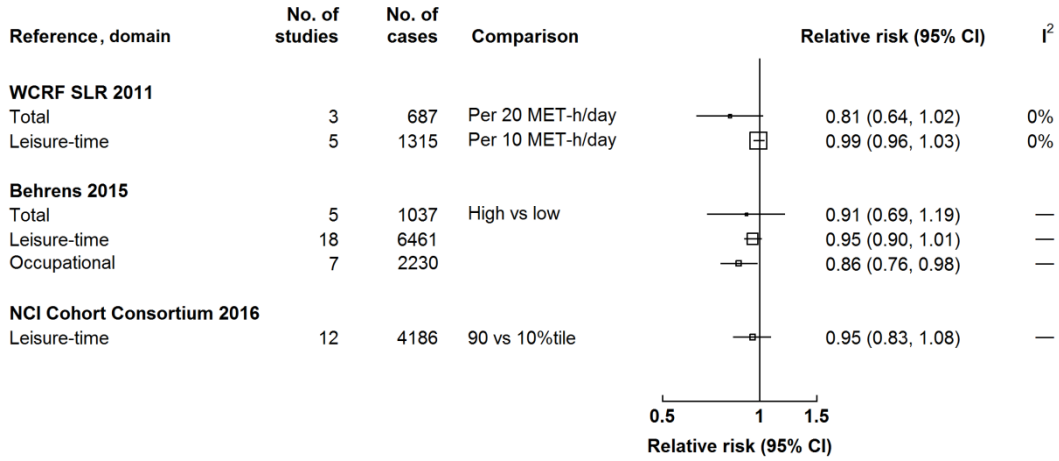
Physical activity is a complex, multidimensional behaviour that is associated with lower adiposity, blood pressure, inflammation, insulin resistance, and improved immune function.[104] Previous prospective studies have shown that higher physical activity is associated with lower risks of diseases including diabetes, CVD, and cancer.[104-106] However, the majority of previous prospective studies have focussed on leisure-time physical activity, with fewer studies examining other domains (i.e. occupational, household, commuting).[36,49,57] Moreover, the majority of previous studies were in high-income countries, where the patterns and levels of physical activity differed importantly from those in low- and middle-income countries including China.[70,107]

2.1.1.1 Pancreatic cancer

Overall prospective studies have shown no clear evidence of associations of total

and leisure-time physical activity with risk of pancreatic cancer, although there was a report of an inverse association for occupational physical activity (**Figure 2.1**).[36,108] The World Cancer Research Fund (WCRF) Systematic Literature Review (SLR) conducted in 2011 suggests that the evidence is limited whether physical activity is associated with risk of pancreatic cancer.[36] The SLR meta-analysis reported pooled RRs of 0.81 ([0.64-1.02], 3 studies and 687 cases) per 20 MET-h/day total physical activity and 0.99 ([0.96-1.03], 5 studies and 1315 cases) per 10 MET-h/day leisure-time physical activity. However, the estimates may be underpowered due to the small number of cases included.

Figure 2.1 Meta-analysis of prospective studies on physical activity and risk of pancreatic cancer



Abbreviations: NCI Cohort Consortium, National Health Institute's Cohort Consortium; WCRF SLR, World Cancer Research Fund Systematic Literature Review.
P for heterogeneity within each subgroup: all >0.05.

A recent meta-analysis involving four times as many cases as the 2011 SLR reported an inverse association of occupational physical activity but not total or leisure-time physical activity.[108] In that meta-analysis of 24 prospective cohort studies with 8538 cases, the pooled RRs comparing the highest and lowest categories were 0.91 (0.69-1.19) for total, 0.95 (0.90-1.01) for leisure-time, and 0.86 (0.76-0.98) for occupational physical activity. However, the associations did

not differ across domains (*p* for heterogeneity 0.2). No subgroup analyses were conducted for domain-specific physical activity. Consistent with this meta-analysis, a pooled analysis of 12 cohort studies in the US and Europe (the National Cancer Institute [NCI]'s Cohort Consortium) with 4186 cases reported a null association for leisure-time physical activity, with a HR of 0.95 (0.83-1.08) comparing 90th and 10th percentile (**Figure 2.1**). Similar associations were observed by sex, among never smokers, and with additional adjustment for BMI.[109] A recent cohort study in urban Chinese (the Shanghai Women's Health Study and the Shanghai Men's Health Study) reported no associations for total and occupational physical activity in both sexes and an inverse association for leisure-time PA in men but not women (HR >1.07 MET-h/day vs none: 0.59 [0.40-0.87] vs 1.06 [0.76-1.44]).[110] However, the study involved only 384 cases, and the difference by sex was nonsignificant (*p* for heterogeneity 0.07).

2.1.1.2 Liver cancer

Although prospective evidence has been limited on physical activity and liver cancer, previous prospective studies have suggested an inverse association for leisure-time physical activity in both Western countries and East Asia (**Figure 2.2**).[49] The NCI Cohort Consortium showed an inverse association of leisure-time physical activity with liver cancer risk (HR comparing 90th and 10th percentile 0.73 [0.55-0.98]; 12 studies, 1384 cases), with similar associations in men and women.[109] The inverse association was stronger among never smokers, while it attenuated towards the null and became nonsignificant when additionally adjusting for BMI. In East Asia, a prospective cohort study of 416,175 individuals and 924 cases in a standard medical screening programme in Taiwan showed an inverse

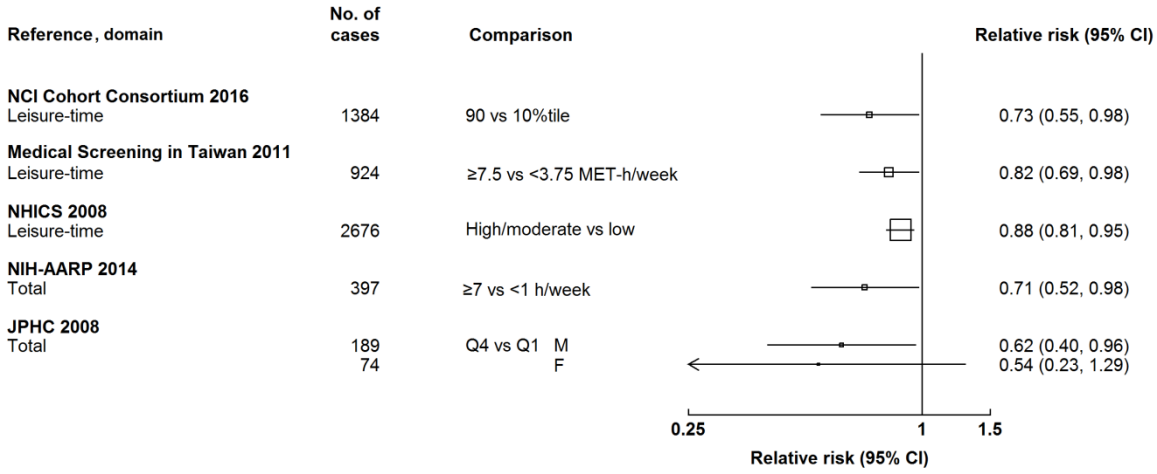
association, with a HR of 0.82 (0.69-0.98) comparing ≥7.5 vs <3.75 MET-h/week.[111] Similarly, the National Health Insurance Corporation Study (NHICS) in Korea involving 44,963 men and 2676 cases showed an inverse association, with a HR of 0.88 (0.81-0.95) comparing high/moderate and low categories.[112]

For total physical activity, the evidence has been limited, with previous studies reporting consistent results (**Figure 2.2**).[113,114]

2.1.1.3 Colorectal cancer

Prospective studies have shown that physical activity is associated with lower risk of colorectal cancer, and the inverse association is stronger for colon cancer and for occupational physical activity (**Figure 2.3**).[57] The WCRF has conducted two meta-analyses on physical activity and colorectal cancer. Although the 2015 SLR included a larger number of studies and cases, a dose-response meta-analysis was only done in the 2010 SLR. The WCRF SLR conducted in 2010, involving a total of eight studies, showed that total physical activity was associated with a 3% lower risk of colorectal cancer (RR 0.97 [0.94-0.99] per 5 MET h/week; 3 studies and 924 cases) and an 8% lower risk of colon cancer (0.92 [0.86-0.99]; 5 studies and 3153 cases).[57] For leisure-time activity, there were also inverse associations, with RRs per 5 MET h/week of 0.97 (0.94-1.00; 3 studies and 2220 cases) for colorectal and 0.98 (0.96-1.00; 5 studies and 2650 cases) for colon cancer. For rectal cancer, there were no associations of total and leisure-time physical activity (HR per 5 MET-h/week: total: 1.02 [0.95-1.10], 483 cases; leisure-time: 1.00 [0.97-1.03], 5 studies and 1275 cases).

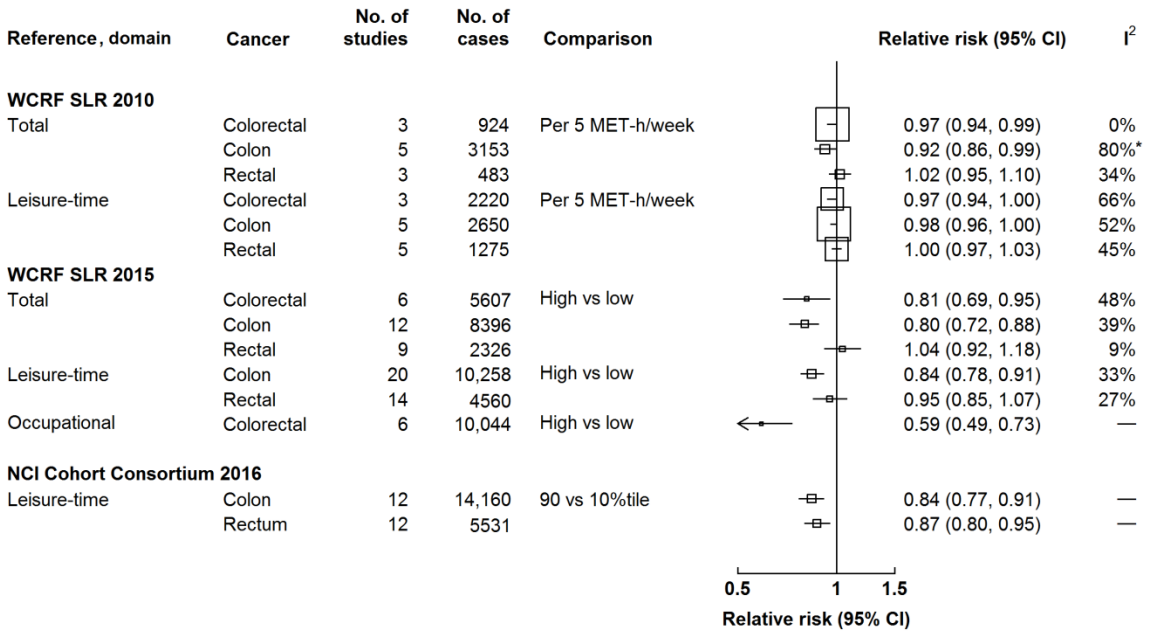
Figure 2.2 Prospective studies on physical activity and risk of liver cancer*



Abbreviations: NCI Cohort Consortium, National Cancer Institute's Cohort Consortium; NHICS, National Health Insurance Corporation Study; NIH-AARP Diet and Health Study, National Institutes of Health-American Association of Retired Persons Diet and Health Study; JPHC, Japan Public Health Centre-based Prospective Study.

* For leisure-time physical activity, the NIH-AARP was included in the NCI Cohort Consortium 2016 paper. The NIH-AARP 2014 paper reported total physical activity.

Figure 2.3 Meta-analysis of prospective studies on physical activity and risk of colorectal cancer



Abbreviations: NCI Cohort Consortium, National Health Institute's Cohort Consortium; WCRF SLR, World Cancer Research Fund Systematic Literature Review.

The WCRF SLR 2010 reported RRs from a dose-response meta-analysis, and the WCRF SLR 2015 reported RRs comparing high vs low categories. The size of boxes between the two SLRs is not directly comparable.

* *P* for heterogeneity within each subgroup <0.05.

Similar to the 2010 SLR, an updated meta-analysis in 2015 involving five times as many cases showed inverse associations of total and leisure-time physical activity with colon cancer and no associations with rectal cancer (**Figure 2.3**).[57] The 2015 SLR also reported an inverse association of occupational activity with colorectal cancer, with a RR of 0.59 ([0.49-0.73], 6 studies and 10,044 cases) comparing the highest and lowest categories. Although individual studies included in these meta-analyses showed similar associations in men and women, sex-specific analyses were not conducted. Consistent with the SLRs, the NCI Cohort Consortium reported an inverse association of leisure-time physical activity with colon cancer (HR comparing the 90th to 10th percentile: 0.84 [0.77-0.91]; 14,160 cases), whereas the study also showed an inverse association for rectal cancer (0.87 [0.80-0.95]; 5531 cases).[108] Similar associations were observed by sex, among never smokers, and with additional adjustment for BMI. Another meta-analysis assessed the associations of physical activity with colon cancer by anatomical site.[115] This meta-analysis involved 12 prospective cohort studies (7938 proximal and 6333 distal colon cancer cases) and reported inverse associations, with RRs comparing the most and least active individuals of 0.78 (0.72-0.86) for proximal and 0.78 (0.70-0.87) for distal colon cancer.

2.1.1.4 Conclusions

The associations of physical activity with specific GI cancers differ by cancer type. There was no clear evidence of associations of total and leisure-time physical activity with pancreatic cancer, while there is an inverse association for occupational physical activity. For liver cancer, there was suggestive evidence of inverse associations with leisure-time and total physical activity. For colorectal

cancer, there were inverse associations of total and domain-specific (including leisure-time and occupational) physical activity with colon cancer but no clear evidence of associations with rectal cancer. However, previous studies included small numbers of cases, particularly for pancreatic and liver cancer, and did not address properly residual confounding and reverse causality (e.g. related to smoking and pre-existing illness). More importantly, previous meta-analyses reported associations by comparing high and low categories without linking to MET-h/day.

2.1.2 Sedentary behaviours

Sedentary behaviours are activities that do not require energy expenditure above the resting level, which include activities of energy expenditure of 1.0-1.5 METs (1 MET is the energy cost of resting quietly) such as sitting, lying down, watching TV, and other screen-based entertainment.[116,117] Previous prospective studies have assessed sedentary behaviours by self-reported time spent on occupational or recreational (e.g. TV viewing or computer use) activities.[118-120] Sedentary behaviours are associated with adiposity and diabetes independently of physical activity and are associated with cancers of multiple sites including colorectal, breast, and endometrial cancer.[119,120] However, there is limited evidence whether sedentary behaviours are associated with risks of pancreatic and liver cancer.[119-121] Moreover, little is known whether the harmful effects of sedentary behaviours are independent of physical activity as sedentary behaviours displace time spent in physical activity.[121]

2.1.2.1 Pancreatic cancer and liver cancer

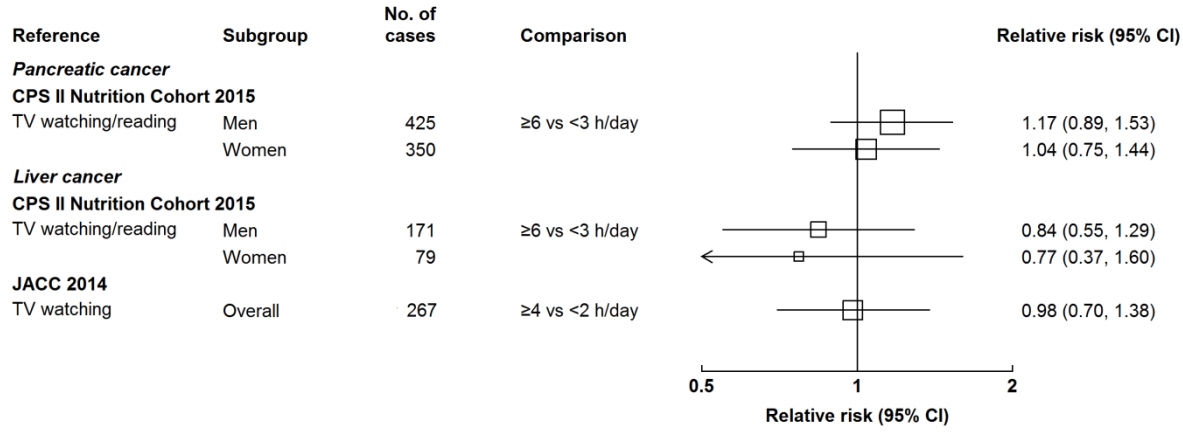
Prospective evidence is limited whether sedentary behaviours assessed by sitting

time are associated with risks of pancreatic and liver cancer. At least two prospective studies have examined the associations of recreational sitting time with risks of pancreatic and liver cancer (**Figure 2.4**). However, these studies involved small numbers of cases (<500) and reported no clear associations.[122,123] The Cancer Prevention Study II Nutrition Cohort in the US reported no associations of TV watching time with risks of pancreatic (HR comparing ≥6 vs <3 h/day: men 1.17 [0.89-1.53], 425 cases; women: 1.04 [0.75-1.44], 350 cases) and liver cancer (men: 0.84 [0.55-1.29], 171 cases; women: 0.77 [0.37-1.60], 79 cases).[123] Similarly, the Japan Collaborative Cohort Study (267 liver cancer deaths) showed a null association of TV watching time with risk of liver cancer, with a HR of 0.98 (0.70-1.38) comparing ≥4 vs 2 h/day.[122]

2.1.2.2 Colorectal cancer

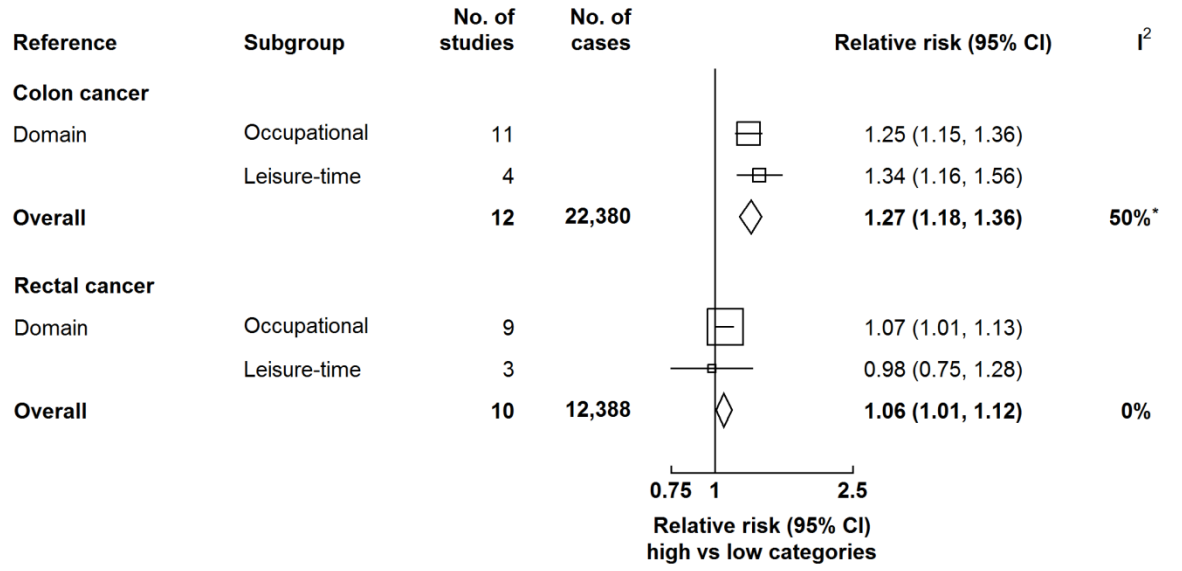
A recent meta-analysis suggested that sitting time, either occupational or recreational, was associated with higher risks of colon and rectal cancer (**Figure 2.5**).[119] In that meta-analysis, Cong et al. synthesised data from 12 cohort or case-control studies on colon and 11 studies on rectal cancer. Among prospective cohort studies, there were positive associations of sitting time (either occupational or recreational) with risks of colon and rectal cancer, with RRs of 1.27 ([1.18-1.36]; 22,380 cases) for colon cancer and 1.06 ([1.01-1.12]; 12,388 cases) for rectal cancer comparing the highest and lowest levels. Among case-control studies, the positive association was stronger for colon cancer (1.46 [1.27-1.68]), while a similar but nonsignificant association was observed for rectal cancer (1.06 [0.85-1.33]).

Figure 2.4 Prospective studies on sitting time and risks of pancreatic cancer and liver cancer



Abbreviations: JACC, Japan Collaborative Cohort Study; CPS II Nutrition Cohort, Cancer Prevention Study II Nutrition Cohort.

Figure 2.5 Meta-analysis of prospective studies on sitting time and risk of colorectal cancer



* *P* for heterogeneity within each subgroup <0.05.

However, findings from case-control studies should be cautiously interpreted as these studies might be affected by recall bias and reverse causality (i.e. individuals may have changed their behaviours close to or after cancer diagnosis), therefore the associations may be biased. Subgroup analyses were conducted combining prospective cohort studies and case-control studies (**Appendix 2.2**). For colon cancer, similar associations were observed by domain (occupational or recreational sitting time, **Figure 2.5**), sex, and with additional adjustment for physical activity, while the positive associations were weaker in North America and Europe and with additional adjustment for BMI. For rectal cancer, however, the associations were nonsignificant in most subgroups examined possibly due to the small numbers of cases involved.

After the publication of this meta-analysis, recent analyses of the UK Biobank involving 1108 colon and 820 rectal cancer cases examined the associations of recreational sitting time (TV watching or computer use) with risks of colon and rectal cancer.[124] Similar to the meta-analysis, positive associations of TV watching time were observed with colon and rectal cancer (HR ≥5 vs <1 h/day: colon 1.32 [1.04-1.68], rectal 1.13 [0.79-1.61], *p* for heterogeneity 0.48), which persisted when additionally adjusting for total physical activity. However, the study showed no associations of computer using time with risks of colon and rectal cancer (HR ≥4 h/day vs none: colon 0.86 [0.56-1.30], rectal 1.10 [0.68-1.79]).

2.1.2.3 Conclusions

Evidence from prospective studies is limited whether sitting time is associated with risks of specific GI cancers and whether the associations differ for occupational or recreational (e.g. TV viewing or computer use) sitting time. Previous studies have

shown positive associations of sitting time (occupational or recreational) with risks of colon and rectal cancer, while there is no clear evidence of associations of sitting time (mainly recreational) with pancreatic and liver cancer. However, previous studies involved small numbers of cases, did not control for physical activity, and did not assess the shape of associations.

2.2 Adiposity and specific GI cancers

Adiposity is associated with insulin resistance, diabetes, hormonal changes, and inflammation, which are associated with higher risk of cancer.[125,126] Individuals with adiposity are at higher risk of cancer, including pancreatic, liver, and colorectal cancer.[127] The majority of previous studies assessed body fatness by BMI, a proxy for general adiposity, while some studies also assessed central adiposity by waist circumference (WC) and/or waist-to-hip ratio (WHR).[36,49,57] This is because central adiposity may be more strongly associated with insulin resistance than BMI,[125,128] and therefore central adiposity may be more strongly associated with cancer risk. However, BMI may not be a good proxy for body fatness as it cannot distinguish between fat mass and lean mass.[129,130] In this context, fat mass (or percent body fat [%BF]) is the direct measurement of body fat stores, often assessed by bioelectrical impedance in population-based studies,[131-134] and may be a better marker for general adiposity. In addition, a number of studies examined young adulthood BMI, usually defined as BMI between ages 18-25.[135] Compared with adulthood BMI, young adulthood BMI is less affected by reverse causality (i.e. weight loss induced by preclinical cancer) and may also capture early life exposures in a similar way as adult attained height.[36,135]

The WCRF has concluded that both general (i.e. BMI) and central adiposity (i.e. WC and WHR) are associated with higher risks of pancreatic and colorectal cancer and that being overweight or obese as measured by BMI is associated with liver cancer.[36,49,57] Furthermore, the IARC Working Group has concluded that there is sufficient evidence that the absence of excess body fatness lowers risks of pancreatic, liver, and colorectal cancer.[136] Although positive associations between BMI and cancer risks have been reported in prospective studies in Western populations, the majority of studies in East Asia have shown weaker or null associations, particularly for pancreatic and liver cancer.[36,49,135] It is possible that individual studies in East Asia included small numbers of events (often less <500) and had limited power. As a result, these studies could not address properly residual confounding and reverse causality (e.g. by excluding smokers and early years of follow-up). It is also possible that the aetiology of cancer differs between Western countries and East Asia.[38] In terms of population attributable fraction, alcohol and HCV are the most important risk factors for liver cancer in North America and Europe, while HBV is the major risk factor in East Asia.[38,137] Moreover, the majority of previous studies have focussed on BMI, with limited evidence on central adiposity (e.g. WC, WHR) and other adiposity traits (e.g. %BF, fat mass, lean mass). It is not clear which adiposity trait is a better indicator of cancer risk and whether central adiposity is associated with cancer risk independently of BMI or vice versa. Although the mean BMI is much lower in Chinese than Western populations,[79] the Chinese population are more likely to develop central adiposity and have higher %BF at given BMI levels compared with their Western counterparts.[138] Assessing the strength and shape of associations between different adiposity measures and cancer in Chinese may address

whether the adiposity-cancer associations differ between Chinese and Western populations.

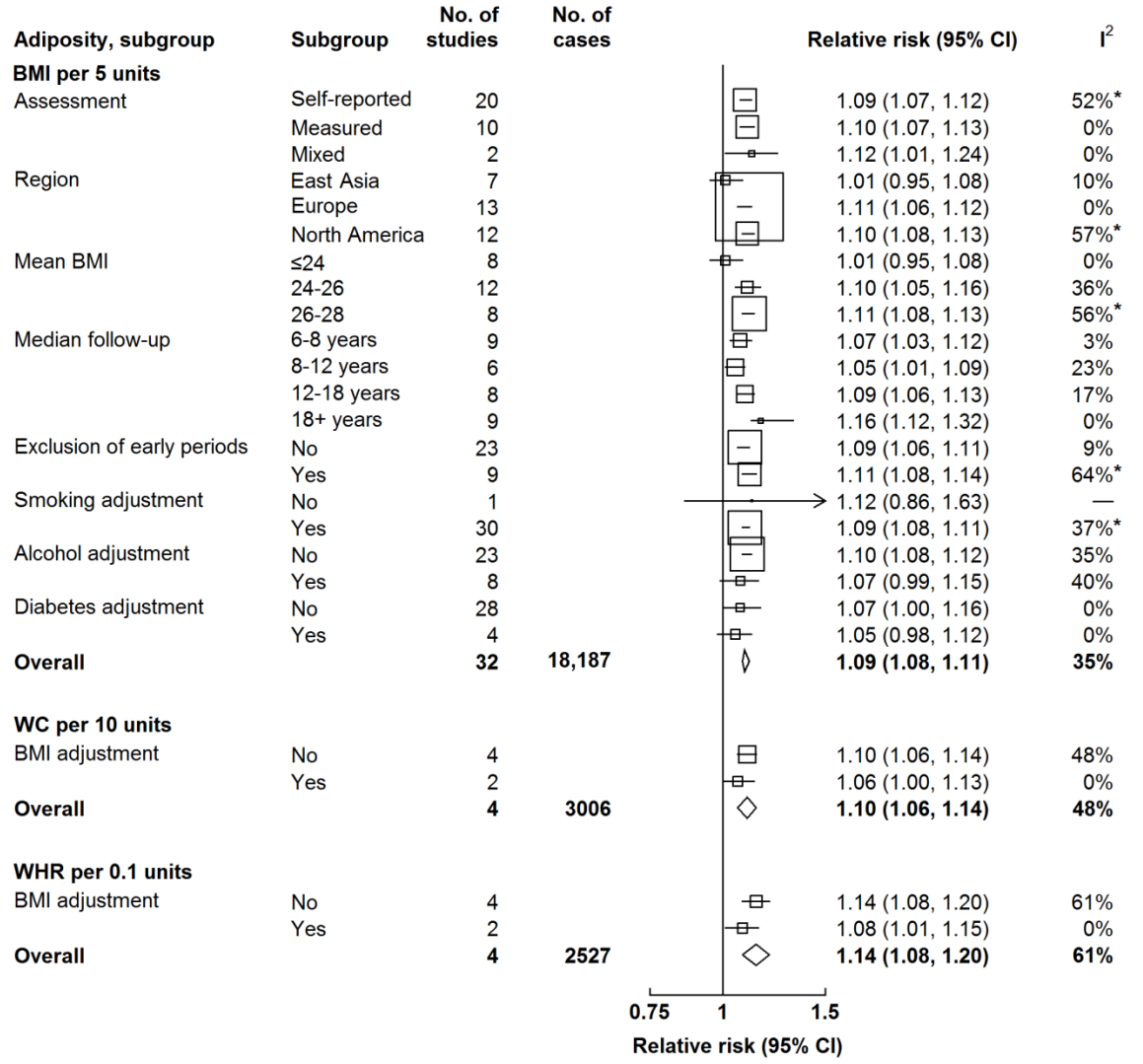
2.2.1 General and central adiposity

2.2.1.1 Pancreatic cancer

Both general (BMI) and central adiposity (WC and WHR) are associated with higher risk of pancreatic cancer, although most studies in East Asia have shown no association for BMI.[36,135] A recent meta-analysis of 32 prospective cohort studies involving 18,187 pancreatic cancer cases reported a positive association for BMI (**Figure 2.6**), with a RR of 1.09 (1.08-1.11) per 5 kg/m^2.[135] The association was weaker in East Asian studies than North American or European studies (RR per 5 kg/m^2: East Asia 1.01 [0.95-1.08], North America 1.10 [1.08-1.13], Europe 1.11 [1.06-1.12]), while the association did not differ by sex, method of BMI assessment, median of follow-up, exclusion of early periods, and adjustment for smoking, alcohol, and diabetes (**Figure 2.6**). The same meta-analysis reported RRs of 1.10 ([1.06-1.14], 4 studies and 3006 cases) per 10 cm higher WC and 1.14 ([1.08-1.20], 4 studies and 2527 cases) per 0.1 higher WHR (**Figure 2.6**). The associations of WC and WHR attenuated when further adjusting for BMI, with RRs of 1.06 (1.00-1.13) per 10 cm higher WC and 1.08 (1.01-1.15) per 0.1 higher WHR.

Similar to this meta-analysis, two pooled analyses have shown no evidence of an association of BMI with pancreatic cancer in East Asians (**Appendix 2.3**).[139,140] The Asia Pacific Cohort Studies Collaboration included 424,519 participants (74% from East Asia) and 324 pancreatic cancer deaths and reported a null association in the range of BMI ≥18.5 kg/m^2, with a HR of 1.02 (0.83-1.25) per 5 kg/m^2.[139]

Figure 2.6 Meta-analysis of prospective studies on adiposity and risk of pancreatic cancer



* *P* for heterogeneity within each subgroup <0.05.

Likewise, the Asian Cohort Collaboration including 16 cohort studies and 1458 cases reported a null association, with RRs of 0.95 (0.80-1.11), 1.01 (0.80-1.29), and 0.96 (0.67-1.37) for BMI of 25.0-27.4, 27.5-29.9, and ≥30 kg/m^2.[140] A recent cohort study in urban Chinese (the Shanghai Women's Health Study) with 195 cases showed no association for BMI (HR per 5 kg/m^2 0.92 [0.74-1.14]).[141] The reasons for the null association in East Asians are not well understood. It is possible that the majority of previous studies in East Asia assessed BMI by self-report, which might have underestimated the association due to measurement

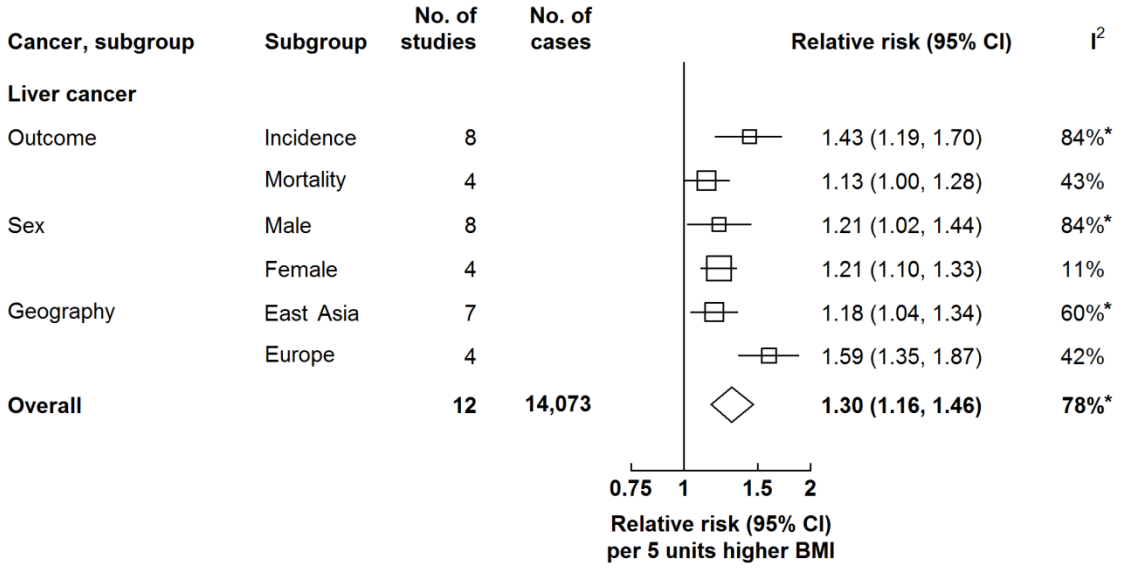
error. When stratifying East Asian studies by BMI assessment, the meta-analysis reported RRs of 1.08 (0.99-1.19) and 0.94 (0.87-1.03) in studies assessing BMI by measurement and by self-report.[135] It is also possible that previous studies in East Asia involved small number of events (often <400) and could not properly address residual confounding and reverse causality, particular related to smoking and pre-existing illness (i.e. individuals with preclinical cancer may lose weight).[135]

At least two prospective cohort studies have assessed the associations of BMI and central adiposity with pancreatic cancer risk by examining HRs comparing high and low categories,[142,143] while a cohort study directly compared the excess risk associated with 1-SD higher adiposity trait.[141] Two small prospective cohort studies (324 and 251 cases) showed that the positive associations of WC and WHR were stronger than that of BMI comparing high and low categories,[142,143] while the Shanghai Women's Health Study (198 cases) reported null associations per 1-SD higher BMI, WC, and WHR.[141] In addition, the pooled analysis of the NCI Cohort Consortium (1947 cases) examined whether WC and WHR were associated with pancreatic cancer with additional adjustment for BMI.[144] In the main model, there were positive associations for BMI, WC, and WHR (HR per 5 kg/m^2 BMI, 1.09 [1.05-1.12]; per 10 cm WC, 1.09 [1.04-1.13]; per 0.1 WHR, 1.11 [1.04-1.19]). When additionally adjusting for BMI, the positive associations for WC and WHR attenuated but remained significant (HR per 10 cm WC, 1.07 [1.00-1.14]; per 0.1 WHR, 1.09 [1.02-1.17]), suggesting that central adiposity may contribute to pancreatic cancer risk beyond BMI. However, no analysis was conducted for BMI with adjustment for WC or WHR.

2.2.1.2 Liver cancer

BMI is positively associated with risk of liver cancer, whereas there has been limited evidence on other measures of adiposity.[49] The WCRF SLR including 12 prospective studies and 14,073 liver cancer cases reported a RR of 1.30 (1.16-1.46) per 5 kg/m^2 higher BMI (**Figure 2.7**), with large between-study heterogeneity (I^2=78%).[49] The positive association was stronger for incidence than mortality (1.43 [1.19-1.70] vs 1.13 [1.00-1.28]) and in European studies than Asian studies (1.59 [1.35-1.87] vs 1.18 [1.04-1.34], *p* for heterogeneity 0.005), whereas no difference by sex was observed (men 1.21 [1.02-1.44], women 1.21 [1.10-1.33]; **Figure 2.7**). The weaker association in Asian studies might be explained by the different aetiology of liver cancer.[38] Several prospective studies have suggested a null association for BMI among HBsAg positive individuals and a positive association among HBsAg negative individuals.[49] However, the majority of East Asian studies did not control for HBV.

Figure 2.7 Meta-analysis of prospective studies on BMI and risk of liver cancer



* *P* for heterogeneity within each subgroup <0.05.

It is important to control for HBV as HBV is associated positively with liver cancer

and inversely with adiposity.[38,145] More importantly, individual studies in East Asia showed that the shape of associations differed from that in Western populations. For example, a cohort study in China with 884 liver cancer deaths reported an inverse trend for BMI in the range of 15-<23.5 kg/m^2 (HR per 5 kg/m^2 0.91 [0.71-1.17]) and a positive trend for BMI in the range of 23.5-<35 kg/m^2 (1.15 [0.74-1.79]).[146] Another cohort study in urban Chinese with 165 cases showed a positive trend for BMI in the range of 18.5-40 kg/m^2 (HR per 5 kg/m^2 1.20 [0.95-1.50]).[141]

For central adiposity, the evidence has been limited. The Liver Cancer Pooling Project in the US involved 14 cohort studies and 2162 cases and reported positive associations for both BMI and WC (**Appendix 2.3**).[147] The HRs per 5 cm higher WC were 1.08 (1.04-1.13) in all participants, 1.07 (1.01-1.13) in men, and 1.11 (1.04-1.18) in women; the corresponding RRs per 5 kg/m^2 higher BMI were 1.26 (1.21-1.32), 1.31 (1.23-1.39), and 1.20 (1.11-1.29).

At least three prospective cohort studies have examined the associations of BMI and central adiposity (WC or WHR) with liver cancer risk when adjusting for the other.[141,147,148] However, evidence has been inconsistent whether general or central adiposity is more strongly associated with liver cancer risk. The Liver Cancer Pooling Project (2162 cases) showed that BMI and WC were equally informative of liver cancer risk by showing similar associations in a model including both measures (HR per 1-SD: BMI 1.15 [1.02-1.29], WC 1.20 [1.05-1.36]).[147] In contrast, the European Prospective Investigation into Cancer and Nutrition (EPIC) study with 177 cases showed that central adiposity (WC, WHR, waist-to-height ratio [WHtR]) was associated with liver cancer beyond BMI, whereas BMI was not associated with liver cancer beyond central adiposity.[148]

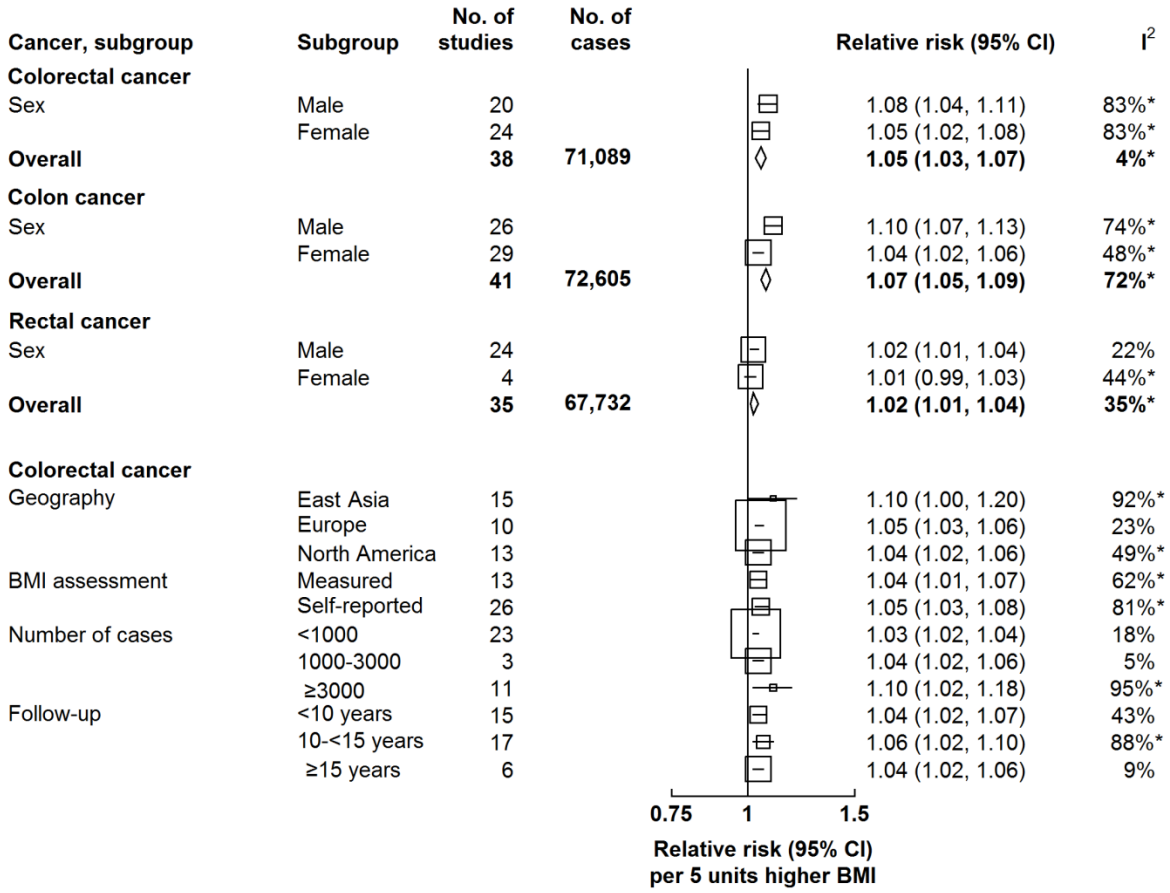
Similarly, the Shanghai Women's Health Study involving 165 liver cancer deaths suggested that WC and WHtR were associated with liver cancer when adjusting for BMI, but BMI was not associated when adjusting for WC or WHtR.[141]

2.2.1.3 Colorectal cancer

Both general and central adiposity are associated with higher risk of colorectal cancer, with stronger associations in men and for colon cancer.[57] The WCRF SLR including 38 prospective studies and 71,089 cases showed that the pooled RR per 5 kg/m^2 BMI was 1.05 (1.03-1.07) for colorectal cancer, with a stronger association for colon than rectal cancer (1.07 [1.05-1.09] vs 1.02 [1.01-1.04], *p* for heterogeneity <0.001; **Figure 2.8**). For colorectal cancer, the association was stronger in men than women (1.08 [1.04-1.11] vs 1.05 [1.02-1.08], *p* for heterogeneity 0.02). The positive association with colorectal cancer was weaker in European or North American studies than Asian studies (Asia 1.10 [1.00-1.20], Europe 1.05 [1.03-1.06], North America 1.04 [1.02-1.06]), but large between-study heterogeneity was observed in Asian studies (I^2=92%). The positive association with colorectal cancer did not differ by method of BMI assessment and duration of follow-up (**Figure 2.8**). For central adiposity, the SLR meta-analysis identified eight studies (4301 cases) for WC and four studies (2564 cases) for WHR and reported positive associations of both WC and WHR with colorectal cancer risk (**Figure 2.9**). The positive associations tended to be stronger for colon than rectal cancer but were similar by sex and by region. However, the sex- and region-specific analyses included small numbers of cases and may have limited power. The pooled RRs per 1 cm higher WC were 1.02 (1.01-1.03) for colorectal, 1.04 (1.02-1.06) for colon, and 1.02 (1.00-1.03) for rectal cancer (colon vs rectal: *p* for

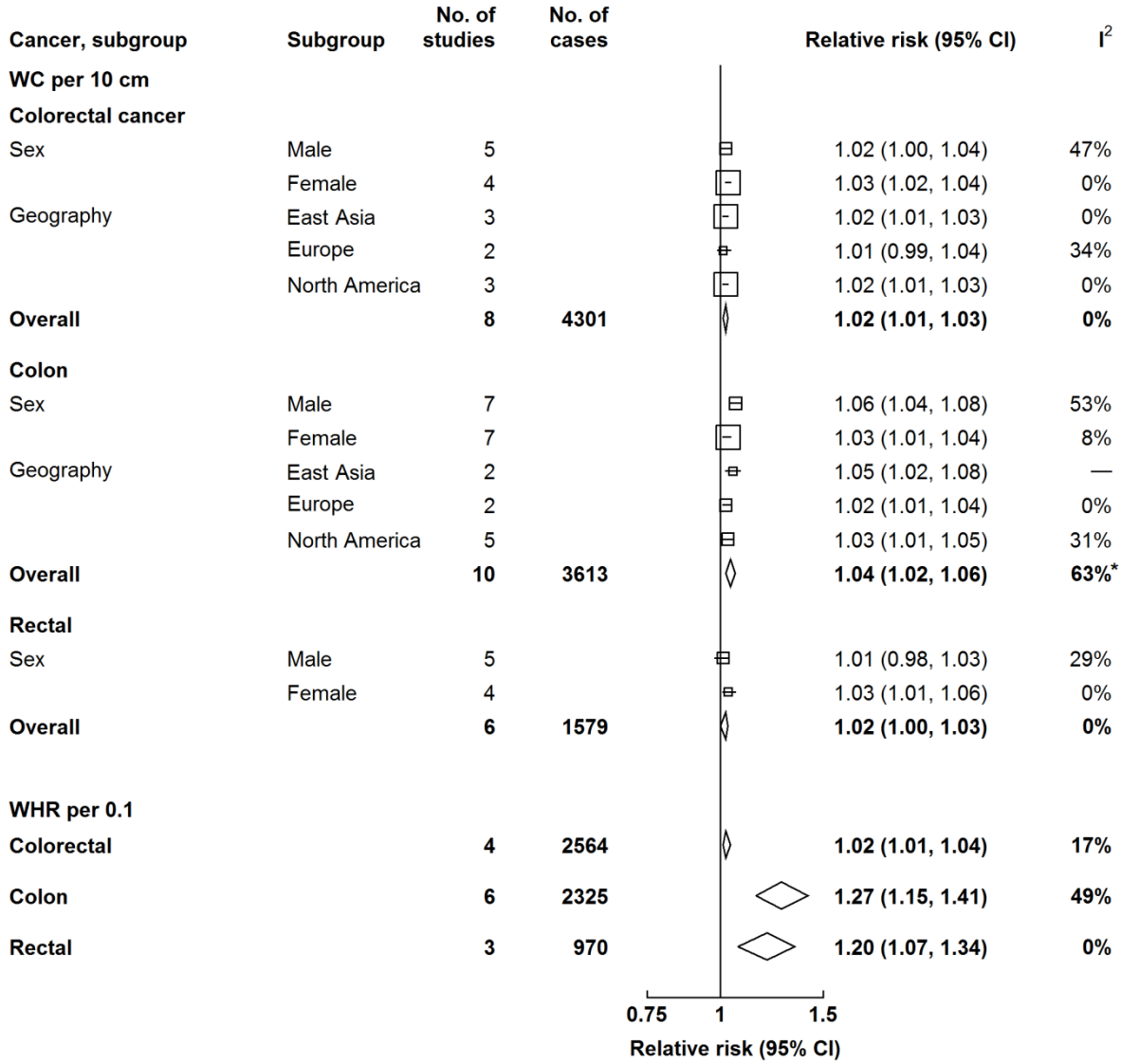
heterogeneity 0.12); the corresponding RRs per 0.1 higher WHR were 1.02 (1.01-1.04), 1.27 (1.15-1.41), and 1.20 (1.07-1.34) (colon vs rectal: *p* for heterogeneity 0.46).

Figure 2.8 Meta-analysis of prospective studies on BMI and risk of colorectal cancer



* *P* for heterogeneity within each subgroup <0.05.

Figure 2.9 Meta-analysis of prospective studies on WC and WHR and risk of colorectal cancer



* *P* for heterogeneity within each subgroup <0.05.

At least six prospective cohort studies have examined the associations of BMI and central adiposity (WC or WHR) when adjusting for or stratified by the other.[57] Three studies showed that WC or WHR was a better indicator of colorectal cancer by showing greater magnitudes of associations comparing top and bottom categories or HRs per 1-SD.[131,149,150] In the Shanghai Men's Health Study and the Shanghai Women's Health Study (935 cases), the positive association of BMI attenuated and became nonsignificant when stratified by WHR, while the positive association of WHR remained when stratified by BMI.[64] In contrast, two studies

showed that BMI was a better indicator than WC or WHR.[151,152]

2.2.1.4 Conclusions

BMI is positively associated with risks of pancreatic, liver, and colorectal cancer, with weaker or null associations for pancreatic and liver cancer in East Asians. For liver and colorectal cancer, between-study heterogeneity was large among East Asian studies (I^2 ≥60%). For central adiposity, WC and WHR are associated with risks of pancreatic and colorectal cancer, while there is a positive association of WC with liver cancer. However, East Asian studies involved small numbers of cases and did not address properly reverse causality and residual confounding particularly related to smoking and pre-existing illness (including HBV infection). It is also not clear whether the associations of adiposity and liver cancer differ by HBV infection. Moreover, the evidence has been inconclusive whether general or central adiposity is a better indicator of cancer risk.

2.2.2 Other measures of adiposity

Apart from BMI and central adiposity (WC and WHR), several prospective studies have examined other measures of adiposity, including %BF, fat mass, lean mass, and young adulthood BMI.[131-135,153,154]

2.2.2.1 Percent body fat

At least three prospective cohort studies have examined the associations of %BF assessed by bioelectrical impedance analysis with risk of colorectal cancer (**Appendix 2.4**).[131-134] Two of these studies suggested a positive association of %BF or fat mass with colon cancer in men,[132-134] while the other study including less than 200 cases reported a null association with colorectal cancer in

postmenopausal women.[131] For example, the Melbourne Collaborative Cohort Study involved 40,628 participants and 518 colon cancer cases.[132,133] In men, there were positive associations of fat mass and fat-free mass (HR per 10 kg: fat mass 1.33 [1.09-1.61], fat-free mass 1.59 [1.22-2.06]) with colon cancer risk; in women, there were positive trends for %BF, fat mass, and fat-free mass (%BF per 10% 1.14 [0.94-1.40], fat mass per 10 kg 1.09 [0.95-1.25], fat-free mass per 10 kg 1.07 [0.78-1.46]). Similarly, recent analyses of the UK Biobank involving 1731 colon cancer cases and 889 rectal cancer cases reported a positive association of %BF with colon cancer and a null association with rectal cancer in men and no associations with both colon and rectal cancer in women.[134] In men, the HRs per 5% higher %BF were 1.12 (1.05-1.19) for colon and 1.05 (0.97-1.14) for rectal cancer; in women, the corresponding HRs were 1.00 (0.94-1.06) and 0.96 (0.87-1.05).

2.2.2.2 Young adulthood BMI

Previous prospective cohort studies have shown that young adulthood BMI is associated with higher risk of pancreatic cancer (**Appendix 2.5**).[135] A recent meta-analysis involving five prospective studies and 4602 pancreatic cancer cases reported a RR of 1.18 (1.12-1.24) per 5 kg/m^2 higher BMI at age ~20,[135] while the WCRF SLT including four studies and 900 cases showed a nonsignificant positive association (1.12 [0.97-1.29] per 5 kg/m^2).[36] In addition, several prospective studies have suggested positive associations of young adulthood BMI with risks of liver and colorectal cancer. For liver cancer, a nested case-control study of 622 liver cancer patients and 660 matched controls showed that overweight (≥25 kg/m^2) and obese (≥30 kg/m^2) participants at mid-20s had a higher risk (HR: overweight 1.6 [1.1-2.3], obese 2.5 [1.3-4.8]),[153] whereas the Japan Collaborative

Cohort Study involving 254 cases showed a null association for BMI at age 20 (HR comparing ≥25 vs 21-22.9 kg/m^2: men 0.98 [0.60-1.62]; women 0.62 [0.29-1.34]).[155] For colorectal cancer, three small prospective cohort studies suggested a positive association of BMI at age ~20 in both sexes (HR per 5 kg/m^2 higher BMI ~1.30),[156-158] whereas the Nurses' Health Study and Health Professionals Follow-up Study (2100 cases) showed a positive association in women but not men (HR comparing ≥27.5 vs 15-19 kg/m^2: women 1.60 [1.07-2.39], men 1.08 [0.69-1.72]).[154]

2.2.2.3 Conclusions

Previous prospective studies have suggested a positive association of %BF with risk of colon cancer in men but not women. Previous prospective studies have shown a positive association of young adulthood BMI with pancreatic cancer and suggested positive associations with liver and colorectal cancer. However, these studies involved small numbers of cases (half <500). Importantly, no previous studies have compared the associations of adiposity with cancer risk across a range of adiposity traits including BMI, central adiposity (e.g. WC and WHR), and young adulthood adiposity.

2.2.3 Mendelian randomisation studies

So far three Mendelian randomisation studies have assessed the causal associations between adiposity and risks of pancreatic and colorectal cancer.[159-161] These studies have suggested that the positive associations of BMI with pancreatic and colorectal cancer reported from observational studies are causal. Mendelian randomisation is a method for obtaining the causal effects of a putative causal variable on disease in observational studies.[162] It utilises the random

assortment of alleles from parents to offspring during gamete formation and uses gene variants associated with the risk factors of interest as unconfounded markers for those factors.[162] Mendelian randomisation studies rely on important assumptions that the selected genetic variants are associated with the exposure of interest, they are not associated with any confounders, and they are not associated with the outcome via any pathway other than through the exposure of interest.[162]

To examine the causal association between BMI and colorectal cancer, Thrift et al. conducted a Mendelian randomisation study including 10,226 colorectal cancer cases and 10,286 controls of European ancestry.[159] In women, a higher genetically influenced BMI was associated with a higher risk of colorectal cancer (OR per 5 kg/m^2 1.82 [1.26-2.61]), which was greater than the association obtained from the conventional analysis. In men, genetically influenced BMI was not associated with colorectal cancer (OR per 5 kg/m^2 1.18 [0.73-1.92]), although this estimate was not statistically different from the conventional estimate. Similarly, the Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium involving 51,537 cancer cases and 61,600 controls showed that genetically influenced BMI was associated with a higher risk of colorectal cancer (OR per 1-SD 1.39 [1.06-1.82]).[160] For pancreatic cancer, a recent Mendelian randomisation study involving 7110 cases and 7264 controls in the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4) suggested a causal association between BMI and pancreatic cancer (OR per 1-SD 1.34 [1.09-1.65]).[161]

In conclusion, both observational and Mendelian randomisation studies have

shown positive associations of BMI with risks of pancreatic and colorectal cancer, while prospective studies have shown a positive association of BMI with liver cancer. For central adiposity, prospective studies have shown positive associations of WC and WHR with risks of pancreatic and colorectal cancer and of WC with liver cancer. However, there is limited evidence whether general or central adiposity is a better indicator of risks of these cancers. Although evidence is limited for other measures of adiposity, prospective studies have shown positive associations of %BF with colon cancer and of young adulthood BMI with pancreatic cancer.

2.3 Diabetes, blood glucose and specific GI cancers

2.3.1 Diabetes

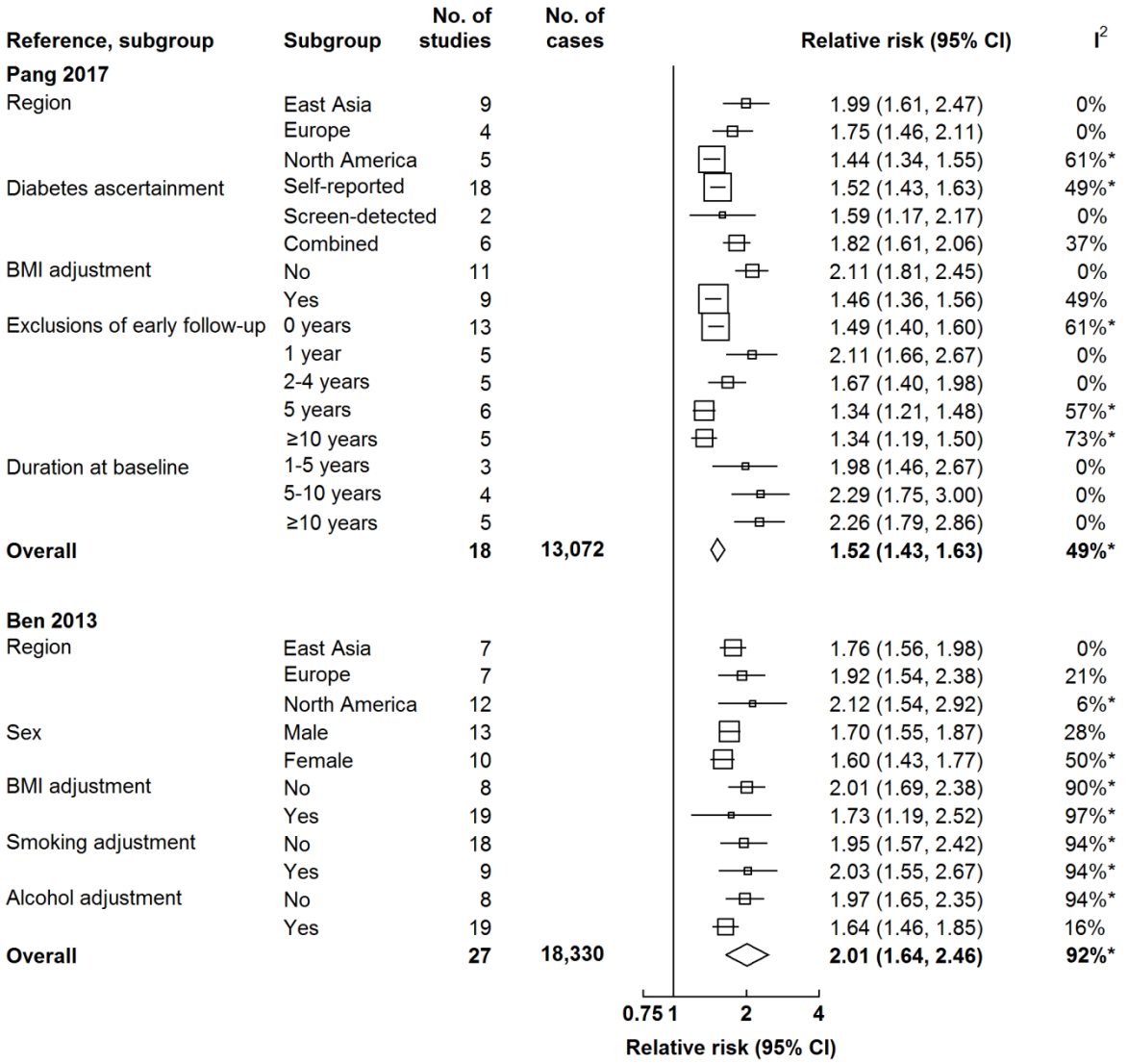
Adiposity and physical inactivity are associated with hyperglycaemia and diabetes, and insulin resistance and subsequent hyperinsulinaemia are the key mediators in this process.[104,125] Insulin is a hormone as well as a growth factor that has growth promoting and mitogenic effects on cancer cells.[125,163] A recent Mendelian randomisation study has suggested a causal association between plasma insulin and pancreatic cancer.[161] Previous prospective studies have shown that individuals with diabetes have higher risks of certain cancers, including pancreatic, liver, and colorectal cancer.[164] Below the range of diabetes, uncertainty remains as to whether blood glucose levels are associated with cancer risk, and, if so, whether the association shows a dose-response relationship. In recent decades, there has been a substantial increase in the incidence of diabetes in China, with a high proportion of undetected diabetes (~60%).[16] However, there is limited

prospective evidence available in China about the associations of diabetes and blood glucose with cancer risk.

2.3.1.1 Pancreatic cancer

Diabetes is associated with higher risk of pancreatic cancer.[165,166] A recent meta-analysis involving 18 prospective cohort studies and 13,072 cases reported that individuals with previously diagnosed diabetes had a 52% higher risk (RR 1.52 [1.43-1.63], **Figure 2.10**).[166] The associations did not differ by diabetes ascertainment (self-reported or screen-detected) and region, although a weaker association was observed in North American studies where large heterogeneity was observed (North America 1.44 [1.34-1.55], Europe 1.75 [1.46-2.11], Asia 1.99 [1.61-2.47]). The positive association attenuated when additionally adjusting for BMI (BMI adjustment: no 2.11 [1.81-2.45], yes 1.46 [1.36-1.56]), a possible mediator or confounder on the pathway between diabetes and pancreatic cancer. However, the results should be cautiously interpreted because not all studies had compared directly the RRs without and with BMI adjustment within the same study. The positive association also attenuated when excluding early years of follow-up, with RRs of 2.11 (1.66-2.67), 1.67 (1.40-1.98), 1.34 (1.21-1.48), and 1.34 (1.19-1.50) when excluding the first 1, 2-4, 5, and ≥10 years (*p* for trend <0.001). When examining the associations by diabetes duration (calculated as the time interval between age at diagnosis and study baseline), the RRs were 1.98 (1.46-2.67), 2.29 (1.75-3.00), and 2.26 (1.79-2.87) for 1-5, 5-10, and ≥10 years (*p* for trend 0.54). The positive association for diabetes persisted when excluding early years of follow-up and among patients with diabetes duration ≥10 years, suggesting that the positive association was not explained by reverse causality.

Figure 2.10 Meta-analysis of prospective studies on diabetes and risk of pancreatic cancer



* *P* for heterogeneity within each subgroup <0.05.

Similar to this meta-analysis, another meta-analysis conducted by Ben et al. involving 27 prospective cohort and record linkage studies and 18,330 cases showed that diabetes was associated with a two-fold higher risk (RR 2.01 [1.64-2.46], **Figure 2.10**).[165] Although a smaller number of prospective cohort studies were included, this meta-analysis showed subgroups by sex, smoking, and alcohol which were not reported in the most recent meta-analysis. The association did not differ by sex, geographic region, study design, and adjustment for smoking status, alcohol consumption, and BMI. In addition to these meta-analyses, three

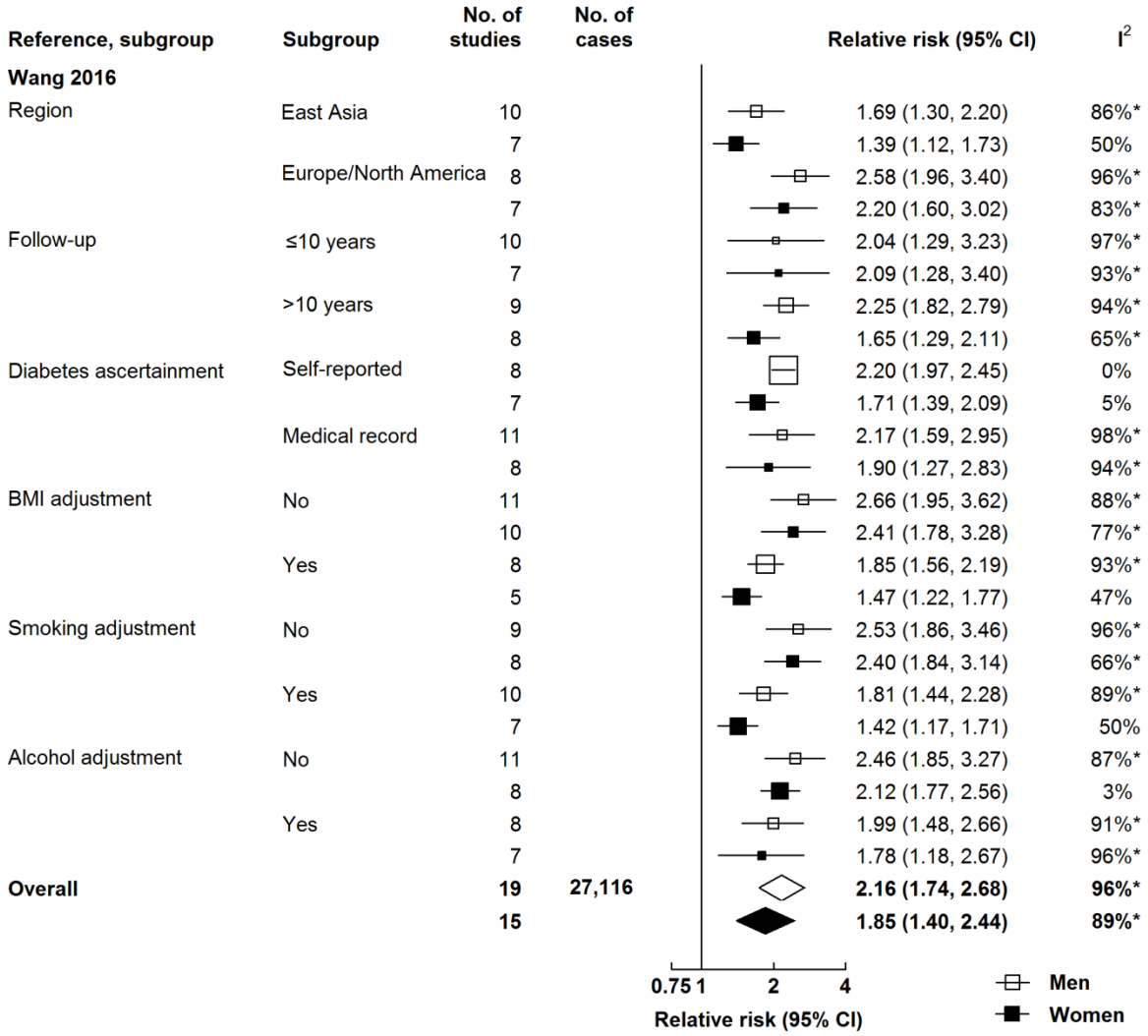
pooled-analyses of prospective cohort studies have examined the association of diabetes with pancreatic cancer mortality (**Appendix 2.6**), with similar associations to these meta-analyses[167-169]

2.3.1.2 Liver cancer

Diabetes is associated with higher risk of liver cancer.[170,171] A meta-analysis of 19 prospective cohort studies with 27,116 cases reported a positive association, with a stronger association in men than women (2.16 [1.74-2.68] vs 1.85 [1.40-2.44], **Figure 2.11**).[171] The associations were stronger in Non-Asians than Asians (Asians: 1.69 [1.30-2.20] in men, 1.39 [1.12-1.73] in women; Non-Asians: 2.58 [1.96-3.40] in men, 2.20 [1.60-3.02] in women). The associations did not differ by diabetes ascertainment (self-reported or medical record) and follow-up period, while the associations tended to be weaker when additionally adjusting for BMI, smoking, and alcohol. Similarly, another meta-analysis identified 18 cohort studies involving 17,466 cases and reported a two-fold higher risk (2.01 [1.61-2.51]).[170] Subgroup analyses showed that the association was similar by geographic region, adjustment for alcohol consumption, HBV, and HCV. However, only six out of 10 studies in East Asia controlled for HBV and it was not clear whether HBV confounded or modified the association between diabetes and liver cancer.[170] It is also not clear whether the association differed for previously diagnosed (medical record or self-reported) and screen-detected diabetes (e.g. by fasting plasma glucose [FPG], postload glucose). The association by diabetes duration was not conducted because different methods were used to assess duration across individual studies. Consistent with these meta-analyses, three pooled-analyses of prospective cohort studies have examined the association of diabetes with liver

cancer mortality (**Appendix 2.5**) and showed similar results.[167-169]

Figure 2.11 Meta-analysis of prospective studies on diabetes and risk of liver cancer



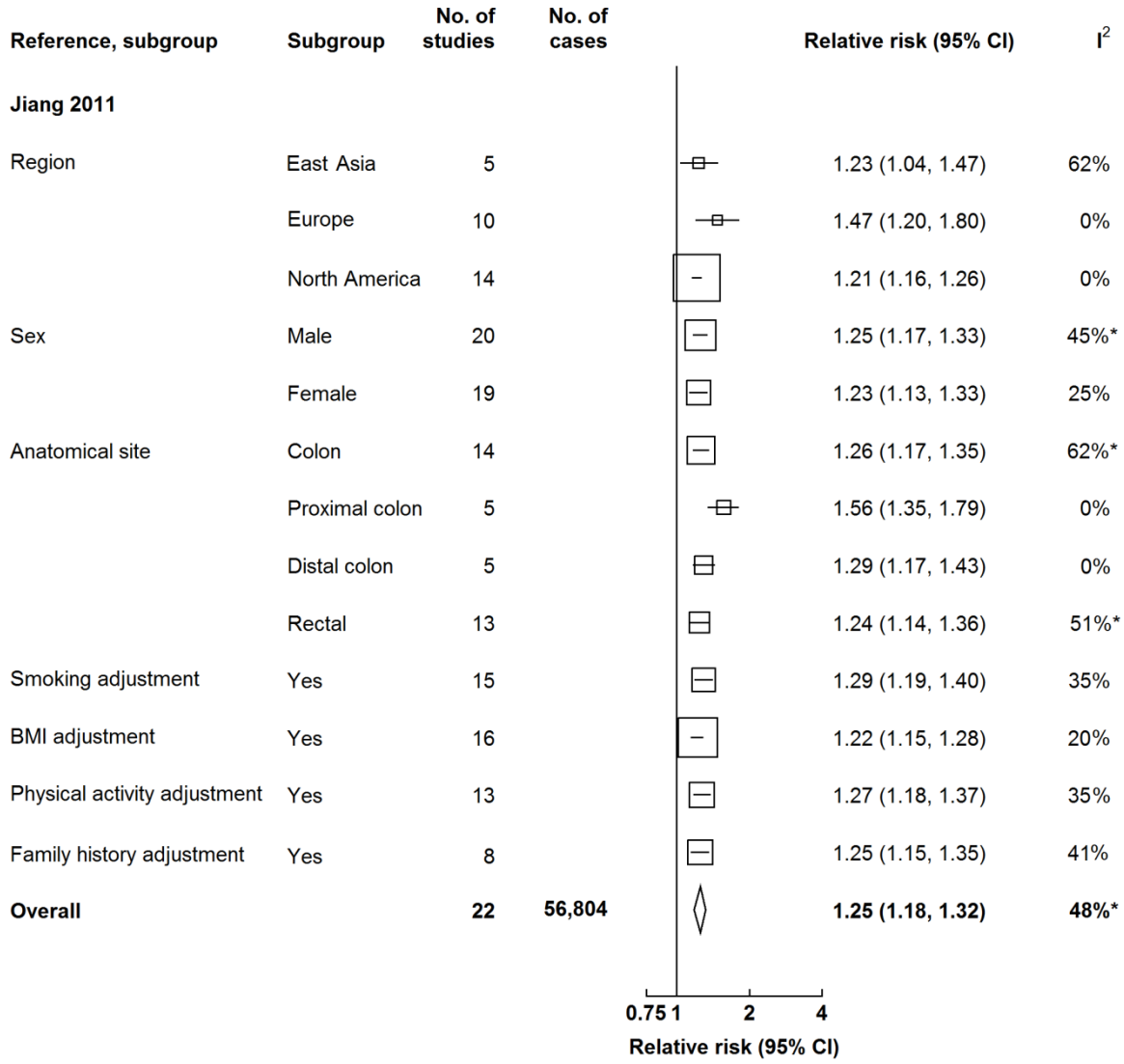
* *P* for heterogeneity within each subgroup <0.05.

2.3.1.3 Colorectal cancer

Diabetes is associated with higher risk of colorectal cancer.[172,173] A meta-analysis including 22 cohort studies and 56,804 cases showed that diabetes was associated with a 25% higher risk (1.25 [1.18-1.32], **Figure 2.12**).[173] The associations were similar by sex, geographic region, and adjustment for smoking, physical activity, BMI, and family history of colorectal cancer. Of note, the associations were similar in men (1.25 [1.17-1.33]) and women (1.23 [1.13-1.33])

and for colon (1.26 [1.17-1.35]) and rectal cancer (1.24 [1.14-1.36]). However, no subgroup analysis was conducted by diabetes ascertainment. For diabetes duration, the analysis was not possible as data were not uniformly reported. Furthermore, diabetes was associated with colorectal cancer mortality (1.25 [1.08-1.44]; ~2300 deaths). Similarly, another meta-analysis involving eight prospective cohort studies and 5229 cases reported a RR of 1.21 (1.02-1.42), with similar associations by sex (1.17 [1.00-1.37] in men, 1.22 [1.01-1.49] in women).[172] In addition, three pooled-analyses of prospective cohort studies have examined the association of diabetes with colorectal cancer mortality (**Appendix 2.6**), which tended to show stronger associations than these meta-analyses.[167-169]

Figure 2.12 Meta-analysis of prospective studies on diabetes and risk of colorectal cancer



* *P* for heterogeneity within each subgroup <0.05.

2.3.1.4 Duration of diabetes

To assess the associations of diabetes duration with cancer risk, previous studies excluded early periods of follow-up, examined cancer risk by diabetes duration since study enrolment, or used a time-dependent approach to account for diabetes duration.[166,170,173] However, given the range of approaches used, it was challenging to combine appropriately the data from different studies.

The majority of previous prospective studies have examined associations with cancer risk by excluding early periods of follow-up or by stratifying diabetes duration since study enrolment. However, the associations by diabetes duration have been inconsistent. In a meta-analysis of five prospective cohort studies, the associations for pancreatic cancer tended to decrease with exclusion of longer periods of follow-up, with RRs of 2.11 (1.66-2.67), 1.67 (1.40-1.98), 1.34 (1.21-1.48), and 1.34 (1.19-1.50) when excluding 1, 2-4, 5, and 10 years (*p* for trend <0.001).[166] In the same meta-analysis, similar RRs were observed by diabetes duration since baseline, with RRs of 1.98 (1.46-2.67), 2.29 (1.75-3.00), and 2.26 (1.79-2.86) for 1-5, 5-10, and >10 years (*p* for trend 0.54).[166] For liver cancer, a prospective cohort study in Taiwan including 231 liver cancer deaths reported similar associations when excluding the first 3.5, 6, or 7.6 years of follow-up (HR 3.38 [2.20-5.18], 2.82 [1.60-4.95], and 3.82 [1.75-5.34]).[174] When assessing the associations by diabetes duration since baseline, a cohort study in Singapore including 499 liver cancer cases reported that the HRs tended to decrease with longer duration, with HRs of 2.41 (1.73-3.35), 2.14 (1.38-3.33), and 1.84 (1.24-2.72) for <5, 5-10, and >10 years (*p* for trend 0.31).[175] For colorectal cancer, two prospective cohort studies examined diabetes duration since baseline and reported that diabetes was not associated with a higher risk 10-15 years after diabetes diagnosis.[176,177] The Netherlands Cohort Study (3056 cases) showed a null association of diabetes for duration >10 years since baseline.[176] In the Nurses' Health Study (892 cases), although an elevated risk was observed for duration 11-15 years, the association was nonsignificant for duration >15 years.[177]

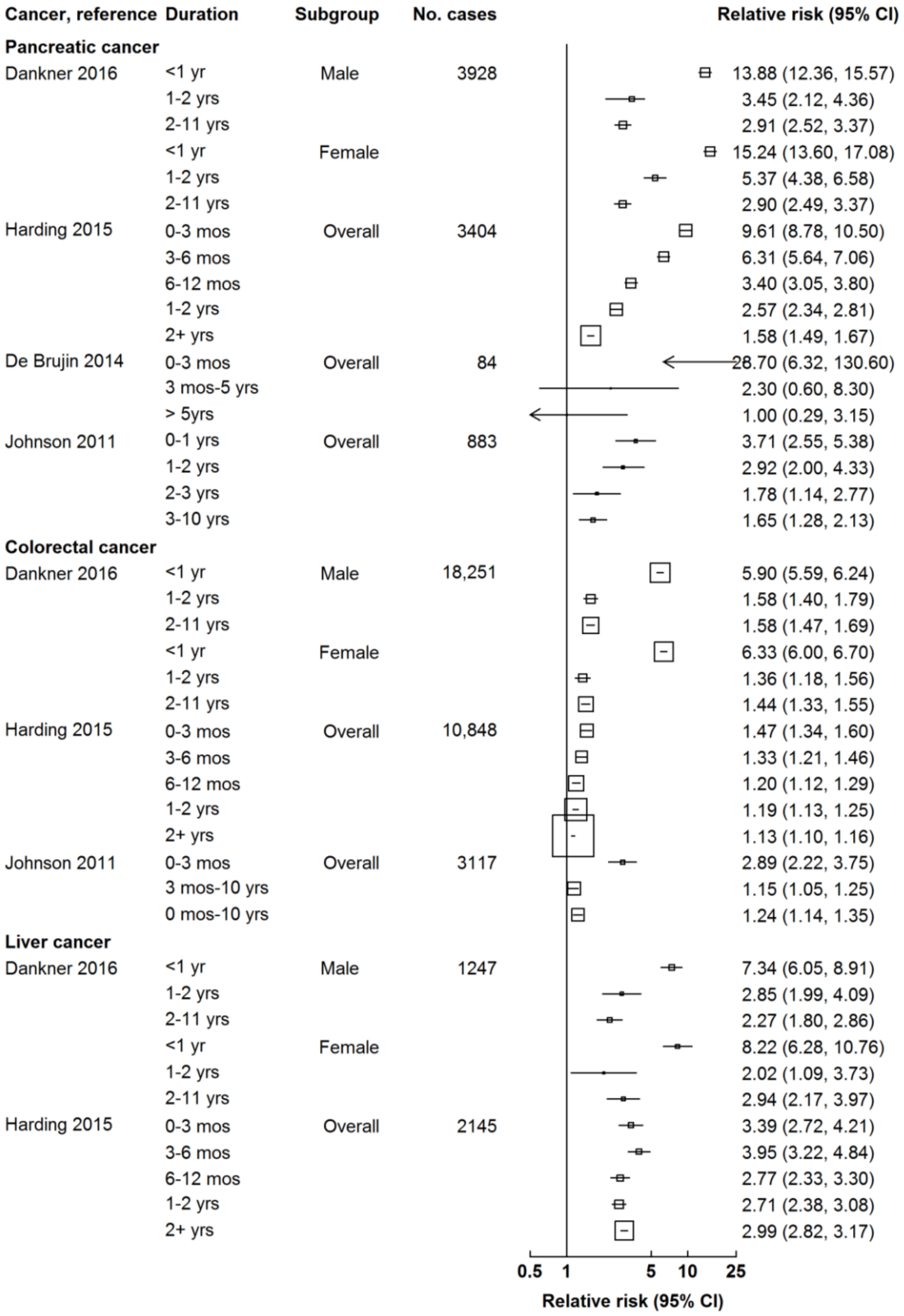
At least four prospective studies have conducted a time-dependent analysis in which diabetes duration was modelled as a time-varying exposure (i.e. time

interval between diabetes diagnosis and cancer diagnosis).[178-181] These studies have shown a three- to ten-fold higher risk of cancer within the first two years following diabetes diagnosis (**Figure 2.13**). These studies have also shown that the elevated risk decreased with longer duration of diabetes but remained elevated ~10 years after diabetes diagnosis (**Figure 2.13**). It is possible that the high risk of cancer among individuals with a shorter duration of diabetes may be due to reverse causality (i.e. diabetes induced by preclinical cancer), particularly for pancreatic and liver cancer.[166,170] It is also possible that the high risk may be due to detection bias, where cancer events are detected as a result of increased screening or medical check-ups at the time of diabetes diagnosis.[178,180,181] However, previous studies have shown similar associations of diabetes with incidence and mortality of cancer,[165,170,171,173] suggesting that the diabetes-cancer association is unlikely to be explained by detection bias.

2.3.1.5 Conclusions

Prospective cohort studies have shown positive associations of diabetes with risks of pancreatic, colorectal, and liver cancer. Consistent patterns were observed in both sexes and across different regions, though large between-study heterogeneity was observed. However, the relevance of diabetes duration and medications is less clear. Moreover, there is limited evidence whether the association between diabetes and cancer differs for previously diagnosed and screen-detected diabetes. This is particularly important in low- and middle-income countries including China, where a high proportion of diabetes cases (>60%) remain undetected.

Figure 2.13 Meta-analyses of diabetes duration and risks of pancreatic cancer, liver cancer, and colorectal cancer

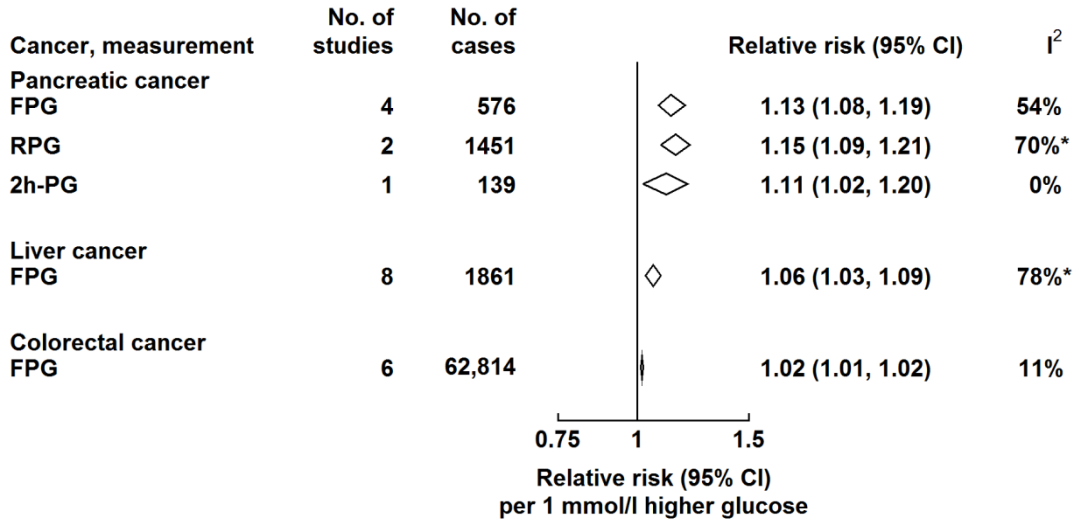


2.3.2 Blood glucose

2.3.2.1 Pancreatic cancer

Previous prospective studies have shown a positive association of blood glucose with risk of pancreatic cancer.[166] A meta-analysis including nine studies and 2408 cases showed a positive association for FPG (**Figure 2.14**).[182] The pooled RR per 1 mmol/L higher FPG was 1.08 (1.03-1.12) in all participants, while the RR was similar when excluding diabetes patients (1.08 [1.03-1.14]). In addition, a recent meta-analysis of nine prospective cohort studies involving 2166 cases reported similar associations by measurement of blood glucose, with RRs per 1 mmol/L increment of 1.13 (1.08-1.19) for FPG, 1.15 (1.09-1.21) for random plasma glucose (RPG), and 1.11 (1.02-1.20) for 2h-postload plasma glucose (**Figure 2.14**).[166] Large between-study heterogeneity was reported for both FPG and RPG (I^2 = 54% and 70%, respectively).

Figure 2.14 Meta-analysis of prospective studies on blood glucose and risks of pancreatic cancer, liver cancer, and colorectal cancer



Abbreviations: FPG, fasting plasma glucose; RPG, random plasma glucose; 2h-PG, 2-hour postload glucose.
* *P* for heterogeneity within each subgroup <0.05.

In both meta-analyses, no subgroup analyses were conducted by sex, region, and

with different adjustment. Consistent with these meta-analyses, the Metabolic Syndrome and Cancer (Me-Can) project involving 862 cases showed a positive association for RPG, which changed little when additionally adjusting for BMI (HR per 1-SD [0.5 mmol/L]: main model vs additional adjustment for BMI: 1.08 [1.00-1.17] in vs 1.09 [1.00-1.18] in men; 1.23 [1.14-1.34] vs 1.20 [1.10-1.32] in women).[183]

2.3.2.2 Liver cancer

Previous prospective studies have shown a positive association of blood glucose with risk of liver cancer.[184] A meta-analysis of eight studies and 1861 cases reported a positive association for FPG (RR per 1 mmol/L 1.06 [1.03-1.09], **Figure 2.14**),[184] with large between-study heterogeneity (I^2=78%). No subgroup analyses were conducted. Similarly, a recent prospective cohort study involving 109,169 men and 267 cases in China (not included in the meta-analysis) reported a positive association for FPG, with a HR of 1.06 (1.04-1.08) per 1 mmol/L.[185] This study showed stronger associations among nonsmokers, current drinkers, HBsAg negative individuals, and individuals with BMI <25 kg/m^2. In addition, the Me-Can project involving 266 cases showed a positive association of RPG which changed little when additional adjusting for BMI (HR per 1-SD [0.5 mmol/L]: 2.38 [1.76-3.14] in main model vs 2.13 [1.55-2.94] with additional adjustment for BMI).[186]

2.3.2.3 Colorectal cancer

Previous prospective studies have shown a positive association of blood glucose with risk of colorectal cancer.[187] A meta-analysis of six prospective cohort studies involving 62,814 cases reported a positive association for FPG, with a RR of 1.02 (1.01-1.02) per 1 mmol/L (**Figure 2.14**).[187] Similar associations were observed by

sex (men 1.02 [1.01-1.02], women 1.01 [0.99-1.03]), for colon and rectal cancer (colon 1.04 [1.01-1.07], rectal 1.03 [0.16-6.82]), and by region (North America 1.05 [1.01-1.08], Europe 1.01 [0.99-1.03], and Asia (1.02 [1.01-1.02]). In addition, the Me-Can Project involving 4695 cases showed that a positive association of RPG with colorectal cancer, which attenuated when additionally adjusting for BMI in men (HR per 1-SD [0.5 mmol/L]: main model vs additional adjustment for BMI: 1.11 [0.94-1.31] vs 0.98 [0.82-1.17] for colon cancer; 1.16 [0.95-1.43] vs 1.08 [0.87-1.34] for rectal cancer) but not in women (1.09 [0.91-1.32] vs 1.08 [0.89-1.32] for colon cancer; 1.24 [0.95, 1.62] vs 1.22 [0.92-1.62] for rectal cancer).[188]

In conclusion, evidence from prospective cohort studies has shown positive associations of blood glucose with risks of pancreatic, liver, and colorectal cancer. However, there is limited evidence whether the association differs by glucose measurement (RPG vs FPG) and whether the positive association continues down to below the range of diabetes, particularly for liver and colorectal cancer.

2.3.3 Mendelian randomisation studies

A recent mendelian randomisation study involving 7110 cases and 7264 controls in the Pancreatic Cancer Case-Control Consortium (PanC4) showed no evidence of a causal association between type 2 diabetes and pancreatic cancer. This suggests that the positive association in observational studies may be partly explained by reverse causality.[161] Nonetheless, this Mendelian randomisation study showed a causal association between plasma insulin and pancreatic cancer, consistent with observational studies showing a positive association for plasma insulin.[189,190]

In conclusion, prospective studies have shown positive associations of diabetes

and blood glucose with risks of pancreatic, liver, and colorectal cancer, although it is not clear whether these associations are causal.

2.4 Mechanisms

2.4.1 Physical activity, sedentary behaviours and cancer

Although high physical activity may prevent cancer by counteracting adiposity and diabetes, physical activity may lower cancer risk independently of adiposity and diabetes.[104,191] Several possible mechanisms have been hypothesised, including lowering inflammation and metabolic hormones and improving insulin sensitivity and immune function.[104,191] Similar to the mechanisms for physical activity, biological mechanisms linking sedentary behaviours and cancer risk include lowering adiposity, insulin resistance, inflammation, and metabolic hormones (more on this in Chapter 6 Section 6.2.6.2).

Physical activity may protect against cancer by lowering insulin resistance and levels of insulin and insulin-like growth factors (IGFs), independently of the effects of weight loss on insulin sensitivity.[49,57] Adipokine is another hormonal system that is linked to physical activity.[192] Physical activity is associated higher levels of adiponectin and lower levels of leptin.[192] Physical activity can also reduce chronic inflammation and oxidative stress.[104] Previous studies have reported that higher physical activity was associated with lower levels of inflammation, including fibrinogen and C-reactive protein (CRP).[193-198] Furthermore, physical activity may be related to liver cancer through its protective effect on nonalcoholic fatty liver disease (NAFLD).[104,199] NAFLD patients are at a higher risk of developing cirrhosis and liver cancer.[199] Physical activity can positively affect liver enzymes, inflammation, and oxidative stress markers in the liver, therefore lowering the risk

of developing NAFLD and progression to nonalcoholic steatohepatitis (NASH).[200-202]

2.4.2 Adiposity and cancer

There are several possible mechanisms linking adiposity and cancer. Adiposity is associated with insulin resistance and diabetes, which increase cancer risk (more on this in Section 2.4.3).[36,49,57] Independently of its effect on diabetes, adiposity can lead to hormonal changes related to body fatness and inflammation that are also associated with cancer risk.[36,49,57]

2.4.2.1 Insulin resistance

Insulin resistance is increased by adiposity, particularly by central adiposity, and subsequent hyperinsulinaemia could occur as the pancreas compensates by increasing insulin production.[203] Hyperinsulinaemia is associated with higher risks of pancreatic and colorectal cancer.[204] Higher circulating levels of insulin subsequently increase bioavailable insulin-like growth factor I (IGF-I) by altering some of its binding proteins (e.g. IGFBP3), which can promote the growth of cancer cells.[205] Although it is hypothesised that the primary role of insulin and IGF is through the Warburg effect and promotion of proliferation (more on this in Section 2.4.3), another attractive mechanism is that insulin and IGF may activate enzymes involved in anti-apoptosis.[206]

2.4.2.2 Circulating hormones

Adiposity can affect circulating levels of sex steroid hormones, including oestrogens, androgens, and progesterone.[207,208] Adipose tissue is the main site of oestrogen synthesis in men and postmenopausal women.[209] Higher levels of sex

hormones may be associated with risk of colorectal cancer (more on this in Chapter 7).[149,210]

2.4.2.3 Inflammation

Adipose tissue can stimulate the inflammatory response, which may promote cancer development.[211] First, the adipocyte produces proinflammatory factors, circulating tumour necrosis factor alpha (TNF-α),[212] interleukin (IL)-6, and CRP, and thus activates the proinflammatory signalling pathways (e.g. c-Jun NH2-terminal kinase [JNK] and IκB kinase-β [IKK-β]).[213] Prospective studies have suggested a positive association of CRP with colorectal cancer[214,215] and of inflammatory cytokines with pancreatic cancer (more on this in Chapter 9).[216] Second, obese people have increased secretion of leptin and decreased secretion of adiponectin.[213,217] Previous prospective studies have reported inverse associations of plasma adiponectin with risks of colorectal, pancreatic, endometrial, and postmenopausal breast cancer[213,217-222] and a positive association of plasma leptin with pancreatic cancer.[223] Third, recent evidence suggests that chronic inflammation associated with obesity is linked to immunosuppression and procancerous outcomes including increased DNA damage and synthesis, cellular proliferation, inhibition of apoptosis, and promotion of angiogenesis and invasion.[126]

2.4.2.4 Oxidative stress

Obesity is a chronic disease state that is associated with oxidative stress as a result of inflammation.[224,225] Oxidative stress can lead to the formation of free radicals and aldehydes, which can induce deleterious gene mutations.[224,225] Obesity may also lower activity of protective antioxidants and enhance systemic

oxidative stress, and such a phenomenon may be particularly relevant to obesity-related cancer.[217]

2.4.2.5 Emerging mechanisms

In addition to the above-mentioned mechanisms, there are several emerging mechanisms.[224,225] First, adipose tissue hypoxia plays a key role in the development of insulin resistance, regulation of systemic inflammation, and gene expressions of adipokines,[226] which may contribute to cancer risk. It has been reported that high levels of tumour hypoxia are associated with increased mortality, and that the key transcription factor hypoxia-inducible factor (HIF)-1α is associated with increased metastatic spread.[227] Second, mesenchymal stromal cells may be recruited to the tumour by hypoxia or inflammation.[228] These cells are present in the circulation at low levels and their sources include bone marrow and white adipose tissue. When recruited to the tumour site, they become tumour stromal cells and promote angiogenesis and tumour progression.[228] Third, obesity can alter the composition of the intestinal microbiome.[229] Recent *in vivo* evidence suggests that the intestinal microbiota may contribute to colorectal carcinogenesis by influencing their metabolites.[230] In addition, it is suggested that metabolites of the intestinal microbiota may "spill over" into the circulation of the host and contribute to the pathogenesis of cancers distant from the GI tract.[231]

2.4.2.6 Site-specific mechanisms

Obesity is associated with higher risk of NAFLD, which may progress to cirrhosis and liver cancer.[232] The low-grade systemic inflammation associated with obesity contributes to metabolic deregulation (peripheral and hepatic insulin resistance) and progression of NAFLD to NASH, cirrhosis, and finally liver cancer.[232]

2.4.3 Diabetes and cancer

Hyperglycaemia, hyperinsulinaemia, and insulin resistance have been hypothesised as the underlying mechanisms linking diabetes and cancer.[204]

2.4.3.1 Hyperglycaemia

Hyperglycaemia might increase cancer risk by providing more glucose to fuel tumour growth, thereby enhancing proliferation and invasion ability of cancer cells.[204,233] Previous prospective studies have shown similar associations of type 1 and type 2 diabetes with cancer risk,[102,180] suggesting a role of hyperglycaemia in the aetiology of cancer.

2.4.3.2 Insulin

Insulin has growth promoting and mitogenic effects on cancer cells, via insulin receptors.[204,234] Several prospective studies have shown positive associations of plasma insulin with risk of pancreatic cancer[190,235-237] and colorectal cancer.[238-240] Insulin also indirectly impacts pancreatic carcinogenesis by increasing bioavailability of IGF, a multifunctional peptide that regulates cell proliferation, differentiation, and apoptosis.[205,233] Elevated insulin concentrations have been shown to lower concentrations of IGF-binding proteins (IGFBPs, mostly IGFBP-3), which in turn contribute to an upregulated level of IGF-I.[205,206] Several prospective studies have shown positive associations of IGF-I and IGFBP-3 with risks of pancreatic and colorectal cancer.[206] Furthermore, insulin resistance leads to increased release of multiple proinflammatory cytokines, including TNF-α, IL-6, and leptin.[203] These proinflammatory cytokines may contribute to the development of inflammation and subsequent cancer (more on this in Chapter 9).

2.4.3.3 Specific mechanisms by cancer subtype

In addition to the above-mentioned mechanisms, diabetes is an important risk factor for NAFLD.[241] Insulin resistance and subsequent inflammatory cascade might contribute to progression of NAFLD to liver cirrhosis and liver cancer.[232] For colorectal cancer, slower bowel transit and constipation are common in diabetic patients, which could contribute to increased exposure to toxic substances and carcinogenic agents and elevated concentrations of faecal bile acids. Increased concentrations of faecal bile acids could lead to DNA damage and other damage to cells, increasing subsequent risk of colorectal cancer.[242]

2.5 Summary of findings and gaps in evidence

2.5.1 Domain-specific physical activity

Previous prospective studies have shown reasonably consistently inverse associations of total and domain-specific physical activity (i.e. leisure-time or occupational) with risks of colorectal, mainly colon, and liver cancer but not with pancreatic cancer. For sedentary behaviours (e.g. occupational or recreational-related sitting time), previous studies have suggested positive associations with risks colon and rectal cancer, with more limited evidence for pancreatic and liver cancer.

The majority of previous studies have involved Western populations and focussed mainly on leisure-time physical activity. Assessing the associations of domain-specific physical activity in China is important as the patterns and levels of physical activity differ from those in Western countries. Moreover, there is limited evidence whether sedentary behaviours are associated with risks of pancreatic

and liver cancer and whether the associations of sedentary behaviours with cancer risk are independent of physical activity.

2.5.2 General and central adiposity

Prospective studies have shown positive associations of BMI with risks of pancreatic, liver, colorectal and cancer, but the associations tended to be weaker in East Asians for pancreatic and liver cancer. In particular, East Asian studies had relatively large between-study heterogeneity which might reflect the small sample size and quality of study. For central adiposity (e.g. WC and WHR), the associations were generally similar to those for BMI, though data are more limited. Although evidence is limited for other measures of adiposity, prospective studies have suggested positive associations of %BF with colon cancer and of young adulthood BMI with pancreatic cancer.

The majority of previous studies have focussed on BMI, with limited evidence on central adiposity (WC, WHR) and other adiposity traits (e.g. %BF, fat mass, lean mass, WHtR). Although several previous studies in Western populations have suggested a stronger association for central adiposity (WC or WHR) than BMI, these have not been assessed systematically.

2.5.3 Diabetes and blood glucose

Prospective studies have shown positive associations of both diabetes and blood glucose with risks of pancreatic, liver, and colorectal cancer. The excess risks of these cancers were highest within two years after diabetes diagnosis, decreased with longer duration, but remain elevated 10 years after diabetes diagnosis.

The majority of previous studies have focussed on previously diagnosed diabetes,

with limited evidence on undetected diabetes, which is higher in China than Western populations. In addition, previous studies have not systematically assessed characterisations of aspects of diabetes including diabetes duration and medications, which are important to understand the mechanisms linking diabetes and cancer risk. For blood glucose, the majority of previous studies examined the association of blood glucose with cancer risk within the range of diabetes, prediabetes, and normoglycaemia without accounting for diabetes treatment, which may have diluted the association of blood glucose with cancer risk. Moreover, most studies have focused on FPG levels, with little data on RPG, which may be a more practical and relevant measure because people spend most time in a nonfasting state.

Chapter 3 Aims and objectives

The aims of the thesis are to characterise the incidence of pancreatic cancer, liver cancer, and colorectal cancer in Chinese adults, and to quantify the associations of metabolic risk factors including physical activity, sedentary leisure time, adiposity, diabetes, and plasma glucose, with the cancer types studied.

The specific objectives of the thesis are to:

1. Examine the incidence of pancreatic, liver, and colorectal cancer within the China Kadoorie Biobank (CKB) population, both overall and by age, sex, region, and socioeconomic status (SES);
2. Assess and quantify the associations of total and domain-specific physical activity and sedentary leisure time with risks of these three cancers;
3. Examine the associations of adiposity with risks of these three cancers;
    a. Examine the associations of each of several measures of general and central adiposity;
    b. Examine the associations of different measures of adiposity simultaneously adjusting for other measures of adiposity (i.e. adjusted associations);
    c. Examine the associations of adiposity-related measures (height, leg length, and sitting height)；
4. Assess and quantify the associations of diabetes and of plasma glucose with risks of these three cancers;
    a. Examine the associations of diabetes and duration of diabetes;
    b. Examine the associations of plasma glucose among participants without previously diagnosed diabetes.

Chapter 4 Methods

This chapter describes the study population, assessments of exposures and outcomes, and methods for statistical analyses.

4.1 China Kadoorie Biobank study population

4.1.1 Baseline survey

512,713 participants were recruited into the study from 10 geographically defined localities (5 urban and 5 rural) in China during 2004-2008.[243] The study areas were selected to provide diversity in risk exposure and disease patterns, while taking into account population stability, quality of mortality and morbidity registries, capacity, and long-term commitment within the areas. Potentially eligible participants in each of 100-150 administrative units (rural villages or urban residential committees) selected for the study within each region were identified through official residential records, and invitation letters (with study information leaflets) were delivered door-to-door by local community leaders or health workers, following extensive publicity campaigns. Approximately 1.8 million persons were originally selected for recruitment to get the sample of 0.5 million (estimated population response rate ~28%). Local, national, and international ethical approval was obtained prior to commencement of the study. All participants provided written informed consent.

At local study assessment clinics, participants completed an interviewer-administered laptop-based questionnaire on sociodemographic characteristics (age, sex, education, occupation, household income, and marital status), lifestyle behaviours (smoking, alcohol consumption, diet, and physical activity), personal

health and family medical history (hypertension, diabetes, chronic hepatitis or cirrhosis, gallstones or cholecystitis, peptic ulcer, and menopausal status [for women only]) and current medications (for CHD, stroke, hypertension, and diabetes). A range of physical measurements were recorded by trained technicians, including height, weight, hip and waist circumference, bioimpedance, lung function, blood pressure, and heart rate, using calibrated instruments with standard protocols. In addition, blood spot tests were used to measure random plasma glucose (RPG) and HBsAg (ACON Biotech, CA, US). The baseline questionnaire is shown in **Appendix 4.1**.

4.1.2 Resurvey

From July to October 2008 (~3 years after the baseline survey), a resurvey was undertaken in 10 study regions, involving 19,788 (~5%) of randomly chosen surviving participants. The participant list was generated using a cluster random sampling approach, and the clinic location (i.e. rural village or urban residential committee) in each of the study areas was used as the basic sampling unit. Apart from measurement for lung function and a few additional questions on recent hospitalisation, much of the data collection and survey procedures at the resurvey was identical to that in the baseline survey, including collection, processing, and shipment of blood samples.

4.2 Exposure assessment

4.2.1 Physical activity and sedentary leisure time

The questions on physical activity and sedentary leisure time were adapted from validated questionnaires used in several other studies, including the European

Prospective Investigation into Cancer and Nutrition (EPIC) and the Shanghai Women's Health Study,[244,245] with some additional modifications after a CKB pilot study. However, no separate validation of these questions in CKB was undertaken. At baseline and subsequent resurveys, participants were asked about their usual type and duration of physical activities related to occupation, commuting, housework, and leisure-time exercise during the past year. To quantify the amount of physical activity, metabolic equivalent of tasks (METs) from the 2011 update of a major compendium of physical activities were used.[246] The MET value for a particular type of physical activity represents the ratio of the energy expended per kilogram of body weight per hour during that activity to that expended when sitting quietly. The number of hours spent per day participating in each activity was multiplied by the MET value for that activity, and the daily amount of total physical activity was obtained by summing the MET-h/day for activities related to occupational and nonoccupational (i.e. commuting, housework, and nonsedentary leisure-time) activities. Hours spent per day on sedentary leisure time activities (such as TV watching, reading, and playing cards or mahjong) and sleeping were also recorded, but were not included in the physical activity calculation. **Appendix 4.2** shows types, MET values, codes, and intensity categories of physical activity.

4.2.2 Adiposity

All anthropometric measurements were taken by trained technicians while participants were wearing light clothes and no shoes, usually to the nearest 0.1 cm or 0.1 kg. Standing height and sitting height were measured using a stadiometer. Sitting height was measured as the length of the body from buttocks to the crown of the head. Weight was measured using a body composition

analyser (TANITA-TBF-300GS, Tanita Corporation, Tokyo, Japan), with subtraction of weight of clothing according to season (ranging from 0.5 kg in summer to 2.0-2.5 kg in winter). Waist circumference (WC) and hip circumference (HC) were measured using a soft nonstretchable tape. WC was measured at the midpoint between the lowest rib margin and the iliac crest. HC was measured around the maximum circumference of the buttocks. WC and HC were measured unclothed or 1-2 cm was subtracted from the WC reading to account for undergarments and 1 and 2.5 cm were subtracted from the HC reading to account for skirt and trousers, respectively. Body mass index (BMI) was calculated as the measured weight in kilograms divided by the square of the measured height in metres. BMI at 25 years (BMI25) was calculated using the recalled weight at age 25 years and the measured height at baseline. Waist-to-hip ratio (WHR) was the ratio of WC to HC. Percent body fat (%BF) was the fraction of total weight that was estimated to be fat weight by the Tanita body composition analyser using proprietary algorithms. Other derived measures of adiposity included fat mass (the product of %BF and body weight), lean mass (the subtraction of fat mass from body weight), waist-to-height ratio (WC divided by standing height), and leg length (the subtraction of sitting height from standing height).

General adiposity measures were BMI, %BF, height-adjusted weight, fat mass, and lean mass; central adiposity measures were WC, HC, WHR, and waist-to-height ratio (WHtR). Anthropometric measures including standing height, sitting height, and leg length were also analysed as adiposity-related measures.

4.2.3 Diabetes and plasma glucose

A 10-ml nonfasting (with the time since the participant last ate recorded) blood

sample was collected from participants into an ethylene diamine tetraacetic acid vacutainer (EDTA) vacutainer (BD Hemogard, NJ, US). Immediate on-site testing of RPG level was undertaken using the SureStep Plus System (Johnson & Johnson, California, US), regularly calibrated with manufacturer quality control solution. Participants with glucose levels ≥7.8 mmol/L and <11.1 mmol/L were invited to return for a fasting plasma glucose (FPG) test the next day. RPG data were unavailable for 8341 participants (because of a delay in making the on-site test available in certain regions).

Previously diagnosed diabetes was defined by the question “Has a doctor ever told you that you had diabetes?”. Among positive respondents, additional information about age at diagnosis and current use of certain medications for the treatment of diabetes (insulin and chlorpropamide or metformin) and CVDs (e.g. aspirin, lipid and blood pressure lowering agents) was collected. Among those without previously diagnosed diabetes, screen-detected diabetes was defined as (1) RPG ≥7.0 mmol/L if the time since last eating was ≥8 h, (2) RPG ≥11.1 mmol/L if the time since last eating was <8 h, or (3) FPG ≥7.0 mmol/L on subsequent testing.[247]

Of all 504,372 participants who provided blood samples, 108,200 participants fasted for at least 8 hours. Of 26,444 participants who did not fast and had an elevated RPG, 13,009 participants returned for an FPG. For screen-detected diabetes, 4413 cases were based on RPG among persons who fasted for ≥8 hours, 8122 cases on RPG among persons who fasted for <8 hours, and 1582 cases on FPG on repeat testing.

4.2.4 Other variables

Data collected on smoking included frequency, amount, and type of tobacco smoked, the ages at which participants started smoking regularly and stopped smoking, and the main reason for smoking cessation. Smoking status was classified as never, occasional, former regular, or current regular smoker. Never smokers were defined as those who reported not smoking at baseline and had smoked <100 cigarettes in lifetime. Former regular smokers (i.e. ex-regular) were defined as those who had smoked a total of at least 100 cigarettes or equivalent but had quit smoking for at least six months before baseline by choice. Occasional smokers were defined as those who did not meet the criteria for never smokers or former smoker, and who had not stopped smoking completely for at least the six months before baseline. Current regular smokers were defined as those who reported having ever smoked one or more cigarettes (or their equivalent) daily for at least six months. Among current regular smokers who had stopped six or more months before recruitment, approximately half did so because of ill health, and they were still counted as current regular smokers in the main analyses. Among current and former regular smokers, information was collected on the types and amount of tobacco smoked when last smoking. Exhaled carbon monoxide was measured to validate smoking status (CareFusion MicroCO meter, CareFusion, Chatham, UK).

Data collected on alcohol drinking included frequency, the ages at which participants began drinking, the type of alcohol (beer, wine or spirits), and the amount of each type consumed on a typical drinking week. Participants were classified into five drinking categories. Abstainers were defined as those who had never or almost never drunk alcohol in the past 12 months and had not drunk weekly in the past. Occasional drinkers were defined as those who in the past 12

months had drunk alcohol occasionally, during certain seasons, or monthly but less than weekly, and had not drunk weekly in the past. Reduced-intake drinkers were those who in the past 12 months had drunk alcohol occasionally, during certain seasons, or monthly but less than weekly, but had drunk weekly in the past. Ex-weekly drinkers were those who had drunk weekly in the past but had never or almost never drunk alcohol in the past 12 months. Weekly drinkers were those who usually drank at least once a week during the past 12 months.

Dietary data covered 12 major food groups: rice, wheat products, other staple food (e.g. corn or millet), red meat, poultry, fish/seafood, fresh eggs, dairy products, fresh vegetables, preserved vegetables, fresh fruit, and soybean products. Respondents were asked about the frequency of habitual consumption during the previous 12 months and chose among five categories of frequency (daily, 4-6 day/week, 1-3 day/week, monthly, or never or rarely).

All participants were asked whether their family members (father, mother, siblings, or children) had any major chronic diseases including stroke, heart attack, diabetes, mental disorder, or cancer. No information about cancer type was collected. A participant was defined as “family cancer history positive” if he or she reported that at least one parent or sibling had cancer. Self-rated health was assessed by the question “How is your current general health status: excellent, good, fair, or poor?”. History of chronic diseases was assessed by the question “Has a doctor ever told you that you had had the following disease?”. Chronic diseases covered CHD, stroke or transient ischaemic attack (TIA), hypertension, rheumatic heart disease, tuberculosis, emphysema/bronchitis, asthma,

cirrhosis/chronic hepatitis, peptic ulcer, gallstone/gallbladder disease, kidney disease, cancer (**Appendix 4.1**).

4.3 Outcome assessment

The vital status of each participant was determined periodically through China Centre for Disease Control and Prevention (CDC)'s Disease Surveillance Points (DSP) system, supplemented by regular checks against local residential records and health insurance records and by annual active confirmation through street committees or village administrators. For the few deaths (<5%) without any recent medical attention, probable causes of death were determined using standardised procedures based on symptoms or signs described by informants (usually family members).[248] Additional information about cancer incidence and any episodes of hospitalisation was collected through linkages, via each participant's unique national identification number, with disease registries (for cancer, CHD, stroke, and diabetes) and national health insurance claims databases, which have almost universal coverage in the study areas. 98% participants had been linked to the health insurance databases, with similar proportions of successful linkage for participants in urban and rural areas.

All events were coded using International Classification of Diseases, 10th Revision (ICD-10) by trained staff who were blinded to baseline information. Information on cancer histological subtypes was also collected for a subset of the cases through cancer registries or reviews of hospital medical notes as part of the ongoing outcome adjudication for major diseases. All diseases on the death certificates were coded using ICD-10 by trained DSP staff who then assigned underlying causes of death. For deceased participants, the information was

entered into the study follow-up system (including scanned images of the original death certificates) and reviewed centrally by trained clinicians, who were unaware of baseline information. Participants were lost to follow-up (1) whose permanent registered residence moved out of the study area, (2) who could not be contacted after at least three reasonable attempts within 1 year, or (3) who could be contacted but the new residence was out of the jurisdiction of the regional coordinating centre. By 1.1.2017, 42,921 (8%) participants had died, and 5276 (1%) were lost to follow-up. Among 510,136 participants without prior cancer at baseline, 26,594 participants had developed cancer (ICD-10: C00-97), including 796 pancreatic (C25), 2847 liver (C22), and 3024 colorectal cancer (C18-20) cases (**Table 4.1**).

Table 4.1 Numbers of cancer cases by ICD-10 code

ICD-10	Descriptions	No. of cases
C18	Malignant neoplasm of colon	1745
C19	Malignant neoplasm of rectosigmoid junction	152
C20	Malignant neoplasm of rectum	1716
C18-C20		3024
C22	Malignant neoplasm of liver and intrahepatic bile ducts	2847
C25	Malignant neoplasm of pancreas	796

4.4 Statistical methods

4.4.1 Study population

The present study excluded individuals with a prior history of cancer (n=2577) or missing data on BMI or %BF (n=244). After these exclusions, 509,892 individuals remained in the main analyses.

4.4.2 Baseline characteristics

Mean values and prevalence of baseline metabolic risk factors were calculated for

categories of age at baseline, sex, and regions, standardised by 5-year age groups, sex, and area structure of the CKB population, where appropriate. Mean values and prevalence of baseline characteristics were calculated for categories of each metabolic risk factor, standardised by 5-year age groups, sex, and area structure of the CKB population. Sex-specific correlations between different adiposity variables were calculated using Pearson partial correlation coefficients (r), adjusted for baseline age (8 categories) and area (10 categories).

4.4.3 Incidence and mortality of cancer

Cancer incidence and mortality rates were presented as per 100,000 persons. The incidence and mortality rates were standardised by age, sex, and region (10 areas), where appropriate. Cancer incidence included any fatal or nonfatal events, and cancer mortality included specific cancer as the underlying cause of death. To allow comparison with the national estimates derived from the Global Burden of Disease Study in 2010,[249] incidence and mortality rates in CKB were standardised by age, sex, and region (i.e. urban/rural) using the population composition of those aged 35 to 79 years from the 2010 Chinese census population. The mortality-to-incidence ratio (MIR) was also calculated to compare cancer disparities between urban and rural areas. MIR is the ratio of the mortality and incidence identified over the same period of time for a specific cancer. MIR can reflect screening, prevention, treatment, and survival of a specific cancer, and has been reported to associate inversely with human development index.[250-253]

4.4.4 Metabolic risk factors and cancer risk

4.4.4.1 Modelling of exposures

Metabolic risk factors including physical activity, sedentary leisure time, adiposity, diabetes, and plasma glucose were analysed as both continuous and categorical variables. For categorical analyses, BMI was modelled as a categorical variable with five categories (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2), and other measures of adiposity were grouped by splitting at sex-specific quintiles. **Appendix 4.3** shows the cut-off points for sex-specific quintiles of adiposity measures. For BMI, the association was also examined using the WHO classifications (<18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 kg/m^2).[80] For WC, the association was also examined using the International Diabetes Federation (IDF) categories for Chinese (≥90 cm in men and ≥80 cm in women).[254] For WHR, the association was also examined using the WHO cut-off points for substantially increased risk of metabolic complications (≥0.90 in men and ≥0.85 in women).[255] RPG was categorised into 4 groups <5.6 (reference), 5.6 to <6.8, 6.8 to <7.8, and ≥7.8 mmol/L as well as into 6 groups <4.3, 4.3 to <5.8, 5.8 to <7.0, 7.0 to <7.8, 7.8 to <11.1, and ≥11.1 mmol/L, selected to include the FPG thresholds for prediabetes and diabetes.[88] Physical activity was grouped by splitting at quintiles, and sedentary leisure time was categorised into 5 groups to ensure adequate cases in each category (0 to <2, 2 to <3, 3 to <4, 4 to <5, and ≥5 h/day). All adiposity variables were also modelled as continuous variables to estimate HRs per 1-SD increment, while for blood glucose HRs per 1 mmol/L were estimated. For physical activity, HRs per 4 MET-h/day increment were estimated (equivalent to 1 hour of moderate physical activity such as brisk walking [3-4 mph]), while for SLT HRs per 1.5 h/day increment were estimated (equivalent to 1-SD increment).

4.4.4.2 Cox proportional hazards model

Cox proportional hazards models were used to estimate adjusted hazard ratios

(HRs) of specific cancer incidence associated with each metabolic risk factor, stratified by age-at-risk (5-year), sex, and region (10 areas), and adjusted for age at baseline, education (4 groups: no formal school, primary school, middle/high school, or college/university), household income (6 groups: <2500, 2500-4999, 5000-9999, 10,000-19,999, 20,000-34,999, ≥35,000 RMB/year), smoking (6 groups: never, occasional, former regular, and among current regular, 0-10, 11-20, ≥20 cigarettes/day), alcohol (5 groups: abstainers, ex-weekly drinkers, reduced-intake drinkers, occasional drinkers, or weekly drinkers), self-rated health (4 groups: excellent, good, fair, or poor), and family history of cancer (yes or no). The models for liver cancer were additionally stratified by HBsAg status (3 groups: positive, negative, unclear or missing). To visualise the shape of associations between metabolic risk factors and risks of cancer, HRs are plotted against the mean level in each category of metabolic risk factors (physical activity, sedentary leisure time, adiposity, and RPG among participants without previously diagnosed diabetes). In these line plots, log-scale is used for the y-axis and the area of the squares is inversely proportional to the variance of the log HRs.

In the analyses of weight, fat mass, and lean mass, standing height was also included in the model as a continuous variable. For blood glucose, the analyses of RPG and FPG were conducted in participants without previously diagnosed diabetes (n=485,775) and were additionally adjusted for fasting time. For physical activity, separate analyses were conducted for domain-specific physical activity (occupational vs nonoccupational; for nonoccupational: commuting, household, and leisure-time). Analyses of physical activity and sedentary leisure time also included mutual adjustment for each other. For analyses involving more than two categories, all HRs are presented with ‘floating’ standard errors to facilitate

comparisons between groups.[256]

In the analyses of general and central adiposity, further analyses additionally adjusted for selected adiposity measures to examine adjusted associations. The analyses of general adiposity (BMI and %BF) were further adjusted for WC, WHR, or HC. The analyses of central adiposity (WC, WHR, and HC) were further adjusted for BMI. The analyses of HC were further adjusted for WC. Both the basic method and the residual method were used to examine adjusted associations. In the basic method, WC was included in the model when examining the adjusted association of BMI with cancer risk, while BMI was included in the model when examining the adjusted association of WC. In the residual method for BMI, the residuals from the regression of BMI on WC were modelled as the main exposure variable and additionally included WC as a covariate in the model. In the residual method for WC, the residuals from the regression of WC on BMI were modelled as the main exposure variable and additionally included BMI as a covariate in the model. The residuals were grouped by splitting at quintiles.

Cox models with a time-updated exposure for diabetes duration were used to estimate the association of diabetes duration with cancer risk, with the same adjustment (except for stratification by age-at-risk). Time since birth was used as the underlying time scale. Among participants without diabetes at baseline (previously diagnosed or screen-detected), incident diabetes cases (ICD-10 code E11, n=18,120) that occurred during the follow-up were also included. Duration was defined as the time interval between diabetes diagnosis and age-at-risk. For previously diagnosed and incident diabetes, duration was calculated as the time interval between age at diagnosis and age-at-risk. For screen-detected diabetes,

duration was calculated as the time interval between age at baseline and age-at-risk. Duration of diabetes was categorised into 4 groups, including 0 to <2, 2 to <5, 5 to <10, and ≥10 years. In the time-updated Cox model, participants were aligned by age and were split into a person-period dataset by 1-year interval. An explanatory variable for diabetes at baseline was included, which took the value 1 throughout follow-up for participants who had diabetes at baseline, and another explanatory variable for incident diabetes was included, which took the value 1 from the time when a participant was diagnosed with diabetes onwards.

4.4.5 Regression dilution

Single measurements of metabolic risk factors may not accurately reflect an individual's usual level because of random measurement error, including within-person variation or change over time. Repeat measurements of physical activity, sedentary leisure time, adiposity, and plasma glucose were available for ~20,000 participants who attended the resurvey ~3 years after baseline and were used to estimate regression dilution ratios (RDRs). The RDRs were calculated using the McMahon-Peto method, which uses the ratio of the ranges (top vs bottom categories, defined by baseline levels of metabolic risk factors) of the mean levels of each metabolic risk factor at resurvey to the range of such measurements at baseline.[257] For comparison, RDRs calculated using the correlation between measurements for participants with baseline and resurvey data were also reported.[258] **Appendices 4.4-4.7** show RDRs calculated for physical activity, sedentary leisure time, adiposity, and RPG. Log HR estimates for each baseline metabolic risk factor (examined as continuous variables) were multiplied by the reciprocal of the RDR to estimate associations of usual metabolic risk factor with

incident cancer risk.

4.4.6 Subgroup analyses

To explore whether the associations of metabolic risk factors with cancer risk differ by population subgroup (sociodemographic, lifestyle, and metabolic factors), I examined the associations for each metabolic risk factor in subgroups defined by age-at-risk (35-59, 60-69, 70-89), sex, region (urban vs rural), education (<6 vs ≥6 years), smoking (never regular, ex-regular, current regular), alcohol (abstainer, ex-regular, weekly drinkers), physical activity (<12.4, 12.4 to <25.4, ≥25.4 MET-h/day), BMI (<25 vs ≥25 kg/m^2), WC (<80 cm in women or <90 cm in men vs ≥80 cm in women or ≥90 cm in men), history of CVD (CHD or TIA), and fasting time (<8 vs ≥8 hours, for RPG), where appropriate. For smoking, never smokers and occasional smokers were combined as one category (i.e. never regular smokers). For the associations of physical activity and sedentary leisure time with cancer risk, I also examined the associations by subgroup of work activity level (farmers, manual workers, and nonmanual workers). This is because the intensity of physical activity differed by work activity level, which may modify the associations of physical activity and sedentary leisure time with cancer risk.[49,57] For liver cancer, I examined whether HBsAg modified the associations of metabolic risk factors with risk of liver cancer. For colorectal cancer, I examined whether the associations of metabolic risk factors differed for colon cancer and rectal cancer.

4.4.7 Sensitivity analyses

First, I repeated the analyses for each metabolic risk factor excluding the first two and five years of follow-up, separately. This is because participants with subclinical or undetected diseases at baseline might be diagnosed with cancer

over early years of follow-up and subclinical diseases may affect adiposity and physical activity at baseline, resulting in reverse causality. For diabetes, preclinical cancer (e.g. pancreatic cancer, liver cancer) can induce diabetes close to cancer diagnosis, resulting in reverse causality.[259,260] Second, I repeated the analyses for each metabolic risk factor excluding current and former regular smokers or weekly and reduced intake drinkers. As both smoking and alcohol are possible risk factors for cancer, restricting the analysis to never regular smokers or never regular drinkers may address residual confounding related to these two factors.[36,49,57] In addition, smoking can affect adiposity, and therefore excluding smokers can limit the effects of reverse causality.[261] Third, I examined the associations of each metabolic risk factor with cancer mortality. Fourth, I additionally adjusted for 12 dietary factors, including rice, wheat products, other staple food (e.g. corn or millet), red meat, poultry, fish/seafood, fresh eggs, dairy products, fresh vegetables, preserved vegetables, fresh fruit, and soybean products (5 groups: daily, 4-6 days/week, 1-3 days/week, monthly, or never/rarely). This is because dietary factors may be associated with metabolic risk factors and with cancer risk, and therefore may confound the associations of metabolic risk factors with cancer risk.[36,49,57] Fifth, I additionally adjusted for the other two metabolic risk factors in the analyses of single metabolic risk factor with cancer risk (i.e. adjusting diabetes and physical activity in the analysis of adiposity and cancer). This is because the association of one metabolic risk factor (e.g. diabetes) with cancer risk may be confounded or mediated by other metabolic risk factors (e.g. adiposity or physical activity). Sixth, I repeated the analyses for each metabolic risk factor excluding participants with poor self-rated health status or major chronic diseases (including CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease,

peptic ulcer, and kidney disease). Poor self-rated health or major chronic diseases may affect adiposity, physical activity, and other lifestyle factors, which may result in reverse causality. Seventh, in the analyses of diabetes and cancer risk, I further adjusted for diabetes medications (i.e. chlorpropamide or metformin and insulin) and reported the HRs for specific cancer associated with diabetes medications. This is because metformin and insulin have been reported to be associated with cancer risk and may confound the associations of diabetes with cancer.[262-264]

All analyses were conducted using SAS version 9.3 and R version 2.14.2.

Chapter 5 Cancer incidence and mortality

The objective of this chapter is to examine the incidence and mortality rates of pancreatic cancer, liver cancer, and colorectal cancer, both overall and by region, age, sex, and socioeconomic status (SES).

5.1 Results

5.1.1 Overall incidence and mortality

During a median of 10 years of follow-up, a total of 26,594 participants had developed cancer (ICD-10: C00-C97), including 13,305 participants who had died of cancer. Of the incident cancers recorded, 796 (3%) were pancreatic cancer, 2847 (10.7%) were liver cancer, and 3024 (11.4%) were colorectal cancer cases; the corresponding numbers of cancer deaths were 569, 2021, and 961, respectively. As more people were being recruited, the numbers of cancer incident cases and deaths increased steadily during the 4-year study recruitment period (i.e. 2004-2008) (**Figure 5.1**). From 2009 onwards, however, the annual numbers of all three cancers remained relatively stable, indicating the completeness of follow-up (**Figure 5.1**). After standardising for age, sex, and region, the standardised incidence rates (per 100,000 persons) were 15.5, 55.9, and 58.7 for pancreatic, liver, and colorectal cancer, respectively (**Table 5.1**); the corresponding standardised mortality rates (per 100,000 persons) were 11.0, 39.2, and 18.4, respectively. Compared with the incidence rates, the standardised mortality rates of pancreatic and liver cancer were ~30% lower, while the mortality rate of colorectal cancer was three-fold lower.

Figure 5.1 Distribution of cancer cases by calendar time

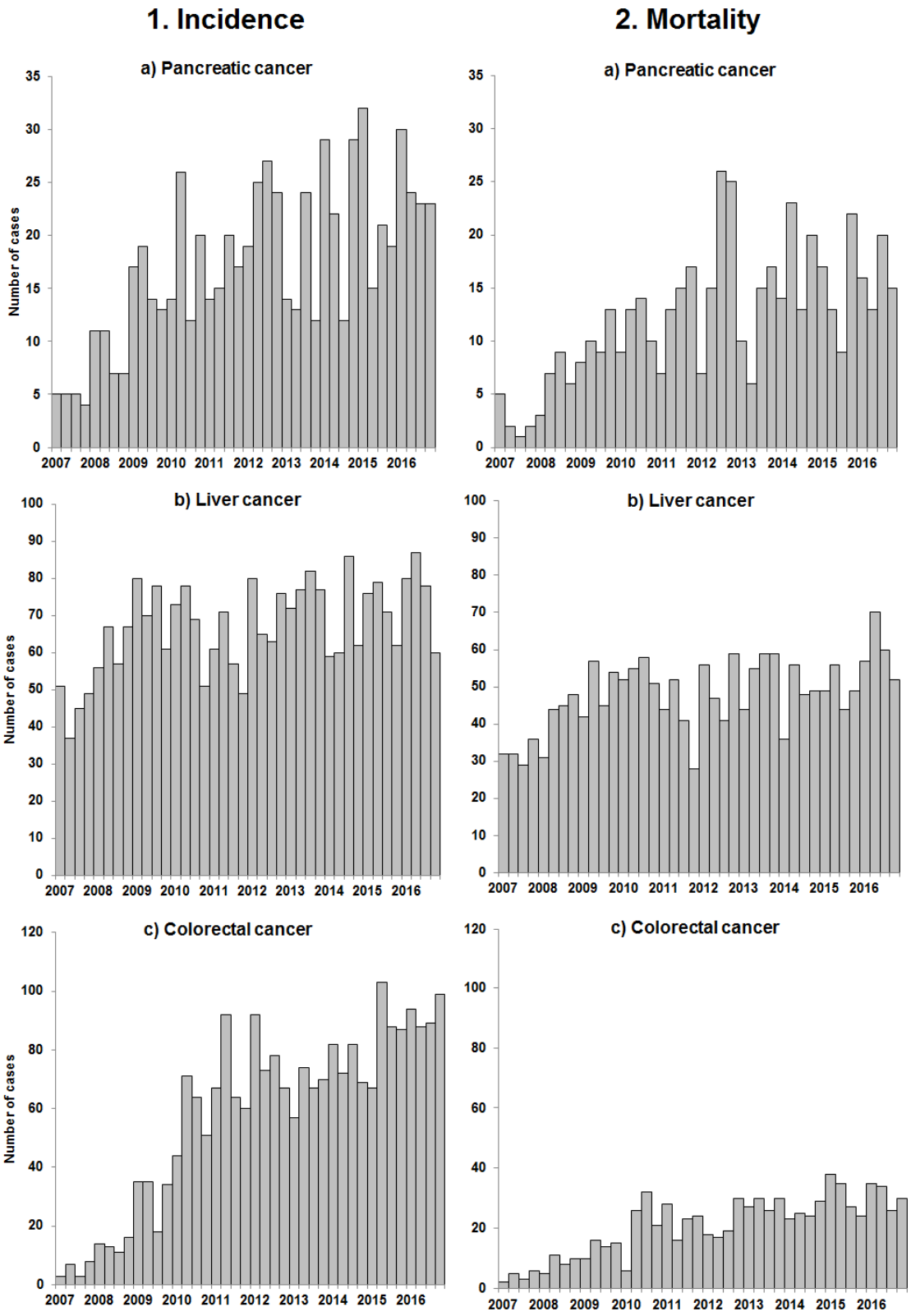


Table 5.1 Standardised incidence and mortality rates of specific GI cancers by sex and region

Area	Sex	No. of cases	Incidence rates (per 100,000)	No. of deaths	Mortality rates (per 100,000)	MIR
Pancreatic cancer						
All	**Both**	**796**	**15.5**	**569**	**11.0**	**0.71**
	Male	397	18.2	282	12.9	0.71
	Female	399	13.5	287	9.4	0.70
Urban	**Both**	**402**	**17.8**	**290**	**12.6**	**0.71**
	Male	206	22.1	145	15.3	0.69
	Female	196	14.7	145	10.7	0.72
Rural	**Both**	**394**	**13.7**	**279**	**9.7**	**0.71**
	Male	191	15.0	137	11.0	0.73
	Female	203	12.5	142	8.5	0.68
Liver cancer						
All	**Both**	**2847**	**55.9**	**2021**	**39.2**	**0.70**
	Male	1849	88.2	1346	63.4	0.72
	Female	998	33.3	675	22.1	0.67
Urban	**Both**	**1209**	**53.1**	**799**	**34.5**	**0.65**
	Male	799	87.9	540	58.9	0.67
	Female	410	29.9	259	18.0	0.60
Rural	**Both**	**1638**	**58.2**	**1222**	**43.0**	**0.74**
	Male	1050	88.4	806	67.0	0.76
	Female	588	36.0	416	25.4	0.71
Colorectal cancer						
All	**Both**	**3024**	**58.7**	**961**	**18.4**	**0.31**
	Male	1511	70.7	490	22.2	0.31
	Female	1513	50.0	471	15.6	0.31
Urban	**Both**	**1725**	**76.5**	**471**	**19.9**	**0.26**
	Male	868	95.7	235	24.5	0.26
	Female	857	63.4	236	16.8	0.26
Rural	**Both**	**1299**	**44.7**	**490**	**17.2**	**0.39**
	Male	643	51.1	255	20.5	0.40
	Female	656	39.6	235	14.7	0.37

Abbreviations: MIR, mortality-to-incidence ratio.
Estimates were standardised by age, sex, and region, where appropriate.

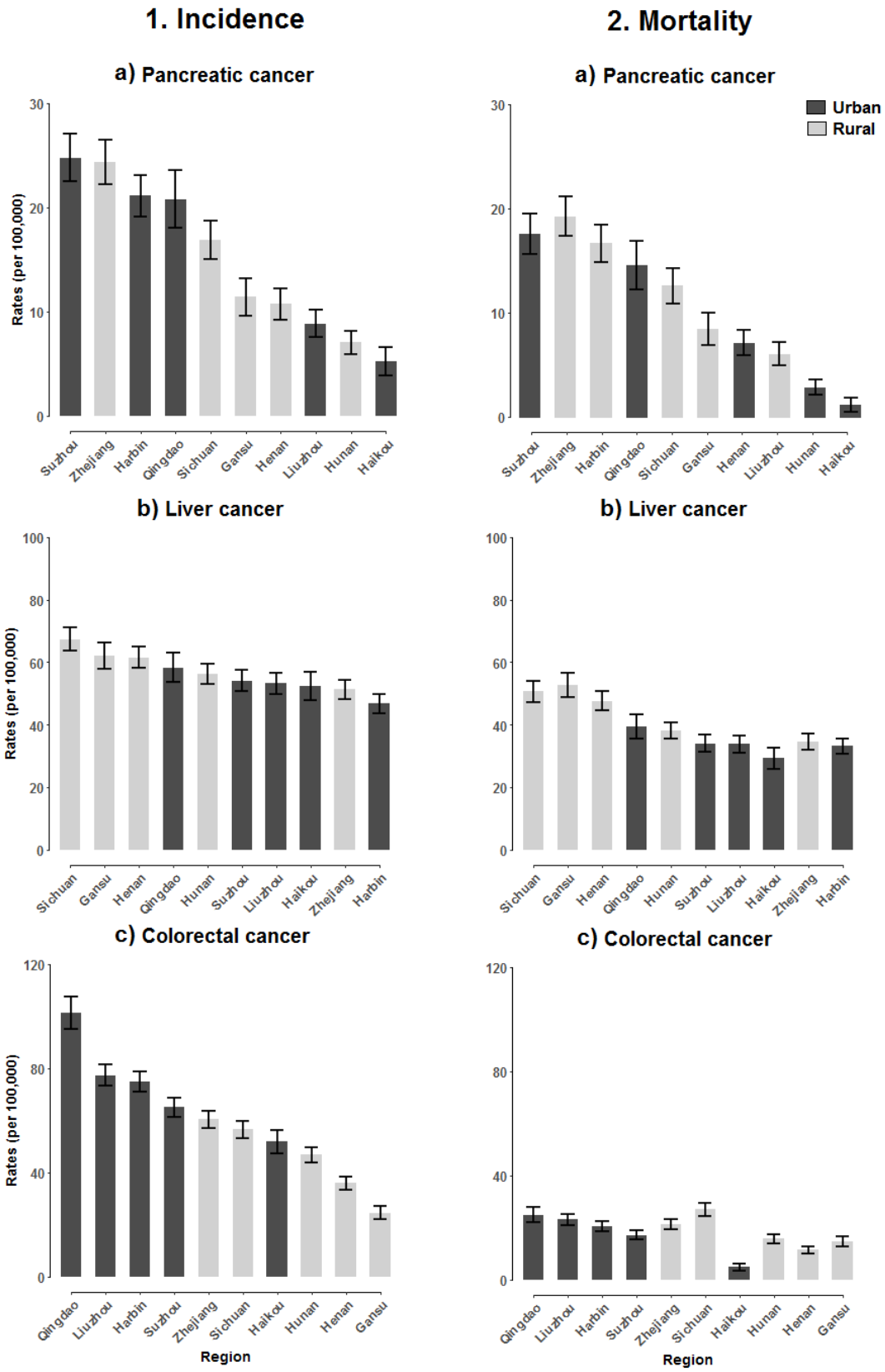
5.1.2 Incidence and mortality by region

Overall, the incidence and mortality rates of pancreatic cancer were higher in urban than rural areas, while the converse was true for liver cancer (**Figure 5.2**). The incidence rates (per 100,000 persons) of pancreatic cancer in urban and rural areas were 17.8 and 13.7 (*p* for heterogeneity <0.001), while the corresponding mortality rates (per 100,000 persons) were 12.6 and 9.7 (*p* for heterogeneity 0.04). The incidence rates of liver cancer in urban and rural areas were 53.1 and 58.2 (*p* for heterogeneity 0.02), while the corresponding mortality rates were 34.5 and 43.0 (*p* for heterogeneity <0.001). For colorectal cancer, while the incidence rate was higher in urban than rural areas (urban vs rural: 76.5 vs 44.7, *p* for heterogeneity <0.001), similar mortality rates were observed (urban vs rural: 19.9 vs 17.2, *p* for heterogeneity 0.32). The mortality-to-incidence ratio (MIR) of pancreatic cancer was similar in urban and rural areas (0.71 vs 0.71), while the MIRs of liver and colorectal cancer were lower in urban than rural areas (liver cancer: 0.65 vs 0.74, colorectal cancer: 0.26 vs 0.39).

For pancreatic cancer (**Figure 5.2**), the incidence rates varied by five-fold across 10 regions, with the highest rate (per 100,000 persons) in Suzhou (24.8) and the lowest in Haikou (5.2). There were even larger variations in mortality rates (per 100,000 persons), ranging from 1.3 in Haikou to 19.0 in Zhejiang. For liver cancer (**Figure 5.2**), the incidence rates varied by ~1.5-fold, with the highest rate in Sichuan (67.4) and the lowest in Harbin (46.8). There were also larger variations in mortality rates, ranging from 29.3 in Haikou to 52.6 in Gansu. For colorectal cancer (**Figure 5.2**), the incidence rates varied by four-fold, with the highest rate in

Qingdao (101.4) and the lowest in Gansu (24.5). The mortality rates ranged from 4.7 in Haikou to 26.9 in Sichuan.

Figure 5.2 Standardised incidence and mortality rates of specific GI cancers in 10 regions

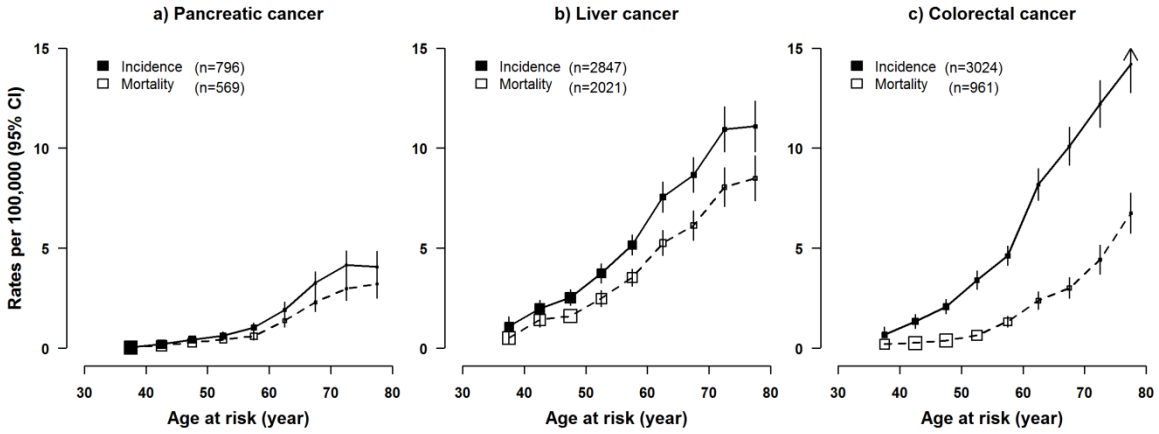


Estimates were standardised by age, sex, and region, where appropriate.

5.1.3 Incidence and mortality by age and sex

The incidence rates of all three cancers increased with age (**Figure 5.3**). For pancreatic cancer, the incidence rate increased slowly between 35-59 years, after which there was a rapid increase. For liver cancer, the incidence rate increased rapidly between 35-74 years. For both pancreatic and liver cancer, the incidence rates levelled off after 75 years. For colorectal cancer, the incidence rate rose steeply between 35-79 years, with a more rapid increase observed after 55 years. While the mortality rates of pancreatic, liver, and colorectal cancer also increased with age, the trends were more modest compared with those observed for incidence rates.

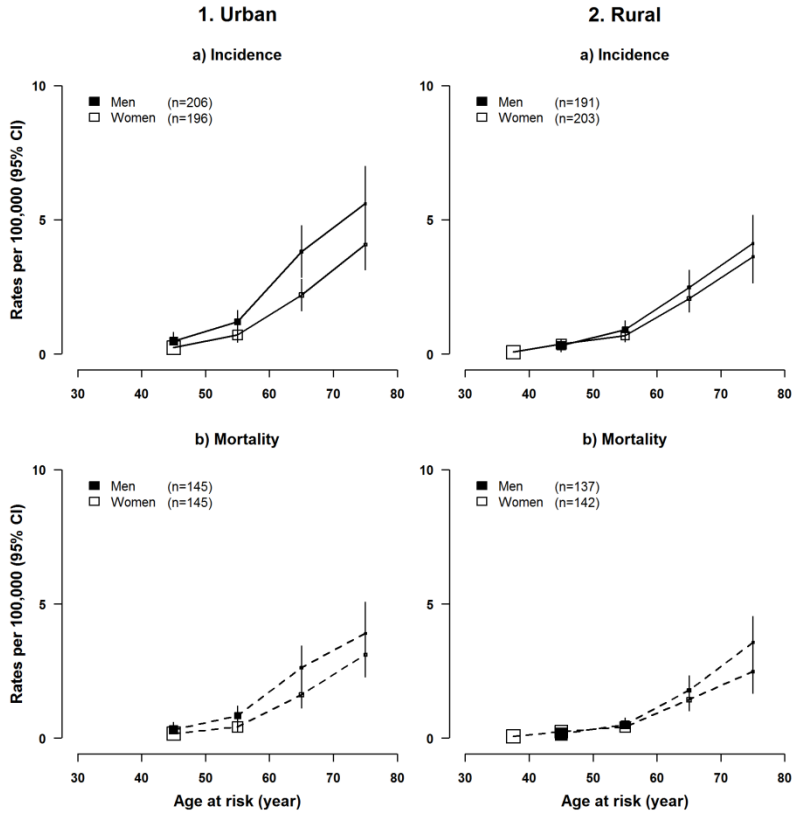
Figure 5.3 Standardised incidence and mortality rates of specific GI cancers



Estimates were standardised by sex and region, where appropriate.

For pancreatic cancer (**Figure 5.4**), the standardised incidence rate (per 100,000 persons) was higher in men than women (18.2 vs 13.5, *p* for heterogeneity <0.001), as was the standardised mortality rate (12.9 vs 9.4, *p* for heterogeneity <0.001). In men, incidence and mortality rates increased more rapidly with age in urban than rural areas, while similar age patterns were observed in women in both urban and rural areas.

Figure 5.4 Standardised incidence and mortality rates of pancreatic cancer by region and by sex



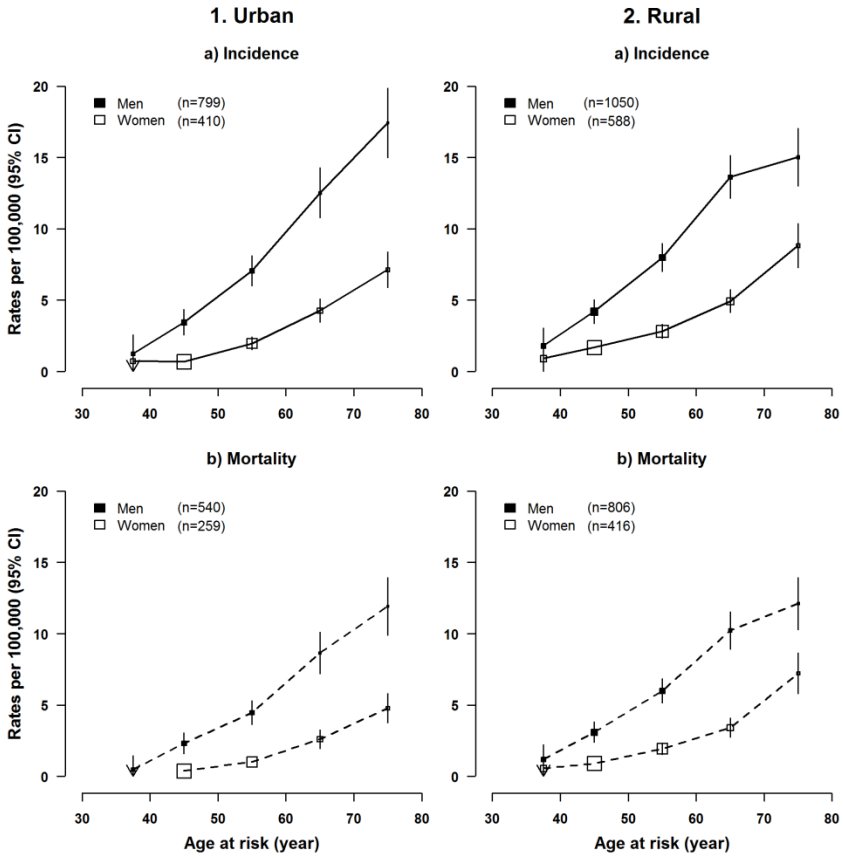
Estimates were standardised by sex and region, where appropriate.

For liver cancer (**Figure 5.5**), the incidence and mortality rates were almost three times higher in men than women. The standardised incidence rates (per 100,000 persons) were 88.2 in men and 33.3 in women (*p* for heterogeneity <0.001), while the standardised mortality rates were 63.4 in men and 22.1 in women (*p* for heterogeneity <0.001). In both men and women, the age patterns of incidence and mortality rates were similar comparing urban and rural areas.

For colorectal cancer (**Figure 5.6**), the standardised incidence rate (per 100,000 persons) was higher in men than women (70.7 vs 50.0, *p* for heterogeneity <0.001), but the difference was nonsignificant in rural areas. The standardised mortality rates were higher in men than women (22.2 vs 15.6, *p* for heterogeneity <0.001) in both urban and rural areas. In both men and women, incidence and

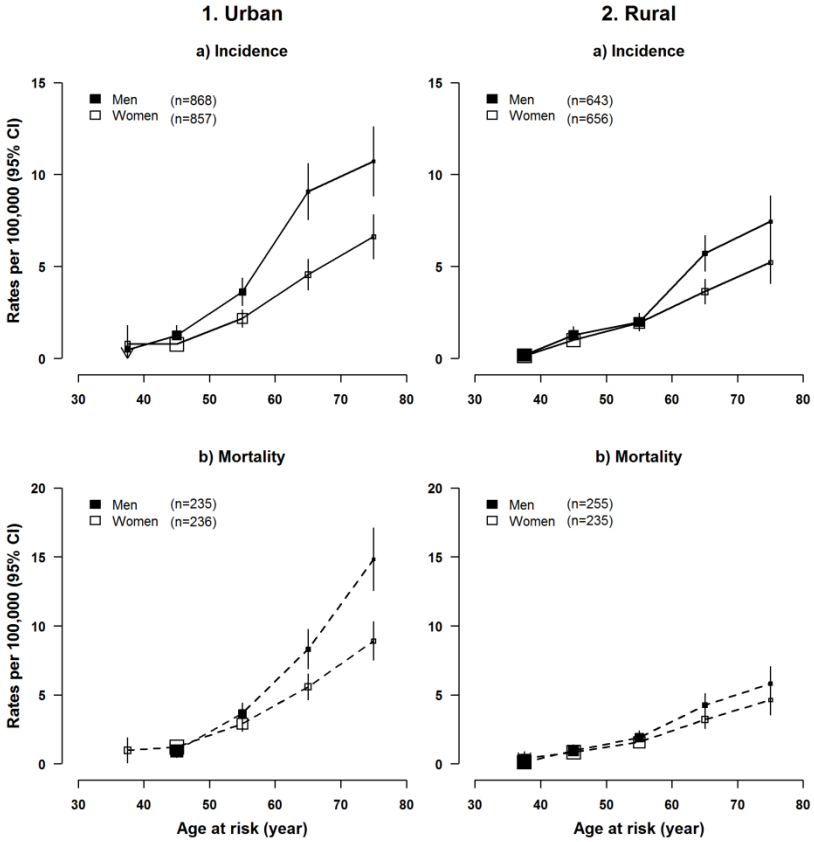
mortality rates increased more rapidly with age in urban than rural areas, particularly after age 55 years.

Figure 5.5 Standardised incidence and mortality rates of liver cancer by region and by sex



Estimates were standardised by sex and region, where appropriate.

Figure 5.6 Standardised incidence and mortality rates of colorectal cancer by region and by sex



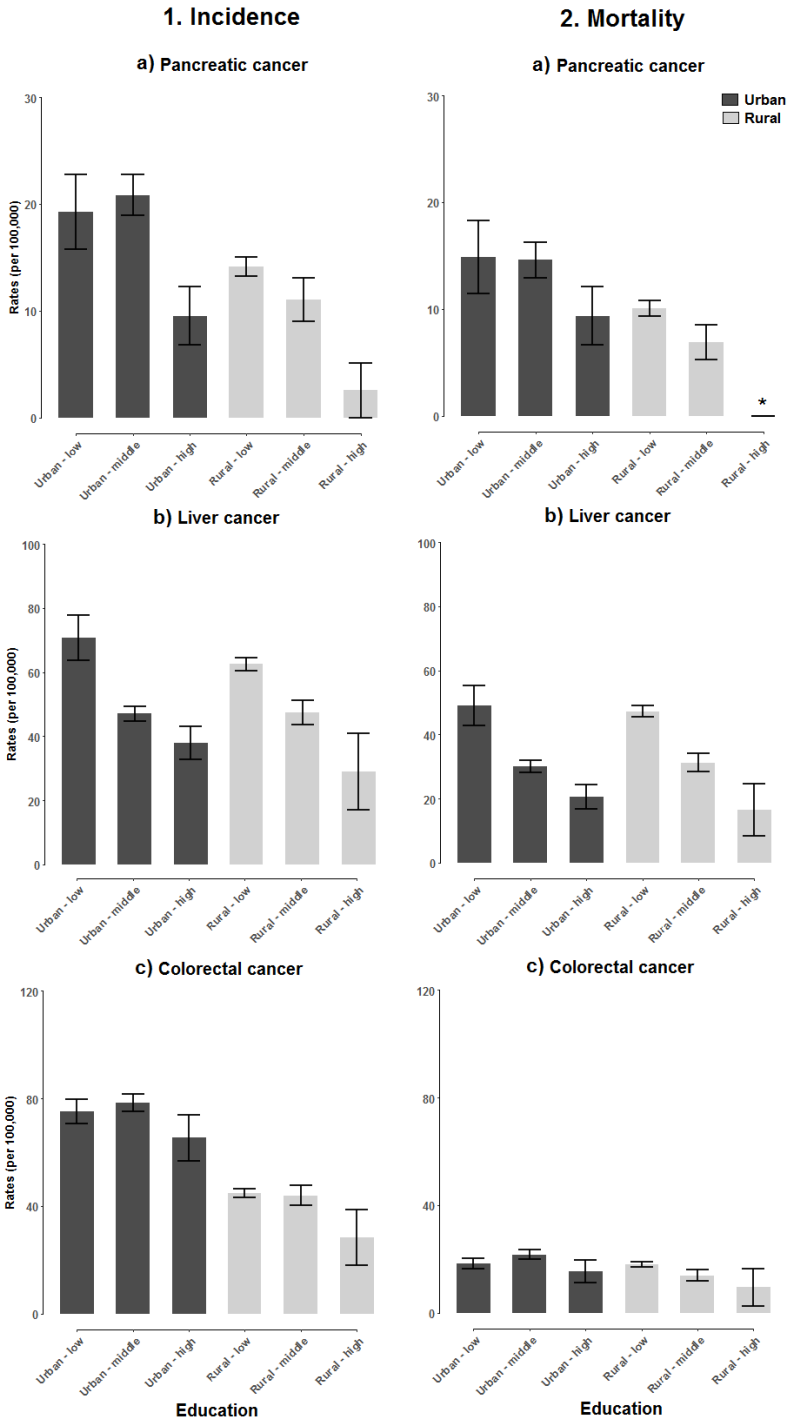
Estimates were standardised by sex and region, where appropriate.

5.1.4 Incidence and mortality by SES

In both urban and rural areas, the standardised incidence rates of pancreatic and liver cancer tended to decrease with higher levels of education (**Figure 5.7**). For pancreatic cancer, the incidence rates (per 100,000 persons) in participants with low, middle, and high levels of education were 19.3, 20.8, and 9.5 in urban areas (*p* for trend 0.008), and were 14.1, 11.1 and 2.6 in rural areas (*p* for trend <0.001). For liver cancer, the incidence rates in participants with low, middle, and high levels of education were 70.7, 47.1, and 38.0 in urban areas (*p* for trend <0.001), and were 62.5, 47.5 and 29.0 in rural areas (*p* for trend <0.001). For colorectal cancer, although there were no trends towards lower incidence rates with higher education, participants that had high levels of education had lower incidence rates

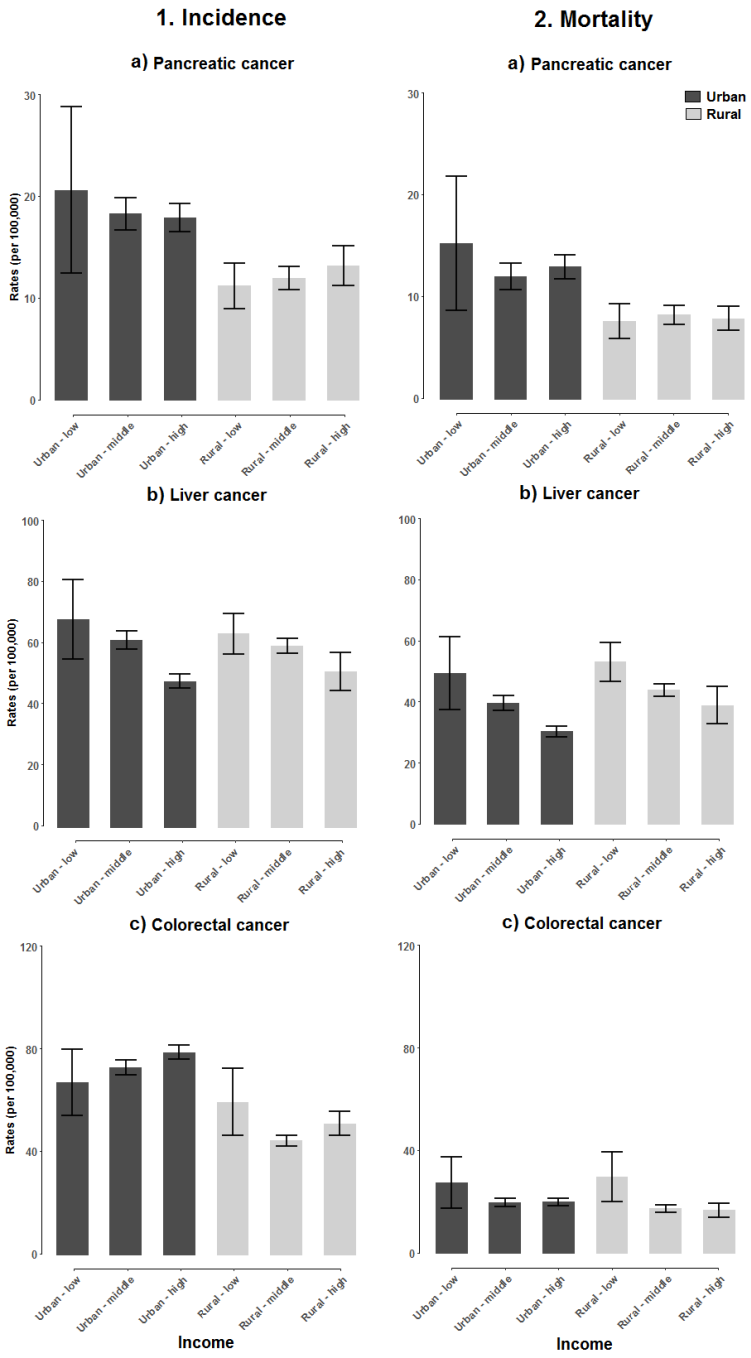
of colorectal cancer than those with low and middle levels (high, middle, low: urban: 75.2, 78.4, and 65.3; rural: 44.9, 43.9 and 28.2).

Figure 5.7 Standardised incidence and mortality rates of cancer by education



Estimates were standardised by age, sex, and region, where appropriate.
Education categories: low, no formal school or primary school; middle, middle or high school; high, technical school, college, or university.
* There were no pancreatic cancer deaths in participants with high education in rural areas.

Figure 5.8 Standardised incidence and mortality rates of cancer by household income



Estimates were standardised by age, sex, and region, where appropriate.
Income categories: low, <5000 RMB/year; middle, 5000-19,999 RMB/year; high, ≥20,000 RMB/year.

In both urban and rural areas, there were inverse trends between household income and incidence rates of liver cancer (**Figure 5.8**). However, such an inverse trend was only significant in urban areas (*p* for trend <0.001). For pancreatic and colorectal cancer (**Figure 5.8**), no clear patterns were identified in both urban and

rural areas. For cancer mortality (**Figures 5.7-5.8**), the patterns of education and household income were similar to those observed of cancer incidence.

5.1.5 Subtypes of colorectal cancer

For colorectal cancer (**Table 5.2**), the proportion of colon cancer was higher in urban than rural areas (62% vs 52%). This pattern was observed consistently across all 10 regions, except for a higher proportion of colon cancer in Zhejiang (rural, 59%) and a lower proportion in Qingdao (urban, 52%). The ratio of incidence rates of colon versus rectal cancer was 1.19 in urban areas and 0.84 in rural areas. Among 909 colorectal cancer cases that were adjudicated (**Table 5.3**), the proportion was 49% for colon cancer and 51% for rectal cancer. For colon cancer, 11% was proximal colon cancer and 12% was distal colon cancer.

Table 5.2 Standardised incidence rates of colon and rectal cancer (per 100,000)

	Incidence				Incident cases			
	CRC	**Colon**	**Rectal**	**Colon:Rectal**	**CRC**	**Colon**	**Rectal**	**% colon**
Urban								
Qingdao	101.4	55.1	61.1	0.90	326	168	206	52%
Liuzhou	77.3	52.8	39.5	1.34	425	288	218	68%
Harbin	74.8	44.6	38.0	1.17	462	285	223	62%
Suzhou	65.1	40.9	30.3	1.35	358	224	176	63%
Haikou	51.8	33.6	26.3	1.28	154	100	75	65%
Total	**76.5**	**47.1**	**39.6**	**1.19**	**1725**	**1065**	**898**	**62%**
Rural								
Zhejiang	60.4	36.9	33.5	1.10	376	223	213	59%
Sichuan	56.4	30.3	38.4	0.79	312	163	218	52%
Hunan	46.8	21.4	32.1	0.67	281	131	185	47%
Henan	35.8	18.0	21.9	0.82	221	110	135	50%
Gansu	24.5	11.3	16.0	0.71	109	53	67	49%
Total	**44.7**	**23.6**	**28.2**	**0.84**	**1299**	**680**	**818**	**52%**
Total	**39.6**	**21.3**	**24.3**	**0.88**	**3024**	**1745**	**1716**	**58%**

Abbreviations: CRC, colorectal cancer.
Estimates were standardised by age, sex, and region, where appropriate.

Table 5.3 Distribution and classification of colorectal cancer by ICD-10 code

ICD-10 code	Descriptions	No. of cases
C18	**Malignant neoplasm of colon**	**444**
C18.0	Caecum	11
C18.1	Appendix	4
C18.2	Ascending colon	26
C18.3	Hepatic flexure	5
C18.4	Transverse colon	4
C18.5	Splenic flexure	0
C18.0-5	**Proximal colon**	**50**
C18.6	Descending colon	2
C18.7	Sigmoid colon	51
C18.6, C18.7	**Distal colon**	**53**
C18.8	Overlapping lesion of colon	1
C18.9	Colon, unspecified	340
C19	**Malignant neoplasm of rectosigmoid junction**	**12**
C20	**Malignant neoplasm of rectum**	**453**

Information on cancer histological subtypes was collected for a subset of the cases through cancer registries or reviews of hospital medical notes as part of the on-going outcome adjudication for major diseases. The on-going outcome adjudication involved ~30% of all colorectal cancer cases (ICD-10 C18-20).

5.1.6 Cancer survival

Figure 5.9 shows the distribution of survival time of three cancers, with their median survival time shown in **Table 5.4**. Of all 796 incident pancreatic cancer cases, 575 (72%) died during follow-up, with 569 (71%) having pancreatic cancer as the underlying cause of death. The median survival was 4 months (IQR 1.8-6.1). Of all 2847 incident liver cancer cases, 2053 (72%) died during follow-up, with 2021 (71%) having liver cancer as the underlying cause of death. The median survival was 3.7 months (interquartile range [IQR] 1.6-10.2). For both pancreatic and colorectal cancer, the median survival was similar by sex, in urban and rural areas, and by education (**Table 5.4**). Of all 3024 incident colorectal cancer cases, 988 (33%) died during follow-up, with 961 (32%) having colorectal cancer as the underlying cause of death. The median survival was 13 months (IQR 5.2-24.9), with similar median survival by sex and longer survival in urban than rural areas (14.3 vs 11.2, p=0.01). For colon cancer, median survival was longer in urban than

rural areas (13.3 vs 9.0, *p*=0.02) and increased with levels of education (*p* for trend 0.02). For rectal cancer, by contrast, similar median survival was observed in urban and rural areas and by education.

Figure 5.9 Distribution of cancer survival

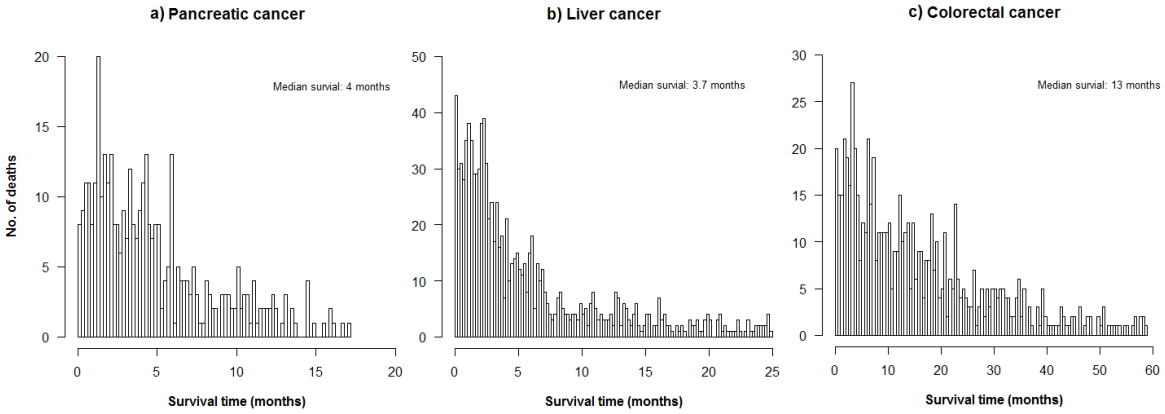


Table 5.4 Median survival in months of specific GI cancers by sex, region, and education

	Pancreatic	Liver	Colorectal	Colon	Rectal
Overall	4.0 (1.8, 6.1)	3.7 (1.6, 10.2)	13.0 (5.2, 24.9)	12.2 (4.0, 24.1)	14.1 (6.2, 26.4)
Sex*					
Male	4.0 (1.9, 7.0)	3.8 (1.7, 10.2)	13.0 (5.6, 25.8)	11.1 (3.6, 23.6)	14.8 (6.6, 27.0)
Female	4.2 (1.7, 8.2)	3.7 (1.6, 10.3)	13.0 (5.0, 24.2)	12.8 (4.4, 24.4)	13.5 (6.0, 19.3)
Region†					
Rural	4.2 (1.8, 6.4)	4.0 (1.9, 10.0)	11.2 (4.6, 22.6)	9.0 (3.5, 20.4)	12.6 (6.04, 24.9)
Urban	3.9 (1.8, 6.8)	3.6 (1.4, 10.3)	14.3 (5.9, 29.0)	13.3 (4.9, 29.6)	16.3 (7.1, 28.0)
Education‡					
Low	4.0 (1.7, 7.1)	3.5 (1.7, 9.0)	12.1 (4.5, 23.7)	9.6 (3.7, 20.7)	13.1 (5.5, 25.2)
Middle	4.2 (2.0, 6.8)	4.3 (1.6, 11.8)	14.0 (6.2, 29.1)	13.3 (4.9, 27.5)	16.2 (7.2, 30.7)
High	3.1 (1.7, 5.7)	4.6 (1.8, 14.1)	14.0 (6.2, 21.7)	19.3 (4.2, 23.7)	12.4 (8.6. 18.7)

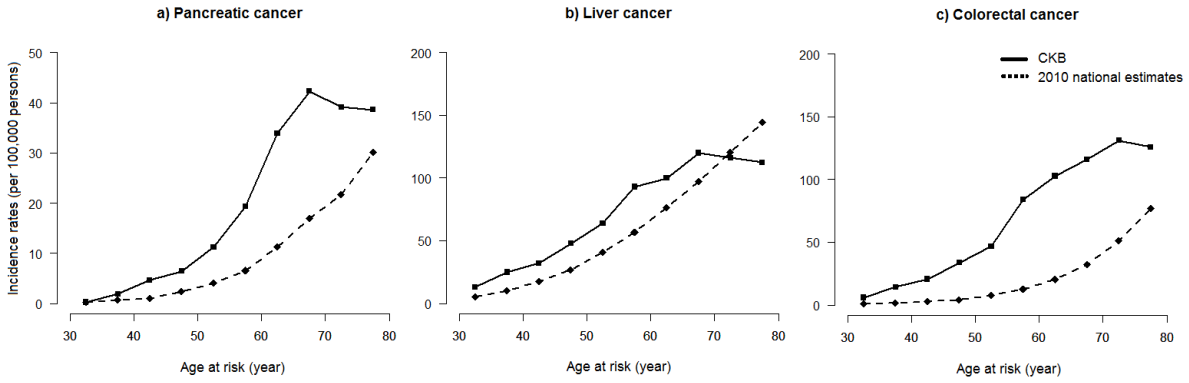
* *P* value for heterogeneity by sex: all >0.05.
† *P* value for heterogeneity by region: colorectal cancer, 0.01; colon cancer, 0.02; others >0.05.
‡ *P* value for heterogeneity by region: colon cancer, 0.02; others >0.05.

5.1.7 Comparison of CKB with national estimates in 2010

When comparing the incidence rates in CKB with national estimates in 2010 (**Figure 5.10**), there were higher rates of pancreatic and colorectal cancer in CKB

than the national estimates. For liver cancer, higher incidence rates were observed in CKB between 35-69 years, while the national rates were higher after 70 years.

Figure 5.10 Comparison of CKB with national estimates in 2010



The national estimates in 2010 were obtained from the Global Burden of Disease Study.[249]
Incidence rates in CKB were standardised to the Chinese census population in 2010.

5.2 Discussion

5.2.1 Summary of findings

In CKB, the incidence rates of pancreatic and colorectal cancer were higher in urban than rural areas, while the converse was true for liver cancer. The incidence rates of all three cancers increased with age, with higher rates in men than women. Participants with higher education had lower incidence rates of all three cancers in both urban and rural areas. Participants with higher household income had lower incidence rates of liver cancer in urban areas, while no patterns were identified for pancreatic and colorectal cancer. For mortality rates, the sex- and region-specific patterns were similar to those of incidence rates. For colorectal cancer, colon cancer accounted for ~60% of total cases, with a higher proportion in urban than rural areas. Similarly, the ratio of colon versus rectal cancer was higher in urban areas, being ~1.2 in urban and ~0.8 in rural areas. When comparing the estimates

in CKB with national estimates, the incidence rates were higher in CKB. During follow-up, over 70% of cancer patients died of pancreatic and liver cancer, while ~30% of patients died of colorectal cancer. The median survival for pancreatic and liver cancer was similar in urban and rural areas, while the median survival was longer for colorectal cancer in urban than rural areas.

When comparing CKB with national estimates in 2010, the incidence rates of all three cancers were higher in CKB. The differences in cancer incidence may be explained by the different sources of incident cancer cases in CKB and national estimates. The national estimates were obtained from the Global Burden of Disease Study 2010, which ascertained cancer cases from death and cancer registries.[249] In CKB, cancer cases were ascertained through linkages to the health insurance system and active follow-up (with 98% coverage till December 2016), as well as death and cancer registries.[243] Additional cancer cases ascertained through linkages to the health insurance system and active follow-up may explain the higher incidence rates observed in CKB.

5.2.2 Urban vs rural differences

As for urban-rural differences, the patterns in CKB are consistent with annual reports released by the National Central Cancer Registry (NCCR) between 2008-2015.[6,17-23] The NCCR is a population-based cancer registry which relied on passive reports from various sources including local hospitals, community health centres, the Urban Resident Basic Medical Insurance programme, and the New Rural Cooperative Medical Scheme. The NCCR was established in 2002 and has published annual reports on cancer in China since 2008. The number of registration sites increased from 56 in 2008 (covering 82 million) to 261 in 2012

(covering 239 million). **Appendix 5.1** shows the distribution of 177 NCCR sites in 2011 and 10 regions in CKB. Similar to CKB, the NCCR reports showed higher incidence rates of pancreatic and colorectal cancer in urban areas and higher incidence rates of liver cancer in rural areas.[6,17,18,20-23,265] The urban-rural differences of the three cancers are also consistent with previous NCCR reports showing higher incidence and mortality rates of pancreatic and colorectal cancer and lower rates of liver cancer in regions with higher urbanisation rates and gross domestic product per capita.[266,267]

Previous studies in Western countries and Japan have reported higher incidence and mortality rates of total cancer in urban than rural areas, as well as higher rates of pancreatic, liver, and colorectal cancer.[268-272] A review compared cancer incidence and mortality in urban and rural residents in 13 populations (Europe, Australia, and Japan) and reported higher rates of pancreatic, liver, and colorectal cancer in urban than rural areas.[268] For pancreatic cancer, the mean ratio of urban to rural rate was 1.2 in both sexes. For liver cancer, the mean ratio was 1.7 in men and 1.1 in women. For colorectal cancer, the mean ratio was ~1.4 in men and ~1.2 in women. Recent reports in North America and Europe have confirmed the urban-rural differences reported in this review.[269-272] While the urban-rural differences in pancreatic and colorectal cancer in CKB were consistent with those in high-income countries, the pattern of liver cancer was different possibly due to different aetiology of liver cancer between China and high-income countries. HBV is the most important risk factor for liver cancer in China (accounting for ~60%),[137,273] while HCV and alcohol are major risk factors in high-income countries (HCV 50-60%, alcohol 20-30%).[38] In the review, the author suggested that alcohol may explain the urban-rural difference in liver cancer in high-income

countries.[268] In Korea, where HBV is also the major risk factor for liver cancer, a higher mortality rate of liver cancer was observed in rural than urban areas.[274]

The urban-rural differences in CKB may be partially explained by the differences in risk factors for these cancers. First, the higher prevalence of lifestyle and metabolic risk factors in urban areas may explain the urban-rural differences in cancer risk. Smoking, excessive alcohol intake, higher consumption of animal origin foods, overweight/obesity, and physical inactivity are all possible risk factors for pancreatic and colorectal cancer.[49,57] Therefore, the higher prevalence of overweight/obesity, physical inactivity, and consumption of animal origin foods in urban areas may explain the higher incidence of pancreatic and colorectal cancer.[12,14,15,71,275] Second, the higher prevalence of infections in rural areas may explain the urban-rural differences in liver cancer risk. HBV is the most important risk factor for liver cancer in China, accounting for approximately 60% of all liver cancer cases.[137] The higher prevalence of chronic HBV infection in rural areas may explain the higher incidence of liver cancer in rural than urban areas. National surveys in 1992 and 2006 showed higher prevalence of HBsAg in rural than urban areas. The prevalence of HBsAg was 10.5% in rural and 8.1% in urban areas in 1992,[7] while the prevalence was 7.3% in rural and 6.8% in urban areas in 2006.[8]

The urban-rural differences in CKB may also be explained by the differences in cancer care. Studies in Western populations have reported greater delays in cancer diagnosis, worse health status of cancer patients, and greater unmet needs for health services (e.g. physical and supportive) in rural than urban residents.[276-279] MIR is the ratio of the mortality and incidence identified over the same period of time for a specific cancer.[250] MIR can reflect screening, prevention,

treatment, and survival of a specific cancer, and has been reported to be inversely associated with human development index.[250-252] A lower MIR suggests a lower mortality rate at a given incidence rate and reflects better survival at a population level. In CKB, the MIR for pancreatic cancer was similar in urban and rural areas, which may reflect the lack of screening methods and effective treatments. Only less than 20% pancreatic cancer patients are eligible for surgical resection as the disease is often diagnosed at a late stage.[24,29] For pancreatic cancer screening, there is no consensus on the definition of high-risk populations and cost-effective modalities for population-based screening.[24,29] For liver and colorectal cancer, the lower MIRs in urban areas may be because of better opportunities of medical services for diagnosis and treatment of cancer.[280] Indeed, the majority of tertiary hospitals are located in urban areas, and thus there is limited access to cancer care for people living in rural areas.[281] In China, there are substantial disparities in access to medical resources between urban and rural areas.[281] For example, there are 8.5 doctors or nurses per 1000 people in eastern China, compared with 2.8 per 1000 people in rural western China.[282] In addition, rural residents are less likely to utilise hospitals than their urban counterparts.[283] Studies in China as well as Western and other East Asian countries have shown that urban residents are more likely to have cancer diagnosed at an early stage, to receive effective treatment, and to have better cancer outcomes.[55,281]

Furthermore, cancer screening may explain the urban-rural differences in liver and colorectal cancer. In China, population-based screening programmes now cover liver and colorectal cancer as well as oesophageal, stomach, breast, cervical, and nasopharynx cancer, whereas there is no nationwide screening programme for pancreatic cancer.[284] For liver cancer, the Chinese guideline recommends

performance of α-fetoprotein (AFP) measurement and liver ultrasound every six months for high-risk population aged 35-40 years (i.e. HBV or HCV-related chronic liver diseases).[285] For colorectal cancer, the Asia Pacific Colorectal Cancer Working Group recommends screening for those aged 50-75 years at average risk (i.e. an asymptomatic population at average risk for colorectal cancer) with a quantitative faecal immunochemical testing (FIT) and colonoscopy for those with a positive FIT test result.[286] In China, cancer screening programmes are not available to the entire population and are particularly limited in rural areas.[281] In 2013, there were five pilot sites for colorectal cancer screening and 11 for liver cancer.[284] Colorectal screening sites were mainly in large cities such as Shanghai, Hangzhou, and Hongkong.[286] Surveys conducted for cervical and breast cancer have shown that women in rural areas were less likely to have screening tests, while women with higher education levels and health insurance were more likely to have screening tests.[287,288]

5.2.3 Individual-level SES

In CKB, participants with higher education had lower incidence of all three cancers, while participants with higher household income had lower incidence of liver cancer but not pancreatic and colorectal cancer. Education level, which captures many aspects of the construct “social class”, is a widely used indicator for SES in epidemiological studies.[289] The association of education with cancer risk is not affected by reverse causality, whereas the associations of occupation and income may be subject to reverse causality. This is because cancer patients may have reduced work-related physical activity and therefore reduced income. Nonetheless, the inverse association between household income and liver cancer in CKB is

consistent with prospective studies in Korea which showed an inverse association of family income with liver cancer mortality.[290,291]

Previous prospective studies mainly from Western countries have reported that individuals with lower education had higher incidence and mortality of pancreatic, liver, and colorectal cancer compared with those with higher education,[292-295] which is consistent with the findings in CKB. Similarly, a recent meta-analysis of 20 prospective cohort studies in Asia showed an inverse association of education with total cancer mortality.[296] The inverse association of education with cancer may be explained by the associations of education with risk factors for these cancers, including smoking, alcohol, dietary factors, and physical inactivity. Indeed, studies in the US, Europe, and Asia have shown higher prevalence of smoking, heavy alcohol intake, and consumption of animal origin foods (e.g. red and processed meat) in individuals with lower education.[292-295] Previous studies in China and Korea have reported higher prevalence of HBV infection in individuals with lower education.[7,8,290,291] In CKB, individuals with lower education were more likely to smoke and consume alcohol and were more likely to have HBV infection (**Appendix 5.2**). They were also less likely to consume fresh fruits and vegetables (**Appendix 5.2**).

Furthermore, the education gradient, as an indicator of overall SES, may be explained by differential access to cancer health services including diagnosis and treatment. First, low SES status is associated with lower utilisation of screening services and later diagnosis of cancer. Several studies in the US reported a lower prevalence of colorectal cancer screening among individuals with low education compared with those with high education.[297,298] In China, although population-

based colorectal cancer screening has not been implemented, individuals with high education may be more likely to get cancer screening and to be diagnosed at an early stage.[281,287,288] Several surveys in China showed that the usage of cancer screening services was low and barriers to utilisation of the screening services included cultural and economic barriers particularly relevant to individuals with low SES.[287,288,299] In addition, previous studies in Western countries, China, and other East Asian countries have shown that individuals with low SES (e.g. education, occupation, health insurance premium) were more likely to be diagnosed at a more advanced stage in both urban and rural areas.[300-303] Second, SES may be related to status and type of insurance and health care-seeking behaviours, and these factors may be associated with both cancer diagnosis and treatment.[287,288,300]

5.2.4 Sex differences

In CKB, the higher incidence and mortality of cancer in men than women are consistent with previous reports in China as well as other countries. In China, the NCCR reports showed higher age-standardised incidence and mortality rates in men than women between 2008-2015.[6,17,18,20-23,265] Similarly, the GLOBOCAN project showed higher age-standardised incidence and mortality rates in men than women in both more and less developed regions.[4]

There are several factors that may contribute to the sex differences in cancer susceptibility, including environmental risk factors, physiological factors, immune surveillance, and genetic differences.[304] First, the higher rates in men may be due to variation in environmental and occupational risk factors.[305] For example, the prevalence of lifestyle risk factors such as smoking and binge drinking is higher in

men than women.[305] These factors are associated with higher risks of pancreatic, liver, and colorectal cancer.[36,49,57] Second, there are physiological differences between men and women that may explain the differences in cancer susceptibility. The higher IL-6 levels in men than women may explain the higher incidence of liver cancer in men,[306] while the sex-specific difference in colorectal cancer may be explained by sex hormones.[149] Third, immune surveillance may be different between men and women. Women have higher innate and adaptive immune responses than men, and therefore women may have faster clearance of pathogens.[307,308] Responses to immunological stimuli are also affected by the expression of X-linked genes and microRNA, as well as sex hormones signalling pathways.[309] Fourth, there are sex-specific differences that are relevant to the efficiency of genomic surveillance mechanisms. For example, women have higher recombination rates and lower DNA repair capacity than men, while women have lower levels of DNA damage and methylation.[304,310] However, evidence is still limited to draw conclusions why men have greater cancer susceptibility than women.[310]

5.2.5 Subtypes of colorectal cancer

In CKB, colon cancer accounted for ~60% of total colorectal cancer cases recorded, similar to those (50-60%) reported in Asian countries but lower than the ~70% reported in Europe and North America.[10,52] However, the proportion of colon cancer in CKB is higher than previous reports in China between 1990 and 2005, which reported ~40%.[311-313] The follow-up period of CKB is from 2004-2008 till 2016. The higher proportion of colon cancer in CKB might reflect a proximal shift in the subsite distribution of colorectal cancer (i.e. a higher proportion of colon

cancer and a lower proportion of rectal cancer) over time, which is also observed in high-income countries.[3,4] In CKB, the ratio of incidence rates of colon and rectal cancer (0.88) was lower than that reported in the US (2-3.5) or in Japan (1.6-2.2), but was comparable to that in Korea (1.0-1.1).[53] When compared with previous reports in China, the CKB estimate in urban areas (1.19) was consistent with those in Guangzhou, Harbin, and Shanghai (1.1-1.8),[53] while the CKB estimate in rural areas was lower (0.84).

The reason for the geographic variation in the distribution of colorectal cancer (e.g. proportions of colon and rectal cancer) is poorly understood.[314] It has been hypothesised that such variation might be due to the distinct aetiology and susceptibility to environmental risk factors between colon and rectal cancer (**Appendix 5.3**).[314,315] Previous prospective studies have suggested stronger associations of smoking and alcohol with risk of rectal cancer and stronger associations of metabolic risk factors (i.e. adiposity and physical inactivity) with risk of colon cancer.[316] For dietary factors, there are inverse associations of dietary fibre and wholegrains with risk of colon cancer and no clear associations with rectal cancer.[57] In addition, the positive associations of red meat and processed meat tended to be stronger for colon than rectal cancer.[57] The higher proportion of colon cancer in Western countries than in China might be due to higher prevalences of physical inactivity, obesity, and different dietary pattern (e.g. higher consumption of animal origin foods) in Western countries.[10,52,316]

5.2.6 Cancer survival

In CKB, the prognosis of pancreatic and liver cancer was worse than colorectal cancer, as indicated by median survival. The median survival of pancreatic and

liver cancer in CKB was comparable to previous reports both in China and Western countries. A population-based study in China (the Shanghai Cancer Registry) reported overall 5-year survival of 4.1% and median survival of 3.9 (95% CI: 3.8-4.0) months.[317] Similarly, the Cancer Research UK data showed median survival of 6-11 months for stage III and of 2-6 months for stage IV pancreatic cancer.[30] For liver cancer, European data showed that the median survival was 4-8 months for stage III and 4 months for stage IV liver cancer.[40] Similar to CKB, national data in China showed that the prognosis of pancreatic and liver cancer was worse than colorectal cancer. A recent report of 17 population-based cancer registries in China (number of participants: half urban, half rural) examined 5-year survival for individuals with cancer between 2003-2015.[31] The age-standardised 5-year survival was 7% for pancreatic, 12% for liver, and 57% for colorectal cancer.

When examining survival by sex, the median survival of pancreatic, liver, and colorectal cancer was similar in men and women in CKB, consistent with the national report.[31] When examining survival in urban and rural areas, the median survival of colorectal cancer was longer in urban areas in CKB, while the median survival of pancreatic and liver cancer did not differ in urban and rural areas possibly due to the limited number of cancer cases. The national report showed better survival of liver and colorectal cancer in urban than rural areas, while similar survival was observed for pancreatic cancer.[31] In Asia, survival of total cancer was worse in rural than urban areas in China, India, Thailand, but not in Korea.[55] The rural-urban difference in cancer survival may reflect differences in early diagnosis, availability of screening programmes, inequalities in health-care infrastructure, health-care-seeking behaviours, and treatment effectiveness.[281]

5.3 Conclusions

In this Chinese population, there were variations in incidence and mortality rates of pancreatic, liver, and colorectal cancer by region, age, sex, and SES. Higher incidence and mortality rates were observed in urban areas for pancreatic and colorectal cancer, while higher rates were observed in rural areas for liver cancer. For all three cancers, the incidence and mortality rates were higher in men than women and increased with age. The sex-, region-, and age-specific patterns in CKB were consistent with national reports. Individuals with higher education had lower incidence and mortality rates of all three cancers, while individuals with higher household income had lower incidence and mortality rates of liver cancer. Survival of colorectal cancer was better than pancreatic and liver cancer, and the medial survival was comparable to previous reports in China and Western countries. For colorectal cancer, better survival was observed in urban than rural areas.

Chapter 6 PA, SLT, and risk of specific GI cancers

The objective of this chapter is to examine the shape and strength of associations of physical activity (PA) and sedentary leisure time (SLT) with risks of pancreatic, liver, and colorectal cancer controlling for each other and possible confounders and adjusting for within-person variation and error in the measurement of PA and SLT. This chapter also describes the associations of domain-specific PA with risks of these cancers, including occupational and nonoccupational (commuting, household, and leisure-time) PA.

6.1 Results

6.1.1 Patterns and correlates of PA and SLT

Among all 509,892 participants, the mean (SD) total PA was 21.1 (13.9) MET-h/day, mainly from occupational PA (75% in men vs 50% in women). The mean SLT was 21.1 (10.8) h/week. In both sexes, the distributions of PA and SLT were right-skewed (**Figures 6.1-6.2**), and for SLT there was a digit preference for integer values. In both sexes, PA and SLT were inversely correlated (Spearman correlation coefficient: r=-0.22 in men and -0.22 in women). The prevalence of meeting PA recommendations by the 2010 WHO guidelines (i.e. leisure-time PA ≥7.5 MET-h/week or 1.07 MET-h/day) was 18.8%.

The mean level of total PA was higher in men than women (22.4 vs 20.2 MET-h/day) and in rural than urban areas (22.9 vs 18.8 MET-h/day). Compared with women, men had higher occupational PA (16.8 vs 10.3 MET-h/day) and lower nonoccupational PA (5.6 vs 9.9 MET-h/day) in both urban and rural areas (**Table 6.1**). Therefore, occupational PA accounted for a higher proportion of total PA in

men than women (75% in men and 51% in women). For nonoccupational PA, the patterns differed by sex and by urbanicity (**Table 6.1**). For household PA, women had almost three-fold higher levels than men (mean 7.7 vs 2.9 MET-h/day) in both urban and rural areas. For leisure-time PA, participants in urban areas had almost ten-fold higher levels than those in rural areas (mean 1.7 vs 0.2 MET-h/day) in both sexes. Similarly, the prevalence of meeting PA recommendations by the 2010 WHO guidelines was much higher in urban than rural areas (34.4% vs 5.9%), while it was similar by sex (19.6% in men vs 18.1% in women). For commuting PA, men tended to have higher levels than women (mean 1.8 vs 1.3 MET-h/day). In contrast to the patterns of PA, the mean SLT was similar in men and women (21.8 vs 20.6 MET-h/day) and in urban and rural areas (21.6 vs 20.6 MET-h/day).

Mean total PA decreased with age, and it was less than half as high between 70-79 years as between 35-39 years (**Figure 6.3**). The decline in total PA was largely driven by the decline in occupational PA (**Figure 6.4**). For nonoccupational PA, the age pattern differed by sex (**Figure 6.4**). In women, nonoccupational PA increased with age between 35-60 years, while there was a slight decrease after age 60 years. In men, nonoccupational PA increased with age between 35-70 years in urban areas, while it changed little with age in rural areas. For SLT, the age pattern differed between urban and rural areas (**Figure 6.3**). In urban men, mean SLT increased with age between 35-79 years, with a more rapid increase after age 60 years. In urban women, mean SLT increased with age between 35-60 years, while it levelled off after age 60 years. In rural men and women, mean SLT tended to decrease with age between 35-60 years, while it levelled off after age 60 years.

Figure 6.1 Distribution of total and domain-specific PA

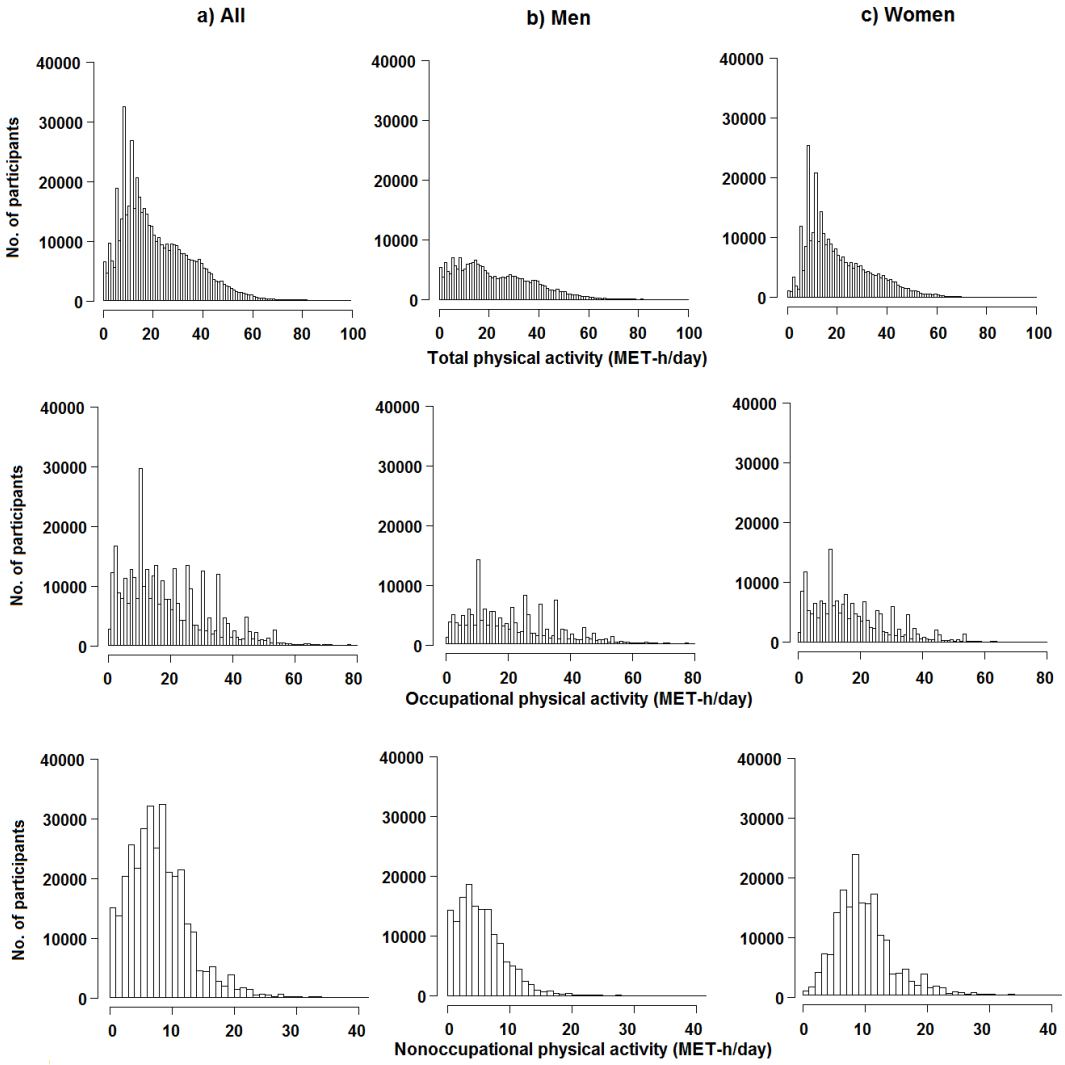


Figure 6.2 Distribution of sedentary leisure time

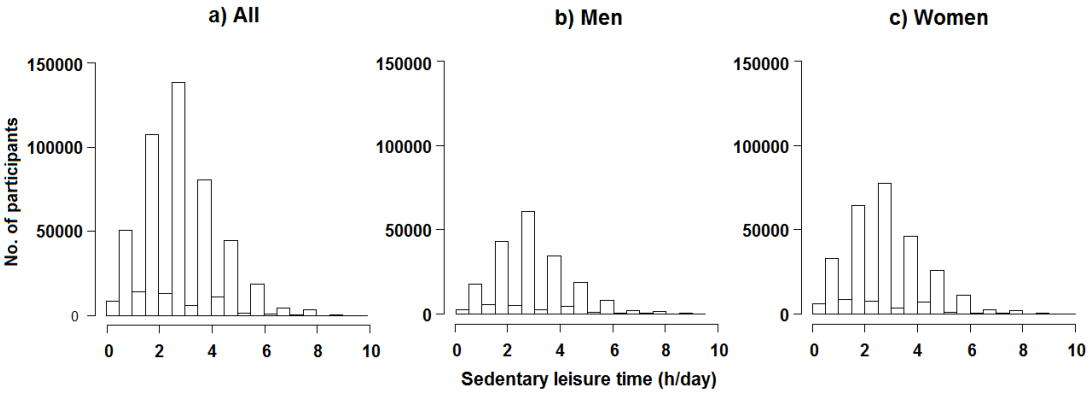


Table 6.1 Means and standard deviations (SDs) of PA and SLT

Domain	Urban			Rural		
	Overall	Male	Female	Overall	Male	Female
Physical activity (MET-h/day)						
Total	18.5 (12.7)	19.4 (13.9)	17.9 (11.7)	23.2 (14.4)	24.8 (16.0)	22.0 (13.2)
Occupational	10.4 (12.9)	13.4 (13.7)	8.3 (11.9)	15.0 (14.3)	19.5 (15.6)	11.9 (12.6)
Nonoccupational	8.1 (4.9)	5.9 (4.2)	9.6 (4.7)	8.2 (5.0)	5.3 (4.0)	10.2 (4.6)
Commuting	1.1 (1.9)	1.4 (2.0)	0.9 (1.7)	1.9 (2.5)	2.2 (2.6)	1.7 (2.4)
Household	5.3 (4.1)	2.8 (2.6)	7.0 (4.0)	6.1 (4.3)	2.9 (2.9)	8.3 (3.7)
Leisure-time	1.7 (3.0)	1.8 (3.1)	1.7 (2.9)	0.2 (1.1)	0.3 (1.2)	0.2 (0.9)
Sedentary leisure time (h/week)	21.6 (11.5)	22.6 (11.4)	21.0 (11.5)	20.6 (10.2)	21.2 (10.0)	20.3 (10.4)

Means were standardised by age (5-year), sex, and region, where appropriate.

Figure 6.3 Distribution of total PA and SLT by sex and by region

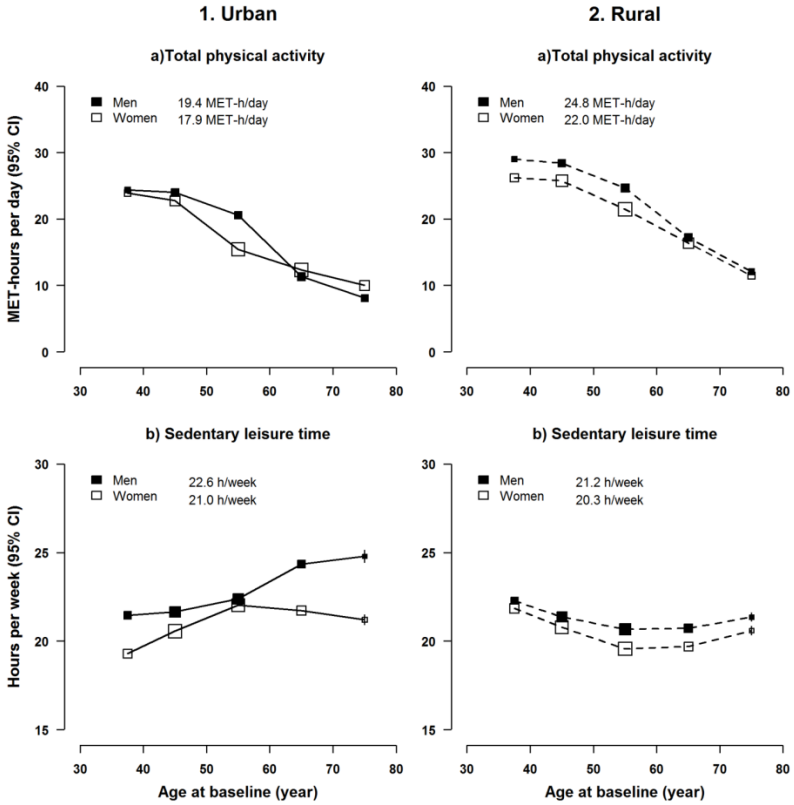
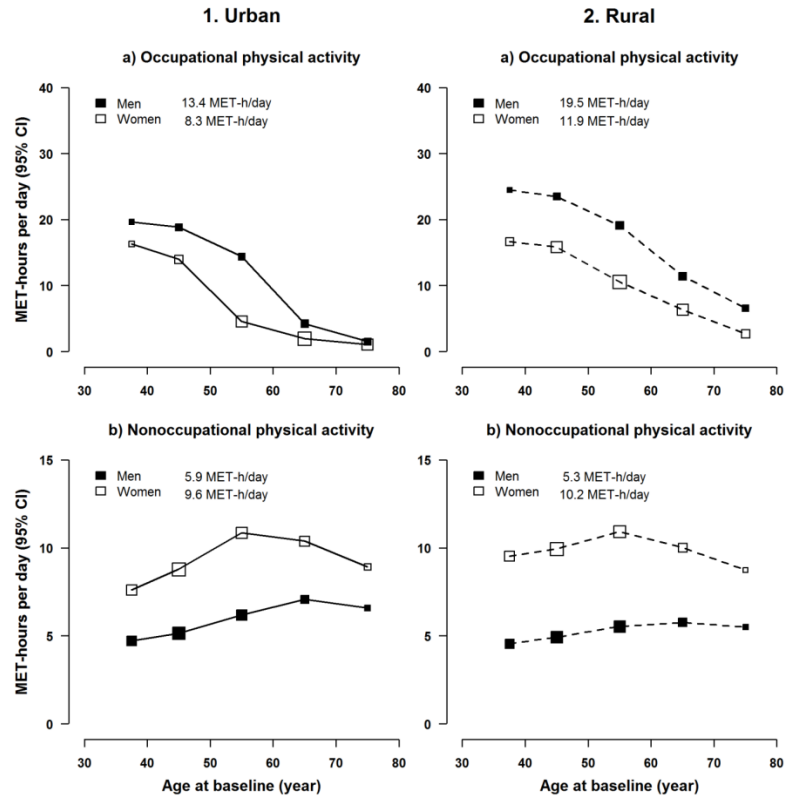


Figure 6.4 Distribution of domain-specific PA by sex and by region



Results were standardised by age, sex, and region (where appropriate).

Participants with higher total PA were more likely to be men, younger, and from rural areas (**Table 6.2**). They were also more likely to have lower levels of SBP, RPG, and adiposity. They were less likely to have diabetes, CVD, and hypertension. In contrast, participants with higher SLT were more likely to be older and from urban areas (**Table 6.3**). They were more likely to have higher education and household income. They were more likely to smoke and consume fresh fruits, fresh vegetables, and red meat on a daily basis, and were more likely to have higher adiposity and prevalent diabetes, CVD, and hypertension. They were also more likely to have a family history of diabetes and cancer.

Table 6.2 Baseline characteristics of participants by levels of total PA

Variable*	Total physical activity (MET-h/day)				
	0 to <8.8 (n=101,720)	**8.8 to <14.3** (n=102,096)	**14.3 to <21.9** (n=102,119)	**21.9 to <33.3** (n=101,885)	**≥33.3** (n=102,072)
Age (SD), year	58.2 (12.2)	54.7 (12.6)	50.3 (10.5)	47.7 (9.2)	45.8 (8.9)
Female, %	59.3	67.4	60.8	55.1	45.0
Socioeconomic and lifestyle factors					
Urban region, %	52.3	47.1	46.4	34.6	30.5
≥9 years of education, %	17.9	23.5	25.6	21.7	17.2
Household income ≥35 000 RMB/year, %	15.6	21.2	21.6	17.8	14.9
Ever regular smoking, %					
Male	69.2	67.7	65.6	67.1	68.0
Female	3.6	2.8	2.6	2.6	2.8
Weekly drinking, %					
Male	30.3	34.6	34.2	34.7	34.4
Female	2.0	2.0	2.2	2.4	2.5
Total physical activity (SD), MET-h/day	5.9 (2.5)	11.7 (1.6)	17.7 (2.2)	27.0 (3.3)	42.2 (8.4)
Sedentary leisure time (SD), h/day	3.6 (1.8)	3.3 (1.5)	3.0 (1.4)	2.7 (1.4)	2.6 (1.3)
Daily consumption, %					
Fresh fruits	18.6	20.8	21.3	19.1	17.2
Fresh vegetables	95.1	96.2	95.4	93.0	95.2
Red meat	30.5	30.9	29.8	28.7	28.2
Blood pressure and anthropometry					
SBP (SD), mmHg	131.8 (23.2)	131.3 (21.9)	130.6 (20.7)	130.4 (20.2)	129.9 (19.3)
RPG (SD), mmol/L	6.2 (2.9)	6.1 (2.6)	6.0 (2.2)	6.0 (2.0)	5.9 (1.8)
BMI (SD), kg/m^2	23.9 (3.6)	23.9 (3.5)	23.7 (3.3)	23.5 (3.2)	23.4 (3.1)
Waist circumference (SD), cm	81.3 (10.3)	81.0 (9.8)	80.3 (9.7)	79.6 (9.4)	79.3 (9.0)
Hip circumference (SD), cm	91.4 (7.5)	91.3 (7.1)	91.0 (6.8)	90.6 (6.5)	90.5 (6.1)
Waist-to-hip ratio (SD)	0.89 (0.07)	0.89 (0.07)	0.88 (0.07)	0.88 (0.07)	0.88 (0.07)
Percent body fat (SD), %	28.7 (9.0)	28.5 (8.6)	28.0 (8.1)	27.4 (8.0)	27.1 (7.9)
Height (SD), cm	158.7 (8.3)	158.9 (8.0)	158.9 (8.4)	158.6 (8.4)	158.5 (7.9)
BMI at age 25 (SD), kg/m^2	21.9 (2.7)	21.8 (2.7)	21.9 (2.6)	21.9 (2.5)	22.0 (2.4)

Variable*	Total physical activity (MET-h/day)				
	0 to <8.8 (n=101,720)	**8.8 to <14.3** (n=102,096)	**14.3 to <21.9** (n=102,119)	**21.9 to <33.3** (n=101,885)	**≥33.3** (n=102,072)
HBsAg positive, %	3.0	3.1	2.9	3.1	2.9
Prior disease history, %					
Diabetes	8.1	6.6	5.4	4.6	3.7
Coronary heart disease	3.8	3.3	2.8	2.3	1.7
Stroke or TIA	3.1	1.6	1.2	1.1	1.0
Hypertension	14.2	13.1	11.1	9.8	8.9
Family history of diabetes	4.9	5.3	5.3	5.0	4.8
Family history of cancer	13.9	14.1	14.2	14.4	13.9

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.
* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.

Table 6.3 Baseline characteristics of participants by levels of SLT

Variable*	Sedentary leisure time (h/day)				
	0 to <2 (n=84,164)	2 to <3 (n=132,125)	3 to <4 (n=133,839)	4 to <5 (n=86,112)	≥5 (n=73,652)
Age (SD), year	51.7 (13.1)	51.2 (10.8)	50.8 (10.6)	51.1 (12.2)	52.0 (15.1)
Female, %	63.7	59.7	54.9	55.8	55.7
Socioeconomic and lifestyle factors					
Urban region, %	42.4	44.6	43.2	43.6	47.7
≥9 years of education, %	18.3	20.3	21.9	22.8	22.5
Household income ≥35 000 RMB/year, %	15.7	17.8	19.7	20.1	21.2
Ever regular smoking, %					
Male	64.8	64.8	67.3	69.9	73.7
Female	2.5	2.5	2.9	3.0	4.2
Weekly drinking, %					
Male	33.9	32.3	32.5	34.0	34.3
Female	2.4	2.0	2.0	2.3	2.6
Total physical activity (SD), MET-h/day	23.7 (15.4)	22.8 (14.0)	21.2 (13.5)	19.2 (12.7)	15.9 (11.5)
Sedentary leisure time (SD), h/day	1.0 (0.4)	2.1 (0.3)	3.1 (0.2)	4.1 (0.1)	5.6 (1.2)
Daily consumption, %					
Fresh fruits	16.9	18.2	19.6	20.3	22.8
Fresh vegetables	88.6	93.5	95.7	97.0	96.7
Red meat	27.3	28.8	30.1	31.0	34.5
Blood pressure and anthropometry					
SBP (SD), mmHg	131.3 (22.3)	131.1 (21.2)	131.1 (20.8)	130.7 (20.9)	130.9 (21.3)
RPG (SD), mmol/L	6.1 (2.1)	6.0 (2.2)	6.1 (2.3)	6.1 (2.4)	6.1 (2.7)
BMI (SD), kg/m^2	23.4 (3.3)	23.5 (3.3)	23.7 (3.3)	23.9 (3.4)	24.1 (3.5)
Waist circumference (SD), cm	79.4 (9.7)	79.8 (9.6)	80.4 (9.6)	80.9 (9.8)	81.5 (9.9)
Hip circumference (SD), cm	90.2 (6.8)	90.6 (6.9)	91.1 (6.8)	91.3 (6.9)	91.6 (6.9)
Waist-to-hip ratio (SD)	0.88 (0.07)	0.88 (0.07)	0.88 (0.07)	0.88 (0.07)	0.89 (0.07)
Percent body fat (SD), %	27.3 (8.2)	27.6 (8.3)	28.1 (8.4)	28.4 (8.5)	29.0 (8.6)
Height (SD), cm	158.2 (8.1)	158.5 (8.2)	158.8 (8.3)	159.0 (8.3)	159.2 (8.3)
BMI at age 25 (SD), kg/m^2	22.0 (2.6)	21.9 (2.6)	21.9 (2.6)	21.9 (2.6)	21.8 (2.7)

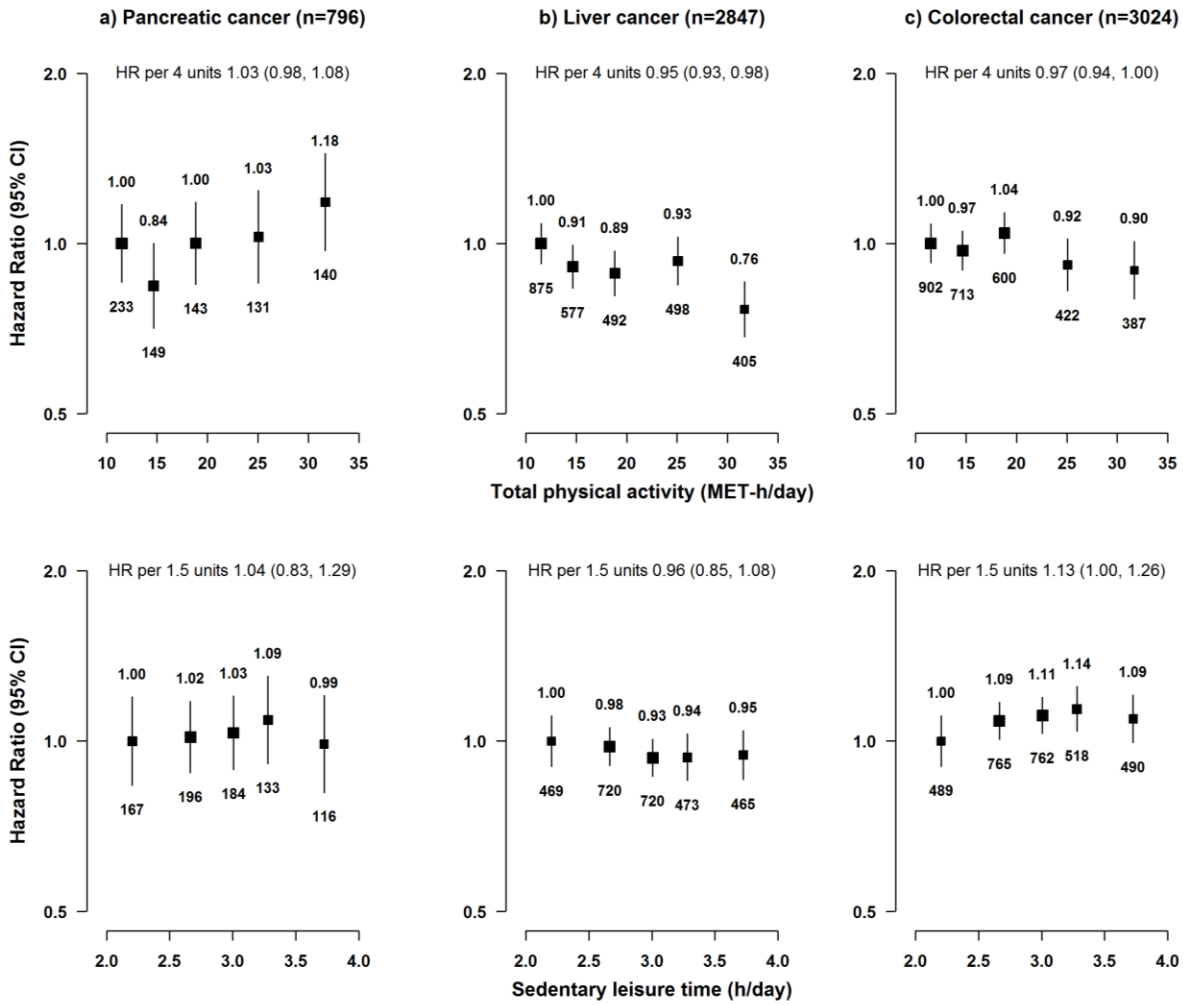
Variable*	Sedentary leisure time (h/day)				
	0 to <2 (n=84,164)	**2 to <3** (n=132,125)	**3 to <4** (n=133,839)	**4 to <5** (n=86,112)	**≥5** (n=73,652)
HBsAg positive, %	2.9	3.1	3.1	3.1	2.9
Prior disease history, %					
Diabetes	5.5	5.5	5.8	6.1	7.4
Coronary heart disease	2.7	2.9	3.1	3.1	3.6
Stroke or TIA	1.6	1.6	1.6	1.6	2.3
Hypertension	10.9	11.3	11.9	12.2	13.2
Family history of diabetes	4.5	4.7	5	5.3	5.8
Family history of cancer	13.6	13.8	14.2	14.4	14.7

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.
* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.

6.1.2 Associations of PA and SLT with specific GI cancers

The main model was stratified by age-at-risk, sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, smoking, alcohol, education, household income, self-rated health, family history of cancer, SLT (for PA), and PA (for SLT). Total PA showed no association with risk of pancreatic cancer and inverse associations with risks of liver and colorectal cancer (**Figure 6.5** and **Tables 6.4-6.6**). The HRs per 4 MET-h/day higher usual total PA were 1.03 (95% CI 0.98-1.08) for pancreatic, 0.95 (0.93-0.98) for liver, and 0.97 (0.94-1.00) for colorectal cancer (**Figure 6.5**). For liver cancer, the HRs were 1.00 (0.92-1.08), 0.91 (0.84-0.99), 0.89 (0.81-0.97), 0.93 (0.85-1.02), and 0.76 (0.69-0.85) for those in the bottom to the top quintile (**Table 6.5**); for colorectal cancer, the corresponding HRs were 1.00 (0.93-1.08), 0.97 (0.90-1.05), 1.04 (0.96-1.13), 0.92 (0.83-1.02), and 0.90 (0.80-1.01) (**Table 6.6**). When modelling total PA with different categories (in multiples of 4 MET-h/day, **Appendix 6.1**), there was no clear association with risk of pancreatic cancer, while the HRs for the top category tended to be more extreme for liver and colorectal cancer. For liver cancer, the HRs were 1.00 (0.92-1.09), 0.92 (0.86-0.99), 0.90 (0.82-0.99), 0.89 (0.79-0.99), 0.81 (0.73-0.91), and 0.68 (0.55-0.84) for those with total PA of 0 to <8, 8 to <16, 16 to <24, 24 to <32, 32 to <48, ≥48 MET-h/day; for colorectal cancer, the corresponding HRs were 1.00 (0.92-1.09), 0.96 (0.90-1.02), 0.98 (0.90-1.07), 0.89 (0.79-1.00), 0.90 (0.80-1.01), and 0.75 (0.58-0.93).

Figure 6.5 Associations of total PA and SLT with specific GI cancers



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

HRs are plotted against the mean level in each category of total PA or SLT. Log-scale is used for the y-axis. The squares represent HRs, and the vertical lines represent 95% CIs. The area of the squares is inversely proportional to the variance of the log HRs. The numbers above the vertical lines are point estimates for HRs, and the numbers below the lines are numbers of events.

Table 6.4 Adjusted HRs for pancreatic cancer by PA and SLT*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Total PA				
0 to <8.8	233	966,732	17.8	1.00 (0.86, 1.17)
8.8 to <14.3	149	1,010,234	16.4	0.84 (0.71, 1.00)
14.3 to <21.9	143	1,025,687	12.3	1.00 (0.85, 1.18)
21.9 to <33.3	131	1,024,862	13.2	1.03 (0.85, 1.23)
≥33.3	140	1,038,119	12.9	1.18 (0.98, 1.44)
per 4 MET-h/day†				*1.03 (0.98, 1.08)*
Occupational PA				
0	341	1,500,764	16.8	1.00 (0.84, 1.20)
>0 to <9.0	121	851,834	17.7	1.32 (1.08, 1.62)
9.0 to <15.5	104	925,459	10.8	1.07 (0.88, 1.29)
15.5 to <26.1	111	906,120	10.7	1.14 (0.94, 1.38)
≥26.1	119	881,456	11.4	1.23 (1.01, 1.51)
per 4 MET-h/day†				*1.02 (0.97, 1.07)*
Nonoccupational PA				
0 to <3.9	167	1,001,278	15.1	1.00 (0.84, 1.19)
3.9 to <6.5	162	1,001,569	17.6	0.99 (0.85, 1.16)
6.5 to <8.5	150	1,020,848	13.5	1.02 (0.87, 1.19)
8.5 to <11.6	145	1,014,472	16.2	0.98 (0.83, 1.16)
≥11.6	172	1,027,467	14.5	1.14 (0.97, 1.35)
per 4 MET-h/day†				*1.10 (0.96, 1.26)*
SLT				
0 to <2	167	846,843	14.1	1.00 (0.84, 1.19)
2 to <3	196	1,319,272	15.3	1.02 (0.88, 1.17)
3 to <4	184	1,323,156	15.6	1.03 (0.89, 1.20)
4 to <5	133	852,252	16.5	1.09 (0.92, 1.30)
≥5	116	724,112	16.5	0.99 (0.82, 1.20)
per 1.5 h/day†				*1.04 (0.83, 1.29)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Table 6.5 Adjusted HRs for liver cancer by PA and SLT*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Total PA				
0 to <8.8	875	966,182	72.3	1.00 (0.92, 1.08)
8.8 to <14.3	577	1,009,861	52.5	0.91 (0.84, 0.99)
14.3 to <21.9	492	1,025,263	55.5	0.89 (0.81, 0.97)
21.9 to <33.3	498	1,024,490	41.0	0.93 (0.85, 1.02)
≥33.3	405	1,037,827	56.8	0.76 (0.69, 0.85)
per 4 MET-h/day†				*0.95 (0.93, 0.98)*
Occupational PA				
0	1122	1,500,065	84.6	1.00 (0.91, 1.10)
>0 to <9.0	500	851,504	53.5	0.90 (0.81, 0.99)
9.0 to <15.5	420	925,115	54.2	0.89 (0.81, 0.98)
15.5 to <26.1	432	905,807	48.6	0.92 (0.83, 1.01)
≥26.1	373	881,131	42.1	0.76 (0.68, 0.85)
per 4 MET-h/day†				*0.96 (0.94, 0.98)*
Nonoccupational PA				
0 to <3.9	755	1,000,739	55.8	1.00 (0.92, 1.09)
3.9 to <6.5	651	1,001,030	54.6	1.08 (1.00, 1.17)
6.5 to <8.5	505	1,020,511	61.6	0.97 (0.89, 1.06)
8.5 to <11.6	483	1,014,123	55.5	0.97 (0.88, 1.06)
≥11.6	453	1,027,219	53.6	0.97 (0.88, 1.08)
per 4 MET-h/day†				*0.95 (0.88, 1.03)*
SLT				
0 to <2	469	846,490	61.1	1.00 (0.90, 1.11)
2 to <3	720	1,318,717	54.9	0.98 (0.91, 1.05)
3 to <4	720	1,322,690	52.2	0.93 (0.87, 1.01)
4 to <5	473	851,860	55.2	0.94 (0.85, 1.03)
≥5	465	723,866	61.9	0.95 (0.86, 1.04)
per 1.5 h/day†				*0.96 (0.85, 1.08)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Table 6.6 Adjusted HRs for colorectal cancer by PA and SLT*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Total PA				
0 to <8.8	902	964,364	64.5	1.00 (0.93, 1.08)
8.8 to <14.3	713	1,008,427	59.9	0.97 (0.90, 1.05)
14.3 to <21.9	600	1,024,061	51.1	1.04 (0.96, 1.13)
21.9 to <33.3	422	1,023,777	65.7	0.92 (0.83, 1.02)
≥33.3	387	1,037,080	58.6	0.90 (0.80, 1.01)
per 4 MET-h/day†				*0.97 (0.94, 1.00)*
Occupational PA				
0	1472	1,496,851	63.7	1.00 (0.91, 1.09)
>0 to <9.0	425	850,765	65.2	1.01 (0.91, 1.13)
9.0 to <15.5	423	924,351	46.7	1.01 (0.92, 1.12)
15.5 to <26.1	365	905,225	47.8	0.95 (0.85, 1.05)
≥26.1	339	880,518	59.4	0.88 (0.78, 0.99)
per 4 MET-h/day†				*0.97 (0.95, 1.00)*
Nonoccupational PA				
0 to <3.9	630	999,664	62.6	1.00 (0.91, 1.09)
3.9 to <6.5	616	1,000,001	55.5	0.95 (0.88, 1.03)
6.5 to <8.5	569	1,019,362	55.0	0.96 (0.88, 1.04)
8.5 to <11.6	590	1,012,845	58.8	0.95 (0.88, 1.04)
≥11.6	619	1,025,837	57.7	0.98 (0.90, 1.07)
per 4 MET-h/day†				*0.99 (0.92, 1.06)*
SLT				
0 to <2	489	845,567	53.3	1.00 (0.91, 1.10)
2 to <3	765	1,317,232	56.7	1.09 (1.01, 1.17)
3 to <4	762	1,321,111	58.9	1.11 (1.03, 1.19)
4 to <5	518	850,947	59.7	1.14 (1.04, 1.24)
≥5	490	722,852	62.5	1.09 (1.00, 1.20)
per 1.5 h/day†				*1.13 (1.00, 1.26)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

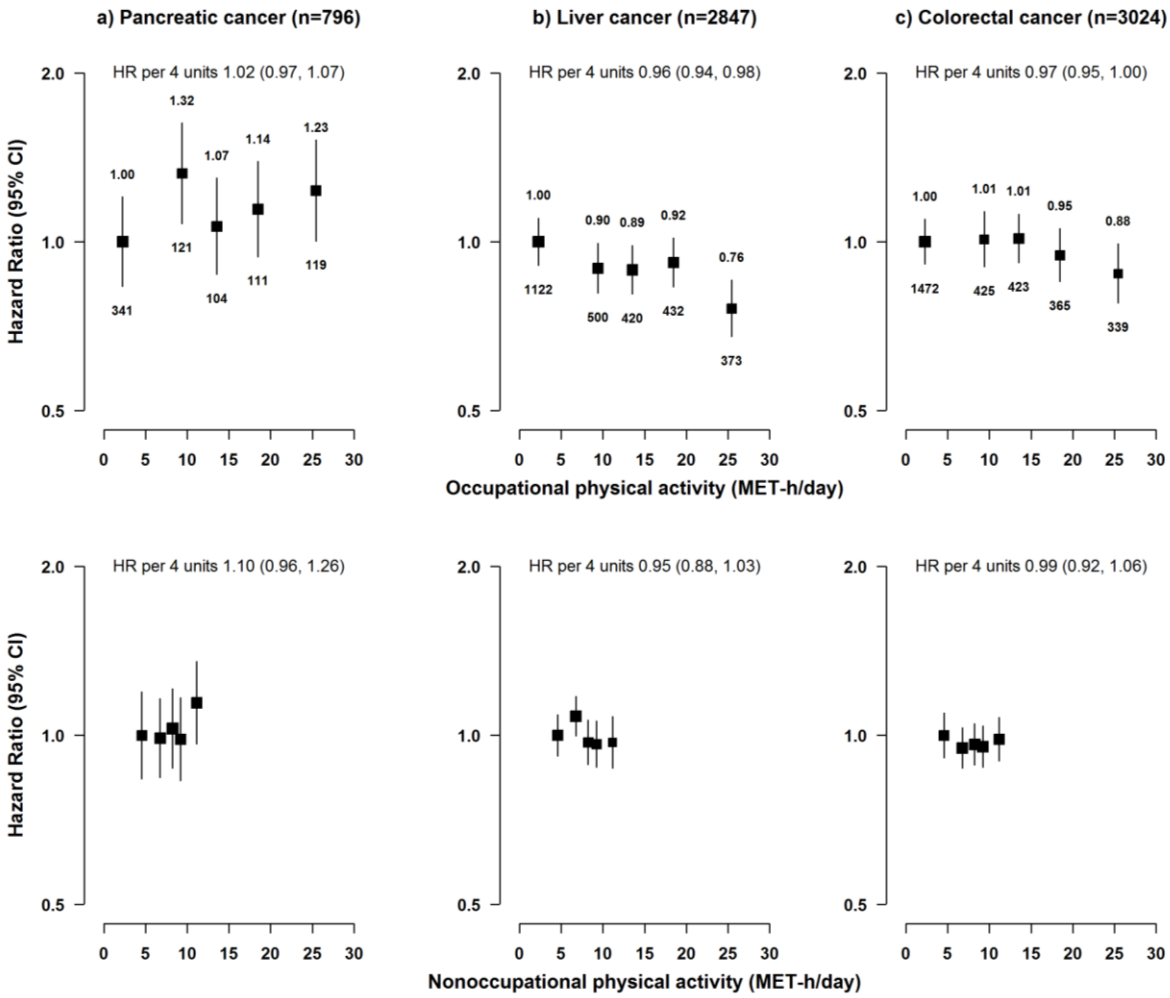
Occupational PA showed similar associations with risks of these three cancers to total PA (**Figure 6.6** and **Tables 6.4-6.6**), with HRs per 4 MET-h/day of 1.02 (0.97-1.07) for pancreatic, 0.96 (0.94-0.98) for liver, and 0.97 (0.95-1.00) for colorectal cancer. For liver cancer, the HRs were 1.00 (0.91-1.10), 0.90 (0.81-0.99), 0.89 (0.81-0.98), 0.92 (0.83-1.01), and 0.76 (0.68-0.85) for those in the bottom to the top quintile (**Table 6.5**); for colorectal cancer, the corresponding HRs were 1.00 (0.91-1.09), 1.01 (0.91-1.13), 1.01 (0.92-1.12), 0.95 (0.85-1.05), and 0.88 (0.78-0.99) (**Table 6.6**). Nonoccupational PA showed no clear associations with these three cancers (**Figure 6.6** and **Tables 6.4-6.6**), with HRs per 4 MET-h/day of 1.10 (0.98-1.26) for pancreatic, 0.95 (0.88-1.03) for liver, and 0.99 (0.92-1.06) for liver cancer.

When examining the associations by domain of nonoccupational PA (i.e. commuting, household, and leisure-time), the associations differed by cancer type (**Table 6.7**). For pancreatic cancer, there was a positive association for commuting PA (HR per 4 MET-h/day 1.45 [1.10-1.93]), while there were no associations for household and leisure-time PA (1.06 [0.90-1.26] vs 0.93 [0.71-1.23]). For liver cancer, there were inverse trends for commuting and leisure-time PA (HR per 4 MET-h/day 0.85 [0.72-1.01] and 0.89 [0.76-1.04], respectively), while there was no association for household PA (1.03 [0.93-1.13]). For colorectal cancer, there were no associations for commuting and household PA (HR per 4 MET-h/day 1.05 [0.88-1.26] and 1.01 [0.93-1.11], respectively), while there was an inverse trend for leisure-time PA (0.92 [0.81-1.04]). According to the PA recommendations by the 2010 WHO guidelines, individuals who had ≥1.07 MET-h/day or ≥7.5 MET-h/day leisure-time PA had a similar risk of pancreatic cancer compared with those

who had no leisure-time PA (HR 0.99 [0.84-1.16] vs 1.08 [0.73-1.60]). Individuals who had ≥1.07 MET-h/day leisure time PA had similar risks of liver and colorectal cancer (HR 0.94 [0.86-1.03] vs 1.06 [0.98-1.14]), while individuals who had ≥7.5 MET-h/day leisure-time PA had a 26% lower risk of liver cancer and a nonsignificant 15% lower risk of colorectal cancer (HR 0.74 [0.57-0.96] vs 0.85 [0.69-1.03]).

SLT were not associated with risks of pancreatic and liver cancer, with HRs per 1.5 h/day higher usual SLT of 1.04 (0.83-1.29) and 0.96 (0.85-1.08), respectively (**Figure 6.5** and **Tables 6.4-6.5**). For colorectal cancer, there was a positive association, with a HR of 1.13 (1.00-1.26) per 1.5 h/day (**Figure 6.5**). The HRs for colorectal cancer were 1.00 (0.91-1.10), 1.09 (1.01-1.17), 1.11 (1.03-1.19), 1.14 (1.04-1.24), and 1.09 (1.00-1.20) for those who had SLT of <2, 2 to <3, 3 to <4, 4 to <5, and ≥5 h/day (**Table 6.6**).

Figure 6.6 Associations of domain-specific PA with specific GI cancers



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.

Table 6.7 Adjusted HRs for specific GI cancers by nonoccupational PA[*]

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Commuting						
0	399	1.00 (0.85, 1.18)	1431	1.00 (0.92, 1.09)	1723	1.00 (0.92, 1.08)
>0 to <1.2	104	1.14 (0.93, 1.39)	369	0.86 (0.78, 0.96)	379	0.97 (0.87, 1.08)
1.2 to <1.8	47	1.07 (0.80, 1.42)	167	0.94 (0.81, 1.10)	184	0.97 (0.84, 1.13)
1.8 to <3.4	149	1.30 (1.10, 1.53)	498	0.92 (0.84, 1.01)	437	0.91 (0.82, 1.00)
≥3.4	97	1.19 (0.96, 1.49)	382	0.89 (0.80, 1.00)	301	1.01 (0.89, 1.14)
per 4 MET-h/day[†]		*1.45 (1.10, 1.93)*		*0.85 (0.72, 1.01)*		*1.05 (0.88, 1.26)*
Household						
0	84	1.00 (0.79, 1.27)	383	1.00 (0.89, 1.12)	291	1.00 (0.88, 1.14)
>0 to <2.8	110	1.02 (0.83, 1.25)	440	1.04 (0.94, 1.15)	413	1.02 (0.92, 1.13)
2.8 to <5.6	155	0.94 (0.80, 1.10)	682	1.17 (1.08, 1.26)	637	1.03 (0.96, 1.12)
5.6 to <8.4	324	0.98 (0.87, 1.11)	1022	1.08 (1.00, 1.16)	1267	1.03 (0.96, 1.10)
≥8.4	123	1.09 (0.90, 1.34)	320	1.11 (0.98, 1.26)	416	1.05 (0.94, 1.17)
per 4 MET-h/day[†]		*1.06 (0.90, 1.26)*		*1.03 (0.93, 1.13)*		*1.01 (0.93, 1.11)*
Leisure-time						
0	571	1.00 (0.89, 1.13)	2129	1.00 (0.94, 1.06)	1975	1.00 (0.94, 1.06)
>0 to ≤1.07	23	1.08 (0.72, 1.62)	86	1.01 (0.82, 1.25)	103	1.17 (0.96, 1.42)
>1.07[‡]	202	0.99 (0.84, 1.16)	632	0.94 (0.86, 1.03)	946	1.06 (0.98, 1.14)
0	571	1.00 (0.87, 1.15)	2129	1.00 (0.93, 1.08)	1975	1.00 (0.93, 1.08)
>0 to <3.75	140	1.06 (0.90, 1.23)	445	0.97 (0.89, 1.05)	629	1.13 (1.05, 1.22)
3.75 to <7.5	59	0.84 (0.65, 1.10)	214	0.98 (0.85, 1.12)	320	1.02 (0.91, 1.14)
≥7.5	26	1.08 (0.73, 1.60)	59	0.74 (0.57, 0.96)	100	0.85 (0.69, 1.03)
per 4 MET-h/day[†]		*0.93 (0.71, 1.23)*		*0.89 (0.76, 1.04)*		*0.92 (0.81, 1.04)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.
[†] Regression dilution ratios: commuting, 0.45; household, 0.53; leisure time, 0.55.
[‡] 1.07 MET-h/day is based on recommended minimum threshold for health benefits by the 2010 WHO guidelines.

6.1.3 Exclusion of early years of follow-up, smokers or drinkers

When excluding the first two or five years of follow-up, similar associations were observed of PA and SLT with risks of pancreatic and liver cancer to those in all participants (**Appendices 6.2-6.3**), suggesting that the associations were not affected by reverse causality (i.e. individuals with preclinical cancer may reduce physical activity). For colorectal cancer (**Appendix 6.4**), similar associations were observed for total, occupational, and nonoccupational PA when excluding the first two or five years, while the positive association for SLT became stronger when excluding the first five years (HR per 1.5 h/day: without and with exclusions: 1.13 [1.00-1.26] vs 1.21 [1.04-1.40]). When restricting the analyses to never regular smokers or never regular drinkers (**Appendices 6.5-6.7**), similar associations were observed of PA and SLT with risks of all three cancers, with the exception of PA and pancreatic cancer in never regular smokers. In never regular smokers, there were positive trends between PA and pancreatic cancer (HR per 4 MET-h/day: total 1.10 [1.02-1.18], occupational 1.07 [1.00-1.14], nonoccupational 1.17 [0.99-1.38]; **Appendix 6.5**).

6.1.4 Associations of PA and SLT with specific GI cancers by work activity level

In CKB, the intensity of PA differed by work activity level, particularly total and occupational PA. The mean MET values of total PA were 15.3, 10.9, and 9.6 among farmers, manual workers, and nonmanual workers. For occupational PA, the mean MET values were 6.9, 3.6, and 2.1 among farmers, manual workers, and nonmanual workers; for nonoccupational PA, the corresponding mean MET

values were 8.4, 7.3, and 7.6. The associations of total and domain-specific PA with all three cancers did not differ by work activity level (*p* for heterogeneity 0.07-0.92, **Table 6.8**, **Figures 6.7-6.9**). Nonetheless, the inverse associations of total PA with liver and colorectal cancer were more robust among nonmanual workers (**Table 6.8**). For liver cancer, the HRs per 4 MET-h/day were 0.98 (0.95-1.02), 0.93 (0.83-1.05), and 0.91 (0.86-0.96) among farmers, manual workers, and nonmanual workers (*p* for heterogeneity 0.07); for colorectal cancer, the corresponding HRs were 0.99 (0.94-1.03), 1.03 (0.92-1.14), and 0.95 (0.91-1.00) (*p* for heterogeneity 0.27). For pancreatic cancer, farmers who had high levels of total PA tended to have a higher risk (HR comparing top vs bottom quintile: 1.31 [1.02-1.69], **Table 6.8**).

For all three cancers, the pattern of occupational PA by work activity level was similar to that of total PA (**Figures 6.7-6.9**). For liver cancer, the HRs per 4 MET-h/day were 0.98 (0.95-1.01), 0.97 (0.87-1.08), and 0.93 (0.88-0.98) among farmers, manual workers, and nonmanual workers (*p* for heterogeneity 0.26, **Figure 6.8**); for colorectal cancer, the corresponding HRs were 0.98 (0.94-1.03), 0.99 (0.89-1.09), and 0.97 (0.92-1.02) (*p* for heterogeneity 0.92, **Figure 6.9**). For pancreatic cancer, farmers who had high levels of occupational PA tended to have a higher risk (HR comparing top vs bottom quintile: 1.32 [1.00-1.75], **Figure 6.7**). For nonoccupational PA, there were positive trends for pancreatic cancer among farmers and manual workers (HR per 4 MET-h/day 1.27 [1.02-1.59] vs 1.37 [0.84-2.24], **Figure 6.7**) and for colorectal cancer among manual workers (1.31 [1.00-1.71], **Figure 6.9**).

For SLT (**Table 6.9**), the null associations with risks of pancreatic and liver cancer did not differ by work activity level (*p* for heterogeneity: 0.41 and 0.43), but there was a positive trend for pancreatic cancer among manual workers (HR per 1.5 h/day 1.75 [0.74-4.14]). For colorectal cancer, however, the association with SLT differed by work activity level (*p* for heterogeneity 0.01), with positive trends among manual and nonmanual workers (HR per 1.5 h/day 2.13 [1.35-3.36] vs 1.10 [0.96-1.26]) and no association among farmers (0.98 [0.76-1.26]).

Among nonfarmers, occupation categories derived from work activity levels were examined to assess the associations of occupational sitting time with these three cancers (**Appendix 6.8**). Compared with nonfarmers who had a nonsedentary occupation, nonfarmers with a sedentary occupation had a higher risk of colorectal cancer (HR 1.29 [1.15-1.44]), with similar HRs for colon and rectal cancer (1.32 [1.14-1.53] vs 1.28 [1.11-1.51], *p* for heterogeneity 0.88). Nonfarmers with a sedentary occupation also had a higher risk of pancreatic cancer (HR 1.17 [0.91-1.49]), albeit nonsignificant. Nonfarmers who were not in paid employment (i.e. retired, homemakers, and unemployed) had higher risks of liver (HR 1.27 [1.12-1.44]) and colorectal cancer (HR 1.12 [1.00-1.24]).

Table 6.8 Adjusted HRs for specific GI cancers associated with total PA by work activity level[*]

	Farmers		Manual workers[‡]		Nonmanual workers[§]	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Pancreatic cancer						
0 to <8.8	32	1.00 (0.67, 1.48)		—	201	1.00 (0.85, 1.18)
8.8 to <14.3	47	1.04 (0.77, 1.42)		—	101	0.77 (0.63, 0.93)
14.3 to <21.9	67	0.98 (0.77, 1.25)	4	1.00 (0.37, 2.71)	73	0.98 (0.78, 1.24)
21.9 to <33.3	89	1.12 (0.90, 1.39)	11	0.65 (0.36, 1.20)	31	0.90 (0.62, 1.31)
≥33.3	70	1.31 (1.02, 1.69)	50	1.22 (0.88, 1.69)	20	0.97 (0.60, 1.56)
per 4 MET-h/day[†]		*1.04 (0.96, 1.13)*		*1.11 (0.92, 1.33)*		*0.99 (0.91, 1.09)*
Liver cancer						
0 to <8.8	187	1.00 (0.85, 1.18)		—	688	1.00 (0.91, 1.10)
8.8 to <14.3	231	1.01 (0.88, 1.16)		—	344	0.88 (0.79, 0.97)
14.3 to <21.9	267	0.88 (0.78, 0.99)	15	1.00 (0.58, 1.72)	212	0.89 (0.78, 1.03)
21.9 to <33.3	332	1.02 (0.90, 1.14)	57	0.80 (0.61, 1.05)	108	0.85 (0.70, 1.04)
≥33.3	240	0.87 (0.76, 1.00)	125	0.78 (0.64, 0.96)	41	0.60 (0.43, 0.83)
per 4 MET-h/day[†]		*0.98 (0.95, 1.02)*		*0.93 (0.83, 1.05)*		*0.91 (0.86, 0.96)*
Colorectal cancer						
0 to <8.8	115	1.00 (0.82, 1.23)		—	785	1.00 (0.92, 1.09)
8.8 to <14.3	160	0.94 (0.79, 1.11)		—	550	1.00 (0.92, 1.09)
14.3 to <21.9	240	1.09 (0.96, 1.24)	16	1.00 (0.60, 1.66)	349	1.07 (0.96, 1.20)
21.9 to <33.3	240	1.08 (0.94, 1.23)	54	0.71 (0.54, 0.93)	128	0.85 (0.71, 1.02)
≥33.3	167	1.00 (0.85, 1.17)	160	0.82 (0.68, 0.98)	60	0.78 (0.59, 1.02)
per 4 MET-h/day[†]		*0.99 (0.94, 1.03)*		*1.03 (0.92, 1.14)*		*0.95 (0.91, 1.00)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.

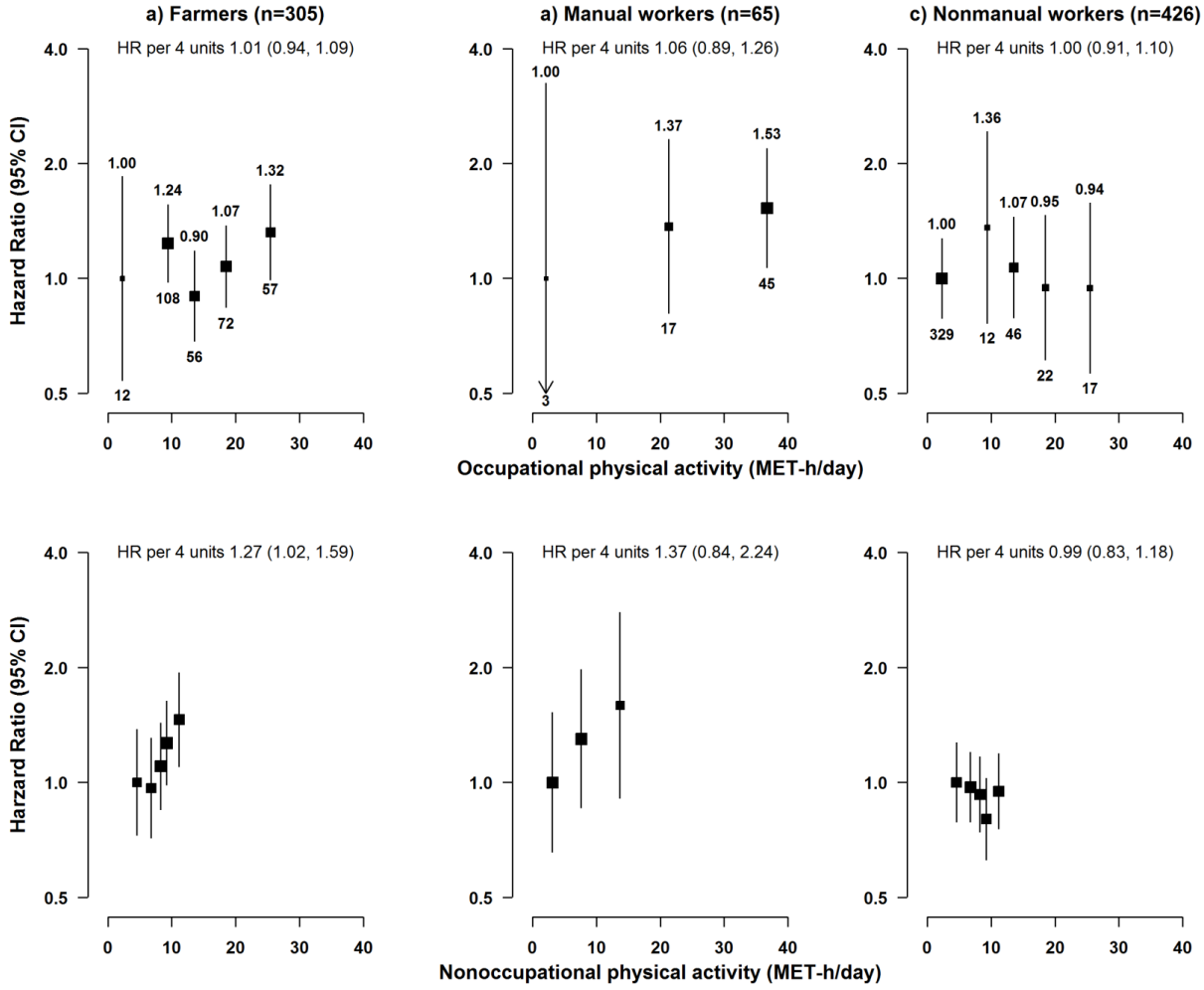
† Regression dilution ratios: total PA, 0.54.

‡ Among manual workers, quintiles 1-3 (0 to <21.9 MET-h/day) were used as the reference.

§ Nonmanual workers include homemakers, retired, unemployed, and other occupation.

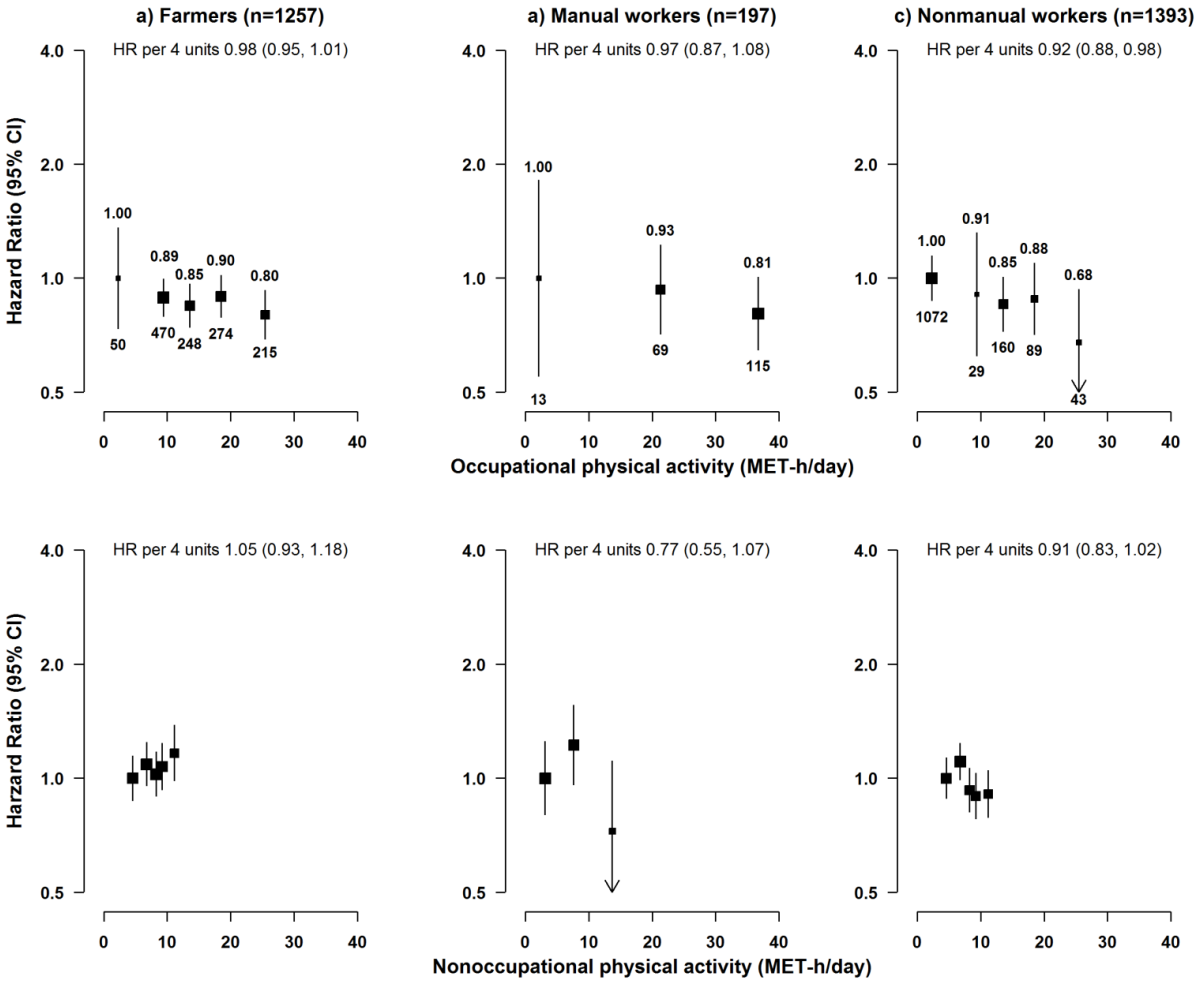
P for heterogeneity by work activity level: pancreatic cancer, 0.50; liver cancer, 0.07; colorectal cancer, 0.27.

Figure 6.7 Associations of domain-specific PA with risk of pancreatic cancer by work activity level



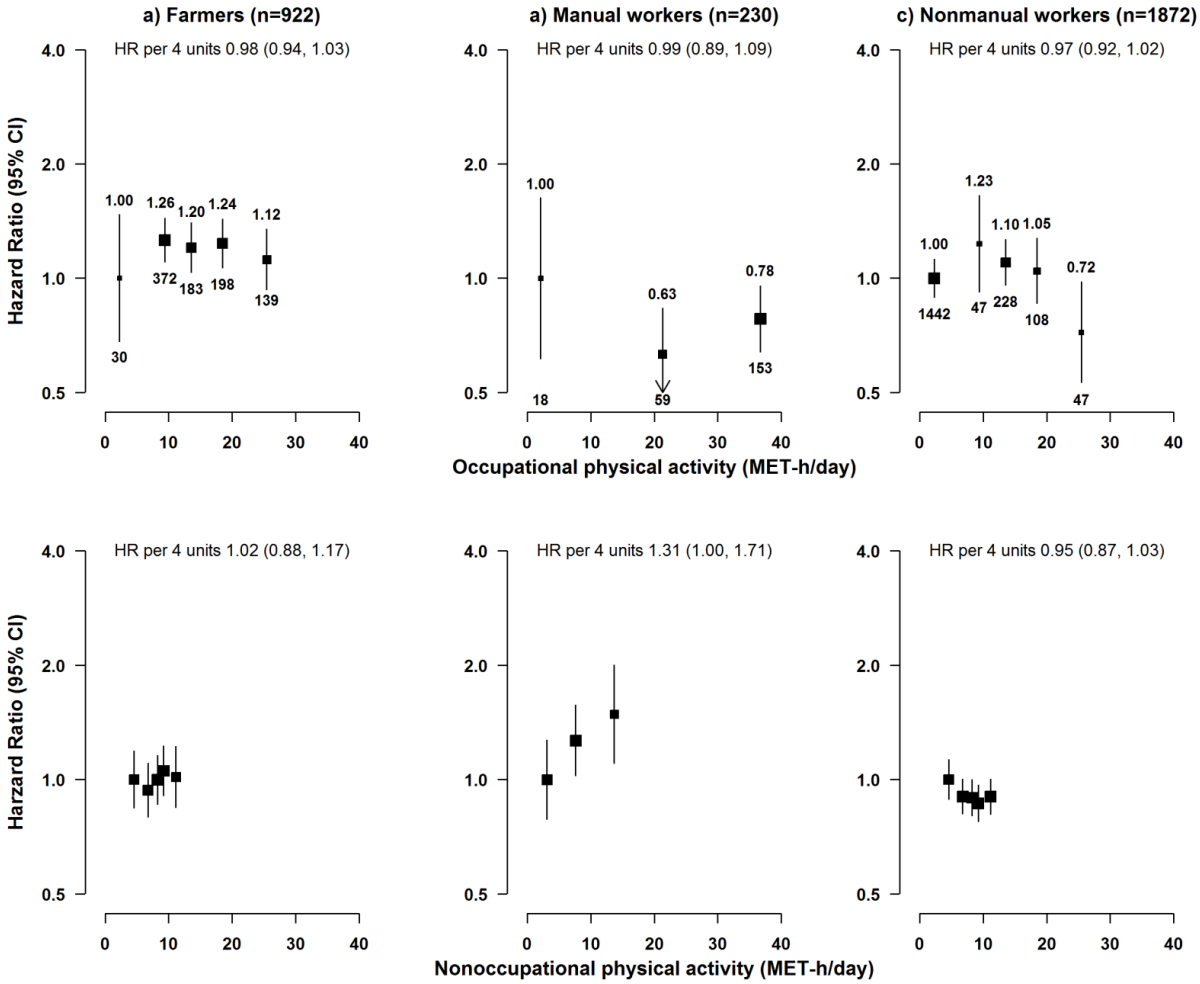
Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.
P for heterogeneity by work activity level: occupational, 0.85; nonoccupational, 0.45.

Figure 6.8 Associations of domain-specific PA with risk of liver cancer by work activity level



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.
P for heterogeneity by work activity level: occupational, 0.26; nonoccupational, 0.54.

Figure 6.9 Associations of domain-specific PA with risk of colorectal cancer by work activity level



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.
P for heterogeneity by work activity level: occupational, 0.92; nonoccupational, 0.09.

Table 6.9 Adjusted HRs for specific GI cancers associated with SLT by work activity level[*]

	Farmers		Manual workers		Nonmanual workers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Pancreatic cancer						
0 to <2	85	1.00 (0.76, 1.32)	16	1.00 (0.58, 1.72)	66	1.00 (0.77, 1.29)
2 to <3	73	0.98 (0.78, 1.24)	19	1.17 (0.74, 1.84)	104	1.04 (0.86, 1.26)
3 to <4	58	0.87 (0.67, 1.12)	14	1.31 (0.77, 2.22)	112	1.14 (0.95, 1.37)
4 to <5	53	1.15 (0.87, 1.53)	10	1.60 (0.84, 3.03)	70	1.00 (0.79, 1.26)
≥5	36	1.05 (0.74, 1.49)	6	1.93 (0.83, 4.48)	74	0.92 (0.72, 1.16)
per 1.5 h/day[†]		*1.10 (0.71, 1.68)*		*1.75 (0.74, 4.14)*		*0.96 (0.73, 1.27)*
Liver cancer						
0 to <2	219	1.00 (0.86, 1.17)	41	1.00 (0.72, 1.39)	209	1.00 (0.87, 1.15)
2 to <3	320	1.01 (0.91, 1.14)	59	1.02 (0.78, 1.32)	341	0.95 (0.86, 1.06)
3 to <4	324	0.93 (0.84, 1.04)	51	0.99 (0.75, 1.32)	345	0.94 (0.84, 1.04)
4 to <5	214	0.97 (0.84, 1.11)	23	0.89 (0.58, 1.36)	236	0.92 (0.81, 1.05)
≥5	180	1.05 (0.90, 1.23)	23	1.45 (0.94, 2.24)	262	0.85 (0.75, 0.97)
per 1.5 h/day[†]		*1.04 (0.84, 1.28)*		*1.16 (0.69, 1.95)*		*0.90 (0.76, 1.05)*
Colorectal cancer						
0 to <2	189	1.00 (0.84, 1.19)	46	1.00 (0.73, 1.37)	254	1.00 (0.88, 1.14)
2 to <3	233	0.99 (0.87, 1.13)	75	1.53 (1.22, 1.93)	457	1.06 (0.97, 1.16)
3 to <4	239	1.03 (0.91, 1.17)	52	1.51 (1.15, 1.99)	471	1.08 (0.98, 1.18)
4 to <5	155	1.06 (0.90, 1.24)	33	1.86 (1.31, 2.65)	330	1.08 (0.97, 1.21)
≥5	106	0.93 (0.76, 1.13)	24	2.70 (1.77, 4.13)	360	1.05 (0.94, 1.17)
per 1.5 h/day[†]		*0.98 (0.76, 1.26)*		*2.13 (1.35, 3.36)*		*1.10 (0.96, 1.26)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and total PA.

[†] Regression dilution ratios: SLT, 0.33.

P for heterogeneity by work activity level: pancreatic, 0.41; liver, 0.43; colorectal, 0.01.

6.1.5 Interactions of PA with SLT and of occupational with nonoccupational PA

The associations of total PA with risks of the three cancers did not differ by level of SLT (**Table 6.10**). For pancreatic cancer, there were no associations with total PA across tertiles of SLT, with HRs per 4 MET-h/day of 1.02 (0.93-1.13), 1.05 (0.95-1.17), and 1.04 (0.97-1.11) for those in the top to the bottom tertiles of SLT (*p* for interaction 0.73). For liver and colorectal cancer, the inverse associations with total PA were similar across tertiles of SLT. For liver cancer, the HRs per 4 MET-h/day were 0.94 (0.89-0.98), 0.95 (0.90-1.00), and 0.97 (0.93-1.01) for those in the top to the bottom tertiles of SLT (*p* for interaction 0.96); for colorectal cancer, the corresponding HRs were 0.98 (0.93-1.03), 0.96 (0.91-1.01), and 0.98 (0.94-1.02) (*p* for interaction 0.61).

The associations of occupational PA with risks of pancreatic and colorectal cancer differed by level of nonoccupational PA (*p* for interaction 0.04 and 0.04, **Table 6.11**). For pancreatic cancer, there were no associations with occupational PA for those in the two bottom tertiles of nonoccupational PA (HR per 4 MET-h/day 0.95 [0.85-1.06] and 0.97 [0.88-1.07]), while there was a positive association for those in the top tertile (1.07 [1.00-1.14]). For colorectal cancer, there were inverse associations for those in the two bottom tertiles of nonoccupational PA (0.92 [0.87-0.98] and 0.96 [0.91-1.01]), while there was no association for those in the top tertile (0.99 [0.96-1.03]). For liver cancer (**Table 6.11**), the associations with occupational PA did not differ by level of nonoccupational PA (*p* for interaction 0.09), with HRs per 4 MET-h/day of 0.96 (0.92-1.01), 0.93 (0.88-0.97), and 0.98 (0.94-1.02) for those in the bottom to top tertiles of nonoccupational PA.

Table 6.10 Adjusted HRs for specific GI cancers associated with total PA by level of SLT*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
SLT ≥3.4 h/day						
Total PA <12.4 MET-h/day	135	1.00 (0.83, 1.20)	548	1.00 (0.91, 1.09)	600	1.00 (0.92, 1.09)
Total PA 12.4-25.4 MET-h/day	87	1.24 (1.00, 1.54)	278	0.89 (0.79, 1.01)	324	1.01 (0.90, 1.13)
Total PA ≥25.4 MET-h/day	50	1.29 (0.96, 1.73)	185	0.86 (0.74, 1.00)	155	0.97 (0.82, 1.15)
per 4 MET-h/day†		*1.02 (0.93, 1.13)*		*0.94 (0.89, 0.98)*		*0.98 (0.93, 1.03)*
SLT 2.1-3.3 h/day						
Total PA <12.4 MET-h/day	95	1.09 (0.88, 1.35)	344	0.94 (0.84, 1.05)	410	1.01 (0.92, 1.12)
Total PA 12.4-25.4 MET-h/day	61	1.02 (0.79, 1.31)	262	0.93 (0.82, 1.05)	271	0.94 (0.83, 1.06)
Total PA ≥25.4 MET-h/day	51	1.12 (0.84, 1.49)	207	0.80 (0.69, 0.92)	186	0.91 (0.78, 1.05)
per 4 MET-h/day†		*1.05 (0.95, 1.17)*		*0.95 (0.90, 1.00)*		*0.96 (0.91, 1.01)*
SLT 0-2 h/day						
Total PA <12.4 MET-h/day	92	0.89 (0.72, 1.10)	386	1.01 (0.91, 1.12)	417	0.99 (0.90, 1.10)
Total PA 12.4-25.4 MET-h/day	118	1.32 (1.09, 1.59)	312	0.96 (0.85, 1.07)	344	0.94 (0.84, 1.05)
Total PA ≥25.4 MET-h/day	107	1.06 (0.85, 1.31)	325	0.84 (0.75, 0.95)	317	0.81 (0.72, 0.92)
per 4 MET-h/day†		*1.04 (0.97, 1.11)*		*0.97 (0.93, 1.01)*		*0.98 (0.94, 1.02)*
P for interactions		*0.73*		*0.96*		*0.61*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. SLT and total PA were grouped by splitting at tertiles.

† Regression dilution ratios: total PA, 0.54.

Table 6.11 Adjusted HRs for cancer associated with occupational PA by level of nonoccupational PA*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Nonoccupational 0-2.9 MET-h/day						
Occupational 0 MET-h/day	54	1.00 (0.75, 1.33)	220	1.00 (0.87, 1.15)	201	1.00 (0.86, 1.16)
Occupational <15.5 MET-h/day	30	0.88 (0.61, 1.29)	163	0.71 (0.60, 0.83)	130	0.91 (0.75, 1.09)
Occupational ≥15.5 MET-h/day	37	0.87 (0.61, 1.22)	177	0.74 (0.63, 0.87)	112	0.69 (0.56, 0.84)
per 4 MET-h/day†		*0.95 (0.85, 1.06)*		*0.96 (0.92, 1.01)*		*0.92 (0.87, 0.98)*
Nonoccupational 3-5.9 MET-h/day						
Occupational 0 MET-h/day	66	0.88 (0.68, 1.14)	233	0.95 (0.83, 1.09)	260	0.89 (0.78, 1.02)
Occupational <15.5 MET-h/day	54	1.03 (0.78, 1.36)	244	0.88 (0.78, 1.00)	224	0.99 (0.86, 1.13)
Occupational ≥15.5 MET-h/day	56	0.83 (0.63, 1.10)	234	0.76 (0.66, 0.87)	207	0.81 (0.70, 0.94)
per 4 MET-h/day†		*0.97 (0.88, 1.07)*		*0.93 (0.88, 0.97)*		*0.96 (0.91, 1.01)*
Nonoccupational ≥6 MET-h/day						
Occupational 0 MET-h/day	221	0.81 (0.68, 0.98)	669	0.85 (0.77, 0.94)	1011	0.87 (0.80, 0.95)
Occupational <15.5 MET-h/day	141	1.03 (0.86, 1.23)	513	0.82 (0.75, 0.90)	494	0.85 (0.78, 0.94)
Occupational ≥15.5 MET-h/day	137	1.15 (0.95, 1.38)	394	0.78 (0.70, 0.87)	385	0.83 (0.75, 0.93)
per 4 MET-h/day†		*1.07 (1.00, 1.14)*		*0.98 (0.94, 1.02)*		*0.99 (0.96, 1.03)*
P for interactions		*0.04*		*0.09*		*0.04*

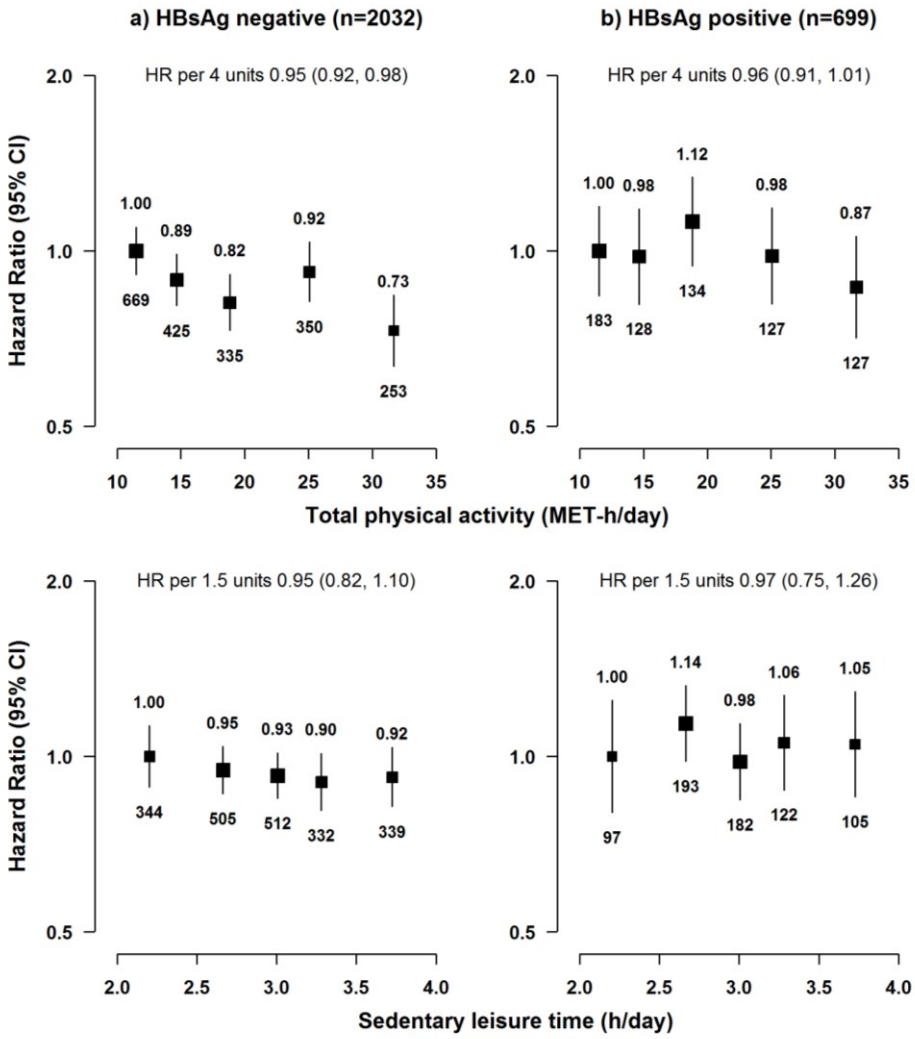
* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT. Occupational and nonoccupational PA were grouped by splitting at tertiles.

† Regression dilution ratios: occupational PA, 0.62.

6.1.6 Associations of PA and SLT with HBsAg negative and positive liver cancer

For both PA and SLT, the associations with liver cancer did not differ by HBsAg status (*p* for heterogeneity 0.26-0.89, **Figure 6.10** and **Table 6.12**). However, the magnitudes of associations tended to differ for total and occupational PA. Among HBsAg negative participants, there were inverse associations of total and occupational PA, with HRs per 4 MET-h/day of 0.95 (0.92-0.98) and 0.95 (0.92-0.98), respectively (**Table 6.12**). For total PA, the HRs among HBsAg negative participants were 1.00 (0.91-1.10), 0.89 (0.81-0.98), 0.82 (0.73-0.91), 0.92 (0.82-1.03), and 0.73 (0.64-0.84) for those in the bottom to the top quintile; for occupational PA, the corresponding HRs were 1.00 (0.90-1.11), 0.87 (0.78-0.98), 0.78 (0.69-0.89), 0.88 (0.78-0.99), and 0.70 (0.60-0.80). Although the linear estimates among HBsAg positive participants were similar to those among HBsAg negative participants (HR per 4 MET-h/day: total 0.96 [0.91-1.01]; occupational: 0.97 [0.93-1.01]), there were no clear associations for total or occupational PA (**Table 6.12**). For total PA, the HRs among HBsAg positive participants were 1.00 (0.84-1.19), 0.98 (0.81-1.17), 1.12 (0.95-1.33), 0.98 (0.81-1.18), and 0.87 (0.71-1.05) for those in the bottom to the top quintile; for occupational PA, the corresponding HRs 1.00 (0.81-1.23), 1.05 (0.85-1.30), 1.29 (1.08-1.54), 1.04 (0.86-1.25), and 0.97 (0.80-1.19). For nonoccupational PA and SLT, there were no associations among HBsAg negative and positive participants (**Table 6.12**). The HRs per 4 MET-h/day nonoccupational PA were 0.99 (0.90-1.08) and 0.89 (0.76-1.05) among HBsAg negative and positive participants, while the HRs per 1.5 h/day SLT were 0.95 (0.82-1.10) and 0.97 (0.75-1.26).

Figure 6.10 Associations of total PA and SLT with risk of liver cancer by HBsAg



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

P for heterogeneity by HBsAg: total PA, 0.75; SLT, 0.89.

Table 6.12 Adjusted HRs for liver cancer associated with PA and SLT by HBsAg*

	HBsAg negative		HBsAg positive	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
Total PA				
0 to <8.8	669	1.00 (0.91, 1.10)	183	1.00 (0.84, 1.19)
8.8 to <14.3	425	0.89 (0.81, 0.98)	128	0.98 (0.81, 1.17)
14.3 to <21.9	335	0.82 (0.73, 0.91)	134	1.12 (0.95, 1.33)
21.9 to <33.3	350	0.92 (0.82, 1.03)	127	0.98 (0.81, 1.18)
≥33.3	253	0.73 (0.64, 0.84)	127	0.87 (0.71, 1.05)
per 4 MET-h/day†		*0.95 (0.92, 0.98)*		*0.96 (0.91, 1.01)*
Occupational PA				
0	876	1.00 (0.90, 1.11)	209	1.00 (0.81, 1.23)
>0 to <9.0	365	0.87 (0.78, 0.98)	122	1.05 (0.85, 1.30)
9.0 to <15.5	268	0.78 (0.69, 0.89)	131	1.29 (1.08, 1.54)
15.5 to <26.1	295	0.88 (0.78, 0.99)	115	1.04 (0.86, 1.25)
≥26.1	228	0.70 (0.60, 0.80)	122	0.97 (0.80, 1.19)
per 4 MET-h/day†		*0.95 (0.92, 0.98)*		*0.97 (0.93, 1.01)*
Nonoccupational PA				
0 to <3.9	505	1.00 (0.90, 1.11)	225	1.00 (0.86, 1.17)
3.9 to <6.5	441	1.03 (0.94, 1.13)	176	1.16 (1.00, 1.34)
6.5 to <8.5	376	0.97 (0.88, 1.07)	109	0.95 (0.78, 1.15)
8.5 to <11.6	365	0.97 (0.87, 1.08)	101	0.98 (0.80, 1.20)
≥11.6	345	0.99 (0.88, 1.12)	88	0.87 (0.69, 1.10)
per 4 MET-h/day†		*0.99 (0.90, 1.08)*		*0.89 (0.76, 1.05)*
SLT				
0 to <2	344	1.00 (0.89, 1.12)	97	1.00 (0.81, 1.24)
2 to <3	505	0.95 (0.87, 1.04)	193	1.14 (0.99, 1.32)
3 to <4	512	0.93 (0.85, 1.01)	182	0.98 (0.85, 1.13)
4 to <5	332	0.90 (0.81, 1.01)	122	1.06 (0.88, 1.27)
≥5	339	0.92 (0.82, 1.03)	105	1.05 (0.86, 1.29)
per 1.5 h/day†		*0.95 (0.82, 1.10)*		*0.97 (0.75, 1.26)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

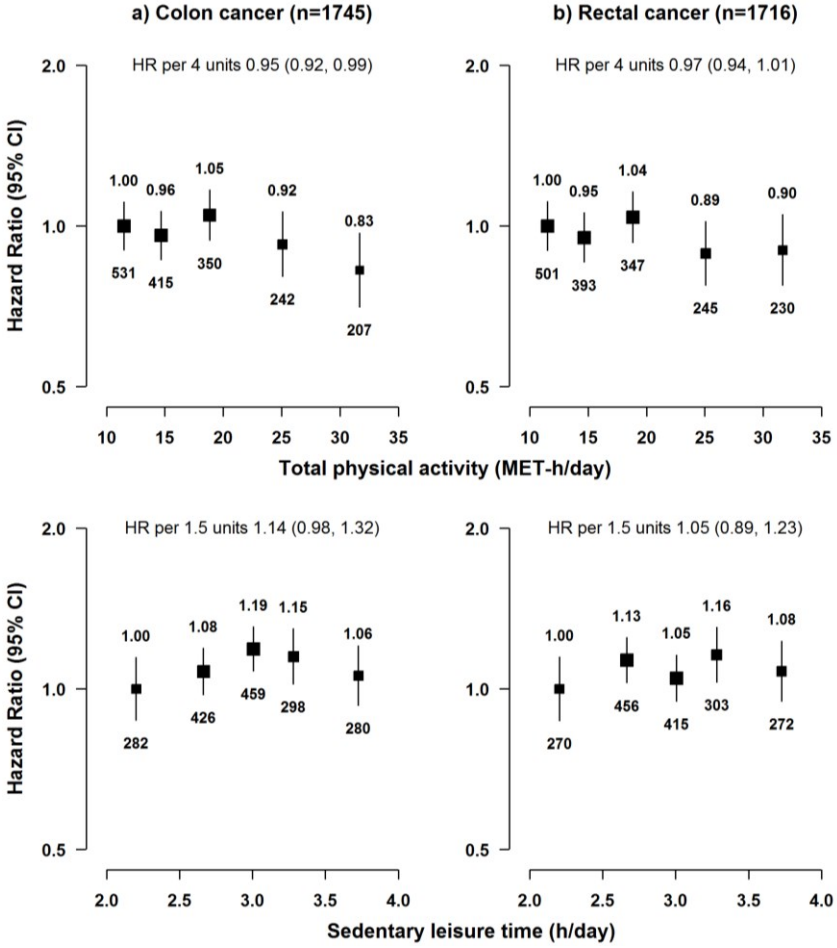
† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

P for heterogeneity by HBsAg: total PA, 0.75; occupational PA, 0.43; nonoccupational PA, 0.26; SLT, 0.89.

6.1.7 Associations of PA and SLT with colon and rectal cancer

For both total PA and SLT, the associations did not differ for colon and rectal cancer (*p* for heterogeneity 0.42 vs 0.47, **Figure 6.11** and **Table 6.13**). For total PA, there was an inverse association for colon cancer and an inverse trend for rectal cancer (HR per 4 MET-h/day 0.95 [0.92-0.99] vs 0.97 [0.94-1.01], *p* for heterogeneity 0.42). For SLT, although the linear estimate tended to be weaker for rectal than colon cancer (HR per 1.5 h/day: 1.05 [0.89-1.23] vs 1.14 [0.98-1.32], *p* for heterogeneity 0.47), participants in the top quintile of SLT had higher risks of both colon and rectal cancer (HR top vs bottom quintile [≥4 vs <2 h/day]: 1.11 [1.01-1.21] vs 1.12 [1.02-1.23]).

Figure 6.11 Associations of total PA and SLT with colon and rectal cancer



For domain-specific PA, the directions and magnitudes of associations tended to differ between colon and rectal cancer, but the differences were nonsignificant (*p* for heterogeneity 0.20-0.78, **Tables 6.13-6.14**). For occupational PA (**Table 6.13**), there was an inverse association for colon cancer and no association for rectal cancer (HR per 4 MET-h/day: 0.95 [0.92-0.98] vs 0.98 [0.95-1.02], *p* for heterogeneity 0.20). The HRs for colon cancer were 1.00 (0.89-1.12), 0.98 (0.84-1.14), 0.94 (0.82-1.07), 0.92 (0.80-1.05), and 0.78 (0.66-0.91) for those in the bottom to the top quintile; the corresponding HRs for rectal cancer were 1.00 (0.89-1.13), 1.04 (0.91-1.20), 1.06 (0.94-1.20), 0.96 (0.83-1.10), and 0.95 (0.81-1.10). When examining the associations of nonoccupational PA by domain (**Table 6.14**), there were no associations of commuting and household PA with colon and rectal cancer. For leisure-time PA, there was a null association for colon cancer and an inverse trend for rectal cancer (HR per 4 MET-h/day 1.01 [0.86-1.18] vs 0.90 [0.75-1.07], *p* for heterogeneity 0.35). According to the recommendations by the 2010 WHO guidelines, individuals who had ≥7.5 MET-h/day leisure-time PA had a nonsignificant 18% lower risk of rectal cancer compared with those who had no leisure-time PA (0.82 [0.63-1.08]), while they had a similar risk of colon cancer (1.03 [0.82-1.31]).

Table 6.13 Adjusted HRs for colon and rectal cancer by PA and SLT*

	Colon cancer		Rectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	531	1.00 (0.91, 1.10)	501	1.00 (0.90, 1.11)
8.8 to <14.3	415	0.96 (0.87, 1.06)	393	0.95 (0.86, 1.06)
14.3 to <21.9	350	1.05 (0.94, 1.16)	347	1.04 (0.93, 1.15)
21.9 to <33.3	242	0.92 (0.81, 1.06)	245	0.89 (0.78, 1.02)
≥33.3	207	0.83 (0.71, 0.97)	230	0.90 (0.78, 1.05)
per 4 MET-h/day†		*0.95 (0.92, 0.99)*		*0.97 (0.94, 1.01)*
Occupational PA				
0	905	1.00 (0.89, 1.12)	775	1.00 (0.89, 1.13)
>0 to <9.0	222	0.98 (0.84, 1.14)	268	1.04 (0.91, 1.20)
9.0 to <15.5	229	0.94 (0.82, 1.07)	254	1.06 (0.94, 1.20)
15.5 to <26.1	208	0.92 (0.80, 1.05)	212	0.96 (0.83, 1.10)
≥26.1	181	0.78 (0.66, 0.91)	207	0.95 (0.81, 1.10)
per 4 MET-h/day†		*0.95 (0.92, 0.98)*		*0.98 (0.95, 1.02)*
Nonoccupational PA	367	1.00 (0.89, 1.13)	374	1.00 (0.89, 1.12)
0 to <3.9	333	0.87 (0.78, 0.97)	349	0.94 (0.84, 1.04)
3.9 to <6.5	323	0.90 (0.81, 1.01)	342	0.98 (0.88, 1.09)
6.5 to <8.5	346	0.92 (0.83, 1.02)	317	0.89 (0.80, 1.00)
8.5 to <11.6	376	0.96 (0.86, 1.08)	334	0.95 (0.84, 1.07)
≥11.6		*1.02 (0.93, 1.12)*		*0.94 (0.85, 1.03)*
per 4 MET-h/day†				
SLT				
0 to <2	282	1.00 (0.88, 1.14)	270	1.00 (0.88, 1.14)
2 to <3	426	1.08 (0.98, 1.19)	456	1.13 (1.03, 1.24)
3 to <4	459	1.19 (1.08, 1.30)	415	1.05 (0.95, 1.15)
4 to <5	298	1.15 (1.02, 1.29)	303	1.16 (1.03, 1.30)
≥5	280	1.06 (0.94, 1.20)	272	1.08 (0.95, 1.22)
per 1.5 h/day†		*1.14 (0.98, 1.32)*		*1.05 (0.89, 1.23)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

P for heterogeneity by colon and rectal cancer: total PA, 0.42; occupational PA, 0.20; nonoccupational PA, 0.23; SLT, 0.47.

Table 6.14 Adjusted HRs for colon and rectal cancer by nonoccupational PA*

	Colon cancer		Rectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Commuting				
0	1035	1.00 (0.90, 1.11)	934	1.00 (0.90, 1.11)
>0 to <1.2	211	0.97 (0.84, 1.11)	237	0.96 (0.84, 1.10)
1.2 to <1.8	99	0.92 (0.75, 1.12)	109	0.96 (0.79, 1.16)
1.8 to <3.4	236	0.89 (0.78, 1.01)	263	0.88 (0.78, 0.99)
≥3.4	164	0.97 (0.82, 1.14)	173	0.96 (0.82, 1.13)
per 4 MET-h/day†		*0.99 (0.78, 1.27)*		*1.04 (0.82, 1.32)*
Household				
0	165	1.00 (0.84, 1.19)	175	1.00 (0.85, 1.18)
>0 to <2.8	228	0.97 (0.84, 1.11)	247	1.02 (0.89, 1.16)
2.8 to <5.6	378	1.05 (0.94, 1.16)	372	1.00 (0.90, 1.11)
5.6 to <8.4	737	1.01 (0.93, 1.10)	687	0.92 (0.84, 1.00)
≥8.4	237	1.02 (0.89, 1.18)	235	0.97 (0.84, 1.12)
per 4 MET-h/day†		*1.03 (0.92, 1.16)*		*0.94 (0.83, 1.06)*
Leisure-time				
0	1073	1.00 (0.92, 1.09)	1172	1.00 (0.92, 1.09)
>0 to ≤1.07	67	1.36 (1.07, 1.72)	57	1.12 (0.86, 1.45)
>1.07	605	1.18 (1.07, 1.29)	487	1.00 (0.90, 1.11)
0	1073	1.00 (0.91, 1.10)	1172	1.00 (0.91, 1.10)
>0 to <3.75	396	1.26 (1.14, 1.38)	336	1.09 (0.98, 1.20)
3.75 to <7.5	205	1.12 (0.97, 1.29)	155	0.91 (0.77, 1.07)
≥7.5	71	1.03 (0.82, 1.31)	53	0.82 (0.63, 1.08)
per 4 MET-h/day†		*1.01 (0.86, 1.18)*		*0.90 (0.75, 1.07)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

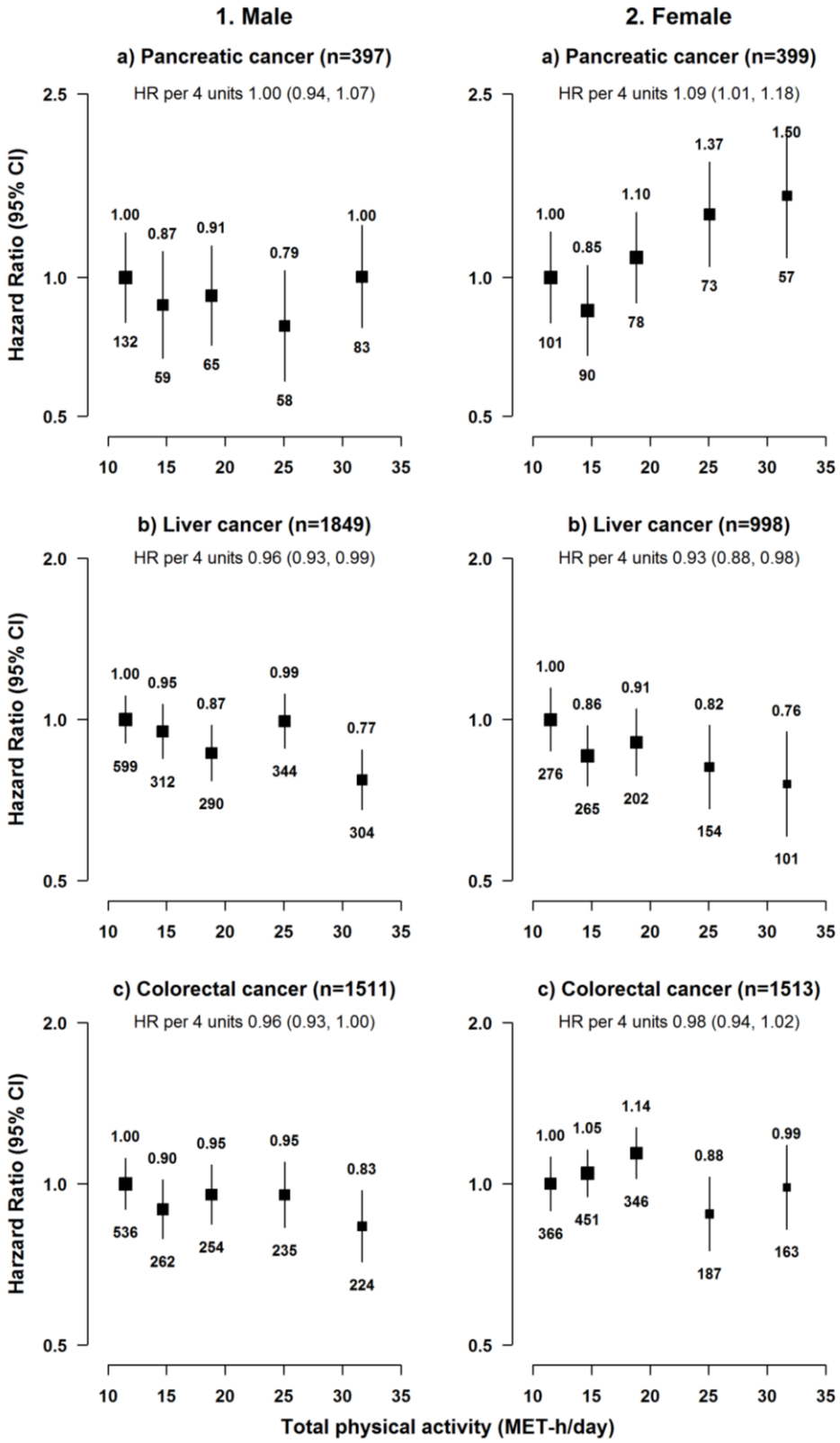
† Regression dilution ratios: commuting, 0.45; household, 0.53; leisure-time, 0.55.

P for heterogeneity by colon and rectal cancer: commuting, 0.78; household, 0.29; leisure-time, 0.35.

6.1.8 Subgroup analyses

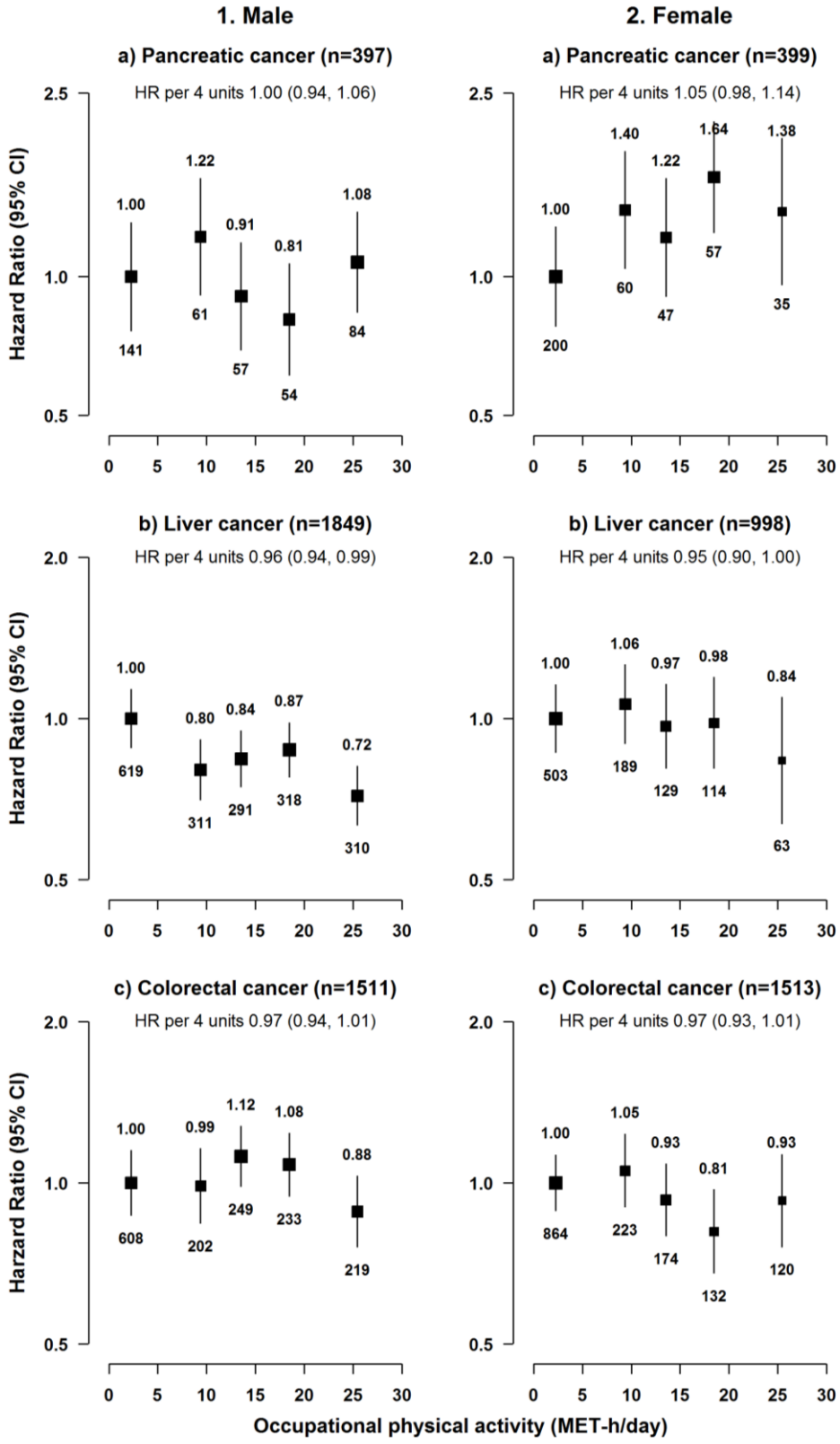
The associations of PA and SLT with risks of three cancers did not differ by sex (*p* for heterogeneity 0.11-0.89, **Figures 6.12-6.15**). However, the direction of association for pancreatic cancer differed by sex. For pancreatic cancer, there was a positive trend for total PA in women and a null association in men (HR per 4 MET-h/day: 1.09 [1.01-1.18] vs 1.00 [0.94-1.07], **Figure 6.12**). The HRs in women were 1.00 (0.80-1.25), 0.85 (0.68-1.06), 1.10 (0.89-1.38), 1.37 (1.06-1.77), and 1.50 (1.11-2.03) for those in the bottom to the top quintiles; the corresponding HRs in men were 1.00 (0.80-1.24), 0.87 (0.67-1.13), 0.91 (0.72-1.16), 0.79 (0.60-1.03), and 1.00 (0.78-1.29). For SLT, there was a positive trend for pancreatic cancer in men but no association in women (HR per 1.5 h/day: 1.25 [0.93-1.68] vs 0.83 [0.60-1.16], **Figure 6.15**). The HRs in women were 1.00 (0.79-1.27), 0.96 (0.78-1.17), 0.98 (0.80-1.20), 0.90 (0.69-1.16), and 0.79 (0.59-1.06) for those who had SLT of <2, 2 to <3, 3 to <4, 4 to <5, and ≥5 h/day; the corresponding HRs in men were 1.00 (0.77-1.30), 1.11 (0.90-1.35), 1.12 (0.91-1.37), 1.35 (1.06-1.71), and 1.24 (0.96-1.61).

Figure 6.12 Associations of total PA with risks of specific GI cancers by sex



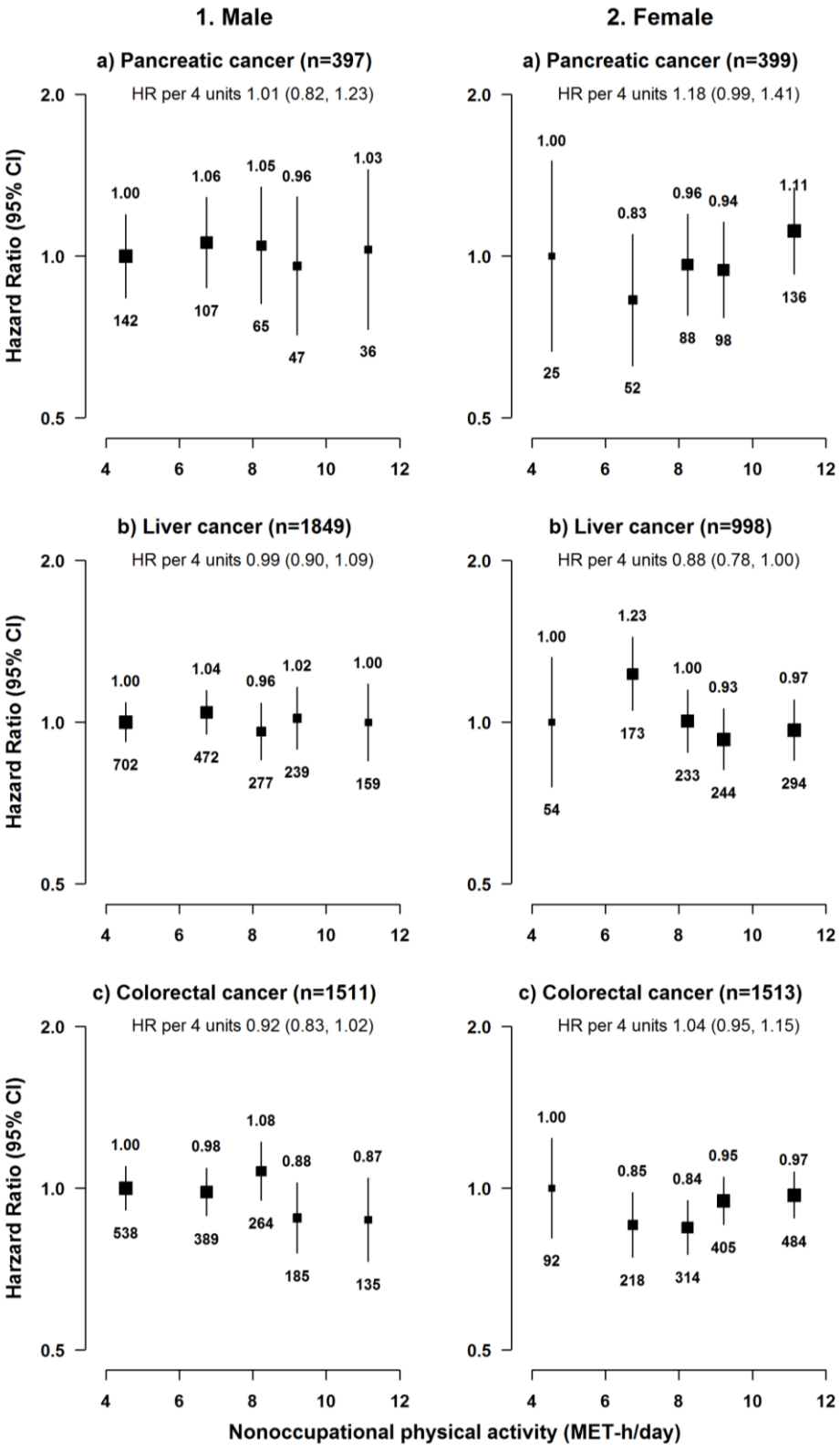
Model was stratified by age-at-risk (5-year), region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT. *P* for heterogeneity by sex: pancreatic, 0.14; liver, 0.32; colorectal, 0.56.

Figure 6.13 Associations of occupational PA with risks of specific GI cancers by sex



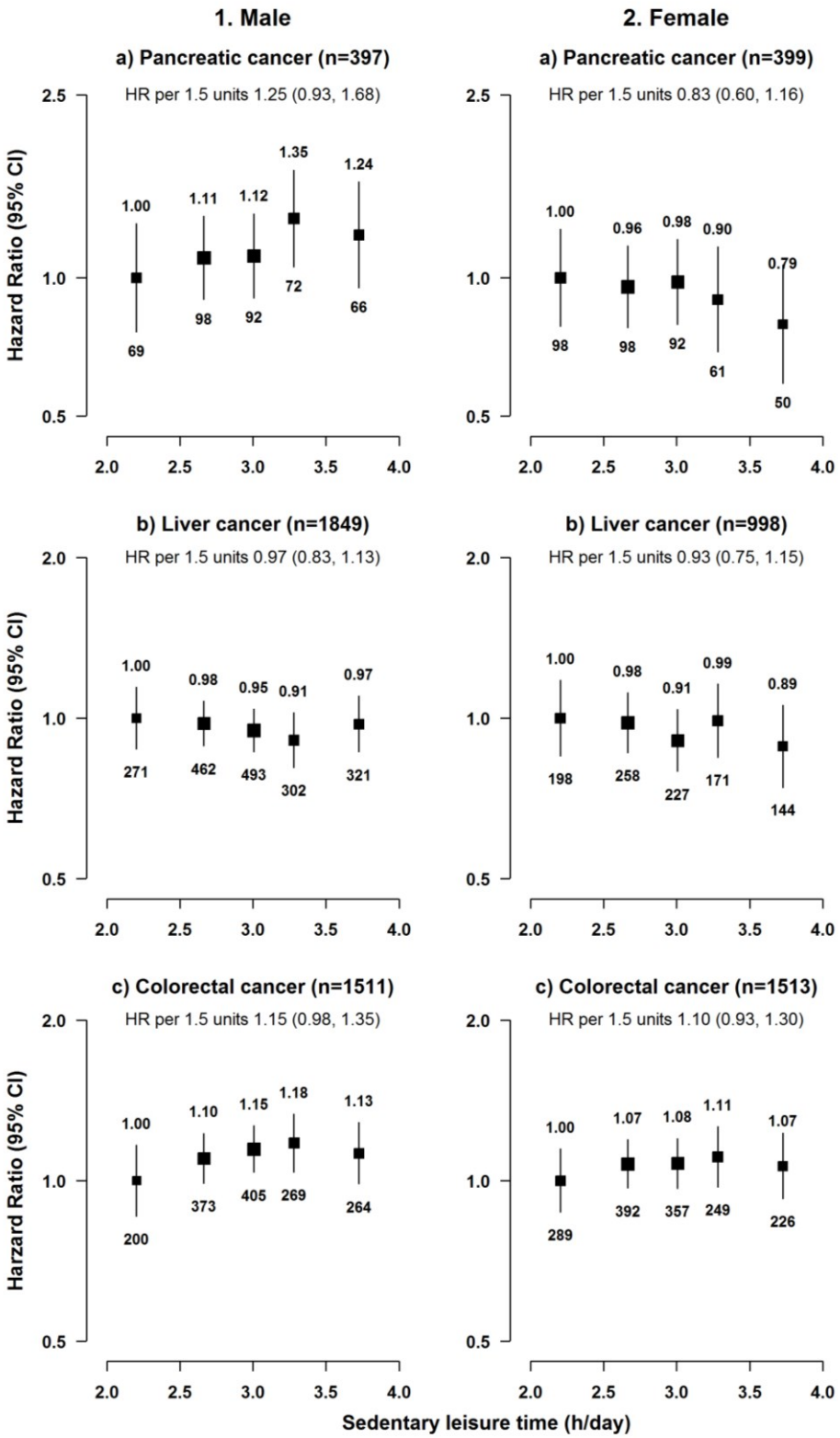
Model was stratified by age-at-risk (5-year), region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT. *P* for heterogeneity: pancreatic, 0.28; liver, 0.72; colorectal, 0.89.

Figure 6.14 Associations of nonoccupational PA with risks of specific GI cancers by sex



Model was stratified by age-at-risk (5-year), region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT. *P* for heterogeneity: pancreatic, 0.32; liver, 0.24; colorectal, 0.12.

Figure 6.15 Associations of SLT with risks of specific GI cancers by sex

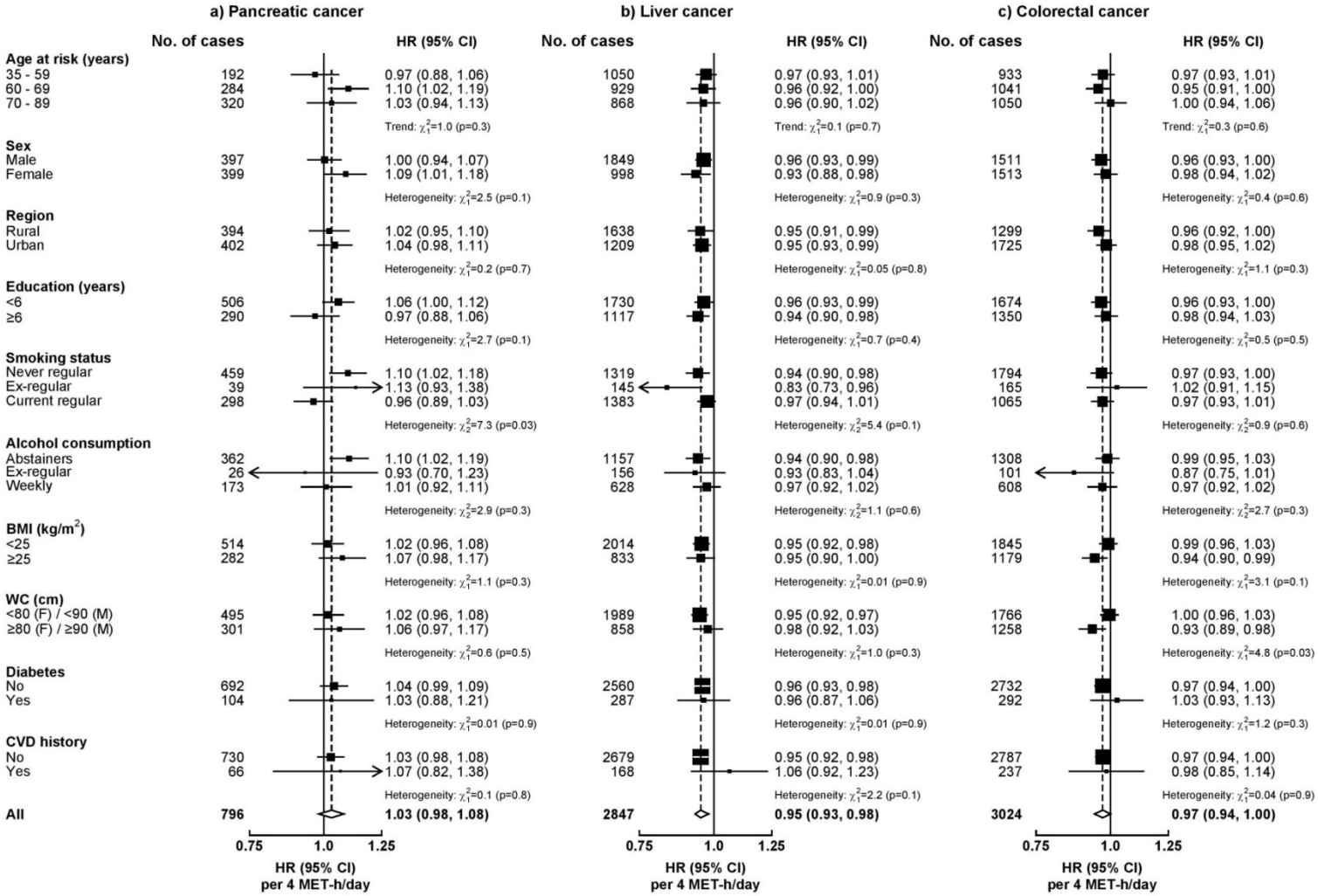


Model was stratified by age-at-risk (5-year), region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and total PA.

P for heterogeneity: pancreatic, 0.11; liver, 0.65; colorectal, 0.68.

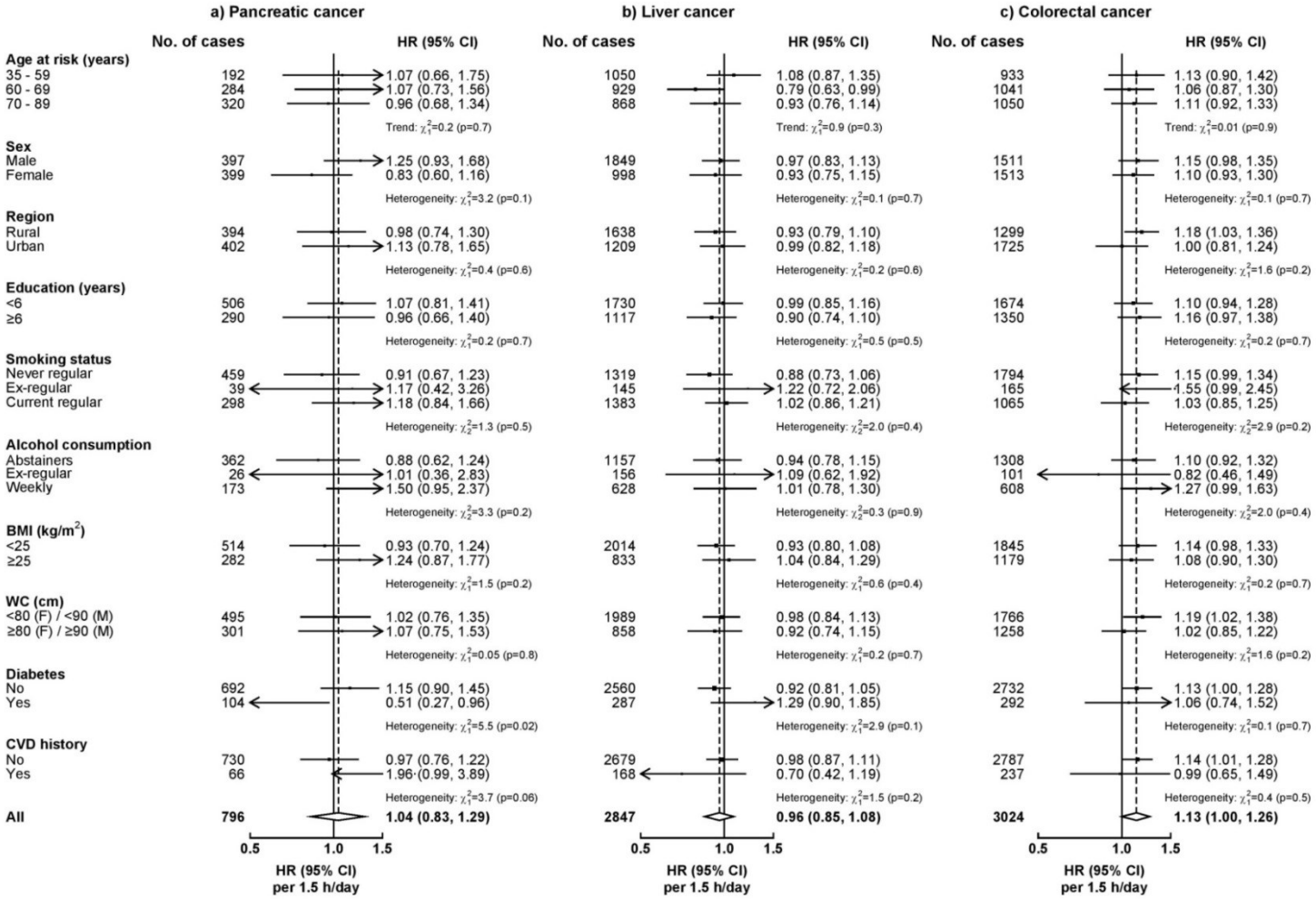
For total PA, the associations with three cancers did not vary across different population subgroups, with the exception of pancreatic cancer by smoking status and colorectal cancer by WC (**Figure 6.16**). For pancreatic cancer, there were positive trends in never and ex-regular smokers (HR per 4 MET-h/day: 1.10 [1.02-1.18] vs 1.13 [0.93-1.38]) and no association in current regular smokers (0.96 [0.89-1.03], *p* for heterogeneity 0.03). For colorectal cancer, there was an inverse association in participants with high WC (HR per 4 MET-h/day 0.93 [0.89-0.98]) and no association in those with low WC (1.00 [0.96-1.03], *p* for heterogeneity 0.03). For occupational PA, the patterns across population subgroups were generally similar to those of total PA (**Appendix 6.9**). For nonoccupational PA, the null associations for all three cancers were generally consistent across population subgroups (**Appendix 6.10**). For SLT (**Figure 6.17**), the HRs differed little by subgroup, except for pancreatic cancer by diabetes history (HR per 1.5 h/day: no vs yes: 1.15 [0.90-1.45] vs 0.51 [0.27-0.96], *p* for heterogeneity 0.02). However, the inverse association in participants with a history of diabetes should be cautiously interpreted considering the wide confidence intervals. For colorectal cancer, there was a positive association in participants with low WC and a null association in those with high WC (HR per 1.5 h/day: 1.19 [1.02-1.38] vs 1.02 [0.85-1.22], *p* for heterogeneity 0.20).

Figure 6.16 Associations of total PA with risks of specific GI cancers by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.

Figure 6.17 Associations of SLT with risks of specific GI cancers by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and total PA.

6.1.9 Sensitivity analyses

6.1.9.1 Additional adjustment for adiposity or diabetes

Compared with the main model, associations of PA and SLT with risks of all three cancers were similar when additionally adjusting for adiposity or diabetes (**Appendices 6.11-6.16**), possible mediators or confounders between PA and cancer risk. When additionally adjusting for BMI, WC, or %BF, the associations of PA and SLT with risks of three cancers were almost identical to those from the main model (**Appendices 6.11-6.13**). For pancreatic cancer, the HRs per 4 MET-h/day total PA were 1.03 (0.98-1.08) and 1.04 (0.99-1.09) when additionally adjusting for BMI or diabetes; the corresponding HRs per 1.5 h/day SLT were 1.03 (0.83-1.29) and 1.03 (0.82-1.28) (**Appendix 6.14**). For liver cancer, the HRs per 4 MET-h/day total PA were 0.95 (0.93-0.98) and 0.96 (0.93-0.98) when additionally adjusting for BMI or diabetes; the corresponding HRs per 1.5 h/day SLT were 0.97 (0.86-1.09) and 0.95 (0.84-1.08) (**Appendix 6.15**). For colorectal cancer, the HRs per 4 MET-h/day total PA were 0.98 (0.95-1.00) and 0.97 (0.95-1.00) when additionally adjusting for BMI or diabetes; the corresponding HRs per 1.5 h/day SLT were 1.10 (0.98-1.23) and 1.12 (1.00-1.26) (**Appendix 6.16**).

6.1.9.2 Additional adjustment for diet

Similar associations were observed when additionally adjusting for dietary factors (**Appendix 6.17**), including fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables. The HRs per 4 MET-h/day total PA were 1.03 (0.98-1.09) for pancreatic, 0.95 (0.93-0.98) for liver, and 0.97 (0.95-1.00) for

colorectal cancer; the corresponding HRs per 1.5 h/day SLT were 1.06 (0.85-1.33), 0.96 (0.85-1.08), and 1.11 (0.99-1.25).

6.1.9.3 Exclusion of poor self-rated health or major chronic diseases

When excluding participants who reported poor self-rated health or who had major chronic diseases (CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease, peptic ulcer, and kidney disease) (**Appendices 6.18-6.20**), similar associations were observed of PA and SLT with risks of three cancers to those in all participants. When excluding participants who reported poor self-rated health, the HRs per 4 MET-h/day total PA were 1.02 (0.97-1.08), 0.96 (0.94-0.99), and 0.97 (0.94-0.99) for pancreatic, liver, and colorectal cancer; the corresponding HRs per 1.5 h/day SLT were 1.12 (0.88-1.43), 0.96 (0.83-1.10), and 1.14 (1.00-1.29). When excluding those who had major chronic diseases, the HRs per 4 MET-h/day total PA were 1.05 (1.00-1.11), 0.98 (0.95-1.01), and 0.97 (0.94-1.00) for pancreatic, liver, and colorectal cancer; the corresponding HRs per 1.5 h/day SLT were 1.03 (0.78-1.35), 0.96 (0.82-1.12), and 1.12 (0.97-1.29).

6.1.9.4 Cancer mortality

For all three cancers, the associations of PA and SLT with cancer mortality were similar to those for cancer incidence, with the exception of SLT and colorectal cancer (**Appendix 6.21**). For total PA, the HRs per 4 MET-h/day were 1.05 (0.99-1.11) for pancreatic, 0.95 (0.92-0.98) for liver, and 0.98 (0.93-1.03) for colorectal cancer mortality. For SLT, the HRs per 1.5 h/day were 1.02 (0.79-1.33) for pancreatic, 0.94 (0.81-1.09) for liver, and 0.97 (0.79-1.20) for colorectal cancer mortality.

6.2 Discussion

6.2.1 Summary of findings

In CKB, there were inverse associations of total PA with risks of liver and colorectal cancer, while there was no association with pancreatic cancer. The associations for occupational PA were similar to those for total PA, while there were no associations for nonoccupational PA. For leisure-time PA, although there was no association with pancreatic cancer, participants with high levels of leisure-time PA tended to have lower risks of liver and colorectal cancer. For SLT, there was a positive association with colorectal cancer, while there were no associations with risks of pancreatic and liver cancer. For liver cancer, although HBsAg status did not modify the associations for PA and SLT, there were no clear associations for PA among HBsAg positive participants. For colorectal cancer, although the inverse associations of total and occupational PA tended to be stronger for colon than for rectal cancer, the differences were nonsignificant. For SLT, the positive association differed little for colon and rectal cancer, particularly when comparing high and low categories. The associations for PA and SLT changed little when excluding the first two or five years of follow-up, or when restricting the analyses to never regular smokers or never regular drinkers. The directions of associations of PA and SLT with risks of all three cancers are generally consistent with previous studies in Western or other East Asian countries. However, given the different distribution of physical activity in China and in the West, it is difficult to compare directly the strengths and shape of associations.

6.2.2 PA and pancreatic cancer

Similar to the findings in CKB, previous prospective studies have shown no clear evidence of association of total or leisure-time PA with risk of pancreatic cancer. The meta-analysis conducted by the WCRF in 2011 showed that each 20 MET-h/day higher total PA was associated with a nonsignificant ~20% lower risk (RR per 20 MET-h/day 0.81 [0.64-1.02], 3 studies and 687 cases), while leisure-time PA was not related (RR per 10 MET-h/day 0.99 [0.96-1.03], 5 studies and 1315 cases).[36] However, this meta-analysis included small numbers of cases, with 687 cases for total and 1315 cases for leisure-time PA. Similar to this meta-analysis, a recent meta-analysis by Behrens et al. involving 24 prospective studies showed that neither total nor leisure-time PA was associated with pancreatic cancer, despite a greater number of cases included (n=8353).[108] The summary RRs comparing high and low categories were 0.91 (0.69-1.19) for total and 0.95 (0.90-1.01) for leisure-time PA. Similarly, prospective cohort studies published after the meta-analysis have shown no association of total or leisure-time PA with pancreatic cancer.[109] The NCI Cohort Consortium involving 12 cohort studies and 4186 cases showed no association for leisure-time PA, with a HR of 0.95 (0.83-1.08) comparing 90th and 10th percentile. Likewise, the Health Professional Follow-up Study with 235 cases showed no association for total PA (HR comparing high vs low categories: 0.95 [0.57-1.57]).[318]

In contrast to the null findings for total and leisure-time PA, the meta-analysis by Behrens et al. showed an inverse association for occupational PA, with a RR of 0.86 (0.76-0.98) comparing high and low categories (7 studies, 2230 cases).[108] However, the association did not differ by domain of PA (*p* for heterogeneity: 0.2). More importantly, these seven studies assessed occupational PA with different methods, including job categories (2 studies),[319,320] perceived workload (1

study),[321] occupational sitting time (3 studies),[322-324] and energy expenditure (1 study).[142] Therefore, it is difficult to combine their estimates. Upon careful inspection of these studies, two small studies suggested a positive trend between occupational PA of vigorous intensity and pancreatic cancer,[142,321] while one study showed that sedentary work was associated with a higher risk.[322] Although the nature of occupational PA is different between China and the West, the findings in the current study were consistent with previous studies in Western populations which showed positive associations for occupational PA of high intensity and occupational sitting time. In EPIC with 310 cases, participants who reported >2 h/week of vigorous work had a nonsignificant higher risk compared with those who reported none (HR 1.21 [0.83-1.77]).[142] In CKB, although the trend was nonsignificant, farmers and manual workers who had higher levels of occupational PA had a higher risk (HR comparing top and bottom categories: 1.32 [1.00-1.75] and 1.53 [1.08-2.17]), while there was no association among nonmanual workers. For occupational sitting time, a Swedish cohort including 109 cases reported a HR of 1.58 (1.01-2.47) comparing sedentary and nonsedentary work.[322] In CKB, participants who had a sedentary occupation had a nonsignificant higher risk compared with those with a nonsedentary occupation (1.17 [0.91-1.49]).

Previous prospective studies in East Asia included small numbers of cases and the results have been inconclusive whether PA is associated with risk of pancreatic cancer.[108] A recent study in urban Chinese reported an inverse association of leisure-time PA with pancreatic cancer among men but not women.[110] The study populations were the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS) (384 cases), which assessed total and domain-specific PA by self-report. While there were no

associations for total and occupational PA in both sexes, there was an inverse association for leisure-time PA among men (HR >1.07 MET-h/day vs none 0.59 [0.40-0.87]) but not women (1.06 [0.78-1.44]). However, the difference by sex for leisure-time PA was nonsignificant (*p* for heterogeneity 0.07). In CKB, there were no associations of leisure-time PA with pancreatic cancer in both sexes. Although the mean level of leisure-time PA was similar in SWHS and SMHS and urban residents in CKB (Shanghai studies vs CKB: men: 2.0 vs 1.8 MET-h/day, women: 1.6 vs 1.7 MET-h/day), the patterns of occupational PA and other risk factors for cancer may differ.[245,325] In addition, small numbers of cases were included in both studies (number of cases: 384 vs 796).

6.2.3 PA and liver cancer

There has been limited prospective evidence whether PA is associated with risk of liver cancer.[49] At least two prospective cohort studies have examined the association of total PA with liver cancer,[113,114] and three (including a pooled analysis of cohort studies) have examined leisure-time PA.[109,111,112] These two cohort studies have suggested an inverse association of total PA with liver cancer. A Japanese cohort study with 263 cases reported a nonsignificant lower risk comparing the highest and lowest levels of activity (HR 0.62 [0.40-0.96] in men, 0.54 [0.23-1.29] in women).[114] Likewise, the NIH-AARP Diet and Health Study with 397 cases examined total PA of moderate to vigorous (MVPA) intensity and showed a lower risk comparing >7 h/week of MVPA with those reporting <1 h/week (HR 0.71 [0.52-0.98]).[113] The current study included a much larger number of cases than previous studies and showed an inverse association for total PA,

directionally concordant with the Japanese cohort and the NIH-AARP Diet and Health Study.

Similar to total PA, previous prospective cohort studies have shown an inverse association of leisure-time PA with liver cancer.[109,111,112] The NCI Cohort Consortium pooled 12 cohort studies with 1384 cases and reported a HR of 0.73 (0.55-0.98) comparing 90th and 10th percentile.[109] Similarly, a prospective cohort study of 416,175 individuals in Taiwan with 924 cases showed that leisure-time PA was associated with a lower risk, with a HR of 0.82 (0.69-0.98) comparing ≥7.5 vs <3.75 MET h/week.[111] A cohort study in Korea with 2676 cases also reported a lower risk associated with leisure-time PA (HR comparing high/moderate vs low: 0.88 [0.81-0.95]).[112] In the current study, there was a nonsignificant 11% lower risk per 4 MET-h/day leisure-time PA (HR 0.89 [0.76-1.04]). When assessing extreme categories, the HR comparing ≥7.5 MET-h/day and none was 0.74 (0.57-0.96), which was directionally consistent with but weaker than the study in Taiwan (HR ≥3.6 vs <0.5 MET-h/day: 0.65 [0.49-0.86]). However, that study recruited healthy participants in a standard medical screening programme of high socioeconomic class, who may have a different pattern of exercise. For studies conducted in Western populations, it is difficult to make direct comparison with findings in the current study because of the different distribution of leisure-time PA. For example, the median of leisure-time PA was 8-11 MET-h/week in the NCI Cohort Consortium,[109] whereas the median in CKB was less than 0.1 MET-h/week.

Similar to the findings in CKB, previous prospective studies have shown similar associations when excluding early years of follow-up.[109,113] Likewise, previous studies as well as CKB have reported similar associations by sex, smoking status,

and alcohol consumption.[109,112,113] While previous studies showed that the inverse associations attenuated towards the null when additionally adjusting for adiposity,[109] similar associations were observed in CKB. This is probably because of the null association between adiposity with liver cancer in the current study (more on this in Chapter 7). None of previous studies examined whether HBV infection confounded or modified the association of PA with liver cancer. The current study showed that there were inverse associations of PA with liver cancer among HBsAg negative participants but no clear associations among HBsAg positive participants.

6.2.4 PA and colorectal cancer

The meta-analysis conducted by WCRF showed that total PA was inversely associated with risks of colorectal (RR comparing high and low 0.81 [0.69-0.95], 6 studies and 5607 cases) and colon cancer (RR 0.80 [0.72-0.88], 12 studies and 8396 cases).[57] Although different categories were used, the estimate in the current study was generally consistent with previous studies, for both colorectal (RR comparing high and low categories: CKB vs meta-analysis: 0.90 [0.80-1.01] vs 0.81 [0.69-0.95]) and colon cancer (CKB vs meta-analysis: 0.83 [0.71-0.97] vs 0.80 [0.72-0.88]). When dose-response analyses were conducted, the meta-analysis reported RRs per 5 MET-h/week of 0.97 (0.94-0.99) for colorectal and 0.92 (0.86-0.99) for colon cancer.[57] In CKB, the linear estimates for both colorectal and colon cancer tended to be weaker than those in the meta-analysis (HR per 4 MET-h/day: colorectal 0.97 [0.94-1.00], colon 0.95 [0.92-0.99]). However, it should be noted that the between-study heterogeneity in the meta-analysis was large for studies assessing dose-response relationships.[57] For rectal cancer, the meta-

analysis showed no association for total PA (RR comparing high and low: meta-analysis 1.04 [0.92-1.18], 9 studies and 2326 cases).[57] After publication of the meta-analysis, a recent report from the UK Biobank including 2391 colorectal cancer cases showed an inverse association of total PA with colon cancer and no association with rectal cancer (HR comparing high vs low categories: colon 0.84 [0.72-0.98], rectal 1.11 [0.90-1.37]).[124] Although the trend was nonsignificant in CKB, participants who had higher levels of total PA tended to have a lower risk of rectal cancer (HR comparing top and bottom quintile: 0.90 [0.78-1.05]), and the association differed little from that with colon cancer (*p* for heterogeneity 0.42).

Similar to CKB, the EPIC study with 1662 colorectal cancer cases examined total and domain-specific PA.[326] Consistent with the findings in CKB, the EPIC study reported a nonsignificant lower risk of colon cancer among participants with high levels of total PA (HR comparing high vs low categories: 0.78 [0.59-1.03]) and a higher risk among those with a sedentary occupation. However, the EPIC study showed no associations of total PA and occupation with rectal cancer (HR comparing high vs low categories: total PA 1.02 [0.73-1.44]),[326] while in CKB the association did not differ for colon and rectal cancer. For nonoccupational PA (i.e. household and leisure-time), no associations were observed with risks of colon and rectal cancer in both EPIC and CKB.

For leisure-time PA, the WCRF meta-analysis reported an inverse association with colon cancer and a null association with rectal cancer.[57] The HRs comparing high and low categories were 0.84 (0.78-0.91) for colon (20 studies and 10,258 cases) and 0.95 (0.85-1.07) for rectal cancer (14 studies and 4560 cases). The HRs per 5 MET-h/week were 0.98 (0.96-1.00) for colon and 1.00 (0.97-1.03) for rectal

cancer.[57] However, the association with colon and rectal cancer did not differ significantly (*p* for heterogeneity 0.27). In the current study, there was an inverse trend between leisure-time PA with colorectal cancer, with a nonsignificant difference between colon and rectal cancer (*p* for heterogeneity 0.35). Participants with high leisure-time PA had a nonsignificant lower risk of colorectal cancer, consistent with a prospective cohort study in Taiwan.[62,111] That study showed a 25% lower risk of colorectal cancer among participants with ≥7.5 MET-h/week leisure-time PA compared with those <3.75 MET-h/week (HR 0.75 [0.58-0.95]), while the HR comparing ≥7.5 MET-h/day and none in CKB was 0.85 (0.69-1.03).[111]

Consistent with the findings in CKB, previous prospective studies have shown similar associations when excluding early years of follow-up.[109,124,149] Likewise, similar associations were observed by sex, smoking, alcohol consumption, and level of BMI.[109,124,149] When further adjusting for adiposity, the UK Biobank reported that the inverse association of total PA with risk of colorectal cancer attenuated towards the null,[124] whereas other studies showed that the results did not change.[109,149,318] In CKB, the association for PA did not change when additionally adjusting for adiposity, and the inverse association was only observed in participants with high WC.

6.2.5 Sitting time and specific GI cancers

Previous prospective studies of primarily Western populations have shown positive associations of sitting time with risks of colon and rectal cancer.[119,120] A meta-analysis involved 35 cohort or case-control studies on colon and 28 studies on rectal cancer and reported positive associations of total sitting time (recreational or occupational) with risks of colon and rectal cancer.[119] Among

prospective cohort studies, the HRs comparing high and low categories were 1.27 (1.18-1.36; 22,380 cases) for colon and 1.06 (1.01-1.12; 12,388 cases) for rectal cancer (*p* for heterogeneity by cancer subtype <0.001). Subgroup analyses were conducted combining cohort and case-control studies, which showed similar associations for recreational and occupational sitting time. In CKB, the positive associations of recreational sitting time (i.e. SLT) with colon and rectal cancer were directionally consistent with the meta-analysis, but the associations did not differ for colon and rectal cancer. Although information on occupation sitting time was not collected in CKB, sedentary and nonsedentary occupations were derived according to work activity level. Among nonfarmers, participants with a sedentary occupation had a higher risk of colorectal cancer compared with those who had a nonsedentary occupation, again with similar associations for colon and rectal cancer. Similar to the findings in CKB, a recent report from the UK Biobank involving 1108 colon and 820 rectal cancer cases showed a positive association for TV watching hours.[124] The HRs comparing ≥5 and ≤1 h/day of TV watching were 1.32 (1.04-1.68) for colon and 1.13 (0.79-1.61) for rectal cancer (*p* for heterogeneity 0.48). The report also examined computer using hours and showed no associations with colon and rectal cancer.

Compared with colorectal cancer, there is limited evidence on the associations of sitting time with risks of pancreatic and liver cancer.[323] For occupational sitting, an occupational cohort of Finnish women (1302 pancreatic and 389 liver cancer cases) reported positive associations with pancreatic and liver cancer, with HRs comparing high and low categories of 1.32 (1.02-1.69) and 1.30 (0.77-2.20), respectively.[122,123,323] Likewise, in CKB, nonfarmers who had a sedentary occupation had nonsignificant higher risks of pancreatic (HR 1.17 [0.91-1.49]) and

liver cancer (1.09 [0.95-1.26]). For recreational sitting, previous prospective studies have shown no associations with risks of pancreatic and liver cancer, consistent with the findings in CKB. For SLT, a US cohort (775 pancreatic and 250 liver cancer cases) reported no associations with pancreatic and liver cancer.[123] The HRs comparing ≥6 h/day and <3 h/day for pancreatic cancer were 1.17 (0.89-1.53) in men and 1.04 (0.75-1.44) in women, and the corresponding HRs for liver cancer were 0.84 (0.55-1.29) and 0.77 (0.37-1.60). Similarly, a Japanese cohort study including 267 liver cancer deaths reported no association of TV watching hours with liver cancer (HR comparing ≥4 vs <2 h/day 0.98 [0.70-1.38]).[122]

6.2.6 Mechanisms

6.2.6.1 PA

There are several hypotheses why PA is associated with lower risk of cancer.[104,191] First, higher PA is associated with lower adiposity and lower risk of developing diabetes,[104,327] which are associated with lower risk of cancer.[127,204] However, previous studies have shown that the associations of PA with cancer risk are independent of adiposity and diabetes.[49,57,109,328] Second, PA improves insulin sensitivity and reduces hyperinsulinaemia and subsequent risk of diabetes.[329,330] Both acute bouts of PA and chronic exercise can improve insulin sensitivity, independently of the changes in body weight.[331] Epidemiological studies have reported that higher PA is associated with lower blood glucose and lower risk of type 2 diabetes.[327] Insulin resistance, hyperinsulinaemia, hyperglycaemia, and diabetes have been reported to be associated with risks of several cancers, including pancreatic, liver, and colorectal cancer.[204,206] Third, PA is associated with lower levels of systemic inflammation by reducing

proinflammatory factors such as CRP or by reducing the production of adipokines,[332] although the underlying mechanisms are unclear. Epidemiological studies have shown that higher levels of PA are associated with lower levels of inflammation markers, including CRP, adiponectin, and IL-6.[193-197] Inflammation has been linked with higher risk of cancer (more on this in Chapter 9).[333-338] Fourth, although the mechanisms between PA and immune function have not been well investigated, PA may have protective effects by influencing the number or function of natural killer cells.[339,340]

6.2.6.2 SLT

Similar to the mechanisms for PA, biological mechanisms that have been hypothesised to explain the association of sitting time with risk of cancer include adiposity, insulin resistance, inflammation, metabolic and sex hormones.[121] First, SLT displaces PA, particularly light intensity activities, leading to weight gain and obesity,[121] which are associated to higher risk of cancer.[191] Although it may be difficult to fully account for the displacement effects in regression models, prospective cohort studies have shown that the harmful effects of sedentary behaviours on cancer risk persist after adjusting for PA.[119] Second, sedentary behaviours are associated with metabolic dysfunction, including increased levels of blood glucose, insulin resistance, and proinflammatory factors (e.g. CRP, IL-6, TNF-α),[341,342] which are associated with risk of cancer.[203,204,343] Third, vitamin D deficiency may be an additional biological pathway underlying the association between sedentary behaviours and cancer risk.[57] Cross-sectional analyses have shown that individuals with higher TV viewing time had lower circulating concentrations of 25-hydroxyvitamin D (25(OH)D), an indicator of vitamin D

status.[344,345] It is hypothesised that increased vitamin D levels are associated with lower risk of colon cancer.[57]

6.3 Conclusions

For pancreatic cancer, both CKB and previous studies have shown no association of total PA or leisure time PA, while participants with high levels of occupational PA are at a higher risk of pancreatic cancer. For liver cancer, both CKB and previous studies have shown an inverse association of total PA. Although the association for leisure-time PA is nonsignificant in CKB, it is consistent with studies in Western countries and East Asia that have shown an inverse association of leisure time PA with risk of liver cancer. For colorectal cancer, both CKB and previous studies have shown inverse associations of total PA, occupational, and leisure time PA. For SLT, both CKB and previous studies have shown no associations with risks of pancreatic and liver cancer and a positive association with risk of colorectal cancer. For colorectal cancer, previous studies have shown that PA is inversely associated with colon cancer but not associated with rectal cancer, while the association does not differ for colon and rectal cancer in CKB. In CKB, the associations of PA and SLT with liver cancer did not differ by HBsAg status. More studies are needed to assess the associations of domain-specific PA with risks of pancreatic, liver, and colorectal cancer in diverse populations with different distributions of PA.

Chapter 7 Adiposity and risks of specific GI cancers

This objective of this chapter is to examine the shape and strength of associations of general (body mass index [BMI], percent body fat [%BF], weight, fat mass, lean mass) and central adiposity (waist circumference [WC], hip circumference [HC], waist-to-hip ratio [WHR], waist-to-height ratio [WHtR]) with risks of pancreatic, liver, and colorectal cancer, after controlling for possible confounders and adjusting for within-person variation and error in adiposity measurements. This chapter also describes young adulthood adiposity (assessed by BMI at age 25 [BMI25]) and adiposity-related traits (height, leg length, sitting height) in relation to risks of these cancers. In this chapter, I will focus on five main adiposity traits (BMI, %BF, WC, WHR, and BMI25) and also describe five other adiposity traits (HC, WHtR, weight, fat mass, and lean mass).

7.1 Results

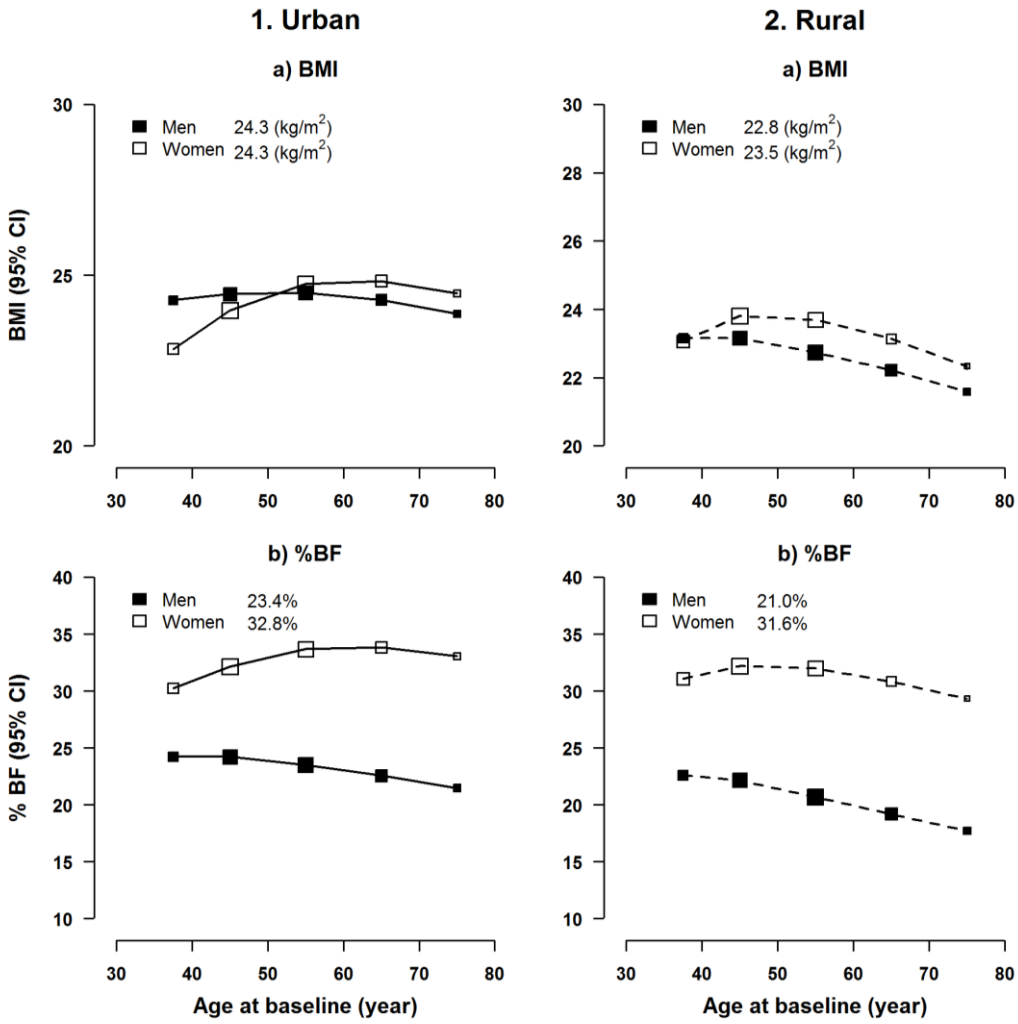
7.1.1 Patterns and correlates of adiposity

Among all 509,892 participants, the mean (SD) measured BMI and WC at baseline were 23.7 (3.3) kg/m^2 and 80.3 (9.8) cm, respectively. Overall, 33% were either overweight or obese (BMI ≥25 kg/m^2), and 4% were obese (BMI ≥30 kg/m^2). 34% had high WC defined by the IDF criterion for Chinese (WC ≥80 cm in women and ≥90 cm in men). The prevalences of overweight and obesity were higher in women and in urban areas (BMI ≥25 kg/m^2: women vs men: 34.3% vs 31.2%, urban vs rural: 39.7% vs 27.3%; BMI ≥30 kg/m^2: women vs men: 4.9% vs 3.0%, urban vs rural: 5.3% vs 3.1%), so was the mean level of BMI (women vs men: 23.8 vs 23.5 kg/m^2, urban vs rural 24.3 vs 23.2 kg/m^2). For %BF, the mean level

was almost 50% higher in women than men (32.1% vs 22.1%) and was slightly higher in urban than rural areas (28.9% vs 27.2%). For WC, the mean level was higher in men than women (82.1 vs 79.1 cm) and in urban than rural areas (81.8 vs 79.0 cm), while the prevalence of high WC was higher in women and in urban areas (women vs men: 43.5% vs 21.1%, urban vs rural: 39.1% vs 29.8%). For WHR, the mean level was higher in men than women (0.90 vs 0.87) and was similar in urban and rural areas (0.88 vs 0.89). For HC, the mean level was similar in men and women (90.7 vs 91.1) and was higher in urban than rural areas (93.3 vs 89.0 cm).

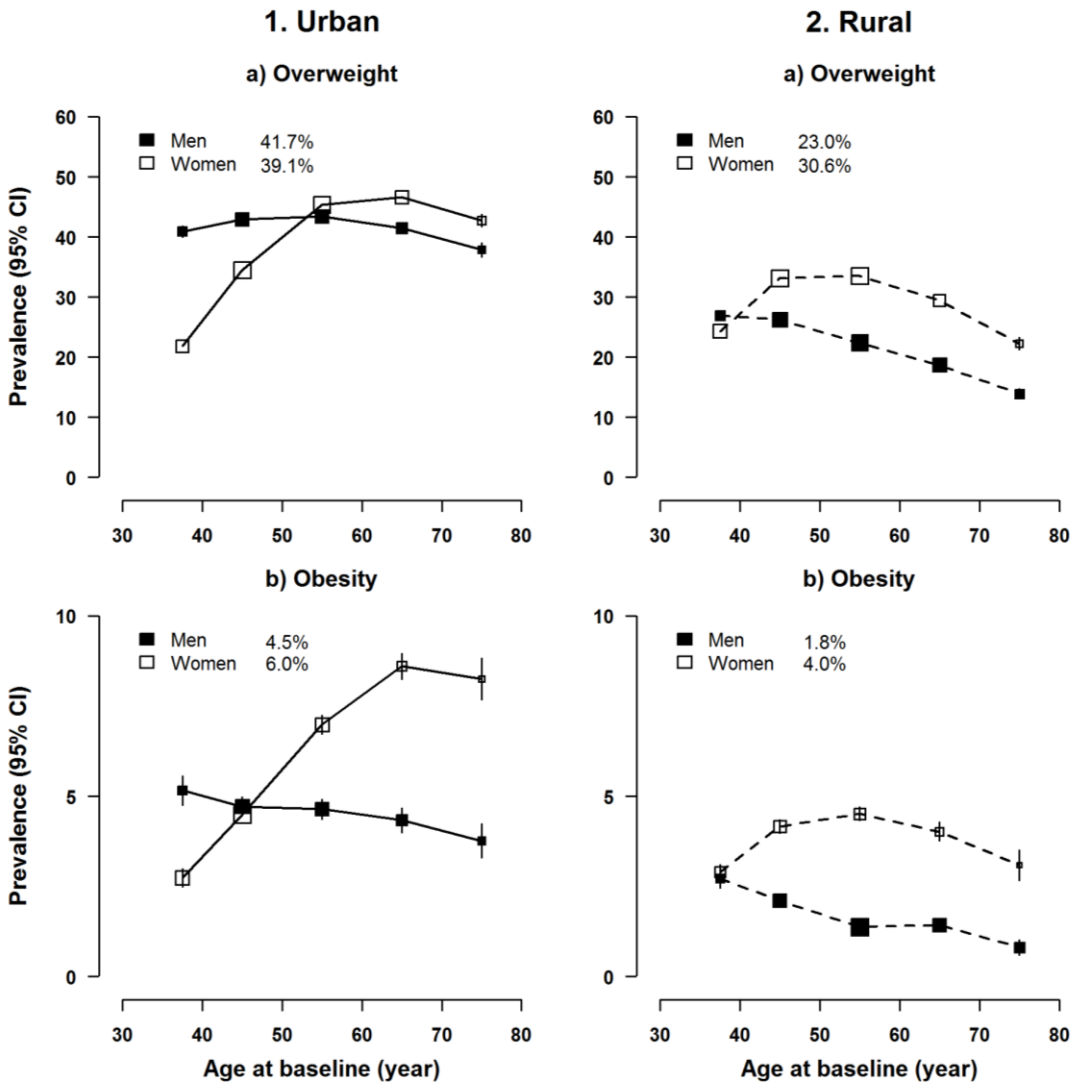
In urban areas, mean BMI in men was stable between 35-54 years and then tended to decrease with age between 55-79 years, whereas mean BMI in women increased with age until 60 years and fell afterwards (**Figure 7.1**). In rural areas, mean BMI in men decreased with age, while in women it increased with age until 50 years and then decreased. The age patterns of overweight and obesity were similar to those of BMI (**Figure 7.2**). For WC (**Figure 7.3**), mean level in men changed little with age in urban areas, while it tended to decrease with age in rural areas. Mean WC in women increased with age in both urban and rural areas, except for a slight decline in rural women after 60 years. The age patterns of WHR were similar to those of WC, except that WHR changed little with age in rural men and women after 60 years (**Figure 7.3**).

Figure 7.1 Distribution of BMI and %BF by region and by sex



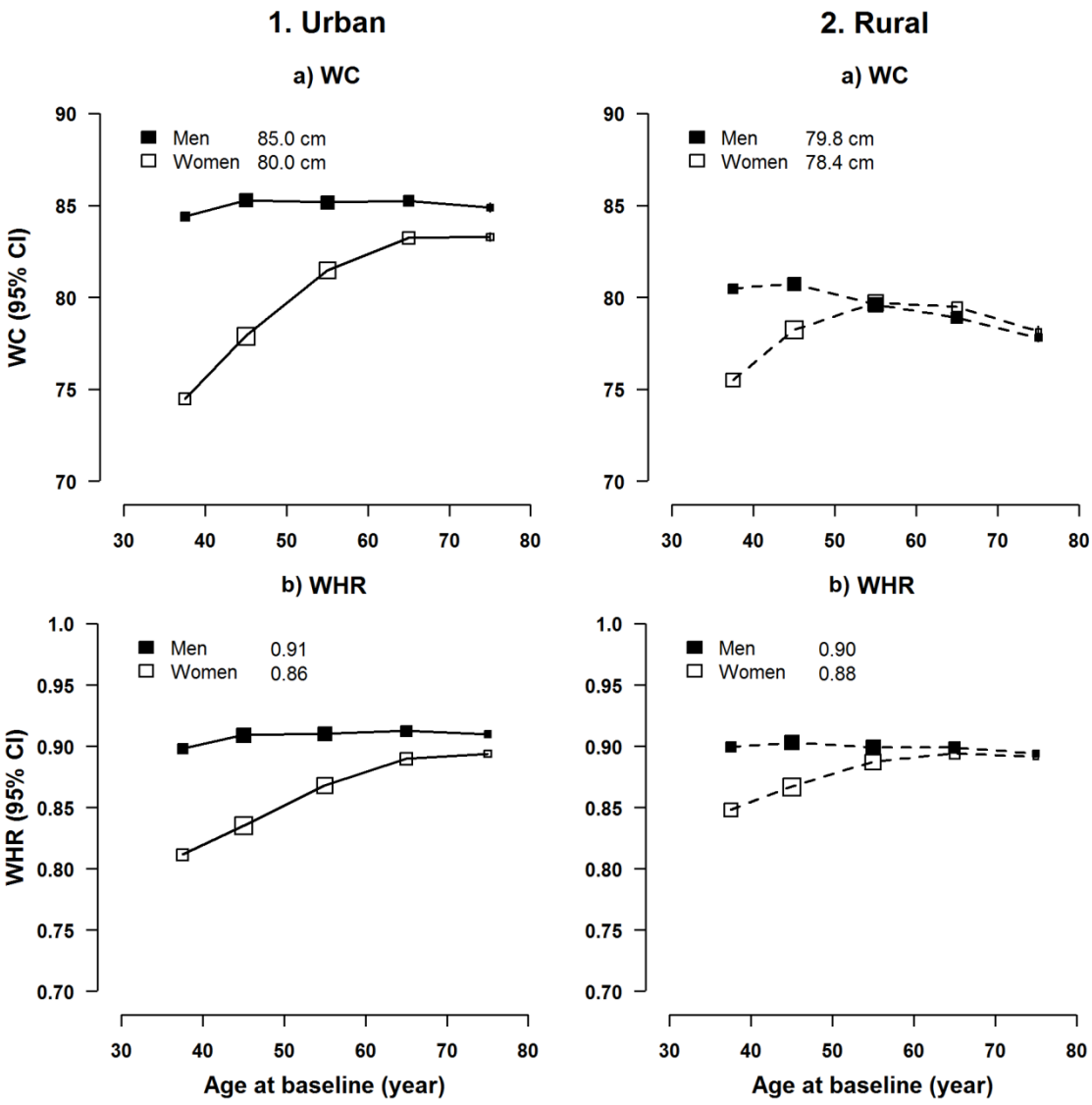
Results were standardised by age, sex, and region (where appropriate).

Figure 7.2 Prevalence of overweight and obesity by region and by sex



Results were standardised by age, sex, and region (where appropriate).

Figure 7.3 Distribution of WC and WHR by region and by sex



Results were standardised by age, sex, and region (where appropriate).

There were moderate to strong correlations between BMI and central adiposity (**Appendix 7.1,** men vs women: WC: 0.86 vs 0.84, WHR: 0.63 vs 0.54, HC: 0.76 vs 0.78, WHtR: 0.86 vs 0.84) and between BMI and other general adiposity traits (men vs women: %BF: 0.80 vs 0.89, weight: 0.88 vs 0.89, fat mass: 0.89 vs 0.94, lean mass: 0.65 vs 0.47), while there was a weak correlation between BMI and BMI25 (men vs women: 0.31 vs 0.34). There were moderate to strong correlations between central adiposity traits (men vs women: WC-HC: 0.81 vs 0.77, WC-WHR: 0.81 vs 0.79, WC-WHtR: 0.95 vs 0.95; WHtR-HC: 0.70 vs 0.67), except for a weak correlation between HC and WHR (men 0.32, women 0.23). BMI25 was weakly correlated with central adiposity (men vs women: WC: 0.15 vs 0.23, HC: 0.12 vs 0.19, WHR: 0.12 vs 0.17, WHtR: 0.21 vs 0.27) and other general adiposity traits (men vs women: %BF: 0.15 vs 0.25, weight: 0.17 vs 0.24, fat mass: 0.17 vs 0.25, lean mass: 0.14 vs 0.12).

Participants with higher levels of BMI were more likely to be female and from urban areas and to have higher household income (**Table 7.1**). They were less likely to be smokers, had lower total physical activity and higher sedentary leisure time, and were more likely to consume fresh fruits and red meat on a daily basis. Participants with higher levels of BMI were more likely to have higher levels of SBP, blood glucose, and adiposity (general, central adiposity, and BMI25). They were less likely to test positive for HBsAg, while they were more likely to have prevalent diabetes, a history of CVD, and hypertension, and a family history of diabetes and cancer. For WC, the patterns of baseline characteristics were similar to those for BMI (**Table 7.2**).

Table 7.1 Baseline characteristics of participants by levels of BMI

Variable*	BMI				
	<20 (n=65,986)	**20 to <22.5** (n=131,198)	**22.5 to <25** (n=144,703)	**25 to <27.5** (n=85,427)	**≥27.5** (n=82,578)
Age (SD), year	52.4 (13.0)	50.7 (10.9)	51.0 (10.3)	51.5 (10.2)	51.6 (10.9)
Female, %	55.8	57.0	59.5	59.5	64.1
Socioeconomic and lifestyle factors					
Urban region, %	31.5	37.2	45.4	51.1	55.7
≥9 years of education, %	20.0	21.1	21.8	21.5	20.4
Household income ≥35 000 RMB/year, %	14.8	16.7	18.6	19.7	20.1
Ever regular smoking, %					
Male	76.0	71.4	65.7	62.8	61.4
Female	4.2	3.0	2.7	2.4	2.6
Weekly drinking, %					
Male	31.5	34.1	33.8	32.7	32.4
Female	2.1	2.1	2.1	2.1	1.9
Total physical activity (SD), MET-h/day	21.4 (13.9)	21.8 (14.3)	21.3 (14.0)	20.6 (13.6)	19.8 (13.0)
Sedentary leisure time (SD), h/day	2.9 (1.5)	2.9 (1.5)	3.0 (1.5)	3.1 (1.6)	3.2 (1.6)
Daily consumption, %					
Fresh fruits	16.3	18.0	19.1	19.7	20.0
Fresh vegetables	93.8	94.6	95.0	95.3	95.2
Red meat	26.8	28.2	29.6	30.7	31.5
Blood pressure and anthropometry					
SBP (SD), mmHg	123.0 (20.9)	127.2 (20.4)	131.2 (20.6)	134.9 (20.8)	139.4 (21.3)
RPG (SD), mmol/L	5.9 (2.1)	5.9 (2.1)	6.0 (2.3)	6.2 (2.5)	6.4 (2.7)
BMI (SD), kg/m^2	18.7 (1.1)	21.3 (0.7)	23.7 (0.7)	25.9 (0.6)	29.0 (2.0)
Waist circumference (SD), cm	68.3 (5.2)	74.5 (5.3)	80.6 (5.8)	86.0 (5.9)	93.0 (7.4)
Hip circumference (SD), cm	83.6 (4.3)	87.4 (4.2)	90.9 (4.4)	94.2 (4.5)	99.0 (5.9)
Waist-to-hip ratio (SD)	0.82 (0.06)	0.85 (0.06)	0.89 (0.06)	0.91 (0.06)	0.94 (0.07)
Percent body fat (SD), %	18.9 (4.9)	23.9 (5.5)	28.3 (5.8)	32.1 (6.2)	36.6 (7.6)
Height (SD), cm	158.6 (8.3)	158.6 (8.1)	158.7 (8.2)	158.9 (8.4)	158.9 (8.5)
BMI at age 25 (SD), kg/m^{2†}	20.5 (2.3)	21.4 (2.3)	21.9 (2.4)	22.4 (2.5)	23.2 (2.8)

Variable*	BMI				
	<20 (n=65,986)	**20 to <22.5** (n=131,198)	**22.5 to <25** (n=144,703)	**25 to <27.5** (n=85,427)	**≥27.5** (n=82,578)
HBsAg positive, %	3.4	3.2	3.0	2.9	2.8
Prior disease history, %					
Diabetes	3.4	4.3	5.8	7.2	9.1
Coronary heart disease	1.9	2.2	2.9	3.5	4.3
Stroke or TIA	1.0	1.4	1.8	2.0	2.3
Hypertension	4.6	7.3	11.2	15.5	21.5
Family history of diabetes	3.7	4.2	5.0	5.4	6.0
Family history of cancer	13.0	13.5	14.2	14.4	14.6

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.
* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.
† BMI25 was missing in 81,880 participants.

Table 7.2 Baseline characteristics of participants by sex-specific quintiles of WC

Variable*	WC				
	Quintile 1 (n=100,973)	**Quintile 2** (n=100,132)	**Quintile 3** (n=103,308)	**Quintile 4** (n=102,588)	**Quintile 5** (n=102,891)
Age (SD), year	50.3 (11.8)	50.0 (10.6)	50.8 (10.2)	51.9 (10.2)	53.4 (10.7)
Socioeconomic and lifestyle factors					
Urban region, %	32.9	37.7	44.1	49.5	53.1
≥9 years of education, %	19.9	21.1	21.6	21.6	20.0
Household income ≥35 000 RMB/year, %	14.1	16.7	18.4	20.0	20.7
Ever regular smoking, %					
Male	73.0	69.6	66.4	64.1	64.3
Female	3.4	2.8	2.6	2.7	3.0
Weekly drinking, %					
Male	29.9	33.7	33.8	34.1	34.0
Female	2.0	2.0	2.2	2.2	2.1
Total physical activity (SD), MET-h/day	22.1 (14.3)	21.8 (14.2)	21.3 (14.0)	20.6 (13.4)	19.7 (12.7)
Sedentary leisure time (SD), h/day	2.9 (1.5)	2.9 (1.5)	3.0 (1.5)	3.1 (1.5)	3.2 (1.6)
Daily consumption, %					
Fresh fruits	17.0	18.3	19.0	19.6	19.5
Fresh vegetables	93.9	94.7	94.9	95.1	95.3
Red meat	26.5	28.5	29.5	30.7	31.3
Blood pressure and anthropometry					
SBP (SD), mmHg	124.6 (20.3)	127.9 (20.2)	130.7 (20.5)	133.6 (20.9)	138.0 (21.3)
RPG (SD), mmol/L	5.7 (1.7)	5.8 (1.9)	6.0 (2.2)	6.2 (2.5)	6.5 (3.0)
BMI (SD), kg/m^2	19.9 (1.8)	21.9 (1.7)	23.4 (1.8)	25.1 (1.9)	27.8 (2.7)
Waist circumference (SD), cm	67.7 (3.5)	74.5 (2.0)	79.6 (2.2)	85.1 (2.5)	94.0 (5.5)
Hip circumference (SD), cm	84.4 (4.4)	87.9 (4.1)	90.5 (4.2)	93.4 (4.4)	98.3 (5.8)
Waist-to-hip ratio (SD)	0.80 (0.05)	0.85 (0.05)	0.88 (0.05)	0.91 (0.05)	0.96 (0.06)
Percent body fat (SD), %	20.8 (6.0)	24.8 (6.4)	27.8 (6.5)	30.9 (6.8)	35.3 (7.9)
Height (SD), cm	157.1 (7.8)	158.1 (7.9)	158.6 (8.0)	159.3 (8.3)	160.4 (8.8)
BMI at age 25 (SD), kg/m^{2†}	21.2 (2.3)	21.7 (2.4)	21.9 (2.5)	22.2 (2.6)	22.7 (2.9)

Variable*	WC				
	Quintile 1 (n=100,973)	**Quintile 2** (n=100,132)	**Quintile 3** (n=103,308)	**Quintile 4** (n=102,588)	**Quintile 5** (n=102,891)
HBsAg positive, %	3.4	3.1	3.0	2.8	2.8
Prior disease history, %					
Diabetes	2.6	3.7	5.2	6.8	9.9
Coronary heart disease	1.9	2.3	2.6	3.3	4.2
Stroke or TIA	1.1	1.3	1.6	1.9	2.4
Hypertension	5.3	7.7	10.5	13.9	19.8
Family history of diabetes	3.6	4.4	4.9	5.5	6.0
Family history of cancer	13.0	13.7	13.9	14.6	14.5

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.
* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.
† BMI25 was missing in 81,880 participants.

7.1.2 Associations of adiposity with pancreatic cancer

7.1.2.1 Main adiposity traits

The main model was stratified by age-at-risk, sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, smoking, alcohol, education, household income, self-rated health, and family history of cancer. BMI was not associated with risk of pancreatic cancer (**Figure 7.4** and **Table 7.3**), with HRs of 0.90 (0.73-1.10), 1.00 (0.87-1.15) (reference), 0.95 (0.83-1.08), 0.96 (0.81-1.13), and 1.02 (0.86-1.20) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2 (HR per 5 kg/m^2 1.02 [0.92-1.14]). When the WHO classifications were used (**Appendix 7.2**), the HRs were 0.99 (0.72-1.36), 1.00 (0.91-1.10), 1.02 (0.90-1.16), and 1.07 (0.78-1.48) for those with BMI of <18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 kg/m^2. Similarly, there was no association for BF% (**Table 7.3**), with a HR per 10% of 0.97 (0.86-1.09). For central adiposity, neither WC nor WHR was associated with pancreatic cancer (**Table 7.3**), with HRs of 1.01 (0.93-1.11) per 10 cm WC and 0.99 (0.85-1.15) per 0.1 WHR. By contrast, there was a positive association for BMI25 (**Table 7.3**), with a HR per 5 kg/m^2 of 1.18 (1.02-1.36). The HR were 0.95 (0.79-1.15), 1.00 (0.88-1.14), 1.08 (0.94-1.24), 1.37 (1.10-1.71), and 1.28 (0.93-1.77) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2.

7.1.2.2 Exclusion of early years of follow-up, smokers or drinkers

When excluding the first two or five years of follow-up (**Figure 7.5** and **Appendix 7.3**), the null associations remained for BMI, %BF, WC, and WHR (HR per 1-SD when excluding first five years: BMI: 1.01 [0.91-1.12]; %BF: 0.99 [0.87-1.13]; WC:

1.02 [0.90-1.14]; WHR: 1.01 [0.87-1.16]). This suggests that the null associations were unaffected by reverse causality. When restricting the analysis to never regular smokers (**Appendix 7.4**), there were positive but nonsignificant trends for BMI and WC but no associations for %BF and WHR (HR per 1-SD: BMI: 1.06 [0.96-1.16]; WC: 1.07 [0.96-1.20]; %BF: 1.01 [0.89-1.14]; WHR: 1.03 [0.90-1.18]). This suggests that the null associations observed in all participants may be partially due to residual confounding related to smoking. When restricting the analysis to never regular drinkers (**Appendix 7.4**), the null associations were similar to those in all participants (HR per 1-SD: BMI: 1.02 [0.93-1.11]; %BF: 0.98 [0.88-1.10]; WC: 0.99 [0.90-1.10]; WHR: 0.95 [0.84-1.07]).

7.1.2.3 Other adiposity traits

For other adiposity traits (**Figure 7.4** and **Table 7.4**), there were no associations of HC, WHtR, height-adjusted weight, fat mass, and lean mass with pancreatic cancer (HR per 1-SD: HC: 1.03 [0.94-1.14]; WHtR: 0.99 [0.91-1.08]; weight: 1.02 [0.93-1.12]; fat mass: 0.99 [0.91-1.08]; lean mass: 1.11 [0.95-1.30]). When excluding the first two or five years of follow-up (**Figure 7.5** and **Appendix 7.5**), the null associations remained for these adiposity traits (HR per 1-SD when excluding first five years: HC: 1.03 [0.91-1.18]; WHtR: 0.99 [0.88-1.11]; weight: 1.01 [0.89-1.15]; fat mass: 1.00 [0.89-1.13]; lean mass: 1.02 [0.82-1.26]). When restricting the analysis to never regular smokers (**Appendix 7.6**), there were positive but nonsignificant trends for HC, height adjusted weight, and lean mass, while the null associations remained for WHtR and fat mass (HR per 1-SD: HC: 1.09 [0.97-1.23]; weight: 1.08 [0.95-1.22]; lean mass: 1.24 [0.98-1.56]; WHtR: 1.04 [0.93-1.16]; fat mass: 1.03 [0.93-1.15]). When restricting the analysis for never

regular drinkers (**Appendix 7.6**), the null associations change little compared with the main model.

Table 7.3 Adjusted HRs for pancreatic cancer by main adiposity traits*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
BMI				
<20.0	101	637,592	16.7	0.90 (0.73, 1.10)
20.0 to <22.5	200	1,305,292	16.2	1.00 (0.87, 1.15)
22.5 to <25.0	213	1,445,796	14.8	0.95 (0.83, 1.08)
25.0 to <27.5	135	853,392	15.6	0.96 (0.81, 1.13)
≥27.5	147	823,562	16.7	1.02 (0.86, 1.20)
per 3.4 kg/m^2†				*1.01 (0.94, 1.10)*
%BF				
Quintile 1	171	985,222	16.8	1.06 (0.91, 1.24)
Quintile 2	143	1,000,348	14.8	1.00 (0.85, 1.18)
Quintile 3	158	1,024,915	15.4	1.04 (0.89, 1.22)
Quintile 4	162	1,022,536	16.1	1.05 (0.90, 1.23)
Quintile 5	162	1,032,614	15.1	1.00 (0.85, 1.18)
per 8.4%†				*0.97 (0.88, 1.07)*
WC				
Quintile 1	163	1,011,268	16.7	1.02 (0.87, 1.20)
Quintile 2	139	1,004,544	14.7	1.00 (0.85, 1.18)
Quintile 3	146	1,031,016	14.0	0.98 (0.84, 1.15)
Quintile 4	161	1,017,076	14.9	1.01 (0.86, 1.17)
Quintile 5	187	1,001,729	16.7	1.01 (0.87, 1.18)
per 9.8 cm†				*1.01 (0.93, 1.10)*
WHR				
Quintile 1	145	1,066,155	15.9	1.06 (0.90, 1.25)
Quintile 2	142	934,095	14.7	1.00 (0.85, 1.18)
Quintile 3	127	878,959	14.1	0.99 (0.84, 1.18)
Quintile 4	173	1,053,118	15.8	1.06 (0.91, 1.23)
Quintile 5	209	1,133,308	16.0	1.03 (0.89, 1.18)
per 0.07†				*0.99 (0.91, 1.08)*
BMI25‡				
<20.0	112	979,621	11.0	0.95 (0.79, 1.15)
20.0 to <22.5	239	1,700,011	14.1	1.00 (0.88, 1.14)
22.5 to <25.0	193	1,114,171	15.7	1.08 (0.94, 1.24)
25.0 to <27.5	80	332,733	21.3	1.37 (1.10, 1.71)
≥27.5	38	147,233	19.9	1.28 (0.93, 1.77)
per 2.6 kg/m^2				*1.09 (1.01, 1.17)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

‡ BMI25 was missing in 81,880 participants.

Table 7.4 Adjusted HRs for pancreatic cancer by other adiposity traits*

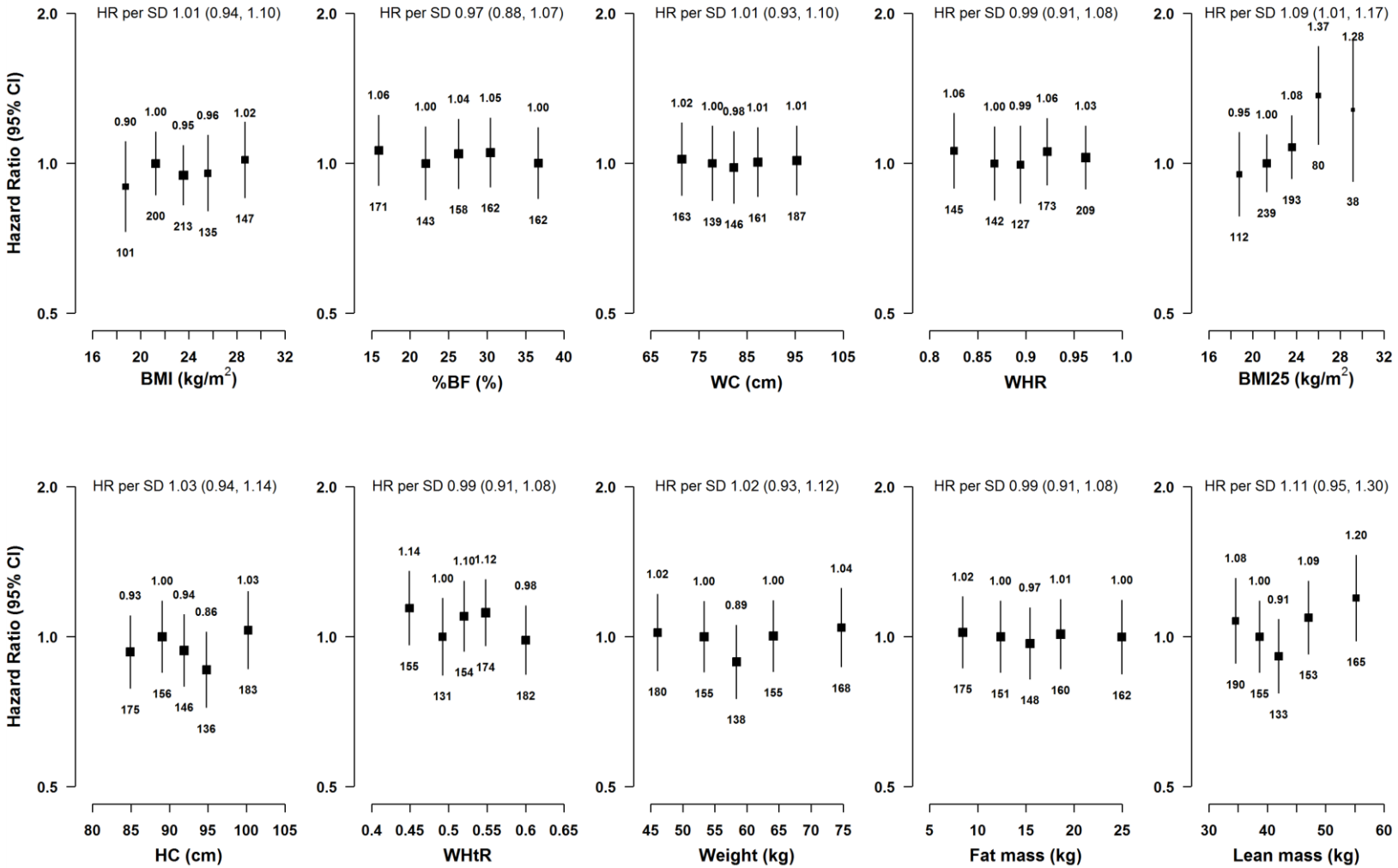
	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
HC				
Quintile 1	175	1,006,770	16.8	0.93 (0.79, 1.10)
Quintile 2	156	971,718	17.8	1.00 (0.85, 1.17)
Quintile 3	146	1,042,382	14.6	0.94 (0.80, 1.10)
Quintile 4	136	1,037,882	13.3	0.86 (0.72, 1.02)
Quintile 5	183	1,006,882	17.2	1.03 (0.87, 1.23)
per 6.9 cm†				*1.03 (0.94, 1.14)*
WHtR				
Quintile 1	155	1,027,983	17.9	1.14 (0.97, 1.35)
Quintile 2	131	1,023,139	13.2	1.00 (0.84, 1.19)
Quintile 3	154	1,016,324	14.7	1.10 (0.94, 1.29)
Quintile 4	174	1,009,621	16.0	1.12 (0.96, 1.30)
Quintile 5	182	988,567	15.3	0.98 (0.84, 1.15)
per 0.06†				*0.99 (0.91, 1.08)*
Height-adjusted weight				
Quintile 1	180	977,845	16.4	1.02 (0.86, 1.21)
Quintile 2	155	1,009,383	15.6	1.00 (0.85, 1.17)
Quintile 3	138	1,033,526	13.7	0.89 (0.76, 1.05)
Quintile 4	155	1,013,478	15.6	1.00 (0.86, 1.18)
Quintile 5	168	1,031,401	17.8	1.04 (0.87, 1.24)
per 10.8 kg†				*1.02 (0.93, 1.12)*
Height-adjusted fat mass				
Quintile 1	175	988,323	17.6	1.02 (0.87, 1.20)
Quintile 2	151	1,015,971	14.8	1.00 (0.85, 1.17)
Quintile 3	148	1,018,195	14.8	0.97 (0.83, 1.14)
Quintile 4	160	1,020,171	15.5	1.01 (0.87, 1.18)
Quintile 5	162	1,022,973	16.3	1.00 (0.85, 1.18)
per 6.9 kg†				*0.99 (0.91, 1.08)*
Height-adjusted lean mass				
Quintile 1	190	993,822	16.6	1.08 (0.89, 1.30)
Quintile 2	155	1,015,431	13.7	1.00 (0.85, 1.17)
Quintile 3	133	1,019,163	13.4	0.91 (0.77, 1.08)
Quintile 4	153	1,019,401	16.0	1.09 (0.93, 1.29)
Quintile 5	165	1,017,816	18.9	1.20 (0.99, 1.45)
per 7.6 kg†				*1.11 (0.95, 1.30)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

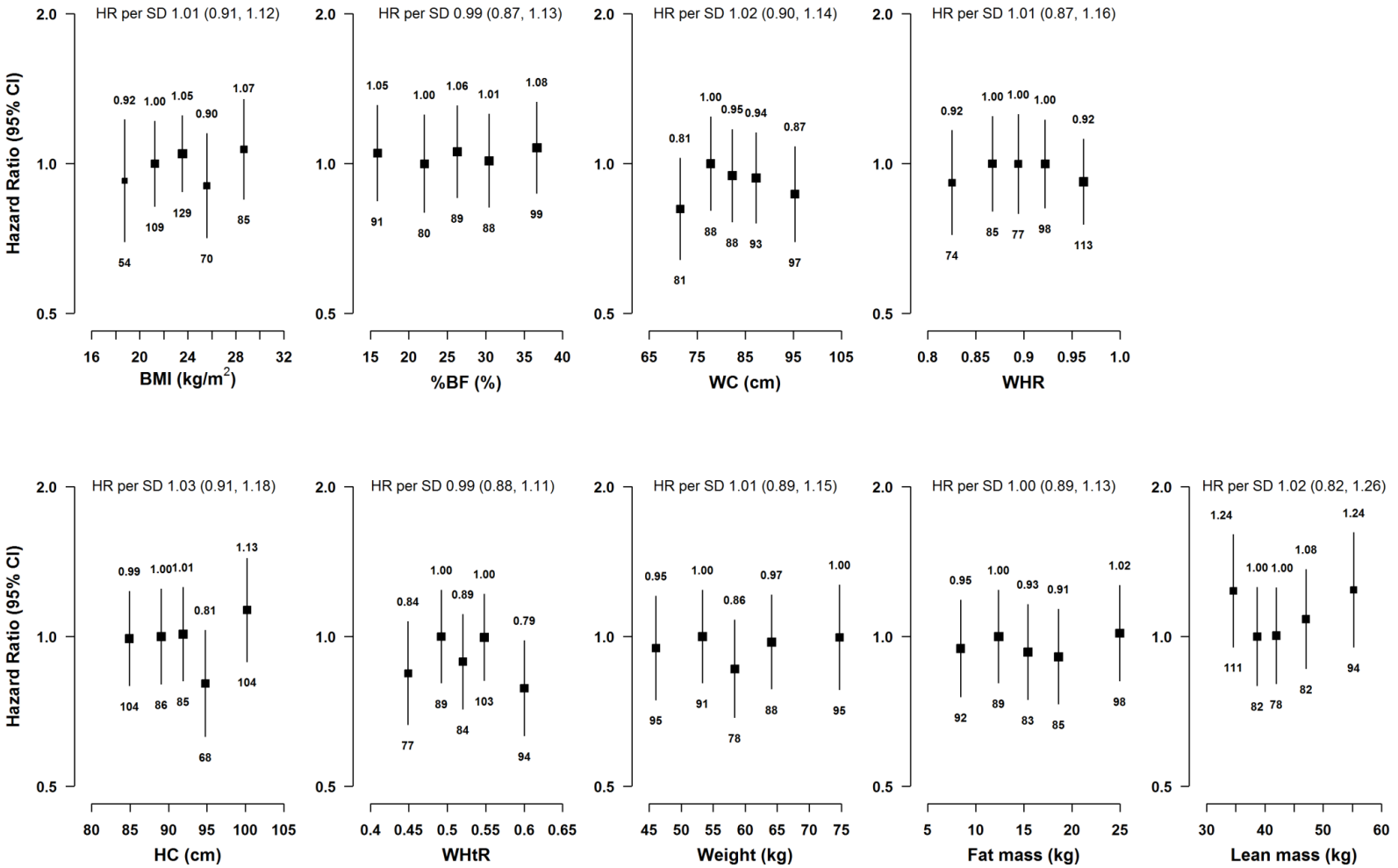
† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Figure 7.4 Associations of adiposity with risk of pancreatic cancer



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weigh, fat mass, and lean mass). For %BF, WC, WHR, HC, WHtR, weight, fat mass, and lean mass, sex-specific quintiles were used.

Figure 7.5 Associations of adiposity with risk of pancreatic cancer excluding the first five years of follow-up



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weigh, fat mass, and lean mass). For %BF, WC, WHR, HC, WHtR, weight, fat mass, and lean mass, sex-specific quintiles were used.

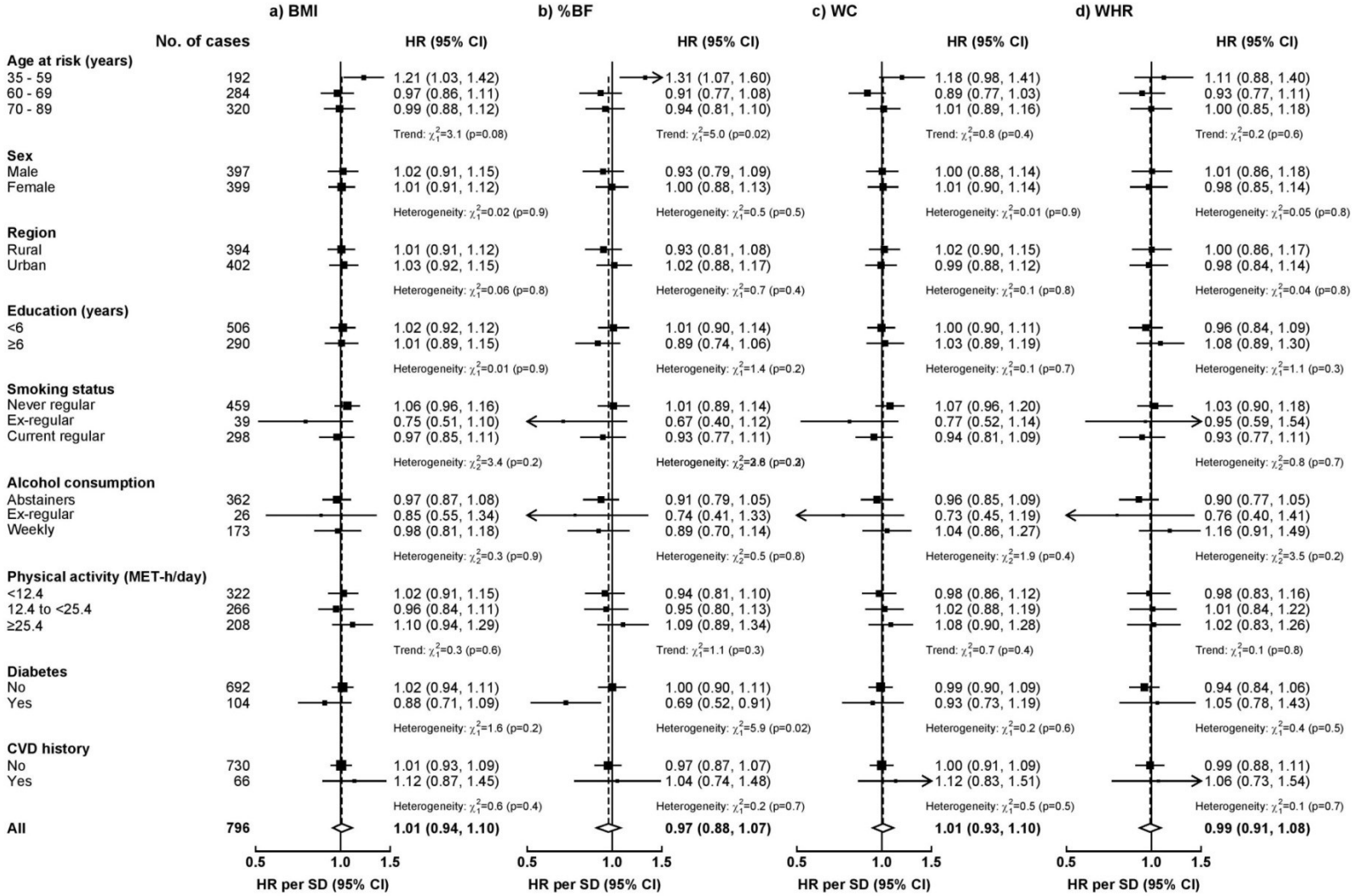
7.1.2.4 Subgroup analyses

Overall similar associations of adiposity with pancreatic cancer were observed in men and women (**Appendices 7.7-7.8**, *p* for heterogeneity 0.53-0.92). In men, the HRs per 1-SD were 1.02 (0.91-1.15) for BMI, 0.93 (0.79-1.09) for %BF, 1.00 (0.88-1.14) for WC, and 1.01 (0.86-1.18) for WHR; in women, the corresponding HRs were 1.01 (0.91-1.12), 1.00 (0.88-1.13), 1.01 (0.90-1.14), and 0.98 (0.85-1.14) (**Appendix 7.7**). According to the IDF categorisations of adiposity for Chinese (**Appendix 7.2**), the HRs associated with high WC were 1.02 (0.79-1.32) in men and 1.03 (0.84-1.27) in women (*p* for heterogeneity 0.95). According to the WHO cut-off points for risk of metabolic complications, the HRs associated with high WHR were 1.12 (0.92-1.37) in men and 0.96 (0.78-1.19) in women (*p* for heterogeneity 0.24). For BMI25, the association was somewhat stronger in men than women (HR per 1-SD: 1.13 [1.01-1.27] vs 1.05 [0.95-1.16]), but the difference was nonsignificant (*p* for heterogeneity 0.32).

The associations of adiposity with pancreatic cancer risk differed little by population subgroup (except for %BF and fat mass by age-at-risk), as indicated by heterogeneity and trend tests (**Figures 7.6**-**7.7**). However, the magnitudes of associations tended to differ by age-at-risk, smoking status, and physical activity. When excluding the first five years of follow-up, there were no clear patterns by population subgroup probably due to the small numbers of events (**Appendices 7.9-7.10**). When stratified by age-at-risk, there were positive trends among participants with younger ages (**Figures 7.6**-**7.7**). For example, the HRs per 1-SD BMI were 1.21 (1.03-1.42), 0.97 (0.86-1.11), and 0.99 (0.88-1.12) for those aged 35-59, 60-69, and 70-89 years. For WC, the corresponding HRs were 1.18 (0.98-

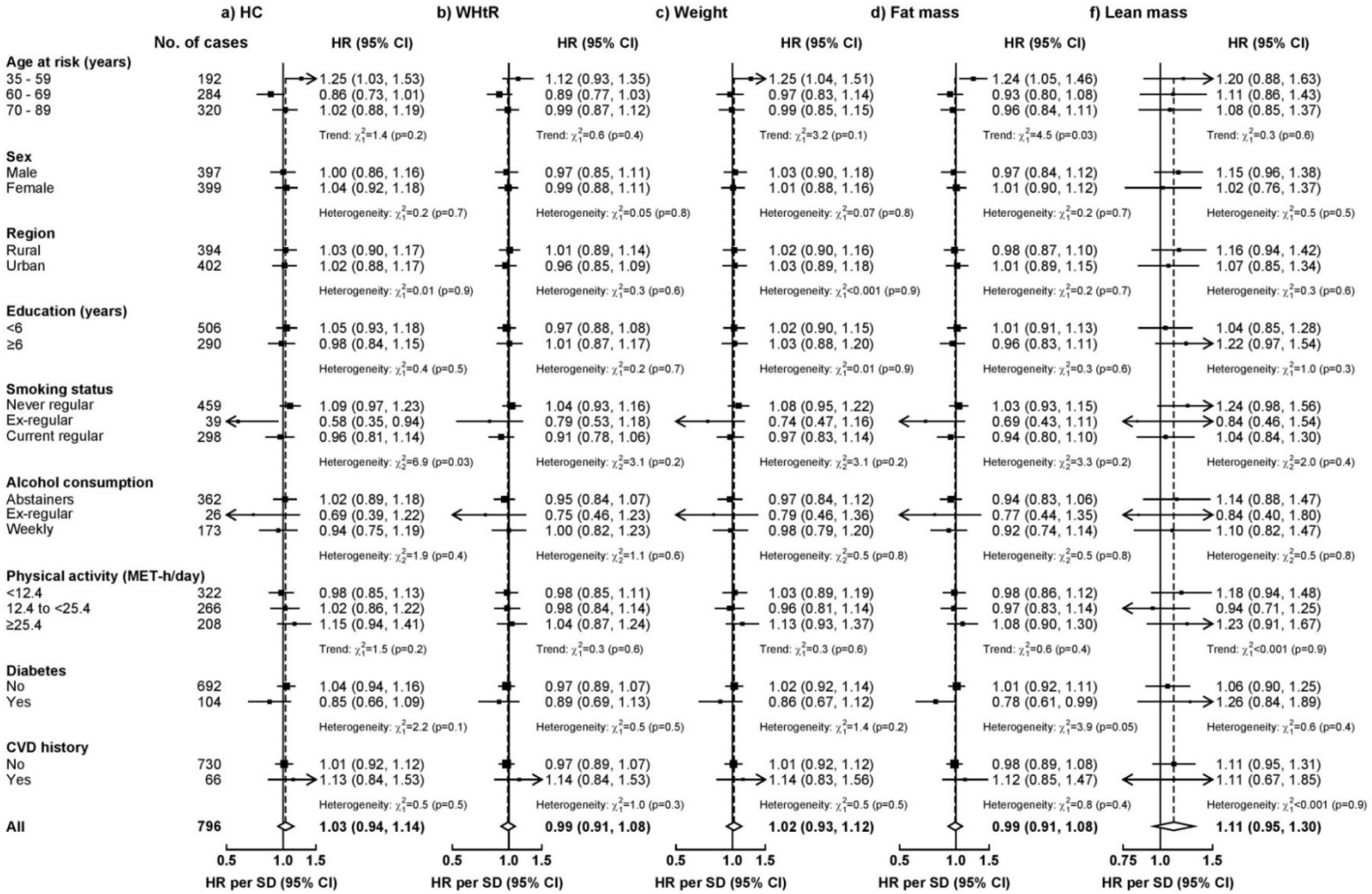
1.41), 0.89 (0.77-1.03), and 1.01 (0.89-1.16). When stratified by smoking status, there were positive trends among never regular smokers and no associations among current regular smokers (**Figures 7.6**-**7.7**). Among ex-regular smokers, there were inverse trends, but the HRs had wide confidence intervals due to the small numbers of cases included. For BMI, the HRs per 1-SD were 1.06 (0.96-1.16), 0.75 (0.51-1.10), and 0.97 (0.85-1.11) among never, ex-regular, and current regular smokers; for WC, the corresponding HRs were 1.07 (0.96-1.20), 0.77 (0.52-1.14), and 0.94 (0.81-1.09). When stratified by physical activity, there were positive trends among participants with higher physical activity (**Figures 7.6**-**7.7**). For example, the HRs per 1-SD higher usual BMI were 1.02 (0.91-1.15), 0.96 (0.84-1.11), and 1.10 (0.94-1.29) for those who had <12.4, 12.4 to <25.4, and ≥25.4 MET-h/day; for WC, the corresponding HRs were 0.98 (0.86-1.12), 1.02 (0.88-1.19), and 1.08 (0.90-1.28).

Figure 7.6 Associations of main adiposity traits with risk of pancreatic cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Figure 7.7 Associations of other adiposity traits with risk of pancreatic cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

7.1.2.5 Adjusted associations for general and central adiposity

Compared with the main model, the null associations for BMI and %BF changed little when additionally adjusting for central adiposity (WC, WHR, or HC; **Table 7.5** and **Figure 7.8**). For BMI, the HRs per 5 kg/m^2 were 1.05 (0.85-1.29), 1.04 (0.91-1.19), and 1.00 (0.84-1.20) when additionally adjusting for WC, WHR, or HC. For %BF, the corresponding HRs per 10% were 0.90 (0.75-1.09), 0.96 (0.83-1.11), and 0.90 (0.77-1.06). For central adiposity (**Table 7.6** and **Figure 7.8**), no associations were observed when additionally adjusting for BMI. When additionally adjusting for BMI, the HRs were 0.98 (0.82-1.16) per 10 cm WC, 0.96 (0.79-1.16) per 0.1 WHR, and 1.03 (0.82-1.31) per 10 cm HC. For HC, the null association remained when further adjusting for WC (HR per 10 cm: 1.07 [0.85-1.34]). In the analyses of both BMI and central adiposity, similar results were observed when the residual method was used (**Appendices 7.11** and **7.12**).

Table 7.5 Adjusted HRs for pancreatic cancer by general adiposity with additional adjustment for central adiposity[*]

	Main	Main + WC	Main + WHR	Main + HC
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI				
<20.0	0.90 (0.73, 1.10)	0.87 (0.67, 1.15)	0.88 (0.70, 1.11)	0.89 (0.70, 1.14)
20.0 to <22.5	1.00 (0.87, 1.15)	1.00 (0.84, 1.19)	1.00 (0.86, 1.16)	1.00 (0.85, 1.17)
22.5 to <25.0	0.95 (0.83, 1.08)	0.97 (0.86, 1.09)	0.96 (0.84, 1.09)	0.94 (0.83, 1.07)
25.0 to <27.5	0.96 (0.81, 1.13)	0.99 (0.82, 1.20)	0.98 (0.82, 1.17)	0.95 (0.79, 1.14)
≥27.5	1.02 (0.86, 1.20)	1.08 (0.84, 1.38)	1.05 (0.87, 1.27)	1.01 (0.80, 1.27)
per 5 kg/m^2[†]	*1.02 (0.92, 1.14)*	*1.05 (0.85, 1.29)*	*1.04 (0.91, 1.19)*	*1.00 (0.84, 1.20)*
%BF				
Quintile 1	1.06 (0.91, 1.24)	1.08 (0.88, 1.33)	1.06 (0.88, 1.27)	1.08 (0.90, 1.30)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.84, 1.19)	1.00 (0.85, 1.18)	1.00 (0.84, 1.18)
Quintile 3	1.04 (0.89, 1.22)	1.03 (0.89, 1.19)	1.04 (0.89, 1.22)	1.03 (0.88, 1.20)
Quintile 4	1.05 (0.90, 1.23)	1.02 (0.87, 1.20)	1.05 (0.90, 1.23)	1.02 (0.87, 1.19)
Quintile 5	1.00 (0.85, 1.18)	0.95 (0.78, 1.17)	1.00 (0.84, 1.19)	0.94 (0.77, 1.14)
per 10%[†]	*0.97 (0.86, 1.09)*	*0.90 (0.75, 1.09)*	*0.96 (0.83, 1.11)*	*0.90 (0.77, 1.06)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, sex-specific quintiles were used.
[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88.

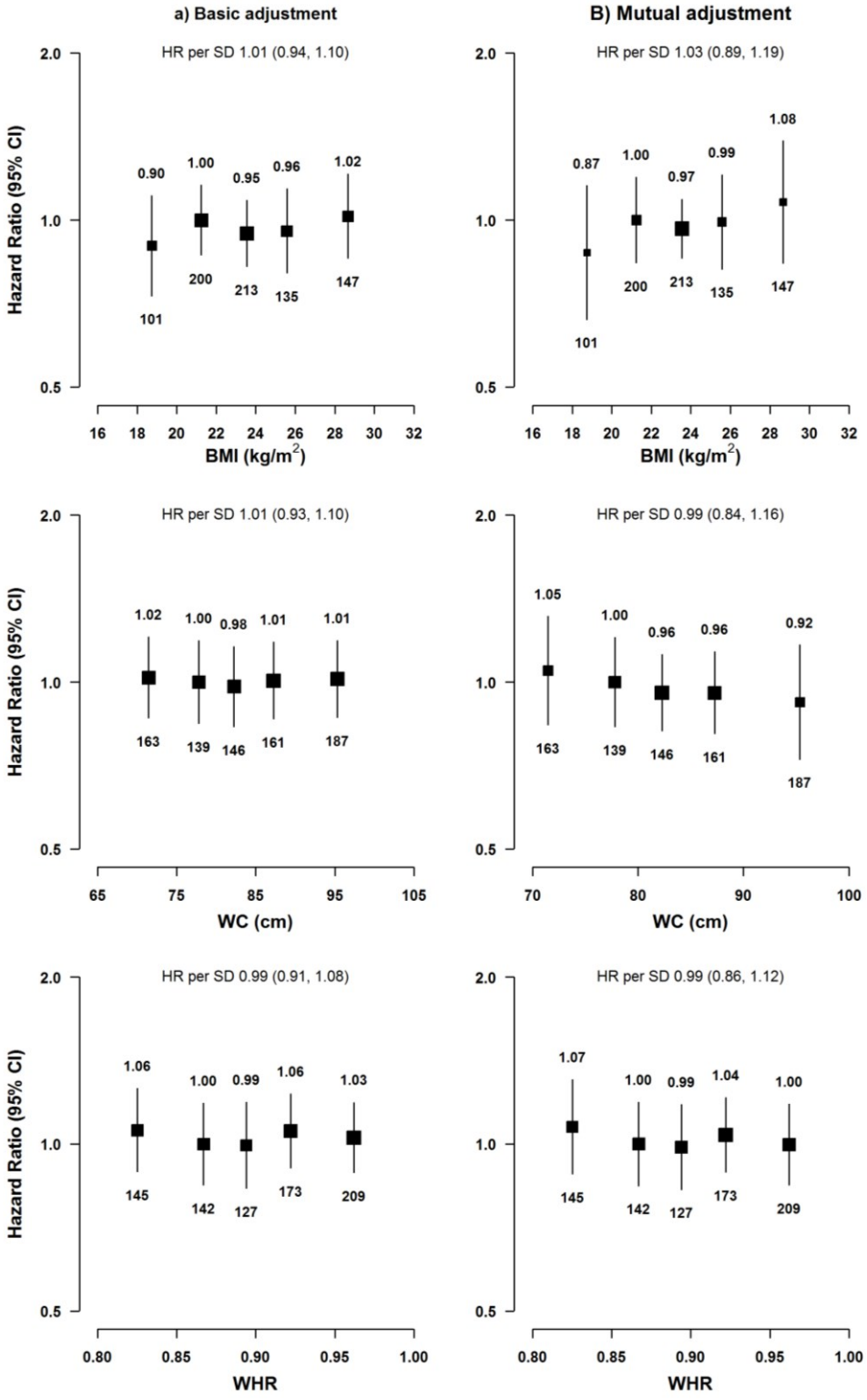
Table 7.6 Adjusted HRs for pancreatic cancer by central adiposity with additional adjustment for other adiposity traits[*]

	Main	Main + BMI	Main + WC
	HR (95% CI)	HR (95% CI)	HR (95% CI)
WC			
Quintile 1	1.02 (0.87, 1.20)	1.05 (0.84, 1.31)	—
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.84, 1.20)	—
Quintile 3	0.98 (0.84, 1.15)	0.96 (0.82, 1.12)	—
Quintile 4	1.01 (0.86, 1.17)	0.96 (0.81, 1.13)	—
Quintile 5	1.01 (0.87, 1.18)	0.92 (0.73, 1.16)	—
per 10 cm[†]	*1.01 (0.93, 1.11)*	*0.98 (0.82, 1.16)*	—
WHR			
Quintile 1	1.06 (0.90, 1.25)	1.07 (0.89, 1.30)	—
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.84, 1.18)	—
Quintile 3	0.99 (0.84, 1.18)	0.99 (0.83, 1.17)	—
Quintile 4	1.06 (0.91, 1.23)	1.04 (0.89, 1.21)	—
Quintile 5	1.03 (0.89, 1.18)	1.00 (0.85, 1.18)	—
per 0.1[†]	*0.99 (0.85, 1.15)*	*0.96 (0.79, 1.16)*	—
HC			
Quintile 1	0.93 (0.79, 1.10)	0.94 (0.77, 1.16)	0.93 (0.76, 1.16)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.85, 1.18)	1.00 (0.84, 1.18)
Quintile 3	0.94 (0.80, 1.10)	0.93 (0.79, 1.08)	0.93 (0.80, 1.09)
Quintile 4	0.86 (0.72, 1.02)	0.84 (0.70, 1.00)	0.85 (0.71, 1.02)
Quintile 5	1.03 (0.87, 1.23)	0.98 (0.77, 1.25)	1.01 (0.80, 1.27)
per 10 cm[†]	*1.05 (0.91, 1.20)*	*1.03 (0.82, 1.31)*	*1.07 (0.85, 1.34)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] Regression dilution ratios: WC, 0.88; WHR, 0.70; HC, 0.81.

Figure 7.8 Associations of adiposity with risk of pancreatic cancer with mutual adjustment



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For WC and WHR, sex-specific quintiles were used. The association of BMI was additionally adjusted for WC. The associations of WC and WHR were additionally adjusted for BMI.

7.1.3 Associations of adiposity with liver cancer

7.1.3.1 Main adiposity traits

BMI was inversely associated with risk of liver cancer (**Figure 7.9** and **Table 7.7**), with HRs of 1.03 (0.93-1.13), 1.00 (0.93-1.07) (reference), 0.96 (0.90-1.03), 0.89 (0.81-0.98), and 0.89 (0.80-0.98) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2 (HR per 5 kg/m^2 0.91 [0.86-0.97], **Table 7.7**). When finer categories of BMI were used, the association appeared to be U-shaped, with the lowest risk at BMI of ~25.0-27.5 kg/m^2. The HRs were 1.12 (0.97-1.31), 1.00 (0.94-1.07), 0.97 (0.90-1.04), 0.89 (0.81-0.97), 0.88 (0.77-1.00), and 0.96 (0.79-1.17) for those with BMI of <18.5, 18.5 to 22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30, and ≥30.0 kg/m^2. When the WHO classifications were used (**Appendix 7.13**), the HRs were 1.13 (0.97-1.32), 1.00 (0.95-1.05), 0.90 (0.84-0.97), and 0.98 (0.81-1.19) for those with BMI of <18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 kg/m^2. Similar to BMI, there was an inverse association for %BF, with HRs of 1.07 (0.99-1.15), 1.00 (0.92-1.08) (reference), 0.86 (0.79-0.94), 0.83 (0.76-0.91), and 0.77 (0.70-0.85) for those in the bottom to the top quintile (HR per 10% 0.82 [0.77-0.88], **Table 7.7**). For central adiposity, there were no associations for WC and WHR, with HRs of 0.98 (0.94-1.03) per 10 cm higher WC and 1.04 (0.96-1.13) per 0.1 higher WHR (**Table 7.7**). By contrast, BMI at age 25 was positively associated with liver cancer (**Table 7.7**), with a HR per 5 kg/m^2 of 1.09 (1.01-1.18). The HRs were 0.97 (0.88-1.07), 1.00 (0.94-1.07), 1.14 (1.06-1.23), 1.03 (0.90-1.19), and 1.11 (0.92-1.35) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2.

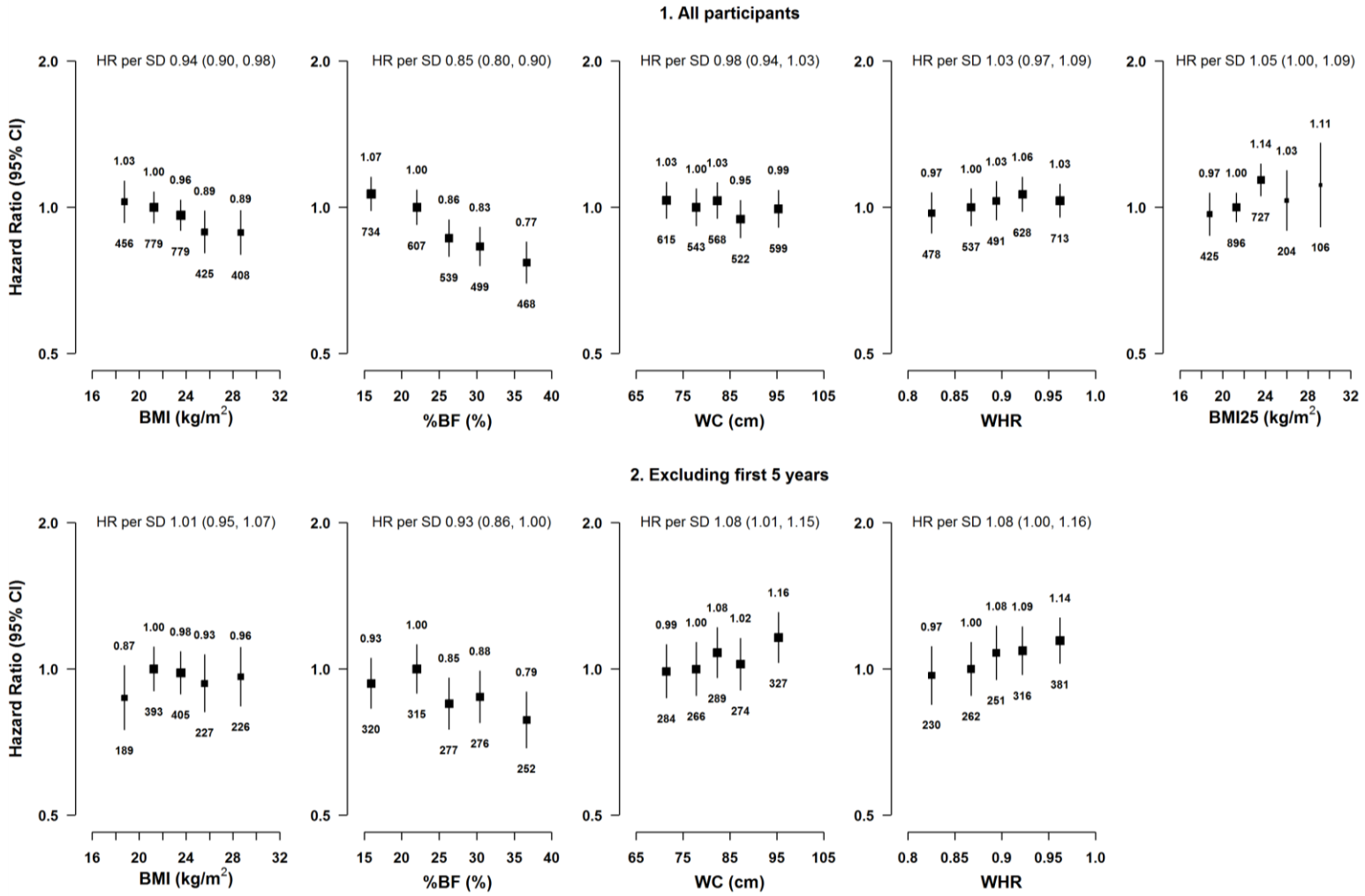
7.1.3.2 Exclusion of early years of follow-up, smokers or drinkers

When excluding early years of follow-up (**Figure 7.9** and **Table 7.8**), the inverse associations for BMI and %BF attenuated towards the null, while there were positive trends for WC and WHR. This suggests that the inverse associations for BMI and %BF and the null associations for WC and WHR in the main model may be due to reverse causality. For BMI (**Table 7.8)**, the inverse association attenuated towards the null when excluding the first two years and was null when excluding the first five years, with HRs per 1-SD of 0.98 (0.93-1.02) and 1.01 (0.95-1.07). Similar to BMI, the inverse associations of %BF attenuated towards the null when excluding the first two and five years, with HRs per 1-SD of 0.90 (0.85-0.96) and 0.93 (0.86-1.00), respectively (**Table 7.8)**. For WC, there was no association when excluding the first two years and a positive trend when excluding the first five years, with HRs per 1-SD of 1.03 (0.98-1.09) and 1.08 (1.01-1.15). For WHR, there was a positive trend when excluding the first two years and a positive association when excluding the first five years, with HRs per 1-SD of 1.04 (0.98-1.11) and 1.08 (1.00-1.16).

When restricting the analysis to never regular smokers (**Appendix 7.14**), the inverse associations for BMI and %BF attenuated towards the null (HR per 1-SD: BMI: 0.97 [0.91-1.03]; %BF: 0.89 [0.83-0.96]), while there was little impact on WC and WHR (WC: 1.01 [0.94-1.08]; WHR: 1.04 [0.96-1.12]). This suggests that the inverse associations for BMI and %BF in the main model may be affected by residual confounding related to smoking. When excluding the first five years (**Appendix 7.15**), there was a positive trend for BMI (HR per 1-SD: 1.06 [0.94-1.18]) and a null association for %BF in never regular smokers (0.96 [0.87-1.07]).

When restricting the analysis to never regular drinkers, the associations changed little for BMI, %BF, WC, and WHR, in all participants (**Appendix 7.14**) or when excluding the first five years (**Appendix 7.15**).

Figure 7.9 Associations of main adiposity traits with risk of liver cancer



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

Table 7.7 Adjusted HRs for liver cancer by main adiposity traits*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
BMI				
<20.0	456	637,276	63.8	1.03 (0.93, 1.13)
20.0 to <22.5	779	1,304,762	60.0	1.00 (0.93, 1.07)
22.5 to <25.0	779	1,445,238	54.3	0.96 (0.90, 1.03)
25.0 to <27.5	425	853,076	48.2	0.89 (0.81, 0.98)
≥27.5	408	823,270	48.5	0.89 (0.80, 0.98)
per 3.4 kg/m^2†				*0.94 (0.90, 0.98)*
%BF				
Quintile 1	734	984,723	70.8	1.07 (0.99, 1.15)
Quintile 2	607	999,931	61.5	1.00 (0.92, 1.08)
Quintile 3	539	1,024,555	52.0	0.86 (0.79, 0.94)
Quintile 4	499	1,022,142	48.3	0.83 (0.76, 0.91)
Quintile 5	468	1,032,271	46.1	0.77 (0.70, 0.85)
per 8.4%†				*0.85 (0.80, 0.90)*
WC				
Quintile 1	615	1,010,822	60.8	1.03 (0.95, 1.12)
Quintile 2	543	1,004,175	55.7	1.00 (0.92, 1.09)
Quintile 3	568	1,030,577	56.4	1.03 (0.95, 1.12)
Quintile 4	522	1,016,694	50.7	0.95 (0.87, 1.03)
Quintile 5	599	1,001,354	51.2	0.99 (0.91, 1.08)
per 9.8 cm†				*0.98 (0.94, 1.03)*
WHR				
Quintile 1	478	1,065,690	56.5	0.97 (0.89, 1.07)
Quintile 2	537	933,801	55.6	1.00 (0.92, 1.09)
Quintile 3	491	878,626	55.4	1.03 (0.94, 1.13)
Quintile 4	628	1,052,635	57.6	1.06 (0.98, 1.15)
Quintile 5	713	1,132,871	54.2	1.03 (0.96, 1.11)
per 0.07†				*1.03 (0.97, 1.09)*
BMI25‡				
<20.0	425	979,305	50.5	0.97 (0.88, 1.07)
20.0 to <22.5	896	1,699,325	52.4	1.00 (0.94, 1.07)
22.5 to <25.0	727	1,113,630	60.8	1.14 (1.06, 1.23)
25.0 to <27.5	204	332,601	57.2	1.03 (0.90, 1.19)
≥27.5	106	147,189	63.1	1.11 (0.92, 1.35)
per 2.6 kg/m^2				*1.05 (1.00, 1.09)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

‡ BMI25 was missing in 81,880 participants.

Table 7.8 Adjusted HRs for liver cancer by main adiposity traits excluding the first two or five years of follow-up[*]

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	346	1.00 (0.89, 1.11)	189	0.87 (0.75, 1.01)
20.0 to <22.5	613	1.00 (0.92, 1.08)	393	1.00 (0.90, 1.11)
22.5 to <25.0	628	0.98 (0.91, 1.06)	405	0.98 (0.89, 1.08)
25.0 to <27.5	355	0.95 (0.85, 1.05)	227	0.93 (0.82, 1.06)
≥27.5	343	0.95 (0.85, 1.07)	226	0.96 (0.84, 1.10)
per 3.4 kg/m^2[†]		*0.98 (0.93, 1.02)*		*1.01 (0.95, 1.07)*
%BF				
Quintile 1	555	1.01 (0.92, 1.10)	320	0.93 (0.83, 1.05)
Quintile 2	492	1.00 (0.92, 1.09)	315	1.00 (0.89, 1.12)
Quintile 3	434	0.86 (0.78, 0.94)	277	0.85 (0.75, 0.95)
Quintile 4	410	0.84 (0.77, 0.93)	276	0.88 (0.78, 0.99)
Quintile 5	394	0.81 (0.73, 0.89)	252	0.79 (0.69, 0.89)
per 8.4%[†]		*0.90 (0.85, 0.96)*		*0.93 (0.86, 1.00)*
WC				
Quintile 1	464	0.98 (0.89, 1.08)	284	0.99 (0.88, 1.12)
Quintile 2	435	1.00 (0.91, 1.10)	266	1.00 (0.89, 1.13)
Quintile 3	452	1.03 (0.94, 1.13)	289	1.08 (0.96, 1.21)
Quintile 4	434	0.99 (0.90, 1.09)	274	1.02 (0.91, 1.15)
Quintile 5	500	1.06 (0.97, 1.16)	327	1.16 (1.03, 1.30)
per 9.8 cm[†]		*1.03 (0.98, 1.09)*		*1.08 (1.01, 1.15)*
WHR				
Quintile 1	377	0.98 (0.88, 1.09)	230	0.97 (0.85, 1.11)
Quintile 2	424	1.00 (0.91, 1.10)	262	1.00 (0.89, 1.13)
Quintile 3	402	1.07 (0.97, 1.18)	251	1.08 (0.95, 1.22)
Quintile 4	501	1.07 (0.98, 1.17)	316	1.09 (0.98, 1.22)
Quintile 5	581	1.08 (0.99, 1.17)	381	1.14 (1.03, 1.27)
per 0.07[†]		*1.04 (0.98, 1.11)*		*1.08 (1.00, 1.16)*

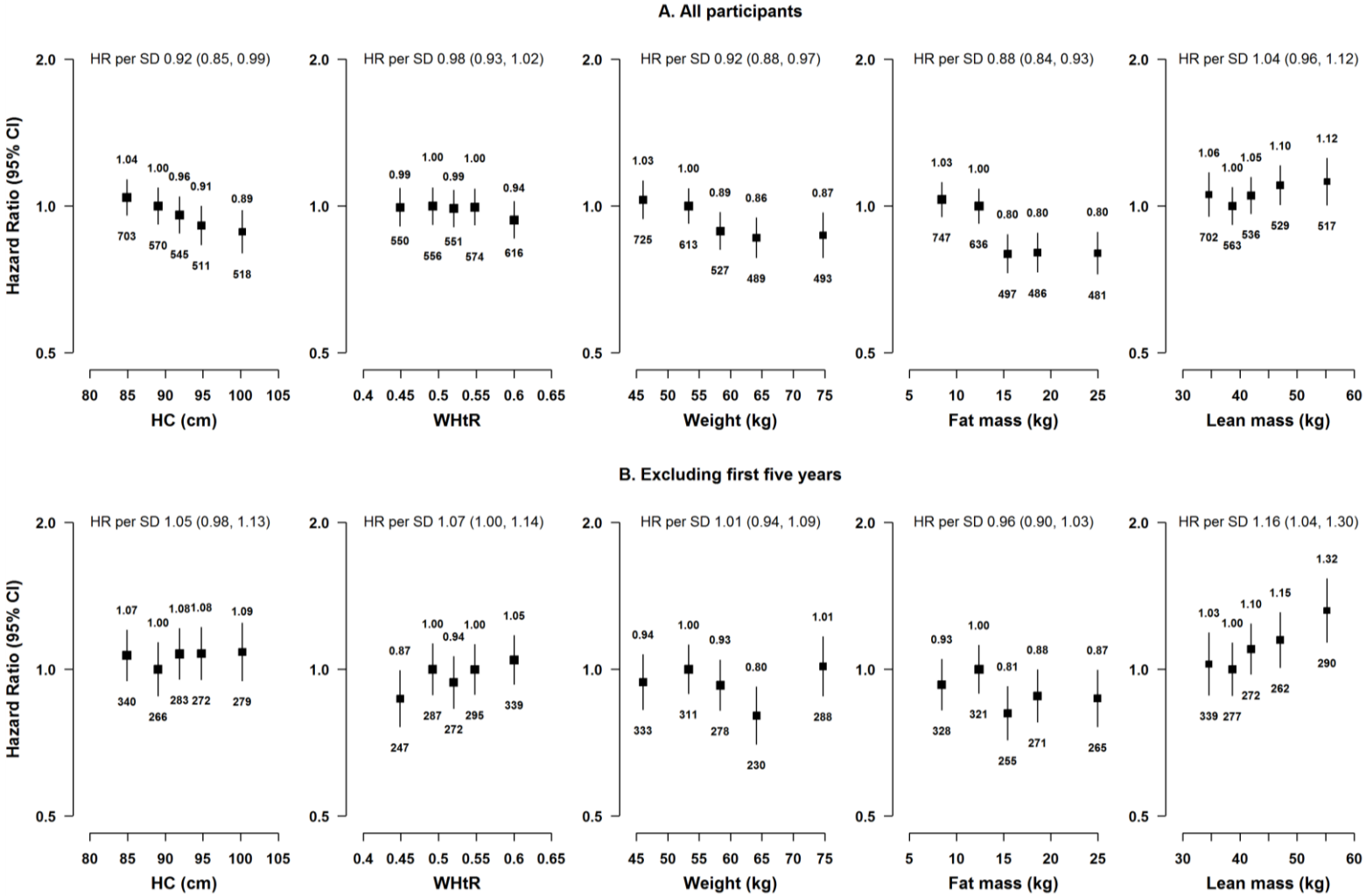
[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

7.1.3.3 Other adiposity traits

For other adiposity traits (**Figure 7.10** and **Table 7.9**), liver cancer showed inverse associations with HC, height-adjusted weight, and height-adjusted fat mass (HR per 1-SD: 0.92 [0.85-0.99], 0.92 [0.88-0.97], and 0.88 [0.84-0.93]) and no associations with WHtR and height-adjusted lean mass (0.98 [0.93-1.02] vs 1.04 [0.96-1.12]). When excluding the first five years of follow-up (**Figure 7.10** and **Table 7.10**), there were no associations for HC, height-adjusted weight, and fat mass (HR per 1-SD: 1.05 [0.98-1.13], 1.01 [0.94-1.09], and 0.96 [0.90-1.03]) and positive associations for WHtR and height-adjusted lean mass (1.07 [1.00-1.14] vs 1.16 [1.04-1.30]). When restricting the analysis to never regular smokers (**Appendix 7.16**), the inverse associations for HC, height-adjusted weight, and height-adjusted fat mass attenuated toward the null (HR per 1-SD: 0.98 [0.91-1.05], 0.96 [0.89-1.04], and 0.93 [0.87-0.99]), while there was a positive association for height-adjusted lean mass (1.11 [0.97-1.26]). When excluding the first five years (**Appendix 7.17**), the positive association for height-adjusted lean mass became stronger among never regular smokers (1.29 [1.08-1.55]). When restricting the analysis to never regular drinkers, the associations changed little for these five adiposity traits (**Appendix 7.16-7.17**).

Figure 7.10 Associations of other adiposity traits with risk of liver cancer



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass). Sex-specific quintiles were used.

Table 7.9 Adjusted HRs for liver cancer by other adiposity traits*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
HC				
Quintile 1	703	1,006,318	58.7	1.04 (0.96, 1.13)
Quintile 2	570	971,273	61.2	1.00 (0.92, 1.09)
Quintile 3	545	1,042,031	53.5	0.96 (0.88, 1.04)
Quintile 4	511	1,037,501	52.3	0.91 (0.84, 1.00)
Quintile 5	518	1,006,500	48.6	0.89 (0.80, 0.98)
per 6.9 cm†				*0.92 (0.85, 0.99)*
WHtR				
Quintile 1	550	1,027,540	58.4	0.99 (0.91, 1.08)
Quintile 2	556	1,022,756	57.3	1.00 (0.92, 1.09)
Quintile 3	551	1,015,870	55.7	0.99 (0.91, 1.07)
Quintile 4	574	1,009,239	54.6	1.00 (0.92, 1.08)
Quintile 5	616	988,217	50.5	0.94 (0.86, 1.02)
per 0.06†				*0.98 (0.93, 1.02)*
Height-adjusted weight				
Quintile 1	725	977,381	64.3	1.03 (0.94, 1.12)
Quintile 2	613	1,009,000	60.4	1.00 (0.92, 1.08)
Quintile 3	527	1,033,156	51.6	0.89 (0.82, 0.97)
Quintile 4	489	1,013,070	52.3	0.86 (0.79, 0.94)
Quintile 5	493	1,031,015	48.5	0.87 (0.79, 0.96)
per 10.8 kg†				*0.92 (0.88, 0.97)*
Height-adjusted fat mass				
Quintile 1	747	987,844	69.6	1.03 (0.95, 1.11)
Quintile 2	636	1,015,546	63.2	1.00 (0.92, 1.08)
Quintile 3	497	1,017,848	49.4	0.80 (0.73, 0.87)
Quintile 4	486	1,019,768	46.7	0.80 (0.73, 0.88)
Quintile 5	481	1,022,616	48.6	0.80 (0.73, 0.88)
per 6.9 kg†				*0.88 (0.84, 0.93)*
Height-adjusted lean mass				
Quintile 1	702	993,380	62.6	1.06 (0.96, 1.17)
Quintile 2	563	1,015,088	54.2	1.00 (0.92, 1.09)
Quintile 3	536	1,018,763	53.4	1.05 (0.97, 1.14)
Quintile 4	529	1,018,992	55.9	1.10 (1.01, 1.21)
Quintile 5	517	1,017,400	55.1	1.12 (1.01, 1.25)
per 7.6 kg†				*1.04 (0.96, 1.12)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Table 7.10 Adjusted HRs for liver cancer by other adiposity traits excluding the first two or five years of follow-up[*]

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	531	0.99 (0.90, 1.09)	340	1.07 (0.95, 1.20)
Quintile 2	452	1.00 (0.91, 1.10)	266	1.00 (0.89, 1.13)
Quintile 3	440	0.98 (0.89, 1.07)	283	1.08 (0.96, 1.21)
Quintile 4	427	0.98 (0.89, 1.08)	272	1.08 (0.95, 1.21)
Quintile 5	435	0.97 (0.87, 1.08)	279	1.09 (0.95, 1.24)
per 6.9 cm[†]		*1.01 (0.96, 1.07)*		*1.05 (0.98, 1.13)*
WHtR				
Quintile 1	422	0.98 (0.88, 1.08)	247	0.87 (0.77, 0.99)
Quintile 2	437	1.00 (0.91, 1.10)	287	1.00 (0.89, 1.12)
Quintile 3	437	1.00 (0.91, 1.10)	272	0.94 (0.83, 1.06)
Quintile 4	472	1.05 (0.96, 1.15)	295	1.00 (0.89, 1.12)
Quintile 5	517	1.03 (0.94, 1.12)	339	1.05 (0.93, 1.17)
per 0.06[†]		*1.02 (0.97, 1.07)*		*1.07 (1.00, 1.14)*
Height-adjusted weight				
Quintile 1	556	0.99 (0.89, 1.09)	333	0.94 (0.83, 1.07)
Quintile 2	490	1.00 (0.91, 1.09)	311	1.00 (0.89, 1.12)
Quintile 3	427	0.90 (0.82, 0.99)	278	0.93 (0.83, 1.04)
Quintile 4	394	0.87 (0.79, 0.96)	230	0.80 (0.70, 0.92)
Quintile 5	418	0.93 (0.84, 1.04)	288	1.01 (0.89, 1.16)
per 10.8 kg[†]		*0.97 (0.91, 1.02)*		*1.01 (0.94, 1.09)*
Height-adjusted fat mass				
Quintile 1	564	0.96 (0.88, 1.05)	328	0.93 (0.83, 1.04)
Quintile 2	519	1.00 (0.92, 1.09)	321	1.00 (0.90, 1.12)
Quintile 3	388	0.77 (0.69, 0.84)	255	0.81 (0.72, 0.92)
Quintile 4	409	0.83 (0.75, 0.91)	271	0.88 (0.78, 0.99)
Quintile 5	405	0.84 (0.75, 0.93)	265	0.87 (0.77, 0.99)
per 6.9 kg[†]		*0.93 (0.88, 0.98)*		*0.96 (0.90, 1.03)*
Height-adjusted lean mass				
Quintile 1	546	1.03 (0.92, 1.15)	339	1.03 (0.89, 1.18)
Quintile 2	452	1.00 (0.91, 1.10)	277	1.00 (0.89, 1.13)
Quintile 3	434	1.06 (0.97, 1.16)	272	1.10 (0.98, 1.23)
Quintile 4	428	1.12 (1.01, 1.23)	262	1.15 (1.01, 1.30)
Quintile 5	425	1.15 (1.03, 1.30)	290	1.32 (1.14, 1.53)
per 7.6 kg[†]		*1.07 (0.98, 1.17)*		*1.16 (1.04, 1.30)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

7.1.3.4 Subgroup analyses

The associations of adiposity with liver cancer risk differed little by HBsAg (**Appendices 7.18**-**7.19**), except that the inverse association for %BF was stronger in HBsAg positive than negative participants (*p* for heterogeneity 0.04). When excluding the first five years of follow-up (**Tables 7.11-7.12**), the direction and strength of associations tended to differ by HBsAg status, though nonsignificantly (*p* for heterogeneity 0.12-0.33). Among HBsAg negative participants, there was an inverse trend for %BF (HR per 1-SD: 0.95 [0.87-1.04]), null associations for BMI, height-adjusted weight, and fat mass (1.04 [0.95-1.15], 1.04 [0.95-1.13], and 0.98 [0.91-1.06]), and positive associations for WC, WHR, HC, WHtR, and height-adjusted lean mass (1.10 [1.02-1.19], 1.11 [1.01-1.23], 1.08 [0.99-1.17], 1.09 [1.01-1.17], and 1.19 [1.04-1.36]). However, among HBsAg positive participants, there were inverse trends for BMI, %BF, height-adjusted weight, and fat mass (HR per 1-SD: 0.90 [0.77-1.06], 0.85 [0.72-0.99], 0.93 [0.80-1.07], and 0.90 [0.79-1.04]), and null associations for WC, WHR, HC, WHtR, and height-adjusted lean mass (0.99 [0.87-1.12], 1.00 [0.86-1.16], 0.98 [0.85-1.13], 0.98 [0.86-1.12], and 1.00 [0.80-1.25]).

Table 7.11 Adjusted HRs for liver cancer associated with main adiposity traits by HBsAg excluding 5 years[*]

	HBsAg negative		HBsAg positive	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	134	0.90 (0.76, 1.08)	49	0.84 (0.62, 1.12)
20.0 to <22.5	264	1.00 (0.88, 1.13)	113	1.00 (0.83, 1.21)
22.5 to <25.0	296	1.04 (0.93, 1.17)	92	0.79 (0.64, 0.97)
25.0 to <27.5	173	1.01 (0.87, 1.18)	44	0.67 (0.49, 0.90)
≥27.5	165	1.03 (0.87, 1.20)	55	0.80 (0.61, 1.06)
per 3.4 kg/m^2[†]		*1.04 (0.95, 1.15)*		*0.90 (0.77, 1.06)*
%BF				
Quintile 1	234	1.02 (0.89, 1.17)	74	0.80 (0.63, 1.01)
Quintile 2	211	1.00 (0.87, 1.14)	89	1.00 (0.81, 1.23)
Quintile 3	206	0.94 (0.82, 1.08)	58	0.65 (0.50, 0.84)
Quintile 4	193	0.91 (0.79, 1.05)	73	0.84 (0.67, 1.06)
Quintile 5	188	0.88 (0.76, 1.02)	59	0.61 (0.47, 0.80)
per 8.4%[†]		*0.95 (0.87, 1.04)*		*0.85 (0.72, 0.99)*
WC				
Quintile 1	192	0.96 (0.83, 1.12)	78	1.02 (0.80, 1.29)
Quintile 2	185	1.00 (0.86, 1.16)	72	1.00 (0.79, 1.27)
Quintile 3	202	1.06 (0.93, 1.22)	72	1.03 (0.82, 1.30)
Quintile 4	210	1.08 (0.94, 1.24)	58	0.88 (0.68, 1.15)
Quintile 5	243	1.19 (1.04, 1.36)	73	1.00 (0.78, 1.28)
per 9.8 cm[†]		*1.10 (1.02, 1.19)*		*0.99 (0.87, 1.12)*
WHR				
Quintile 1	155	0.98 (0.83, 1.15)	64	0.90 (0.69, 1.15)
Quintile 2	181	1.00 (0.86, 1.16)	75	1.00 (0.80, 1.26)
Quintile 3	172	1.04 (0.90, 1.21)	67	1.08 (0.85, 1.37)
Quintile 4	230	1.10 (0.97, 1.26)	78	1.09 (0.87, 1.36)
Quintile 5	294	1.18 (1.05, 1.33)	69	0.91 (0.71, 1.16)
per 0.07[†]		*1.11 (1.01, 1.23)*		*1.00 (0.86, 1.16)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

P for heterogeneity by HBsAg: BMI, 0.12; %BF, 0.24; WC, 0.20; WHR, 0.22.

Table 7.12 Adjusted HRs for liver cancer associated with other adiposity traits by HBsAg excluding 5 years[*]

	HBsAg negative		HBsAg positive	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	242	1.06 (0.93, 1.22)	83	1.13 (0.89, 1.43)
Quintile 2	187	1.00 (0.86, 1.16)	67	1.00 (0.78, 1.28)
Quintile 3	201	1.10 (0.95, 1.26)	66	0.95 (0.74, 1.20)
Quintile 4	208	1.16 (1.01, 1.33)	57	0.88 (0.68, 1.14)
Quintile 5	194	1.10 (0.94, 1.29)	80	1.07 (0.84, 1.38)
per 6.9 cm[†]		*1.08 (0.99, 1.17)*		*0.98 (0.85, 1.13)*
WHtR				
Quintile 1	157	0.83 (0.71, 0.97)	78	0.95 (0.75, 1.20)
Quintile 2	195	1.00 (0.87, 1.15)	82	1.00 (0.80, 1.25)
Quintile 3	206	1.01 (0.89, 1.16)	56	0.75 (0.58, 0.98)
Quintile 4	215	1.00 (0.87, 1.14)	68	1.00 (0.78, 1.27)
Quintile 5	259	1.08 (0.95, 1.23)	69	0.91 (0.71, 1.17)
per 0.06[†]		*1.09 (1.01, 1.17)*		*0.98 (0.86, 1.12)*
Height-adjusted weight				
Quintile 1	248	0.98 (0.84, 1.13)	74	0.97 (0.74, 1.27)
Quintile 2	215	1.00 (0.87, 1.14)	80	1.00 (0.80, 1.25)
Quintile 3	191	0.92 (0.80, 1.06)	73	0.90 (0.72, 1.14)
Quintile 4	174	0.89 (0.76, 1.03)	49	0.60 (0.45, 0.80)
Quintile 5	204	1.10 (0.93, 1.29)	77	0.85 (0.65, 1.11)
per 10.8 kg[†]		*1.04 (0.95, 1.13)*		*0.93 (0.80, 1.07)*
Height-adjusted fat mass				
Quintile 1	243	1.01 (0.88, 1.15)	71	0.75 (0.58, 0.96)
Quintile 2	216	1.00 (0.87, 1.14)	91	1.00 (0.81, 1.23)
Quintile 3	182	0.85 (0.74, 0.98)	62	0.69 (0.54, 0.89)
Quintile 4	200	0.96 (0.83, 1.10)	60	0.67 (0.52, 0.87)
Quintile 5	191	0.96 (0.82, 1.11)	69	0.71 (0.55, 0.92)
per 6.9 kg[†]		*0.98 (0.91, 1.06)*		*0.90 (0.79, 1.04)*
Height-adjusted lean mass				
Quintile 1	247	0.95 (0.81, 1.13)	80	1.52 (1.12, 2.04)
Quintile 2	208	1.00 (0.87, 1.15)	55	1.00 (0.76, 1.32)
Quintile 3	199	1.09 (0.95, 1.25)	64	1.24 (0.97, 1.57)
Quintile 4	186	1.11 (0.96, 1.29)	65	1.26 (0.98, 1.62)
Quintile 5	192	1.28 (1.07, 1.52)	89	1.44 (1.09, 1.89)
per 7.6 kg[†]		*1.19 (1.04, 1.36)*		*1.00 (0.80, 1.25)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

P for heterogeneity by HBsAg: HC, 0.33; WHtR, 0.18; height-adjusted weight, 0.22; height-adjusted fat mass, 0.20; height-adjusted lean mass, 0.28.

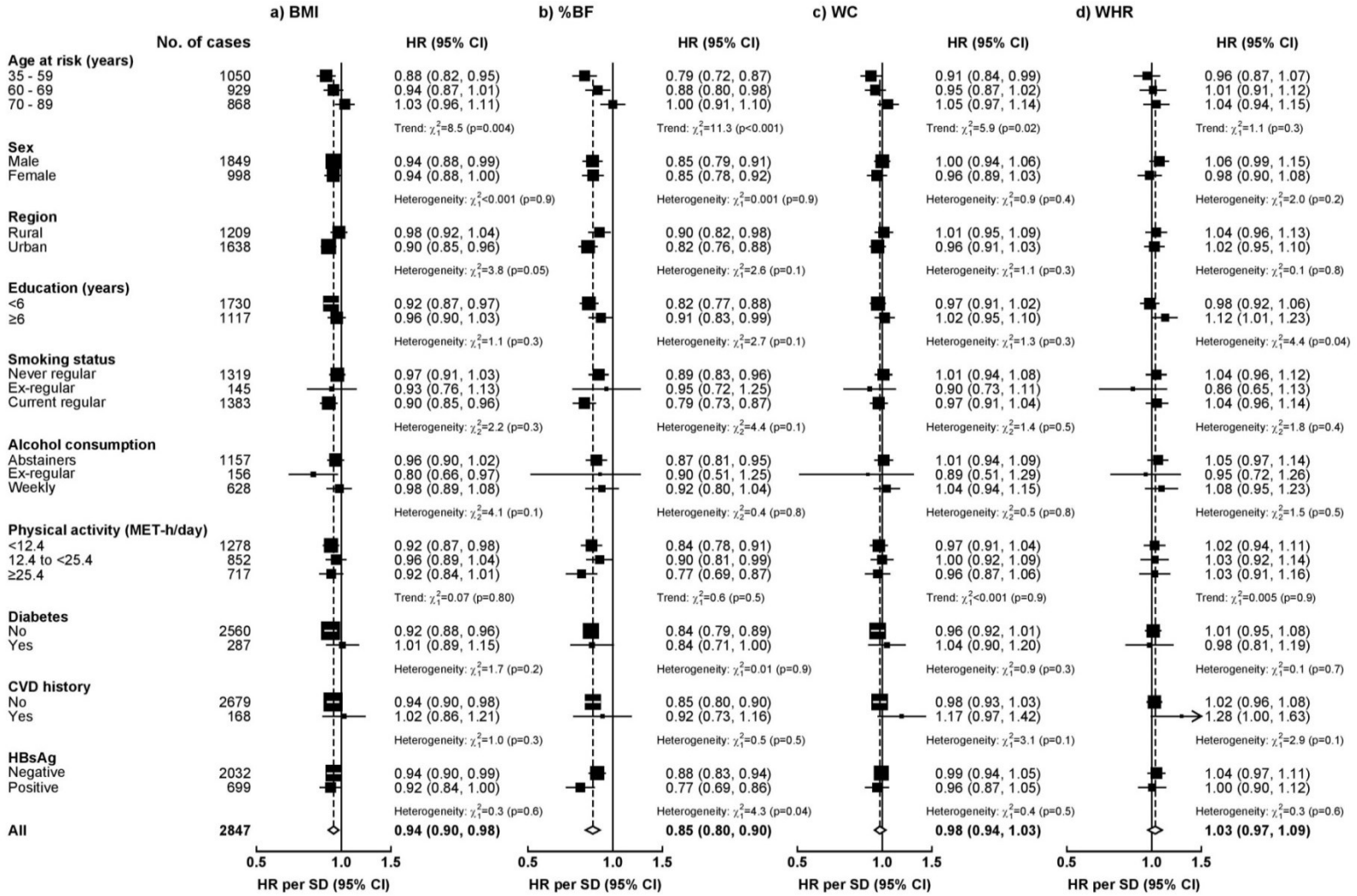
The associations of adiposity with liver cancer risk did not differ by sex (**Appendices 7.20**-**7.21**, *p* for heterogeneity 0.18-0.90). The HRs per 1-SD in men were 0.94 (0.88-0.99) for BMI, 0.85 (0.79-0.91) for %BF, 1.00 (0.94-1.06) for WC, and 1.06 (0.99-1.15) for WHR; the corresponding HRs in women were 0.94 (0.88-1.00), 0.85 (0.78-0.92), 0.96 (0.89-1.03), and 0.98 (0.90-1.08). When excluding the first five years of follow-up (**Appendix 7.13**), the HRs associated with high WC were 1.08 (0.91-1.28) in men and 1.05 (0.88-1.25) in women (*p* for heterogeneity 0.82); the HRs associated with high WHR were 1.17 (1.02-1.33) in men and 1.07 (0.89-1.29) in women (*p* for heterogeneity 0.45). For BMI25, the HRs per 1-SD were 1.05 (1.00-1.11) in men and 1.04 (0.97-1.11) in women.

When stratified by population subgroup (**Figures 7.11**-**7.12**), heterogeneity and trend tests showed that the differences were nonsignificant except for age-at-risk (all traits except for WHR and height adjusted lean mass), region (for height adjusted weight and fat mass), and education (for WHR only). While there was little evidence of heterogeneity across subgroups by alcohol, physical activity, diabetes, or CVD, the magnitudes of associations tended to differ by smoking status. Similar patterns across subgroups were observed when excluding the first five years of follow-up (**Appendices 7.22** and **7.23**).

When stratified by age-at-risk (**Figures 7.11**-**7.12**), there were inverse associations among younger participants (35-49 and 50-59 years) and null associations among older participants (60-79 years). For example, the HRs per 1-SD BMI were 0.88 (0.82-0.95), 0.94 (0.87-1.01), and 1.03 (0.96-1.11) for those aged 35-59, 60-69, and 70-89 years (*p* for heterogeneity 0.004); the corresponding HRs per 1-SD WC were 0.91 (0.84-0.99), 0.95 (0.87-1.02), and

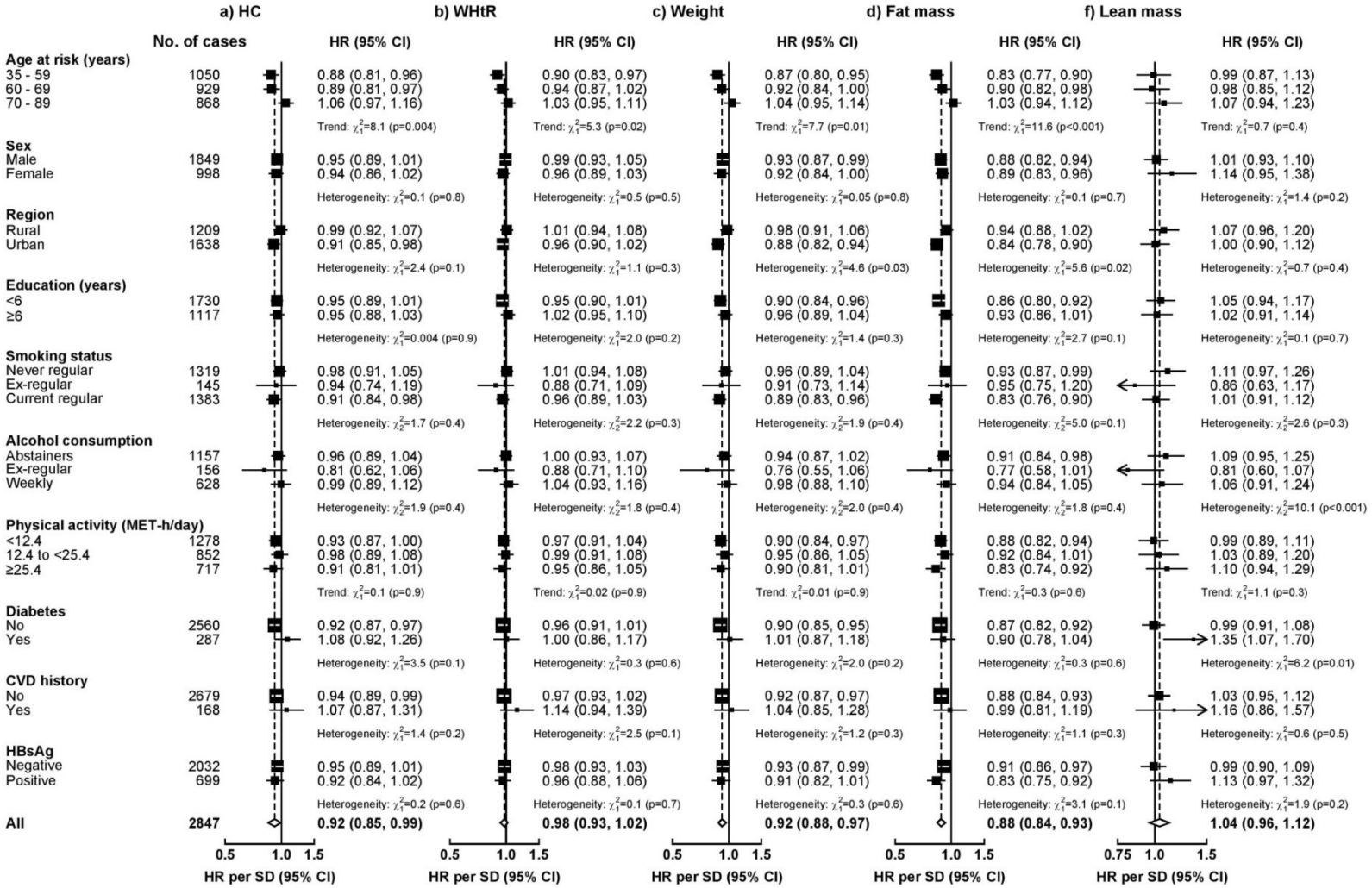
1.05 (0.97-1.14) (*p* for heterogeneity 0.02). Similar patterns were observed for %BF, WHR, HC, WHtR, height-adjusted weight, fat mass, and lean mass. When stratified by region (**Figure 7.12**), the inverse associations of height-adjusted weight and fat mass were stronger in urban than rural areas. The HRs per 1-SD height-adjusted weight were 0.88 (0.82-0.94) in urban and 0.98 (0.91-1.06) in rural areas (*p* for heterogeneity 0.03), while the corresponding HRs per 1-SD height-adjusted fat mass were 0.84 (0.78-0.90) and 0.94 (0.88-1.02) (*p* for heterogeneity 0.02). Similarly, the inverse trends were stronger in urban areas for BMI, %BF, and HC, but the differences were nonsignificant. When stratified by smoking status (**Figure 7.11**), the inverse associations for BMI and %BF were stronger among current than never regular smokers, while the associations for WC and WHR differed little. The HRs per 1-SD BMI were 0.97 (0.91-1.03) and 0.90 (0.85-0.96) in never and current regular smokers, while the corresponding HRs per 1-SD %BF were 0.89 (0.83-0.95) and 0.79 (0.73-0.87). When excluding the first five years (**Appendix 7.22**), the inverse associations among current regular smokers attenuated towards the null (HR per 1-SD: BMI 0.97 [0.85-1.11], %BF 0.87 [0.77-0.99]), while there was a positive trend for BMI among never regular smokers (1.06 [0.94-1.18]).

Figure 7.11 Associations of main adiposity traits with risk of liver cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Figure 7.12 Associations of other adiposity traits with risk of liver cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

7.1.3.5 Adjusted associations for general and central adiposity

As the associations of adiposity with liver cancer risk may be affected by reverse causality, the first five years of follow-up were excluded when examining the adjusted associations for general and central adiposity. In the main model, BMI was not associated with risk of liver cancer when excluding the first five years. In the model with additional adjustment for central adiposity (**Table 7.13** and **Figure 7.13**), the null association for BMI became inverse when additionally adjusting for WC and HC but changed little when adjusting for WHR. However, it should be noted that it is difficult to interpret such an inverse association as these traits were highly correlated (**Appendix 7.1**). The HRs per 5 kg/m^2 higher usual BMI were 0.78 (0.66-0.91), 0.95 (0.87-1.05), and 0.90 (0.78-1.03) when additionally adjusting for WC, WHR, and HC (**Table 7.13**). When additionally adjusting for WC, the HRs were 0.97 (0.80-1.19), 1.00 (0.88-1.13), 0.88 (0.81-0.96), 0.77 (0.66-0.89), and 0.70 (0.58-0.86) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2; when additionally adjusting for WHR, the corresponding HRs were 0.90 (0.77-1.06), 1.00 (0.90-1.11), 0.95 (0.86-1.05), 0.88 (0.77-1.01), and 0.89 (0.77-1.03). When additionally adjusting for central adiposity, the patterns of %BF were similar to those of BMI.

Compared with the main model, the positive associations became stronger for WC and HC when further adjusting for BMI but changed little for WHR (**Table 7.14** and **Figure 7.13**), with HRs per 10 cm of 1.29 (1.13-1.46) for WC and 1.21 (1.02-1.45) for HC. In the model with additional adjustment for BMI, the HRs for WC were 0.93 (0.79-1.10), 1.00 (0.88-1.14), 1.13 (1.01-1.26), 1.12 (0.99-1.28), and 1.37 (1.15-1.64) for those in the bottom to the top quintile. For HC, the positive association in

the main model attenuated and became nonsignificant when additionally adjusting for WC (HR per 10 cm 0.96 [0.81-1.14]). For both general and central adiposity, similar associations were observed when the residual method was used (**Appendices 7.24** and **7.25**).

Table 7.13 Adjusted HRs for liver cancer by general adiposity with additional adjustment for central adiposity excluding the first five years of follow-up[*]

	Main	Main + WC	Main + WHR	Main + HC
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI				
<20.0	0.87 (0.75, 1.01)	0.97 (0.80, 1.19)	0.90 (0.77, 1.06)	0.92 (0.76, 1.10)
20.0 to <22.5	1.00 (0.90, 1.11)	1.00 (0.88, 1.13)	1.00 (0.90, 1.11)	1.00 (0.89, 1.12)
22.5 to <25.0	0.98 (0.89, 1.08)	0.88 (0.81, 0.96)	0.95 (0.86, 1.05)	0.94 (0.86, 1.03)
25.0 to <27.5	0.93 (0.82, 1.06)	0.77 (0.66, 0.89)	0.88 (0.77, 1.01)	0.86 (0.74, 0.99)
≥27.5	0.96 (0.84, 1.10)	0.70 (0.58, 0.86)	0.89 (0.77, 1.03)	0.83 (0.69, 1.00)
per 5 kg/m^2[†]	*1.01 (0.93, 1.10)*	*0.78 (0.66, 0.91)*	*0.95 (0.87, 1.05)*	*0.90 (0.78, 1.03)*
%BF				
Quintile 1	0.93 (0.83, 1.05)	1.08 (0.93, 1.25)	0.98 (0.87, 1.11)	1.00 (0.88, 1.15)
Quintile 2	1.00 (0.89, 1.12)	1.00 (0.89, 1.12)	1.00 (0.89, 1.12)	1.00 (0.89, 1.12)
Quintile 3	0.85 (0.75, 0.95)	0.76 (0.68, 0.85)	0.82 (0.73, 0.92)	0.80 (0.71, 0.90)
Quintile 4	0.88 (0.78, 0.99)	0.71 (0.62, 0.80)	0.82 (0.73, 0.92)	0.78 (0.69, 0.89)
Quintile 5	0.79 (0.69, 0.89)	0.54 (0.46, 0.64)	0.71 (0.62, 0.81)	0.64 (0.55, 0.75)
per 10%[†]	*0.91 (0.83, 1.00)*	*0.66 (0.57, 0.77)*	*0.84 (0.76, 0.93)*	*0.77 (0.68, 0.87)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, sex-specific quintiles were used.
[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88.

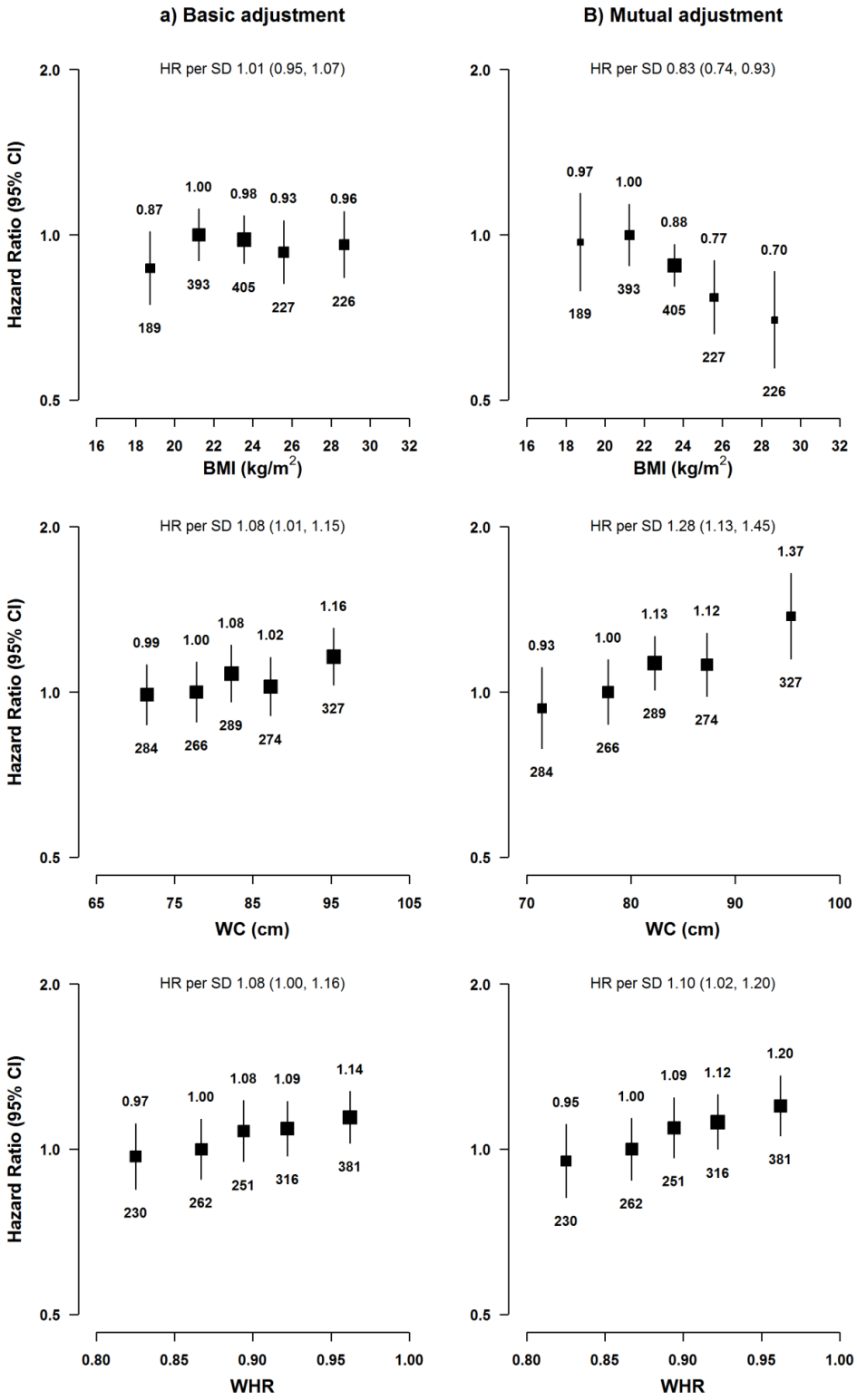
Table 7.14 Adjusted HRs for liver cancer by central adiposity with additional adjustment for other adiposity traits excluding the first five years of follow-up[*]

	Main	Main + BMI	Main + WC
	HR (95% CI)	HR (95% CI)	HR (95% CI)
WC			
Quintile 1	0.99 (0.88, 1.12)	0.93 (0.79, 1.10)	—
Quintile 2	1.00 (0.89, 1.13)	1.00 (0.88, 1.14)	—
Quintile 3	1.08 (0.96, 1.21)	1.13 (1.01, 1.26)	—
Quintile 4	1.02 (0.91, 1.15)	1.12 (0.99, 1.28)	—
Quintile 5	1.16 (1.03, 1.30)	1.37 (1.15, 1.64)	—
per 10 cm[†]	*1.08 (1.01, 1.15)*	*1.29 (1.13, 1.46)*	—
WHR			
Quintile 1	0.97 (0.85, 1.11)	0.95 (0.82, 1.11)	—
Quintile 2	1.00 (0.89, 1.13)	1.00 (0.88, 1.13)	—
Quintile 3	1.08 (0.95, 1.22)	1.09 (0.97, 1.24)	—
Quintile 4	1.09 (0.98, 1.22)	1.12 (1.00, 1.25)	—
Quintile 5	1.14 (1.03, 1.27)	1.20 (1.06, 1.36)	—
per 0.1[†]	*1.12 (1.01, 1.24)*	*1.15 (1.03, 1.29)*	—
HC			
Quintile 1	1.07 (0.95, 1.20)	1.07 (0.92, 1.24)	1.15 (0.99, 1.35)
Quintile 2	1.00 (0.89, 1.13)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)
Quintile 3	1.08 (0.96, 1.21)	1.08 (0.96, 1.20)	1.02 (0.91, 1.13)
Quintile 4	1.08 (0.95, 1.21)	1.08 (0.95, 1.23)	0.96 (0.84, 1.09)
Quintile 5	1.09 (0.95, 1.24)	1.09 (0.91, 1.31)	0.87 (0.73, 1.05)
per 10 cm[†]	*1.08 (0.98, 1.20)*	*1.21 (1.02, 1.45)*	*0.96 (0.81, 1.14)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: WC, 0.88; WHR, 0.70; HC, 0.81.

Figure 7.13 Associations of adiposity with risk of liver cancer with mutual adjustment excluding the first five years



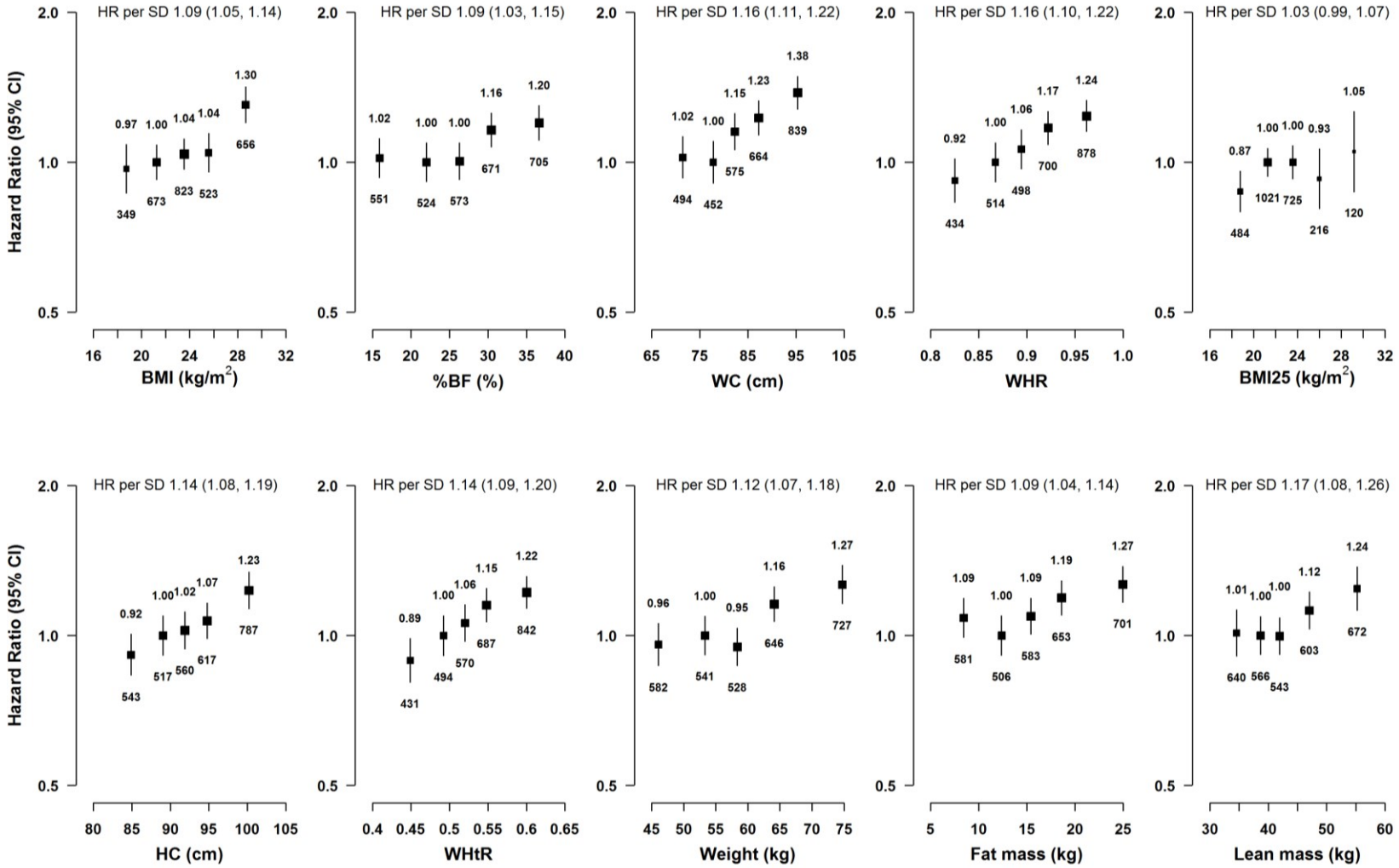
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. The association of BMI was additionally adjusted for WC. The associations of WC and WHR were additionally adjusted for BMI. For WC and WHR, sex-specific quintiles were used.

7.1.4 Associations of adiposity with colorectal cancer

7.1.4.1 Main adiposity traits

BMI was positively associated with risk of colorectal cancer (**Figure 7.14** and **Table 7.15**), with HRs of 0.97 (0.87-1.08), 1.00 (0.93-1.08), 1.04 (0.97-1.11), 1.04 (0.96-1.14), and 1.30 (1.20-1.41) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2 (HR per 5 kg/m^2 1.13 [1.07-1.20]). When the WHO classifications were used (**Appendix 7.26**), the HRs were 1.01 (0.85-1.20), 1.00 (0.95-1.05), 1.14 (1.07-1.21), and 1.29 (1.11-1.51) for those with BMI of <18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 kg/m^2. For %BF, there was also a positive association, with HRs of 1.02 (0.93-1.11), 1.00 (0.92-1.09), 1.00 (0.93-1.09), 1.16 (1.08-1.25), and 1.20 (1.11-1.30) for those in the bottom to the top quintile (HR per 10% 1.11 [1.04-1.18]). For central adiposity, both WC and WHR showed positive associations (**Table 7.15**), with HRs of 1.17 (1.11-1.22) per 10 cm WC and 1.23 (1.14-1.32) per 0.1 WHR. For WC, the HRs were 1.02 (0.93-1.11), 1.00 (0.91-1.10), 1.15 (1.06-1.25), 1.23 (1.14-1.33), and 1.38 (1.28-1.48) for those in the bottom to the top quintiles. For WHR, the HRs were 0.92 (0.83-1.01), 1.00 (0.92-1.09), 1.06 (0.97-1.16), 1.17 (1.09-1.26), and 1.24 (1.16-1.33) for those in the bottom to the top quintiles. For BMI25, there was a positive trend (**Table 7.15**), with HRs of 0.87 (0.80-0.96), 1.00 (0.94-1.06), 1.00 (0.93-1.08), 0.93 (0.81-1.06), and 1.05 (0.88-1.26) for those with BMI <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2 (HR per 5 kg/m^2 1.06 [0.99-1.15]).

Figure 7.14 Associations of adiposity with risk of colorectal cancer



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass). For %BF, WC, WHR, HC, weight, fat mass, and lean mass, sex-specific quintiles were used.

Table 7.15 Adjusted HRs for colorectal cancer by main adiposity traits*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
BMI				
<20.0	349	636,760	56.2	0.97 (0.87, 1.08)
20.0 to <22.5	673	1,303,621	54.8	1.00 (0.93, 1.08)
22.5 to <25.0	823	1,443,510	56.8	1.04 (0.97, 1.11)
25.0 to <27.5	523	851,920	58.6	1.04 (0.96, 1.14)
≥27.5	656	821,898	74.8	1.30 (1.20, 1.41)
per 3.4 kg/m^2†				*1.09 (1.05, 1.14)*
%BF				
Quintile 1	551	983,951	58.0	1.02 (0.93, 1.11)
Quintile 2	524	998,949	52.7	1.00 (0.92, 1.09)
Quintile 3	573	1,023,391	54.1	1.00 (0.93, 1.09)
Quintile 4	671	1,020,589	63.7	1.16 (1.08, 1.25)
Quintile 5	705	1,030,829	67.3	1.20 (1.11, 1.30)
per 8.4%†				*1.09 (1.03, 1.15)*
WC				
Quintile 1	494	1,010,051	54.7	1.02 (0.93, 1.12)
Quintile 2	452	1,003,318	49.6	1.00 (0.91, 1.10)
Quintile 3	575	1,029,568	56.7	1.15 (1.06, 1.25)
Quintile 4	664	1,015,211	61.3	1.23 (1.14, 1.33)
Quintile 5	839	999,562	72.1	1.38 (1.28, 1.48)
per 9.8 cm†				*1.16 (1.11, 1.22)*
WHR				
Quintile 1	434	1,064,809	51	0.92 (0.83, 1.01)
Quintile 2	514	932,845	53.3	1.00 (0.92, 1.09)
Quintile 3	498	877,636	55.2	1.06 (0.97, 1.16)
Quintile 4	700	1,051,279	64.5	1.17 (1.09, 1.26)
Quintile 5	878	1,131,141	66.4	1.24 (1.16, 1.33)
per 0.07†				*1.16 (1.10, 1.22)*
BMI25‡				
<20.0	484	978,315	50.6	0.87 (0.80, 0.96)
20.0 to <22.5	1021	1,697,225	60.2	1.00 (0.94, 1.06)
22.5 to <25.0	725	1,112,264	61.9	1.00 (0.93, 1.08)
25.0 to <27.5	216	332,174	57.9	0.93 (0.81, 1.06)
≥27.5	120	146,956	67.7	1.05 (0.88, 1.26)
per 2.6 kg/m^2				*1.03 (0.99, 1.07)*

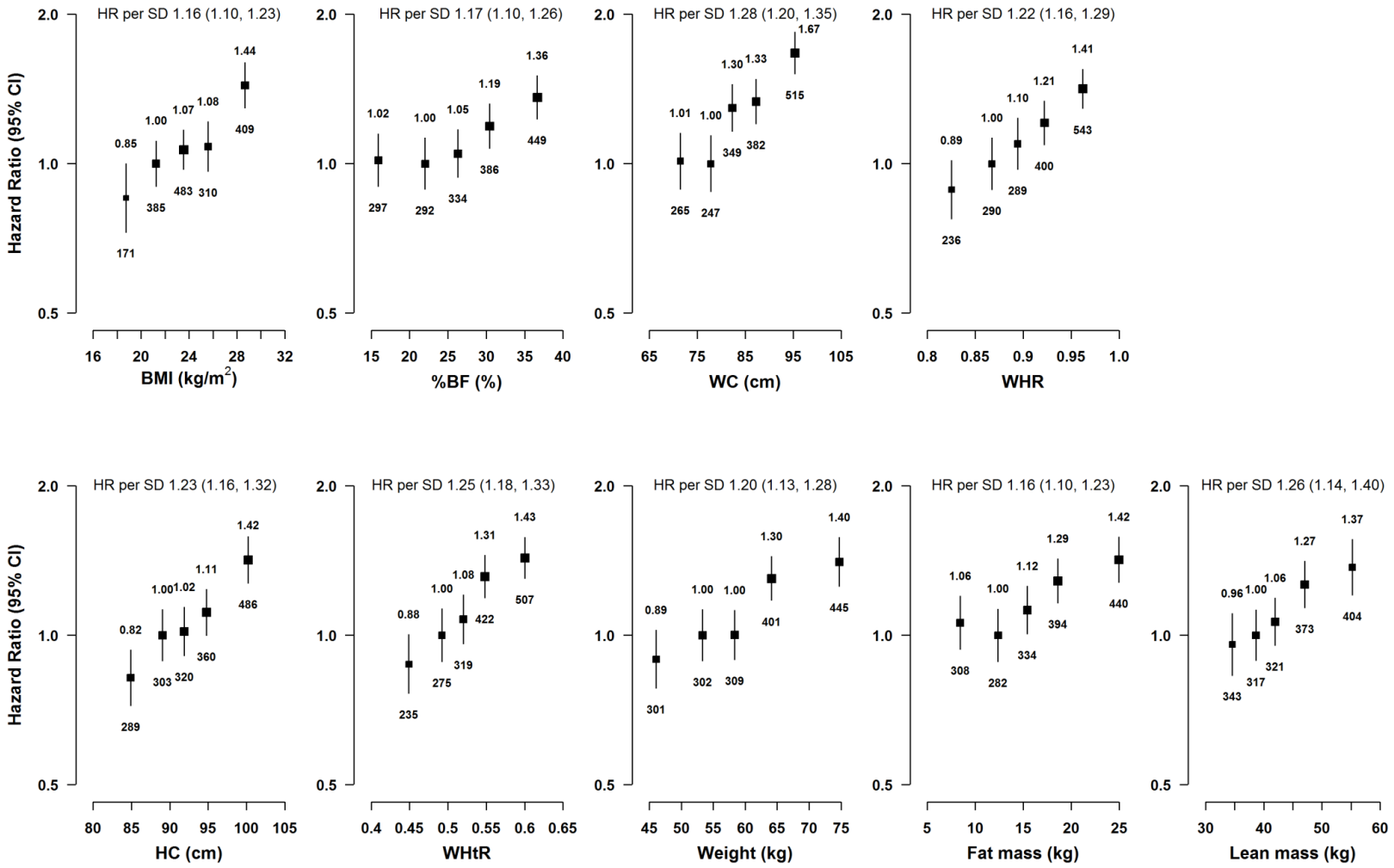
* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

7.1.4.2 Exclusion of early years of follow-up, smokers or drinkers

When excluding early years of follow-up (**Figure 7.15** and **Appendix 7.27**), the positive associations of adiposity with colorectal cancer risk became progressively stronger for BMI, %BF, WC, and WHR. For example, the HRs per 1-SD higher usual BMI were 1.09 (1.05-1.14), 1.12 (1.08-1.17), and 1.16 (1.10-1.23) in all participants, when excluding the first two and five years of follow-up; the corresponding HRs per 1-SD higher usual WC were 1.16 (1.11-1.22), 1.20 (1.14-1.26), and 1.28 (1.20-1.35). When restricting the analysis to never regular smokers or never regular drinkers (**Appendix 7.28**), the positive associations of %BF, WC, and WHR attenuated towards the null, though slightly, compared with the results in all participants. For %BF, the HRs per 1-SD were 1.09 (1.03-1.15), 1.06 (1.00-1.12), and 1.07 (1.01-1.13) in all participants, never regular smokers, and never regular drinkers; for WC, the corresponding HRs were 1.16 (1.11-1.22), 1.12 (1.06-1.19), and 1.13 (1.08-1.19). For BMI, similar associations were observed in all participants, never regular smokers, and never regular drinkers, with HRs per 1-SD of 1.09 (1.05-1.14), 1.08 (1.02-1.13), and 1.08 (1.04-1.13), respectively.

Figure 7.15 Associations of adiposity with risk of colorectal cancer excluding the first five years



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass). For %BF, WC, WHR, HC, weight, fat mass, and lean mass, sex-specific quintiles were used.

7.1.4.3 Other adiposity traits

There were positive associations of HC, WHtR, height-adjusted weight, fat mass, and lean mass with colorectal cancer risk (**Figure 7.14** and **Table 7.16**). The HRs per 1-SD were 1.14 (1.08-1.19) for HC, 1.14 (1.09-1.20) for WHtR, 1.12 (1.07-1.18) for height-adjusted weight, 1.09 (1.04-1.14) for height-adjusted fat mass, and 1.17 (1.08-1.26) for height-adjusted lean mass. When excluding the first two or five years of follow-up (**Figure 7.15** and **Appendix 7.29**), the positive associations became progressively stronger. When restricting the analysis to never regular smokers (**Appendix 7.30**), the positive associations attenuated slightly towards the null for HC, WHtR, height-adjusted weight, and fat mass, but changed little for height-adjusted lean mass. When restricting the analysis for never regular drinkers (**Appendix 7.30**), the positive associations changed little.

Table 7.16 Adjusted HRs for colorectal cancer by other adiposity traits*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
HC				
Quintile 1	543	1,005,495	53.9	0.92 (0.83, 1.00)
Quintile 2	517	970,440	56.3	1.00 (0.92, 1.09)
Quintile 3	560	1,040,814	57.6	1.02 (0.94, 1.11)
Quintile 4	617	1,036,251	58.5	1.07 (0.99, 1.16)
Quintile 5	787	1,004,710	72.7	1.23 (1.14, 1.34)
per 6.9 cm†				*1.14 (1.08, 1.19)*
WHtR				
Quintile 1	431	1,026,900	50.7	0.89 (0.81, 0.98)
Quintile 2	494	1,021,793	54.3	1.00 (0.91, 1.09)
Quintile 3	570	1,014,796	56.8	1.06 (0.98, 1.15)
Quintile 4	687	1,007,804	63.4	1.15 (1.07, 1.24)
Quintile 5	842	986,416	67.8	1.22 (1.14, 1.31)
per 0.06†				*1.14 (1.09, 1.20)*
Height-adjusted weight				
Quintile 1	582	976,534	59.5	0.96 (0.87, 1.05)
Quintile 2	541	1,007,916	55.0	1.00 (0.92, 1.09)
Quintile 3	528	1,032,127	51.8	0.95 (0.87, 1.03)
Quintile 4	646	1,011,725	64.6	1.16 (1.07, 1.25)
Quintile 5	727	1,029,407	70.8	1.27 (1.16, 1.38)
per 10.8 kg†				*1.12 (1.07, 1.18)*
Height-adjusted fat mass				
Quintile 1	581	986,999	60.3	1.09 (0.99, 1.18)
Quintile 2	506	1,014,659	50.5	1.00 (0.92, 1.09)
Quintile 3	583	1,016,554	56.5	1.09 (1.01, 1.19)
Quintile 4	653	1,018,364	62.7	1.19 (1.10, 1.29)
Quintile 5	701	1,021,133	69.0	1.27 (1.17, 1.37)
per 6.9 kg†				*1.09 (1.04, 1.14)*
Height-adjusted lean mass				
Quintile 1	640	992,344	60.4	1.01 (0.91, 1.12)
Quintile 2	566	1,013,872	54.7	1.00 (0.92, 1.09)
Quintile 3	543	1,017,791	54.8	1.00 (0.92, 1.08)
Quintile 4	603	1,017,824	63.9	1.12 (1.03, 1.22)
Quintile 5	672	1,015,879	64.4	1.24 (1.13, 1.37)
per 7.6 kg†				*1.17 (1.08, 1.26)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

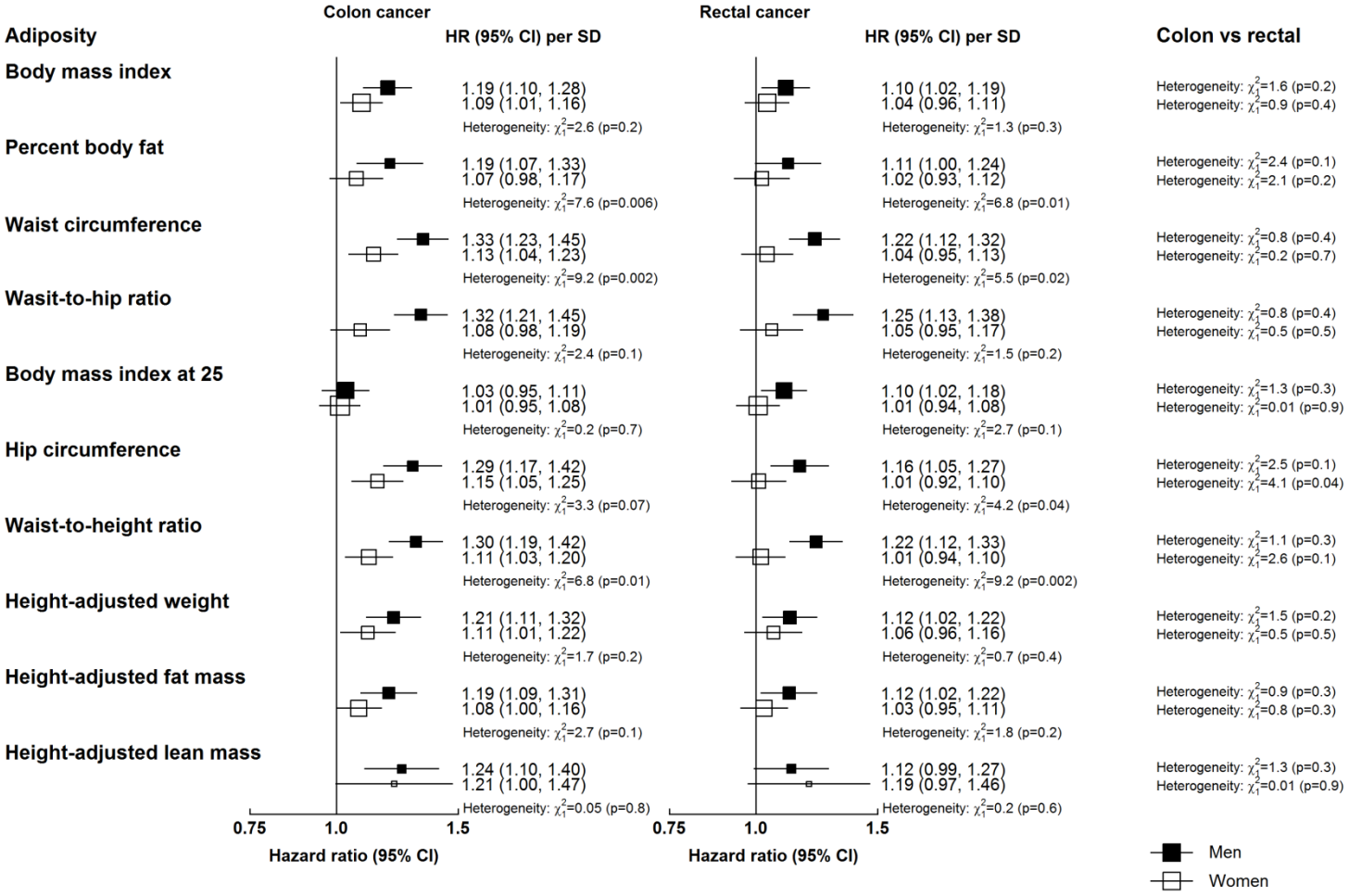
† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

7.1.4.4 Colorectal cancer by sex and by site

For general adiposity (**Figure 7.16**), the associations with risks of colon and rectal cancer tended to be stronger in men than women, but the differences were nonsignificant (*p* for heterogeneity=0.11-0.78). For central adiposity, the associations with risks of colon and rectal cancer were stronger in men than women (*p* for heterogeneity=0.002-0.07). In both men and women, the associations of adiposity tended to be stronger for colon than rectal cancer, though nonsignificantly (*p* for heterogeneity=0.11-0.93). According to the IDF categorisations of adiposity for Chinese (**Appendix 7.26**), the HRs associated with high WC were 1.35 (1.19-1.52) in men and 1.09 (0.98-1.21) in women (*p* for heterogeneity by sex 0.009). According to the WHO cut-off points for risk of metabolic complications (**Appendix 7.26**), the HRs associated with high WHR were 1.25 (1.13-1.39) in men and 1.11 (0.99-1.23) in women (*p* for heterogeneity by sex 0.09).

In men (**Appendices 7.31-7.32**), there were positive associations of adiposity (BMI, %BF, WC, WHR, HC, WHtR, height-adjusted weight, fat mass, lean mass) with risk of colon cancer, while there was a positive trend for BMI25. In women (**Appendices 7.31-7.32**), there were positive but weaker associations for BMI, WC, HC, WHtR, height-adjusted weight, fat mass, and lean mass, while there were positive trends for %BF and WHR. For rectal cancer (**Appendices 7.33-7.34**), there were positive associations of all adiposity traits in men, except for a nonsignificant positive trend for lean mass. In women (**Appendices 7.33-7.34**), the positive trends for adiposity with rectal cancer risk were overall weak, particularly for %BF, HC, WHtR, and fat mass.

Figure 7.16 Associations of adiposity with risks of colon and rectal cancer by sex



Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

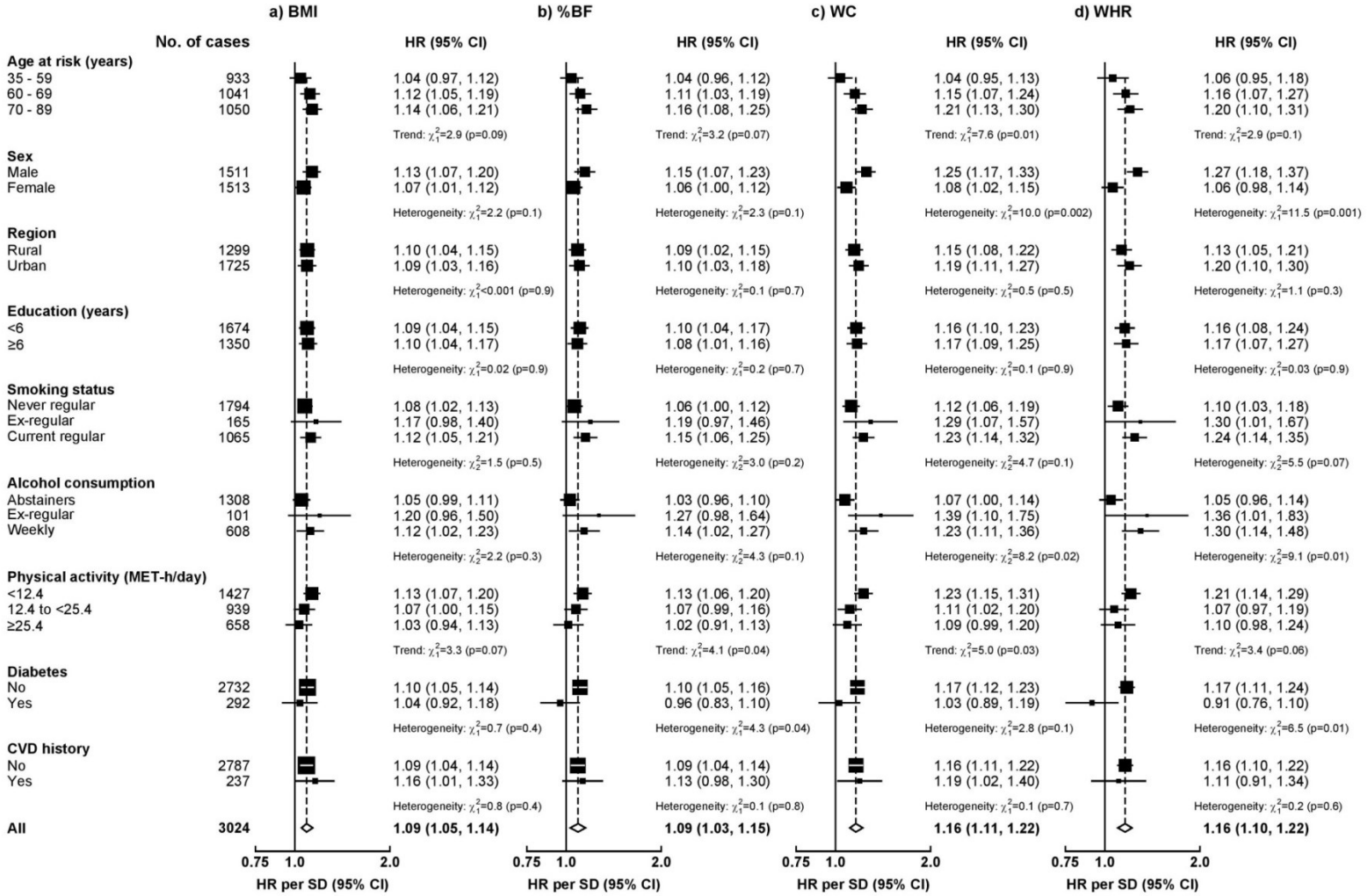
7.1.4.5 Subgroup analyses

When stratified by population subgroup, the associations of adiposity with risk of colorectal cancer differed by age-at-risk, alcohol consumption, and physical activity, as suggested by heterogeneity and trend tests (**Figures 7.17**-**7.18**). When excluding the first five years of follow-up, the patterns of associations by population subgroup were similar to those in all participants (**Appendices 7.35-7.36**).

When stratified by age-at-risk (**Figures 7.17**-**7.18)**, the positive associations were stronger with increasing age. For example, the HRs per 1-SD BMI were 1.04 (0.97-1.12), 1.12 (1.05-1.19), and 1.14 (1.06-1.21) for those aged 35-59, 60-69, and 70-89 years (*p* for heterogeneity 0.09); the corresponding HRs per 1-SD WC were 1.04 (0.95-1.13), 1.15 (1.07-1.24), and 1.21 (1.13-1.30) (*p* for heterogeneity 0.01). When stratified by alcohol consumption (**Figures 7.17**-**7.18)**, the positive associations were weaker among abstainers than ex-regular or regular drinkers. For example, the HRs per 1-SD BMI were 1.05 (0.99-1.11), 1.20 (0.96-1.50), and 1.12 (1.02-1.23) among abstainers, ex-regular, and regular drinkers (*p* for heterogeneity 0.3); the corresponding HRs per 1-SD WC were 1.07 (1.00-1.14), 1.39 (1.10-1.75), and 1.23 (1.11-1.36) (*p* for heterogeneity 0.02). When stratified by physical activity (**Figures 7.17**-**7.18)**, the positive associations attenuated with higher physical activity. For example, the HRs per 1-SD BMI were 1.13 (1.07-1.15), 1.07 (1.00-1.15), and 1.03 (0.94-1.13) for those who had <12.4, 12.4 to <25.4, and ≥25.4 MET-h/day (*p* for heterogeneity 0.07); the corresponding HRs per 1-SD WC were 1.23 (1.15-1.31), 1.11 (1.02-1.20), and 1.09 (0.99-1.20) (*p* for heterogeneity 0.03). Although the associations of adiposity with colorectal cancer did not differ

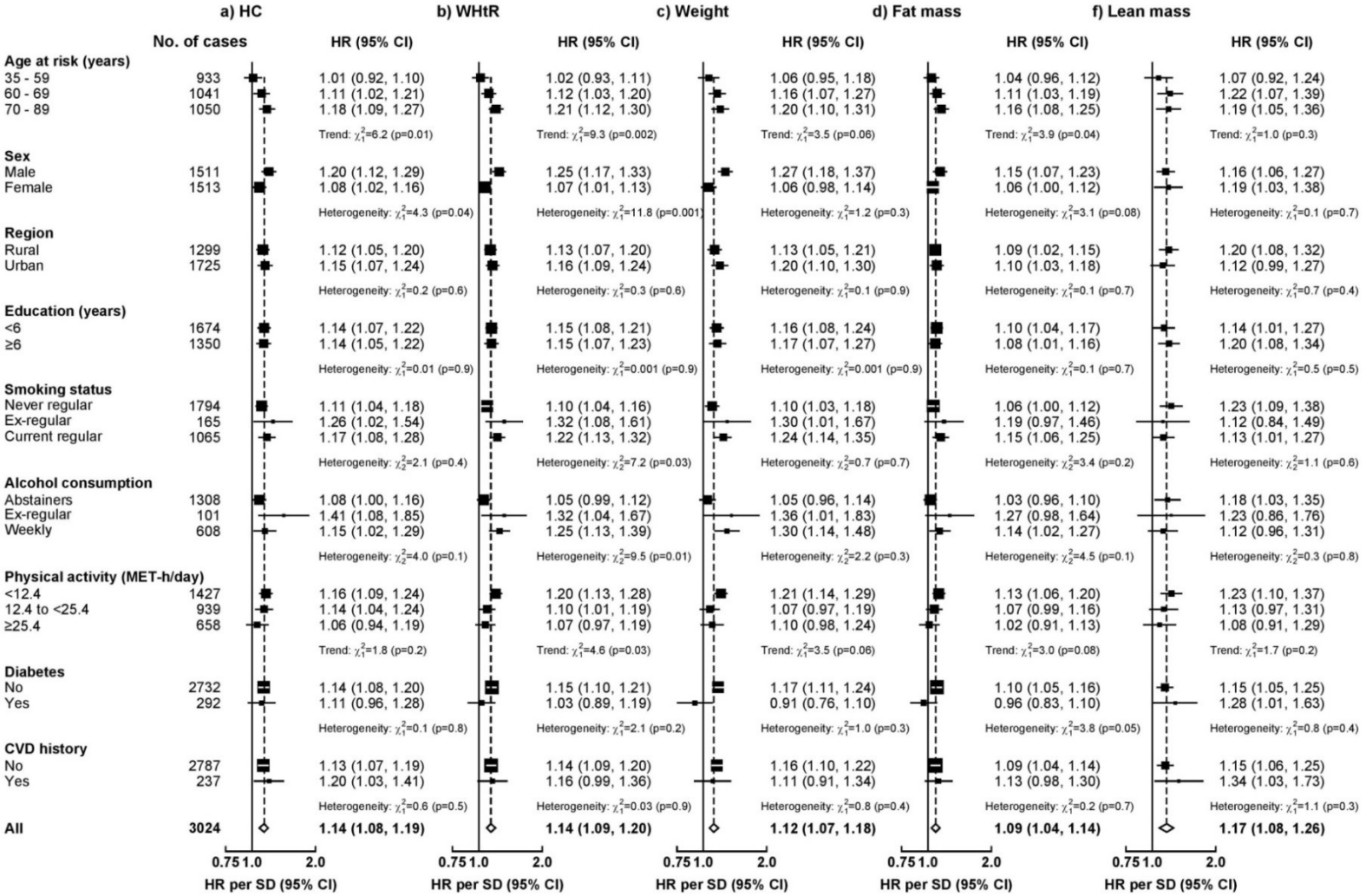
by smoking status, the positive associations tended to be weaker among never than ex-regular or regular smokers (**Figures 7.17**-**7.18)**. The HRs per 1-SD higher usual BMI were 1.08 (1.02-1.13), 1.17 (0.98-1.40), and 1.12 (1.05-1.21) among never, ex-regular, and regular smokers; the corresponding HRs for WC were 1.12 (1.06-1.19), 1.29 (1.07-1.57), and 1.23 (1.14-1.32).

Figure 7.17 Associations of main adiposity traits with risk of colorectal cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Figure 7.18 Associations of other adiposity traits with risk of colorectal cancer by population subgroup



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

7.1.4.6 Adjusted associations for general and central adiposity

In the main model, there was a positive association of BMI with risk of colorectal cancer. In the model with additional adjustment for central adiposity (**Table 7.17**), the positive association for BMI attenuated towards the null when additionally adjusting for WHR and HC and became inverse when additionally adjusting for WC. The HRs per 5 kg/m^2 higher usual BMI were 0.89 (0.80-0.99), 1.06 (1.00-1.14), and 1.03 (0.94-1.13) when additionally adjusting for WC, WHR, and HC. When additionally adjusting for WC, the HRs were 1.08 (0.94-1.25), 1.00 (0.91-1.10), 0.94 (0.88-1.00), 0.87 (0.79-0.95), and 0.96 (0.85-1.09) for those with BMI of <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, and ≥27.5 kg/m^2; when additionally adjusting for WHR, the corresponding HRs 1.02 (0.90-1.15), 1.00 (0.92-1.08), 1.00 (0.93-1.07), 0.97 (0.89-1.07), and 1.18 (1.08-1.29).

In the main model, there were positive associations of WC, WHR, and HC with risk of colorectal cancer. In the model with additional adjustment for BMI (**Table 7.18**), the positive associations for WHR and HC were similar to those in the main model, while the positive association became somewhat stronger for WC. For WC, the HRs per 10 cm were 1.17 (1.11-1.22) in the main model and 1.27 (1.16-1.38) and when additionally adjusting for BMI. For WHR, the HRs were 1.23 (1.14-1.32) in the main model and 1.17 (1.07-1.28) and when additionally adjusting for BMI; for HC, the corresponding HRs were 1.20 (1.12-1.29) and 1.17 (1.04-1.32). In the model with additional adjustment for BMI, the HRs for WC were 1.02 (0.90-1.15), 1.00 (0.90-1.11), 1.16 (1.07-1.25), 1.24 (1.14-1.34), and 1.40 (1.26-1.57) from the bottom to the top quintile. For HC, the positive association attenuated towards the

null and became nonsignificant when additionally adjusting for WC (HR per 10 cm 0.99 [0.88-1.11]).

In the analysis of both BMI and central adiposity, similar patterns were observed for colon and rectal cancer (**Figures 7.19-7.20, Appendices 7.37-7.38**). Similar results were observed when the residual method was used, although the associations were less extreme for high adiposity categories when the residual method was used (**Appendices 7.37-7.38**).

Table 7.17 Adjusted HRs for colorectal cancer by general adiposity with additional adjustment for central adiposity*

	Main	Main + WC	Main + WHR	Main + HC
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI				
<20.0	0.97 (0.87, 1.08)	1.08 (0.94, 1.25)	1.02 (0.90, 1.15)	1.01 (0.89, 1.15)
20.0 to <22.5	1.00 (0.93, 1.08)	1.00 (0.91, 1.10)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
22.5 to <25.0	1.04 (0.97, 1.11)	0.94 (0.88, 1.00)	1.00 (0.93, 1.07)	1.00 (0.94, 1.07)
25.0 to <27.5	1.04 (0.96, 1.14)	0.87 (0.79, 0.95)	0.97 (0.89, 1.06)	0.97 (0.89, 1.07)
≥27.5	1.30 (1.20, 1.41)	0.96 (0.85, 1.09)	1.18 (1.08, 1.29)	1.15 (1.03, 1.29)
per 5 kg/m^2†	*1.13 (1.07, 1.20)*	*0.89 (0.80, 0.99)*	*1.06 (1.00, 1.14)*	*1.03 (0.94, 1.13)*
%BF				
Quintile 1	1.02 (0.93, 1.11)	1.13 (1.01, 1.26)	1.07 (0.97, 1.18)	1.07 (0.97, 1.18)
Quintile 2	1.00 (0.92, 1.09)	1.00 (0.91, 1.10)	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)
Quintile 3	1.00 (0.93, 1.09)	0.93 (0.86, 1.01)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
Quintile 4	1.16 (1.08, 1.25)	1.00 (0.93, 1.09)	1.09 (1.01, 1.18)	1.08 (1.00, 1.17)
Quintile 5	1.20 (1.11, 1.30)	0.94 (0.85, 1.03)	1.10 (1.01, 1.19)	1.06 (0.96, 1.16)
per 10%†	*1.11 (1.04, 1.18)*	*0.88 (0.80, 0.96)*	*1.02 (0.95, 1.10)*	*0.98 (0.90, 1.07)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88.

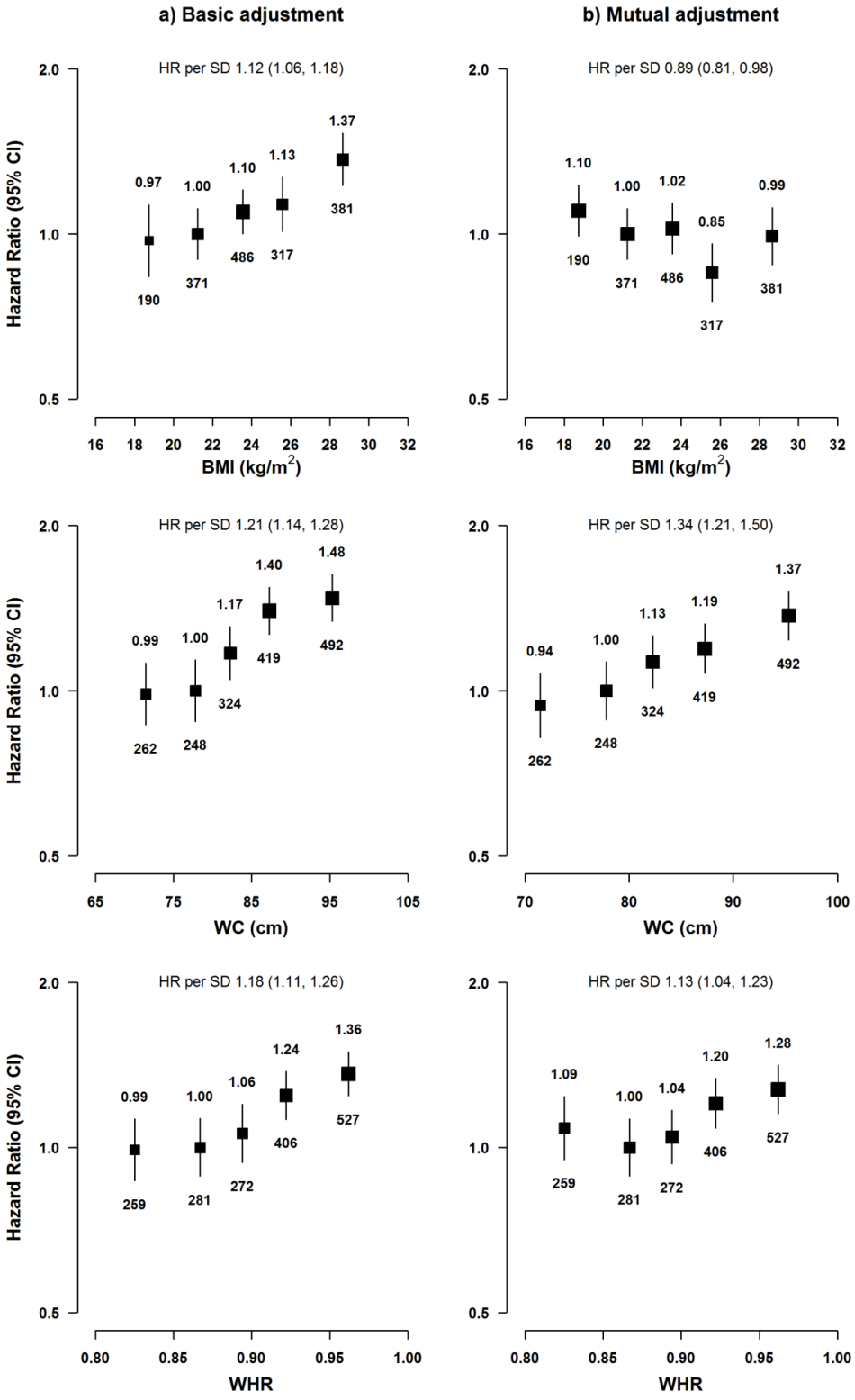
Table 7.18 Adjusted HRs for colorectal cancer by central adiposity with additional adjustment for other adiposity traits[*]

	Main	Main + BMI	Main + WC
	HR (95% CI)	HR (95% CI)	HR (95% CI)
WC			
Quintile 1	1.02 (0.93, 1.12)	1.02 (0.90, 1.15)	—
Quintile 2	1.00 (0.91, 1.10)	1.00 (0.90, 1.11)	—
Quintile 3	1.15 (1.06, 1.25)	1.16 (1.07, 1.25)	—
Quintile 4	1.23 (1.14, 1.33)	1.24 (1.14, 1.34)	—
Quintile 5	1.38 (1.28, 1.48)	1.40 (1.26, 1.57)	—
per 10 cm[†]	*1.17 (1.11, 1.22)*	*1.27 (1.16, 1.38)*	—
WHR			
Quintile 1	0.92 (0.83, 1.01)	0.94 (0.84, 1.04)	—
Quintile 2	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)	—
Quintile 3	1.06 (0.97, 1.16)	1.05 (0.96, 1.14)	—
Quintile 4	1.17 (1.09, 1.26)	1.14 (1.06, 1.23)	—
Quintile 5	1.24 (1.16, 1.33)	1.19 (1.10, 1.29)	—
per 0.1[†]	*1.23 (1.14, 1.32)*	*1.17 (1.07, 1.28)*	—
HC			
Quintile 1	0.92 (0.83, 1.00)	0.94 (0.84, 1.05)	1.00 (0.89, 1.12)
Quintile 2	1.00 (0.92, 1.09)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Quintile 3	1.02 (0.94, 1.11)	1.01 (0.93, 1.09)	0.96 (0.89, 1.04)
Quintile 4	1.07 (0.99, 1.16)	1.03 (0.95, 1.12)	0.94 (0.87, 1.03)
Quintile 5	1.23 (1.14, 1.34)	1.15 (1.02, 1.28)	0.98 (0.87, 1.09)
per 10 cm[†]	*1.20 (1.12, 1.29)*	*1.17 (1.04, 1.32)*	*0.99 (0.88, 1.11)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

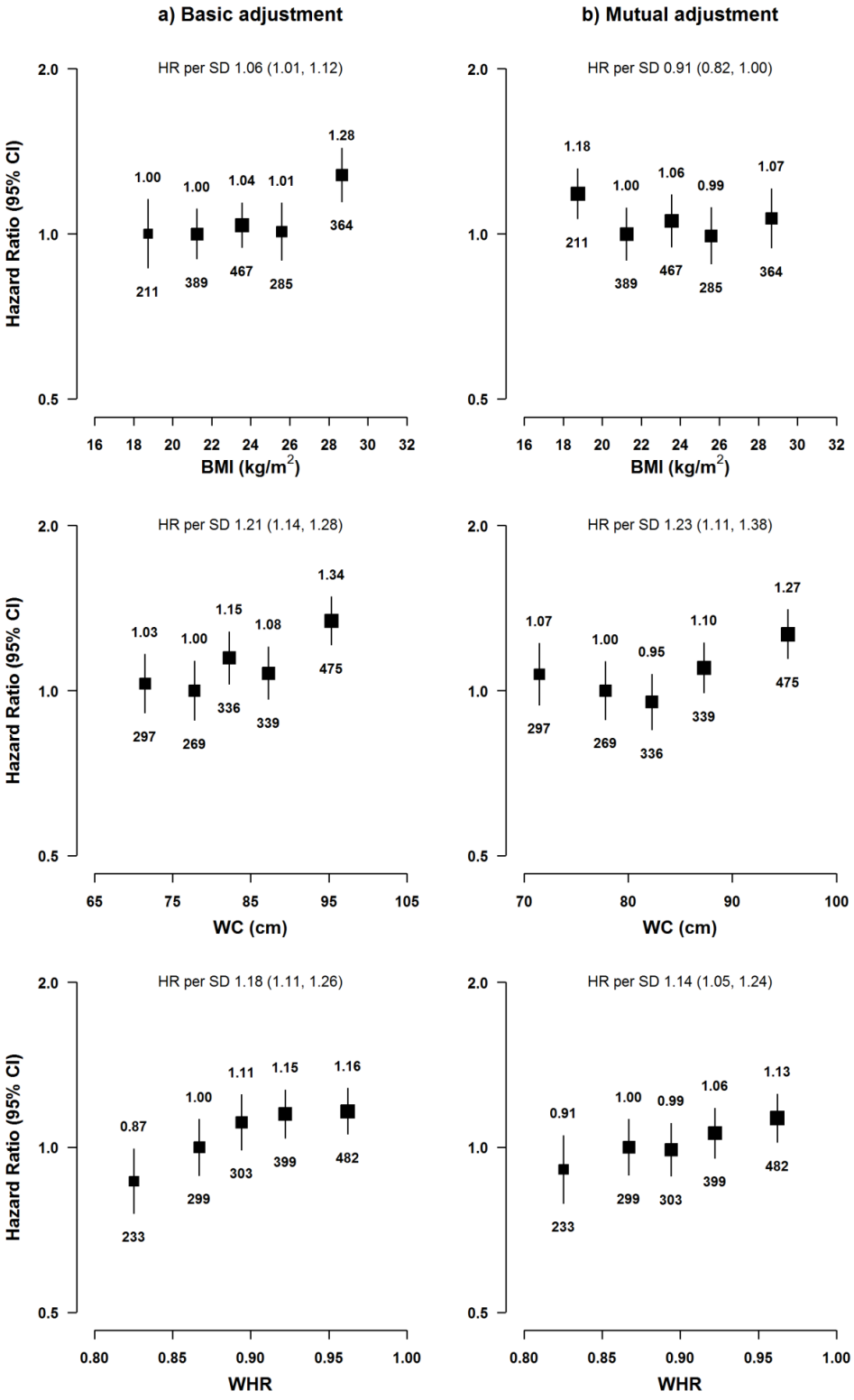
[†] Regression dilution ratios: WC, 0.88; WHR, 0.70; HC, 0.81.

Figure 7.19 Associations of adiposity with risk of colon cancer with mutual adjustment



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. The association of BMI was additionally adjusted for WC. The associations of WC and WHR were additionally adjusted for BMI. For WC and WHR, sex-specific quintiles were used.

Figure 7.20 Associations of adiposity with risk of rectal cancer with mutual adjustment

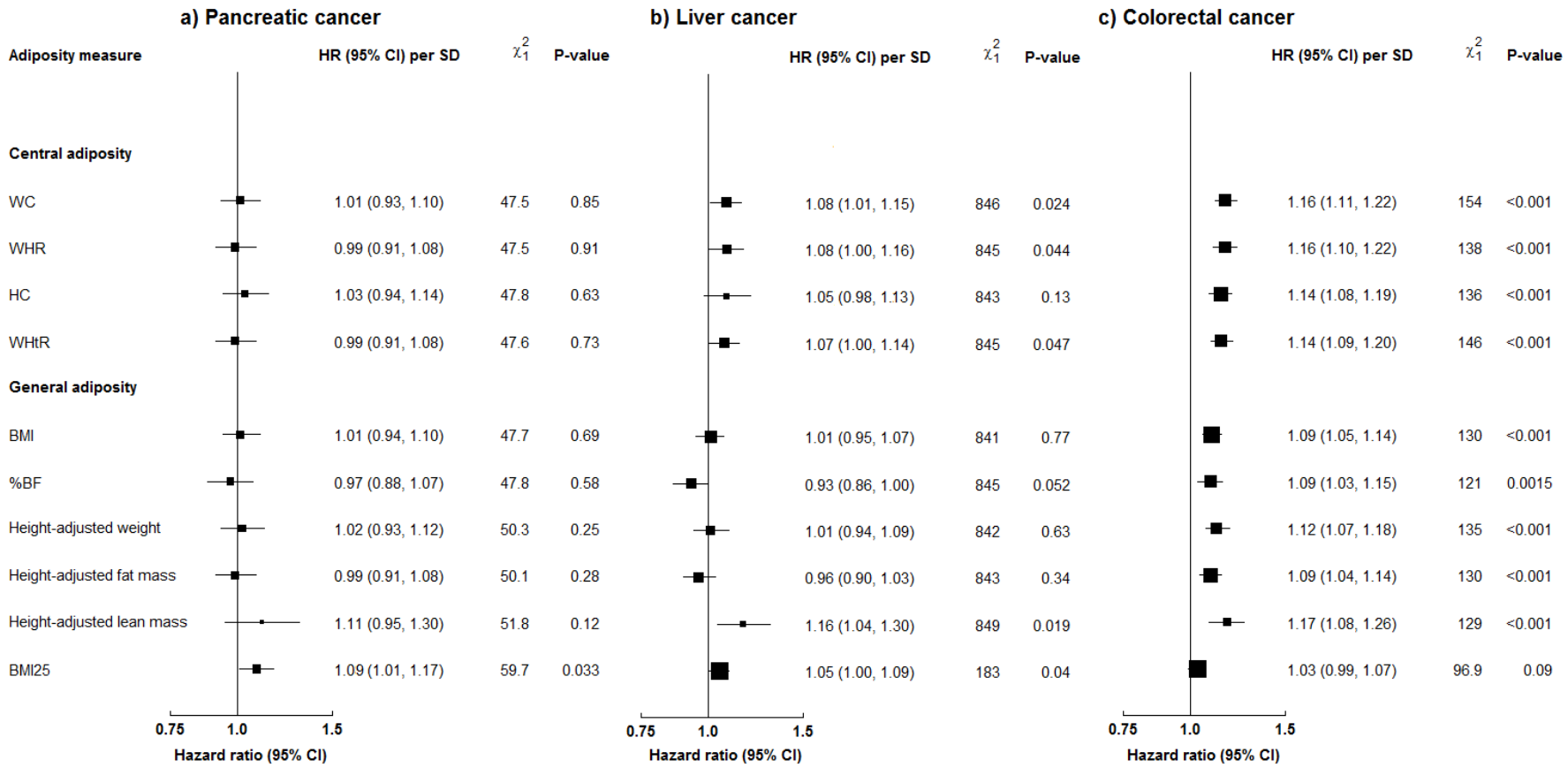


Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. The association of BMI was additionally adjusted for WC. The associations of WC and WHR were additionally adjusted for BMI. For WC and WHR, sex-specific quintiles were used.

7.1.5 Comparison across adiposity traits

Figure 7.21 shows the HRs for pancreatic cancer (all participants), liver cancer (excluding the first five years of follow-up), and colorectal cancer (all participants) per 1-SD increment of usual adiposity across all traits. For pancreatic cancer, there were no associations for WC, WHR, HC, WHtR, BMI, %BF, height-adjusted weight, and fat mass. In contrast, there was a positive association for BMI25 and a positive trend for height-adjusted lean mass. BMI25 and height-adjusted lean mass showed the strongest associations with pancreatic cancer risk (HR per 1-SD: BMI25, 1.09 [1.01-1.17]; height-adjusted lean mass 1.11 [0.95-1.30]; chi-square 59.7 for BMI25, 51.8 for height-adjusted lean mass). However, there was no clear dose-response relationship for height-adjusted lean mass (**Figure 7.4**). For liver cancer, positive associations were observed for WC, WHR, WHtR, height-adjusted lean mass, and BMI25. In contrast, there were no associations for HC, BMI, height-adjusted weight, and height-adjusted fat mass, and an inverse association for %BF. Height-adjusted lean mass, WC, and WHR showed the strongest associations with liver cancer risk (HR per 1-SD: 1.16 [1.04-1.30] for height-adjusted lean mass, 1.08 [1.01-1.15] for WC, 1.08 [1.00-1.16] for WHR; chi-square: 849 for height-adjusted lean mass, 846 for WC, 845 for WHR). For colorectal cancer, there were positive associations for all measures of general and central adiposity, except for a positive trend for BMI25. WC and WHtR showed the strongest associations with colorectal cancer risk (HR per 1-SD: 1.16 [1.11-1.22] for WC, 1.14 [1.09-1.20] for WHtR; chi-square: 154 for WC, 146 for WHtR).

Figure 7.21 Associations of adiposity with risks of pancreatic, liver, and colorectal cancer



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Model 1 included all covariates in the main model. Model 2 included variables in model 1 plus each adiposity trait. The likelihood ratio test was used to compare model 1 and model 2. χ^2 and *p*-value from the comparison were reported for each adiposity trait.

7.1.6 Sensitivity analyses

7.1.6.1 Additional adjustment for diabetes

When additionally adjusting for diabetes (**Appendices 7.39-7.40**), a potential confounder or mediator between adiposity and cancer risk, the associations changed little for pancreatic, liver, and colorectal cancer. For pancreatic cancer, the HRs per 1-SD were 1.00 (0.93-1.08) for BMI, 0.95 (0.86-1.06) for %BF, 0.98 (0.90-1.07) for WC, and 0.96 (0.90-1.07) for WHR. For liver cancer, the HRs per 1-SD were 0.93 (0.89-0.97) for BMI, 0.84 (0.79-0.89) for %BF, 0.97 (0.93-1.02) for WC, and 1.01 (0.96-1.07) for WHR. For colorectal cancer, the HRs per 1-SD were 1.09 (1.05-1.14) for BMI, 1.08 (1.03-1.14) for %BF, 1.16 (1.11-1.21) for WC, and 1.15 (1.09-1.21) for WHR.

7.1.6.2 Additional adjustment for physical activity or diet

For all three cancers, almost identical associations were observed when further adjusting for total physical activity and sedentary leisure time (**Appendices 7.41-7.42**) or dietary factors (fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables) (**Appendices 7.43-7.44**).

7.1.6.3 Exclusion of poor self-rated health or major chronic diseases

For all three cancers, the associations changed little when excluding participants with poor self-rated health or major chronic diseases (CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease, peptic ulcer, and kidney disease) (**Appendices 7.45-7.47**).

7.1.6.4 Adiposity and cancer mortality

For pancreatic cancer, the associations of adiposity with mortality were similar to those with incidence (**Appendix 7.48-7.49**). In all participants, the HRs per 1-SD were 1.03 (0.94-1.13) for BMI, 0.99 (0.88-1.11) for %BF, 1.01 (0.91-1.12) for WC, and 0.99 (0.87-1.12) for WHR; when excluding the first five years of follow-up, the corresponding HRs were 1.05 (0.93-1.18), 1.01 (0.87-1.19), 1.02 (0.89-1.18), and 0.98 (0.83-1.17). For BMI25, the positive association was somewhat stronger for mortality than incidence (HR per 1-SD 1.14 [1.04-1.24] vs 1.09 [1.01-1.17]).

For liver cancer, the associations of adiposity with mortality were similar to those with incidence (**Appendix 7.50-7.51**). In all participants, the HRs per 1-SD were 0.92 (0.87-0.97) for BMI, 0.82 (0.77-0.87) for %BF, 0.97 (0.92-1.03) for WC, 1.02 (0.95-1.09) for WHR, and 1.05 (1.00-1.11) for BMI25; when excluding the first five years of follow-up, the HRs per 1-SD were 1.00 (0.93-1.08) for BMI, 0.91 (0.82-1.00) for %BF, 1.06 (0.98-1.15) for WC, 1.06 (0.96-1.16) for WHR.

For colorectal cancer (**Appendix 7.52-7.53**), the positive associations tended to be weaker for mortality than incidence in all participants. The HRs per 1-SD were 1.05 (0.98-1.13) for BMI, 1.04 (0.95-1.14) for %BF, 1.10 (1.02-1.19) for WC, and 1.13 (1.03-1.25) for WHR. When excluding the first five years, the HRs per 1-SD were 1.16 (1.05-1.29) for BMI, 1.20 (1.06-1.37) for %BF, 1.28 (1.14-1.43) for WC, and 1.26 (1.12-1.41) for WHR, similar to HRs for incidence. For BMI25, the positive association tended to be stronger for mortality than incidence (HR per 1-SD 1.11 [1.04-1.19] vs 1.03 [0.99-1.07]).

7.1.7 Associations of adiposity-related measures with specific GI cancers

For height, there was a positive trend for pancreatic cancer, a null association for liver cancer, and a positive association for colorectal cancer (**Appendices 7.54-7.55**), with HRs per 10 cm of 1.12 (0.98-1.28), 1.04 (0.96-1.13), and 1.08 (1.01-1.16), respectively. For pancreatic cancer, the HRs were 0.96 (0.82-1.13), 1.00 (0.86-1.16), 1.09 (0.94-1.27), 1.10 (0.93-1.29), and 1.18 (0.98-1.42) for those in the bottom to the top quintile. For colorectal cancer, the HRs were 0.98 (0.91-1.07), 1.00 (0.93-1.08), 0.98 (0.91-1.07), 1.04 (0.96-1.13), and 1.18 (1.07-1.29) for those in the bottom to the top quintile, with a somewhat stronger association for colon than rectal cancer (HR per 10 cm: 1.15 [1.05-1.26] vs 1.07 [0.97-1.17], *p* for heterogeneity 0.78). The associations did not differ by population subgroup (**Appendix 7.56**). In particular, similar associations were observed in men and women (**Appendix 7.56**).

There were no associations of leg length with risks of liver and colorectal cancer, while there was a positive trend for pancreatic cancer (**Appendices 7.54-7.55**). The HRs per 10 cm higher usual leg length were 1.16 (0.95-1.41) for pancreatic, 1.02 (0.90-1.16) for liver, and 1.01 (0.91-1.12) for colorectal cancer. When examining the associations of leg length by population subgroup (**Appendix 7.57**), the associations differed little including by sex. For sitting height, there were positive trends for risks of pancreatic and liver cancer (HR per 10 cm: 1.16 [0.92-1.46] vs 1.11 [0.98-1.25]) and a positive association with colorectal cancer (1.25 [1.11-1.41], **Appendix 7.54** and **Appendix 7.58**). No differences were observed across population subgroups (**Appendix 7.59**).

7.2 Discussion

7.2.1 Adiposity and pancreatic cancer

In this Chinese population, there was no evidence of associations of general and central adiposity at baseline with risk of pancreatic cancer. When excluding the first two or five years of follow-up, the null associations remained for general and central adiposity. There were positive trends when restricting the analysis to never regular smokers, while the null associations were unaltered among never regular drinkers. In contrast, there was a positive association for BMI25.

Previous prospective studies conducted in North America and Europe have shown that both general and central adiposity are associated with higher risk of pancreatic cancer.[36] A meta-analysis showed that each 5 kg/m^2 higher BMI was associated with a 9% higher risk (RR 1.09 [1.08-1.11], 32 studies, 18,187 cases), while each 10 cm higher WC was associated with a 10% higher risk (RR 1.10 [1.06-1.14], 4 studies, 3006 cases).[135] In contrast, ten prospective cohort studies and two pooled analyses of prospective studies in East Asia have reported a null association for BMI.[135] Similarly, a prospective cohort study in urban Chinese (the Shanghai Women's Health Study) with 195 incident cases reported no associations for BMI and WHR (HR per 5 kg/m^2 higher BMI 0.92 [0.74-1.14] and HR per 1-SD higher WHR 1.08 [0.94-1.24]).[141] Consistent with previous studies in East Asia, there were no associations for BMI, WC, and WHR in CKB, as well as other adiposity traits (HC, WHtR, height-adjusted weight, fat mass, and lean mass).

There are several possible reasons for the null associations in East Asian populations. First, the majority of previous studies in East Asia assessed BMI by self-report, which might result in measurement error. Previous meta-analysis reported a stronger association in East Asian studies using measured than self-reported BMI (RR per 5 kg/m^2: 1.08 [0.99-1.19] vs 0.94 [0.87-1.03]).[135] However, similar associations by BMI assessment were observed in North American or European studies (measured vs self-reported: 1.11 [1.08-1.13] vs 1.10 [1.07-1.13]).[135] Second, previous East Asian studies were small in size (most <400 cases) and were not able to exclude early years of follow-up.[135] It is possible that individuals with undetected cancer at baseline may lose weight (i.e. so-called reverse causality),[346,347] resulting in a false negative association for BMI. Indeed, previous meta-analysis showed that the positive association was somewhat stronger when excluding early years of follow-up (with and without exclusion: 1.11 [1.08-1.14] vs 1.09 [1.06-1.11]).[135]

Both smoking and heavy alcohol intake (≥3 drinks/day) are risk factors for pancreatic cancer.[35] Previous prospective studies including CKB have shown that smoking is associated with 20-70% excess risk of pancreatic cancer.[35,37] Smoking is also associated lower BMI,[348] suggesting that smoking may be a negative confounder between the association of BMI with pancreatic cancer. Consistent with the findings in CKB, previous studies in Western populations showed a stronger association for BMI among never smokers than smokers.[142,186,349-351] However, East Asian studies showed no differences by smoking status possibly due to the small numbers of cases.[352-354] For alcohol consumption, the current

study showed similar associations when excluding never regular drinkers or when stratified by alcohol consumption, consistent with previous studies in Western countries.[355]

Despite the null findings for pancreatic cancer incidence in CKB, the risk estimate for pancreatic cancer mortality was directionally concordant with previous studies in North America and Europe.[135] The HR per 5 kg/m^2 BMI was 1.07 (0.90-1.27) in CKB (excluding the first five years), consistent with the meta-analysis (1.09 [1.08-1.11]).[135] Although the findings in CKB are largely consistent with previous studies in East Asia,[135] the null associations between adiposity and pancreatic cancer incidence may be a chance finding. A previous report in CKB included 585 incident pancreatic cancer cases over a median of 8 years of follow-up.[135] That study showed a HR of 1.11 (0.97-1.27) per 5 kg/m^2 BMI after excluding the first five years of follow-up (484 cases).[135] This finding was consistent with the meta-analysis but was in contrast to the null association reported in my thesis (HR per 5 kg/m^2 1.01 [0.87-1.16] when excluding the first five years).

7.2.2 Adiposity and liver cancer

7.2.2.1 Summary of findings

In this Chinese population, there were inverse associations of general adiposity and null associations of central adiposity with liver cancer risk, both of which may reflect reverse causality. When excluding the first five years of follow-up, the inverse associations for general adiposity attenuated towards the null, while there were positive associations for central adiposity. When restricting the analyses to never regular smokers, the inverse associations for general adiposity attenuated

towards the null, while the positive associations for central adiposity became stronger. When excluding the first five years of follow-up, there were positive associations for central adiposity and a null association for BMI in HBsAg negative participants, whereas there were no associations for central adiposity and were inverse trends for BMI and %BF in HBsAg positive participants. BMI25 was positively associated with risk of liver cancer.

7.2.2.2 BMI

Previous prospective studies have shown that BMI is associated with a higher risk of liver cancer, with a stronger association in Western populations than East Asians.[49] A meta-analysis of 12 prospective studies and 14,073 cases reported a 30% higher risk per 5 kg/m^2 BMI (RR 1.30 [1.16-1.46]), with RRs of 1.18 (1.04-1.34) in East Asian studies and 1.59 (1.35-1.87) in European studies (*p* for heterogeneity 0.005).[49] Similarly, a recent pooled analysis of the Liver Cancer Pooling Project in the US involving 2162 cases reported a HR of 1.26 (1.12-1.32) per 5 kg/m^2 BMI.[147] Upon careful inspection of individual studies in East Asia, the shape and strength of associations between BMI and liver cancer risk were inconsistent. The Asia Pacific Cohort Studies Collaboration involving 44 cohorts and 774 liver cancer deaths reported a nonsignificant 11% higher risk per 5 kg/m^2 BMI (HR 1.11 [0.94-1.31], BMI ≥18.5 kg/m^2),[356] similar to a small cohort study of Chinese women (HR per 5 kg/m^2 1.20 [0.95-1.50], 165 cases; BMI ≥18.5 kg/m^2).[141] Two large prospective studies in Korea involving over one million participants and 10,820 cases showed a null association in the range of 15-30 kg/m^2, whereas only individuals with BMI ≥30 kg/m^2 were at a higher risk (HR 1.4-

1.6).[352,353] Another prospective study in Japan involving 72,563 participants and 527 cases reported a U-shaped association, with higher risks in both underweight (BMI <20 kg/m^2) and obese (BMI ≥30 kg/m^2) participants (HR 1.5-2.0).[155] Similarly, a prospective study in China involving 884 liver cancer deaths reported HRs per 5 kg/m^2 of 0.91 (0.71-1.17) in the range of 15 to <23.5 kg/m^2 and 1.15 (0.74-1.79) in the range of 23.5 to <35 kg/m^2.[146] Other prospective studies included less than 200 cases and the associations reported have been null or inverse.[49]

Unlike CKB, nine out of 13 East Asian studies did not exclude early years of follow-up,[49] and therefore the higher risk for participants with low BMI may reflect reverse causality. Although studies in Western populations reported similar associations when excluding the first two to five years of follow-up,[147,357] the Asia Pacific Cohort Studies Collaboration showed a somewhat stronger association when excluding the first three years of follow-up (with and without exclusion: 1.11 [0.94-1.31] vs 1.07 [0.94-1.22]).[356] Given the long latency period of liver cancer, individuals are likely to lose weight over the course of chronic liver diseases and progression to liver cancer,[38] thereby resulting in a false negative association for BMI. Indeed, when excluding the first five years of follow-up, the inverse association for BMI in CKB attenuated and became nonsignificant.

Another explanation for the weaker or null associations for BMI may be the different aetiology of liver cancer between East Asia and Western countries. HBV is the most important risk factor for liver cancer in East Asia, while alcohol, HCV, and NAFLD are main risk factors in North America and Europe.[38] In East Asia, the prevalence of HBsAg is approximately 5.5% in Mainland China, 13.7% in Taiwan, 4.4% in Korea, and 1.0% in Japan.[44] Chronic HBV carriers have a 100-fold higher

risk of developing liver cancer than noncarriers.[38] At least seven studies have assessed the association of BMI with liver cancer stratified by or adjusting for HBsAg.[49] Of the three cohort studies (in the US, Japan, and Taiwan) that stratified the analysis by HBsAg, there was a null association among HBsAg positive participants and a positive association among HBsAg negative participants.[147,290,358] In CKB, the findings for central adiposity were consistent with these studies (when excluding the first five years). However, for BMI, there was a null association among HBsAg negative participants and an inverse trend among HBsAg positive participants. It has been hypothesised that obesity is linked to liver cancer through development of NAFLD and progression to cirrhosis.[38,359,360] In North America and Europe, NAFLD is an important risk factor for liver cancer,[38] where the prevalence of obesity is high.[79] In contrast, HBV is the major risk factor for liver cancer in East Asia,[38] where up to 40% patients with HBV-related liver cancer do not have underlying cirrhosis and liver cancer is caused by integration of the HBV genome into the host's intracellular DNA.[38,361]

Smoking is a risk factor for liver cancer and has been reported to be inversely associated with BMI,[47,348] therefore may confound the association of BMI with liver cancer risk. Previous prospective studies have reported stronger associations among never than current smokers,[350,362,363] suggesting that smoking is a negative confounder. In CKB, a positive trend was observed among never regular smokers and a null association among current smokers (when excluding the first five years), consistent with previous studies. For alcohol consumption, both CKB and EPIC showed similar associations when restricting the analysis to never regular drinkers to those in all participants.[148]

7.2.2.3 WC and WHR

Three prospective studies have shown positive associations of central adiposity with risk of liver cancer.[141,147,148] The Liver Cancer Pooling Project involving 2162 cases reported an 8% higher risk per 5 cm WC (HR 1.08 [1.04-1.13]), with similar associations when excluding the first two or five years of follow-up.[147] Likewise, the EPIC study with 177 cases reported positive associations of central adiposity with liver cancer, including WC, WHR, HC, and WHtR.[148] The adjusted HRs were 1.25 (1.17-1.33) per 5 cm WC, 1.66 (1.37-2.02) per 0.1 WHR, 1.24 (1.13-1.35) per 5 cm higher HC, and 2.08 (1.67-2.58) per 0.1 WHtR. In CKB, the positive associations for WC and other central adiposity traits were weaker than the US pooled analysis and EPIC. A recent report from a cohort study in urban Chinese (the Shanghai Women's Health Study [SWHS], 165 cases) showed positive associations for WC and WHtR, a null association for WHR, and a positive trend for BMI.[141] The HRs per 1-SD were 1.19 (1.02-1.38) for WC, 1.19 (1.01-1.40) for WHtR, 1.01 (0.93-1.09) for WHR, and 1.12 (0.97-1.30) for BMI. While the magnitudes of positive associations for WC and WHtR were lower in CKB than SWHS, the current study showed a consistent pattern across measures of central adiposity. Similar to BMI, the weaker associations for WC and WHR might be due to the different aetiology of liver cancer between East Asians and Western populations.[38] In CKB, there were positive associations of WC and WHR with liver cancer risk among HBsAg negative participants, while there were no associations among HBsAg positive participants.

In addition to central adiposity, these studies also examined the association of general and central adiposity with liver cancer risk with adjustment for each

other.[141,147,148] The Liver Cancer Pooling Project reported similar HRs per 1-SD when including both BMI and WC in a model (BMI 1.15 [1.02-1.29], WC 1.20 [1.05-1.36]), suggesting that BMI and WC are equally informative of liver cancer risk. On the other hand, the EPIC study and the SWHS suggested that central adiposity was more important than general adiposity in predicting liver cancer risk.[141,148] In EPIC, the positive association for BMI attenuated and became nonsignificant when further adjusting for WC, while the positive associations for WC and WHR became stronger when further adjusting for BMI.[148] In SWHS, the positive trend for BMI attenuated when further adjusting for WC, WHR, or WHtR, while the positive associations for WC and WHtR remained when further adjusting for BMI.[141] Consistent with EPIC and SWHS, the current study suggests that central adiposity is more important than general adiposity in predicting liver cancer risk. When excluding the first five years of follow-up, the positive associations for WC and WHR became stronger when further adjusting for BMI. For BMI, the null association became inverse when further adjusting for WC or WHR.

7.2.3 Adiposity and colorectal cancer

7.2.3.1 Summary of findings

In this Chinese population, both general and central adiposity were positively associated with risk of colorectal cancer. When excluding the first five years of follow-up, the positive associations for adiposity became stronger. When restricting the analysis to never regular smokers or never regular drinkers, the positive associations for adiposity changed little. For colon and rectal cancer, the associations for general and central adiposity were stronger in men than women, but the differences were significant only for central adiposity. When comparing

colon and rectal cancer, the positive associations were stronger for colon than rectal cancer, but the differences were nonsignificant. BMI25 showed trends towards a higher risk of colorectal cancer.

7.2.3.2 BMI

Previous prospective studies of mostly Western populations have shown a positive association of BMI with risk of colorectal cancer.[57] A recent meta-analyses of 38 prospective cohort studies (71,089 cases) reported a 5% higher risk per 5 kg/m^2 BMI (HR 1.05 [1.03-1.07]), with somewhat stronger associations in men than women (1.08 [1.04-1.11] vs 1.05 [1.02-1.08], *p* for heterogeneity 0.02) and for colon than rectal cancer (1.07 [1.05-1.09] vs 1.02 [1.01-1.04], *p* for heterogeneity <0.001).[364] When stratified by region, a stronger association was observed in East Asia than Europe or North America (HR per 5 kg/m^2: East Asia 1.10 [1.00-1.20], Europe 1.05 [1.03-1.06], North America 1.04 [1.02-1.06]), although large heterogeneity existed (I^2: East Asia 92%, Europe 23%, North America 49%).[364] The risk estimate in the current study tended to be stronger than the meta-analysis (HR per 5 kg/m^2: 1.13 [1.07-1.20] vs 1.05 [1.03-1.07]). The estimate for linear association in CKB was stronger probably because BMI was measured in the current study, which was less affected by measurement error.

In contrast to the positive association reported in Western populations, East Asian studies have shown inconsistent results.[364] Previous East Asian studies reported a positive association of BMI with colon cancer. However, the evidence is inconsistent whether the association differed by sex, and the majority of previous studies reported a null association of BMI with rectal cancer.[64,352,354,357,365-371] Eight out of the 11 studies involved less than 1000 colorectal cancer cases (three less

than 500 cases), and therefore they might not have enough power to conduct subgroup analyses by sex and by anatomical site. The current study involved 3024 colorectal cancer cases over 10 years of follow-up (>700 in each sex for each cancer site), measured adiposity at study baseline, and prespecified subgroup analyses by sex and by anatomical site. In addition, the estimates by sex and by anatomical site in the current study were generally consistent with three East Asian studies involving >5000 cases,[352,366,369] though these studies reported nonsignificant associations in women and for rectal cancer in both sexes.

The meta-analysis also examined the associations with colon cancer by subsite and showed similar associations of BMI with proximal and distal colon cancer (HR per 5 kg/m^2: proximal 1.05 [1.03-1.08], distal 1.08 [1.04-1.11]).[364] Likewise, a pooled analysis of eight prospective cohort studies in Japan reported similar associations with proximal and distal colon cancer (HR per 1 kg/m^2: men: proximal 1.03 [1.00-1.06], distal 1.05 [1.03-1.08]; women: proximal 1.03 [1.01-1.06], distal 1.02 [0.99-1.05]).[366] Although information of subsites was only available in ~30% of all colorectal cancer cases, a previous report in CKB showed similar associations of BMI with proximal and distal colon cancer (HR per 1-SD: 1.23 [1.10-1.38] vs 1.14 [1.02-1.27], *p* for heterogeneity 0.35).[372]

Previous studies reported similar associations of BMI with risk of colorectal cancer when excluding early years of follow-up.[354,357,362,363] In CKB, the associations became somewhat stronger when excluding the first two or five years of follow-up. Consistent with the findings in CKB, the majority of previous studies showed that the positive associations changed little when restricting the analyses to never smokers.[350,352-354,363] For alcohol drinking, a prospective cohort study in Japan

reported a positive association for BMI among never drinkers and inverse associations among ex-drinkers and those who consumed ≥22.8 g/day.[365] In CKB, by contrast, the positive associations tended to be stronger in ex-drinkers and weekly drinkers than those in abstainers.

7.2.3.3 WC and WHR

In addition to BMI, the meta-analysis reported positive associations of WC and WHR with colorectal cancer risk (8 studies [4301 cases] and 4 studies [2564 cases]), with similar RRs by sex and by anatomical site.[364] The pooled RRs per 10cm WC were 1.02 (1.01-1.03) in all studies and were 1.02 (1.01-1.03) in East Asia, while the pooled RR per 0.1 of WHR was 1.02 (1.01-1.04).[364] Again, the estimates in the current study were stronger than the meta-analysis (CKB: WC per 10 cm: 1.17 [1.11-1.22]; WHR per 0.1: 1.23 [1.14-1.32]). In the meta-analysis, no clear patterns were identified by sex and by anatomical site possibly due to the small number of cases included (<1000 cases by sex and by anatomical site).[364] While similar patterns were identified by anatomical site in CKB, stronger associations of WC and WHR with colorectal cancer risk were observed in men than women.

Of all included studies, at least six prospective cohort studies have examined the associations of BMI and central adiposity (WC or WHR) when adjusting for or stratified by the other.[364] Four studies showed that WC or WHR was a better indicator of colorectal cancer risk,[64,131,149,150] while the converse was true for the other two studies. In particular, the Shanghai Men's Health Study and the Shanghai Women's Health Study involving 935 colorectal cancer cases reported a positive association for BMI in men but not women.[64] This study showed that the

positive association for BMI attenuated and became nonsignificant when stratified by WHR, while the positive association for WHR remained when stratified by BMI. Consistent with previous studies, the current study showed that the association of BMI with colorectal cancer risk attenuated when further adjusting for WC or WHR, while the associations of WC and WHR persisted when further adjusting for BMI.[151,152] In CKB, the positive association for BMI became inverse when adjusting for WC. However, the interpretation is not straightforward considering the precision of measurement, the functional form of the variables in the model, and the high correlation between these adiposity traits. A possible explanation may be that BMI adjusted for WC may reflect body mass not explained by central adiposity. When regressing lean mass on BMI adjusted for WC (the residuals from the regression of BMI on WC), there were approximately linear relationships in both men and women (**Appendix 7.60**). This suggests that BMI adjusted for WC may be a measure of lean mass.

7.2.3.4 Other adiposity measures

Three prospective cohort studies in Western populations have examined the associations of %BF with risk of colorectal cancer, as assessed by bioelectrical impedance analysis.[131-134] Two studies showed positive associations of %BF or fat mass with risk of colon cancer in men,[133,134] while the other study included less than 200 cases and showed a null association of %BF with colorectal cancer in postmenopausal women.[131] In the Melbourne Collaborative Cohort Study (40,628 participants and 518 colon cancer cases), there were positive associations of fat mass and fat-free mass with risk of colon cancer in men (fat mass per 10 kg 1.33 [1.09-1.61], fat-free mass 1.59 [1.22-2.06]),[133] while there were positive trends

for %BF, fat mass, and fat-free mass in women (%BF per 10% 1.14 [0.94-1.40], fat mass per 10 kg 1.09 [0.95-1.25], fat-free mass per 10 kg 1.07 [0.78-1.46]).[132] Similarly, recent analyses of the UK Biobank (1731 colon and 889 rectal cancer cases) reported a positive association of %BF with colon cancer in men and a null association in women, while it showed no associations with rectal cancer in both sexes.[134] In men, the HRs per 5% increase were 1.12 (1.05-1.19) for colon and 1.05 (0.97-1.14) for rectal cancer; in women, the corresponding HRs were 1.00 (0.94-1.06) and 0.96 (0.87-1.05). In CKB, the positive associations for %BF, fat mass, and lean mass were consistent with the Australian study and the UK Biobank. Although the associations tended to be weaker in women and for rectal cancer, the associations did not differ by sex and for colon and rectal cancer in CKB.

7.2.4 Young adulthood adiposity and specific GI cancers

A meta-analysis of five prospective cohort studies involving 4602 pancreatic cancer cases showed that each 5 kg/m^2 higher young adulthood BMI was associated with an 18% higher risk (RR 1.18 [1.12-1.24]).[135] The meta-analysis also showed that the positive association did not differ by region, although two cohort studies in East Asia included in the meta-analysis showed no associations, probably due to the small numbers of cases (402 and 52 cases).[135] In CKB, the positive association of BMI25 with pancreatic cancer was consistent with previous studies in primarily Western populations.[135] A pooled analysis of 20 cohort studies in the US (also included in the meta-analysis) compared the associations of adulthood and young adulthood BMI and showed that the positive association was stronger for young adulthood BMI (1.18 [1.11-1.25] vs 1.09 [1.05-1.12] per 5

kg/m^2).[144] Although the association for adulthood BMI was null in CKB, the stronger association for young adulthood BMI (1.02 [0.92-1.14] vs 1.18 [1.02-1.36] per 5 kg/m^2) is consistent with the pooled analysis.

At least two studies have assessed the associations of both adulthood and young adulthood BMI with risk of liver cancer, with inconsistent findings.[153,155] The Japan Collaborative Cohort Study involving 254 liver cancer cases reported a U-shaped association for BMI at baseline (mean age 57), with higher risks among those with low (<18.5) and high BMI (≥25.0) (HR 1.5-2.0).[155] However, they showed no evidence of an association for BMI at age 20. A nested case-control study involving 622 liver cancer cases in Sweden compared associations of BMI assessed at different ages with liver cancer risk.[153] The strongest associations were observed for BMI assessed at mid-20s, with HRs of 1.6 (1.1-2.3) and 2.5 (1.3-4.8) for overweight (≥25 kg/m^2) and obese participants (≥30 kg/m^2), compared with participants with normal BMI (<18.5 kg/m^2). The positive associations attenuated with age and were null for BMI assessed at mid-50s (0.6 [0.4-1.1] for overweight and 0.9 [0.6-1.5] for overweight). In CKB, there was a positive association of BMI25 with liver cancer risk, which is stronger than the null association of BMI at baseline (mean age 52; 1.01 [0.93-1.10] vs 1.09 [1.01-1.18] per 5 kg/m^2). Although the association for adulthood BMI was null in CKB, the stronger association for young adulthood than adulthood BMI is consistent with the Swedish study.[153]

Several prospective studies have examined the association of BMI in young adulthood with risk of colorectal cancer.[154,156-158] Three prospective studies involving less than 1000 colorectal cancer cases reported a positive association

for BMI at age 20 (HR per 5 kg/m^2 higher BMI ~1.30),[156-158] stronger than the weak positive trend in CKB. However, these studies did not examine adulthood BMI. Another prospective cohort study in the US with 2100 cases reported a positive association of BMI at age ~20 with colon cancer risk in women and a null association in men (HR comparing ≥27.5 and 15-19 kg/m^2: women 1.60 [1.07-2.39], men 1.08 [0.69-1.72]).[154] The US study also examined associations of adulthood BMI and showed stronger positive associations than BMI at age 20 in both men and women. Consistent with the US study,[154] in CKB, the positive association of colorectal cancer risk was stronger for adulthood than young adulthood BMI.

7.2.5 Comparison across adiposity traits

Of all adiposity traits examined, height-adjusted lean mass, WC, and WHR showed the strongest associations with risk of liver cancer, while WC and WHtR showed the strongest associations with colorectal cancer. For pancreatic cancer, BMI25 showed the strongest association.

BMI is a measure of general adiposity but cannot distinguish between fat mass and lean mass.[129,130] In the current study, the null association of BMI with pancreatic cancer and the inverse association with liver cancer may reflect reverse causality and residual confounding, particularly related to smoking and HBV (for liver cancer). When excluding the first five years of follow-up, the inverse association with liver cancer became null. When restricting the analysis to never regular smokers, there were positive trends between BMI and risks of pancreatic cancer (in all participants) and liver cancer (when excluding the first five years). Similar to BMI, %BF and height-adjusted fat mass showed no associations with

pancreatic cancer and inverse associations with liver cancer. This probably reflects the strong correlations between BMI, %BF, and fat mass (Pearson correlation r=0.80-0.94). For lean mass, there were positive associations with pancreatic and liver cancer, particularly among never regular smokers and when excluding the first five years. The reason for the different associations of fat mass and lean mass with pancreatic and liver cancer is poorly understood. It is possible that lean mass is associated with nutritional and developmental factors that are associated with higher risk of cancer.[373,374] In the current study, strong correlations were observed between lean mass and height in both men and women (Pearson correlation r=0.68 vs 0.74).

For both liver and colorectal cancer, central adiposity showed stronger associations than BMI and %BF, suggesting that fat distribution may be more important than body fatness in relation to cancer risk. Indeed, central adiposity is associated with insulin resistance, a key mechanism linking adiposity and cancer risk,[204] and the association persists after adjusting for BMI.[203,209] However, the positive association between BMI and insulin resistance became null when additionally adjusting for central adiposity.[375] Moreover, previous studies have shown that visceral adipose tissue (a marker for fat distribution) is associated with risks of diabetes and cancer when additionally adjusting for BMI.[376,377]

7.2.6 Mechanisms

7.2.6.1 General mechanisms

Insulin resistance, sex hormones, and inflammation have been suggested as the underlying mechanisms linking adiposity and cancer risk. First, adiposity is

associated with insulin resistance and subsequent hyperinsulinaemia.[203] Prospective studies have shown that hyperinsulinaemia is associated with higher risks of pancreatic, liver, and colorectal cancer.[149,189,190,378,379] Higher circulating levels of insulin subsequently increase bioavailable IGF-I, which can promote carcinogenesis.[205,206] Second, adiposity can affect circulating levels of sex steroid hormones, including oestrogens, androgens, and progesterone.[208] Prospective studies have suggested a positive association of endogenous oestradiol with colorectal cancer risk in postmenopausal women and an inverse association of testosterone levels in men.[210] Third, adipose tissue can stimulate inflammatory response, which may promote cancer development.[203,211] On one hand, the adipocyte produces proinflammatory factors, circulating TNF-α, IL-6, and CRP.[212,213] Prospective studies have suggested a positive association of CRP with colorectal cancer[214,215] and of inflammatory cytokines with pancreatic cancer (more on this in **Appendix 9.1**).[216] On the other, obese people have increased secretion of leptin and decreased secretion of adiponectin (i.e. adipose-tissue-derived hormones).[213,217] Prospective studies have reported inverse associations of plasma adiponectin with risks of colorectal and pancreatic cancer,[213,217-222] and a positive association of leptin with pancreatic cancer.[223]

7.2.6.2 Central vs general adiposity

For both liver and colorectal cancer, the stronger association with central adiposity may be explained by the stronger link between central adiposity with insulin resistance than general adiposity. Insulin resistance has been hypothesised as the key mechanism underlying the association between central adiposity and cancer risk.[203,260] Epidemiological studies have shown a positive association of central

adiposity (WC or abdominal fat) with insulin resistance assessed by euglycaemic clamp or the insulin sensitivity index.[375,380] Furthermore, central adiposity is less affected by muscle loss during aging or with chronic diseases, while the association with BMI may be influenced by reverse causality particularly due to smoking and pre-existing diseases,[347] biasing the association towards the null. In addition, the positive association of BMI with risks of liver and colorectal cancer may be partially explained by the correlation with central adiposity. Epidemiological studies showed that the positive association of BMI with insulin resistance became null when further adjusting for central adiposity.[375]

7.2.6.3 Colon vs rectal cancer

Although not well understood, the mechanisms underlying the sex difference are hypothesised to be related to sex steroid hormone exposures.[149,210] In Western populations, the association between adiposity and colorectal cancer may be modified by exogenous oestrogens (in the form of postmenopausal hormone replacement therapy [HRT]).[364] This has been supported by the inverse relationship between postmenopausal oral hormone therapy and colorectal cancer in both prospective cohort studies and RCTs.[381,382] Therefore, effect modification by postmenopausal HRT use may be a possible explanation for the weaker association between adiposity and colorectal cancer risk in women. In CKB, HRT use was not collected at baseline, and therefore it was not possible to investigate the association by HRT status. Nonetheless, similar associations were observed when restricting to premenopausal women (HR per 5 kg/m^2 BMI 1.07 [0.89-1.29] for colorectal, 1.13 [0.89-1.43] for colon, and 0.96 [0.74-1.24] for rectal cancer; all women: 1.13 [1.07-1.20] for colorectal, 1.12 [1.02-1.23] for colon, 1.05 [0.95-1.16]

for rectal cancer). However, HRT use may not affect endogenous oestrogen levels. In fact, it has been hypothesised that the protective role of HRT may be independent of oestrogen,[383,384] and evidence has been inconclusive whether endogenous oestrogen is associated with risk of colorectal cancer.[385] Nonetheless, recent Mendelian randomisation studies have reported that genetically raised BMI is associated with higher risk of colorectal cancer in both sexes,[386,387] suggesting a causal role of adiposity in the aetiology of colorectal cancer in both men and women.

7.2.6.4 Young adulthood adiposity

Higher BMI in young adulthood might reflect longer duration of adiposity, which contributes to a higher risk of cancer. Overweight young adults tend to remain overweight into middle age. In CKB, 25.9% of obese and 56.3% of overweight participants in young adulthood remained obese or overweight at baseline (mean age ~52). Stolzenberg-Solomon et al. reported that a longer duration of BMI ≥25.0 kg/m^2 was associated with higher risk of pancreatic cancer.[351] Moreover, young adulthood BMI marks developmental factors that lead to acquisition of both lean and fat body mass in childhood and adolescence.[36] Higher BMI in young adulthood might also correspond to larger body size, and therefore reflects factors related to development and maturation that influence later risk of cancer.[36]

Young adulthood BMI showed a stronger association with risks of pancreatic and liver cancer than adulthood BMI. Compared with adulthood BMI, the association for young adulthood BMI is less likely affected by reverse causality. Pancreatic cancer has a long latency period, during which unintentional weight loss might occur as a result of preclinical cancer.[24] Yachida et al. performed a quantitative

analysis of the timing of the genetic evolution of pancreatic cancer.[388] They showed that it took at least five years for parental nonmetastatic cells to acquire metastatic ability, and it may take up to 20 years for pancreatic cancer to become clinically evident.[388] For HBV-related liver cancer, there is a long latency period between HBV infection and development of liver cancer (~30 years). Weight loss is likely to occur in patients with chronic viral hepatitis and in the progression to liver cancer.[390] Reverse causality might bias the relative risks for adulthood BMI towards the null, while young adulthood BMI, 20-30 years before baseline, is less likely affected by preclinical cancer or liver diseases.

7.3 Conclusions

For pancreatic cancer, there were no associations for general and central adiposity, with similar associations when excluding the first five years of follow-up. For liver cancer, there were inverse associations for general adiposity and null associations for central adiposity, which may reflect reverse causality. When excluding the first five years, the inverse associations for general adiposity attenuated towards the null, while there were positive associations for central adiposity. Although HBsAg did not modify the associations of adiposity with liver cancer risk, the associations were generally null or inverse among HBsAg positive participants. For colorectal cancer, there were positive associations for general and central adiposity. When excluding the first five years of follow-up, the positive associations for adiposity became stronger. For both general and central adiposity, the associations with colon and rectal cancer were stronger in men than women, but the differences were significant only for central adiposity. When comparing colon and rectal cancer, the associations of adiposity tended to be stronger for

colon than rectal cancer, albeit nonsignificantly. Young adulthood adiposity as assessed by BMI25 showed positive associations with risks of pancreatic and liver cancer, while there was a positive trend for colorectal cancer.

Chapter 8 Diabetes and risk of GI cancer

The objective of this chapter is to examine the associations of diabetes with risks of pancreatic, liver, and colorectal cancer and of plasma glucose with risks of these cancers controlling for possible confounders and adjusting for within-person variation and error in the measurement of plasma glucose.

8.1 Results

8.1.1 Patterns and correlates of diabetes and plasma glucose

Among all 509,892 participants, the prevalence of previously diagnosed and screen-detected diabetes was 3.1% and 2.8%, respectively. After standardising for age, sex, and region, the prevalence of diabetes was higher in urban than rural areas (8.2% vs 4.3%, **Appendix 8.1**), so were the prevalences of previously diagnosed and screen-detected diabetes (urban vs rural: previously diagnosed: 4.6% vs 2.0%, screen-detected: 3.6% vs 2.2%). After standardising for age and region, the prevalence of diabetes was higher in women than men (women vs men: total diabetes, 6.3% vs 5.5%; previously diagnosed diabetes, 3.4% vs 2.9%). However, such a sex difference was only evident in rural areas (women vs men: total diabetes, 4.7% vs 3.4%; previously diagnosed diabetes, 2.2% vs 1.6%). In urban areas, the prevalences of total and screen-detected diabetes were slightly higher in men (women vs men: total diabetes, 8.0% vs 8.3%; screen-detected diabetes, 3.3% vs 3.7%), while the prevalence of previously diagnosed diabetes was similar (women vs men: 4.6% vs 4.6%). In both urban and rural areas, the prevalence of diabetes increased with age, with a more rapid increase in women between 35-64 years (**Figure 8.1**). After age 65 years, there was a slight decline

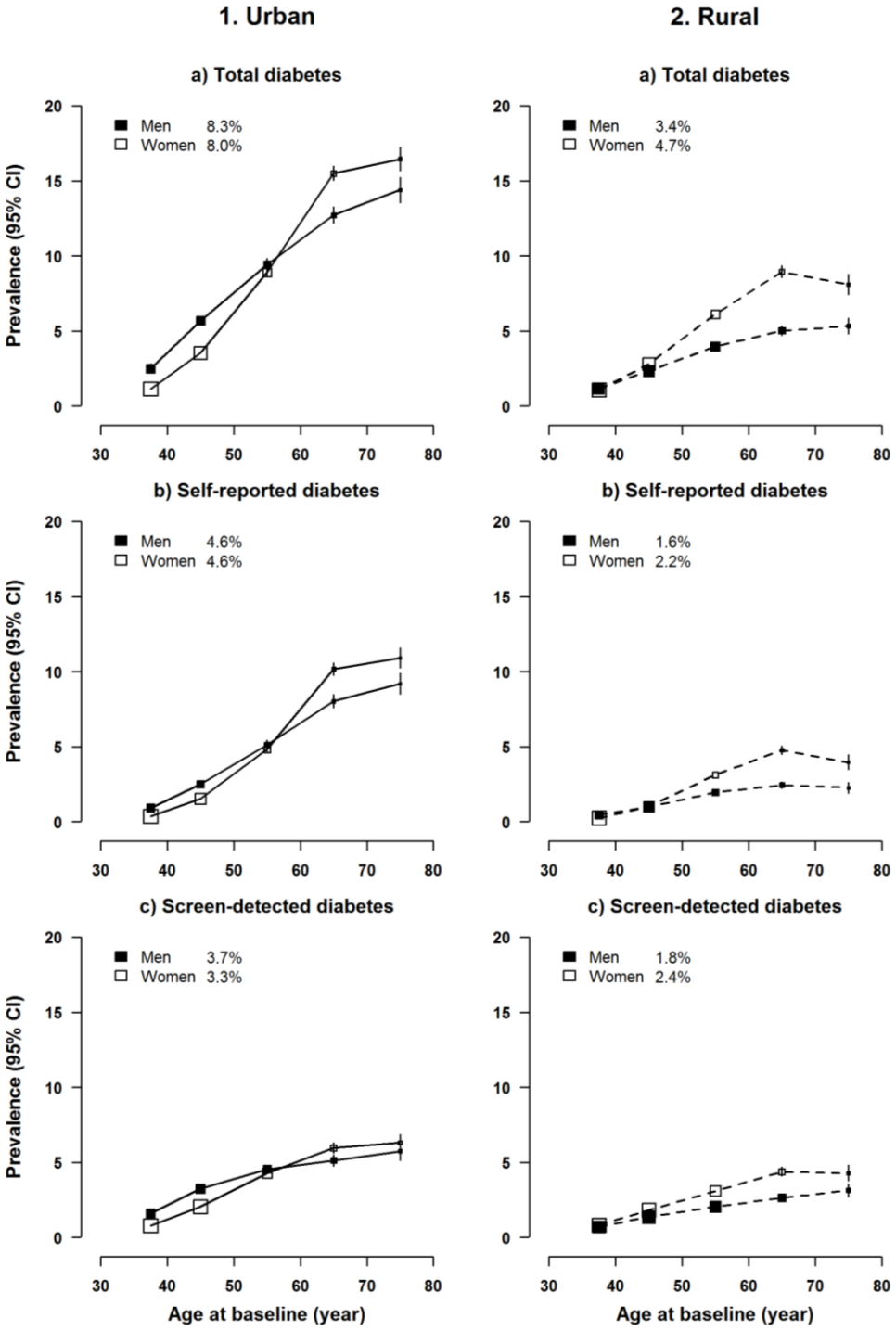
in the prevalence of diabetes in rural women (**Figure 8.1**). Among all 15,993 participants with previously diagnosed diabetes, the median age at first diagnosis was 53 years and the median duration since diagnosis was 6.5 years. 65% of participants with previously diagnosed diabetes reported use of diabetes medications (81% metformin or chlorpropamide, 15% insulin, and 4% both), and the proportion was slightly higher in rural than urban areas (66.9% vs 64.0%, **Appendix 8.1**).

The mean (SD) RPG was 5.7 (1.1), 13.3 (5.4), and 11.8 (5.7) mmol/L among participants without any diabetes, with screen-detected diabetes, and with previously diagnosed diabetes, respectively. Among participants without previously diabetes, the mean RPG was higher in women than men (6.2 vs 6.0 mmol/L) and in urban than rural areas (6.3 vs 5.9 mmol/L, **Appendix 8.1**). However, the sex difference was only observed in rural (women vs men: 6.0 vs 5.7 mmol/L) but not urban areas (6.3 vs 6.3 mmol/L). Similar to diabetes, mean RPG level increased with age (**Figure 8.2**). In urban areas, the age pattern was similar in men and women between 35-54 years, while after age 55 years women had higher RPG levels than men. In rural areas, mean RPG increased with age between 35-79 years and was higher in women than men.

Participants with diabetes were older and more likely to be from urban areas and to have higher household income (**Table 8.1**). Participants with diabetes were less likely to drink alcohol on a weekly basis and to consume fresh fruits on a daily basis, and they had lower total PA and higher SLT. Participants with diabetes had higher levels of SBP, RPG, and adiposity (e.g. BMI, WC), while they were also more likely to have a history of CVD and hypertension, and a family history of

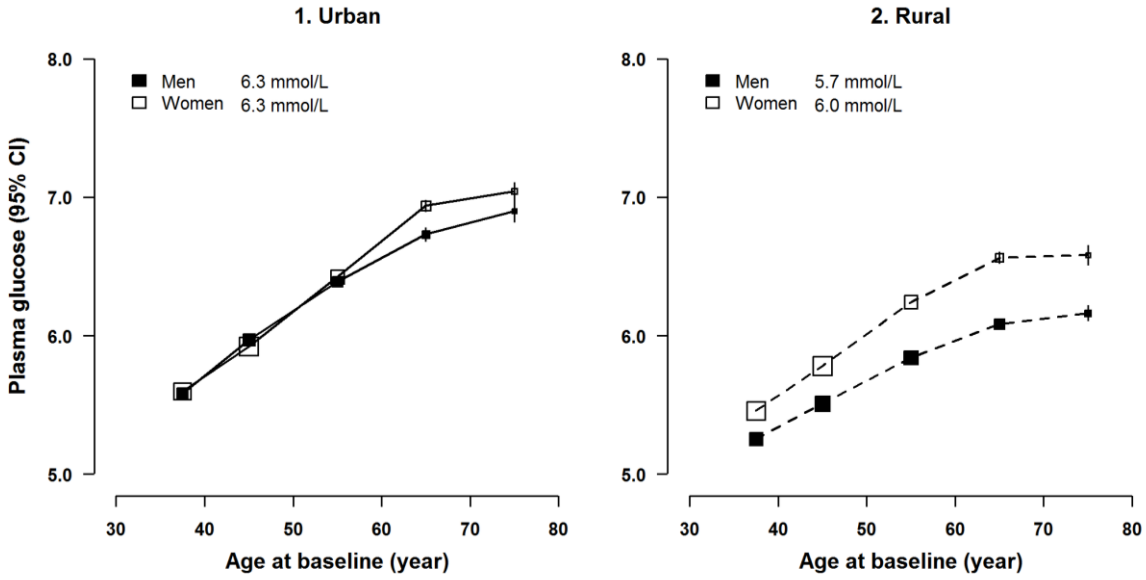
diabetes. Among participants without previously diagnosed diabetes (**Table 8.2**), participants with higher RPG levels were older and more likely to be from urban areas. In contrast to the patterns observed by diabetes status, fresh fruits consumption, total PA, and SLT did not differ much by RPG level. Similar to diabetes patients, participants with higher RPG were more likely to have higher levels of SBP and adiposity, and to have a history of CVD and hypertension, and a family history of diabetes.

Figure 8.1 Prevalence of diabetes at baseline by region and by sex



Results were standardised by age, sex, and region (where appropriate).

Figure 8.2 Mean levels of RPG at baseline by region and by sex



Results were standardised by age, sex, and region (where appropriate).

Table 8.1 Baseline characteristics of participants by diabetes status

Variable*	Diabetes		
	No diabetes (n=479,899)	**Screen-detected** (n=14,000)	**Diagnosed** (n=15,993)
Age (SD), year	51.1 (10.5)	55.9 (10.3)	58.3 (10.1)
Female, %	58.8	61.0	59.2
Socioeconomic and lifestyle factors			
Urban region, %	43.1	54.1	60.8
≥9 years of education, %	21.0	18.7	20.5
Household income ≥35 000 RMB/year, %	17.9	18.6	19.9
Ever regular smoking, %			
Male	67.7	67.6	64.3
Female	2.8	3.1	3.1
Weekly drinking, %			
Male	33.6	36.0	21.8
Female	2.1	1.9	0.7
Total physical activity (SD), MET-h/day	21.2 (13.9)	19.8 (12.9)	17.5 (10.6)
Sedentary leisure time (SD), h/day	3.0 (1.5)	3.1 (1.6)	3.2 (1.7)
Daily consumption, %			
Fresh fruits	19.1	18.1	13.7
Fresh vegetables	94.7	94.7	95.3
Red meat	29.2	29.7	30.4
Blood pressure and anthropometry			
SBP (SD), mmHg	130.6 (21.0)	139.3 (22.7)	137.5 (22.6)
RPG (SD), mmol/L	5.7 (1.1)	13.3 (5.4)	11.8 (5.7)
BMI (SD), kg/m^2	23.6 (3.3)	25.1 (3.7)	24.6 (3.5)
Waist circumference (SD), cm	80.0 (9.6)	85.2 (10.3)	84.3 (9.8)
Hip circumference (SD), cm	90.9 (6.8)	92.6 (7.7)	91.8 (7.5)
Waist-to-hip ratio (SD)	0.88 (0.07)	0.92 (0.07)	0.92 (0.07)
Percent body fat (SD), %	27.8 (8.3)	31.0 (8.8)	29.4 (8.5)
Height (SD), cm	158.7 (8.3)	158.6 (8.4)	159.1 (8.3)
BMI at age 25 (SD), kg/m^2	21.9 (2.5)	22.5 (2.9)	23.2 (3.2)
HBsAg positive, %	3.0	3.5	3.1
Prior disease history, %			
Coronary heart disease	2.8	3.2	6.9
Stroke or TIA	1.6	2.2	3.9
Hypertension	10.8	17.4	27.8
Family history of diabetes	4.5	9.2	16.0
Family history of cancer	13.9	13.4	15.2

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.

* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.

Table 8.2 Baseline characteristics of participants by levels of RPG among participants without diabetes

Variable*	RPG			
	<5.6 (n=242,503)	**5.6 to <6.8** (n=158,177)	**6.8 to <7.8** (n=51,036)	**≥7.8** (n=34,059)
Age (SD), year	49.5 (10.3)	52.2 (10.6)	54.0 (10.9)	55.4 (10.7)
Female, %	54.8	63.6	63.0	59.4
Socioeconomic and lifestyle factors				
Urban region, %	40.3	47.5	45.2	51.0
≥9 years of education, %	21.6	20.8	20.6	19.7
Household income ≥35 000 RMB/year, %	18.1	18.0	17.3	17.9
Ever regular smoking, %				
Male	68.7	66.4	66.9	68.0
Female	3.0	2.5	2.5	3.0
Weekly drinking, %				
Male	33.2	33.8	33.0	35.3
Female	2.1	2.0	1.9	1.8
Total physical activity (SD), MET-h/day	21.3 (14.2)	21.3 (13.5)	21.2 (13.2)	20.8 (12.9)
Sedentary leisure time (SD), h/day	3.0 (1.5)	3.0 (1.5)	3.0 (1.5)	3.0 (1.6)
Daily consumption, %				
Fresh fruits	18.9	18.8	18.2	17.8
Fresh vegetables	94.9	94.5	94.4	94.5
Red meat	29.5	28.5	28.2	29.0
Blood pressure and anthropometry				
SBP (SD), mmHg	129.7 (20.6)	130.9 (21.1)	132.3 (21.5)	136.4 (22.5)
RPG (SD), mmol/L	4.9 (0.5)	6.0 (0.3)	7.2 (0.3)	10.6 (4.0)
BMI (SD), kg/m^2	23.4 (3.2)	23.7 (3.4)	24.0 (3.6)	24.6 (3.7)
Waist circumference (SD), cm	79.2 (9.3)	80.5 (9.6)	81.6 (10.1)	83.4 (10.5)
Hip circumference (SD), cm	90.6 (6.6)	91.1 (6.9)	91.3 (7.1)	91.9 (7.6)
Waist-to-hip ratio (SD)	0.87 (0.07)	0.88 (0.07)	0.89 (0.07)	0.91 (0.07)
Percent body fat (SD), %	27.6 (8.1)	27.8 (8.3)	28.3 (8.8)	29.6 (9.1)
Height (SD), cm	158.8 (8.3)	158.7 (8.2)	158.5 (8.2)	158.3 (8.4)
BMI at age 25 (SD), kg/m^2	21.8 (2.5)	21.9 (2.6)	21.9 (2.7)	22.2 (2.8)
HBsAg positive, %	3.1	3.0	3.2	3.3
Prior disease history, %				
Diabetes	0.0†	0.0†	5.2	35.0
Coronary heart disease	2.6	2.7	3.0	3.1
Stroke or TIA	1.4	1.6	1.8	2.0
Hypertension	9.6	11.0	12.6	15.1
Family history of diabetes	4.4	4.7	5.1	7.1
Family history of cancer	14.1	13.8	13.7	14.0

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.

* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.

† Prevalence of diabetes <0.001%.

8.1.2 Associations of diabetes and plasma glucose with specific GI cancers

8.1.2.1 Diabetes

The main model was stratified by age-at-risk, sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, smoking, alcohol, education, household income, self-rated health, and family history of cancer (**Tables 8.3-8.5**). Individuals with diabetes had a 62% higher risk of pancreatic cancer (HR 1.62 [1.31-2.00], **Table 8.3**), with HRs of 1.71 (1.33-2.21) and 1.49 (1.10-2.04) for previously diagnosed and screen-detected diabetes (*p* for heterogeneity 0.50). Similarly, individuals with diabetes had a 43% higher risk of liver cancer (HR 1.43 [1.26-1.62], **Table 8.4**), with HRs of 1.35 (1.15-1.59) and 1.53 (1.29-1.81) for previously diagnosed and screen-detected diabetes (*p* for heterogeneity 0.30). For colorectal cancer, there was a 16% higher risk associated with diabetes (HR 1.16 [1.02-1.31], **Table 8.5**), with a positive association for screen-detected (1.40 [1.20-1.65]) and a null association for previously diagnosed diabetes (0.97 [0.83-1.15], *p* for heterogeneity 0.002).

During a median of 10 years of follow-up, 18,120 participants had an incident diagnosis of diabetes (ICD-10 code: E11). The median age at diagnosis was 62 years, and the median duration since diagnosis was 4.0 years (IQR 1.7-7.0). When individuals with incident diabetes after baseline were also considered as exposed from their time of diagnosis, the HRs were 2.69 (2.09-3.45) for pancreatic, 1.74 (1.46-1.98) for liver, and 1.30 (1.08-1.56) for colorectal cancer (**Table 8.6**), compared with participants without diabetes at baseline.

Table 8.3 Associations of diabetes and RPG with risk of pancreatic cancer[*]

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Diabetes status				
No diabetes	692	4,785,520	14.5	Reference
Total diabetes	104	280,114	25.3	1.62 (1.31, 2.00)
Diabetes status				
No diabetes	692	4,787,520	14.5	1.00 (0.92, 1.09)
Screen-detected	40	132,399	23.6	1.49 (1.10, 2.04)
Previously diagnosed	64	147,714	24.9	1.71 (1.33, 2.21)
RPG (mmol/L)				
<5.6	303	2,443,888	13.5	1.00 (0.88, 1.13)
5.6 to <6.8	239	1,557,789	14.6	1.07 (0.95, 1.21)
6.8 to <7.8	90	495,417	17.4	1.22 (0.99, 1.51)
≥7.8	77	325,212	19.9	1.39 (1.10, 1.74)
RPG (mmol/L)				
<4.3	36	290,175	13.6	1.00 (0.72, 1.39)
4.3 to <5.8	334	2,554,251	13.4	1.08 (0.96, 1.21)
5.8 to <7.0	197	1,297,878	14.2	1.09 (0.95, 1.25)
7.0 to <7.8	65	354,788	16.4	1.27 (0.99, 1.62)
7.8 to <11.1	53	243,251	17.4	1.32 (1.01, 1.74)
≥11.1	24	81,961	24.6	1.75 (1.17, 2.62)
per 1 mmol/L[†]	*709*			*1.09 (1.04, 1.15)*

Abbreviations: PYAR=person years at risk.

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Table 8.4 Associations of diabetes and RPG with risk of liver cancer*

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Diabetes status				
No diabetes	2560	4,783,671	54.0	Reference
Total diabetes	287	279,951	87.6	1.43 (1.26, 1.62)
Diabetes status				
No diabetes	2560	4,783,671	54.0	1.00 (0.96, 1.05)
Screen-detected	135	132,343	87.0	1.53 (1.29, 1.81)
Previously diagnosed	152	147,608	88.1	1.35 (1.15, 1.59)
RPG (mmol/L)				
<5.6	1160	2,442,965	50.5	1.00 (0.94, 1.06)
5.6 to <6.8	847	1,557,251	55.1	1.09 (1.02, 1.17)
6.8 to <7.8	334	495,199	62.4	1.20 (1.07, 1.33)
≥7.8	297	325,033	78.0	1.44 (1.28, 1.62)
RPG (mmol/L)				
<4.3	175	290,106	43.2	1.00 (0.86, 1.16)
4.3 to <5.8	1199	2,553,270	51.6	1.13 (1.06, 1.20)
5.8 to <7.0	720	1,297,427	55.2	1.19 (1.10, 1.28)
7.0 to <7.8	247	354,612	62.1	1.32 (1.16, 1.50)
7.8 to <11.1	203	243,115	71.1	1.44 (1.25, 1.66)
≥11.1	94	81,919	88.0	1.92 (1.57, 2.36)
per 1 mmol/L†	*2638*			*1.09 (1.06, 1.12)*

Abbreviations: PYAR=person years at risk.

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

† Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Table 8.5 Associations of diabetes and RPG with risk of colorectal cancer[*]

	No. cases	Person-time, PYAR	Incidence rates per 100,000	HR (95% CI)
Diabetes status				
No diabetes	2732	4,778,334	57.9	Reference
Total diabetes	292	279,376	71.9	1.16 (1.02, 1.31)
Diabetes status				
No diabetes	2732	4,778,334	57.9	1.00 (0.96, 1.05)
Screen-detected	148	132,057	85.8	1.40 (1.20, 1.65)
Previously diagnosed	144	147,319	57.5	0.97 (0.83, 1.15)
RPG (mmol/L)				
<5.6	1197	2,440,652	55.2	1.00 (0.94, 1.06)
5.6 to <6.8	998	1,555,262	61.0	1.11 (1.04, 1.18)
6.8 to <7.8	338	494,553	60.1	1.09 (0.98, 1.21)
≥7.8	297	324,442	73.1	1.30 (1.16, 1.46)
RPG (mmol/L)				
<4.3	148	289,867	57.8	1.00 (0.85, 1.18)
4.3 to <5.8	1290	2,550,709	54.3	1.05 (0.99, 1.12)
5.8 to <7.0	829	1,295,788	59.0	1.12 (1.05, 1.20)
7.0 to <7.8	266	354,104	66.0	1.23 (1.09, 1.39)
7.8 to <11.1	215	242,682	68.6	1.32 (1.15, 1.51)
≥11.1	82	81,760	76.5	1.44 (1.16, 1.79)
per 1 mmol/L[†]	*2830*			*1.06 (1.03, 1.09)*

Abbreviations: PYAR=person years at risk.

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

8.1.2.2 Duration of diabetes

Compared with participants without diabetes, there were 1.5- to four-fold higher risks of all three cancers 0 to <2 years following diabetes diagnosis (**Table 8.6**). After two years following diabetes diagnosis, the excess risks decreased but remained elevated even ≥10 years after diabetes diagnosis (**Table 8.6**), except for a null association for ≥10 years of diabetes with colorectal cancer (HR 0.97 [0.79-1.18]). For pancreatic cancer, the HRs were 3.74 (2.60-5.38), 1.66 (1.12-2.46), 1.70 (1.27-2.27), and 1.57 (1.15-2.16) for 0 to <2, 2 to <5, 5 to <10, and ≥10 years (*p* for trend 0.001). The corresponding HRs were 2.15 (1.64-2.81), 1.48 (1.18-1.86), 1.42 (1.19-1.69), and 1.33 (1.09-1.62) for liver cancer (*p* for trend 0.01), and were 1.54 (1.15-2.06), 1.23 (0.97-1.54), 1.37 (1.17-1.61), and 0.97 (0.79-1.18) for colorectal cancer (*p* for trend 0.02). Similar patterns for all three cancers were observed when incident diabetes cases were not counted as exposed in the calculation of diabetes duration (**Table 8.6**).

8.1.2.3 Diabetes medications

Compared with participants without diabetes (**Table 8.7**), diabetes patients taking insulin had nonsignificant higher risks of pancreatic and liver cancer (HR 1.96 [0.97-3.96] vs 1.53 [0.95-2.47]), while diabetes patients taking metformin or chlorpropamide had a nonsignificant higher risk of pancreatic cancer (HR 1.45 [0.99-2.12]). The numbers of cancer cases taking both insulin and metformin or chlorpropamide were too small to yield reliable results. However, there were no differences in HRs across categories of diabetes medications (*p* for heterogeneity: pancreatic 0.47, liver 0.48, colorectal 0.09). When diabetes patients not taking any medications were used as the reference (**Table 8.7**), there were no associations

of diabetes medications with risks of these three cancers. However, the analysis may be underpowered, and the HRs had wide confidence intervals.

In the analysis of diabetes by treatment status (**Table 8.7**), similar associations were observed with pancreatic cancer for untreated (i.e. screen-detected diabetes and previously diagnosed diabetes not taking medications) and treated diabetes (i.e. previously diagnosed diabetes on medications), with HRs of 1.59 (1.23-2.06) for untreated and 1.54 (1.10-2.14) for treated diabetes (*p* for heterogeneity 0.60). For liver and colorectal cancer, the associations were stronger for untreated than treated diabetes (liver: 1.53 [1.32-1.78] vs 1.16 [0.94-1.43], *p* for heterogeneity 0.03; colorectal: 1.32 [1.14-1.52] vs 0.96 [0.78-1.18], *p* for heterogeneity 0.01).

When additionally adjusting for diabetes medications, the associations of previously diagnosed diabetes became somewhat stronger with pancreatic and liver cancer. For pancreatic cancer, the HRs were 1.71 (1.33-2.21) in the main model and 2.22 (1.25-3.95) when further adjusting for diabetes medications; for liver cancer, the corresponding HR were 1.35 (1.15-1.59) and 1.71 (1.19-2.45). For colorectal cancer, additional adjustment for diabetes medications had little impact on the association (0.97 [0.83-1.15] in the main model and 1.01 [0.66-1.54] when further adjusting for diabetes medications).

Table 8.6 Associations of duration of diabetes with risks of specific GI cancers[*]

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Incident diabetes	104	2.69 (2.09, 3.45)	195	1.74 (1.46, 1.98)	191	1.30 (1.08, 1.56)
Diabetes[†]						
No diabetes	646	1.00 (0.92, 1.09)	2484	1.00 (0.96, 1.05)	2639	1.00 (0.96, 1.04)
0 to <2 year	36	3.74 (2.60, 5.38)	64	2.15 (1.64, 2.81)	62	1.54 (1.15, 2.06)
2 to <5 years	26	1.66 (1.12, 2.46)	79	1.48 (1.18, 1.86)	72	1.23 (0.97, 1.54)
5 to <10 years	48	1.70 (1.27, 2.27)	122	1.42 (1.19, 1.69)	152	1.37 (1.17, 1.61)
≥10 years	40	1.57 (1.15, 2.16)	98	1.33 (1.09, 1.62)	99	0.97 (0.79, 1.18)
p for trend[§]		*0.001*		*0.01*		*0.02*
Diabetes[‡]						
No diabetes	692	1.00 (0.92, 1.09)	2560	1.00 (0.96, 1.05)	2732	1.00 (0.96, 1.04)
0 to <2 year	8	2.78 (1.32, 5.83)	28	2.88 (1.97, 4.20)	20	1.84 (1.17, 2.88)
2 to <5 years	12	1.19 (0.67, 2.09)	46	1.29 (0.97, 1.72)	42	1.02 (0.76, 1.38)
5 to <10 years	44	1.76 (1.31, 2.37)	115	1.44 (1.20, 1.72)	131	1.32 (1.11, 1.56)
≥10 years	40	1.51 (1.11, 2.07)	98	1.31 (1.07, 1.60)	99	0.96 (0.78, 1.17)
p for trend[§]		*0.44*		*0.009*		*0.04*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Duration of diabetes was missing in 20 participants.
[†] For previously diagnosed diabetes and incident diabetes, duration was calculated as the time interval between age of diabetes diagnosis and age at risk. For screen-detected diabetes, duration was calculated as the time interval between age at baseline and age at risk.
[‡] Incident diabetes cases were not counted as exposed in the calculation of diabetes duration.
[§] *P* for trend was calculated among participants with diabetes.

Table 8.7 Associations of diabetes medications with risks of specific GI cancers*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Diabetes medications						
No diabetes	692	1.00 (0.91, 1.10)	2560	1.00 (0.95, 1.05)	2732	1.00 (0.95, 1.05)
Previously diagnosed						
No medication	16	1.88 (1.15, 3.08)	34	1.45 (1.03, 2.03)	31	1.01 (0.71, 1.43)
Insulin	8	1.96 (0.97, 3.96)	17	1.53 (0.95, 2.47)	19	1.25 (0.80, 1.97)
Metformin/chlorpropamide	27	1.45 (0.99, 2.12)	67	1.09 (0.85, 1.38)	71	0.92 (0.73, 1.17)
Insulin and metformin	1	1.37 (0.19, 9.78)	4	1.56 (0.59, 4.17)	1	0.31 (0.04, 2.22)
p for heterogeneity		*0.47*		*0.48*		*0.09*
Diabetes medications						
Previously diagnosed						
No medication	16	1.00 (0.60, 1.66)	34	1.00 (0.70, 1.42)	31	1.00 (0.70, 1.43)
Insulin	8	0.92 (0.44, 1.91)	17	1.25 (0.75, 2.07)	19	1.13 (0.70, 1.84)
Metformin/chlorpropamide	27	0.79 (0.54, 1.17)	67	0.79 (0.62, 1.01)	71	0.87 (0.68, 1.10)
Insulin and metformin	1	0.80 (0.11, 5.73)	4	1.19 (0.44, 3.21)	1	0.28 (0.04, 2.01)
p for heterogeneity		*0.39*		*0.69*		*0.09*
Diabetes medications						
No diabetes	692	1.00 (0.91, 1.10)	2560	1.00 (0.95, 1.05)	2732	1.00 (0.95, 1.05)
Untreated diabetes†	56	1.59 (1.23, 2.06)	169	1.53 (1.32, 1.78)	179	1.32 (1.14, 1.52)
Treated diabetes†	36	1.54 (1.10, 2.14)	88	1.16 (0.94, 1.43)	91	0.96 (0.78, 1.18)
p for heterogeneity		*0.60*		*0.03*		*0.01*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Diabetes medications were missing in 2447 participants with previously diagnosed diabetes.

† Untreated diabetes included screen-detected diabetes and previously diagnosed diabetes not taking medications. Treated diabetes included previously diagnosed diabetes on medications.

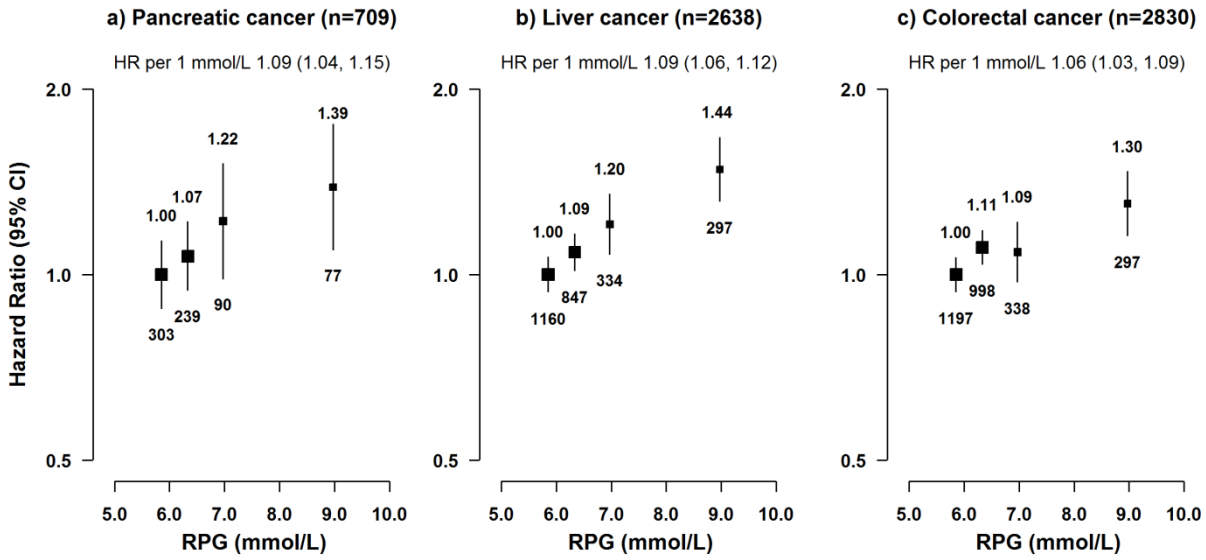
8.1.2.4 Plasma glucose among participants without previously diagnosed diabetes

The main model was stratified by age-at-risk, sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, smoking, alcohol, education, household income, self-rated health, family history of cancer, and fasting time (**Tables 8.3-8.5**). In participants without previously diagnosed diabetes, there were positive associations of RPG with risks of all three cancers (**Tables 8.3-8.5**). For pancreatic cancer, the association was log-linear, with each 1 mmol/L higher usual RPG associated with a 9% higher risk after adjusting for regression dilution bias (1.09 [1.04-1.15], **Figure 8.3**). The HRs were 1.00 (0.88-1.13), 1.07 (0.95-1.21), 1.22 (0.99-1.51), and 1.39 (1.10-1.74) for those with RPG of <5.6, 5.6 to <6.8, 6.8 to <7.8, and ≥7.8 mmol/L (**Table 8.3**). For liver cancer, a log-linear association was also observed (**Figure 8.3**), with a HR of 1.09 (1.06-1.12) per 1 mmol/L higher usual RPG. The HRs were 1.00 (0.94-1.06), 1.09 (1.02-1.17), 1.20 (1.07-1.33), and 1.44 (1.28-1.62) for those with RPG of <5.6, 5.6 to <6.8, 6.8 to <7.8, and ≥7.8 mmol/L (**Table 8.4**). For colorectal cancer, there was a positive association (**Table 8.5** and **Figure 8.3**), with HRs of 1.00 (0.94-1.06), 1.11 (1.04-1.18), 1.09 (0.98-1.21), and 1.30 (1.16-1.46) for those with RPG of <5.6, 5.6 to <6.8, 6.8 to <7.8, and ≥7.8 mmol/L (HR per 1 mmol/L 1.06 [1.03-1.09]).

When stratified by fasting time (**Figure 8.4** and **Table 8.8**), the associations tended to be stronger for fasting than nonfasting plasma glucose (fasting time <8 hours). However, the differences were only significant for colorectal cancer (*p* for heterogeneity: pancreatic 0.22, liver 0.43, colorectal 0.04). The HR per 1 mmol/L higher usual nonfasting plasma glucose were 1.08 (1.02-1.14) for pancreatic, 1.08

(1.04-1.11) for liver, and 1.06 (1.03-1.09) for colorectal cancer, while the corresponding HR per 1 mmol/L higher usual FPG were 1.20 (1.02-1.42), 1.11 (0.99-1.24), and 1.17 (1.07-1.28). However, when examining the dose-response relationships, the HRs for the top two FPG categories had wide confidence intervals due to the small numbers of cases included (**Figure 8.4**).

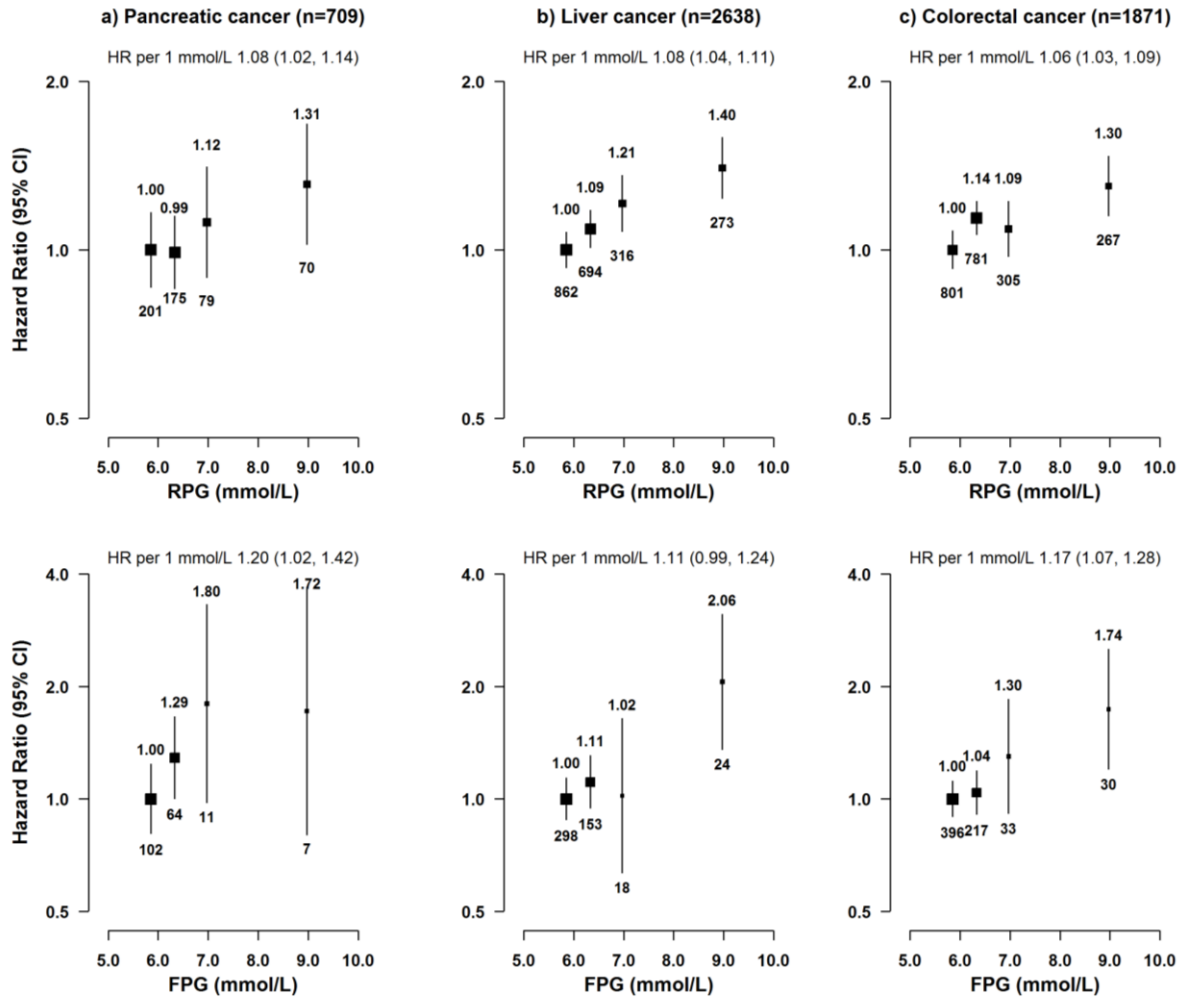
Figure 8.3 Adjusted HRs for specific GI cancers by RPG among individuals without previously diagnosed diabetes



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.

HRs are plotted against the mean level in each category of RPG. Log-scale is used for the y-axis. The squares represent HRs, and the vertical lines represent 95% CIs. The area of the squares is inversely proportional to the variance of the log HRs. The numbers above the vertical lines are point estimates for HRs, and the numbers below the lines are numbers of events.

Figure 8.4 Adjusted HRs for specific GI cancers by RPG among individuals without previously diagnosed diabetes by fasting time*



* The top panel shows nonfasting plasma glucose (fasting time <8 hours), and the bottom panel shows FPG (≥8 hours).
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.
P value for heterogeneity by fasting hours: pancreatic cancer, 0.22; liver cancer, 0.43; colorectal cancer 0.04.

Table 8.8 Associations of plasma glucose with risks of specific GI cancers among participants without previously diagnosed diabetes by fasting time*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Nonfasting (mmol/L)						
<5.6	201	1.00 (0.86, 1.16)	862	1.00 (0.93, 1.07)	801	1.00 (0.93, 1.08)
5.6 to <6.8	175	0.99 (0.86, 1.15)	694	1.09 (1.01, 1.17)	781	1.14 (1.07, 1.22)
6.8 to <7.8	79	1.12 (0.90, 1.40)	316	1.21 (1.08, 1.35)	305	1.09 (0.98, 1.22)
≥7.8	70	1.31 (1.03, 1.67)	273	1.40 (1.24, 1.58)	267	1.30 (1.15, 1.46)
per 1 mmol/L†	*525*	*1.08 (1.02, 1.14)*	*2145*	*1.08 (1.04, 1.11)*	*2154*	*1.06 (1.03, 1.09)*
Fasting (mmol/L)						
<5.6	102	1.00 (0.81, 1.23)	298	1.00 (0.88, 1.13)	396	1.00 (0.90, 1.11)
5.6 to <6.8	64	1.29 (1.01, 1.65)	153	1.11 (0.95, 1.30)	217	1.04 (0.91, 1.18)
6.8 to <7.8	11	1.80 (0.99, 3.27)	18	1.02 (0.64, 1.62)	33	1.30 (0.92, 1.83)
≥7.8	7	1.72 (0.81, 3.61)	24	2.06 (1.37, 3.09)	30	1.74 (1.21, 2.49)
per 1 mmol/L†	*184*	*1.20 (1.02, 1.42)*	*493*	*1.11 (0.99, 1.24)*	*676*	*1.17 (1.07, 1.28)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours. Nonfasting: <8 hours, fasting: ≥8 hours.

† Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

P for heterogeneity by fasting status: pancreatic cancer, 0.22; liver cancer, 0.43; colorectal cancer 0.04.

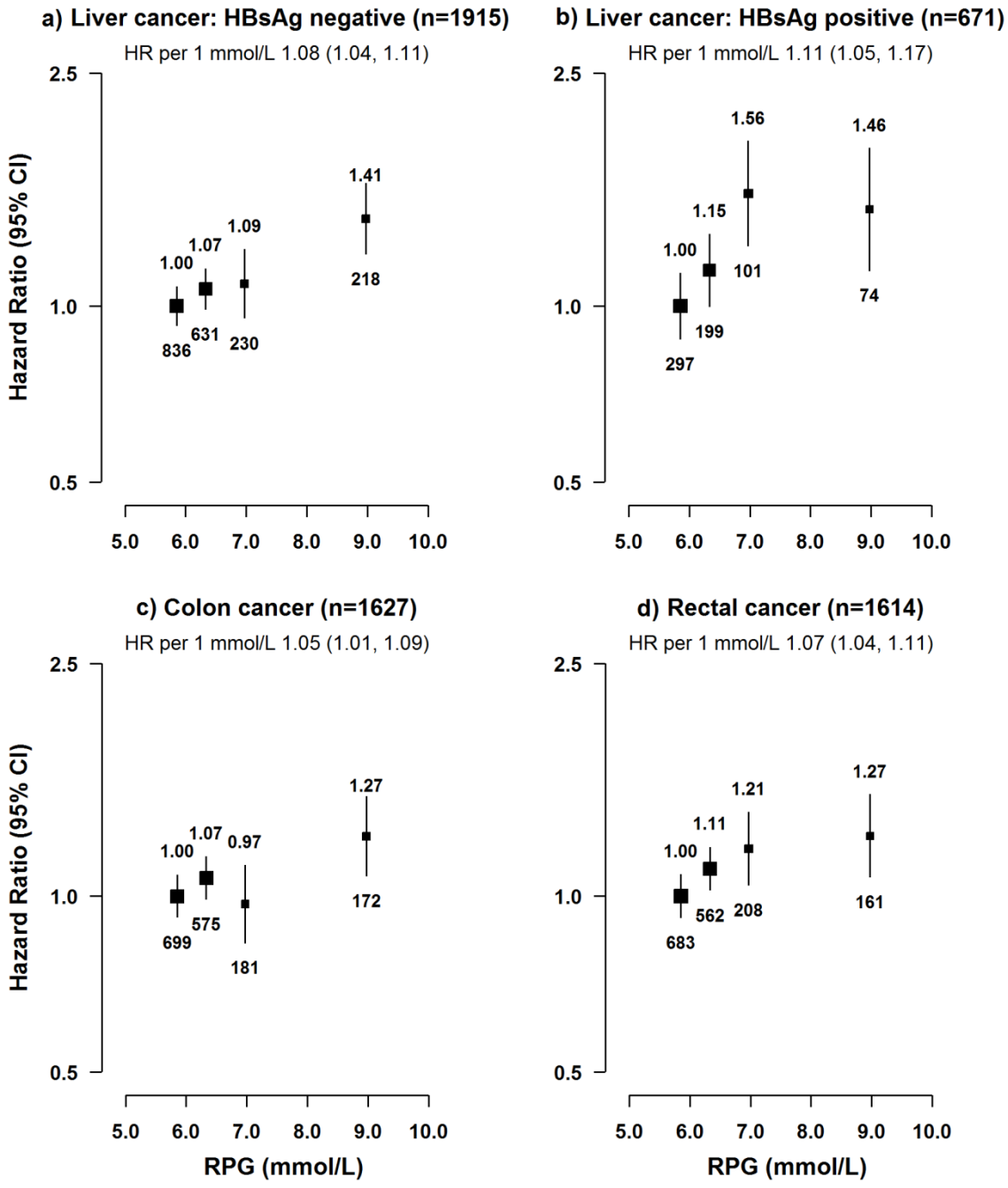
8.1.2.5 HBsAg negative vs positive liver cancer

For liver cancer, the associations of diabetes and RPG did not differ by HBsAg status (**Figure 8.5** and **Table 8.9**). Among participants who tested negative for HBsAg, the HRs were 1.40 (1.21-1.63), 1.45 (1.18-1.77), and 1.37 (1.14-1.65) for total, screen-detected, and previously diagnosed diabetes, while the corresponding HRs were 1.46 (1.13-1.89), 1.73 (1.27-2.37), and 1.19 (0.81-1.74) among HBsAg positive participants (*p* for heterogeneity: total diabetes, 0.94). Among participants without previously diagnosed diabetes, the HRs per 1 mmol/L RPG were 1.08 (1.04-1.11) and 1.11 (1.05-1.17) among HBsAg negative and positive participants (*p* for heterogeneity 0.83). However, for diabetes duration, the number of HBsAg positive participants was too small to permit such an analysis.

8.1.2.6 Colon vs rectal cancer

For colon and rectal cancer, similar associations were observed for diabetes and RPG (**Figure 8.5** and **Tables 8.10-8.11**). Participants with diabetes had nonsignificant higher risks of colon and rectal cancer, with HRs of 1.17 (0.99-1.37) and 1.13 (0.95-1.33) (*p* for heterogeneity 0.92). Similar to colorectal cancer, there were positive associations for screen-detected diabetes and no associations for previously diagnosed diabetes (colon: 1.38 [1.12-1.71] vs 1.01 [0.82-1.25], *p* for heterogeneity 0.04; rectal: 1.44 [1.16-1.78] vs 0.88 [0.70-1.12], *p* for heterogeneity 0.002). Among participants without previously diagnosed diabetes, there were positive associations for RPG, with the HRs per 1 mmol/L RPG of 1.05 (1.01-1.09) for colon and 1.07 (1.03-1.11) for rectal cancer (*p* for heterogeneity 0.86).

Figure 8.5 Adjusted HRs for colorectal and liver cancer by RPG among individuals without previously diagnosed diabetes



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.
P value for heterogeneity: liver cancer by HBsAg, 0.83; colon vs rectal cancer, 0.85.

Table 8.9 Associations of diabetes and RPG with risk of liver cancer by HBsAg*

	HBV negative		HBV positive	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Diabetes status				
No diabetes	1822	Reference	631	Reference
Total diabetes	210	1.40 (1.21, 1.63)	68	1.46 (1.13, 1.89)
Diabetes status				
No diabetes	1822	1.00 (0.95, 1.06)	631	1.00 (0.91, 1.09)
Screen-detected	93	1.45 (1.18, 1.77)	40	1.73 (1.27, 2.37)
Previously diagnosed	117	1.37 (1.14, 1.65)	28	1.19 (0.81, 1.74)
RPG (mmol/L)				
<5.6	836	1.00 (0.93, 1.08)	297	1.00 (0.88, 1.13)
5.6 to <6.8	631	1.07 (0.99, 1.15)	199	1.15 (1.00, 1.32)
6.8 to <7.8	230	1.09 (0.96, 1.24)	101	1.56 (1.27, 1.90)
≥7.8	218	1.41 (1.23, 1.62)	74	1.46 (1.16, 1.85)
per 1 mmol/L†	*1915*	*1.08 (1.04, 1.11)*	*671*	*1.11 (1.05, 1.17)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).
† Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.
P for heterogeneity by HBsAg: total diabetes, 0.94; RPG, 0.83.

Table 8.10 Associations of diabetes and RPG with risks of colon and rectal cancer*

	Colon cancer		Rectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Diabetes status				
No diabetes	1570	Reference	1561	Reference
Total diabetes	175	1.17 (0.99, 1.37)	155	1.13 (0.95, 1.33)
Diabetes status				
No diabetes	1570	1.00 (0.94, 1.06)	1561	1.00 (0.94, 1.06)
Screen-detected	85	1.38 (1.12, 1.71)	85	1.44 (1.16, 1.78)
Previously diagnosed	90	1.01 (0.82, 1.25)	70	0.88 (0.70, 1.12)
RPG (mmol/L)				
<5.6	699	1.00 (0.92, 1.08)	683	1.00 (0.92, 1.08)
5.6 to <6.8	575	1.07 (0.99, 1.16)	562	1.11 (1.03, 1.21)
6.8 to <7.8	181	0.97 (0.84, 1.12)	208	1.21 (1.05, 1.39)
≥7.8	172	1.27 (1.09, 1.48)	161	1.27 (1.09, 1.49)
per 1 mmol/L†	*1627*	*1.05 (1.01, 1.09)*	*1614*	*1.07 (1.04, 1.11)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).
† Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.
P for heterogeneity for colon and rectal cancer: total diabetes, 0.92; RPG, 0.86.

Table 8.11 Associations of duration of diabetes with risks of colon and rectal cancer[*]

	Colon cancer		Rectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Incident diabetes	120	1.39 (1.10, 1.74)	98	1.29 (0.99, 1.63)
Diabetes[†]				
No diabetes	1504	1.00 (0.95, 1.06)	1518	1.00 (0.95, 1.06)
0 to <2 year	41	1.76 (1.23, 2.52)	30	1.39 (0.92, 2.09)
2 to <5 years	47	1.32 (0.98, 1.76)	31	1.00 (0.71, 1.41)
5 to <10 years	97	1.50 (1.23, 1.83)	84	1.37 (1.10, 1.70)
≥10 years	56	0.92 (0.71, 1.20)	53	0.96 (0.73, 1.26)
p for trend[§]		*0.91*		*0.80*
Diabetes[‡]				
No diabetes	1570	1.00 (0.95, 1.06)	1561	1.00 (0.95, 1.06)
0 to <2 year	11	1.89 (1.04, 3.41)	11	1.67 (0.90, 3.11)
2 to <5 years	26	0.83 (0.53, 1.30)	19	1.09 (0.74, 1.60)
5 to <10 years	82	1.31 (1.04, 1.65)	72	1.40 (1.12, 1.73)
≥10 years	56	0.95 (0.73, 1.25)	53	0.90 (0.69, 1.17)
p for trend[§]		*0.17*		*0.07*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Duration of diabetes was missing in 20 participants.
[†] For previously diagnosed diabetes and incident diabetes, duration was calculated as the time interval between age of diabetes diagnosis and age at risk. For screen-detected diabetes, duration was calculated as the time interval between age at baseline and age at risk.
[‡] Incident diabetes cases were not counted as exposed in the calculation of diabetes duration.
[§] *P* for trend was calculated among participants with diabetes.

8.1.3 Exclusion of early years of follow-up, smokers or drinkers

When excluding the first two or five years of follow-up, the positive associations of diabetes and RPG with all three cancers persisted (**Appendix 8.2**), suggesting that the positive associations were mainly not due to reverse causality (i.e. diabetes induced by cancer). For pancreatic cancer, the associations of diabetes were similar in all participants and when excluding the first five years (with and without exclusions of first five years: 1.67 [1.25-2.23] vs 1.62 [1.31-2.00]), while the association of RPG was somewhat stronger when excluding the first five years (with and without exclusions: 1.18 [1.11-1.26] vs 1.09 [1.04-1.15] per 1 mmol/L). For liver cancer, the association of diabetes was stronger when excluding the first five years (with and without exclusions: 1.73 [1.46-2.06] vs 1.43 [1.26-1.62]), while

the association of RPG was similar (with and without exclusions: 1.12 [1.07-1.17] vs 1.09 [1.06-1.21] per 1 mmol/L). For colorectal cancer, the associations of diabetes and RPG were similar in all participants and when excluding the first five years (with and without exclusions: diabetes: 1.19 [1.00-1.40] vs 1.16 [1.02-1.31], RPG: 1.07 [1.00-1.15] vs 1.06 [1.03-1.09] per 1 mmol/L).

Similar associations were observed for all three cancers when restricting the analysis to never regular smokers or never regular drinkers (**Appendix 8.3**). These suggested that the positive associations in the main model were not affected by residual confounding by smoking or alcohol drinking. For pancreatic cancer, the HRs for diabetes were 1.53 (1.16-2.01) in never regular smokers and 1.51 (1.19-1.93) in never regular drinkers, while the HRs per 1 mmol/L RPG were 1.11 (1.04-1.18) and 1.06 (1.00-1.13). For liver cancer, the HRs for diabetes were 1.44 (1.21-1.71) in never regular smokers and 1.38 (1.19-1.59) in never regular drinkers, while the HRs per 1 mmol/L RPG were 1.08 (1.04-1.13) and 1.07 (1.03-1.10). For colorectal cancer, the HRs for diabetes were 1.10 (0.93-1.29) in never regular smokers and 1.15 (1.00-1.33) in never regular drinkers, while the HRs per 1 mmol/L RPG were 1.04 (1.00-1.08) and 1.05 (1.02-1.09).

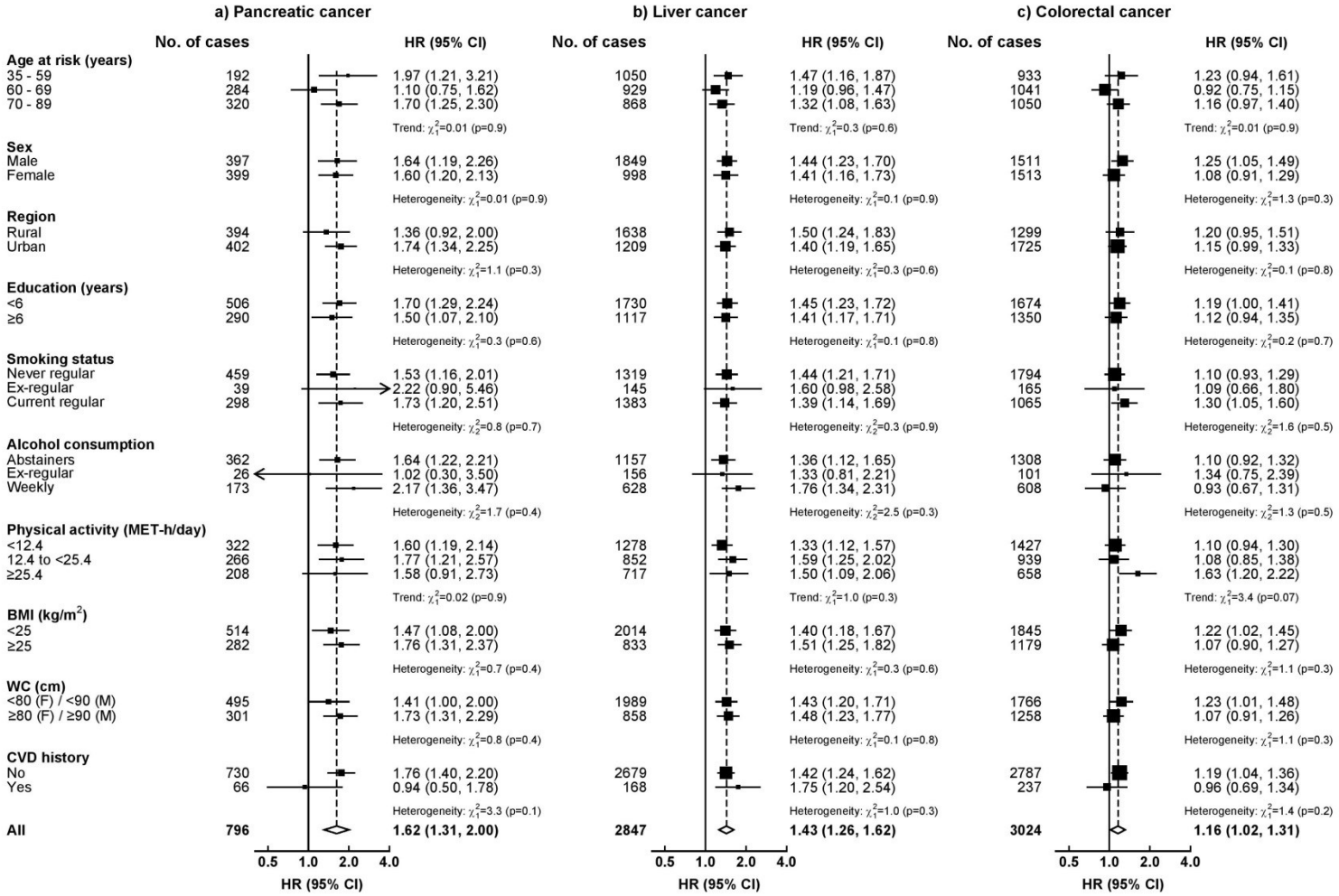
8.1.4 Subgroup analyses

There were no differences between men and women in the associations of diabetes and RPG with risks of all three cancers (*p* for heterogeneity 0.24-0.89, **Appendix 8.4**). However, the associations with colorectal cancer tended to be stronger in men. For diabetes, the HRs for colorectal cancer were 1.25 (1.05-1.49) in men and 1.08 (0.91-1.29) in women, and the HRs per 1 mmol/L RPG were 1.08 (1.04-1.12) and 1.04 (1.00-1.08). Similar associations by sex were observed for

pancreatic and liver cancer. For pancreatic cancer, the HRs for diabetes were 1.64 (1.19-2.26) in men and 1.60 (1.20-2.13) in women, while the HRs per 1 mmol/L RPG were 1.07 (0.99-1.16) and 1.11 (1.03-1.18). For liver cancer, the HRs for diabetes were 1.44 (1.23-1.70) in men and 1.41 (1.16-1.73) in women, and the HRs per 1 mmol/L RPG were 1.09 (1.05-1.13) and 1.08 (1.03-1.13).

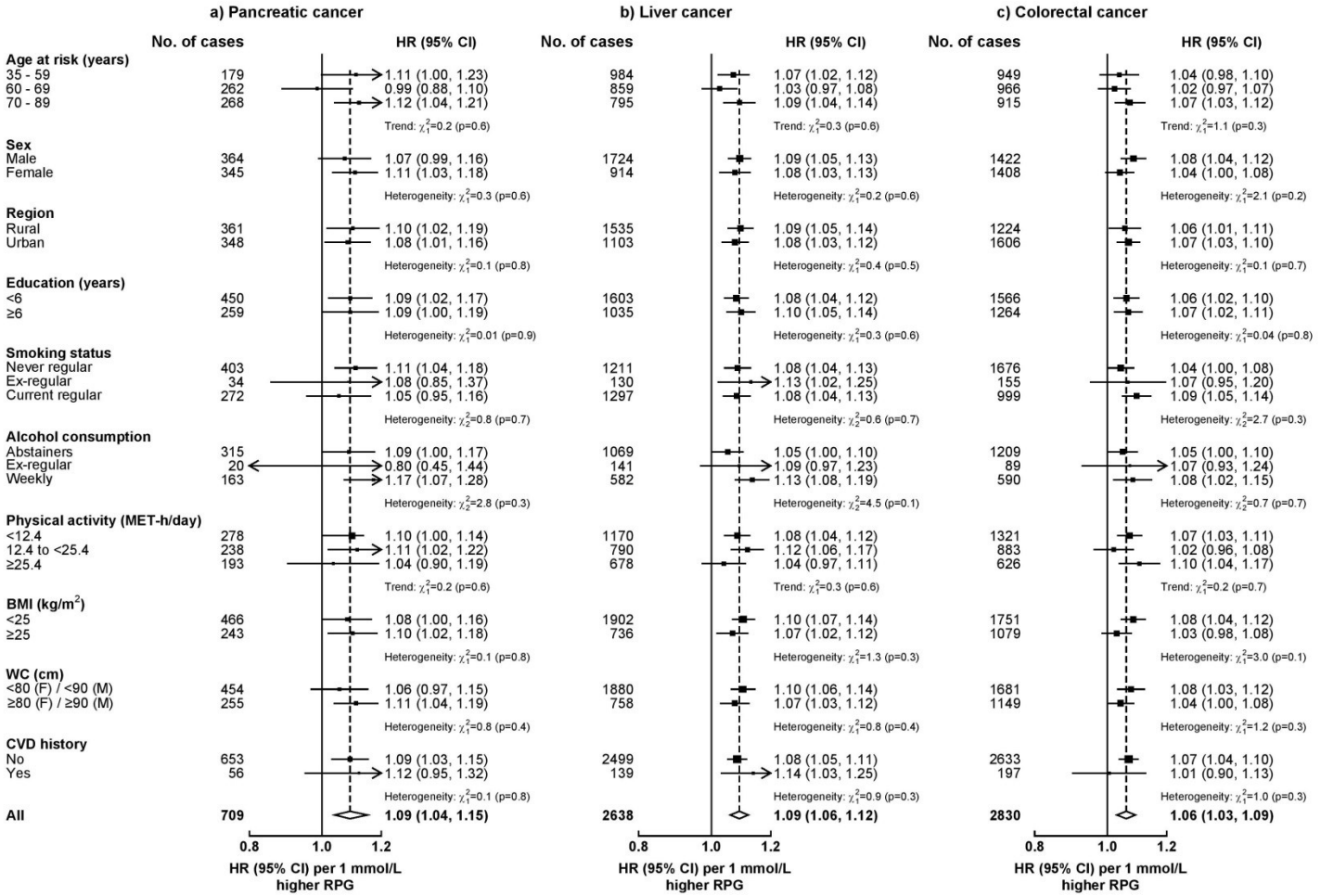
The associations of diabetes with risks of all three cancers were similar across population subgroups (**Figure 8.6**), although the magnitudes of associations tended to differ by alcohol drinking, physical activity, and adiposity for some cancers. When stratified by alcohol drinking, the association with liver cancer tended to be stronger in weekly drinkers (1.36 [1.12-1.65] for abstainers, 1.33 [0.81-2.21] for ex-regular, 1.76 [1.34-2.31] for weekly drinkers). When stratified by physical activity, the association with colorectal cancer was stronger among participants with high physical activity (1.10 [0.94-1.30] for <12.4 MET-h/day; 1.08 [0.85-1.38] for 12.4 to <25.4 MET-h/day; 1.63 [1.20-2.22] for ≥25.4 MET-h/day). When stratified by adiposity, the association with colorectal cancer was stronger in participants with low BMI (<25 kg/m^2) or low WC (<90 cm in men and <80 cm in women). For example, the HRs in those with low and high BMI were 1.22 (1.02-1.45) and 1.07 (0.90-1.27). Among participants without previously diagnosed diabetes, the patterns across population subgroups were similar to those of diabetes (**Figure 8.7**). For example, the association with liver cancer was stronger in weekly drinkers (1.05 [1.00-1.10] for abstainers, 1.09 [0.97-1.23] for ex-regular, 1.13 [1.08-1.19] for weekly drinkers). For adiposity, the association with colorectal cancer was stronger in participants with low BMI or WC (BMI <25 kg/m^2: 1.08 [1.04-1.12], BMI 25 kg/m^2: 1.03 [0.98-1.08]).

Figure 8.6 Adjusted HRs for specific GI cancers associated with diabetes by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Figure 8.7 Adjusted HRs for specific GI cancers associated with 1 mmol/L higher usual RPG among individuals without previously diagnosed diabetes by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.

8.1.5 Sensitivity analyses

8.1.5.1 Type 1 diabetes

At the baseline survey, participants reported whether they had a previous diagnosis of diabetes, but information on types of diabetes was not collected. These individuals were asked to provide additional information about age at first diagnosis and current use of certain medications for diabetes. In a sensitivity analysis, information on age at diagnosis and insulin use was used to differentiate between type 1 and type 2 diabetes. Of all 15,993 participants that had previously diagnosed diabetes, 35 reported age of diagnosis <30 and insulin use. These participants were considered to have type 1 diabetes (less than 1% of all cases). When excluding type 1 diabetes from the analysis, the associations of previously diagnosed diabetes with risks of all three cancers were similar to those from the main analysis. When including all previously diagnosed diabetes, the HRs were 1.71 (1.33-2.11), 1.35 (1.15-1.59), and 0.97 (0.83-1.15) for pancreatic, liver, and colorectal cancer; when excluding 35 cases of type 1 diabetes, the corresponding HRs were 1.72 (1.33-2.21), 1.35 (1.15-1.59), and 0.98 (0.83-1.15).

8.1.5.2 Additional adjustment for adiposity or physical activity

When additionally adjusting for adiposity (BMI, WC, and %BF), the associations of diabetes and RPG with risks of pancreatic and liver cancer did not change compared with the main model (**Appendix 8.5**). For colorectal cancer, the association of diabetes attenuated when additionally adjusting for BMI (1.13 [1.00-1.28]), WC (1.10 [0.97-1.25]), or % BF (1.14 [1.01-1.29]), but similar associations were observed for RPG (HR per 1 mmol/L: BMI 1.06 [1.03-1.09], WC 1.05 [1.02

-1.08], %BF 1.06 [1.03-1.09]). When additionally adjusting for physical activity and sedentary leisure time (**Appendix 8.6**), the associations of diabetes and RPG with risks of all three cancers were similar to those from the main model.

8.1.5.3 Additional adjustment for diet

Additional adjustment for dietary factors (fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables) had little impact on the associations of diabetes and RPG with risks of all three cancers (**Appendix 8.7**).

8.1.5.4 Exclusion of poor self-rated health or major chronic diseases

When excluding participants who reported poor self-rated health at baseline (**Appendix 8.8**), the associations of diabetes with risks of three cancers were similar to those in all participants. When excluding participants who had major chronic diseases at baseline (CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease, peptic ulcer, and kidney disease) (**Appendix 8.8**), the associations tended to be stronger than those in all participants, with HRs of 1.75 (1.35-2.27) for pancreatic, 1.52 (1.30-1.78) for liver, and 1.28 (1.10-1.48) for colorectal cancer. Among participants without previously diagnosed diabetes, similar associations of RPG with three cancers were observed when excluding those who reported poor self-rated death or those who had major chronic diseases at baseline (**Appendix 8.8**).

8.1.5.5 Cancer mortality

When examining the associations of diabetes and RPG with cancer mortality, similar associations were observed to those with incidence (**Appendix 8.9**). The

HRs for mortality were 1.59 (1.24-2.04) for pancreatic, 1.52 (1.32-1.76) for liver, and 1.18 (0.95-1.47) for colorectal cancer. Among participants without previously diagnosed diabetes, the HRs for mortality per 1 mmol/L RPG were 1.09 (1.04-1.15) for pancreatic, 1.09 (1.06-1.12) for liver, and 1.06 (1.03-1.09) for colorectal cancer.

8.2 Discussion

8.2.1 Summary of findings

In this Chinese population, individuals with diabetes had higher risks of pancreatic, liver, and colorectal cancer. The associations with pancreatic and liver cancer were similar for previously diagnosed and screen-detected diabetes, while there was no evidence of association of previously diagnosed diabetes with colorectal cancer. The associations of diabetes with all three cancers were strongest within two years following diabetes diagnosis and tended to decrease with longer duration of diabetes. For pancreatic and liver cancer, the excess risks remained elevated 10 years after diabetes diagnosis. For colorectal cancer, the excess risk tended to decrease with longer duration of diabetes and became nonsignificant 10 years after diabetes diagnosis. Among participants without previously diagnosed diabetes, there were positive associations of RPG with risks of all three cancers.

For all three cancers, the positive associations of diabetes and RPG persisted when excluding the first two or five years of follow-up, and when restricting the analyses to never regular smokers or never regular drinkers. When additionally adjusting for adiposity, the associations of diabetes and RPG with risks of pancreatic and liver cancer changed little, while the associations with colorectal cancer attenuated slightly. For liver cancer, the associations of diabetes and RPG did not differ by HBsAg status at baseline. For colorectal cancer, the associations of diabetes and RPG tended to be stronger in men than women, though nonsignificantly, but did not differ for colon and rectal cancer. The results for both diabetes and blood glucose are largely consistent with previous studies in Western and other East Asian populations.

8.2.2 Diabetes

8.2.2.1 Pancreatic cancer

The association of diabetes with risk of pancreatic cancer in CKB is consistent with previous meta-analyses of prospective cohort studies,[165,166] as well as a recent pooled analysis of the Asia Cohort Consortium.[169] The Asia Cohort Consortium involving 19 prospective cohort studies and 2433 pancreatic cancer deaths reported a 53% higher risk associated with previously diagnosed diabetes (RR 1.53 [1.32-1.77]).[169] Likewise, a meta-analysis of 18 prospective cohort studies with 13,072 cases reported a 52% higher risk associated with previously diagnosed diabetes (RR 1.52 [1.43-1.63]), with a stronger association in East Asia (1.99 [1.61-2.47]).[166] When excluding the first five or ten years of follow-up, the association attenuated but remain elevated (RR 1.34 [1.21-1.48] vs 1.34 [1.19-1.50]).[166] In CKB, the association changed little when excluding the first five years, which is consistent with the Asia Cohort Consortium.[169] In the meta-analysis, only six previous studies defined total diabetes using both previously diagnosed and screen-detected diabetes (i.e. fasting blood glucose [FBG] ≥7.0 mmol/L or post-load blood glucose ≥7.8 mmol/L), and the pooled RR associated with total diabetes was overall similar to that in CKB (1.82 vs 1.62 in CKB).[166] Only a European study (185 cases) assessed previously diagnosed and screen-detected diabetes (2h-postload glucose) separately.[391] Similar to CKB, this study reported a weaker association for screen-detected than previously diagnosed diabetes (screen-detected vs previously diagnosed: 1.67 [0.97-2.85] vs 2.34 [1.27-4.32]; CKB: 1.49 [1.10-2.04] vs 1.71 [1.33-2.21]). When comparing studies by BMI adjustment, studies with additional adjustment for BMI tended to yield a weaker

association (1.46 [1.36-1.56] vs 2.11 [1.81-2.45]).[166] However, not all previous studies presented simultaneously the risk estimates before and after adjustment for BMI. Therefore, it is difficult to assess whether the difference in risk estimates was due to difference in adjustment for BMI or other factors. In CKB, by contrast, additional adjustment for adiposity had little impact on the association, which may be due to the null association of adiposity with pancreatic cancer (more on this in Chapter 7). Previous meta-analyses did not report the associations by smoking or alcohol consumption. In CKB, similar associations were observed when restricting the analysis to never regular smokers or never regular drinkers. Similar to CKB, the Asia Cohort Consortium reported similar associations when restricting the analysis to never smokers (1.53 [1.32-1.77] in all vs 1.47 [1.17-1.84] in never smokers), whereas they reported a stronger association when restricting to nondrinkers (1.72 [1.36-2.17] in nondrinkers).[169]

8.2.2.2 Liver cancer

The association of diabetes with risk of liver cancer in CKB is broadly consistent with previous prospective studies in Western and other East Asian populations.[170,171] A meta-analysis of 19 prospective cohort studies and 27,116 liver cancer cases reported a positive association for diabetes (RR 2.16 [1.74-2.68] in men and 1.85 [1.40-2.44] in women), with a weaker association in Asian studies (1.69 [1.30-2.20] in men and 1.39 [1.12-1.73] in women).[171] The magnitude of the risk estimate in CKB was lower than the meta-analysis as well as three pooled analyses of prospective studies (i.e. the Emerging Risk Factors Collaboration, the Asia-Pacific Cohort Studies Collaboration, and the Asia Cohort Consortium, **Appendix 2.6**).[167-169] These pooled analyses used liver cancer mortality as the

endpoint, did not control for viral hepatitis, and two involved small numbers of cases (533 and 93 deaths vs 2021 deaths in CKB). For example, the Asia Cohort Consortium (19 prospective studies and 3752 liver cancer deaths) reported a HR of 2.05 (1.77-2.38) associated with previously diagnosed diabetes.[169] In CKB, the risk estimate for liver cancer incidence was generally comparable to those shown in prospective cohort studies in Korea (800 cases, HR=1.54)[392] and China (344 cases, HR=1.64),[393] as well as a large record linkage study in Taiwan (19,207 cases, HR=1.78),[394] where the prevalence of HBV was comparable to that in CKB.

Unlike previous studies, which reported similar associations when excluding the first five or 10 years of follow-up,[170,171] the associations in CKB became progressively stronger when excluding the first two or five years. When comparing studies that used different diabetes ascertainment, the meta-analysis reported similar associations for diabetes ascertained by self-report and by medical records.[171] At least seven previous studies ascertained diabetes using both self-report and screening.[171] Four of these studies were from East Asia and reported similar prevalence of HBV and proportion of screen-detected diabetes to CKB.[392,395-397] In these studies, the estimates for total diabetes were consistent with that in CKB. When comparing studies by BMI adjustment, studies with additional adjustment for BMI tended to yield weaker associations (adjustment for BMI: no 2.66 [1.95-3.62] in men and 2.41 [1.78-3.28] in women; yes 1.85 [1.56-2.19] in men and 1.47 [1.22-1.77] in women).[171] However, in CKB, a similar association was observed with additional adjustment for adiposity, possibly due to the null association of adiposity with liver cancer (more on this in Chapter 7). The meta-analysis did not report the associations by smoking or alcohol consumption. In CKB, similar associations were observed when restricting to never regular

smokers or never regular drinkers, which is consistent with the Asia Cohort Consortium (all: 2.05 [1.77-2.38], never smokers: 1.84 [1.48-2.30], nondrinkers: 1.82 [1.51-2.20]).[169]

In East Asia, HBV is the most important risk factor for liver cancer.[38] However, evidence has been inconsistent whether the association of diabetes differs by HBV infection status. Three previous prospective studies reported that the positive association was weaker in HBsAg positive than negative participants,[175,396,398] while three studies did not report any difference by HBsAg.[358,397,399] For example, a cohort in Taiwan including 111 cases reported a higher RR among seronegative (for both HBsAg and HCV) than HBsAg positive participants (RR: negative 5.4 [1.7-17.1], positive 1.3 [0.3-5.6]).[396] Likewise, a nested case-control study in the Singapore Chinese Health Study involving 499 cases reported a RR of 5.2 among seronegative participants (for both HBsAg and HCV) and 1.3 among HBsAg positive participants (RR 5.2 [2.1-12.7] vs 1.3 [0.3-3.4]).[175] In contrast, three prospective cohort studies in Taiwan reported similar associations in HBsAg negative and positive participants.[358,397,399] However, each of these studies included less than 500 cases, so the power to detect any difference was limited. The current study involved >2500 liver cancer cases and showed little difference in risk estimates by HBsAg status. However, the sensitivity of the HBsAg test in CKB was relatively low and participants may have developed HBV infection during follow-up, which may have affected the risk estimate (more on this in Chapter 9).

The interactions of diabetes with alcohol and obesity in relation to liver cancer risk may explain the stronger association in Western countries than East Asia. Although the majority of previous studies in Western countries included small

numbers of liver cancer cases (<300) and were not powered to examine the association by subgroup, two prospective studies showed that the association was stronger in alcohol drinkers and individuals with high BMI.[147,400] The Liver Cancer Pooling Project including 14 prospective cohort studies in the US and 2162 incident liver cancer cases reported a HR of 2.61 (2.34-2.91) associated with diabetes.[147] When stratified by baseline BMI, there were stronger associations among overweight (25-<30 kg/m^2: 3.31 [2.77-3.95]) and obese participants (≥30 kg/m^2: 4.28 [3.59-5.10]) than those with normal BMI (18.5-<25 kg/m^2: 2.93 [2.28-3.77]). The Multi-Ethnic Cohort in the US involving 168,679 participants and 470 incident liver cancer cases reported two- to three-fold higher risk associated with diabetes across racial/ethnic groups.[400] When stratified by alcohol intake, the associations tended to be stronger among drinkers than nondrinkers. The HRs were 3.25 (1.92-5.51), 2.91 (2.00-4.22), and 2.35 (1.78-3.13) among those who had ≥2, <2 drinks/day, and nondrinkers. Compared with Western countries, the mean BMI is much lower in East Asia (23-24 kg/m^2 in China vs 26-28 kg/m^2 in North America or Europe), and a smaller proportion of individuals are obese (4% in China vs 20-35% in North America or Europe).[79] In Western countries, a larger proportion of liver cancer is attributed to alcohol drinking than in East Asia (4% in China vs 20-30% in North America or Europe).[38] Therefore, differences in adiposity and the aetiology of liver cancer may explain the weaker association for diabetes in CKB.

8.2.2.3 Colorectal cancer

The association of diabetes with risk of colorectal cancer is consistent with previous prospective studies in Western and other East Asian populations.[172,173]

However, the magnitude of association in CKB is somewhat lower than previous studies. A meta-analysis of 22 prospective cohort studies (56,804 cases) reported a 25% higher risk (RR 1.25 [1.18-1.32]) and a similar association in Asian studies (1.23 [1.04-1.47]).[173] When examining the association by sex and anatomical site, the meta-analysis showed similar associations in men and women and for colon and rectal cancer (by sex: 1.25 [1.17-1.33] in men, 1.23 [1.13-1.33] in women; by anatomical site: 1.26 [1.17-1.35] for colon cancer, 1.24 [1.14-1.36] for rectal cancer).[173] The Asian Cohort Consortium involving 19 prospective cohort studies and 4194 colorectal cancer deaths reported a RR of 1.41 (1.26-1.57) associated with previously diagnosed diabetes, which is comparable to a meta-analysis of seven prospective cohort studies (HR for colorectal cancer death: 1.25 [1.08-1.44]; ~2300 deaths).[169] The same report showed similar associations by sex (1.42 [1.22-1.65] in men, 1.45 [1.22-1.72] in women) and a stronger association for colon than rectal cancer (1.50 [1.30-1.73] for colon, 1.30 [1.07-1.58] for rectal cancer).[169] In the meta-analysis, adjustment for BMI attenuated slightly the association (RR 1.22 [1.15-1.28] and 1.25 [1.08-1.44] in models with and without additional adjustment for BMI), consistent with the findings in CKB. When restricting the analysis to never regular smokers or never regular drinkers, the positive associations in CKB changed little, which is consistent with the Asia Cohort Consortium (all: 1.41 [1.26-1.57], never smokers: 1.49 [1.27-1.74], non-drinkers: 1.45 [1.19-1.76]).[169]

Although the magnitude of the risk estimate in CKB was lower than the meta-analysis and the Asia Cohort Consortium,[169] the estimate was comparable to two large prospective studies in Korea. [369,392] Like CKB, these two studies included both previously diagnosed and screen-detected diabetes defined by FBG and had

a similar proportion of screen-detected diabetes to CKB.[369,392] The Korea Cancer Prevention Study included 637 cases and reported HRs of 1.11 in men and 1.17 in women (1.11 [1.01-1.24] vs 1.17 [0.98-1.40]),[392] while another cohort study in Korea involving 5108 cases reported HRs of 1.14 in men and 1.06 in women (1.14 [1.02-1.27] vs 1.06 [0.91-1.22]).[369]

There are several possible explanations for the weaker association of diabetes with colorectal cancer in CKB, particularly when compared with studies in Western populations. First, the weaker association may be explained by the larger proportion of distal colon cancer. In CKB, although only 26% of colon cancer cases had been adjudicated, the proportion of distal colon cancer was 55%, higher than the 30-40% in the US and Europe.[53] A meta-analysis involving five prospective studies with >6000 colorectal cancer cases reported that the positive association was weaker with distal than proximal colon cancer (1.29 [1.17-1.43] vs 1.56 [1.35-1.79]).[173] After publication of this meta-analysis, three previous studies also showed a weaker association of diabetes with distal colon cancer.[176,401,402] For example, the Netherlands Cohort Study reported that the HRs in men were 1.13 (0.76-1.68) for proximal and 0.77 (0.49-1.21) for distal colon cancer, while the corresponding HRs in women were 1.44 (1.05-1.99) and 0.75 (0.44-1.27).[176] Second, the null association for previously diagnosed diabetes in CKB might reflect diabetes treatment. In CKB, the association for treated diabetes was weaker than untreated diabetes (0.96 [0.78-1.18] vs 1.32 [1.14-1.52]).

8.2.3 Duration of diabetes

At least 20 prospective cohort studies have assessed the associations of duration of diabetes with risks of pancreatic, liver, and colorectal cancer.[166,170,173] However,

these studies used different approaches, including exclusion of early periods of follow-up, examination of cancer risk by diabetes duration since study enrolment, and a time-dependent approach to account for diabetes duration.[166,170,173] Four prospective cohort studies have examined the association using a time-dependent approach (**Figure 2.13** in Chapter 2).[178-181] Although these studies varied in study design, numbers of cancer cases, duration of follow-up, and categorisation of duration, they tended to show a three- to ten-fold higher risk within the first two years following diabetes diagnosis,[178-181] consistent with the estimates in CKB. Like CKB, these studies also reported that the excess risks decreased with longer duration of diabetes but remained elevated ~10 years after diabetes diagnosis (except for colorectal cancer). For example, a prospective cohort study in the US including 489 colorectal cancer cases reported a decreasing trend in colorectal cancer risk with longer duration of diabetes, with HRs of 2.36 (0.96-5.79), 1.71 (0.63-4.61), and 1.01 (0.48-2.13) for 4-8, 8-12, and ≥12 years of diabetes.[403]

The elevated risk of cancer in the first few years following diabetes diagnosis might be explained by reverse causality and surveillance bias. It is possible that the high risks of pancreatic and liver cancer among individuals with a shorter duration of diabetes might be due to reverse causality (i.e. diabetes induced by preclinical pancreatic cancer or liver diseases).[259,260] Both laboratory and epidemiological evidence have supported that new-onset diabetes might be a manifestation rather than an aetiological factor for pancreatic cancer.[259] Indeed, pancreatic cancer induces diabetes in about 30% of patients.[404,405] Chari et al. found a marked and continuous increase in the prevalence of diabetes in pancreatic cancer patients up to 36 months before the diagnosis.[404] It is hypothesised that diabetes induced by pancreatic cancer might be a

paraneoplastic phenomenon caused by the cancer through dysfunction of β cells.[406] For liver cancer, reverse causality may be due to the bidirectional association of diabetes with NAFLD and the strong association of NAFLD with liver cancer.[260] Diabetes is a risk factor for NAFLD in both Western countries and East Asia as well as in CKB,[260,407] while NAFLD is the hepatic manifestation of the metabolic syndrome and predicts type 2 diabetes after adjusting for obesity.[199] NAFLD can increase the amount of insulin needed to keep hepatic glucose production in the nondiabetic range.[408,409] In individuals with hepatic insulin resistance, β cells cannot sustain insulin secretion, leading to β-cell failure and type 2 diabetes.[408,409] On the other hand, surveillance bias occurs as patients with newly diagnosed diabetes are under increased medical surveillance and thus might be more likely to be diagnosed with cancer or vice versa.[179,181] Indeed, a Danish prospective cohort study reported an almost 30-fold higher risk of pancreatic cancer following three months after diabetes diagnosis, which decreased with longer duration since diabetes diagnosis.[181]

Furthermore, the inverse trend between diabetes duration and cancer risk might reflect a switch from initial hyperinsulinaemia to subsequent hypoinsulinaemia and improved glycaemic control over the course of diabetes. In the natural history of type 2 diabetes, there is a dynamic interaction between insulin sensitivity and insulin secretion.[410,411] Hyperinsulinaemia occurs in the early stage of type 2 diabetes.[410,411] Compared with nondiabetic and nonobese individuals, patients with early stage diabetes have been shown to have elevated levels of plasma insulin.[412] Following an initial increase in plasma insulin, insulin levels are decreasing in diabetic patients.[412] Over the course of diabetes, hyperfunction of β cells may exhaust themselves leading to β cell dysfunction.[412,413] As a result, there

might be a shift from hyperinsulinaemia to hypoinsulinaemia.[413,414]

8.2.4 Diabetes medications

Although several prospective cohort studies have reported that metformin use is associated with a lower risk of colorectal cancer among diabetic patients, these studies may have time-related bias (i.e. immortal time bias and time-window bias).[415] Immortal time bias occurs when the analysis of a time-fixed cohort misclassifies unexposed time as exposed, while time-window bias occurs when the time windows for exposure opportunity are different between individuals.[416] For example, immortal time bias occurs when a patient was on sulfonylureas at the start of follow-up and switched to metformin during follow-up, but was classified as metformin exposed during entire follow-up. Immortal time refers to the period between the sulfonylurea prescription and the first metformin prescription, during which the individual must survive to receive the metformin prescription (i.e. “immortal”). Because of misclassification of exposure, immortal time bias tends to exaggerate the protective effect of a drug when it may have no effect.[415] Time-window bias occurs when controls were not matched to cases on duration of follow-up in the design of nested case-control study.[417] As a result, controls may have had a shorter or longer duration of follow-up than cases and therefore a lower or higher opportunity to receive additional medications, therefore biasing the association in either direction.[417,418] In addition, risk estimates from observational studies are subject to confounding by indication as individuals on different medications may have different prognoses. Metformin is frequently prescribed to patients with fair glycaemic control, whereas insulin tends to be prescribed to patients with a more advanced disease and worse glycaemic

control.[262,419] In contrast to findings of observational studies, RCTs have shown that diabetes patients taking metformin had a similar risk of developing cancer compared with those taking other first-line therapies (e.g. sulfonylureas).[420] A recent meta-analysis of 41 observational studies (1,029,389 patients) reported that diabetes patients on metformin had lower risks of all cancer (OR 0.73 [0.61-0.88]; 18 studies, 561,836 patients), pancreatic (0.56 [0.36-0.86]; 9 studies, 847,248 patients), liver (0.34 [0.19-0.60]; 8 studies, 312,742 patients), and colorectal cancer (0.83 [0.74-0.92]; 12 studies, 871,365 patients).[420] However, there were no associations in RCTs. The ORs were 0.93 (0.07-13.14) for pancreatic (2 RCTs, 6575 patients) and 1.02 (0.41-2.5) for colorectal cancer (2 RCTs, 6575 patients).[420] However, these were based on *post hoc* analyses of RCTs and may not be sufficiently powered to examine the associations with cancer outcomes due to the very few events reported.

To overcome limitations in observational studies, recent analyses of the UK Clinical Practice Research Datalink adopted an "intention-to-treat" approach and compared users of metformin and sulfonylurea or other first-line oral hypoglycaemic agents.[421] Participants with type 2 diabetes who started taking metformin and other oral anti-diabetes medications within one year of diagnosis were considered initiators and were followed-up for incident cancer. At baseline, participants were categorised into mutually exclusive groups according to monotherapy of medications (e.g. metformin, sulfonylureas, thiazolidinediones, other oral hypoglycaemic agents, insulin) and any subsequent changes in medications were not taken into account. After five years of follow-up, the study showed that initiators of metformin had similar risks of total cancer and colorectal cancer compared with initiators of sulfonylurea.[421]

Both *in vitro* and *in vivo* studies have suggested that metformin might inhibit growth of cancer cells and lower cancer risk, including pancreatic and colorectal cancer.[422] Metformin can systematically reduce levels of circulating insulin and IGF-I by improving insulin sensitivity and promoting weight loss.[423,424] Metformin may also directly inhibit growth of cancer cells, potentially through partial inhibition of oxidative phosphorylation.[423,424] Although the anti-neoplastic activity of metformin has only been demonstrated in experimental studies, there have been more than 100 RCTs of metformin for a range of indications, particularly in oncology.[262-264] Results from two RCTs have been reported, as well as a pilot study with biomarker endpoints.[425] The NCIC Clinical Trials Group (NCIC CTG) MA.32 is a randomised, placebo controlled adjuvant trial that investigates the effect of metformin vs placebo on invasive cancer-free survival in early breast cancer, as well as weight and metabolic factors.[425] At six months, significant decreases in weight and biomarkers were observed in the metformin arm compared with the placebo (p=0.03), including homeostasis model assessment (HOMA), plasma glucose, insulin, leptin, and CRP.[425] Another double-blind, randomised, placebo-controlled phase 2 trial assessed the efficacy of the addition of metformin to a standard systemic therapy in patients with advanced pancreatic cancer with a survival endpoint.[426] This trial was complete in January 2014 and showed no difference in overall survival between groups (gemcitabine and erlotinib with either placebo or metformin). Likewise, another open-label, randomised phase II trial also showed that addition of metformin to standard systemic therapy (i.e. cisplatin, epirubicin, capecitabine, and gemcitabine) did not improve survival in patients with metastatic pancreatic cancer.[427]

For insulin, prospective cohort studies and case-control studies have reported

higher risk of cancer among participants receiving exogenous insulin treatment.[262-264] However, the positive association may reflect the severity of diabetes and poor glycaemic control among participants on insulin treatment as insulin tends to be prescribed to patients with a more advanced disease.[262-264] Although there was a strong positive association between insulin use and cancer risk shortly following insulin initiation, excess risks were not observed with longer duration of insulin use.[419] For example, a pooled analysis of 15 case-control studies in the International Pancreatic Cancer Case-Control Consortium (8305 cases and 13,987 controls) reported an OR of 5.60 (3.75-8.35) for diabetes patients with <5 years of insulin use compared with those who did not use insulin.[419] The elevated risk decreased with longer duration of insulin use, with ORs of 1.87 (1.08-3.23) and 1.66 (0.90-3.06) for 5 to <10 and 10 to <15 years. For diabetes patients with ≥15 years of insulin use, the association became null (0.95 [0.53-1.70]).[419] The excess risk for a shorter duration of insulin use might suggest reverse causality, where the excess risk may be due to worsening of diabetes shortly after a diagnosis pancreatic cancer.

8.2.5 Type 1 diabetes

The majority of prospective studies on diabetes and cancer risk did not distinguish between type 1 and type 2 diabetes.[165,166,170,173] Type 1 diabetes accounts for 7-12% of all diabetes cases in high-income countries.[92] Although there are no national data on prevalence of type 1 diabetes in China, the incidence rate of type 1 diabetes in China is much lower than high-income countries.[103] While hyperglyceamia is similar between type 1 and type 2 diabetes, insulin resistance and hyperinsulineamia are more prominent in type 2 than type 1 diabetes.[89,428] It

is hypothesised that hyperinsulineamia might be an underlying biological link between diabetes and cancer.[161,204] If such a hypothesis is valid and it is the only mechanism linking diabetes and cancer, then one would anticipate that type 1 diabetes is not or weakly associated with cancer risk. Therefore, the inclusion of type 1 diabetes would have diluted the observed association between diabetes and cancer. Nonetheless, previous prospective studies have shown similar associations of type 1 and type 2 diabetes with cancer risk.[102,180]

A recent record linkage study in Austria showed similar associations of type 1 and type 2 diabetes with risks of pancreatic, liver, and colorectal cancer.[180] The standardised incidence ratios (SIRs) for type 1 diabetes were 2.48 (1.95-3.15) for pancreatic, 2.76 (2.11-3.62) for liver, and 1.21 (1.06-1.37) for colorectal cancer, while the corresponding SIRs for type 2 diabetes was 2.37 (2.29-2.45), 2.96 (2.84-3.09), and 1.18 (1.15-2.20). Similarly, a meta-analysis of three prospective cohort and six case-control studies reported a two-fold higher risk of pancreatic cancer associated with type 1 diabetes (RR 2.00 [1.37-3.01]).[102] However, the association of type 1 diabetes with cancer risk may be complicated by the use of exogeneous insulin.[89,428] Taking into account the interactions between hyperinsulinaemia, diabetes treatment, and cancer, the association of type 1 diabetes with cancer risk in observational studies should be cautiously interpreted.

8.2.6 Plasma glucose

Previous prospective studies have reported a positive association of blood glucose with risk of pancreatic cancer.[166,182] A recent meta-analysis including nine prospective studies and 2408 pancreatic cancer cases reported an 8% higher risk per 1 mmol/L higher fasting blood glucose (RR 1.08 [1.03-1.12]), with a similar

association when excluding diabetes (1.08 [1.03-1.14]).[182] Consistent with this meta-analysis, an updated meta-analysis with 2166 cases showed that each 1 mmol/L higher blood glucose was associated with a 13% higher risk among individuals without previously diagnosed diabetes (RR 1.13 [1.08-1.19]), with little statistical heterogeneity in risk estimates by different blood glucose measures (RPG, FPG, or 2h-postload glucose).[166] Similar to this meta-analysis, the present study showed that the positive association did not differ between RPG and FPG. Of all previous studies, the Me-Can assessed the association of RPG with pancreatic cancer with further adjustment for BMI and stratification by smoking status.[183] Consistent with the findings in CKB, a similar association was observed to the main model when additionally adjusting for adiposity or restricting the analysis to never smokers.[183]

For liver cancer, at least 10 prospective cohort studies have reported on the association of blood glucose.[184] These studies have shown a positive association between blood glucose and liver cancer, regardless of how it was measured (RPG or FPG).[184] A meta-analysis of eight prospective studies and 1861 cases reported a pooled RR of 1.06 (1.03-1.09) per 1 mmol/L higher FPG.[184] The Me-Can included 266 cases and reported a positive association for RPG (HR per 0.5 mmol/L: 2.38 [1.76-3.14]).[186] In the Me-Can project, the association changed little when further adjusting for BMI,[186] consistent with the finding in CKB. A recent cohort study of 109,169 male workers in China reported a positive association between FPG and liver cancer, with a HR of 1.06 (1.04-1.08) per 1 mmol/L.[185] That study suggested that the association tended to be stronger among HBsAg negative participants,[185] while the association differed little by HBsAg in CKB. Another prospective cohort study reported a positive association of FPG with liver

cancer (138 cases) among participants without previously diagnosed diabetes.[379] The association for FPG was stronger than the estimate in CKB (HR per 1 mmol/L FPG: 1.89 [1.27-2.83] vs 1.11 [0.99-1.24] in CKB), so was the association of previously diagnosed diabetes (2.48 [1.20-5.12] vs 1.35 [1.15-1.59] in CKB).[379]

For colorectal cancer, a meta-analysis of six prospective cohort studies (62,814 cases) reported a pooled RR of 1.02 (1.01-1.02) per 1 mmol/L higher FPG.[187] Similar RRs by sex and by anatomical site were observed, with RRs of 1.02 (1.01-1.02) in men, 1.01 (0.99-1.03) in women, 1.04 (1.01-1.07) for colon cancer, and 1.03 (0. 16-6.82) for rectal cancer.[187] In CKB, the estimate for FPG was stronger than the meta-analysis (1.17 [1.07-1.28] vs 1.02 [1.01-1.02]). In the present study, there was also a positive association for RPG, although the positive association was weaker than FPG possibly due to measurement error (1.06 [1.03-1.09] vs 1.17 [1.07-1.28]).

Taken together, the findings in CKB suggest that the positive associations between blood glucose and risks of pancreatic, liver, and colorectal cancer extend down to below the diabetic and prediabetic range. As both RPG and FPG are positively associated with risks of these three cancers, RPG may be a more practical and relevant measure than FPG as people spend most of the time in a nonfasting state.

8.2.7 Mechanisms

Hyperglycaemia, insulin resistance, and hyperinsulinaemia have been hypothesised as the underlying mechanisms linking diabetes and cancer.

8.2.7.1 Hyperglycaemia

The Warburg effect is a hypothesis to explain the role of hyperglycaemia in the development of cancer.[233,429] Briefly, the Warburg effect is the phenomenon in which the majority of cancer cells produce energy through aerobic glycolysis, rather than oxidative phosphorylation.[429] Although aerobic glycolysis is an inefficient way to generate adenosine 5'-triphosphate, it may enable proliferation by generating additional metabolites needed to sustain cell proliferation.[233] As a result, there is a significant increase in the use of glucose for fuel by the cancer cells.[233,430] Consistent with this hypothesis, previous prospective cohort studies have shown positive associations of plasma glucose with risk of cancer, including pancreatic, liver, and colorectal cancer.[166,182,184,187,431] However, hyperglycaemia may serve as a surrogate for other potential causative factors such as hyperinsulinaemia.

8.2.7.2 Insulin resistance and hyperinsulinaemia

Insulin has direct growth promoting and mitogenic effects on cancer cells, via insulin receptors.[204,234] Insulin is not only a hormone that regulates the metabolism of carbohydrates, lipids, and proteins, but also an important growth factor that has mitogenic effects by promoting cell proliferation and migration and inhibiting apoptosis.[432] In the presence of insulin resistance, insulin modulates the mitogenic responsiveness of cells and tissues to other growth factors through activation of farnesyltransferase,[410,432] which is a critical step in the pathophysiology of cancer.[163,433]

Insulin also indirectly impacts pancreatic carcinogenesis by increasing bioavailability of IGF.[205] IGF-I bioactivity is regulated in part by its six binding proteins (i.e. IGFBP-1 to IGFBP-6).[163,205] Insulin can inhibit hepatic production of

IGFBP-1 and IGFBP-2, leading to increasing levels of unbound, biologically active IGF-I.[163,205] Insulin may also increase ratio of circulating IGF-I/IGFBP-3 by increasing the sensitivity of hepatic growth hormone.[205] Experimental studies have demonstrated that IGF-I has both mitogenic and antiapoptotic effects on tumour cells, including colorectal cancer.[205,206] Prospective studies have shown a positive association of IGF-I and null associations of IGFBP-1 and IGFBP-3 with colorectal cancer, while prospective studies have reported null associations of IGF-I, IGFBP1, and IGFBP3 with pancreatic cancer.[206]

To approximate insulin resistance in large numbers of participants, epidemiological studies have assessed HOMA, plasma C-peptide, and fasting insulin.[149,189,190,239,378,379,434-436] The majority of previous prospective studies have reported no associations of HOMA and plasma C-peptide with risks of pancreatic, liver, and colorectal cancer,[239,378,434-436] which may be partially due to measurement error, whereas several prospective studies have shown positive associations of fasting insulin with risks of pancreatic,[189,190] liver,[379] and colorectal cancer.[149]

8.2.7.3 Insights from Mendelian randomisation

The limitations of observational epidemiological studies are the inability to fully account for reverse causality and residual confounding. In the case of diabetes and cancer risk, the positive association may be explained by reverse causality (i.e. diabetes as an early manifestation of cancer rather than being a causal factor).[259,260] More importantly, it has been suggested that insulin may act as a confounder for the observed association between diabetes and cancer due to the occurrence of hyperinsulinaemia in the early stage type 2 diabetes.[414] In this

context, a recent Mendelian randomisation study showed no evidence of a causal relationship between type 2 diabetes and pancreatic cancer, while genetically increased fasting insulin was causally associated with pancreatic cancer (OR 1.66 [1.05-2.63], per SD [44.4 pmol/L]).[161]

8.2.7.4 Specific mechanisms for liver cancer

Insulin resistance leads to increased release of multiple proinflammatory cytokines (e.g. TNF-α, IL-6, and leptin),[409,437] which may be associated with higher risk of liver cancer.[38,438] In addition, diabetes and insulin resistance are risk factors for NAFLD,[260] which is an important risk factor for liver cancer.[38,199] *De novo* lipogenesis produces saturated fatty acids from excess sugars, the relative proportion of which increases in the liver in direct proportion to liver fat.[439] Saturated fatty acids produced by *de novo* lipogenesis might cause increased lipotoxic injury.[439] Moreover, insulin resistance and the subsequent inflammatory cascade might contribute to progression of NAFLD to cirrhosis and liver cancer.[440,441]

8.3 Conclusions

Both CKB and previous studies have shown that diabetes is associated with higher risks of pancreatic, liver, and colorectal cancer. For duration of diabetes, the associations with these three cancers were strongest within two years following diabetes diagnosis and tended to decrease with longer duration of diabetes. The excess risks remained elevated 10 years after diabetes diagnosis for pancreatic and liver cancer, while for colorectal cancer the excess risk became nonsignificant 10 years after diabetes diagnosis. Among participants without

diabetes, there were positive associations of blood glucose with all three cancers. For both diabetes and blood glucose, similar associations were observed for liver cancer among HBsAg negative and positive participants as well as for colon and rectal cancer.

Chapter 9 General discussion

The objectives of this chapter are to summarise findings in previous chapters, to discuss consistency of the study findings with previous studies, and to describe strengths and limitations, future directions, and implications of the study findings. This chapter also describes preliminary analyses of associations between BMI and proteomics in a case-subcohort study to explore possible mechanisms linking adiposity and cancer risk.

9.1 Summary of findings

9.1.1 Cancer incidence and mortality

In this Chinese population, the incidence rates of pancreatic, liver, and colorectal cancer increased with age, with similar patterns by sex and by region. The incidence rates of all three cancers were higher in men than women. The incidence rates of pancreatic and colorectal cancer were higher in urban than rural areas, while the converse was true for liver cancer. In both urban and rural areas, individuals with higher education had lower incidence rates of all three cancers. Similarly, individuals with higher household income had lower incidence rates of liver cancer, while no patterns were identified for pancreatic and colorectal cancer. For mortality rates, the patterns by age, sex, region, education, and household income were similar to those for incidence rates. During 10 years of follow-up, over 70% of cancer patients died of pancreatic and liver cancer, while ~30% of patients died of colorectal cancer, with median survival of 4 months for pancreatic cancer, 3.7 months for liver cancer, and 13 months for colorectal cancer. For liver and colorectal cancer, the mortality-to-incidence ratio (MIR) was lower in urban

than rural areas, possibly reflecting the urban-rural differences in cancer care (i.e. screening, diagnosis, and treatment).

9.1.2 Associations of PA and SLT with specific GI cancers

In CKB, total PA was inversely associated with risks of liver and colorectal cancer but showed little association with pancreatic cancer. SLT was positively associated with risk of colorectal cancer but not associated with pancreatic and liver cancer. For liver cancer, the associations of PA and SLT were not modified by HBsAg status, but there was no clear association of total PA among HBsAg positive participants. For colorectal cancer, the associations of PA and SLT did not differ for colon and rectal cancer, although the inverse association of total PA was nonstatistically stronger for colon cancer. Similar associations were observed of PA and SLT with risks of these cancers when excluding the first two or five years of follow-up.

9.1.3 Associations of adiposity with specific GI cancers

In this relatively lean Chinese population, BMI was not associated with risk of pancreatic cancer, inversely associated with liver cancer, and positively associated with colorectal cancer. After excluding the first five years of follow-up, the inverse association of BMI with liver cancer risk attenuated towards the null and became nonsignificant, while the positive association with colorectal cancer became stronger. For pancreatic cancer, however, the null association for BMI persisted when excluding the first five years. For most other measures of general adiposity (e.g. %BF, height-adjusted fat mass, and height-adjusted weight), the associations were similar to those for BMI, whereas height-adjusted lean mass

showed positive associations with all three cancers. For central adiposity, WC was not associated with risks of pancreatic and liver cancer and positively associated with colorectal cancer. After excluding the first five years, there was a positive association of WC with liver cancer risk, while the positive association with colorectal cancer became somewhat stronger. For pancreatic cancer, however, the null association with WC was unaltered when excluding the first five years. For WHR, HC, and WHtR, the associations with risks of these cancers were similar to those for WC. For BMI25, there were positive associations for pancreatic and liver cancer and a positive trend for colorectal cancer.

HBsAg status tended to modify, though nonsignificantly, the associations of adiposity with liver cancer risk. Among HBsAg negative participants, there were generally positive associations of central adiposity with liver cancer risk, particularly when excluding the first five years of follow-up. Among HBsAg positive participants, by contrast, there was no evidence of associations of general and central adiposity with liver cancer risk. For colorectal cancer, the sex-specific associations differed for general and central adiposity. For general adiposity, the associations with colon and rectal cancer were stronger in men than women, but heterogeneity tests showed that the differences were nonsignificant. For central adiposity, the associations for colon and rectal cancer were significantly stronger in men than women. When comparing colon and rectal cancer, the associations of adiposity were nonsignificantly stronger with colon than rectal cancer.

When comparing the associations across these adiposity traits, height-adjusted lean mass, WC, and WHR showed the strongest associations with risk of liver

cancer, while WC and WHtR showed the strongest associations with colorectal cancer. For pancreatic cancer, BMI25 showed the strongest association.

9.1.4 Associations of diabetes and RPG with specific GI cancers

In this Chinese population, individuals with diabetes had higher risks of pancreatic, liver, and colorectal cancer. The associations with pancreatic and liver cancer were similar for previously diagnosed and screen-detected diabetes, while there was no evidence of association of previously diagnosed diabetes with colorectal cancer. The associations of diabetes with risks of three cancers were strongest within two years following diabetes diagnosis and tended to decrease with longer duration. Ten years after diabetes diagnosis, the excess risks remained elevated for pancreatic and liver cancer, while the excess risk became nonsignificant for colorectal cancer. Among participants without previously diagnosed diabetes, there were positive associations of RPG with risks of all three cancers. For liver cancer, similar associations of diabetes and RPG were observed in participants tested HBsAg positive and negative at baseline. For colorectal cancer, the associations with diabetes and RPG tended to be stronger in men than women, though nonsignificantly, but did not differ for colon and rectal cancer. For all three cancers, similar results were observed when excluding the first two or five years of follow-up.

9.2 Consistency of CKB findings with literatures

9.2.1 Cancer incidence and mortality

Compared with national estimates, the incidence rates for these three cancers were higher in CKB. This is possibly because incident cancer cases in CKB were

ascertained through multiple sources, particularly linkages to the health insurance system, rather than just cancer registries. Similar patterns of cancer rates by sex and by region were observed in CKB and in national estimates. Compared with men, the incidence rates were 1/3 lower in women for pancreatic cancer, 2/3 lower for liver cancer, and 1/4 lower for colorectal cancer. As for urban-rural differences, the incidence rates were higher in urban than rural areas for pancreatic and colorectal cancer, while the converse was true for liver cancer. The urban-rural differences may be explained by the differences in risk factors for these cancers (e.g. higher prevalences of metabolic risk factors in urban areas and HBV in rural areas). As expected, pancreatic and liver cancer had worse survival than colorectal cancer. Median survival of pancreatic and liver cancer was generally consistent with previous reports in Western populations.

9.2.2 Associations of PA and SLT with specific GI cancers

In CKB, the directions of associations of PA and SLT with risks of pancreatic, liver, and colorectal cancer are generally consistent with previous prospective studies in Western and other East Asian countries. However, given the different distributions of physical activity in China and in the West, it is difficult to compare directly the strengths and shape of associations. Both CKB and previous studies have shown no clear associations of total and leisure-time PA with pancreatic cancer and inverse associations of total and leisure-time PA with liver cancer, although the association between leisure-time PA and liver cancer is nonsignificant in CKB. For colorectal cancer, CKB is consistent with previous studies showing inverse associations of total and leisure-time PA with colon cancer risk. Although previous studies showed no associations with rectal cancer, the associations of total and

domain-specific PA did not differ for colon and rectal cancer in CKB. For SLT, findings in CKB are generally consistent with previous studies showing a positive association for colorectal cancer and no associations for pancreatic and liver cancer.

9.2.3 Associations of adiposity with specific GI cancers

The null associations in CKB of BMI with risks of pancreatic and liver cancer are consistent with previous studies in East Asians, while they are in contrast to the positive associations in Western populations. However, the null association between BMI and pancreatic cancer in CKB may be a chance finding due to the small number of cases. In CKB, the positive associations of BMI with risks of colon and rectal cancer are consistent with previous studies in Western populations, but they are in contrast to the weak positive or null associations in East Asians. For central adiposity, previous studies in Western populations have shown positive associations of WC and WHR with risks of all three cancers. In CKB, the positive associations with liver and colorectal cancer are consistent with findings in Western populations (WC and WHR were positively associated with liver cancer risk when excluding the first five years of follow-up), while WC and WHR were not associated with pancreatic cancer. Although findings in CKB suggest that the associations of adiposity with liver cancer risk were not modified by HBsAg, both CKB and previous studies showed a null association among HBsAg positive participants and a positive association among HBsAg negative participants (in CKB, there was a null association among HBsAg positive participants and a positive trend among HBsAg negative participants excluding the first five years of follow-up). Consistent with several studies in Western populations, the positive

associations of WC with risks of liver and colorectal cancer remained when additionally adjusting for BMI, suggesting that central adiposity is associated with these cancers beyond BMI. For colorectal cancer, both CKB and previous studies in Western populations have shown greater magnitudes of associations in men and for colon cancer.

9.2.4 Associations of diabetes and RPG with specific GI cancers

In CKB, the positive associations of diabetes and blood glucose with risks of pancreatic, liver, and colorectal cancer are largely consistent with previous studies in Western and other East Asian populations. While the excess risk associated with diabetes is similar for pancreatic cancer in CKB and in previous studies, the excess risks for liver and colorectal cancer in CKB are lower than studies in Western populations. For diabetes duration, both CKB and previous studies that used a time-dependent approach have shown a higher risk within the first two years following diabetes diagnosis, which decreased with longer duration of diabetes but remained elevated even 10 years after diabetes diagnosis (except for colorectal cancer). Although the majority of previous studies examined the associations of blood glucose with cancer risk in the range of hyperglycaemia and normoglycaemia, they have shown similar positive associations to the findings in CKB. In addition, positive associations are observed for fasting and nonfasting blood glucose. For diabetes and blood glucose, both CKB and previous studies have shown similar associations for colon and rectal cancer. For liver cancer, although evidence has been inconclusive whether HBV infection modifies the associations of diabetes and blood glucose, the findings in CKB are consistent with several reports in Taiwan showing similar associations by HBsAg status.

9.3 Mechanisms of adiposity and proteomics

To explore the mechanisms linking adiposity and cancer, I examined the associations of BMI with inflammation and immune proteins that are involved in tumorigenesis in a case-subcohort study. The study population, proteomics assay, statistical methods, detailed results, and discussion are presented in **Appendix 9.1**.

Overall, BMI was associated with a range of protein biomarkers which included chemokines, interleukins (ILs), tumour necrosis factor (TNF) and TNF receptor (TNFR) superfamily, growth factors (including VEGF), enzymes, cell surface proteins, and other secreted proteins. These protein biomarkers have a role in apoptosis, chemotaxis, metabolism and autophagy, promotion and suppression of tumour immunity, and vascular and tissue remodelling. In the current study, the associations of BMI with proteomics are generally consistent with previous studies examining the correlations or associations of BMI with a limited set of inflammatory cytokines and growth factors, including MCP1, CXCL10, IL6, IL10, IL12, TRAIL, VEGF, and HGF.[442-457] The associations of BMI with proteomics in CKB are generally in the expected direction of associations of protein biomarkers with cancer risk in previous studies, either assessing gene polymorphisms or plasma concentrations of these proteins (**Appendix 9.1**). In addition, there is agreement between the associations of BMI with proteomics and of proteomics with risk of pancreatic cancer in CKB. However, more studies are needed to examine whether proteomics may explain the associations of adiposity with cancer risk.

9.4 Strengths and limitations

9.4.1 Strengths

Apart from the diverse population and large numbers of cancer cases, there are several strengths of the current study. First, the use of standardised protocols and extensive training across study centres ensured the reliability of exposure measurements. Second, the reported cancer cases in CKB have been shown to be of good quality. On-going outcome adjudication, which involves retrieval and review of clinical notes and test reports by specialists, shows a 95% confirmation rate for cancer. Third, the current study assessed different activity measures including total, occupational, nonoccupational PA, and SLT. Fourth, the current study assessed a wide range of general and central adiposity traits in a relatively lean study population, which enabled investigations of a uniquely wide range of adiposity. Fifth, proteomics were measured in a random subcohort, which allowed explorations of possible mechanisms underlying adiposity and cancer risk. Other strengths are the assessment of a range of risk factors for cancer, including lifestyle risk factors, anthropometry, and past medical history, and the examination of the associations across important population subgroups such as age, sex, smoking, and alcohol.

9.4.2 Limitations

9.4.2.1 PA and SLT

For PA, limitations of the current study include self-reported PA, no data on objectively measured PA, and no data on cardiorespiratory fitness. First, the questionnaire on PA has not been validated in CKB, and the questions were adapted from EPIC and the Shanghai Women's Health Study (SWHS). The PA

questionnaires (PAQs) in both studies have been shown to have good validity.[245,458] In a random sample of 200 participants in the SWHS (original cohort: 75,000 Chinese women aged 40-70 years), validity was evaluated by comparing Spearman correlations (r) between the PAQ and two criterion measures administered over a period of 1 year (7-day PA logs and 7-day PAQs).[245] There were moderate to strong correlations between the PAQ and criterion measures for adult exercise (PA logs, r=0.74; 7-day PAQs, r=0.80) and between PAQ lifestyle activities and the 7-day PAQs (r=0.51-0.92). The Spearman correlation coefficients for stairs climbing, walking, cycling, housework, and transportation to work were 0.92, 0.59, 0.51, 0.76, and 0.82-0.88. Although no separate validation study has been conducted on the CKB questionnaire, the observed associations of PA with adiposity and CVD risk in CKB provide support for the validity of the PAQ.[107,459] In addition, data from CKB showed good reliability of the PAQ. In CKB, following completion of the baseline survey, a quality control (QC) survey was done involving 923 participants with repeated measurements within 1 year after the baseline survey. Results indicated that the reliability of exercise participation (kappa=0.60) and total PA (intraclass correlation coefficient [ICC]=0.72) was reasonable. The reliability of PAQ in CKB is comparable to other studies, including EPIC and SWHS, that estimated their ICC for total PA to be 0.75 (EPIC men), 0.68 (EPIC women), and 0.70 (SWHS), respectively.[245,458] In addition, the kappa statistic for exercise participation is comparable to that in SWHS (0.64).

Second, there were no data on objectively measured PA in CKB. Compared to objective assessments of PA, PAQs are subject to measurement error due to recall bias, social desirability bias (e.g. overreport in participants with low levels of PA), and difficulties to capture low-intensity activities. Moreover, misclassification

may have occurred because the same MET value was assigned to each type of activity regardless of between-person differences in intensity. Previous studies comparing objectively measured PA (e.g. accelerometry, heart rate monitoring) and activity measured by questionnaires have shown low to moderate correlations ranging from -0.71 to 0.96 (mean r=0.37, SD 0.25).[460] Although differences in the measurement instruments and the sociodemographic characteristics of study populations (e.g. age, sex, and education) may have affected the correlations,[461] the inconsistency is still poorly understood. In epidemiological studies, self-reported and device-based methods are measuring different constructs of PA. Device-based methods provide an objective indicator of movement of the body part to which the devices are attached or other physiologic signals over short time periods (generally fractions of a second to a minute), but the majority of devices provide little information on the type and purpose of activities.[462] In contrast, self-reported methods attempt to quantify PA based on reported time periods engaged in specific behaviours of longer duration, incorporating an individual's perception of their activity behaviours.[463] Differences in interpretation can affect whether a particular behaviour is reported as PA, as well as the frequency, duration, intensity, and type of activities.[463]

Third, despite public health recommendations to increase PA, it is not clear whether high levels of PA energy expenditure or physical fitness yield greater health benefits. PA is defined as any bodily movement produced by the contraction of skeletal muscle that results in energy expenditure.[67] Physical fitness, on the other hand, is a set of physiological attributes that reflect "the ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies".[67]

Cardiorespiratory fitness is the most commonly used measure of physical fitness in epidemiological studies, which reflects the ability of the body to transport and use oxygen during sustained PA.[464] Previous prospective studies have shown an inverse association of cardiorespiratory fitness with total cancer mortality, suggesting a protective effect of physical fitness on cancer death.[464] Although both PA and physical fitness have been shown to be associated with a lower risk of cancer, previous studies showed stronger associations of cardiorespiratory fitness with cardiometabolic risk factors (e.g. WC, insulin, triglycerides, LDL cholesterol) than PA.[465] These findings have public health significance as increased cardiorespiratory fitness can be achieved through aerobic exercise. More studies are warranted to examine the associations of physical fitness with cancer risk.

9.4.2.2 Adiposity

First, as a measure of general adiposity, the major limitation of BMI is that the numerator cannot distinguish between fat mass and lean mass.[129,466] In CKB, %BF was assessed by bioimpedence, which was used to derive fat mass and lean mass. In the current study, strong correlations were observed between BMI and %BF and between BMI and fat mass, while moderate correlations were observed between BMI and lean mass. The similar patterns of %BF and height-adjusted fat mass with cancer risks to those of BMI reflect the strong correlations. Second, the major limitation of WC is that WC is a surrogate marker for central adiposity and captures both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).[78] While VAT has been shown to be associated with insulin resistance, diabetes, CVD, and cancer,[377,467,468] SAT is not associated with risks of CVD and cancer.[377] Third, BMI25 was calculated from self-reported weight at

age 25 assuming the same height as at study baseline. Such an approach might lead to overestimation of BMI25 as height generally decreases with ageing.[469] However, it is unlikely that the decrease in height with age differed by BMI25 or risk of cancer. Fourth, BMI25 was missing in 81,880 participants because participants could not recall weight at age 25. In a sensitivity analysis, BMI25 was imputed for those with missing BMI25 values using multiple imputation ("mice" package in R) (**Appendix 9.2**). In the imputed dataset, the HRs per 5 kg/m^2 higher BMI25 were 1.16 (1.00-1.33), 1.08 (1.00-1.17), and 1.06 (0.99-1.14) for risks of pancreatic, liver, and colorectal cancer, which are similar to the estimates among participants with available BMI25 data (HR per 5 kg/m^2 higher BMI25: 1.18 [1.02-1.36] for pancreatic, 1.09 [1.01-1.18] for liver, and 1.06 [0.99-1.15] for colorectal cancer).

9.4.2.3 Diabetes and RPG

First, while the prevalence of previously diagnosed diabetes in this study was comparable to a nationally representative survey in 2010 (3.1% in CKB vs 3.5% in the national survey), the prevalence of screen-detected diabetes was lower (2.8% in CKB vs 8.1% in the national survey).[97] The difference may be due to different tests to ascertain screen-detected diabetes (fasting glucose in CKB vs HbA1c, fasting glucose, and 2-hour glucose in the national survey) as well as differences in sampling schemes and temporal trends in diabetes. Nonetheless, undetected diabetes at baseline could result in underestimation of the associations of diabetes with cancer risk. Second, there are no data on the prevalence of type 1 diabetes in CKB at baseline. In a sensitivity analysis based on insulin use and age at diagnosis (<30 years), the prevalence of type 1 diabetes was less than 1%.

Similar associations of diabetes with cancer risks were observed when excluding these possible type 1 diabetes cases. Although there are no national data in China, the prevalence of type 1 diabetes is likely to be much lower than the 7-12% reported in high-income countries.[92] Furthermore, previous prospective studies have shown similar associations of type 1 and type 2 diabetes with cancer risks including pancreatic, liver, and colorectal cancer.[102,180] Therefore, inclusion of type 1 diabetes should have little impact on the diabetes-cancer associations. Third, among participants without previously diagnosed diabetes, higher risks of cancer at higher glucose levels may reflect undiagnosed or future diabetes. When excluding further screen-detected diabetes, the linear estimates tended to be weaker compared with estimates from the main model (**Appendix 9.3**). Nonetheless, individuals with high RPG (≥7.8 mmol/L) had higher risks of all three cancers (**Appendix 9.3**). Fourth, 1.5% of the study participants did not have RPG measurements, mainly because of delay in getting the supply in three regions (Qingdao, Sichuan, and Zhejiang) at beginning of the study. In a sensitivity analysis, RPG was imputed for those with missing RPG values using multiple imputation ("mice" package in R) (**Appendix 9.4**). After correcting for regression dilution, the HRs per 1 mmol/L higher RPG were 1.09 (1.04-1.15), 1.09 (1.06-1.12), and 1.06 (1.03-1.09) for pancreatic, liver, and colorectal cancer, which are almost identical to the estimates among participants with available RPG (HR per 1 mmol/L higher RPG: 1.09 [1.04-1.15] for pancreatic, 1.09 [1.06-1.12] for liver, and 1.06 [1.03-1.09] for colorectal cancer).

9.4.2.4 Cancer subtypes

In CKB, histological information was not available for all cancer cases. Information on cancer histological subtypes was collected for a subset of the cases through cancer registries or reviews of hospital medical notes as part of the on-going outcome adjudication for major diseases (~30% of all cancer cases). On-going outcome adjudication shows a 95% confirmation rate for cancer. For colorectal cancer, of all cases that medical notes could be retrieved, 96% were confirmed, and 94% were adenocarcinoma. Moreover, a previous report in CKB has shown similar associations of adiposity with risk of colorectal cancer when using adjudicated and all outcomes.[372]

9.4.2.5 Undetected HBV infections

The HBsAg test used was point-of-care test using strip so had a low sensitivity, leading to a high false negative rate.[470,471] In addition, compared with the immune-tolerant phase and the immune-clearance phase, serum HBsAg titres are low in the non/low-replicative phase and the HBV e-antigen (HBeAg) negative hepatitis phase.[472] Serum HBsAg could be undetectable if serum HBsAg titres are lower than the limit of detection (LOD) of the HBsAg assay. However, in a sensitivity analysis censoring viral hepatitis (mostly viral hepatitis B) that had occurred during follow-up, similar associations of metabolic risk factors with liver cancer risk were observed to those in HBsAg negative participants (**Appendices 9.5-9.8**). Although undetected HBV infections cannot be all identified, the null association of adiposity with liver cancer among HBsAg positive participants would lead to underestimation of the association among HBsAg negative participants. For PA and diabetes, undetected HBV infections should have little impact on the

associations as similar associations were observed in HBsAg negative and positive participants.

9.4.2.6 Residual confounding and reverse causality

As in all observational studies, residual confounding may still persist, particularly related to dietary factors (e.g. coffee), nutrients (e.g. fibre and fructose), medical history (e.g. allergy), infections (e.g. *Helicobacter pylori* and HCV), certain medications (e.g. oral contraceptives and HRT), and specific family history (e.g. pancreatic, liver, colorectal cancer).[29,36,38,49,52,57,473,474] In addition, although the first five years were excluded, reverse causality may still not be fully accounted for because of the long latency of cancer.

9.5 Future studies

9.5.1 Objective measurements of PA

Given the limitations of self-reported measurements, future studies should incorporate objective assessment of PA (e.g. wrist-worn accelerometer) to complement self-reported PA and to identify the aspects or patterns of PA that are most important for health. The UK Biobank has collected accelerometer measured PA in over 100,000 participants and derived a summary measure of overall PA (i.e. vector magnitude).[475] In CKB, objective assessment of PA using the same wrist-worn accelerometer as the UK Biobank has been planned for a resurvey in 2019.

9.5.2 Fat distribution

To understand the association of fat distribution with cancer risk, future investigations are needed to examine the associations of systemic and local

ectopic fat with cancer risk and with progression of diseases of the GI system. Simultaneous assessments of several body fat measures may improve understanding of the associations of adipose tissue distribution with risk of diseases.[476] VAT reflects systemic ectopic fat which is often assessed by imaging technologies (e.g. CT, MRI).[377,477] A small prospective study showed a positive association of VAT with risk of total cancer which persisted with additional adjustment for BMI and WC.[377] In addition, obesity is positively associated with liver fat and pancreatic fat, both of which have been shown to be associated with insulin resistance and type 2 diabetes.[478-481] Liver fat is also associated with progression of NAFLD to fibrosis, cirrhosis, and liver cancer.[479,482] It has been hypothesised that inflammation associated with ectopic fat may be the mechanism linking adiposity and cancer risk.[483]

9.5.3 Diabetes and RPG

Although prospective studies have shown positive associations of diabetes with risks of cancer including pancreatic, liver, and colorectal cancer, a recent Mendelian randomisation study has suggested that the association between diabetes and pancreatic cancer risk is not causal.[161] Future investigations are warranted to understand the mechanisms linking diabetes and cancer risk and to address whether diabetes is causally associated with cancer risk. Although several prospective studies have suggested positive associations of blood glucose with risks of several cancers within the range of normoglycaemia,[182,379] evidence from RCTs and Mendelian randomisation studies is needed to assess whether lowering blood glucose may confer a lower risk of cancer.

9.5.4 Combinations of multiple metabolic risk factors

In addition to the effect of single metabolic risk factor on cancer risk, future studies can investigate the associations of multiple metabolic risk factors in relation to cancer risk as well as lifestyle risk factors such as smoking, alcohol, and diet. Previous studies in Western populations have shown that adherence to a combination of healthy lifestyle factors is associated with lower risks of pancreatic and colorectal cancer.[484,485] However, there is little evidence whether a combination of modifiable lifestyle risk factors is associated with cancer risk in the Chinese population where the aetiologies of cancer differ from those in the West. Moreover, it is of public health significance to estimate the proportion of cancer cases that could potentially be prevented by adherence to a healthy lifestyle assuming a causal effect.

9.5.5 Mendelian randomisation studies

As observational studies are affected by residual confounding and reverse causality, future studies should aim to investigate the causal associations of metabolic risk factors with cancer risk. Assessing the causal associations of metabolic risk factors with cancer risk is important to understand the underlying mechanisms and to inform the plan and design of RCTs. Previous Mendelian randomisation studies have shown that genetically influenced BMI is positively associated with risks of pancreatic, colorectal, lung, and ovarian cancer,[159,160] whereas there is no evidence of a causal association between diabetes and pancreatic cancer risk.[161] However, Mendelian randomisation relies on important assumptions that the chosen genetic variants are associated with the exposure of interest, they are not associated with any confounders, and they are not

associated with the outcome via any pathway other than through the exposure of interest.[162]

9.5.6 Multi-omics investigations to explore mechanisms

Future research can investigate the mechanisms linking metabolic risk factors with cancer risk using a multi-omics approach and explore whether biomarkers could explain the associations between metabolic risk factors and cancer risk. The majority of previous multi-omics studies have used nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) methodologies to quantify circulating metabolomics and proteomics.[486,487] These studies have yielded a wide range of metabolic and protein biomarkers associated with PA, adiposity, insulin resistance, incident diabetes, CVD, and cancer.[488-494] However, several studies have shown that the associations of biomarkers with cancer risk are only observed <5 years prior to cancer diagnosis, suggesting that these markers may not be aetiologically relevant.[333,335,338,495-497] In this context, Mendelian randomisation is a useful tool to examine the causal associations between metabolic risk factors, metabolomics, proteomics, and cancer risk. A case-subcohort study of pancreatic cancer in CKB currently underway, including NMR metabolomics and proteomics, is using a multi-omics approach to understand cancer aetiology, and thus will provide novel insights into the mechanisms linking metabolic risk factors and pancreatic cancer risk.

9.6 Implications

The current study shows inverse associations of total PA on risks of liver and colorectal cancer in this Chinese population, and the inverse associations are

largely independent of lifestyle risk factors such as smoking, alcohol, and SLT. These findings suggest that engaging in PA may lower risks of liver and colorectal cancer. Previous cancer recommendations are based on studies conducted in Western populations and focus on leisure-time PA.[36,49,57] Given the different nature of PA, recommendations of leisure-time PA may not be generalisable to the Chinese population. A previous report in this Chinese population has shown inverse associations of total and domain-specific PA with CVD risks, reinforcing the current Chinese guidelines on CVD prevention that promote PA of any kind.[459] Although the associations of nonoccupational PA with risks of specific GI cancers are inconclusive in this Chinese population, tailored recommendations may be needed for cancer prevention at least taking into account occupational and nonoccupational PA.

Obesity remains a public health concern in China.[498] Of the various adiposity traits investigated in the current study, both general and central adiposity are consistently associated with risk of colorectal cancer, providing a basis for a public health recommendation to avoid adiposity in order to reduce risk of colorectal cancer. Although the inverse associations of general adiposity (BMI and %BF) with liver cancer risk may be affected by reverse causality, the current study suggests that central adiposity is more strongly associated with risks of liver and colorectal cancer. These findings suggest that central adiposity may be more important than general adiposity in relation to risks of these cancers. Given that Chinese populations are more likely to have central adiposity at given BMI levels compared with Western populations,[138] control of central adiposity may be needed even BMI is within the normal range. The modifiable nature of PA and central

adiposity suggests that, assuming cause and effect, many cases of liver and colorectal cancer in Chinese might be prevented with lifestyle modifications.

Although a recent Mendelian randomisation study has suggested that diabetes is not an aetiological factor for pancreatic cancer,[161] prevention and early detection of diabetes may still be beneficial in lowering insulin resistance, blood glucose, and subsequent changes in other hormones. Indeed, the same Mendelian randomisation study has suggested a causal association between plasma insulin and pancreatic cancer risk.[161] Given that the majority of diabetes cases are undiagnosed in China,[16,96] early detection of diabetes via screening could help identify a group of individuals at higher risks of pancreatic, liver, and colorectal cancer. In addition to liver cancer, a previous report in CKB showed positive associations of diabetes and blood glucose with risks of NAFLD and cirrhosis.[407] Early detection of diabetes could also help identify individuals at a higher risk of chronic liver diseases and prevent possible progression to cirrhosis and liver cancer. With numbers of cancer cases predicted to increase in China over the next decade,[6] and obesity and diabetes on the rise,[16,498] coherent public health strategies for cancer prevention are needed.

References

1. Global Burben of Disease 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390(10100): 1151-210.

2. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2016; 3(4): 524-48.

3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127(12): 2893-917.

4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136(5): E359-86.

5. Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, et al. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. *Lancet* 2016; 387(10015): 251-72.

6. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66(2): 115-32.

7. Xia GL, Liu CB, Cao HL, Bi SL, Zhan MY, Su CA, et al. Prevalence of hepatitis B and C virus infections in the general Chinese population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China, 1992. *International Hepatology Communications* 1996; 5(1): 62-73.

8. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009; 27(47): 6550-7.

9. Nagy P, Johansson S, Molloy-Bland M. Systematic review of time trends in the prevalence of Helicobacter pylori infection in China and the USA. *Gut Pathog* 2016; 8: 8.

10. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009; 59(6): 366-78.

11. Li LD, Lu FZ, Zhang SW, Mu R, Sun, XD, Huangpu XM, et al. Analysis of cancer mortality and distribution in China from year 1990 through 1992, an epidemiologic study. *Chin J Oncol* 1997; 18: 403-7.

12. Zhi K, Wang L, Han Y, Vaughn MG, Qian Z, Chen Y, et al. Trends in cigarette smoking among older male adults in China: an urban-rural comparison. *J Appl Gerontol* 2017: 733464817716967.

13. Zhai FY, Du SF, Wang ZH, Zhang JG, Du WW, Popkin BM. Dynamics of the Chinese diet and the role of urbanicity, 1991-2011. *Obes Rev* 2014; 15 Suppl 1: 16-26.

14. Jaacks LM, Gordon-Larsen P, Mayer-Davis EJ, Adair LS, Popkin B. Age, period and cohort effects on adult body mass index and overweight from 1991 to 2009 in China: the China Health and Nutrition Survey. *Int J Epidemiol* 2013; 42(3): 828-37.

15. Ng SW, Norton EC, Popkin BM. Why have physical activity levels declined among Chinese adults? Findings from the 1991-2006 China Health and Nutrition Surveys. *Soc Sci Med* 2009; 68(7): 1305-14.

16. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. *JAMA* 2017; 317(24): 2515-23.

17. Chen WQ, Zheng RS, Zhang SW, Li N, Zhao P, Li GL, et al. Report of incidence and mortality in china cancer registries, 2008. *Chin J Cancer Res* 2012; 24(3): 171-80.

18. Chen W, Zheng R, Zhang S, Zhao P, Li G, Wu L, et al. Report of incidence and mortality in China cancer registries, 2009. *Chin J Cancer Res* 2013; 25(1): 10-21.

19. Chen W, Zheng R, Zhang S, Zhao P, Zeng H, Zou X, et al. Annual report on status of cancer in China, 2010. *Chin J Cancer Res* 2014; 26(1): 48-58.

20. Chen W, Zheng R, Zeng H, Zhang S, He J. Annual report on status of cancer in China, 2011. *Chin J Cancer Res* 2015; 27(1): 2-12.

21. Chen W, Zheng R, Zuo T, Zeng H, Zhang S, He J. National cancer incidence and mortality in China, 2012. *Chin J Cancer Res* 2016; 28(1): 1-11.

22. Zheng R, Zeng H, Zhang S, Chen W. Estimates of cancer incidence and mortality in China, 2013. *Chin J Cancer* 2017; 36(1): 66.

23. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, et al. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 2018; 30(1): 1-12.

24. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. *Lancet* 2016; 388(10039): 73-85.

25. Oberg K. Pancreatic endocrine tumors. *Semin Oncol* 2010; 37(6): 594-618.

26. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014; 371(22): 2140-1.

27. Neeleman S, Demeure MJ. Nonfunctioning islet cell carcinoma of the pancreas. *Curr Treat Options Oncol* 2002; 3(4): 355-60.

28. Solorzano CC, Lee JE, Pisters PW, Vauthey JN, Ayers GD, Jean ME, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* 2001; 130(6): 1078-85.

29. Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010; 362(17): 1605-17.

30. Cancer Research UK. Pancreatic cancer survival statistics. 2018. https://community.endnote.com/t5/EndNote-How-To/Organization-as-author/td-p/23965 (accessed April 15 2017).

31. Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health* 2018; 6(5): e555-e67.

32. American Cancer Society. Pancreatic cancer survival rates, by stage. 2018. https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html (accessed April 15 2017).

33. American Cancer Society. Liver cancer survival rates. 2018. https://www.cancer.org/cancer/liver-cancer/detection-diagnosis-staging/survival-rates.html (accessed April 15 2017).

34. American Cancer Society. Survival rates of colorectal cancer, by stage. 2018. https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html (accessed April 15 2017).

35. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol* 2015; 44(1): 186-98.

36. World Cancer Research Fund/American Institue for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer. Available at dietandcancerreport.org.

37. Pang Y, Holmes MV, Guo Y, Yang L, Bian Z, Chen Y, et al. Smoking, alcohol, and diet in relation to risk of pancreatic cancer in China: a prospective study of 0.5 million people. *Cancer Med* 2018; 7(1): 229-39.

38. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379(9822): 1245-55.

39. Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. *Int J Cancer* 2016; 139(7): 1534-45.

40. Cancer Research UK. Liver cancer survival statistics. 2018. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/survival (accessed April 15 2017).

41. Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. *Vaccine* 1999; 17(13-14): 1730-3.

42. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; 5(9): 558-67.

43. International Agency for Research on Cancer. Hepatitis B and C viruses. In: The Evaluation of Carcinogenic Risks to Humans: IARC Monogr no. 100B., 2012.

44. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; 386(10003): 1546-55.

45. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; 57(4): 1333-42.

46. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and

chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(9995): 743-800.

47. Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol* 2009; 38(6): 1497-511.

48. Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. *Eur J Cancer* 2012; 48(14): 2125-36.

49. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and liver cancer. 2015. Available at: wcrf.org/sites/default/files/Liver-Cancer-2015-Report.pdf.

50. International Agency for Research on Cancer. Pharmaceuticals. In: The Evaluation of Carconogenic Risks to Humans, 2012.

51. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol* 2012; 3(3): 153-73.

52. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; 383(9927): 1490-502.

53. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al. Cancer incidence in five continents, Vol. IX. Lyon: International Agency for Research on Cancer, 2007.

54. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014; 15(1): 23-34.

55. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010; 11(2): 165-73.

56. Cancer Research UK. Bowel cancer survival statistics. 2018. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival (accessed April 15 2017).

57. World Cancer Research Fund/American Institue for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and colorectal cancer. 2017. Available at: wcrf.org/colorectal-cancer-2017.

58. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011; 22(9): 1958-72.

59. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer* 2009; 124(10): 2406-15.

60. Zhong X, Fang YJ, Pan ZZ, Lu MS, Zheng MC, Chen YM, et al. Dietary fiber and fiber fraction intakes and colorectal cancer risk in Chinese adults. *Nutr Cancer* 2014; 66(3): 351-61.

61. Vogtmann E, Xiang YB, Li HL, Levitan EB, Yang G, Waterbor JW, et al. Fruit and vegetable intake and the risk of colorectal cancer: results from the Shanghai Men's Health Study. *Cancer Causes Control* 2013; 24(11): 1935-45.

62. Lee SA, Shu XO, Yang G, Li H, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer* 2009; 61(2): 194-205.

63. Ji BT, Dai Q, Gao YT, Hsing AW, McLaughlin JK, Fraumeni JF, Jr., et al. Cigarette and alcohol consumption and the risk of colorectal cancer in Shanghai, China. *Eur J Cancer Prev* 2002; 11(3): 237-44.

64. Li H, Yang G, Xiang YB, Zhang X, Zheng W, Gao YT, et al. Body weight, fat distribution and colorectal cancer risk: a report from cohort studies of 134255 Chinese men and women. *Int J Obes (Lond)* 2013; 37(6): 783-9.

65. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, et al. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. *Circulation* 2013; 127(14): 1493-502, 502e1-8.

66. Global Burden of Disease 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(10010): 2287-323.

67. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985; 100(2): 126-31.

68. World Health Organisation. Global recommendations on physical activity for health. Geneva, 2010.

69. World Health Organisation. Physical activity. 2018. http://www.who.int/news-room/fact-sheets/detail/physical-activity (accessed July 1 2018).

70. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 2012; 380(9838): 247-57.

71. Tian Y, Jiang C, Wang M, Cai R, Zhang Y, He Z, et al. BMI, leisure-time physical activity, and physical fitness in adults in China: results from a series of national surveys, 2000-14. *Lancet Diabetes Endocrinol* 2016; 4(6): 487-97.

72. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics--2016 update: a report from the American Heart Association. *Circulation* 2016; 133(4): 447-54.

73. British Heart Foundation. Physical activity statistics 2015. https://www.bhf.org.uk/informationsupport/publications/statistics/physical-activity-statistics-2015 (accessed July 1 2017).

74. Ng SW, Howard AG, Wang HJ, Su C, Zhang B. The physical activity transition among adults in China: 1991-2011. *Obes Rev* 2014; 15 Suppl 1: 27-36.

75. Kohl HW, 3rd, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. *Lancet* 2012; 380(9838): 294-305.

76. Bauman A, Ainsworth BE, Sallis JF, Hagstromer M, Craig CL, Bull FC, et al. The descriptive epidemiology of sitting. A 20-country comparison using the International Physical Activity Questionnaire (IPAQ). *Am J Prev Med* 2011; 41(2): 228-35.

77. Muntner P, Gu D, Wildman RP, Chen J, Qan W, Whelton PK, et al. Prevalence of physical activity among Chinese adults: results from the International Collaborative Study of Cardiovascular Disease in Asia. *Am J Public Health* 2005; 95(9): 1631-6.

78. Anderson AS, Key TJ, Norat T, Scoccianti C, Cecchini M, Berrino F, et al. European Code against Cancer 4th Edition: Obesity, body fatness and cancer. *Cancer Epidemiol* 2015; 39 Suppl 1: S34-45.

79. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384(9945): 766-81.

80. World Health Organisation. Obesity and overweight. 2018. http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed July 1 2017).

81. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008; 32(9): 1431-7.

82. Popkin BM, Du S, Zhai F, Zhang B. Cohort Profile: The China Health and Nutrition Survey--monitoring and understanding socio-economic and health change in China, 1989-2011. *Int J Epidemiol* 2010; 39(6): 1435-40.

83. Xi B, Liang Y, He T, Reilly KH, Hu Y, Wang Q, et al. Secular trends in the prevalence of general and abdominal obesity among Chinese adults, 1993-2009. *Obes Rev* 2012; 13(3): 287-96.

84. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA* 2010; 303(3): 235-41.

85. Ford ES, Maynard LM, Li C. Trends in mean waist circumference and abdominal obesity among US adults, 1999-2012. *JAMA* 2014; 312(11): 1151-3.

86. Health Survey for England. Trend tables 2015. https://www.gov.uk/government/statistics/health-survey-for-england-trend-tables-health-survey-for-england-trend-tables-2015 (accessed June 1 2017).

87. Haffner SM. Epidemiology of type 2 diabetes: risk factors. *Diabetes Care* 1998; 21 Suppl 3: C3-6.

88. World Health Organisation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Geneva, 2006.

89. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014; 37 Suppl 1: S81-90.

90. World Health Organisation. Use of glycated heamoglobin (HbA1c) in the diagnosis of diabetes mellitus. Geneva, 2011.

91. International Diabetes Federation Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: estimates for the year 2011. *Diabetes Res Clin Pract* 2013; 100(2): 277-9.

92. International Diabetes Federation. IDF Diabetes Atlas Eighth edition 2017, 2018.

93. Chan JC, Cho NH, Tajima N, Shaw J. Diabetes in the Western Pacific Region--past, present and future. *Diabetes Res Clin Pract* 2014; 103(2): 244-55.

94. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin Pract* 2014; 103(2): 150-60.

95. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014; 103(2): 137-49.

96. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; 362(12): 1090-101.

97. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. *JAMA* 2013; 310(9): 948-59.

98. National Diabetes Research Group. A mass survey of diabetes mellitus in a population of 300,000 in 14 provinces and municipalities in China. *Zhonghua Nei Ke Za Zhi* 1981; 20(11): 678-83.

99. Pan XR, Yang WY, Li GW, Liu J. Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997; 20(11): 1664-9.

100. Weng J, Zhou Z, Guo L, Zhu D, Ji L, Luo X, et al. Incidence of type 1 diabetes in China, 2010-13: population based study. *BMJ* 2018; 360: j5295.

101. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ* 2018; 362: k1497.

102. Gordon-Dseagu VL, Shelton N, Mindell JS. Epidemiological evidence of a relationship between type-1 diabetes mellitus and cancer: a review of the existing literature. *Int J Cancer* 2013; 132(3): 501-8.

103. Patterson C, Guariguata L, Dahlquist G, Soltesz G, Ogle G, Silink M. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014; 103(2): 161-75.

104. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006; 174(6): 801-9.

105. Leitzmann M, Powers H, Anderson AS, Scoccianti C, Berrino F, Boutron-Ruault MC, et al. European Code against Cancer 4th Edition: Physical activity and cancer. *Cancer Epidemiol* 2015; 39 Suppl 1: S46-55.

106. Colpani V, Baena CP, Jaspers L, van Dijk GM, Farajzadegan Z, Dhana K, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-

aged and elderly women: a systematic review and meta-analysis. *Eur J Epidemiol* 2018; 33(9): 831-45.

107. Du H, Bennett D, Li L, Whitlock G, Guo Y, Collins R, et al. Physical activity and sedentary leisure time and their associations with BMI, waist circumference, and percentage body fat in 0.5 million adults: the China Kadoorie Biobank study. *Am J Clin Nutr* 2013; 97(3): 487-96.

108. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. *Eur J Epidemiol* 2015; 30(4): 279-98.

109. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med* 2016; 176(6): 816-25.

110. Wu L, Zheng W, Xiang YB, Gao YT, Li HL, Cai H, et al. Physical activity and pancreatic cancer risk among urban Chinese: results from two prospective cohort studies. *Cancer Epidemiol Biomarkers Prev* 2018; 27(4): 479-87.

111. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011; 378(9798): 1244-53.

112. Yun YH, Lim MK, Won YJ, Park SM, Chang YJ, Oh SW, et al. Dietary preference, physical activity, and cancer risk in men: national health insurance corporation study. *BMC Cancer* 2008; 8: 366.

113. Arem H, Moore SC, Park Y, Ballard-Barbash R, Hollenbeck A, Leitzmann M, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer* 2014; 135(2): 423-31.

114. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S, et al. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. *Am J Epidemiol* 2008; 168(4): 391-403.

115. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012; 104(20): 1548-61.

116. Owen N, Bauman A, Brown W. Too much sitting: a novel and important predictor of chronic disease risk? *Br J Sports Med* 2009; 43(2): 81-3.

117. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; 32(9 Suppl): S498-504.

118. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. *Int J Epidemiol* 2012; 41(5): 1338-53.

119. Cong YJ, Gan Y, Sun HL, Deng J, Cao SY, Xu X, et al. Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. *Br J Cancer* 2014; 110(3): 817-26.

120. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. *J Natl Cancer Inst* 2014; 106(7).

121. Lynch BM. Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. *Cancer Epidemiol Biomarkers Prev* 2010; 19(11): 2691-709.

122. Ukawa S, Tamakoshi A, Wakai K, Kurozawa Y. Associations of daily walking and television viewing time with liver cancer mortality: findings from the Japan Collaborative Cohort Study. *Cancer Causes Control* 2014; 25(7): 787-93.

123. Patel AV, Hildebrand JS, Campbell PT, Teras LR, Craft LL, McCullough ML, et al. Leisure-time spent sitting and site-specific cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev* 2015; 24(9): 1350-9.

124. Morris JS, Bradbury KE, Cross AJ, Gunter MJ, Murphy N. Physical activity, sedentary behaviour and colorectal cancer risk in the UK Biobank. *Br J Cancer* 2018; 118(6): 920-9.

125. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; 444(7121): 840-6.

126. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. *Nat Rev Gastroenterol Hepatol* 2018.

127. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ* 2017; 356: j477.

128. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetol Metab Syndr* 2011; 3: 12.

129. Frankenfield DC, Rowe WA, Cooney RN, Smith JS, Becker D. Limits of body mass index to detect obesity and predict body composition. *Nutrition* 2001; 17(1): 26-30.

130. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond)* 2010; 34(5): 791-9.

131. Kabat GC, Heo M, Wactawski-Wende J, Messina C, Thomson CA, Wassertheil-Smoller S, et al. Body fat and risk of colorectal cancer among postmenopausal women. *Cancer Causes Control* 2013; 24(6): 1197-205.

132. MacInnis RJ, English DR, Hopper JL, Gertig DM, Haydon AM, Giles GG. Body size and composition and colon cancer risk in women. *Int J Cancer* 2006; 118(6): 1496-500.

133. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev* 2004; 13(4): 553-9.

134. Ortega LS, Bradbury KE, Cross AJ, Morris JS, Gunter MJ, Murphy N. A prospective investigation of body size, body fat composition and colorectal cancer risk in the UK Biobank. *Sci Rep* 2017; 7(1): 17807.

135. Pang Y, Holmes MV, Kartsonaki C, Guo Y, Yang L, Bian Z, et al. Young adulthood and adulthood adiposity in relation to incidence of pancreatic cancer: a

prospective study of 0.5 million Chinese adults and a meta-analysis. *J Epidemiol Community Health* 2017; 71(11): 1059-67.

136. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer--Viewpoint of the IARC Working Group. *N Engl J Med* 2016; 375(8): 794-8.

137. Chen JG, Zhang SW. Liver cancer epidemic in China: past, present and future. *Semin Cancer Biol* 2011; 21(1): 59-69.

138. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 10(363): 157-63.

139. Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev* 2006; 15(12): 2435-40.

140. Lin Y, Fu R, Grant E, Chen Y, Lee JE, Gupta PC, et al. Association of body mass index and risk of death from pancreas cancer in Asians: findings from the Asia Cohort Consortium. *Eur J Cancer Prev* 2013; 22(3): 244-50.

141. Liu Y, Warren Andersen S, Wen W, Gao YT, Lan Q, Rothman N, et al. Prospective cohort study of general and central obesity, weight change trajectory and risk of major cancers among Chinese women. *Int J Cancer* 2016; 139(7): 1461-70.

142. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2006; 15(5): 879-85.

143. Luo J, Margolis KL, Adami HO, LaCroix A, Ye W, Women's Health Initiative I. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). *Br J Cancer* 2008; 99(3): 527-31.

144. Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol* 2015; 26(11): 2257-66.

145. Trepo C, Chan HL, Lok A. Hepatitis B virus infection. *Lancet* 2014; 384(9959): 2053-63.

146. Chen Z, Yang G, Offer A, Zhou M, Smith M, Peto R, et al. Body mass index and mortality in China: a 15-year prospective study of 220 000 men. *Int J Epidemiol* 2012; 41(2): 472-81.

147. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. adults. *Cancer Res* 2016; 76(20): 6076-83.

148. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M, Trepo E, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. *Int J Cancer* 2013; 132(3): 645-57.

149. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res* 2008; 68(1): 329-37.

150. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006; 98(13): 920-31.

151. Larsson SC, Rutegard J, Bergkvist L, Wolk A. Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men. *Eur J Cancer* 2006; 42(15): 2590-7.

152. Wang Y, Jacobs EJ, Patel AV, Rodriguez C, McCullough ML, Thun MJ, et al. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control* 2008; 19(7): 783-92.

153. Hassan MM, Abdel-Wahab R, Kaseb A, Shalaby A, Phan AT, El-Serag HB, et al. Obesity Early in Adulthood Increases Risk but Does Not Affect Outcomes of Hepatocellular Carcinoma. *Gastroenterology* 2015; 149(1): 119-29.

154. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, et al. Early life body fatness and risk of colorectal cancer in U.S. Women and men-results from two large cohort studies. *Cancer Epidemiol Biomarkers Prev* 2015; 24(4): 690-7.

155. Li Y, Yatsuya H, Yamagishi K, Wakai K, Tamakoshi A, Iso H, et al. Body mass index and weight change during adulthood are associated with increased mortality from liver cancer: the JACC Study. *J Epidemiol* 2013; 23(3): 219-26.

156. Win AK, Dowty JG, English DR, Campbell PT, Young JP, Winship I, et al. Body mass index in early adulthood and colorectal cancer risk for carriers and non-carriers of germline mutations in DNA mismatch repair genes. *Br J Cancer* 2011; 105(1): 162-9.

157. Lee IM, Paffenbarger RS, Jr. Quetelet's index and risk of colon cancer in college alumni. *J Natl Cancer Inst* 1992; 84(17): 1326-31.

158. Burton A, Martin R, Galobardes B, Davey Smith G, Jeffreys M. Young adulthood body mass index and risk of cancer in later adulthood: historical cohort study. *Cancer Causes Control* 2010; 21(12): 2069-77.

159. Thrift AP, Gong J, Peters U, Chang-Claude J, Rudolph A, Slattery ML, et al. Mendelian randomization study of body mass index and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2015; 24(7): 1024-31.

160. Gao C, Patel CJ, Michailidou K, Peters U, Gong J, Schildkraut J, et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Int J Epidemiol* 2016; 45(3): 896-908.

161. Carreras-Torres R, Johansson M, Gaborieau V, Haycock PC, Wade KH, Relton CL, et al. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a Mendelian randomization study. *J Natl Cancer Inst* 2017; 109(9).

162. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003; 32(1): 1-22.

163. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008; 8(12): 915-28.

164. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* 2015; 350: g7607.

165. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *Eur J Cancer* 2011; 47(13): 1928-37.

166. Pang Y, Kartsonaki C, Guo Y, Bragg F, Yang L, Bian Z, et al. Diabetes, plasma glucose and incidence of pancreatic cancer: A prospective study of 0.5 million Chinese adults and a meta-analysis of 22 cohort studies. *Int J Cancer* 2017; 140(8): 1781-8.

167. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364(9): 829-41.

168. Lam EK, Batty GD, Huxley RR, Martiniuk AL, Barzi F, Lam TH, et al. Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. *Ann Oncol* 2011; 22(3): 730-8.

169. Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* 2017; 60(6): 1022-32.

170. Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Int J Cancer* 2012; 130(7): 1639-48.

171. Wang Y, Wang B, Yan S, Shen F, Cao H, Fan J, et al. Type 2 diabetes and gender differences in liver cancer by considering different confounding factors: a meta-analysis of cohort studies. *Ann Epidemiol* 2016; 26(11): 764-72.

172. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J Gastroenterol* 2015; 21(19): 6026-31.

173. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol* 2011; 26(11): 863-76.

174. Chiang CH, Lee LT, Hung SH, Lin WY, Hung HF, Yang WS, et al. Opposite association between diabetes, dyslipidemia, and hepatocellular carcinoma mortality in the middle-aged and elderly. *Hepatology* 2014; 59(6): 2207-15.

175. Koh WP, Wang R, Jin A, Yu MC, Yuan JM. Diabetes mellitus and risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Br J Cancer* 2013; 108(5): 1182-8.

176. de Kort S, Simons CC, van den Brandt PA, Goldbohm RA, Arts IC, de Bruine AP, et al. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer. *Eur J Gastroenterol Hepatol* 2016; 28(8): 896-903.

177. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, et al. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst* 1999; 91(6): 542-7.

178. Dankner R, Boffetta P, Balicer RD, Boker LK, Sadeh M, Berlin A, et al. Time-dependent risk of cancer after a diabetes diagnosis in a cohort of 2.3 million adults. *Am J Epidemiol* 2016; 183(12): 1098-106.

179. de Bruijn KM, Ruiter R, de Keyser CE, Hofman A, Stricker BH, van Eijck CH. Detection bias may be the main cause of increased cancer incidence among diabetics: results from the Rotterdam Study. *Eur J Cancer* 2014; 50(14): 2449-55.

180. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. *Diabetes Care* 2015; 38(2): 264-70.

181. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. *Diabetologia* 2011; 54(9): 2263-71.

182. Liao WC, Tu YK, Wu MS, Lin JT, Wang HP, Chien KL. Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. *BMJ* 2015; 350: g7371.

183. Johansen D, Stocks T, Jonsson H, Lindkvist B, Bjorge T, Concin H, et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. *Cancer Epidemiol Biomarkers Prev* 2010; 19(9): 2307-17.

184. Han H, Zhang T, Jin Z, Guo H, Wei X, Liu Y, et al. Blood glucose concentration and risk of liver cancer: systematic review and meta-analysis of prospective studies. *Oncotarget* 2017; 8(30): 50164-73.

185. Feng X, Wang G, Li N, Lyu Z, Chen S, Wei L, et al. The association between fasting blood glucose and the risk of primary liver cancer in Chinese males: a population-based prospective study. *Br J Cancer* 2017; 117(9): 1405-11.

186. Borena W, Strohmaier S, Lukanova A, Bjorge T, Lindkvist B, Hallmans G, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int J Cancer* 2012; 131(1): 193-200.

187. Shi J, Xiong L, Li J, Cao H, Jiang W, Liu B, et al. A linear dose-response relationship between fasting plasma glucose and colorectal cancer risk: systematic review and meta-analysis. *Sci Rep* 2015; 5: 17591.

188. Stocks T, Lukanova A, Bjorge T, Ulmer H, Manjer J, Almquist M, et al. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can). *Cancer* 2011; 117(11): 2398-407.

189. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* 2005; 294(22): 2872-8.

190. Wolpin BM, Bao Y, Qian ZR, Wu C, Kraft P, Ogino S, et al. Hyperglycemia, insulin resistance, impaired pancreatic beta-cell function, and risk of pancreatic cancer. *J Natl Cancer Inst* 2013; 105(14): 1027-35.

191. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer* 2008; 8(3): 205-11.

192. Bouassida A, Chamari K, Zaouali M, Feki Y, Zbidi A, Tabka Z. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. *Br J Sports Med* 2010; 44(9): 620-30.

193. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; 282(22): 2131-5.

194. Mora S, Lee IM, Buring JE, Ridker PM. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA* 2006; 295(12): 1412-9.

195. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 2001; 153(3): 242-50.

196. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002; 13(5): 561-8.

197. Elwood PC, Yarnell JW, Pickering J, Fehily AM, O'Brien JR. Exercise, fibrinogen, and other risk factors for ischaemic heart disease. Caerphilly Prospective Heart Disease Study. *Br Heart J* 1993; 69(2): 183-7.

198. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 2002; 162(11): 1286-92.

199. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut* 2017; 66(6): 1138-53.

200. Tsunoda K, Kai Y, Uchida K, Kuchiki T, Nagamatsu T. Physical activity and risk of fatty liver in people with different levels of alcohol consumption: a prospective cohort study. *BMJ Open* 2014; 4(8): e005824.

201. Tsunoda K, Kai Y, Kitano N, Uchida K, Kuchiki T, Nagamatsu T. Impact of physical activity on nonalcoholic steatohepatitis in people with nonalcoholic simple fatty liver: A prospective cohort study. *Prev Med* 2016; 88: 237-40.

202. Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB, et al. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol* 2011; 106(3): 460-8; quiz 9.

203. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007; 132(6): 2169-80.

204. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010; 60(4): 207-21.

205. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst* 2002; 94(13): 972-80.

206. Clayton PE, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol* 2011; 7(1): 11-24.

207. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med* 2003; 54: 131-52.

208. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 2002; 11(12): 1531-43.

209. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; 4(8): 579-91.

210. Lin JH, Zhang SM, Rexrode KM, Manson JE, Chan AT, Wu K, et al. Association between sex hormones and colorectal cancer risk in men and women. *Clin Gastroenterol Hepatol* 2013; 11(4): 419-24 e1.

211. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. *FASEB J* 1998; 12(1): 57-65.

212. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. Relationship of total and abdominal adiposity with CRP and IL-6 in women. *Ann Epidemiol* 2003; 13(10): 674-82.

213. Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: a systematic review. *Br J Cancer* 2006; 94(9): 1221-5.

214. Aleksandrova K, Jenab M, Boeing H, Jansen E, Bueno-de-Mesquita HB, Rinaldi S, et al. Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European Prospective Investigation into Cancer and Nutrition. *Am J Epidemiol* 2010; 172(4): 407-18.

215. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *J Clin Oncol* 2006; 24(33): 5216-22.

216. Yako YY, Kruger D, Smith M, Brand M. Cytokines as biomarkers of pancreatic ductal adenocarcinoma: a systematic review. *PLoS One* 2016; 11(5): e0154016.

217. Garofalo C, Surmacz E. Leptin and cancer. *J Cell Physiol* 2006; 207(1): 12-22.

218. Bao Y, Giovannucci EL, Kraft P, Stampfer MJ, Ogino S, Ma J, et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J Natl Cancer Inst* 2013; 105(2): 95-103.

219. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab* 2007; 92(1): 255-63.

220. Michalakis K, Williams CJ, Mitsiades N, Blakeman J, Balafouta-Tselenis S, Giannopoulos A, et al. Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. *Cancer Epidemiol Biomarkers Prev* 2007; 16(2): 308-13.

221. Tworoger SS, Eliassen AH, Kelesidis T, Colditz GA, Willett WC, Mantzoros CS, et al. Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metab* 2007; 92(4): 1510-6.

222. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst* 2005; 97(22): 1688-94.

223. Stolzenberg-Solomon RZ, Newton CC, Silverman DT, Pollak M, Nogueira LM, Weinstein SJ, et al. Circulating leptin and risk of pancreatic cancer: a pooled analysis from 3 cohorts. *Am J Epidemiol* 2015; 182(3): 187-97.

224. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 2015; 15(8): 484-98.

225. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* 2010; 61: 301-16.

226. Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? *Br J Nutr* 2008; 100(2): 227-35.

227. Vaupel P, Hoeckel M. Predictive power of the tumor oxygenation status. *Adv Exp Med Biol* 1999; 471: 533-9.

228. Bertolini F, Petit JY, Kolonin MG. Stem cells from adipose tissue and breast cancer: hype, risks and hope. *Br J Cancer* 2015; 112(3): 419-23.

229. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature* 2012; 489(7415): 242-9.

230. Schulz MD, Atay C, Heringer J, Romrig FK, Schwitalla S, Aydin B, et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* 2014; 514(7523): 508-12.

231. Ohtani N. Microbiome and cancer. *Semin Immunopathol* 2015; 37(1): 65-72.

232. Alzahrani B, Iseli TJ, Hebbard LW. Non-viral causes of liver cancer: does obesity led inflammation play a role? *Cancer Lett* 2014; 345(2): 223-9.

233. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; 324(5930): 1029-33.

234. Li D. Diabetes and pancreatic cancer. *Mol Carcinog* 2012; 51(1): 64-74.

235. Grote VA, Rohrmann S, Nieters A, Dossus L, Tjonneland A, Halkjaer J, et al. Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Diabetologia* 2011; 54(12): 3037-46.

236. Michaud DS, Wolpin B, Giovannucci E, Liu S, Cochrane B, Manson JE, et al. Prediagnostic plasma C-peptide and pancreatic cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev* 2007; 16(10): 2101-9.

237. Wolpin BM, Michaud DS, Giovannucci EL, Schernhammer ES, Stampfer MJ, Manson JE, et al. Circulating insulin-like growth factor axis and the risk of pancreatic cancer in four prospective cohorts. *Br J Cancer* 2007; 97(1): 98-104.

238. Ortiz AP, Thompson CL, Chak A, Berger NA, Li L. Insulin resistance, central obesity, and risk of colorectal adenomas. *Cancer* 2012; 118(7): 1774-81.

239. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999; 91(13): 1147-54.

240. Yoon YS, Keum N, Zhang X, Cho E, Giovannucci EL. Hyperinsulinemia, insulin resistance and colorectal adenomas: A meta-analysis. *Metabolism* 2015; 64(10): 1324-33.

241. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; 346(16): 1221-31.

242. Kajiura K, Ohkusa T, Okayasu I. Relationship between fecal bile acids and the occurrence of colorectal neoplasia in experimental murine ulcerative colitis. *Digestion* 1998; 59(1): 69-72.

243. Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol* 2011; 40(6): 1652-66.

244. Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. *Int J Epidemiol* 2002; 31(1): 168-74.

245. Matthews CE, Shu XO, Yang G, Jin F, Ainsworth BE, Liu D, et al. Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. *Am J Epidemiol* 2003; 158(11): 1114-22.

246. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011; 43(8): 1575-81.

247. Bragg F, Li L, Smith M, Guo Y, Chen Y, Millwood I, et al. Associations of blood glucose and prevalent diabetes with risk of cardiovascular disease in 500 000 adult Chinese: the China Kadoorie Biobank. *Diabet Med* 2014; 31(5): 540-51.

248. Yang G, Rao C, Ma J, Wang L, Wan X, Dubrovsky G, et al. Validation of verbal autopsy procedures for adult deaths in China. *Int J Epidemiol* 2006; 35(3): 741-8.

249. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 381(9882): 1987-2015.

250. Asadzadeh Vostakolaei F, Karim-Kos HE, Janssen-Heijnen ML, Visser O, Verbeek AL, Kiemeney LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur J Public Health* 2011; 21(5): 573-7.

251. Choi E, Lee S, Nhung BC, Suh M, Park B, Jun JK, et al. Cancer mortality-to-incidence ratio as an indicator of cancer management outcomes in Organization for Economic Cooperation and Development countries. *Epidemiol Health* 2017; 39: e2017006.

252. Lee HL, Peng CM, Huang CY, Wu SY, Tsai MC, Wang CC, et al. Is mortality-to-incidence ratio associated with health disparity in pancreatic cancer? A cross-sectional database analysis of 57 countries. *BMJ Open* 2018; 8(7): e020618.

253. Sunkara V, Hebert JR. The application of the mortality-to-incidence ratio for the evaluation of cancer care disparities globally. *Cancer* 2016; 122(3): 487-8.

254. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic symdrome. Brussels, 2006.

255. World health Organisation. Waist circumference and waist-hip ratio. Report of a WHO Expert Consultation. Geneva, 2008.

256. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; 10(7): 1025-35.

257. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335(8692): 765-74.

258. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; 150(4): 341-53.

259. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009; 10(1): 88-95.

260. Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. *Lancet Diabetes Endocrinol* 2014; 2(11): 901-10.

261. Collaboration GBM. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016; 388(10046): 776-86.

262. Singh S, Singh H, Singh PP, Murad MH, Limburg PJ. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2013; 22(12): 2258-68.

263. Singh S, Singh PP, Singh AG, Murad MH, McWilliams RR, Chari ST. Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108(4): 510-9.

264. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108(6): 881-91; quiz 92.

265. Wei KR, Yu X, Zheng RS, Peng XB, Zhang SW, Ji MF, et al. Incidence and mortality of liver cancer in China, 2010. *Chin J Cancer* 2014; 33(8): 388-94.

266. Chen W, Zheng R, Zhang S, Zeng H, Zuo T, Xia C, et al. Cancer incidence and mortality in China in 2013: an analysis based on urbanization level. *Chin J Cancer Res* 2017; 29(1): 1-10.

267. Yang Z, Zheng R, Zhang S, Zeng H, Xia C, Li H, et al. Comparison of cancer incidence and mortality in three GDP per capita levels in China, 2013. *Chin J Cancer Res* 2017; 29(5): 385-94.

268. Doll R. Urban and rural factors in the aetiology of cancer. *Int J Cancer* 1991; 47(6): 803-10.

269. Gartner A, Farewell D, Roach P, Dunstan F. Rural/urban mortality differences in England and Wales and the effect of deprivation adjustment. *Soc Sci Med* 2011; 72(10): 1685-94.

270. Lagace C, Desmeules M, Pong RW, Heng D. Non-communicable disease and injury-related mortality in rural and urban places of residence: a comparison between Canada and Australia. *Can J Public Health* 2007; 98 Suppl 1: S62-9.

271. Puigpinos R, Borrell C, Antunes JL, Azlor E, Pasarin MI, Serral G, et al. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. *BMC Public Health* 2009; 9: 35.

272. Singh GK, Williams SD, Siahpush M, Mulhollen A. Socioeconomic, rural-urban, and racial inequalities in US cancer mortality: Part I-All cancers and lung cancer and Part II-Colorectal, prostate, breast, and cervical cancers. *J Cancer Epidemiol* 2011; 2011: 107497.

273. Fan JH, Wang JB, Jiang Y, Xiang W, Liang H, Wei WQ, et al. Attributable causes of liver cancer mortality and incidence in china. *Asian Pac J Cancer Prev* 2013; 14(12): 7251-6.

274. Choi KM. Investigation of cancer mortality inequalities between rural and urban areas in South Korea. *Aust J Rural Health* 2016; 24(1): 61-6.

275. Ma YX, Zhang B, Wang HJ, Du WW, Su C, Zhai FY. Status and trend of alcohol consumption among adults in nine provinces (antonomous region) of China from 1993 to 2006. *Zhonghua Yu Fang Yi Xue Za Zhi* 2011; 45(4): 323-9.

276. Butow PN, Phillips F, Schweder J, White K, Underhill C, Goldstein D, et al. Psychosocial well-being and supportive care needs of cancer patients living in urban and rural/regional areas: a systematic review. *Support Care Cancer* 2012; 20(1): 1-22.

277. Mollica MA, Weaver KE, McNeel TS, Kent EE. Examining urban and rural differences in perceived timeliness of care among cancer patients: A SEER-CAHPS study. *Cancer* 2018; 124(15): 3257-65.

278. Weaver KE, Geiger AM, Lu L, Case LD. Rural-urban disparities in health status among US cancer survivors. *Cancer* 2013; 119(5): 1050-7.

279. Weaver KE, Palmer N, Lu L, Case LD, Geiger AM. Rural-urban differences in health behaviors and implications for health status among US cancer survivors. *Cancer Causes Control* 2013; 24(8): 1481-90.

280. Sunkara V, Hebert JR. The colorectal cancer mortality-to-incidence ratio as an indicator of global cancer screening and care. *Cancer* 2015; 121(10): 1563-9.

281. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, Fan L, Li J, Chavarri-Guerra Y, et al. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol* 2014; 15(5): 489-538.

282. China Health Statistics Yearbook. 2011. http://wsb.moh.gov.cn/htmlfiles/zwgkzt/ptjnj/year2011/index2011.html (accessed May 1 2018).

283. Liu M, Zhang Q, Lu M, Kwon CS, Quan H. Rural and urban disparity in health services utilization in China. *Med Care* 2007; 45(8): 767-74.

284. Kang LN, Qiao, R.L. Cancer screening and prevention in China. *Cancer Control* 2014: 131-3.

285. Chinese Anti-Cancer Association Society of Liver Cancer, Chinese Society of Hepatology Liver Cancer Study Group. The expert consensus on the treatment standards for hepatocellular carcinoma. *Digestive Disease and Endoscopy* 2009; 3: 40-51.

286. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; 64(10): 1637-49.

287. Wang B, He M, Wang L, Engelgau MM, Zhao W, Wang L. Breast cancer screening among adult women in China, 2010. *Prev Chronic Dis* 2013; 10: E183.

288. Wang B, He M, Chao A, Engelgau MM, Saraiya M, Wang L, et al. Cervical cancer screening among adult women in China, 2010. *Oncologist* 2015; 20(6): 627-34.

289. Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc* 2007; 99(9): 1013-23.

290. Joshi S, Song YM, Kim TH, Cho SI. Socio-economic status and the risk of liver cancer mortality: a prospective study in Korean men. *Public Health* 2008; 122(11): 1144-51.

291. Yun EH, Lim MK, Oh JK, Park JH, Shin A, Sung J, et al. Combined effect of socioeconomic status, viral hepatitis, and lifestyles on hepatocelluar carcinoma risk in Korea. *Br J Cancer* 2010; 103(5): 741-6.

292. Tavani A, Fioretti F, Franceschi S, Gallus S, Negri E, Montella M, et al. Education, socioeconomic status and risk of cancer of the colon and rectum. *Int J Epidemiol* 1999; 28(3): 380-5.

293. Menvielle G, Rey G, Jougla E, Luce D. Diverging trends in educational inequalities in cancer mortality between men and women in the 2000s in France. *BMC Public Health* 2013; 13: 823.

294. Jemal A, Simard EP, Xu J, Ma J, Anderson RN. Selected cancers with increasing mortality rates by educational attainment in 26 states in the United States, 1993-2007. *Cancer Causes Control* 2013; 24(3): 559-65.

295. Doubeni CA, Laiyemo AO, Major JM, Schootman M, Lian M, Park Y, et al. Socioeconomic status and the risk of colorectal cancer: an analysis of more than a

half million adults in the National Institutes of Health-AARP Diet and Health Study. *Cancer* 2012; 118(14): 3636-44.

296. Vathesatogkit P, Batty GD, Woodward M. Socioeconomic disadvantage and disease-specific mortality in Asia: systematic review with meta-analysis of population-based cohort studies. *J Epidemiol Community Health* 2014; 68(4): 375-83.

297. Cole AM, Jackson JE, Doescher M. Urban-rural disparities in colorectal cancer screening: cross-sectional analysis of 1998-2005 data from the Centers for Disease Control's Behavioral Risk Factor Surveillance Study. *Cancer Med* 2012; 1(3): 350-6.

298. Wang KS, Liu X, Ategbole M, Xie X, Liu Y, Xu C, et al. Generalized linear mixed model analysis of urban-rural differences in social and behavioral factors for colorectal cancer screening. *Asian Pac J Cancer Prev* 2017; 18(9): 2581-9.

299. Shi J, Huang H, Guo L, Ren J, Ren Y, Lan L, et al. Acceptance and willingness-to-pay for colorectal colonoscopy screening among high-risk populations for colorectal cancer in urban China. *Zhonghua Yu Fang Yi Xue Za Zhi* 2015; 49(5): 381-6.

300. Parikh-Patel A, Bates JH, Campleman S. Colorectal cancer stage at diagnosis by socioeconomic and urban/rural status in California, 1988-2000. *Cancer* 2006; 107(5 Suppl): 1189-95.

301. Kweon SS, Kim MG, Kang MR, Shin MH, Choi JS. Difference of stage at cancer diagnosis by socioeconomic status for four target cancers of the National Cancer Screening Program in Korea: Results from the Gwangju and Jeonnam cancer registries. *J Epidemiol* 2017; 27(7): 299-304.

302. Li Y, Shi J, Yu S, Wang L, Liu J, Ren J, et al. Effect of socioeconomic status on stage at diagnosis of lung cancer in a hospital-based multicenter retrospective clinical epidemiological study in China, 2005-2014. *Cancer Med* 2017; 6(10): 2440-52.

303. Ueda K, Tsukuma H, Ajiki W, Oshima A. Socioeconomic factors and cancer incidence, mortality, and survival in a metropolitan area of Japan: a cross-sectional ecological study. *Cancer Sci* 2005; 96(10): 684-8.

304. Dorak MT, Karpuzoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue. *Front Genet* 2012; 3: 268.

305. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev* 2011; 20(8): 1629-37.

306. Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, et al. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007; 317(5834): 121-4.

307. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007; 117(5): 1137-46.

308. Cramer DW, Finn OJ. Epidemiologic perspective on immune-surveillance in cancer. *Curr Opin Immunol* 2011; 23(2): 265-71.

309. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology* 2012; 153(6): 2544-50.

310. Kirsch-Volders M, Bonassi S, Herceg Z, Hirvonen A, Moller L, Phillips DH. Gender-related differences in response to mutagens and carcinogens. *Mutagenesis* 2010; 25(3): 213-21.

311. Li M, Gu J. Changing patterns of colorectal cancer in China over a period of 20 years. *World J Gastroenterol* 2005; 11(30): 4685-8.

312. Xu AG, Yu ZJ, Jiang B, Wang XY, Zhong XH, Liu JH, et al. Colorectal cancer in Guangdong Province of China: a demographic and anatomic survey. *World J Gastroenterol* 2010; 16(8): 960-5.

313. Jiang SX, Wang XS, Geng CH, Wang GY. Altering trend of clinical characteristics of colorectal cancer: a report of 3,607 cases. *Ai Zheng* 2009; 28(1): 54-6.

314. Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer* 2002; 101(5): 403-8.

315. Yamauchi M, Lochhead P, Morikawa T, Huttenhower C, Chan AT, Giovannucci E, et al. Colorectal cancer: a tale of two sides or a continuum? *Gut* 2012; 61(6): 794-7.

316. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer* 2004; 108(3): 433-42.

317. Long J, Luo GP, Xiao ZW, Liu ZQ, Guo M, Liu L, et al. Cancer statistics: current diagnosis and treatment of pancreatic cancer in Shanghai, China. *Cancer Lett* 2014; 346(2): 273-7.

318. Keum N, Bao Y, Smith-Warner SA, Orav J, Wu K, Fuchs CS, et al. Association of physical activity by type and intensity with digestive system cancer risk. *JAMA Oncol* 2016; 2(9): 1146-53.

319. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). *Cancer Causes Control* 2002; 13(5): 417-26.

320. Paffenbarger RS, Jr., Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am J Clin Nutr* 1987; 45(1 Suppl): 312-7.

321. Nilsen TI, Vatten LJ. A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. *Cancer Causes Control* 2000; 11(7): 645-52.

322. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer* 2002; 98(3): 480-2.

323. Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E. Occupational exposures and gastrointestinal cancers among Finnish women. *J Occup Environ Med* 2003; 45(3): 305-15.

324. Heinen MM, Verhage BA, Goldbohm RA, Lumey LH, van den Brandt PA. Physical activity, energy restriction, and the risk of pancreatic cancer: a prospective study in the Netherlands. *Am J Clin Nutr* 2011; 94(5): 1314-23.

325. Jurj AL, Wen W, Xiang YB, Matthews CE, Liu D, Zheng W, et al. Reproducibility and validity of the Shanghai Men's Health Study physical activity questionnaire. *Am J Epidemiol* 2007; 165(10): 1124-33.

326. Friedenreich C, Norat T, Steindorf K, Boutron-Ruault MC, Pischon T, Mazuir M, et al. Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2006; 15(12): 2398-407.

327. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; 29(6): 1433-8.

328. Keum N, Cao Y, Oh H, Smith-Warner SA, Orav J, Wu K, et al. Sedentary behaviors and light-intensity activities in relation to colorectal cancer risk. *Int J Cancer* 2016; 138(9): 2109-17.

329. Mayer-Davis EJ, D'Agostino R, Jr., Karter AJ, Haffner SM, Rewers MJ, Saad M, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 1998; 279(9): 669-74.

330. Kelley DE, Goodpaster BH. Effects of physical activity on insulin action and glucose tolerance in obesity. *Med Sci Sports Exerc* 1999; 31(11 Suppl): S619-23.

331. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010; 33(12): e147-67.

332. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol* 2005; 45(10): 1563-9.

333. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 2014; 60(3): 858-71.

334. Brenner DR, Fanidi A, Grankvist K, Muller DC, Brennan P, Manjer J, et al. Inflammatory cytokines and lung cancer risk in 3 prospective studies. *Am J Epidemiol* 2017; 185(2): 86-95.

335. Dossus L, Franceschi S, Biessy C, Navionis AS, Travis RC, Weiderpass E, et al. Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study. *Int J Cancer* 2018; 142(7): 1332-42.

336. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst* 2011; 103(14): 1112-22.

337. Trabert B, Eldridge RC, Pfeiffer RM, Shiels MS, Kemp TJ, Guillemette C, et al. Prediagnostic circulating inflammation markers and endometrial cancer risk in

the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Int J Cancer* 2017; 140(3): 600-10.

338. Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecol Oncol* 2014; 135(2): 297-304.

339. Woods JA. Physical activity, exercise, and immune function. *Brain Behav Immun* 2005; 19(5): 369-70.

340. Pedersen BK, Ullum H. NK cell response to physical activity: possible mechanisms of action. *Med Sci Sports Exerc* 1994; 26(2): 140-6.

341. Patterson R, McNamara E, Tainio M, de Sa TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol* 2018; 33(9): 811-829.

342. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metab* 2010; 35(6): 725-40.

343. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; 140(6): 883-99.

344. Hypponen E, Berry D, Cortina-Borja M, Power C. 25-Hydroxyvitamin D and pre-clinical alterations in inflammatory and hemostatic markers: a cross sectional analysis in the 1958 British Birth Cohort. *PLoS One* 2010; 5(5): e10801.

345. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. *Pediatrics* 2009; 124(3): e362-70.

346. Flegal KM, Graubard BI, Williamson DF, Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. *Am J Epidemiol* 2011; 173(1): 1-9.

347. Lawlor DA, Hart CL, Hole DJ, Davey Smith G. Reverse causality and confounding and the associations of overweight and obesity with mortality. *Obesity (Silver Spring)* 2006; 14(12): 2294-304.

348. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. *Am J Clin Nutr* 2008; 87(4): 801-9.

349. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control* 2007; 18(2): 165-75.

350. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF, Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control* 2006; 17(7): 901-9.

351. Stolzenberg-Solomon RZ, Schairer C, Moore S, Hollenbeck A, Silverman DT. Lifetime adiposity and risk of pancreatic cancer in the NIH-AARP Diet and Health Study cohort. *Am J Clin Nutr* 2013; 98(4): 1057-65.

352. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. Body mass index and cancer risk in Korean men and women. *Int J Cancer* 2008; 123(8): 1892-6.

353. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol* 2005; 23(21): 4742-54.

354. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. *J Clin Oncol* 2008; 26(20): 3395-402.

355. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol* 2012; 23(4): 843-52.

356. Batty GD, Barzi F, Huxley R, Chang CY, Jee SH, Jamrozik K, et al. Obesity and liver cancer mortality in Asia: The Asia Pacific Cohort Studies Collaboration. *Cancer Epidemiol* 2009; 33(6): 469-72.

357. Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncol* 2010; 11(8): 741-52.

358. Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008; 135(1): 111-21.

359. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; 129(1): 113-21.

360. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology* 2010; 51(2): 679-89.

361. Tiollais P, Pourcel C, Dejean A. The hepatitis B virus. *Nature* 1985; 317(6037): 489-95.

362. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348(17): 1625-38.

363. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007; 335(7630): 1134.

364. Abar L, Vieira AR, Aune D, Sobiecki JG, Vingeliene S, Polemiti E, et al. Height and body fatness and colorectal cancer risk: an update of the WCRF-AICR systematic review of published prospective studies. *Eur J Nutr* 2018; 57(5): 1701-20.

365. Akhter M, Kuriyama S, Nakaya N, Shimazu T, Ohmori K, Nishino Y, et al. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: the Miyagi Cohort Study. *Eur J Cancer* 2007; 43(2): 383-90.

366. Matsuo K, Mizoue T, Tanaka K, Tsuji I, Sugawara Y, Sasazuki S, et al. Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan. *Ann Oncol* 2012; 23(2): 479-90.

367. Odegaard AO, Koh WP, Yu MC, Yuan JM. Body mass index and risk of colorectal cancer in Chinese Singaporeans: the Singapore Chinese Health Study. *Cancer* 2011; 117(16): 3841-9.

368. Otani T, Iwasaki M, Inoue M, Shoichiro Tsugane for the Japan Public Health Center-based Prospective Study G. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. *Cancer Causes Control* 2005; 16(7): 839-50.

369. Shin CM, Han K, Lee DH, Choi YJ, Kim N, Park YS, et al. Association among obesity, metabolic health, and the risk for colorectal cancer in the general population in Korea using the National Health Insurance Service-National Sample Cohort. *Dis Colon Rectum* 2017; 60(11): 1192-200.

370. Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, et al. A prospective study of body size and colon cancer mortality in Japan: The JACC Study. *Int J Obes Relat Metab Disord* 2004; 28(4): 551-8.

371. Yeh CC, You SL, Chen CJ, Sung FC. Peanut consumption and reduced risk of colorectal cancer in women: a prospective study in Taiwan. *World J Gastroenterol* 2006; 12(2): 222-7.

372. Pang Y, Kartsonaki C, Guo Y, Chen Y, Yang L, Bian Z, et al. Adiposity and risks of colorectal and small intestine cancer in Chinese adults: a prospective study of 0.5 million people. *Br J Cancer* 2018.

373. Roubenoff R, Kehayias JJ. The meaning and measurement of lean body mass. *Nutr Rev* 1991; 49(6): 163-75.

374. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A. Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? *Am J Clin Nutr* 2003; 77(3): 726-30.

375. Racette SB, Evans EM, Weiss EP, Hagberg JM, Holloszy JO. Abdominal adiposity is a stronger predictor of insulin resistance than fitness among 50-95 year olds. *Diabetes Care* 2006; 29(3): 673-8.

376. Abraham TM, Pedley A, Massaro JM, Hoffmann U, Fox CS. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. *Circulation* 2015; 132(17): 1639-47.

377. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol* 2013; 62(10): 921-5.

378. Kabat GC, Kim MY, Strickler HD, Shikany JM, Lane D, Luo J, et al. A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. *Br J Cancer* 2012; 106(1): 227-32.

379. Loftfield E, Freedman ND, Lai GY, Weinstein SJ, McGlynn KA, Taylor PR, et al. Higher glucose and insulin levels are associated with risk of liver cancer and

chronic liver disease mortality among men without a history of diabetes. *Cancer Prev Res (Phila)* 2016; 9(11): 866-74.

380. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996; 45(5): 633-8.

381. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004; 350(10): 991-1004.

382. Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; 93(5 Pt 2): 880-8.

383. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. *J Clin Endocrinol Metab* 1991; 72(2): 374-81.

384. English MA, Kane KF, Cruickshank N, Langman MJ, Stewart PM, Hewison M. Loss of estrogen inactivation in colonic cancer. *J Clin Endocrinol Metab* 1999; 84(6): 2080-5.

385. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res* 2008; 68(1): 329-37.

386. Gao C, Patel CJ, Michailidou K, Peters U, Gong J, Schildkraut J, et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Int J Epidemiol* 2016; 45(3): 896-908.

387. Jarvis D, Mitchell JS, Law PJ, Palin K, Tuupanen S, Gylfe A, et al. Mendelian randomisation analysis strongly implicates adiposity with risk of developing colorectal cancer. *Br J Cancer* 2016; 115(2): 266-72.

388. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; 467(7319): 1114-7.

389. Srivatanakul P, Sriplung H, Deerasamee S. Epidemiology of liver cancer: an overview. *Asian Pac J Cancer Prev* 2004; 5(2): 118-25.

390. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; 142(6): 1264-73 e1.

391. Zhou XH, Qiao Q, Zethelius B, Pyorala K, Soderberg S, Pajak A, et al. Diabetes, prediabetes and cancer mortality. *Diabetologia* 2010; 53(9): 1867-76.

392. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293(2): 194-202.

393. Yang WS, Shu XO, Gao J, Li HL, Cai H, Yang G, et al. Prospective evaluation of type 2 diabetes mellitus on the risk of primary liver cancer in Chinese men and women. *Ann Oncol* 2013; 24(6): 1679-85.

394. Lo SF, Chang SN, Muo CH, Chen SY, Liao FY, Dee SW, et al. Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. *Int J Cancer* 2013; 132(1): 182-8.

395. Khan M, Mori M, Fujino Y, Shibata A, Sakauchi F, Washio M, et al. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev* 2006; 7(2): 253-9.

396. Wang CS, Yao WJ, Chang TT, Wang ST, Chou P. The impact of type 2 diabetes on the development of hepatocellular carcinoma in different viral hepatitis statuses. *Cancer Epidemiol Biomarkers Prev* 2009; 18(7): 2054-60.

397. Chen CT, Chen JY, Wang JH, Chang KC, Tseng PL, Kee KM, et al. Diabetes mellitus, metabolic syndrome and obesity are not significant risk factors for hepatocellular carcinoma in an HBV- and HCV-endemic area of Southern Taiwan. *Kaohsiung J Med Sci* 2013; 29(8): 451-9.

398. Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol* 2012; 107(1): 46-52.

399. Lai MS, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. *Hepatology* 2006; 43(6): 1295-302.

400. Setiawan VW, Hernandez BY, Lu SC, Stram DO, Wilkens LR, Le Marchand L, et al. Diabetes and racial/ethnic differences in hepatocellular carcinoma risk: the multiethnic cohort. *J Natl Cancer Inst* 2014; 106(12).

401. de Kort S, Masclee AAM, Sanduleanu S, Weijenberg MP, van Herk-Sukel MPP, Oldenhof NJJ, et al. Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation. *Sci Rep* 2017; 7: 46527.

402. Peeters PJ, Bazelier MT, Leufkens HG, de Vries F, De Bruin ML. The risk of colorectal cancer in patients with type 2 diabetes: associations with treatment stage and obesity. *Diabetes Care* 2015; 38(3): 495-502.

403. Flood A, Strayer L, Schairer C, Schatzkin A. Diabetes and risk of incident colorectal cancer in a prospective cohort of women. *Cancer Causes Control* 2010; 21(8): 1277-84.

404. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005; 129(2): 504-11.

405. Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008; 134(1): 95-101.

406. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol* 2013; 10(7): 423-33.

407. Pang Y, Kartsonaki C, Turnbull I, Guo Y, Clarke R, Chen Y, et al. Diabetes, plasma glucose and incidence of fatty liver, cirrhosis and liver cancer: A prospective study of 0.5 million people. *Hepatology* 2018.

408. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia* 2005; 48(4): 634-42.

409. Tilg H, Moschen AR. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. *Trends Endocrinol Metab* 2008; 19(10): 371-9.

410. Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol (Lausanne)* 2013; 4: 37.

411. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104(6): 787-94.

412. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 1988; 37(6): 667-87.

413. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; 46(1): 3-19.

414. Ammon HP. Hyper- and hypoinsulinemia in type-2 diabetes: what may be wrong in the secretory mechanism of the B-cell. *Exp Clin Endocrinol Diabetes* 1997; 105 Suppl 2: 43-7.

415. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care* 2012; 35(12): 2665-73.

416. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006; 29(2): 254-8.

417. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. *Epidemiology* 2011; 22(2): 228-31.

418. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 2010; 33(6): 1304-8.

419. Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol* 2014; 25(10): 2065-72.

420. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS One* 2013; 8(8): e71583.

421. Tsilidis KK, Capothanassi D, Allen NE, Rizos EC, Lopez DS, van Veldhoven K, et al. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. *Diabetes Care* 2014; 37(9): 2522-32.

422. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Ann N Y Acad Sci* 2011; 1243: 54-68.

423. Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK, Gans RO, et al. Metformin: taking away the candy for cancer? *Eur J Cancer* 2010; 46(13): 2369-80.

424. Pernicova I, Korbonits M. Metformin--mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 2014; 10(3): 143-56.

425. Goodwin PJ, Parulekar WR, Gelmon KA, Shepherd LE, Ligibel JA, Hershman DL, et al. Effect of metformin vs placebo on and metabolic factors in NCIC CTG MA.32. *J Natl Cancer Inst* 2015; 107(3).

426. Kordes S, Pollak MN, Zwinderman AH, Mathot RA, Weterman MJ, Beeker A, et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2015; 16(7): 839-47.

427. Reni M, Dugnani E, Cereda S, Belli C, Balzano G, Nicoletti R, et al. (Ir)relevance of metformin treatment in patients with metastatic pancreatic cancer: an open-label, randomized phase II trial. *Clin Cancer Res* 2016; 22(5): 1076-85.

428. Daneman D. Type 1 diabetes. *Lancet* 2006; 367(9513): 847-58.

429. Warburg O. On the origin of cancer cells. *Science* 1956; 123(3191): 309-14.

430. Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. *Cancer Res* 2006; 66(18): 8927-30.

431. Xu J, Ye Y, Wu H, Duerksen-Hughes P, Zhang H, Li P, et al. Association between markers of glucose metabolism and risk of colorectal cancer. *BMJ Open* 2016; 6(6): e011430.

432. Draznin B. Mitogenic action of insulin: friend, foe or 'frenemy'? *Diabetologia* 2010; 53(2): 229-33.

433. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control* 1995; 6(2): 164-79.

434. Chao LT, Wu CF, Sung FY, Lin CL, Liu CJ, Huang CJ, et al. Insulin, glucose and hepatocellular carcinoma risk in male hepatitis B carriers: results from 17-year follow-up of a population-based cohort. *Carcinogenesis* 2011; 32(6): 876-81.

435. Limburg PJ, Stolzenberg-Solomon RZ, Vierkant RA, Roberts K, Sellers TA, Taylor PR, et al. Insulin, glucose, insulin resistance, and incident colorectal cancer in male smokers. *Clin Gastroenterol Hepatol* 2006; 4(12): 1514-21.

436. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, et al. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2005; 14(4): 850-5.

437. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 2004; 25(1): 4-7.

438. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43(2 Suppl 1): S99-S112.

439. Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology* 2014; 146(3): 726-35.

440. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology* 2005; 42(5): 987-1000.

441. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; 51(5): 1820-32.

442. Azizian M, Mahdipour E, Mirhafez SR, Shoeibi S, Nematy M, Esmaily H, et al. Cytokine profiles in overweight and obese subjects and normal weight individuals matched for age and gender. *Ann Clin Biochem* 2016; 53(6): 663-8.

443. Denis GV, Sebastiani P, Andrieu G, Tran AH, Strissel KJ, Lombardi FL, et al. Relationships among obesity, type 2 diabetes, and plasma cytokines in African American women. *Obesity (Silver Spring)* 2017; 25(11): 1916-20.

444. Doupis J, Rahangdale S, Gnardellis C, Pena SE, Malhotra A, Veves A. Effects of diabetes and obesity on vascular reactivity, inflammatory cytokines, and growth factors. *Obesity (Silver Spring)* 2011; 19(4): 729-35.

445. Hashimoto I, Wada J, Hida A, Baba M, Miyatake N, Eguchi J, et al. Elevated serum monocyte chemoattractant protein-4 and chronic inflammation in overweight subjects. *Obesity (Silver Spring)* 2006; 14(5): 799-811.

446. Lim JP, Leung BP, Ding YY, Tay L, Ismail NH, Yeo A, et al. Monocyte chemoattractant protein-1: a proinflammatory cytokine elevated in sarcopenic obesity. *Clin Interv Aging* 2015; 10: 605-9.

447. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation* 2007; 116(11): 1234-41.

448. Wong E, Freiberg M, Tracy R, Kuller L. Epidemiology of cytokines: the Women On the Move through Activity and Nutrition (WOMAN) Study. *Am J Epidemiol* 2008; 168(4): 443-53.

449. Evans J, Collins M, Jennings C, van der Merwe L, Soderstrom I, Olsson T, et al. The association of interleukin-18 genotype and serum levels with metabolic risk factors for cardiovascular disease. *Eur J Endocrinol* 2007; 157(5): 633-40.

450. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. *Arterioscler Thromb Vasc Biol* 2005; 25(6): 1268-73.

451. Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. *JPEN J Parenter Enteral Nutr* 2004; 28(6): 410-5.

452. Kuo SM, Halpern MM. Lack of association between body mass index and plasma adiponectin levels in healthy adults. *Int J Obes (Lond)* 2011; 35(12): 1487-94.

453. Marques-Vidal P, Bochud M, Bastardot F, Luscher T, Ferrero F, Gaspoz JM, et al. Association between inflammatory and obesity markers in a Swiss population-based sample (CoLaus Study). *Obes Facts* 2012; 5(5): 734-44.

454. Piva SJ, Tatsch E, De Carvalho JA, Bochi GV, Kober H, Duarte T, et al. Assessment of inflammatory and oxidative biomarkers in obesity and their associations with body mass index. *Inflammation* 2013; 36(1): 226-31.

455. Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. *PLoS One* 2015; 10(3): e0121971.

456. Strohacker K, Wing RR, McCaffery JM. Contributions of body mass index and exercise habits on inflammatory markers: a cohort study of middle-aged adults living in the USA. *BMJ Open* 2013; 3(5).

457. Welsh P, Woodward M, Rumley A, Lowe G. Associations of circulating TNFalpha and IL-18 with myocardial infarction and cardiovascular risk markers: the Glasgow Myocardial Infarction Study. *Cytokine* 2009; 47(2): 143-7.

458. Pols MA, Peeters PH, Ocke MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. *Int J Epidemiol* 1997; 26 Suppl 1: S181-9.

459. Bennett DA, Du H, Clarke R, Guo Y, Yang L, Bian Z, et al. Association of physical activity with risk of major cardiovascular diseases in Chinese men and women. *JAMA Cardiol* 2017; 2(12): 1349-58.

460. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act* 2008; 5: 56.

461. Sabia S, van Hees VT, Shipley MJ, Trenell MI, Hagger-Johnson G, Elbaz A, et al. Association between questionnaire- and accelerometer-assessed physical activity: the role of sociodemographic factors. *Am J Epidemiol* 2014; 179(6): 781-90.

462. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. *Br J Sports Med* 2014; 48(13): 1019-23.

463. Troiano RP, Pettee Gabriel KK, Welk GJ, Owen N, Sternfeld B. Reported physical activity and sedentary behavior: why do you ask? *J Phys Act Health* 2012; 9 Suppl 1: S68-75.

464. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015; 26(2): 272-8.

465. Dvorak RV, Tchernof A, Starling RD, Ades PA, DiPietro L, Poehlman ET. Respiratory fitness, free living physical activity, and cardiovascular disease risk in older individuals: a doubly labeled water study. *J Clin Endocrinol Metab* 2000; 85(3): 957-63.

466. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002; 3(3): 141-6.

467. Ding J, Hsu FC, Harris TB, Liu Y, Kritchevsky SB, Szklo M, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* 2009; 90(3): 499-504.

468. McNeely MJ, Shofer JB, Leonetti DL, Fujimoto WY, Boyko EJ. Associations among visceral fat, all-cause mortality, and obesity-related mortality in Japanese Americans. *Diabetes Care* 2012; 35(2): 296-8.

469. KL Minaker. Common clinical sequelae of aging. In: Goldman L SA, ed. Goldman's Cecil Medicine 24th ed. Philadelphia: Elsevier Saunders; 2011.

470. Chan HL, Wong VW, Wong GL, Tse CH, Chan HY, Sung JJ. A longitudinal study on the natural history of serum hepatitis B surface antigen changes in chronic hepatitis B. *Hepatology* 2010; 52(4): 1232-41.

471. Scheiblauer H, El-Nageh M, Diaz S, Nick S, Zeichhardt H, Grunert HP, et al. Performance evaluation of 70 hepatitis B virus (HBV) surface antigen (HBsAg) assays from around the world by a geographically diverse panel with an array of HBV genotypes and HBsAg subtypes. *Vox Sang* 2010; 98(3 Pt 2): 403-14.

472. Nguyen T, Thompson AJ, Bowden S, Croagh C, Bell S, Desmond PV, et al. Hepatitis B surface antigen levels during the natural history of chronic hepatitis B: a perspective on Asia. *J Hepatol* 2010; 52(4): 508-13.

473. Fernandez E, La Vecchia C, D'Avanzo B, Negri E, Franceschi S. Family history and the risk of liver, gallbladder, and pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 1994; 3(3): 209-12.

474. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994; 331(25): 1669-74.

475. Doherty A, Jackson D, Hammerla N, Plotz T, Olivier P, Granat MH, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank Study. *PLoS One* 2017; 12(2): e0169649.

476. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 2000; 21(6): 697-738.

477. Linge J, Borga M, West J, Tuthill T, Miller MR, Dumitriu A, et al. Body composition profiling in the UK Biobank Imaging Study. *Obesity (Silver Spring)* 2018 May 22. doi: 10.1002/oby.22210.

478. Bamberg F, Hetterich H, Rospleszcz S, Lorbeer R, Auweter SD, Schlett CL, et al. Subclinical disease burden as assessed by whole-body MRI in subjects with prediabetes, subjects with diabetes, and normal control subjects from the general population: the KORA-MRI Study. *Diabetes* 2017; 66(1): 158-69.

479. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; 44(4): 865-73.

480. Le KA, Ventura EE, Fisher JQ, Davis JN, Weigensberg MJ, Punyanitya M, et al. Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers. *Diabetes Care* 2011; 34(2): 485-90.

481. Lingvay I, Esser V, Legendre JL, Price AL, Wertz KM, Adams-Huet B, et al. Noninvasive quantification of pancreatic fat in humans. *J Clin Endocrinol Metab* 2009; 94(10): 4070-6.

482. Wattacheril J, Chalasani N. Nonalcoholic fatty liver disease (NAFLD): is it really a serious condition? *Hepatology* 2012; 56(4): 1580-4.

483. Vongsuvanh R, George J, Qiao L, van der Poorten D. Visceral adiposity in gastrointestinal and hepatic carcinogenesis. *Cancer Lett* 2013; 330(1): 1-10.

484. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med* 2014; 12: 168.

485. Jiao L, Mitrou PN, Reedy J, Graubard BI, Hollenbeck AR, Schatzkin A, et al. A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. *Arch Intern Med* 2009; 169(8): 764-70.

486. Evans AM, DeHaven CD, Barrett T, Mitchell M, Milgram E. Integrated, nontargeted ultrahigh performance liquid chromatography/electrospray ionization tandem mass spectrometry platform for the identification and relative quantification of the small-molecule complement of biological systems. *Anal Chem* 2009; 81(16): 6656-67.

487. Soininen P, Kangas AJ, Wurtz P, Tukiainen T, Tynkkynen T, Laatikainen R, et al. High-throughput serum NMR metabonomics for cost-effective holistic studies on systemic metabolism. *Analyst* 2009; 134(9): 1781-5.

488. Kujala UM, Makinen VP, Heinonen I, Soininen P, Kangas AJ, Leskinen TH, et al. Long-term leisure-time physical activity and serum metabolome. *Circulation* 2013; 127(3): 340-8.

489. Xiao Q, Moore SC, Keadle SK, Xiang YB, Zheng W, Peters TM, et al. Objectively measured physical activity and plasma metabolomics in the Shanghai Physical Activity Study. *Int J Epidemiol* 2016; 45(5): 1433-44.

490. Enroth S, Johansson A, Enroth SB, Gyllensten U. Strong effects of genetic and lifestyle factors on biomarker variation and use of personalized cutoffs. *Nat Commun* 2014; 5: 4684.

491. Wurtz P, Wang Q, Kangas AJ, Richmond RC, Skarp J, Tiainen M, et al. Metabolic signatures of adiposity in young adults: Mendelian randomization analysis and effects of weight change. *PLoS Med* 2014; 11(12): e1001765.

492. Tillin T, Hughes AD, Wang Q, Wurtz P, Ala-Korpela M, Sattar N, et al. Diabetes risk and amino acid profiles: cross-sectional and prospective analyses of ethnicity, amino acids and diabetes in a South Asian and European cohort from the SABRE (Southall And Brent REvisited) Study. *Diabetologia* 2015; 58(5): 968-79.

493. Wurtz P, Makinen VP, Soininen P, Kangas AJ, Tukiainen T, Kettunen J, et al. Metabolic signatures of insulin resistance in 7,098 young adults. *Diabetes* 2012; 61(6): 1372-80.

494. Harlid S, Myte R, Van Guelpen B. The metabolic syndrome, inflammation, and colorectal cancer risk: an evaluation of large panels of plasma protein

markers using repeated, prediagnostic samples. *Mediators Inflamm* 2017; 2017: 4803156.

495. Shiels MS, Pfeiffer RM, Hildesheim A, Engels EA, Kemp TJ, Park JH, et al. Circulating inflammation markers and prospective risk for lung cancer. *J Natl Cancer Inst* 2013; 105(24): 1871-80.

496. Ose J, Schock H, Tjonneland A, Hansen L, Overvad K, Dossus L, et al. Inflammatory markers and risk of epithelial ovarian cancer by tumor subtypes: the EPIC Cohort. *Cancer Epidemiol Biomarkers Prev* 2015; 24(6): 951-61.

497. Shiels MS, Katki HA, Hildesheim A, Pfeiffer RM, Engels EA, Williams M, et al. Circulating inflammation markers, risk of lung cancer, and utility for risk stratification. *J Natl Cancer Inst* 2015; 107(10).

498. Chen CM. Overview of obesity in Mainland China. *Obes Rev* 2008; 9 Suppl 1: 14-21.

Appendix

Chapter 1 386
Chapter 2 390
Chapter 4 399
Chapter 5 422
Chapter 6 426
Chapter 7 447
Chapter 8 507
Chapter 9 516

Appendix 1.1 Risk factors for pancreatic cancer from published meta-analyses

Reference	Year	Risk factor	Category	No. studies	No. cases	Results	I^2
Iodice[1]	2008	Smoking	Former vs never	19	–	1.21 (1.10, 1.35)	–
			Current vs never	26	–	1.70 (1.53, 1.90)	–
Tramacere[2]	2010	Alcohol	<3 drinks/day*	7	4384	0.91 (0.86, 0.95)	–
			≥3 drinks/day*	5	797	1.30 (1.16, 1.47)	–
WCRF SLR[3]	2011	Alcohol	Per 1 drink/week*	6	9522	1.00 (0.99, 1.01)	93%
		Fruit	Per 100g/day	10	3739	1.00 (0.95, 1.05)	15%
		Red meat	Per 100g/day	7	2704	1.14 (0.95, 1.38)	47%
		Processed meat	Per 50g/day	7	2748	1.17 (1.01, 1.34)	0%
		Fish	Per 20g/day	7	3372	1.03 (0.97, 1.08)	0%
		Coffee	Per cup/day	13	1460	1.02 (0.95, 1.09)	29%
		Saturated fatty acids	Per 10g/day	5	2740	1.11 (1.01, 1.21)	43%
		Fructose	Per 25g/day	6	2831	1.22 (1.08, 1.37)	0%
Duell[4]	2012	Pancreatitis (>2 years)	Yes vs no	10	5048	2.71 (1.96, 3.74)	–

Abbreviations: BMI, body mass index; MET, metabolic equivalent of tasks; WCRF SLR, World Cancer Research Fund Systematic Literature Review; WC, waist circumference; WHR, waist-to-hip ratio.

* 1 drink/day = 12.5 g ethanol.

References:

1. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008; 393(4): 535-45.
2. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. *Int J Cancer* 2010; 126(6): 1474-86.
3. World Cancer Research Fund/American Institue for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer. Available at dietandcancerreport.org.
4. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, Silverman, DT. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012; 23(11): 2964-70.

Appendix 1.2 Risk factors for liver cancer from published meta-analyses

Reference	Year	Risk factor	Categories	No. studies	No. cases	Results	I^2
Lee[1]	2009	Smoking	Former vs never	4	–	1.51 (0.80, 2.85)	–
			Current vs never	7	–	1.52 (1.31, 1.78)	–
WCRF SLR[2]	2014	Alcohol	Per 10 g/day	19	5650	1.04 (1.02, 1.06)	64%
		Fish	Per 20 g/day	4	1812	0.94 (0.89, 0.99)	53%
		Coffee	Per 1 cup/day	6	1582	0.86 (0.81, 0.90)	18%
Liu[3]	2012	Aflatoxins	Any vs none	9	1680	4.75 (2.78, 8.11)	76%

Abbreviations: WCRF SLR, World Cancer Research Fund Systematic Literature Review.

References:

1. Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol* 2009; 38(6): 1497-511.
2. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and liver cancer. 2015. Available at: wcrf.org/sites/default/files/Liver-Cancer-2015-Report.pdf.
3. Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: systematic review and meta-analysis. *Eur J Cancer* 2012; 48(14): 2125-36.

Appendix 1.3 Risk factors for colorectal cancer from published meta-analyses

Reference	Year	Risk factor	Categories	No. studies	No. cases	Results	I^2
Liang[1]	2009	Smoking	Current	22	–	1.15 (1.00, 1.32)	–
			Former	22	–	1.20 (1.04, 1.38)	–
Fedirko[2]	2011	Alcohol	Drinker vs nondrinker	23	–	1.12 (1.03, 1.22)	–
			≤12.5 g/day	23	–	1.02 (0.96, 1.08)	–
			12.6-49.9 g/day	22	–	1.24 (1.13, 1.28)	–
			≥50 g/day	7	–	1.57 (1.38, 1.80)	–
WCRF SLR[3]	2016	Alcohol	Per 10 g/day	16	15,896	1.07 (1.05, 1.09)	25%
		Fruit	Per 100 g/day	10	10,999	0.98 (0.97, 0.99)	14%
		Vegetables	Per 100 g/day	11	14,136	0.98 (0.96, 0.99)	0%
		Red meat	Per 100 g/day	8	6662	1.12 (1.00, 1.25)	24%
		Processed meat	Per 50 g/day	10	10,738	1.16 (1.08, 1.26)	20%
		Fish	Per 100 g/day	11	10,356	0.89 (0.80, 0.99)	0%
		Dietary fibre	Per 10 g/day	21	16,562	0.93 (0.87, 1.00)	72%
		Wholegrain	Per 3 servings/day	6	8320	0.83 (0.79, 0.89)	18%
		Dairy products	Per 400 g/day	10	14,859	0.87 (0.83, 0.90)	18%
		Calcium supplements	High vs low	5	2625	0.76 (0.65, 0.89)	–

Abbreviations: WCRF SLR, World Cancer Research Fund Systematic Literature Review.

References:
1. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer* 2009; 124(10): 2406-15.
2. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011; 22(9): 1958-72.
3. World Cancer Research Fund/American Institue for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and colorectal cancer. 2017. Available at: wcrf.org/colorectal-cancer-2017.

Appendix 1.4 Prevalence of diabetes, prediabetes, and awareness, treatment, and control of diabetes among Chinese adults*

	Total†	Diagnosed†	Prediabetes‡	Awareness§	Treatment‖	Control¶
2010[1]						
Overall	11.6	3.5	50.1	30.1	25.8	39.7
Sex						
Men	12.1	3.6	52.1	29.7	25.5	40.7
Women	11.0	3.4	48.1	30.5	26.2	38.6
Location						
Urban	14.3	5.6	48.4	38.7	32.7	40.8
Rural	10.3	2.5	50.9	24.6	21.5	38.6
2013[2]						
Overall	10.9	4.0	35.7	36.5	32.2	49.2
Sex						
Men	11.7	3.9	36.4	33.5	29.5	49.9
Women	10.2	4.1	35.0	39.8	35.3	48.5
Location						
Urban	12.6	5.4	34.3	43.1	38.4	53.3
Rural	9.5	2.8	37.0	29.1	25.2	42.3

* Weighted prevalence to be representative of the Chinese census data in 2010 was calculated.

† Total diabetes included persons with diagnosed and undiagnosed diabetes. Diagnosed diabetes was defined as a self-reported previous diagnosis by health care professionals. Undiagnosed diabetes was defined according to the American Diabetes Association 2010 criteria, which included diagnosis of diabetes with an FPG level of 126 mg/dL or greater, 2-hour PG level of 200 mg/dL or greater (after 75 g glucose), or HbA1c level of 6.5% or higher. Diabetes based on information with diagnosed diabetes, FPG level, and 2-hour PG level corresponded to the 1999 World Health Organization criteria.

‡ Prediabetes was defined as any participants who did not have diabetes but who had an HbA1c level of 5.7% to 6.4%, FPG level of 100 to 125 mg/dL, or 2-hour PG level of 140 to 199 mg/dL.

§ Awareness was defined as the proportion of individuals with a self-reported history of physician-diagnosed diabetes among all patients with total diabetes.

‖ Treatment was defined as the proportion of individuals receiving diabetes medications among all patients with diabetes. The analytic sample for awareness and treatment was all patients with diabetes.

¶ Control was defined as the proportion of individuals with an HbA1c concentration of less than 7.0% among patients with diabetes who were treated. The analytic sample for control was all patients with diabetes who were treated.

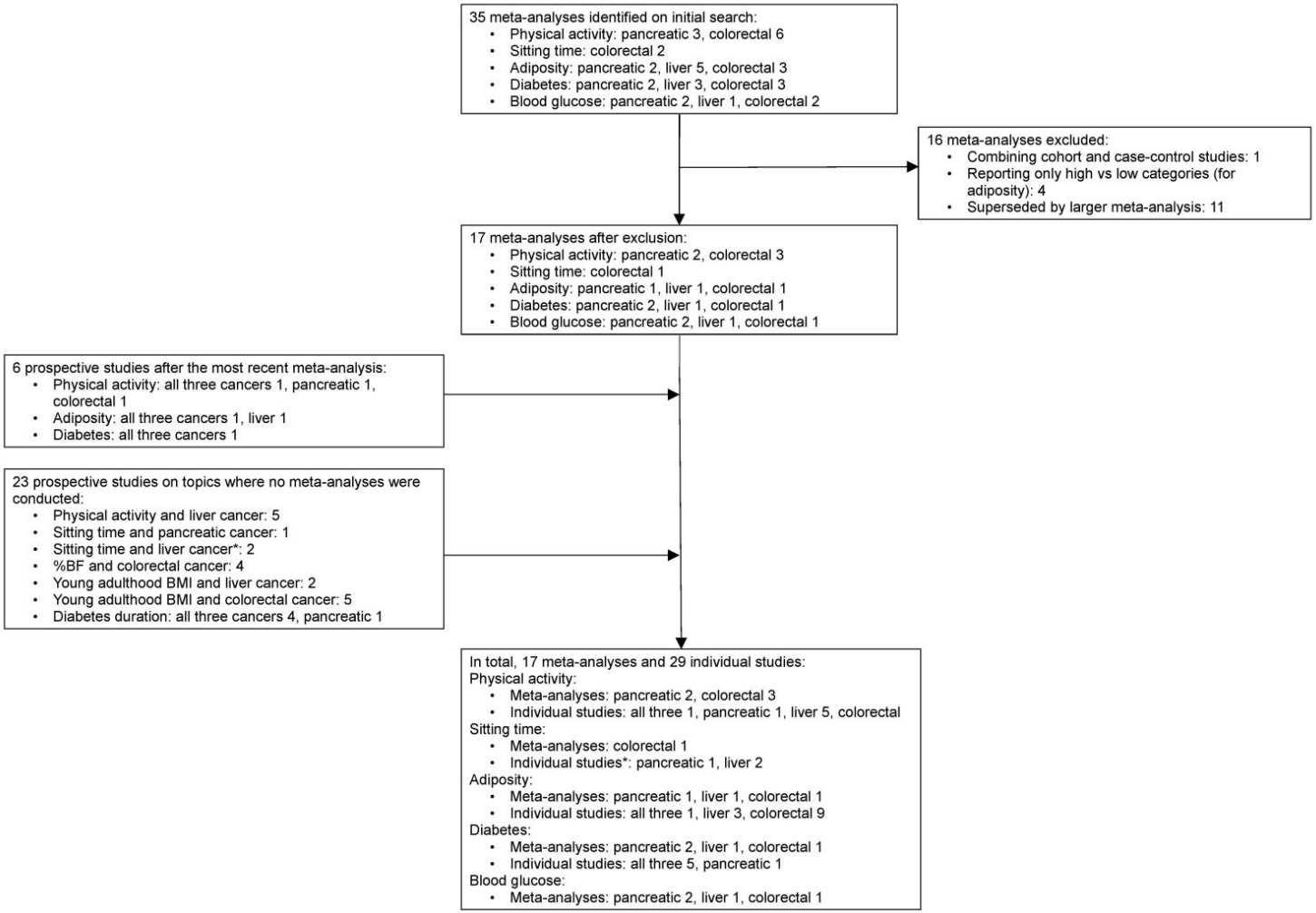
References:

1. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. *JAMA* 2013; 310(9): 948-59.
2. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. *JAMA* 2017; 317(24): 2515-23.

Appendix 2.1 Search strategies and flow chart for the literature review

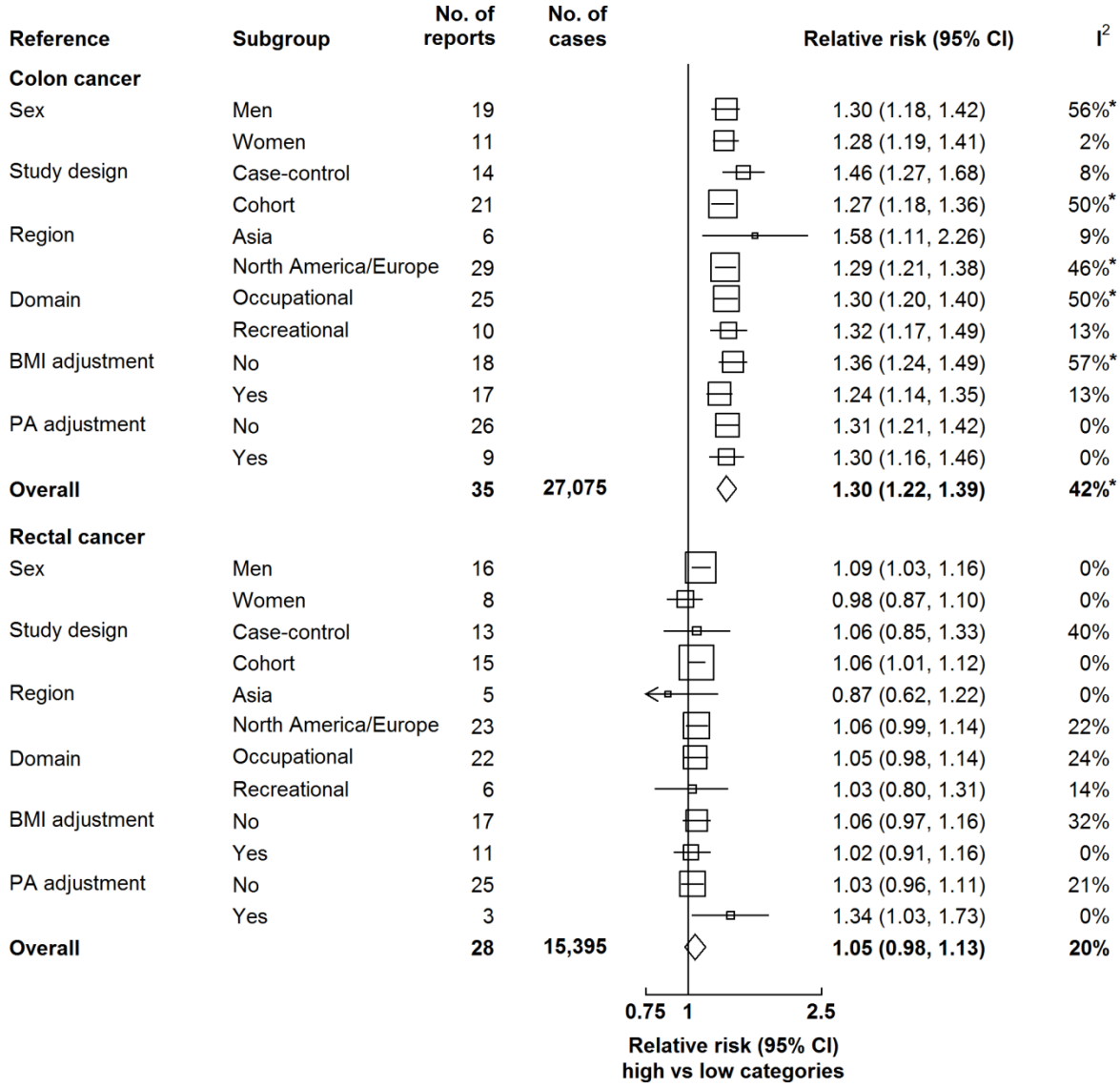
I conducted a narrative review of systematic reviews and meta-analyses published in the past five years (January 2013 to May 2018) and identified individual prospective cohort studies and pooled analyses of prospective studies since the most recent meta-analyses. Where no meta-analyses were conducted on specific topics, I identified individual prospective cohort studies and pooled analyse of prospective studies. Pooled RRs both overall and by population subgroup from the most recent meta-analyses were reported. For certain metabolic risk factors (e.g. diabetes and physical activity), more than one meta-analyses were included in the literature review because the previous meta-analyses included key subgroup analyses (e.g. smoking and alcohol) and dose-response meta-analyses (e.g. MET-h/day).

Appendix 2.1 Search strategies and flow chart for the literature review



* One study reported both pancreatic and liver cancer in the same paper.

Appendix 2.2 Meta-analysis of prospective studies on sitting time and risk of colorectal cancer



* *P* for heterogeneity within each subgroup: <0.05.

Reference:
Cong YJ, Gan Y, Sun HL, Deng J, Cao SY, Xu X, et al. Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. *Br J Cancer* 2014; 110(3): 817-26.

Appendix 2.3 Published pooled analyses of prospective studies on adiposity and specific GI cancers

Study population	BMI measure	No. cases	Cancer	Subgroup	Adiposity	Comparison	RR (95% CI)
Parr/2010/Asia[1]							
The Asia Pacific Cohort Studies Collaboration: 424,519 Asian study participants from 44 cohort studies	Mixed	302	Pancreas	Overall	BMI	Per 5 kg/m^2	1.02 (0.83, 1.25)
Lin/2013/Asia[2]							
A pooled analysis of 883,529 participants from 16 cohort studies in Asian countries: 8 Japan, 2 China, 1 Taiwan, 2 Korea, 2 India, 1 Bangladesh	Mixed	1458	Pancreas	Overall	BMI	22.5-24.9	1
						25-27.4	0.95 (0.80, 1.11)
						27.5-29.9	1.01 (0.80, 1.29)
						≥30	0.96 (0.67, 1.37)
Campbell/2017/US[3]							
The Liver Cancer Pooling Project: 1.57 million participants enrolled in 14 US-based cohort studies	Mixed	2162	Liver	Overall	BMI	Per 5 kg/m^2	1.26 (1.21, 1.32)
				Male			1.31 (1.23, 1.39)
				Female			1.20 (1.11, 1.29)
				Overall	WC	Per 5 cm	1.08 (1.04, 1.13)
				Male			1.07 (1.01, 1.13)
				Female			1.11 (1.04, 1.18)

Abbreviations: BMI, body mass index; RR, relative risk; WC, waist circumference; WHR, waist-to-hip ratio.

References:
1. Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncol* 2010; 11(8): 741-52.
2. Lin Y, Fu R, Grant E, Chen Y, Lee JE, Gupta PC, et al. Association of body mass index and risk of death from pancreas cancer in Asians: findings from the Asia Cohort Consortium. *Eur J Cancer Prev* 2013; 22(3): 244-50.
3 Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. adults. *Cancer Res* 2016; 76(20): 6076-83.

Appendix 2.4 Published prospective studies on body fat and specific GI cancers

Study population	No. cases	Subtype	Measure	Comparison	RR (95% CI)
MacInnis/2004/Australia[1]					
The Melbourne Collaborative Cohort Study: 16,556 men	306	Colon	Fat mass	Per 10 kg	1.33 (1.09, 1.61)
			Fat-free mass	Per 10 kg	1.59 (1.22, 2.06)
			BMI	Per 5 kg/m^2	1.29 (1.04, 1.60)
MacInnis/2006/Australia[2]					
The Melbourne Collaborative Cohort Study: 24,072 women	212	Colon	Body fat %	Per 10%	1.14 (0.94, 1.40)
			Fat mass	Per 10 kg	1.09 (0.95, 1.25)
			Fat-free mass	Per 10 kg	1.07 (0.78, 1.46)
			BMI	Per 5 kg/m^2	1.04 (0.90, 1.20)
Kabat/2013/US[3]					
The Women's Health Initiative: 11,124 postmenopausal women	169	Colorectal	Fat mass	Q2 vs Q1	1.45 (0.93, 2.28)
				Q3 vs Q1	1.07 (0.66, 1.74)
				Q4 vs Q1	1.39 (0.86, 2.23)
			Body fat %	Q2 vs Q1	1.17 (0.75, 1.82)
				Q3 vs Q1	1.01 (0.64, 1.60)
				Q4 vs Q1	1.07 (0.68, 1.69)
			BMI	Q2 vs Q1	0.88 (0.54, 1.43)
				Q3 vs Q1	1.21 (0.77, 1.91)
				Q4 vs Q1	1.07 (0.66, 1.75)
Ortega/2017/UK[4]					
The UK Biobank: 472,526 participants	901	Colon M	Body fat %	Q2 vs Q1	1.00 (0.78, 1.29)
				Q3 vs Q1	1.18 (0.92, 1.50)
				Q4 vs Q1	1.24 (0.97, 1.57)
				Q5 vs Q1	1.36 (1.07, 1.72)
				Per 5%	1.12 (1.05, 1.19)
	575	Rectal M	Body fat %	Q2 vs Q1	1.05 (0.78, 1.41)
				Q3 vs Q1	1.10 (0.83, 1.48)
				Q4 vs Q1	1.25 (0.94, 1.66)
				Q5 vs Q1	1.18 (0.88, 1.58)
				Per 5%	1.05 (0.97, 1.14)

Study population	No. cases	Subtype	Measure	Comparison	RR (95% CI)
The UK Biobank: 472,526 participants	807	Colon F	Body fat %	Q2 vs Q1	0.95 (0.74, 1.21)
				Q3 vs Q1	0.99 (0.79, 1.27)
				Q4 vs Q1	1.01 (0.79, 1.28)
				Q5 vs Q1	1.00 (0.78, 1.28)
				Per 5%	1.00 (0.94, 1.06)
	296	Rectal F	Body fat %	Q2 vs Q1	1.34 (0.91, 1.97)
				Q3 vs Q1	1.29 (0.87, 1.91)
				Q4 vs Q1	0.99 (0.65, 1.51)
				Q5 vs Q1	1.02 (0.66, 1.57)
				Per 5%	0.96 (0.87, 1.05)

Abbreviations: BMI, body mass index; F, female; M, male; RR, relative risk.

References:
1. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev* 2004; 13(4): 553-9.
2. MacInnis RJ, English DR, Hopper JL, Gertig DM, Haydon AM, Giles GG. Body size and composition and colon cancer risk in women. *Int J Cancer* 2006; 118(6): 1496-500.
3. Kabat GC, Heo M, Wactawski-Wende J, Messina C, Thomson CA, Wassertheil-Smoller S, et al. Body fat and risk of colorectal cancer among postmenopausal women. *Cancer Causes Control* 2013; 24(6): 1197-205.
4. Ortega LS, Bradbury KE, Cross AJ, Morris JS, Gunter MJ, Murphy N. A prospective investigation of body size, body fat composition and colorectal cancer risk in the UK Biobank. *Sci Rep* 2017; 7(1): 17807.

Appendix 2.5 Published prospective studies on young adulthood BMI and specific GI cancers

Design	Study	Measure	Subgroup	Comparison	No. case	RR (95% CI)
Liver						
Hassan/2015/US[2]						
Nested case-control	622 patients newly diagnosed with liver cancer from January 2004 through December 2013, along with 660 healthy controls (frequency-matched by age and sex)	Self-reported at age 20	Mid-20s	≥25 vs 18.5-<24.9	622	1.6 (1.1, 2.3)
			Mid-30s			1.2 (0.9, 1.8)
			Mid-40s			0.9 (0.6, 1.2)
			Mid-50s			0.6 (0.4, 1.1)
			Mid-20s	≥30 vs 18.5-<24.9		2.5 (1.3, 4.8)
			Mid-30s			2.9 (1.7, 5.1)
			Mid-40s			2.1 (1.3, 3.3)
			Mid-50s			0.9 (0.6, 1.5)
Li/2013/Japan[1]						
Cohort	The Japan Collaborative Cohort Study for Evaluation of Cancer Risk: 31,108 men and 41,455 women	Self-reported at age 20	Male	<18.5	164	0.50 (0.18, 1.39)
				18.5-20.9		1.05 (0.71, 1.54)
				21.0-22.9		1
				23.0-24.9		0.81 (0.53, 1.25)
				≥25.0		0.98 (0.60, 1.62)
			Female	<18.5	90	1.28 (0.59, 2.76)
				18.5-20.9		1.24 (0.72, 2.15)
				21.0-22.9		1
				23.0-24.9		1.22 (0.68, 2.21)
				≥25.0		0.62 (0.29, 1.34)
Colorectal						
Zhang/2015/US[3]						
Cohort	The Nurses' Health Study and Health Professionals Follow-up Study: 75,238 women and 34,533 men	Self-reported F 18 M 21	Male	15-18.9	2100	1
				19-20.4		1.11 (0.84, 1.47)
				20.5-21.9		1.13 (0.84, 1.52)
				22.0-24.9		1.08 (0.78, 1.49)
				25.0-27.4		1.12 (0.75, 1.67)
				27.5-45		1.08 (0.69, 1.72)

Design	Study	Measure	Subgroup	Comparison	No. case	RR (95% CI)
	The Nurses' Health Study and Health Professionals Follow-up Study: 75,238 women and 34,533 men		Female	15-18.9		1
				19-20.4		1.05 (0.88, 1.26)
				20.5-21.9		1.16 (0.91, 1.48)
				22.0-24.9		1.26 (0.95, 1.67)
				25.0-27.4		1.33 (0.89, 2.00)
				27.5-45		1.60 (1.07, 2.39)
Win/2011/US[4]						
Cohort	1324 carriers of MMR gene mutations and 1219 noncarriers from the Colon Cancer Family Registry	Self-reported at age 20	Carrier	BMI per 5 kg/m^2	695	1.30 (1.08, 1.58)
			Noncarrier			1.64 (1.02, 2.64)
Burton/2010/UK[5]						
Retrospective	9,549 men and 2,657 women had weight and height measured while at university (1948-1968)	Self-reported at age 20	Overall	BMI per 1 kg/m^2	131	1.06 (0.98, 1.15)
Lee/1992/US[6]						
Cohort	17,595 alumni of Harvard University	Measured at college entry	Overall	BMI per 1 kg/m^2	302	1.05 (1.00, 1.10)

Abbreviations: F, female; M, male; RR, relative risk.

References:
1. Li Y, Yatsuya H, Yamagishi K, Wakai K, Tamakoshi A, Iso H, et al. Body mass index and weight change during adulthood are associated with increased mortality from liver cancer: the JACC Study. *J Epidemiol* 2013; 23(3): 219-26.
2. Hassan MM, Abdel-Wahab R, Kaseb A, Shalaby A, Phan AT, El-Serag HB, et al. Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. *Gastroenterology* 2015; 149(1): 119-29.
3. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, et al. Early life body fatness and risk of colorectal cancer in u.s. Women and men-results from two large cohort studies. *Cancer Epidemiol Biomarkers Prev* 2015; 24(4): 690-7.
4. Win AK, Dowty JG, English DR, Campbell PT, Young JP, Winship I, et al. Body mass index in early adulthood and colorectal cancer risk for carriers and non-carriers of germline mutations in DNA mismatch repair genes. *Br J Cancer* 2011; 105(1): 162-9.
5. Burton A, Martin R, Galobardes B, Davey Smith G, Jeffreys M. Young adulthood body mass index and risk of cancer in later adulthood: historical cohort study. *Cancer Causes Control* 2010; 21(12): 2069-77.
6. Lee IM, Paffenbarger RS, Jr. Quetelet's index and risk of colon cancer in college alumni. *J Natl Cancer Inst* 1992; 84(17): 1326-31.

Appendix 2.6 Published pooled analyses of prospective studies on diabetes and specific GI cancers

Study	Diabetes	Subgroup	No. cases	Cancer	RR (95% CI)
Chen/2017/Asia[1]					
The Asia Cohort Consortium: 19 prospective cohorts and 771,297 participants	Previously diagnosed	Overall	2433	Pancreas	1.53 (1.32, 1.77)
		Male	1291		1.74 (1.44, 2.09)
		Female	1142		1.32 (1.05, 1.68)
		Overall	3752	Liver	2.05 (1.77, 2.38)
		Male	2659		2.27 (1.96, 2.62)
		Female	1093		1.77 (1.30, 2.26)
		Overall	4194	Colorectal	1.41 (1.26, 1.57)
		Male	2346		1.42 (1.22, 1.65)
		Female	1848		1.45 (1.22, 1.72)
		Overall	2681	Colon	1.50 (1.30, 1.73)
		Male	1408		1.57 (1.27, 1.93)
		Female	1273		1.48 (1.20, 1.81)
		Overall	1513	Rectal	1.30 (1.07, 1.58)
		Male	938		1.26 (0.99, 1.61)
		Female	575		1.55 (1.12, 2.16)
Seshasai/2011/worldwide[2]					
The Emerging Risk Factor Collaboration: 97 prospective cohorts and 820,900 participants	Mixed	Overall	2189	Pancreas	1.51 (1.24, 1.83)
			533	Liver	2.16 (1.62, 2.88)
			3876	Colorectal	1.40 (1.20, 1.63)
Lam/2011/Asia[3]					
The Asia-Pacific Cohort Studies Collaboration: 36 prospective cohorts and 367,361 participants	Mixed	Overall	161	Pancreas	1.85 (1.03, 3.31)
			93	Liver	2.14 (1.08, 4.25)
			596	Colorectal	1.32 (0.98, 1.78)

Abbreviations: RR, relative risk.

References:

1. Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* 2017; 60(6): 1022-32.
2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364(9): 829-41.
3. Lam EK, Batty GD, Huxley RR, Martiniuk AL, Barzi F, Lam TH, et al. Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. *Ann Oncol* 2011; 22(3): 730-8.

Appendix 4.1 Baseline survey questionnaire

Section 1: Background information

1.1 Study ID: ☐☐☐☐☐☐☐☐☐☐ *(The date & time of interview will be recorded by computer)*

1.2 Name_____, **Sex :** Male ☐ Female ☐ , **Name of spouse**_____

1.3 Date of birth: ☐☐☐☐ Year ☐☐ Month ☐☐ Day

1.4 National ID number (if no, put #) ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.5 Home address : _____ Province _____ City_____ District/County _____ Street/Village

Home telephone: Not available ☐ , Yes: ☐☐☐-☐☐☐☐☐☐☐☐☐☐☐

1.6 What is the highest level of school education you ever received?

- ☐ No formal school
- ☐ Primary School
- ☐ Middle School
- ☐ High School
- ☐ Technical school / college
- ☐ University

1.7 What is your current occupation?

- ☐ Agriculture & related workers
- ☐ Factory worker
- ☐ Administrator / manager
- ☐ Professional / technical
- ☐ Sales & service workers
- ☐ Retired
- ☐ House wife / husband
- ☐ Self-employed
- ☐ Unemployed
- ☐ Other or not stated

1.8 How many people living together in the household? ☐☐ persons

1.9 What is your current marital status?

- ☐ Married
- ☐ Widowed
- ☐ Separated / divorced
- ☐ Never married

1.10 What is the total income last year in your household?

- ☐ <2,500 yuan
- ☐ 2,500-4,999 yuan
- ☐ 5,000-9,999 yuan
- ☐ 10,000-19,999 yuan
- ☐ 20,000-34,999 yuan
- ☐ ≥35,000 yuan

1.11 Do you have any health care cover and following items in your household?

Yes	No	
☐	☐	Health care cover
☐	☐	Own house / apartment
☐	☐	Toilet for private use
☐	☐	Telephone or mobile phone
☐	☐	Motor vehicle (e.g. car or motorbike)
☐	☐	Holiday during last five years

Section 2: Tea drinking

2.1 During the past 12 months, how often did you drink any tea?

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → ***Go to Q2.3*** (were2.2)

2.2(were 2.1a) **In the past, did you ever have a period of at least 1 year during which you usually drank tea at least once a week?**

- ☐ Yes, → (were 2.1b) if so, how long ago did it end? ☐☐ Years } ***Go to section 3***
- ☐ No

2.3(were 2.2) **During the past 12 months, on how many days did you drink tea in a typical week?**

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

2.4(were2.3)**At about what age did you start drinking tea in most weeks?** ····· ☐☐ Years

---

2.5(were2.4)**On days when you drink tea, how many cups do you usually drink?** (choose one only)

Green /Jasmine tea ·····	☐☐	cups/day
Oolong tea ·····	☐☐	cups/day
Black tea ·····	☐☐	cups/day
Other tea ·····	☐☐	cups/day

2.6(were2.5) **How often do you change tea leaves during a day?** ····· ☐☐ times

---

2.7(were2.6) **About how much tea leaves do you usually add each time?** ☐☐ Grams

---

2.8(were2.7) **What strength of tea do you usually prefer to drink?**

- ☐ Weak
- ☐ Moderate
- ☐ Strong

2.9(were2.8) **At about what temperature do you usually drink your tea?**

- ☐ Room temperature / warm
- ☐ Hot
- ☐ Burning hot

2.10(were2.9)**Has your tea consumption changed significantly compared with that some years ago?** ☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 3: Alcohol consumption

3.1(were3.0) **Have you drunk any alcohol today?** ☐ Yes , ☐ No

3.2(were3.1)**During the past 12 months, how often did you drink any alcohol?**

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → ***Go to Q3.4*** (wereQ3.2)

3.3(were3.1a)**In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?**

- ☐ Yes, →(were 3.1b) If so, how long ago did it e☐☐ Years } ***Go to section 4***
- ☐ No

3.4(were3.2)**During the past 12 months, on how many days did you drink alcohol in a typical week?**

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

3.5(were3.3)**At about what age did you start drinking some alcohol in most weeks?** ☐☐ Years

---

3.6(were3.4) **On days when you drink, how much alcohol do you usually drink in a day?**
(Can choose up to 3 types of alcohol for special occasions; for beer, 1 large bottle=2 small ones)

Alcohol type	On a typical day (choose one)		On a special day when you drink a lot		Last time when you drank	
Beer (large)	☐☐	Bottle	☐☐	Bottle	☐☐	Bottle
Rice Wine	☐☐	liang	☐☐	liang	☐☐	liang
Wine	☐☐	liang	☐☐	liang	☐☐	liang
Spirit (≥50% alcohol)	☐☐	liang	☐☐	liang	☐☐	liang
Spirit (<50% alcohol)	☐☐	liang	☐☐	liang	☐☐	liang

3.7(were3.5)**On a typical day when you drink alcohol, when do you usually take the drink?**

- ☐ Usually drink with the meal
- ☐ Usually drink between or after the meals
- ☐ No regular pattern

3.8(were3.6)**After drinking alcohol, do you usually experience hot flushes or dizziness?**

- ☐ Yes, soon after first mouthful
- ☐ Yes, after drinking small amount of alcohol
- ☐ Yes, but only after drinking large amount of alcohol
- ☐ No

3.9(were3.7)**During the past month, how often have you drunk alcohol in the morning?**

- ☐ Never
- ☐ <1 day/week
- ☐ A few days a week
- ☐ Daily or almost daily

3.10(were3.8)**During the past month, have you ever had the following experiences?**

Yes	No	
☐	☐	Unable to work or to do anything because of drinking
☐	☐	Felt depressed, irritated or couldn't control yourself after drinking
☐	☐	Could not keep away from drinking
☐	☐	Had shakes when you stopped drinking

3.11(were3.9) **Has your alcohol consumption changed significantly compared with that some years ago?**

- ☐ About the same as before
- ☐ Has increased a lot
- ☐ Has decreased a lot

Section 4: Smoking history

4.1(were4.0) **Have you smoked any tobacco today?** ☐ **Yes ,** ☐ **No,** →if yes, how many: __ total, __in last hour

4.2(were4.1)**How often do you smoke tobacco now?**

- ☐ Do not smoke now
- ☐ Only occasionally
- ☐ Yes, on most days
- ☐ Yes, daily or almost every day

→ *Go to Q4.7* (were Q4.5)

4.3(were4.2)**In the past, how frequently did you smoke?**

- ☐ Did not smoke
- ☐ Smoked only occasionally
- ☐ Smoked on most days
- ☐ Smoked daily or almost every day

→ *Go to Q 4.5* (were Q4.3)

4.4(were4.2a)**In your life time, have you smoked a total of at least 100 cigarettes or equivalent?**

- ☐ Yes
- ☐ No

→ *Please go to section 5*

4.5(were4.3)**How many years ago did you last stop smoking regularly?** ☐☐ Years

4.6(were4.4)**What was your main reason for stopping?**

- ☐ Physical illness that you already had
- ☐ Money
- ☐ Health concerns (about future illness)
- ☐ Family against
- ☐ Other

4.7(were4.5)**At about what age did you first start smoking on most days?** ☐☐ Years

4.8(were4.6)**What tobacco did you use when you first started smoking on most days?**

Mainly cigarette ☐, Mainly non-cigarette ☐, Mixed types ☐

↳ (4.6a) If so, have you always smoked some cigarettes on most days, never having a month or more without them? Yes ☐, No ☐

4.9(were4.7)**How much tobacco do you usually smoke (or did you smoke before giving up)?**

Filter cigarettes (factory) ·····	☐☐	number/day
Non-filter cigarettes (factory)·····	☐☐	number/day
Hand-rolled cigarettes ····· ····· ·····	☐☐	liang/month
Pipe or water pipe ·····	☐☐	liang/month
Cigars ·····	☐☐	number/day

4.10(were4.9) **How deeply do you usually inhale the smoke?**

- ☐ Mouth only
- ☐ Throat
- ☐ Lung → 4.9a Have you always inhaled the smoke into your lung when smoking? Yes ☐, No ☐

4.11(were4.10)**Has your tobacco consumption changed significantly compared with that some years ago?**

☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 5: Diet

5.1(were5.2)**During the past 12 months, about how often did you eat the following foods?**

	Daily	4-6 days per week	1-3 days per week	Monthly	Never/rarely
Rice	☐	☐	☐	☐	☐
Wheat	☐	☐	☐	☐	☐
Other staple food (corn, millet etc.)	☐	☐	☐	☐	☐
Meat	☐	☐	☐	☐	☐
Poultry	☐	☐	☐	☐	☐
Fish/sea food	☐	☐	☐	☐	☐
Fresh eggs	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐
Soybean products	☐	☐	☐	☐	☐
Preserved vegetables	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐
Dairy products (milk, yogurt)	☐	☐	☐	☐	☐

5.2(were5.3)**During the past 12 months, have you taken the following supplements regularly?**

Yes	No	
☐	☐	Fish oil/cod liver oil
☐	☐	Vitamins
☐	☐	Calcium/iron/zinc
☐	☐	Ginshen (at least 5 or more times during a year)
☐	☐	Other herbal products

5.3(were5.3a)**Have you ever experienced any severe food shortage?** ☐Yes, ☐ No → *Go to Q5.6(wereQ5.3c)*

5.4(were5.3a1)**What year was the worst food shortage you experienced?** _____ **years**

5.5(were5.3b)**During the most severe food shortage you experienced:**

5.5.1– did you lose weight? ☐ Yes, ☐ No, → If yes, about how much? _____ *jin*,

5.5.2– did you develop any specific disease related to food shortage? ☐ Yes, ☐ No

5.6(were5.3c)**How many years have you had a refrigerator in your home?** ☐☐ Years

---

5.7(were5.4) **During the past month, about how often did you eat hot spicy food?**

☐ Never or almost never
☐ Only occasionally } → ***Go to section 6***
☐ 1-2 days/week
☐ 3-5 days/week
☐ Daily or almost every day

5.8(were5.5)**At what age did you start to eat spicy food at least once a week?** ☐☐ Years

5.9(were5.6)**What strength of spicy food do you usually prefer to eat?**

☐ Weak, ☐ Moderate, ☐ Strong

5.10(were5.7)**On day when you eat spicy food, what are the main sources of spice usually used?**

Yes	No	
☐	☐	Chili sauce
☐	☐	Chili oil
☐	☐	Dried chili pepper
☐	☐	Fresh chili pepper
☐	☐	Other or don't know

5.1(were5.2)**During the past 12 months, about how often did you eat the following foods?**

	Daily	4-6 days per week	1-3 days per week	Monthly	Never/rarely
Rice	☐	☐	☐	☐	☐
Wheat	☐	☐	☐	☐	☐
Other staple food (corn, millet etc.)	☐	☐	☐	☐	☐
Meat	☐	☐	☐	☐	☐
Poultry	☐	☐	☐	☐	☐
Fish/sea food	☐	☐	☐	☐	☐
Fresh eggs	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐
Soybean products	☐	☐	☐	☐	☐
Preserved vegetables	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐
Dairy products (milk, yogurt)	☐	☐	☐	☐	☐

5.2(were5.3)**During the past 12 months, have you taken the following supplements regularly?**

Yes	No	
☐	☐	Fish oil/cod liver oil
☐	☐	Vitamins
☐	☐	Calcium/iron/zinc
☐	☐	Ginshen (at least 5 or more times during a year)
☐	☐	Other herbal products

5.3(were5.3a)**Have you ever experienced any severe food shortage?** ☐Yes, ☐ No → *Go to Q5.6(wereQ5.3c)*

5.4(were5.3a1)**What year was the worst food shortage you experienced?** _____ **years**

5.5(were5.3b)**During the most severe food shortage you experienced:**

5.5.1– did you lose weight? ☐ Yes, ☐ No, → If yes, about how much? _____ *jin*,

5.5.2– did you develop any specific disease related to food shortage? ☐ Yes, ☐ No

5.6(were5.3c)**How many years have you had a refrigerator in your home?** ☐☐ Years

5.7(were5.4) **During the past month, about how often did you eat hot spicy food?**

☐ Never or almost never
☐ Only occasionally } → ***Go to section 6***
☐ 1-2 days/week
☐ 3-5 days/week
☐ Daily or almost every day

5.8(were5.5)**At what age did you start to eat spicy food at least once a week?** ☐☐ Years

5.9(were5.6)**What strength of spicy food do you usually prefer to eat?**

☐ Weak, ☐ Moderate, ☐ Strong

5.10(were5.7)**On day when you eat spicy food, what are the main sources of spice usually used?**

Yes	No	
☐	☐	Chili sauce
☐	☐	Chili oil
☐	☐	Dried chili pepper
☐	☐	Fresh chili pepper
☐	☐	Other or don't know

Section 6: Passive smoking & indoor air pollution

6.1 Have you ever lived with smoker in the same house for at least 6 months?

- ☐ Never
- ☐ Yes, but not now
- ☐ Yes, at present

→ ***If yes, duration of living together*** ☐☐ years

6.2 How frequently are you exposed to other people's tobacco smoke either at home, workplace or in public places? *(i.e. a minimum of 5 consecutive minutes each time)*

- ☐ Never or almost never
- ☐ Occasionally (<1 time/week)

→ ***Go to Q6.4***

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

6.3 What is the usual duration of your exposure per week? ☐☐ Hours

---

6.4 During past year, how long did you store pesticides at home? ☐☐ Months

---

6.5(were6.4a)**Please tell us the duration you lived in 3 most recent houses** (each for at least 1 year)?

Present house	☐☐	years
Previous house	☐☐	years
The house before previous	☐☐	years

6.6(were6.5) **In your present & two previous houses, how often did you cook at home?**

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Never/Rarely → ***Go to Q6.10*** (wereQ6.8)
- ☐ No cooking facility → ***Go to Q6.11*** (wereQ6.11)

6.7(were6.6)**In your present & two previous houses, what was the main cooking fuel used?**

- ☐ Gas
- ☐ Coal
- ☐ Wood
- ☐ Eletricity
- ☐ Other

6.8(were6.7)**In your present & two previous houses, what was the main cooking oil used?**

- ☐ Rapeseed
- ☐ Peanut
- ☐ Soybean
- ☐ Lard
- ☐ Other

6.9(were6.7a)**How much time have you spent on cooking so far today?** ☐☐ minutes

---

6.10(were6.8)**In your present & two previous houses, did your stove(s) all have a chimney / extractor?**

☐ Yes ☐ Not all stoves ☐ No

6.11(were6.9)**In your present & two previous houses, was your stove always kept under slow burning throughout the day?**

☐ Yes, always ☐ Yes, sometimes ☐ No → if ticked, ***Go to Q6.14***

6.12(were 6.9a) **If yes , types of the fuel most commonly used?**

☐ Smokeless coal ☐ Coal brick / Coalite

☐ Smoky coal ☐ Other

6.13(were 6.9b) **And , the place where stove was usually kept?**

☐ Inside the house ☐ Outside the house

6.14(were6.11)**In winter, did you normally heat your house?**

☐ Yes, ☐ No

6.15 If yes, what was the main heating fuel used?

☐ Central heating ☐ Wood

☐ Gas ☐ Electricity

☐ Coal ☐ Other

6.16(were6.12)**From what year did the inside of your house tend to be coal-smoky in winter?**

☐ Never → if ticked, ***Go to section 7***

☐ Ever since childhood

☐ Since the year: _____ year

6.17(were6.13)**In what year did the inside of your house stop being really coal-smoky in winter?**

☐ In the year: _____ year

☐ Still is

Section 7: Personal & family medical history

7.1 How is your current general health status?

7.1.1 Self-rated health status?
- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor

7.1.2. Compared to someone of your own age?
- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Don't know

7.2 If you were walking on level ground with other healthy people of the same age, would you usually:

7.2.1 Become short of breath? ☐ Yes ☐ No ☐ Disabled

7.2.2 Slow down due to chest discomfort? ☐ Yes ☐ No ☐ Disabled

---

7.3 During the past 12 months, have you usually had the following symptoms?

7.3.1 Cough frequently?
- ☐ No
- ☐ Yes, for <3 months
- ☐ Yes, for ≥3months

7.3.2 Cough up sputum after getting up in the morning?
- ☐☐ No
- ☐☐ Yes, for <3 months
- ☐☐ Yes, for ≥3 months

7.4 Has a doctor EVER told you that you had had the following disease?

	Diagnosed disease? Yes	Diagnosed disease? No	Age at first diagnosis	Still on treatment? Yes	Still on treatment? No
Diabetes	☐	☐	_____	☐	☐
CHD	☐	☐	_____	☐	☐
Stroke or TIA	☐	☐	_____	☐	☐
Hypertension	☐	☐	_____	☐	☐
Rheumatic heart dis.	☐	☐	_____	☐	☐
TB	☐	☐	_____	☐	☐
Emphysema/bronchitis	☐	☐	_____	☐	☐
Asthma	☐	☐	_____	☐	☐
Cirrhosis/chronic hepatitis	☐	☐	_____	☐	☐
Peptic ulcer	☐	☐	_____	☐	☐
Gallstone/gallbladder dis.	☐	☐	_____	☐	☐
Kidney disease	☐	☐	_____	☐	☐
Fracture	☐	☐	_____	☐	☐
Rheumatoid arthritis	☐	☐	_____	☐	☐
Psychiatric disorders	☐	☐	_____	☐	☐
Neurasthenia	☐	☐	_____	☐	☐
Head injury	☐	☐	_____	☐	☐
Cancer*	☐	☐	_____	☐	☐

For CHD, stroke, and hypertension what is the current medication:

1. Aspirin
2. ACE-I
3. Beta-blocker
4. Statins
5. Diuretics
6. Ca^{++} antagonist

& for diabetes, the above list plus

7. Chlorpropamide or metformin
8. Insulin

***If yes, please indicate the site of cancer** ☐ *(If more than one, choose the one that occurred first)*

0. Lung 1. Esophagus 2. Stomach 3. Liver 4. Intestine 5. Breast 6. Prostate 7. Cervix 8. Other

7.5 **Have many blood transfusions have you ever received?** *(If none, put 0)* ☐☐ times

7.6(were7.5a)**How many times have you ever donated blood for financial payment?**

(If none, put 0) ☐☐ times

7.7(were7.6)**About how often do you have bowel movements each week?**

- ☐ More than once on most days
- ☐ About daily
- ☐ Once every 2-3 days
- ☐ Less than 3 times a week

7.8(were7.7)**How often do your gums bleed when you brush your teeth?**

- ☐ Occasionally, rarely or never
- ☐ Sometimes
- ☐ Always
- ☐ Brush teeth rarely or never

7.9(were7.8)**How many brothers & sisters do you have?** *(Including half siblings. If unknown, put#)* ☐☐

7.10(were7.9)**How many children do you have?** *(Including only biological ones)* ☐☐

7.11(were7.9a)**Is your mother still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.12(were7.9b)**Is your father still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.13(were7.10) **Did any of your parents, siblings or children have following diseases?** *(For sibling and children, please record the number with disease)*

	Stroke	Heart attack	Diabetes	Mental disorder	Cancer
Mother *(tick box)*	☐	☐	☐	☐	☐
Father *(tick box)*	☐	☐	☐	☐	☐
Siblings *(inclu. half)*	☐	☐	☐	☐	☐
Children	☐	☐	☐	☐	☐

Section 8U: Physical activities (Urban)

8.1 During the past 12 months, how active were you at work?

- ☐ Mainly sedentary (e.g. office worker)
- ☐ Standing occupation (e.g. guard, shop assistant)
- ☐ Manual work (e.g. plumber, carpenter)
- ☐ Heavy manual work (e.g. miner, construction worker)
- ☐ Retired or housewife/husband or unemployed or disabled → *If ticked, please go to Q8.8*

8.2(were8.1a) **In a typical week, about how many hours did you usually work?** _____ **hours**

8.3(were8.2) **During the past 12 months, how did you usually get to work?**

- ☐ Mainly walk
- ☐ By motorbike
- ☐ By bicycle
- ☐ By bus/car/ferry/train
- ☐ Mainly stay at home or work near home

↳*If ticked, please go to Q8.8*

8.4(were8.3) **How much time did you spend each day on journey to & from work?** ____**minutes**

Section 8F: Physical activities (New section for rural farmers)

8.1 During the past 12 months, did your farming work change seasonally?

- ☐ No → *go to Q8.3*
- ☐ Yes

8.2 During the farming season in the last 12 months:

8.2.1 How many months did it usually last? ☐☐ month

8.2.2 What types of work did it usually involve?

☐ manual ☐ Semi-mechanized ☐ Fully mechanized

8.2.3 How many hours did you usually work each day? ☐☐ hours

8.2.4 Of which , how many hours did you sweat or have a much faster heartbeat? ☐☐ hours

---

8.3 In a typical week, how many hours did you usually work in the field? ☐☐ hours

---

8.4 Apart from agriculture work, did you have any other job?

- ☐ No → *go to Q8.7*
- ☐ Yes

8.5 How active were you at work with other job?

- ☐ Mainly sedentary
- ☐ Mainly standing
- ☐ Mainly general manual work
- ☐ Mainly heavy manual work

8.6 In a typical week, about how many hours did you work at other job? ☐☐ hours

---

8.7 In a typical day how much time did you usually spend on the journey to and from work on foot or by bicycle? ☐☐☐ minutes

---

Section 8C: Physical activities (Common to both rural farmers and urban)

8.8 During the past 12 months, how often did you do exercise in your leisure time?

- ☐ Never or almost never } → *If ticked, please go to Q8.11*
- ☐ 1-3 times/month } → *If ticked, please go to Q8.11*
- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.9 What is your main type of exercise? *(tick one box only)*

- ☐ Taichi / Qigong
- ☐ Jogging/aerobic exercise
- ☐ Ball games (basketball, table tennis, etc)
- ☐ Walking
- ☐ Swimming
- ☐ Other (eg. mountain climbing)

8.10 About how many hours per week did you do such exercise in leisure time? ___ hours

---

8.11 In a typical week during the past 12 months, how often did you sweat or have a much faster heartbeat because of heavy physical activities/exercise?

- ☐ Never or almost never } → *If ticked, please go to Q8.13*
- ☐ <1 time / week } → *If ticked, please go to Q8.13*
- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.12 About how many hours per week did you do such activities? _____ hours

---

8.13 About how many hours per week did you do house work? _____ hours

8.14 About how many hours per week did you watch TV or read? _____ hours

---

8.15 During the past 12 months, has your weight changed significantly?

☐ About the same as before ☐ Yes, gained ≥2.5 kg ☐ Yes, lost ≥2.5 kg

---

8.16 Have you tried to reduce weight in the past 12 months? No ☐, Yes ☐

8.17 How much did you weigh when you were at age 25? (If unknown put #) ☐☐☐ jin

---

Section 9: Reproductive history (for women)

9.1 How old were you when you had your first menstrual period? ☐☐ Year

---

9.2 Have you had your menopause?

☐ No
☐ Yes, currently
☐ Yes, had menopause → If so, age of completion of menopause: ☐☐ Year

---

9.3 How many times have you ever been pregnant? (if none, put 0. Go to Q9.6) ☐☐ times

— **Of which,**

Live birth ☐☐ times → If none, Go to Q9.5 (wereQ9.6)

Still birth ☐☐ times, Spontaneous abortion ☐☐ times, Induced abortion ☐☐ times

---

9.4 Age and length of breastfeeding at each live birth (twins=one birth)?

Live Birth	Age at end of pregnancy	Months of breastfeeding
1st	☐☐	☐☐
2nd	☐☐	☐☐
3rd	☐☐	☐☐
4th	☐☐	☐☐
5th	☐☐	☐☐

9.5(were9.6)Have you ever used oral contraceptive pills?

☐ Never → ***If ticked, please go to Q9.8*** (were Q9.9)
☐ Past use → **if ticked,** age when you last stopped the pill: ☐☐ Year
☐ Current use

9.6(were9.7)How old were you when you first used oral contraceptives? ☐☐ Year

9.7(were9.8)For how long altogether have you used oral contraceptives? ☐☐ Year

---

9.8(were9.9)Have you had a hysterectomy?

☐ No , ☐ Yes → If yes, age when you had the operation ☐☐ Year

---

9.9(were9.10)Have you had one or both ovaries removed?

☐ No , ☐ Yes → If yes, age when you had the most recent operation ☐☐ Year

---

9.10(were9.11) Have you ever had surgery to remove a breast lump?

☐ No, ☐ Yes → If yes, age when you most recently had the operation ☐☐ Year

---

Section 10: Sleeping, mood & mental situation

10.1 In general, how satisfied are you with your life?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Unsatisfied
- ☐ Very unsatisfied

10.2 Over the past two years have you had any of the following major events in your life?

Yes	No		Yes	No	
☐	☐	Marital separation/divorce	☐	☐	Major injury or traffic accident
☐	☐	Loss of job/retirement	☐	☐	Death /major illness of spouse
☐	☐	Business bankrupt	☐	☐	Death/major illness of other close family member
☐	☐	Violence	☐	☐	Major natural disaster (e.g. flood & drought)
☐	☐	Major conflict within family	☐	☐	Loss of income / living on debt

---

10.3 During the past month, did you have any of the following for ≥3 days each week?

Yes	No	
☐	☐	Taking >30 minutes to fall asleep after going to bed or waking up in the middle of the night
☐	☐	Waking up early and not being able to go back to sleep
☐	☐	Needing to take medicine (including herbal or sleeping pills) at least once a week to help sleep
☐	☐	Having difficulty staying alert while at work, eating or meeting people during daytime

---

10.4 Do you usually take a daytime nap? ☐ Yes usually, ☐ Yes ,but only in summer , ☐ No

10.5(were10.4a) **Do you snore during sleep?** ☐ Yes, Frequently, ☐ Yes, Sometimes, ☐ No / Don't know

10.6(were10.5)**How many hours do you typically sleep per day (incl. naps)?** ☐☐ Hours

---

10.7(were10.6)**During the past 12 months, have you had following situations for 2 or more weeks?**
(If answer yes to any of the questions, complete CIDI-A)

Yes	No	
☐	☐	Feeling much more sad, or depressed than usual
☐	☐	Loss of interest in most things like hobbies or activities that usually give you pleasure
☐	☐	Felt so hopeless that you had no appetite to eat even your favourite food
☐	☐	Feeling worthless and useless, everything went wrong was your fault and life is very difficult that there was no way out

---

10.8(were10.7) **During the past 12 months, have you experienced the following situations?**

Yes	No	
☐	☐	Having a period lasting one month or longer when most of time you felt worried, tense, or anxious and it interfered your life *(if yes, complete CIDI-B)*
☐	☐	Having a pain or discomfort in your body lasting ≥3 months that interfered with your life
☐	☐	Having had a spell or an attack when all of sudden felt frightened, anxious, or very uneasy
☐	☐	Having had inexplicable strong fear in situations such as closed space (cave, elevator, airplane etc), in the crowds or public such that you would avoid such situations

---

Section 11: Physical examination

11.1 **Standing height** (without shoes) ..... [ ][ ][ ].[ ] m

11.2 **Sitting height** ..... [ ][ ][ ].[ ] cm

11.3 **Waist** ..... [ ][ ][ ].[ ] cm

11.4 **Hip** ..... [ ][ ][ ].[ ] cm

11.5 **Weight** (without shoes, but in light clothing) ..... [ ][ ][ ].[ ] Kg

11.6 **BMI** ..... [ ][ ].[ ] Kg/m^2

11.7 **Impedance** ..... [ ][ ][ ] **Ω** *Staff code*

11.8 **Fat %** (with one decimal point) ..... [ ][ ].[ ] [ ][ ][ ]

11.9 **Did you take any drugs to lower blood pressure in the last 2 days?** ☐ Yes ☐ No

11.10 **Blood pressure & heart rate** (to be measured after 5 minutes in the seated position)

	First	Second	
SBP	[ ][ ][ ]	[ ][ ][ ]	mmHg
DBP	[ ][ ][ ]	[ ][ ][ ]	mmHg
Heart rate	[ ][ ][ ]	[ ][ ][ ]	bpm

11.11(were11.10a)**Hours since last ate anything (ignore any drinks)?** _____ **hours** *Staff code*

11.12(were11.11)**Blood sample collected:** Yes (, . Failed ([ ][ ][ ]

11.13 (were11. 12) **Lung function & CO levels:**

	First	Second		
CO	[ ][ ][ ]	[ ][ ][ ]		
%COHB	[ ][ ].[ ][ ]	[ ][ ].[ ][ ]	%	*Staff code*
FEV1	[ ].[ ][ ]	[ ].[ ][ ]	Liter	[ ][ ][ ]
FVC	[ ].[ ][ ]	[ ].[ ][ ]	Liter	

11.14(were11.13)Assessment of subject's cooperation and the reliability of data collected?

Assessment of subject's cooperation?	11.15 Assessment of the reliability of the information collected?
☐ Good	☐ Good
☐ Fair	☐ Fair
☐ Poor	☐ Poor

Date of interview _____Year_____Month____Day, **Signature of interviewer**_____

Appendix 4.2 Physical activity types, MET values, codes, and intensity categories

Activity type	MET	Intensity	Code
Sedentary work	1.8	Low	Mean of 11580, 11585, and 11590
Standing work	3.8	Moderate	Mean of 11610 and 11630
Manual work	4.5	Moderate	11476
Heavy manual work	6.5	Vigorous	11477
Work outside the farming season	2.0	Low	11147
Fully mechanised work in the farming season	2.4	Low	Mean of 11147 and 11170
Semi-mechanised work in the farming season	3.4	Moderate	Mean of 11146 and 11147
Manual work in the farming season	6.3	Vigorous	Mean of 11145 and 11146
Walking	4.0	Moderate	17270
Bicycle	6.8	Vigorous	1011
Motorbike	3.5	Moderate	16030
Private or public transportation	1.7	Low	Mean of 16010, 16015, and 16016
Household activity	2.8	Low	Mean of 05030*, 05040*, 05035, 05055, 05070, 05090*, 05092*, 05184, 05197, and 05200
Tai-Chi/qigong/leisure walking	3.3	Moderate	Mean of 15670 and 17160
Jogging/aerobic exercise	7.4	Vigorous	Mean of 03015, 12020, and 12150
Ball games	5.5	Moderate	Mean of 15020*, 15030*, 15055, 15080, 15090, 15255, 15605*, 15610*, 15652, 15660, 15675, 15710*, and 15711*
Brisk walking/gymnastics/folk dancing	4.2	Moderate	Mean of 03025, 15300, and 17200
Swimming	7.2	Vigorous	Mean of 18230, 18240, and 18310
Other exercise, e.g. mountain walking, home exercise and rope jumping	5.9	Moderate	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

Abbreviations: MET, Metabolic equivalent of tasks.
* 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.

Appendix 4.3 Cut-off points for sex-specific quintiles of adiposity measures

Adiposity measure	Sex	Cut-off points
%BF (%)	Men:	16.5, 20.0, 23.4, 27.2
	Women:	26.1, 30.0, 33.5, 37.9
WC (cm)	Men:	73.1, 79.0, 84.3, 90.5
	Women:	70.8, 76.0, 81.0, 87.0
WHR	Men:	0.85, 0.89, 0.92, 0.96
	Women:	0.81, 0.85, 0.88, 0.92
HC (cm)	Men:	84.7, 88.5, 92.0, 96.3
	Women:	85.4, 89.0, 92.3, 96.5
WHtR	Men:	0.45, 0.48, 0.51, 0.54
	Women:	0.46, 0.49, 0.53, 0.56
Weight (kg)	Men:	54.7, 60.5, 66.2, 73.2
	Women:	48.7, 53.7, 58.4, 64.2
Fat mass (kg)	Men:	9.2, 12.2, 15.4, 19.6
	Women:	12.9, 16.2, 19.5, 23.9
Lean mass (kg)	Men:	44.4, 47.7, 50.8, 54.5
	Women:	34.6, 36.8, 38.8, 41.3
Height (cm)	Men:	159.8, 163.6, 166.8, 170.6
	Women:	149.2, 152.7, 155.7, 159.1
Leg length (cm)	Men:	73.5, 75.8, 77.8, 80.2
	Women:	67.9, 70.0, 71.8, 74.0
Sitting height (cm)	Men:	85.1, 87.5, 89.4, 91.7
	Women:	80.1, 82.3, 84.2, 86.3

Appendix 4.4 Estimated regression dilution ratios of physical activity (PA) and sedentary leisure time (SLT)

Baseline groups	Mean baseline value	Mean resurvey value	Ratios of the ranges estimate	Self-correlation estimate
Total PA (MET-h/day)				
<8.80 (1)	5.71	11.50	0.54	0.51
8.80 to <14.25 (2)	11.59	14.66		
14.25 to <21.86 (3)	17.71	18.82		
21.86 to <33.25 (4)	27.32	25.06		
≥33.25 (5)	43.23	31.67		
Difference (5 - 1)	***37.52***	***20.17***		
Occupational PA (MET-h/day)				
0 (1)	0	2.25	0.62	0.57
0.1 to <9.0 (2)	4.57	9.37		
9.0 to <15.53 (3)	11.85	13.53		
15.53 to <26.06 (4)	20.98	18.46		
≥26.06 (5)	37.42	25.44		
Difference (5 - 1)	***37.42***	***23.19***		
Nonoccupational PA (MET-h/day)				
<3.93 (1)	2.11	4.54	0.49	0.48
3.93 to <6.05 (2)	5.30	6.74		
6.50 to <8.47 (3)	7.71	8.23		
8.47 to <11.62 (4)	10.10	9.21		
≥11.62 (5)	15.53	11.14		
Difference (5 - 1)	***13.42***	***6.60***		
Sedentary leisure time (h/week)				
<14 (1)	6.70	15.42	0.33	0.31
14 to <18 (2)	14.18	18.51		
18 to <21 (3)	19.05	19.65		
21 to <28 (4)	21.36	21.04		
≥28 (5)	33.66	24.43		
Difference (5 - 1)	***26.96***	***9.01***		

Abbreviations: MET, metabolic equivalent of task; PA, physical activity.

Appendix 4.5 Estimated regression dilution ratios of adiposity measures

Baseline groups	Mean baseline value	Mean resurvey value	Ratios of the ranges estimate	Self-correlation estimate
BMI (kg/m^2)				
<20.0 (1)	18.68	18.74	0.95	0.94
20.0 to <22.5 (2)	21.28	21.24		
22.5 to <25.0 (3)	23.67	23.55		
25.0 to <27.5 (4)	25.88	25.57		
≥27.5 (5)	29.10	28.66		
Difference (5 - 1)	***10.42***	***9.92***		
WC (cm)				
<71.8 (1)	67.43	71.44	0.88	0.84
71.8 to <77.0 (2)	74.33	77.78		
77.0 to <82.2 (3)	79.50	82.25		
82.2 to <88.5 (4)	85.15	87.24		
≥88.5 (5)	94.51	95.33		
Difference (5 - 1)	***27.08***	***23.89***		
WHR				
<0.82 (1)	0.780	0.825	0.70	0.67
0.82 to <0.86 (2)	0.836	0.867		
0.86 to <0.90 (3)	0.875	0.894		
0.90 to <0.94 (4)	0.914	0.922		
≥0.94 (5)	0.977	0.962		
Difference (5 - 1)	***0.197***	***0.137***		
HC (cm)				
<85.1 (1)	81.92	84.87	0.81	0.82
85.1 to <89.0 (2)	87.03	89.02		
89.0 to <92.2 (3)	90.51	91.87		
92.2 to <96.4 (4)	94.14	94.78		
≥96.4 (5)	100.90	100.20		
Difference (5 - 1)	***18.89***	***15.33***		
WHtR				
<0.45 (1)	0.427	0.449	0.92	0.84
0.45 to <0.49 (2)	0.471	0.492		
0.49 to <0.52 (3)	0.503	0.522		
0.52 to <0.56 (4)	0.537	0.551		
≥0.56 (5)	0.595	0.604		
Difference (5 - 1)	***0.168***	***0.155***		

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Appendix 4.5 Continued

Baseline groups	Mean baseline value	Mean resurvey value	Ratios of the ranges estimate	Self-correlation estimate
%BF (%)				
<20.5 (1)	16.47	15.92	0.88	0.90
20.5 to <25.5 (2)	23.07	22.01		
25.5 to <29.9 (3)	27.66	26.30		
29.9 to <35.0 (4)	32.27	30.42		
≥35.0 (5)	39.98	36.65		
Difference (5 - 1)	***23.51***	***20.73***		
Weight (kg)				
<50.7 (1)	45.99	46.05	0.96	0.96
50.7 to <56.2 (2)	53.49	53.37		
56.2 to <61.5 (3)	58.74	58.41		
61.5 to <68.4 (4)	64.65	64.12		
≥68.4 (5)	75.83	74.71		
Difference (5 - 1)	***29.84***	***28.66***		
Fat mass (kg)				
<11.1 (1)	8.59	8.32	0.99	0.91
11.1 to <14.6 (2)	12.87	12.89		
14.6 to <17.9 (3)	16.21	16.21		
17.9 to <22.4 (4)	19.97	19.94		
≥22.4 (5)	27.52	27.15		
Difference (5 - 1)	***18.93***	***18.83***		
Lean mass (kg)				
<36.1 (1)	33.57	34.55	0.99	0.96
36.1 to <39.4 (2)	37.77	38.64		
39.4 to <43.5 (3)	41.33	42.00		
43.5 to <49.6 (4)	46.36	47.06		
≥49.6 (5)	54.57	55.24		
Difference (5 - 1)	***21.00***	***20.69***		

Abbreviations: %BF, percent body fat.

Appendix 4.6 Estimated regression dilution ratios of adiposity-related measures

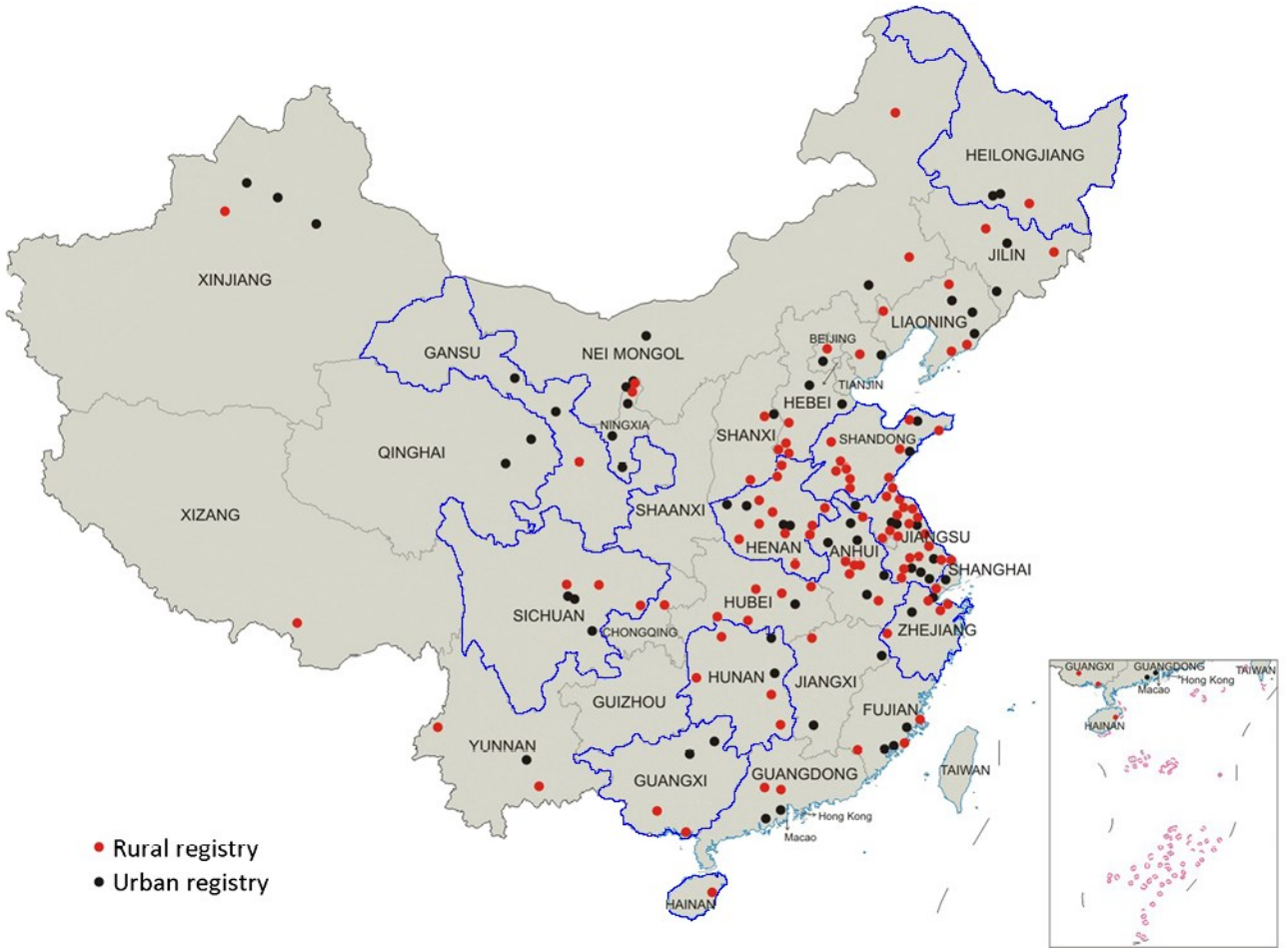
Baseline groups	Mean baseline value	Mean resurvey value	Ratios of the ranges estimate	Self-correlation estimate
Height (cm)				
<151.5 (1)	147.60	147.50	0.99	0.96
151.5 to <156.0 (2)	153.70	153.80		
156.0 to <160.5 (3)	158.10	158.30		
160.5 to <166.0 (4)	163.00	163.20		
≥166.0 (5)	170.80	170.60		
Difference (5 - 1)	***23.20***	***23.10***		
Leg (cm)				
<69.2 (1)	67.85	68.25	0.94	0.93
69.2 to <71.9 (2)	70.57	70.73		
71.9 to <74.4 (3)	73.08	73.04		
74.4 to <77.5 (4)	75.81	75.7		
≥77.5 (5)	80.29	79.92		
Difference (5 - 1)	***12.44***	***11.67***		
Sitting height (cm)				
<81.4 (1)	78.78	79.34	0.93	0.92
81.4 to <84.0 (2)	82.70	82.94		
84.0 to <86.4 (3)	85.13	85.14		
86.4 to <89.2 (4)	87.67	87.60		
≥89.2 (5)	91.76	91.46		
Difference (5 - 1)	***12.98***	***12.12***		

Appendix 4.7 Estimated regression dilution ratios of RPG

Baseline groups	Mean baseline value	Mean resurvey value	Ratios of the ranges estimate	Self-correlation estimate
RPG (mmol/L)				
<5.6 (1)	4.78	5.85	0.53	0.45
5.6 to <6.8 (2)	6.04	6.33		
6.8 to <7.8 (3)	7.21	6.97		
≥7.8 (4)	10.72	8.97		
Difference (4 - 1)	***5.94***	***3.12***		

Abbreviations: RPG, random plasma glucose.

Appendix 5.1 Distributions of NCCR sites and 10 regions in CKB*



* 10 regions in CKB are outlined in blue.

Appendix 5.2 Baseline characteristics of participants by levels of highest education

Variable*	Highest education					
	No formal school (n=94,627)	Primary school (n=164,204)	Middle school (n=144,212)	High school (n=77,093)	Technical/college (n=18,148)	University (n=11,608)
Age (SD), year	52.3 (10.2)	51.8 (4.4)	51.1 (3.6)	51.2 (5.0)	51.0 (8.1)	50.9 (8.1)
Female, %	59.0	59.0	59.0	58.9	58.4	55.8
Socioeconomic and lifestyle factors						
Urban region, %	44.1	44.1	44.1	44.2	44.7	47.8
Household income ≥35 000 RMB/year, %	9.6	12.3	17.8	27.3	43.6	54.8
Ever regular smoking, %						
Male	69.6	71.5	68.6	61.8	51.5	43.2
Female	5.3	4.0	2.4	1.5	1.2	0.2
Weekly drinking %						
Male	31.9	33.7	33.7	31.2	30.3	29.5
Female	2.3	1.8	2.0	1.8	2.0	2.0
Total physical activity (SD), MET-h/day	20.4 (14.3)	21.1 (14.3)	20.7 (14.3)	19.3 (12.7)	17.3 (9.0)	17.3 (8.1)
Sedentary leisure time (SD), h/day	2.8 (1.7)	3.0 (1.5)	3.2 (1.5)	3.3 (1.5)	3.4 (1.5)	3.3 (1.5)
Daily consumption, %						
Fresh fruits	11.7	14.6	21.0	28.2	40.0	41.7
Fresh vegetables	93.1	94.3	95.3	95.9	97.1	98.3
Red meat	23.8	26.8	30.6	35.4	43.7	46.0
Blood pressure and anthropometry						
SBP (SD), mmHg	133.3 (23.3)	131.6 (21.4)	130.4 (19.4)	129.3 (19.2)	127.6 (19.2)	126.1 (19.3)
RPG (SD), mmol/L	6.2 (2.5)	6.1 (2.4)	6.1 (2.3)	6.0 (2.1)	6.1 (2.2)	6.0 (2.2)
BMI (SD), kg/m^2	23.7 (3.5)	23.7 (3.4)	23.7 (3.3)	23.7 (3.3)	23.8 (3.2)	23.9 (3.2)
Waist circumference (SD), cm	80.3 (10.0)	80.6 (9.7)	80.5 (9.6)	80.4 (9.7)	80.7 (9.9)	81.1 (10.0)
Hip circumference (SD), cm	90.5 (6.8)	90.9 (6.7)	91.2 (6.8)	91.4 (6.6)	92.0 (6.2)	92.5 (6.3)
Waist-to-hip ratio (SD)	0.89 (0.07)	0.89 (0.07)	0.88 (0.07)	0.88 (0.07)	0.88 (0.08)	0.88 (0.07)
Percent body fat (SD), %	28.1 (8.8)	28.1 (8.9)	28.1 (8.1)	27.9 (7.6)	28.2 (6.9)	27.8 (6.8)

Appendix 5.2 Continued

Variable*	Highest education					
	No formal school (n=94,627)	Primary school (n=164,204)	Middle school (n=144,212)	High school (n=77,093)	Technical/college (n=18,148)	University (n=11,608)
Blood pressure and anthropometry						
Height (SD), cm	157.3 (7.2)	158.1 (7.8)	159.0 (8.0)	159.8 (8.0)	160.8 (7.8)	161.3 (7.9)
BMI at age 25 (SD), kg/m^2	22.2 (2.8)	22.2 (2.6)	21.9 (2.5)	21.6 (2.5)	21.3 (2.4)	21.2 (2.4)
HBsAg positive, %	3.3	3.3	3.0	2.8	2.6	1.9
Prior disease history, %						
Diabetes	7.3	6.4	6.4	6.3	6.6	6.9
Coronary heart disease	2.4	3.0	3.1	3.9	4.1	4.9
Stroke or TIA	2.2	2.0	1.8	1.8	1.8	1.2
Hypertension	10.9	11.6	12.6	14.1	18.4	13.9
Family history of diabetes	2.7	3.1	5.2	7.0	8.4	8.6
Family history of cancer	11.9	13.3	15.3	15.9	19.0	16.3

Abbreviations: BMI=body mass index, MET=metabolic equivalent of task, RPG=random plasma glucose, SBP=systolic blood pressure, TIA=transient ischaemic attack.

* Results were standardised by age, sex, and region (where appropriate). Values are means unless otherwise stated.

Appendix 5.3 Meta-analyses of prospective studies on risk factors for colon and rectal cancer

		Colon cancer				Rectal cancer			
		Relative risk	I^2 (%)	No. studies	No. cases	Relative risk	I^2 (%)	No. studies	No. cases
Wholegrains[1]	Per 90 g/day	0.82 (0.73, 0.92)	0	4	3875	0.82 (0.57, 1.16)	84	3	1548
Dietary fibre[1]	Per 10 g/day	0.91 (0.84, 1.00)	69	21	12601	0.93 (0.85, 1.01)	31	21	5809
Nonstarchy vegetables[1]	Per 100 g/day	0.97 (0.95, 0.99)	0	12	>6308	0.99 (0.96, 1.02)	0	8	>2435
Fruits[1]	Per 100 g/day	0.98 (0.96, 1.01)	39	12	>6317	0.98 (0.93, 1.03)	55	9	>2444
Red meat[1]	Per 100 g/day	1.22 (1.06, 1.39)	12	11	4081	1.13 (0.96, 1.34)	0	8	1772
Processed meat[1]	Per 50 g/day	1.23 (1.11, 1.35)	26	12	8599	1.08 (1.00, 1.18)	0	10	3029
Fish[1]	Per 100 g/day	0.91 (0.80, 1.03)	0	11	10,512	0.84 (0.69, 1.02)	15	10	3944
Dairy products[1]	Per 400 g/day	0.87 (0.81, 0.94)	24	6	3991	0.93 (0.82, 1.06)	49	5	2152
Plasma/serum vitamin D[1]	Per 30 nmol/L	0.90 (0.81, 1.01)	63	9	2037	0.83 (0.69, 1.00)	43	7	1579
Alcoholic drinks[2]	Drinkers vs nondrinkers*	1.05 (0.99, 1.12)†	–	42	–	1.19 (1.09, 1.31)	–	38	–
	Heavy drinkers vs nondrinkers*	1.43 (1.23, 1.67)†	–	16	–	1.59 (1.18, 2.15)	–	15	–
Smoking[3]	Current vs never	1.00 (0.91, 1.10)‡	–	25	–	1.11 (1.00, 1.23)	–	25	–
	Former vs never	1.13 (1.06, 1.20)‡	–	26	–	1.15 (1.07, 1.24)	–	26	–
Total PA[1]	High vs low	0.80 (0.72, 0.88)	39	12	8396	1.04 (0.92, 1.18)	9	9	2326
Leisure-time PA[1]	High vs low	0.84 (0.78, 0.91)	33	20	10,258	0.95 (0.85, 1.07)	27	14	4560
BMI[1]	Per 5 kg/m^2	1.07 (1.05, 1.09)	41	41	72,605	1.02 (1.01, 1.04)	59	35	67,732
WC[1]	Per 10 cm	1.04 (1.02, 1.06)	63	10	3613	1.02 (1.00, 1.03)	0	6	1579

Abbreviations: BMI, body mass index; PA, physical activity; WC, waist circumference.

* Nondrinkers included nondrinkers and occasional drinkers. Heavy drinkers were defined as drinking ≥50 g/day.

† Colon vs rectal cancer: *p* for heterogeneity, drinkers vs nondrinkers, *p*=0.03; heavy drinkers vs nondrinkers, *p*=0.56.

‡ Colon vs rectal cancer: *p* for heterogeneity, current vs never smokers, *p*=0.02; former vs never smokers, *p*=0.70.

References:

1. World Cancer Research Fund/American Institue for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and colorectal cancer. 2017. Available at: wcrf.org/colorectal-cancer-2017.
2. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011; 22(9): 1958-72.
3. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA* 2008; 300(23): 2765-78.

Appendix 6.1 Adjusted HRs for specific GI cancers by total PA*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)
Total PA (MET-h/day)						
0 to <8	181	1.00 (0.84, 1.19)	698	1.00 (0.92, 1.09)	708	1.00 (0.92, 1.09)
8 to <16	238	0.86 (0.74, 0.98)	897	0.92 (0.86, 0.99)	1095	0.96 (0.90, 1.02)
16 to <24	146	1.09 (0.93, 1.28)	466	0.90 (0.82, 0.99)	510	0.98 (0.90, 1.07)
24 to <32	77	0.86 (0.68, 1.09)	331	0.89 (0.79, 0.99)	287	0.89 (0.79, 1.00)
32 to <48	129	1.23 (1.01, 1.49)	360	0.81 (0.73, 0.91)	348	0.90 (0.80, 1.01)
≥48	25	0.88 (0.59, 1.33)	95	0.68 (0.55, 0.84)	76	0.74 (0.58, 0.93)

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.
† Regression dilution ratios: total PA, 0.54.

Appendix 6.2 Adjusted HRs for pancreatic cancer by PA and SLT excluding early years of follow-up*

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	196	1.00 (0.84, 1.18)	125	1.00 (0.81, 1.23)
8.8 to <14.3	123	0.79 (0.66, 0.95)	75	0.72 (0.57, 0.92)
14.3 to <21.9	127	1.01 (0.85, 1.20)	88	1.01 (0.82, 1.24)
21.9 to <33.3	114	1.04 (0.85, 1.26)	74	0.95 (0.75, 1.21)
≥33.3	120	1.21 (0.98, 1.49)	85	1.22 (0.95, 1.56)
per 4 MET-h/day†		*1.04 (0.99, 1.10)*		*1.03 (0.97, 1.10)*
Occupational PA				
0	286	1.00 (0.82, 1.22)	180	1.00 (0.78, 1.28)
>0 to <9.0	102	1.34 (1.07, 1.66)	72	1.38 (1.06, 1.78)
9.0 to <15.5	93	1.14 (0.93, 1.39)	58	1.00 (0.77, 1.29)
15.5 to <26.1	94	1.19 (0.97, 1.46)	67	1.18 (0.93, 1.51)
≥26.1	105	1.36 (1.10, 1.69)	70	1.31 (1.01, 1.71)
per 4 MET-h/day†		*1.04 (0.98, 1.09)*		*1.03 (0.97, 1.09)*
Nonoccupational PA				
0 to <3.9	140	1.00 (0.83, 1.21)	88	1.00 (0.79, 1.27)
3.9 to <6.5	145	1.03 (0.88, 1.22)	103	1.16 (0.95, 1.41)
6.5 to <8.5	129	1.00 (0.84, 1.19)	80	0.97 (0.78, 1.21)
8.5 to <11.6	126	0.95 (0.80, 1.14)	80	0.94 (0.75, 1.18)
≥11.6	140	1.03 (0.86, 1.24)	96	1.07 (0.86, 1.34)
per 4 MET-h/day†		*1.03 (0.89, 1.19)*		*1.05 (0.88, 1.26)*
SLT				
0 to <2	133	1.00 (0.82, 1.22)	83	1.00 (0.78, 1.28)
2 to <3	168	1.09 (0.94, 1.27)	118	1.28 (1.06, 1.54)
3 to <4	161	1.14 (0.98, 1.33)	102	1.22 (1.01, 1.49)
4 to <5	120	1.25 (1.04, 1.50)	82	1.45 (1.16, 1.81)
≥5	98	1.06 (0.86, 1.31)	62	1.16 (0.90, 1.51)
per 1.5 h/day†		*1.11 (0.87, 1.41)*		*1.15 (0.85, 1.55)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.3 Adjusted HRs for liver cancer by PA and SLT excluding early years of follow-up*

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	691	1.00 (0.92, 1.09)	432	1.00 (0.89, 1.12)
8.8 to <14.3	469	0.91 (0.83, 1.00)	290	0.87 (0.77, 0.98)
14.3 to <21.9	398	0.89 (0.81, 0.98)	256	0.88 (0.78, 0.99)
21.9 to <33.3	400	0.93 (0.84, 1.04)	261	0.96 (0.84, 1.09)
≥33.3	327	0.78 (0.69, 0.88)	201	0.75 (0.64, 0.88)
per 4 MET-h/day†		*0.96 (0.93, 0.99)*		*0.96 (0.92, 0.99)*
Occupational PA				
0	888	1.00 (0.90, 1.11)	552	1.00 (0.87, 1.14)
>0 to <9.0	400	0.91 (0.82, 1.02)	251	0.92 (0.80, 1.06)
9.0 to <15.5	338	0.92 (0.82, 1.02)	222	0.94 (0.83, 1.08)
15.5 to <26.1	362	0.99 (0.89, 1.10)	231	1.02 (0.89, 1.16)
≥26.1	297	0.80 (0.70, 0.90)	184	0.80 (0.69, 0.94)
per 4 MET-h/day†		*0.97 (0.94, 1.00)*		*0.97 (0.94, 1.00)*
Nonoccupational PA				
0 to <3.9	592	1.00 (0.91, 1.10)	371	1.00 (0.89, 1.13)
3.9 to <6.5	527	1.10 (1.01, 1.20)	336	1.12 (1.01, 1.25)
6.5 to <8.5	409	0.98 (0.89, 1.08)	247	0.95 (0.84, 1.08)
8.5 to <11.6	398	0.98 (0.89, 1.09)	253	0.99 (0.87, 1.12)
≥11.6	359	0.92 (0.82, 1.03)	233	0.93 (0.80, 1.07)
per 4 MET-h/day†		*0.92 (0.84, 1.00)*		*0.91 (0.81, 1.01)*
SLT				
0 to <2	363	1.00 (0.89, 1.12)	228	1.00 (0.87, 1.15)
2 to <3	584	1.00 (0.92, 1.09)	365	0.99 (0.89, 1.10)
3 to <4	577	0.95 (0.87, 1.03)	374	0.98 (0.88, 1.08)
4 to <5	388	0.99 (0.89, 1.09)	245	0.99 (0.87, 1.13)
≥5	373	0.98 (0.88, 1.10)	228	0.95 (0.83, 1.09)
per 1.5 h/day†		*0.98 (0.85, 1.12)*		*0.98 (0.82, 1.16)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.4 Adjusted HRs for colorectal cancer by PA and SLT excluding early years of follow-up*

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	779	1.00 (0.92, 1.09)	508	1.00 (0.90, 1.11)
8.8 to <14.3	611	0.94 (0.86, 1.02)	423	0.95 (0.86, 1.05)
14.3 to <21.9	531	1.03 (0.95, 1.12)	359	0.99 (0.89, 1.10)
21.9 to <33.3	357	0.87 (0.78, 0.97)	229	0.79 (0.69, 0.91)
≥33.3	333	0.88 (0.78, 0.99)	239	0.92 (0.80, 1.07)
per 4 MET-h/day†		*0.97 (0.94, 1.00)*		*0.97 (0.94, 1.01)*
Occupational PA				
0	1271	1.00 (0.91, 1.10)	842	1.00 (0.89, 1.12)
>0 to <9.0	360	0.97 (0.86, 1.09)	245	0.92 (0.79, 1.06)
9.0 to <15.5	376	1.00 (0.91, 1.11)	259	0.94 (0.83, 1.06)
15.5 to <26.1	315	0.92 (0.82, 1.03)	207	0.85 (0.74, 0.98)
≥26.1	289	0.87 (0.76, 0.99)	205	0.88 (0.76, 1.03)
per 4 MET-h/day†		0.97 (0.95, 1.00)		0.97 (0.94, 1.01)
Nonoccupational PA				
0 to <3.9	543	1.00 (0.91, 1.10)	374	1.00 (0.89, 1.12)
3.9 to <6.5	534	0.94 (0.86, 1.03)	360	0.91 (0.82, 1.01)
6.5 to <8.5	496	0.94 (0.86, 1.03)	330	0.90 (0.81, 1.00)
8.5 to <11.6	504	0.92 (0.84, 1.00)	318	0.83 (0.74, 0.93)
≥11.6	534	0.95 (0.86, 1.04)	376	0.95 (0.85, 1.06)
per 4 MET-h/day†		*0.98 (0.90, 1.05)*		*0.99 (0.90, 1.08)*
SLT				
0 to <2	410	1.00 (0.90, 1.11)	266	1.00 (0.88, 1.14)
2 to <3	670	1.13 (1.04, 1.22)	460	1.19 (1.08, 1.30)
3 to <4	665	1.15 (1.06, 1.24)	428	1.14 (1.04, 1.26)
4 to <5	443	1.16 (1.05, 1.27)	317	1.28 (1.15, 1.44)
≥5	423	1.13 (1.02, 1.25)	287	1.20 (1.06, 1.35)
per 1.5 h/day†		*1.14 (1.01, 1.29)*		*1.21 (1.04, 1.40)*

Footnotes as in Appendix 6.2.

Appendix 6.5 Adjusted HRs for pancreatic cancer by PA and SLT excluding smokers or drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	122	1.00 (0.81, 1.23)	183	1.00 (0.84, 1.19)
8.8 to <14.3	98	0.87 (0.71, 1.07)	121	0.84 (0.70, 1.01)
14.3 to <21.9	88	1.17 (0.95, 1.44)	109	1.03 (0.86, 1.25)
21.9 to <33.3	78	1.32 (1.03, 1.68)	94	1.05 (0.84, 1.31)
≥33.3	73	1.60 (1.22, 2.09)	97	1.26 (1.00, 1.59)
per 4 MET-h/day†		*1.10 (1.02, 1.18)*		*1.04 (0.98, 1.11)*
Occupational PA				
0	225	1.00 (0.79, 1.26)	284	1.00 (0.82, 1.22)
>0 to <9.0	67	1.52 (1.16, 1.99)	97	1.39 (1.11, 1.75)
9.0 to <15.5	54	1.21 (0.92, 1.58)	69	1.05 (0.83, 1.34)
15.5 to <26.1	61	1.47 (1.13, 1.90)	79	1.23 (0.98, 1.54)
≥26.1	52	1.56 (1.16, 2.10)	75	1.27 (0.99, 1.64)
per 4 MET-h/day†		*1.07 (1.00, 1.14)*		*1.02 (0.96, 1.08)*
Nonoccupational PA				
0 to <3.9	48	1.00 (0.73, 1.36)	97	1.00 (0.80, 1.25)
3.9 to <6.5	72	0.92 (0.73, 1.17)	115	1.04 (0.87, 1.26)
6.5 to <8.5	96	1.04 (0.85, 1.27)	114	0.99 (0.82, 1.19)
8.5 to <11.6	104	1.03 (0.85, 1.25)	125	1.04 (0.87, 1.25)
≥11.6	139	1.20 (1.00, 1.44)	153	1.18 (1.00, 1.41)
per 4 MET-h/day†		*1.17 (0.99, 1.38)*		*1.15 (0.99, 1.33)*
SLT				
0 to <2	113	1.00 (0.80, 1.24)	137	1.00 (0.82, 1.22)
2 to <3	118	0.97 (0.81, 1.16)	145	0.91 (0.77, 1.08)
3 to <4	97	0.89 (0.73, 1.09)	137	0.92 (0.78, 1.09)
4 to <5	74	0.98 (0.78, 1.24)	101	1.00 (0.82, 1.22)
≥5	57	0.84 (0.64, 1.11)	84	0.87 (0.69, 1.09)
per 1.5 h/day†		*0.91 (0.67, 1.23)*		*0.94 (0.73, 1.22)*

Footnotes as in Appendix 6.2.

Appendix 6.6 Adjusted HRs for liver cancer by PA and SLT excluding smokers or drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	402	1.00 (0.89, 1.12)	665	1.00 (0.91, 1.09)
8.8 to <14.3	317	0.87 (0.78, 0.98)	447	0.90 (0.81, 0.99)
14.3 to <21.9	247	0.94 (0.83, 1.06)	356	0.88 (0.79, 0.98)
21.9 to <33.3	214	0.92 (0.79, 1.07)	356	0.91 (0.81, 1.02)
≥33.3	139	0.76 (0.63, 0.91)	267	0.72 (0.63, 0.83)
per 4 MET-h/day†		*0.94 (0.90, 0.98)*		*0.94 (0.91, 0.97)*
Occupational PA				
0	635	1.00 (0.88, 1.14)	900	1.00 (0.90, 1.11)
>0 to <9.0	230	1.05 (0.90, 1.22)	377	0.92 (0.82, 1.03)
9.0 to <15.5	183	1.03 (0.89, 1.20)	292	0.90 (0.81, 1.02)
15.5 to <26.1	171	1.06 (0.91, 1.24)	288	0.90 (0.80, 1.02)
≥26.1	100	0.80 (0.65, 0.99)	234	0.72 (0.63, 0.83)
per 4 MET-h/day†		*0.96 (0.92, 1.00)*		*0.94 (0.92, 0.97)*
Nonoccupational PA				
0 to <3.9	180	1.00 (0.85, 1.18)	461	1.00 (0.90, 1.11)
3.9 to <6.5	253	1.07 (0.94, 1.22)	464	1.14 (1.03, 1.25)
6.5 to <8.5	294	1.03 (0.91, 1.15)	395	0.99 (0.89, 1.09)
8.5 to <11.6	281	0.91 (0.81, 1.03)	377	0.95 (0.85, 1.05)
≥11.6	311	0.91 (0.81, 1.03)	394	1.01 (0.90, 1.13)
per 4 MET-h/day†		*0.89 (0.79, 0.99)*		*0.97 (0.89, 1.06)*
SLT				
0 to <2	259	1.00 (0.87, 1.15)	354	1.00 (0.89, 1.12)
2 to <3	342	0.93 (0.83, 1.03)	535	0.98 (0.90, 1.07)
3 to <4	325	0.90 (0.80, 1.00)	535	0.95 (0.88, 1.04)
4 to <5	210	0.89 (0.77, 1.02)	348	0.96 (0.87, 1.07)
≥5	183	0.83 (0.72, 0.97)	319	0.93 (0.83, 1.05)
per 1.5 h/day†		*0.88 (0.73, 1.06)*		*0.94 (0.82, 1.09)*

Footnotes as in Appendix 6.3.

Appendix 6.7 Adjusted HRs for colorectal cancer by PA and SLT excluding smokers or drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Total PA				
0 to <8.8	493	1.00 (0.91, 1.10)	669	1.00 (0.92, 1.09)
8.8 to <14.3	494	0.99 (0.90, 1.09)	580	1.00 (0.91, 1.08)
14.3 to <21.9	385	1.07 (0.97, 1.19)	467	1.09 (1.00, 1.20)
21.9 to <33.3	231	0.87 (0.76, 1.00)	317	0.97 (0.86, 1.09)
≥33.3	191	0.86 (0.73, 1.01)	267	0.92 (0.80, 1.06)
per 4 MET-h/day†		*0.97 (0.93, 1.00)*		*0.98 (0.94, 1.01)*
Occupational PA				
0	998	1.00 (0.90, 1.12)	1195	1.00 (0.91, 1.10)
>0 to <9.0	252	1.06 (0.92, 1.22)	333	1.03 (0.91, 1.16)
9.0 to <15.5	221	0.96 (0.84, 1.09)	298	1.03 (0.92, 1.16)
15.5 to <26.1	170	0.82 (0.70, 0.96)	250	0.94 (0.83, 1.07)
≥26.1	153	0.86 (0.73, 1.03)	224	0.89 (0.77, 1.02)
per 4 MET-h/day†		*0.96 (0.93, 1.00)*		*0.98 (0.95, 1.01)*
Nonoccupational PA				
0 to <3.9	190	1.00 (0.86, 1.17)	378	1.00 (0.89, 1.12)
3.9 to <6.5	296	0.91 (0.81, 1.02)	435	0.95 (0.86, 1.04)
6.5 to <8.5	374	0.96 (0.86, 1.06)	443	0.92 (0.84, 1.01)
8.5 to <11.6	436	0.99 (0.90, 1.09)	492	0.95 (0.87, 1.04)
≥11.6	498	1.01 (0.91, 1.10)	552	1.00 (0.91, 1.09)
per 4 MET-h/day†		*1.02 (0.93, 1.11)*		*1.00 (0.93, 1.08)*
SLT				
0 to <2	319	1.00 (0.88, 1.13)	400	1.00 (0.89, 1.12)
2 to <3	464	1.08 (0.99, 1.19)	582	1.02 (0.94, 1.11)
3 to <4	447	1.13 (1.03, 1.24)	583	1.06 (0.98, 1.15)
4 to <5	294	1.12 (1.00, 1.26)	375	1.05 (0.95, 1.16)
≥5	270	1.12 (0.99, 1.27)	360	1.05 (0.94, 1.17)
per 1.5 h/day†		*1.15 (0.99, 1.34)*		*1.10 (0.96, 1.26)*

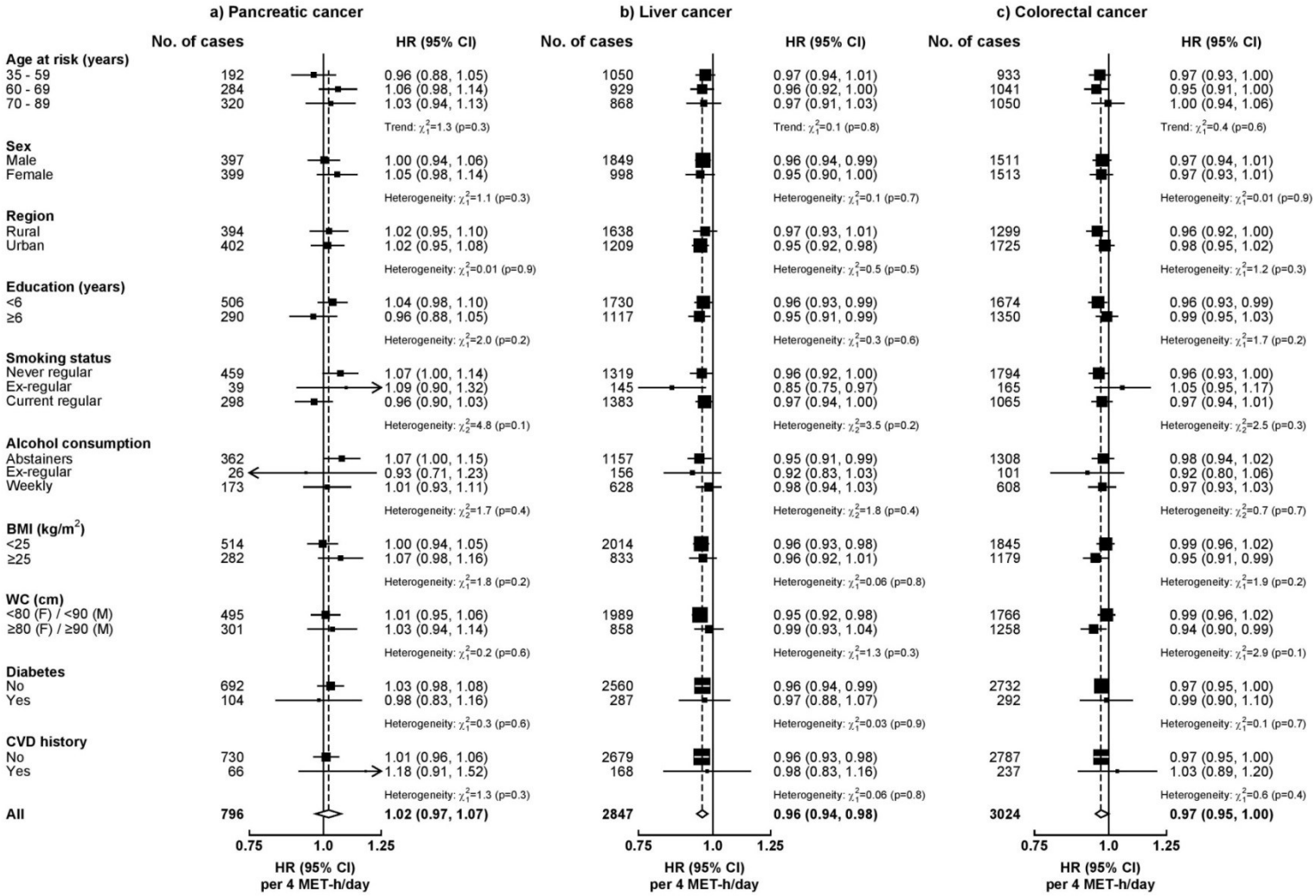
Footnotes as in Appendix 6.2.

Appendix 6.8 Adjusted HRs for specific GI cancers by occupations among nonfarmers*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)
Among nonfarmers†						
Nonsedentary	99	1.00 (0.80, 1.25)	319	1.00 (0.89, 1.13)	363	1.00 (0.89, 1.12)
Sedentary	63	1.17 (0.91, 1.49)	199	1.09 (0.95, 1.26)	297	1.29 (1.15, 1.44)
Not in paid employment	329	1.03 (0.82, 1.29)	1072	1.27 (1.12, 1.44)	1442	1.12 (1.00, 1.24)

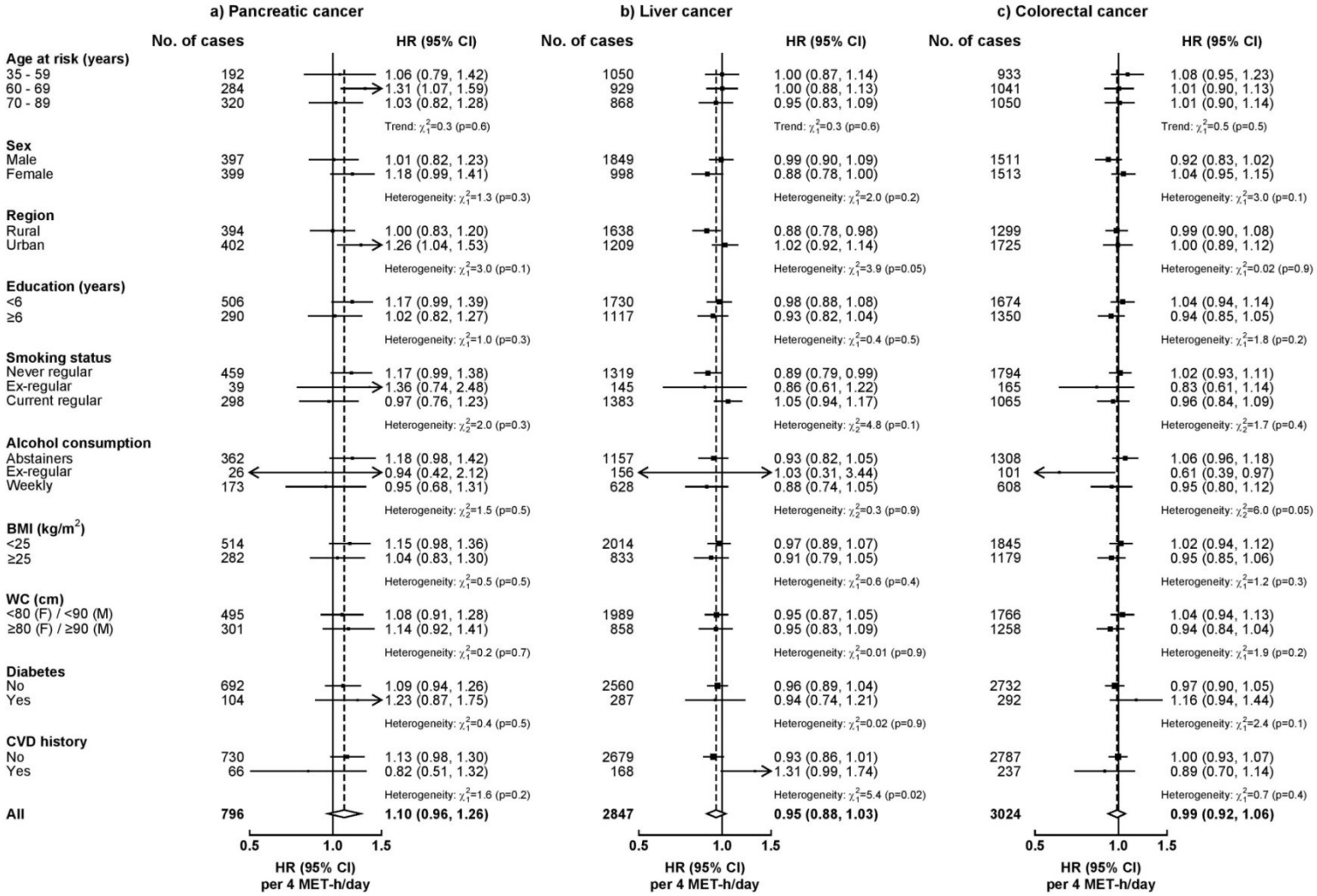
* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and sedentary leisure time.
† Nonsedentary occupations included standing occupation, manual work, and heavy manual work. Not in paid employment included retired, homemakers, and unemployed.

Appendix 6.9 Associations of occupational PA with risks of specific GI cancers by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.

Appendix 6.10 Associations of nonoccupational PA with risks of specific GI cancers by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and SLT.

Appendix 6.11 Adjusted HRs for pancreatic cancer by PA and SLT with additional adjustment for adiposity*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.86, 1.17)	1.00 (0.86, 1.17)	1.00 (0.86, 1.17)
8.8 to <14.3	0.84 (0.71, 1.00)	0.84 (0.71, 1.00)	0.84 (0.71, 1.00)
14.3 to <21.9	1.00 (0.85, 1.18)	1.00 (0.85, 1.18)	1.00 (0.85, 1.17)
21.9 to <33.3	1.03 (0.86, 1.24)	1.03 (0.85, 1.23)	1.02 (0.85, 1.23)
≥33.3	1.19 (0.98, 1.44)	1.18 (0.98, 1.44)	1.18 (0.97, 1.43)
per 4 MET-h/day†	*1.03 (0.98, 1.08)*	*1.03 (0.98, 1.08)*	*1.03 (0.98, 1.08)*
Occupational PA			
0	1.00 (0.84, 1.20)	1.00 (0.84, 1.20)	1.00 (0.84, 1.20)
>0 to <9.0	1.33 (1.09, 1.62)	1.32 (1.08, 1.62)	1.32 (1.08, 1.61)
9.0 to <15.5	1.07 (0.88, 1.29)	1.06 (0.88, 1.29)	1.06 (0.88, 1.29)
15.5 to <26.1	1.15 (0.95, 1.39)	1.14 (0.94, 1.38)	1.14 (0.94, 1.38)
≥26.1	1.24 (1.01, 1.51)	1.23 (1.01, 1.51)	1.23 (1.00, 1.50)
per 4 MET-h/day†	*1.02 (0.97, 1.07)*	*1.02 (0.97, 1.07)*	*1.02 (0.97, 1.07)*
Nonoccupational PA			
0 to <3.9	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)
3.9 to <6.5	1.00 (0.85, 1.16)	0.99 (0.85, 1.16)	0.99 (0.85, 1.16)
6.5 to <8.5	1.02 (0.87, 1.19)	1.02 (0.87, 1.19)	1.02 (0.87, 1.19)
8.5 to <11.6	0.98 (0.83, 1.16)	0.98 (0.83, 1.16)	0.98 (0.83, 1.16)
≥11.6	1.14 (0.97, 1.35)	1.14 (0.97, 1.35)	1.14 (0.97, 1.34)
per 4 MET-h/day†	*1.10 (0.96, 1.26)*	*1.10 (0.96, 1.26)*	*1.10 (0.96, 1.26)*
SLT			
0 to <2	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)
2 to <3	1.02 (0.88, 1.17)	1.02 (0.88, 1.17)	1.02 (0.88, 1.17)
3 to <4	1.03 (0.89, 1.19)	1.03 (0.89, 1.20)	1.04 (0.90, 1.20)
4 to <5	1.09 (0.92, 1.30)	1.09 (0.92, 1.30)	1.09 (0.92, 1.30)
≥5	0.99 (0.81, 1.19)	0.99 (0.82, 1.20)	0.99 (0.82, 1.20)
per 1.5 h/day†	*1.03 (0.83, 1.29)*	*1.04 (0.83, 1.29)*	*1.04 (0.83, 1.30)*

* Main model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA). Model 1: main model plus BMI. Model 2: main model plus WC. Model 3: main model plus %BF.

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.12 Adjusted HRs for liver cancer by PA and SLT with additional adjustment for adiposity*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)
8.8 to <14.3	0.91 (0.84, 0.99)	0.91 (0.84, 0.99)	0.90 (0.83, 0.98)
14.3 to <21.9	0.88 (0.81, 0.97)	0.89 (0.81, 0.97)	0.87 (0.80, 0.95)
21.9 to <33.3	0.93 (0.85, 1.02)	0.93 (0.85, 1.03)	0.91 (0.83, 1.00)
≥33.3	0.76 (0.68, 0.85)	0.77 (0.69, 0.86)	0.75 (0.67, 0.83)
per 4 MET-h/day†	*0.95 (0.93, 0.98)*	*0.95 (0.93, 0.98)*	*0.95 (0.93, 0.97)*
Occupational PA			
0	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
>0 to <9.0	0.89 (0.81, 0.99)	0.90 (0.81, 0.99)	0.88 (0.80, 0.97)
9.0 to <15.5	0.89 (0.81, 0.98)	0.89 (0.81, 0.98)	0.88 (0.79, 0.96)
15.5 to <26.1	0.92 (0.83, 1.01)	0.92 (0.84, 1.02)	0.90 (0.81, 0.99)
≥26.1	0.76 (0.68, 0.85)	0.76 (0.68, 0.85)	0.74 (0.66, 0.83)
per 4 MET-h/day†	*0.96 (0.94, 0.98)*	*0.96 (0.94, 0.98)*	*0.96 (0.93, 0.98)*
Nonoccupational PA			
0 to <3.9	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
3.9 to <6.5	1.08 (1.00, 1.17)	1.08 (1.00, 1.17)	1.07 (0.99, 1.16)
6.5 to <8.5	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)	0.96 (0.88, 1.05)
8.5 to <11.6	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)	0.96 (0.87, 1.05)
≥11.6	0.97 (0.88, 1.08)	0.97 (0.88, 1.08)	0.96 (0.86, 1.06)
per 4 MET-h/day†	*0.95 (0.88, 1.03)*	*0.96 (0.89, 1.03)*	*0.94 (0.88, 1.02)*
SLT			
0 to <2	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
2 to <3	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)	0.99 (0.92, 1.06)
3 to <4	0.94 (0.87, 1.01)	0.93 (0.87, 1.00)	0.95 (0.88, 1.02)
4 to <5	0.94 (0.86, 1.03)	0.94 (0.85, 1.03)	0.96 (0.87, 1.05)
≥5	0.95 (0.86, 1.04)	0.94 (0.86, 1.04)	0.97 (0.88, 1.07)
per 1.5 h/day†	*0.97 (0.86, 1.09)*	*0.96 (0.85, 1.08)*	*0.98 (0.87, 1.11)*

Footnotes as in Appendix 6.11.

Appendix 6.13 Adjusted HRs for colorectal cancer by PA and SLT with additional adjustment for adiposity*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)
8.8 to <14.3	0.98 (0.91, 1.06)	0.98 (0.90, 1.05)	0.97 (0.90, 1.05)
14.3 to <21.9	1.06 (0.98, 1.15)	1.05 (0.97, 1.14)	1.05 (0.97, 1.14)
21.9 to <33.3	0.94 (0.85, 1.04)	0.93 (0.84, 1.03)	0.93 (0.84, 1.02)
≥33.3	0.92 (0.82, 1.03)	0.91 (0.81, 1.02)	0.91 (0.81, 1.02)
per 4 MET-h/day†	*0.98 (0.95, 1.00)*	*0.97 (0.95, 1.00)*	*0.97 (0.95, 1.00)*
Occupational PA			
0	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)
>0 to <9.0	1.03 (0.93, 1.15)	1.02 (0.92, 1.14)	1.02 (0.91, 1.14)
9.0 to <15.5	1.03 (0.94, 1.14)	1.02 (0.93, 1.13)	1.02 (0.93, 1.12)
15.5 to <26.1	0.97 (0.87, 1.08)	0.96 (0.87, 1.07)	0.96 (0.86, 1.06)
≥26.1	0.90 (0.80, 1.02)	0.89 (0.79, 1.01)	0.89 (0.79, 1.00)
per 4 MET-h/day†	*0.98 (0.95, 1.00)*	*0.98 (0.95, 1.00)*	*0.97 (0.95, 1.00)*
Nonoccupational PA			
0 to <3.9	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)
3.9 to <6.5	0.96 (0.89, 1.04)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
6.5 to <8.5	0.97 (0.89, 1.05)	0.96 (0.89, 1.04)	0.96 (0.88, 1.04)
8.5 to <11.6	0.96 (0.89, 1.05)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
≥11.6	1.00 (0.91, 1.09)	0.99 (0.91, 1.08)	0.99 (0.91, 1.08)
per 4 MET-h/day†	*1.00 (0.93, 1.07)*	*0.99 (0.93, 1.07)*	*0.99 (0.93, 1.06)*
SLT			
0 to <2	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
2 to <3	1.08 (1.00, 1.16)	1.08 (1.01, 1.16)	1.08 (1.01, 1.17)
3 to <4	1.09 (1.02, 1.17)	1.10 (1.03, 1.18)	1.10 (1.03, 1.19)
4 to <5	1.12 (1.03, 1.22)	1.13 (1.04, 1.23)	1.13 (1.04, 1.24)
≥5	1.06 (0.97, 1.17)	1.08 (0.98, 1.19)	1.08 (0.99, 1.19)
per 1.5 h/day†	*1.10 (0.98, 1.23)*	*1.11 (0.99, 1.25)*	*1.11 (0.99, 1.25)*

Footnotes as in Appendix 6.11.

Appendix 6.14 Adjusted HRs for pancreatic cancer by PA and SLT with additional adjustment for adiposity and diabetes*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.86, 1.17)	1.00 (0.86, 1.17)	1.00 (0.86, 1.17)
8.8 to <14.3	0.84 (0.71, 1.00)	0.85 (0.72, 1.00)	0.85 (0.72, 1.00)
14.3 to <21.9	1.00 (0.85, 1.18)	1.01 (0.86, 1.19)	1.01 (0.86, 1.19)
21.9 to <33.3	1.03 (0.86, 1.24)	1.05 (0.87, 1.26)	1.05 (0.87, 1.26)
≥33.3	1.19 (0.98, 1.44)	1.21 (1.00, 1.46)	1.21 (1.00, 1.47)
per 4 MET-h/day†	*1.03 (0.98, 1.08)*	*1.04 (0.99, 1.09)*	*1.04 (0.99, 1.09)*
Occupational PA			
0	1.00 (0.84, 1.20)	1.00 (0.84, 1.20)	1.00 (0.83, 1.20)
>0 to <9.0	1.33 (1.09, 1.62)	1.35 (1.10, 1.65)	1.35 (1.10, 1.65)
9.0 to <15.5	1.07 (0.88, 1.29)	1.08 (0.89, 1.32)	1.09 (0.89, 1.32)
15.5 to <26.1	1.15 (0.95, 1.39)	1.17 (0.97, 1.41)	1.17 (0.97, 1.42)
≥26.1	1.24 (1.01, 1.51)	1.26 (1.03, 1.55)	1.26 (1.03, 1.55)
per 4 MET-h/day†	*1.02 (0.97, 1.07)*	*1.02 (0.97, 1.07)*	*1.02 (0.97, 1.07)*
Nonoccupational PA			
0 to <3.9	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)
3.9 to <6.5	1.00 (0.85, 1.16)	0.99 (0.85, 1.16)	0.99 (0.85, 1.16)
6.5 to <8.5	1.02 (0.87, 1.19)	1.03 (0.88, 1.21)	1.03 (0.88, 1.21)
8.5 to <11.6	0.98 (0.83, 1.16)	0.99 (0.84, 1.17)	0.99 (0.84, 1.17)
≥11.6	1.14 (0.97, 1.35)	1.15 (0.98, 1.36)	1.15 (0.98, 1.36)
per 4 MET-h/day†	*1.10 (0.96, 1.26)*	*1.10 (0.97, 1.26)*	*1.10 (0.97, 1.26)*
SLT			
0 to <2	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)
2 to <3	1.02 (0.88, 1.17)	1.02 (0.88, 1.17)	1.02 (0.88, 1.17)
3 to <4	1.03 (0.89, 1.19)	1.03 (0.89, 1.19)	1.03 (0.89, 1.19)
4 to <5	1.09 (0.92, 1.30)	1.09 (0.91, 1.29)	1.09 (0.91, 1.29)
≥5	0.99 (0.81, 1.19)	0.98 (0.81, 1.19)	0.98 (0.81, 1.18)
per 1.5 h/day†	*1.03 (0.83, 1.29)*	*1.03 (0.82, 1.28)*	*1.03 (0.82, 1.28)*

* Main model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA). Model 1: main model plus BMI. Model 2: main model plus diabetes. Model 3: main model plus BMI and diabetes.

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.15 Adjusted HRs for liver cancer by PA and SLT with additional adjustment for adiposity and diabetes*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)
8.8 to <14.3	0.91 (0.84, 0.99)	0.91 (0.84, 0.99)	0.91 (0.84, 0.99)
14.3 to <21.9	0.88 (0.81, 0.97)	0.89 (0.82, 0.98)	0.89 (0.81, 0.97)
21.9 to <33.3	0.93 (0.85, 1.02)	0.94 (0.86, 1.03)	0.93 (0.85, 1.03)
≥33.3	0.76 (0.68, 0.85)	0.77 (0.69, 0.86)	0.77 (0.69, 0.86)
per 4 MET-h/day†	*0.95 (0.93, 0.98)*	*0.96 (0.93, 0.98)*	*0.95 (0.93, 0.98)*
Occupational PA			
0	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
>0 to <9.0	0.89 (0.81, 0.99)	0.91 (0.82, 1.00)	0.90 (0.81, 0.99)
9.0 to <15.5	0.89 (0.81, 0.98)	0.90 (0.82, 0.99)	0.90 (0.81, 0.99)
15.5 to <26.1	0.92 (0.83, 1.01)	0.93 (0.85, 1.03)	0.92 (0.84, 1.02)
≥26.1	0.76 (0.68, 0.85)	0.77 (0.69, 0.86)	0.76 (0.68, 0.85)
per 4 MET-h/day†	*0.96 (0.94, 0.98)*	*0.96 (0.94, 0.98)*	*0.96 (0.94, 0.98)*
Nonoccupational PA			
0 to <3.9	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
3.9 to <6.5	1.08 (1.00, 1.17)	1.09 (1.01, 1.17)	1.08 (1.00, 1.17)
6.5 to <8.5	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)
8.5 to <11.6	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)
≥11.6	0.97 (0.88, 1.08)	0.98 (0.88, 1.08)	0.97 (0.88, 1.08)
per 4 MET-h/day†	*0.95 (0.88, 1.03)*	*0.96 (0.89, 1.03)*	*0.96 (0.89, 1.03)*
SLT			
0 to <2	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
2 to <3	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)	0.98 (0.91, 1.06)
3 to <4	0.94 (0.87, 1.01)	0.93 (0.87, 1.00)	0.94 (0.87, 1.01)
4 to <5	0.94 (0.86, 1.03)	0.93 (0.85, 1.02)	0.94 (0.86, 1.03)
≥5	0.95 (0.86, 1.04)	0.94 (0.85, 1.04)	0.95 (0.87, 1.05)
per 1.5 h/day†	*0.97 (0.86, 1.09)*	*0.95 (0.84, 1.08)*	*0.96 (0.85, 1.09)*

Footnotes as in Appendix 6.14.

Appendix 6.16 Adjusted HRs for colorectal cancer by PA and SLT with additional adjustment for adiposity and diabetes*

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)	1.00 (0.93, 1.08)
8.8 to <14.3	0.98 (0.91, 1.06)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
14.3 to <21.9	1.06 (0.98, 1.15)	1.05 (0.97, 1.13)	1.05 (0.97, 1.14)
21.9 to <33.3	0.94 (0.85, 1.04)	0.92 (0.83, 1.02)	0.93 (0.84, 1.03)
≥33.3	0.92 (0.82, 1.03)	0.90 (0.80, 1.01)	0.91 (0.81, 1.02)
per 4 MET-h/day†	*0.98 (0.95, 1.00)*	*0.97 (0.95, 1.00)*	*0.97 (0.95, 1.00)*
Occupational PA			
0	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)
>0 to <9.0	1.03 (0.93, 1.15)	1.01 (0.91, 1.13)	1.03 (0.92, 1.14)
9.0 to <15.5	1.03 (0.94, 1.14)	1.02 (0.92, 1.12)	1.03 (0.93, 1.13)
15.5 to <26.1	0.97 (0.87, 1.08)	0.95 (0.86, 1.06)	0.96 (0.87, 1.07)
≥26.1	0.90 (0.80, 1.02)	0.88 (0.78, 0.99)	0.89 (0.79, 1.01)
per 4 MET-h/day†	*0.98 (0.95, 1.00)*	*0.97 (0.95, 1.00)*	*0.97 (0.95, 1.00)*
Nonoccupational PA			
0 to <3.9	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)
3.9 to <6.5	0.96 (0.89, 1.04)	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)
6.5 to <8.5	0.97 (0.89, 1.05)	0.97 (0.89, 1.05)	0.97 (0.89, 1.05)
8.5 to <11.6	0.96 (0.89, 1.05)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
≥11.6	1.00 (0.91, 1.09)	0.99 (0.90, 1.07)	0.99 (0.91, 1.08)
per 4 MET-h/day†	*1.00 (0.93, 1.07)*	*0.99 (0.92, 1.06)*	*0.99 (0.92, 1.06)*
SLT			
0 to <2	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
2 to <3	1.08 (1.00, 1.16)	1.09 (1.01, 1.17)	1.08 (1.01, 1.16)
3 to <4	1.09 (1.02, 1.17)	1.11 (1.03, 1.19)	1.10 (1.02, 1.18)
4 to <5	1.12 (1.03, 1.22)	1.14 (1.04, 1.24)	1.13 (1.03, 1.23)
≥5	1.06 (0.97, 1.17)	1.09 (0.99, 1.20)	1.07 (0.98, 1.18)
per 1.5 h/day†	*1.10 (0.98, 1.23)*	*1.12 (1.00, 1.26)*	*1.11 (0.99, 1.24)*

Footnotes as in Appendix 6.13.

Appendix 6.17 Adjusted HRs for specific GI cancers by PA and SLT with additional adjustment for diet*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total PA			
0 to <8.8	1.00 (0.86, 1.17)	1.00 (0.92, 1.08)	1.00 (0.93, 1.08)
8.8 to <14.3	0.84 (0.71, 1.00)	0.91 (0.83, 0.99)	0.97 (0.90, 1.04)
14.3 to <21.9	1.00 (0.85, 1.18)	0.88 (0.81, 0.96)	1.04 (0.96, 1.13)
21.9 to <33.3	1.03 (0.86, 1.24)	0.93 (0.85, 1.02)	0.92 (0.83, 1.02)
≥33.3	1.20 (0.99, 1.45)	0.76 (0.68, 0.85)	0.90 (0.80, 1.01)
per 4 MET-h/day†	*1.03 (0.98, 1.09)*	*0.95 (0.93, 0.98)*	*0.97 (0.95, 1.00)*
Occupational PA			
0	1.00 (0.83, 1.20)	1.00 (0.91, 1.10)	1.00 (0.91, 1.09)
>0 to <9.0	1.31 (1.07, 1.60)	0.90 (0.81, 0.99)	1.02 (0.92, 1.14)
9.0 to <15.5	1.05 (0.87, 1.28)	0.89 (0.81, 0.99)	1.02 (0.93, 1.13)
15.5 to <26.1	1.14 (0.94, 1.38)	0.92 (0.84, 1.02)	0.96 (0.86, 1.07)
≥26.1	1.24 (1.01, 1.52)	0.76 (0.68, 0.85)	0.89 (0.79, 1.00)
per 4 MET-h/day†	*1.02 (0.97, 1.07)*	*0.96 (0.94, 0.98)*	*0.97 (0.95, 1.00)*
Nonoccupational PA			
0 to <3.9	1.00 (0.84, 1.19)	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)
3.9 to <6.5	1.00 (0.85, 1.17)	1.08 (1.00, 1.17)	0.95 (0.87, 1.03)
6.5 to <8.5	1.04 (0.88, 1.22)	0.96 (0.88, 1.05)	0.97 (0.89, 1.05)
8.5 to <11.6	1.00 (0.84, 1.18)	0.96 (0.87, 1.05)	0.95 (0.88, 1.04)
≥11.6	1.16 (0.99, 1.37)	0.96 (0.87, 1.07)	0.98 (0.90, 1.07)
per 4 MET-h/day†	*1.11 (0.97, 1.27)*	*0.95 (0.88, 1.02)*	*0.99 (0.92, 1.06)*
SLT			
0 to <2	1.00 (0.84, 1.19)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
2 to <3	1.03 (0.89, 1.18)	0.97 (0.90, 1.05)	1.08 (1.00, 1.16)
3 to <4	1.06 (0.92, 1.22)	0.93 (0.87, 1.00)	1.10 (1.03, 1.18)
4 to <5	1.12 (0.94, 1.34)	0.94 (0.86, 1.03)	1.13 (1.03, 1.23)
≥5	1.02 (0.84, 1.24)	0.94 (0.86, 1.04)	1.08 (0.98, 1.18)
per 1.5 h/day†	*1.06 (0.85, 1.33)*	*0.96 (0.85, 1.08)*	*1.11 (0.99, 1.25)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), SLT (for PA), and dietary variables (fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables).
† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.18 Adjusted HRs for pancreatic cancer by PA and SLT excluding poor self-rated health or major chronic diseases*

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	HR (95% CI)[1]	No. cases	HR (95% CI)[1]
Total PA				
0 to <8.8	192	1.00 (0.84, 1.18)	143	1.00 (0.82, 1.21)
8.8 to <14.3	130	0.86 (0.71, 1.03)	106	0.93 (0.76, 1.14)
14.3 to <21.9	126	1.01 (0.84, 1.20)	101	1.02 (0.84, 1.23)
21.9 to <33.3	110	0.96 (0.79, 1.17)	101	1.08 (0.87, 1.32)
≥33.3	126	1.15 (0.94, 1.42)	116	1.32 (1.07, 1.63)
per 4 MET-h/day†		*1.02 (0.97, 1.08)*		*1.05 (1.00, 1.11)*
Occupational PA				
0	282	1.00 (0.82, 1.22)	209	1.00 (0.80, 1.24)
>0 to <9.0	107	1.41 (1.14, 1.75)	86	1.25 (0.98, 1.59)
9.0 to <15.5	92	1.07 (0.87, 1.31)	83	1.15 (0.93, 1.43)
15.5 to <26.1	94	1.08 (0.88, 1.33)	90	1.23 (1.00, 1.52)
≥26.1	109	1.26 (1.02, 1.55)	99	1.38 (1.10, 1.72)
per 4 MET-h/day†		*1.01 (0.96, 1.06)*		*1.04 (0.99, 1.10)*
Nonoccupational PA				
0 to <3.9	149	1.00 (0.83, 1.20)	126	1.00 (0.82, 1.22)
3.9 to <6.5	140	0.95 (0.80, 1.12)	107	0.87 (0.72, 1.06)
6.5 to <8.5	129	0.97 (0.82, 1.15)	112	0.99 (0.82, 1.19)
8.5 to <11.6	125	0.94 (0.79, 1.13)	109	0.99 (0.81, 1.20)
≥11.6	141	1.03 (0.86, 1.24)	113	1.03 (0.84, 1.27)
per 4 MET-h/day†		*1.06 (0.91, 1.22)*		*1.07 (0.91, 1.26)*
SLT				
0 to <2	143	1.00 (0.83, 1.21)	127	1.00 (0.82, 1.23)
2 to <3	165	0.99 (0.85, 1.16)	131	0.92 (0.77, 1.09)
3 to <4	163	1.07 (0.92, 1.25)	137	1.07 (0.91, 1.27)
4 to <5	116	1.13 (0.93, 1.36)	100	1.16 (0.95, 1.42)
≥5	97	1.04 (0.84, 1.28)	72	0.94 (0.74, 1.20)
per 1.5 h/day†		*1.12 (0.88, 1.43)*		*1.03 (0.78, 1.35)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA). Major chronic diseases included CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease, peptic ulcer, and kidney disease.

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 6.19 Adjusted HRs for liver cancer by PA and SLT excluding poor self-rated health or major chronic diseases*

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	HR (95% CI)[1]	No. cases	HR (95% CI)[1]
Total PA				
0 to <8.8	701	1.00 (0.92, 1.09)	523	1.00 (0.90, 1.11)
8.8 to <14.3	483	0.90 (0.82, 0.99)	376	0.94 (0.84, 1.04)
14.3 to <21.9	425	0.91 (0.82, 1.00)	346	0.94 (0.84, 1.04)
21.9 to <33.3	436	0.98 (0.88, 1.08)	361	1.00 (0.89, 1.11)
≥33.3	369	0.80 (0.72, 0.90)	312	0.87 (0.77, 0.99)
per 4 MET-h/day†		*0.96 (0.94, 0.99)*		*0.98 (0.95, 1.01)*
Occupational PA				
0	910	1.00 (0.90, 1.11)	672	1.00 (0.89, 1.12)
>0 to <9.0	419	0.94 (0.84, 1.05)	348	0.86 (0.77, 0.98)
9.0 to <15.5	364	0.95 (0.85, 1.05)	305	0.93 (0.83, 1.04)
15.5 to <26.1	380	0.99 (0.89, 1.10)	314	0.94 (0.84, 1.05)
≥26.1	341	0.82 (0.73, 0.92)	279	0.81 (0.72, 0.93)
per 4 MET-h/day†		*0.97 (0.94, 0.99)*		*0.98 (0.95, 1.01)*
Nonoccupational PA				
0 to <3.9	645	1.00 (0.91, 1.09)	502	1.00 (0.90, 1.11)
3.9 to <6.5	540	1.04 (0.95, 1.13)	418	1.05 (0.95, 1.15)
6.5 to <8.5	421	0.94 (0.85, 1.03)	350	0.97 (0.88, 1.08)
8.5 to <11.6	413	0.95 (0.86, 1.05)	330	0.98 (0.88, 1.10)
≥11.6	395	0.98 (0.88, 1.09)	318	1.01 (0.89, 1.14)
per 4 MET-h/day†		*0.96 (0.88, 1.04)*		*0.98 (0.89, 1.08)*
SLT				
0 to <2	406	1.00 (0.90, 1.11)	333	1.00 (0.89, 1.13)
2 to <3	618	0.96 (0.88, 1.04)	477	0.90 (0.82, 0.99)
3 to <4	619	0.93 (0.86, 1.00)	497	0.89 (0.81, 0.97)
4 to <5	411	0.95 (0.86, 1.05)	316	0.88 (0.78, 0.98)
≥5	360	0.92 (0.83, 1.03)	295	0.93 (0.82, 1.05)
per 1.5 h/day†		*0.96 (0.83, 1.10)*		*0.96 (0.82, 1.12)*

Footnotes as in Appendix 6.18.

Appendix 6.20 Adjusted HRs for colorectal cancer by PA and SLT excluding poor self-rated health or major chronic diseases*

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	HR (95% CI)[1]	No. cases	HR (95% CI)[1]
Total PA				
0 to <8.8	785	1.00 (0.92, 1.08)	615	1.00 (0.91, 1.10)
8.8 to <14.3	649	0.98 (0.90, 1.06)	512	0.96 (0.88, 1.05)
14.3 to <21.9	534	1.02 (0.93, 1.11)	453	1.01 (0.92, 1.10)
21.9 to <33.3	378	0.90 (0.80, 1.00)	325	0.87 (0.77, 0.97)
≥33.3	357	0.88 (0.78, 0.99)	323	0.90 (0.80, 1.02)
per 4 MET-h/day†		*0.97 (0.94, 0.99)*		*0.97 (0.94, 1.00)*
Occupational PA				
0	1314	1.00 (0.91, 1.10)	987	1.00 (0.90, 1.11)
>0 to <9.0	365	0.94 (0.84, 1.06)	351	1.03 (0.91, 1.16)
9.0 to <15.5	373	0.96 (0.86, 1.06)	329	0.97 (0.87, 1.08)
15.5 to <26.1	338	0.93 (0.83, 1.04)	281	0.88 (0.78, 0.99)
≥26.1	313	0.84 (0.74, 0.95)	280	0.87 (0.76, 0.99)
per 4 MET-h/day†		*0.97 (0.94, 0.99)*		*0.97 (0.94, 1.00)*
Nonoccupational PA				
0 to <3.9	559	1.00 (0.91, 1.10)	441	1.00 (0.90, 1.11)
3.9 to <6.5	539	0.93 (0.85, 1.01)	456	1.02 (0.93, 1.12)
6.5 to <8.5	525	0.97 (0.89, 1.06)	432	1.01 (0.92, 1.11)
8.5 to <11.6	531	0.95 (0.87, 1.04)	446	1.03 (0.93, 1.13)
≥11.6	549	0.97 (0.88, 1.06)	453	1.06 (0.96, 1.18)
per 4 MET-h/day†		*0.98 (0.91, 1.06)*		*1.02 (0.94, 1.11)*
SLT				
0 to <2	443	1.00 (0.90, 1.11)	365	1.00 (0.89, 1.12)
2 to <3	686	1.06 (0.98, 1.14)	595	1.13 (1.04, 1.23)
3 to <4	680	1.09 (1.01, 1.17)	551	1.09 (1.00, 1.18)
4 to <5	467	1.14 (1.04, 1.25)	375	1.15 (1.04, 1.27)
≥5	427	1.10 (0.99, 1.22)	342	1.14 (1.02, 1.27)
per 1.5 h/day†		*1.14 (1.00, 1.29)*		*1.12 (0.97, 1.29)*

Footnotes as in Appendix 6.18.

Appendix 6.21 Adjusted HRs for cancer mortality by PA and SLT*

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)
Total PA						
0 to <8.8	166	1.00 (0.83, 1.20)	632	1.00 (0.91, 1.10)	290	1.00 (0.88, 1.14)
8.8 to <14.3	101	0.81 (0.66, 1.00)	412	0.92 (0.83, 1.02)	242	1.08 (0.95, 1.23)
14.3 to <21.9	111	1.11 (0.92, 1.33)	335	0.86 (0.77, 0.96)	176	1.04 (0.89, 1.20)
21.9 to <33.3	93	1.05 (0.84, 1.30)	358	0.93 (0.83, 1.04)	143	1.03 (0.87, 1.24)
≥33.3	98	1.24 (0.99, 1.56)	284	0.75 (0.66, 0.85)	110	0.90 (0.73, 1.12)
per 4 MET-h/day†		*1.05 (0.99, 1.11)*		*0.95 (0.92, 0.98)*		*0.98 (0.93, 1.03)*
Occupational PA						
0	246	1.00 (0.81, 1.24)	796	1.00 (0.89, 1.12)	474	1.00 (0.85, 1.17)
>0 to <9.0	88	1.44 (1.14, 1.82)	370	0.87 (0.77, 0.97)	148	1.01 (0.84, 1.21)
9.0 to <15.5	73	1.05 (0.83, 1.32)	300	0.86 (0.77, 0.97)	123	0.98 (0.82, 1.17)
15.5 to <26.1	78	1.13 (0.90, 1.42)	299	0.85 (0.76, 0.96)	115	0.97 (0.80, 1.17)
≥26.1	84	1.28 (1.01, 1.63)	256	0.70 (0.61, 0.80)	101	0.91 (0.73, 1.13)
per 4 MET-h/day†		*1.03 (0.97, 1.09)*		*0.95 (0.92, 0.98)*		*0.98 (0.94, 1.03)*
Nonoccupational PA						
0 to <3.9	124	1.00 (0.82, 1.22)	542	1.00 (0.91, 1.10)	201	1.00 (0.85, 1.17)
3.9 to <6.5	110	0.92 (0.76, 1.11)	455	1.09 (1.00, 1.20)	186	0.93 (0.80, 1.08)
6.5 to <8.5	103	0.94 (0.78, 1.15)	367	1.01 (0.91, 1.12)	190	1.00 (0.87, 1.15)
8.5 to <11.6	100	0.92 (0.76, 1.13)	335	0.99 (0.88, 1.10)	180	0.92 (0.79, 1.06)
≥11.6	132	1.18 (0.98, 1.43)	322	1.00 (0.88, 1.13)	204	1.01 (0.86, 1.17)
per 4 MET-h/day†		*1.15 (0.99, 1.34)*		*0.98 (0.90, 1.07)*		*0.98 (0.86, 1.11)*
SLT						
0 to <2	123	1.00 (0.81, 1.23)	328	1.00 (0.89, 1.13)	172	1.00 (0.84, 1.19)
2 to <3	138	1.04 (0.88, 1.23)	524	1.03 (0.94, 1.12)	236	1.00 (0.88, 1.14)
3 to <4	133	1.09 (0.92, 1.30)	510	0.94 (0.86, 1.02)	217	0.92 (0.80, 1.05)
4 to <5	94	1.10 (0.90, 1.36)	323	0.89 (0.80, 0.99)	173	1.07 (0.92, 1.25)
≥5	81	0.97 (0.77, 1.22)	336	0.95 (0.85, 1.07)	163	0.99 (0.84, 1.16)
per 1.5 h/day†		*1.02 (0.79, 1.33)*		*0.94 (0.81, 1.09)*		*0.97 (0.79, 1.20)*

Footnotes as in Appendix 6.18.

Appendix 7.1 Partial correlations between adiposity traits

		Standing height	Weight	BMI	WC	HC	WHR	WHtR	BF%	BMI25	Fat mass	Lean mass
Leg	Men:	0.83	0.34	-0.06	0.14	0.22	0.003	-0.14	-0.03	-0.18	0.12	0.47
length	Women:	0.81	0.30	-0.08	0.10	0.18	-0.005	-0.15	-0.07	-0.13	0.09	0.53
Standing		Men:	0.53	0.07	0.27	0.42	0.02	-0.06	0.04	-0.19	0.24	0.68
height		Women:	0.48	0.03	0.20	0.36	-0.04	-0.12	-0.0006	-0.14	0.21	0.74
Weight			Men:	0.88	0.85	0.84	0.54	0.71	0.70	0.17	0.87	0.87
			Women:	0.89	0.83	0.85	0.46	0.68	0.78	0.24	0.92	0.75
BMI				Men:	0.86	0.76	0.63	0.86	0.80	0.31	0.89	0.65
				Women:	0.84	0.78	0.54	0.84	0.89	0.34	0.94	0.47
WC					Men:	0.81	0.81	0.95	0.74	0.15	0.84	0.65
					Women:	0.77	0.79	0.95	0.78	0.23	0.84	0.49
HC						Men:	0.32	0.70	0.62	0.12	0.75	0.72
						Women:	0.23	0.67	0.70	0.19	0.81	0.59
WHR							Men:	0.84	0.59	0.12	0.60	0.36
							Women:	0.81	0.53	0.17	0.52	0.19
WHtR								Men:	0.75	0.21	0.78	0.45
								Women:	0.79	0.27	0.78	0.26
BF%									Men:	0.15	0.95	0.27
									Women:	0.25	0.95	0.19
BMI25										Men:	0.17	0.14
										Women:	0.25	0.12
Fat mass											Men:	0.52
											Women:	0.43

Pearson partial correlation coefficients were adjusted for age and regions.

Appendix 7.2 Adjusted HRs for pancreatic cancer by BMI, WC, and WHR*

	No exclusions		Excluding 2 years		Excluding 5 years	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)
BMI						
<18.5	39	0.99 (0.72, 1.36)	30	0.91 (0.63, 1.30)	20	0.97 (0.62, 1.51)
18.5-24.9	475	1.00 (0.91, 1.10)	412	1.00 (0.90, 1.11)	272	1.00 (0.88, 1.13)
25.0-29.9	243	1.02 (0.90, 1.16)	205	0.99 (0.86, 1.14)	132	0.96 (0.80, 1.14)
≥30.0	39	1.07 (0.78, 1.48)	33	1.06 (0.75, 1.50)	23	1.07 (0.71, 1.63)
WC						
<90 (M) / 80 (F)	508	Reference	441	Reference	291	Reference
≥90 (M) / 80 (F)	288	1.03 (0.88, 1.21)	239	0.98 (0.82, 1.16)	156	0.97 (0.78, 1.20)
Men	86	1.02 (0.79, 1.32)	68	0.95 (0.72, 1.26)	42	0.94 (0.65, 1.34)
Women	202	1.03 (0.84, 1.27)	171	0.98 (0.79, 1.23)	114	0.98 (0.75, 1.28)
WHR						
<0.90 (M) / 0.85 (F)	345	Reference	297	Reference	194	Reference
≥0.90 (M) / 0.85 (F)	451	1.02 (0.86, 1.20)	383	1.05 (0.88, 1.26)	253	1.07 (0.85, 1.33)
Men	202	1.12 (0.92, 1.37)	171	1.15 (0.92, 1.43)	112	1.22 (0.92, 1.60)
Women	249	0.96 (0.78, 1.19)	212	0.90 (0.72, 1.12)	141	0.86 (0.66, 1.13)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.3 Adjusted HRs for pancreatic cancer by main adiposity traits excluding the first two or five years of follow-up*

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	83	0.89 (0.71, 1.11)	54	0.92 (0.70, 1.22)
20.0 to <22.5	169	1.00 (0.86, 1.17)	109	1.00 (0.83, 1.21)
22.5 to <25.0	190	1.00 (0.86, 1.15)	129	1.05 (0.88, 1.24)
25.0 to <27.5	115	0.96 (0.80, 1.16)	70	0.90 (0.71, 1.14)
≥27.5	123	1.01 (0.84, 1.22)	85	1.07 (0.85, 1.34)
per 3.4 kg/m^2†		*1.02 (0.94, 1.11)*		*1.01 (0.91, 1.12)*
%BF				
Quintile 1	143	1.08 (0.91, 1.28)	91	1.05 (0.85, 1.30)
Quintile 2	120	1.00 (0.84, 1.20)	80	1.00 (0.80, 1.25)
Quintile 3	134	1.06 (0.89, 1.25)	89	1.06 (0.86, 1.30)
Quintile 4	143	1.11 (0.94, 1.30)	88	1.01 (0.82, 1.25)
Quintile 5	140	1.04 (0.87, 1.23)	99	1.08 (0.88, 1.32)
per 8.4%†		*0.99 (0.88, 1.10)*		*0.99 (0.87, 1.13)*
WC				
Quintile 1	128	0.89 (0.74, 1.06)	81	0.81 (0.65, 1.02)
Quintile 2	126	1.00 (0.84, 1.19)	88	1.00 (0.81, 1.24)
Quintile 3	132	0.98 (0.83, 1.16)	88	0.95 (0.77, 1.17)
Quintile 4	141	0.98 (0.83, 1.15)	93	0.94 (0.76, 1.15)
Quintile 5	153	0.93 (0.79, 1.11)	97	0.87 (0.70, 1.08)
per 9.8 cm†		*1.02 (0.93, 1.12)*		*1.02 (0.90, 1.14)*
WHR				
Quintile 1	116	0.96 (0.80, 1.16)	74	0.92 (0.72, 1.16)
Quintile 2	126	1.00 (0.84, 1.19)	85	1.00 (0.81, 1.24)
Quintile 3	116	1.02 (0.85, 1.23)	77	1.00 (0.80, 1.25)
Quintile 4	145	1.00 (0.85, 1.17)	98	1.00 (0.82, 1.22)
Quintile 5	177	0.98 (0.84, 1.14)	113	0.92 (0.76, 1.11)
per 0.07†		*1.00 (0.89, 1.13)*		*1.01 (0.87, 1.16)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.4 Adjusted HRs for pancreatic cancer by main adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	49	0.81 (0.61, 1.09)	78	0.85 (0.68, 1.08)
20.0 to <22.5	113	1.00 (0.83, 1.21)	156	1.00 (0.85, 1.17)
22.5 to <25.0	110	0.79 (0.66, 0.96)	149	0.84 (0.72, 0.99)
25.0 to <27.5	82	0.91 (0.74, 1.14)	105	0.94 (0.78, 1.14)
≥27.5	105	1.05 (0.86, 1.29)	116	0.98 (0.81, 1.19)
per 3.4 kg/m^2†		*1.06 (0.96, 1.16)*		*1.02 (0.93, 1.11)*
%BF				
Quintile 1	93	1.17 (0.95, 1.45)	141	1.20 (1.01, 1.43)
Quintile 2	73	1.00 (0.79, 1.26)	101	1.00 (0.82, 1.22)
Quintile 3	91	1.16 (0.94, 1.42)	113	1.07 (0.89, 1.29)
Quintile 4	100	1.18 (0.97, 1.44)	125	1.16 (0.97, 1.38)
Quintile 5	102	1.10 (0.90, 1.35)	124	1.09 (0.91, 1.31)
per 8.4%†		*1.01 (0.89, 1.14)*		*0.98 (0.88, 1.10)*
WC				
Quintile 1	81	1.03 (0.82, 1.29)	125	1.03 (0.85, 1.23)
Quintile 2	73	1.00 (0.79, 1.26)	106	1.00 (0.83, 1.21)
Quintile 3	77	0.93 (0.74, 1.16)	108	0.94 (0.78, 1.14)
Quintile 4	100	1.06 (0.87, 1.29)	118	0.96 (0.80, 1.15)
Quintile 5	128	1.15 (0.95, 1.39)	147	1.02 (0.85, 1.21)
per 9.8 cm†		*1.07 (0.96, 1.20)*		*0.99 (0.90, 1.10)*
WHR				
Quintile 1	80	1.25 (0.99, 1.56)	118	1.15 (0.96, 1.39)
Quintile 2	71	1.00 (0.79, 1.26)	105	1.00 (0.83, 1.21)
Quintile 3	67	1.03 (0.81, 1.30)	93	0.98 (0.80, 1.21)
Quintile 4	96	1.11 (0.91, 1.35)	125	1.02 (0.86, 1.22)
Quintile 5	145	1.26 (1.06, 1.49)	163	1.03 (0.88, 1.21)
per 0.07†		*1.03 (0.90, 1.18)*		*0.95 (0.84, 1.07)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.5 Adjusted HRs for pancreatic cancer by other adiposity traits excluding the first two or five years of follow-up[*]

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	149	0.93 (0.78, 1.11)	104	0.99 (0.80, 1.23)
Quintile 2	132	1.00 (0.84, 1.19)	86	1.00 (0.81, 1.24)
Quintile 3	129	0.99 (0.83, 1.17)	85	1.01 (0.82, 1.25)
Quintile 4	116	0.88 (0.73, 1.06)	68	0.81 (0.63, 1.02)
Quintile 5	154	1.06 (0.88, 1.28)	104	1.13 (0.90, 1.43)
per 6.9 cm[†]		*1.04 (0.93, 1.15)*		*1.03 (0.91, 1.18)*
WHtR				
Quintile 1	123	1.02 (0.85, 1.23)	77	0.84 (0.67, 1.06)
Quintile 2	117	1.00 (0.83, 1.20)	89	1.00 (0.81, 1.23)
Quintile 3	135	1.08 (0.91, 1.28)	84	0.89 (0.72, 1.10)
Quintile 4	153	1.10 (0.94, 1.29)	103	1.00 (0.82, 1.21)
Quintile 5	152	0.94 (0.79, 1.11)	94	0.79 (0.64, 0.98)
per 0.06[†]		*1.00 (0.92, 1.10)*		*0.99 (0.88, 1.11)*
Height-adjusted weight				
Quintile 1	151	1.00 (0.83, 1.20)	95	0.95 (0.75, 1.20)
Quintile 2	133	1.00 (0.84, 1.19)	91	1.00 (0.81, 1.23)
Quintile 3	124	0.94 (0.79, 1.12)	78	0.86 (0.69, 1.07)
Quintile 4	135	1.03 (0.87, 1.22)	88	0.97 (0.79, 1.20)
Quintile 5	137	1.01 (0.83, 1.23)	95	1.00 (0.79, 1.26)
per 10.8 kg[†]		*1.03 (0.92, 1.14)*		*1.01 (0.89, 1.15)*
Height-adjusted fat mass				
Quintile 1	145	1.00 (0.84, 1.19)	92	0.95 (0.76, 1.18)
Quintile 2	129	1.00 (0.84, 1.19)	89	1.00 (0.81, 1.23)
Quintile 3	130	1.00 (0.84, 1.18)	83	0.93 (0.75, 1.15)
Quintile 4	142	1.06 (0.90, 1.25)	85	0.91 (0.74, 1.13)
Quintile 5	134	0.98 (0.82, 1.18)	98	1.02 (0.82, 1.26)
per 6.9 kg[†]		*1.00 (0.91, 1.10)*		*1.00 (0.89, 1.13)*
Height-adjusted lean mass				
Quintile 1	162	1.03 (0.83, 1.26)	111	1.24 (0.96, 1.59)
Quintile 2	136	1.00 (0.84, 1.19)	82	1.00 (0.80, 1.25)
Quintile 3	113	0.90 (0.75, 1.07)	78	1.00 (0.81, 1.25)
Quintile 4	132	1.10 (0.92, 1.31)	82	1.08 (0.87, 1.36)
Quintile 5	137	1.18 (0.95, 1.45)	94	1.24 (0.96, 1.61)
per 7.6 kg[†]		*1.10 (0.93, 1.30)*		*1.02 (0.82, 1.26)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.6 Adjusted HRs for pancreatic cancer by other adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	94	0.91 (0.73, 1.14)	142	1.03 (0.86, 1.24)
Quintile 2	84	1.00 (0.80, 1.24)	113	1.00 (0.83, 1.21)
Quintile 3	77	0.85 (0.68, 1.06)	104	0.90 (0.74, 1.09)
Quintile 4	82	0.90 (0.72, 1.12)	98	0.86 (0.70, 1.05)
Quintile 5	122	1.13 (0.91, 1.39)	147	1.14 (0.94, 1.39)
per 6.9 cm†		*1.09 (0.97, 1.23)*		*1.04 (0.93, 1.16)*
WHtR				
Quintile 1	78	1.25 (0.99, 1.57)	122	1.24 (1.03, 1.50)
Quintile 2	65	1.00 (0.78, 1.28)	95	1.00 (0.82, 1.22)
Quintile 3	82	1.11 (0.89, 1.38)	111	1.08 (0.90, 1.31)
Quintile 4	104	1.20 (0.99, 1.46)	133	1.16 (0.98, 1.37)
Quintile 5	130	1.23 (1.02, 1.48)	143	1.01 (0.85, 1.21)
per 0.06†		*1.04 (0.93, 1.16)*		*0.98 (0.89, 1.08)*
Height-adjusted weight				
Quintile 1	99	1.04 (0.82, 1.30)	147	1.07 (0.89, 1.30)
Quintile 2	85	1.00 (0.81, 1.24)	117	1.00 (0.83, 1.20)
Quintile 3	74	0.85 (0.68, 1.06)	100	0.86 (0.71, 1.05)
Quintile 4	85	0.95 (0.77, 1.17)	105	0.92 (0.76, 1.12)
Quintile 5	116	1.21 (0.98, 1.50)	135	1.17 (0.96, 1.42)
per 10.8 kg†		*1.08 (0.95, 1.22)*		*1.03 (0.92, 1.15)*
Height-adjusted fat mass				
Quintile 1	94	1.05 (0.85, 1.30)	143	1.08 (0.90, 1.28)
Quintile 2	81	1.00 (0.80, 1.25)	113	1.00 (0.83, 1.20)
Quintile 3	79	0.94 (0.75, 1.17)	103	0.91 (0.75, 1.10)
Quintile 4	95	1.05 (0.86, 1.28)	116	0.99 (0.83, 1.19)
Quintile 5	110	1.13 (0.93, 1.39)	129	1.09 (0.91, 1.32)
per 6.9 kg†		*1.03 (0.93, 1.15)*		*1.01 (0.91, 1.11)*
Height-adjusted lean mass				
Quintile 1	104	1.03 (0.79, 1.34)	151	1.06 (0.86, 1.32)
Quintile 2	87	1.00 (0.81, 1.24)	122	1.00 (0.84, 1.20)
Quintile 3	77	0.94 (0.75, 1.17)	94	0.84 (0.69, 1.02)
Quintile 4	87	1.10 (0.89, 1.37)	114	1.08 (0.89, 1.30)
Quintile 5	104	1.36 (1.06, 1.74)	123	1.22 (0.98, 1.53)
per 7.6 kg†		*1.24 (0.98, 1.56)*		*1.11 (0.92, 1.34)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.7 Adjusted HRs for pancreatic cancer by main adiposity traits in men and women, separately*

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	57	1.02 (0.78, 1.34)	44	0.78 (0.58, 1.06)
20.0 to <22.5	100	1.00 (0.82, 1.22)	100	1.00 (0.82, 1.22)
22.5 to <25.0	117	1.12 (0.94, 1.34)	96	0.78 (0.64, 0.96)
25.0 to <27.5	59	0.92 (0.71, 1.19)	76	0.97 (0.77, 1.21)
≥27.5	64	1.18 (0.91, 1.52)	83	0.88 (0.70, 1.11)
per 3.4 kg/m^2†		*1.02 (0.91, 1.15)*		*1.01 (0.91, 1.12)*
%BF				
Quintile 1	88	0.99 (0.79, 1.24)	83	1.15 (0.92, 1.44)
Quintile 2	78	1.00 (0.80, 1.25)	65	1.00 (0.78, 1.28)
Quintile 3	86	1.04 (0.85, 1.29)	72	1.05 (0.83, 1.32)
Quintile 4	76	0.98 (0.78, 1.23)	86	1.13 (0.91, 1.39)
Quintile 5	69	0.93 (0.73, 1.19)	93	1.07 (0.86, 1.32)
per 8.4%†		*0.93 (0.79, 1.09)*		*1.00 (0.88, 1.13)*
WC				
Quintile 1	97	1.17 (0.95, 1.46)	66	0.86 (0.67, 1.10)
Quintile 2	70	1.00 (0.79, 1.27)	69	1.00 (0.79, 1.27)
Quintile 3	71	1.01 (0.80, 1.27)	75	0.95 (0.76, 1.19)
Quintile 4	76	1.05 (0.84, 1.32)	85	0.95 (0.77, 1.18)
Quintile 5	83	1.09 (0.86, 1.38)	104	0.93 (0.76, 1.15)
per 9.8 cm†		*1.00 (0.88, 1.14)*		*1.01 (0.90, 1.14)*
WHR				
Quintile 1	77	0.88 (0.70, 1.11)	68	1.34 (1.05, 1.71)
Quintile 2	85	1.00 (0.81, 1.24)	57	1.00 (0.77, 1.30)
Quintile 3	64	0.87 (0.68, 1.11)	63	1.18 (0.92, 1.51)
Quintile 4	93	1.04 (0.85, 1.28)	80	1.10 (0.88, 1.36)
Quintile 5	78	0.85 (0.68, 1.06)	131	1.24 (1.04, 1.49)
per 0.07†		*1.01 (0.86, 1.18)*		*0.98 (0.85, 1.14)*
BMI25‡				
<20.0	49	0.94 (0.71, 1.25)	63	0.95 (0.74, 1.22)
20.0 to <22.5	136	1.00 (0.84, 1.18)	103	1.00 (0.82, 1.21)
22.5 to <25.0	102	1.04 (0.85, 1.26)	91	1.13 (0.92, 1.38)
25.0 to <27.5	44	1.71 (1.27, 2.31)	36	1.10 (0.79, 1.52)
≥27.5	15	1.31 (0.78, 2.17)	23	1.26 (0.83, 1.90)
per 2.6 kg/m^2		*1.13 (1.01, 1.27)*		*1.05 (0.95, 1.16)*

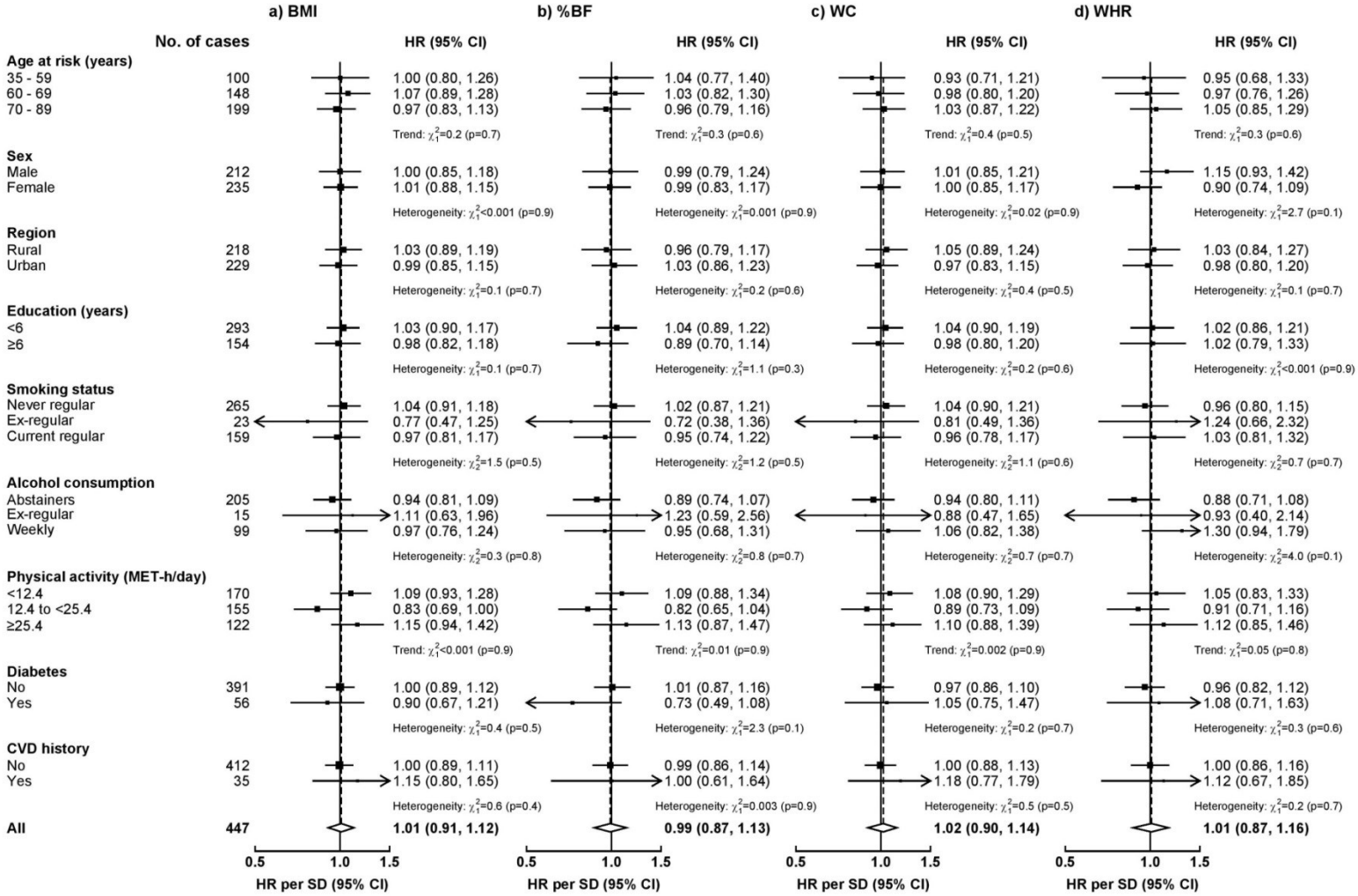
* Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.
‡ BMI25 was missing in 81,880 participants.
P for heterogeneity by sex: BMI, 0.92; %BF, 0.53; WC, 0.87; WHR, 0.82; BMI25, 0.32.

Appendix 7.8 Adjusted HRs for pancreatic cancer by other adiposity traits in men and women, separately*

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	85	1.01 (0.79, 1.27)	90	0.86 (0.69, 1.08)
Quintile 2	79	1.00 (0.80, 1.25)	77	1.00 (0.80, 1.25)
Quintile 3	80	1.09 (0.88, 1.36)	66	0.79 (0.62, 1.01)
Quintile 4	69	0.88 (0.69, 1.11)	67	0.84 (0.66, 1.07)
Quintile 5	84	1.05 (0.81, 1.36)	99	1.00 (0.79, 1.26)
per 6.8 cm†		*1.00 (0.86, 1.16)*		*1.04 (0.92, 1.18)*
WHtR				
Quintile 1	91	1.19 (0.96, 1.48)	64	1.08 (0.84, 1.39)
Quintile 2	70	1.00 (0.79, 1.27)	61	1.00 (0.78, 1.29)
Quintile 3	76	1.08 (0.86, 1.35)	78	1.12 (0.90, 1.39)
Quintile 4	88	1.19 (0.96, 1.47)	86	1.04 (0.85, 1.29)
Quintile 5	72	0.90 (0.70, 1.14)	110	1.05 (0.86, 1.28)
per 0.06†		*0.97 (0.85, 1.11)*		*0.99 (0.88, 1.11)*
Height-adjusted weight				
Quintile 1	84	0.92 (0.71, 1.18)	96	1.14 (0.91, 1.45)
Quintile 2	85	1.00 (0.81, 1.24)	70	1.00 (0.79, 1.27)
Quintile 3	70	0.82 (0.65, 1.04)	68	0.97 (0.77, 1.23)
Quintile 4	83	0.99 (0.79, 1.24)	72	1.02 (0.81, 1.28)
Quintile 5	75	0.91 (0.69, 1.19)	93	1.19 (0.94, 1.50)
per 10.8 kg†		*1.03 (0.90, 1.18)*		*1.01 (0.88, 1.16)*
Height-adjusted fat mass				
Quintile 1	90	1.03 (0.82, 1.29)	85	1.01 (0.81, 1.27)
Quintile 2	78	1.00 (0.80, 1.25)	73	1.00 (0.79, 1.26)
Quintile 3	83	1.05 (0.85, 1.30)	65	0.88 (0.69, 1.12)
Quintile 4	75	0.96 (0.76, 1.21)	85	1.06 (0.86, 1.31)
Quintile 5	71	0.97 (0.75, 1.24)	91	1.02 (0.81, 1.27)
per 6.9 kg†		*0.97 (0.84, 1.11)*		*1.01 (0.90, 1.12)*
Height-adjusted lean mass				
Quintile 1	80	0.87 (0.66, 1.15)	110	1.34 (1.02, 1.75)
Quintile 2	87	1.00 (0.81, 1.24)	68	1.00 (0.79, 1.27)
Quintile 3	66	0.79 (0.62, 1.00)	67	1.07 (0.85, 1.35)
Quintile 4	75	0.91 (0.73, 1.15)	78	1.33 (1.05, 1.67)
Quintile 5	89	1.08 (0.83, 1.41)	76	1.33 (1.01, 1.77)
per 7.6 kg†		*1.15 (0.96, 1.38)*		*1.02 (0.76, 1.37)*

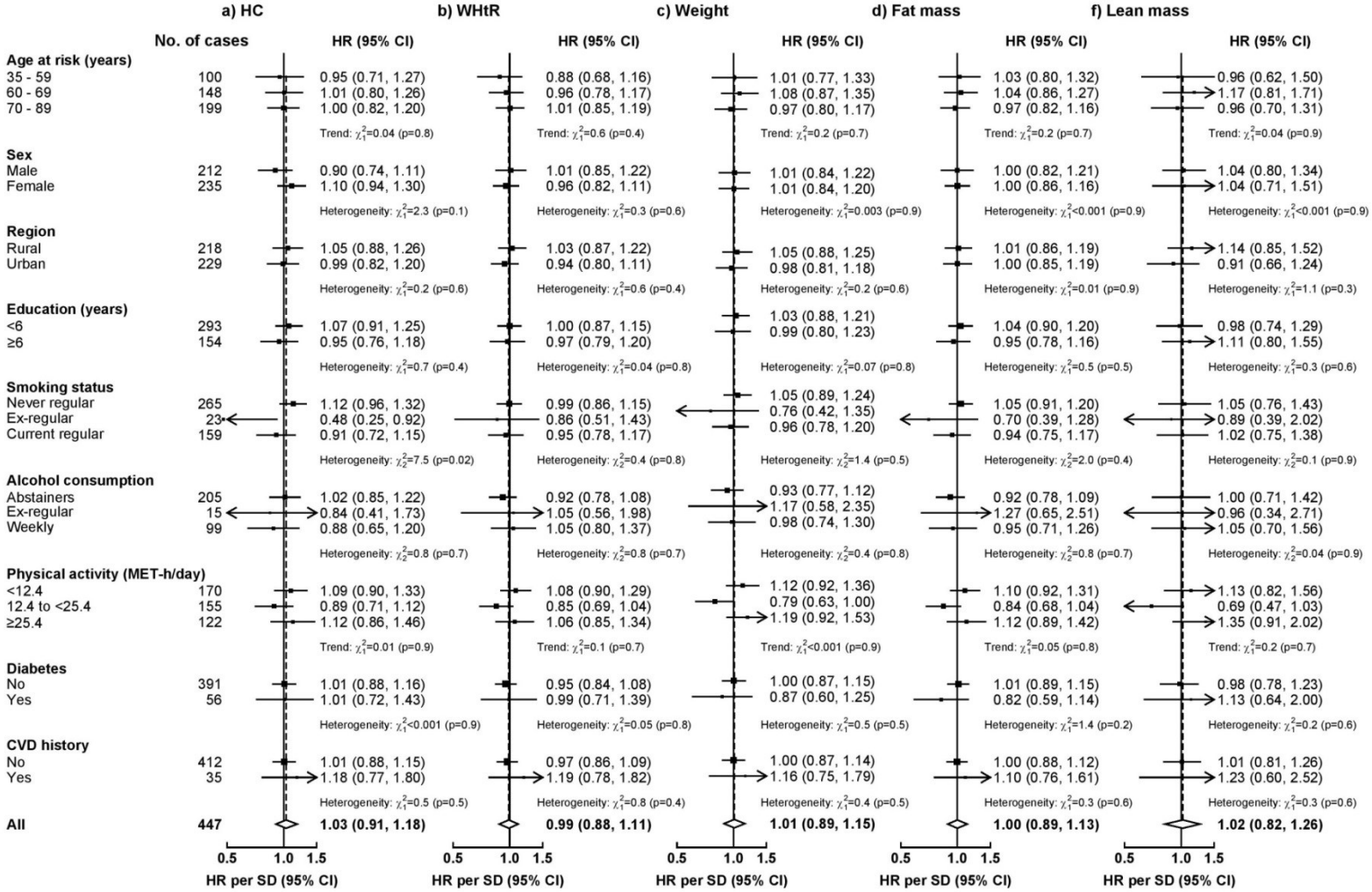
* Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.
P for heterogeneity by sex: HC, 0.73; WHtR, 0.78; height-adjusted weight, 0.77; height-adjusted fat mass, 0.65; height-adjusted lean mass, 0.54.

Appendix 7.9 Associations of main adiposity traits with risk of pancreatic cancer by population subgroup excluding the first five years



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.10 Associations of other adiposity traits with risk of pancreatic cancer by population subgroup excluding the first five years



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

Appendix 7.11 Adjusted HRs for pancreatic cancer by BMI with additional adjustment for central adiposity*

	Basic	Residual
	HR (95% CI)	HR (95% CI)
BMI adjusted for WC		
Quintile 1	0.87 (0.67, 1.15)	0.85 (0.72, 1.00)
Quintile 2	1.00 (0.84, 1.19)	1.00 (0.86, 1.16)
Quintile 3	0.97 (0.86, 1.09)	1.06 (0.91, 1.22)
Quintile 4	0.99 (0.82, 1.20)	0.88 (0.75, 1.04)
Quintile 5	1.08 (0.84, 1.38)	0.92 (0.77, 1.10)
BMI adjusted for WHR		
Quintile 1	0.88 (0.70, 1.11)	1.03 (0.87, 1.20)
Quintile 2	1.00 (0.86, 1.16)	1.00 (0.85, 1.17)
Quintile 3	0.96 (0.84, 1.09)	1.09 (0.93, 1.27)
Quintile 4	0.98 (0.82, 1.17)	1.00 (0.85, 1.18)
Quintile 5	1.05 (0.87, 1.27)	1.08 (0.91, 1.27)
BMI adjusted for HC		
Quintile 1	0.89 (0.70, 1.14)	1.18 (0.99, 1.39)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.84, 1.18)
Quintile 3	0.94 (0.83, 1.07)	1.05 (0.89, 1.23)
Quintile 4	0.95 (0.79, 1.14)	1.14 (0.98, 1.33)
Quintile 5	1.01 (0.80, 1.27)	1.13 (0.97, 1.32)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† In the residual method, the residuals from the regression of BMI on WC, WHR, or HC were modelled as the main exposure variable and additionally included WC, WHR, or HC as a covariate in the model.

Appendix 7.12 Adjusted HRs for pancreatic cancer by central adiposity with additional adjustment for BMI*

	Basic	Residual
	HR (95% CI)	HR (95% CI)
WC adjusted for BMI		
Quintile 1	1.05 (0.84, 1.31)	0.92 (0.77, 1.11)
Quintile 2	1.00 (0.84, 1.20)	1.00 (0.85, 1.17)
Quintile 3	0.96 (0.82, 1.12)	0.88 (0.75, 1.03)
Quintile 4	0.96 (0.81, 1.13)	1.01 (0.87, 1.17)
Quintile 5	0.92 (0.73, 1.16)	0.90 (0.76, 1.06)
WHR adjusted for BMI		
Quintile 1	1.07 (0.89, 1.30)	1.13 (0.94, 1.37)
Quintile 2	1.00 (0.84, 1.18)	1.00 (0.84, 1.19)
Quintile 3	0.99 (0.83, 1.17)	1.22 (1.06, 1.42)
Quintile 4	1.04 (0.89, 1.21)	1.18 (1.02, 1.37)
Quintile 5	1.00 (0.85, 1.18)	1.05 (0.90, 1.22)
HC adjusted for BMI		
Quintile 1	0.94 (0.77, 1.16)	1.14 (0.97, 1.34)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.85, 1.18)
Quintile 3	0.93 (0.79, 1.08)	1.30 (1.12, 1.51)
Quintile 4	0.84 (0.70, 1.00)	1.09 (0.92, 1.30)
Quintile 5	0.98 (0.77, 1.25)	1.21 (1.01, 1.46)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† In the residual method, the residuals from the regression of WC, WHR, or HC on BMI were modelled as the main exposure variable and additionally included BMI as a covariate in the model.

Appendix 7.13 Adjusted HRs for liver cancer by BMI, WC, and WHR*

	No exclusions		Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI						
<18.5	176	1.13 (0.97, 1.32)	125	1.03 (0.86, 1.23)	60	0.81 (0.62, 1.05)
18.5-24.9	1838	1.00 (0.95, 1.05)	1462	1.00 (0.95, 1.05)	927	1.00 (0.94, 1.07)
25.0-29.9	726	0.90 (0.84, 0.97)	608	0.95 (0.88, 1.04)	389	0.94 (0.85, 1.05)
≥30.0	107	0.98 (0.81, 1.19)	90	1.05 (0.85, 1.29)	64	1.16 (0.90, 1.49)
WC						
<90 (M) / 80 (F)	2013	Reference	1584	Reference	992	Reference
≥90 (M) / 80 (F)	834	0.97 (0.89, 1.06)	701	1.04 (0.95, 1.15)	448	1.06 (0.94, 1.20)
Men	367	0.98 (0.86, 1.10)	305	1.05 (0.92, 1.20)	195	1.08 (0.91, 1.28)
Women	467	0.97 (0.85, 1.10)	396	1.04 (0.90, 1.20)	253	1.05 (0.88, 1.25)
WHR						
<0.90 (M) / 0.85 (F)	1279	Reference	1013	Reference	622	Reference
≥0.90 (M) / 0.85 (F)	1568	1.08 (0.99, 1.17)	1272	1.09 (0.99, 1.19)	818	1.13 (1.00, 1.27)
Men	948	1.11 (1.01, 1.22)	757	1.13 (1.02, 1.26)	482	1.17 (1.02, 1.33)
Women	620	0.99 (0.87, 1.13)	515	1.03 (0.89, 1.19)	336	1.07 (0.89, 1.29)

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.14 Adjusted HRs for liver cancer by main adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	190	1.14 (0.98, 1.32)	351	1.03 (0.93, 1.15)
20.0 to <22.5	306	1.00 (0.89, 1.12)	570	1.00 (0.92, 1.09)
22.5 to <25.0	372	1.04 (0.94, 1.15)	570	0.96 (0.89, 1.04)
25.0 to <27.5	209	0.94 (0.82, 1.08)	297	0.85 (0.76, 0.96)
≥27.5	242	1.04 (0.92, 1.19)	303	0.88 (0.78, 0.99)
per 3.4 kg/m^2†		*0.97 (0.91, 1.03)*		*0.93 (0.89, 0.98)*
%BF				
Quintile 1	330	1.15 (1.03, 1.29)	576	1.06 (0.98, 1.16)
Quintile 2	251	1.00 (0.88, 1.13)	451	1.00 (0.91, 1.10)
Quintile 3	232	0.85 (0.75, 0.97)	374	0.81 (0.74, 0.90)
Quintile 4	261	0.94 (0.83, 1.06)	355	0.80 (0.72, 0.89)
Quintile 5	245	0.86 (0.75, 0.97)	335	0.76 (0.68, 0.85)
per 8.4%†		*0.89 (0.83, 0.96)*		*0.84 (0.79, 0.90)*
WC				
Quintile 1	251	1.05 (0.92, 1.19)	467	1.05 (0.95, 1.15)
Quintile 2	229	1.00 (0.88, 1.14)	396	1.00 (0.91, 1.10)
Quintile 3	251	0.97 (0.86, 1.10)	407	0.99 (0.90, 1.09)
Quintile 4	253	0.91 (0.81, 1.03)	383	0.95 (0.86, 1.05)
Quintile 5	335	1.08 (0.97, 1.22)	438	0.99 (0.89, 1.09)
per 9.8 cm†		*1.01 (0.94, 1.08)*		*0.98 (0.93, 1.03)*
WHR				
Quintile 1	194	0.94 (0.82, 1.09)	377	1.02 (0.92, 1.13)
Quintile 2	237	1.00 (0.88, 1.14)	396	1.00 (0.91, 1.10)
Quintile 3	215	0.99 (0.87, 1.13)	339	0.99 (0.89, 1.11)
Quintile 4	293	1.02 (0.91, 1.14)	455	1.09 (0.99, 1.19)
Quintile 5	380	1.04 (0.94, 1.16)	524	1.04 (0.95, 1.14)
per 0.07†		*1.04 (0.96, 1.12)*		*1.03 (0.96, 1.10)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.15 Adjusted HRs for liver cancer by main adiposity traits in never regular smokers or never regular drinkers excluding 5 years[*]

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	88	1.01 (0.82, 1.25)	140	0.86 (0.73, 1.02)
20.0 to <22.5	162	1.00 (0.86, 1.17)	282	1.00 (0.89, 1.13)
22.5 to <25.0	198	1.04 (0.91, 1.20)	288	0.97 (0.86, 1.09)
25.0 to <27.5	113	0.97 (0.80, 1.16)	152	0.87 (0.75, 1.03)
≥27.5	142	1.18 (0.99, 1.40)	168	0.97 (0.83, 1.14)
per 3.4 kg/m^2[†]		*1.06 (0.94, 1.18)*		*1.01 (0.94, 1.08)*
%BF				
Quintile 1	158	1.10 (0.93, 1.29)	241	0.92 (0.80, 1.05)
Quintile 2	130	1.00 (0.84, 1.19)	227	1.00 (0.88, 1.14)
Quintile 3	131	0.93 (0.79, 1.11)	194	0.84 (0.73, 0.96)
Quintile 4	147	1.03 (0.87, 1.21)	187	0.83 (0.72, 0.96)
Quintile 5	137	0.93 (0.78, 1.11)	181	0.80 (0.69, 0.93)
per 8.4%[†]		*0.96 (0.87, 1.07)*		*0.93 (0.85, 1.02)*
WC				
Quintile 1	123	0.97 (0.81, 1.17)	207	0.98 (0.85, 1.13)
Quintile 2	120	1.00 (0.83, 1.20)	190	1.00 (0.87, 1.15)
Quintile 3	136	1.00 (0.85, 1.19)	204	1.03 (0.90, 1.19)
Quintile 4	135	0.96 (0.81, 1.13)	192	0.99 (0.86, 1.14)
Quintile 5	189	1.25 (1.07, 1.45)	237	1.16 (1.01, 1.32)
per 9.8 cm[†]		*1.10 (1.00, 1.21)*		*1.08 (1.00, 1.16)*
WHR				
Quintile 1	101	0.95 (0.78, 1.16)	175	0.97 (0.83, 1.13)
Quintile 2	121	1.00 (0.84, 1.20)	194	1.00 (0.87, 1.15)
Quintile 3	125	1.13 (0.95, 1.34)	168	1.00 (0.86, 1.16)
Quintile 4	148	1.01 (0.86, 1.19)	222	1.07 (0.94, 1.22)
Quintile 5	208	1.15 (1.00, 1.32)	271	1.10 (0.97, 1.25)
per 0.07[†]		*1.08 (0.99, 1.19)*		*1.08 (0.99, 1.17)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.
[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.16 Adjusted HRs for liver cancer by other adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	304	1.05 (0.93, 1.18)	518	1.07 (0.97, 1.17)
Quintile 2	243	1.00 (0.88, 1.14)	415	1.00 (0.91, 1.10)
Quintile 3	261	0.97 (0.86, 1.10)	410	0.97 (0.88, 1.07)
Quintile 4	233	0.89 (0.78, 1.01)	376	0.93 (0.84, 1.03)
Quintile 5	278	0.95 (0.83, 1.09)	372	0.89 (0.79, 0.99)
per 6.9 cm†		*0.98 (0.91, 1.05)*		*0.94 (0.88, 1.00)*
WHtR				
Quintile 1	217	0.99 (0.87, 1.14)	420	0.99 (0.90, 1.09)
Quintile 2	237	1.00 (0.88, 1.14)	414	1.00 (0.91, 1.10)
Quintile 3	235	0.90 (0.79, 1.02)	383	0.92 (0.83, 1.01)
Quintile 4	283	0.97 (0.86, 1.08)	422	0.97 (0.88, 1.07)
Quintile 5	347	0.99 (0.89, 1.11)	452	0.90 (0.82, 0.99)
per 0.06†		*1.01 (0.94, 1.08)*		*0.97 (0.92, 1.02)*
Height-adjusted weight				
Quintile 1	327	1.02 (0.90, 1.16)	554	1.06 (0.96, 1.17)
Quintile 2	274	1.00 (0.89, 1.13)	449	1.00 (0.91, 1.10)
Quintile 3	228	0.83 (0.73, 0.94)	386	0.89 (0.81, 0.99)
Quintile 4	228	0.85 (0.75, 0.97)	361	0.88 (0.79, 0.98)
Quintile 5	262	0.97 (0.85, 1.12)	341	0.86 (0.77, 0.97)
per 10.8 kg†		*0.96 (0.89, 1.04)*		*0.91 (0.86, 0.97)*
Height-adjusted fat mass				
Quintile 1	342	1.16 (1.04, 1.30)	588	1.07 (0.98, 1.16)
Quintile 2	256	1.00 (0.88, 1.13)	463	1.00 (0.91, 1.10)
Quintile 3	218	0.83 (0.72, 0.94)	352	0.78 (0.70, 0.87)
Quintile 4	254	0.95 (0.84, 1.08)	347	0.80 (0.72, 0.89)
Quintile 5	249	0.92 (0.81, 1.05)	341	0.81 (0.72, 0.91)
per 6.9 kg†		*0.93 (0.87, 0.99)*		*0.88 (0.83, 0.93)*
Height-adjusted lean mass				
Quintile 1	318	1.00 (0.86, 1.16)	519	1.07 (0.95, 1.20)
Quintile 2	255	1.00 (0.88, 1.13)	412	1.00 (0.91, 1.10)
Quintile 3	252	1.10 (0.98, 1.24)	403	1.09 (0.99, 1.20)
Quintile 4	250	1.16 (1.02, 1.32)	398	1.16 (1.05, 1.28)
Quintile 5	244	1.21 (1.04, 1.42)	359	1.12 (0.99, 1.27)
per 7.6 kg†		*1.11 (0.97, 1.26)*		*1.02 (0.93, 1.12)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.17 Adjusted HRs for liver cancer by other adiposity traits in never regular smokers or never regular drinkers excluding 5 years*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	156	1.11 (0.94, 1.32)	240	1.09 (0.95, 1.25)
Quintile 2	115	1.00 (0.83, 1.20)	185	1.00 (0.86, 1.16)
Quintile 3	151	1.19 (1.02, 1.40)	207	1.10 (0.96, 1.26)
Quintile 4	128	1.08 (0.91, 1.29)	204	1.16 (1.01, 1.33)
Quintile 5	153	1.20 (1.00, 1.43)	194	1.09 (0.94, 1.28)
per 6.9 cm†		*1.08 (0.98, 1.20)*		*1.05 (0.97, 1.15)*
WHtR				
Quintile 1	106	0.92 (0.75, 1.12)	184	0.87 (0.75, 1.01)
Quintile 2	126	1.00 (0.84, 1.19)	208	1.00 (0.87, 1.15)
Quintile 3	122	0.89 (0.74, 1.06)	185	0.88 (0.76, 1.01)
Quintile 4	155	1.03 (0.88, 1.20)	213	0.98 (0.85, 1.12)
Quintile 5	194	1.12 (0.97, 1.30)	240	0.99 (0.87, 1.13)
per 0.06†		*1.09 (1.00, 1.19)*		*1.06 (0.98, 1.14)*
Height-adjusted weight				
Quintile 1	161	0.96 (0.80, 1.14)	240	0.93 (0.80, 1.07)
Quintile 2	144	1.00 (0.85, 1.18)	227	1.00 (0.88, 1.14)
Quintile 3	130	0.89 (0.75, 1.06)	197	0.90 (0.79, 1.04)
Quintile 4	108	0.78 (0.64, 0.94)	168	0.80 (0.69, 0.94)
Quintile 5	160	1.16 (0.97, 1.39)	198	1.00 (0.85, 1.17)
per 10.8 kg†		*1.05 (0.95, 1.17)*		*1.01 (0.93, 1.10)*
Height-adjusted fat mass				
Quintile 1	162	1.08 (0.92, 1.28)	249	0.95 (0.84, 1.09)
Quintile 2	134	1.00 (0.84, 1.19)	228	1.00 (0.88, 1.14)
Quintile 3	119	0.88 (0.73, 1.05)	173	0.78 (0.67, 0.91)
Quintile 4	143	1.04 (0.88, 1.22)	193	0.89 (0.77, 1.03)
Quintile 5	145	1.05 (0.88, 1.25)	187	0.89 (0.77, 1.04)
per 6.9 kg†		*1.00 (0.91, 1.09)*		*0.97 (0.89, 1.05)*
Height-adjusted lean mass				
Quintile 1	158	0.92 (0.75, 1.14)	236	0.99 (0.83, 1.17)
Quintile 2	135	1.00 (0.84, 1.19)	203	1.00 (0.87, 1.15)
Quintile 3	138	1.14 (0.97, 1.34)	201	1.10 (0.96, 1.26)
Quintile 4	133	1.21 (1.01, 1.44)	196	1.17 (1.01, 1.35)
Quintile 5	139	1.35 (1.09, 1.66)	194	1.23 (1.04, 1.47)
per 7.6 kg†		*1.29 (1.08, 1.55)*		*1.15 (1.00, 1.32)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.18 Adjusted HRs for liver cancer associated with main adiposity traits by HBsAg status*

	HBsAg negative		HBsAg positive	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	337	1.10 (0.98, 1.23)	100	0.85 (0.69, 1.05)
20.0 to <22.5	527	1.00 (0.92, 1.09)	216	1.00 (0.87, 1.15)
22.5 to <25.0	559	1.00 (0.92, 1.09)	189	0.87 (0.75, 1.00)
25.0 to <27.5	308	0.92 (0.83, 1.03)	99	0.78 (0.64, 0.95)
≥27.5	301	0.95 (0.85, 1.07)	95	0.74 (0.60, 0.91)
per 3.4 kg/m^2†		*0.94 (0.90, 0.99)*		*0.92 (0.84, 1.00)*
%BF				
Quintile 1	520	1.13 (1.03, 1.23)	181	0.94 (0.81, 1.10)
Quintile 2	407	1.00 (0.91, 1.10)	169	1.00 (0.86, 1.16)
Quintile 3	396	0.95 (0.86, 1.05)	121	0.69 (0.57, 0.82)
Quintile 4	357	0.89 (0.80, 0.99)	124	0.73 (0.61, 0.87)
Quintile 5	352	0.87 (0.78, 0.97)	104	0.57 (0.47, 0.70)
per 8.4%†		*0.88 (0.83, 0.94)*		*0.77 (0.69, 0.86)*
WC				
Quintile 1	436	1.05 (0.95, 1.16)	145	0.95 (0.80, 1.12)
Quintile 2	379	1.00 (0.90, 1.11)	143	1.00 (0.85, 1.18)
Quintile 3	389	1.00 (0.91, 1.11)	156	1.09 (0.93, 1.28)
Quintile 4	386	0.97 (0.88, 1.07)	122	0.90 (0.75, 1.08)
Quintile 5	442	1.02 (0.93, 1.13)	133	0.86 (0.72, 1.03)
per 9.8 cm†		*0.99 (0.94, 1.05)*		*0.96 (0.87, 1.05)*
WHR				
Quintile 1	327	1.00 (0.89, 1.11)	127	0.89 (0.75, 1.07)
Quintile 2	367	1.00 (0.90, 1.11)	151	1.00 (0.85, 1.17)
Quintile 3	342	1.03 (0.93, 1.15)	126	1.00 (0.84, 1.19)
Quintile 4	451	1.08 (0.98, 1.18)	161	1.10 (0.94, 1.28)
Quintile 5	545	1.07 (0.98, 1.17)	134	0.85 (0.71, 1.01)
per 0.07†		*1.04 (0.97, 1.11)*		*1.00 (0.90, 1.12)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

P for heterogeneity by HBsAg: BMI, 0.56; %BF, 0.04; WC, 0.52; WHR, 0.64.

Appendix 7.19 Adjusted HRs for liver cancer associated with other adiposity traits by HBsAg status*

	HBsAg negative		HBsAg positive	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	525	1.13 (1.03, 1.24)	148	0.87 (0.73, 1.04)
Quintile 2	387	1.00 (0.90, 1.11)	153	1.00 (0.85, 1.18)
Quintile 3	386	1.01 (0.92, 1.12)	132	0.80 (0.68, 0.95)
Quintile 4	374	0.99 (0.89, 1.09)	122	0.76 (0.63, 0.91)
Quintile 5	360	0.95 (0.84, 1.06)	144	0.76 (0.63, 0.91)
per 6.9 cm†		*0.95 (0.89, 1.01)*		0.92 (0.84, 1.02)
WHtR				
Quintile 1	371	0.97 (0.87, 1.08)	148	1.00 (0.85, 1.18)
Quintile 2	389	1.00 (0.90, 1.11)	148	1.00 (0.85, 1.18)
Quintile 3	399	0.99 (0.90, 1.10)	134	0.98 (0.83, 1.16)
Quintile 4	406	0.95 (0.86, 1.04)	144	1.10 (0.94, 1.30)
Quintile 5	467	0.95 (0.86, 1.04)	125	0.85 (0.71, 1.02)
per 0.06†		*0.98 (0.93, 1.03)*		*0.96 (0.88, 1.06)*
Height-adjusted weight				
Quintile 1	547	1.11 (1.01, 1.23)	151	0.95 (0.79, 1.14)
Quintile 2	413	1.00 (0.91, 1.10)	160	1.00 (0.85, 1.17)
Quintile 3	368	0.92 (0.83, 1.02)	140	0.87 (0.74, 1.03)
Quintile 4	359	0.95 (0.85, 1.05)	113	0.71 (0.59, 0.86)
Quintile 5	345	0.95 (0.84, 1.07)	135	0.79 (0.65, 0.96)
per 10.8 kg†		*0.93 (0.87, 0.99)*		*0.91 (0.82, 1.01)*
Height-adjusted fat mass				
Quintile 1	545	1.11 (1.01, 1.21)	169	0.87 (0.74, 1.03)
Quintile 2	426	1.00 (0.91, 1.10)	176	1.00 (0.86, 1.16)
Quintile 3	354	0.85 (0.77, 0.94)	123	0.69 (0.58, 0.82)
Quintile 4	359	0.88 (0.80, 0.98)	111	0.64 (0.53, 0.77)
Quintile 5	348	0.89 (0.80, 1.00)	120	0.63 (0.52, 0.76)
per 6.9 kg†		*0.91 (0.86, 0.97)*		*0.83 (0.75, 0.92)*
Height-adjusted lean mass				
Quintile 1	528	1.03 (0.92, 1.16)	146	1.24 (1.00, 1.54)
Quintile 2	420	1.00 (0.91, 1.10)	115	1.00 (0.83, 1.21)
Quintile 3	378	1.00 (0.91, 1.11)	138	1.28 (1.09, 1.51)
Quintile 4	361	1.03 (0.92, 1.15)	145	1.35 (1.14, 1.59)
Quintile 5	345	1.06 (0.93, 1.21)	155	1.35 (1.11, 1.65)
per 7.6 kg†		*0.99 (0.90, 1.09)*		*1.13 (0.97, 1.32)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

P for heterogeneity by HBsAg: HC, 0.59; WHtR, 0.72; height-adjusted weight, 0.63; height-adjusted fat mass, 0.10; height-adjusted lean mass, 0.19.

Appendix 7.20 Adjusted HRs for liver cancer by main adiposity traits in men and women, separately*

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	291	0.93 (0.82, 1.05)	165	1.26 (1.08, 1.48)
20.0 to <22.5	554	1.00 (0.92, 1.09)	225	1.00 (0.88, 1.14)
22.5 to <25.0	505	0.93 (0.85, 1.01)	274	1.05 (0.93, 1.18)
25.0 to <27.5	275	0.87 (0.77, 0.98)	150	0.94 (0.80, 1.11)
≥27.5	224	0.82 (0.72, 0.94)	184	1.01 (0.87, 1.18)
per 3.4 kg/m^2†		*0.94 (0.88, 0.99)*		*0.94 (0.88, 1.00)*
%BF				
Quintile 1	464	1.00 (0.91, 1.10)	270	1.19 (1.05, 1.35)
Quintile 2	412	1.00 (0.91, 1.10)	195	1.00 (0.87, 1.15)
Quintile 3	383	0.91 (0.82, 1.00)	156	0.78 (0.66, 0.91)
Quintile 4	315	0.82 (0.74, 0.92)	184	0.85 (0.74, 0.99)
Quintile 5	275	0.74 (0.66, 0.84)	193	0.82 (0.71, 0.95)
per 8.4%†		*0.85 (0.79, 0.91)*		*0.85 (0.78, 0.92)*
WC				
Quintile 1	405	1.01 (0.91, 1.12)	210	1.08 (0.94, 1.24)
Quintile 2	367	1.00 (0.90, 1.11)	176	1.00 (0.86, 1.16)
Quintile 3	397	1.13 (1.02, 1.24)	171	0.86 (0.74, 1.00)
Quintile 4	329	0.97 (0.87, 1.08)	193	0.91 (0.79, 1.04)
Quintile 5	351	0.99 (0.89, 1.11)	248	0.99 (0.87, 1.13)
per 9.8 cm†		1.00 (0.94, 1.06)		0.96 (0.89, 1.03)
WHR				
Quintile 1	323	0.95 (0.85, 1.06)	155	1.02 (0.87, 1.20)
Quintile 2	364	1.00 (0.90, 1.11)	173	1.00 (0.86, 1.16)
Quintile 3	346	1.09 (0.98, 1.21)	145	0.92 (0.78, 1.08)
Quintile 4	406	1.08 (0.98, 1.19)	222	1.03 (0.90, 1.18)
Quintile 5	410	1.05 (0.96, 1.16)	303	1.00 (0.89, 1.12)
per 0.07†		1.06 (0.99, 1.15)		0.98 (0.90, 1.08)
BMI25‡				
<20.0	268	1.00 (0.89, 1.13)	157	0.91 (0.77, 1.06)
20.0 to <22.5	642	1.00 (0.93, 1.08)	254	1.00 (0.88, 1.13)
22.5 to <25.0	512	1.15 (1.05, 1.25)	215	1.11 (0.97, 1.27)
25.0 to <27.5	124	1.03 (0.86, 1.23)	80	1.03 (0.83, 1.28)
≥27.5	61	1.15 (0.90, 1.49)	45	1.05 (0.78, 1.42)
per 2.6 kg/m^2		*1.05 (1.00, 1.11)*		*1.04 (0.97, 1.11)*

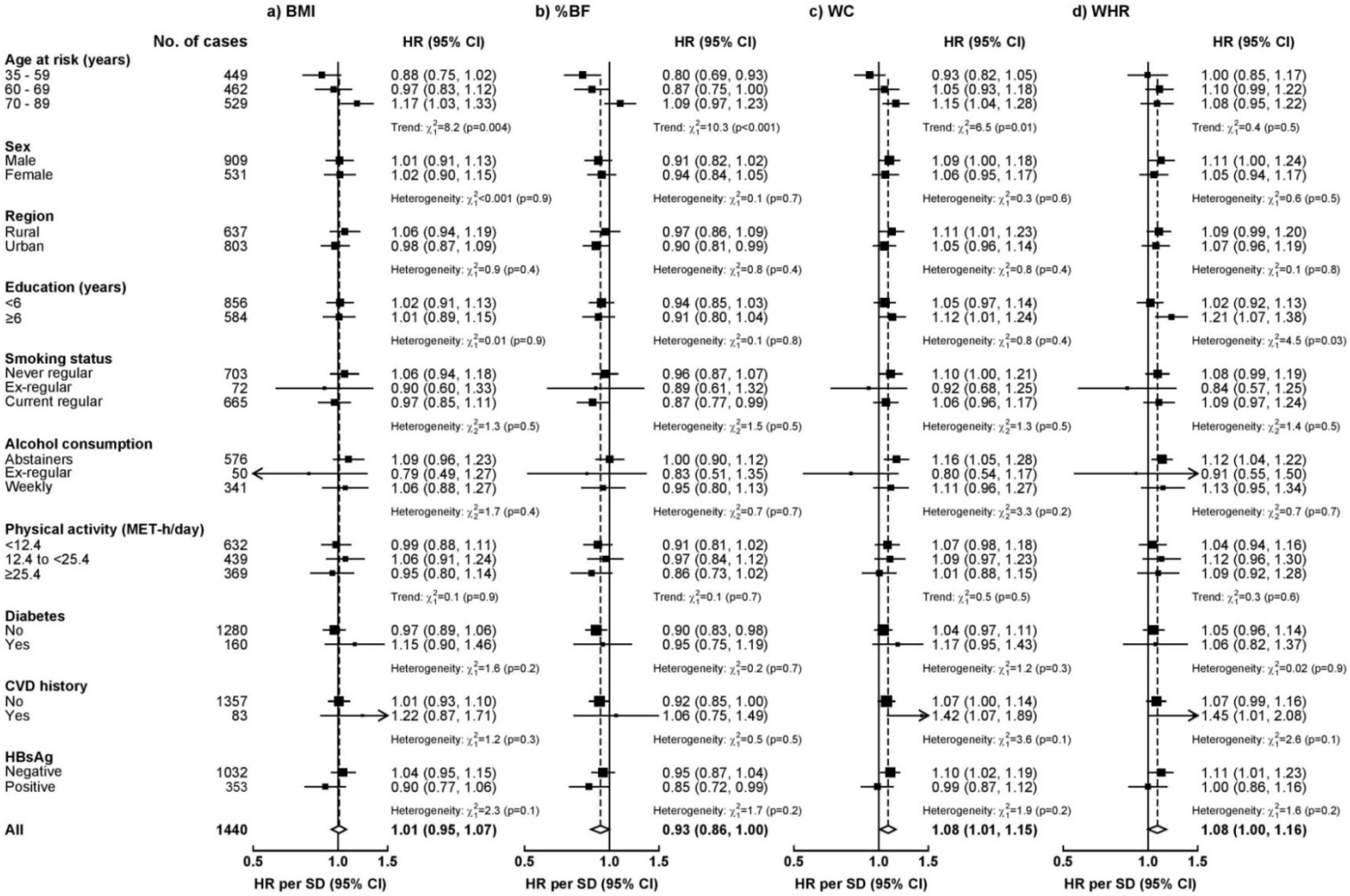
* Model was stratified by age-at-risk (5-year), region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.
‡ BMI25 was missing in 81,880 participants.
P for heterogeneity by sex: BMI, 0.88; %BF, 0.90; WC, 0.44; WHR, 0.21; BMI25, 0.76.

Appendix 7.21 Adjusted HRs for liver cancer by other adiposity traits in men and women, separately*

	Men		Women	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	435	1.00 (0.90, 1.10)	268	1.13 (0.99, 1.29)
Quintile 2	385	1.00 (0.90, 1.11)	185	1.00 (0.87, 1.16)
Quintile 3	358	0.97 (0.88, 1.08)	187	0.94 (0.82, 1.09)
Quintile 4	353	0.95 (0.85, 1.05)	158	0.85 (0.73, 0.99)
Quintile 5	318	0.85 (0.75, 0.96)	200	0.96 (0.82, 1.12)
per 6.8 cm†		0.95 (0.89, 1.01)		0.94 (0.86, 1.02)
WHtR				
Quintile 1	360	0.92 (0.83, 1.03)	190	1.16 (1.00, 1.34)
Quintile 2	385	1.00 (0.90, 1.11)	171	1.00 (0.86, 1.16)
Quintile 3	382	1.04 (0.94, 1.15)	169	0.90 (0.77, 1.04)
Quintile 4	370	1.03 (0.93, 1.14)	204	0.95 (0.83, 1.09)
Quintile 5	352	0.90 (0.80, 1.00)	264	1.01 (0.89, 1.15)
per 0.06†		0.99 (0.93, 1.05)		0.96 (0.89, 1.03)
Height-adjusted weight				
Quintile 1	441	0.97 (0.86, 1.08)	284	1.15 (1.01, 1.32)
Quintile 2	413	1.00 (0.91, 1.10)	200	1.00 (0.87, 1.15)
Quintile 3	363	0.91 (0.82, 1.00)	164	0.85 (0.73, 0.99)
Quintile 4	333	0.87 (0.78, 0.97)	156	0.84 (0.72, 0.99)
Quintile 5	299	0.81 (0.71, 0.92)	194	0.99 (0.84, 1.16)
per 10.8 kg†		0.93 (0.87, 0.99)		0.92 (0.84, 1.00)
Height-adjusted fat mass				
Quintile 1	460	0.92 (0.83, 1.01)	287	1.29 (1.14, 1.46)
Quintile 2	450	1.00 (0.91, 1.10)	186	1.00 (0.87, 1.15)
Quintile 3	342	0.78 (0.70, 0.87)	155	0.84 (0.72, 0.98)
Quintile 4	308	0.74 (0.66, 0.83)	178	0.94 (0.81, 1.09)
Quintile 5	289	0.74 (0.65, 0.83)	192	0.95 (0.82, 1.10)
per 6.9 kg†		0.88 (0.82, 0.94)		0.89 (0.83, 0.96)
Height-adjusted lean mass				
Quintile 1	427	1.06 (0.93, 1.20)	275	1.05 (0.89, 1.25)
Quintile 2	365	1.00 (0.90, 1.11)	198	1.00 (0.87, 1.15)
Quintile 3	349	1.03 (0.93, 1.14)	187	1.09 (0.95, 1.25)
Quintile 4	358	1.11 (0.99, 1.23)	171	1.10 (0.94, 1.28)
Quintile 5	350	1.09 (0.96, 1.24)	167	1.20 (0.99, 1.44)
per 7.6 kg†		1.01 (0.93, 1.10)		1.14 (0.95, 1.38)

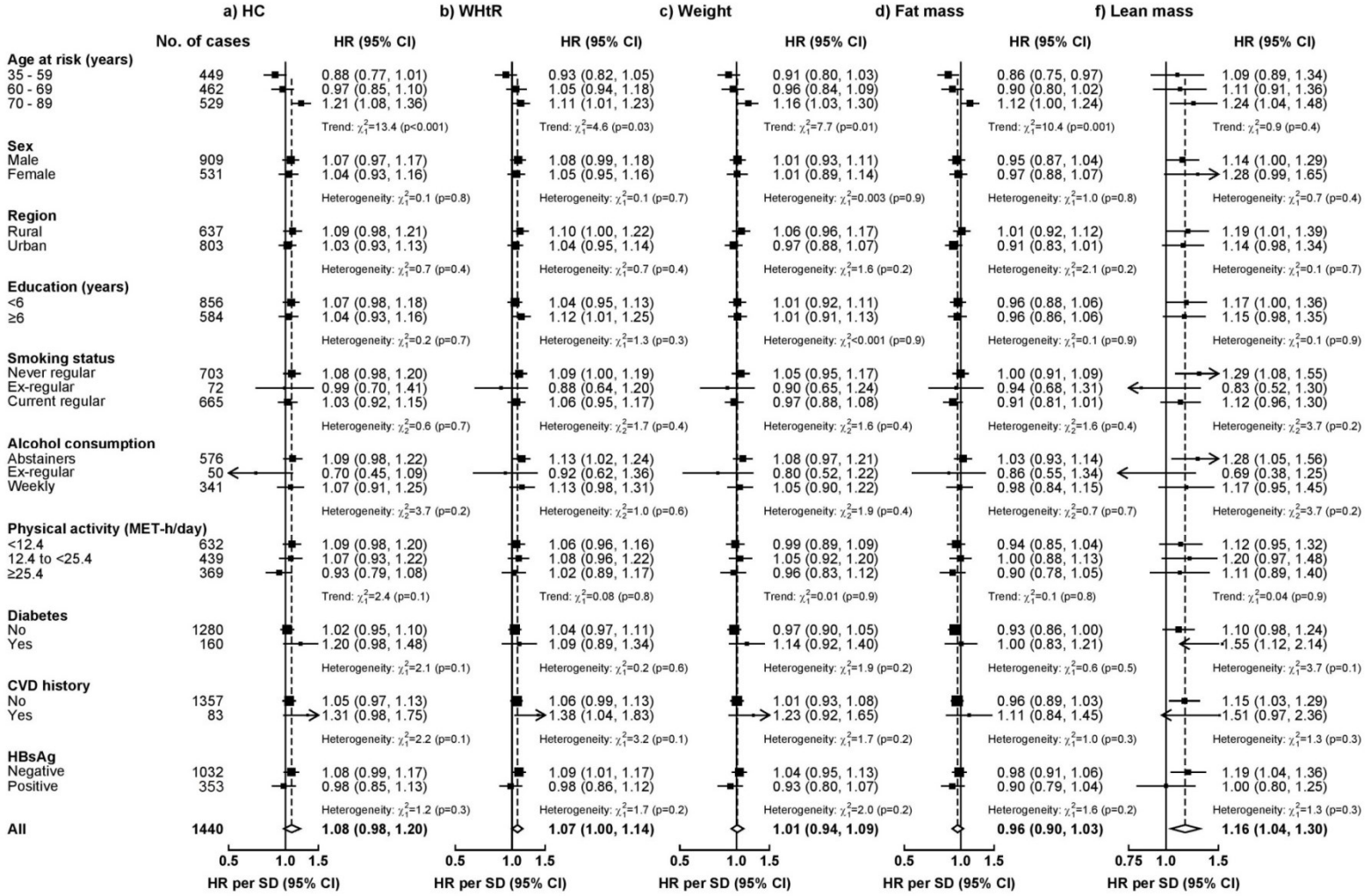
* Model was stratified by age-at-risk (5-year), region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.
P for heterogeneity by sex: HC, 0.83; WHtR, 0.54; height-adjusted weight, 0.78; height-adjusted fat mass, 0.73; height-adjusted lean mass, 0.18.

Appendix 7.22 Associations of main adiposity traits with risk of liver cancer by population subgroup excluding the first five years



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.23 Associations of other adiposity traits with risk of liver cancer by population subgroups excluding the first five years



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

Appendix 7.24 Adjusted HRs for liver cancer by BMI with additional adjustment for central adiposity excluding the first five years of follow-up[*]

	Basic	Residual
	HR (95% CI)	HR (95% CI)
BMI adjusted for WC		
Quintile 1	0.97 (0.80, 1.19)	1.01 (0.91, 1.13)
Quintile 2	1.00 (0.88, 1.13)	1.00 (0.90, 1.11)
Quintile 3	0.88 (0.81, 0.96)	0.93 (0.83, 1.04)
Quintile 4	0.77 (0.66, 0.89)	0.79 (0.69, 0.90)
Quintile 5	0.70 (0.58, 0.86)	0.75 (0.64, 0.87)
BMI adjusted for WHR		
Quintile 1	0.90 (0.77, 1.06)	0.95 (0.86, 1.06)
Quintile 2	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
Quintile 3	0.95 (0.86, 1.05)	0.85 (0.75, 0.96)
Quintile 4	0.88 (0.77, 1.01)	0.92 (0.81, 1.04)
Quintile 5	0.89 (0.77, 1.03)	0.82 (0.71, 0.95)
BMI adjusted for HC		
Quintile 1	0.92 (0.76, 1.10)	1.13 (1.00, 1.28)
Quintile 2	1.00 (0.89, 1.12)	1.00 (0.89, 1.13)
Quintile 3	0.94 (0.86, 1.03)	1.04 (0.93, 1.16)
Quintile 4	0.86 (0.74, 0.99)	0.96 (0.85, 1.08)
Quintile 5	0.83 (0.69, 1.00)	0.99 (0.87, 1.11)

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
[†] In the residual method, the residuals from the regression of BMI on WC, WHR, or HC were modelled as the main exposure variable and additionally included WC, WHR, or HC as a covariate in the model.

Appendix 7.25 Adjusted HRs for liver cancer by central adiposity with additional adjustment for BMI excluding the first five years of follow-up[*]

	Basic	Residual
	HR (95% CI)	HR (95% CI)
WC adjusted for BMI		
Quintile 1	0.93 (0.79, 1.10)	0.99 (0.85, 1.15)
Quintile 2	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)
Quintile 3	1.13 (1.01, 1.26)	1.05 (0.93, 1.18)
Quintile 4	1.12 (0.99, 1.28)	1.16 (1.04, 1.29)
Quintile 5	1.37 (1.15, 1.64)	1.38 (1.24, 1.53)
WHR adjusted for BMI		
Quintile 1	0.95 (0.82, 1.11)	1.22 (1.05, 1.44)
Quintile 2	1.00 (0.88, 1.13)	1.00 (0.87, 1.15)
Quintile 3	1.09 (0.97, 1.24)	1.15 (1.03, 1.30)
Quintile 4	1.12 (1.00, 1.25)	1.25 (1.13, 1.39)
Quintile 5	1.20 (1.06, 1.36)	1.35 (1.22, 1.50)
HC adjusted for BMI		
Quintile 1	1.07 (0.92, 1.24)	0.93 (0.83, 1.05)
Quintile 2	1.00 (0.88, 1.14)	1.00 (0.89, 1.12)
Quintile 3	1.08 (0.96, 1.20)	0.84 (0.74, 0.95)
Quintile 4	1.08 (0.95, 1.23)	1.04 (0.93, 1.18)
Quintile 5	1.09 (0.91, 1.31)	1.12 (0.98, 1.28)

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] In the residual method, the residuals from the regression of WC, WHR, or HC on BMI were modelled as the main exposure variable and additionally included BMI as a covariate in the model.

Appendix 7.26 Adjusted HRs for colorectal cancer by BMI, WC, and WHR*

	No exclusions		Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI						
<18.5	131	1.01 (0.85, 1.20)	106	0.97 (0.80, 1.18)	57	0.81 (0.62, 1.05)
18.5-24.9	1714	1.00 (0.95, 1.05)	1461	1.00 (0.95, 1.06)	982	1.00 (0.94, 1.07)
25.0-29.9	1009	1.14 (1.07, 1.21)	890	1.18 (1.10, 1.26)	608	1.19 (1.10, 1.29)
≥30.0	170	1.29 (1.11, 1.51)	154	1.39 (1.18, 1.64)	111	1.50 (1.24, 1.82)
WC						
<90 (M) / 80 (F)	1810	Reference	1552	Reference	1030	Reference
≥90 (M) / 80 (F)	1214	1.19 (1.10, 1.29)	1059	1.23 (1.13, 1.34)	728	1.32 (1.19, 1.46)
Men	431	1.35 (1.19, 1.52)	385	1.45 (1.27, 1.64)	261	1.53 (1.31, 1.79)
Women	783	1.09 (0.98, 1.21)	674	1.08 (0.97, 1.21)	467	1.17 (1.02, 1.34)
WHR						
<0.90 (M) / 0.85 (F)	1212	Reference	1032	Reference	680	Reference
≥0.90 (M) / 0.85 (F)	1812	1.18 (1.08, 1.29)	1579	1.23 (1.12, 1.35)	1078	1.31 (1.17, 1.47)
Men	854	1.25 (1.13, 1.39)	754	1.34 (1.20, 1.50)	515	1.44 (1.25, 1.65)
Women	958	1.11 (0.99, 1.23)	825	1.10 (0.97, 1.23)	563	1.13 (0.98, 1.30)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.27 Adjusted HRs for colorectal cancer by main adiposity traits excluding the first two or five years of follow-up[*]

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	289	0.95 (0.85, 1.08)	171	0.85 (0.73, 1.00)
20.0 to <22.5	571	1.00 (0.92, 1.09)	385	1.00 (0.90, 1.11)
22.5 to <25.0	707	1.05 (0.98, 1.13)	483	1.07 (0.98, 1.17)
25.0 to <27.5	463	1.09 (1.00, 1.20)	310	1.08 (0.97, 1.21)
≥27.5	581	1.37 (1.26, 1.50)	409	1.44 (1.30, 1.59)
per 3.4 kg/m^2[†]		*1.12 (1.08, 1.17)*		*1.16 (1.10, 1.23)*
%BF				
Quintile 1	455	0.97 (0.88, 1.07)	297	1.02 (0.90, 1.14)
Quintile 2	458	1.00 (0.91, 1.10)	292	1.00 (0.89, 1.12)
Quintile 3	496	0.99 (0.91, 1.09)	334	1.05 (0.94, 1.17)
Quintile 4	569	1.13 (1.04, 1.22)	386	1.19 (1.08, 1.31)
Quintile 5	633	1.24 (1.14, 1.34)	449	1.36 (1.23, 1.50)
per 8.4%[†]		*1.12 (1.06, 1.19)*		*1.17 (1.10, 1.26)*
WC				
Quintile 1	416	1.03 (0.93, 1.14)	265	1.01 (0.89, 1.15)
Quintile 2	380	1.00 (0.90, 1.11)	247	1.00 (0.88, 1.13)
Quintile 3	505	1.21 (1.11, 1.32)	349	1.30 (1.17, 1.44)
Quintile 4	574	1.27 (1.17, 1.38)	382	1.33 (1.21, 1.47)
Quintile 5	736	1.47 (1.36, 1.59)	515	1.67 (1.52, 1.83)
per 9.8 cm[†]		*1.20 (1.14, 1.26)*		*1.28 (1.20, 1.35)*
WHR				
Quintile 1	370	0.92 (0.83, 1.02)	236	0.89 (0.78, 1.01)
Quintile 2	439	1.00 (0.91, 1.10)	290	1.00 (0.89, 1.12)
Quintile 3	425	1.06 (0.97, 1.17)	289	1.10 (0.98, 1.23)
Quintile 4	604	1.19 (1.10, 1.29)	400	1.21 (1.10, 1.33)
Quintile 5	773	1.30 (1.21, 1.40)	543	1.42 (1.30, 1.55)
per 0.07[†]		*1.18 (1.12, 1.25)*		*1.22 (1.16, 1. 29)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.28 Adjusted HRs for colorectal cancer by main adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	168	0.85 (0.73, 0.99)	273	0.99 (0.87, 1.12)
20.0 to <22.5	400	1.00 (0.91, 1.10)	508	1.00 (0.92, 1.09)
22.5 to <25.0	488	0.96 (0.88, 1.05)	624	1.03 (0.95, 1.11)
25.0 to <27.5	330	1.00 (0.90, 1.12)	399	1.05 (0.95, 1.15)
≥27.5	408	1.15 (1.04, 1.27)	496	1.26 (1.15, 1.38)
per 3.4 kg/m^2†		*1.08 (1.02, 1.13)*		*1.08 (1.04, 1.13)*
%BF				
Quintile 1	307	0.96 (0.86, 1.08)	442	1.03 (0.93, 1.14)
Quintile 2	321	1.00 (0.90, 1.12)	407	1.00 (0.91, 1.10)
Quintile 3	334	0.94 (0.85, 1.05)	427	0.98 (0.89, 1.07)
Quintile 4	403	1.07 (0.97, 1.18)	501	1.12 (1.03, 1.23)
Quintile 5	429	1.10 (0.99, 1.21)	523	1.16 (1.06, 1.26)
per 8.4%†		*1.06 (1.00, 1.12)*		*1.07 (1.01, 1.13)*
WC				
Quintile 1	260	0.92 (0.81, 1.05)	387	1.03 (0.93, 1.14)
Quintile 2	283	1.00 (0.89, 1.12)	352	1.00 (0.90, 1.11)
Quintile 3	360	1.09 (0.98, 1.20)	446	1.13 (1.03, 1.24)
Quintile 4	399	1.08 (0.98, 1.20)	501	1.18 (1.08, 1.29)
Quintile 5	492	1.18 (1.07, 1.29)	614	1.29 (1.18, 1.40)
per 9.8 cm†		*1.12 (1.06, 1.19)*		*1.13 (1.08, 1.19)*
WHR				
Quintile 1	267	1.03 (0.91, 1.16)	346	0.92 (0.83, 1.03)
Quintile 2	291	1.00 (0.89, 1.12)	403	1.00 (0.91, 1.10)
Quintile 3	294	1.10 (0.98, 1.23)	380	1.04 (0.94, 1.15)
Quintile 4	423	1.21 (1.10, 1.33)	532	1.15 (1.06, 1.25)
Quintile 5	519	1.20 (1.10, 1.32)	639	1.14 (1.05, 1.24)
per 0.07†		*1.10 (1.03, 1.18)*		*1.11 (1.05, 1.18)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.29 Adjusted HRs for colorectal cancer by other adiposity traits excluding the first two or five years of follow-up[*]

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	460	0.91 (0.83, 1.01)	289	0.82 (0.72, 0.93)
Quintile 2	437	1.00 (0.91, 1.10)	303	1.00 (0.89, 1.12)
Quintile 3	480	1.04 (0.95, 1.14)	320	1.02 (0.91, 1.13)
Quintile 4	541	1.12 (1.03, 1.22)	360	1.11 (1.00, 1.23)
Quintile 5	693	1.31 (1.20, 1.43)	486	1.42 (1.28, 1.57)
per 6.9 cm[†]		*1.17 (1.11, 1.23)*		*1.23 (1.16, 1.32)*
WHtR				
Quintile 1	362	0.88 (0.79, 0.98)	235	0.88 (0.77, 1.00)
Quintile 2	419	1.00 (0.91, 1.10)	275	1.00 (0.89, 1.13)
Quintile 3	495	1.09 (1.00, 1.19)	319	1.08 (0.96, 1.20)
Quintile 4	594	1.18 (1.09, 1.28)	422	1.31 (1.19, 1.44)
Quintile 5	741	1.30 (1.20, 1.40)	507	1.43 (1.31, 1.57)
per 0.06[†]		*1.18 (1.13, 1.24)*		*1.25 (1.18, 1.33)*
Height-adjusted weight				
Quintile 1	489	0.96 (0.87, 1.07)	301	0.89 (0.78, 1.02)
Quintile 2	452	1.00 (0.91, 1.10)	302	1.00 (0.89, 1.12)
Quintile 3	465	1.00 (0.92, 1.10)	309	1.00 (0.90, 1.12)
Quintile 4	567	1.22 (1.13, 1.33)	401	1.30 (1.18, 1.44)
Quintile 5	638	1.35 (1.23, 1.47)	445	1.40 (1.26, 1.57)
per 10.8 kg[†]		*1.16 (1.10, 1.22)*		*1.20 (1.13, 1.28)*
Height-adjusted fat mass				
Quintile 1	477	1.03 (0.94, 1.14)	308	1.06 (0.94, 1.19)
Quintile 2	440	1.00 (0.91, 1.10)	282	1.00 (0.89, 1.13)
Quintile 3	513	1.11 (1.02, 1.21)	334	1.12 (1.01, 1.25)
Quintile 4	554	1.17 (1.07, 1.27)	394	1.29 (1.16, 1.42)
Quintile 5	627	1.31 (1.21, 1.43)	440	1.42 (1.28, 1.57)
per 6.9 kg[†]		*1.12 (1.07, 1.17)*		*1.16 (1.10, 1.23)*
Height-adjusted lean mass				
Quintile 1	541	1.00 (0.89, 1.12)	343	0.96 (0.83, 1.10)
Quintile 2	481	1.00 (0.91, 1.10)	317	1.00 (0.89, 1.12)
Quintile 3	471	1.03 (0.94, 1.12)	321	1.06 (0.96, 1.18)
Quintile 4	528	1.17 (1.07, 1.28)	373	1.27 (1.14, 1.40)
Quintile 5	590	1.31 (1.18, 1.46)	404	1.37 (1.21, 1.55)
per 7.6 kg[†]		*1.22 (1.12, 1.33)*		*1.26 (1.14, 1.40)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.30 Adjusted HRs for colorectal cancer by other adiposity traits in never regular smokers or never regular drinkers*

	Never regular smokers		Never regular drinkers	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	308	0.91 (0.81, 1.03)	426	0.96 (0.87, 1.07)
Quintile 2	302	1.00 (0.89, 1.12)	387	1.00 (0.90, 1.11)
Quintile 3	345	0.99 (0.89, 1.10)	434	1.03 (0.94, 1.13)
Quintile 4	360	1.00 (0.90, 1.11)	462	1.07 (0.98, 1.17)
Quintile 5	479	1.14 (1.03, 1.27)	591	1.23 (1.12, 1.36)
per 6.9 cm†		*1.11 (1.04, 1.18)*		*1.12 (1.06, 1.19)*
WHtR				
Quintile 1	244	0.95 (0.83, 1.08)	342	0.91 (0.82, 1.02)
Quintile 2	279	1.00 (0.89, 1.13)	381	1.00 (0.90, 1.11)
Quintile 3	366	1.14 (1.03, 1.26)	438	1.05 (0.95, 1.15)
Quintile 4	412	1.13 (1.03, 1.24)	515	1.11 (1.02, 1.21)
Quintile 5	493	1.16 (1.06, 1.28)	624	1.16 (1.06, 1.26)
per 0.06†		*1.10 (1.04, 1.16)*		*1.11 (1.05, 1.17)*
Height-adjusted weight				
Quintile 1	324	0.97 (0.85, 1.10)	458	0.99 (0.89, 1.10)
Quintile 2	318	1.00 (0.89, 1.12)	412	1.00 (0.91, 1.10)
Quintile 3	318	0.94 (0.84, 1.04)	398	0.94 (0.85, 1.03)
Quintile 4	397	1.13 (1.03, 1.25)	488	1.14 (1.05, 1.25)
Quintile 5	437	1.17 (1.05, 1.30)	544	1.25 (1.14, 1.38)
per 10.8 kg†		*1.10 (1.03, 1.18)*		*1.11 (1.05, 1.17)*
Height-adjusted fat mass				
Quintile 1	321	1.03 (0.92, 1.16)	459	1.08 (0.98, 1.19)
Quintile 2	307	1.00 (0.89, 1.12)	392	1.00 (0.91, 1.10)
Quintile 3	353	1.06 (0.95, 1.17)	442	1.07 (0.98, 1.18)
Quintile 4	386	1.09 (0.99, 1.21)	480	1.13 (1.03, 1.24)
Quintile 5	427	1.15 (1.04, 1.28)	527	1.24 (1.13, 1.36)
per 6.9 kg†		*1.06 (1.00, 1.12)*		*1.07 (1.02, 1.13)*
Height-adjusted lean mass				
Quintile 1	361	1.00 (0.87, 1.15)	487	0.98 (0.87, 1.11)
Quintile 2	336	1.00 (0.89, 1.12)	449	1.00 (0.91, 1.10)
Quintile 3	315	0.95 (0.85, 1.06)	403	0.93 (0.85, 1.03)
Quintile 4	377	1.14 (1.02, 1.26)	464	1.09 (1.00, 1.20)
Quintile 5	405	1.21 (1.07, 1.37)	497	1.18 (1.05, 1.32)
per 7.6 kg†		*1.23 (1.09, 1.38)*		*1.18 (1.07, 1.30)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.31 Adjusted HRs for colon cancer by main adiposity traits in men and women, separately*

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	100	1.07 (0.87, 1.31)	90	0.88 (0.71, 1.09)
20.0 to <22.5	173	1.00 (0.86, 1.16)	198	1.00 (0.87, 1.15)
22.5 to <25.0	253	1.30 (1.15, 1.47)	233	0.93 (0.82, 1.06)
25.0 to <27.5	151	1.24 (1.06, 1.46)	166	1.04 (0.90, 1.22)
≥27.5	173	1.68 (1.44, 1.96)	208	1.15 (0.99, 1.32)
per 3.4 kg/m^2†		*1.19 (1.10, 1.28)*		*1.09 (1.01, 1.16)*
%BF				
Quintile 1	146	0.97 (0.82, 1.15)	156	0.98 (0.83, 1.15)
Quintile 2	146	1.00 (0.85, 1.18)	159	1.00 (0.86, 1.17)
Quintile 3	181	1.11 (0.96, 1.29)	157	0.92 (0.79, 1.07)
Quintile 4	201	1.32 (1.15, 1.52)	200	1.08 (0.94, 1.24)
Quintile 5	176	1.25 (1.08, 1.46)	223	1.13 (0.99, 1.30)
per 8.4%†		*1.19 (1.07, 1.33)*		*1.07 (0.98, 1.17)*
WC				
Quintile 1	131	1.04 (0.86, 1.25)	131	0.94 (0.79, 1.12)
Quintile 2	113	1.00 (0.83, 1.21)	135	1.00 (0.84, 1.19)
Quintile 3	145	1.21 (1.02, 1.42)	179	1.14 (0.99, 1.32)
Quintile 4	212	1.67 (1.46, 1.91)	207	1.20 (1.05, 1.37)
Quintile 5	249	1.86 (1.62, 2.12)	243	1.21 (1.06, 1.38)
per 9.8 cm†		*1.33 (1.23, 1.45)*		*1.13 (1.04, 1.23)*
WHR				
Quintile 1	104	0.75 (0.62, 0.92)	155	1.25 (1.06, 1.48)
Quintile 2	147	1.00 (0.85, 1.18)	134	1.00 (0.84, 1.19)
Quintile 3	141	1.04 (0.88, 1.23)	131	1.08 (0.91, 1.29)
Quintile 4	214	1.27 (1.11, 1.45)	192	1.22 (1.06, 1.40)
Quintile 5	244	1.36 (1.20, 1.55)	283	1.37 (1.21, 1.55)
per 0.07†		*1.32 (1.21, 1.45)*		*1.08 (0.98, 1.19)*
BMI25‡				
<20.0	124	0.86 (0.72, 1.03)	166	0.84 (0.72, 0.99)
20.0 to <22.5	332	1.00 (0.90, 1.11)	281	1.00 (0.89, 1.12)
22.5 to <25.0	215	0.94 (0.83, 1.08)	197	0.95 (0.83, 1.10)
25.0 to <27.5	54	0.91 (0.70, 1.19)	66	0.82 (0.64, 1.04)
≥27.5	31	1.15 (0.81, 1.65)	40	0.96 (0.70, 1.32)
per 2.6 kg/m^2		*1.03 (0.95, 1.11)*		*1.01 (0.95, 1.08)*

* Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.
‡ BMI25 was missing in 81,880 participants.
P for heterogeneity by sex: BMI, 0.22; %BF, 0.11; WC, 0.006; WHR, 0.002; BMI25, 0.71.

Appendix 7.32 Adjusted HRs for colon cancer by other adiposity traits in men and women, separately[*]

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	134	1.00 (0.83, 1.21)	163	0.91 (0.77, 1.08)
Quintile 2	124	1.00 (0.83, 1.20)	150	1.00 (0.85, 1.18)
Quintile 3	161	1.32 (1.13, 1.54)	173	1.00 (0.86, 1.16)
Quintile 4	200	1.50 (1.31, 1.72)	159	0.92 (0.79, 1.07)
Quintile 5	231	1.79 (1.53, 2.08)	250	1.23 (1.06, 1.42)
per 6.8 cm[†]		*1.29 (1.17, 1.42)*		*1.15 (1.05, 1.25)*
WHtR				
Quintile 1	109	0.77 (0.64, 0.94)	132	1.01 (0.85, 1.21)
Quintile 2	138	1.00 (0.84, 1.18)	137	1.00 (0.84, 1.18)
Quintile 3	139	0.95 (0.81, 1.12)	173	1.12 (0.97, 1.30)
Quintile 4	218	1.37 (1.20, 1.57)	199	1.14 (0.99, 1.31)
Quintile 5	246	1.37 (1.20, 1.56)	254	1.24 (1.09, 1.42)
per 0.06[†]		*1.30 (1.19, 1.42)*		*1.11 (1.03, 1.20)*
Height-adjusted weight				
Quintile 1	150	1.03 (0.86, 1.25)	184	0.96 (0.81, 1.15)
Quintile 2	135	1.00 (0.84, 1.19)	163	1.00 (0.85, 1.17)
Quintile 3	153	1.09 (0.93, 1.27)	142	0.87 (0.74, 1.02)
Quintile 4	199	1.43 (1.24, 1.64)	191	1.21 (1.05, 1.39)
Quintile 5	213	1.63 (1.39, 1.92)	207	1.34 (1.13, 1.58)
per 10.8 kg[†]		*1.21 (1.11, 1.32)*		*1.11 (1.01, 1.22)*
Height-adjusted fat mass				
Quintile 1	148	1.02 (0.86, 1.22)	183	1.24 (1.06, 1.46)
Quintile 2	140	1.00 (0.85, 1.18)	136	1.00 (0.84, 1.19)
Quintile 3	175	1.16 (1.00, 1.34)	184	1.31 (1.14, 1.51)
Quintile 4	203	1.36 (1.19, 1.57)	195	1.42 (1.23, 1.64)
Quintile 5	184	1.37 (1.17, 1.60)	189	1.47 (1.25, 1.71)
per 6.9 kg[†]		*1.19 (1.09, 1.31)*		*1.08 (1.00, 1.16)*
Height-adjusted lean mass				
Quintile 1	160	1.14 (0.93, 1.38)	198	1.10 (0.91, 1.32)
Quintile 2	134	1.00 (0.84, 1.19)	159	1.00 (0.85, 1.17)
Quintile 3	164	1.24 (1.07, 1.44)	143	0.94 (0.80, 1.11)
Quintile 4	168	1.27 (1.09, 1.48)	194	1.29 (1.11, 1.49)
Quintile 5	224	1.68 (1.42, 1.99)	193	1.25 (1.04, 1.49)
per 7.6 kg[†]		*1.24 (1.10, 1.40)*		*1.21 (1.00, 1.47)*

[*] Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.
P for heterogeneity by sex: HC, 0.07; WHtR, 0.01; height-adjusted weight, 0.18; height-adjusted fat mass, 0.10; height-adjusted lean mass, 0.78.

Appendix 7.33 Adjusted HRs for rectal cancer by main adiposity traits in men and women, separately[*]

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	124	1.12 (0.93, 1.35)	87	0.87 (0.70, 1.08)
20.0 to <22.5	201	1.00 (0.87, 1.15)	188	1.00 (0.87, 1.16)
22.5 to <25.0	237	1.09 (0.96, 1.24)	230	0.98 (0.86, 1.12)
25.0 to <27.5	148	1.11 (0.94, 1.31)	137	0.92 (0.77, 1.08)
≥27.5	177	1.54 (1.31, 1.80)	187	1.08 (0.93, 1.26)
per 3.4 kg/m^2[†]		*1.10 (1.02, 1.19)*		*1.04 (0.96, 1.11)*
%BF				
Quintile 1	169	1.09 (0.93, 1.28)	153	1.05 (0.89, 1.23)
Quintile 2	147	1.00 (0.85, 1.18)	141	1.00 (0.85, 1.18)
Quintile 3	182	1.15 (0.99, 1.32)	150	0.99 (0.85, 1.17)
Quintile 4	202	1.35 (1.18, 1.55)	182	1.10 (0.95, 1.27)
Quintile 5	187	1.31 (1.13, 1.52)	203	1.11 (0.96, 1.29)
per 8.4%[†]		*1.11 (1.00, 1.24)*		*1.02 (0.93, 1.12)*
WC				
Quintile 1	157	0.99 (0.84, 1.17)	140	1.07 (0.90, 1.27)
Quintile 2	143	1.00 (0.85, 1.18)	126	1.00 (0.84, 1.19)
Quintile 3	167	1.14 (0.98, 1.32)	169	1.16 (1.00, 1.35)
Quintile 4	175	1.15 (0.99, 1.33)	164	1.01 (0.87, 1.18)
Quintile 5	245	1.52 (1.33, 1.74)	230	1.19 (1.04, 1.37)
per 9.8 cm[†]		*1.22 (1.12, 1.33)*		*1.04 (0.95, 1.13)*
WHR				
Quintile 1	126	0.92 (0.77, 1.10)	107	0.81 (0.67, 0.99)
Quintile 2	149	1.00 (0.85, 1.17)	150	1.00 (0.85, 1.18)
Quintile 3	174	1.29 (1.11, 1.50)	129	0.93 (0.78, 1.11)
Quintile 4	197	1.21 (1.05, 1.39)	202	1.09 (0.95, 1.25)
Quintile 5	241	1.41 (1.24, 1.60)	241	0.96 (0.84, 1.09)
per 0.07[†]		*1.25 (1.13, 1.38)*		*1.05 (0.95, 1.17)*
BMI25[‡]				
<20.0	119	0.91 (0.76, 1.09)	145	0.84 (0.71, 0.99)
20.0 to <22.5	308	1.00 (0.89, 1.12)	256	1.00 (0.88, 1.13)
22.5 to <25.0	245	1.16 (1.03, 1.32)	174	0.91 (0.78, 1.05)
25.0 to <27.5	72	1.28 (1.02, 1.62)	56	0.75 (0.58, 0.98)
≥27.5	29	1.15 (0.80, 1.66)	37	0.96 (0.69, 1.33)
per 2.6 kg/m^2		*1.10 (1.02, 1.18)*		*1.01 (0.94, 1.08)*

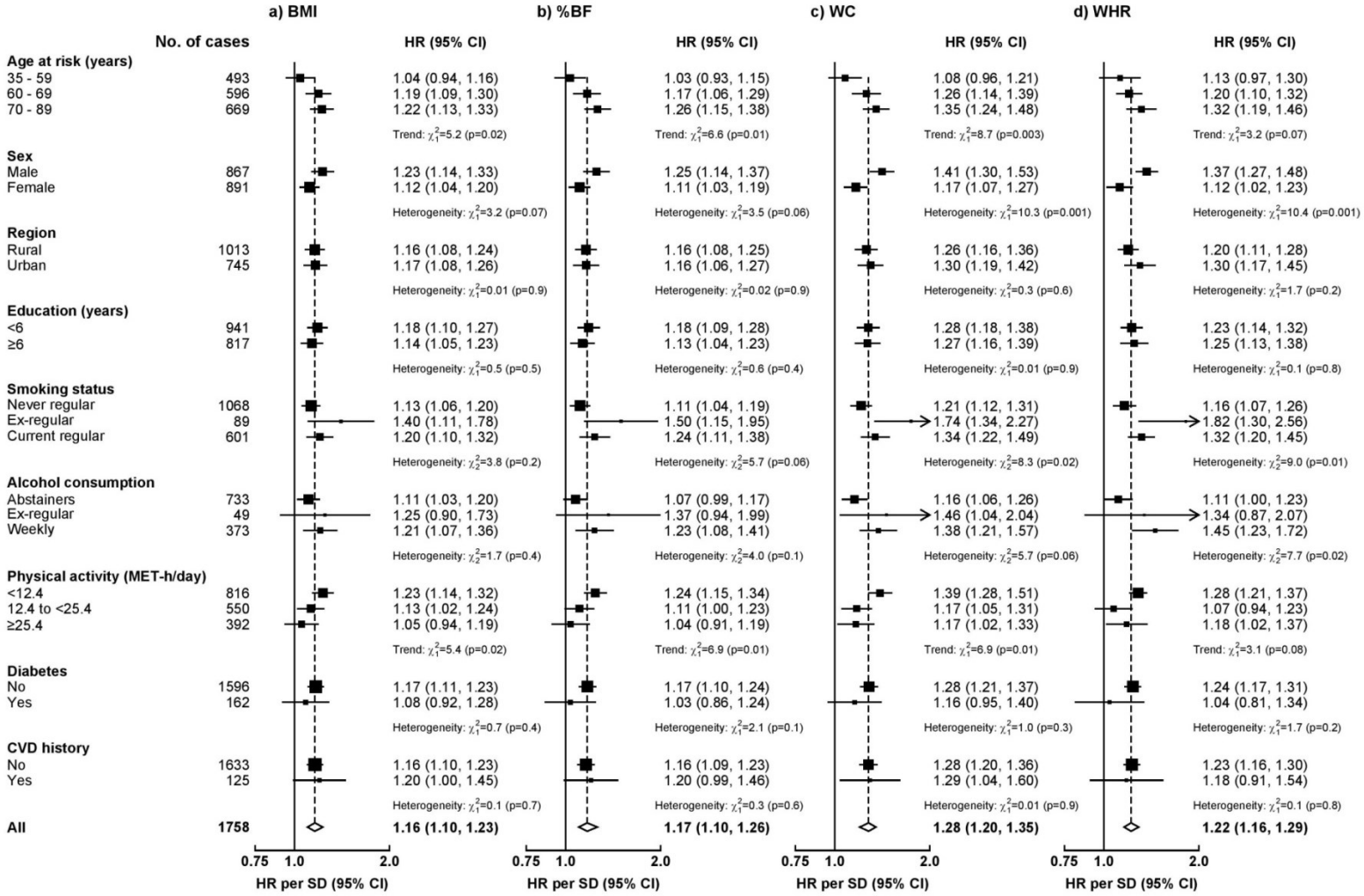
[*] Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
[†] Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.
[‡] BMI25 was missing in 81,880 participants.
P for heterogeneity by sex: BMI, 0.33; %BF, 0.23; WC, 0.01; WHR, 0.02; BMI25, 0.14.

Appendix 7.34 Adjusted HRs for rectal cancer by other adiposity traits in men and women, separately[*]

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	160	0.86 (0.73, 1.03)	178	1.02 (0.87, 1.20)
Quintile 2	162	1.00 (0.85, 1.17)	141	1.00 (0.85, 1.18)
Quintile 3	157	1.01 (0.86, 1.18)	156	0.99 (0.84, 1.15)
Quintile 4	190	1.12 (0.97, 1.29)	162	1.03 (0.88, 1.20)
Quintile 5	218	1.23 (1.05, 1.44)	192	1.00 (0.85, 1.18)
per 6.8 cm[†]		*1.16 (1.05, 1.27)*		*1.01 (0.92, 1.10)*
WHtR				
Quintile 1	131	0.91 (0.76, 1.09)	119	0.91 (0.76, 1.10)
Quintile 2	143	1.00 (0.85, 1.18)	140	1.00 (0.85, 1.18)
Quintile 3	177	1.20 (1.04, 1.39)	171	1.08 (0.93, 1.25)
Quintile 4	195	1.25 (1.09, 1.44)	178	0.98 (0.84, 1.13)
Quintile 5	*241*	*1.40 (1.23, 1.60)*	*221*	*1.00 (0.87, 1.15)*
per 0.06[†]		1.22 (1.12, 1.33)		1.01 (0.94, 1.10)
Height-adjusted weight				
Quintile 1	184	0.96 (0.81, 1.15)	176	1.10 (0.93, 1.30)
Quintile 2	163	1.00 (0.85, 1.17)	140	1.00 (0.85, 1.18)
Quintile 3	142	0.87 (0.74, 1.02)	157	1.10 (0.94, 1.28)
Quintile 4	191	1.21 (1.05, 1.39)	157	1.08 (0.92, 1.26)
Quintile 5	207	1.34 (1.13, 1.58)	199	1.24 (1.05, 1.45)
per 10.8 kg[†]		*1.12 (1.02, 1.22)*		*1.06 (0.96, 1.16)*
Height-adjusted fat mass				
Quintile 1	183	1.24 (1.06, 1.46)	164	1.07 (0.91, 1.26)
Quintile 2	136	1.00 (0.84, 1.19)	142	1.00 (0.85, 1.18)
Quintile 3	184	1.31 (1.14, 1.51)	156	1.05 (0.90, 1.23)
Quintile 4	195	1.42 (1.23, 1.64)	166	1.05 (0.90, 1.22)
Quintile 5	189	1.47 (1.25, 1.71)	201	1.15 (0.99, 1.33)
per 6.9 kg[†]		*1.12 (1.02, 1.22)*		*1.03 (0.95, 1.11)*
Height-adjusted lean mass				
Quintile 1	198	1.10 (0.91, 1.32)	211	1.20 (0.99, 1.46)
Quintile 2	159	1.00 (0.85, 1.17)	151	1.00 (0.85, 1.18)
Quintile 3	143	0.94 (0.80, 1.11)	124	0.87 (0.73, 1.03)
Quintile 4	194	1.29 (1.11, 1.49)	160	1.16 (0.99, 1.36)
Quintile 5	193	1.25 (1.04, 1.49)	183	1.34 (1.11, 1.62)
per 7.6 kg[†]		*1.12 (0.99, 1.27)*		*1.19 (0.97, 1.46)*

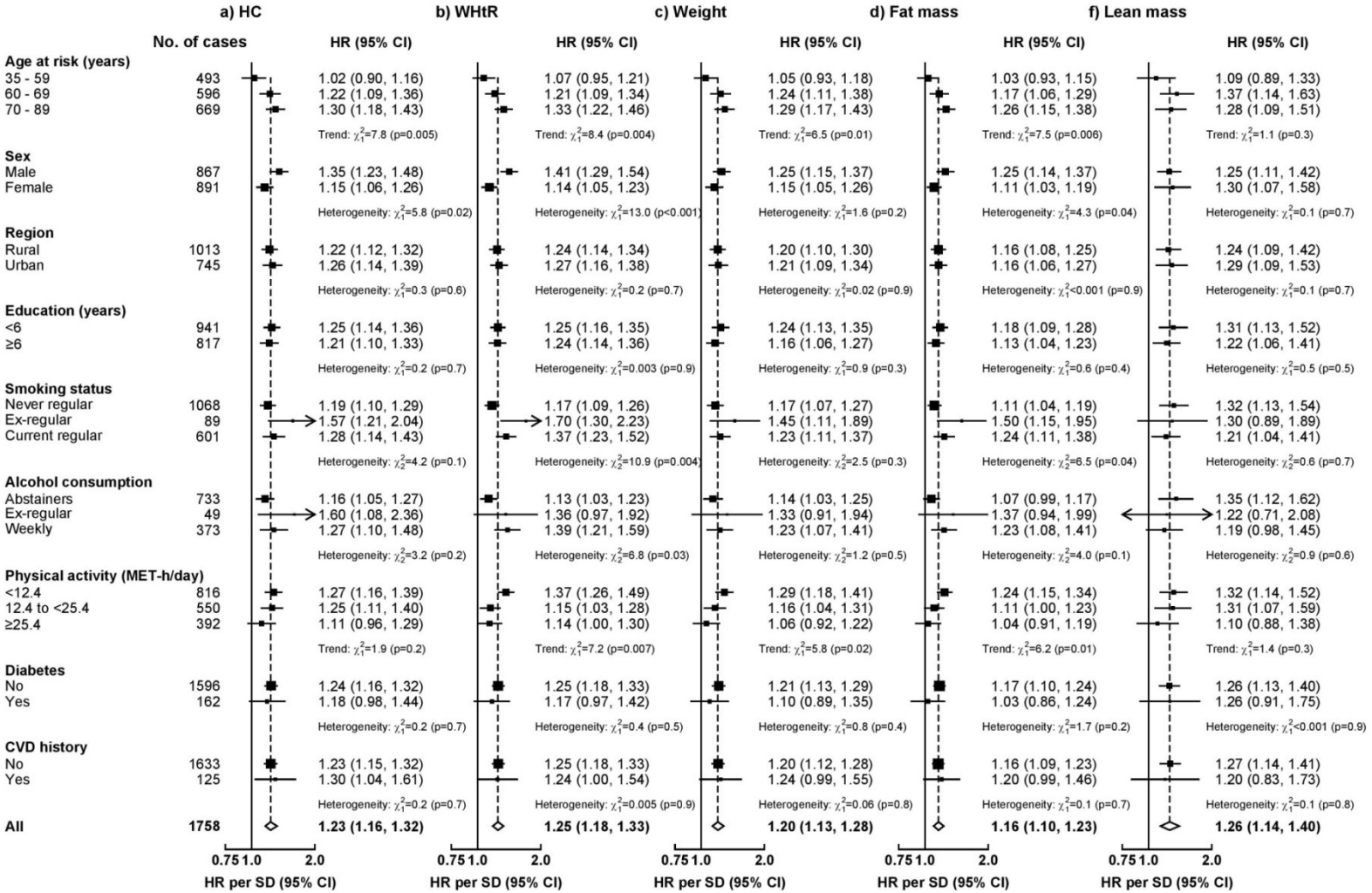
[*] Model was stratified by age-at-risk (5-year) and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
[†] Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.
P for heterogeneity by sex: HC, 0.04; WHtR, 0.002; height-adjusted weight, 0.44; height-adjusted fat mass, 0.21; height-adjusted lean mass, 0.56.

Appendix 7.35 Associations of main adiposity traits with risk of colorectal cancer by population subgroups excluding the first five years



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.36 Associations of other adiposity traits with risk of colorectal cancer by population subgroups excluding the first five years



Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and standing height (for weight, fat mass, and lean mass).

Appendix 7.37 Adjusted HRs for colon and rectal cancer by BMI with additional adjustment for central adiposity*

	Colon		Rectal	
	Basic HR (95% CI)	Residual HR (95% CI)	Basic HR (95% CI)	Residual HR (95% CI)
BMI adjusted for WC				
Quintile 1	1.14 (0.94, 1.38)	1.10 (1.00, 1.22)	1.08 (0.90, 1.30)	1.18 (1.07, 1.31)
Quintile 2	1.00 (0.88, 1.13)	1.00 (0.90, 1.11)	1.00 (0.89, 1.13)	1.00 (0.90, 1.11)
Quintile 3	0.95 (0.88, 1.03)	1.02 (0.92, 1.13)	0.97 (0.89, 1.05)	1.06 (0.95, 1.17)
Quintile 4	0.86 (0.76, 0.98)	0.85 (0.76, 0.96)	0.89 (0.78, 1.01)	0.99 (0.88, 1.11)
Quintile 5	0.88 (0.75, 1.03)	0.99 (0.88, 1.11)	1.04 (0.88, 1.22)	1.07 (0.95, 1.20)
BMI adjusted for WHR				
Quintile 1	1.03 (0.87, 1.21)	1.02 (0.91, 1.14)	1.05 (0.90, 1.23)	1.02 (0.91, 1.14)
Quintile 2	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
Quintile 3	1.05 (0.96, 1.14)	1.04 (0.93, 1.15)	1.00 (0.91, 1.09)	1.02 (0.91, 1.13)
Quintile 4	1.04 (0.93, 1.17)	1.02 (0.92, 1.14)	0.94 (0.83, 1.06)	0.96 (0.86, 1.08)
Quintile 5	1.22 (1.09, 1.37)	1.14 (1.02, 1.27)	1.16 (1.03, 1.31)	1.08 (0.97, 1.21)
BMI adjusted for HC				
Quintile 1	1.06 (0.89, 1.26)	0.98 (0.87, 1.10)	1.00 (0.84, 1.18)	0.84 (0.75, 0.95)
Quintile 2	1.00 (0.89, 1.12)	1.00 (0.90, 1.11)	1.00 (0.89, 1.12)	1.00 (0.90, 1.11)
Quintile 3	1.02 (0.94, 1.11)	0.92 (0.82, 1.02)	1.04 (0.96, 1.13)	0.89 (0.80, 0.99)
Quintile 4	0.98 (0.87, 1.11)	0.97 (0.88, 1.08)	1.01 (0.90, 1.15)	0.93 (0.83, 1.03)
Quintile 5	1.06 (0.92, 1.24)	1.04 (0.94, 1.16)	1.29 (1.11, 1.50)	0.96 (0.87, 1.07)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

† In the residual method, the residuals from the regression of BMI on WC, WHR, or HC were modelled as the main exposure variable and additionally included WC, WHR, or HC as a covariate in the model.

Appendix 7.38 Adjusted HRs for colon and rectal cancer by central adiposity with additional adjustment for BMI*

	Colon		Rectal	
	Basic HR (95% CI)	Residual HR (95% CI)	Basic HR (95% CI)	Residual HR (95% CI)
WC adjusted for BMI				
Quintile 1	0.98 (0.83, 1.15)	0.94 (0.82, 1.07)	1.01 (0.86, 1.18)	1.07 (0.94, 1.22)
Quintile 2	1.00 (0.87, 1.15)	1.00 (0.89, 1.13)	1.00 (0.88, 1.14)	1.00 (0.89, 1.12)
Quintile 3	1.18 (1.06, 1.31)	1.13 (1.02, 1.26)	1.17 (1.05, 1.29)	0.95 (0.85, 1.07)
Quintile 4	1.42 (1.29, 1.57)	1.19 (1.08, 1.32)	1.11 (0.99, 1.24)	1.10 (0.99, 1.22)
Quintile 5	1.52 (1.32, 1.75)	1.37 (1.24, 1.51)	1.43 (1.23, 1.65)	1.27 (1.15, 1.40)
WHR adjusted for BMI				
Quintile 1	1.02 (0.89, 1.18)	1.09 (0.95, 1.23)	0.87 (0.75, 1.01)	0.91 (0.79, 1.05)
Quintile 2	1.00 (0.89, 1.13)	1.00 (0.89, 1.12)	1.00 (0.89, 1.12)	1.00 (0.89, 1.12)
Quintile 3	1.04 (0.92, 1.17)	1.04 (0.94, 1.16)	1.11 (0.99, 1.24)	0.99 (0.89, 1.10)
Quintile 4	1.19 (1.08, 1.32)	1.20 (1.09, 1.33)	1.14 (1.04, 1.26)	1.06 (0.96, 1.17)
Quintile 5	1.27 (1.15, 1.41)	1.28 (1.16, 1.41)	1.15 (1.04, 1.28)	1.13 (1.03, 1.25)
HC adjusted for BMI				
Quintile 1	0.98 (0.84, 1.14)	0.97 (0.86, 1.10)	0.97 (0.84, 1.13)	1.03 (0.92, 1.16)
Quintile 2	1.00 (0.88, 1.14)	1.00 (0.90, 1.12)	1.00 (0.89, 1.13)	1.00 (0.90, 1.11)
Quintile 3	1.12 (1.01, 1.24)	1.15 (1.03, 1.27)	0.97 (0.88, 1.08)	1.06 (0.95, 1.18)
Quintile 4	1.13 (1.02, 1.26)	1.01 (0.91, 1.14)	1.02 (0.91, 1.14)	0.94 (0.84, 1.06)
Quintile 5	1.37 (1.18, 1.59)	1.29 (1.15, 1.45)	1.00 (0.86, 1.17)	1.06 (0.94, 1.19)

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† In the residual method, the residuals from the regression of WC, WHR, or HC on BMI were modelled as the main exposure variable and additionally included BMI as a covariate in the model.

Appendix 7.39 Adjusted HRs for specific GI cancers by main adiposity traits with additional adjustment for diabetes*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI			
<20.0	0.91 (0.74, 1.11)	1.03 (0.94, 1.14)	0.97 (0.87, 1.08)
20.0 to <22.5	1.00 (0.87, 1.15)	1.00 (0.93, 1.07)	1.00 (0.93, 1.08)
22.5 to <25.0	0.93 (0.82, 1.07)	0.96 (0.89, 1.03)	1.04 (0.97, 1.11)
25.0 to <27.5	0.94 (0.79, 1.11)	0.88 (0.80, 0.97)	1.04 (0.95, 1.13)
≥27.5	0.98 (0.83, 1.17)	0.87 (0.78, 0.96)	1.30 (1.20, 1.41)
per 3.4 kg/m^2†	*1.00 (0.93, 1.08)*	*0.93 (0.89, 0.97)*	*1.09 (1.05, 1.14)*
%BF			
Quintile 1	1.08 (0.92, 1.26)	1.07 (0.99, 1.16)	1.02 (0.94, 1.12)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	1.04 (0.89, 1.21)	0.86 (0.79, 0.93)	1.00 (0.92, 1.09)
Quintile 4	1.04 (0.89, 1.21)	0.82 (0.75, 0.90)	1.16 (1.07, 1.25)
Quintile 5	0.98 (0.83, 1.15)	0.75 (0.69, 0.83)	1.19 (1.10, 1.29)
per 8.4%†	*0.95 (0.86, 1.06)*	*0.84 (0.79, 0.89)*	*1.08 (1.03, 1.14)*
WC			
Quintile 1	1.03 (0.87, 1.21)	1.04 (0.96, 1.13)	1.03 (0.93, 1.12)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.91, 1.10)
Quintile 3	0.97 (0.83, 1.14)	1.03 (0.95, 1.11)	1.15 (1.06, 1.25)
Quintile 4	0.98 (0.84, 1.15)	0.93 (0.86, 1.02)	1.22 (1.13, 1.32)
Quintile 5	0.97 (0.83, 1.13)	0.96 (0.88, 1.05)	1.37 (1.27, 1.47)
per 9.8 cm†	*0.98 (0.90, 1.07)*	*0.97 (0.93, 1.02)*	*1.16 (1.11, 1.21)*
WHR			
Quintile 1	1.07 (0.91, 1.27)	0.98 (0.89, 1.08)	0.92 (0.84, 1.02)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.99 (0.83, 1.17)	1.03 (0.94, 1.12)	1.06 (0.97, 1.16)
Quintile 4	1.03 (0.89, 1.20)	1.05 (0.97, 1.14)	1.17 (1.09, 1.26)
Quintile 5	0.98 (0.85, 1.13)	1.00 (0.93, 1.08)	1.23 (1.15, 1.32)
per 0.07†	*0.96 (0.86, 1.07)*	*1.01 (0.96, 1.07)*	*1.15 (1.09, 1.21)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and diabetes. For %BF, WC, and WHR, sex-specific quintiles were used.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.40 Adjusted HRs for specific GI cancers by other adiposity traits with additional adjustment for diabetes*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
HC			
Quintile 1	0.94 (0.80, 1.10)	1.05 (0.97, 1.14)	0.92 (0.84, 1.00)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.93 (0.79, 1.10)	0.96 (0.88, 1.04)	1.02 (0.94, 1.11)
Quintile 4	0.85 (0.72, 1.01)	0.91 (0.83, 0.99)	1.07 (0.99, 1.16)
Quintile 5	1.01 (0.85, 1.21)	0.88 (0.79, 0.97)	1.23 (1.13, 1.33)
per 6.8 cm†	*1.01 (0.92, 1.12)*	*0.94 (0.90, 0.99)*	*1.13 (1.08, 1.19)*
WHtR			
Quintile 1	1.15 (0.98, 1.36)	1.00 (0.92, 1.09)	0.89 (0.81, 0.98)
Quintile 2	1.00 (0.84, 1.19)	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)
Quintile 3	1.09 (0.93, 1.27)	0.98 (0.90, 1.07)	1.06 (0.97, 1.15)
Quintile 4	1.09 (0.94, 1.27)	0.98 (0.90, 1.07)	1.15 (1.06, 1.24)
Quintile 5	0.94 (0.81, 1.10)	0.91 (0.84, 0.99)	1.21 (1.13, 1.30)
per 0.06†	*0.97 (0.89, 1.06)*	*0.96 (0.92, 1.01)*	*1.14 (1.09, 1.19)*
Height-adjusted weight			
Quintile 1	1.03 (0.87, 1.23)	1.04 (0.95, 1.13)	0.96 (0.87, 1.06)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.88 (0.75, 1.04)	0.88 (0.81, 0.96)	0.95 (0.87, 1.03)
Quintile 4	0.98 (0.84, 1.15)	0.85 (0.78, 0.93)	1.15 (1.07, 1.25)
Quintile 5	1.01 (0.84, 1.21)	0.85 (0.77, 0.94)	1.26 (1.15, 1.37)
per 10.8 kg†	*1.00 (0.91, 1.10)*	*0.91 (0.87, 0.96)*	*1.12 (1.06, 1.17)*
Height-adjusted fat mass			
Quintile 1	1.03 (0.88, 1.21)	1.04 (0.96, 1.12)	1.09 (1.00, 1.19)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.96 (0.82, 1.13)	0.79 (0.73, 0.87)	1.09 (1.01, 1.18)
Quintile 4	1.00 (0.85, 1.16)	0.79 (0.72, 0.87)	1.19 (1.10, 1.28)
Quintile 5	0.97 (0.82, 1.14)	0.78 (0.71, 0.86)	1.26 (1.16, 1.36)
per 6.9 kg†	*0.98 (0.89, 1.07)*	*0.87 (0.83, 0.92)*	*1.09 (1.04, 1.14)*
Height-adjusted lean mass			
Quintile 1	1.09 (0.90, 1.32)	1.06 (0.96, 1.17)	1.01 (0.92, 1.12)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.91 (0.77, 1.07)	1.05 (0.96, 1.14)	1.00 (0.92, 1.08)
Quintile 4	1.08 (0.92, 1.27)	1.09 (1.00, 1.20)	1.12 (1.03, 1.22)
Quintile 5	1.17 (0.96, 1.42)	1.11 (0.99, 1.23)	1.24 (1.12, 1.36)
per 7.6 kg†	*1.09 (0.93, 1.27)*	*1.02 (0.95, 1.11)*	*1.16 (1.07, 1.26)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and diabetes. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.41 Adjusted HRs for specific GI cancers by main adiposity traits with additional adjustment for total PA and SLT*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI			
<20.0	0.89 (0.73, 1.10)	1.02 (0.93, 1.12)	0.97 (0.87, 1.08)
20.0 to <22.5	1.00 (0.87, 1.15)	1.00 (0.93, 1.07)	1.00 (0.93, 1.08)
22.5 to <25.0	0.95 (0.83, 1.08)	0.96 (0.90, 1.03)	1.03 (0.97, 1.11)
25.0 to <27.5	0.96 (0.81, 1.14)	0.89 (0.81, 0.98)	1.04 (0.95, 1.13)
≥27.5	1.02 (0.86, 1.21)	0.88 (0.80, 0.98)	1.29 (1.19, 1.40)
per 3.4 kg/m^2†	*1.02 (0.94, 1.10)*	*0.94 (0.90, 0.98)*	*1.09 (1.05, 1.13)*
%BF			
Quintile 1	1.06 (0.90, 1.24)	1.06 (0.99, 1.15)	1.02 (0.94, 1.12)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	1.05 (0.90, 1.22)	0.86 (0.79, 0.94)	1.00 (0.92, 1.09)
Quintile 4	1.05 (0.90, 1.23)	0.83 (0.76, 0.90)	1.15 (1.07, 1.24)
Quintile 5	1.01 (0.86, 1.18)	0.76 (0.69, 0.84)	1.18 (1.10, 1.28)
per 8.4%†	*0.98 (0.88, 1.08)*	*0.84 (0.80, 0.89)*	*1.08 (1.02, 1.14)*
WC			
Quintile 1	1.02 (0.86, 1.20)	1.03 (0.95, 1.12)	1.03 (0.94, 1.13)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.91, 1.10)
Quintile 3	0.98 (0.83, 1.15)	1.03 (0.95, 1.12)	1.15 (1.06, 1.24)
Quintile 4	1.00 (0.86, 1.17)	0.94 (0.87, 1.03)	1.22 (1.13, 1.32)
Quintile 5	1.01 (0.86, 1.18)	0.99 (0.91, 1.08)	1.36 (1.27, 1.47)
per 9.8 cm†	*1.01 (0.93, 1.10)*	*0.98 (0.94, 1.03)*	*1.16 (1.10, 1.21)*
WHR			
Quintile 1	1.06 (0.90, 1.25)	0.97 (0.89, 1.07)	0.92 (0.84, 1.02)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	1.00 (0.84, 1.19)	1.03 (0.94, 1.13)	1.06 (0.97, 1.16)
Quintile 4	1.06 (0.91, 1.23)	1.06 (0.98, 1.15)	1.17 (1.08, 1.26)
Quintile 5	1.03 (0.90, 1.19)	1.03 (0.95, 1.11)	1.23 (1.15, 1.32)
per 0.07†	*1.00 (0.89, 1.11)*	*1.03 (0.97, 1.09)*	*1.15 (1.09, 1.21)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA, and SLT. For %BF, WC, and WHR, sex-specific quintiles were used.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.42 Adjusted HRs for specific GI cancers by other adiposity traits with additional adjustment for total PA and STL*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
HC			
Quintile 1	0.93 (0.79, 1.10)	1.04 (0.96, 1.13)	0.92 (0.84, 1.01)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.94 (0.80, 1.10)	0.96 (0.88, 1.04)	1.02 (0.94, 1.11)
Quintile 4	0.85 (0.72, 1.01)	0.91 (0.84, 1.00)	1.06 (0.98, 1.15)
Quintile 5	1.02 (0.85, 1.21)	0.89 (0.80, 0.98)	1.22 (1.12, 1.32)
per 6.8 cm†	*1.03 (0.93, 1.13)*	*0.95 (0.90, 1.00)*	*1.13 (1.07, 1.18)*
WHtR			
Quintile 1	1.14 (0.97, 1.35)	0.99 (0.91, 1.08)	0.89 (0.81, 0.99)
Quintile 2	1.00 (0.84, 1.19)	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)
Quintile 3	1.10 (0.94, 1.29)	0.99 (0.91, 1.07)	1.06 (0.97, 1.15)
Quintile 4	1.12 (0.96, 1.30)	0.99 (0.91, 1.08)	1.14 (1.06, 1.23)
Quintile 5	0.98 (0.84, 1.15)	0.93 (0.86, 1.02)	1.21 (1.12, 1.30)
per 0.06†	*0.99 (0.91, 1.08)*	*0.98 (0.93, 1.02)*	*1.14 (1.09, 1.19)*
Height-adjusted weight			
Quintile 1	1.01 (0.85, 1.21)	1.03 (0.94, 1.12)	0.96 (0.88, 1.06)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.89 (0.76, 1.05)	0.89 (0.82, 0.97)	0.95 (0.87, 1.03)
Quintile 4	1.01 (0.86, 1.18)	0.86 (0.78, 0.94)	1.15 (1.06, 1.24)
Quintile 5	1.05 (0.88, 1.25)	0.87 (0.78, 0.96)	1.25 (1.15, 1.36)
per 10.8 kg†	*1.03 (0.93, 1.13)*	*0.92 (0.88, 0.97)*	*1.11 (1.06, 1.17)*
Height-adjusted fat mass			
Quintile 1	1.01 (0.86, 1.19)	1.03 (0.95, 1.11)	1.09 (1.00, 1.19)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.97 (0.83, 1.14)	0.80 (0.73, 0.87)	1.09 (1.00, 1.18)
Quintile 4	1.02 (0.87, 1.19)	0.80 (0.73, 0.87)	1.18 (1.09, 1.28)
Quintile 5	1.00 (0.85, 1.18)	0.79 (0.72, 0.87)	1.25 (1.15, 1.36)
per 6.9 kg†	*1.00 (0.91, 1.09)*	*0.88 (0.84, 0.93)*	*1.08 (1.04, 1.13)*
Height-adjusted lean mass			
Quintile 1	1.07 (0.89, 1.30)	1.05 (0.95, 1.16)	1.01 (0.91, 1.12)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.91 (0.77, 1.08)	1.05 (0.97, 1.14)	1.00 (0.92, 1.08)
Quintile 4	1.09 (0.93, 1.29)	1.11 (1.01, 1.21)	1.12 (1.03, 1.22)
Quintile 5	1.19 (0.98, 1.45)	1.13 (1.01, 1.25)	1.24 (1.13, 1.37)
per 7.6 kg†	*1.11 (0.95, 1.29)*	*1.04 (0.96, 1.13)*	*1.16 (1.08, 1.26)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA, and SLT. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.43 Adjusted HRs for specific GI cancers by main adiposity traits with additional adjustment for diet*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI			
<20.0	0.89 (0.73, 1.10)	1.02 (0.93, 1.13)	0.97 (0.87, 1.09)
20.0 to <22.5	1.00 (0.87, 1.15)	1.00 (0.93, 1.07)	1.00 (0.93, 1.08)
22.5 to <25.0	0.95 (0.83, 1.09)	0.97 (0.90, 1.04)	1.04 (0.97, 1.11)
25.0 to <27.5	0.97 (0.82, 1.15)	0.90 (0.81, 0.99)	1.04 (0.95, 1.13)
≥27.5	1.03 (0.87, 1.23)	0.90 (0.81, 0.99)	1.29 (1.19, 1.40)
per 3.4 kg/m^2†	*1.02 (0.95, 1.11)*	*0.94 (0.90, 0.98)*	*1.09 (1.05, 1.14)*
%BF			
Quintile 1	1.05 (0.90, 1.24)	1.06 (0.98, 1.15)	1.02 (0.93, 1.11)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	1.04 (0.89, 1.22)	0.87 (0.80, 0.94)	1.00 (0.92, 1.09)
Quintile 4	1.06 (0.90, 1.23)	0.83 (0.76, 0.91)	1.15 (1.07, 1.24)
Quintile 5	1.01 (0.86, 1.19)	0.78 (0.71, 0.85)	1.19 (1.10, 1.28)
per 8.4%†	*0.98 (0.89, 1.08)*	*0.86 (0.81, 0.90)*	*1.08 (1.03, 1.14)*
WC			
Quintile 1	1.02 (0.86, 1.20)	1.03 (0.95, 1.12)	1.03 (0.94, 1.13)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.91, 1.10)
Quintile 3	0.99 (0.84, 1.16)	1.04 (0.95, 1.12)	1.15 (1.06, 1.24)
Quintile 4	1.02 (0.87, 1.19)	0.95 (0.87, 1.04)	1.22 (1.13, 1.32)
Quintile 5	1.03 (0.88, 1.20)	1.00 (0.92, 1.09)	1.37 (1.27, 1.47)
per 9.8 cm†	*1.01 (0.93, 1.10)*	*0.99 (0.95, 1.04)*	*1.16 (1.11, 1.21)*
WHR			
Quintile 1	1.06 (0.90, 1.25)	0.97 (0.89, 1.07)	0.92 (0.83, 1.01)
Quintile 2	1.00 (0.85, 1.18)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.99 (0.83, 1.18)	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)
Quintile 4	1.05 (0.91, 1.22)	1.07 (0.99, 1.16)	1.17 (1.08, 1.26)
Quintile 5	1.03 (0.89, 1.18)	1.04 (0.96, 1.12)	1.24 (1.15, 1.32)
per 0.07†	*0.99 (0.89, 1.10)*	*1.04 (0.98, 1.10)*	*1.15 (1.09, 1.21)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Dietary variables included fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.44 Adjusted HRs for specific GI cancers by other adiposity traits with additional adjustment for diet*

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	HR (95% CI)	HR (95% CI)
HC			
Quintile 1	0.92 (0.78, 1.09)	1.04 (0.96, 1.13)	0.92 (0.84, 1.01)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.94 (0.80, 1.11)	0.96 (0.88, 1.05)	1.02 (0.94, 1.11)
Quintile 4	0.87 (0.73, 1.02)	0.92 (0.84, 1.00)	1.06 (0.98, 1.15)
Quintile 5	1.06 (0.89, 1.26)	0.89 (0.81, 0.99)	1.22 (1.12, 1.32)
per 6.8 cm†	*1.03 (0.94, 1.14)*	*0.95 (0.90, 1.00)*	*1.13 (1.07, 1.18)*
WHtR			
Quintile 1	1.14 (0.96, 1.34)	1.00 (0.91, 1.09)	0.89 (0.81, 0.98)
Quintile 2	1.00 (0.84, 1.19)	1.00 (0.92, 1.09)	1.00 (0.91, 1.09)
Quintile 3	1.10 (0.94, 1.29)	0.99 (0.92, 1.08)	1.06 (0.97, 1.15)
Quintile 4	1.12 (0.97, 1.30)	1.00 (0.92, 1.09)	1.15 (1.06, 1.23)
Quintile 5	0.99 (0.85, 1.16)	0.95 (0.87, 1.03)	1.21 (1.13, 1.30)
per 0.06†	*1.00 (0.91, 1.09)*	*1.07 (1.01, 1.15)*	*1.14 (1.09, 1.19)*
Height-adjusted weight			
Quintile 1	1.02 (0.85, 1.21)	1.03 (0.94, 1.12)	0.96 (0.88, 1.06)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.90 (0.76, 1.06)	0.89 (0.82, 0.97)	0.95 (0.87, 1.03)
Quintile 4	1.02 (0.87, 1.19)	0.87 (0.79, 0.95)	1.15 (1.07, 1.25)
Quintile 5	1.06 (0.89, 1.27)	0.88 (0.80, 0.98)	1.26 (1.15, 1.37)
per 10.8 kg†	*1.03 (0.94, 1.14)*	*0.93 (0.88, 0.98)*	*1.11 (1.06, 1.17)*
Height-adjusted fat mass			
Quintile 1	1.01 (0.86, 1.19)	1.03 (0.95, 1.11)	1.09 (1.00, 1.19)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)
Quintile 3	0.97 (0.82, 1.14)	0.80 (0.73, 0.87)	1.09 (1.01, 1.18)
Quintile 4	1.02 (0.87, 1.19)	0.81 (0.74, 0.88)	1.18 (1.10, 1.28)
Quintile 5	1.01 (0.86, 1.20)	0.81 (0.73, 0.89)	1.25 (1.16, 1.36)
per 6.9 kg†	*1.00 (0.92, 1.09)*	*0.89 (0.85, 0.94)*	*1.09 (1.04, 1.14)*
Height-adjusted lean mass			
Quintile 1	1.07 (0.89, 1.30)	1.05 (0.95, 1.16)	1.02 (0.92, 1.13)
Quintile 2	1.00 (0.85, 1.17)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Quintile 3	0.91 (0.77, 1.08)	1.05 (0.97, 1.14)	1.00 (0.92, 1.08)
Quintile 4	1.10 (0.94, 1.30)	1.11 (1.01, 1.21)	1.12 (1.03, 1.22)
Quintile 5	1.21 (1.00, 1.47)	1.13 (1.02, 1.26)	1.24 (1.12, 1.36)
per 7.6 kg†	*1.12 (0.96, 1.31)*	*1.04 (0.96, 1.13)*	*1.16 (1.07, 1.26)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Dietary variables included fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.45 Adjusted HRs for pancreatic cancer by main adiposity traits excluding poor self-rated health or major chronic diseases*

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	170	1.00 (0.86, 1.17)	152	1.00 (0.85, 1.18)
20.0 to <22.5	86	0.94 (0.75, 1.17)	68	0.83 (0.65, 1.06)
22.5 to <25.0	188	0.98 (0.85, 1.13)	158	0.95 (0.81, 1.11)
25.0 to <27.5	112	0.93 (0.77, 1.13)	98	0.97 (0.79, 1.18)
≥27.5	128	1.07 (0.89, 1.29)	91	0.91 (0.73, 1.13)
per 3.4 kg/m^2†		*1.02 (0.93, 1.11)*		*1.00 (0.91, 1.09)*
%BF				
Quintile 1	121	1.00 (0.84, 1.20)	108	1.00 (0.83, 1.21)
Quintile 2	149	1.12 (0.94, 1.33)	120	0.99 (0.82, 1.20)
Quintile 3	131	1.02 (0.86, 1.21)	114	1.03 (0.85, 1.23)
Quintile 4	146	1.13 (0.96, 1.33)	120	1.08 (0.90, 1.29)
Quintile 5	137	1.03 (0.87, 1.23)	105	0.93 (0.76, 1.13)
per 8.4%†		*0.95 (0.85, 1.07)*		*0.97 (0.86, 1.09)*
WC				
Quintile 1	125	1.00 (0.84, 1.19)	106	1.00 (0.83, 1.21)
Quintile 2	138	0.99 (0.83, 1.18)	113	0.94 (0.78, 1.15)
Quintile 3	128	0.95 (0.80, 1.13)	115	1.04 (0.86, 1.24)
Quintile 4	137	0.95 (0.80, 1.12)	114	1.00 (0.83, 1.20)
Quintile 5	156	0.95 (0.80, 1.13)	119	0.95 (0.78, 1.15)
per 9.8 cm†		*0.99 (0.90, 1.09)*		*1.00 (0.90, 1.11)*
WHR				
Quintile 1	126	1.00 (0.84, 1.19)	93	1.00 (0.82, 1.23)
Quintile 2	129	1.06 (0.89, 1.27)	106	1.21 (0.99, 1.47)
Quintile 3	112	1.00 (0.83, 1.20)	98	1.19 (0.98, 1.45)
Quintile 4	147	1.02 (0.87, 1.20)	124	1.20 (1.00, 1.43)
Quintile 5	170	0.99 (0.84, 1.15)	146	1.17 (0.99, 1.39)
per 0.07†		*0.95 (0.85, 1.07)*		*1.01 (0.88, 1.15)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Major chronic diseases included CVD, tuberculosis, respiratory disease, chronic liver disease, gallbladder disease, peptic ulcer, and kidney disease. For %BF, WC, and WHR, sex-specific quintiles were used.
† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

Appendix 7.46 Adjusted HRs for liver cancer by main adiposity traits excluding poor self-rated health or major chronic diseases[*]

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	651	1.00 (0.92, 1.08)	535	1.00 (0.92, 1.09)
20.0 to <22.5	373	1.05 (0.94, 1.16)	314	1.07 (0.95, 1.20)
22.5 to <25.0	665	0.98 (0.91, 1.06)	517	0.95 (0.88, 1.04)
25.0 to <27.5	374	0.93 (0.84, 1.03)	275	0.87 (0.77, 0.98)
≥27.5	351	0.94 (0.84, 1.05)	277	0.95 (0.84, 1.07)
per 3.4 kg/m^2[†]		*0.95 (0.91, 1.00)*		*0.94 (0.89, 0.99)*
%BF				
Quintile 1	517	1.00 (0.92, 1.09)	422	1.00 (0.91, 1.10)
Quintile 2	597	1.05 (0.96, 1.14)	496	1.04 (0.95, 1.15)
Quintile 3	460	0.86 (0.79, 0.94)	338	0.80 (0.71, 0.88)
Quintile 4	430	0.85 (0.77, 0.93)	342	0.85 (0.77, 0.95)
Quintile 5	410	0.82 (0.74, 0.91)	320	0.80 (0.72, 0.90)
per 8.4%[†]		*0.87 (0.82, 0.93)*		*0.86 (0.80, 0.92)*
WC				
Quintile 1	455	1.00 (0.91, 1.10)	376	1.00 (0.90, 1.11)
Quintile 2	508	1.05 (0.96, 1.15)	418	1.05 (0.95, 1.16)
Quintile 3	487	1.06 (0.97, 1.15)	395	1.07 (0.97, 1.18)
Quintile 4	454	0.98 (0.90, 1.08)	333	0.91 (0.82, 1.01)
Quintile 5	510	1.04 (0.95, 1.14)	396	1.05 (0.94, 1.16)
per 9.8 cm[†]		*1.00 (0.95, 1.05)*		*0.99 (0.94, 1.05)*
WHR				
Quintile 1	457	1.00 (0.91, 1.10)	368	1.00 (0.90, 1.11)
Quintile 2	418	1.00 (0.90, 1.10)	329	1.00 (0.89, 1.12)
Quintile 3	412	1.01 (0.92, 1.11)	333	1.04 (0.93, 1.15)
Quintile 4	531	1.06 (0.97, 1.16)	398	0.99 (0.90, 1.10)
Quintile 5	596	1.05 (0.97, 1.14)	490	1.10 (1.00, 1.20)
per 0.07[†]		*1.03 (0.97, 1.10)*		*1.05 (0.98, 1.12)*

Footnotes as in Appendix 7.45.

Appendix 7.47 Adjusted HRs for colorectal cancer by adiposity traits excluding poor self-rated health or major chronic diseases*

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	612	1.00 (0.92, 1.08)	537	1.00 (0.92, 1.09)
20.0 to <22.5	290	0.92 (0.81, 1.03)	239	0.86 (0.76, 0.98)
22.5 to <25.0	751	1.03 (0.96, 1.11)	619	1.00 (0.93, 1.09)
25.0 to <27.5	467	1.02 (0.93, 1.11)	376	0.99 (0.89, 1.10)
≥27.5	583	1.29 (1.19, 1.41)	457	1.25 (1.13, 1.37)
per 3.4 kg/m^2†		*1.09 (1.05, 1.14)*		*1.10 (1.05, 1.15)*
%BF				
Quintile 1	469	1.00 (0.91, 1.10)	425	1.00 (0.91, 1.10)
Quintile 2	481	1.02 (0.93, 1.12)	406	0.94 (0.85, 1.04)
Quintile 3	522	1.02 (0.93, 1.11)	410	0.91 (0.82, 1.00)
Quintile 4	606	1.17 (1.08, 1.27)	492	1.09 (1.00, 1.19)
Quintile 5	625	1.21 (1.12, 1.31)	495	1.11 (1.01, 1.22)
per 8.4%†		*1.10 (1.04, 1.16)*		*1.09 (1.02, 1.15)*
WC				
Quintile 1	407	1.00 (0.91, 1.10)	356	1.00 (0.90, 1.11)
Quintile 2	426	1.00 (0.91, 1.11)	368	0.98 (0.88, 1.09)
Quintile 3	526	1.16 (1.07, 1.27)	440	1.14 (1.04, 1.25)
Quintile 4	599	1.23 (1.13, 1.33)	486	1.20 (1.10, 1.32)
Quintile 5	745	1.38 (1.28, 1.50)	578	1.35 (1.24, 1.48)
per 9.8 cm†		*1.17 (1.11, 1.22)*		*1.17 (1.11, 1.23)*
WHR				
Quintile 1	451	1.00 (0.91, 1.10)	405	1.00 (0.91, 1.10)
Quintile 2	393	0.95 (0.86, 1.05)	317	0.86 (0.77, 0.97)
Quintile 3	456	1.11 (1.01, 1.22)	377	1.03 (0.93, 1.14)
Quintile 4	638	1.22 (1.13, 1.32)	515	1.13 (1.03, 1.23)
Quintile 5	765	1.27 (1.18, 1.36)	614	1.17 (1.08, 1.27)
per 0.07†		*1.16 (1.10, 1.22)*		*1.16 (1.09, 1.23)*

Footnotes as in Appendix 7.45.

Appendix 7.48 Adjusted HRs for pancreatic cancer mortality by main adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
BMI				
<20.0	73	0.91 (0.72, 1.16)	34	0.84 (0.59, 1.19)
20.0 to <22.5	138	1.00 (0.84, 1.19)	73	1.00 (0.79, 1.26)
22.5 to <25.0	154	0.99 (0.85, 1.16)	92	1.11 (0.91, 1.36)
25.0 to <27.5	98	1.01 (0.82, 1.23)	46	0.89 (0.66, 1.18)
≥27.5	106	1.05 (0.86, 1.29)	65	1.19 (0.92, 1.55)
per 3.4 kg/m^2†		*1.03 (0.94, 1.13)*		*1.05 (0.93, 1.18)*
%BF				
Quintile 1	123	1.04 (0.86, 1.25)	62	1.09 (0.84, 1.42)
Quintile 2	102	1.00 (0.82, 1.21)	51	1.00 (0.76, 1.32)
Quintile 3	103	0.95 (0.79, 1.15)	55	1.02 (0.78, 1.33)
Quintile 4	121	1.10 (0.92, 1.31)	70	1.26 (0.99, 1.59)
Quintile 5	120	1.03 (0.86, 1.24)	72	1.21 (0.95, 1.54)
per 8.4%†		*0.99 (0.88, 1.11)*		*1.01 (0.87, 1.19)*
WC				
Quintile 1	128	1.20 (1.00, 1.45)	63	1.04 (0.80, 1.35)
Quintile 2	90	1.00 (0.81, 1.23)	52	1.00 (0.76, 1.32)
Quintile 3	94	0.98 (0.80, 1.19)	54	0.97 (0.75, 1.27)
Quintile 4	119	1.14 (0.95, 1.36)	68	1.13 (0.89, 1.44)
Quintile 5	138	1.13 (0.95, 1.36)	73	1.06 (0.83, 1.36)
per 9.8 cm†		*1.01 (0.91, 1.12)*		*1.02 (0.89, 1.18)*
WHR				
Quintile 1	112	1.10 (0.91, 1.33)	57	0.94 (0.72, 1.23)
Quintile 2	103	1.00 (0.82, 1.21)	62	1.00 (0.78, 1.28)
Quintile 3	81	0.87 (0.70, 1.09)	46	0.82 (0.61, 1.09)
Quintile 4	125	1.06 (0.89, 1.26)	68	0.95 (0.75, 1.20)
Quintile 5	148	1.01 (0.85, 1.19)	77	0.85 (0.67, 1.07)
per 0.07†		*0.99 (0.87, 1.12)*		*0.98 (0.83, 1.17)*
BMI25‡				
<20.0	69	0.84 (0.66, 1.06)		—
20.0 to <22.5	168	1.00 (0.86, 1.17)		—
22.5 to <25.0	139	1.10 (0.93, 1.29)		—
25.0 to <27.5	60	1.44 (1.12, 1.86)		—
≥27.5	30	1.40 (0.98, 2.02)		—
per 2.6 kg/m^2		*1.14 (1.04, 1.24)*		—

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

‡ BMI25 was missing in 81,880 participants.

Appendix 7.49 Adjusted HRs for pancreatic cancer mortality by other adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	132	1.04 (0.92, 1.16)	72	1.04 (0.80, 1.34)
Quintile 2	105	1.00 (0.82, 1.22)	54	1.00 (0.76, 1.31)
Quintile 3	95	0.91 (0.75, 1.11)	56	1.05 (0.81, 1.36)
Quintile 4	99	0.92 (0.76, 1.12)	47	0.88 (0.66, 1.17)
Quintile 5	138	1.11 (0.91, 1.36)	81	1.34 (1.03, 1.76)
per 6.9 cm†		*1.06 (0.90, 1.26)*		*1.07 (0.92, 1.25)*
WHtR				
Quintile 1	120	1.29 (1.06, 1.55)	58	0.99 (0.75, 1.29)
Quintile 2	88	1.00 (0.81, 1.23)	56	1.00 (0.77, 1.30)
Quintile 3	107	1.14 (0.94, 1.37)	58	0.97 (0.75, 1.25)
Quintile 4	122	1.16 (0.97, 1.38)	68	1.02 (0.80, 1.29)
Quintile 5	132	1.05 (0.88, 1.26)	70	0.90 (0.70, 1.15)
per 0.06†		*0.99 (0.89, 1.10)*		*1.00 (0.87, 1.15)*
Height-adjusted weight				
Quintile 1	140	1.27 (1.04, 1.55)	68	1.09 (0.82, 1.44)
Quintile 2	96	1.00 (0.82, 1.22)	55	1.00 (0.77, 1.31)
Quintile 3	96	1.00 (0.82, 1.22)	54	0.98 (0.76, 1.28)
Quintile 4	113	1.17 (0.97, 1.41)	59	1.07 (0.83, 1.38)
Quintile 5	124	1.21 (0.99, 1.49)	74	1.25 (0.95, 1.64)
per 10.8 kg†		*1.04 (0.93, 1.17)*		*1.06 (0.91, 1.24)*
Height-adjusted fat mass				
Quintile 1	131	1.11 (0.92, 1.34)	67	1.13 (0.87, 1.46)
Quintile 2	101	1.00 (0.82, 1.22)	53	1.00 (0.76, 1.31)
Quintile 3	106	1.03 (0.86, 1.25)	59	1.10 (0.86, 1.42)
Quintile 4	111	1.04 (0.86, 1.26)	56	1.00 (0.77, 1.30)
Quintile 5	120	1.08 (0.89, 1.32)	75	1.27 (0.99, 1.62)
per 6.9 kg†		*1.01 (0.91, 1.12)*		*1.04 (0.91, 1.19)*
Height-adjusted lean mass				
Quintile 1	144	1.25 (1.00, 1.57)	77	1.38 (1.02, 1.88)
Quintile 2	101	1.00 (0.82, 1.22)	49	1.00 (0.75, 1.33)
Quintile 3	89	0.93 (0.76, 1.14)	53	1.14 (0.88, 1.48)
Quintile 4	116	1.25 (1.03, 1.50)	62	1.37 (1.06, 1.77)
Quintile 5	119	1.27 (1.01, 1.59)	69	1.50 (1.11, 2.04)
per 7.6 kg†		*1.12 (0.93, 1.34)*		*1.12 (0.87, 1.44)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.50 Adjusted HRs for liver cancer mortality by main adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
BMI				
<20.0	333	1.03 (0.92, 1.15)	135	0.93 (0.78, 1.11)
20.0 to <22.5	562	1.00 (0.92, 1.09)	258	1.00 (0.88, 1.13)
22.5 to <25.0	550	0.96 (0.88, 1.04)	261	0.97 (0.86, 1.10)
25.0 to <27.5	306	0.91 (0.81, 1.01)	155	0.98 (0.84, 1.15)
≥27.5	270	0.83 (0.73, 0.94)	146	0.95 (0.81, 1.13)
per 3.4 kg/m^2†		*0.92 (0.87, 0.97)*		*1.00 (0.93, 1.08)*
%BF				
Quintile 1	538	1.07 (0.98, 1.17)	212	0.89 (0.77, 1.03)
Quintile 2	436	1.00 (0.91, 1.10)	214	1.00 (0.87, 1.14)
Quintile 3	395	0.89 (0.80, 0.98)	196	0.89 (0.77, 1.02)
Quintile 4	345	0.81 (0.73, 0.90)	182	0.86 (0.75, 1.00)
Quintile 5	307	0.71 (0.63, 0.80)	151	0.70 (0.59, 0.83)
per 8.4%†		*0.82 (0.77, 0.87)*		*0.91 (0.82, 1.00)*
WC				
Quintile 1	436	0.98 (0.89, 1.08)	189	0.94 (0.81, 1.09)
Quintile 2	407	1.00 (0.91, 1.10)	187	1.00 (0.86, 1.16)
Quintile 3	395	0.97 (0.88, 1.07)	182	0.96 (0.83, 1.11)
Quintile 4	364	0.89 (0.81, 0.99)	178	0.94 (0.81, 1.09)
Quintile 5	419	0.93 (0.84, 1.03)	219	1.08 (0.94, 1.25)
per 9.8 cm†		*0.97 (0.92, 1.03)*		*1.06 (0.98, 1.15)*
WHR				
Quintile 1	338	0.96 (0.86, 1.07)	156	0.99 (0.84, 1.16)
Quintile 2	386	1.00 (0.90, 1.11)	176	1.00 (0.86, 1.16)
Quintile 3	358	1.05 (0.95, 1.16)	167	1.06 (0.91, 1.24)
Quintile 4	441	1.04 (0.95, 1.14)	207	1.04 (0.91, 1.20)
Quintile 5	498	0.99 (0.90, 1.08)	249	1.08 (0.94, 1.22)
per 0.07†		*1.02 (0.95, 1.09)*		*1.06 (0.96, 1.16)*
BMI25‡				
<20.0	286	0.94 (0.84, 1.06)		—
20.0 to <22.5	634	1.00 (0.92, 1.08)		—
22.5 to <25.0	526	1.15 (1.05, 1.25)		—
25.0 to <27.5	144	1.01 (0.86, 1.19)		—
≥27.5	80	1.16 (0.93, 1.45)		—
per 2.6 kg/m^2		*1.05 (1.00, 1.11)*		—

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

‡ BMI25 was missing in 81,880 participants.

Appendix 7.51 Adjusted HRs for liver cancer mortality by other adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	516	1.08 (0.99, 1.19)	232	1.13 (0.98, 1.30)
Quintile 2	400	1.00 (0.91, 1.10)	170	1.00 (0.86, 1.16)
Quintile 3	389	0.98 (0.89, 1.08)	191	1.13 (0.98, 1.31)
Quintile 4	360	0.93 (0.84, 1.03)	180	1.12 (0.96, 1.29)
Quintile 5	356	0.88 (0.78, 0.99)	182	1.10 (0.93, 1.30)
per 6.9 cm†		*0.94 (0.88, 1.00)*		*1.06 (0.97, 1.15)*
WHtR				
Quintile 1	387	0.96 (0.86, 1.06)	159	0.80 (0.68, 0.94)
Quintile 2	409	1.00 (0.91, 1.10)	204	1.00 (0.87, 1.15)
Quintile 3	382	0.94 (0.85, 1.04)	162	0.79 (0.67, 0.92)
Quintile 4	411	0.98 (0.89, 1.08)	200	0.95 (0.82, 1.09)
Quintile 5	432	0.89 (0.81, 0.99)	230	0.97 (0.85, 1.11)
per 0.06†		*0.97 (0.92, 1.02)*		*1.06 (0.98, 1.15)*
Height-adjusted weight				
Quintile 1	536	1.06 (0.95, 1.17)	239	1.03 (0.88, 1.19)
Quintile 2	434	1.00 (0.91, 1.10)	197	1.00 (0.87, 1.15)
Quintile 3	384	0.93 (0.84, 1.02)	193	1.03 (0.90, 1.18)
Quintile 4	343	0.87 (0.78, 0.97)	145	0.82 (0.69, 0.96)
Quintile 5	324	0.83 (0.74, 0.95)	181	1.05 (0.88, 1.24)
per 10.8 kg†		*0.90 (0.84, 0.95)*		*1.00 (0.91, 1.09)*
Height-adjusted fat mass				
Quintile 1	554	1.04 (0.95, 1.14)	229	0.95 (0.83, 1.09)
Quintile 2	460	1.00 (0.91, 1.10)	211	1.00 (0.87, 1.15)
Quintile 3	360	0.81 (0.73, 0.89)	178	0.87 (0.75, 1.01)
Quintile 4	329	0.76 (0.68, 0.85)	169	0.85 (0.73, 1.00)
Quintile 5	318	0.74 (0.66, 0.84)	168	0.86 (0.73, 1.01)
per 6.9 kg†		*0.85 (0.80, 0.90)*		*0.94 (0.86, 1.02)*
Height-adjusted lean mass				
Quintile 1	512	1.02 (0.91, 1.15)	239	1.00 (0.85, 1.19)
Quintile 2	412	1.00 (0.91, 1.10)	190	1.00 (0.87, 1.16)
Quintile 3	366	1.00 (0.91, 1.11)	162	0.98 (0.85, 1.14)
Quintile 4	376	1.11 (1.00, 1.23)	175	1.18 (1.01, 1.37)
Quintile 5	355	1.11 (0.98, 1.26)	189	1.37 (1.14, 1.64)
per 7.6 kg†		*1.03 (0.94, 1.13)*		*1.17 (1.02, 1.34)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.52 Adjusted HRs for colorectal cancer mortality by main adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
BMI				
<20.0	147	1.16 (0.98, 1.38)	54	0.94 (0.71, 1.24)
20.0 to <22.5	218	1.00 (0.87, 1.14)	98	1.00 (0.82, 1.22)
22.5 to <25.0	252	1.04 (0.92, 1.18)	132	1.25 (1.06, 1.48)
25.0 to <27.5	149	1.01 (0.86, 1.18)	77	1.21 (0.96, 1.51)
≥27.5	195	1.32 (1.14, 1.54)	92	1.48 (1.19, 1.83)
per 3.4 kg/m^2†		*1.05 (0.98, 1.13)*		*1.16 (1.05, 1.29)*
%BF				
Quintile 1	209	1.07 (0.93, 1.24)	81	0.90 (0.72, 1.14)
Quintile 2	173	1.00 (0.86, 1.16)	79	1.00 (0.80, 1.25)
Quintile 3	183	1.01 (0.88, 1.17)	91	1.12 (0.91, 1.37)
Quintile 4	190	1.07 (0.93, 1.23)	94	1.19 (0.97, 1.45)
Quintile 5	206	1.15 (1.00, 1.33)	108	1.37 (1.13, 1.67)
per 8.4%†		*1.04 (0.95, 1.14)*		*1.20 (1.06, 1.37)*
WC				
Quintile 1	181	1.08 (0.92, 1.25)	70	0.96 (0.75, 1.23)
Quintile 2	150	1.00 (0.85, 1.18)	64	1.00 (0.78, 1.28)
Quintile 3	183	1.15 (1.00, 1.33)	93	1.40 (1.14, 1.72)
Quintile 4	197	1.17 (1.02, 1.35)	101	1.49 (1.23, 1.81)
Quintile 5	250	1.30 (1.14, 1.49)	125	1.70 (1.41, 2.05)
per 9.8 cm†		*1.10 (1.02, 1.19)*		*1.28 (1.14, 1.43)*
WHR				
Quintile 1	131	0.78 (0.66, 0.93)	59	0.83 (0.64, 1.08)
Quintile 2	180	1.00 (0.86, 1.16)	76	1.00 (0.80, 1.25)
Quintile 3	155	0.96 (0.82, 1.12)	69	1.02 (0.81, 1.30)
Quintile 4	214	1.03 (0.90, 1.17)	101	1.16 (0.96, 1.42)
Quintile 5	281	1.08 (0.95, 1.22)	148	1.40 (1.18, 1.66)
per 0.07†		*1.13 (1.03, 1.25)*		*1.26 (1.12, 1.41)*
BMI25‡				
<20.0	116	0.71 (0.59, 0.85)		—
20.0 to <22.5	310	1.00 (0.89, 1.12)		—
22.5 to <25.0	227	0.99 (0.87, 1.13)		—
25.0 to <27.5	81	1.05 (0.84, 1.31)		—
≥27.5	46	1.14 (0.85, 1.53)		—
per 2.6 kg/m^2		*1.11 (1.04, 1.19)*		—

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. For %BF, WC, and WHR, sex-specific quintiles were used.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.70.

‡ BMI25 was missing in 81,880 participants.

Appendix 7.53 Adjusted HRs for colorectal cancer mortality by other adiposity traits*

	No exclusions		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
HC				
Quintile 1	220	0.99 (0.86, 1.15)	91	0.84 (0.67, 1.06)
Quintile 2	178	1.00 (0.86, 1.16)	83	1.00 (0.80, 1.25)
Quintile 3	164	0.92 (0.79, 1.07)	76	0.94 (0.75, 1.18)
Quintile 4	183	1.01 (0.87, 1.17)	90	1.16 (0.95, 1.43)
Quintile 5	216	1.07 (0.91, 1.25)	113	1.41 (1.14, 1.76)
per 6.9 cm†		*1.05 (0.96, 1.15)*		*1.22 (1.08, 1.39)*
WHtR				
Quintile 1	150	0.89 (0.75, 1.05)	63	0.91 (0.70, 1.17)
Quintile 2	169	1.00 (0.86, 1.16)	69	1.00 (0.79, 1.27)
Quintile 3	175	0.97 (0.84, 1.13)	79	1.10 (0.88, 1.37)
Quintile 4	203	1.02 (0.89, 1.17)	103	1.32 (1.09, 1.60)
Quintile 5	264	1.11 (0.97, 1.26)	139	1.56 (1.30, 1.86)
per 0.06†		*1.08 (1.00, 1.17)*		*1.24 (1.11, 1.39)*
Height-adjusted weight				
Quintile 1	238	1.11 (0.95, 1.29)	87	0.78 (0.61, 1.00)
Quintile 2	173	1.00 (0.86, 1.16)	86	1.00 (0.81, 1.24)
Quintile 3	163	0.97 (0.83, 1.13)	87	1.08 (0.88, 1.33)
Quintile 4	188	1.15 (0.99, 1.33)	105	1.38 (1.14, 1.68)
Quintile 5	199	1.23 (1.04, 1.44)	88	1.19 (0.94, 1.52)
per 10.8 kg†		*1.06 (0.97, 1.16)*		*1.20 (1.06, 1.36)*
Height-adjusted fat mass				
Quintile 1	230	1.25 (1.08, 1.44)	87	1.05 (0.84, 1.32)
Quintile 2	158	1.00 (0.85, 1.17)	70	1.00 (0.79, 1.27)
Quintile 3	192	1.21 (1.05, 1.39)	104	1.51 (1.25, 1.83)
Quintile 4	186	1.19 (1.03, 1.37)	98	1.47 (1.21, 1.80)
Quintile 5	195	1.27 (1.09, 1.48)	94	1.46 (1.17, 1.81)
per 6.9 kg†		*1.06 (0.98, 1.15)*		*1.17 (1.04, 1.31)*
Height-adjusted lean mass				
Quintile 1	254	1.13 (0.95, 1.34)	103	0.86 (0.66, 1.12)
Quintile 2	182	1.00 (0.86, 1.16)	88	1.00 (0.81, 1.24)
Quintile 3	159	0.96 (0.83, 1.12)	78	1.03 (0.83, 1.28)
Quintile 4	176	1.11 (0.95, 1.30)	91	1.31 (1.06, 1.62)
Quintile 5	190	1.24 (1.03, 1.48)	93	1.47 (1.13, 1.90)
per 7.6 kg†		*1.06 (0.92, 1.23)*		*1.23 (1.00, 1.51)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

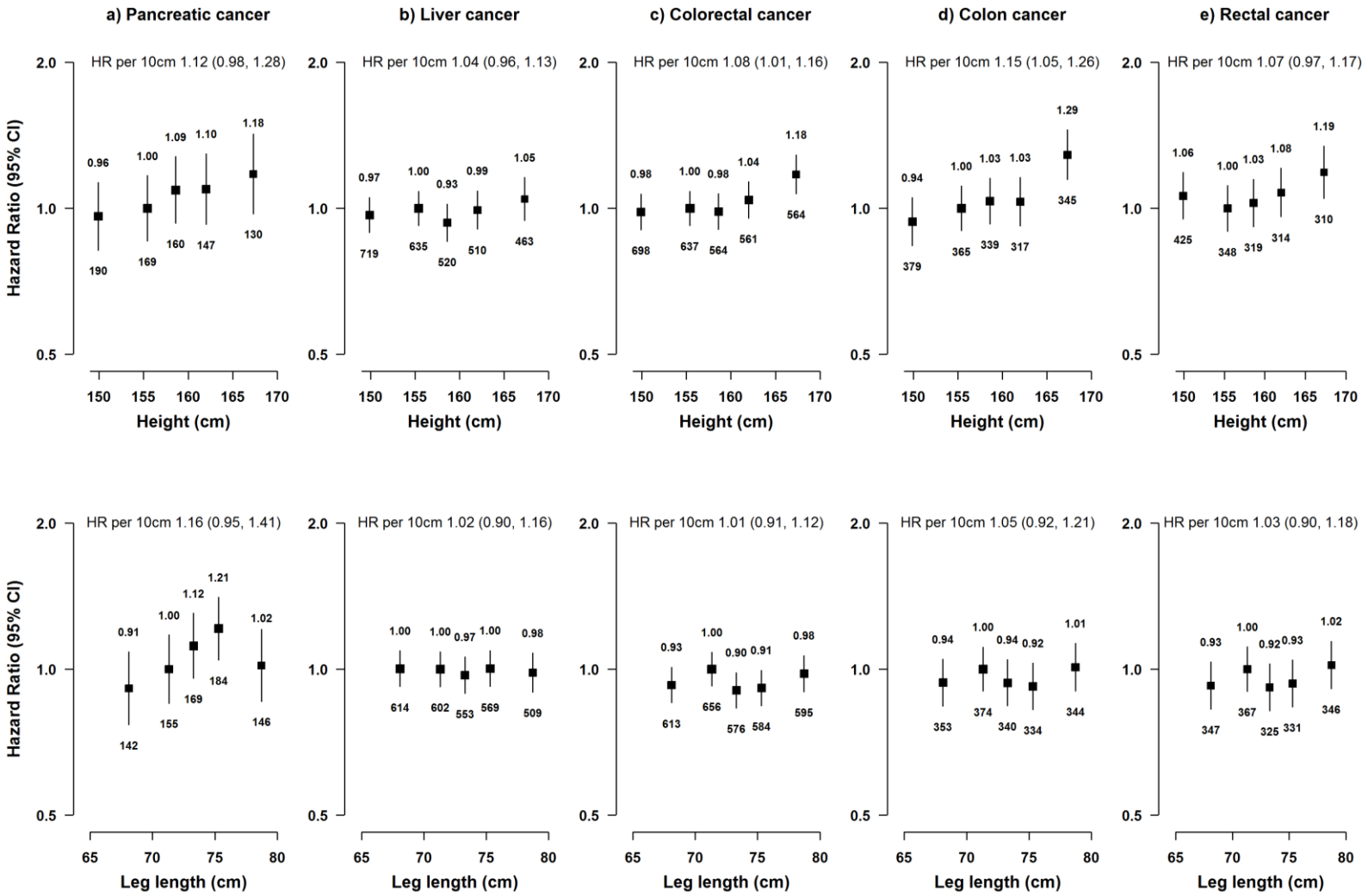
† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.99.

Appendix 7.54 Adjusted HRs for cancer by anthropometry traits*

	Height		Leg length		Sitting height	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Pancreatic cancer						
Quintile 1	190	0.96 (0.82, 1.13)	142	0.91 (0.77, 1.08)	205	0.82 (0.70, 0.96)
Quintile 2	169	1.00 (0.86, 1.16)	155	1.00 (0.85, 1.17)	187	1.00 (0.87, 1.16)
Quintile 3	160	1.09 (0.94, 1.27)	169	1.12 (0.96, 1.30)	148	0.95 (0.81, 1.11)
Quintile 4	147	1.10 (0.93, 1.29)	184	1.21 (1.05, 1.40)	133	0.98 (0.82, 1.16)
Quintile 5	130	1.18 (0.98, 1.42)	146	1.02 (0.86, 1.20)	123	1.11 (0.90, 1.35)
per 10 cm†		*1.12 (0.98, 1.28)*		*1.16 (0.95, 1.41)*		*1.16 (0.92, 1.46)*
Liver cancer						
Quintile 1	719	0.97 (0.89, 1.05)	614	1.00 (0.92, 1.09)	725	0.89 (0.82, 0.97)
Quintile 2	635	1.00 (0.93, 1.08)	602	1.00 (0.92, 1.08)	672	1.00 (0.93, 1.08)
Quintile 3	520	0.93 (0.86, 1.02)	553	0.97 (0.89, 1.06)	510	0.90 (0.82, 0.98)
Quintile 4	510	0.99 (0.91, 1.08)	569	1.00 (0.92, 1.09)	506	0.98 (0.89, 1.07)
Quintile 5	463	1.05 (0.95, 1.15)	509	0.98 (0.90, 1.08)	434	1.01 (0.90, 1.12)
per 10 cm†		*1.04 (0.96, 1.13)*		*1.02 (0.90, 1.16)*		*1.11 (0.98, 1.25)*
Colorectal cancer						
Quintile 1	698	0.98 (0.91, 1.07)	613	0.93 (0.85, 1.01)	674	0.83 (0.76, 0.90)
Quintile 2	637	1.00 (0.93, 1.08)	656	1.00 (0.93, 1.08)	674	1.00 (0.93, 1.08)
Quintile 3	564	0.98 (0.91, 1.07)	576	0.90 (0.83, 0.98)	567	0.94 (0.87, 1.02)
Quintile 4	561	1.04 (0.96, 1.13)	584	0.91 (0.84, 0.99)	585	1.06 (0.97, 1.15)
Quintile 5	564	1.18 (1.07, 1.29)	595	0.98 (0.90, 1.06)	524	1.09 (0.99, 1.21)
per 10 cm†		*1.08 (1.01, 1.16)*		*1.01 (0.91, 1.12)*		*1.25 (1.11, 1.41)*

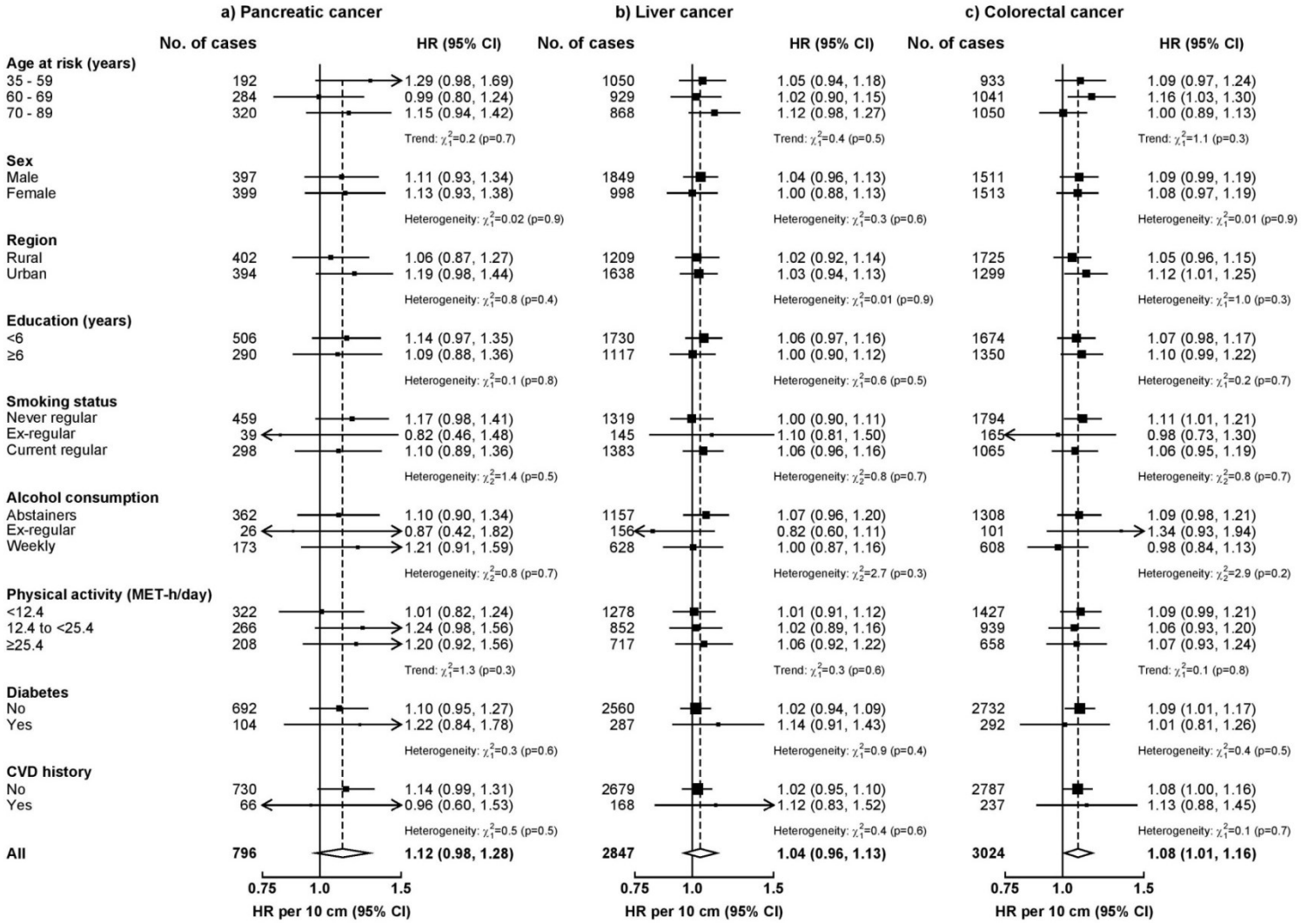
* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.
† Regression dilution ratios: height, 0.99; leg length, 0.94; sitting height, 0.93

Appendix 7.55 Associations of height and leg length with specific GI cancers



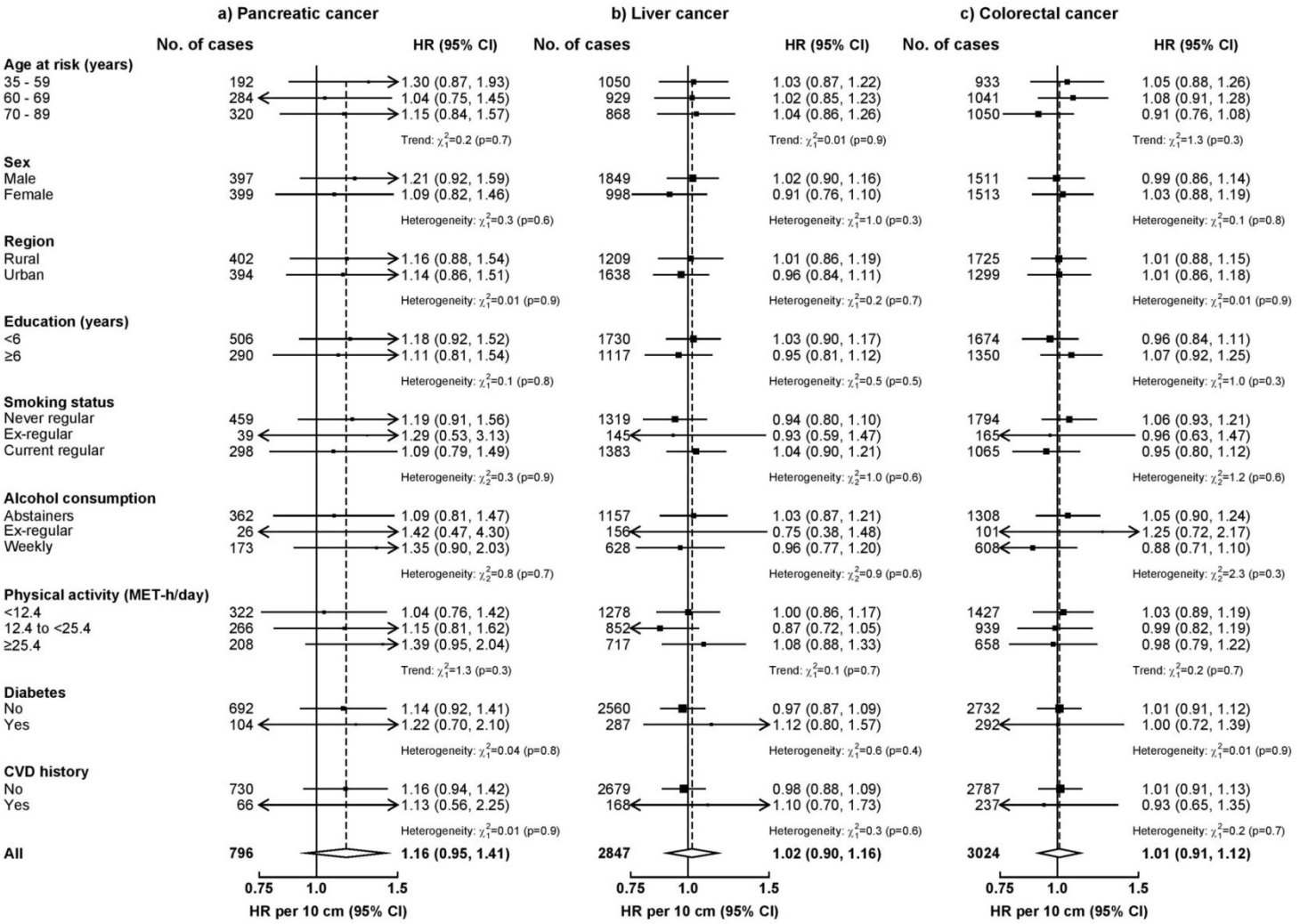
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

Appendix 7.56 Associations of height with specific GI cancers by population subgroup



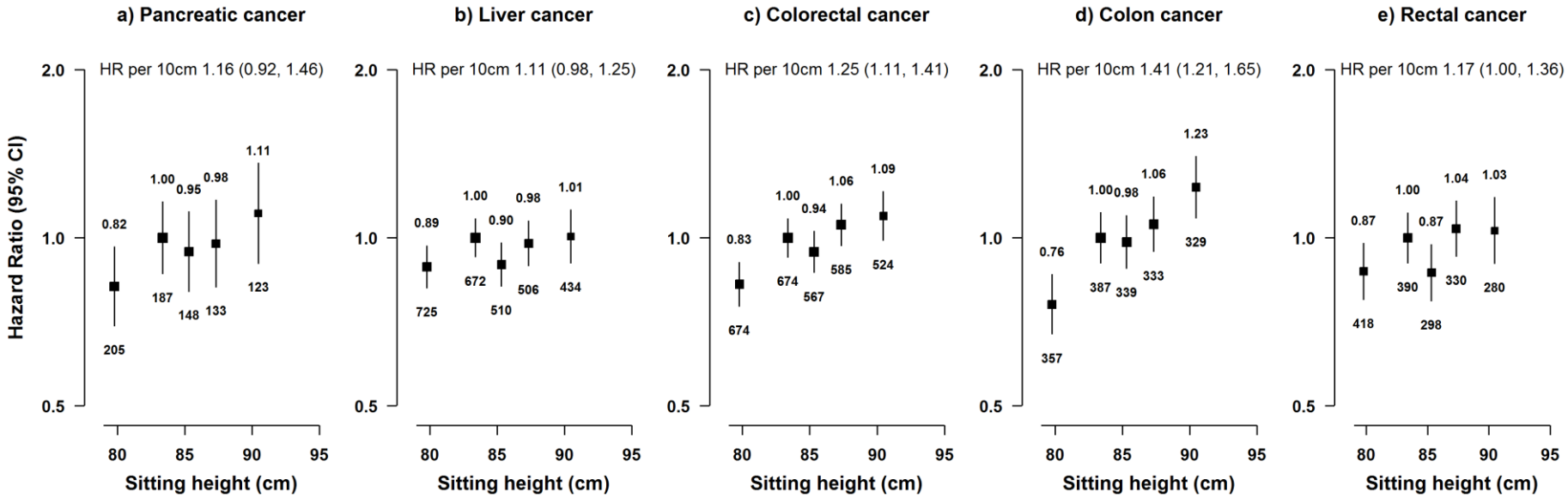
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.57 Associations of leg length with specific GI cancers by population subgroup



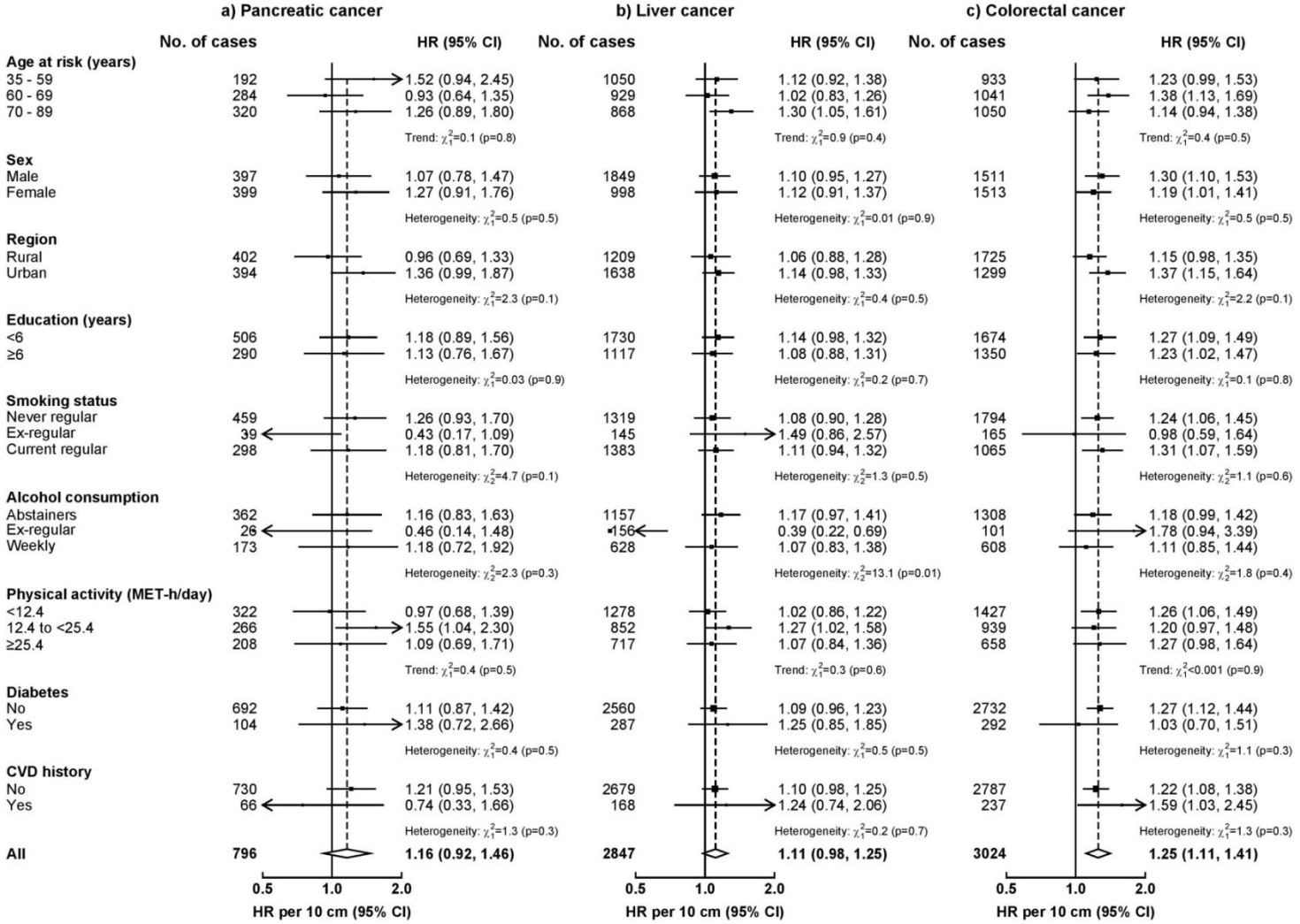
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.58 Associations of sitting height with specific GI cancers



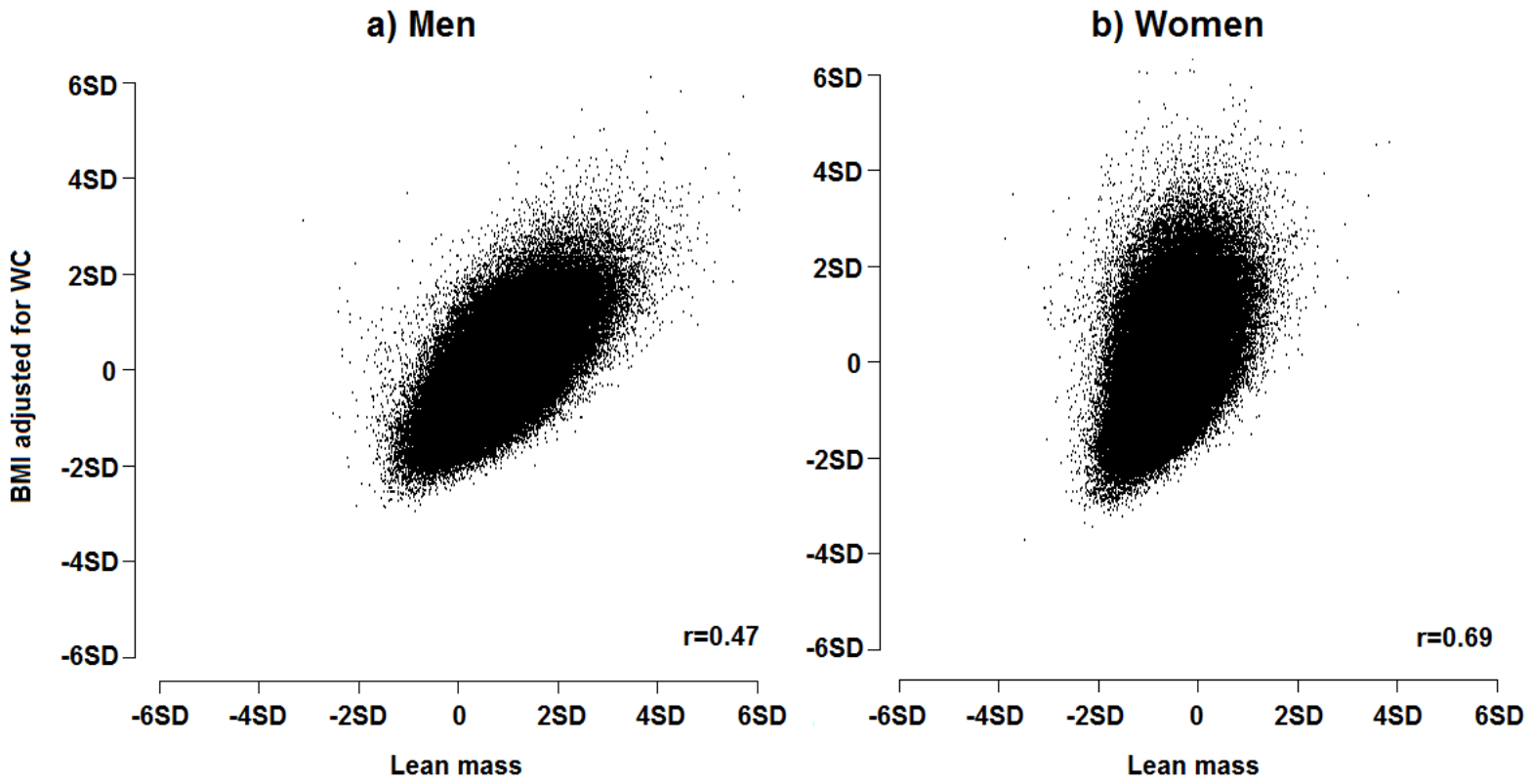
Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer. Sex-specific quintiles were used.

Appendix 7.59 Associations of sitting height with specific GI cancers by population subgroup



Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

Appendix 7.60 Correlation between BMI adjusted for WC and lean mass in men and women, separately



BMI adjusted for WC were the residuals from the regression of BMI on WC.

Appendix 8.1 Prevalence of diabetes and mean (SD) of RPG among participants without previously diagnosed diabetes*

	Urban			Rural		
	Overall	**Male**	**Female**	**Overall**	**Male**	**Female**
Diabetes, %						
Total	8.2	8.3	8.0	4.3	3.4	4.7
Previously diagnosed	4.6	4.6	4.6	2.0	1.6	2.2
Screen-detected	3.6	3.7	3.3	2.2	1.8	2.4
Medications	64.0	61.9	65.5	66.9	67.1	66.9
Random plasma glucose (mmol/L)	6.3 (2.5)	6.3 (2.6)	6.3 (2.4)	5.9 (2.2)	5.7 (2.0)	6.0 (2.3)

* Results were standardised by age, sex, and region (where appropriate).

Appendix 8.2 Associations of diabetes and RPG with specific GI cancers excluding early years of follow-up

	Excluding 2 years		Excluding 5 years	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
		Pancreatic cancer		
Diabetes status				
No diabetes	599	Reference	391	Reference
Total diabetes	81	1.49 (1.18, 1.90)	56	1.67 (1.25, 2.23)
RPG (mmol/L)				
<5.6	256	1.00 (0.88, 1.14)	166	1.00 (0.85, 1.18)
5.6 to <6.8	207	1.10 (0.96, 1.25)	129	1.10 (0.93, 1.30)
6.8 to <7.8	80	1.29 (1.03, 1.61)	55	1.46 (1.12, 1.91)
≥7.8	69	1.49 (1.17, 1.89)	50	1.80 (1.35, 2.38)
per 1 mmol/L[†]	*612*	*1.10 (1.04, 1.16)*	*400*	*1.18 (1.11, 1.26)*
		Liver cancer		
Diabetes status				
No diabetes	2060	Reference	1280	Reference
Total diabetes	225	1.46 (1.27, 1.68)	160	1.73 (1.46, 2.06)
RPG (mmol/L)				
<5.6	945	1.00 (0.93, 1.07)	587	1.00 (0.92, 1.09)
5.6 to <6.8	680	1.08 (1.00, 1.16)	432	1.13 (1.03, 1.24)
6.8 to <7.8	256	1.12 (0.99, 1.27)	156	1.14 (0.97, 1.33)
≥7.8	233	1.38 (1.21, 1.58)	146	1.45 (1.23, 1.71)
per 1 mmol/L[†]	*2114*	*1.08 (1.05, 1.12)*	*1321*	*1.12 (1.07, 1.17)*
		Colorectal cancer		
Diabetes status				
No diabetes	2362	Reference	1596	Reference
Total diabetes	249	1.17 (1.02, 1.33)	162	1.19 (1.00, 1.40)
RPG (mmol/L)				
<5.6	1040	1.00 (0.94, 1.07)	697	1.00 (0.92, 1.08)
5.6 to <6.8	858	1.10 (1.03, 1.18)	577	1.13 (1.04, 1.22)
6.8 to <7.8	292	1.09 (0.97, 1.22)	211	1.20 (1.05, 1.38)
≥7.8	250	1.27 (1.12, 1.44)	160	1.25 (1.06, 1.46)
per 1 mmol/L[†]	*2440*	*1.06 (1.03, 1.09)*	*1645*	*1.07 (1.00, 1.15)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.3 Associations of diabetes and RPG with specific GI cancers excluding smokers or drinkers

	Never regular smokers		Never regular drinkers	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
		Pancreatic cancer		
Diabetes status				
No diabetes	395	Reference	524	Reference
Total diabetes	64	1.53 (1.16, 2.01)	80	1.51 (1.19, 1.93)
RPG (mmol/L)				
<5.6	155	1.00 (0.84, 1.18)	228	1.00 (0.87, 1.15)
5.6 to <6.8	142	1.07 (0.91, 1.26)	179	1.01 (0.87, 1.16)
6.8 to <7.8	58	1.30 (1.00, 1.69)	70	1.15 (0.90, 1.45)
≥7.8	48	1.50 (1.12, 2.00)	54	1.21 (0.92, 1.58)
per 1 mmol/L[†]	*403*	*1.11 (1.04, 1.18)*	*531*	*1.06 (1.00, 1.13)*
		Liver cancer		
Diabetes status				
No diabetes	1169	Reference	1880	Reference
Total diabetes	150	1.44 (1.21, 1.71)	211	1.38 (1.19, 1.59)
RPG (mmol/L)				
<5.6	479	1.00 (0.91, 1.10)	858	1.00 (0.93, 1.08)
5.6 to <6.8	430	1.14 (1.04, 1.25)	622	1.06 (0.98, 1.14)
6.8 to <7.8	164	1.19 (1.02, 1.39)	249	1.16 (1.02, 1.31)
≥7.8	138	1.45 (1.22, 1.72)	210	1.38 (1.20, 1.58)
per 1 mmol/L[†]	*1211*	*1.08 (1.04, 1.13)*	*1939*	*1.07 (1.03, 1.10)*
		Colorectal cancer		
Diabetes status				
No diabetes	1620	Reference	2069	Reference
Total diabetes	174	1.10 (0.93, 1.29)	231	1.15 (1.00, 1.33)
RPG (mmol/L)				
<5.6	684	1.00 (0.92, 1.08)	886	1.00 (0.93, 1.07)
5.6 to <6.8	611	1.07 (0.99, 1.16)	773	1.13 (1.05, 1.21)
6.8 to <7.8	214	1.10 (0.96, 1.27)	264	1.11 (0.98, 1.25)
≥7.8	167	1.25 (1.07, 1.46)	217	1.29 (1.13, 1.48)
per 1 mmol/L[†]	*1676*	*1.04 (1.00, 1.08)*	*2140*	*1.05 (1.02, 1.09)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.4 Associations of diabetes and RPG with specific GI cancers by sex

	Men		Women	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
		Pancreatic cancer		
Diabetes status				
No diabetes	352	Reference	340	Reference
Total diabetes	45	1.64 (1.19, 2.26)	59	1.60 (1.20, 2.13)
RPG (mmol/L)				
<5.6	174	1.00 (0.85, 1.18)	129	1.00 (0.83, 1.20)
5.6 to <6.8	115	1.09 (0.91, 1.30)	124	1.06 (0.90, 1.26)
6.8 to <7.8	37	1.10 (0.80, 1.53)	53	1.32 (1.00, 1.74)
≥7.8	38	1.40 (1.01, 1.93)	39	1.38 (1.00, 1.90)
per 1 mmol/L[†]	*364*	*1.07 (0.99, 1.16)*	*345*	*1.11 (1.03, 1.18)*
		Liver cancer		
Diabetes status				
No diabetes	1675	Reference	885	Reference
Total diabetes	174	1.44 (1.23, 1.70)	113	1.41 (1.16, 1.73)
RPG (mmol/L)				
<5.6	807	1.00 (0.93, 1.08)	353	1.00 (0.89, 1.12)
5.6 to <6.8	512	1.07 (0.98, 1.17)	335	1.14 (1.02, 1.26)
6.8 to <7.8	206	1.17 (1.02, 1.35)	128	1.24 (1.04, 1.48)
≥7.8	199	1.47 (1.28, 1.70)	98	1.38 (1.13, 1.69)
per 1 mmol/L[†]	*1724*	*1.09 (1.05, 1.13)*	*914*	*1.08 (1.03, 1.13)*
		Colorectal cancer		
Diabetes status				
No diabetes	1367	Reference	1365	Reference
Total diabetes	144	1.25 (1.05, 1.49)	148	1.08 (0.91, 1.29)
RPG (mmol/L)				
<5.6	646	1.00 (0.92, 1.09)	551	1.00 (0.91, 1.09)
5.6 to <6.8	459	1.08 (0.99, 1.19)	539	1.13 (1.04, 1.22)
6.8 to <7.8	156	1.04 (0.89, 1.22)	182	1.13 (0.97, 1.31)
≥7.8	161	1.37 (1.17, 1.60)	136	1.23 (1.03, 1.46)
per 1 mmol/L[†]	*1422*	*1.08 (1.04, 1.12)*	*1408*	*1.04 (1.00, 1.08)*

[*] Model was stratified by age-at-risk (5-year), region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

P for heterogeneity by sex: diabetes: pancreatic, 0.89, liver 0.87, colorectal 0.33; RPG: pancreatic, 0.56, liver 0.62, colorectal 0.24.

Appendix 8.5 Associations of diabetes and RPG with specific GI cancers with additional adjustment for adiposity

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
	Pancreatic cancer		
Diabetes status			
No diabetes	Reference	Reference	Reference
Total diabetes	1.62 (1.31, 2.00)	1.62 (1.31, 2.01)	1.63 (1.32, 2.02)
RPG (mmol/L)			
<5.6	1.00 (0.88, 1.13)	1.00 (0.88, 1.13)	1.00 (0.88, 1.13)
5.6 to <6.8	1.07 (0.95, 1.21)	1.07 (0.95, 1.21)	1.07 (0.95, 1.21)
6.8 to <7.8	1.21 (0.98, 1.50)	1.22 (0.99, 1.50)	1.22 (0.99, 1.51)
≥7.8	1.37 (1.09, 1.73)	1.38 (1.10, 1.74)	1.39 (1.10, 1.74)
per 1 mmol/L[†]	*1.09 (1.03, 1.15)*	*1.09 (1.03, 1.15)*	*1.09 (1.04, 1.15)*
	Liver cancer		
Diabetes status			
No diabetes	Reference	Reference	Reference
Total diabetes	1.46 (1.29, 1.66)	1.45 (1.27, 1.64)	1.49 (1.31, 1.69)
RPG (mmol/L)			
<5.6	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.10 (1.03, 1.18)	1.10 (1.03, 1.17)	1.10 (1.03, 1.18)
6.8 to <7.8	1.21 (1.09, 1.35)	1.21 (1.08, 1.34)	1.21 (1.09, 1.35)
≥7.8	1.48 (1.32, 1.66)	1.46 (1.30, 1.64)	1.49 (1.33, 1.68)
per 1 mmol/L[†]	*1.09 (1.06, 1.12)*	*1.09 (1.06, 1.12)*	*1.09 (1.06, 1.12)*
	Colorectal cancer		
Diabetes status			
No diabetes	Reference	Reference	Reference
Total diabetes	1.13 (1.00, 1.28)	1.10 (0.97, 1.25)	1.14 (1.01, 1.29)
RPG (mmol/L)			
<5.6	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.10 (1.03, 1.17)	1.09 (1.03, 1.16)	1.11 (1.04, 1.17)
6.8 to <7.8	1.07 (0.96, 1.19)	1.05 (0.95, 1.18)	1.08 (0.97, 1.20)
≥7.8	1.27 (1.13, 1.43)	1.24 (1.10, 1.39)	1.28 (1.14, 1.44)
per 1 mmol/L[†]	*1.06 (1.03, 1.09)*	*1.05 (1.02, 1.08)*	*1.06 (1.03, 1.09)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG). Model 1: main model plus BMI. Model 2: main model plus WC. Model 3: main model plus %BF.

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.6 Associations of diabetes and RPG with specific GI cancers with additional adjustment for PA and SLT

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Diabetes status			
No diabetes	Reference	Reference	Reference
Total diabetes	1.63 (1.32, 2.02)	1.42 (1.25, 1.61)	1.15 (1.01, 1.30)
RPG (mmol/L)			
<5.6	1.00 (0.88, 1.13)	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.07 (0.95, 1.21)	1.09 (1.02, 1.17)	1.11 (1.04, 1.18)
6.8 to <7.8	1.22 (0.99, 1.51)	1.20 (1.07, 1.33)	1.09 (0.98, 1.21)
≥7.8	1.39 (1.10, 1.74)	1.43 (1.28, 1.61)	1.30 (1.16, 1.46)
per 1 mmol/L[†]	*1.09 (1.04, 1.15)*	*1.08 (1.06, 1.11)*	*1.06 (1.03, 1.09)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, fasting hours (for RPG), total PA, and SLT.
[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.7 Associations of diabetes and RPG with specific GI cancers with additional adjustment for diet

	Pancreatic cancer	Liver cancer	Colorectal cancer
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Diabetes status			
No diabetes	Reference	Reference	Reference
Total diabetes	1.55 (1.24, 1.92)	1.44 (1.27, 1.63)	1.14 (1.01, 1.29)
RPG (mmol/L)			
<5.6	1.00 (0.88, 1.13)	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.07 (0.95, 1.22)	1.09 (1.02, 1.17)	1.11 (1.04, 1.18)
6.8 to <7.8	1.22 (0.99, 1.50)	1.19 (1.07, 1.33)	1.09 (0.98, 1.22)
≥7.8	1.39 (1.11, 1.74)	1.44 (1.28, 1.62)	1.30 (1.16, 1.46)
per 1 mmol/L[†]	*1.09 (1.04, 1.15)*	*1.09 (1.06, 1.12)*	*1.06 (1.03, 1.09)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, fasting hours (for RPG), and dietary variables (fresh fruits, fresh vegetables, red meat, poultry, fish/seafood, dairy products, soybean products, fresh eggs, rice, wheat, other staple food, and preserved vegetables).
[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.8 Associations of diabetes and RPG with specific GI cancers excluding poor self-rated health or major chronic diseases

	Excluding poor self-rated health		Excluding major chronic diseases	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
		Pancreatic cancer		
Diabetes status				
No diabetes	605	Reference	498	Reference
Total diabetes	79	1.61 (1.27, 2.05)	69	1.75 (1.35, 2.27)
RPG (mmol/L)				
<5.6	275	1.00 (0.88, 1.14)	224	1.00 (0.87, 1.15)
5.6 to <6.8	201	1.02 (0.89, 1.16)	171	1.05 (0.91, 1.22)
6.8 to <7.8	79	1.22 (0.98, 1.53)	66	1.25 (0.98, 1.60)
≥7.8	69	1.41 (1.11, 1.80)	52	1.33 (1.01, 1.75)
per 1 mmol/L[†]	*624*	*1.09 (1.03, 1.15)*	*513*	*1.08 (1.01, 1.15)*
		Liver cancer		
Diabetes status				
No diabetes	2196	Reference	1736	Reference
Total diabetes	218	1.44 (1.25, 1.66)	182	1.52 (1.30, 1.78)
RPG (mmol/L)				
<5.6	1005	1.00 (0.94, 1.07)	808	1.00 (0.93, 1.08)
5.6 to <6.8	729	1.10 (1.02, 1.18)	557	1.04 (0.96, 1.13)
6.8 to <7.8	277	1.16 (1.03, 1.31)	227	1.18 (1.03, 1.35)
≥7.8	246	1.41 (1.24, 1.60)	194	1.39 (1.20, 1.60)
per 1 mmol/L[†]	*2257*	*1.08 (1.05, 1.12)*	*1786*	*1.08 (1.05, 1.12)*
		Colorectal cancer		
Diabetes status				
No diabetes	2459	Reference	2021	Reference
Total diabetes	244	1.20 (1.05, 1.37)	207	1.28 (1.10, 1.48)
RPG (mmol/L)				
<5.6	1091	1.00 (0.94, 1.07)	906	1.00 (0.93, 1.07)
5.6 to <6.8	896	1.10 (1.04, 1.18)	736	1.11 (1.03, 1.19)
6.8 to <7.8	307	1.11 (0.99, 1.25)	249	1.12 (0.99, 1.27)
≥7.8	260	1.29 (1.14, 1.46)	216	1.34 (1.17, 1.54)
per 1 mmol/L[†]	*2554*	*1.07 (1.04, 1.10)*	*2107*	*1.07 (1.04, 1.11)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG). Major chronic diseases included CVD, tuberculosis, respiratory diseases, chronic liver diseases, gall bladder disease, peptic ulcer, and kidney disease.

[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 8.9 Associations of diabetes and RPG with mortality of cancer

	Pancreatic cancer		Liver cancer		Colorectal cancer	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Diabetes status						
No diabetes	493	Reference	1807	Reference	866	Reference
Total diabetes	76	1.59 (1.24, 2.04)	214	1.52 (1.32, 1.76)	95	1.18 (0.95, 1.47)
Diabetes status						
No diabetes	493	1.00 (0.90, 1.11)	1807	1.00 (0.95, 1.06)	866	1.00 (0.92, 1.08)
Screen-detected	27	1.39 (0.95, 2.02)	103	1.65 (1.36, 2.00)	50	1.48 (1.12, 1.95)
Previously diagnosed	49	1.74 (1.30, 2.32)	111	1.42 (1.17, 1.72)	45	0.96 (0.71, 1.29)
RPG (mmol/L)						
<5.6	214	1.00 (0.86, 1.16)	807	1.00 (0.93, 1.08)	373	1.00 (0.90, 1.12)
5.6 to <6.8	166	1.05 (0.90, 1.22)	613	1.15 (1.07, 1.24)	317	1.10 (0.99, 1.23)
6.8 to <7.8	66	1.27 (1.00, 1.63)	245	1.27 (1.12, 1.45)	99	0.97 (0.80, 1.19)
≥7.8	57	1.46 (1.12, 1.91)	206	1.45 (1.26, 1.67)	108	1.47 (1.21, 1.78)
RPG (mmol/L)						
<4.3	21	1.00 (0.65, 1.54)	121	1.00 (0.83, 1.20)	50	1.00 (0.75, 1.32)
4.3 to <5.8	238	1.27 (1.11, 1.46)	840	1.17 (1.09, 1.25)	406	0.99 (0.89, 1.10)
5.8 to <7.0	142	1.30 (1.10, 1.53)	525	1.29 (1.18, 1.40)	259	1.02 (0.90, 1.15)
7.0 to <7.8	45	1.46 (1.09, 1.96)	179	1.42 (1.23, 1.65)	74	0.96 (0.76, 1.21)
7.8 to <11.1	39	1.62 (1.18, 2.23)	132	1.39 (1.17, 1.66)	82	1.44 (1.15, 1.79)
≥11.1	18	2.21 (1.39, 3.52)	74	2.27 (1.81, 2.86)	26	1.32 (0.90, 1.95)
per 1 mmol/L[†]	*503*	*1.09 (1.04, 1.15)*	*1871*	*1.09 (1.06, 1.12)*	*897*	*1.06 (1.03, 1.09)*

[*] Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).
[†] Regression dilution ratios: RPG, 0.53. RPG was missing in 8124 participants.

Appendix 9.1 Associations of BMI and proteomics in CKB

1. Methods

1.1 Study population

The case-subcohort study was designed to examine the associations of proteomics with risk of pancreatic cancer. All 700 cases of pancreatic cancer (ICD-10: C25) that accumulated until 1 January 2016 were included. A subcohort of 700 participants was sampled at random from the baseline cohort. The analysis of BMI and proteomics was conducted in the subcohort.

1.2 Proteomics assay

The OLINK Immuno-Oncology assay measures 92 protein biomarkers selected to include proteins involved in promotion and inhibition of tumour immunity, chemotaxis, vascular and tissue remodelling, apoptosis and cell killing, and metabolism and autophagy. **Table A1** shows the 92 protein markers quantified by the OLINK assay. The OLINK method is based on the proximity extension assay (PEA).[1] In the PEA technology, there are 92 oligonucleotide labelled antibody probe pairs that are allowed to bind to their respective target protein in the sample. A polymerase chain reaction (PCR) reporter sequence is formed by a proximity dependent DNA polymerisation event and amplified, which is then detected and quantified by the use of real-time PCR. Details of the OLINK assay have been reported elsewhere, including measurements of assay performance and validations of the OLINK method.[1,2]

The stored baseline plasma samples for the cases and subcohort were retrieved, thawed, and subaliquoted at the Wolfson laboratory, CTSU, and 100 uL aliquots

were shipped on dry ice to the OLINK Laboratory at Uppsala, Sweden, for the OLINK Immuno-Oncology assay (Olink Biosciences, Uppsala, Sweden) to quantify 92 circulating protein markers. Samples from cases and subcohort were analysed in random order, with laboratory staff blinded to case or subcohort status. The native scale of OLINK protein measurements is log(2) to ensure normal distributions. In the OLINK assay, limit of detection (LOD) was defined as 3 standard deviations above background. The LODs for 92 proteins are shown in **Table A2**. For samples below the LOD, a value equal to the LOD was assigned. Samples that had either a quality control warning or precipitation were excluded from the analysis. In total 638 participants in the subcohort remained in the analysis.

1.3 Statistical methods

All protein biomarkers were standardised to have a standard deviation (SD) of 1. Linear regression was used to assess the associations of BMI with protein markers, adjusted for age at baseline (continuous), sex, region (10 regions), education (4 groups: no formal school, primary school, middle/high school, or college/university), household income (6 groups: <2500, 2500-4999, 5000-9999, 10,000-19,999, 20,000-34,999, ≥35,000 RMB), smoking (3 groups: never regular, former regular, or current regular), alcohol (5 groups: abstainers, ex-drinkers, reduced-intake drinkers, occasional drinkers, or drinkers), self-rated health (4 groups: excellent, good, fair, or poor), intake of fruit and meat (5 groups: daily, 4-6 days/week, 1-3 days/week, monthly, or never/rarely), and fasting time (continuous). For each biomarker, adjusted SD differences and 95% CI associated with 1-SD higher (3.4 kg/m^2) usual BMI were estimated, adjusting for regression dilution

using repeated measures of adiposity in the resurvey. For the 12 protein markers with >70% of samples below the LOD, a dichotomous variable was generated for each individual (1 >LOD, 0 ≤LOD), and logistic regression was used to assess the associations of BMI with protein markers >LOD. To explore the dose-response relationships between BMI and proteomics, BMI was also modelled as a categorical variable (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, ≥27.5 kg/m^2). To account for the large number of highly correlated protein markers, false discovery rate-corrected (FDR) *p*-values <0.05 were used.[3]

Table A1. List of 92 proteins quantified by the OLINK assay

Label	Names	Biological process			
ADA	Adenosine Deaminase	M			V
ADGRG1	Adhesion G-protein coupled receptor G1				
ANG1	Angiopoietin-1				V
ANGPT2	Angiopoietin-2				V
ARG1	Arginase-1				
CAIX	Carbonic anhydrase IX	M			V
CASP8	Caspase-8	A			
CCL3	C-C motif chemokine 3	C			
CCL4	C-C motif chemokine 4	C			
CCL17	C-C motif chemokine 17	C		S	
CCL19	C-C motif chemokine 19	C		S	
CCL20	C-C motif chemokine 20	C		S	
CCL23	C-C motif chemokine 23	C			V
CD4	T-cell surface glycoprotein CD4		P	S	
CD5	T-cell surface glycoprotein CD5		P	S	
CD8A	T-cell surface glycoprotein CD8 alpha chain		P		
CD27	CD27 antigen		P		
CD28	T-cell surface glycoprotein CD28		P		
CD40	CD40L receptor		P		
CD40L	CD40-L	A	P		
CD70	CD70 antigen		P		
CD83	CD83 antigen		P		
CD244	Natural killer cell receptor 2B4		P		
CRTAM	Cytotoxic and regulatory T-cell molecule		P		
CSF1	Macrophage colony-stimulating factor 1			S	
CX3CL1	Fractalkine	C	P		
CXCL1	C-X-C motif chemokine 1	C		S	V
CXCL5	C-X-C motif chemokine 5	C		S	V
CXCL9	C-X-C motif chemokine 9	C	P		V
CXCL10	C-X-C motif chemokine 10	C	P		V
CXCL11	C-X-C motif chemokine 11	C	P	S	V
CXCL12	Stromal cell-derived factor 1	C		S	V
CXCL13	C-X-C motif chemokine 13	C	P	S	
DCN	Decorin				V
EGF	Pro-epidermal growth factor				V
FasL	Fas antigen ligand	A			
FGF2	Fibroblast growth factor 2				V
Gal1	Galectin-1			S	V
Gal9	Galectin-9	A		S	V
GZMA	Granzyme A	A			
GZMB	Granzyme B	A			
GZMH	Granzyme H	A			
HGF	Hepatocyte growth factor				V
HO1	Heme oxygenase 1	M			
ICOSLG	ICOS ligand		P		
IFN beta	Interferon beta		P		
IFN gamma	Interferon gamma		P		
IL1 alpha	Interleukin-1 alpha		P	S	V

Abbreviations: A, apoptosis/cell killing; C, chemotaxis; M, metabolism/autophagy; P, promote tumour immunity; S, supress tumour immunity; V, vascular & tissue remodelling.

Table A1. Continued

Label	Names	Biological process			
IL2	Interleukin-2		P		
IL4	Interleukin-4			S	
IL5	Interleukin-5			S	
IL6	Interleukin-6		P	S	
IL7	Interleukin-7		P		
IL8	Interleukin-8	C		S	V
IL10	Interleukin-10			S	
IL12	Interleukin-12				
IL12RB1	Interleukin-12 receptor subunit beta-1		P		
IL13	Interleukin-13			S	
IL18	Interleukin-18		P	S	
IL21	Interleukin-21		P		
IL33	Interleukin-33			S	
IL35	Interleukin-35			S	
KLRD1	Natural killer cells antigen CD94		P		
LAMP3	Lysosome-associated membrane glycoprotein 3			S	
LAP TGF-beta-1	Latency-associated peptide transforming growth factor beta-1			S	
MCP1	Monocyte chemotactic protein 1	C			V
MCP2	Monocyte chemotactic protein 2	C			
MCP3	Monocyte chemotactic protein 3	C			
MCP4	Monocyte chemotactic protein 4	C		S	V
MIC-A/B	MHC class I polypeptide-related sequence A/B			S	
MMP7	Matrix metalloproteinase-7	A		S	
MMP12	Matrix metalloproteinase-12			S	V
NCR1	Natural cytotoxicity triggering receptor 1		P		
NOS3	Nitric oxide synthase, endothelial				V
PD L1	Programmed cell death 1 ligand 1			S	
PD L2	Programmed cell death 1 ligand 2			S	
PDCD1	Programmed cell death protein 1			S	
PDGF subunit B	Platelet-derived growth factor subunit B				V
PGF	Placenta growth factor				V
PTN	Pleiotrophin				V
TIE2	Angiopoietin-1 receptor				V
TNF	Tumour necrosis factor alpha		P	S	V
TNFRSF4	Tumour necrosis factor receptor superfamily member 4		P		
TNFRSF9	Tumour necrosis factor receptor superfamily member 9		P		
TNFRSF12A	Tumour necrosis factor receptor superfamily member 12A	A			V
TNFRSF21	Tumour necrosis factor receptor superfamily member 21	A			
TNFSF14	Tumour necrosis factor ligand superfamily member 14		P		
TRAIL	TNF-related apoptosis-inducing ligand	A			
TWEAK	Tumour necrosis factor (Ligand) superfamily, member 12	A			V
VEGFA	Vascular endothelial growth factor A				V
VEGFC	Vascular endothelial growth factor C				V
VEGFR2	Vascular endothelial growth factor receptor 2				V

Abbreviations: A, apoptosis/cell killing; C, chemotaxis; M, metabolism/autophagy; P, promote tumour immunity; S, supress tumour immunity; V, vascular & tissue remodelling.

Table A2. Limit of detection (LOD) of 92 protein biomarkers*

Protein	LOD	No. <LOD	% <LOD
ADA	0.267	0	0
ADGRG1	1.152	430	67.4
ANG1	0.800	0	0
ANGPT2	0.620	0	0
ARG1	1.591	74	11.6
CAIX	0.149	0	0
CASP8	1.299	0	0
CCL3	0.925	0	0
CCL4	0.645	0	0
CCL17	0.483	0	0
CCL19	1.101	0	0
CCL20	1.217	0	0
CCL23	0.338	0	0
CD4	-1.608	0	0
CD5	-0.071	0	0
CD8A	0.776	0	0
CD27	0.391	0	0
CD28	0.538	32	5.0
CD40	0.807	0	0
CD40L	1.506	1	0.2
CD70	1.065	0	0
CD83	0.110	0	0
CD244	1.476	0	0
CRTAM	0.749	0	0
CSF1	1.012	0	0
CX3CL1	1.044	0	0
CXCL1	0.986	0	0
CXCL5	1.564	0	0
CXCL9	0.721	0	0
CXCL10	0.877	0	0
CXCL11	0.785	0	0
CXCL12	0.920	295	46.2
CXCL13	1.379	0	0
DCN	0.366	0	0
EGF	0.289	0	0
FasL	0.479	0	0
FGF2	0.479	527	82.6
Gal1	1.537	0	0
Gal9	0.606	0	0
GZMA	0.991	2	0.3
GZMB	0.758	0	0
GZMH	1.600	0	0
HGF	0.608	0	0
HO1	1.431	0	0
ICOSLG	0.901	0	0
IFN beta	0.442	624	97.8
IFN gamma	0.760	625	98.0
IL1 alpha	0.423	632	99.1

Table A2. Continued

Protein	LOD	No. <LOD	% <LOD
IL2	0.923	637	99.8
IL4	0.995	629	98.6
IL5	2.199	451	70.7
IL6	1.118	0	0
IL7	0.924	0	0
IL8	1.028	0	0
IL10	1.465	47	7.4
IL12	1.296	0	0
IL12RB1	1.101	8	1.3
IL13	1.429	633	99.2
IL18	1.640	0	0
IL21	1.437	638	99.8
IL33	0.930	624	97.8
IL35	2.463	638	99.0
8KLRD1	0.721	0	0
LAMP3	1.043	0	0
LAP TGF-beta-1	-0.712	0	0
MCP1	0.662	0	0
MCP2	0.897	0	0
MCP3	1.219	210	32.9
MCP4	0.125	0	0
MIC-A/B	0.545	149	23.4
MMP12	0.480	0	0
MMP7	1.556	5	0.8
NCR1	1.702	0	0
NOS3	1.383	381	59.7
PD L1	1.804	0	0
PD L2	0.728	1	0.2
PDCD1	1.426	1	0.2
PDGF subunit B	0.164	0	0
PGF	0.698	0	0
PTN	0.078	178	27.9
TIE2	0.553	0	0
TNF	1.804	601	94.2
TNFRSF4	1.545	0	0
TNFRSF9	-0.385	0	0
TNFRSF12A	0.503	0	0
TNFRSF21	0.136	0	0
TNFSF14	0.306	0	0
TRAIL	0.156	0	0
TWEAK	-0.421	0	0
VEGFA	0.762	0	0
VEGFC	-0.284	177	27.7
VEGFR2	0.068	0	0

2. Results

Table A3 shows the associations of BMI with proteomics. After correcting for multiple comparisons, BMI showed significant associations with 35 protein biomarkers, including positive associations for 32 and inverse associations for 3 protein biomarkers (i.e. CAIX, FasL, and TWEAK). **Table A4** shows the associations of BMI with proteomics by protein classes. However, it should be noted that one protein may belong to multiple classes. For example, CXCL1, IL6, and CSF1 are both cytokines and growth factors. BMI showed associations with chemokines, inflammatory cytokines and receptors (IL, IFN, TNF, and TNFR families), growth factors and receptors (including VEGF family), enzymes, cell surface proteins, and other secreted proteins (DCN, Gal1, and Gal9). For chemokines, BMI was positively associated with CCL3, CCL19, CCL20, CXCL10, MCP1, and MCP3. For ILs, BMI showed positive associations with IL6, IL12, and IL18. For TNF, BMI was positively associated with CD70, TNFSF14, and TRAIL, and inversely with FasL and TWEAK. For TNFR, there was a positive association for TNFRSF12A. For growth factors, BMI was positively related to CSF1, HGF, PGF, PTN, and VEGFA, and was also positively associated with a growth factor receptor VEGFR2. For enzymes, there were positive associations for ADA, ARG1, CASP8, GZMA, GZMB, and NOS3, and an inverse association for CAIX. For cell surface proteins, the associations were overall weak, including positive associations for ADGRG1, CD5, CD83, and KLRD1. For other secreted proteins, there were strong positive associations for DCN, Gal1, and Gal9. For the 12 protein markers with >70% below the LOD, BMI was associated with higher levels of ADGRG1 and NOS3 (OR for >LOD per 1-SD higher BMI: ADGRG1 1.37 [1.11-9.76], NOS3 1.54 [1.26-10.91]) but not with other protein markers. When

examining the dose-response relationships (**Figures A1-A7**), the associations with BMI were approximately linear for chemokines (MCP1, MCP3, CCL3, CCL4, CCL19, CCL20, and CXCL10), ILs (IL6 and IL18), TNF and TNFR (FasL, TNFRSF12A, TNFSF14, TRAIL, and TWEAK), growth factors (HGF and PGF), enzymes (ADA and GZMA), and other secreted proteins (DCN, Gal1, and Gal9).

Table A3. Associations of BMI with proteomics

Proteins	SD difference (95% CI)	*P*-value
ADA	0.181 (0.099, 0.263)	**
ADGRG1	0.104 (0.023, 0.186)	*
ANG1	0.028 (-0.050, 0.106)	-
ANGPT2	0.045 (-0.040, 0.130)	-
ARG1	0.168 (0.081, 0.254)	**
CAIX	-0.114 (-0.199, -0.028)	*
CASP8	0.228 (0.135, 0.320)	***
CCL3	0.159 (0.073, 0.244)	**
CCL4	0.079 (-0.009, 0.168)	-
CCL17	-0.001 (-0.078, 0.076)	-
CCL19	0.225 (0.142, 0.308)	***
CCL20	0.122 (0.031, 0.213)	*
CCL23	-0.035 (-0.119, 0.049)	-
CD4	0.094 (0.008, 0.180)	-
CD5	0.099 (0.018, 0.181)	*
CD8A	0.052 (-0.040, 0.143)	-
CD27	-0.015 (-0.095, 0.065)	-
CD28	0.058 (-0.017, 0.134)	-
CD40	0.091 (0.007, 0.174)	-
CD40L	0.040 (-0.044, 0.124)	-
CD70	0.137 (0.057, 0.218)	**
CD83	0.106 (0.023, 0.189)	*
CD244	0.074 (-0.011, 0.159)	-
CRTAM	-0.001 (-0.083, 0.080)	-
CSF1	0.208 (0.126, 0.290)	***
CX3CL1	-0.012 (-0.098, 0.074)	-
CXCL1	0.044 (-0.039, 0.128)	-
CXCL5	0.051 (-0.029, 0.131)	-
CXCL9	0.006 (-0.079, 0.092)	-
CXCL10	0.146 (0.063, 0.229)	**
CXCL11	0.043 (-0.047, 0.134)	-
CXCL12	-0.055 (-0.145, 0.036)	-
CXCL13	0.012 (-0.069, 0.094)	-
DCN	0.147 (0.064, 0.229)	**
EGF	0.086 (0.001, 0.171)	-
FasL	-0.101 (-0.181, -0.021)	*
FGF2	0.027 (-0.059, 0.113)	-
Gal1	0.288 (0.210, 0.366)	***
Gal9	0.220 (0.143, 0.297)	***
GZMA	0.135 (0.049, 0.221)	**
GZMB	0.151 (0.066, 0.237)	**
GZMH	0.063 (-0.023, 0.149)	-
HGF	0.336 (0.263, 0.409)	***
HO1	0.064 (-0.020, 0.148)	-
ICOSLG	-0.098 (-0.190, -0.006)	-
IFN beta	0.010 (-0.080, 0.100)	-
IFN gamma	-0.033 (-0.105, 0.039)	-

Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.
P-value: - $p>0.05$; * $p<0.05$; ** $p<0.01$; ***$p<0.001$.

Table A3. Continued

Proteins	SD difference (95% CI)	*P*-value
IL1 alpha	0.017 (-0.079, 0.114)	-
IL2	-0.001 (-0.002, 0.001)	-
IL4	0.003 (-0.103, 0.108)	-
IL5	0.086 (-0.014, 0.185)	-
IL6	0.254 (0.167, 0.340)	***
IL7	0.050 (-0.041, 0.140)	-
IL8	0.046 (-0.045, 0.136)	-
IL10	0.074 (-0.010, 0.158)	-
IL12	0.138 (0.060, 0.216)	**
IL12RB1	0.045 (-0.042, 0.131)	-
IL13	-0.071 (-0.173, 0.030)	-
IL18	0.175 (0.092, 0.258)	**
IL21	0.000 (-0.000, 0.000)	-
IL33	-0.031 (-0.078, 0.016)	-
IL35	0.000 (-0.000, 0.000)	-
KLRD1	0.103 (0.018, 0.189)	*
LAMP3	0.007 (-0.068, 0.081)	-
LAP TGF-beta-1	0.088 (0.002, 0.173)	-
MCP1	0.145 (0.059, 0.230)	**
MCP2	-0.020 (-0.106, 0.065)	-
MCP3	0.115 (0.046, 0.183)	**
MCP4	0.080 (-0.001, 0.161)	-
MIC-A/B	0.055 (-0.031, 0.141)	-
MMP7	0.068 (-0.021, 0.158)	-
MMP12	-0.008 (-0.082, 0.067)	-
NCR1	0.073 (-0.017, 0.163)	-
NOS3	0.120 (0.039, 0.201)	*
PD L1	0.056 (-0.034, 0.147)	-
PD L2	0.013 (-0.069, 0.096)	-
PDCD1	0.032 (-0.063, 0.126)	-
PDGF subunit B	0.047 (-0.032, 0.127)	-
PGF	0.195 (0.113, 0.278)	***
PTN	0.071 (0.013, 0.130)	*
TIE2	0.049 (-0.037, 0.135)	-
TNF	-0.011 (-0.104, 0.082)	-
TNFRSF4	0.054 (-0.029, 0.137)	-
TNFRSF9	0.065 (-0.019, 0.150)	-
TNFRSF12A	0.151 (0.070, 0.232)	**
TNFRSF21	0.017 (-0.069, 0.102)	-
TNFSF14	0.309 (0.222, 0.396)	***
TRAIL	0.256 (0.162, 0.351)	***
TWEAK	-0.145 (-0.230, -0.060)	**
VEGFA	0.246 (0.169, 0.323)	***
VEGFC	0.003 (-0.081, 0.087)	-
VEGFR2	0.180 (0.094, 0.265)	**

Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.
P-value: - $p>0.05$; * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Table A4. Associations of BMI with proteomics by classes

Proteins	SD difference (95% CI)	*P*-value
Chemokines		
CCL3	0.159 (0.073, 0.244)	**
CCL4	0.079 (-0.009, 0.168)	-
CCL17	-0.001 (-0.078, 0.076)	-
CCL19	0.225 (0.142, 0.308)	***
CCL20	0.122 (0.031, 0.213)	*
CCL23	-0.035 (-0.119, 0.049)	-
CX3CL1	-0.012 (-0.098, 0.074)	-
CXCL1	0.044 (-0.039, 0.128)	-
CXCL5	0.051 (-0.029, 0.131)	-
CXCL9	0.006 (-0.079, 0.092)	-
CXCL10	0.146 (0.063, 0.229)	**
CXCL11	0.043 (-0.047, 0.134)	-
CXCL12	-0.055 (-0.145, 0.036)	-
CXCL13	0.012 (-0.069, 0.094)	-
MCP1	0.145 (0.059, 0.230)	**
MCP2	-0.020 (-0.106, 0.065)	-
MCP3	0.115 (0.046, 0.183)	**
MCP4	0.080 (-0.001, 0.161)	-
Interleukins family		
IL1 alpha	0.017 (-0.079, 0.114)	-
IL2	-0.001 (-0.002, 0.001)	-
IL4	0.003 (-0.103, 0.108)	-
IL5	0.086 (-0.014, 0.185)	-
IL6	0.254 (0.167, 0.340)	***
IL7	0.050 (-0.041, 0.140)	-
IL8	0.046 (-0.045, 0.136)	-
IL10	0.074 (-0.010, 0.158)	-
IL12	0.138 (0.060, 0.216)	**
IL12RB1	0.045 (-0.042, 0.131)	-
IL13	-0.071 (-0.173, 0.030)	-
IL18	0.175 (0.092, 0.258)	**
IL21	0.000 (-0.000, 0.000)	-
IL33	-0.031 (-0.078, 0.016)	-
IL35	0.000 (-0.000, 0.000)	-
IFN family		
IFN beta	0.010 (-0.080, 0.100)	-
IFN gamma	-0.033 (-0.105, 0.039)	-

Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.
P-value: - $p>0.05$; * $p<0.05$; ** $p<0.01$; ***$p<0.001$.

Table A4. Continued

Proteins	SD difference (95% CI)	*P*-value
TNF/TNFR family		
CD27	-0.015 (-0.095, 0.065)	-
CD40	0.091 (0.007, 0.174)	-
CD40L	0.040 (-0.044, 0.124)	-
CD70	0.137 (0.057, 0.218)	**
FasL	-0.101 (-0.181, -0.021)	*
TNF	-0.011 (-0.104, 0.082)	-
TNFRSF4	0.054 (-0.029, 0.137)	-
TNFRSF9	0.065 (-0.019, 0.150)	-
TNFRSF12A	0.151 (0.070, 0.232)	**
TNFRSF21	0.017 (-0.069, 0.102)	-
TNFSF14	0.309 (0.222, 0.396)	***
TRAIL	0.256 (0.162, 0.351)	***
TWEAK	-0.145 (-0.230, -0.060)	**
Growth factors		
ANG1	0.028 (-0.050, 0.106)	-
ANGPT2	0.045 (-0.040, 0.130)	-
CSF1	0.208 (0.126, 0.290)	***
EGF	0.086 (0.001, 0.171)	-
FGF2	0.027 (-0.059, 0.113)	-
HGF	0.336 (0.263, 0.409)	***
LAP TGF-beta-1	0.088 (0.002, 0.173)	-
PDGF subunit B	0.047 (-0.032, 0.127)	-
PGF	0.195 (0.113, 0.278)	***
PTN	0.071 (0.013, 0.130)	*
VEGFA	0.246 (0.169, 0.323)	***
VEGFC	0.003 (-0.081, 0.087)	-
VEGFR2	0.180 (0.094, 0.265)	**
Enzymes		
ADA	0.181 (0.099, 0.263)	**
ARG1	0.168 (0.081, 0.254)	**
CAIX	-0.114 (-0.199, -0.028)	*
CASP8	0.228 (0.135, 0.320)	***
GZMA	0.135 (0.049, 0.221)	**
GZMB	0.151 (0.066, 0.237)	**
GZMH	0.063 (-0.023, 0.149)	-
HO1	0.064 (-0.020, 0.148)	-
MMP7	0.068 (-0.021, 0.158)	-
MMP12	-0.008 (-0.082, 0.067)	-
NOS3	0.120 (0.039, 0.201)	*
TIE2	0.049 (-0.037, 0.135)	-

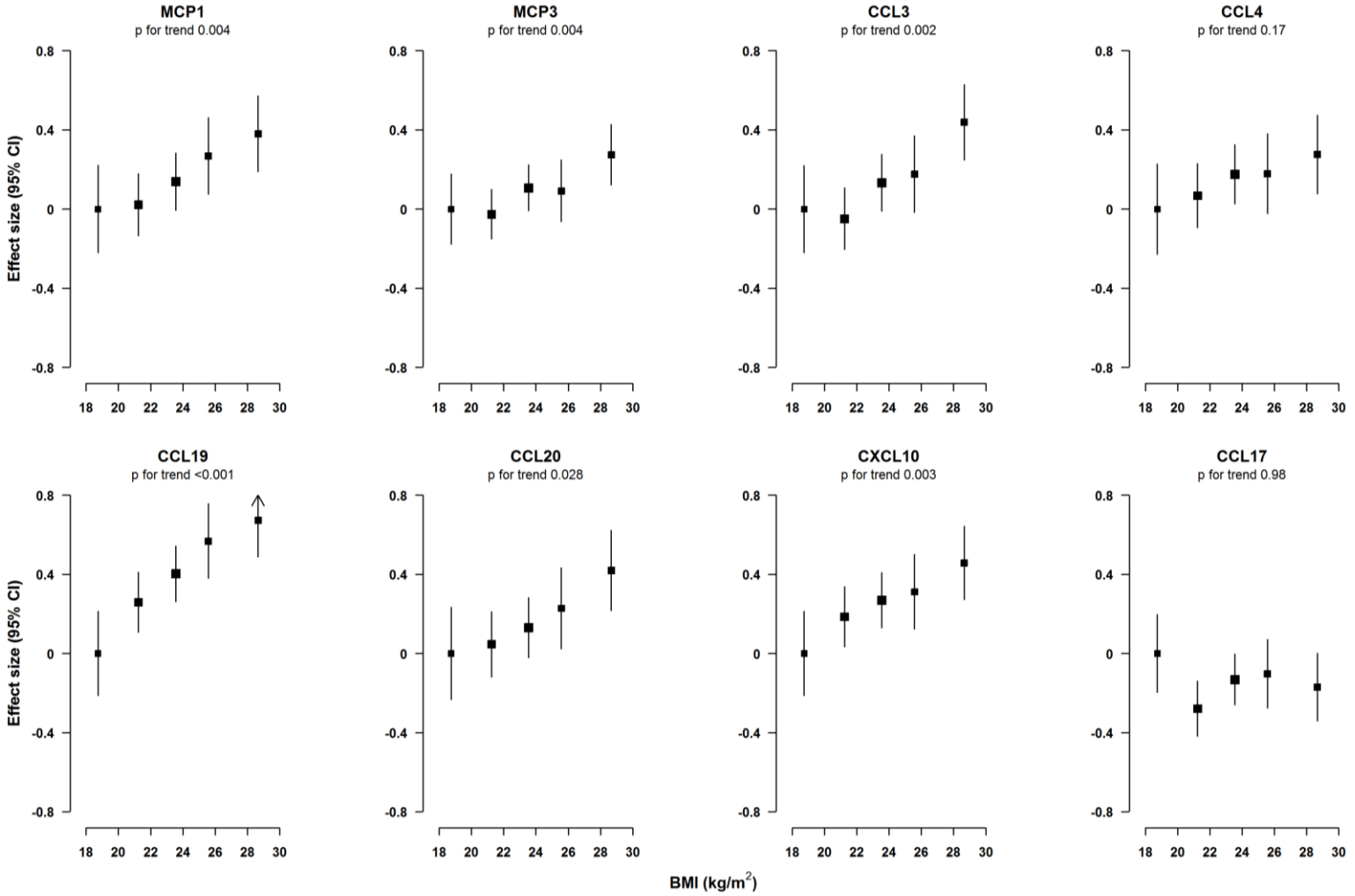
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.
P-value: - $p>0.05$; * $p<0.05$; ** $p<0.01$; ***$p<0.001$.

Table A4. Continued

Proteins	SD difference (95% CI)	*P*-value
Cell surface proteins		
ADGRG1	0.104 (0.023, 0.186)	*
CD4	0.094 (0.008, 0.180)	-
CD5	0.099 (0.018, 0.181)	*
CD8A	0.052 (-0.040, 0.143)	-
CD28	0.058 (-0.017, 0.134)	-
CD83	0.106 (0.023, 0.189)	*
CD244	0.074 (-0.011, 0.159)	-
CRTAM	-0.001 (-0.083, 0.080)	-
ICOSLG	-0.098 (-0.190, -0.006)	-
KLRD1	0.103 (0.018, 0.189)	*
LAMP3	0.007 (-0.068, 0.081)	-
MIC-A/B	0.055 (-0.031, 0.141)	-
NCR1	0.073 (-0.017, 0.163)	-
PD L1	0.056 (-0.034, 0.147)	-
PD L2	0.013 (-0.069, 0.096)	-
PDCD1	0.032 (-0.063, 0.126)	-
Other secreted proteins		
DCN	0.147 (0.064, 0.229)	**
Gal1	0.288 (0.210, 0.366)	***
Gal9	0.220 (0.143, 0.297)	***

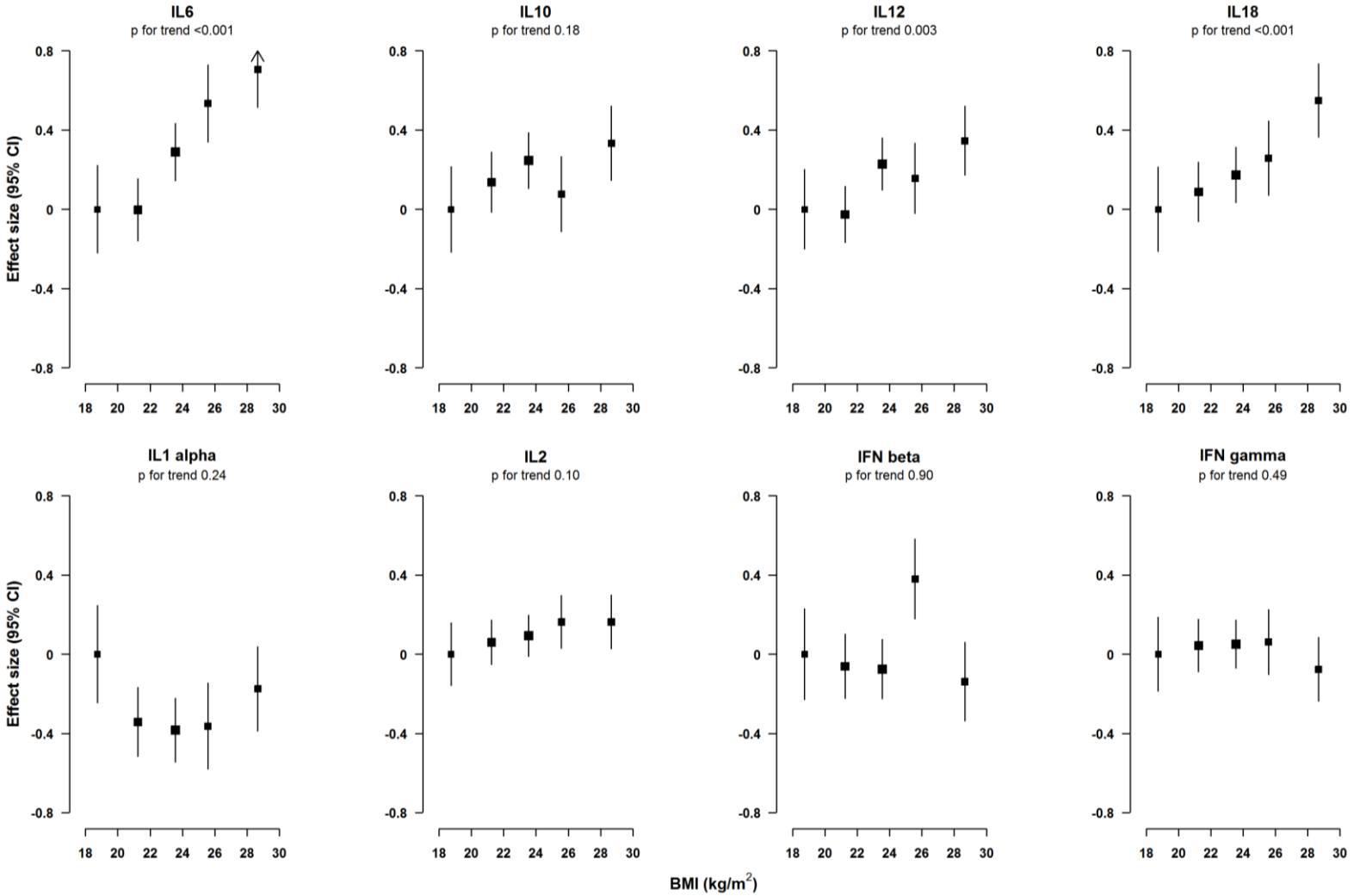
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.
P-value: - $p>0.05$; * $p<0.05$; ** $p<0.01$; ***$p<0.001$.

Figure A1. Associations of BMI with chemokines



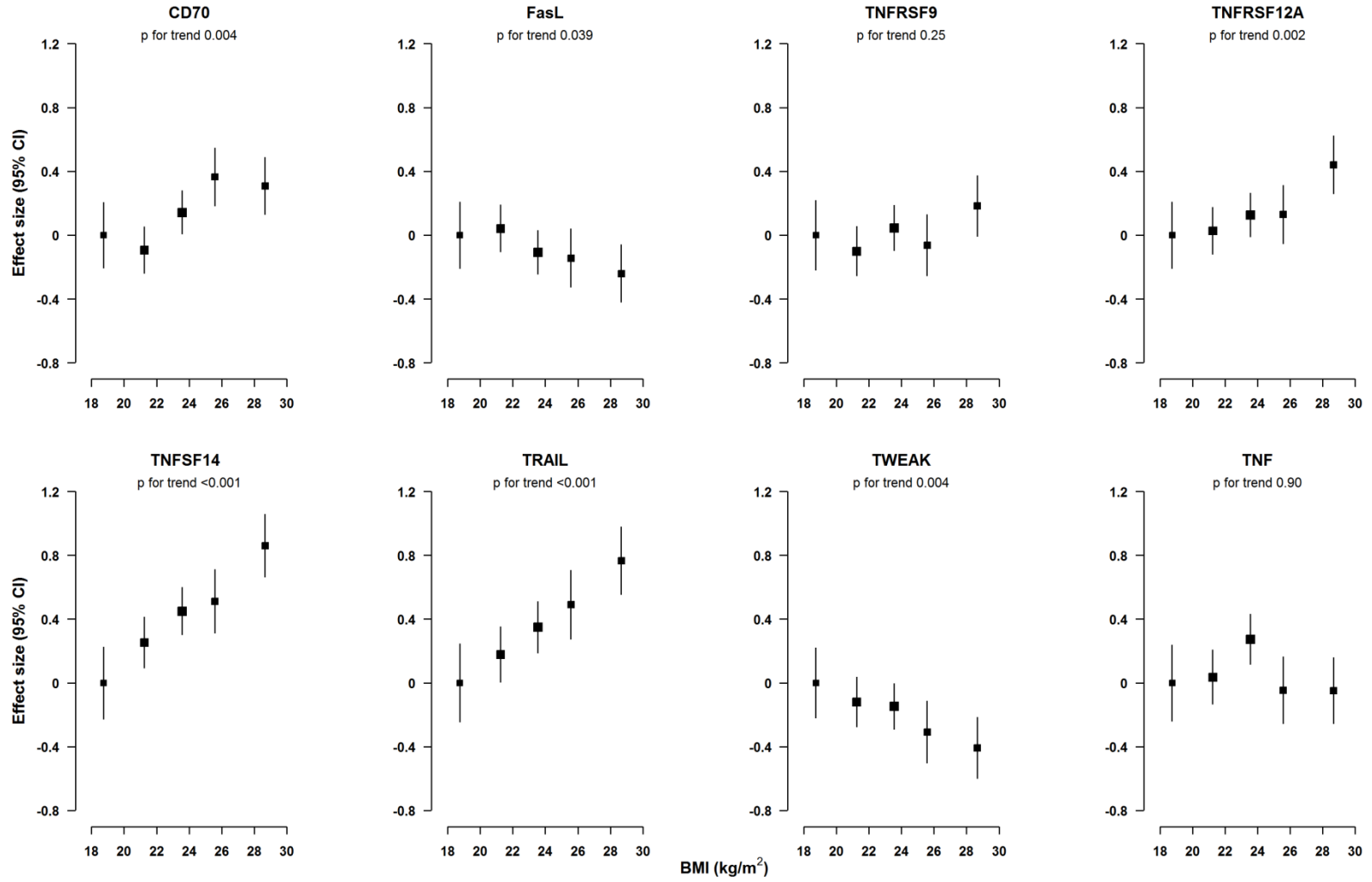
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

Figure A2. Associations of BMI with interleukins



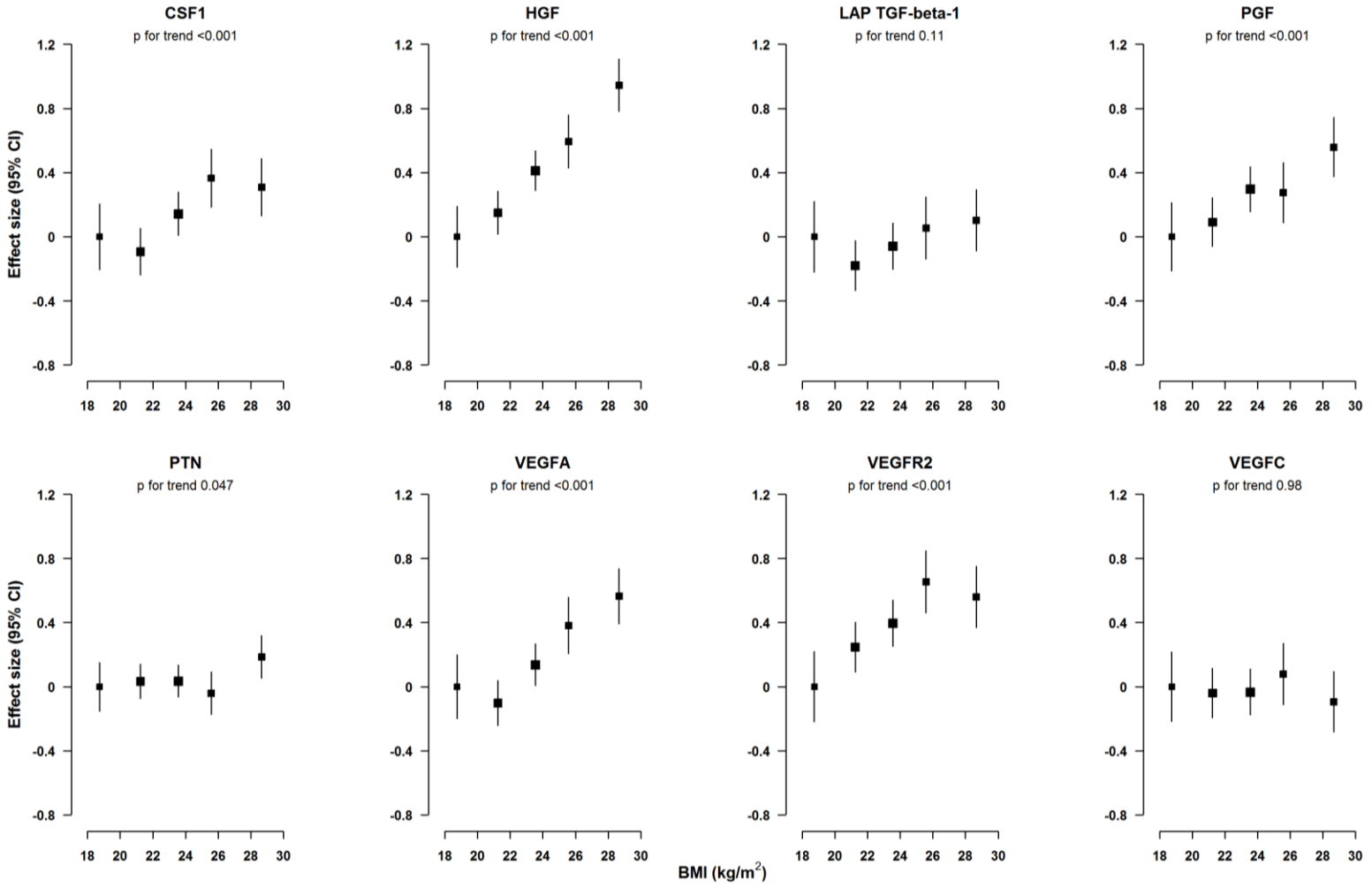
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

Figure A3. Associations of BMI with TNF and TNFR



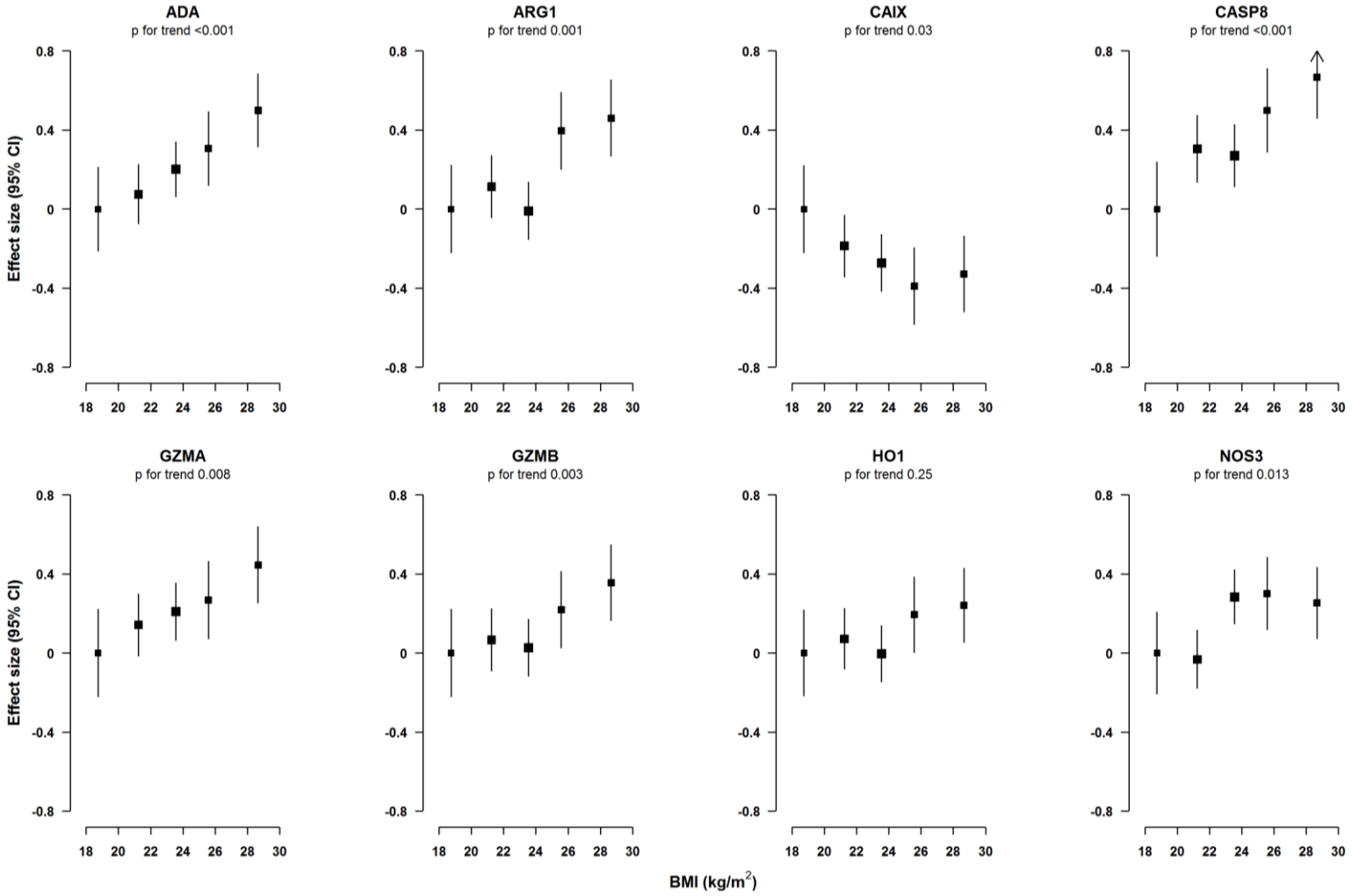
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time

Figure A4. Associations of BMI with growth factors



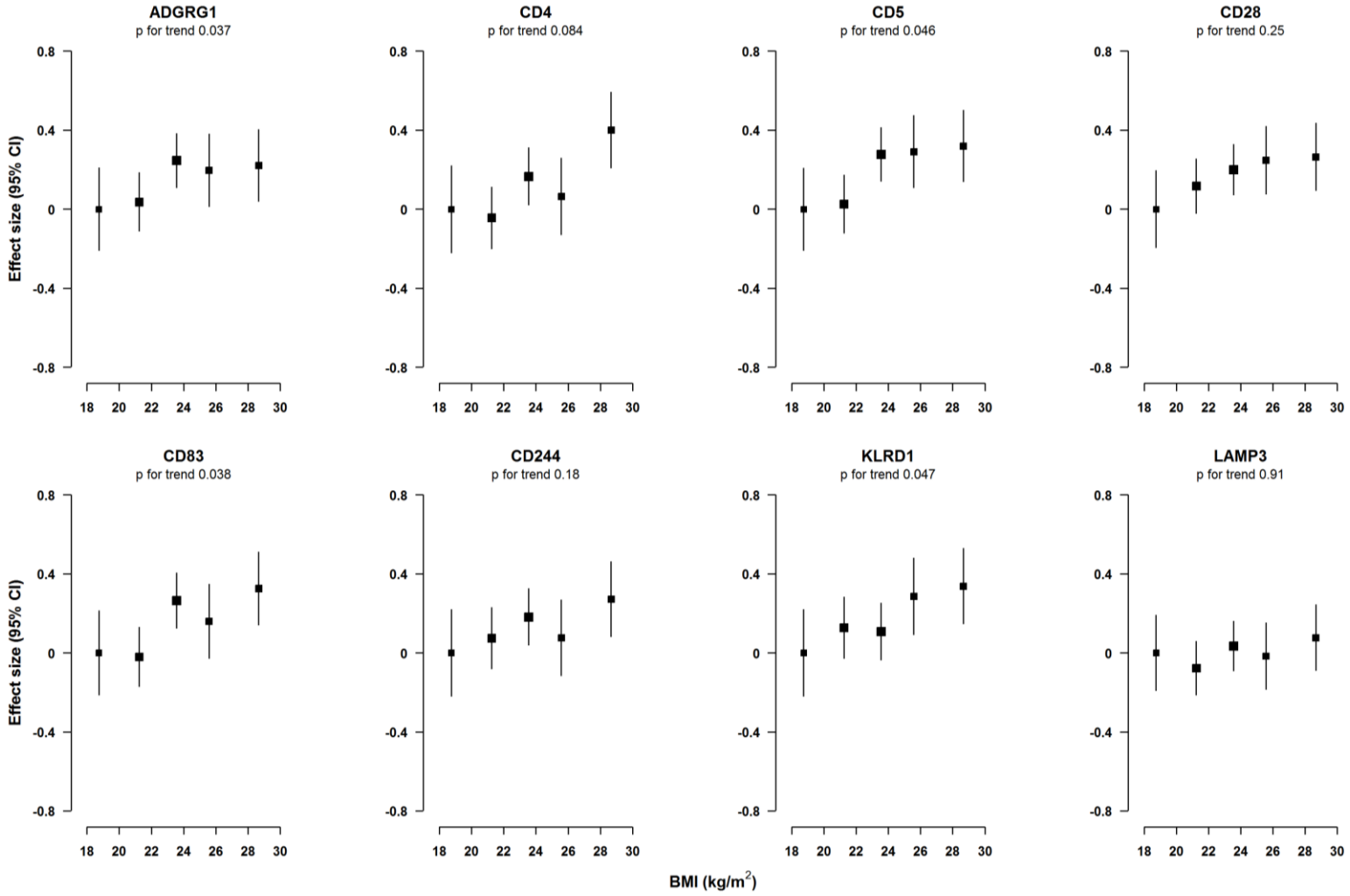
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

Figure A5. Associations of BMI with enzymes



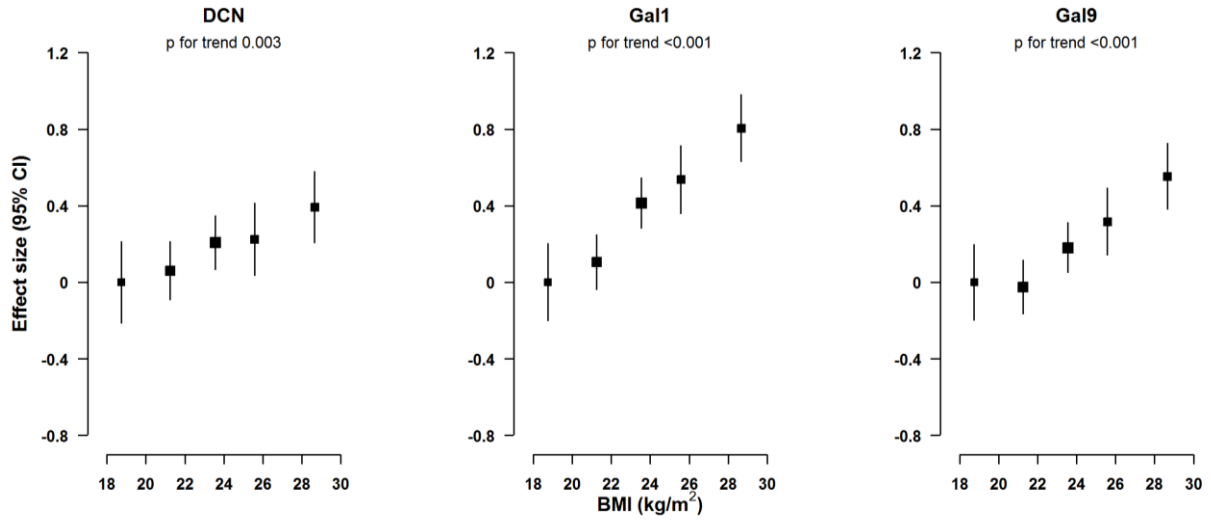
Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

Figure A6. Associations of BMI with cell surface proteins



Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

Figure A7. Associations of BMI with other secreted proteins



Model was adjusted for age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, intake of fruit and meat, and fasting time.

3. Discussion

3.1 Chemokines

In the current study, BMI showed positive associations with a wide range of chemokines, with the strongest associations observed for MCP1, MCP3, CCL3, CCL19, CCL20, and CXCL10. The current study findings are consistent with previous cross-sectional studies showing positive correlations between BMI and chemokines.[4-10] The chemokines identified in the current study have been implicated in tumorigenesis in both experimental and observational studies.[11]

Chemokines, a family of small-molecule cytokines, are chemotactic cytokines induced by inflammatory cytokines, growth factors, and pathogenic stimuli, and can induce directed migration of leukocytes along a chemical gradient of ligand (i.e. chemokine gradient).[12] Chemokine signalling leads to the transcription of target genes involved in cell invasion, motility, angiogenesis, interactions with the extracellular matrix, and apoptosis.[12] Based on the position of the first two cysteines adjacent to the amino terminus, the small chemokine proteins (8-10 kDa) are classified into four subfamilies: CXC, CC, C, and CX3C.[13] For many cancers, a complex chemokine network is crucial in immune-cell infiltration, tumour cell growth, survival, migration, angiogenesis, and metastasis.[11] Previous experimental studies have reported increased expression of chemokines in adipose tissue under chronic inflammation associated with obesity.[14] Previous case-control studies nested in cohort studies have shown associations of various chemokines with risks of several cancers (**Figure A8**).[15-20]

3.2 Interleukins

In addition to chemokines, BMI showed positive associations with interleukins, with the strongest associations observed for IL6, IL12, and IL18. The findings for interleukins are consistent with previous cross-sectional studies showing positive correlations between BMI and interleukins.[4,6,9,10,21-29] The interleukins identified in the current study have a key role in tumorigenesis in experimental and observational studies,[30] while some are potential targets in cancer therapy (i.e. IL6, IL10, IL12).[31,32]

Interleukins are a group of cytokines that were first reported to be expressed by leukocytes and play an important role in the function of the immune system.[33] Interleukins have both inflammatory and anti-inflammatory effects.[33] For example, IL1α, IL6, and IL8 are proinflammatory cytokines, while IL4 and IL10 are anti-inflammatory cytokines.

IL6 plays a key role in inflammatory responses.[34] IL6 has a wide variety of biological functions and is a potent inducer of the acute phase response.[34] Upon binding to its receptor soluble IL6 receptor (sIL6R), IL6 promotes the transition from acute to chronic inflammation.[34-36] IL6 is overexpressed in almost all tumours that have been investigated and is associated with more advanced tumour stages and shorter survival of several cancers, including colorectal, breast, and ovarian cancer.[36] IL6 is a potential therapeutic target for cancer.[32] Previous case-control studies have shown that IL6 polymorphisms are associated with risks of liver and lung cancer.[37-39] A previous case-control study has suggested that IL6 is positively associated with risk of gallbladder cancer,[41] while previous nested case-control studies have shown positive associations of IL6 with risks of colorectal, liver, and

endometrial cancer.[19,40,42-44] A recent nested case-control study has suggested a positive association of sIL6R with lung cancer, which remained significant 7.5 years prior to cancer diagnosis.[16] IL18 is a proinflammatory cytokine that plays an important role in the regulations of innate and acquired immune responses.[45] IL18 induces the release of IFN-γ in combination with IL12 and is involved in several inflammation-related diseases including atherosclerosis and rheumatoid arthritis.[46] Previous case-control studies have shown that IL18 gene polymorphisms are associated with risks of liver cirrhosis, oesophageal cancer, and nasopharyngeal cancer.[47,48]

3.3 TNF and TNFR

BMI showed positive associations with TNF and TNFR, except for inverse associations with TWEAK and FasL. The positive associations were strongest for CD70, TNFSF14, TRAIL, and TNFSF12A. The majority of these proteins are involved in apoptosis, a critical step in tumorigenesis.[49,50] Apoptosis plays a key role in the initiation of inflammation and dysfunction of adipose tissue.[49] In both human and animal studies, increased apoptosis of adipocytes has been observed in individuals with obesity, which may contribute to the development of systemic inflammation.[50]

Apoptosis is characterised by distinct morphological and biochemical changes mediated by caspases, a family of cysteine proteases involved in programmed cell death.[51] There are two separable pathways leading to activation of caspases.[52] The extrinsic pathway is initiated through apoptotic signal transduction cascades, which involves binding of transmembrane death receptors (TNF receptor, TRAIL receptor, and FasL) to activate membrane-proximal caspases (caspase-8 and

caspase-10).[52] The intrinsic pathway is controlled by Bcl family proteins at the mitochondria and involves disruption of the mitochondrial membrane and the release of mitochondrial proteins.[52] The balance between cell proliferation and apoptosis has an important impact on tumorigenesis.[53] In normal cells, apoptosis has been recognised as an innate defense against carcinogens.[51]

The TNF family is a key mediator of inflammation, which is involved in both normal functions and tumorigenesis.[54] TNF can regulate normal biological functions including immune responses, cellular proliferation, differentiation, and apoptosis. TNF is also involved in fibroblast growth, angiogenesis, tissue remodelling, tumour growth, and metastasis.[55] Several cytokines of the TNF family have a role in apoptosis (e.g. TRAIL, TWEAK, FasL).[55] A nested case-control study has suggested a positive association of TNF-α with risk of ovarian cancer.[56] Case-control studies have shown associations of TRAIL gene polymorphisms with risks of stomach cancer and lymphomas[57,58] and of FasL gene polymorphisms with risks of lung, oesophageal, stomach, and breast cancer.[59-61]

4.4 Growth factors

In the current study, BMI showed positive associations with a wide range of growth factors, including the VEGF family. The strongest associations were observed for CSF1, HGF, PGF, PTN, VEGFA, and VEGFR2. The current study findings are consistent with previous cross-sectional studies showing positive correlations between BMI and growth factors.[4,6,62-67] These growth factors have a key role in angiogenesis, a hallmark of tumour pathogenesis, in which VEGF family and its receptors are the major mediators.[68]

Adipogenesis, the formation of new blood vessels from the pre-existing vascular bed, is closely related to angiogenesis.[69] Adipose tissue stimulates angiogenesis, while inhibition of angiogenesis supresses the development of adipose tissue.[69] Adipose tissue produces cytokines in angiogenesis, such as VEGF, TNF-α, and plasminogen activator inhibitor-1 (PAI-1).[69-71] Previous studies have shown overexpression of angiogenic factors including VEGF in both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) of obese individuals.[69] Angiogenesis is a fundamental event in the process of tumour growth and the formation of metastases.[72] Tumour cells are dependent on angiogenesis for supply of oxygen, nutrients, enzymes, growth factors, and hormones, for control of coagulation and fibrinolysis, and for dissemination of tumour cells.[72] Angiogenesis is a highly complex process regulated by a wide range of activators and inhibitors, where the “angiogenic switch” is “on” when the effects of inhibitors (i.e. antiangiogenic molecules) are balanced by those of activators (i.e. proangiogenic molecules).[73,74]

VEGF is a subfamily of growth factors that play an important role in both vasculogenesis and angiogenesis.[75] Previous studies have shown overexpression of VEGF in a variety of tumours, and elevated levels of VEGF are associated with poor prognosis.[75,76] There are five VEGF ligands (i.e. VEGFA, VEFGB, VEGFC, VEGFD, and PGF) and three receptors (i.e. VEGFR1, VEGFR2, VEGFR3).[75] VEGFA is a member of the VEGF family, and upon binding to VEGFR1 and VEGFR2 it induces proliferation and migration of endothelial cell and inhibits apoptosis.[75] VEGFA is involved in promotion of blood vessel dilation and permeability as well as induction of new blood vessel formation.[75] The VEGFA pathway has been the target of anti-tumour therapy (e.g. VEGFA inhibition or

VEGFR2 inhibition), either as monotherapy or in combination with chemotherapy and radiation therapy.[77] However, improvement in survival is only modest, and tumour resistance has been observed.[77] VEGFR2 plays a role in the regulation of angiogenesis, development and permeability of vascular, and promotion of proliferation, survival, and migration of endothelial cells.[75] Previous case-control studies have shown that VEGFA gene polymorphisms are associated with risks of liver, stomach, breast cancer, and glioma.[19,78-81] Previous nested case-control studies have suggested a positive association of VEGFA with risk of endometrial cancer.[19] In addition, previous nested case-control studies have suggested a positive association of VEGFR2 with risk of non-Hodgkin lymphoma (NHL) and an inverse association with lung cancer among never smokers.[16,20]

Apart from the VEGF family, there are other growth factors involved in angiogenesis and tumorigenesis. HGF is an endothelial growth factor, as well as a motility and morphogenic factor, that has a key role in angiogenesis, tumorigenesis, and tissue regeneration.[82] HGF can act synergistically with VEGF both *in vivo* and *in vitro*, thereby augmenting the angiogenic effects.[82] HGF is overexpressed in liver diseases and a wide range of tumours.[83] A case-control study has suggested a positive association of HGF with risk of liver cancer.[84]

3.5 Enzymes

In the current study, BMI was associated with enzymes involved in apoptosis and angiogenesis, including positive associations with ADA, ARG1, CASP8, GZMA, GZMB, and NOS3 and an inverse association with CAIX.

HO1 is an isoform of the heme oxygenase (HO) system that controls heme catabolism and has anti-apoptosis functions by removing excessive free heme.[85]

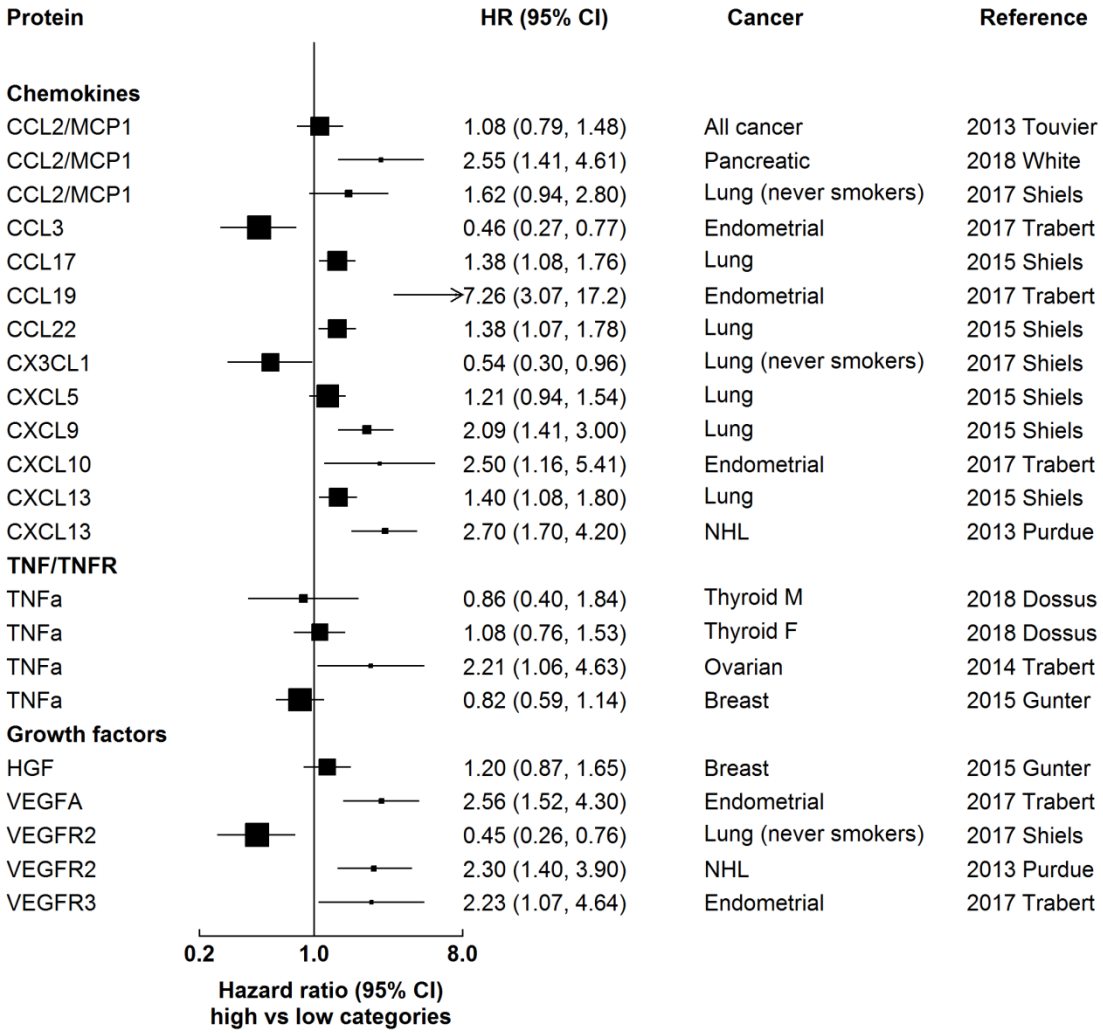
HO1 is also anti-inflammatory and controls growth and cell proliferation.[86] HO1 is overexpressed in several cancers[87,88] and may play a role in cellular resistance against chemo- and radio-therapy.[86,89] Recent evidence suggests that inhibition of HO1 increases the responsiveness of pancreatic cancer cells to anti-cancer treatment.[90] Previous case-control studies have shown that HO1 gene polymorphisms are associated with risks of lung cancer and melanoma.[91-93] Granzymes are a family of serine proteases that are expressed specifically in the cytoplasmic granules of cytotoxic T cells and natural killer cells, inducing programmed cell death in the target cell.[94] Granzyme A activates apoptosis independently of caspase, while granzyme B induces apoptosis by activating caspases (particularly caspase-3).[94] However, previous studies are limited whether granzymes are associated with cancer risk.

3.6 Potential mediations: adiposity, proteomics, and cancer risk

Although the current study did not examine proteomics in relation to cancer outcomes, the associations of BMI with proteomics in the current study were generally in the expected direction of associations between protein biomarkers and cancer risk reported in previous studies (**Figures A8-A9**). This suggests that proteomics can be promising candidates to explore potential mediation between adiposity and cancer risk. In CKB, analyses of the associations of proteomics with risk of pancreatic cancer have identified 13 protein biomarkers that are associated with higher risk of pancreatic cancer. These biomarkers are (ordered by effect sizes) ANGPT2, MCP3, IL18, LAMP3, IL6, CD8A, CCL3, CD4, HO1, HGF, CD40, TNFSF9, and GZMA. Of these biomarkers, MCP3, IL18, IL6, CCL3, HGF, and GZMA are also positively associated with BMI, suggesting that these proteins may

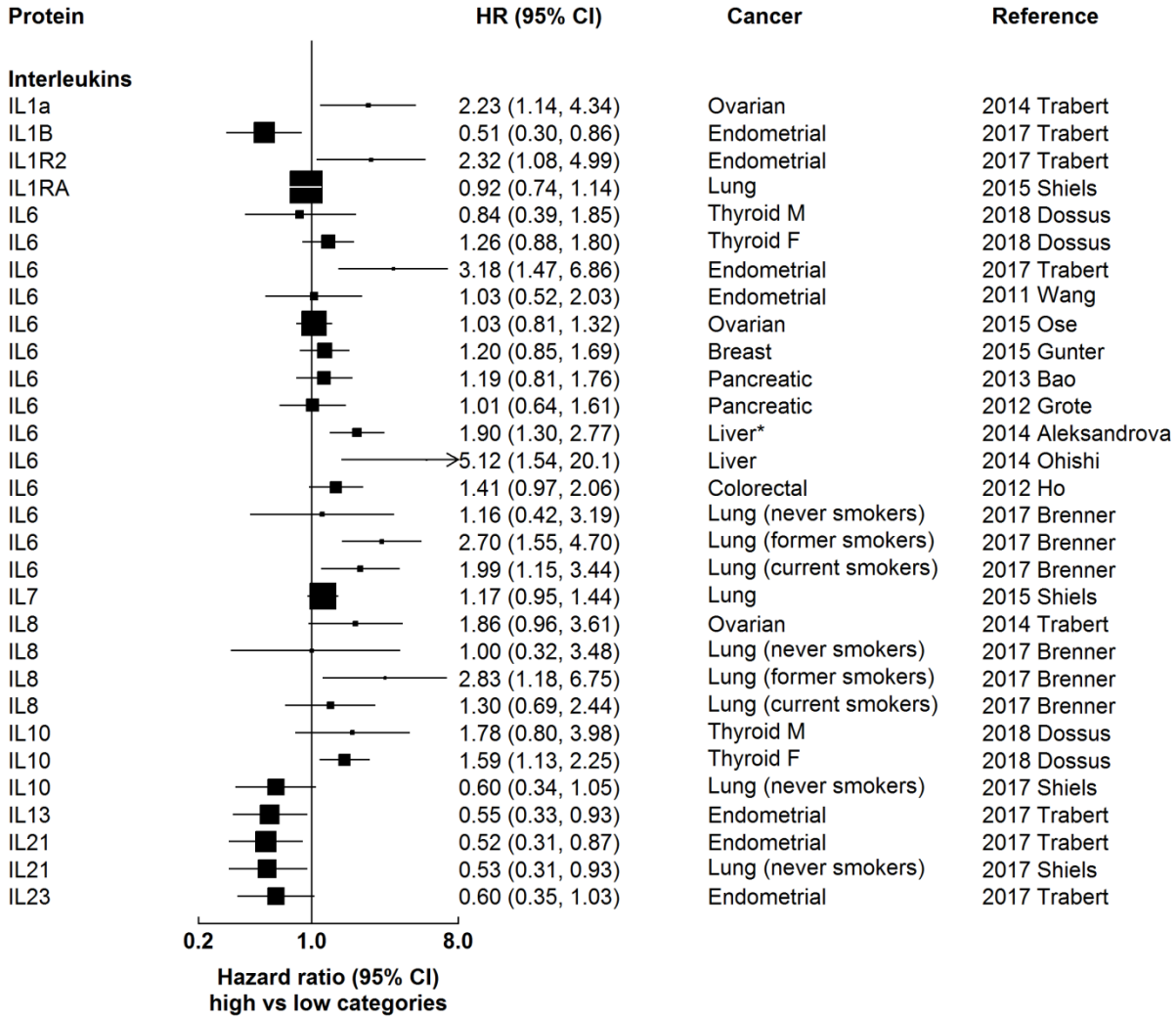
explain the associations of adiposity with risk of pancreatic cancer. Given the strong associations of BMI and protein biomarkers and associations of protein biomarkers with cancer risk, more studies are warranted to examine whether protein biomarkers may explain the association between adiposity and cancer risk.

Figure A8. Prospective studies on chemokines, TNF, TNFR, growth factors and cancer risk



Abbreviations: NHL, non-Hodgkin lymphoma; M, male; F, female.

Figure A9. Prospective studies on interleukins and cancer risk



Abbreviations: M, male; F, female.
* HR per doubling of IL6.

References:

1. Lundberg M, Thorsen SB, Assarsson E, Villablanca A, Tran B, Gee N, et al. Multiplexed homogeneous proximity ligation assays for high-throughput protein biomarker research in serological material. *Mol Cell Proteomics* 2011; 10(4): M110.004978.
2. Assarsson E, Lundberg M, Holmquist G, Bjorkesten J, Thorsen SB, Ekman D, et al. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. *PLoS One* 2014; 9(4): e95192. doi: 10.1371/journal.pone.0095192.
3. Benjamini Y and Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)* 1995: 289-300.
4. Azizian M, Mahdipour E, Mirhafez SR, Shoeibi S, Nematy M, Esmaily H, et al. Cytokine profiles in overweight and obese subjects and normal weight individuals matched for age and gender. *Ann Clin Biochem* 2016; 53(6): 663-8.
5. Denis GV, Sebastiani P, Andrieu G, Tran AH, Strissel KJ, Lombardi FL, et al. Relationships among obesity, type 2 diabetes, and plasma cytokines in African American women. *Obesity (Silver Spring)* 2017; 25(11): 1916-20.
6. Doupis J, Rahangdale S, Gnardellis C, Pena SE, Malhotra A, Veves A. Effects of diabetes and obesity on vascular reactivity, inflammatory cytokines, and growth factors. *Obesity (Silver Spring)* 2011; 19(4): 729-35.
7. Hashimoto I, Wada J, Hida A, Baba M, Miyatake N, Eguchi J, et al. Elevated serum monocyte chemoattractant protein-4 and chronic inflammation in overweight subjects. *Obesity (Silver Spring)* 2006; 14(5): 799-811.
8. Lim JP, Leung BP, Ding YY, Tay L, Ismail NH, Yeo A, et al. Monocyte chemoattractant protein-1: a proinflammatory cytokine elevated in sarcopenic obesity. *Clin Interv Aging* 2015; 10: 605-9.
9. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation* 2007; 116(11): 1234-41.
10. Wong E, Freiberg M, Tracy R, Kuller L. Epidemiology of cytokines: the Women On the Move through Activity and Nutrition (WOMAN) Study. *Am J Epidemiol* 2008; 168(4): 443-53.
11. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer* 2004; 4(7): 540-50.
12. Rossi D, Zlotnik A. The biology of chemokines and their receptors. *Annu Rev Immunol* 2000; 18: 217-42.
13. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity* 2000; 12(2): 121-7.

14. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009; 18(10): 2569-78.

15. White DL, Hoogeveen RC, Chen L, Richardson P, Ravishankar M, Shah P, et al. A prospective study of soluble receptor for advanced glycation end products and adipokines in association with pancreatic cancer in postmenopausal women. *Cancer Med* 2018; 7(5): 2180-91.

16. Shiels MS, Shu XO, Chaturvedi AK, Gao YT, Xiang YB, Cai Q, et al. A prospective study of immune and inflammation markers and risk of lung cancer among female never smokers in Shanghai. *Carcinogenesis* 2017; 38(10): 1004-10.

17. Shiels MS, Katki HA, Hildesheim A, Pfeiffer RM, Engels EA, Williams M, et al. Circulating inflammation markers, risk of lung cancer, and utility for risk stratification. *J Natl Cancer Inst* 2015; 107(10).

18. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, et al. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: a nested case-control study. *Am J Epidemiol* 2013; 177(1): 3-13.

19. Trabert B, Eldridge RC, Pfeiffer RM, Shiels MS, Kemp TJ, Guillemette C, et al. Prediagnostic circulating inflammation markers and endometrial cancer risk in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Int J Cancer* 2017; 140(3): 600-10.

20. Purdue MP, Hofmann JN, Kemp TJ, Chaturvedi AK, Lan Q, Park JH, et al. A prospective study of 67 serum immune and inflammation markers and risk of non-Hodgkin lymphoma. *Blood* 2013; 122(6): 951-7.

21. Evans J, Collins M, Jennings C, van der Merwe L, Soderstrom I, Olsson T, et al. The association of interleukin-18 genotype and serum levels with metabolic risk factors for cardiovascular disease. *Eur J Endocrinol* 2007; 157(5): 633-40.

22. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. *Arterioscler Thromb Vasc Biol* 2005; 25(6): 1268-73.

23. Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. *JPEN J Parenter Enteral Nutr* 2004; 28(6): 410-5.

24. Kuo SM, Halpern MM. Lack of association between body mass index and plasma adiponectin levels in healthy adults. *Int J Obes (Lond)* 2011; 35(12): 1487-94.

25. Marques-Vidal P, Bochud M, Bastardot F, Luscher T, Ferrero F, Gaspoz JM, et al. Association between inflammatory and obesity markers in a Swiss population-based sample (CoLaus Study). *Obes Facts* 2012; 5(5): 734-44.

26. Piva SJ, Tatsch E, De Carvalho JA, Bochi GV, Kober H, Duarte T, et al. Assessment of inflammatory and oxidative biomarkers in obesity and their associations with body mass index. *Inflammation* 2013; 36(1): 226-31.

27. Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. *PLoS One* 2015; 10(3): e0121971. doi: 10.1371/journal/pone.0121971.

28. Strohacker K, Wing RR, McCaffery JM. Contributions of body mass index and exercise habits on inflammatory markers: a cohort study of middle-aged adults living in the USA. *BMJ Open* 2013; 3(5).

29. Welsh P, Woodward M, Rumley A, Lowe G. Associations of circulating TNFalpha and IL-18 with myocardial infarction and cardiovascular risk markers: the Glasgow Myocardial Infarction Study. *Cytokine* 2009; 47(2): 143-7.

30. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; 140(6): 883-99.

31. Lasek W, Zagozdzon R, Jakobisiak M. Interleukin 12: still a promising candidate for tumor immunotherapy? *Cancer Immunol Immunother* 2014; 63(5): 419-35.

32. Guo Y, Xu F, Lu T, Duan Z, Zhang Z. Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treat Rev* 2012; 38(7): 904-10.

33. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. *J Allergy Clin Immunol* 2010; 125(2 Suppl 2): S53-72.

34. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, et al. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J Clin Invest* 1998; 101(2): 311-20.

35. Heikkila K, Ebrahim S, Lawlor DA. Systematic review of the association between circulating interleukin-6 (IL-6) and cancer. *Eur J Cancer* 2008; 44(7): 937-45.

36. Naugler WE, Karin M. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. *Trends Mol Med* 2008; 14(3): 109-19.

37. Lin J, Lu C, Stewart DJ, Gu J, Huang M, Chang DW, et al. Systematic evaluation of apoptotic pathway gene polymorphisms and lung cancer risk. *Carcinogenesis* 2012; 33(9): 1699-706.

38. Tian G, Mi J, Wei X, Zhao D, Qiao L, Yang C, et al. Circulating interleukin-6 and cancer: A meta-analysis using Mendelian randomization. *Sci Rep* 2015; 5: 11394.

39. Lim WY, Chen Y, Ali SM, Chuah KL, Eng P, Leong SS, et al. Polymorphisms in inflammatory pathway genes, host factors and lung cancer risk in Chinese female never-smokers. *Carcinogenesis* 2011; 32(4): 522-9.

40. Ho GY, Wang T, Gunter MJ, Strickler HD, Cushman M, Kaplan RC, et al. Adipokines linking obesity with colorectal cancer risk in postmenopausal women. *Cancer Res* 2012; 72(12): 3029-37.

41. Koshiol J, Gao YT, Corbel A, Kemp TJ, Shen MC, Hildesheim A, et al. Circulating inflammatory proteins and gallbladder cancer: Potential for risk

stratification to improve prioritization for cholecystectomy in high-risk regions. *Cancer Epidemiol* 2018; 54: 25-30.

42. Brenner DR, Fanidi A, Grankvist K, Muller DC, Brennan P, Manjer J, et al. Inflammatory cytokines and lung cancer risk in 3 prospective studies. *Am J Epidemiol* 2017; 185(2): 86-95.
43. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 2014; 60(3): 858-71.
44. Ohishi W, Cologne JB, Fujiwara S, Suzuki G, Hayashi T, Niwa Y, et al. Serum interleukin-6 associated with hepatocellular carcinoma risk: a nested case-control study. *Int J Cancer* 2014; 134(1): 154-63.
45. Dinarello CA. IL-18: A TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. *J Allergy Clin Immunol* 1999; 103(1 Pt 1): 11-24.
46. Okamura H, Kashiwamura S, Tsutsui H, Yoshimoto T, Nakanishi K. Regulation of interferon-gamma production by IL-12 and IL-18. *Curr Opin Immunol* 1998; 10(3): 259-64.
47. Lu Y, Bao JG, Deng Y, Rong CZ, Liu YQ, Huang XL, et al. Role of IL-18 gene promoter polymorphisms, serum IL-18 levels, and risk of hepatitis B virus-related liver disease in the Guangxi Zhuang population: a retrospective case-control study. *Asian Pac J Cancer Prev* 2015; 16(14): 6019-26.
48. Wang M, Zhu XY, Wang L, Lin Y. The -607C/A polymorphisms in interleukin-18 gene promoter contributes to cancer risk: evidence from a meta-analysis of 22 case-control studies. *PLoS One* 2013; 8(10): e76915. doi: 10.1371/journal.pone.0076915.
49. Alkhouri N, Gornicka A, Berk MP, Thapaliya S, Dixon LJ, Kashyap S, et al. Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis. *J Biol Chem* 2010; 285(5): 3428-38.
50. Chen W, Tang WR, Zhang M, Chang K, Wei YL. Association of DR4 (TRAIL-R1) polymorphisms with cancer risk in Caucasians: an updated meta-analysis. *Asian Pac J Cancer Prev* 2014; 15(6): 2889-92.
51. Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. *Science* 1998; 281(5381): 1305-8.
52. Evan GI, Vousden KH. Proliferation, cell cycle and apoptosis in cancer. *Nature* 2001; 411(6835): 342-8.
53. Goldsworthy TL, Conolly RB, Fransson-Steen R. Apoptosis and cancer risk assessment. *Mutat Res* 1996; 365(1-3): 71-90.
54. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell* 2001; 104(4): 487-501.
55. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003; 3(9): 745-56.
56. Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in

the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecol Oncol* 2014; 135(2): 297-304.

57. Wang C, Xu S, Yi F, Wang X, Lei Y, Huang S, et al. Tumor necrosis factor-related apoptosis inducing ligand gene polymorphisms are correlated with gastric cancer in central China. *Pharm Res* 2015; 32(3): 762-8.
58. Heredia-Galvez B, Ruiz-Cosano J, Torres-Moreno D, Espanol I, Morales-Lara MJ, Perez-Ceballos E, et al. Association of polymorphisms in TRAIL1 and TRAILR1 genes with susceptibility to lymphomas. *Ann Hematol* 2014; 93(2): 243-7.
59. Xu Y, He B, Li R, Pan Y, Gao T, Deng Q, et al. Association of the polymorphisms in the Fas/FasL promoter regions with cancer susceptibility: a systematic review and meta-analysis of 52 studies. *PLoS One* 2014; 9(3): e90090. doi: 10.1371/journal.pone/journal.pone.0090090.
60. Yu X, Li Y, Yu Y, Lei J, Wan G, Cao F. Associations between FAS rs2234767 and FASL rs763110 polymorphisms and the risk of lung cancer: a meta-analysis of 39,736 subjects. *Onco Targets Ther* 2016; 9: 2049-56.
61. Zhao H, Zheng L, Li X, Wang L. FasL gene -844T/C mutation of esophageal cancer in South China and its clinical significance. *Sci Rep* 2014; 4: 3866.
62. Faber DR, van der Graaf Y, Westerink J, Kanhai DA, Monajemi H, Visseren FL, et al. Hepatocyte growth factor and interferon-gamma inducible protein-10 are related to visceral adiposity. *Eur J Clin Invest* 2013; 43(4): 369-78.
63. Kitahara CM, Trabert B, Katki HA, Chaturvedi AK, Kemp TJ, Pinto LA, et al. Body mass index, physical activity, and serum markers of inflammation, immunity, and insulin resistance. *Cancer Epidemiol Biomarkers Prev* 2014; 23(12): 2840-9.
64. Loebig M, Klement J, Schmoller A, Betz S, Heuck N, Schweiger U, et al. Evidence for a relationship between VEGF and BMI independent of insulin sensitivity by glucose clamp procedure in a homogenous group healthy young men. *PLoS One* 2010; 5(9): e12610. doi: 10.1371/journal.pone.0012610.
65. Rehman J, Considine RV, Bovenkerk JE, Li J, Slavens CA, Jones RM, et al. Obesity is associated with increased levels of circulating hepatocyte growth factor. *J Am Coll Cardiol* 2003; 41(8): 1408-13.
66. Sandhofer A, Tatarczyk T, Kirchmair R, Iglseder B, Paulweber B, Patsch JR, et al. Are plasma VEGF and its soluble receptor sFlt-1 atherogenic risk factors? Cross-sectional data from the SAPHIR study. *Atherosclerosis* 2009; 206(1): 265-9.
67. Vistoropsky Y, Trofimov S, Malkin I, Kobyliansky E, Livshits G. Genetic and environmental determinants of hepatocyte growth factor levels and their association with obesity and blood pressure. *Ann Hum Biol* 2008; 35(1): 93-103.
68. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; 1(1): 27-31.
69. Cao Y. Angiogenesis modulates adipogenesis and obesity. *J Clin Invest* 2007; 117(9): 2362-8.

70. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 2004; 145(5): 2273-82.

71. Silha JV, Krsek M, Sucharda P, Murphy LJ. Angiogenic factors are elevated in overweight and obese individuals. *Int J Obes (Lond)* 2005; 29(11): 1308-14.

72. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; 407(6801): 249-57.

73. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 2003; 3(6): 401-10.

74. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. *Cell* 1991; 64(2): 327-36.

75. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; 23(5): 1011-27.

76. Vecchiarelli-Federico LM, Cervi D, Haeri M, Li Y, Nagy A, Ben-David Y. Vascular endothelial growth factor--a positive and negative regulator of tumor growth. *Cancer Res* 2010; 70(3): 863-7.

77. Cardones AR, Banez LL. VEGF inhibitors in cancer therapy. *Curr Pharm Des* 2006; 12(3): 387-94.

78. Wu X, Xin Z, Zhang W, Wu J, Chen K, Wang H, et al. Polymorphisms in the VEGFA promoter are associated with susceptibility to hepatocellular carcinoma by altering promoter activity. *Int J Cancer* 2013; 133(5): 1085-93.

79. Liu H, Wang S, Huang C. VEGFA+936C/T and -634G/C polymorphisms and gastric cancer risk: a meta-analysis. *Asian Pac J Cancer Prev* 2011; 12(8): 1979-83.

80. Li R, Zhao Y, Fan W, Chen H, Chen Y, Liu Y, et al. Possible association between polymorphisms of human vascular endothelial growth factor A gene and susceptibility to glioma in a Chinese population. *Int J Cancer* 2011; 128(1): 166-75.

81. Slattery ML, John EM, Torres-Mejia G, Lundgreen A, Lewinger JP, Stern MC, et al. Angiogenesis genes, dietary oxidative balance and breast cancer risk and progression: the Breast Cancer Health Disparities Study. *Int J Cancer* 2014; 134(3): 629-44.

82. Molnarfi N, Benkhoucha M, Funakoshi H, Nakamura T, Lalive PH. Hepatocyte growth factor: A regulator of inflammation and autoimmunity. *Autoimmun Rev* 2015; 14(4): 293-303.

83. Jiang WG, Martin TA, Parr C, Davies G, Matsumoto K, Nakamura T. Hepatocyte growth factor, its receptor, and their potential value in cancer therapies. *Crit Rev Oncol Hematol* 2005; 53(1): 35-69.

84. Yamagamim H, Moriyama M, Matsumura H, Aoki H, Shimizu T, Saito T, et al. Serum concentrations of human hepatocyte growth factor is a useful indicator for predicting the occurrence of hepatocellular carcinomas in C-viral chronic liver diseases. *Cancer* 2002; 95(4): 824-34.

85. Otterbein LE, Choi AM. Heme oxygenase: colors of defense against cellular stress. *Am J Physiol Lung Cell Mol Physiol* 2000; 279(6): L1029-37.

86. Jozkowicz A, Was H, Dulak J. Heme oxygenase-1 in tumors: is it a false friend? *Antioxid Redox Signal* 2007; 9(12): 2099-117.

87. Liu ZM, Chen GG, Ng EK, Leung WK, Sung JJ, Chung SC. Upregulation of heme oxygenase-1 and p21 confers resistance to apoptosis in human gastric cancer cells. *Oncogene* 2004; 23(2): 503-13.

88. Sunamura M, Duda DG, Ghattas MH, Lozonschi L, Motoi F, Yamauchi J, et al. Heme oxygenase-1 accelerates tumor angiogenesis of human pancreatic cancer. *Angiogenesis* 2003; 6(1): 15-24.

89. Chau LY. Heme oxygenase-1: emerging target of cancer therapy. *J Biomed Sci* 2015; 22: 22.

90. Berberat PO, Dambrauskas Z, Gulbinas A, Giese T, Giese N, Kunzli B, et al. Inhibition of heme oxygenase-1 increases responsiveness of pancreatic cancer cells to anticancer treatment. *Clin Cancer Res* 2005; 11(10): 3790-8.

91. Wu MM, Lee CH, Hsu LI, Cheng WF, Lee TC, Wang YH, et al. Effect of heme oxygenase-1 gene promoter polymorphism on cancer risk by histological subtype: A prospective study in arseniasis-endemic areas in Taiwan. *Int J Cancer* 2016; 138(8): 1875-86.

92. Okamoto I, Krogler J, Endler G, Kaufmann S, Mustafa S, Exner M, et al. A microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with risk for melanoma. *Int J Cancer* 2006; 119(6): 1312-5.

93. Kikuchi A, Yamaya M, Suzuki S, Yasuda H, Kubo H, Nakayama K, et al. Association of susceptibility to the development of lung adenocarcinoma with the heme oxygenase-1 gene promoter polymorphism. *Hum Genet* 2005; 116(5): 354-60.

94. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol* 2015; 15(6): 388-400.

Additional references in Figures A8-A9:

Bao Y, Giovannucci EL, Kraft P, Stampfer MJ, Ogino S, Ma J, et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J Natl Cancer Inst* 2013; 105(2): 95-103.

Dossus L, Franceschi S, Biessy C, Navionis AS, Travis RC, Weiderpass E, et al. Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: the EPIC study. *Int J Cancer* 2018; 142(7): 1332-42.

Gunter MJ, Wang T, Cushman M, Xue X, Wassertheil-Smoller S, Strickler HD, et al. Circulating adipokines and inflammatory markers and postmenopausal breast cancer risk. *J Natl Cancer Inst* 2015; 107(9).

Grote VA, Kaaks R, Nieters A, Tjonneland A, Halkjaer J, Overvad K, et al. Inflammation marker and risk of pancreatic cancer: a nested case-control study within the EPIC cohort. *Br J Cancer* 2012; 106(11): 1866-74.

Ose J, Schock H, Tjonneland A, Hansen L, Overvad K, Dossus L, et al. Inflammatory markers and risk of epithelial ovarian cancer by tumor subtypes: the EPIC Cohort. *Cancer Epidemiol Biomarkers Prev* 2015; 24(6): 951-61.

Wang T, Rohan TE, Gunter MJ, Xue X, Wactawski-Wende J, Rajpathak SN, et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. *Cancer Epidemiol Biomarkers Prev* 2011; 20(5): 971-7.

Appendix 9.2 Adjusted HRs for specific GI cancers associated with BMI25*

	Main model HR (95% CI)	Imputed BMI25† HR (95% CI)
Pancreatic cancer		
<20.0	0.95 (0.79, 1.15)	0.92 (0.76, 1.11)
20.0 to <22.5	1.00 (0.88, 1.14)	1.00 (0.90, 1.11)
22.5 to <25.0	1.08 (0.94, 1.24)	1.03 (0.89, 1.18)
25.0 to <27.5	1.37 (1.10, 1.71)	1.29 (1.04, 1.61)
≥27.5	1.28 (0.93, 1.77)	1.20 (0.87, 1.66)
per 5 kg/m^2	*1.18 (1.02, 1.36)*	*1.16 (1.00, 1.33)*
Liver cancer		
<20.0	0.97 (0.88, 1.07)	0.97 (0.88, 1.06)
20.0 to <22.5	1.00 (0.94, 1.07)	1.00 (0.95, 1.06)
22.5 to <25.0	1.14 (1.06, 1.23)	1.13 (1.05, 1.21)
25.0 to <27.5	1.03 (0.90, 1.19)	1.02 (0.89, 1.17)
≥27.5	1.11 (0.92, 1.35)	1.10 (0.90, 1.33)
per 5 kg/m^2	*1.09 (1.01, 1.18)*	*1.08 (1.00, 1.17)*
Colorectal cancer		
<20.0	0.87 (0.80, 0.96)	0.87 (0.80, 0.96)
20.0 to <22.5	1.00 (0.94, 1.06)	1.00 (0.95, 1.05)
22.5 to <25.0	1.00 (0.93, 1.08)	1.00 (0.93, 1.07)
25.0 to <27.5	0.93 (0.81, 1.06)	0.92 (0.81, 1.06)
≥27.5	1.05 (0.88, 1.26)	1.05 (0.88, 1.26)
per 5 kg/m^2	*1.06 (0.99, 1.15)*	*1.06 (0.99, 1.14)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.
† Imputation model included age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, family history of cancer, and cumulative hazard of cancer.

Appendix 9.3 Associations of RPG with specific GI cancers excluding participants with diabetes*

	Excluding previously diagnosed diabetes		Excluding further screen-detected diabetes	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Pancreatic cancer				
<5.6	303	1.00 (0.88, 1.13)	303	1.00 (0.88, 1.13)
5.6 to <6.8	239	1.07 (0.95, 1.21)	239	1.06 (0.94, 1.20)
6.8 to <7.8	90	1.22 (0.99, 1.51)	84	1.20 (0.96, 1.49)
≥7.8	77	1.39 (1.10, 1.74)	43	1.21 (0.89, 1.64)
per 1 mmol/L†	*709*	*1.09 (1.04, 1.15)*	*669*	*1.05 (0.98, 1.12)*
Liver cancer				
<5.6	1160	1.00 (0.94, 1.06)	1160	1.00 (0.94, 1.06)
5.6 to <6.8	847	1.09 (1.02, 1.17)	847	1.09 (1.03, 1.17)
6.8 to <7.8	334	1.20 (1.07, 1.33)	324	1.21 (1.08, 1.35)
≥7.8	297	1.44 (1.28, 1.62)	172	1.27 (1.09, 1.48)
per 1 mmol/L†	*2638*	*1.09 (1.06, 1.12)*	*2503*	*1.06 (1.02, 1.09)*
Colorectal cancer				
<5.6	1197	1.00 (0.94, 1.06)	1197	1.00 (0.94, 1.06)
5.6 to <6.8	998	1.11 (1.04, 1.18)	998	1.10 (1.04, 1.17)
6.8 to <7.8	338	1.09 (0.98, 1.21)	314	1.05 (0.94, 1.18)
≥7.8	297	1.30 (1.16, 1.46)	174	1.20 (1.03, 1.39)
per 1 mmol/L†	*2830*	*1.06 (1.03, 1.09)*	*2683*	*1.05 (1.01, 1.08)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.

† Regression dilution ratio: RPG, 0.53.

Appendix 9.4 Adjusted HRs for specific GI cancers associated with RPG among participants without previously diagnosed diabetes*

	Main model HR (95% CI)	Imputed RPG† HR (95% CI)
Pancreatic cancer		
<5.6	1.00 (0.88, 1.13)	1.00 (0.89, 1.13)
5.6 to <6.8	1.07 (0.95, 1.21)	1.08 (0.96, 1.22)
6.8 to <7.8	1.22 (0.99, 1.51)	1.22 (0.99, 1.51)
≥7.8	1.39 (1.10, 1.74)	1.38 (1.10, 1.74)
per 1 mmol/L‡	*1.09 (1.04, 1.15)*	*1.09 (1.04, 1.15)*
Liver cancer		
<5.6	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.09 (1.02, 1.17)	1.10 (1.03, 1.17)
6.8 to <7.8	1.20 (1.07, 1.33)	1.20 (1.07, 1.33)
≥7.8	1.44 (1.28, 1.62)	1.44 (1.28, 1.62)
per 1 mmol/L‡	*1.09 (1.06, 1.12)*	*1.09 (1.06, 1.12)*
Colorectal cancer		
<5.6	1.00 (0.94, 1.06)	1.00 (0.94, 1.06)
5.6 to <6.8	1.11 (1.04, 1.18)	1.10 (1.03, 1.16)
6.8 to <7.8	1.09 (0.98, 1.21)	1.09 (0.97, 1.21)
≥7.8	1.30 (1.16, 1.46)	1.30 (1.16, 1.46)
per 1 mmol/L‡	*1.06 (1.03, 1.09)*	*1.06 (1.03, 1.09)*

* Model was stratified by age-at-risk (5-year), sex, region, and HBsAg (for liver cancer), and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours.

† Imputation model included age at baseline, sex, region, education, household income, smoking, alcohol, self-rated health, family history of cancer, and cumulative hazard of cancer.

‡ Regression dilution ratio: RPG, 0.53.

Appendix 9.5 Adjusted HRs for liver cancer associated with main adiposity traits*

	HBsAg negative		Censoring viral hepatitis	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
BMI				
<20.0	337	1.10 (0.98, 1.23)	320	1.09 (0.97, 1.22)
20.0 to <22.5	527	1.00 (0.92, 1.09)	501	1.00 (0.91, 1.09)
22.5 to <25.0	559	1.00 (0.92, 1.09)	532	1.01 (0.92, 1.09)
25.0 to <27.5	308	0.92 (0.83, 1.03)	301	0.95 (0.85, 1.07)
≥27.5	301	0.95 (0.85, 1.07)	294	0.99 (0.87, 1.11)
per 5 kg/m^2†		*0.92 (0.86, 0.99)*		*0.94 (0.88, 1.01)*
%BF				
Quintile 1	520	1.13 (1.03, 1.23)	492	1.13 (1.03, 1.24)
Quintile 2	407	1.00 (0.91, 1.10)	382	1.00 (0.90, 1.11)
Quintile 3	396	0.95 (0.86, 1.05)	386	0.99 (0.90, 1.10)
Quintile 4	357	0.89 (0.80, 0.99)	344	0.92 (0.82, 1.02)
Quintile 5	352	0.87 (0.78, 0.97)	344	0.92 (0.82, 1.02)
per 10%†		*0.86 (0.80, 0.93)*		*0.88 (0.82, 0.96)*
WC				
Quintile 1	436	1.05 (0.95, 1.16)	421	1.07 (0.96, 1.18)
Quintile 2	379	1.00 (0.90, 1.11)	358	1.00 (0.90, 1.11)
Quintile 3	389	1.00 (0.91, 1.11)	365	1.00 (0.90, 1.11)
Quintile 4	386	0.97 (0.88, 1.07)	374	1.00 (0.90, 1.11)
Quintile 5	442	1.02 (0.93, 1.13)	430	1.07 (0.96, 1.18)
per 10 cm†		*0.99 (0.94, 1.05)*		*1.01 (0.95, 1.07)*
WHR				
Quintile 1	327	1.00 (0.89, 1.11)	312	0.99 (0.88, 1.11)
Quintile 2	367	1.00 (0.90, 1.11)	351	1.00 (0.90, 1.11)
Quintile 3	342	1.03 (0.93, 1.15)	323	1.02 (0.92, 1.14)
Quintile 4	451	1.08 (0.98, 1.18)	438	1.10 (1.00, 1.20)
Quintile 5	545	1.07 (0.98, 1.17)	524	1.09 (0.99, 1.19)
per 0.1†		*1.06 (0.96, 1.16)*		*1.07 (0.97, 1.19)*
BMI25				
<20.0	294	0.97 (0.86, 1.09)	280	0.96 (0.85, 1.09)
20.0 to <22.5	611	1.00 (0.92, 1.08)	587	1.00 (0.92, 1.09)
22.5 to <25.0	498	1.10 (1.01, 1.20)	481	1.10 (1.01, 1.21)
25.0 to <27.5	164	1.13 (0.97, 1.32)	160	1.15 (0.98, 1.34)
≥27.5	84	1.16 (0.94, 1.44)	80	1.15 (0.92, 1.43)
per 5 kg/m^2		*1.10 (1.00, 1.20)*		*1.10 (1.00, 1.21)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

† Regression dilution ratios: BMI, 0.95; %BF, 0.88; WC, 0.88; WHR, 0.92.

Appendix 9.6 Adjusted HRs for liver cancer associated with other adiposity traits*

	HBsAg negative		Censoring viral hepatitis	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
HC				
Quintile 1	525	1.13 (1.03, 1.24)	505	1.12 (1.02, 1.23)
Quintile 2	387	1.00 (0.90, 1.11)	371	1.00 (0.90, 1.11)
Quintile 3	386	1.01 (0.92, 1.12)	363	1.00 (0.90, 1.11)
Quintile 4	374	0.99 (0.89, 1.09)	359	1.00 (0.90, 1.11)
Quintile 5	360	0.95 (0.84, 1.06)	350	0.97 (0.86, 1.10)
per 10 cm†		*0.93 (0.85, 1.01)*		*0.95 (0.87, 1.04)*
WHtR				
Quintile 1	371	0.97 (0.87, 1.08)	359	0.99 (0.89, 1.11)
Quintile 2	389	1.00 (0.90, 1.11)	365	1.00 (0.90, 1.11)
Quintile 3	399	0.99 (0.90, 1.10)	381	1.01 (0.92, 1.12)
Quintile 4	406	0.95 (0.86, 1.04)	385	0.96 (0.87, 1.06)
Quintile 5	467	0.95 (0.86, 1.04)	458	1.00 (0.91, 1.10)
per 0.06†		*0.98 (0.93, 1.03)*		*0.99 (0.94, 1.05)*
Height-adjusted weight				
Quintile 1	547	1.11 (1.01, 1.23)	526	1.13 (1.02, 1.25)
Quintile 2	413	1.00 (0.91, 1.10)	388	1.00 (0.91, 1.10)
Quintile 3	368	0.92 (0.83, 1.02)	350	0.94 (0.85, 1.04)
Quintile 4	359	0.95 (0.85, 1.05)	347	0.98 (0.88, 1.10)
Quintile 5	345	0.95 (0.84, 1.07)	337	1.00 (0.88, 1.13)
per 10.8 kg†		*0.93 (0.87, 0.99)*		*0.95 (0.89, 1.01)*
Height-adjusted fat mass				
Quintile 1	545	1.11 (1.01, 1.21)	513	1.09 (0.99, 1.19)
Quintile 2	426	1.00 (0.91, 1.10)	406	1.00 (0.91, 1.10)
Quintile 3	354	0.85 (0.77, 0.94)	341	0.86 (0.78, 0.96)
Quintile 4	359	0.88 (0.80, 0.98)	350	0.91 (0.82, 1.01)
Quintile 5	348	0.89 (0.80, 1.00)	338	0.92 (0.82, 1.03)
per 6.9 kg†		*0.91 (0.86, 0.97)*		*0.93 (0.88, 0.99)*
Height-adjusted lean mass				
Quintile 1	528	1.03 (0.92, 1.16)	509	1.02 (0.91, 1.15)
Quintile 2	420	1.00 (0.91, 1.10)	407	1.00 (0.91, 1.10)
Quintile 3	378	1.00 (0.91, 1.11)	358	0.98 (0.89, 1.09)
Quintile 4	361	1.03 (0.92, 1.15)	343	1.01 (0.91, 1.13)
Quintile 5	345	1.06 (0.93, 1.21)	331	1.06 (0.93, 1.21)
per 7.6 kg†		*0.99 (0.90, 1.09)*		*1.00 (0.91, 1.10)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, and family history of cancer.

† Regression dilution ratios: HC, 0.81; WHtR, 0.92; weight, 0.96; fat mass, 0.99; lean mass, 0.90.

Appendix 9.7 Adjusted HRs for liver cancer associated with PA and SLT*

	HBsAg negative		Censoring viral hepatitis	
	No. cases	HR (95% CI)	No. cases	HR (95% CI)
Total PA				
0 to <8.8	669	1.00 (0.91, 1.10)	644	1.00 (0.84, 1.19)
8.8 to <14.3	425	0.89 (0.81, 0.98)	407	0.90 (0.79, 1.02)
14.3 to <21.9	335	0.82 (0.73, 0.91)	318	0.83 (0.75, 0.91)
21.9 to <33.3	350	0.92 (0.82, 1.03)	339	0.98 (0.81, 1.17)
≥33.3	253	0.73 (0.64, 0.84)	240	0.77 (0.54, 1.10)
per 4 MET-h/day†		*0.95 (0.92, 0.98)*		*0.95 (0.92, 0.98)*
Occupational PA				
0	876	1.00 (0.90, 1.11)	839	1.00 (0.86, 1.17)
>0 to <9.0	365	0.87 (0.78, 0.98)	347	0.89 (0.77, 1.01)
9.0 to <15.5	268	0.78 (0.69, 0.89)	263	0.84 (0.75, 0.94)
15.5 to <26.1	295	0.88 (0.78, 0.99)	280	0.93 (0.80, 1.09)
≥26.1	228	0.70 (0.60, 0.80)	219	0.76 (0.58, 0.99)
per 4 MET-h/day†		*0.95 (0.92, 0.98)*		*0.95 (0.92, 0.98)*
Nonoccupational PA				
0 to <3.9	505	1.00 (0.90, 1.11)	487	1.00 (0.90, 1.11)
3.9 to <6.5	441	1.03 (0.94, 1.13)	420	1.05 (0.96, 1.16)
6.5 to <8.5	376	0.97 (0.88, 1.07)	368	1.02 (0.92, 1.13)
8.5 to <11.6	365	0.97 (0.87, 1.08)	351	1.02 (0.92, 1.14)
≥11.6	345	0.99 (0.88, 1.12)	322	1.06 (0.94, 1.21)
per 4 MET-h/day†		*0.99 (0.90, 1.08)*		*0.98 (0.89, 1.07)*
SLT				
Quintile 1	344	1.00 (0.89, 1.12)	330	1.00 (0.89, 1.13)
Quintile 2	505	0.95 (0.87, 1.04)	490	0.97 (0.88, 1.06)
Quintile 3	512	0.93 (0.85, 1.01)	491	0.94 (0.86, 1.03)
Quintile 4	332	0.90 (0.81, 1.01)	314	0.90 (0.81, 1.01)
Quintile 5	339	0.92 (0.82, 1.03)	323	0.93 (0.82, 1.04)
per 1.5 h/day†		*0.95 (0.82, 1.10)*		*0.94 (0.81, 1.09)*

* Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, total PA (for SLT), and SLT (for PA).

† Regression dilution ratios: total PA, 0.54; occupational PA, 0.62; nonoccupational PA, 0.49; SLT, 0.33.

Appendix 9.8 Adjusted HRs for liver cancer associated with diabetes and RPG among participants without previously diagnosed diabetes[*]

	HBsAg negative		Censoring viral hepatitis	
	No. cases	**HR (95% CI)**	**No. cases**	**HR (95% CI)**
Diabetes status				
No diabetes	1822	Reference	1743	Reference
Total diabetes	210	1.40 (1.21, 1.63)	205	1.43 (1.23, 1.65)
Diabetes status				
No diabetes	1822	1.00 (0.95, 1.06)	1743	1.00 (0.95, 1.06)
Screen-detected	93	1.45 (1.18, 1.77)	91	1.47 (1.20, 1.81)
Previously diagnosed	117	1.37 (1.14, 1.65)	114	1.39 (1.15, 1.67)
RPG (mmol/L)				
<5.6	836	1.00 (0.93, 1.08)	800	1.00 (0.93, 1.08)
5.6 to <6.8	631	1.07 (0.99, 1.15)	601	1.06 (0.98, 1.15)
6.8 to <7.8	230	1.09 (0.96, 1.24)	222	1.10 (0.96, 1.26)
≥7.8	218	1.41 (1.23, 1.62)	211	1.43 (1.25, 1.64)
per 1 mmol/L[†]	*1915*	*1.08 (1.04, 1.11)*	*1834*	*1.08 (1.05, 1.12)*

[*] Model was stratified by age-at-risk (5-year), sex, and region, and adjusted for age at baseline, education, household income, smoking, alcohol, self-rated health, family history of cancer, and fasting hours (for RPG).

[†] Regression dilution ratio: RPG, 0.53.