Understanding the role of vegetarian diet, adiposity and grip strength in cancer risk

Solange Liliana Parra Soto

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Abstract

Cancer is a leading cause of death with rising incidence every year. Lifestyle factors play crucial roles in the risk of this disease. However, more evidence is needed to understand the association between diet, adiposity and physical activity with different cancer site, because most of the evidence still being inconclusive. Therefore, this thesis aims to determine the associations of type of diet, adiposity, grip strength with cancer risk.

The thesis includes four research papers that were conducted in order to achieve its general aim. These studies were conducted utilising data from the UK Biobank. Across these manuscripts, the associations between the different exposures (diet, adiposity and grip strength) and cancer outcomes were studied.

The cancer risks of four types of diet (meat eaters, poultry eaters, pescatarians, and vegetarians) were investigated in the first paper. The study found that vegetarians had a lower risk of all cancer than meat eaters. The study also found that vegetarians had a lower risk of 7 out of the 19 cancer sites studied, including stomach, bladder, and blood cancers. Pescatarians also had a lower risk of colorectal cancer than meat-eaters. The meta-analysis, which included 15 studies with 1,180,523 participants, supported the findings of the UK Biobank study, with vegetarians having a lower risk of all cancer and fish-eaters having a lower risk of gastric cancer than to meat-eaters.

The second study found that higher levels of all six adiposity-related markers were associated with a higher risk of developing and dying from cancer. BMI, waist circumference, hip circumference, and waist-to-hip ratio were positively associated with the incidence and mortality from several cancer types, including liver, lung, and

pancreas cancers. The third study identified that both general obesity (defined as BMI ≥30 kg/m^2) and central obesity (defined as waist circumference >90 cm for men and >84 cm for women) were independently associated with a higher risk of developing and dying from cancer. The combined presence of general and central obesity was associated with a higher risk of developing and dying from several colorectal, liver, and pancreatic cancers.

Finally, the fourth study found that both absolute and relative grip strength were inversely associated with the risk of cancer. The association between grip strength and cancer risk was consistent across different cancer types and subgroups of participants.

In conclusion, these four papers provide important insights into the roles of lifestyle factors on cancer risk and highlight the importance of maintaining a healthy diet, maintaining muscle strength, and maintaining a healthy body weight for cancer prevention. All of the studies included in the thesis were observational. Therefore, they cannot establish that a particular diet, adiposity, or grip strength caused cancer. However, they are in line with the current research on cancer prevention.

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Publications

Included in this thesis.

Parra-Soto, S., Ahumada, D *et al*. (2022). 'Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank prospective cohort study and meta-analysis'. *BMC medicine*. **IF: 8.775. Cited by: 13**

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Parra-Soto, S., et al. (2020). ‘Obesity and Cancer-The two scenarios that Chile will lead’. Rev Med Chile. Article in Spanish. **IF: 0.22. Cited by: 3.**

Posters and Abstracts

Parra-Soto, S, et al (Dec 2022). **22nd IUNS-ICN**: Joint European Congress on Obesity. 'Association between food preference and health outcomes: findings from the UK Biobank prospective cohort study'. Oral presentation

Parra-Soto, S, et al (May 2022). **ZoomFoward 2022: Joint European Congress on Obesity.** 'Visceral adiposity index and its association with cancer risk in the UK Biobank cohort'. Oral poster

Parra-Soto, S., et al. (November 2021). **AICR 2021 Research Conference- Online conference.** 'Adherence to the AICR/WCRF Cancer Prevention Recommendations among 110,727 participants in the UK Biobank prospective study'. Oral poster.

Parra-Soto, S., et al. (November 2021). **National Cancer Research Institute (NCRI) Festival: Making cancer research better together- Online conference**. 'Is A Body Shape Index (ABSI) associated with incident cancer? – Findings from the UK Biobank prospective cohort study'. Oral Presentation- *NCRI Award winner*

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Parra-Soto, S., et al. *(May 2021).* **28th European and International Congress on**

Obesity (EASO) – Online conference. 'Is A Body Shape Index (ABSI) associated with incident cancer? – Findings from the UK Biobank prospective cohort study'. Oral poster.

Parra-Soto, S., et al. *(May 2021).* **Canada Obesity Conference – Online conference.** 'Cancer cases and deaths attributable to adiposity- Findings from the UK Biobank prospective cohort study." Canada Obesity Conference'. Oral poster.

Parra-Soto, S., et al. *(September 2020).* **ESPEN– Online conference.** 'The association of type of diet and all-cause cancer incidence and mortality: prospective study from UK Biobank'. Poster.

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Parra-Soto, S., et al. *(September 2020).* **2nd International DKFZ Conference on Cancer Prevention– Online conference.** 'Joint association of body mass index and waist circumference with cancer risk at 24 sites'. Poster.

Parra-Soto, S., et al. *(September 2020).* **European and International Congress on Obesity (EASO)– Online conference.** 'Sex differences in the associations between adiposity-related markers and incidence from 24 cancer sites in the UK Biobank prospective cohort study'. Poster.

Parra-Soto, S., et al. (November 2020). **National Cancer Research Institute (NCRI) Virtual Showcase– Online conference**. 'Does insulin like growth factor moderate the association between height and risk of cancer at 24 sites?'. Poster.

My journey to become an early career researcher.

I always thought Ph.D. is for improving skills such as improving subject knowledge, running experiments, and developing data analysis skills. Before starting, I had aimed to strengthen my data analysis skills and the use of English language. Still, after these three years of learning, I have developed not just quantitative skills but also a lot of other skills through the development of the different papers I included in this thesis. My time management skill has improved because Ph.D. is not just writing articles. There are also training, meetings, teaching, journal submissions, and revisions. I learned how to use effective my time and the best tactics to help me with this, also problem-solving, at the beginning I support a lot with my supervisor. Still, during these years, I took more responsibilities and was in charge of my research and team.

I never felt confident to be a leader, so I never thought developing leadership skills was needed in my Ph.D. In my last year, I went to the European Nutrition Leadership Platform course, where I learned that we can be leaders in any position, the importance of team working and focusing on our current skills and improving them more than focusing on having the skills we lack because more people in your team could have it. I have considerably improved my writing style in Spanish and English and polished my presentations. I wrote as many papers as I could during these years, read and learned from different writing styles, and I continue having red revisions from my supervisor until now. I continue to find my style.

Another skill that I learned during a PhD is academic presentation. Most of my presentations were online due to the COVID-19 pandemic. Still, I tried to go to at least 3 conferences per year to show my results to explain my research to others; In 2021, I went to my first conference in person; it was a multidisciplinary conference, and I had

the opportunity to tell others about my job, no one was an expert in my field, and I enjoyed to say to others what I was doing, what was my contribution in my area. This year I had the opportunity to tell people in my field part of what I was doing face to face. I received many questions and was happy again to show my contribution in English. Both experiences were vibrant for me; all my presentations allowed me to improve and express myself in a foreign language.

Finally, I did not say before that one of my main motivations for doing a Ph.D. is to become a lecturer; due to the pandemic, most of the teaching was online, and I had the opportunity to teach at a Chilean University about the different skills I was developing during my Ph.D., such as statistics and epidemiology. I did lecturing for almost two years, and it was amazing how all the knowledge was there I could teach someone else. I am grateful for this experience; it gave me not just skills I wanted but also skills for my life.

Acknowledgement

I am deeply grateful to my supervisors, Professor. Jill Pell, Dr. Frederick Ho and Dr. Carlos Celis, for their guidance and support throughout this project. Their mentorship has been invaluable, and I am so fortunate to have had them as mentors. I am incredibly grateful for Dr. Celis willingness to meet with me at all moments I needed him to discuss my research until today. His insights and feedback have been essential to the development of this thesis and my career.

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Finally, I would like to thank my family for their love and support. My parents always believed in me and be proud of every step I have done.

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I cannot express everything in a page, but I am so grateful to have all of them in my life.

Author's Declaration

I declare that this thesis is the result of my own work. In those cases that a contribution of others was used, explicit reference was included. The manuscripts included are open access; therefore, they can be openly shared in this thesis.

The contents of this thesis have not been submitted for any other degree at the University of Glasgow or any other institution.

Solange Parra Soto

August 2023

Main Abbreviations

BMI	Body mass index
WC	Waist circumference
UK	United Kingdom
GLOBOCAN	Global Cancer Observatory
WCRF	World Cancer Research Fund
AICR	American Institute for Cancer Research
GBD	Global Burden of Diseases
NCDs	Non-communicable diseases
BF%	Body fat percentage and
BFI	Body fat index
WHR	Waist-hip ratio
WHtR	Waist-height ratio
HGS	Handgrip strength
HC	Hip circumference
ICD	International Classification of Diseases
BIA	Bioimpedance
CI	Confidence interval
CVD	Cardiovascular disease
DXA	Dual-energy x-ray absorptiometry
EAC	Ethics Advisory Committee
HES	Health Episode Statistics
HR	Hazard ratio

MRC	Medical Research Council
NHS	National Health Service
OR	Odds ratio
RR	Risk Ratio
SD	Standard deviation
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Epidemiology of cancer

Cancer is one of the most important challenges in contemporary public health (Sung et al., 2021, Bray et al., 2018). The Global Cancer Observatory (GLOBOCAN) estimated 18.1 million incident cancers and 9.6 million cancer deaths in 2018 (Bray et al., 2018). In 2020, this estimation was updated to 19.3 million new cases and 10.0 million deaths due to cancer worldwide (Sung et al., 2021) (Figure 1-1), and this number is expected to increase to 28.4 million new cancer cases by 2040 (Sung et al., 2021).

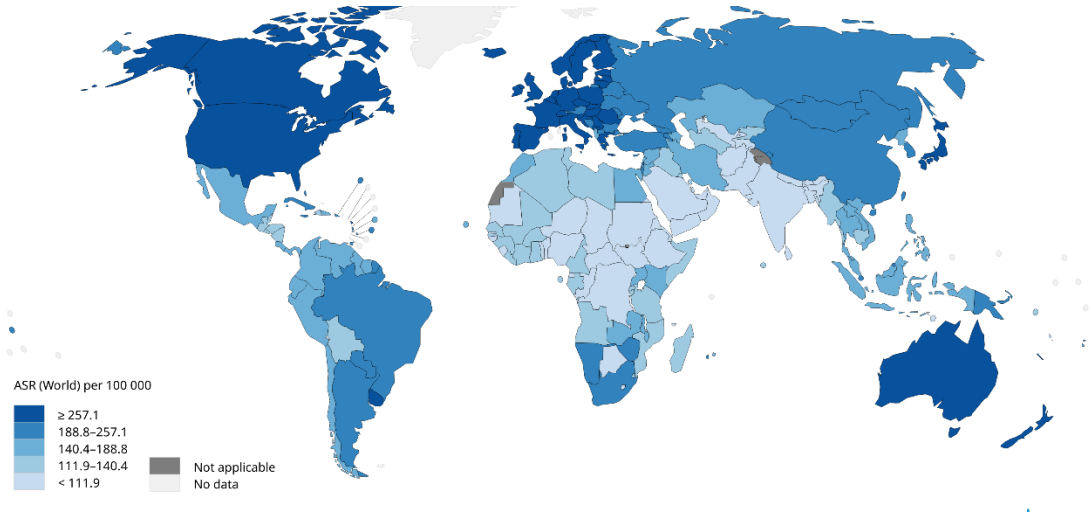

Figure 1-1. Estimated age-standardized incidence rates in 2020.

Source: Adapted from GLOBOCAN, 2020

In 2020, the highest proportion of cancer deaths (58.3%) occurred in Asia, with 19.6% of cancer deaths in Europe and 7.2% of deaths in Africa (Sung et al., 2021). The most commonly diagnosed cancer, which accounted for 11.7% of total cancer cases in the world, was breast cancer. This was closely followed by lung cancer (which accounted for 11.4% of cancer cases), colorectal cancer (10%), prostate cancer (7.3%) and finally stomach cancer (5.6%) (1). The leading cause of cancer deaths was lung cancer (18%), followed by colorectal (9.4%), liver (8.3%), and stomach (7.7%) cancer, and breast cancer in women (6.9%). The leading cause of cancer death in women was breast cancer and, for men, lung cancer, followed by prostate and colorectal cancers (Figure 1-2) (Sung et al., 2021). In

countries with a high Human Development Index (HDI), such as the United Kingdom (UK), death from cancer has surpassed death from cardiovascular diseases (Dagenais et al., 2020).

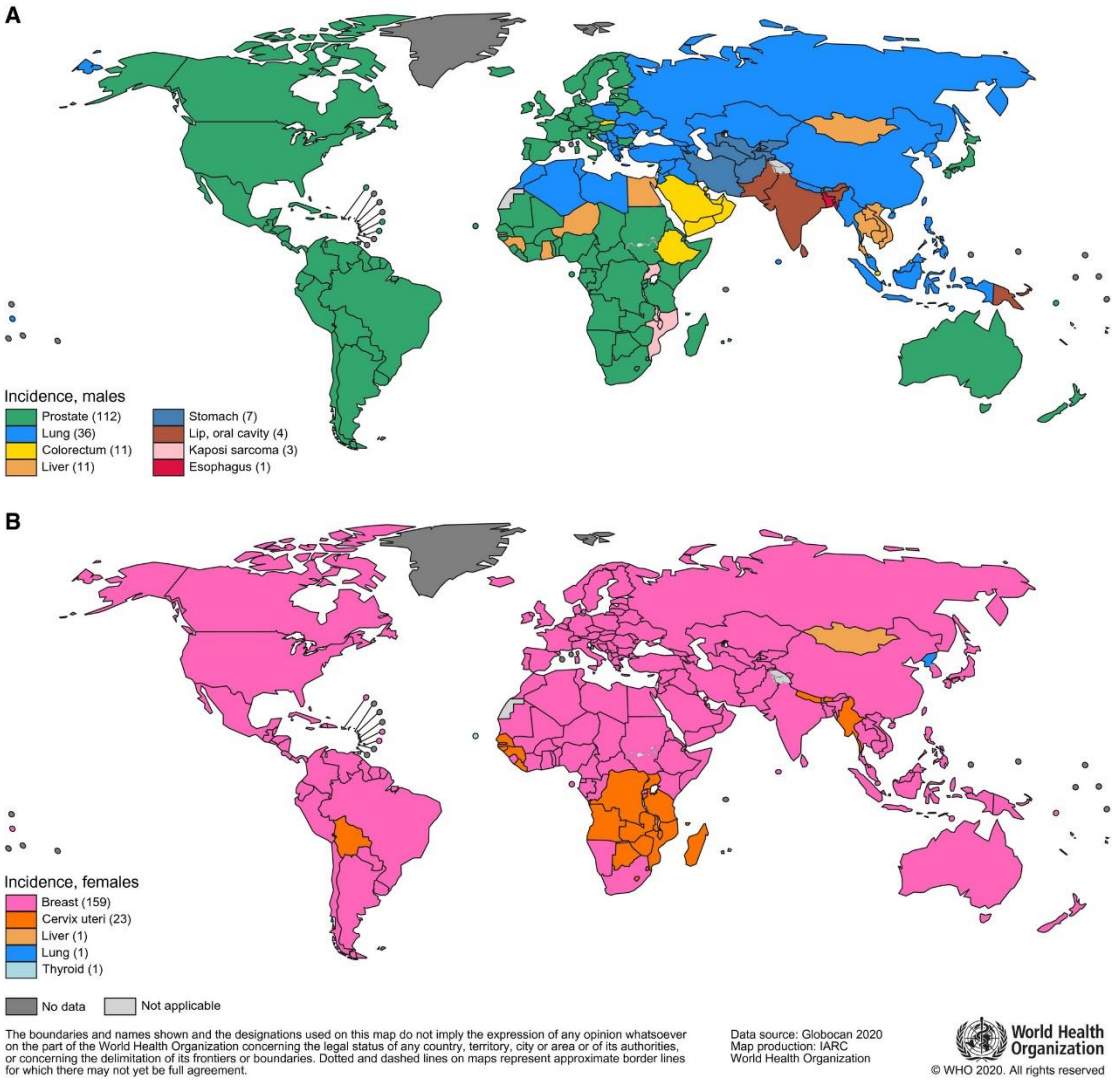

Figure 1-2. Most Common Type of Cancer Incidence in 2020 in Each Country Among (A) Men and (B) Women.

Source: Adapted from GLOBOCAN, 2020

Cancer is a significant health problem in the United Kingdom (UK). Cancer Research UK (CRUK) reported that between 2016 to 2018 there were 375,400 new cancers diagnosed in the UK and cancer caused 167,000 deaths. It is further projected that there will be around 514,000 new cases of cancer diagnosed per year in 2035 (Cancer Research UK, 2022). In 2017, breast, prostate, lung and bowel cancers accounted for 53% of new cancer cases in the UK (Cancer Research UK, 2022). Cancer is the second leading cause of

death in the UK, accounting for around 29% of all deaths. The most common types of cancer in the UK are prostate, breast, colorectal, and lung cancer, which together account for more than half of all new cancer cases (Figure 1-3) (Bray et al., 2018, Cancer Research UK, 2022).

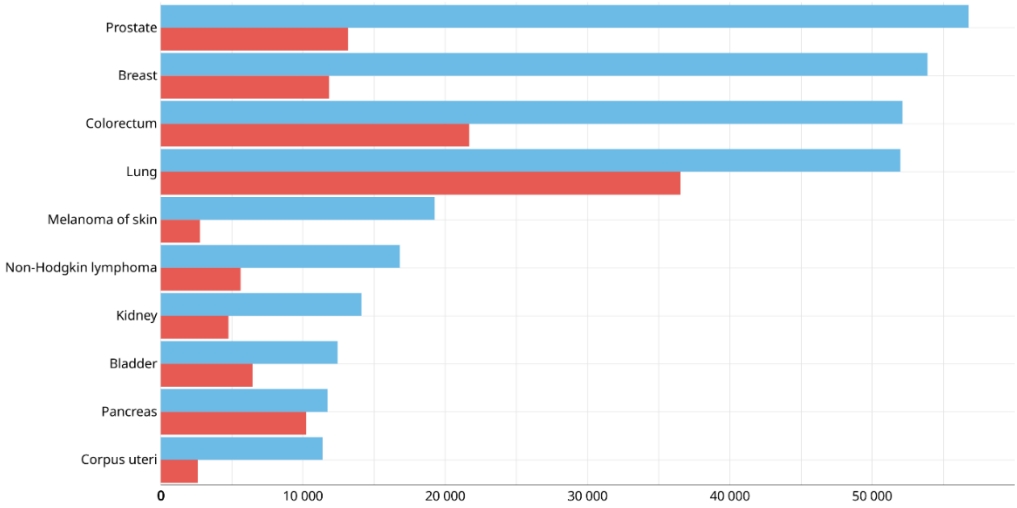

Figure 1-3. Estimated number of incident and deaths in the UK, both sex and age.

Source: Adapted from GLOBOCAN, 2020

1.2 Cancer Aetiology

Cancer is a disease characterized by the abnormal and uncontrolled growth of cells in the body. Cancer develops when the usual mechanisms that control cell behaviour break down and a cell becomes the ancestor of a population of cells with similar functional abnormalities. Cancer cells divide and grow uncontrollably, forming a mass of tissue called a tumour (Cooper GM, 2000, National Institutes of Health, 2007). Cancer can occur in any part of the body and can spread to other parts through the bloodstream or lymphatic system. There are many different types of cancer, each with its own set of causes, symptoms and treatment options (Cooper G., 2000, Annad P., et al, 2008).

(Figure 1-4) (World Cancer Research Fund/American Institute for Cancer Research, 2018b).

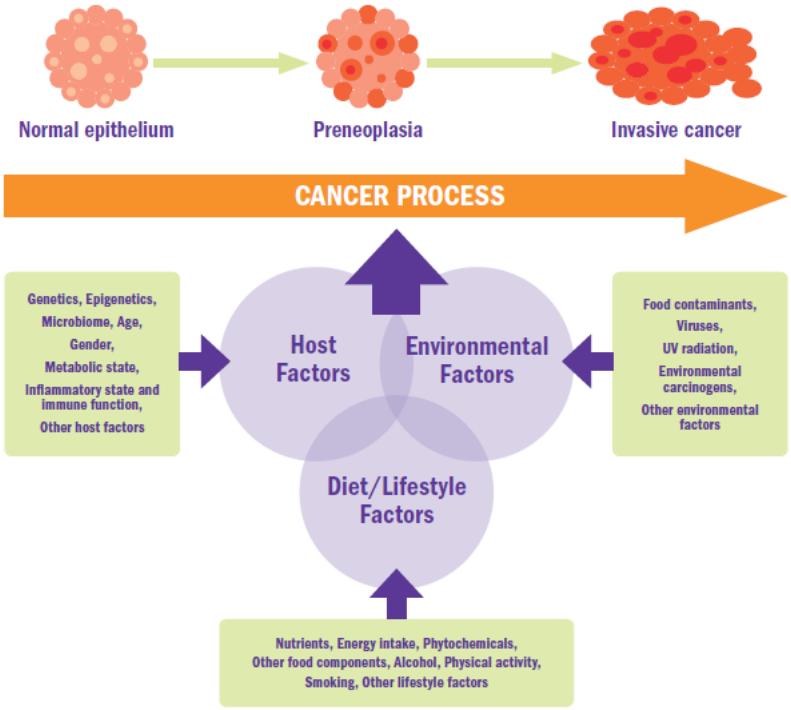

Figure 1-4. Diet, nutrition and physical activity, other environmental exposure and host factors interact to affect the cancer process.

Source: Adapted from World Cancer Research Fund/American Institute for Cancer Research, 2018

1.3 Cancer and Lifestyle

Cancer is caused by a complex interaction of environmental, lifestyle, and biological variables, according to epidemiological and molecular studies (Song et al., 2018). A lower risk of several types of cancer has been linked to leading a healthy lifestyle, which includes a good diet, frequent exercise, maintaining healthy body weight, and abstaining from alcohol and tobacco (Spring et al., 2015, Khan et al., 2010). According to recent research, 30-50% of all malignancies are caused by modifiable risk factors (Whiteman et al., 2015, Brown et al., 2018, Islami et al., 2018). Therefore, according to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) worldwide expert group, improving food, physical activity, and lifestyle choices could prevent at least one-third of all malignancies. (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). The most recent research from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)

2019, stated that environmental and lifestyle factors contributed to over 44% of all cancer deaths. Smoking, drinking, and having a high body mass index (BMI) ranked as the three biggest risk factors for cancer risk (Collaborators, 2022)

1.3.1 Diet and Cancer

Diet is an important modifiable lifestyle factor for prevention of cancer (Afshin et al., 2019, World Cancer Research Fund/American Institute for Cancer Research, 2018b, Collaborators, 2022). Globally in 2017, 913,090 cancer deaths were attributable to diet (Afshin et al., 2019). The current dietary guidelines prioritise the reduced consumption of unhealthy food items like red meat, processed meat, sugary drinks, and salt, while encouraging the intake of healthy food items such as fruit, vegetables, oily fish, and whole grains (Public Health England, 2016).

The WCRF/AICR presented consistent evidence for the association between unhealthy food and cancer. For instance, there is strong evidence that colorectal cancer is associated with consumption of processed meat, and convincing evidence that it is associated with red meat consumption (Zhao Z., et al, 2017). Red and processed meat have also been associated with other types of cancer: nasopharyngeal, oesophageal, pancreatic, stomach, lung, and all-cause cancer mortality (Figure 1-5) (World Cancer Research Fund/American Institute for Cancer Research, 2018b). Indeed, the fraction of colorectal cancer deaths attributable to red and processed meat is 25% in the UK (Brown et al., 2018). Cantonese-style salty fish was consistently found to be associated with higher risk of colorectal cancer (Figure 1-5) (World Cancer Research Fund/American Institute for Cancer Research, 2018b).

On the other hand, fruits and vegetables were found to be associated with lower cancer risk (Ubago-Guisado et al., 2021, World Cancer Research Fund/American Institute for Cancer Research, 2018b). Evidence from observational studies has shown

that 100g/day of vegetable consumption reduces the risk by around 10% for oesophageal and lung cancer (Risk Estimate (RE): 0.89, 95%CI: 0.80-0.99, RE:0.88, 95%CI: 0.79-0.99) and 200g/day reduces the risk of breast cancer by around 20% (RE: 0.79, 95%CI: 0.63-0.98) (World Cancer Research Fund/American Institute for Cancer Research, 2018b). Similar results have been shown in relation to fruits, specifically citric fruits, and stomach cancer, as well as foods containing carotenoids and lung, breast and prostate cancer (Ubago-Guisado et al., 2021). There is convincing evidence that consumption of whole grains and fibre are associated with lower risk of colorectal cancer (Figure 1-5) (World Cancer Research Fund/American Institute for Cancer Research, 2018b).

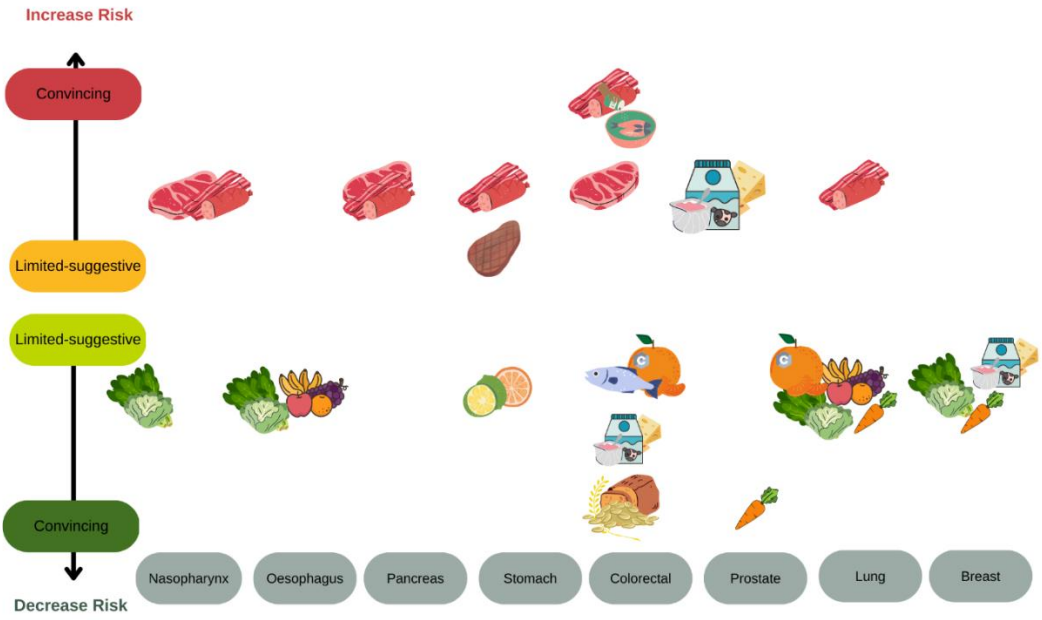

Figure 1-5: Summary Matrix level of evidence available for wholegrains, vegetables and fruits, Meat, fish and dairy products and the risk of cancer.

Source: Adapted from WCRF/AIRC, 2018, using canva and flaticon.

The majority of evidence that nutrient and food intake may be protective of health comes from studies that investigated either a single food/nutrient or used a more comprehensive assessment of macronutrient intake (Lim et al., 2012, World Cancer Research Fund/American Institute for Cancer Research, 2018b). However,

dietary patterns are a better indicator of the actual consumption of nutrients and foods which are typically eaten together and, therefore, it may be more appropriate to examine their combined effects by analysing the overall dietary pattern (Figure 1-6) (Hu, 2002). Indeed, what we eat and the type of dietary pattern we follow are influenced by many factors such as socioeconomic status, environment, culture and personal beliefs (Hu, 2002, Cespedes and Hu, 2015).

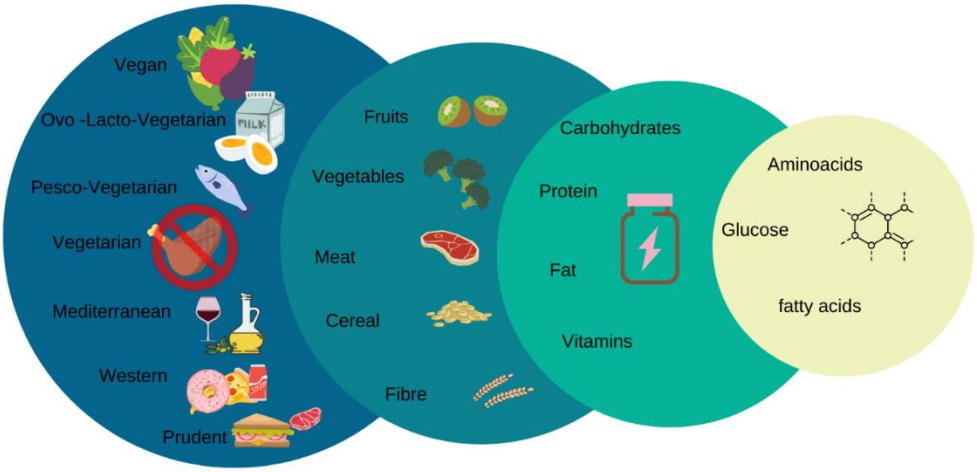

Figure 1-6. The spectrum of elements to study in nutrition epidemiology could be related to cancer risk.

Source: Adapted from Melinda et al, using canva and flaticon.

Plant-based diets are an integral part of evidence-based recommendations for the primary prevention of cancer and other non-communicable diseases (NCDs) (Hardt et al., 2022, World Cancer Research Fund/American Institute for Cancer Research, 2018b). Therefore, diets rich in whole grains, vegetables, fruit, nuts and legumes with limited consumption of red and processed meat are promoted. Of these, the vegetarian diet has become more popular through the years (Melina et al., 2016). It has been hypothesised that a vegetarian diet reduces the risk of cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018b).

1.3.1.1 Current Evidence on Vegetarian Diet

Vegetarians have been defined as people who do not consume meat, poultry or fish. Among them there are sub classifications including

pescatarians, lacto-ovo-vegetarians, and vegan (Melina et al., 2016). To date most of the evidence on vegetarianism has been focused on all-cause mortality (Appleby et al., 2016, Key et al., 2009b, Orlich et al., 2013), with limited and conflicted evidence on cancer (Key et al., 2009a, Tantamango-Bartley et al., 2013, Cade et al., 2010, Dinu et al., 2017, Godos et al., 2017, Orlich et al., 2013). For instance, Orlish et al. conducted a study on 73,308 Seventh-day Adventist men and women who were followed up for 5.7 years and reported no associations between a vegetarian diet and either all-cause cancer incidence or mortality, compared with a non-vegetarian diet (Orlich et al., 2013). In contrast, Key et al. found that pooled data from two British prospective cohorts, covering 61,647 men and women, with a follow up of 14.9 years, and reported that vegetarians had 12% lower risk of all-cause cancer, compared with meat-eaters (Key et al., 2009a). This same study also showed that fish-eaters had the same 12% lower risk of all-cause cancer and a 38% and 34% lower risk of stomach and colorectal cancer, respectively (Key et al., 2009a).

Other studies have been focused on specific cancer sites (Key et al., 2009a, Penniecook-Sawyers et al., 2016, Dinu et al., 2017, Godos et al., 2017, Tantamango-Bartley et al., 2016) but found no differences for breast (Penniecook-Sawyers et al., 2016) or prostate (Tantamango-Bartley et al., 2016) cancer. Two systematic reviews were published in 2017 (Dinu et al., 2017, Godos et al., 2017). Dinu et al. reported an 8% lower risk of all-cause cancer among vegetarians (Dinu et al., 2017), while Godos et al. found no associations with breast, colorectal and prostate cancer when the study results were pooled (Godos et al., 2017). However, these reviews were limited all-cause cancer or the most common cancer sites. In addition, the comparison group was not well defined and comparable across studies, and different populations were included with diverse dietary patterns and lifestyles. Some of the studies included had a higher risk of bias and definitions of vegetarian diet differed across the studies. In summary, existing evidence shows that investigations of the associations with dietary patterns have been restricted to a limited number of cancer sites (~5000 cases)

and have produced equivocal findings.

1.3.2 Adiposity and cancer

Around the world, the prevalence of obesity has tripled since 1975 and, in 2016, over 650 million were people with obesity (Dai et al., 2020). Strong epidemiological and clinical data support the hypothesis that people with overweight and obesity raises the risk of a number of non-communicable diseases, including cardiovascular diseases, respiratory diseases, and several types of cancer (Lauby-Secretan et al., 2016, Ortega et al., 2016, Williams et al., 2015). Several factors have been associated with obesity, including for instance; poor diet, sedentary lifestyles, genetics, psychological factors, and environmental factors (World Health Organization, 2000a, Williams et al., 2015, Ortega et al., 2016).

The WCRF/AIRC showed that there is strong evidence linking adiposity, measured using body mass index (BMI), and the risk of several cancers including oesophagus, pancreas, liver, colorectum, breast (post-menopause) and endometrium. However, the evidence was graded as only probable for mouth, pharyngeal, laryngeal, stomach, gallbladder, ovary and prostate cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018b) (Figure 1-7).

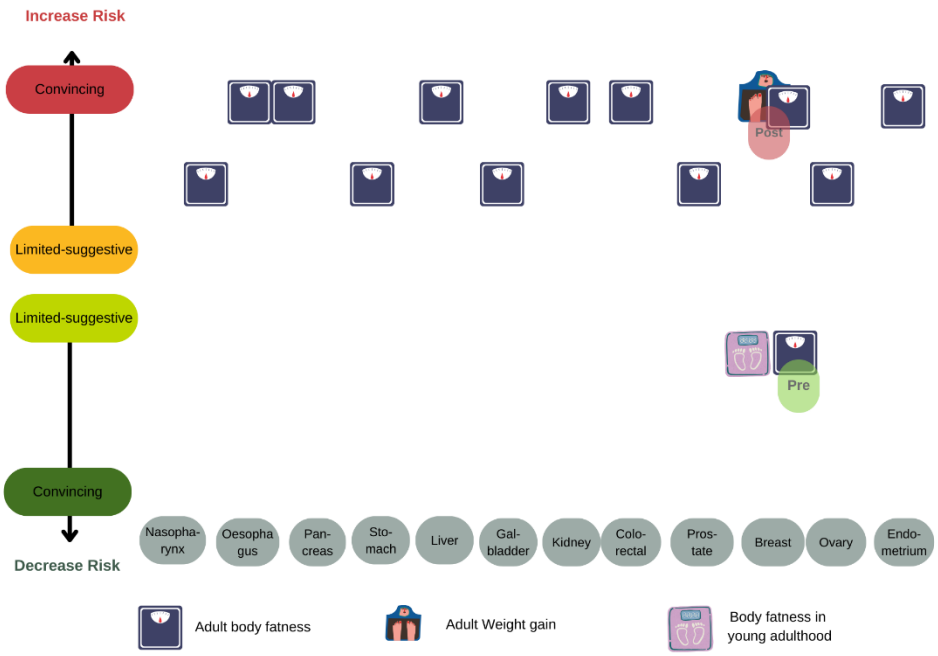

Figure 1-7. Summary Matrix for level of evidence on Body fatness and weight gain and the risk of cancer.

Source: Adapted from WCRF/AIRC 2018 report, using canva and flaticon

Whilst the current evidence has tended to focus on BMI, other measurements such as waist circumference (WC), body fat percentage (BF%), and waist-hip ratio (WHR) might be better measures of adiposity in cancer studies, as is the case for cardiovascular risk (Table 1.1) (World Cancer Research Fund/American Institute for Cancer Research, 2018b, Barberio et al., 2019, Tang et al., 2017, Snijder et al., 2006). Few studies have compared the effect estimates for BMI and WC in relation to multiple site-specific cancers (Freisling et al., 2017, Barberio et al., 2019), and none have studied emerging adiposity markers in different cancer types or combinations of these markers.

In a study of 26,607 Canadians, Barberio et al., showed that WC could be a better predictor of cancer than BMI. When BMI analyses were adjusted for WC, the effect size of BMI attenuated, especially among women (Barberio et al., 2019). Existing studies of associations between adiposity and cancer have considered BMI and WC separately (Freisling et al., 2017, Barberio et al., 2019). However, the distribution of excess fat also plays a role in its association with cancer (Britton et al., 2013, Gupta et al., 2017), and BMI does not capture fat distribution (Arnold et al., 2016). A study of 2,627 Americans showed that greater lower body subcutaneous fat was associated with lower cancer risk (Gupta et al., 2017). Conversely, in 3,086 participants of the Framingham study, visceral adiposity was associated with incident cancer (Britton et al., 2013).

The evidence supporting an association between body fat percentage and cancer risk is scarce. This is partially because it can be difficult to measure body fat percentage reliably in largescale epidemiological studies. In 2019, a study of 3,460 postmenopausal women found that higher body fat percentage was associated with increased risk of breast cancer (Iyengar et al., 2019). However, further studies are needed to corroborate these results.

There is limited evidence specifically on the relationship between combined adiposity markers and cancer risk. Sun et al. showed that women of normal weight with central adiposity had higher risk of cancer mortality (Sun et al., 2019). However, this analysis was restricted to women and did not apply the WCRF/IARC cut offs for WC cancer prevention (≤80cm in women, ≤94cm in men) (World Cancer Research Fund/American Institute for Cancer Research, 2018b). To date, no other studies have combined measurements of adiposity.

In summary, the current evidence has been focussed principally on BMI and WC, and not investigated newer, or more sophisticated markers. Firstly, I hypothesised that other markers, such as BF%, WHR, and waist hip ratio, may have stronger associations with specific cancer sites. Secondly, I hypothesised that using BMI and WC combined better risk stratification, for instance, with people who have both higher BMI and higher WC having higher risk of cancer compared with people who have only one adiposity marker, and even more so compared with people having normal BMI and WC.

Table 1-1. Summary table on adiposity markers

Marker	**Definition**	**Cut-off for obesity**	**Reference**
Body mass index	Weight (kg) divided by height square (m^2).	≥30kg/m^2	(World Health Organization, 2000a)
Waist circumference	The distance around your waist, just above your hips	Men ≥94cm Women ≥80cm	(World Cancer Research Fund/American Institute for Cancer Research, 2018b)
Waist-hip ratio	Waist circumference divided by hip circumference	Men ≥0.90 Women ≥0.85	(World Health Organization, 2008)
Waist-height ratio	Waist circumference divided by height	≥0.5	(NICE, 2022)
Body fat percentage	Proportion of fat mass	Men ≥25% Women ≥35%	(World Health Organization, 1995)
Muscle mass	Lean mass	Men <20 kg Women <15 kg	(Studenski et al., 2014)

1.3.3 Grip strength and cancer

While body composition, such as BF%, has been linked to increased risk of cancer, and lean mass has been inversely associated to cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018b). Muscular weakness can be defined as low grip strength (Bhasin et al., 2020). Indeed, the latest American Physical Activity guidelines included “Each week adults need 150 minutes of moderate-intensity physical activity and 2 days of muscle strengthening activity” (U.S. Department of Health and Human Services, 2018).

Handgrip strength (HGS), a common muscle strength marker, is often used in clinical and research settings to assess muscle strength because it is simple and inexpensive to measure, and has a good correlation with overall strength (Ho et al., 2019, Cooper et al., 2010, Bohannon, 2015). HGS, measured using a handheld dynamometer, measures the maximal amount of force exerted during an isometric hand squeeze (Bohannon, 2015, Celis-Morales et al., 2018).

Existing evidence has shown a strong association between low HGS and mortality from all-cause and CVD (Celis-Morales et al., 2018, Leong et al., 2015, Wu et al., 2017, Cooper et al., 2010). However, published evidence of an association with cancer has been less conclusive (Leong et al., 2015, Celis-Morales et al., 2018, Yates et al., 2017). The Prospective Urban Rural Epidemiology study (PURE), which included 139,691 participants in 17 countries, reported that

lower absolute HGS (reported as per 5 kg reduction in HGS) was associated with increased cancer risk, particularly in participants from high-income countries (HR: 0.916, 95% CI: 0.880; 0.953) (Leong et al., 2015).

Previous studies conducted on UK Biobank have been inconsistent. For instance, Yates et al. showed no association between HGS and all-cause cancer mortality among 420,727 participants (230,670 women and 190,057 men) but specific cancer sites were not studied (Yates et al., 2017). Meanwhile, Celis-Morales et al., in 477,074 participants, reported associations of absolute HGS with all-cause cancer, as well as colorectal, lung, and breast incident cancer and mortality (Celis-Morales et al., 2018). Wu et al., in a meta-analysis that included 42 studies, did not find an association between HGS and overall cancer [hazard ratio (HR): 0.89, 95% confidence interval (CI): 0.66–1.20] (Wu et al., 2017). Similar results were found by García-Hermoso et al. who, in a meta-analysis published in 2018, which included 309,413 participants and 9,787 cancer cases, found no association between HGS and overall cancer mortality. However, the categorization of HGS and adjustment for covariates was heterogeneous between studies, and there was no stratification by cancer site (García-Hermoso et al., 2018). The current studies included different definitions of HGS and adjusted for potential confounders to a different extent, which could explain some of the inconsistency in their results.

Absolute strength refers to the maximum amount of force that a muscle or muscle group can generate, typically measured in

kilograms or pounds. It is influenced by factors such as muscle size, fibre type, and neurological efficiency (Baechle and Earle 2008). Relative strength, on the other hand, takes into account an individual's body weight or size. It is calculated by dividing absolute strength by body weight and is often expressed as a ratio or percentage. Relative strength may be a better indicator of functional ability and performance, as it accounts for differences in body size and composition (Stone et al., 2002).

Most of the evidence has been focused on cancer mortality with limited evidence for other cancer sites and HGS has only been considered as an absolute value. Therefore, I hypostatised that measures of relative grip strength may be more strongly associated with specific cancer sites.

1.3.4 The Role of Diet, Adiposity and Grip Strength in Cancer

Deregulation of cellular energetics, evasion of growth suppressors, avoidance of immune destruction, and tumor-promoting inflammation, among others, are crucial components of the biology of cancer cells, and lifestyle variables can affect them all. Therefore, nutrition, physical capability and adiposity play a key role in determining whether a healthy cell has the capacity to develop cancerous features (Figure 1-8).

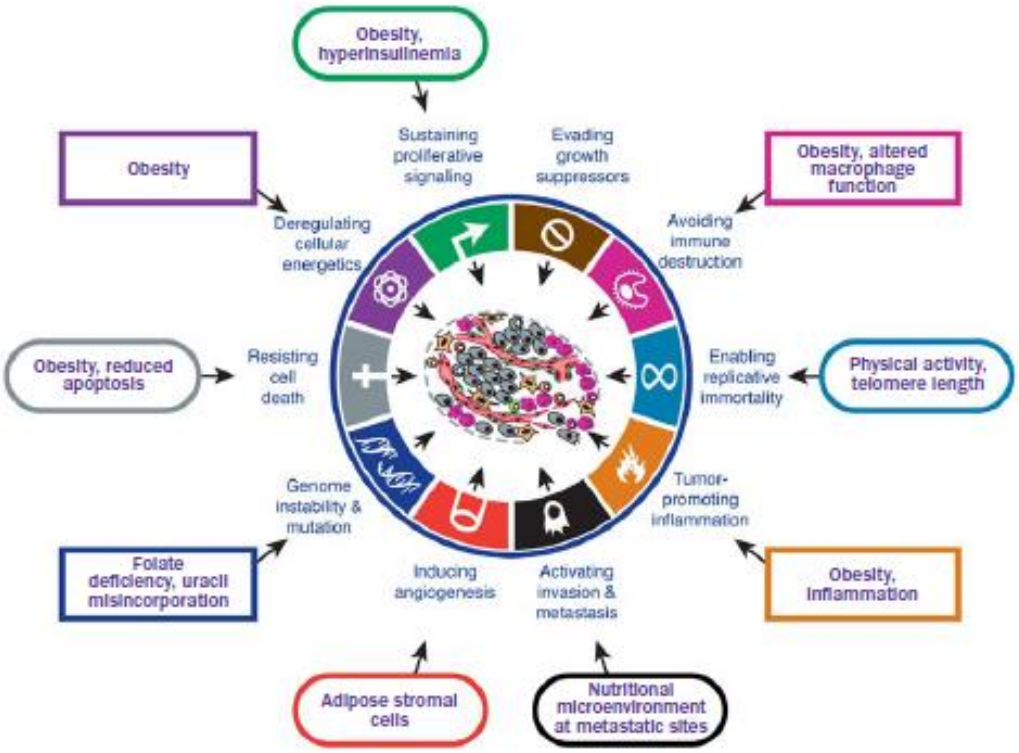

Figure 1-8: Nutrition, physical activity and the hallmarks of cancer

Source: Adapted from WCRF/AIRC

The link between diet, strength, and adiposity is complex and multi-factorial. Here are some potential ways in which they may be linked:

Diet and adiposity: Diet is a key factor in the development and maintenance of adiposity. Consuming a diet high in calories, saturated and trans fats, and added sugars can lead to excess energy intake and increased adiposity. Conversely, consuming a diet that is high in fibre, lean protein, healthy fats, and whole foods may help to promote a healthy body weight and reduce adiposity (Clemente-Suárez., et al 2022, World Cancer Research Fund/American Institute for Cancer Research, 2018b).

Diet and strength: Adequate nutrition is essential for the development and maintenance of muscle strength (Robinson et al.,

2019). Specifically, consuming sufficient amounts of protein, carbohydrates, and fat can support muscle growth and repair, which in turn may improve strength (Carbone et al., 2019). Conversely, a diet lacking in these macronutrients may impair muscle strength and function (World Cancer Research Fund/American Institute for Cancer Research, 2018b).

Adiposity and strength: Higher levels of adiposity, or body fat, may be associated with lower muscle strength. This is thought to occur via several mechanisms, such as increased mechanical loading on the joints, decreased mobility, and metabolic dysfunction (Rubio-Ruiz et al., 2019). Additionally, excess body fat may interfere with the proper functioning of muscle cells, which can impair strength (Addison, et al., 2014).

The Third Expert Report, Diet, Nutrition, Physical Activity Cancer, from WCRF/AICR collated the latest evidence on cancer prevention (World Cancer Research Fund/American Institute for Cancer Research, 2018b). However, this same report highlighted the current need for more research to increase the strength of the evidence and produce the strongest recommendations to generate the best possible answer to the most important questions related to diet, nutrition and physical activity (World Cancer Research Fund/American Institute for Cancer Research, 2018b). Therefore, this thesis will explore diet through broad dietary patterns, nutrition through obesity and physical activity through muscular strength, and their association with most common cancer sites.

1.4 Aim

1.4.1 General aim

To determine the associations between type of diet, adiposity, and grip strength and cancer risk.

1.4.2 Specific objectives

I. To investigate the association of type of diet with all cancers and site-specific incident cancers in a prospective cohort study and then in a meta-analysis of published prospective cohort studies.

II. To investigate the associations of adiposity markers with all cancers and site-specific incident cancers in a prospective cohort study

III. To investigate the associations of combinations of BMI and WC with all cancers and site-specific incident cancers in a prospective cohort study.

IV. To compare the associations of absolute and relative grip strength with all cancers and site-specific incident cancers in a prospective cohort study.

1.5 Thesis Overview

Throughout this thesis, each objective mentioned above will be systematically covered across four published papers. Using the published version of each one. **Chapter 2** summarises my prospective cohort study's design and general methodology. One published paper is included in ***Chapter 3***. which covered the association of type of diet and cancer. ***Paper 1*** - *"Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank prospective cohort study and meta-analysis"*. The association of obesity and cancer will be covered in **Chapter 4 and Chapter 5**. One paper published was included in **Chapter 4**. In this chapter, **Paper 2** - "*Associations of six adiposity-related markers with incidence and mortality from 24 cancers—findings from the UK Biobank prospective cohort study*" - Adiposity is a strong risk factor for cancer incidence and mortality. However, most of the evidence available has focused on body mass index (BMI) as a marker of adiposity. There is limited evidence on relationships of cancer with other adiposity markers, and if these associations are linear or not. In **chapter 5** one published paper was included **Paper 3** -"*Combined association of general and central obesity with incidence and mortality of cancers in 22 sites*" - Body mass index (BMI) and waist circumference (WC) are measures of general and central obesity, respectively, and both have been shown to be associated with cancer. However, there is insufficient evidence of their combined association with the risk of cancer. One published paper is included in **Chapter 6**. In this chapter, the association of grip strength

will be covered. **Paper 5** - *"Absolute and relative grip strength as predictors of cancer: prospective cohort study of 445 552 participants in UK Biobank"* - Reduced muscular strength, as measured by absolute grip strength, has been associated with increased risk of some site-specific cancers. The ability of grip strength to predict other diseases may be affected by whether it is expressed in absolute or relative terms, but the evidence for cancer is scarce.

Finally, ***Chapter 7*** provides a general summary of the key findings obtained in the aforementioned manuscripts, the studies' strengths, limitations, and the implications of the findings for future research and practice.

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Chapter 2 General Methods UK Biobank

2.1 UK Biobank

UK Biobank is general population-based prospective cohort study. The main aim of UK Biobank is to investigate the lifestyle and genetic determinants of a range of health outcomes that occur in middle and old age (Sudlow et al., 2015).

2.2 Design and Methods

2.2.1 Population and recruitment

UK Biobank is an ongoing prospective cohort study of approximately 500,000 individuals (229,171 men and 273,461 women). The inclusion of a half-million individuals to allow investigate common causes of morbidity and mortality, in order to generate appropriate statistical power to reliably identify odds ratios of 1.3 to 1.5 (based on UK age- and sex-specific rates) over a 10- to 20-year follow-up period.

Adults aged 40 to 69 who were NHS-registered and lived within 25 miles of a research assessment centre received a letter inviting them to join UK Biobank. No exclusion criteria were applied. The age range was set so that participants would be expected to have incident disease outcomes in the early years of follow-up, while still permitting baseline exposure assessment with minimal influence from incipient disease (Palmer, 2007, Sudlow et al., 2015).

Twenty-two assessment centres were in operation across England, Wales and Scotland between 2006 and 2010. Invitation mailings were stratified according to age, gender and postcode area (as a measure of social deprivation). Approximately 9 million invitations were issued to achieve the eventual cohort size of 502,664, indicating an overall response rate of around 5.5% (Sudlow et al., 2015).

2.2.2 Cohort characteristic

Available data as of 01st October 2019 (n = 502,535). Indicated that participant ages ranged from 37 to 73 years. More women (n = 273,391,

54.4%) than men (229,129, 45.6%) took. The majority self-reported white ethnicity (n = 472,709, 94.59%;), followed by Asian/Asian British (n = 9,882; 2.0%), black/black British (n = 8,061; 1.6%), mixed ethnic background (7,517, 1.5%) and Chinese (n = 1,574; 0.3%).

A comparison of the UK Biobank cohort with UK Biobank invitees who did not participate, and with findings from nationally representative surveys, confirmed that the cohort is not representative with regard to gender and deprivation; the proportion reporting white ethnicity is representative of the 2001 UK census but is higher than that reported in the 2011 census (Fry et al., 2017). Those who were finally registered were older, more likely to be women, and lived in less socioeconomically challenged areas than non-responders. (Fry et al., 2017). On the other hand, Fry et al. found that UK Biobank members were less likely to be people with obesity, smoke, report fewer self-reported health issues, and drink alcohol on a daily basis than the general UK population. (Fry et al., 2017). Even though risk factor levels and death rates were better in UK Biobank participants compared to the Health Surveys for England and the Scottish Health Surveys, Batty et al. pointed out that the UK Biobank study's relationships appear generalisable. (Batty et al., 2020). Therefore, as UK Biobank is not representative of the general population, these studies suggested that the summary statistics obtained from the UK Biobank study should not be generalised. However, effect sizes estimated from UK Biobank were generally consistent with those from population-representative cohorts, as it was shown for Batty et al. (Batty et al., 2020)

2.3 Outcomes

The primary outcome is all-cause incident cancer, and the secondary outcome is site specific incident cancer. Incident cancer was defined as including both fatal and non-fatal events derived from death and hospital admission data respectively.

The date and cause of death for the participants was obtained from the death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central

Register Scotland (Scotland). The date and cause of hospitalization were obtained via record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Hospital admission data used in this thesis were available until 31 March 2017 for Scotland and Wales and until 1 June 2020 for England, resulting in analyses of incident outcomes being censored at these dates or the date of relevant hospitalisation or death, whichever occurred earlier.

Both the death certificate databases and hospitalisation databases used the World Health Organization's ICD (International Classification of Diseases and Related Health Problems) disease codes. The International Classification of Diseases, 10th revision (ICD-10), was used to define the following cancers sites: overall cancer (C00–C97, excluding C44), oral (lip, pharynx and larynx) (C00–C14), oesophagus (C15), stomach (C16), colorectal (C18, C19, and C20), colon proximal (C 18.0–18.5), colon distal (C18.6, C18.7), colon (C18.0-C18.9), rectum (C19–C20), liver (C22), gallbladder (C23), pancreas (C25), lung (C34), malignant melanoma (C43), breast (C50), uterine (C54–C55), cervix (C53), endometrium (C54), ovary (C56), prostate (C61), testis (C62), kidney (C64-C65), bladder (C67), brain (C71), thyroid (C73), lymphatic and haematopoietic tissue (C81–C96), non-Hodgkin lymphoma (C82–C85), multiple myeloma (C90), and leukaemia (C91–C95).

This method offers a thorough assessment of cancer incidence since hospitalization and mortality from cancer include both fatal and non-fatal occurrences. This definition makes sure that a variety of cancer cases—including those that end in hospitalization or death—are taken into account in the research. Also, we did not have access to cancer registry data and that primary care data are only available on a sub-group of UK Biobank participants.

2.4 Exposures included in this thesis.

Full-scale recruitments of volunteers began in 2006 and finished in June 2010. At the baseline assessment visits, evidence about lifestyles, past medical history, medications and other health-related information was collected through self- completed touch-screen questionnaires and face to

face interviews. Physical measurements and biological samples were also collected.

2.4.1 Type of Diet

The self-completed touch-screen questionnaire (completed at baseline) was used to collect the frequency of consumption of food items over the previous year to assess dietary habits. 29 questions related to dietary intake were assessed: cooked vegetables, salad/raw vegetables, fresh fruit, dried fruit, oily fish, non-oily fish, processed meat, poultry, beef, lamb, pork, cheese, milk type used, spread type, bread type, cereal intake, cereal type, salt added to food, tea, coffee, water, age when last ate meat, never eat (eggs, dairy, wheat, sugar), non-butter spread type details, hot drink temperatures, major dietary changes in the last five years and variation in diet. Except for those variables that had a numerical answer, the other questions were categorised as: never, less than once a week, 2-4 times a week, 5-6 times a week and once or more daily.

Participants were asked to specify how often they consumed various food items, ranging from "Never" to "Once or more daily." The included food items were cheese, milk, fish (both oily and non-oily), poultry, and red meat (processed meat, beef, lamb or mutton, pork, chicken, turkey, or other poultry). Additionally, participants were queried about their adherence to specific diets, such as gluten-free, lactose-free, low calorie, vegetarian, and vegan diets.

Based on their responses, participants were categorized into different diets: vegetarian, which encompassed lacto-ovo-vegetarians (those consuming cheese and/or milk but abstaining from fish, poultry, or red meat) and vegans (those reporting no consumption of milk, cheese, fish, poultry, or red meat); pescatarians (those consuming cheese, milk, and fish but avoiding poultry and red meat); fish-poultry eaters (those consuming cheese, milk, fish, and poultry but avoiding red meat); and meat-eaters (those consuming cheese, milk, fish, poultry, and red meat). Due to the limited number of participants following a vegan diet (n=57), they were combined with vegetarians.

To account for potential changes in dietary habits, individuals who self-reported that their diet often varied at baseline were excluded (n=45,028, 8.99%). Additionally, participants who identified as vegetarians but reported consuming any meat products were excluded from the study (n=57).

Dietary information for total energy and macro- and micro-nutrients was collected via the Oxford WebQ, a web-based 24-hour dietary questionnaire, obtain data regarding the quantities of up to 206 different meal categories and 32 different drink types that were consumed the day before. It is ideal for recurrent use in large-scale prospective studies and is quick (about 12 minutes) to complete on your own (Galante et al., 2016). Bradbury et al. reported that data collected using the dietary touchscreen questionnaire, which was applied to the entire cohort, correctly ranked subjects according to their primary food group intakes (Bradbury et al., 2018).

2.4.2 Adiposity and body composition

The exposures were six adiposity-related markers (BMI, WC, WHR, WHtR, HC, and BF%) measured by trained staff using standardised protocols across the assessment centres at baseline. Weight (in kg) and body composition were measured, through bioimpedance (BIA), using a Tanita BC-418 MA body composition analyser. Standing and sitting height were measured in cm using a Seca 202 height measure. Waist circumference – at the level of the umbilicus – and hip circumference were measured in cm using a Wessex non-stretchable sprung tape measure. BMI was calculated as weight (kg) divided by height (m) squared and classified into the following categories: underweight ($< 18.5\,kg/m^2$), normal weight (≥ 18.5 to $< 25\,kg/m^2$), overweight (≥ 25 to $< 30\,kg/m^2$), and obese ($\geq 30\,kg/m^2$) (World Health Organization, 2000b)
BF% was measured using the Tanita BC-418 MA body composition analyser (fat mass divided by the total body mass).

The natural indent was used to measure WC (the umbilicus was used if the natural indent could not be observed) and used to determine central

obesity (WC ≥ 88 cm for women and WC ≥ 102 cm for men). HC was recorded at the widest part of the hips. WHR and WHtR are the ratios of the waist-to-hip circumference and waist circumference to height, respectively.

Muscle mass index was derived from appendicular lean muscle mass (kg) dividedby height (m) squared, using the total body composition measured by BIA by trained nurses (Biobank, 2007).

2.4.3 Grip strength

Right- and left-hand grip strengths were measured in kg using a Jamar J00105 hydraulic hand dynamometer (Patterson Medical). The dynamometer measures grip force isometrically and can be adjusted for hand size in five half-inch increments. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm wasfacing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses (Arnold et al., 2010, Celis-Morales et al., 2017). Five representations of HGS were analysed: (1) absolute HGS in kg, (2) HGS divided by height, (3) HGS divided by weight, (4) HGS divided by BMI, (5) HGS divided by body fat mass (BFM) in kilogramme. All these variables were standardized using sex-specific mean and standard deviation of the whole sample ([X Mean] ÷ SD).
In table 2-1 is presented the number of cases by cancer site. Due availability of exposures and the lower number of events for some cancers, the papers included in this thesis can vary, in table 2-2 are the events available for cancer by each of the exposures. In addition, for two papers included, there was shown just for 15 cancer sites due their association with lifestyle factor according to WCRF(World Cancer Research Fund/American Institute for Cancer Research, 2018a).

Table 2-1: Number of cancers outcomes used in this thesis.

Name cancer	ICD 10 code	n

All cause	C0-C97, D37-D48	54,019
Bladder	C67	2,853
Brain	C71	1,039
Breast	C50	10,490
Colorectal	C18-C20	6,352
Colon	C18	4,507
Colon Distal	C18.6, C18.7	1,908
Colon Proximal	C18.8, C18.9	2,208
Rectum	C19, C20	2,799
Gallbladder	C23	431
Kidney	C64, C65	1,730
Liver	C22	945
Lung	C34	4,842
Lymphatic	C81-C95	5,412
Leukaemia	C81, C86, C88, C96	1,753
Multiple Myeloma	C90	1,345
Non-Hodgkin Lymphoma	C91-C95	2,563
Melanoma	C43	2,758
Oesophagus	C15	1,405
Head & neck	C00 -C14	1,229
Pancreas	C25	1,562
Prostate	C61	9,941
Stomach	C16	1,063
Stomach Gastric Cardia	C16.0	556
Stomach Gastric Noncardiac	C16.1-C16.5	265
Testis	C62	108
Thyroid	C73	433
Vulva	C51	145
Uterine	C53-C55	1,602
Cervix	C53	186
Endometrium	C54	1,526
Ovary	C56	1,327

Table 2-2: Number of cancers total people and cases by exposure.

Exposures Marker	All cause cancer	Head cancer	Bladder cancer	Brain cancer
BMI	499524/53676	499524/1221	499524/2832	499524/1035
WC	500224/53769	500224/1221	500224/2835	500224/1036
WHR	500178/53758	500178/1221	500178/2834	500178/1036
WHtR	499412/53660	499412/1221	499412/2830	499412/1035
HIP	500224/53769	500224/1221	500224/2835	500224/1036
BFI	491468/52690	491468/1201	491468/2777	491468/1019
Grip	499571/53698	499571/1225	499571/2833	499571/1036
HGS BFM	490963/52631	490963/1201	490963/2774	490963/1018
HGS BMI	498979/53610	498979/1221	498979/2829	498979/1034
HGS FFM	491760/52709	491760/1211	491760/2777	491760/1018
HGS FFP	491758/52709	491758/1211	491758/2777	491758/1018
HGS Height	498977/53610	498977/1221	498977/2829	498977/1034
HGS Weight	499052/53619	499052/1221	499052/2830	499052/1034
Normal weight without central obesity	133425/12228	133425/363	133425/547	133425/245
Normal weight with central obesity	28965/3149	28965/72	28965/118	28965/64
Overweight without central obesity	59189/5550	59189/143	59189/333	59189/137
Overweight with central obesity	274061/32372	274061/625	274061/1811	274061/582
Meat eaters	425055/46145	425055/1037	425055/2451	425055/891
Pescatarian	10316/841	10316/27	0/0	0/0
Poultry eaters	5144/507	5144/11	5144/24	5144/12
Vegetarian	7910/557	7910/19	10316/40	10316/17

Exposures Marker	Oesophagus cancer	Stomach cancer	Pancreas cancer	Colorectal cancer
BMI	499524/1391	499524/1057	499524/1551	499524/6310
WC	500224/1398	500224/1060	500224/1556	500224/6319
WHR	500178/1398	500178/1060	500178/1556	500178/6317
WHtR	499412/1391	499412/1057	499412/1551	499412/6305
HIP	500224/1398	500224/1060	500224/1556	500224/6319

BFI	491468/1341	491468/1028	491468/1514	491468/6198
Grip	499571/1396	499571/1060	499571/1551	499571/6315
HGS BFM	490963/1341	490963/1028	490963/1510	490963/6192
HGS BMI	498979/1389	498979/1056	498979/1547	498979/6304
HGS FFM	491760/1348	491760/1030	491760/1511	491760/6201
HGS FFP	491758/1348	491758/1030	491758/1511	491758/6201
HGS Height	498977/1389	498977/1056	498977/1547	498977/6304
HGS Weight	499052/1389	499052/1056	499052/1547	499052/6304
Normal weight without central obesity	133425/250	133425/191	133425/339	133425/1339
Normal weight with central obesity	28965/65	28965/46	28965/68	28965/328
Overweight without central obesity	59189/132	59189/115	59189/167	59189/640
Overweight with central obesity	274061/925	274061/699	274061/971	274061/3969
Meat eaters	425055/1208	425055/906	425055/1328	425055/5488
Pescatarian	10316/11	10316/13	10316/24	10316/85
Poultry eaters	5144/14	5144/10	5144/9	5144/51
Vegetarian	7910/14	7910/10	7910/12	7910/51
Exposure	**Gallbladder cancer**	**Kidney cancer**	**Thyroid cancer**	**Liver cancer**
BMI	499524/429	499524/1723	499524/431	499524/941
WC	500224/430	500224/1726	500224/431	500224/942
WHR	500178/430	500178/1725	500178/431	500178/942
WHtR	499412/429	499412/1722	499412/431	499412/941
HIP	500224/430	500224/1726	500224/431	500224/942
BFI	491468/420	491468/1690	491468/424	491468/916
Grip	499571/428	499571/1726	499571/429	499571/939
HGS BFM	490963/419	490963/1689	490963/423	490963/913
HGS BMI	498979/428	498979/1722	498979/429	498979/938
HGS FFM	491760/419	491760/1693	491760/423	491760/913
HGS FFP	491758/419	491758/1693	491758/423	491758/913
HGS Height	498977/428	498977/1722	498977/429	498977/938
HGS Weight	499052/428	499052/1723	499052/429	499052/938

Normal weight without central obesity	133425/80	133425/269	133425/97	133425/168
Normal weight with central obesity	28965/22	28965/84	28965/25	28965/42
Overweight without central obesity	59189/46	59189/179	59189/36	59189/73
Overweight with central obesity	274061/281	274061/1175	274061/271	274061/653
Meat eaters	425055/369	425055/1493	425055/358	425055/810
Pescatarian	10316/10	10316/21	10316/6	10316/12
Poultry eaters	5144/3	5144/18	5144/4	5144/5
Vegetarian	7910/3	7910/14	7910/10	7910/6
Exposure	**Lung cancer**	**Lymphatic cancer**	**Leukaemia cancer**	**Multiple Myeloma cancer**
BMI	499524/4794	499524/5381	499524/1743	499524/1339
WC	500224/4811	500224/5386	500224/1744	500224/1340
WHR	500178/4811	500178/5385	500178/1744	500178/1339
WHtR	499412/4793	499412/5380	499412/1743	499412/1338
HIP	500224/4811	500224/5386	500224/1744	500224/1340
BFI	491468/4686	491468/5279	491468/1706	491468/1312
Grip	499571/4805	499571/5382	499571/1740	499571/1340
HGS BFM	490963/4681	490963/5271	490963/1701	490963/1310
HGS BMI	498979/4788	498979/5373	498979/1738	498979/1337
HGS FFM	491760/4694	491760/5280	491760/1703	491760/1311
HGS FFP	491758/4694	491758/5280	491758/1703	491758/1311
HGS Height	498977/4788	498977/5373	498977/1738	498977/1337
HGS Weight	499052/4789	499052/5373	499052/1738	499052/1337
Normal weight without central obesity	133425/1118	133425/1247	133425/401	133425/302
Normal weight with central obesity	28965/360	28965/302	28965/78	28965/72
Overweight without central obesity	59189/384	59189/560	59189/181	59189/146
Overweight with central obesity	274061/2873	274061/3248	274061/1077	274061/813
Meat eaters	425055/4063	425055/4608	425055/1488	425055/1164
Pescatarian	10316/58	10316/84	10316/30	10316/29

Poultry eaters	5144/40	5144/47	5144/13	5144/12
Vegetarian	7910/35	7910/63	7910/19	7910/17
Exposures Marker	**Breast cancer**	**Cervix cancer**	**Prostate cancer**	
BMI	271913/10433	271913/184	227611/9888	
WC	272239/10445	272239/183	227985/9903	
WHR	272215/10441	272215/183	227963/9903	
WHtR	271845/10429	271845/183	227567/9888	
HIP	272239/10445	272239/183	227985/9903	
BFI	268136/10288	268136/183	223332/9712	
Grip	271611/10424	271611/184	227960/9896	
HGS BFM	267818/10277	267818/183	223145/9705	
HGS BMI	271581/10422	271581/184	227398/9879	
HGS FFM	267901/10279	267901/183	223859/9717	
HGS FFP	267899/10279	267899/183	223859/9717	
HGS Height	271580/10422	271580/184	227397/9879	
HGS Weight	271611/10424	271611/184	227441/9880	
Normal weight without central obesity	82435/2724	82435/52	50990/2060	
Normal weight with central obesity	23190/968	23190/8	5775/317	
Overweight without central obesity	19658/651	19658/13	39531/1578	
Overweight with central obesity	144147/6008	144147/109	129914/5896	
Meat eaters	226565/8753	226565/153	198490/8759	
Pescatarian	7425/256	7425/3	2891/88	
Poultry eaters	3894/157	3894/2	1250/46	
Vegetarian	5262/159	5262/3	2648/54	

*Total population/cancer cases

2.5 Variables included as confounders in the manuscripts.

A wide range of potential confounders was included in the analyses. These confounders were selected due to, they association with the exposure, with cancer and they were no intermediate factors between the exposure and the outcome. Baseline questionnaires focused on potential risk factors, both in adulthood and early life, for important public health concerns for the adult population were implemented.

2.5.1 Sociodemographic characteristics

Age, gender, and ethnicity were self-reported during the baseline evaluation via a touch-screen questionnaire.

Sex and year of birth were acquired from the National Health Service Central Register at recruitment, but in some cases were updated by the participant. Age was calculated from date of birth and from baseline assessment.

Participants responded to their ethnic background from a set of fixed categories in the questionaries. Ethnicity was categorised as White (British, Irish, any other white background), South Asian/Asian British, Mixed, Black/Black British and Other groups. “Prefer not to answer” and “Don’t know” responses were grouped together.

Townsend area deprivation index has been derived from the postcode of residence of the participants using data aggregated on unemployment, car and homeownership, and household overcrowding (1988). A score was calculated based on the four census variables. A higher Townsend code equated to higher levels of socioeconomic deprivation. Data on household income was self-reported by the participants, and educational attainment was also derived from the highest self-reported qualification which was based on the International Standard Classification of Education. Tertiles were created to compare the lowest or most affluent to the highest deprived or less affluent groups.

2.5.2 Lifestyle factors

Smoking status was self-reported during the baseline evaluation via a touch-screen questionnaire, which was categorized into never, former, and current smoking. The information collected included current smoking status, amount smoked, duration of smoking and time since quitting.

The frequency of alcohol intake was also self-reported at baseline and categorised into daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only, never and prefer not to answer. If participants' alcohol intake varied significantly, they were encouraged to include the average intake over the previous year.

Self-reported physical activity was estimated using the International Physical Activity Questionnaire, short forms which include time spent in different physical activity domains including, walking, moderate and vigorous physical activity. Other physical activity related questions were also included in the assessment questionnaire which assess physical activity levels across a comprehensive set of domains including (IPAQ, Craig et al., 2003). Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Walking pace was also self- reported and categorised into slow, average or brisk. Nonetheless, the majority of the lifestyle variables were self-reported, which are prone to recall bias and misclassification.

2.5.3 Medical history and other health-related self-reported covariates

Medical history (physician diagnosis of depression, stroke, angina, heart attack,hypertension, cancer, diabetes, hypertension, or other illness) was collected from the self-completed baseline assessment questionnaire (Biobank, 2007b).

2.6 Ethics

UK Biobank was approved by the NHS Northwest Multicentre Research Ethics Committee (Ref: 11/NW/0382). Data and samples are only used for ethically andscientifically approved research and confidentiality of the participants’ data andsamples are maintaining in all processes.

Additionally, UK Biobank has the EthicsAdvisory Committee (EAC) who provides advice to the UK Biobank Board and Funders on ethical issues that occurs during the maintenance, development and use for current and future activities of the UK Biobank study. The EAC was established in 2018 and replaced the Ethics and Governance Council (Biobank, 2007a)
My study was done as part of an approved UK Biobank project (reference application number 7155) for which the University of Glasgow has an existing material transfer agreement. I registered with UK Biobank and was approved by UK Biobank as an investigator on this study. I was provided with an anonymised extract of the relevant data that was encrypted and password protected. I analysed this data on a password protected computer which no one had access to. In accordance with data protection requirements, the findings from this research are only reported as aggregated results. No individual participants can be identified. Given the existing NHS ethical approval, no additional ethical approval was required from the university ethics committee.

2.7 Statistical Methods

Associations between exposure and cancer sites were investigated using Cox-proportional hazard models. The time of follow-up was used as the time-dependent variable. The results were reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). A hazard ratio represents the proportionate instantaneous risk over time of an event (such failure, or death) between two groups. It is commonly used in survival analysis to compare the hazard functions of different groups (Sashegyi et al., 2017). The proportional hazard assumptions were checked using Schoenfeld residuals. Because of potentially inflated type-I errors, multiple testing was done using Holm’s method. Holm's method is preferred over Bonferroni's for multiple testing due to increased power, adaptability to diverse hypotheses, better control in the presence of dependencies, sequential testing flexibility, and ease of implementation. Its nuanced approach considers the scientific context, providing a balanced solution for controlling familywise error rates while maintaining statistical power and interpretability (AICKIN, et al., 1996).

2.8 Reference Chapter 2

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Chapter 3. Association of meat, vegetarian, pescatarian, and fish-poultry diets with risk of 19 cancer sites and all cancer: Findings from the UK Biobank prospective cohort study and meta-analysis

3.1 Abstract

Background: The associations of cancer with types of diets, including vegetarian, fish and poultry-containing diets, remain unclear. The aim of this study was, therefore, to investigate the association of type of diet with all cancers and 19 site-specific incident cancers in a prospective cohort study and then in a meta-analysis of published prospective cohort studies.

Methods: 409,110 participants from the UK Biobank study, recruited between 2006 and 2010, were included. The outcomes were incidence of all cancers combined and 19 cancer sites. Associations between types of diets and cancer were investigated using Cox proportional hazards models. Previously published prospective cohort studies were identified from four databases and a meta-analysis was conducted using random-effects models.

Results: The mean follow-up period was 10.6 years (IQR: 10.0; 11.3). Compared with meat-eaters, vegetarians (Hazard Ratio (HR): 0.87 [95% CI: 0.79 to 0.96]) and pescatarians (HR: 0.93 [95% CI: 0.87 to 1.00]) had lower overall cancer risk. Vegetarians also had a lower risk of colorectal and prostate cancers compared with meat-eaters. In the meta-analysis, vegetarians (Risk Ratio (RR): 0.90 [0.86;0.94]) and pescatarians (RR: 0.91 [0.86; 0.96]), had lower risk of overall cancer. No associations between types of diets cancer-specific cancer were found in the meta-analysis.

Conclusions: Compared with meat-eaters, vegetarians and pescatarians had a lower risk of overall, colorectal and prostate cancer. When results were pooled in a meta-analysis, the overall associations with overall cancer persisted, but the results relating to specific cancer sites were inconclusive.

3.2 Introduction

Unhealthy diets have been associated with a higher risk of several adverse health outcomes, including cancer (Collaborators, 2019, Sung et al., 2021). Over 11 million deaths were attributed to poor diet in 2017, among which more than 930,000 were attributed to cancer, particularly breast and colorectal cancer (Collaborators, 2019). Although there is considerable evidence regarding the associations between diet and cancer risk, most studies have focused on single nutrients (Key et al., 2020, Negri et al., 1998) or food items (Key et al., 2020, Franceschi et al., 1997), which do not provide insights into how the widely varying combinations of these foods within whole dietary patterns impact risk.

What we eat and the type of dietary pattern we follow are influenced by socioeconomic status, environmental factors, and cultural and personal beliefs (Collaborators, 2019). Recently there has been a growing concern about the impact of food consumption on not just human health but also planetary health. This has led to an increasing number of people worldwide changing from diets that include meat to other types of diet such as vegetarian, vegan and pescatarian (Johnston et al., 2019, Rosenfeld and Burrow, 2017, Leitzmann, 2014, Key et al., 2006). Recent estimates indicate that 4% of the worldwide population are vegetarian, with almost 40% reporting frequent consumption of vegetarian meals (Vegetarian Resource Group, 2019). Although there is increasing evidence regarding the health benefits associated with these types of diets, most studies have focused on outcomes such as all-cause mortality and cardiovascular diseases, with limited and conflicting evidence for all cancers combined and specific cancers (Appleby et al., 2016, Key et al., 2009b, Key et al., 2014, Orlich et al., 2013). One study conducted in 73,308 Seventh-day

Adventist men and women who were followed up for 5.7 years reported a 12% lower risk of all-cause mortality in vegetarians compared with non-vegetarians (Orlich et al., 2013). Although no associations were observed for the incidence of all cancer combined or mortality (Orlich et al., 2013), vegetarians had a lower risk of cancers of the gastrointestinal tract (Tantamango-Bartley et al., 2013). Another study that pooled data from two prospective cohorts, covering 61,647 British men and women who were followed for 14.9 years, reported that fish-eaters had 38%, 34% and 12% lower risk of stomach, colorectal and all cancers, respectively (Key et al., 2014), while vegetarians had 63% and 12% lower risk of stomach and all cancers, respectively, compared with meat-eaters (Key et al., 2014). A combined analysis of EPIC-Oxford and the Oxford Vegetarian Study, also from the UK, reported that vegetarians (including vegans) had lower risk of all cancers and cancers of the stomach, bladder, lymphatic and hematopoietic system, but higher risk of cervical cancer compared with meat-eaters (Key et al., 2009a). In the UK Women's Cohort Study, a vegetarian diet was not associated with differences in the risk of breast cancer (Cade et al., 2010). The latest meta-analysis for overall cancer, published in 2017, pooled only two prospective cohort studies and showed an 8% reduction in overall incident cancers associated with vegetarian diets (Dinu et al., 2017). Another meta-analysis, conducted in 2017, included nine studies (n=686,629 participants) and reported no associations between a vegetarian diet and the risk of breast, colorectal or prostate cancers (Godos et al., 2017).

In summary, existing evidence shows that investigations of associations with dietary patterns have been restricted to a limited number of cancer sites with equivocal findings. We addressed these research gaps using data from the UK Biobank, a large prospective cohort study, to investigate associations between

type of diet and all incident cancers combined and 19 site-specific cancers. In addition, we combined our findings with those from past studies to provide an up-to-date meta-analysis of prospective cohort studies.

3.2 Methods

UK Biobank

Between April 2007 and December 2010, the UK Biobank recruited over 500,000 participants, aged 37 to 73 years from the general population (Collins, 2012). Participants attended one of 22 assessment centres across England, Wales and Scotland (Palmer, 2007, Sudlow et al., 2015), where they completed a touchscreen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere (Palmer, 2007, Sudlow et al., 2015).

Outcomes

The primary outcome was incident cancer defined as the first record of hospitalization for cancer or death due to cancer, if no prior record of hospitalization. Date and cause of death were obtained from death certificates available up to 1 June 2020. Dates and causes of hospital admissions were obtained from the Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Follow-up for incident events was censored on this date or the date of event (cancer diagnosis or death), whichever came first. The International Classification of Diseases, 10th revision (ICD-10) was used to define overall cancer (C00-C97, excluding non-melanoma skin cancer (C44)) and the following 19 cancers and four subgroups of colorectal cancer: head & neck (C00-C14), oesophagus (C15), stomach (C16), colorectal (C18, C19, and C20), [colon (C18.0), colon proximal (C 18.0-18.4), colon distal (C18.5, C18.7), rectum (C19-C20)], pancreas (C25), lung (C33-34), malignant melanoma (C43), breast in

premenopausal and postmenopausal women (C50), uterus (C54-C55), ovary (C56), prostate (C61), kidney (C64-C65), bladder (C67), brain (C70-72), lymphatic and hematopoietic tissue (C81-C96), non-Hodgkin lymphoma (C82-C86, C96), multiple myeloma (C88-90), and leukaemia (C91-C95). Further details of these measurements can be found in the UK Biobank online protocol (UK Biobank).

Types of diets

A touchscreen dietary intake questionnaire, containing 29 questions about diet and 18 questions about alcohol, completed at recruitment (baseline), was used to collect data on the frequency of food intake over the past year. Participants chose a frequency of intake ranging from “Never” to “Once or more daily” for each food item. The food items included were cheese, milk, fish (oily and non-oily), poultry and red meat (processed meat, beef, lamb or mutton, pork, chicken, turkey or other poultry). Participants were also asked to report whether they followed any particular diet, including gluten-free, lactose-free, low calorie, vegetarian and vegan diets. Based on their responses, participants were categorized into one of the following diets: vegetarian, which included: lacto-ovo-vegetarian (who consumed cheese and/or milk but they never consumed fish, poultry or red meat) and vegan (who reported never consuming milk, cheese, fish, poultry or red meat); pescatarian (who consumed cheese, milk and fish but never consumed poultry or red meat); fish-poultry eaters (who consumed cheese, milk, fish and poultry but never consumed red meat); and meat-eaters (who consumed cheese, milk, fish, poultry and red meat). Due to the low number of participants following a vegan diet (n=57), these were pooled with vegetarians. To take account of people changing their dietary patterns, we excluded people who self-reported at baseline that their diet often varied (n=45,028, 8.99%). In addition, those participants who reported being

vegetarians but who self-reported eating any meat products were excluded from the study (n=57). The same approach was used for pescatarians and fish-poultry eaters (Petermann-Rocha et al., 2020). Dietary information for total energy and macro- and micro-nutrients was collected via the Oxford WebQ, a web-based 24-hour dietary questionnaire (Galante et al., 2016). Bradbury et al. reported that data collected using the dietary touchscreen questionnaire, which was applied to the entire cohort, correctly ranked subjects according to their primary food group intakes (Bradbury et al., 2018).

Covariates

Sociodemographic factors (sex and ethnicity) were self-reported at the baseline assessment visit using a touchscreen questionnaire. Age was calculated from the date of birth at baseline assessment. Area-based socioeconomic status was derived from the postcode of residence using the Townsend score (16), which generates a deprivation score based on four Census variables: unemployment, non-car ownership, non-house ownership and household overcrowding. Self-reported smoking status was categorized as never, former or current smoker. Body mass index (BMI) was calculated from weight and height expressed in kg/m2, and the World Health Organization (WHO) criteria were applied to classify participants into: underweight (<18.5 kg/m2), normal weight (18.5-24.9 kg/m2); overweight (25.0-29.9 kg/m2); and obese (≥30.0 kg/m2) (17). Data were also collected from women on hormonal replacement therapy, menopausal status and parity. Self-reported levels of physical activity were collected via the International Physical Activity Questionnaire and reported as metabolic equivalent of task (MET) per week (IPAQ). Multimorbidity (physician diagnosis of depression, hypertension, and diabetes) was self-reported at baseline. For this study, an average of up to five 24-h recalls was used. However, as the average

of the 24-h recalls was not available for the whole UK Biobank population (~200,000 individuals), the number of individuals with data available for each variable is shown in Additional file 1: Table S2.

Statistical analyses

We excluded people who had cancer diagnoses at baseline and people with missing data for all covariates studied and for the exposure of interest. Descriptive characteristics for the cohort, categorized by type of diet, were summarized using means with standard deviations (SD) for quantitative variables and percentages for categorical variables.

Associations between types of diet and all cancer combined, and the individual cancer sites were investigated using Cox-proportional hazard models. Individuals who were classified as meat-eaters were used as the reference group. The time of follow-up was used as the time-dependent variable. The results were reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard assumptions were checked using Schoenfeld residuals.

We ran four models for each outcome, including an increasing number of covariates: “model 0” unadjusted, "model 1" (minimally adjusted) included sociodemographic covariates (age, sex, deprivation index, and ethnicity); "model 2" additionally included lifestyle factors (smoking, alcohol intake and total physical activity); "model 3" additionally included multimorbidity; and “model 4” (maximally adjusted) additionally included BMI. The models for breast, ovarian, cervical, endometrial and uterine cancer were also adjusted for hormone replacement therapy and parity. To minimize the effect of reverse causation, we additionally conducted 2-year landmark sensitivity analyses, excluding cancer events in the first two years of follow-up. All analyses were undertaken using R

statistical software, version 3.6.2 with the package "survival". Two-sided P-values below 0.05 were interpreted as statistically significant.

Meta-analysis

The systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and registered in PROSPERO with the number CRD42021240456. The research question was: "Do vegetarians, vegan, fish- and poultry-eaters have a lower overall and site-specific cancer risk compared to meat-eaters?". The population included was adults aged ≥18 years with and without a cancer diagnosis. The exposure was types of diet, including vegan, vegetarian, poultry eaters, fish eaters and meat eaters. Outcomes included all cause and site-specific (colorectal, breast, prostate, digestive tract, and lung) cancers. Only prospective cohort studies were included. As recorded in PROSPERO, two authors (SP-S and DA) searched MEDLINE/PubMed, Scopus, Embase and Web of Science using the search terms described in the Additional file 1: Methods. Two stages of screening (1) title and abstract and (2) full text of potentially eligible papers was performed. Data extraction was carried out independently by the authors SP-S and DA in Rayyan, and results were then extracted to an excel spreadsheet. Inclusion was restricted to prospective cohort studies published any time up to and including 31 August 2021, that were conducted in adults, included some/all of the following types of diets (meat, vegetarian, pescatarian, fish & poultry diet), provided results for some/all of the relevant cancer outcomes and was written in English. We excluded case-control studies and studies that did not define the type of diet. Meta-analysis was undertaken using a random-effects model, stratified by type of diet (vegetarian, pescatarian or both) and only included specific cancer sites that were reported by at least three independent studies. Manuscripts that met the inclusion criteria were assessed independently

by the two authors using RAYYAN software (Ouzzani et al., 2016). We used funnel plots to assess potential bias within the studies included in the meta-analyses. The quality of the studies was also assessed using the Newcastle-Ottawa Scale (Additional file 1: Table S1) (Stang, 2010). Heterogeneity between studies was tested using the I-squared statistic. All analyses were undertaken using R statistical software, version 3.6.2 with the package "meta".

3.3 Results

UK Biobank

Of the 508,492 UK participants, 99,382 were excluded as they had cancer diagnoses at baseline (n=41,416) and missing data for types of diet or relevant covariates (n=57,976) (baseline characteristics of people with missing variables are in Additional file 1: Table S2). Therefore, this study included 409,110 participants, of whom 53.4% were women. Overall, 7,256 (1.8%) were vegetarian, 9,498 (2.3%) were pescatarian, 4,625 (1.1%) were fish-poultry eaters and 387,731 (94.8%) were meat-eaters (Additional file 1: Fig. S1). The median follow-up period was 10.6 years (interquartile range: 10.0-11.3) and 39,596 participants developed cancers during follow-up. The sociodemographic characteristics of the population by type of diet are presented in Table 1. In comparison with the other groups, meat-eaters were older, and more likely to be overweight or obese, and to smoke (Table 3-1). The characteristics of dietary intake across types of diets are presented in Additional file 1: Table S2. Energy consumption was similar in the diet groups. However, intake of fibre, polyunsaturated fat and water was slightly higher in participants with vegetarian and pescatarian diets. In contrast, protein intake was lower in vegetarians (mean 12.4 ± 2.3 SD % of total energy) than meat-eaters (mean 15.7± 3.6 SD % of total energy) respectively to food, crisp and pizza were more consumed for vegetarian and pescatarian. Additional file 1: Table S3 shows the characteristics

of the UK Biobank population excluded from the study (n=57,976). Briefly, compared with the cohort included in the present study, those excluded were more likely to be women, individuals from more deprived backgrounds, of non-white ethnicity and have a higher BMI.

The findings for the associations of types of diets with incident cancer are shown in Table 3.2. In the unadjusted model, vegetarians had a lower risk of liver, pancreatic, lung, prostate, bladder, colorectal, melanoma, kidney, non-Hodgkin lymphoma and lymphatic cancer as well as overall cancer, with hazard ratios ranging from 0.29 to 0.70 (Table 3-2). However, when the models were fully adjusted for sociodemographic and lifestyle factors, multimorbidity and BMI (model 4) the associations remained statistically significant only for prostate cancer (HR: 0.57 [95% CI: 0.43 to 0.76]), colorectal cancer (HR: 0.73 [95% CI: 0.54; 0.99]), and all cancers combined (HR: 0.87 [95% CI: 0.79 to 0.96]). When colorectal cancer was stratified according to subtypes, a lower risk was observed for colon (HR: 0.69 [95%CI: 0.48; 0.99]) and proximal colon (HR: 0.43 [95% CI: 0.22; 0.82]) in vegetarians compared with meat-eaters, but not for rectum or distal cancer.

Table 3-1. Sociodemographic characteristics of the study population by types of diet.

Characteristics	Meat-eaters	Vegan & vegetarian	Pescatarian	Fish & poultry	Overall
Sociodemographic					
N (%)	387,731 (94.8%)	7,256 (1.8%)	9,498 (2.3%)	4,625 (1.1%)	409,110
Age, mean (SD)	56.4 (8.09)	52.9 (7.92)	53.9 (8.03)	56.2 (8.12)	56.3 (8.11)
Sex, n (%)					
Females	203,550 (52.5%)	4,770 (65.7%)	6,770 (71.3%)	3,477 (75.2%)	218,567 (53.4%)
Males	184,181 (47.5%)	2,486 (34.3%)	2,728 (28.7%)	1,148 (24.8%)	190,543 (46.6%)
Deprivation, n (%)					
Lower	133,296 (34.4%)	1,882 (25.9%)	2,766 (29.1%)	1,300 (28.1%)	139,244 (34.0%)
Middle	130,632 (33.7%)	2,337 (32.2%)	3,155 (33.2%)	1,466 (31.7%)	137,590 (33.6%)
Higher	123,803 (31.9%)	3,037 (41.9%)	3,577 (37.7%)	1,859 (40.2%)	132,276 (32.3%)
Ethnicity, n (%)					
White	368,509 (95.0%)	5,825 (80.3%)	8,882 (93.5%)	4,150 (89.7%)	387,366 (94.7%)
Mixed	5,309 (1.4%)	116 (1.6%)	142 (1.5%)	96 (2.1%)	5,663 (1.4%)
South Asian	5,776 (1.5%)	1,235 (17.0%)	284 (3.0%)	217 (4.7%)	7,512 (1.8%)
Black	5,775 (1.5%)	30 (0.4%)	131 (1.4%)	143 (3.1%)	6,079 (1.5%)
Chinese	1,206 (0.3%)	9 (0.1%)	10 (0.1%)	5 (0.1%)	1,230 (0.3%)
Any other	1156 (0.3%)	41 (0.6%)	49 (0.5%)	14 (0.3%)	1260 (0.3%)
Anthropometric					
Height (m), mean (SD)	1.68 (0.09)	1.66 (0.09)	1.67 (0.09)	1.65 (0.09)	1.68 (0.09)
Weight (Kg), mean (SD)	78.4 (15.81)	71.5 (14.66)	70.7 (13.82)	70.3 (14.15)	78.0 (15.82)
Waist (cm), mean (SD)	90.4 (13.35)	85.1 (12.80)	83.2 (12.07)	83.3 (12.57)	90.1 (13.38)
Body Mass index (kg/m2), mean (SD)	27.4 (4.71)	25.7 (4.63)	25.2 (4.24)	25.6 (4.60)	27.3 (4.72)
BMI (kg/m2), n (%)					
Underweight	1,752 (0.5%)	118 (1.6%)	155 (1.6%)	71 (1.5%)	2,096 (0.5%)
Normal	124,548 (32.1%)	3,556 (49.0%)	5,010 (52.7%)	2,285 (49.4%)	135,399 (33.1%)
Overweight	167,563 (43.2%)	2,531 (34.9%)	3,215 (33.8%)	1,572 (34.0%)	174,881 (42.7%)

Obese	93,868 (24.2%)	1,051 (14.5%)	1,118 (11.8%)	697 (15.1%)	96,734 (23.6%)
Lifestyle					
Smoking, n (%)					
Never	214,263 (55.3%)	4,676 (64.4%)	5,437 (57.2%)	2,763 (59.7%)	227,139 (55.5%)
Previous	133,411 (34.4%)	2,086 (28.7%)	3,390 (35.7%)	1,511 (32.7%)	140,398 (34.3%)
Current	40,057 (10.3%)	494 (6.8%)	671 (7.1%)	351 (7.6%)	41,573 (10.2%)
Alcohol intake, n (%)					
Daily or almost daily	79,854 (20.6%)	1,015 (14.0%)	1,825 (19.2%)	641 (13.9%)	83,335 (20.4%)
3-4 times a week	91,813 (23.7%)	1,283 (17.7%)	2,296 (24.2%)	828 (17.9%)	96,220 (23.5%)
Once or twice a week	102,119 (26.3%)	1,449 (20.0%)	2,202 (23.2%)	1,063 (23.0%)	106,833 (26.1%)
1-3 times a month	43,093 (11.1%)	849 (11.7%)	1,103 (11.6%)	522 (11.3%)	45,567 (11.1%)
Special occasions only	42,704 (11.0%)	1,026 (14.1%)	1,065 (11.2%)	822 (17.8%)	45,617 (11.2%)
Never	27,915 (7.2%)	1,632 (22.5%)	1,004 (10.6%)	743 (16.1%)	31,294 (7.6%)
Missing	233 (0.1%)	2 (0.0%)	3 (0.0%)	6 (0.1%)	244 (0.1%)
Sedentary time, (h/day), mean (SD)	5.1 (2.26)	4.3 (2.23)	4.3 (2.09)	4.5 (2.33)	5.0 (2.26)
Physical activity (MET/min/week), mean (SD)	2912.6 (3220.45)	2850.0 (3040.25)	2896.8 (2938.19)	3288.2 (3329.61)	2915.5 (3212.13)
Health					
Multimorbidity, n (%)					
No	145,488 (37.5%)	3,140 (43.3%)	4,217 (44.4%)	1,787 (38.6%)	154,632 (37.8%)
Yes	242,243 (62.5%)	4,116 (56.7%)	5,281 (55.6%)	2,838 (61.4%)	254,478 (62.2%)

BMI: body mass index; n: number; PA: physical activity; MET: metabolic-equivalent; SD: standard deviation. Multimorbidity was defined as the existence of 2 or more chronic diseases.

Table 3-2. Association between types of diet and cancer incidence for Models 0 and 4

Cancer site	Total	Events	Meat-eaters	Events	Vegan & Vegetarian		Events	Pescatarian		Events	Fish & Poultry	
Model 0 (unadjusted)			REF		HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	409,110	38,042	1.00 (Ref.)	463	0.64 (0.58; 0.70)	<0.001	686	0.73 (0.67; 0.78)	<0.001	405	0.89 (0.81; 0.99)	0.024
Head & neck	409,110	848	1.00 (Ref.)	12	0.76 (0.43; 1.34)	0.341	21	1.01 (0.66; 1.56)	0.960	9	0.89 (0.46; 1.73)	0.740
Oesophagus	409,110	1,010	1.00 (Ref.)	11	0.59 (0.32; 1.06)	0.077	7	0.28 (0.13; 0.60)	0.001	13	1.09 (0.63; 1.88)	0.764
Stomach	409,110	775	1.00 (Ref.)	8	0.55 (0.28; 1.11)	0.096	11	0.58 (0.32; 1.05)	0.072	7	0.76 (0.36; 1.60)	0.472
Colorectal	409,110	4,679	1.00 (Ref.)	43	0.49 (0.36; 0.66)	<0.001	75	0.65 (0.52; 0.82)	<0.001	42	0.76 (0.56; 1.02)	0.070
Colon	409,110	3,340	1.00 (Ref.)	29	0.46 (0.32; 0.67)	<0.001	52	0.64 (0.48; 0.84)	0.001	29	0.73 (0.51; 1.05)	0.093
Proximal	409,110	1,680	1.00 (Ref.)	9	0.29 (0.15; 0.55)	<0.001	29	0.70 (0.49; 1.02)	0.061	15	0.75 (0.45; 1.25)	0.272
Distal	409,110	1,444	1.00 (Ref.)	17	0.63 (0.39; 1.02)	0.059	18	0.51 (0.32; 0.81)	0.004	15	0.88 (0.53; 1.46)	0.608
Rectum	409,110	2,045	1.00 (Ref.)	18	0.47 (0.30; 0.75)	0.001	35	0.70 (0.50; 0.98)	0.035	24	0.99 (0.66; 1.48)	0.957
Pancreas	409,110	1,133	1.00 (Ref.)	9	0.43 (0.22; 0.82)	0.011	21	0.76 (0.49; 1.17)	0.207	6	0.45 (0.20; 1.00)	0.049
Lung	409,110	3,306	1.00 (Ref.)	27	0.44 (0.30; 0.64)	<0.001	46	0.57 (0.42; 0.76)	<0.001	28	0.71 (0.49; 1.03)	0.075
Melanoma	409,110	1,979	1.00 (Ref.)	19	0.51 (0.33; 0.81)	0.004	28	0.58 (0.40; 0.84)	0.004	17	0.72 (0.45; 1.17)	0.184
Breast	218,391	6,901	1.00 (Ref.)	138	0.85 (0.72; 1.01)	0.065	195	0.85 (0.73; 0.98)	0.022	127	1.08 (0.91; 1.29)	0.375
Premenopausal	54,775	1,776	1.00 (Ref.)	50	1.02 (0.77; 1.36)	0.872	52	0.81 (0.61; 1.07)	0.136	22	0.93 (0.61; 1.41)	0.726
Postmenopausal	130,625	3,668	1.00 (Ref.)	71	0.86 (0.68; 1.09)	0.211	114	0.89 (0.74; 1.07)	0.210	79	1.05 (0.84; 1.31)	0.678
Uterine	218,391	1,132	1.00 (Ref.)	23	0.87 (0.58; 1.31)	0.509	30	0.80 (0.55; 1.14)	0.216	18	0.94 (0.59; 1.49)	0.777
Ovary	218,391	870	1.00 (Ref.)	19	0.94 (0.59; 1.47)	0.772	28	0.97 (0.66; 1.41)	0.859	18	1.22 (0.76; 1.94)	0.409
Prostate	190,543	7,492	1.00 (Ref.)	47	0.46 (0.35; 0.61)	<0.001	82	0.74 (0.59; 0.92)	0.006	41	0.88 (0.65; 1.20)	0.422
Kidney	409,110	1,227	1.00 (Ref.)	12	0.52 (0.30; 0.93)	0.026	17	0.57 (0.35; 0.91)	0.020	12	0.82 (0.47; 1.46)	0.505
Bladder	409,110	2,054	1.00 (Ref.)	18	0.47 (0.30; 0.75)	0.001	35	0.70 (0.50; 0.97)	0.033	16	0.66 (0.40; 1.07)	0.093
Brain	409,110	760	1.00 (Ref.)	8	0.56 (0.28; 1.13)	0.107	12	0.64 (0.36; 1.14)	0.131	10	1.11 (0.59; 2.07)	0.745
Haematological	409,110	3,583	1.00 (Ref.)	47	0.70 (0.53; 0.94)	0.016	66	0.75 (0.59; 0.96)	0.021	38	0.89 (0.65; 1.23)	0.490
Non-Hodgkin lymphoma	409,110	1,744	1.00 (Ref.)	21	0.65 (0.42; 0.99)	0.046	27	0.63 (0.43; 0.92)	0.018	19	0.92 (0.58; 1.44)	0.712
Multiple Myeloma	409,110	921	1.00 (Ref.)	13	0.76 (0.44; 1.31)	0.319	21	0.93 (0.60; 1.43)	0.745	11	1.01 (0.56; 1.82)	0.983
Leukaemia	409,110	1,116	1.00 (Ref.)	16	0.77 (0.47; 1.26)	0.295	25	0.91 (0.62; 1.36)	0.658	11	0.83 (0.46; 1.50)	0.541
Model 4 (fully adjusted)					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	409,110	38,042	1.00 (Ref.)	463	0.87 (0.79; 0.96)	0.004	686	0.93 (0.87; 1.00)	0.047	405	0.99 (0.90; 1.09)	0.845
Head & neck	409,110	848	1.00 (Ref.)	12	0.94 (0.53; 1.66)	0.824	21	1.23 (0.80; 1.91)	0.344	9	1.05 (0.54; 2.03)	0.889
Oesophagus	409,110	1,010	1.00 (Ref.)	11	1.13 (0.62; 2.06)	0.679	7	0.51 (0.24; 1.07)	0.075	13	1.64 (0.95; 2.85)	0.076
Stomach	409,110	775	1.00 (Ref.)	8	0.94 (0.47; 1.90)	0.870	11	0.99 (0.54; 1.80)	0.967	7	1.08 (0.51; 2.28)	0.836
Colorectal	409,110	4,679	1.00 (Ref.)	43	0.73 (0.54; 0.99)	0.042	75	0.90 (0.71; 1.14)	0.355	42	0.89 (0.66; 1.21)	0.468
Colon	409,110	3,340	1.00 (Ref.)	29	0.69 (0.48; 0.99)	0.046	52	0.87 (0.66; 1.15)	0.321	29	0.84 (0.59; 1.22)	0.367
Proximal	409,110	1,680	1.00 (Ref.)	9	0.43 (0.22; 0.82)	0.011	29	0.96 (0.67; 1.39)	0.847	15	0.84 (0.51; 1.41)	0.515
Distal	409,110	1,444	1.00 (Ref.)	17	0.94 (0.58; 1.51)	0.784	18	0.70 (0.44; 1.12)	0.141	15	1.07 (0.64; 1.78)	0.805
Rectum	409,110	2,045	1.00 (Ref.)	18	0.72 (0.45; 1.15)	0.163	35	0.98 (0.70; 1.37)	0.904	24	1.25 (0.83; 1.86)	0.287

Pancreas	409,110	1,133	1.00 (Ref.)	9	0.65 (0.34; 1.26)	0.204	21	1.08 (0.70; 1.66)	0.741	6	0.52 (0.23; 1.15)	0.108
Lung	409,110	3,306	1.00 (Ref.)	27	0.76 (0.52; 1.11)	0.150	46	0.86 (0.64; 1.15)	0.300	28	0.81 (0.56; 1.18)	0.282
Melanoma	409,110	1,979	1.00 (Ref.)	19	0.68 (0.43; 1.07)	0.096	28	0.68 (0.47; 0.98)	0.041	17	0.80 (0.50; 1.29)	0.364
Breast	218,391	6,895	1.00 (Ref.)	138	0.95 (0.80; 1.13)	0.555	194	0.90 (0.78; 1.04)	0.153	127	1.11 (0.93; 1.32)	0.243
Premenopausal	54,775	1,776	1.00 (Ref.)	50	1.00 (0.75; 1.33)	0.970	52	0.78 (0.59; 1.03)	0.082	22	0.91 (0.60; 1.39)	0.657
Postmenopausal	130,625	3,668	1.00 (Ref.)	71	0.92 (0.73; 1.16)	0.300	113	0.91 (0.75; 1.10)	0.186	79	1.06 (0.85; 1.33)	0.604
Uterine	218,391	1,131	1.00 (Ref.)	23	1.15 (0.76; 1.74)	0.522	30	1.09 (0.75; 1.56)	0.655	18	1.07 (0.67; 1.71)	0.764
Ovary	218,391	870	1.00 (Ref.)	19	1.14 (0.72; 1.80)	0.583	28	1.07 (0.73; 1.57)	0.716	18	1.20 (0.75; 1.91)	0.455
Prostate	190,543	7,492	1.00 (Ref.)	47	0.57 (0.43; 0.76)	<0.001	82	0.89 (0.71; 1.11)	0.280	41	0.87 (0.64; 1.18)	0.373
Kidney	409,110	1,227	1.00 (Ref.)	12	0.88 (0.50; 1.56)	0.662	17	0.93 (0.57; 1.50)	0.765	12	1.14 (0.64; 2.02)	0.652
Bladder	409,110	2,054	1.00 (Ref.)	18	0.91 (0.57; 1.45)	0.685	35	1.25 (0.89; 1.75)	0.196	16	0.99 (0.61; 1.63)	0.979
Brain	409,110	760	1.00 (Ref.)	8	0.73 (0.36; 1.47)	0.379	12	0.78 (0.44; 1.38)	0.394	10	1.25 (0.67; 2.34)	0.485
Thyroid	409,110	287	1.00 (Ref.)	8	1.37 (0.68; 2.79)	0.379	6	0.78 (0.35; 1.76)	0.551	3	0.76 (0.24; 2.38)	0.640
Haematological	409,110	3,583	1.00 (Ref.)	47	0.98 (0.73; 1.31)	0.885	66	1.00 (0.78; 1.28)	0.987	38	1.01 (0.74; 1.40)	0.934
Non-Hodgkin lymphoma	409,110	1,744	1.00 (Ref.)	21	0.89 (0.58; 1.38)	0.612	27	0.81 (0.55; 1.19)	0.285	19	1.01 (0.64; 1.59)	0.956
Multiple Myeloma	409,110	921	1.00 (Ref.)	13	0.99 (0.57; 1.72)	0.968	21	1.24 (0.80; 1.92)	0.330	11	1.13 (0.62; 2.04)	0.697
Leukaemia	409,110	1,116	1.00 (Ref.)	16	1.14 (0.69; 1.87)	0.611	25	1.29 (0.87; 1.93)	0.206	11	0.99 (0.55; 1.80)	0.981

Data presented as adjusted hazard ratio (HR) with 95% confidence interval (95% CI) by type of diet. Meat-eaters were used as the reference group.
Model 0 was unadjusted, Model 4 included sociodemographic covariates (age, sex, deprivation, and ethnicity); lifestyle factors (smoking, alcohol, total physical activity, fruits and vegetables) and comorbidities (presence of 43 diseases), women-reproductive factors; and body mass index. Models 1, 2 and 3 are presented in Additional file 1: table S2.

Lower risk of overall cancer and nine cancer sites was found for pescatarians compared with meat-eaters in the unadjusted analyses - kidney, lung, melanoma, non-Hodgkin lymphoma, colorectal (overall and for colon and rectum individually), bladder, prostate, lymphatic and breast - with hazard ratios ranging from 0.57 to 0.65. However, in the maximally adjusted model (model 4), only overall cancer (HR: 0.93 [95% CI: 0.87 to 1.00]) and melanoma (HR: 0.68 [95% CI: 0.47; 0.98]) remained significant. The hazard ratios for intermediate models 2 and 3 are presented in Additional file 1: Table S4.

Similar results were found when the models were repeated using the 2-year landmark analysis. In the maximally adjusted models (model 4), the associations for vegetarians were slightly attenuated but remained significant for overall (HR: 0.88 [95% CI: 0.80 to 0.97]), proximal colon (HR: 0.48 [95% CI: 0.25; 0.93]) and prostate (HR: 0.59 [95% CI: 0.44; 0.79]) cancer. However, the associations of vegetarian diet with colorectal and colon cancer were no longer significant. Meanwhile, the associations for pescatarians remained significant for overall cancer (HR: 0.90 [95% CI: 0.83 to 0.98]) and melanoma (HR: 0.67 [95% CI: 0.44; 1.00]). There was a lower risk of oesophageal cancer among pescatarians when the 2-year landmark analyses were performed (HR: 0.41 [95% CI: 0.17; 0.99]) (Additional file 1: Table S5).

Meta-analysis

A total of 1,468 (189 Scopus; 227 Web of Science; 433 EMBASE; 619 PubMed) articles were identified from the search terms. Following the exclusion of duplicates, 1,044 abstracts were screened, and 34 manuscripts were reviewed in full. Of these, 25 manuscripts were excluded as they did not meet the inclusion criteria (16 did not report the exposure of interest; 8 did not report cancer outcomes, and one did not report relevant effect sizes, i.e. HR or RR). After

adding our UK Biobank study, ten studies in total were included in the meta-analysis. (Cade et al., 2010, Gilsing et al., 2015, Gilsing et al., 2016, Key et al., 2014, Orlich et al., 2015, Penniecook-Sawyers et al., 2016, Tantamango-Bartley et al., 2013, Tantamango-Bartley et al., 2016, Travis et al., 2008) (Figure 3-1). Of the 28 cancer sites reported in these papers, only overall cancer and four individual cancer sites could be included in the meta-analysis as they had been reported by at least three independent studies (Additional file 1: Table S6). The definitions used for vegetarian and pescatarian diets in each study are presented in Additional file 1: Table S7. Related to qualitative methodology, most of the studies had moderate risk (Additional file 1: Table S8 and Additional file 1: Table S9).

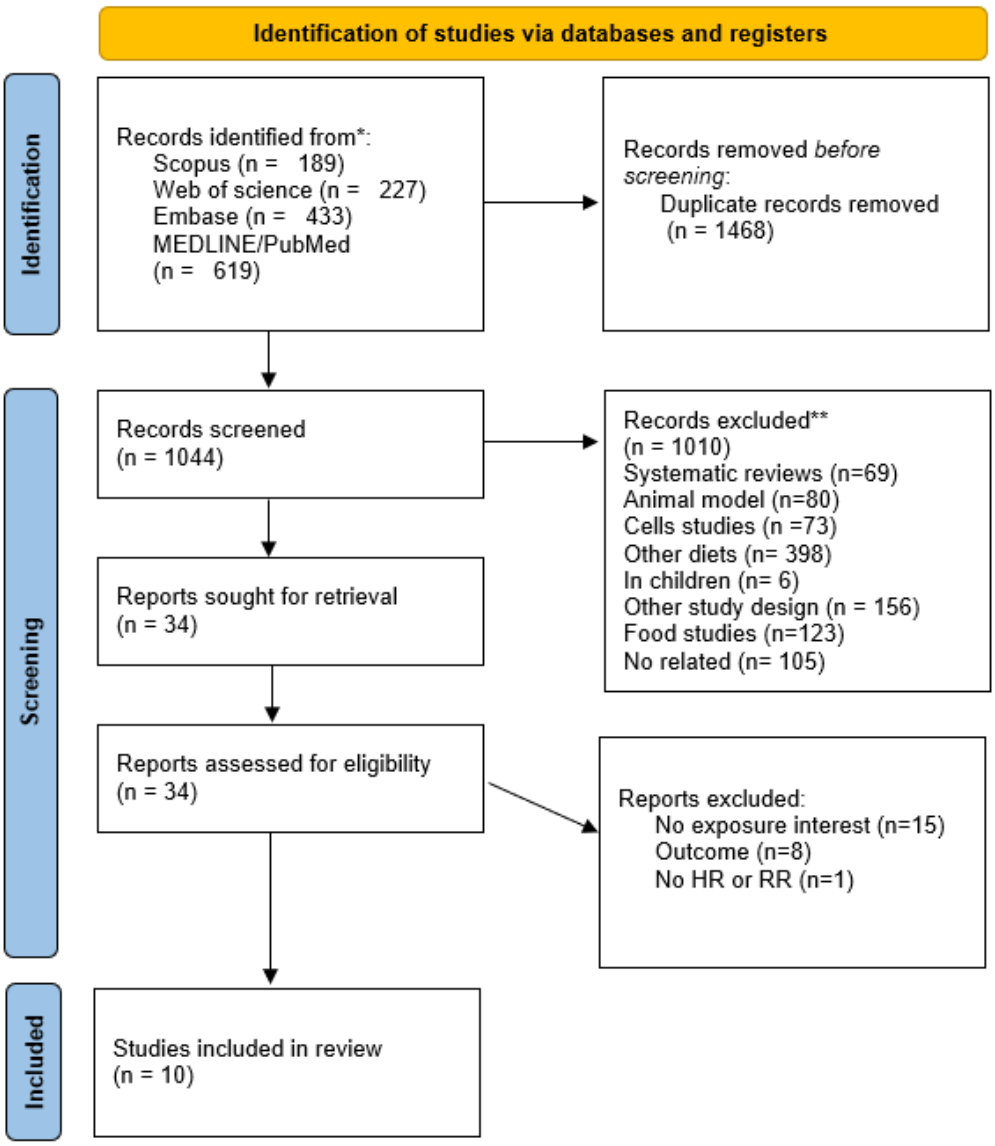

Figure 3-1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection process (Presented according to PRISMA guidelines).

For vegetarian diets, there were 3 eligible studies (539,877 participants; 3,192 events) for overall cancer (Key et al., 2014, Tantamango-Bartley et al., 2013), 4 studies (558,626 participants; 471 events) for colorectal cancer (Gilsing et al., 2015, Key et al., 2014, Orlich et al., 2015), 3 studies (481,839 subjects, 92 events) for lung cancer (Gilsing et al., 2016, Key et al., 2014), 4 studies (509,027 participants, 499 events) for prostate cancer (Gilsing et al., 2016, Key et al.,

2014, Tantamango-Bartley et al., 2016) and 5 studies (569,968 participants, 1,116 events) for breast cancer (Gilsing et al., 2016, Key et al., 2014, Penniecook-Sawyers et al., 2016, Cade et al., 2010) (Figure 3.2). The meta-analysis heterogeneity ranged from 0% to 74% across cancer sites, with the highest heterogeneity found for prostate and colorectal cancer (Figure 3.2), and the funnel plots were reasonably symmetrical (Additional file 1: Fig. S2, S3, S4 and S5). For overall cancer, the pooled results suggested a 10% lower risk among vegetarians compared with meat-eaters (RR: 0.90, 95% CI: 0.86; 0.94) and there was a borderline significant lower risk for colorectal cancer (RR: 0.86, 95% CI: 0.72; 1.02). No associations were observed for lung (RR: 0.92, 95% CI: 0.69; 1.21), prostate (RR: 0.83, 95% CI: 0.63; 1.08) or breast cancer (RR: 0.94, 95% CI: 0.84, 1.05) (Figure 3-2). When a sensitivity analysis was performed by replacing vegetarians for lacto-ovo vegetarians defined by Tantamango et al., (Tantamango-Bartley et al., 2013) for overall cancer, Orlish et al [33] for colorectal cancer, and Penniecook et al (Penniecook-Sawyers et al., 2016) for breast cancer, similar results were found (Additional file 1: Fig S6). When studies for which the definition of vegetarians included a low meat consumption (less than once a month) were excluded (Orlish et al [33], Tantamango et al., (Tantamango-Bartley et al., 2013) and Penniecook et al (Penniecook-Sawyers et al., 2016)) the association of vegetarians with overall cancer remained significant (RR: ;0.89, 95% CI: 0.84; 0.94), while the association for colorectal cancer remained no significant (Additional file 1: Fig S7).

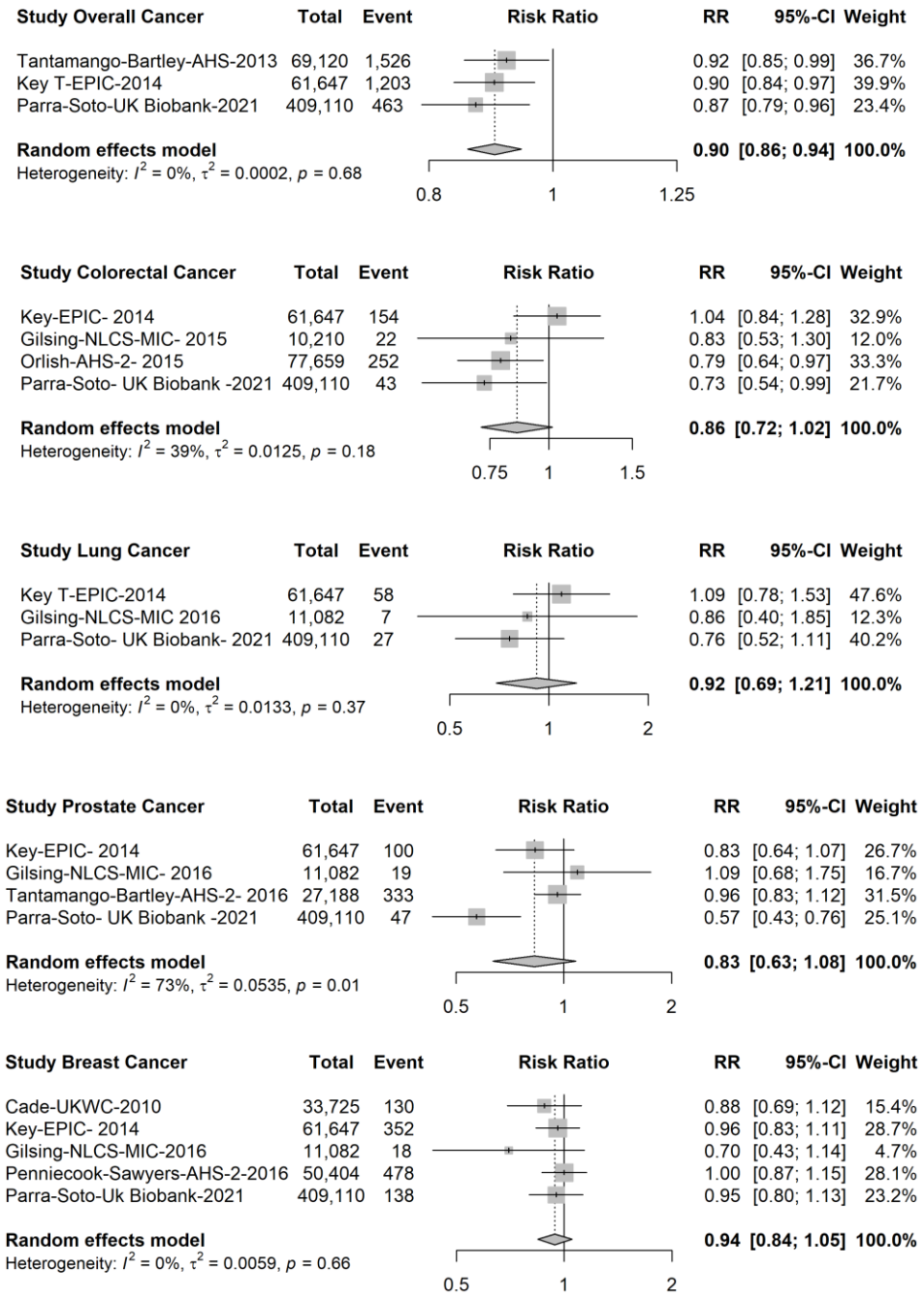

Figure 3-2. Forest plot of prospective cohort studies evaluating summary risk ratios of colorectal, lung, prostate, breast and overall cancer of vegetarians compared with meat-eaters (reference). RR: Risk ratio, CI: confidence interval

For pescatarian diets, there were 3 studies (1,482 events) for overall cancer (Key et al., 2014, Tantamango-Bartley et al., 2013), 4 studies (167 events) for colorectal cancer (Gilsing et al., 2015, Key et al., 2014, Orlich et al., 2015), 3 studies (61 events) for lung cancer (Gilsing et al., 2016, Key et al., 2014), 4

studies (250 events) for prostate cancer (Gilsing et al., 2016, Key et al., 2014, Tantamango-Bartley et al., 2016), and 5 studies (585 events) for breast cancer (Gilsing et al., 2016, Key et al., 2014, Penniecook-Sawyers et al., 2016, Cade et al., 2010) (Figure 3-3).

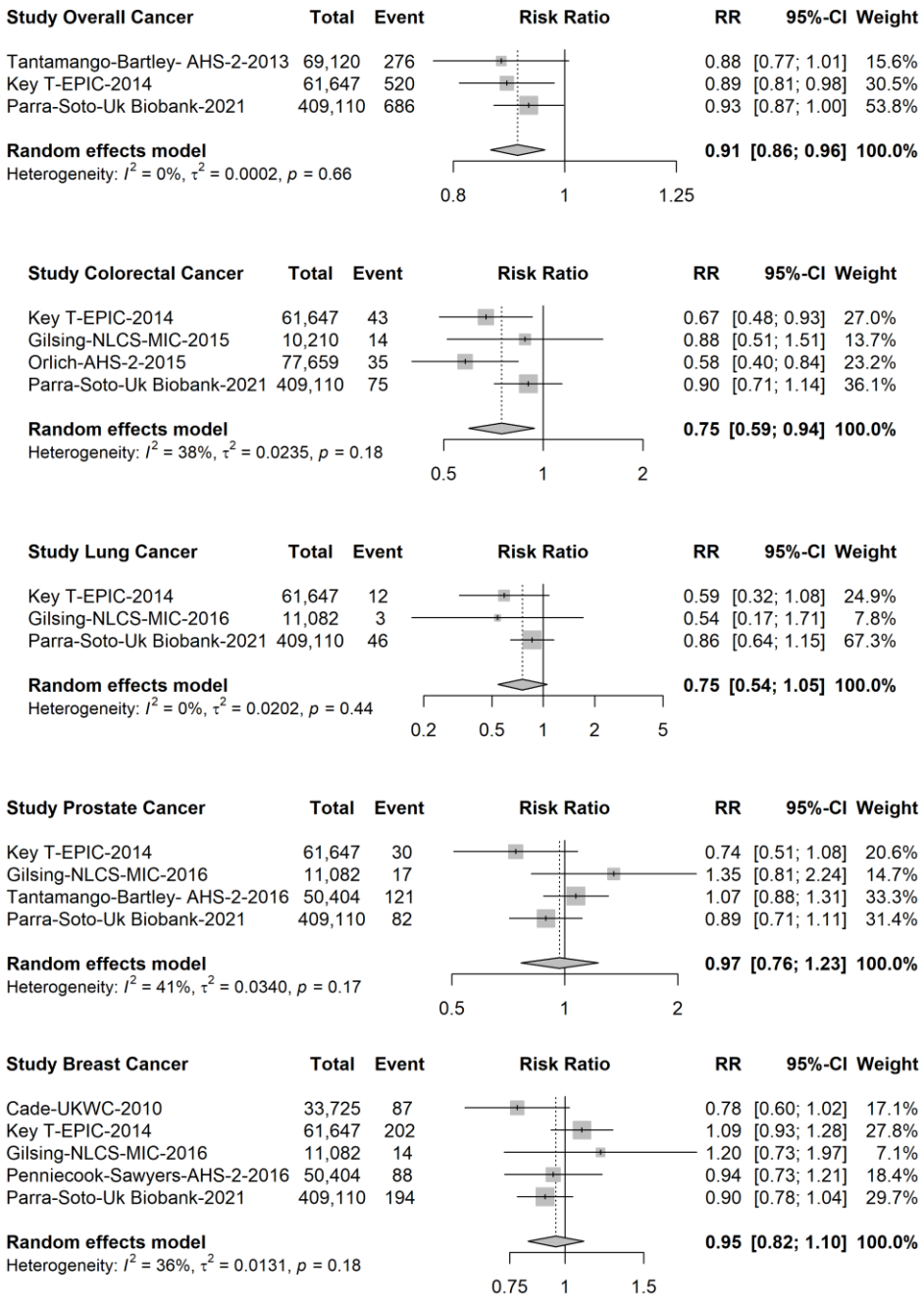

Figure 3-3. Forest plot of prospective cohort studies evaluating summary risk ratios of colorectal, lung, prostate, breast and overall cancer of pescatarians compared with meat-eaters (reference). RR: Risk ratio, CI: confidence interval

Compared with meat-eaters, pescatarians had a 9% lower risk of overall cancer (pooled RR: 0.91, 95% CI: 0.86; 0.96) and a significant association for colorectal

cancer (RR: 0.75, 95% CI: 0.59; 0.94), but no significant associations were observed for lung (RR: 0.75, 95% CI: 0.54; 1.05), prostate (RR: 0.97, 95%CI: 0.76; 1.23) or breast cancer (RR: 0.95, 95% CI: 0.82; 1.10) (Figure 3-3).

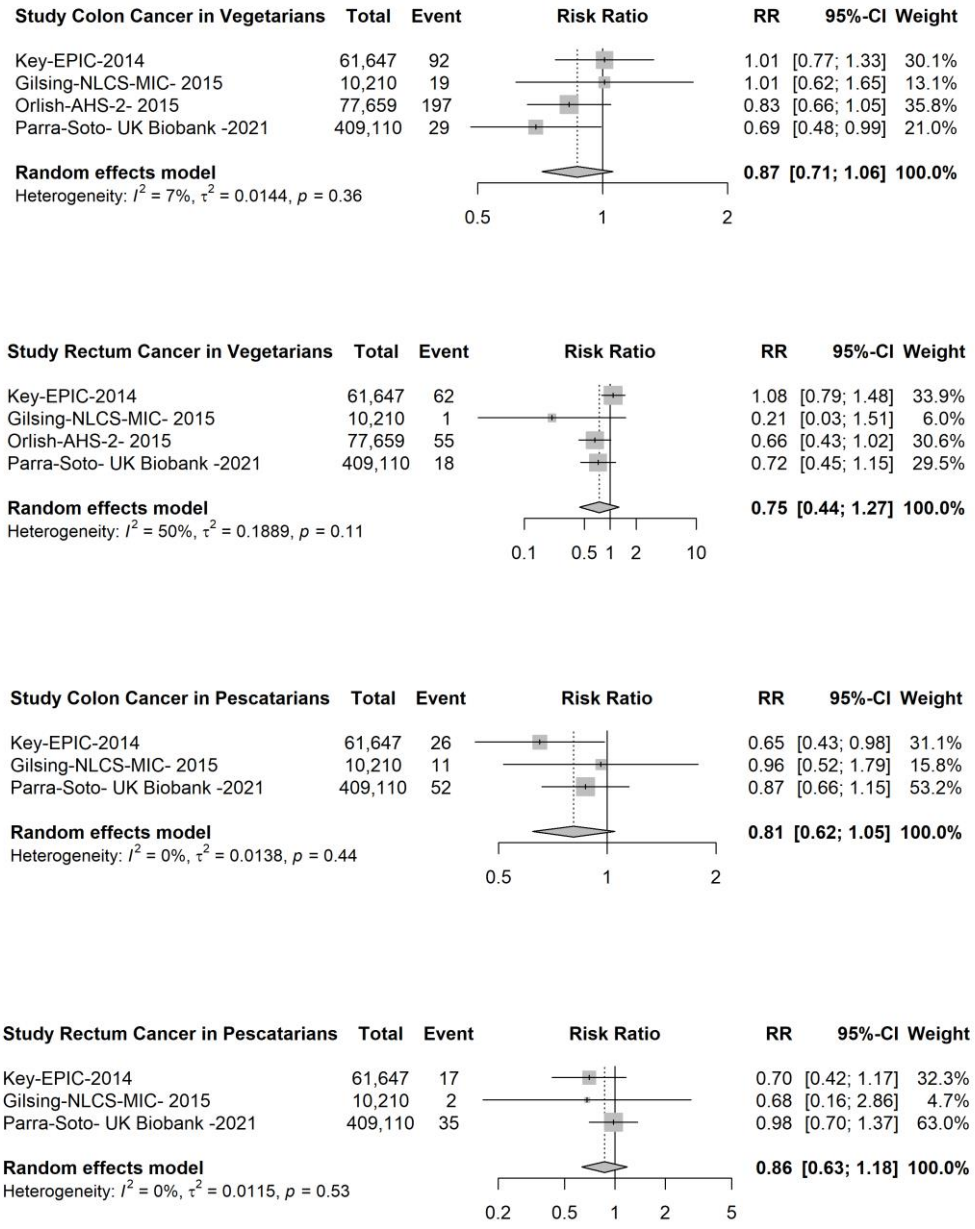

Figure 3-4. Forest plot of prospective cohort studies evaluating summary risk ratios of colon and rectal cancer of vegetarians and pescatarians compared with meat-eaters (reference). RR: Risk ratio, CI: confidence interval

When the pooled data were examined for colon and rectum cancer separately, there were no differences in risk for vegetarians or pescatarians compared with meat-eaters (Figure 3-4). Similarly, when breast cancer was stratified by

menopausal status, risk did not differ between vegetarians, pescatarians and meat-eaters (Figure 3-5) and when and Penniecook et al (Penniecook-Sawyers et al., 2016)) was removed (Additional file 1: Fig S9). Finally, when Orlish et al [33] was removed from the analysis since they include low meat consumption (less than once a month) on their definition of pescatarian, the association became non-significant (RR: 0.81, 95% CI: 0.65; 1.01) (Additional file 1: Fig S8).

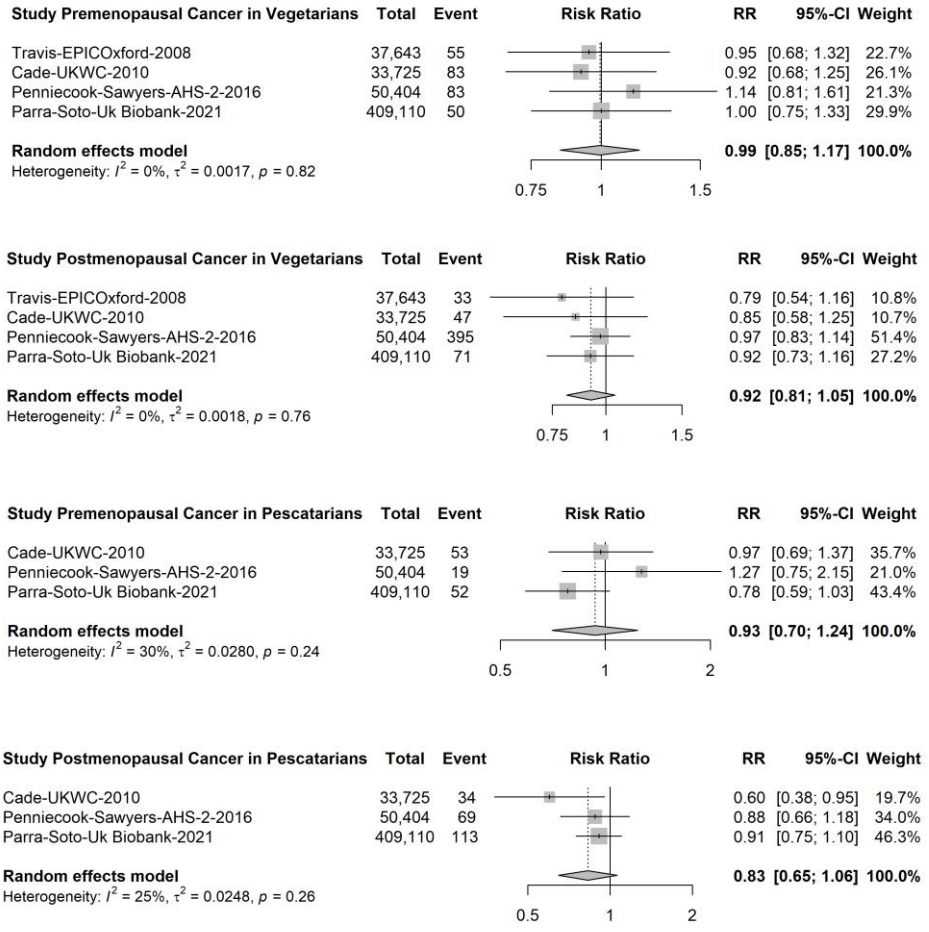

Figure 3-5. Forest plot of prospective cohort studies evaluating summary risk ratios of breast cancer in premenopausal and postmenopausal women for vegetarians and pescatarians compared with meat-eaters (reference). RR: Risk ratio, CI: confidence interval

3.4 Discussion

This analysis of the UK Biobank cohort suggests that, compared to meat-eaters, vegetarians had a lower risk of all cancers combined and of colorectal (especially colon and proximal colon) and prostate cancer, and that pescatarians had a lower risk of all cancers and melanoma. These associations were independent of major confounding factors, including socio-demographics, lifestyle, multimorbidity and adiposity. When the results were pooled with nine previous studies in a meta-analysis, the overall associations with all cancers persisted, but the results relating to specific cancer sites were inconclusive.

Although evidence for associations between red and processed meat consumption and increased risk of cancer has been widely reported (Anderson et al., 2018, Bradbury et al., 2019, Handel et al., 2019, Johnston et al., 2019, World Cancer Research Fund/American Institute for Cancer Research, 2018), there is limited and equivocal evidence for alternative diets, such as vegetarian or pescatarian, on cancer risk (Dinu et al., 2017, Godos et al., 2017, Veettil et al., 2021). In our study, vegetarians and pescatarians had a 10% and 9% lower risk of overall cancer compared with meat-eaters, respectively. These findings of lower risk agree with evidence reported in previous studies (Dinu et al., 2017). A meta-analysis published in 2017, which included 38,033 participants from two prospective cohort studies from the USA and UK, of whom 1,976 developed incident all-cause cancers, showed that vegetarians had an 8% lower risk (Dinu et al., 2017). However, an earlier meta-analysis by Huang et al. in 2012, which included 124,706 participants from the UK, Netherlands and Germany, reported a larger reduction of 18% for overall cancer incidence in vegetarians compared with meat-eaters (Huang et al., 2012).

Regarding specific cancers, in a study including 77,659 participants who were followed-up for 7.3 years, Orlich et al. (2015), reported that vegetarians had a 22% lower incidence risk of colorectal cancer (HR: 0.78 [95% CI, 0.64; 0.95] (490 cases)) compared with meat-eaters. The reduction in risk was stronger for pescatarians, who had a 43% lower risk of colorectal cancer (HR: 0.57 [95% CI, 0.40; 0.82]) (Orlich et al., 2015). In a relatively recent meta-analysis, Godos et al. (Godos et al., 2017), which included a total of nine studies including six cohorts accounting for 686 629 individuals, and 3441, 4062 and 1935 cases of breast, colorectal and prostate cancer, respectively, reported no significant differences between vegetarians and non-vegetarians in the risk of breast and prostate cancer. However, they did find a lower risk of colorectal cancer in semi-vegetarians (RR:0.86 [95% CI, 0.79; 0.94]) and pescatarians (RR:0.67 [95% CI, 0.53; 0.83]) (Godos et al., 2017). In our study using UK Biobank data, we found a 27% lower risk of colorectal cancer in vegetarians. When the analyses were stratified by subtype, cancers in the proximal colon and colon showed a 57% and 31% lower risk in vegetarians, respectively, with no associations observed for distal colon or rectal cancer. Interestingly, for pescatarians, we observed significant associations for colorectal and colon cancer only in the minimally adjusted model, and these associations were completely attenuated when the analyses were adjusted for socio-demographics, lifestyle and BMI. Similar to breast and lung cancer, the associations with diet type were significant in the unadjusted model; but disappeared completely in the most adjusted model. Indeed, these results are in agreement with previous studies, especially for breast cancer, where associations were attenuated after accounting for BMI (Cade et al., 2010, Gilsing et al., 2016, Penniecook-Sawyers

et al., 2016, Key et al., 2014). No studies have reported significant differences in lung cancer risk for vegetarians or pescatarians versus meat-eaters in maximal adjusted models (Cade et al., 2010, Gilsing et al., 2016, Key et al., 2014). Our finding of no significant associations with site-specific cancers among poultry eaters was similar to those reported by Cade et al. in 2010 (Cade et al., 2010). Some of the mechanisms that could explain the associations between vegetarian diet and cancer risk are the presence of bioactive compounds in plant-based diets, such as fibre, phenol, polyphenol, and sulphuric compounds, and other antioxidants compounds, including vitamins. These compounds have been shown to have anti-carcinogenic effects in experimental models and epidemiological studies (Subramaniam et al., 2019, Silveira et al., 2020). On the other hand, this dietary pattern has some deficient intake of certain nutrients such as iron and vitamin B12. For instance, long-chain n-3 fatty acids, such as eicosapentaenoic acid, and docosahexaenoic acid, are lower in vegetarians (Burns-Whitmore et al., 2019). Therefore, decreased intakes of some of these nutrients have been related to a higher cancer incidence in some studies (Siriwardhana et al., 2012). We cannot discard that some of the associations described may be mediated through other risk factors such as adiposity(Arnold et al., 2016, Arnold et al., 2015, Brown et al., 2018) or smoking(Brown et al., 2018).

It is important to notice that not all vegetarians' diets are healthy (Gehring et al., 2021); higher consumption of ultra-processed food could reduce the benefit of a vegetarian diet on cancer risk. In our sample, vegetarian and pescatarians reported eating more crisps and pizza than meat-eaters.

Despite low/moderate heterogeneity in our meta-analysis, studies differed in a variety of ways that could lead to inconsistencies in their findings. Some of these include the length of follow-up (ranging from 4.1 to 20.3 years), differences in

confounding factors controlled for in each study, differences in sample size across cohorts (ranging from 10,210 to 409,110), as well as risks of bias attributable to the design of the studies which varied from low to moderate (Dinu et al., 2017). Studies also differed in how vegetarian and other types of diets were defined and for how long participants had been following their attributed type of diet (Huang et al., 2012). However, the measured heterogeneity between studies included in the meta-analyses was low.

Strength and limitations

UK Biobank is a large, prospective, general population cohort with data on diet and a wide range of potential confounders and health outcomes. However, UK Biobank is not representative of the general UK population regarding lifestyle and baseline health (Batty et al., 2020). Moreover, the participants who have full data available and therefore were included in this study were leaner and more affluent than those excluded due to missing data and prevalent cancer at baseline (Additional file 1: Table S3). Regardless of these differences, our risk estimates were similar to other more population-representative cohorts (Collins, 2012). In the UK Biobank, dietary data were collected from all participants on one occasion; therefore, we cannot rule out that the type of diet reported was not modified over the length of the study. However, an analysis of the repeatability of the touchscreen questionnaire in a sub-set of participants (n=20 348), who repeated the assessment centre visit approximately four years after recruitment, showed that the dietary touchscreen variables, available for the full cohort, reliably rank participants according to intakes of the main food groups. In our study, we were unable to investigate the association of vegan diet with cancer risk because there were very small numbers (n=57) of participants

who were vegan. Also, we were not able to include energy intake as a covariate as data were available for only half of the cohort population. Moreover, exposure specificity is also a limitation as there was a lack of data on what alternative nutrients or food sources were used to replace meat or fish consumption. An additional limitation of the UK Biobank findings is that data were collected at a single timepoint resulting in the inability to properly adjust for changes in the exposure or covariates over time.

For the meta-analysis, some data limitations should be considered when interpreting the results. The only available evidence was from high-income countries in Europe and North America i.e., the USA, Canada, UK and the Netherlands. Therefore, associations between dietary patterns and cancer in other continents and in low-income and middle-income countries remain to be investigated. The number of available studies was generally low for the cancer-specific analyses. This limited the possibility of exploring subgroup analysis, but the heterogeneity across studies was low. The definitions used for different types of diets differed between studies, which could introduce bias and influence the likelihood of detecting associations. Future research in this area should aim to standardize types of diet classifications relating to the types of food consumed and their frequency of consumption.

3.5 Conclusion

Our UK Biobank findings suggest that, compared with meat-eaters, vegetarians had a lower risk of cancer overall, probably due to lower risk of colorectal and prostate cancer. Pescatarians also had lower overall risk of cancer, but the relationships with specific contributory cancers were unclear. However, when our risk estimates were pooled with those from previous prospective cohort

studies, there was no conclusive evidence in relation to site-specific cancers, even though the associations with overall cancer risk were significant. Larger studies with longer follow-up periods and better classification of diet types are needed to elucidate the benefits, or otherwise, of vegetarian and pescatarian diets on risk of individual cancers.

3.6 References Chapter 3

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3.7 Additional File Chapter 3

Methods

Key search terms used in the systematic review

#1 Vegetarian, #2 Vegetarianism, #3 "Vegetarian Diet", #4Vegan, #5Veganism, #6 "Vegan Diet", #7Veg$, #8 "Plant-Based", #9 Cancer, #10Neoplasms, #11 Cohort, #12 cohort Study, #13Prospective, #14 "Prospective Cohort Study", #15 Incidence, #16 "Incidence Studies" and MESH terms: #17 "Diet, vegetarian", #18 "Neoplasm" y #19 "cohort studies. They were combined in the following the following search codes: ((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #17) AND (#9 OR #10 OR #18) AND (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #19)).

EMBASE

(vegetarian:ab,ti OR vegetarianism OR vegan OR veganism OR (vegan AND diet) OR (plant AND based) OR (vegetarian AND diet)) AND (cancer OR 'neoplasm') AND ('cohort analysis' OR (cohort AND study) OR (retrospective AND cohort AND study) OR (retrospective AND cohort) OR (retrospective AND cohort AND study) OR (prospective AND cohort AND study) OR (prospective AND cohort) OR (incidence AND studies)) AND ([article]/lim OR [article in press]/lim) AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [embase]/lim

WEB OF SCIENCE

AB = (vegetarian OR vegetarianism OR vegan OR veganism OR "vegan diet" OR "plant based"OR "vegetarian diet)" AND cancer OR neoplasm AND "cohort analysis" OR "cohort study" OR "retrospective cohort study" OR "retrospective cohort" OR "retrospective cohort study" OR "prospective cohort study" OR "prospective cohort" OR "incidence studies")

AND AB = (cancer OR neoplasm) AND AB = ("cohort" OR "cohort study")

SCOPUS

TITLE-ABS-KEY ((vegetarian OR vegetarianism OR vegan OR veganism OR "plant based" OR "vegetarian diet" AND cancer OR neoplasm AND "cohort" OR "cohort study" OR retrospective)) AND (LIMIT-TO (DOCTYPE , "ar"))

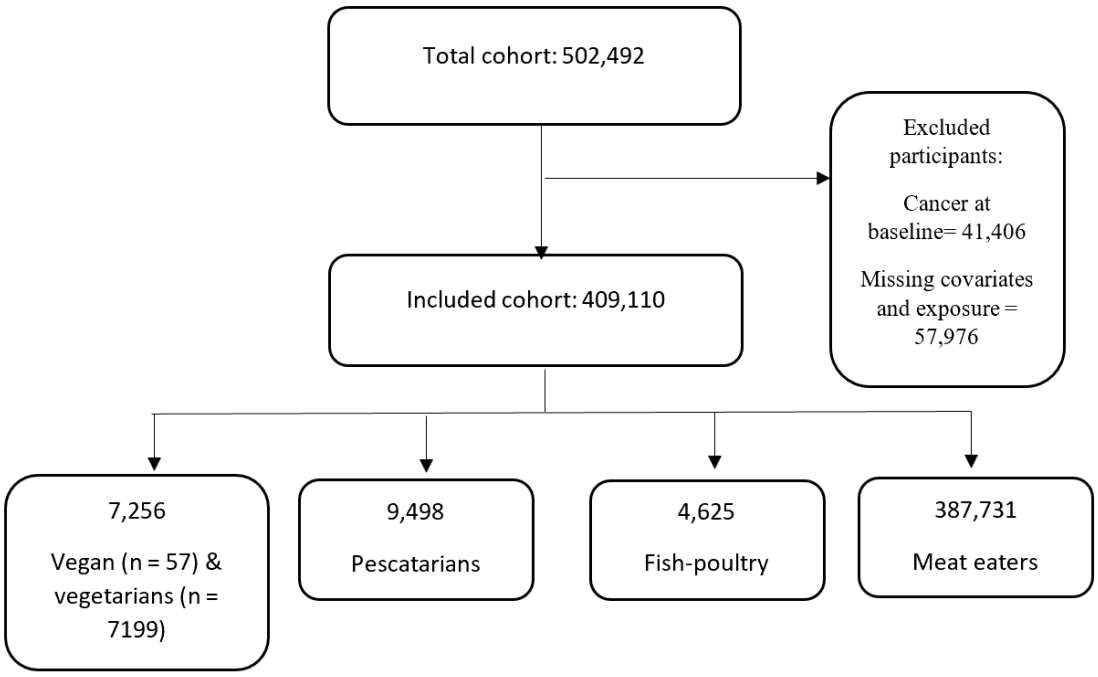

Fig. S1: Flowchart of UK Biobank participants.

Table S1: Criteria for the Newcastle-Ottawa Scale regarding star allocation to assess quality of studies (out of a total of seven stars).

Criteria	Acceptable (star awarded):	Unacceptable (star not awarded):
Representativeness of exposed cohort	Population-based	Hospital-based
Selection of non-exposed cohort	Same setting as exposed cohort	Different setting from exposed cohort
Ascertainment of exposure	Secure records or directly measured	Self-reported information
Comparability	Excluded or adjusted for prior outcome in analysis Adjusted for age, race, smoking	No exclusion of prior outcome Did not adjust for age, race, smoking
Outcome of interest	Secure records or directly measured	Self-reported information
Adequacy of follow-up	Adjusted for missing data or follow-up > 1 month.	No statement regarding missing data. No follow-up after birth

Table S2: Details of dietary characteristics for 175,499 UK Biobank participants.

	Meat-eaters	Vegan & vegetarian	Pescatarian	Fish & poultry	Overall
N (%)	164,492 (93.7%)	3,846 (2.2%)	5,159 (2.9%)	2,002 (1.1%)	175,499
Total energy intake (kcal/day), mean (SD)	2123.7 (645.76)	2071.2 (717.53)	2074.7 (655.92)	1985.1 (699.11)	2119.5 (648.60)
CHO intake (% of TE), mean (SD)	47.0 (8.04)	52.1 (8.11)	50.1 (8.06)	50.3 (8.53)	47.3 (8.10)
Sugar intake (% of TE), mean (SD)	22.4 (6.94)	24.1 (7.34)	23.7 (7.02)	25.1 (7.63)	22.5 (6.97)
Fibre intake (g/day), mean (SD)	16.4 (7.62)	21.0 (9.22)	20.0 (8.90)	19.5 (9.63)	16.6 (7.78)
Protein intake (% of TE), mean (SD)	15.7 (3.61)	12.4 (2.31)	13.5 (2.71)	15.2 (3.52)	15.5 (3.61)
Fat intake (% of TE), mean (SD)	32.1 (6.68)	31.7 (7.15)	31.9 (6.97)	30.8 (7.27)	32.0 (6.71)
Polyunsaturated fat intake (% of TE), mean (SD)	5.9 (2.22)	6.3 (2.47)	6.3 (2.34)	6.0 (2.27)	5.9 (2.23)
Saturated fat intake (% of TE), mean (SD)	12.4 (3.31)	12.0 (3.60)	11.8 (3.40)	11.3 (3.53)	12.3 (3.32)
Vitamin D, (ug), mean (SD)*	2.8 (3.29)	1.2 (1.90)	3.3 (4.34)	3.14 (4.22)	2.8 (3.32)
Iron, (mg), mean (SD)*	13.6 (5.23)	14.3 (6.15)	14.6 (5.74)	13.74 (5.77)	13.7 (5.28)
Fruit and vegetable intake (g/day), mean (SD)	328.3 (181.81)	403.8 (223.13)	406.7 (212.51)	426.0 (229.14)	333.4 (185.44)
Water intake (glasses/day), mean (SD)	2.9 (2.20)	3.4 (2.66)	3.4 (2.43)	3.6 (2.57)	2.9 (2.22)
Fried potatoes					
< quarter portion	121,425 (74.6%)	3,114 (81.4%)	4,181 (81.8%)	1,676 (84.4%)	130,396 (75.1%)
Between quarter portion and Half portion	7,130 (4.4%)	133 (3.5%)	171 (3.3%)	67 (3.4%)	7,501 (4.3%)
Between Half portion and 1 portion	30,680 (18.9%)	509 (13.3%)	686 (13.4%)	219 (11.0%)	32,094 (18.5%)
Between 1 portion and 3 portions	2,636 (1.6%)	56 (1.5%)	55 (1.1%)	19 (1.0%)	2,766 (1.6%)
More than 2 portions	803 (0.5%)	14 (0.4%)	18 (0.4%)	5 (0.3%)	840 (0.5%)
Fizzy drinks					
< 1 portion	157,865 (97.0%)	3,734 (97.6%)	5,021 (98.2%)	1,949 (98.1%)	168,569 (97.1%)
Between 1 portion and 2 portions	3,642 (2.2%)	74 (1.9%)	71 (1.4%)	27 (1.4%)	3,814 (2.2%)
Between 2 portion and 3 portions	782 (0.5%)	9 (0.2%)	9 (0.2%)	7 (0.4%)	807 (0.5%)
More than 3 portions	385 (0.2%)	9 (0.2%)	10 (0.2%)	3 (0.2%)	407 (0.2%)
Crisp					
< half portion	130,692 (80.3%)	2,965 (77.5%)	4,172 (81.6%)	1,711 (86.2%)	139,540 (80.4%)
Between half portion and 1 portion	27,813 (17.1%)	739 (19.3%)	800 (15.7%)	239 (12.0%)	29,591 (17.0%)
Between 1 portion and 3 portions	3,802 (2.3%)	108 (2.8%)	124 (2.4%)	30 (1.5%)	4,064 (2.3%)
More than 3 portions	367 (0.2%)	14 (0.4%)	15 (0.3%)	6 (0.3%)	402 (0.2%)
Pizza					
< quarter portion	155,165 (95.4%)	3,530 (92.3%)	4,803 (94.0%)	1,903 (95.8%)	165,401 (95.3%)
Between quarter portion and Half portion	1,375 (0.8%)	39 (1.0%)	46 (0.9%)	7 (0.4%)	1,467 (0.8%)
Between Half portion and 3 portion	2,206 (1.4%)	84 (2.2%)	91 (1.8%)	28 (1.4%)	2,409 (1.4%)
More than 3 portions	2,376 (1.5%)	101 (2.6%)	111 (2.2%)	30 (1.5%)	2,618 (1.5%)
Missing	1553 (1.0%)	72 (1.9%)	60 (1.2%)	18 (0.9%)	1703 (1.0%)

*Available for 58,496

Table S3: Baseline characteristics people with missing data who were not included in the study.

	No included (N=57,976)	Included (N=409,110)
Age, mean (SD)	56.2 (8.17)	56.3 (8.11)
Sex, n (%)		
Females	32,192 (55.5%)	218,567 (53.4%)
Males	25,768 (44.4%)	190,543 (46.6%)
Townsend deprivation index, n(%)		
Lower deprivation	16,143 (27.7 %)	139,244 (34.0%)
Middle	17,798 (30.5 %)	137,590 (33.6%)
Higher deprivation	23,692 (40.7 %)	132,276 (32.3%)
Missing	639 (1.1 %)	-
Ethnicity, n (%)		
White	51,289 (88.0 %)	387,366 (94.7%)
Mixed	1,527 (2.6 %)	5,663 (1.4%)
South Asian	2,059 (3.5 %)	7,512 (1.8%)
Black	1,691 (2.9 %)	6,079 (1.5%)
Chinese	282 (0.5 %)	1,230 (0.3%)
Missing	1,424 (2.4 %)	1260 (0.3%)
Nutritional status		
Height (m), mean (SD)	1.7 (0.09)	1.68 (0.09)
Weight (Kg), mean (SD)	79.9 (17.01)	78.0 (15.82)
Waist (cm), mean (SD)	92.3 (14.10)	90.1 (13.38)
Body Mass index (kg/m2), mean (SD)	28.3 (5.26)	27.3 (4.72)
BMI classification, n (%)		
Underweight	304 (0.5 %)	2,096 (0.5%)
Normal	15,331 (26.3 %)	135,399 (33.1%)
Overweight	22,730 (39.0 %)	174,881 (42.7%)
Obese	16,972 (29.1 %)	96,734 (23.6%)
Missing	2,935 (5.0 %)	-
Smoking, n (%)		
Never	28,483 (48.9 %)	227,139 (55.5%)
Previous	18,805 (32.3 %)	140,398 (34.3%)
Current	8,035 (13.8 %)	41,573 (10.2%)
Missing	2,949 (5.1 %)	-
Alcohol intake, n (%)		
Daily or almost daily	11,160 (19.2 %)	83,335 (20.4%)
3-4 times a week	11,653 (20.0 %)	96,220 (23.5%)
Once or twice a week	13,659 (23.4 %)	106,833 (26.1%)
1-3 times a month	6,452 (11.1 %)	45,567 (11.1%)
Special occasions only	7,819 (13.4 %)	45,617 (11.2%)
Never	6,278 (10.8 %)	31,294 (7.6%)
Missing	1,251 (2.1 %)	244 (0.1%)
Sedentary time (h/day), mean (SD)	5.0 (2.54)	5.0 (2.26)
Physical activity (MET/min/week)	3138.8 (3534.36)	2915.5 (3212.13)
Multimorbidity, n (%)		
No	18,467 (32.7 %)	154,632 (37.8%)
Yes	39,804 (68.3 %)	254,478 (62.2%)

Table S4: Association between types of diet and cancer incidence for Models 1-3.

Cancer site	Total	Events	Meat-eaters	Events	Vegan & Vegetarian		Events	Pescatarian		Events	Fish & Poultry	
Model 1					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	409,110	38,042	1.00 (Ref.)	463	0.83 (0.76; 0.91)	<0.001	686	0.89 (0.82; 0.95)	0.002	405	0.95 (0.86; 1.05)	0.310
Head & neck	409,110	848	1.00 (Ref.)	12	0.91 (0.51; 1.61)	0.740	21	1.22 (0.79; 1.88)	0.379	9	1.03 (0.54; 2.00)	0.919
Oesophagus	409,110	1,010	1.00 (Ref.)	11	0.97 (0.53; 1.76)	0.919	7	0.43 (0.20; 0.90)	0.025	13	1.43 (0.82; 2.47)	0.203
Stomach	409,110	775	1.00 (Ref.)	8	0.83 (0.41; 1.66)	0.594	11	0.85 (0.47; 1.55)	0.605	7	0.96 (0.45; 2.02)	0.908
Colorectal	409,110	4,679	1.00 (Ref.)	43	0.70 (0.51; 0.94)	0.018	75	0.85 (0.68; 1.07)	0.171	42	0.85 (0.63; 1.16)	0.310
Colon	409,110	3,340	1.00 (Ref.)	29	0.65 (0.45; 0.94)	0.021	52	0.82 (0.62; 1.08)	0.152	29	0.80 (0.56; 1.16)	0.241
Proximal	409,110	1,680	1.00 (Ref.)	9	0.40 (0.21; 0.77)	0.006	29	0.89 (0.62; 1.29)	0.548	15	0.79 (0.48; 1.32)	0.375
Distal	409,110	1,444	1.00 (Ref.)	17	0.89 (0.55; 1.43)	0.619	18	0.67 (0.42; 1.07)	0.091	15	1.02 (0.61; 1.69)	0.949
Rectum	409,110	2,045	1.00 (Ref.)	17	0.68 (0.43; 1.09)	0.110	35	0.94 (0.67; 1.31)	0.712	24	1.19 (0.80; 1.78)	0.392
Pancreas	409,110	1,133	1.00 (Ref.)	9	0.60 (0.31; 1.16)	0.129	21	0.99 (0.64; 1.52)	0.959	6	0.48 (0.22; 1.07)	0.074
Lung	409,110	3,306	1.00 (Ref.)	27	0.62 (0.43; 0.91)	0.014	46	0.72 (0.54; 0.96)	0.025	28	0.70 (0.48; 1.01)	0.060
Melanoma	409,110	1,979	1.00 (Ref.)	19	0.68 (0.43; 1.07)	0.095	28	0.67 (0.46; 0.98)	0.039	17	0.80 (0.50; 1.29)	0.358
Breast	218,391	6,901	1.00 (Ref.)	138	0.93 (0.79; 1.10)	0.400	195	0.89 (0.77; 1.02)	0.104	127	1.09 (0.92; 1.30)	0.328
Premenopausal	54,775	1,776	1.00 (Ref.)	50	1.02 (0.77; 1.36)	0.872	52	0.81 (0.61; 1.07)	0.136	22	0.93 (0.61; 1.41)	0.726
Postmenopausal	130,625	3,668	1.00 (Ref.)	71	0.86 (0.68; 1.09)	0.211	114	0.89 (0.74; 1.07)	0.210	79	1.05 (0.84; 1.31)	0.678
Uterine	218,391	1,132	1.00 (Ref.)	23	1.03 (0.68; 1.55)	0.907	30	0.90 (0.62; 1.29)	0.550	18	0.93 (0.58; 1.48)	0.757
Ovary	218,391	870	1.00 (Ref.)	19	1.17 (0.74; 1.84)	0.507	28	1.11 (0.76; 1.61)	0.597	18	1.23 (0.77; 1.96)	0.388
Prostate	190,543	7,492	1.00 (Ref.)	47	0.59 (0.44; 0.78)	<0.001	82	0.92 (0.74; 1.14)	0.446	41	0.90 (0.66; 1.22)	0.484
Kidney	409,110	1,227	1.00 (Ref.)	12	0.76 (0.43; 1.35)	0.358	17	0.79 (0.49; 1.28)	0.343	12	1.01 (0.57; 1.78)	0.976
Bladder	409,110	2,054	1.00 (Ref.)	18	0.82 (0.51; 1.30)	0.394	35	1.13 (0.81; 1.58)	0.484	16	0.90 (0.55; 1.48)	0.691
Brain	409,110	760	1.00 (Ref.)	8	0.74 (0.37; 1.48)	0.389	12	0.79 (0.45; 1.40)	0.416	10	1.26 (0.67; 2.35)	0.473
Haematological	409,110	3,583	1.00 (Ref.)	47	0.95 (0.71; 1.27)	0.731	66	0.97 (0.76; 1.24)	0.792	38	0.99 (0.72; 1.36)	0.934
Non-Hodgkin lymphoma	409,110	1,744	1.00 (Ref.)	21	0.88 (0.57; 1.36)	0.564	27	0.79 (0.54; 1.16)	0.234	19	1.00 (0.64; 1.57)	0.997
Multiple Myeloma	409,110	921	1.00 (Ref.)	13	0.97 (0.56; 1.67)	0.900	21	1.20 (0.78; 1.85)	0.406	11	1.10 (0.60; 1.99)	0.763
Leukaemia	409,110	1,116	1.00 (Ref.)	16	1.09 (0.66; 1.79)	0.728	25	1.24 (0.84; 1.85)	0.281	11	0.96 (0.53; 1.74)	0.893
Model 2					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	409,110	38,042	1.00 (Ref.)	463	0.85 (0.78; 0.93)	0.001	686	0.90 (0.84; 0.97)	0.008	405	0.97 (0.88; 1.07)	0.538
Head & neck	409,110	848	1.00 (Ref.)	12	1.00 (0.56; 1.77)	0.993	21	1.32 (0.85; 2.03)	0.217	9	1.11 (0.58; 2.15)	0.749
Oesophagus	409,110	1,010	1.00 (Ref.)	11	1.05 (0.58; 1.90)	0.877	7	0.46 (0.22; 0.97)	0.043	13	1.54 (0.89; 2.66)	0.123
Stomach	409,110	775	1.00 (Ref.)	8	0.86 (0.43; 1.74)	0.679	11	0.89 (0.49; 1.62)	0.709	7	1.00 (0.47; 2.10)	0.991
Colorectal	409,110	4,679	1.00 (Ref.)	43	0.71 (0.52; 0.96)	0.024	75	0.87 (0.69; 1.09)	0.214	42	0.86 (0.64; 1.17)	0.348
Colon	409,110	3,340	1.00 (Ref.)	29	0.66 (0.46; 0.95)	0.027	52	0.83 (0.63; 1.09)	0.185	29	0.81 (0.56; 1.17)	0.264
Proximal	409,110	1,680	1.00 (Ref.)	9	0.41 (0.21; 0.78)	0.007	29	0.91 (0.63; 1.32)	0.623	15	0.80 (0.48; 1.34)	0.402
Distal	409,110	1,444	1.00 (Ref.)	17	0.90 (0.56; 1.45)	0.661	18	0.67 (0.42; 1.07)	0.097	15	1.03 (0.62; 1.71)	0.924
Rectum	409,110	2,045	1.00 (Ref.)	17	0.70 (0.44; 1.11)	0.130	35	0.95 (0.68; 1.33)	0.768	24	1.21 (0.81; 1.81)	0.353
Pancreas	409,110	1,133	1.00 (Ref.)	9	0.62 (0.32; 1.20)	0.159	21	1.02 (0.66; 1.57)	0.933	6	0.50 (0.22; 1.11)	0.087
Lung	409,110	3,306	1.00 (Ref.)	27	0.77 (0.53; 1.12)	0.176	46	0.86 (0.65; 1.16)	0.326	28	0.83 (0.57; 1.21)	0.334
Melanoma	409,110	1,979	1.00 (Ref.)	19	0.67 (0.43; 1.05)	0.084	28	0.67 (0.46; 0.97)	0.033	17	0.79 (0.49; 1.27)	0.334
Breast	218,391	6,895	1.00 (Ref.)	138	0.93 (0.78; 1.10)	0.375	194	0.87 (0.76; 1.01)	0.067	127	1.08 (0.91; 1.29)	0.385
Premenopausal	54,775	1,776	1.00 (Ref.)	50	1.03 (0.78; 1.37)	0.838	52	0.80 (0.61; 1.06)	0.119	22	0.93 (0.61; 1.42)	0.734
Postmenopausal	130,625	3,668	1.00 (Ref.)	71	0.89 (0.70; 1.12)	0.317	114	0.90 (0.74; 1.08)	0.250	79	1.07 (0.86; 1.34)	0.530

Ovary	218,391	870	1.00 (Ref.)	19	1.13 (0.72; 1.79)	0.597	28	1.07 (0.73; 1.56)	0.739	18	1.19 (0.75; 1.90)	0.467
Prostate	190,543	7,492	1.00 (Ref.)	47	0.58 (0.43; 0.77)	<0.001	82	0.90 (0.73; 1.12)	0.360	41	0.88 (0.65; 1.20)	0.428
Kidney	409,110	1,227	1.00 (Ref.)	12	0.80 (0.45; 1.41)	0.439	17	0.83 (0.51; 1.34)	0.437	12	1.04 (0.59; 1.84)	0.888
Bladder	409,110	2,054	1.00 (Ref.)	18	0.88 (0.55; 1.40)	0.578	35	1.20 (0.86; 1.67)	0.293	16	0.97 (0.59; 1.58)	0.890
Brain	409,110	760	1.00 (Ref.)	8	0.73 (0.36; 1.48)	0.386	12	0.78 (0.44; 1.39)	0.404	10	1.26 (0.67; 2.35)	0.475
Haematological	409,110	3,583	1.00 (Ref.)	47	0.95 (0.71; 1.27)	0.749	66	0.97 (0.76; 1.24)	0.823	38	0.99 (0.72; 1.36)	0.949
Non-Hodgkin lymphoma	409,110	1,744	1.00 (Ref.)	21	0.88 (0.57; 1.36)	0.563	27	0.80 (0.54; 1.17)	0.243	19	1.00 (0.64; 1.57)	0.999
Multiple Myeloma	409,110	921	1.00 (Ref.)	13	0.96 (0.55; 1.67)	0.888	21	1.20 (0.78; 1.86)	0.404	11	1.09 (0.60; 1.99)	0.766
Leukaemia	409,110	1,116	1.00 (Ref.)	16	1.11 (0.67; 1.82)	0.693	25	1.25 (0.84; 1.86)	0.269	11	0.97 (0.53; 1.75)	0.912
Model 3					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	409,110	38,042	1.00 (Ref.)	463	0.86 (0.78; 0.94)	0.001	686	0.91 (0.84; 0.98)	0.011	405	0.97 (0.88; 1.07)	0.562
Head & neck	409,110	848	1.00 (Ref.)	12	1.00 (0.56; 1.77)	0.999	21	1.32 (0.86; 2.04)	0.209	9	1.11 (0.58; 2.15)	0.747
Oesophagus	409,110	1,010	1.00 (Ref.)	11	1.06 (0.59; 1.93)	0.838	7	0.47 (0.23; 1.00)	0.050	13	1.55 (0.89; 2.68)	0.119
Stomach	409,110	775	1.00 (Ref.)	8	0.87 (0.43; 1.75)	0.695	11	0.90 (0.50; 1.64)	0.740	7	1.00 (0.47; 2.11)	0.998
Colorectal	409,110	4,679	1.00 (Ref.)	43	0.71 (0.52; 0.96)	0.024	75	0.87 (0.69; 1.09)	0.217	42	0.86 (0.64; 1.17)	0.348
Colon	409,110	3,340	1.00 (Ref.)	29	0.66 (0.46; 0.96)	0.028	52	0.83 (0.63; 1.10)	0.194	29	0.81 (0.56; 1.17)	0.266
Proximal	409,110	1,680	1.00 (Ref.)	9	0.41 (0.21; 0.79)	0.007	29	0.92 (0.63; 1.32)	0.642	15	0.81 (0.48; 1.34)	0.406
Distal	409,110	1,444	1.00 (Ref.)	17	0.90 (0.56; 1.45)	0.664	18	0.67 (0.42; 1.07)	0.098	15	1.03 (0.62; 1.71)	0.922
Rectum	409,110	2,045	1.00 (Ref.)	17	0.70 (0.44; 1.11)	0.128	35	0.95 (0.68; 1.33)	0.759	24	1.21 (0.81; 1.81)	0.355
Pancreas	409,110	1,133	1.00 (Ref.)	9	0.63 (0.33; 1.21)	0.167	21	1.03 (0.67; 1.59)	0.881	6	0.50 (0.22; 1.11)	0.090
Lung	409,110	3,306	1.00 (Ref.)	27	0.78 (0.53; 1.14)	0.202	46	0.88 (0.66; 1.18)	0.411	28	0.84 (0.58; 1.22)	0.352
Melanoma	409,110	1,979	1.00 (Ref.)	19	0.67 (0.43; 1.06)	0.084	28	0.67 (0.46; 0.97)	0.034	17	0.79 (0.49; 1.27)	0.334
Breast	218,391	6,895	1.00 (Ref.)	138	0.93 (0.78; 1.10)	0.375	194	0.87 (0.76; 1.01)	0.067	127	1.08 (0.91; 1.29)	0.385
Premenopausal	54,775	1,776	1.00 (Ref.)	50	1.01 (0.76; 1.33)	0.970	52	0.78 (0.59; 1.03)	0.082	22	0.91 (0.60; 1.39)	0.657
Postmenopausal	130,625	3,668	1.00 (Ref.)	71	0.88 (0.70; 1.12)	0.300	113	0.88 (0.73; 1.06)	0.186	79	1.06 (0.85; 1.33)	0.604
Uterine	218,391	1,131	1.00 (Ref.)	23	0.97 (0.64; 1.46)	0.870	30	0.88 (0.61; 1.27)	0.493	18	0.90 (0.56; 1.43)	0.649
Ovary	218,391	870	1.00 (Ref.)	19	1.13 (0.72; 1.79)	0.594	28	1.07 (0.73; 1.56)	0.734	18	1.19 (0.75; 1.90)	0.465
Prostate	190,543	7,492	1.00 (Ref.)	47	0.58 (0.43; 0.77)	<0.001	82	0.90 (0.72; 1.12)	0.348	41	0.88 (0.65; 1.20)	0.427
Kidney	409,110	1,227	1.00 (Ref.)	12	0.81 (0.46; 1.44)	0.472	17	0.85 (0.52; 1.37)	0.502	12	1.05 (0.59; 1.85)	0.870
Bladder	409,110	2,054	1.00 (Ref.)	18	0.89 (0.56; 1.41)	0.608	35	1.21 (0.87; 1.70)	0.256	16	0.97 (0.59; 1.59)	0.901
Brain	409,110	760	1.00 (Ref.)	8	0.73 (0.36; 1.48)	0.386	12	0.78 (0.44; 1.39)	0.405	10	1.26 (0.67; 2.35)	0.475
Haematological	409,110	3,583	1.00 (Ref.)	47	0.96 (0.72; 1.28)	0.765	66	0.98 (0.77; 1.25)	0.855	38	0.99 (0.72; 1.37)	0.957
Non-Hodgkin lymphoma	409,110	1,744	1.00 (Ref.)	21	0.88 (0.57; 1.36)	0.576	27	0.80 (0.55; 1.17)	0.257	19	1.00 (0.64; 1.58)	0.994
Multiple Myeloma	409,110	921	1.00 (Ref.)	13	0.96 (0.55; 1.67)	0.887	21	1.20 (0.78; 1.86)	0.405	11	1.09 (0.60; 1.99)	0.767
Leukaemia	409,110	1,116	1.00 (Ref.)	16	1.11 (0.67; 1.82)	0.683	25	1.26 (0.85; 1.87)	0.258	11	0.97 (0.53; 1.76)	0.916

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by type of diets. Meat-eaters were used as the reference group.
"model 1" (minimally adjusted) included sociodemographic covariates (age, sex, deprivation, and ethnicity); "model 2" additionally included lifestyle factors (smoking, alcohol intake and total physical activity); and "model 3" included model 2 plus multimorbidity.

Table S5: Landmark sensitivity analysis: Association between types of diet and cancer incidence for all Models after excluding events in the first 2 years of follow-up.

Cancer site	Total	Event	Meat-eaters	Event	Vegan & Vegetarian		Event	Pescatarian		Event	Fish & Poultry	
Model 0					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	403805	32960	1.00 (Ref.)	405	0.65 (0.59; 0.71)	<0.001	578	0.71 (0.65; 0.77)	<0.001	348	0.89 (0.80; 0.98)	0.025
Head & neck	408996	739	1.00 (Ref.)	9	0.65 (0.34; 1.26)	0.204	21	1.16 (0.75; 1.79)	0.501	7	0.80 (0.38; 1.68)	0.555
Oesophagus	408980	887	1.00 (Ref.)	10	0.61 (0.32; 1.13)	0.115	5	0.23 (0.10; 0.55)	0.001	9	0.86 (0.45; 1.65)	0.648
Stomach	409013	686	1.00 (Ref.)	4	0.31 (0.12; 0.84)	0.020	8	0.48 (0.24; 0.96)	0.037	6	0.74 (0.33; 1.65)	0.458
Colorectal	408405	3996	1.00 (Ref.)	39	0.52 (0.38; 0.72)	<0.001	61	0.62 (0.48; 0.80)	<0.001	38	0.80 (0.58; 1.10)	0.172
Colon	408604	2847	1.00 (Ref.)	27	0.51 (0.35; 0.74)	<0.001	43	0.62 (0.46; 0.83)	0.002	27	0.80 (0.55; 1.17)	0.246
Proximal	408900	1473	1.00 (Ref.)	9	0.33 (0.17; 0.63)	0.001	26	0.72 (0.49; 1.06)	0.097	15	0.86 (0.52; 1.43)	0.557
Distal	408872	1213	1.00 (Ref.)	16	0.71 (0.43; 1.16)	0.170	14	0.47 (0.28; 0.80)	0.005	13	0.90 (0.52; 1.56)	0.717
Rectum	408833	1779	1.00 (Ref.)	16	0.48 (0.29; 0.79)	0.004	28	0.64 (0.44; 0.93)	0.020	22	1.04 (0.68; 1.59)	0.845
Pancreas	409002	1032	1.00 (Ref.)	6	0.31 (0.14; 0.70)	0.004	17	0.67 (0.42; 1.09)	0.105	6	0.49 (0.22; 1.09)	0.082
Lung	408732	2941	1.00 (Ref.)	24	0.44 (0.29; 0.65)	<0.001	39	0.54 (0.39; 0.74)	<0.001	25	0.72 (0.48; 1.06)	0.097
Melanoma	408857	1735	1.00 (Ref.)	17	0.53 (0.33; 0.85)	0.008	24	0.56 (0.38; 0.84)	0.005	14	0.68 (0.40; 1.15)	0.151
Breast	217207	5794	1.00 (Ref.)	115	0.85 (0.70; 1.02)	0.078	160	0.83 (0.71; 0.97)	0.018	105	1.07 (0.88; 1.29)	0.510
Premenopausal	54,590	1,240	1.00 (Ref.)	41	0.93 (0.68; 1.27)	0.647	41	0.72 (0.53; 0.99)	0.040	20	0.96 (0.62; 1.49)	0.860
Postmenopausal	129,922	3,656	1.00 (Ref.)	57	0.78 (0.60; 1.01)	0.063	96	0.87 (0.71; 1.07)	0.182	63	1.00 (0.78; 1.28)	0.987
Uterine	218222	970	1.00 (Ref.)	21	0.93 (0.60; 1.43)	0.734	28	0.87 (0.59; 1.26)	0.453	15	0.91 (0.55; 1.52)	0.717
Ovary	218251	739	1.00 (Ref.)	17	0.99 (0.61; 1.59)	0.952	23	0.93 (0.62; 1.42)	0.749	16	1.27 (0.78; 2.09)	0.337
Prostate	189754	6721	1.00 (Ref.)	44	0.48 (0.36; 0.64)	<0.001	70	0.70 (0.55; 0.89)	0.003	38	0.91 (0.66; 1.25)	0.570
Kidney	408969	1088	1.00 (Ref.)	12	0.59 (0.33; 1.04)	0.070	15	0.56 (0.34; 0.94)	0.027	12	0.93 (0.53; 1.64)	0.803
Bladder	408832	1783	1.00 (Ref.)	17	0.51 (0.32; 0.82)	0.006	32	0.73 (0.52; 1.04)	0.081	13	0.61 (0.36; 1.06)	0.080

Brain	408996	650	1.00 (Ref.)	7	0.58 (0.27; 1.22)	0.148	10	0.63 (0.34; 1.17)	0.145	9	1.17 (0.60; 2.25)	0.644
Haematological	408676	3162	1.00 (Ref.)	44	0.75 (0.55; 1.00)	0.053	59	0.76 (0.59; 0.98)	0.038	35	0.93 (0.67; 1.30)	0.684
Non-Hodgkin lymphoma	408877	1522	1.00 (Ref.)	18	0.63 (0.40; 1.01)	0.055	21	0.56 (0.37; 0.87)	0.009	17	0.94 (0.58; 1.52)	0.807
Multiple Myeloma	409022	835	1.00 (Ref.)	12	0.77 (0.44; 1.36)	0.371	20	0.98 (0.63; 1.52)	0.921	11	1.11 (0.61; 2.01)	0.729
Leukaemia	408994	1002	1.00 (Ref.)	16	0.86 (0.52; 1.40)	0.537	24	0.98 (0.65; 1.47)	0.913	10	0.84 (0.45; 1.57)	0.588
Model 1					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	403805	32960	1.00 (Ref.)	405	0.84 (0.76; 0.92)	<0.001	578	0.86 (0.79; 0.93)	<0.001	348	0.95 (0.85; 1.05)	0.317
Head & neck	408996	739	1.00 (Ref.)	9	0.77 (0.40; 1.50)	0.444	21	1.39 (0.90; 2.15)	0.139	7	0.92 (0.43; 1.93)	0.816
Oesophagus	408980	887	1.00 (Ref.)	10	0.99 (0.53; 1.85)	0.970	5	0.34 (0.14; 0.83)	0.018	9	1.12 (0.58; 2.16)	0.734
Stomach	409013	686	1.00 (Ref.)	4	0.46 (0.17; 1.22)	0.119	8	0.69 (0.35; 1.40)	0.305	6	0.92 (0.41; 2.05)	0.829
Colorectal	408405	3996	1.00 (Ref.)	39	0.73 (0.53; 1.00)	0.052	61	0.80 (0.62; 1.03)	0.088	38	0.90 (0.65; 1.24)	0.519
Colon	408604	2847	1.00 (Ref.)	27	0.70 (0.48; 1.03)	0.070	43	0.78 (0.58; 1.06)	0.114	27	0.87 (0.60; 1.28)	0.488
Proximal	408900	1473	1.00 (Ref.)	9	0.45 (0.24; 0.88)	0.018	26	0.91 (0.61; 1.34)	0.615	15	0.90 (0.54; 1.50)	0.698
Distal	408872	1213	1.00 (Ref.)	16	0.98 (0.60; 1.61)	0.932	14	0.61 (0.36; 1.03)	0.067	13	1.05 (0.61; 1.81)	0.872
Rectum	408833	1779	1.00 (Ref.)	16	0.69 (0.42; 1.14)	0.146	28	0.86 (0.59; 1.24)	0.417	22	1.25 (0.82; 1.90)	0.303
Pancreas	409002	1032	1.00 (Ref.)	6	0.44 (0.20; 0.98)	0.045	17	0.88 (0.54; 1.42)	0.594	6	0.53 (0.24; 1.18)	0.122
Lung	408732	2941	1.00 (Ref.)	24	0.61 (0.41; 0.92)	0.018	39	0.68 (0.49; 0.93)	0.016	25	0.70 (0.47; 1.03)	0.072
Melanoma	408857	1735	1.00 (Ref.)	17	0.70 (0.43; 1.12)	0.137	24	0.66 (0.44; 0.99)	0.045	14	0.76 (0.45; 1.28)	0.296
Breast	217207	5794	1.00 (Ref.)	115	0.91 (0.76; 1.09)	0.315	160	0.86 (0.73; 1.01)	0.060	105	1.07 (0.89; 1.30)	0.469
Premenopausal	54,590	1,240	1.00 (Ref.)	41	0.97 (0.71; 1.32)	0.823	41	0.73 (0.54; 1.00)	0.052	20	0.97 (0.63; 1.52)	0.908
Postmenopausal	129,922	3,656	1.00 (Ref.)	57	0.82 (0.63; 1.06)	0.133	96	0.89 (0.73; 1.09)	0.275	63	1.00 (0.78; 1.29)	0.972
Uterine	218222	970	1.00 (Ref.)	21	1.09 (0.71; 1.69)	0.695	28	0.97 (0.67; 1.42)	0.885	15	0.91 (0.54; 1.51)	0.706
Ovary	218251	739	1.00 (Ref.)	17	1.21 (0.75; 1.97)	0.433	23	1.07 (0.70; 1.62)	0.758	16	1.28 (0.78; 2.11)	0.324
Prostate	189754	6721	1.00 (Ref.)	44	0.61 (0.45; 0.82)	0.001	70	0.87 (0.69; 1.10)	0.239	38	0.93 (0.68; 1.28)	0.651

Kidney	408969	1088	1.00 (Ref.)	12	0.86 (0.48; 1.52)	0.599	15	0.79 (0.47; 1.31)	0.358	12	1.14 (0.64; 2.01)	0.661
Bladder	408832	1783	1.00 (Ref.)	17	0.88 (0.55; 1.42)	0.607	32	1.18 (0.83; 1.68)	0.350	13	0.85 (0.49; 1.46)	0.550
Brain	408996	650	1.00 (Ref.)	7	0.75 (0.36; 1.59)	0.456	10	0.76 (0.41; 1.42)	0.393	9	1.32 (0.68; 2.55)	0.408
Haematological	408676	3162	1.00 (Ref.)	44	1.01 (0.75; 1.37)	0.932	59	0.98 (0.76; 1.27)	0.888	35	1.03 (0.74; 1.44)	0.855
Non-Hodgkin lymphoma	408877	1522	1.00 (Ref.)	18	0.87 (0.55; 1.39)	0.563	21	0.71 (0.46; 1.09)	0.118	17	1.03 (0.64; 1.66)	0.918
Multiple Myeloma	409022	835	1.00 (Ref.)	12	0.99 (0.56; 1.76)	0.978	20	1.26 (0.81; 1.97)	0.307	11	1.22 (0.67; 2.21)	0.520
Leukaemia	408994	1002	1.00 (Ref.)	16	1.21 (0.74; 1.99)	0.447	24	1.34 (0.89; 2.00)	0.163	10	0.97 (0.52; 1.81)	0.928
Model 2					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	403805	32960	1.00 (Ref.)	405	0.86 (0.78; 0.95)	0.002	578	0.88 (0.81; 0.95)	0.002	348	0.97 (0.87; 1.07)	0.526
Head & neck	408996	739	1.00 (Ref.)	9	0.85 (0.44; 1.65)	0.631	21	1.50 (0.97; 2.32)	0.067	7	0.98 (0.47; 2.08)	0.967
Oesophagus	408980	887	1.00 (Ref.)	10	1.07 (0.57; 2.00)	0.838	5	0.37 (0.15; 0.90)	0.028	9	1.21 (0.63; 2.33)	0.575
Stomach	409013	686	1.00 (Ref.)	4	0.48 (0.18; 1.27)	0.139	8	0.72 (0.36; 1.45)	0.364	6	0.95 (0.42; 2.13)	0.901
Colorectal	408405	3996	1.00 (Ref.)	39	0.74 (0.54; 1.02)	0.065	61	0.81 (0.63; 1.05)	0.108	38	0.91 (0.66; 1.25)	0.565
Colon	408604	2847	1.00 (Ref.)	27	0.71 (0.49; 1.04)	0.082	43	0.79 (0.59; 1.07)	0.136	27	0.88 (0.60; 1.29)	0.520
Proximal	408900	1473	1.00 (Ref.)	9	0.46 (0.24; 0.89)	0.020	26	0.92 (0.62; 1.36)	0.678	15	0.91 (0.55; 1.52)	0.729
Distal	408872	1213	1.00 (Ref.)	16	0.99 (0.60; 1.63)	0.974	14	0.61 (0.36; 1.04)	0.069	13	1.06 (0.61; 1.82)	0.848
Rectum	408833	1779	1.00 (Ref.)	16	0.71 (0.43; 1.16)	0.167	28	0.86 (0.59; 1.26)	0.447	22	1.27 (0.83; 1.93)	0.274
Pancreas	409002	1032	1.00 (Ref.)	6	0.45 (0.20; 1.02)	0.055	17	0.90 (0.56; 1.45)	0.661	6	0.55 (0.24; 1.22)	0.139
Lung	408732	2941	1.00 (Ref.)	24	0.76 (0.51; 1.14)	0.186	39	0.82 (0.59; 1.12)	0.209	25	0.83 (0.56; 1.23)	0.354
Melanoma	408857	1735	1.00 (Ref.)	17	0.69 (0.43; 1.11)	0.124	24	0.65 (0.44; 0.98)	0.039	14	0.75 (0.44; 1.26)	0.276
Breast	217207	5794	1.00 (Ref.)	115	0.90 (0.75; 1.09)	0.286	159	0.85 (0.72; 0.99)	0.037	5	1.06 (0.88; 1.29)	0.535
Premenopausal	54,590	1,240	1.00 (Ref.)									
Postmenopausal	129,922	3,656	1.00 (Ref.)									
Uterine	218222	970	1.00 (Ref.)	21	1.02 (0.66; 1.58)	0.916	28	0.95 (0.65; 1.39)	0.799	15	0.87 (0.52; 1.46)	0.606

Ovary	218251	739	1.00 (Ref.)	17	1.18 (0.73; 1.91)	0.508	23	1.03 (0.68; 1.56)	0.893	16	1.24 (0.76; 2.04)	0.388
Prostate	189754	6721	1.00 (Ref.)	44	0.60 (0.44; 0.81)	0.001	70	0.85 (0.67; 1.08)	0.188	38	0.92 (0.67; 1.26)	0.587
Kidney	408969	1088	1.00 (Ref.)	12	0.89 (0.50; 1.58)	0.701	15	0.82 (0.49; 1.37)	0.447	12	1.17 (0.66; 2.07)	0.586
Bladder	408832	1783	1.00 (Ref.)	17	0.95 (0.59; 1.53)	0.819	32	1.25 (0.88; 1.78)	0.208	13	0.90 (0.52; 1.56)	0.712
Brain	408996	650	1.00 (Ref.)	7	0.75 (0.35; 1.58)	0.444	10	0.75 (0.40; 1.41)	0.371	9	1.31 (0.68; 2.54)	0.419
Thyroid	409060	241	1.00 (Ref.)	7	1.40 (0.66; 2.98)	0.386	3	0.44 (0.14; 1.37)	0.155	3	0.87 (0.28; 2.71)	0.805
Haematological	408676	3162	1.00 (Ref.)	44	1.02 (0.75; 1.37)	0.916	59	0.99 (0.76; 1.28)	0.914	35	1.03 (0.74; 1.44)	0.844
Non-Hodgkin lymphoma	408877	1522	1.00 (Ref.)	18	0.87 (0.55; 1.39)	0.559	21	0.71 (0.46; 1.10)	0.122	17	1.03 (0.63; 1.65)	0.919
Multiple Myeloma	409022	835	1.00 (Ref.)	12	0.99 (0.56; 1.75)	0.967	20	1.26 (0.81; 1.97)	0.307	11	1.21 (0.67; 2.20)	0.523
Leukaemia	408994	1002	1.00 (Ref.)	16	1.23 (0.75; 2.02)	0.417	24	1.34 (0.89; 2.01)	0.157	10	0.98 (0.52; 1.83)	0.946
Model 3					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	403805	32960	1.00 (Ref.)	405	0.86 (0.78; 0.95)	0.003	578	0.88 (0.81; 0.96)	0.002	348	0.97 (0.87; 1.08)	0.546
Head & neck	408996	739	1.00 (Ref.)	9	0.85 (0.44; 1.65)	0.634	21	1.51 (0.97; 2.33)	0.066	7	0.98 (0.47; 2.08)	0.968
Oesophagus	408980	887	1.00 (Ref.)	10	1.08 (0.58; 2.03)	0.799	5	0.38 (0.16; 0.92)	0.032	9	1.21 (0.63; 2.34)	0.564
Stomach	409013	686	1.00 (Ref.)	4	0.48 (0.18; 1.28)	0.143	8	0.73 (0.36; 1.47)	0.380	6	0.95 (0.43; 2.13)	0.906
Colorectal	408405	3996	1.00 (Ref.)	39	0.74 (0.54; 1.02)	0.064	61	0.81 (0.63; 1.05)	0.108	38	0.91 (0.66; 1.25)	0.565
Colon	408604	2847	1.00 (Ref.)	27	0.71 (0.49; 1.05)	0.084	43	0.80 (0.59; 1.08)	0.140	27	0.88 (0.60; 1.29)	0.523
Proximal	408900	1473	1.00 (Ref.)	9	0.46 (0.24; 0.89)	0.021	26	0.92 (0.63; 1.36)	0.690	15	0.91 (0.55; 1.52)	0.732
Distal	408872	1213	1.00 (Ref.)	16	0.99 (0.60; 1.63)	0.975	14	0.61 (0.36; 1.04)	0.070	13	1.06 (0.61; 1.82)	0.847
Rectum	408833	1779	1.00 (Ref.)	16	0.70 (0.43; 1.15)	0.164	28	0.86 (0.59; 1.25)	0.438	22	1.26 (0.83; 1.93)	0.276
Pancreas	409002	1032	1.00 (Ref.)	6	0.46 (0.21; 1.03)	0.058	17	0.91 (0.56; 1.48)	0.709	6	0.55 (0.25; 1.22)	0.143
Lung	408732	2941	1.00 (Ref.)	24	0.77 (0.52; 1.16)	0.211	39	0.84 (0.61; 1.15)	0.267	25	0.84 (0.56; 1.24)	0.372
Melanoma	408857	1735	1.00 (Ref.)	17	0.69 (0.43; 1.11)	0.124	24	0.65 (0.44; 0.98)	0.039	14	0.75 (0.44; 1.26)	0.277
Breast	217207	5794	1.00 (Ref.)	115	0.90 (0.75; 1.09)	0.287	159	0.85 (0.72; 0.99)	0.037	105	1.06 (0.88; 1.29)	0.534

Premenopausal	54,590	1,240	1.00 (Ref.)	41	0.97 (0.71; 1.32)	0.837	41	0.73 (0.53; 0.99)	0.046	20	0.98 (0.63; 1.52)	0.912
Postmenopausal	129,922	3,656	1.00 (Ref.)	57	0.84 (0.65; 1.10)	0.203	96	0.90 (0.74; 1.10)	0.311	63	1.03 (0.80; 1.32)	0.819
Uterine	218222	970	1.00 (Ref.)	21	1.03 (0.67; 1.59)	0.898	28	0.96 (0.66; 1.40)	0.835	15	0.88 (0.53; 1.46)	0.615
Ovary	218251	739	1.00 (Ref.)	17	1.18 (0.73; 1.91)	0.506	23	1.03 (0.68; 1.56)	0.889	16	1.24 (0.76; 2.04)	0.387
Prostate	189754	6721	1.00 (Ref.)	44	0.60 (0.44; 0.80)	0.001	70	0.85 (0.67; 1.08)	0.179	38	0.91 (0.66; 1.26)	0.585
Kidney	408969	1088	1.00 (Ref.)	12	0.91 (0.51; 1.61)	0.741	15	0.84 (0.50; 1.40)	0.508	12	1.18 (0.67; 2.09)	0.571
Bladder	408832	1783	1.00 (Ref.)	17	0.95 (0.59; 1.54)	0.846	32	1.27 (0.89; 1.80)	0.184	13	0.91 (0.52; 1.56)	0.721
Brain	408996	650	1.00 (Ref.)	7	0.75 (0.35; 1.58)	0.443	10	0.75 (0.40; 1.40)	0.369	9	1.31 (0.68; 2.54)	0.420
Haematological	408676	3162	1.00 (Ref.)	44	1.02 (0.76; 1.38)	0.898	59	0.99 (0.77; 1.28)	0.947	35	1.04 (0.74; 1.45)	0.836
Non-Hodgkin lymphoma	408877	1522	1.00 (Ref.)	18	0.87 (0.55; 1.39)	0.572	21	0.72 (0.47; 1.10)	0.131	17	1.03 (0.64; 1.66)	0.912
Multiple Myeloma	409022	835	1.00 (Ref.)	12	0.99 (0.56; 1.75)	0.967	20	1.26 (0.81; 1.97)	0.306	11	1.21 (0.67; 2.21)	0.523
Leukaemia	408994	1002	1.00 (Ref.)	16	1.23 (0.75; 2.03)	0.410	24	1.35 (0.90; 2.02)	0.150	10	0.98 (0.53; 1.83)	0.950
Model 4					HR 95% CI	P value		HR 95% CI	P value		HR 95% CI	P value
Overall	403805	32960	1.00 (Ref.)	405	0.88 (0.80; 0.97)	0.009	578	0.90 (0.83; 0.98)	0.013	348	0.99 (0.89; 1.10)	0.827
Head & neck	408996	739	1.00 (Ref.)	9	0.80 (0.41; 1.55)	0.511	21	1.41 (0.91; 2.19)	0.122	7	0.93 (0.44; 1.96)	0.847
Oesophagus	408980	887	1.00 (Ref.)	10	1.16 (0.62; 2.17)	0.641	5	0.41 (0.17; 0.99)	0.048	9	1.30 (0.67; 2.50)	0.440
Stomach	409013	686	1.00 (Ref.)	4	0.52 (0.19; 1.40)	0.197	8	0.81 (0.40; 1.62)	0.543	6	1.04 (0.46; 2.33)	0.926
Colorectal	408405	3996	1.00 (Ref.)	39	0.77 (0.56; 1.06)	0.106	61	0.85 (0.66; 1.09)	0.197	38	0.94 (0.69; 1.30)	0.727
Colon	408604	2847	1.00 (Ref.)	27	0.75 (0.51; 1.09)	0.131	43	0.83 (0.62; 1.13)	0.240	27	0.92 (0.63; 1.35)	0.673
Proximal	408900	1473	1.00 (Ref.)	9	0.48 (0.25; 0.93)	0.031	26	0.98 (0.66; 1.44)	0.910	15	0.96 (0.58; 1.60)	0.886
Distal	408872	1213	1.00 (Ref.)	16	1.03 (0.63; 1.70)	0.895	14	0.64 (0.38; 1.09)	0.100	13	1.10 (0.64; 1.90)	0.735
Rectum	408833	1779	1.00 (Ref.)	16	0.73 (0.44; 1.19)	0.209	28	0.89 (0.61; 1.30)	0.559	22	1.31 (0.86; 1.99)	0.214
Pancreas	409002	1032	1.00 (Ref.)	6	0.48 (0.21; 1.06)	0.071	17	0.95 (0.59; 1.53)	0.829	6	0.57 (0.25; 1.27)	0.167
Lung	408732	2941	1.00 (Ref.)	24	0.75 (0.50; 1.12)	0.164	39	0.81 (0.59; 1.11)	0.196	25	0.81 (0.55; 1.21)	0.307

Melanoma	408857	1735	1.00 (Ref.)	17	0.70 (0.43; 1.13)	0.143	24	0.67 (0.44; 1.00)	0.049	14	0.76 (0.45; 1.29)	0.307
Breast	217207	5794	1.00 (Ref.)	115	0.93 (0.77; 1.12)	0.423	159	0.87 (0.74; 1.02)	0.084	105	1.09 (0.90; 1.32)	0.375
Premenopausal	54,590	1,240	1.00 (Ref.)	41	0.94 (0.69; 1.29)	0.701	41	0.71 (0.52; 0.97)	0.030	20	0.95 (0.61; 1.48)	0.820
Postmenopausal	129,922	3,656	1.00 (Ref.)	57	0.87 (0.67; 1.14)	0.318	95	0.92 (0.75; 1.13)	0.439	63	1.06 (0.83; 1.36)	0.644
Uterine	218222	970	1.00 (Ref.)	21	1.23 (0.79; 1.89)	0.360	28	1.20 (0.82; 1.74)	0.354	15	1.06 (0.64; 1.76)	0.827
Ovary	218251	739	1.00 (Ref.)	17	1.18 (0.73; 1.92)	0.494	23	1.04 (0.68; 1.57)	0.870	16	1.25 (0.76; 2.05)	0.377
Prostate	189754	6721	1.00 (Ref.)	44	0.59 (0.44; 0.79)	<0.001	70	0.84 (0.66; 1.06)	0.140	38	0.90 (0.65; 1.24)	0.522
Kidney	408969	1088	1.00 (Ref.)	12	0.99 (0.56; 1.76)	0.975	15	0.93 (0.56; 1.55)	0.773	12	1.29 (0.73; 2.28)	0.382
Bladder	408832	1783	1.00 (Ref.)	17	0.98 (0.61; 1.58)	0.930	32	1.30 (0.92; 1.85)	0.139	13	0.93 (0.54; 1.60)	0.788
Brain	408996	650	1.00 (Ref.)	7	0.74 (0.35; 1.57)	0.437	10	0.75 (0.40; 1.40)	0.363	9	1.31 (0.68; 2.53)	0.426
Haematological	408676	3162	1.00 (Ref.)	44	1.04 (0.77; 1.41)	0.776	59	1.02 (0.79; 1.32)	0.895	35	1.06 (0.76; 1.48)	0.730
Non-Hodgkin lymphoma	408877	1522	1.00 (Ref.)	18	0.88 (0.55; 1.41)	0.606	21	0.73 (0.47; 1.12)	0.147	17	1.04 (0.64; 1.68)	0.874
Multiple Myeloma	409022	835	1.00 (Ref.)	12	1.02 (0.57; 1.81)	0.949	20	1.31 (0.84; 2.04)	0.242	11	1.25 (0.69; 2.27)	0.460
Leukaemia	408994	1002	1.00 (Ref.)	16	1.27 (0.77; 2.08)	0.354	24	1.39 (0.92; 2.08)	0.116	10	1.01 (0.54; 1.88)	0.986

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by type of diets. Meat-eaters were used as the reference group. “Model 0” was unadjusted "model 1" (minimally adjusted) included sociodemographic covariates (age, sex, deprivation, and ethnicity); "model 2" additionally included lifestyle factors (smoking, alcohol intake and total physical activity); "model 3" included model 2 plus multimorbidity: and “model 4” include model 3 plus body mass index.

Table S6: Characteristics of the cohorts included in systematic review; data in italics are those included in the meta-analysis.

Author (year)	Cancer site	Study cohort	Years Follow-up	Age range	Number of individuals	Number cases	Adjusted
Travis et al (2008)	Breast cancer	EPICOxford	7.4 years	20 - 89	37,643	585	Height, body mass index (BMI), age at menarche, age at first birth and parity, menopausal status, current HRT use, alcohol consumption and daily energy intake
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Breast	108	Vegetarian v/s Non-vegetarian	0.91	0.72	1.14	
	Premenopausal	55	Vegetarian v/s Non-vegetarian	0.95	0.68	1.32	
	Postmenopausal	33	Vegetarian v/s Non-vegetarian	0.79	0.54	1.16	
Cade et al., (2010)	Breast cancer	UKWCS, (UK)	9 years	35-69	33,725	783	Age, energy intake, menopausal status (combined analysis), calorie adjusted fat, BMI, physical activity, OCP use, HRT use, smoking status, parity, age at menarche, ethanol, total days breast feeding, socioeconomic class, level of education
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Breast	130	Vegetarian v/s Red meat eater	0.88	0.69	1.11	
	Breast	87	Pescatarian v/s Red meat eater	0.78	0.6	1.03	
	Premenopausal	83	Vegetarian v/s Red meat eater	0.92	0.67	1.24	
	Premenopausal	53	Pescatarian v/s Red meat eater	0.97	0.69	1.37	
	Postmenopausal	47	Vegetarian v/s Red meat eater	0.85	0.58	1.25	
	Postmenopausal	34	Pescatarian v/s Red meat eater	0.60	0.38	0.96	
Tantamango-Bartley et al.,-2013	Overall cancer	Adventist Health Study-2.	4,14 years	30- 70	69,120	2939	Race, family history of cancer, education, smoking, alcohol, age at menarche,
		Number cases	Comparison	Results			

				HR	Lower CI	Upper CI	pregnancies, breastfeeding, oral contraceptives, hormone replacement therapy, and menopause status.
		1526	Vegetarian v/s Non vegetarian	0.92	0.85	0.99	
		878	Lacto-vegetarian	0.93	0.85	1.02	
		276	Pescatarian v/s No vegetarian	0.88	0.77	1.01	
Key TJ et al., (2014)	15 sites	OVS and EPIC–Oxford Cohort, (UK)	14.9 years	20-89	61,647		Smoking, alcohol consumption, physical activity level, BMI; + parity and oral contraceptive use for breast cancer *corrected from misprinting in original paper
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Overall	1203	Vegetarian v/s No vegetarian	0.90	0.83*	0.96	
	Overall	520	Pescatarian v/s No vegetarian	0.89	0.81	0.98	
	Stomach	11	Vegetarian v/s No vegetarian	0.38	0.2	0.71	
	Stomach	6	Pescatarian v/s No vegetarian	0.64	0.27	1.5	
	Pancreas	22	Vegetarian v/s No vegetarian	0.70	0.42	1.17	
	Pancreas	10	Pescatarian v/s No vegetarian	0.77	0.39	1.52	
	Kidney	21	Vegetarian v/s No vegetarian	1.02	0.58	1.78	
	Kidney	2	Pescatarian v/s No vegetarian	0.23	0.05	0.99	
	Bladder	24	Vegetarian v/s No vegetarian	0.65	0.40	1.03	
	Bladder	9	Pescatarian v/s No vegetarian	0.72	0.36	1.43	
	Colorectal	154	Vegetarian v/s No vegetarian	1.04	0.84	1.28	
	Colorectal	43	Pescatarian v/s No vegetarian	0.67	0.48	0.92	
	Colon	92	Vegetarian v/s No vegetarian	1.01	0.77	1.33	

	Colon	26	Pescatarian v/s No vegetarian	0.65	0.43	0.98	
	Rectum	62	Vegetarian v/s No vegetarian	1.08	0.79	1.48	
	Rectum	17	Pescatarian v/s No vegetarian	0.70	0.42	1.17	
	Lung	58	Vegetarian v/s No vegetarian	1.09	0.78	1.53	
	Lung	12	Pescatarian v/s No vegetarian	0.59	0.32	1.07	
	Prostate	100	Vegetarian v/s No vegetarian	0.83	0.64	1.06	
	Prostate	30	Pescatarian v/s No vegetarian	0.74	0.51	1.09	
	Breast	352	Vegetarian v/s No vegetarian	0.96	0.83	1.10	
	Breast	202	Pescatarian v/s No vegetarian	1.09	0.93	1.28	
	Endometrium	42	Vegetarian v/s No vegetarian	0.99	0.67	1.45	
	Endometrium	17	Pescatarian v/s No vegetarian	0.82	0.48	1.38	
	Cervix	27	Vegetarian v/s No vegetarian	1.90	1.00	3.60	
	Cervix	13	Pescatarian v/s No vegetarian	2.11	1.02	4.37	
	Ovary	56	Vegetarian v/s No vegetarian	0.87	0.61	1.22	
	Ovary	17	Pescatarian v/s No vegetarian	0.56	0.33	0.94	
Gilsing et al., (2015)	Colorectal	NLCS-MIC, (Netherlands)	20.3 years	55–69	10,210	437	Age sex, total energy intake, cigarette smoking, alcohol consumption, BMI, non-occupational physical activity, and level of education
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Colorectal	22	Vegetarian v/s No vegetarian	0.83	0.53	1.31	
	Colorectal	14	Pescatarian v/s Meat consumption group	0.88	0.51	1.51	

	Colon	19	Vegetarian v/s No vegetarian	1.01	0.62	1.66	Landmark data no show.
	Colon	11	Pescatarian v/s Meat consumption group	0.96	0.52	1.80	
	Rectum	1	Vegetarian v/s No vegetarian	0.21	0.03	1.55	
	Rectum	2	Pescatarian v/s Meat consumption group	0.68	0.16	2.84	
Orlich et al., (2015)	Colorectal	AHS-2, (USA and Canada)	7.3 years	≥25	77,659	490	Age , race and sex, educational level, moderate or vigorous exercise, smoking, alcohol use , family history of colorectal cancer, history of peptic ulcer, history of inflammatory bowel disease, treatment for diabetes mellitus within the past year, used aspirin at least weekly at least 2 of the past 5 years, used statins at least 2 of the past 5 years, prior colonoscopy or flexible sigmoidoscopy , supplemental calcium use, supplemental vitamin D, dietary energy, and hormone therapy among menopausal women and body mass index
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Colorectal	252	Vegetarian v/s No vegetarian	0.79	0.64	0.97	
	Colorectal	35	Pescatarian v/s No vegetarian	0.58	0.40	0.84	
	Colorectal	147	Lactoovo v/s No vegetarian	0.83	0.66	1.05	
	Colon	197	Vegetarian v/s No vegetarian	0.83	0.66	1.05	
	Rectum	55	Vegetarian v/s No vegetarian	0.66	0.43	1.02	
Gilsing et al., (2016)	Prostate Breast and	NLCS-MIC, 20.3 years		55–69	11,082		

	Lung	(Netherlands)					age, total energy intake, cigarette smoking, education. Landmark data no show
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Prostate	19	Vegetarian v/s No vegetarian	1.09	0.68	1.76	
	Prostate	17	Pescatarian v/s No vegetarian	1.35	0.81	2.23	
	Breast	18	Vegetarian v/s No vegetarian	0.70	0.43	1.14	
	Breast	14	Pescatarian v/s No vegetarian	1.20	0.78	2.11	
	Lung	7	Vegetarian v/s No vegetarian	0.86	0.40	1.85	
	Lung	3	Pescatarian v/s No vegetarian	0.54	0.17	1.70	
Tantamango-Bartley et al., -2016	Prostate	AHS-2, (USA and Canada)	7.8 years	≥30	27,188	1079	Race, family history of prostate cancer, education, screening for prostate cancer, energy intake and body mass index
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Prostate	333	Lacto-Vegetarian v/s No vegetarian	0.96	0.83	1.12	
	Prostate	121	Pescatarian v/s No vegetarian	1.07	0.88	1.31	
Penniecook-Sawyers et al., 2016	Breast	AHS-2, (USA and Canada)	7.8 years	≥30	50,404	892	Race, height, physical activity, family history of cancer, mammography in the last 2 years after age 42 years, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children,
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Breast	478	Vegetarian v/s No vegetarian	1.00	0.87	1.16	
	Breast	289	Lacto-Vegetarian v/s No vegetarian	1.08	0.92	1.27	
	Breast	88	Pescatarian v/s No vegetarian	0.94	0.73	1.21	

							breastfeeding, educational level, smoking, alcohol, and body mass index
	Premenopausal	83	Vegetarian v/s No vegetarian	1.14	0.81	1.61	
	Premenopausal	41	Lacto-Vegetarian v/s No vegetarian	0.98	0.64	1.48	
	Premenopausal	19	Pescatarian v/s No vegetarian	1.27	0.75	2.14	
	Postmenopausal	395	Vegetarian v/s No vegetarian	0.97	0.83	1.14	
	Postmenopausal	248	Lacto-Vegetarian v/s No vegetarian	1.10	0.92	1.31	
	Postmenopausal	69	Pescatarian v/s No vegetarian	0.88	0.66	1.18	
Parra-Soto et al., (2021)		UK Biobank (UK)	8.8 years	37-73	409,110		Age, sex, deprivation, and ethnicity, smoking, alcohol intake, total physical activity, multimorbidity and body mass index
		Number cases	Comparison	Results			
				HR	Lower CI	Upper CI	
	Overall	463	Vegetarian v/s No vegetarian	0.87	0.79	0.96	
	Overall	686	Pescatarian v/s No vegetarian	0.93	0.87	1.00	
	Colorectal	43	Vegetarian v/s No vegetarian	0.73	0.54	0.99	
	Colorectal	75	Pescatarian v/s No vegetarian	0.90	0.71	1.14	
	Colon	29	Vegetarian v/s No vegetarian	0.69	0.48	0.99	
	Colon	52	Pescatarian v/s No vegetarian	0.87	0.66	1.15	
	Rectum	18	Vegetarian v/s No vegetarian	0.72	0.45	1.15	
	Rectum	35	Pescatarian v/s No vegetarian	0.98	0.70	1.37	

Lung	27	Vegetarian v/s No vegetarian	0.76	0.52	1.11
Lung	46	Pescatarian v/s No vegetarian	0.86	0.64	1.15
Prostate	47	Vegetarian v/s No vegetarian	0.57	0.43	0.76
Prostate	82	Pescatarian v/s No vegetarian	0.89	0.71	1.11
Breast	138	Vegetarian v/s No vegetarian	0.95	0.80	1.13
Breast	194	Pescatarian v/s No vegetarian	0.90	0.78	1.04
Premenopausal	50	Vegetarian v/s No vegetarian	1.00	0.75	1.33
Premenopausal	52	Pescatarian v/s No vegetarian	0.78	0.59	1.03
Postmenopausal	71	Vegetarian v/s No vegetarian	0.92	0.73	1.16
Postmenopausal	113	Pescatarian v/s No vegetarian	0.91	0.75	1.10

Table S7: Definitions of vegetarian, lacto-ovo-vegetarian, pescatarian and poultry diets used in the various studies.

	Vegetarian	Pescatarian	Lacto- Ovo-Vegetarian	Poultry
Travis et al., (2008)	Did not eat meat, or fish	N/I	N/I	N/I
Cade et al., (2010)	Red meat, poultry, or fish less than once a week	Fish at least once a week but not poultry or red meat	N/I	Poultry at least once a week and can eat fish but not red meat
Tantamango-Bartley et al., (2014)	Red meat and poultry <1 per month	Red meat and poultry < 1 per month, and fish ≥ 1 per month	Red meat, poultry and fish <1 per month, and eggs and dairy ≥ 1 per month.	N/I
Key TJ et al., (2014)	Did not eat meat, fish, eggs, or dairy products	Did not eat meat, but ate fish	N/I	N/I
Gilsing et al., (2015)	N/I	N/I	N/I	N/I
Orlich et al., (2015)	Red meat and poultry <1 per month	Fish one or more times a month, but all other meats less than once a month	Eggs / dairy 1 or more times a month, but fish and all other meats less than 1 time a month	N/I
Gilsing et al., (2016)	Do not eat meat or fish (including vegans, lacto-ovo-, lacto- and ovo-vegetarians)	Did not eat meat, but ate fish	N/I	N/I
Tantamango-Bartley et al., (2016)	Red meat, poultry, fish <1 time / month	Red meat or poultry <1 time / month, but fish ≥1 time / month and had no restrictions on the consumption of dairy products and / or eggs	Red meat, poultry and fish <1 time / month and eggs or dairy ≥1 time / month	N/I
Penniecook-Sawyers et al., (2016)	Do not eat meat or fish (including vegans, lacto-ovo-, lacto- and ovo-vegetarians)	Fish was ≥1 time a month, while red meat and poultry were consumed less than once a month, but no restrictions on dairy products or eggs	Fish, poultry and red meat were less than once a month and their intake of eggs or dairy products was greater than or equal to once a month	N/I
Parra-Soto et al., (2021)	Consumption of cheese and/or milk but not fish, poultry or red meat	Consumption of cheese, milk and fish but not poultry or red meat	N/I	Consumption of cheese, milk, fish and poultry but not red meat

Table S8: Quality assessment of studies using a modified Newcastle-Ottawa scale for assessing studies in the systematic review of vegetarian diet and cancer risk.

Study ID	Selection			Comparability*	Outcome		Total
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	(⋆⋆)	Assessment of outcome (⋆)	Adequacy of follow up (⋆)	Total (7⋆)
Travis et al., (2008)	⋆	⋆		⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆ ⋆ (5)
Cade et al., (2010)	⋆	⋆		⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆ ⋆ (5)
Tantamango-Bartley et al., (2014)	⋆	⋆			⋆	⋆	⋆ ⋆ ⋆ ⋆ (4)
Key TJ et al., (2014)	⋆	⋆		⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆ ⋆ (5)
Gilsing et al., (2015)				⋆	⋆	⋆	⋆ ⋆ ⋆ (3)
Orlich et al., (2015)	⋆	⋆		⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆ ⋆ (5)
Gilsing et al., (2016)	⋆	⋆			⋆	⋆	⋆ ⋆ ⋆ ⋆ (4)
Tantamango-Bartley et al., (2016)	⋆	⋆			⋆	⋆	⋆ ⋆ ⋆ ⋆ (4)
Penniecook-Sawyers et al., (2016)	⋆	⋆		⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆ ⋆ (5)
Parra-Soto et al., (2021)	⋆	⋆		⋆ ⋆	⋆	⋆	⋆ ⋆ ⋆ ⋆⋆ ⋆ (6)

* Comparability assessed as the following: one star rewarded if study excluded or adjusted for outcome, another star rewarded if study adjusted for age, race, smoking

Table S9: Risk of bias assessment (modified from Cochrane Tool to Assess Risk of Bias in Cohort Studies and EPOC Data Collection Form)

Study ID	Allocation concealment (selection bias)	Assessment of exposure (self-report)	Outcome of interest present at beginning	Incomplete data	Selective reporting (reporting bias)	Total score*
Travis et al., (2008)	+	-	+	+	+	4
Cade et al., (2010)	+	-	+	+	+	4
Tantamango-Bartley et al., (2014)	+	-	+	+	+	4
Key TJ et al., (2014)	+	-	+	+	+	4
Gilsing et al., (2015)	+	-	+	-	+	3
Orlich et al., (2015)	+	-	+	+	+	4
Gilsing et al., (2016)	+	-	+	+	+	4
Tantamango-Bartley et al., (2016)	+	-	+	+	+	4
Penniecook-Sawyers et al., (2016)	+	-	+	+	+	4
Parra-Soto et al., (2021)	+	-	+	+	+	4

*Total score: points awarded based on number of "+" or low risk of bias
+ = Low risk of bias, ? = Unclear risk of bias, - = High risk of bias

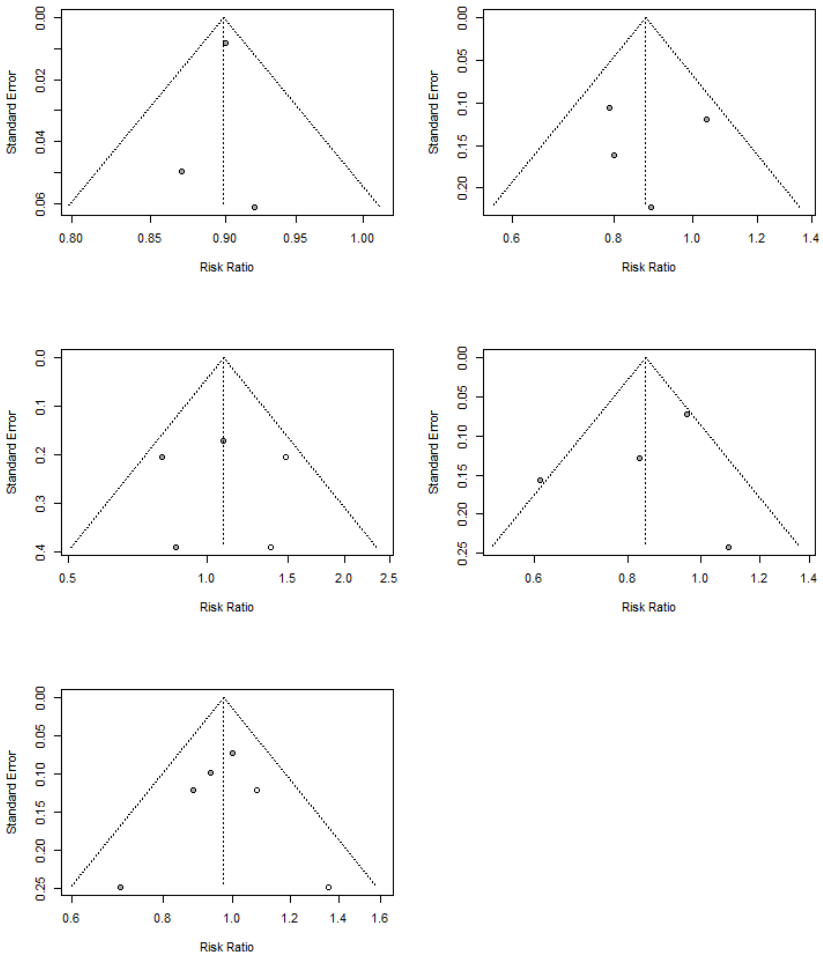

Fig. S2: Funnel plot of prospective cohort studies evaluating summary hazard ratios of colorectal, lung, prostate, breast and overall cancer for vegetarians versus meat-eaters (reference).

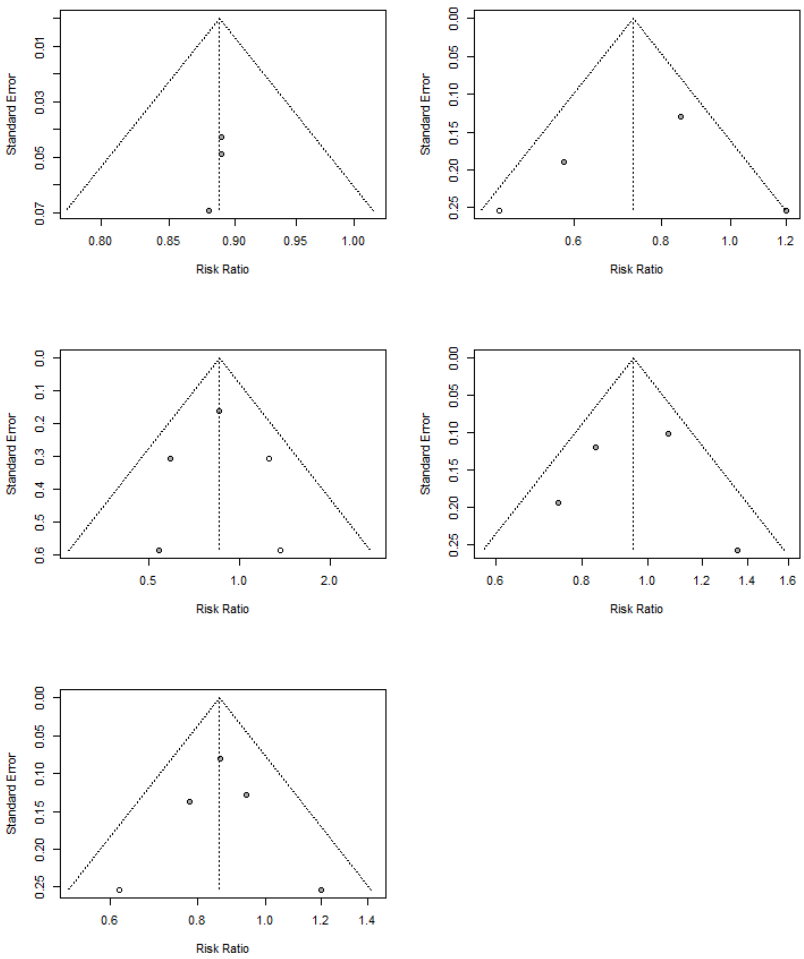

Fig.S3: Funnel plot of prospective cohort studies evaluating summary hazard ratios of colorectal, lung, prostate, breast and overall cancer for pescatarians versus meat-eaters (reference).

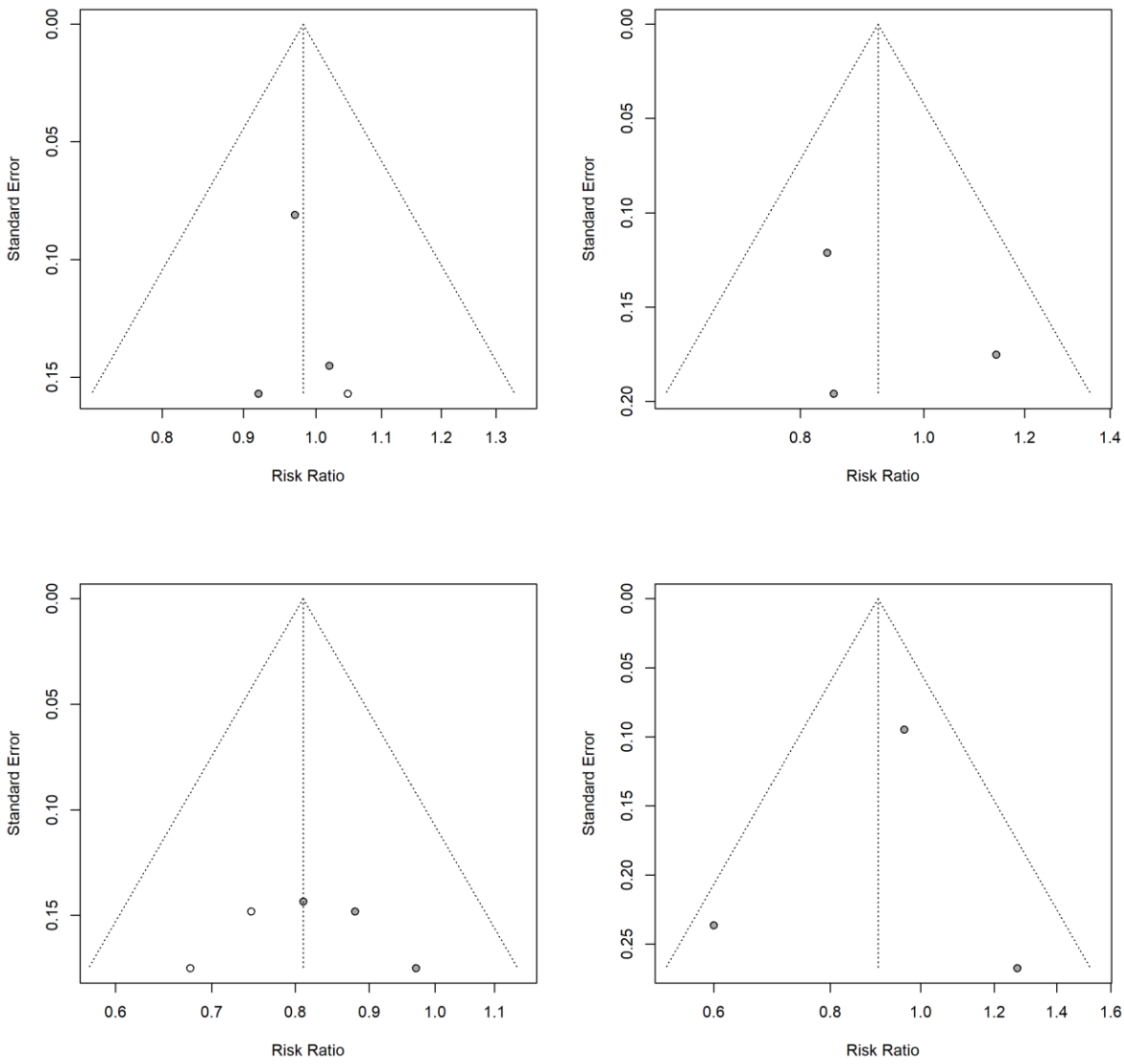

Fig S4: Funnel plot of prospective cohort studies evaluating summary hazard ratios of colon and rectum cancer for vegetarian and pescatarians versus meat-eaters (reference).

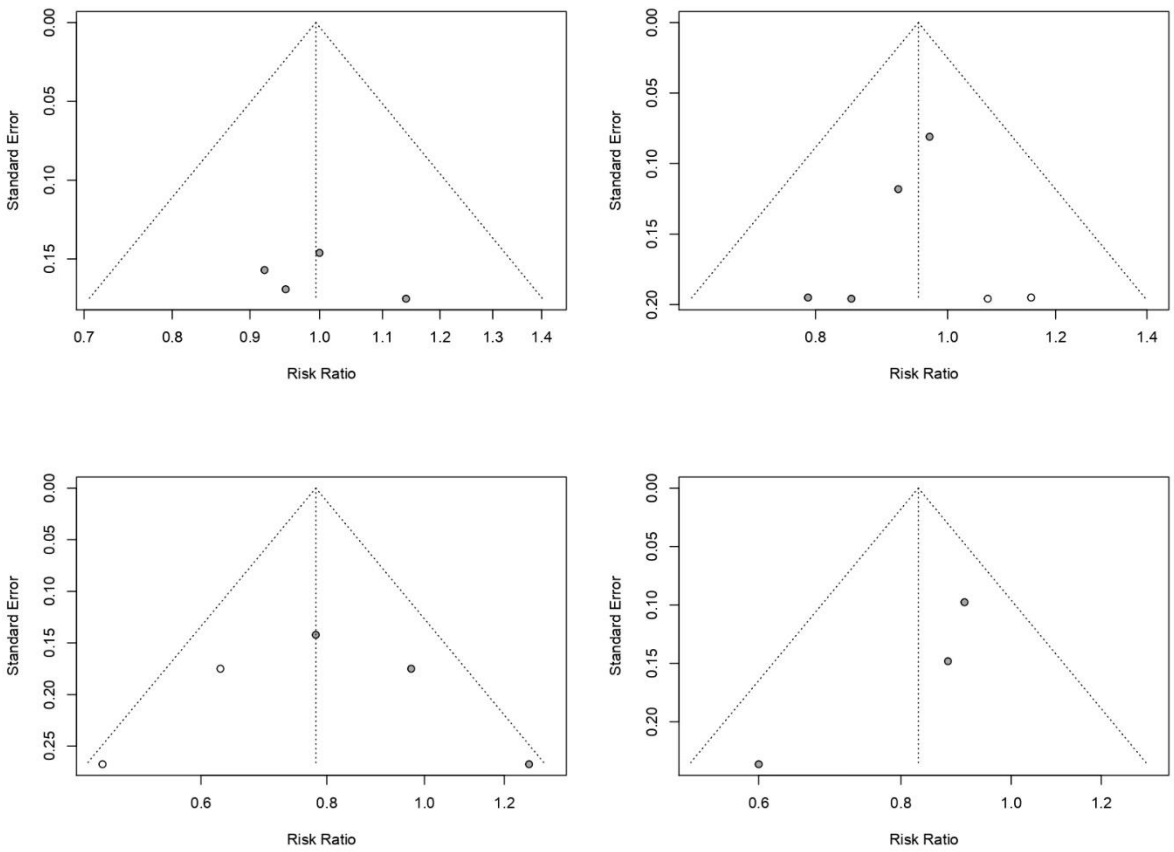

Fig S5: Funnel plot of prospective cohort studies evaluating summary hazard ratios of breast cancer in premenopausal and postmenopausal for vegetarian and pescatarians versus meat-eaters (reference).

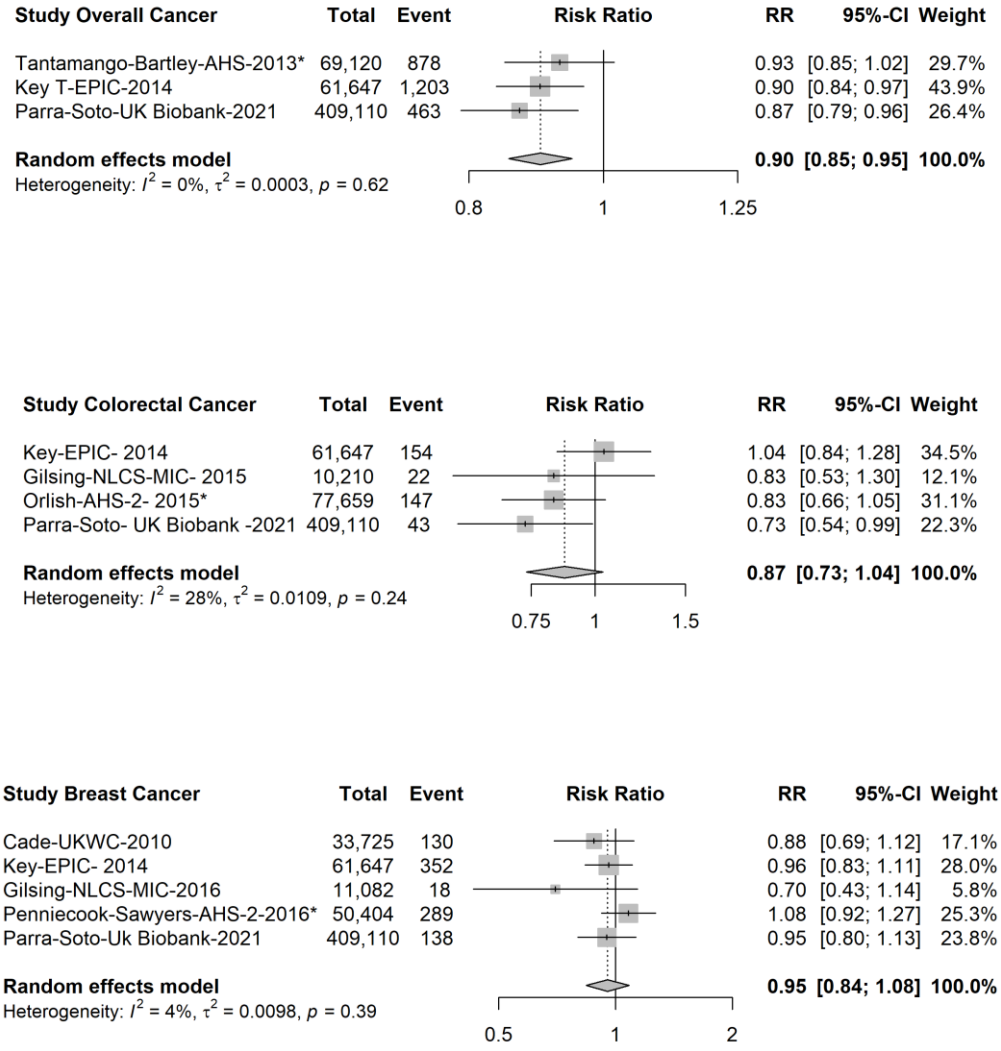

Fig S6: Sensitivity analysis of prospective cohort studies evaluating summary risk ratios of Lacto-Ovo vegetarians defined by Tantamango et al. for overall cancer, Orlish et al. for colorectal cancer, and Penniecook et al for breast cancer, compared with non-vegetarians (reference). RR: Risk ratio, CI: confidence interval.
*study change RR

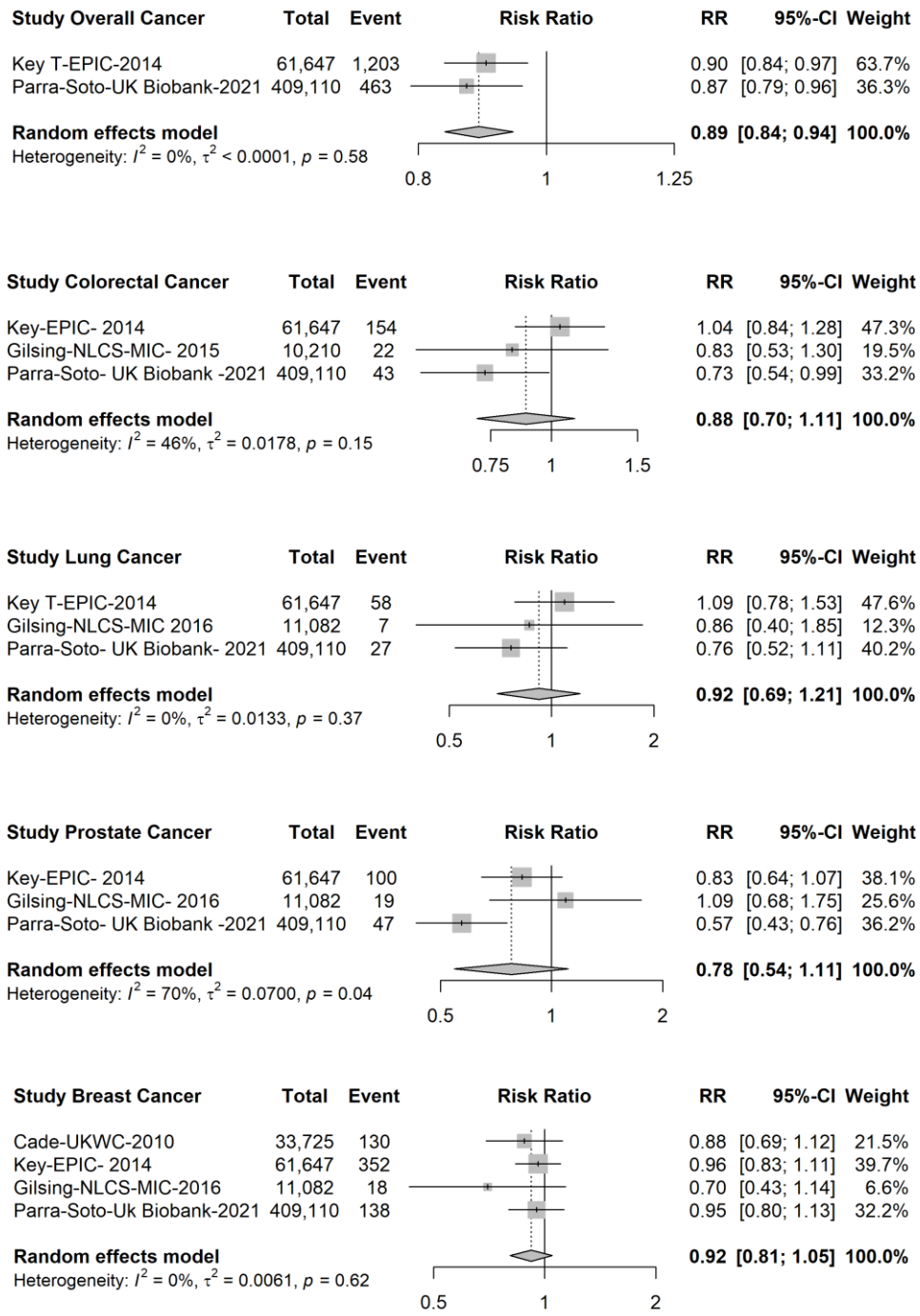

Fig S7: Sensitivity analysis of prospective cohort studies evaluating summary risk ratios of overall, colorectal, lung, prostate and breast cancer for vegetarians compared with meat-eaters (defined as reference). This sensitivity analysis excluded the study of Tantamango-Bartley et al., 2013 for overall cancer, Orlich et al 2015 for colorectal and Pennie-cook Sawyers et al., 2016 for breast cancer as their definition of vegetarians included a low intake of meat (less than once a month). RR: Risk ratio, CI: confidence interval

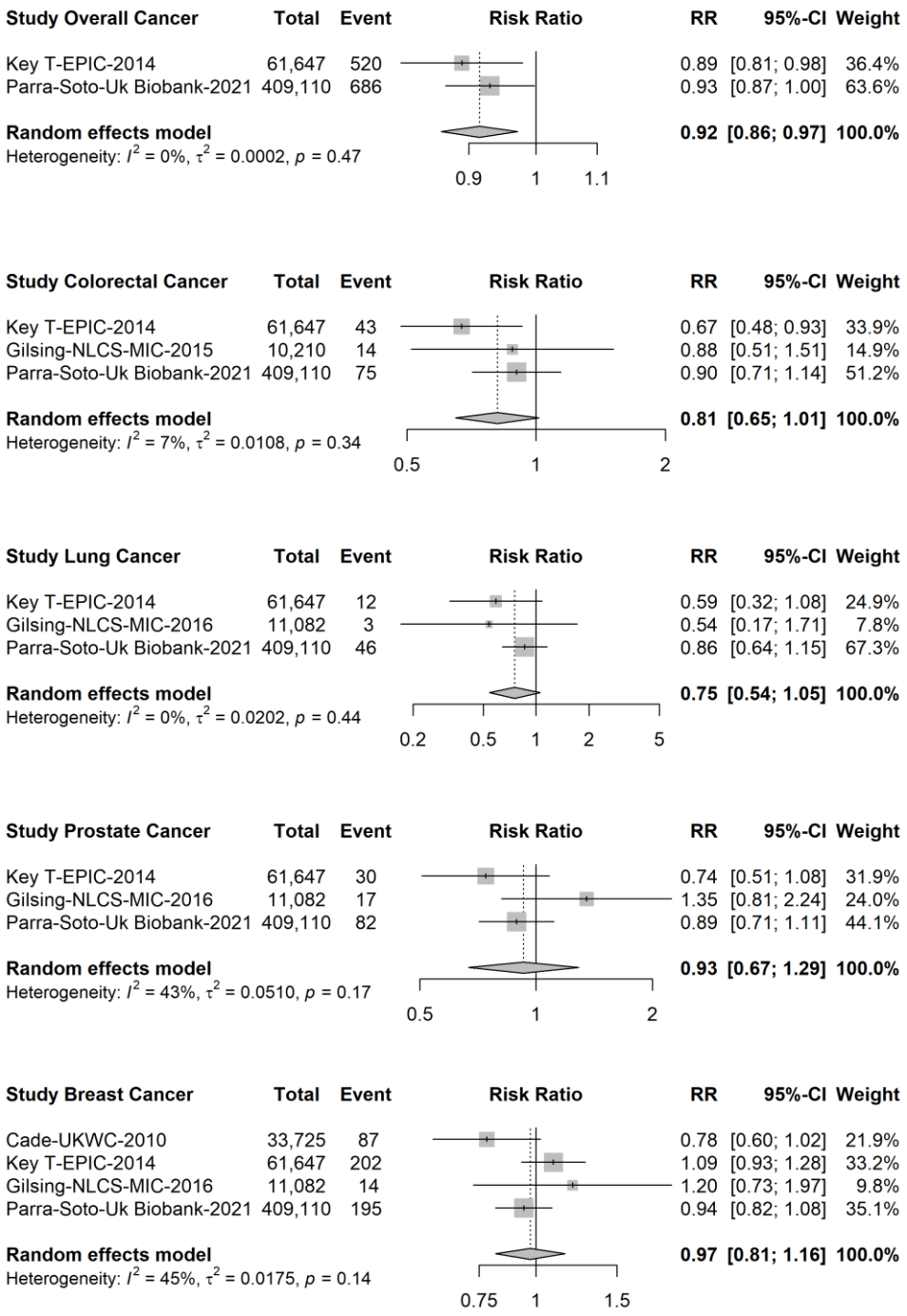

Fig S8: Sensitivity analysis of prospective cohort studies evaluating summary risk ratios of colorectal, lung, prostate, breast and overall cancer of pescatarians compared with meat-eaters (reference group). The studies of Tanta mango-Bartley et al., 2013 for overall cancer, Orlich et al 2015 for colorectal and Pennie-cook Sawyers et al., 2016 for breast cancer were removed as these included a definition of pescatarians who consumed meat less than once a month. RR: Risk ratio, CI: confidence interval

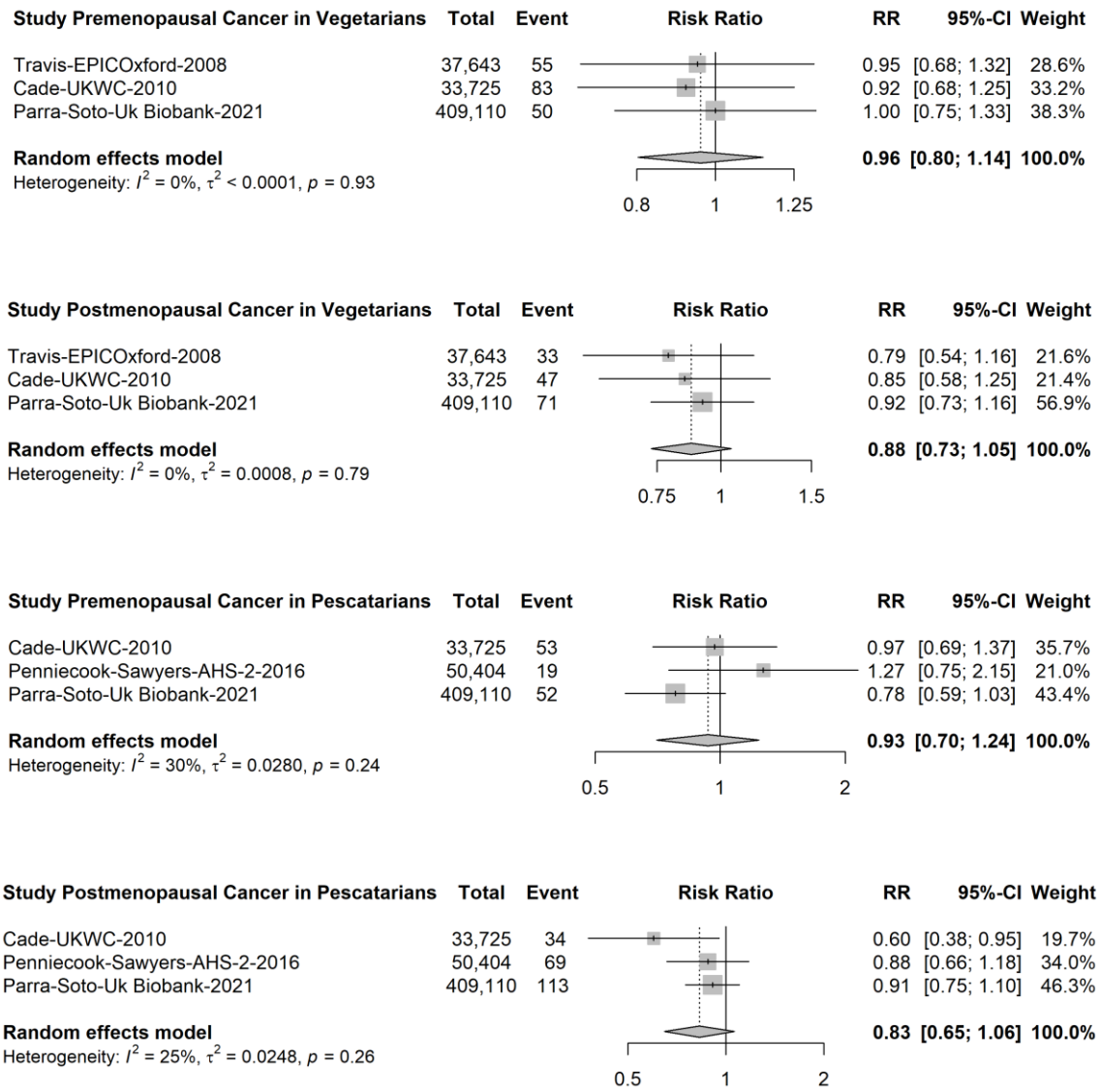

Figure S9: Forest plot of prospective cohort studies evaluating summary risk ratios of breast cancer in premenopausal and postmenopausal women for vegetarians and pescatarians compared with meat-eaters (reference). RR: Risk ratio, CI: confidence interval. Removing Pennie-cook Sawyers et al., 2016

Chapter 4. Associations of six adiposity-related markers with incidence and mortality from 24 cancers – Findings from the UK Biobank prospective cohort study

4.1 Abstract

Background: Adiposity is a strong risk factor for cancer incidence and mortality. However, most of the evidence available has focused on body mass index (BMI) as a marker of adiposity. There is limited evidence on relationships of cancer with other adiposity markers, and if these associations are linear or not. The aim of this study was to investigate the associations of six adiposity markers with incidence and mortality from 24 cancers by accounting for potential non-linear associations.

Methods: 437,393 participants (53.8% women; mean age 56.3 years) from the UK Biobank prospective cohort study were included in this study. The median follow-up was 8.8 years (interquartile range 7.9 to 9.6) for mortality and 9.3 years (IQR: 8.6 to 9.9) for cancer incidence. Adiposity-related exposures were BMI, body fat percentage, waist-hip ratio, waist-height ratio, waist and hip circumference. Incidence and mortality of 24 cancers sites were the outcomes. Cox proportional hazard models were used with each of the exposure variables fitted separately on penalised cubic splines.

Results: During follow-up, 47,882 individuals developed cancer and 11,265 died due to cancer during the follow-up period. All adiposity markers had similar associations with overall cancer incidence. BMI was associated with a higher incidence of 10 cancers (stomach cardia (Hazard ratio per 1 SD increment (1.35, 95% CI: 1.23; 1.47), gallbladder (1.33 (1.12; 1.58)), liver (1.27 (1.19; 1.36)), kidney (1.26 (1.20; 1.33)), pancreas (1.12 (1.06; 1.19)), bladder (1.09 (1.04; 1.14)), colorectal (1.10 (1.06; 1.13)), endometrial (1.73 (1.65; 1.82)), uterine (1.68 (1.60; 1.75)) and breast cancer (1.08 (1.05; 1.11))) and overall cancer (1.03 (1.02; 1.04)). All these associations were linear except for breast cancer in postmenopausal women. Similar results were observed when other markers of

central and overall adiposity were used. For mortality, nine cancer sites were linearly associated with BMI and eight with waist circumference and body fat percentage.

Conclusion: Adiposity, regardless of the marker used, was associated with an increased risk in 10 cancer sites.

4.2 Background

Currently, 67% of men and 62% of women are overweight or obese in the United Kingdom. Obesity has strong association with increased incidence of, and premature mortality from, some types of cancer (Mokdad et al., 2003, Bhaskaran et al., 2014). A recent report by the World Cancer Research Fund (WCRF) summarises the evidence showing that high BMI is associated with higher risk of 12 cancers, including colorectal, breast in postmenopausal women, oesophageal, pancreatic, liver, kidney, oral, pharynx and larynx, stomach cardia, gallbladder, ovarian, (advanced) prostate, and womb cancers (World Cancer Research Fund, 2018a). However, the WCRF report also highlighted the lack of evidence regarding the association of cancer with other markers of adiposity (i.e. central adiposity and body fat).

Although previous studies have reported the association of several cancer sites with different markers of adiposity (Bhaskaran et al., 2014, Freisling et al., 2017, Keimling et al., 2013), most of these studies have been conducted in Asian populations (Wang et al., 2020, Lee et al., 2018), Lee et al., reported the associations of 18 cancers with waist circumference (WC) in 22.9 million Korean adults (Lee et al., 2018), Similarly, Wang et al., reported the associations of four markers of adiposity including BMI, WC, waist-to-hip ratio (WHR) and body fat percentage (BF%) with 15 cancers in the China Kadoorie Biobank (Wang et al., 2020). Evidence derived from white or British populations has focused mainly on a small number of cancer sites (i.e. breast, colon, endometrium and prostate) (Guo et al., 2019, Ortega et al., 2017, Perez-Cornago et al., 2017, Omiyale et al., 2020), or has been restricted to BMI as a marker of adiposity (Bhaskaran et al., 2014, Freisling et al., 2017, Keimling et al., 2013). In 2014, Bhaskaran et al., (Bhaskaran et al., 2014) reported that BMI was associated with 17 cancers in 5.2

million British adults. This study also highlighted the need for further evidence for other adiposity markers since measures of body fat distribution, such as central obesity and body fat might be stronger determinants of specific cancer sites than BMI (Barberio et al., 2019), as observed for other health outcomes such as cardiovascular diseases (Ross et al., 2020). Moreover, most of the evidence available to date have assumed a linear association between markers of adiposity and cancer risk from most common sites (colorectal, breast cancer, liver, kidney and gallbladder) (Freisling et al., 2017, Barberio et al., 2019), with a limited number of studies investigating non-linear association (Bhaskaran et al., 2014, World Cancer Research Fund, 2018b, Aune et al., 2012). To address these limitations, we used data from the UK Biobank cohort, a large prospective cohort study, to investigate the associations of six adiposity markers with incidence and mortality from 24 cancers by accounting for potential non-linear associations.

4.3 Methods

Study design

UK Biobank recruited more than 500,000 participants (aged 37-73 years, 56.3% were women) between 2006 and 2010 (Collins, 2012). Participants attended one of 22 assessment centres across England, Scotland, and Wales, where they completed a self-administered, touch-screen questionnaire and face-to-face interviews (Sudlow et al., 2015, Palmer, 2007). After excluding participants with a prevalent cancer diagnosis at baseline (n=41,460), those with missing data for exposures and covariates (n=21,064), and participants who were classified as underweight (n=2,629), 437,393 participants were finally included in the study. The outcomes defined for this study were incidence and mortality for overall cancer and 24 specific cancers. Of the 24 cancers, 17 were relevant to both men

and women, two were specific to men (testicular and prostate cancer), and five were specific to women (breast, endometrium, uterine, cervix and ovary). The exposures were six adiposity-related markers, including BMI, WC, WHR, waist-to-height ratio (WHtR), hip circumference (HC) and BF%. The covariates were sociodemographic factors (age, ethnicity, education, and Townsend deprivation), smoking status, dietary intake (red meat, processed meat, fruit and vegetables, oily fish, and alcohol), physical activity, and sedentary behaviour. Additional cancer-specific covariates were added for women-related cancer (hormonal replacement, ages first live birth, last live birth and at menarche). Additionally, sun exposition was added as a covariate for melanoma cancer and for lung, oesophageal and oral cancer we restricted the analysis to never smoker only.

Procedures

Date of death was obtained from death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Date and cause of hospital admissions were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Detailed information about the linkage procedures can be found at http://content.digital.nhs.uk/services. At the time of analysis, mortality data were available up to 01 June 2020. Mortality analysis was therefore censored at this date or date of death, whichever occurred earlier. Hospital admission data were available until 31 March 2017 for Scotland and Wales and until 01 June 2020 for England, resulting in analyses of incident outcomes being censored at this date or the date of relevant hospitalisation or death, whichever occurred earlier. We defined incident cancer as fatal or nonfatal events. The International Classification of Diseases, 10th revision (ICD-10) was used to define the following

27 cancers: overall cancer (C00-C97, D37, D48), oral (lip, pharynx and larynx) (C00-C14), oesophagus (C15) upper oesophagus (C15.0,15.1,15.3 and 15.4), stomach (C16) stomach cardia (C16.0), stomach non cardia (C16.1-16.6), colorectal (C18, C19, and C20), colon proximal (C 18.0-18.5), colon distal (C18.6, C18.7), colon (C18.0-C18.9), rectum (C19-C20), liver (C22), gallbladder (C23), pancreas (C25), lung (C34), malignant melanoma (C43), breast (C50), uterine (C54-C55), cervix (C53), endometrium (C54), ovary (C56), prostate (C61), testis (C62), kidney (C64-C65), bladder (C67), brain (C71), thyroid (C73), lymphatic and hematopoietic tissue (C81-C96), non-Hodgkin lymphoma (C82-C85), multiple myeloma (C90), and leukaemia (C91-C95).

The exposures were six adiposity-related markers (BMI, WC, WHR, WHtR, HC and BF%) measured by trained staff using standardised protocols across the assessment centres at baseline. Height was measured to the nearest centimetre, using a Seca 202 stadiometer, and body weight to the nearest 0.1 kg, using a Tanita BC-418 body composition analyser. BMI was calculated as weight (kg) divided by height (m) squared and classified into the following categories: underweight (<18.5 kg/m2), normal weight (18.5 to <25 kg/m2), overweight (25 to <30 kg/m2), obese (>30 kg/m2) (World Health Organization, 2000).

BF% was measured using the Tanita BC-418 MA body composition analyser (fat mass divided by the total body mass).

The natural indent was used to measure WC (the umbilicus was used if the natural indent could not be observed) and used to determine central obesity (WC ≥88 cm for women and WC ≥102 cm for men). HC was recorded at the widest part of the hips. WHR and WHtR are the ratios of the waist-to-hip circumference and waist circumference to height, respectively.

Age, sex, ethnicity, smoking status, diet (portions of fruits & vegetables, red & processed meat, and oily fish) and alcohol intake (daily, 2-4 times a week, once or twice a week, 1-3 time a month, special occasions and never) sun exposition (do not go out in the sunshine, rarely, sometimes, most of the time, always), and female specific factors were self-reported at the baseline assessment by touch-screen questionnaire. Townsend area deprivation index was derived from the postcode of residence using aggregated data on unemployment, car and homeownership, and household overcrowding. (Townsend P et al., 1988) Educational qualification was self-reported. Physical activity level over a typical week was self-reported using the International Physical Activity Questionnaire and reported as metabolic equivalent of task (MET) per week. (IPAQ) Time spent on discretionary sedentary behaviours was derived from the questionnaire and included time spent in front of a TV or computer or driving during leisure time. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals for each adiposity marker (BMI, WC, BF%, WHR, WHtR and HC) separately with incidence and mortality for 24 cancers and all-cause cancer. Duration of follow-up was used as the timeline variable. The exposure variables were fitted separately on penalised cubic splines to investigate non-linear associations between each adiposity exposure and the outcomes. Penalised spline is a variation of basis spline (Govindarajulu et al., 2009). Non-linearity was tested by likelihood ratio tests. To compare the associations between cancer across different adiposity markers, all adiposity

exposures were standardised by sex and HR were expressed per 1-standard deviation increment (1-SD was equivalent to BMI units of 4.2 and 5.1 kg/m2, WC 11.3 and 12.5 cm, WHR 0.07 and 0.07, WHtR 6.5 and 7.9, HC 7,6 and 10,4 cm, BF% 5.8 and 6.9% and BFI 2.6 and 3.8 kg/m2 for men and women, respectively). Participants with prevalent cancer at the baseline assessment were excluded from the study (n=41,406). Underweight participants were also excluded from the study (n=2,629). In addition, a landmark analysis was performed to reduce the potential for reverse causality, with follow-up commencing two years after recruitment. The association between adiposity and oesophageal, oral and lung cancer was restricted to participants who reported being never smokers, to avoid reverse causation bias. For breast cancer, all analyses were stratified by menopausal status. Additional analyses were performed including underweight people and adding height as a covariate.

Population attributable fractions (PAFs), assuming causality, were calculated based on the BMI distribution of Health Surveys of England, Scotland, and Wales in 2018 (Cabinet Secretary for Health and Sport, 2020, Lifestyles Team, 2019, National Survey for Wales, 2020) and the HRs derived from this study using the standard formula with 95% Confidence Interval (CI) and p-values estimated using bootstrapping (formula shown in Additional file 1: Figure S1) (Vander Hoorn S et al., 2004).

To compare cancer risk discrimination between BMI and the remaining five adiposity markers, we calculated Harrell's C-index (the probability of concordance between observed and predicted responses) for a model that included the adiposity marker and covariates (age, ethnicity, deprivation, education, smoking, alcohol consumption, intakes of fruit and vegetables, red and processed meat, oily fish, physical activity, and sedentary behaviours). The

model with BMI was defined as baseline model. The C-indices of the baseline model and the C-index difference between other adiposity model and the baseline model were reported. The variance of the C-indices were calculated using formula as described previously (Hanley and Mcneil, 1982). These were then used to calculate confidence intervals and p-values using normal approximation.

Competing risk due to non-cancer mortality was handled using a cause-specific model (Lau et al., 2009). Participants who died due to non-cancer causes were marked as censored at their date of death. This approach was used instead of the sub distribution proportional hazards model because there is no evidence that the competing events influence the risk of cancer events, and because the current study aims to investigate associations rather than absolute risk.

Finally, because of potentially inflated type-I errors due to multiple tests, all analyses were corrected for multiple testing using Holm's method (ETH Zurich), which performed similarly to Bonferroni's method while retaining higher statistical power (Holm, 1979). The multiple testing corrected p-value are denoted as Padj P value for testing overall significance against no association, and Pnonlinear for p-value testing non-linearity.

All analyses were adjusted for age, ethnicity, deprivation, education, smoking, alcohol consumption, intakes of fruit and vegetables, red and processed meat, oily fish, physical activity, and sedentary behaviours. Additionally, breast cancer was further adjusted for hormonal replacement, age menarche, age at first and last live birth. Prostate cancer was additionally adjusted for family history of prostate cancer, and melanoma was further

adjusted for sun exposure. All analyses were performed using R Statistical Software, version 3.6.2, with the package survival and pifpaf.

4. Results

This study included 437,393 participants who were followed-up for 8.8 years (interquartile range (IQR) 7.9 to 9.6) for cancer incidence and 9.3 (IQR: 8.6 to 9.9) for cancer mortality, after excluding the 2-years landmark analysis. Over this period, 47,882 incident cancer cases and 11,265 cancer deaths occurred (Additional file 1: Table S1and S2). The characteristics of participants stratified by BMI categories are shown in Table 4-1. In summary, 53.8% of the study population were women, 94.6% were of white European background. The mean population age was 56.3 years, 55.3% of subjects had never smoked and 10.4% were current smokers.

*Table 4-1. **Cohort baseline characteristics***

	Normal weight	Overweight	Obese	Overall
n	143,460 (32.8%)	187,563 (42.9%)	106,370 (24.3%)	437,393
Age, Mean (SD)	55.4 (8.22)	56.7 (8.07)	56.6 (7.90)	56.3 (8.10)
Sex				
Females	92,922 (64.8%)	87,097 (46.4%)	55,246 (51.9%)	235,265 (53.8%)
Males	50,538 (35.2%)	100,466 (53.6%)	51,124 (48.1%)	202,128 (46.2%)
Townsend deprivation index				
Lower deprivation	51,511 (35.9%)	65,530 (34.9%)	30,740 (28.9%)	147,781 (33.8%)
Middle deprivation	48,183 (33.6%)	63,918 (34.1%)	34,366 (32.3%)	146,467 (33.5%)
Higher deprivation	43,766 (30.5%)	58,115 (31.0%)	41,264 (38.8%)	143,145 (32.7%)
Education				
College or University degree	64,263 (44.8%)	69,351 (37.0%)	32,442 (30.5%)	166,056 (38.0%)
A levels/AS levels or equivalent	17,455 (12.2%)	20,738 (11.1%)	11,116 (10.5%)	49,309 (11.3%)
O levels/GCSEs or equivalent	29,336 (20.4%)	40,223 (21.4%)	23,510 (22.1%)	93,069 (21.3%)
SEs or equivalent/NVQ or HND or HNC or equivalent	13,885 (9.7%)	23,548 (12.6%)	15,352 (14.4%)	52,785 (12.1%)
Missing	18,521 (12.9%)	33,703 (18.0%)	23950 (22.5%)	76174 (17.4%)
Ethnicity				
White	136,331 (95.0%)	177574 (94.7%)	99866 (93.9%)	413771 (94.6%)
Mixed	2,101 (1.5%)	2,703 (1.4%)	1,741 (1.6%)	6,545 (1.5%)
South Asian	2,830 (2.0%)	3,965 (2.1%)	1,869 (1.8%)	8,664 (2.0%)
Black	1,327 (0.9%)	2,905 (1.5%)	2,813 (2.6%)	7,045 (1.6%)
Chinese	871 (0.6%)	416 (0.2%)	81 (0.1%)	1368 (0.3%)
Height (m), Mean (SD)	1.68 (0.08)	1.69 (0.09)	1.68 (0.09)	1.69 (0.09)
Weight (kg), Mean (SD)	64.7 (8.47)	78.6 (9.63)	95.9 (14.3)	78.2 (15.8)
Waist circumference (cm), Mean (SD)	78.6 (8.10)	91.0 (8.36)	105 (11.0)	90.3 (13.3)
Body Mass index (kg/m2), Mean (SD)	22.9 (1.53)	27.3 (1.40)	33.9 (3.83)	27.4 (4.71)
Smoking				
Never	85,608 (59.7%)	101,285 (54.0%)	54,809 (51.5%)	241,702 (55.3%)
Previous	41,891 (29.2%)	67,116 (35.8%)	41,239 (38.8%)	150,246 (34.4%)
Current	15,961 (11.1%)	19,162 (10.2%)	10,322 (9.7%)	45,445 (10.4%)
Alcohol intake				
Daily or almost daily	32,389 (22.6%)	40,452 (21.6%)	16,463 (15.5%)	89,304 (20.4%)
3-4 times a week	35,702 (24.9%)	46,235 (24.7%)	20,550 (19.3%)	10,2487 (23.4%)
Once or twice a week	36,313 (25.3%)	49,273 (26.3%)	28,077 (26.4%)	113,663 (26.0%)

1-3 times a month	14,853 (10.4%)	19,717 (10.5%)	14,346 (13.5%)	48,916 (11.2%)
Special occasions only	14,027 (9.8%)	18,826 (10.0%)	16,405 (15.4%)	49,258 (11.3%)
Never	10,176 (7.1%)	13,060 (7.0%)	10,529 (9.9%)	33,765 (7.7%)
Fruit and vegetable intake (portion/day), Mean (SD)	2.01 (0.825)	1.95 (0.827)	1.94 (0.832)	1.97 (0.828)
Red meat (portion/week), Mean (SD)	1.93 (1.38)	2.14 (1.42)	2.28 (1.53)	2.11 (1.44)
Processed meat (portion/week), Mean (SD)	1.69 (1.08)	1.92 (1.04)	2.03 (1.04)	1.87 (1.06)
Oily fish (portion/week), Mean (SD)	1.65 (0.919)	1.65 (0.921)	1.59 (0.946)	1.64 (0.927)
Sedentary time (hours/day), Mean (SD)	4.48 (2.03)	5.12 (2.22)	5.64 (2.51)	5.03 (2.28)
Physical activity(hours/day), Mean (SD)	1.62 (1.44)	1.76 (1.58)	2.22 (2.00)	1.83 (1.67)
Diabetes at baseline	2,398 (1.7%)	7,325 (3.9%)	11,485 (10.8%)	21,208 (4.8%)
Hypertension at baseline	20,636 (14.4%)	48,570 (25.9%)	44,758 (42.1%)	11,3964 (26.1%)

Data are presented as numbers (percentages) unless stated otherwise. SD: Standard deviation, BMI: Body Mass Index. Participants classified as underweight (BMI <18.5 kg/m2 were excluded from the analyses (n=2,629).

Figure 4-1 shows the association of six adiposity markers with overall, liver and colorectal cancer incidence. Although there was no evidence against linear associations with these cancer sites for all adiposity markers, the magnitude of association was higher for liver cancer incidence (HR ranging from 1.19 to 1.33 per 1-SD higher adiposity) compared with colorectal cancer (HR ranging from 1.07 to 1.13 per 1-SD higher adiposity), as shown in Additional file 1: Table S2. Similar results were found for overall, liver, pancreatic and colorectal cancer mortality as shown in Additional file 1: Table S2. However, the association for WC and HC with colorectal cancer mortality was not significant (Additional file 1: Fig. S2). Although a similar shape of association was observed for risk of pancreatic cancer incidence across all adiposity markers, only BMI was significantly associated with a higher risk after adjusting for multiple testing (Figure 4-1). Similar results were observed for mortality from pancreas cancer (Additional file 1: Fig. S2). When the analyses were performed by segments of the digestive tract, distal, proximal and colon cancer incidence were linearly associated with a higher risk across all adiposity markers (Additional file 1: Fig. S3), but these associations were not observed for mortality (Additional file 1: Table S1 and Fig. S4).

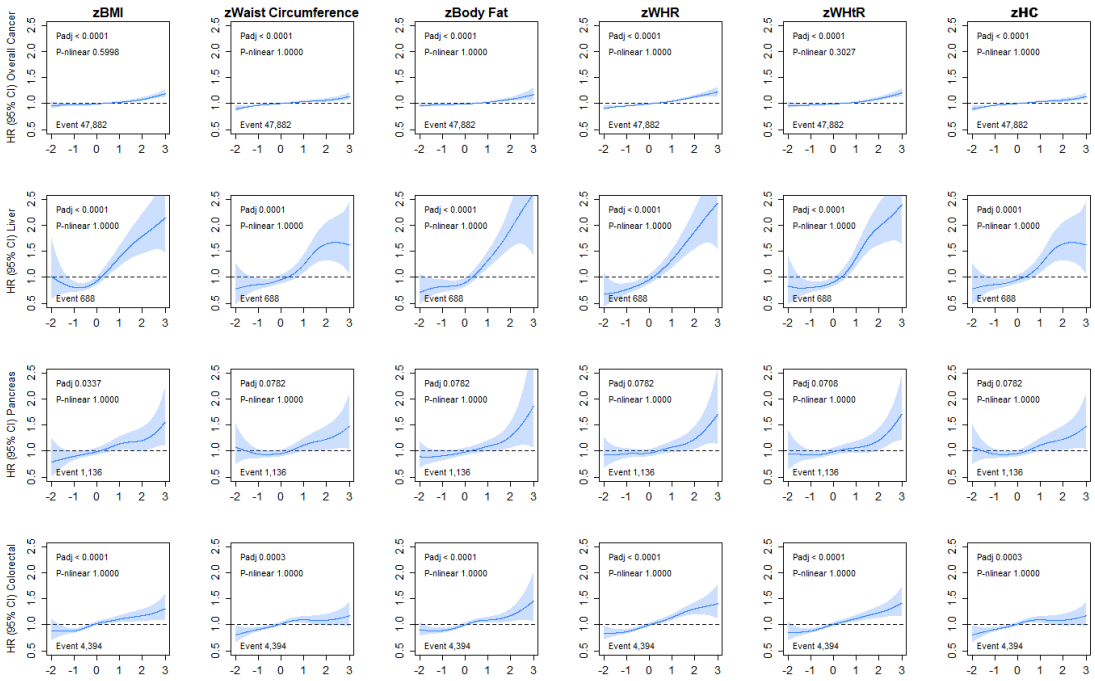

Figure 4-1. Association of adiposity markers with overall, liver, pancreas and colorectal cancer incidence.

The association of adiposity markers with gallbladder and stomach (cardia and non-cardia) cancer incidence are shown in Figure 4-2. There was no evidence of non-linear associations for gallbladder cancer across all six adiposity markers (HR varied from 1.28 to 1.50 per 1-SD higher adiposity). For stomach cancer incidence, a linear association was observed across all adiposity markers (HR ranged from 1.14 to 1.24 per 1-SD higher adiposity). However, when the analyses were stratified by stomach cardia and non-cardia, only stomach cardia was linearly associated with all adiposity markers (HR varied from 1.25 to 1.35 per 1-SD higher adiposity) (Additional file 1: Table S1). Similar patterns of associations were observed for mortality from gallbladder, stomach, and stomach cardia cancer (Additional file 1: Fig. S5).

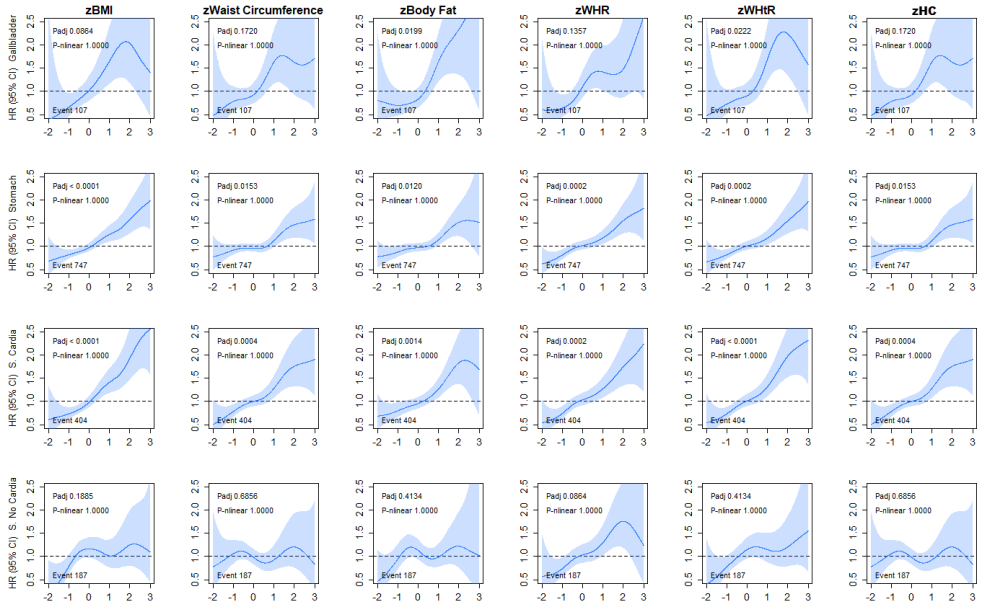

Figure 4-2 Association of adiposity markers with gallbladder and stoma4h cancer incidence

The associations between adiposity and respiratory-related cancers in never smokers are shown in Figure 4-3. Although similar shaped associations were observed for oesophageal cancer incidence across all adiposity markers, only WHtR was significant (HR ranged from 1.19 to 1.26 per 1-SD higher adiposity) (Additional file 1: Table S1). Similar associations were observed for oesophageal cancer mortality (Additional file 1: Fig. S6). No associations were observed for upper oesophagus, oral and lung cancer incidence and mortality across any of the adiposity markers.

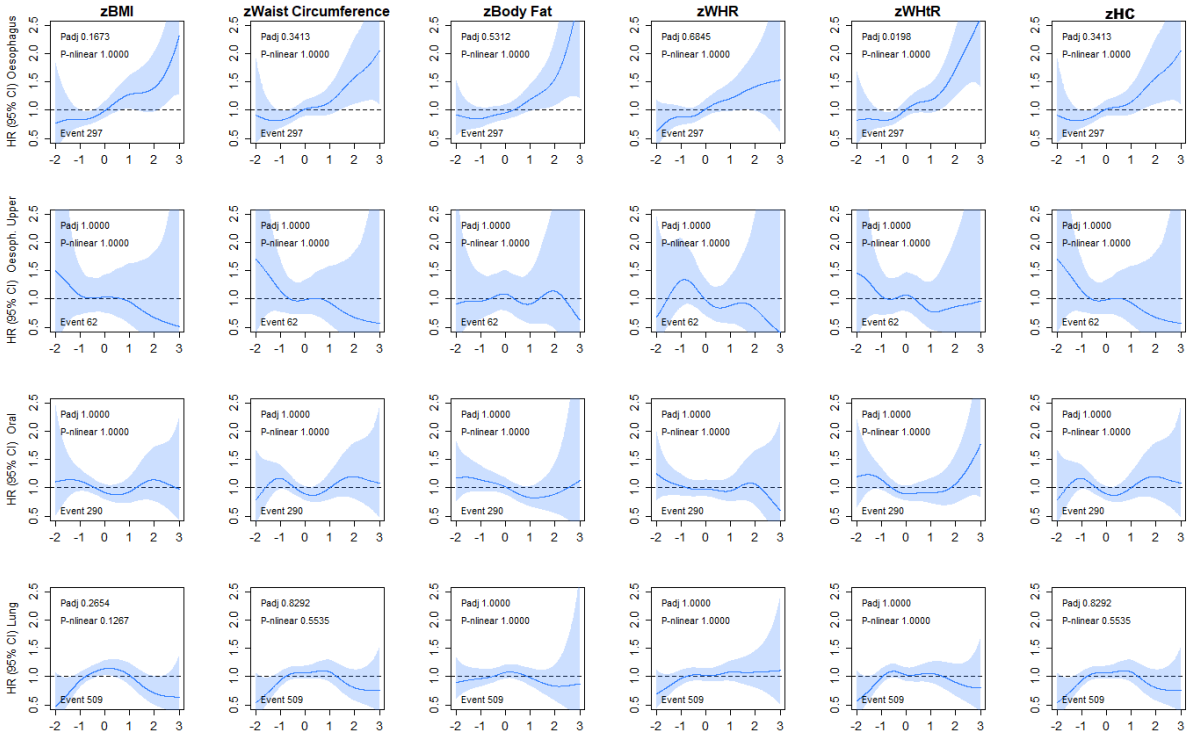

Figure 4-3. Association of adiposity markers with oesophagus, oral and lung cancer incidence in never smoker.

Lymphatic cancer was linearly associated with BMI, WC and HC, for incidence (HR ranged from 1.06 to 1.08 per 1-SD higher adiposity, Additional file 1: Table S1). However, no association were observed for leukaemia, non-Hodgkin and myeloma cancer incidence and mortality across any of the adiposity markers (Figure 4 and Additional file 1: Fig. S7).

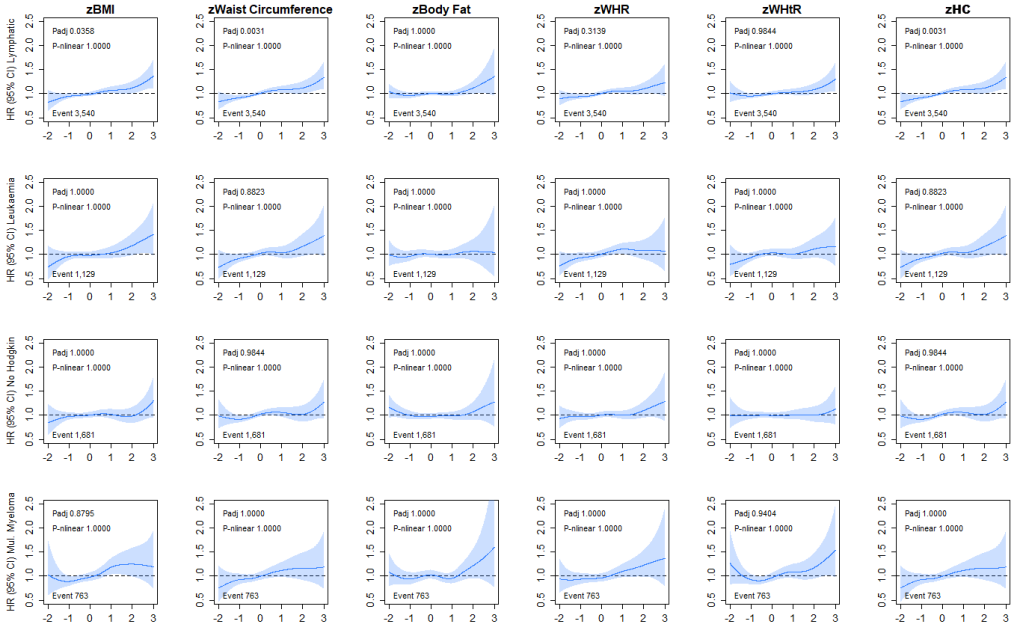

Figure 4-4. Association of adiposity markers with lymphatic cancer incidence

For sex-specific cancers, we observed a steeper linear association for uterine (HR ranged from 1.26 to 1.70) and endometrial (HR ranged from 1.29 to 1.78) cancer incidence (Figure 4-5 and Additional file 1: Table S1).

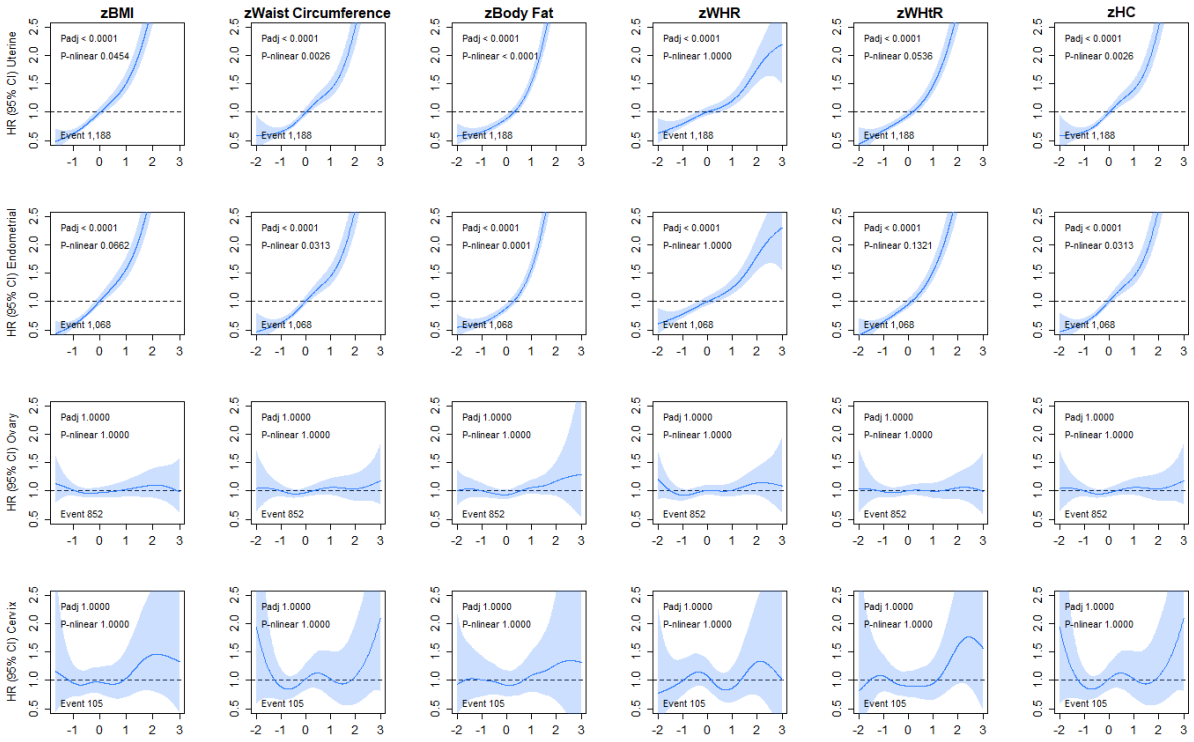

Figure 4-5. Association of adiposity markers with sexual women cancer incidence.

The strongest magnitude of association for both uterine and endometrial cancer incidence was observed for body fat % whereas WHR shows the smallest magnitude of association of any adiposity marker (Additional file 1: Table S1). Although similar associations were observed for uterine and endometrial cancer mortality across all adiposity markers, mortality from cervical cancer showed a borderline U-shaped association with BMI, WC, body fat, WHtR and HC (Additional file 1: Fig. S9 and Table S2). No association was found between adiposity and ovarian cancer incidence and mortality. For breast cancer incidence, a linear association was observed for BMI, body fat %, WHtR and WHR; however, a slight departure from linearity was observed for WC and HC (Figure 4-6). When the analyses were stratified into pre and post menopause, the adiposity markers were associated with breast cancer incidence in

postmenopausal women only (Figure 4-6). No associations were observed for breast cancer mortality (Additional file 1: Fig. S10). The associations for female-related cancers remained largely unchanged when the analyses were further adjusted for use of hormonal replacement therapy, age at menarche, age at first and date of last live birth (Additional file 1: Fig. S8 and S11). For men, only prostate cancer incidence, but not mortality, was inversely associated with WC and HC (Figure 4-6 and Additional file 1: Fig. S10).

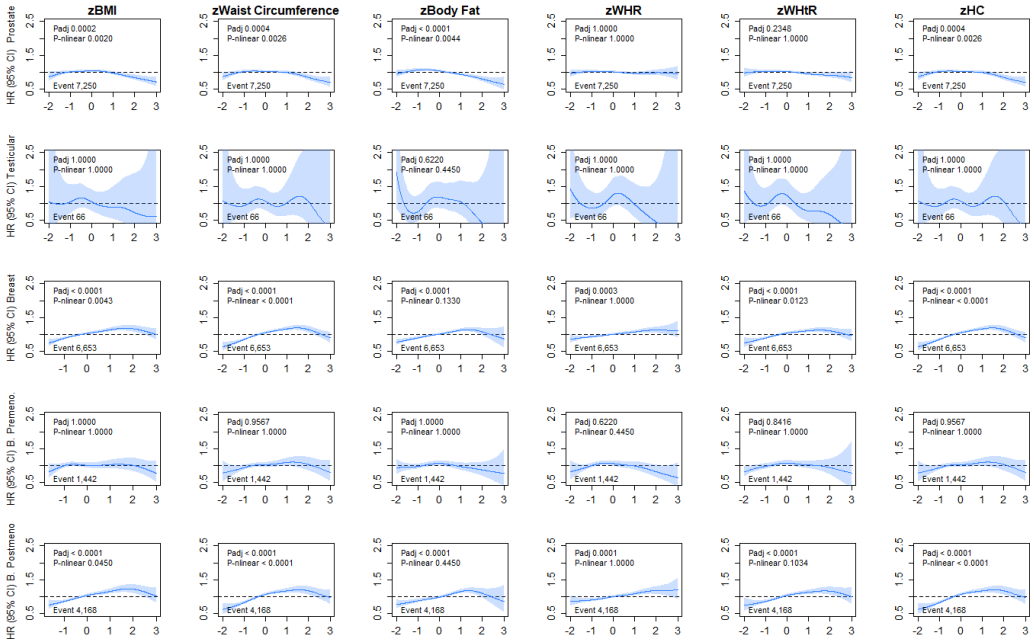

Figure 4.6. Association of adiposity markers with prostate, testicular cancer in men and breast

Kidney cancer incidence and mortality were linearly associated with all adiposity markers, with HR ranging from 1.18 to 1.27 per 1-SD higher adiposity (Figure 4-7 and Additional file 1: Fig. S12). For bladder cancer we observed a higher risk of cancer incidence only at the higher end of the BMI and WHtR ranges (Figure 4-7). However, these associations were not observed for bladder cancer mortality (Additional file 1: Fig. S12). For melanoma cancer incidence, only WC and HC were linearly associated with a higher risk (Figure 4-7).

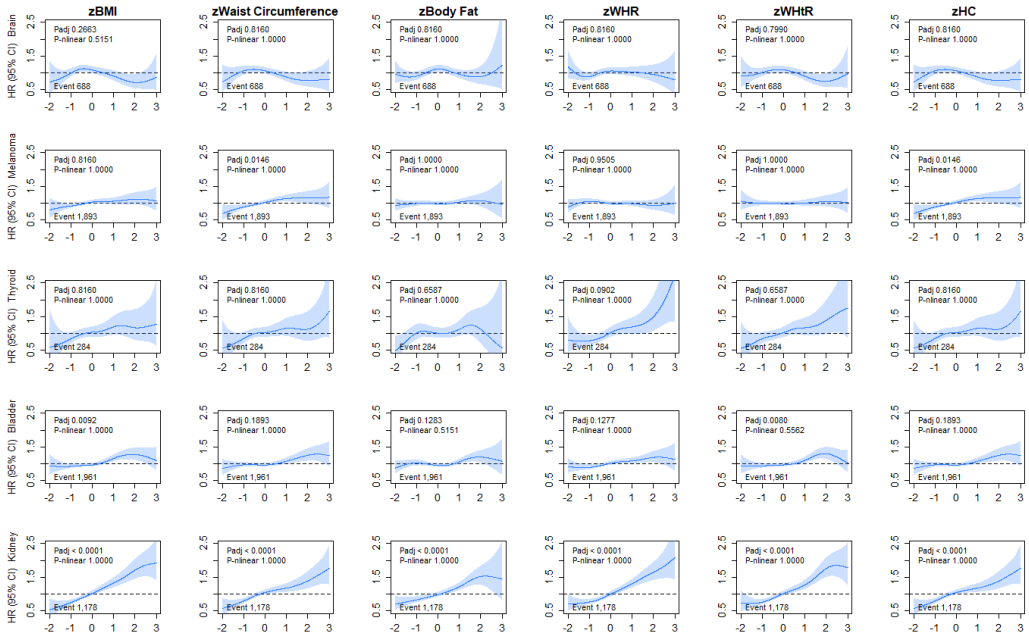

Figure 4-7. Association of adiposity markers with brain, melanoma, thyroid, bladder and kidney cancer incidence.

Our PAF analyses show that the proportions of cancer attributable to BMI vary considerably by cancer site. Endometrial, uterine and gallbladder were the top three cancers for which obesity accounted for 43.8%, 39.2%, and 29.9% incident cases and 63.8%, 46.1%, and 39.8% of deaths, respectively (Figure 4-8). When the predictive ability of BMI was compared with the other adiposity markers using C-index, there were no evidence of a significant improvement in C-indices from models using WC, BF%, WHR, WHtR and HC over the model with BMI (Additional file 1: Table S3). The associations for overall, liver, kidney, stomach, pancreatic, bladder, gallbladder, colorectal cancer, endometrium, uterine, and breast (postmenopausal in women) cancer remained significant and largely unchanged when the analyses were adjusted for competing events (Additional file 1: Table S4).

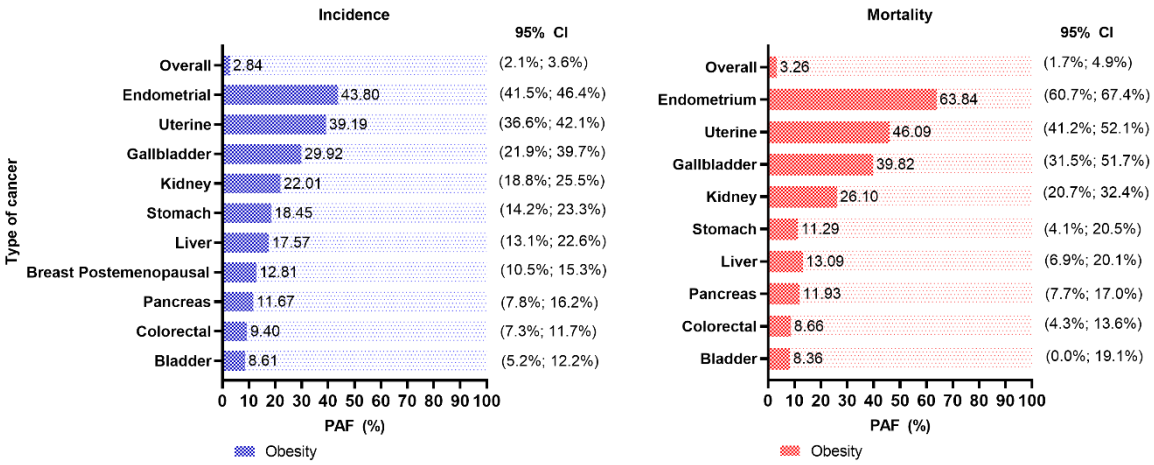

Figure 4-8. Population attributable fraction (PAF) for cancer incidence and mortality attributable to been obese.

When we did the analyses, including underweight people the association between adiposity and cancer remained linear (Additional file 1: Fig. S13 and Fig. S14). Similar results were found for cancer incidence and mortality when we added height as a covariate; some associations were slightly stronger as was the association between BMI and overall cancer mortality (HR: 1.04, 95% CI: 1.03; 1.05, previous was HR: 1.03, 95% CI: 1.02;1.04 (Additional file 1: Table S1, Table S5 and Table S6).

4.5 Discussion

This study provides adds important evidence regarding the risk of 24 cancer sites associated with multiple adiposity markers. Higher levels of adiposity, regardless of the adiposity marker used, were associated in a linear manner with a higher incidence of liver, kidney, stomach, pancreatic, bladder, gallbladder, colorectal cancer, endometrial, uterine, and breast (postmenopausal in women) cancer. If the associations observed were causal, reducing the BMI of obese individuals to the normal range could prevent 43.8%, 39.2%, and 29.9% incidence and 63.8%,

46.1%, and 39.8% deaths from endometrial, uterine and gallbladder cancers, respectively.

Our findings corroborate previous evidence, including the WCRF obesity and cancer 2018 report and meta-analyses from protective cohort studies (Fang et al., 2018, Wei et al., 2018, Renehan et al., 2008, Stolzenberg-Solomon et al., 2013), that adult adiposity (assessed using BMI) is associated with higher risk of oesophageal, pancreatic, liver, colorectal, postmenopausal breast and endometrial cancers. Furthermore, our findings add strength to previously weak evidence of links between BMI and stomach cancer risk (Kubo and Corley, 2006). On the other hand, our findings did not find evidence for an association between BMI (or any other markers of adiposity) and ovarian cancer as reported by others (Kyrgiou et al., 2017), which could be attributed to our comprehensive confounder adjustments. We also found inverse associations between five adiposity markers and risk of prostate cancer. Although excess adiposity has been associated with multiple cancers, evidence of its association with prostate cancer has been restricted to advanced prostate cancer only (Harrison et al., 2020, Lauby-Secretan et al., 2016). However, a recent systematic review of data from 78 studies, including a meta-analysis of 67 studies, reported no association between BMI and prostate cancer (Harrison et al., 2020, Lauby-Secretan et al., 2016). These authors also concluded that previously reported inverse associations between BMI and prostate cancer may be due to incomplete diagnosis (not all men being biopsied). The assumption that men who have not been tested for prostate do not have prostate cancer may lead to bias and inverse associations (Harrison et al., 2020). BMI and WHTR were positively associated with bladder cancer, in concordance with the metanalysis of 15 cohort studies, published by Sun et al., which showed a linear association between adiposity and bladder cancer (Sun et al., 2015).

We did not find a significant association between adiposity and lung cancer in never smokers. These agree with a recent meta-analysis with considerable statistical power, which pooled data from 29 observational studies, including 15 million never smokers, where BMI was inversely associated with lung cancer (Zhu and Zhang, 2018). Our findings in current smokers agree with previous studies showing that BMI was inversely associated with lung cancer in current smokers.

There is convincing evidence (Johnson et al., 2013) that greater adiposity is associated with increased risk of colorectal cancer, assessed mainly as BMI in prospective cohort studies (Jarvis et al., 2016, Johnson et al., 2013, Kubo and Corley, 2006, Lee et al., 2018, Guo et al., 2016, Thrift et al., 2015). Our study corroborates these findings and adds novel evidence that other adiposity markers are also consistently associated with an increased risk of colorectal cancer. We also observed that all adiposity markers were positively associated with higher liver cancer risk with broadly consistent effect sizes. Furthermore, we found that all adiposity markers were associated with an increased risk of breast cancer. But the association appeared to occur in postmenopausal women only. These findings confirm previous evidence from prospective cohort studies (Renehan et al., 2008, Benn et al., 2016, Guo et al., 2018).

Implications of findings

The findings of this study have important clinical implications. First, it provides evidence that central (waist and hip circumference) and overall adiposity (BMI and BF%) markers produced similar relative risk estimates. Therefore, the use of BMI, a simple and low-cost measurement, is adequate for clinical screening in terms of cancer risk, and there is no advantage in using more complicated or more expensive measures such as WC or BF%. We also

found that a significant proportion of cancers could be prevented by reducing obesity, especially liver and kidney cancer in men and endometrial and uterine cancer in women.

Strengths and *Limitations*

UK Biobank is not a representative sample of the UK older adult population, so that we should be cautious in generalising summary statistics to the general population. However, relative risks derived from UK Biobank are consistent with more representative population cohorts (Batty et al., 2020). The adiposity exposures used in the study were measured by trained staff using standardised protocols; therefore this minimises the chance of measurement error and misclassification. However, there are several limitations that should be taken into account. Reverse causation is a concern in prospective cohort studies investigating the association between adiposity and cancer. However, to minimise the effect of reverse causation in our study, we excluded all cancers diagnosed within the first 2-years of follow up and baseline cancers. Residual confounding is also possible even though we have adopted a comprehensive adjustment scheme. In addition, although we used data from hospital admission and deaths registers, available in the UK, we cannot exclude misclassification for cancer specific sites or uncommon cancers. Although UK Biobank is a large observational study, some cancers had limited numbers of events, which limited our power to identify some associations with adiposity markers.

4.6 Conclusion

Adiposity, regardless of the marker used, was associated with an increased risk of 10 cancer sites. Furthermore, the associations were mostly linear among all

adiposity markers. We found no evidence that the use of other adiposity markers, such as central adiposity or body fat, improves the prediction ability for cancer risk beyond the risk attributable to BMI.

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4.8 Additional File Chapter 4

****Figures with red lines are for mortality; those with blue lines for incidence.**

Figure S1: Formula Population Attributable Fraction

$$\text{PAF} = \frac{\int_{\mathbb{R}^p} RR(X;\theta) f(X) dX - 1}{\int_{\mathbb{R}^p} RR(X;\theta) f(X) dX} \quad \text{if } X \text{ is continuous.}$$

PAF: Population Attributable Fraction
$RR(X_i;\theta)$: Relative Risk
X_i: i^{th} category of the exposure variable

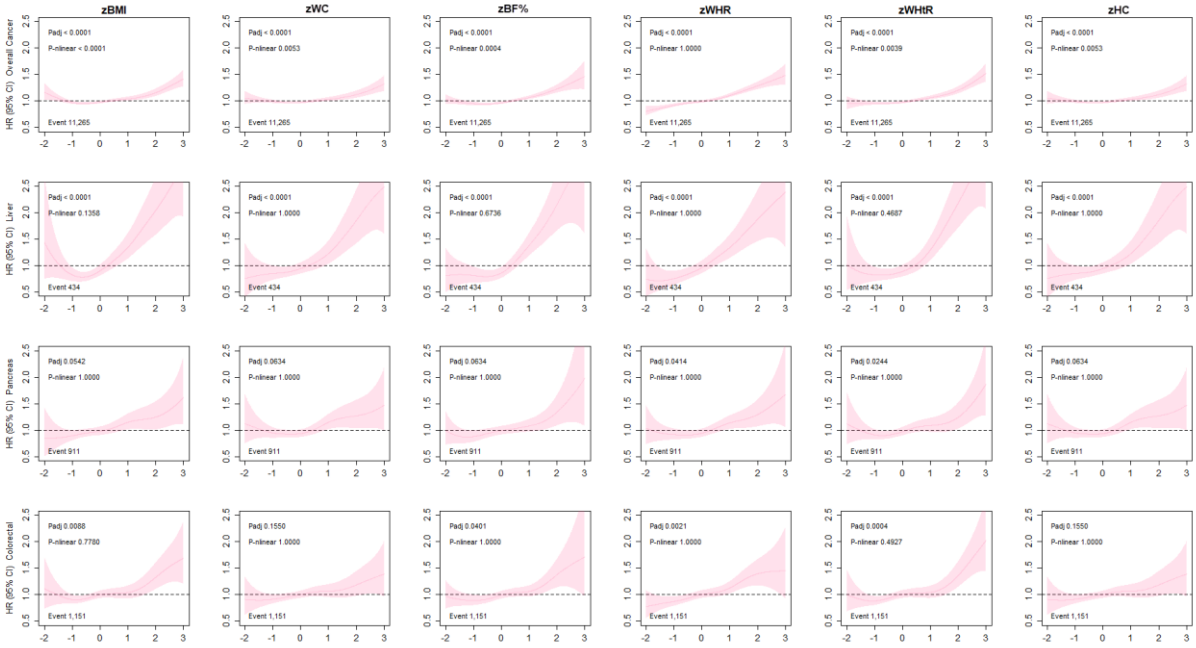

Figure S2. Association of adiposity markers with overall, liver, pancreas and colorectal cancer mortality.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

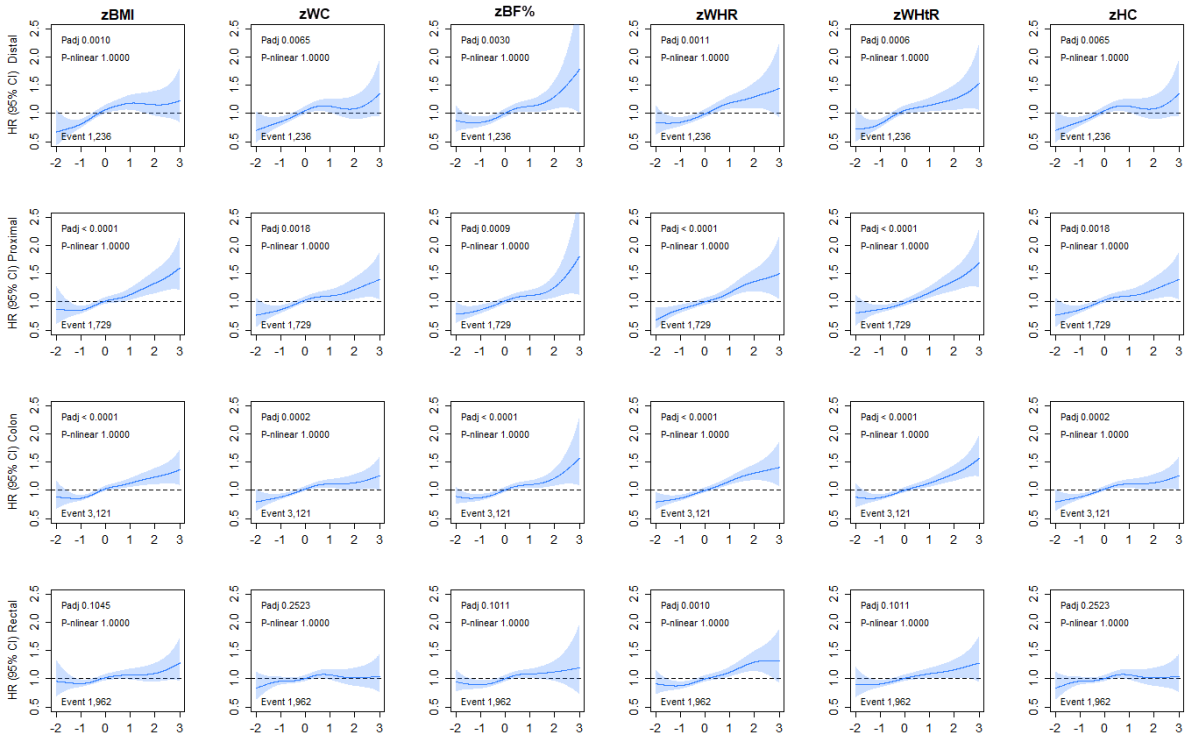

Figure S3. Association of adiposity markers with distal, proximal, colon and rectal cancer incidence.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

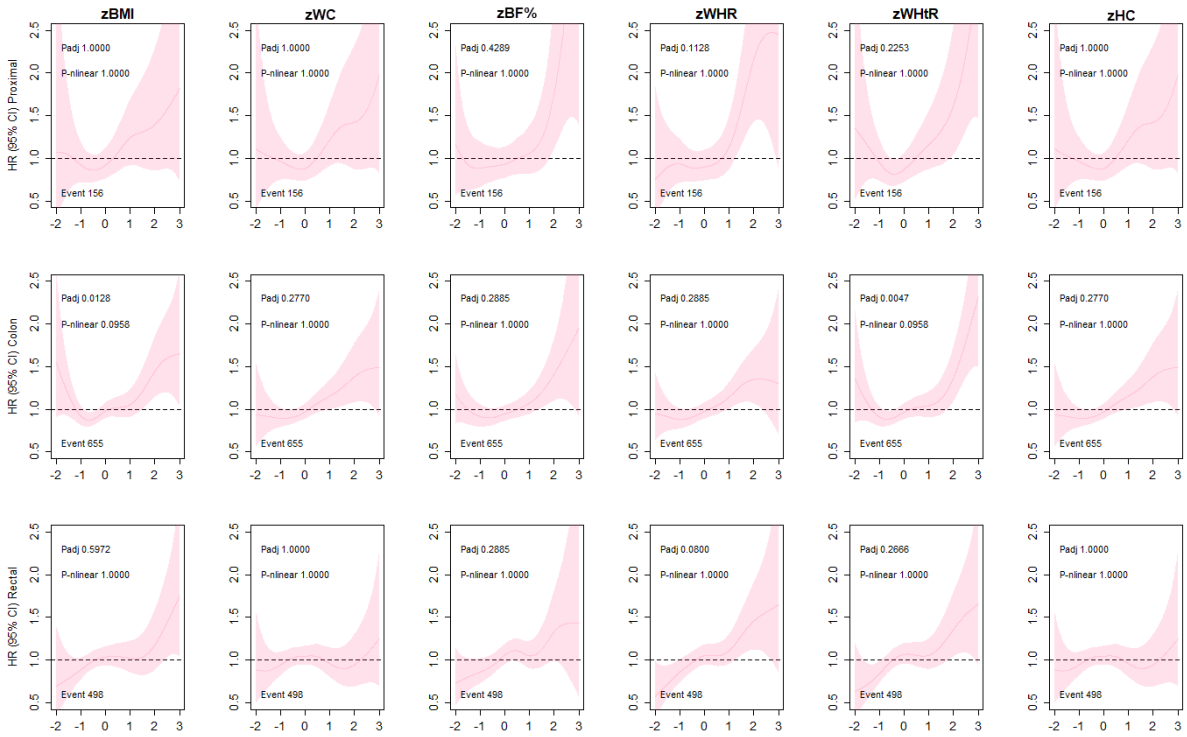

Figure S4. Association of adiposity markers with proximal, colon and rectal cancer mortality.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

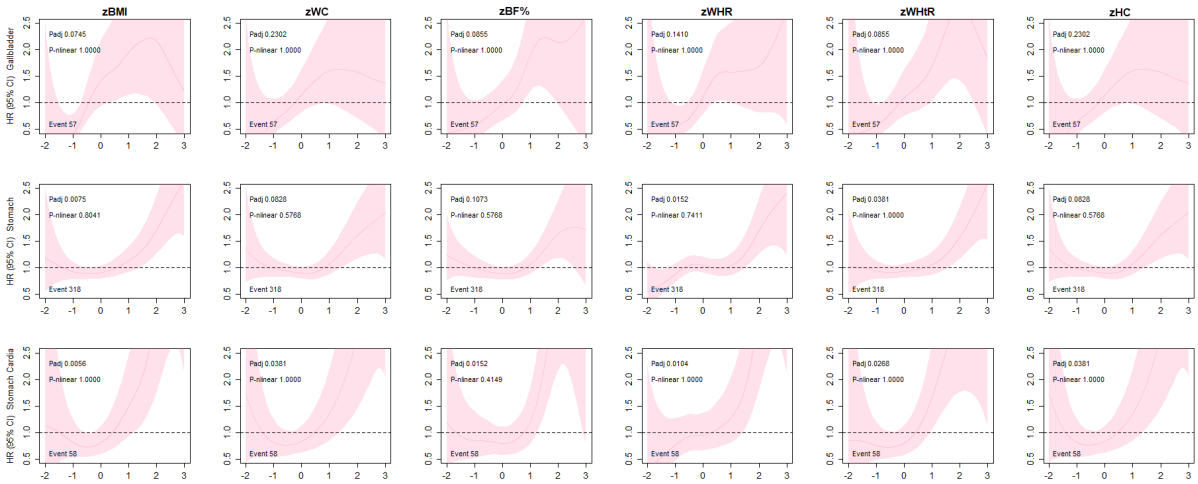

Figure S5. Association of adiposity markers with gallbladder and stomach cancer mortality.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. Stomach no cardia did not have enough cases to perform the analyses for mortality (n>5). P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

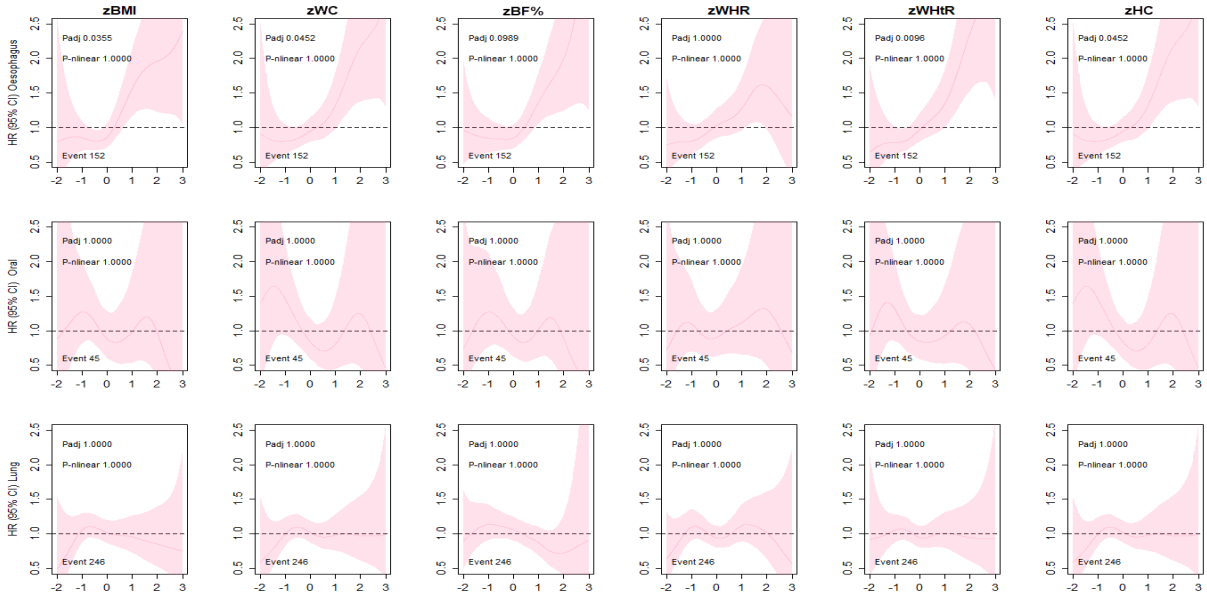

Figure S6. Association of adiposity markers oesophagus, oral and lung cancer mortality in never smokers.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. Oesophagus upper did not have enough cases to perform the mortality analysis (n>5). P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

Figure S7. Association of adiposity markers with lymphatic cancer mortality. Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

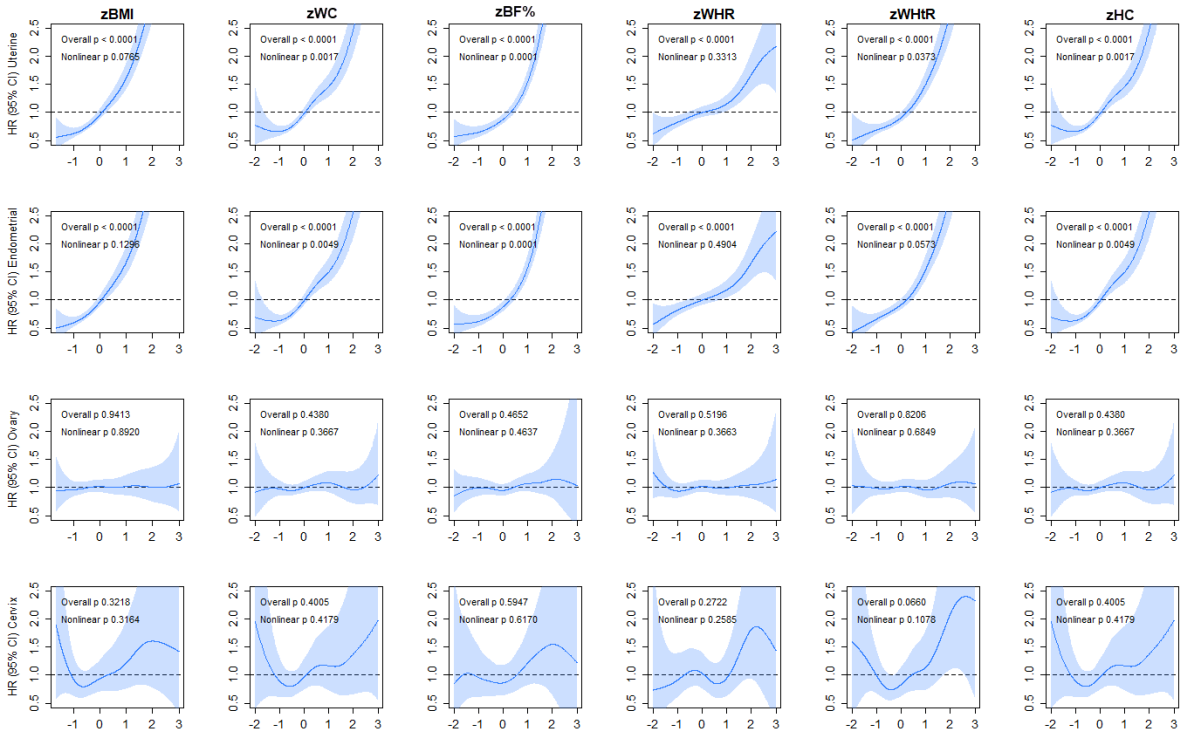

Figure S8. Association of adiposity markers with uterine, endometrial, ovary and cervical cancer incidence adjusted for sex-related covariates.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour, physical activity, age menarche, hormonal replacement, age first and las live birth. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. Stomach no cardia did not have enough cases to perform the analyses for mortality (n>5). P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

Figure S9. Association of adiposity markers with uterine, endometrial, ovary and cervical cancer mortality.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

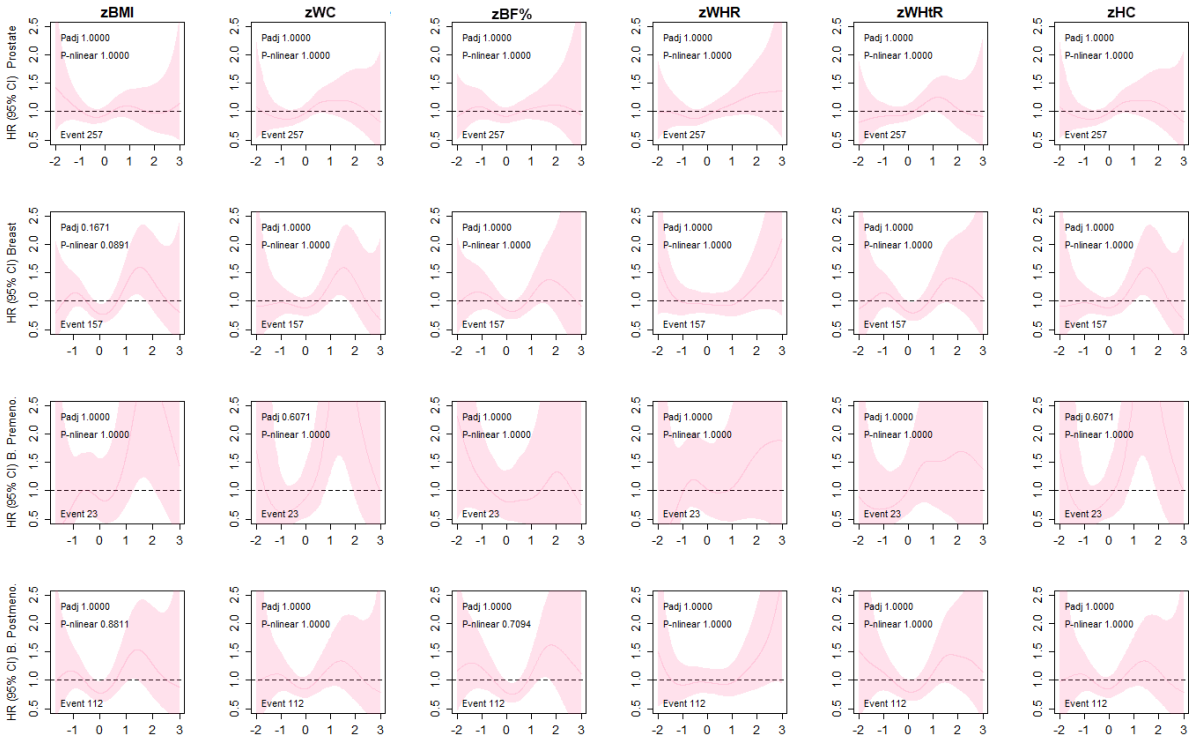

Figure S10. Association of adiposity markers with prostate, testicular cancer in men and breast cancer in pre- and post-menopausal women mortality. Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

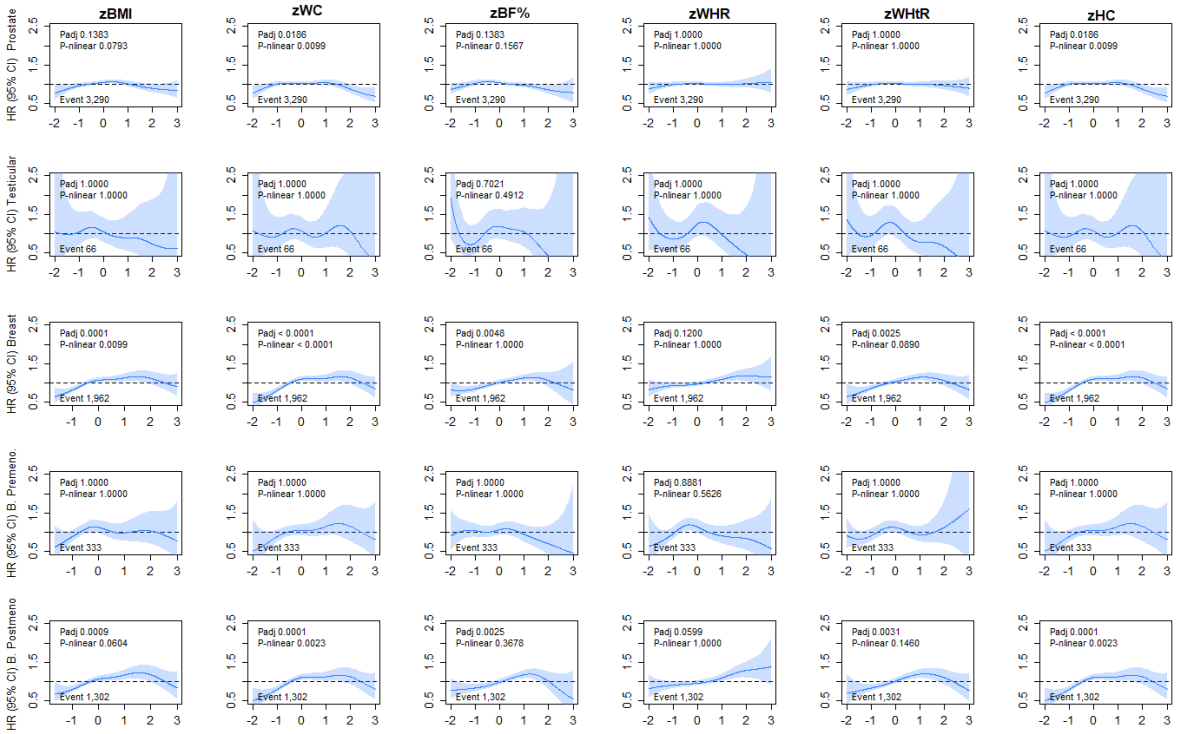

Figure S11. Association of adiposity markers with prostate, testicular, and breast cancer incidence additionally adjusted for sex-related covariates. Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour, physical activity, hormonal replacement, age menarche, age first and last live birth for breast and family history for prostate cancer. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

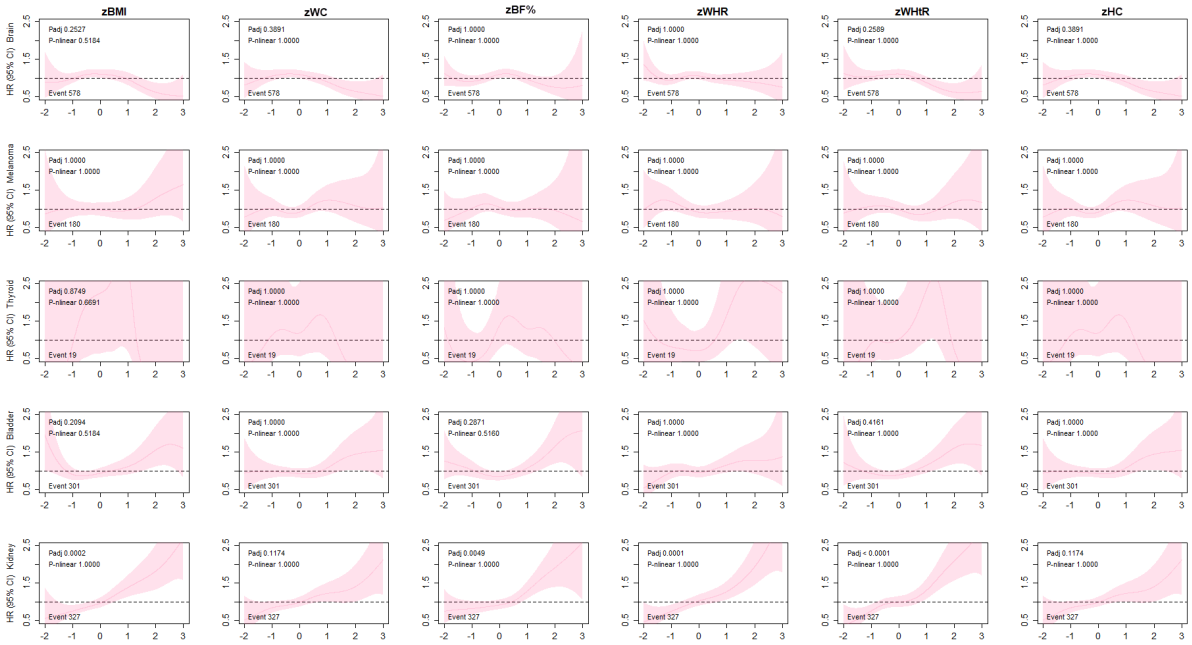

Figure S12. Association of adiposity markers with brain, melanoma, thyroid, bladder and kidney cancer mortality.

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity, melanoma cancer also was adjusted for sun exposition. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear). Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

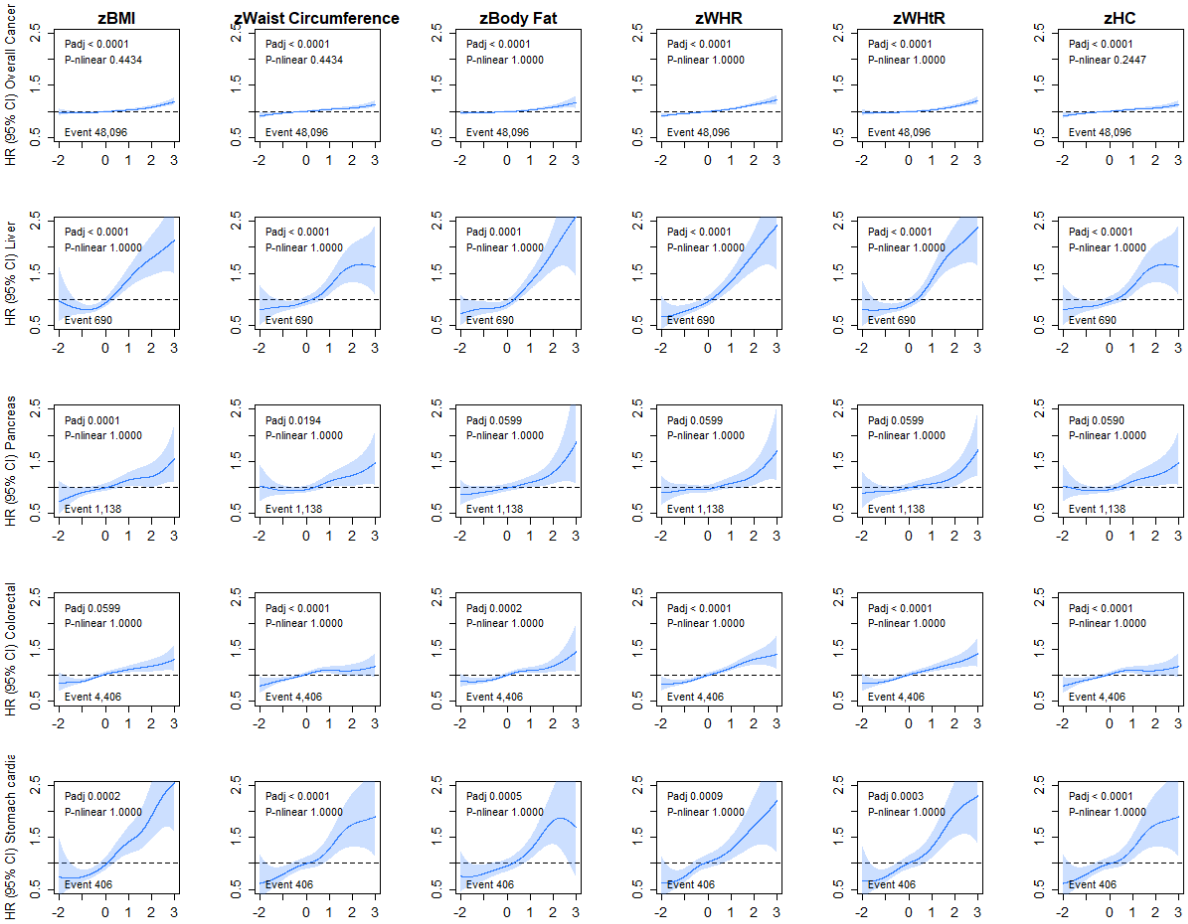

Figure S13. Association of Adiposity markers with overall, liver, pancreas, colorectal cancer and stomach cardia incidence with underweight people Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear).

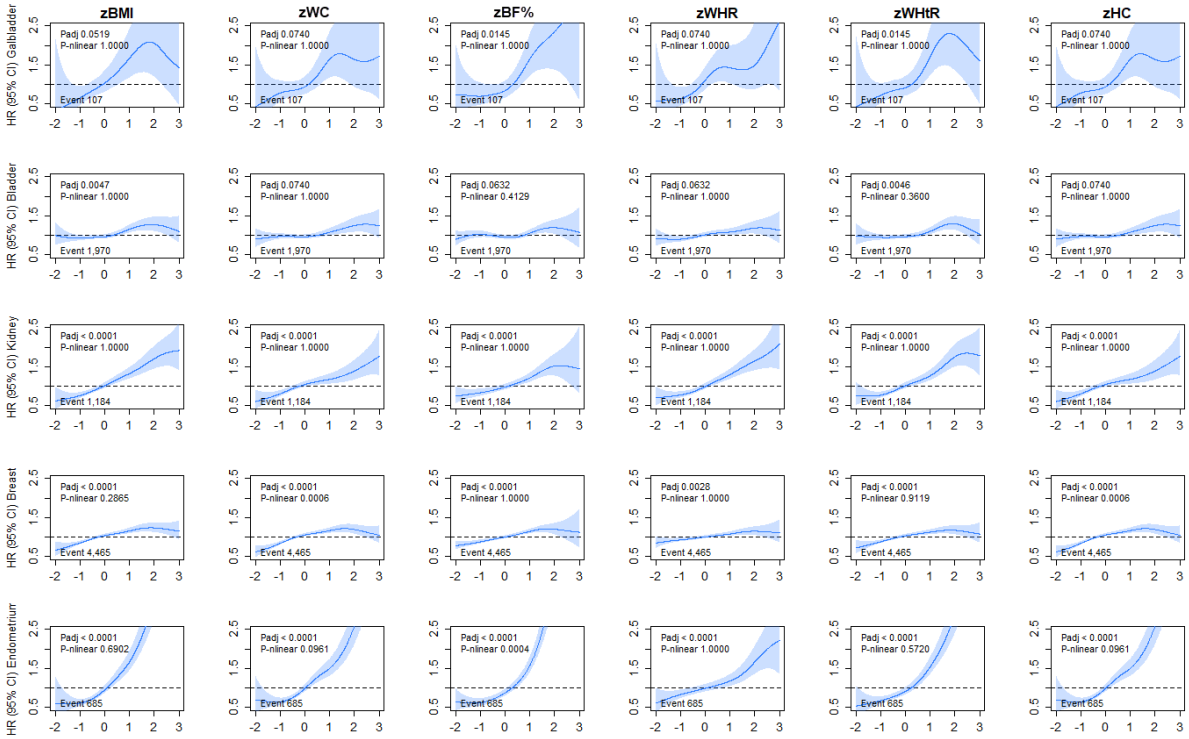

Figure S14. Association of Adiposity markers with gallbladder, bladder, kidney, breast and endometrium cancer incidence with underweight people

Penalised splines were used to present the association between adiposity markers and cancer outcomes. The adiposity markers were sex-standardised to 1-SD increment. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference, HR: Hazard Ratio. Shaded areas represent 95% confidence intervals. P-value for linear association corrected for multiple testing (Padj), p-value for non-linear association corrected for multiple testing (P-nlinear).

Table S1: Association of adiposity markers with incidence from 24 cancer sites per 1 SD increase in adiposity markers.

Cancer site	Total/Event	BMI	WC	BF%	HC	WHR	WHTR
Overall	429,976/47,882	**1.03 (1.02; 1.04)**	**1.04 (1.03; 1.05)**	**1.03 (1.02; 1.04)**	**1.04 (1.03; 1.05)**	**1.05 (1.04; 1.06)**	**1.04 (1.03; 1.05)**
Bladder	437,087/1,961	**1.09 (1.04; 1.14)**	1.07 (1.02; 1.11)	1.05 (1.00; 1.10)	1.07 (1.02; 1.11)	**1.08 (1.03; 1.13)**	**1.08 (1.03; 1.13)**
Brain	437,279/688	0.95 (0.88; 1.04)	0.94 (0.87; 1.02)	1.01 (0.93; 1.10)	0.94 (0.87; 1.02)	1.01 (0.93; 1.09)	0.95 (0.87; 1.03)
Breast	234,007/6,653	**1.08 (1.05; 1.11)**	**1.09 (1.06; 1.12)**	**1.10 (1.07; 1.13)**	**1.09 (1.06; 1.12)**	**1.07 (1.04; 1.09)**	**1.08 (1.05; 1.10)**
Breast Postmenopausal	139,546/4,168	**1.10 (1.07; 1.14)**	**1.11 (1.08; 1.15)**	**1.12 (1.08; 1.16)**	**1.11 (1.08; 1.15)**	**1.09 (1.05; 1.12)**	**1.10 (1.07; 1.14)**
Breast Premenopausal	58,701/1,442	0.99 (0.94; 1.05)	1.03 (0.97; 1.08)	1.04 (0.99; 1.10)	1.03 (0.97; 1.08)	1.00 (0.94; 1.06)	0.98 (0.92; 1.04)
Cervix	235,241/105	1.09 (0.90; 1.32)	1.09 (0.90; 1.31)	1.06 (0.86; 1.30)	1.09 (0.90; 1.31)	1.02 (0.84; 1.25)	1.09 (0.89; 1.33)
Colorectal	436,640/4,394	**1.10 (1.06; 1.13)**	**1.07 (1.04; 1.11)**	**1.09 (1.05; 1.13)**	**1.07 (1.04; 1.11)**	**1.13 (1.10; 1.17)**	**1.12 (1.08; 1.15)**
Colon	436859/3121	**1.12 (1.08; 1.16)**	**1.10 (1.06; 1.13)**	**1.10 (1.06; 1.15)**	**1.10 (1.06; 1.13)**	**1.14 (1.10; 1.18)**	**1.13 (1.09; 1.18)**
Distal	437155/1236	**1.13 (1.07; 1.20)**	**1.11 (1.05; 1.18)**	**1.13 (1.07; 1.21)**	**1.11 (1.05; 1.18)**	**1.15 (1.08; 1.22)**	**1.15 (1.09; 1.22)**
Proximal	437154/1729	**1.14 (1.09; 1.20)**	**1.12 (1.07; 1.17)**	**1.13 (1.07; 1.19)**	**1.12 (1.07; 1.17)**	**1.16 (1.10; 1.22)**	**1.16 (1.11; 1.22)**
Rectum	437092/1962	**1.07 (1.02; 1.12)**	1.04 (1.00; 1.09)	**1.07 (1.02; 1.13)**	1.04 (1.00; 1.09)	**1.11 (1.06; 1.17)**	**1.09 (1.04; 1.14)**
Endometrium	235,095/1,068	**1.73 (1.65; 1.82)**	**1.63 (1.55; 1.71)**	**1.78 (1.66; 1.91)**	**1.63 (1.55; 1.71)**	**1.29 (1.22; 1.37)**	**1.69 (1.60; 1.79)**
Gallbladder	437,380/107	**1.33 (1.12; 1.58)**	**1.28 (1.08; 1.52)**	**1.50 (1.21; 1.86)**	**1.28 (1.08; 1.52)**	**1.32 (1.10; 1.59)**	**1.40 (1.16; 1.67)**
Kidney	437,240/1,178	**1.26 (1.20; 1.33)**	**1.18 (1.12; 1.25)**	**1.21 (1.13; 1.28)**	**1.18 (1.12; 1.25)**	**1.27 (1.20; 1.34)**	**1.26 (1.19; 1.33)**
Leukaemia	437,276/1,129	1.07 (1.01; 1.14)	1.08 (1.02; 1.15)	1.02 (0.96; 1.09)	1.08 (1.02; 1.15)	1.07 (1.01; 1.14)	1.05 (0.99; 1.12)
Liver	437,322/688	**1.27 (1.19; 1.36)**	**1.19 (1.11; 1.27)**	**1.32 (1.21; 1.43)**	**1.19 (1.11; 1.27)**	**1.32 (1.23; 1.42)**	**1.33 (1.23; 1.43)**
Lung	241,636/509	0.99 (0.90; 1.09)	0.92 (0.92; 1.11)	1.00 (0.91; 1.10)	0.91 (0.87; 0.95)	1.07 (0.97; 1.17)	1.01 (0.92; 1.12)
Lymphatic	436,947/3,540	**1.07 (1.04; 1.11)**	**1.08 (1.04; 1.12)**	1.02 (0.99; 1.06)	**1.08 (1.04; 1.12)**	**1.06 (1.02; 1.10)**	1.05 (1.01; 1.08)
Melanoma	437,124/1,893	1.06 (1.01; 1.11)	**1.10 (1.05; 1.15)**	1.03 (0.98; 1.08)	**1.10 (1.05; 1.15)**	0.98 (0.93; 1.03)	1.01 (0.96; 1.06)
Multiple Myeloma	437,306/763	1.10 (1.02; 1.18)	1.08 (1.01; 1.16)	1.02 (0.95; 1.11)	1.08 (1.01; 1.16)	1.09 (1.01; 1.17)	1.08 (1.00; 1.16)
Non-Hodgkin	437,155/1,681	1.03 (0.98; 1.09)	1.05 (1.00; 1.11)	0.99 (0.94; 1.05)	1.06 (1.00; 1.11)	1.04 (0.99; 1.09)	1.01 (0.96; 1.06)
Oesophagus	241,662/297	**1.23 (1.11; 1.38)**	**1.21 (1.09; 1.35)**	**1.19 (1.05; 1.35)**	**1.21 (1.09; 1.35)**	**1.18 (1.05; 1.32)**	**1.26 (1.13; 1.42)**
Oral	241,661/290	0.96 (0.85; 1.09)	0.99 (0.87; 1.11)	0.90 (0.79; 1.02)	0.99 (0.87; 1.11)	0.95 (0.84; 1.08)	0.97 (0.85; 1.10)
Ovary	23,111/852	1.01 (0.93; 1.08)	1.02 (0.95; 1.10)	1.03 (0.96; 1.11)	1.02 (0.95; 1.10)	1.03 (0.96; 1.10)	1.01 (0.94; 1.09)
Pancreas	437,271/1,136	**1.12 (1.06; 1.19)**	**1.09 (1.03; 1.16)**	**1.11 (1.04; 1.18)**	**1.09 (1.03; 1.16)**	1.08 (1.02; 1.15)	**1.10 (1.03; 1.17)**
Prostate	436,554/7,252	**0.92 (0.90; 0.95)**	**0.94 (0.91; 0.96)**	**0.91 (0.89; 0.93)**	**0.94 (0.91; 0.96)**	**0.95 (0.92; 0.97)**	**0.92 (0.90; 0.95)**
Stomach	437,294/747	**1.24 (1.15; 1.32)**	**1.14 (1.07; 1.22)**	**1.16 (1.08; 1.26)**	**1.14 (1.07; 1.22)**	**1.21 (1.13; 1.30)**	**1.22 (1.13; 1.31)**
S. Cardia	437338/404	**1.35 (1.23; 1.47)**	**1.25 (1.14; 1.36)**	**1.27 (1.15; 1.42)**	**1.25 (1.14; 1.36)**	**1.29 (1.17; 1.42)**	**1.33 (1.21; 1.46)**
S. No Cardia	437370/187	1.11 (0.97; 1.28)	0.99 (0.86; 1.14)	1.08 (0.93; 1.26)	0.99 (0.86; 1.14)	**1.26 (1.09; 1.45**)	1.15 (1.00; 1.33)
Testis	437,379/67	0.86 (0.66; 1.13)	0.93 (0.72; 1.20)	0.84 (0.65; 1.08)	0.93 (0.72; 1.20)	0.90 (0.70; 1.17)	0.83 (0.63; 1.09)
Thyroid	437,340/284	1.11 (0.99; 1.25)	1.13 (1.01; 1.27)	1.11 (0.98; 1.26)	1.13 (1.01; 1.27)	**1.23 (1.10; 1.38)**	1.19 (1.05; 1.33)
Uterine	235,061/1,188	**1.68 (1.60; 1.75)**	**1.58 (1.51; 1.66)**	**1.70 (1.60; 1.82)**	**1.58 (1.51; 1.66)**	**1.26 (1.19; 1.34)**	**1.63 (1.55; 1.72)**

Data is presented as Hazar Ratio and their 95% confidence interval. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference. P-values are corrected for multiple testing by using the Holm's method. In **bold** are those associations statistically significant after correcting for multiple testing.

Table S2: Association of adiposity markers with mortality from 24 cancer sites per 1 SD increase in adiposity markers.

Cancer site	Total/Event	BMI	WC	BF%	HC	WHR	WHTR
Overall	435,378/11,265	**1.05 (1.03; 1.07)**	**1.03 (1.02; 1.07)**	**1.06 (1.04; 1.08)**	**1.04 (1.02; 1.06)**	**1.08 (1.06; 1.10)**	**1.08 (1.06; 1.10)**
Bladder	437,383/301	1.11 (0.99; 1.24)	1.10 (0.98; 1.22)	1.09 (0.97; 1.24)	1.10 (0.98; 1.22)	1.13 (1.01; 1.27)	1.16 (1.03; 1.30)
Brain	437,339/578	0.92 (0.84; 1.01)	0.91 (0.83; 0.99)	0.98 (0.90; 1.07)	0.91 (0.83; 0.99)	0.95 (0.87; 1.04)	0.89 (0.82; 0.98)
Breast	235,252/477	**1.12 (1.02; 1.23)**	**1.13 (1.03; 1.23)**	**1.17 (1.06; 1.30)**	**1.13 (1.03; 1.23)**	1.09 (1.00; 1.20)	**1.11 (1.01; 1.22)**
Breast Postmenopausal	140,365/307	1.14 (1.01; 1.28)	1.13 (1.01; 1.26)	1.19 (1.05; 1.36)	1.13 (1.01; 1.26)	1.15 (1.03; 1.29)	1.15 (1.02; 1.29)
Breast Premenopausal	58,936/89	1.16 (0.96; 1.41)	1.19 (0.99; 1.45)	1.23 (1.00; 1.52)	1.19 (0.99; 1.45)	0.98 (0.78; 1.23)	1.06 (0.86; 1.32)
Cervix	235,263/21	1.24 (0.83; 1.85)	1.12 (0.74; 1.69)	1.36 (0.85; 2.19)	1.12 (0.74; 1.69)	1.00 (0.64; 1.55)	1.10 (0.71; 1.70)
Colorectal	437,336/1,151	**1.11 (1.04; 1.17)**	1.08 (1.02; 1.15)	1.10 (1.03; 1.17)	1.08 (1.02; 1.15)	**1.14 (1.08; 1.21)**	**1.13 (1.06; 1.20)**
Colon	437355/655	1.11 (1.02; 1.20)	**1.13 (1.04; 1.22)**	1.08 (0.99; 1.18)	**1.13 (1.04; 1.22)**	1.12 (1.04; 1.22)	1.12 (1.04; 1.22)
Proximal	437390/156	1.16 (0.99; 1.36)	1.14 (0.98; 1.34)	1.16 (0.97; 1.38)	1.14 (0.98; 1.34)	1.26 (1.08; 1.47)	1.22 (1.04; 1.43)
Rectum	437374/498	1.10 (1.01; 1.21)	1.02 (0.93; 1.12)	1.13 (1.03; 1.24)	1.02 (0.93; 1.12)	**1.17 (1.07; 1.28)**	1.14 (1.04; 1.25)
Endometrium	235,263/128	**1.70 (1.47; 1.97)**	**1.56 (1.34; 1.81)**	**1.84 (1.50; 2.26)**	**1.56 (1.34; 1.81)**	**1.35 (1.14; 1.60)**	**1.67 (1.42; 1.97)**
Gallbladder	437,389/57	1.38 (1.09; 1.75)	1.30 (1.03; 1.64)	**1.61 (1.20; 2.16)**	1.30 (1.03; 1.64)	1.41 (1.11; 1.80)	**1.50 (1.18; 1.92)**
Kidney	437,371/327	**1.32 (1.19; 1.46)**	**1.21 (1.09; 1.34)**	**1.30 (1.15; 1.46)**	**1.21 (1.09; 1.34)**	**1.36 (1.23; 1.50)**	**1.37 (1.24; 1.53)**
Leukaemia	437,367/405	1.10 (0.99; 1.22)	1.12 (1.02; 1.23)	1.05 (0.95; 1.17)	1.12 (1.02; 1.23)	1.01 (0.91; 1.12)	1.05 (0.95; 1.16)
Liver	437,361/434	**1.31 (1.21; 1.43)**	**1.25 (1.15; 1.36)**	**1.37 (1.23; 1.51)**	**1.25 (1.15; 1.36)**	**1.31 (1.20; 1.43)**	**1.36 (1.24; 1.49)**
Lung	241,684/246	0.996(0.83; 1.10)	1.00 (0.87; 1.15)	1.00 (0.91; 1.10)	0.91 (0.80; 1.05)	1.02 (0.90; 1.17)	0.98 (0.85; 1.13)
Lymphatic	437,333/1,063	**1.10 (1.04; 1.18)**	**1.10 (1.04; 1.17)**	1.03 (0.96; 1.10)	**1.10 (1.04; 1.17)**	1.08 (1.01; 1.15)	1.07 (1.01; 1.15)
Melanoma	437,387/180	1.06 (0.90; 1.24)	1.07 (0.92; 1.25)	1.02 (0.87; 1.19)	1.07 (0.92; 1.25)	0.92 (0.79; 1.08)	0.99 (0.84; 1.16)
Multiple Myeloma	437,383/221	1.13 (0.98; 1.30)	1.21 (1.06; 1.37)	1.03 (0.89; 1.19)	1.21 (1.06; 1.37)	1.00 (0.87; 1.15)	1.08 (0.94; 1.24)
Non-Hodgkin	437,372/416	1.07 (0.96; 1.18)	1.01 (0.91; 1.11)	0.98 (0.88; 1.09)	1.01 (0.91; 1.11)	**1.18 (1.07; 1.30)**	1.07 (0.97; 1.19)
Oesophagus	241,696/152	**1.35 (1.16; 1.56)**	1.35 (1.18; 1.55)	**1.31 (1.10; 1.55)**	1.35 (1.18; 1.55)	**1.22 (1.04; 1.43)**	**1.40 (1.20; 1.63)**
Oral	241,700/45	0.86 (0.63; 1.18)	0.82 (0.60; 1.12)	0.94 (0.69; 1.27)	0.82 (0.60; 1.12)	1.06 (0.78; 1.42)	0.89 (0.65; 1.21)
Ovary	235,252/390	1.02 (0.91; 1.13)	1.03 (0.93; 1.15)	1.03 (0.93; 1.16)	1.03 (0.93; 1.15)	0.95 (0.86; 1.06)	0.98 (0.88; 1.09)
Pancreas	437,320/911	**1.13 (1.06; 1.21)**	1.10 (1.03; 1.17)	1.11 (1.03; 1.19)	1.10 (1.03; 1.17)	1.11 (1.03; 1.18)	**1.11 (1.04; 1.19)**
Prostate	202,112/632	1.04 (0.96; 1.13)	1.04 (0.96; 1.12)	1.01 (0.93; 1.10)	1.04 (0.96; 1.12)	1.11 (1.02; 1.21)	1.07 (0.98; 1.16)
Stomach	437,368/318	**1.22 (1.10; 1.35)**	1.12 (1.01; 1.24)	1.09 (0.97; 1.22)	1.12 (1.01; 1.24)	**1.20 (1.07; 1.34)**	**1.19 (1.06; 1.33)**
S. Cardia	437390/58	1.55 (1.26; 1.92)	1.40 (1.14; 1.73)	1.47 (1.11; 1.94)	1.40 (1.14; 1.73)	1.53 (1.29; 1.80)	1.56 (1.23; 1.97)
Thyroid	437,390/19	1.11 (0.58; 2.12)	0.77 (0.37; 1.60)	1.13 (0.54; 2.36)	0.77 (0.37; 1.60)	2.01 (1.16; 3.48)	1.51 (0.81; 2.80)
Uterine	235,260/193	**1.54 (1.36; 1.75)**	**1.45 (1.28; 1.64)**	**1.59 (1.35; 1.87)**	**1.45 (1.28; 1.64)**	**1.22 (1.06; 1.41)**	**1.48 (1.29; 1.70)**

Data is presented as Hazar Ratio and their 95% confidence interval. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference. P-values are corrected for multiple testing by using the Holm's method. In **bold** are those associations statistically significant after correcting for multiple testing.

Table S3: C-Index for the predictive ability of BMI versus other adiposity markers.

	BMI	Fat %		WC	
	C (95% CI)	ΔC (95% CI)	P	ΔC (95% CI)	P
Incidence					
Overall	0.6546 (0.6521 to 0.6570)	-0.0003 (-0.0038 to 0.0031)	0.85	<0.0001 (-0.0035 to 0.0035)	0.99
Bladder	0.7764 (0.7658 to 0.7871)	-0.0005 (-0.0157 to 0.0146)	0.95	-0.0006 (-0.0158 to 0.0145)	0.93
Brain	0.6277 (0.6078 to 0.6477)	-0.0008 (-0.0290 to 0.0274)	0.96	-0.0005 (-0.0288 to 0.0277)	0.97
Colorectal	0.6789 (0.6695 to 0.6882)	-0.0016 (-0.0148 to 0.0116)	0.81	-0.0003 (-0.0135 to 0.0129)	0.96
Gall bladder	0.7313 (0.6822 to 0.7805)	-0.0041 (-0.0737 to 0.0655)	0.91	0.0006 (-0.0689 to 0.0701)	0.99
Kidney	0.7171 (0.7021 to 0.7322)	-0.0063 (-0.0276 to 0.0150)	0.56	-0.0042 (-0.0255 to 0.0171)	0.70
Leukaemia	0.6924 (0.6769 to 0.7080)	-0.0013 (-0.0233 to 0.0207)	0.90	0.0001 (-0.0218 to 0.0221)	0.99
Liver	0.7270 (0.7071 to 0.7469)	-0.0006 (-0.0288 to 0.0275)	0.96	-0.0020 (-0.0302 to 0.0261)	0.89
Lung	0.8210 (0.8130 to 0.8289)	-0.0008 (-0.0121 to 0.0104)	0.88	0.0003 (-0.0110 to 0.0116)	0.96
Lymphoma	0.6712 (0.6623 to 0.6801)	-0.0005 (-0.0131 to 0.0121)	0.94	0.0004 (-0.0122 to 0.0130)	0.95
Melanoma	0.6239 (0.6118 to 0.6359)	<0.0001 (-0.0171 to 0.0170)	1.00	0.0014 (-0.0156 to 0.0185)	0.87
Multiple myeloma	0.6797 (0.6604 to 0.6989)	0.0007 (-0.0266 to 0.0279)	0.96	-0.0002 (-0.0274 to 0.0270)	0.99
Non-Hodgkin lymphoma	0.6637 (0.6508 to 0.6766)	-0.0001 (-0.0183 to 0.0181)	0.99	0.0006 (-0.0176 to 0.0188)	0.95
Oesophageal	0.7703 (0.7545 to 0.7862)	<0.0001 (-0.0224 to 0.0225)	1.00	-0.0010 (-0.0234 to 0.0214)	0.93
Oral	0.6761 (0.6583 to 0.6940)	0.0011 (-0.0241 to 0.0264)	0.93	0.0002 (-0.0250 to 0.0255)	0.99
Pancreatic	0.7006 (0.6849 to 0.7163)	-0.0022 (-0.0244 to 0.0200)	0.84	-0.0002 (-0.0224 to 0.0220)	0.99
Stomach	0.7474 (0.7291 to 0.7657)	-0.0049 (-0.0309 to 0.0211)	0.71	-0.0021 (-0.0280 to 0.0239)	0.88
Thyroid	0.6389 (0.6083 to 0.6694)	0.0005 (-0.0427 to 0.0437)	0.98	0.0009 (-0.0423 to 0.0441)	0.97
Breast	0.5565 (0.5500 to 0.5629)	0.0003 (-0.0088 to 0.0095)	0.94	0.0009 (-0.0083 to 0.0100)	0.85
Cervix	0.5933 (0.5458 to 0.6408)	-0.0025 (-0.0697 to 0.0647)	0.94	-0.0011 (-0.0683 to 0.0661)	0.97
Endometrium	0.6974 (0.6815 to 0.7132)	-0.0135 (-0.0359 to 0.0090)	0.24	-0.0114 (-0.0339 to 0.0111)	0.32
Ovary	0.6213 (0.6036 to 0.6389)	0.0013 (-0.0237 to 0.0262)	0.92	0.0005 (-0.0244 to 0.0255)	0.97
Uterine	0.6801 (0.6651 to 0.6951)	-0.0127 (-0.0340 to 0.0085)	0.24	-0.0099 (-0.0312 to 0.0113)	0.36
Prostate	0.6866 (0.6802 to 0.6929)	0.0013 (-0.0077 to 0.0102)	0.78	-0.0003 (-0.0092 to 0.0087)	0.95
Testis	0.6376 (0.5746 to 0.7007)	-0.0013 (-0.0904 to 0.0879)	0.98	-0.0008 (-0.0899 to 0.0884)	0.99
Mortality					
Overall	0.7269 (0.7219 to 0.7320)	-0.0012 (-0.0083 to 0.0059)	0.74	<0.0001 (-0.0072 to 0.0071)	0.99

Bladder	0.8150 (0.7871 to 0.8428)	-0.0027 (-0.0422 to 0.0368)	0.89	-0.0001 (-0.0395 to 0.0393)	1.00
Brain	0.6544 (0.6316 to 0.6773)	-0.0023 (-0.0346 to 0.0300)	0.89	-0.0002 (-0.0325 to 0.0320)	0.99
Colorectal	0.6916 (0.6702 to 0.7130)	-0.0013 (-0.0316 to 0.0290)	0.93	0.0008 (-0.0295 to 0.0310)	0.96
Gallbladder	0.7754 (0.7108 to 0.8400)	-0.0114 (-0.1034 to 0.0805)	0.81	<0.0001 (-0.0914 to 0.0914)	1.00
Kidney	0.7694 (0.7413 to 0.7976)	-0.0030 (-0.0428 to 0.0369)	0.88	-0.0045 (-0.0444 to 0.0354)	0.83
Leukaemia	0.7516 (0.7257 to 0.7775)	-0.0016 (-0.0382 to 0.0350)	0.93	0.0005 (-0.0361 to 0.0371)	0.98
Liver	0.7373 (0.7120 to 0.7625)	-0.0019 (-0.0377 to 0.0339)	0.92	-0.0009 (-0.0367 to 0.0349)	0.96
Lung	0.8498 (0.8403 to 0.8593)	-0.0011 (-0.0145 to 0.0124)	0.88	0.0001 (-0.0133 to 0.0136)	0.98
Lymphoma	0.7445 (0.7284 to 0.7606)	-0.0010 (-0.0238 to 0.0218)	0.93	<0.0001 (-0.0228 to 0.0228)	1.00
Melanoma	0.6848 (0.6431 to 0.7265)	-0.0012 (-0.0601 to 0.0578)	0.97	0.0005 (-0.0585 to 0.0594)	0.99
Multiple myeloma	0.7582 (0.7230 to 0.7933)	0.0013 (-0.0484 to 0.0509)	0.96	0.0026 (-0.0470 to 0.0523)	0.92
Non-Hodgkin lymphoma	0.7381 (0.7120 to 0.7642)	-0.0018 (-0.0387 to 0.0351)	0.92	-0.0006 (-0.0375 to 0.0363)	0.97
Oesophageal	0.7915 (0.7705 to 0.8125)	0.0008 (-0.0289 to 0.0306)	0.96	-0.0013 (-0.0311 to 0.0285)	0.93
Oral	0.7927 (0.7529 to 0.8325)	-0.0003 (-0.0566 to 0.0561)	0.99	<0.0001 (-0.0563 to 0.0563)	1.00
Pancreatic	0.7085 (0.6907 to 0.7262)	-0.0024 (-0.0275 to 0.0227)	0.85	-0.0003 (-0.0254 to 0.0248)	0.98
Stomach	0.7388 (0.7095 to 0.7682)	-0.0050 (-0.0466 to 0.0366)	0.81	-0.0028 (-0.0444 to 0.0387)	0.89
Thyroid	0.7801 (0.6681 to 0.8922)	0.0047 (-0.1533 to 0.1627)	0.95	-0.0004 (-0.1590 to 0.1581)	1.00
Breast	0.5917 (0.5660 to 0.6174)	0.0050 (-0.0314 to 0.0413)	0.79	0.0022 (-0.0342 to 0.0385)	0.91
Cervix	0.7750 (0.6622 to 0.8878)	0.0095 (-0.1490 to 0.1681)	0.91	-0.0011 (-0.1606 to 0.1585)	0.99
Endometrium	0.7922 (0.7476 to 0.8367)	-0.0043 (-0.0675 to 0.0589)	0.89	-0.0097 (-0.0731 to 0.0537)	0.76
Ovary	0.6819 (0.6538 to 0.7100)	-0.0007 (-0.0404 to 0.0391)	0.97	-0.0001 (-0.0399 to 0.0396)	1.00
Uterine	0.7587 (0.7212 to 0.7963)	-0.0019 (-0.0551 to 0.0513)	0.94	-0.0038 (-0.0570 to 0.0494)	0.89
Prostate	0.7727 (0.7521 to 0.7932)	-0.0013 (-0.0304 to 0.0277)	0.93	<0.0001 (-0.0291 to 0.0290)	1.00
Testis	0.9708 (0.8372 to 1.1045)	-0.0077 (-0.2082 to 0.1927)	0.94	-0.0083 (-0.2096 to 0.1930)	0.94

ΔC (95% CI): Difference between C-indices with the model with BMI and their 95% confidence interval, P: p-value for ΔC

Table S3 continuation: C-Index for adiposity markers.

	HC		WHR		WHtR	
	ΔC (95% CI)	**P**	**ΔC (95% CI)**	**P**	**ΔC (95% CI)**	**P**
Incidence						
Overall	<0.0001 (-0.0035 to 0.0035)	0.99	0.0003 (-0.0032 to 0.0037)	0.88	<0.0001 (-0.0034 to 0.0035)	0.99
Bladder	-0.0006 (-0.0158 to 0.0145)	0.93	-0.0003 (-0.0154 to 0.0148)	0.97	0.0001 (-0.0151 to 0.0152)	0.99
Brain	-0.0005 (-0.0288 to 0.0277)	0.97	-0.0008 (-0.0290 to 0.0275)	0.96	0.0004 (-0.0278 to 0.0286)	0.98
Colorectal	-0.0003 (-0.0135 to 0.0129)	0.96	0.0010 (-0.0122 to 0.0142)	0.88	0.0006 (-0.0126 to 0.0138)	0.93
Gallbladder	0.0006 (-0.0689 to 0.0701)	0.99	-0.0014 (-0.0710 to 0.0681)	0.97	0.0023 (-0.0671 to 0.0718)	0.95
Kidney	-0.0042 (-0.0255 to 0.0171)	0.70	<0.0001 (-0.0213 to 0.0212)	1.00	-0.0009 (-0.0221 to 0.0204)	0.94
Leukaemia	0.0001 (-0.0218 to 0.0221)	0.99	<0.0001 (-0.0220 to 0.0220)	1.00	-0.0004 (-0.0224 to 0.0216)	0.97
Liver	-0.0020 (-0.0302 to 0.0261)	0.89	0.0039 (-0.0241 to 0.0320)	0.78	0.0032 (-0.0249 to 0.0313)	0.83
Lung	0.0003 (-0.0110 to 0.0116)	0.96	0.0009 (-0.0103 to 0.0122)	0.87	-0.0001 (-0.0114 to 0.0111)	0.98
Lymphoma	0.0004 (-0.0122 to 0.0130)	0.95	-0.0001 (-0.0127 to 0.0125)	0.99	-0.0003 (-0.0129 to 0.0123)	0.96
Melanoma	0.0014 (-0.0156 to 0.0185)	0.87	-0.0003 (-0.0173 to 0.0168)	0.98	-0.0007 (-0.0177 to 0.0164)	0.94
Multiple myeloma	-0.0002 (-0.0274 to 0.0270)	0.99	-0.0003 (-0.0276 to 0.0269)	0.98	-0.0002 (-0.0274 to 0.0270)	0.99
Non-Hodgkin lymphoma	0.0006 (-0.0176 to 0.0188)	0.95	0.0003 (-0.0180 to 0.0185)	0.98	-0.0002 (-0.0184 to 0.0180)	0.98
Oesophageal	-0.0010 (-0.0234 to 0.0214)	0.93	0.0029 (-0.0195 to 0.0252)	0.80	0.0024 (-0.0200 to 0.0248)	0.83
Oral	0.0002 (-0.0250 to 0.0255)	0.99	-0.0004 (-0.0256 to 0.0249)	0.98	<0.0001 (-0.0253 to 0.0252)	1.00
Pancreatic	-0.0002 (-0.0224 to 0.0220)	0.99	0.0006 (-0.0216 to 0.0228)	0.96	-0.0001 (-0.0223 to 0.0221)	0.99
Stomach	-0.0021 (-0.0280 to 0.0239)	0.88	-0.0006 (-0.0265 to 0.0254)	0.97	-0.0007 (-0.0266 to 0.0253)	0.96
Thyroid	0.0009 (-0.0423 to 0.0441)	0.97	0.0020 (-0.0412 to 0.0452)	0.93	0.0017 (-0.0415 to 0.0449)	0.94
Breast	0.0009 (-0.0083 to 0.0100)	0.85	-0.0026 (-0.0118 to 0.0065)	0.58	-0.0016 (-0.0107 to 0.0076)	0.73
Cervix	-0.0011 (-0.0683 to 0.0661)	0.97	-0.0006 (-0.0678 to 0.0665)	0.98	0.0009 (-0.0663 to 0.0681)	0.98
Endometrium	-0.0114 (-0.0339 to 0.0111)	0.32	**-0.0425 (-0.0651 to -0.0199)**	**0.0002**	-0.0080 (-0.0304 to 0.0145)	0.49
Ovary	0.0005 (-0.0244 to 0.0255)	0.97	0.0004 (-0.0246 to 0.0254)	0.98	<0.0001 (-0.0250 to 0.0250)	1.00
Uterine	-0.0099 (-0.0312 to 0.0113)	0.36	**-0.0392 (-0.0605 to -0.0179)**	**0.0003**	-0.0076 (-0.0288 to 0.0136)	0.48
Prostate	-0.0003 (-0.0092 to 0.0087)	0.95	-0.0005 (-0.0095 to 0.0084)	0.91	<0.0001 (-0.0090 to 0.0089)	0.99
Testis	-0.0008 (-0.0899 to 0.0884)	0.99	-0.0004 (-0.0896 to 0.0887)	0.99	-0.0011 (-0.0902 to 0.0881)	0.98
Mortality						
Overall	<0.0001 (-0.0072 to 0.0071)	0.99	0.0012 (-0.0059 to 0.0083)	0.75	0.0005 (-0.0067 to 0.0076)	0.90

Bladder	-0.0001 (-0.0395 to 0.0393)	1.00	0.0001 (-0.0393 to 0.0395)	1.00	0.0005 (-0.0389 to 0.0399)	0.98
Brain	-0.0002 (-0.0325 to 0.0320)	0.99	-0.0007 (-0.0330 to 0.0316)	0.97	0.0011 (-0.0311 to 0.0334)	0.95
Colorectal	0.0008 (-0.0295 to 0.0310)	0.96	0.0013 (-0.0290 to 0.0315)	0.93	0.0004 (-0.0299 to 0.0307)	0.98
Gall bladder	<0.0001 (-0.0914 to 0.0914)	1.00	0.0010 (-0.0903 to 0.0923)	0.98	0.0035 (-0.0877 to 0.0946)	0.94
Kidney	-0.0045 (-0.0444 to 0.0354)	0.83	0.0016 (-0.0382 to 0.0414)	0.94	0.0016 (-0.0381 to 0.0414)	0.94
Leukaemia	0.0005 (-0.0361 to 0.0371)	0.98	-0.0013 (-0.0379 to 0.0354)	0.95	-0.0009 (-0.0375 to 0.0357)	0.96
Liver	-0.0009 (-0.0367 to 0.0349)	0.96	0.0017 (-0.0340 to 0.0374)	0.93	0.0019 (-0.0339 to 0.0376)	0.92
Lung	0.0001 (-0.0133 to 0.0136)	0.98	0.0004 (-0.0131 to 0.0138)	0.96	-0.0004 (-0.0139 to 0.0131)	0.95
Lymphoma	<0.0001 (-0.0228 to 0.0228)	1.00	-0.0004 (-0.0233 to 0.0224)	0.97	-0.0004 (-0.0232 to 0.0225)	0.97
Melanoma	0.0005 (-0.0585 to 0.0594)	0.99	<0.0001 (-0.0590 to 0.0589)	1.00	-0.0015 (-0.0605 to 0.0575)	0.96
Multiple myeloma	0.0026 (-0.0470 to 0.0523)	0.92	-0.0032 (-0.0530 to 0.0466)	0.90	-0.0011 (-0.0508 to 0.0487)	0.97
Non-Hodgkin lymphoma	-0.0006 (-0.0375 to 0.0363)	0.97	0.0031 (-0.0337 to 0.0400)	0.87	0.0005 (-0.0364 to 0.0374)	0.98
Oesophageal	-0.0013 (-0.0311 to 0.0285)	0.93	0.0045 (-0.0251 to 0.0342)	0.76	0.0036 (-0.0260 to 0.0333)	0.81
Oral	<0.0001 (-0.0563 to 0.0563)	1.00	0.0014 (-0.0549 to 0.0576)	0.96	0.0008 (-0.0555 to 0.0571)	0.98
Pancreatic	-0.0003 (-0.0254 to 0.0248)	0.98	0.0008 (-0.0243 to 0.0259)	0.95	-0.0003 (-0.0254 to 0.0248)	0.98
Stomach	-0.0028 (-0.0444 to 0.0387)	0.89	-0.0007 (-0.0422 to 0.0408)	0.97	-0.0011 (-0.0426 to 0.0404)	0.96
Thyroid	-0.0004 (-0.1590 to 0.1581)	1.00	0.0047 (-0.1532 to 0.1627)	0.95	0.0035 (-0.1546 to 0.1616)	0.97
Breast	0.0022 (-0.0342 to 0.0385)	0.91	-0.0023 (-0.0386 to 0.0341)	0.90	0.0001 (-0.0363 to 0.0364)	1.00
Cervix	-0.0011 (-0.1606 to 0.1585)	0.99	-0.0018 (-0.1614 to 0.1579)	0.98	-0.0022 (-0.1619 to 0.1574)	0.98
Endometrium	-0.0097 (-0.0731 to 0.0537)	0.76	-0.0160 (-0.0796 to 0.0477)	0.62	-0.0020 (-0.0651 to 0.0611)	0.95
Ovary	-0.0001 (-0.0399 to 0.0396)	1.00	0.0002 (-0.0396 to 0.0399)	0.99	-0.0001 (-0.0399 to 0.0396)	0.99
Uterine	-0.0038 (-0.0570 to 0.0494)	0.89	-0.0118 (-0.0653 to 0.0416)	0.66	-0.0028 (-0.0561 to 0.0504)	0.92
Prostate	<0.0001 (-0.0291 to 0.0290)	1.00	0.0008 (-0.0283 to 0.0298)	0.96	0.0003 (-0.0288 to 0.0293)	0.98
Testis	-0.0083 (-0.2096 to 0.1930)	0.94	0.0197 (-0.1347 to 0.1741)	0.80	0.0005 (-0.1879 to 0.1888)	1.00

ΔC (95% CI): Difference between C-indices with the model with BMI and their 95% confidence interval, P: p-value for ΔC

Table S4: Association of adiposity markers with incidence from 24 cancer sites after accounting for competing risk.

Cancer site	Total/event	BMI	WC	BF%	WHR	WHTR	HC
Overall	425,604/43,458	**1.08 (1.07; 1.09)**	**1.07 (1.06; 1.08)**	**1.06 (1.05; 1.07)**	**1.09 (1.08; 1.10)**	**1.09 (1.08; 1.10)**	**1.07 (1.06; 1.08)**
Bladder	436,819/1,688	**1.13 (1.07; 1.19)**	**1.10 (1.05; 1.15)**	**1.08 (1.03; 1.14)**	**1.13 (1.08; 1.19)**	**1.13 (1.08; 1.19)**	**1.10 (1.05; 1.15)**
Brain	437,199/603	1.00 (0.91; 1.09)	0.97 (0.89; 1.06)	1.05 (0.96; 1.15)	1.03 (0.95; 1.12)	0.99 (0.91; 1.08)	0.97 (0.89; 1.06)
Breast	435,620/6,203	**1.16 (1.13; 1.19)**	**1.16 (1.13; 1.19)**	**1.18 (1.15; 1.22)**	**1.14 (1.11; 1.17)**	**1.17 (1.14; 1.20)**	**1.16 (1.13; 1.19)**
Breast Postmenopausal	139,183/3,804	**1.16 (1.12; 1.20)**	**1.16 (1.12; 1.20)**	**1.16 (1.12; 1.20)**	**1.12 (1.08; 1.16)**	**1.16 (1.12; 1.20)**	**1.16 (1.12; 1.20)**
Breast Premenopausal	58,656/1,396	1.02 (0.97; 1.08)	1.06 (1.00; 1.12)	1.07 (1.01; 1.13)	1.02 (0.96; 1.08)	1.01 (0.95; 1.07)	1.06 (1.00; 1.12)
Cervix	437,358/94	1.21 (0.99; 1.47)	1.21 (1.00; 1.47)	1.15 (0.92; 1.42)	1.08 (0.88; 1.34)	1.21 (0.98; 1.48)	1.21 (1.00; 1.47)
Colorectal	436,183/3,936	**1.15 (1.11; 1.18)**	**1.11 (1.08; 1.15)**	**1.13 (1.09; 1.17)**	**1.19 (1.15; 1.23)**	**1.18 (1.14; 1.21)**	**1.11 (1.08; 1.15)**
Endometrium	437,123/968	**1.84 (1.75; 1.93)**	**1.71 (1.63; 1.79)**	**1.91 (1.78; 2.05)**	**1.37 (1.30; 1.45)**	**1.82 (1.72; 1.93)**	**1.71 (1.63; 1.79)**
Gallbladder	437,364/91	**1.46 (1.22; 1.76)**	**1.38 (1.15; 1.65)**	**1.61 (1.27; 2.03)**	**1.39 (1.15; 1.68)**	**1.55 (1.28; 1.89)**	**1.38 (1.15; 1.65)**
Kidney	437,072/1,008	**1.31 (1.23; 1.39)**	**1.21 (1.14; 1.28)**	**1.24 (1.16; 1.33)**	**1.33 (1.25; 1.41)**	**1.32 (1.24; 1.41)**	**1.21 (1.14; 1.28)**
Leukaemia	437,120/964	**1.15 (1.07; 1.22)**	**1.15 (1.08; 1.23)**	1.07 (1.00; 1.14)	**1.14 (1.07; 1.22)**	**1.13 (1.05; 1.21)**	**1.15 (1.08; 1.23)**
Liver	437,215/580	**1.34 (1.24; 1.44)**	**1.23 (1.14; 1.33)**	**1.38 (1.26; 1.51)**	**1.39 (1.29; 1.49)**	**1.41 (1.30; 1.52)**	**1.23 (1.14; 1.33)**
Lung	436,467/2,731	0.97 (0.93; 1.01)	0.95 (0.92; 0.99)	1.03 (0.99; 1.08)	**1.16 (1.11; 1.20)**	1.05 (1.01; 1.09)	0.95 (0.92; 0.99)
Lymphatic	436,523/3,105	**1.12 (1.08; 1.16)**	**1.12 (1.08; 1.17)**	1.06 (1.02; 1.10)	**1.11 (1.07; 1.15)**	**1.10 (1.06; 1.15)**	**1.12 (1.08; 1.17)**
Melanoma	436,931/1,698	**1.08 (1.03; 1.14)**	**1.12 (1.06; 1.17)**	1.04 (0.99; 1.10)	0.99 (0.94; 1.05)	1.03 (0.97; 1.08)	**1.12 (1.06; 1.17)**
Multiple Myeloma	437,217/672	**1.14 (1.05; 1.24)**	**1.13 (1.04; 1.22)**	1.06 (0.97; 1.15)	**1.14 (1.05; 1.23)**	**1.14 (1.05; 1.24)**	**1.13 (1.04; 1.22)**
Non-Hodgkin	436,948/1,473	1.07 (1.01; 1.13)	**1.08 (1.02; 1.14)**	1.01 (0.96; 1.07)	1.08 (1.02; 1.14)	1.05 (1.00; 1.12)	**1.08 (1.02; 1.14)**
Oesophagus	437,121/0,000	**1.26 (1.18; 1.35)**	**1.17 (1.09; 1.25)**	**1.27 (1.18; 1.37)**	**1.36 (1.28; 1.45)**	**1.35 (1.26; 1.44)**	**1.17 (1.09; 1.25)**
Oral	437,180/740	0.93 (0.86; 1.01)	0.93 (0.86; 1.01)	0.95 (0.88; 1.03)	1.05 (0.97; 1.13)	0.99 (0.91; 1.07)	0.93 (0.86; 1.01)
Ovary	437,172/787	1.08 (1.00; 1.16)	1.08 (1.00; 1.16)	1.09 (1.01; 1.18)	1.10 (1.02; 1.18)	1.09 (1.01; 1.17)	1.08 (1.00; 1.16)
Pancreas	437,125/990	**1.19 (1.11; 1.27)**	**1.14 (1.07; 1.22)**	**1.16 (1.08; 1.24)**	**1.15 (1.08; 1.23)**	**1.18 (1.11; 1.26)**	**1.14 (1.07; 1.22)**
Prostate	435,777/6,470	0.97 (0.94; 1.00)	0.97 (0.95; 1.00)	**0.94 (0.92; 0.97)**	0.99 (0.96; 1.01)	0.98 (0.95; 1.00)	0.97 (0.95; 1.00)
Stomach	437,192/645	**1.27 (1.17; 1.36)**	**1.15 (1.07; 1.24)**	**1.16 (1.07; 1.27)**	**1.27 (1.17; 1.37)**	**1.26 (1.17; 1.36)**	**1.15 (1.07; 1.24)**
Testis	437,375/63	0.91 (0.69; 1.20)	0.94 (0.72; 1.23)	0.85 (0.65; 1.10)	0.93 (0.71; 1.22)	0.86 (0.65; 1.14)	0.94 (0.72; 1.23)
Thyroid	437,309/253	1.16 (1.02; 1.31)	**1.19 (1.06; 1.34)**	1.13 (0.99; 1.29)	**1.21 (1.07; 1.37)**	**1.22 (1.08; 1.38)**	**1.19 (1.06; 1.34)**
Uterine	437,077/1,076	**1.79 (1.71; 1.88)**	**1.67 (1.59; 1.75)**	**1.83 (1.71; 1.95)**	**1.35 (1.28; 1.43)**	**1.77 (1.67; 1.86)**	**1.67 (1.59; 1.75)**

Data is presented as Hazar Ratio and their 95% confidence interval. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour and physical activity. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference. A landmark analysis was performed to reduce the potential for reverse causality, with follow-up commencing two years after recruitment. P-values are corrected for multiple testing by using the Holm's method. In **bold** are those associations statistically significant after correcting for multiple testing. Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629).

Table S5: Association of adiposity markers with incidence from 24 cancer sites per 1 SD increase in adiposity markers with height as covariate.

Cancer site	Total/Event	BMI	WC	BF%	HC	WHR	WHTR
Overall	429,976/47,882	**1.04 (1.03; 1.05)**	**1.02 (1.01; 1.03)**	**1.03 (1.02; 1.04)**	**1.02 (1.01; 1.03)**	**1.05 (1.04; 1.06)**	**1.05 (1.04; 1.06)**
Bladder	437,087/1,961	**1.09 (1.04; 1.14)**	1.06 (1.01; 1.11)	1.05 (1.00; 1.10)	1.06 (1.01; 1.11)	**1.08 (1.03; 1.13)**	**1.09 (1.04; 1.14)**
Brain	437,279/688	0.95 (0.88; 1.04)	0.93 (0.85; 1.01)	1.01 (0.93; 1.10)	0.93 (0.85; 1.01)	1.01 (0.93; 1.09)	0.95 (0.88; 1.03)
Breast	234,007/6,653	**1.09 (1.06; 1.12)**	**1.08 (1.05; 1.10)**	**1.09 (1.06; 1.12)**	**1.08 (1.05; 1.10)**	**1.07 (1.05; 1.10)**	**1.10 (1.07; 1.13)**
Breast Postmenopausal	139,546/4,168	**1.11 (1.08; 1.15)**	**1.10 (1.06; 1.13)**	**1.11 (1.07; 1.15)**	**1.10 (1.06; 1.13)**	**1.09 (1.06; 1.13)**	**1.13 (1.09; 1.17)**
Breast Premenopausal	58,700/1,442	1.00 (0.95; 1.06)	1.00 (0.95; 1.06)	1.04 (0.98; 1.09)	1.00 (0.95; 1.06)	1.00 (0.95; 1.06)	1.00 (0.94; 1.06)
Cervix	235,241/105	1.09 (0.90; 1.32)	1.09 (0.90; 1.32)	1.06 (0.86; 1.31)	1.09 (0.90; 1.32)	1.02 (0.84; 1.25)	1.09 (0.89; 1.33)
Colorectal	436,640/4,394	**1.10 (1.07; 1.13)**	**1.07 (1.03; 1.10)**	**1.09 (1.06; 1.13)**	**1.07 (1.03; 1.10)**	**1.13 (1.10; 1.17)**	**1.13 (1.10; 1.17)**
Colon	436,859/3,121	**1.12 (1.08; 1.16)**	**1.08 (1.05; 1.12)**	**1.11 (1.06; 1.15)**	**1.08 (1.05; 1.12)**	**1.14 (1.10; 1.19)**	**1.15 (1.11; 1.19)**
Distal	437,155/1,236	**1.14 (1.07; 1.20)**	**1.11 (1.04; 1.17)**	**1.13 (1.07; 1.21)**	**1.11 (1.04; 1.17)**	**1.15 (1.09; 1.22)**	**1.17 (1.10; 1.24)**
Proximal	437,154/1,729	**1.15 (1.09; 1.20)**	**1.11 (1.06; 1.16)**	**1.13 (1.07; 1.19)**	**1.11 (1.06; 1.16)**	**1.16 (1.11; 1.22)**	**1.18 (1.12; 1.24)**
Rectum	437,092/1,962	**1.07 (1.02; 1.12)**	1.03 (0.99; 1.08)	1.07 (1.02; 1.13)	1.03 (0.99; 1.08)	**1.12 (1.06; 1.17)**	**1.10 (1.05; 1.15)**
Endometrium	235,095/1,068	**1.74 (1.66; 1.82)**	**1.64 (1.56; 1.72)**	**1.78 (1.66; 1.91)**	**1.64 (1.56; 1.72)**	**1.29 (1.22; 1.37)**	**1.72 (1.63; 1.82)**
Gallbladder	437,380/107	**1.34 (1.13; 1.59)**	1.28 (1.08; 1.52)	**1.50 (1.21; 1.86)**	1.28 (1.08; 1.52)	**1.32 (1.10; 1.59)**	**1.42 (1.18; 1.71)**
Kidney	437,240/1,178	**1.27 (1.20; 1.34)**	**1.17 (1.10; 1.23)**	**1.21 (1.14; 1.29)**	**1.17 (1.10; 1.23)**	**1.27 (1.20; 1.35)**	**1.29 (1.22; 1.36)**
Leukaemia	437,276/1,129	1.08 (1.02; 1.15)	1.05 (0.99; 1.12)	1.02 (0.96; 1.09)	1.05 (0.99; 1.12)	1.07 (1.01; 1.14)	1.08 (1.01; 1.15)
Liver	437,322/688	**1.27 (1.19; 1.36)**	**1.19 (1.11; 1.28)**	**1.32 (1.21; 1.43)**	**1.19 (1.11; 1.28)**	**1.32 (1.23; 1.42)**	**1.34 (1.25; 1.44)**
Lung	241,636/509	1.00 (0.90; 1.10)	0.99 (0.90; 1.09)	1.00 (0.91; 1.10)	0.99 (0.90; 1.09)	1.07 (0.98; 1.17)	1.04 (0.94; 1.14)
Lymphatic	436,947/3,540	**1.08 (1.04; 1.12)**	1.05 (1.01; 1.09)	1.02 (0.99; 1.06)	1.05 (1.01; 1.09)	**1.06 (1.02; 1.10)**	**1.07 (1.04; 1.11)**
Melanoma	437,124/1,893	1.07 (1.02; 1.12)	1.06 (1.01; 1.12)	1.03 (0.98; 1.08)	1.06 (1.01; 1.12)	0.98 (0.94; 1.03)	1.03 (0.98; 1.09)
Multiple Myeloma	437,306/763	1.11 (1.03; 1.19)	1.06 (0.98; 1.14)	1.02 (0.95; 1.10)	1.06 (0.98; 1.14)	1.09 (1.01; 1.18)	1.10 (1.02; 1.19)
Non-Hodgkin	437,155/1,681	1.04 (0.99; 1.10)	1.02 (0.97; 1.07)	0.99 (0.94; 1.05)	1.02 (0.97; 1.07)	1.04 (0.99; 1.09)	1.04 (0.98; 1.09)
Oesophagus	241,662/297	**1.24 (1.11; 1.38)**	**1.22 (1.09; 1.36)**	1.19 (1.05; 1.35)	**1.22 (1.09; 1.36)**	1.18 (1.05; 1.32)	**1.27 (1.14; 1.43)**
Oral	241,661/290	0.96 (0.85; 1.09)	0.98 (0.87; 1.12)	0.90 (0.79; 1.02)	0.98 (0.87; 1.12)	0.95 (0.84; 1.08)	0.97 (0.85; 1.10)
Ovary	235,111/0,852	1.01 (0.94; 1.09)	1.01 (0.94; 1.09)	1.03 (0.95; 1.11)	1.01 (0.94; 1.09)	1.03 (0.96; 1.11)	1.03 (0.95; 1.10)
Pancreas	437,271/1,136	**1.13 (1.06; 1.19)**	1.08 (1.02; 1.15)	**1.11 (1.04; 1.18)**	1.08 (1.02; 1.15)	1.09 (1.02; 1.15)	**1.11 (1.04; 1.18)**
Stomach	437,294/0,747	**1.24 (1.16; 1.32)**	**1.14 (1.06; 1.22)**	**1.17 (1.08; 1.26)**	**1.14 (1.06; 1.22)**	**1.21 (1.13; 1.30)**	**1.23 (1.14; 1.32)**
S. Cardia	437,338/0,404	**1.35 (1.24; 1.48)**	**1.24 (1.13; 1.36)**	**1.28 (1.15; 1.42)**	**1.24 (1.13; 1.36)**	**1.29 (1.17; 1.42)**	**1.36 (1.23; 1.49)**
S. No Cardia	437,370/0,187	1.11 (0.96; 1.27)	1.01 (0.87; 1.17)	1.08 (0.93; 1.26)	1.01 (0.87; 1.17)	**1.26 (1.09; 1.45)**	1.14 (0.99; 1.32)
Prostate	201,290/7,250	0.97 (0.94; 0.99)	0.96 (0.94; 0.99)	**0.95 (0.92; 0.97)**	0.96 (0.94; 0.99)	0.99 (0.96; 1.01)	0.97 (0.94; 0.99)
Testis	202,114/66	0.91 (0.70; 1.18)	0.91 (0.69; 1.19)	0.90 (0.69; 1.16)	0.91 (0.69; 1.19)	0.93 (0.72; 1.21)	0.90 (0.68; 1.17)
Thyroid	437,340/284	1.12 (1.00; 1.26)	1.11 (0.99; 1.24)	1.11 (0.98; 1.26)	1.11 (0.99; 1.24)	**1.24 (1.10; 1.39)**	**1.22 (1.08; 1.37)**
Uterine	235,061/1,188	**1.68 (1.61; 1.76)**	**1.59 (1.52; 1.67)**	**1.70 (1.60; 1.82)**	**1.59 (1.52; 1.67)**	**1.26 (1.20; 1.34)**	**1.66 (1.57; 1.75)**

Data is presented as Hazar Ratio and their 95% confidence interval. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour physical activity and height. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference. P-values are corrected for multiple testing by using the Holm's method. In **bold** are those associations statistically significant after correcting for multiple testing. Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629)

Table S6: Association of adiposity markers with mortality from 24 cancer sites per 1 SD increase in adiposity markers with height as covariate.

Cancer site	Total/Event	BMI	WC	BF%	HC	WHR	WHTR
Overall	436,695/11,265	**1.06 (1.04; 1.08)**	1.03 (1.01; 1.05)	1.06 (1.04; 1.08)	**1.11 (1.09; 1.14)**	**1.09 (1.07; 1.11)**	1.03 (1.01; 1.05)
Bladder	437,383/301	1.11 (0.99; 1.24)	1.10 (0.99; 1.24)	1.09 (0.97; 1.24)	1.13 (1.01; 1.27)	1.16 (1.03; 1.31)	1.10 (0.99; 1.24)
Brain	437,339/578	0.93 (0.85; 1.01)	0.90 (0.82; 0.98)	0.98 (0.90; 1.07)	0.95 (0.87; 1.04)	0.90 (0.82; 0.98)	0.90 (0.82; 0.98)
Breast	235,252/477	1.13 (1.03; 1.24)	1.11 (1.01; 1.21)	1.17 (1.05; 1.29)	1.10 (1.00; 1.21)	1.15 (1.04; 1.26)	1.11 (1.01; 1.21)
Breast Postmenopausal	140,365/307	1.16 (1.03; 1.30)	1.11 (0.98; 1.24)	1.18 (1.04; 1.35)	1.16 (1.03; 1.30)	1.18 (1.05; 1.33)	1.11 (0.98; 1.24)
Breast Premenopausal	58,935/89	1.18 (0.97; 1.43)	1.16 (0.95; 1.41)	1.21 (0.98; 1.50)	0.99 (0.79; 1.24)	1.11 (0.89; 1.38)	1.16 (0.95; 1.41)
Cervix	235,263/21	1.24 (0.83; 1.85)	1.13 (0.74; 1.71)	1.37 (0.85; 2.20)	1.00 (0.64; 1.55)	1.10 (0.70; 1.71)	1.13 (0.74; 1.71)
Colorectal	437,336/1,151	**1.11 (1.04; 1.18)**	1.07 (1.01; 1.14)	1.10 (1.03; 1.17)	**1.15 (1.08; 1.22)**	**1.15 (1.08; 1.22)**	1.07 (1.01; 1.14)
Colon	437,355/655	1.12 (1.03; 1.21)	1.10 (1.02; 1.19)	1.08 (0.99; 1.18)	1.13 (1.04; 1.22)	**1.16 (1.07; 1.26)**	1.10 (1.02; 1.19)
Distal	437,392/91	0.85 (0.67; 1.07)	0.95 (0.76; 1.20)	0.95 (0.76; 1.19)	0.96 (0.77; 1.20)	0.94 (0.75; 1.19)	0.95 (0.76; 1.20)
Proximal	437,390/156	1.17 (1.00; 1.37)	1.11 (0.95; 1.31)	1.16 (0.97; 1.38)	1.26 (1.08; 1.48)	1.26 (1.07; 1.48)	1.11 (0.95; 1.31)
Rectum	437,374/498	1.10 (1.00; 1.21)	1.04 (0.95; 1.14)	1.13 (1.02; 1.24)	**1.17 (1.07; 1.28)**	1.13 (1.03; 1.25)	1.04 (0.95; 1.14)
Endometrium	235,263/128	**1.71 (1.48; 1.98)**	**1.56 (1.35; 1.81)**	1.84 (1.50; 2.26)	**1.35 (1.14; 1.60)**	**1.70 (1.44; 2.01)**	**1.56 (1.35; 1.81)**
Gallbladder	437,389/57	1.38 (1.09; 1.75)	1.31 (1.04; 1.66)	1.61 (1.20; 2.16)	1.41 (1.11; 1.79)	**1.51 (1.18; 1.94)**	1.31 (1.04; 1.66)
Kidney	437,371/327	**1.32 (1.19; 1.46)**	**1.22 (1.10; 1.35)**	1.30 (1.15; 1.46)	**1.36 (1.23; 1.50)**	**1.38 (1.24; 1.54)**	**1.22 (1.10; 1.35)**
Leukaemia	437,367/405	1.11 (1.00; 1.23)	1.09 (0.99; 1.21)	1.06 (0.95; 1.18)	1.02 (0.92; 1.12)	1.08 (0.97; 1.20)	1.09 (0.99; 1.21)
Liver	437,361/434	**1.32 (1.21; 1.44)**	**1.25 (1.14; 1.36)**	1.37 (1.23; 1.52)	**1.31 (1.20; 1.44)**	**1.39 (1.27; 1.52)**	**1.25 (1.14; 1.36)**
Lung	241,684/246	0.97 (0.84; 1.11)	0.97 (0.84; 1.12)	0.91 (0.80; 1.05)	0.97 (0.84; 1.12)	1.03 (0.90; 1.17)	1.00 (0.87; 1.16)
Lymphatic	437,333/1,063	**1.11 (1.05; 1.18)**	1.07 (1.01; 1.14)	1.03 (0.96; 1.10)	1.08 (1.02; 1.15)	1.10 (1.03; 1.18)	1.07 (1.01; 1.14)
Melanoma	437,387/180	1.06 (0.90; 1.24)	1.07 (0.91; 1.25)	1.02 (0.87; 1.20)	0.92 (0.79; 1.08)	0.99 (0.84; 1.17)	1.07 (0.91; 1.25)
Multiple Myeloma	437,383/221	1.15 (1.00; 1.32)	1.17 (1.02; 1.34)	1.03 (0.89; 1.19)	1.00 (0.87; 1.15)	1.12 (0.97; 1.29)	1.17 (1.02; 1.34)
Non-Hodgkin	437,372/416	1.07 (0.97; 1.19)	0.98 (0.89; 1.09)	0.98 (0.88; 1.09)	**1.18 (1.07; 1.30)**	1.10 (0.99; 1.21)	0.98 (0.89; 1.09)
Oesophagus	241,696/152	**1.35 (1.16; 1.56)**	**1.37 (1.19; 1.57)**	**1.30 (1.10; 1.55)**	**1.37 (1.19; 1.57)**	1.22 (1.04; 1.43)	**1.41 (1.21; 1.65)**
Oral	241,700/45	0.86 (0.63; 1.18)	0.79 (0.57; 1.10)	0.94 (0.69; 1.28)	0.79 (0.57; 1.10)	1.06 (0.78; 1.43)	0.90 (0.65; 1.23)
Ovary	235,252/390	1.02 (0.91; 1.14)	1.03 (0.92; 1.14)	1.03 (0.92; 1.15)	0.96 (0.86; 1.06)	0.99 (0.89; 1.11)	1.03 (0.92; 1.14)
Pancreas	437,320/911	**1.13 (1.06; 1.21)**	1.09 (1.02; 1.16)	1.11 (1.03; 1.19)	1.11 (1.04; 1.19)	**1.13 (1.05; 1.21)**	1.09 (1.02; 1.16)
Prostate	202,112/632	1.04 (0.96; 1.14)	1.02 (0.93; 1.11)	1.01 (0.93; 1.10)	1.11 (1.03; 1.21)	1.08 (1.00; 1.18)	1.02 (0.93; 1.11)
Stomach	437,368/318	**1.22 (1.10; 1.36)**	1.11 (1.00; 1.24)	1.09 (0.97; 1.23)	**1.20 (1.07; 1.34)**	**1.21 (1.08; 1.35)**	1.11 (1.00; 1.24)
S. Cardia	437,390/58	**1.58 (1.27; 1.95)**	1.35 (1.09; 1.68)	1.48 (1.12; 1.97)	**1.55 (1.30; 1.86)**	**1.64 (1.30; 2.08)**	1.35 (1.09; 1.68)
Thyroid	437,390/19	1.05 (0.64; 1.70)	1.02 (0.63; 1.66)	1.23 (0.74; 2.03)	1.38 (0.93; 2.05)	1.21 (0.75; 1.94)	1.02 (0.63; 1.66)
Uterine	235,260/193	**1.55 (1.37; 1.76)**	**1.46 (1.28; 1.65)**	1.59 (1.35; 1.87)	1.22 (1.06; 1.41)	**1.51 (1.32; 1.74)**	**1.46 (1.28; 1.65)**

Data is presented as Hazar Ratio and their 95% confidence interval. Analyses were adjusted age, sex, ethnicity, education, deprivation, smoking, dietary intake (alcohol, fruits & vegetables, red & processed meat, and oily fish), discretionary sedentary behaviour, physical activity and height. BMI: Body Mass Index, BF%: Body Fat Percentage, WHR: waits hip ratio, WHTR: Waist height ratio, HC: hip circumference. P-values are corrected for multiple testing by using the Holm's method. In **bold** are those associations statistically significant after correcting for multiple testing. Participants classified as underweight (BMI < 18.5 kg/m2 were excluded from the analyses (n = 2629)

Chapter 5. Combined association of general and central obesity with incidence and mortality of cancers in 22 sites

5.1 Abstract

Background: Body mass index (BMI) and waist circumference (WC) are measures of general and central obesity, respectively, and both have been shown to be associated with cancer. However, there is insufficient evidence of their combined association with the risk of cancer.

Objectives: This study aimed to investigate the associations of combinations of BMI and WC with cancer at 22 sites.

Methods: A total of 386,101 (54.5% women) UK Biobank participants aged from 37 to 73 y were included. The outcomes were incidence of and mortality from cancer at 22 sites. Participants were categorized as normal weight (BMI 18.5–24.9) or overweight. (Including obese, BMI ≥ 25) and as normal WC or centrally obese (WC ≥ 94 cm for men and ≥80 cm for women). Four mutually exclusive groups were derived: 1) normal weight without central obesity, 2) normal weight with central obesity, 3) overweight without central obesity, and 4) overweight with central obesity. We used Cox proportional hazards models to estimate HRs and 95% CIs.

Results: The mean follow-up period was 8.8 y. Compared with participants with normal weight and WC, men who were overweight and centrally obese had higher cancer incidence risk at 3 sites [stomach (HR: 1.75; 95% CI: 1.33, 2.32; Padj = 0.002), kidney (HR: 1.45; 95% CI: 1.17, 1.81; Padj = 0.016), and colorectal (HR: 1.31; 95% CI: 1.17, 1.47; Padj < 0.001) cancer]. Similar associations were found at 4 sites in women [endometrial (HR: 2.48; 95% CI: 2.06, 2.98; Padj < 0.001), uterine (HR: 2.23; 95% CI: 1.89, 2.64;

Padj < 0.001), kidney (HR: 1.84; 95% CI: 1.37, 2.46; Padj = 0.001), and breast (HR: 1.24; 95% CI: 1.16, 1.32; Padj < 0.001) cancer] and for all-cause cancer (HR: 1.07; 95% CI: 1.03, 1.10; Padj = 0.003). Only endometrial cancer mortality (HR: 3.28; 95% CI: 1.77, 6.07; Padj = 0.004) was significantly associated with being overweight and centrally obese.

Conclusions: The combination of general and central obesity was associated with a higher risk at several cancer sites and some associations were sex-specific. Am J Clin Nutr 2020;00:1–9.

5.2 Introduction

Body mass index (BMI) is the most commonly used indicator of adiposity and has been shown to be a strong risk factor for several non-communicable diseases (World Health Organization, 1997). However, whilst BMI is a measure of general obesity, it does not provide any information on body fat distribution (World Health Organization, 1997). This is important as body fat distribution, particularly accumulation of fat in central depots, has been shown to be a risk factor for several non-communicable diseases independent of general obesity. For example, waist circumference (WC), a measure of central obesity, has been demonstrated to be a stronger predictor of cardiometabolic risk than BMI (Ross et al., 2020, Lofgren et al., 2004, Barberio et al., 2019, Janssen et al., 2004). These studies indicate the potential utility of using WC, in addition to BMI, in clinical practice for cardio-metabolic risk assessment (Janssen et al., 2004). Obesity and central obesity are not only associated with cardiometabolic disease but also with certain cancers. Most of the evidence regarding adiposity and cancer comes from studies that have considered BMI and WC separately (Bhaskaran et al., 2014, Arnold et al., 2016, Barberio et al., 2019, Renehan et al., 2008). Bhaskaran et al. (Bhaskaran et al., 2014), found an association with BMI with 17, out of 22, cancer sites in a cohort study of 5.24 million UK adults. BMI has been associated with many cancers including: colorectal, postmenopausal breast, esophageal, pancreatic, liver, endometrial, kidney, oral, stomach, gallbladder, ovarian, advanced prostate, and cervical cancer (Key et al., 2020, Vithayathil et al., 2020, Mokdad et al., 2003, World Cancer Research Fund/American Institute for Cancer Research, 2018). However, Barberio et al.(Barberio et al., 2019) in a recent study, highlighted that WC could be a better predictor than BMI. High BMI and high WC were associated with high risk

of all-cancer. Adjustment for WC attenuated the effect size of BMI, especially among women. Existing evidence on adiposity and cancer has considered BMI and WC separately or studied only all-cause cancer in a selective population (Bhaskaran et al., 2014, Barberio et al., 2019, Arnold et al., 2016, Renehan et al., 2008, Sun et al., 2019). It should also be noted that the association between adiposity and cancer could vary by sex (Kim and Giovannucci, 2017, Renehan et al., 2008).

Sun et al, showed that women with normal weight and central adiposity had higher risk of cancer mortality (13). However, this analysis was restricted to women and used World Health Organization cut-offs, rather than the current cut-off recommendation for central adiposity based on cancer risk (12). Consistent with the evidence for cardiovascular disease, where BMI and WC provide complementary information for risk stratification (Bhaskaran et al., 2014, Barberio et al., 2019), we hypothesized that people with higher BMI and WC had higher risk of cancer compared with people having only one adiposity marker, and even more so compared with people having normal BMI and WC. To test this hypothesis, we used data from the UK Biobank prospective cohort study and investigated the associations of different combinations of BMI and WC with cancer at 22 sites.

5.3 Methods

Subjects and Data sources

Between 2006 and 2010 UK Biobank recruited over 502,000 participants (53.4% women) aged from 37 to 73 years. Participants attended one of 22 assessment centers across England, Scotland, and Wales where they completed a self-administered, touch-screen questionnaire and face-to-face interview (Sudlow et al., 2015). Our analyses excluded participants who reported prevalent cancer at

baseline (n=41,437), and people who were underweight (n=2,122). In addition, 72,832 individuals were excluded due to missing exposure or covariate data. The study population comprised the remaining 386,101 (76,8%) participants.

Study outcomes and exposure

The outcomes for this study were cancer incidence and mortality; overall and at 22 sites. The date and cause of death were obtained from death certificates held by the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Dates and causes of hospital admission were obtained from the Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Detailed information about the record linkage procedures can be found at http://content.digital.nhs.uk/services. Incident cancer was defined as the first record of the cancer of interest, at hospitalization or death. At the time of analysis, mortality data were available up to 01 June 2020. Mortality analyses were, therefore, censored at this date or date of death, whichever occurred earlier. Hospital admission data were available until 31 March 2017 for Scotland and Wales and until 01 June 2020 for England. Therefore, analyses of incident cancers were censored at these dates, or the date of first hospitalization for, or death from, the cancer of interest, whichever occurred earlier.

The International Classification of Diseases, 10th revision (ICD-10) was used to define the following 24 cancers: all-cause (C00-C97, D37, D48), oral (C00-C14), esophageal (C15), stomach (C16), colorectal (C18, C19, and C20), liver (C22), gallbladder (C23), pancreatic (C25), lung (C34), malignant melanoma (C43), breast (C50), uterine (C53-C55), endometrial (C54), cervical (C53), ovarian (C56), prostate (C61), testicular (C62), kidney (C64-C65), bladder (C67), brain (C71), thyroid (C73), and lymphatic and hematopoietic tissue (C81-C96) cancers, and non-Hodgkin lymphoma (C82-C85), multiple myeloma (C90), and leukemia

(C91-C95). Of these, 17 cancer sites were studied for both men and women; two were specific to men (testicular and prostate) and five to women (breast, endometrial, uterine, cervical and ovarian).

Body mass index and waist circumference categories

Height was measured to the nearest centimeter, using a Seca 202 stadiometer, and body weight to the nearest 0.1 kg, using a Tania BC-418 body composition analyzer. Body mass index (BMI) was calculated as weight divided by height^2, and the World Health Organization's criteria were used to derive the following categories: underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (>30 kg/m^2) (World Health Organization, 2000). The natural indent was used to measure waist circumference (or umbilicus if not visible). In accordance with the latest recommendation from the WCRF, the following cut-off values for central obesity were used: ≥94 cm for men and ≥80 cm for women (World Cancer Research Fund/American Institute for Cancer Research, 2018). For the purpose of this study, the following category combinations were derived: (1) normal weight without central obesity (BMI 18.5-24.9 kg/m^2; WC <88 cm for women and <94 cm for men), (2) normal weight with central obesity (BMI 18.5-24.9 kg/m^2; WC ≥80 cm for women and ≥94 cm for men), (3) overweight without central obesity (BMI 25.0-29.9 kg/m^2; WC <88 cm for women and <94 cm for men), (4) overweight with central obesity (BMI 25.0-29.9 kg/m^2; WC ≥80 cm for women and ≥94 cm for men), (5) obese without central obesity (BMI ≥30.0 kg/m^2; WC <88 cm for women and <94 cm for men), and (6) obese with central obesity (BMI ≥30.0 kg/m^2; WC ≥80 for women and ≥94 for men). Due to insufficient numbers in category 5 (n=1,145), categories 3 with 5 were combined, as were categories 4 and 6.

Covariates

Sociodemographic factors (age, sex, educational qualifications and ethnicity)

were self-reported at the baseline assessment using a touch screen questionnaire. Townsend area deprivation index was derived from the postcode of residence using aggregated data on unemployment, car and homeownership, and household overcrowding (1988). Past and current physician-diagnosed medical conditions were self-reported at baseline and used to derive a multimorbidity count of the following: stroke, angina, heart attack, hypertension, cancer, diabetes, hypertension, chronic obstructive pulmonary disease, or longstanding illness (Jani et al., 2019). A diet score representing cumulative dietary risk factors was derived from ten foods items (processed meat, red meat, oily fish, milk type, spread type, cereal intake, salt added to food, water, and fruit and vegetables). The score ranged from 0 to 9, with each point representing one dietary risk factor (Petermann-Rocha et al., 2020). Level of physical activity level over a typical week was self-reported using the International Physical Activity Questionnaire and presented as MET-mins per week (Guo et al., 2015). Time spent on sedentary behaviors included watching television and leisure-time computer use. Smoking was self-reported and categorized into never, ex- and current smokers. The other covariates were specific to women, including menopausal status, hormone replacement therapy, ages at menarche, first and last birth, and number live births, and were self-reported at baseline using the touch screen questionnaire. Further details of these measurements are contained in the UK Biobank protocol (http://www.ukbiobank.ac.uk).

Ethics

All participants provided written informed consent before enrolment in the study, which was conducted in accordance with the Declaration of Helsinki. The study was approved by the NHS National Research Ethics Service (Ref: 11/NW/0382).

Statistical analyses

Descriptive characteristics were presented as means with standard deviations (SD) for quantitative variables and percentages for categorical variables. The results were reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard assumption was checked based on Schoenfeld residuals. Age violated the assumption, and this was addressed by treating age as an ordinal variable, which produced largely similar results. Firstly, to investigate differences in cancer risk between BMI and WC, ratios of hazard ratios were estimated for the obesity (binary variable) x WC (continuous variable) interaction terms using Cox models. Secondly, Cox proportional hazard models with follow-up time as the time-dependent variable were used to investigate associations of combined categories of BMI and WC with incidence (fatal and not fatal) and mortality for 24 cancer sites and all-cause cancer. Individuals with normal weight and normal WC were the reference group.

All analyses were conducted for both sexes, as well as women and men separately, and adjusted for age (ordinal variable), sex, deprivation, ethnicity, education, multimorbidity, smoking, alcohol consumption, diet risk score, physical activity and discretionary sedentary time. The association of combined categories of BMI and WC with lung, oral and esophageal cancers were restricted to never smokers only because these cancers are strongly influenced by smoking. For analyses specific to women, we also conducted subgroup analyses by pre and postmenopausal status. These subgroup analyses were conducted because of potential moderations menopausal status. To minimize potential reverse causation, all analyses excluded participants who had cancer events within two years of follow-up. Sensitivity analyses were conducted excluding participants with comorbidities at baseline (study population 144,311) and non-white participants (study population=366,450). Due to reduced statistical power, the

sensitivity analyses were not sex-specific, and results were not reported for combined BMI/WC categories with fewer than 5 events. Finally, in order to avoid inflated type-I errors, all p-values were corrected for multiple testing using Holm's method (ETH Zurich), which performs similarly to Bonferroni's method while retaining higher statistical power (Holm, 1979). The multiple testing corrected p-values are denoted as P_{adj}.

All analyses were performed using R version 3.6.2. A two-sided P-value <0.05 was considered statistically significant.

5.4 Results

Characteristics of the study population

Of the 24 cancers studied, cervical and gallbladder cancers did not have sufficient events and were removed, resulting in 22 cancer sites. The median follow-up period was 8.8 years [IQR 8.6-9.9] for incidence and 9.3 years [IQR 8.6-9.9] for mortality. Over the follow-up period, 42,189 people developed cancer, and 9,826 died from cancer. Table 5-1 and Supplementary Table 1 present the characteristics of the study population at baseline. In summary, the study sample contained more women and had a mean age of 56.2 years; 55.6% of participants were never smokers and 37.4% did not have multimorbidity. Among women, 31.1%, were normal weight without central obesity. Compared with this sub-group, overweight women with central obesity, were 2.3 years older and had a similar proportion of never smokers. Among men, 22.5% had normal weight and no central obesity, and 56.8% were overweight with central obesity.

Table 5-1: Characteristics by BMI and WC categories and sex.

	Women				Men			
	Normal weight (18.5 - 24.9 kg/m²)		Overweight (≥25 kg/m²)		Normal weight (18.5 - 24.9 kg/m²)		Overweight (≥25 kg/m²)	
	Without central obesity	With central obesity	Without central obesity	With central obesity	Without central obesity	With central obesity	Without central obesity	With central obesity
N (%)	65,396 (31.1)	17,958 (8.5)	15,954 (7.6)	110,951 (52.85)	39,588 (22.5)	4,360 (2.5)	32,013 (18.2)	99,881 (56.8)
Age, Mean (SD)	54.6 (8.13)	56.9 (7.91)	55.2 (8.10)	56.9 (7.83)	55.6 (8.41)	58.4 (7.81)	55.1 (8.44)	57.2 (7.99)
Townsend deprivation index								
Lower deprivation	24,400 (37.3%)	6,325 (35.2%)	5,920 (37.1%)	34,846 (31.4%)	13,827 (34.9%)	1,489 (34.2%)	11,471 (35.8%)	33,565 (33.6%)
Middle	22,587 (34.5%)	6,185 (34.4%)	5,530 (34.7%)	37,358 (33.7%)	12,776 (32.3%)	1,493 (34.2%)	10,882 (34.0%)	33,230 (33.3%)
Higher deprivation	18,409 (28.2%)	5,448 (30.3%)	4,504 (28.2%)	38,748 (34.9%)	12,985 (32.8%)	1,378 (31.6%)	9,660 (30.2%)	33,086 (33.1%)
Height (m), Mean (SD)	1.63 (0.0618)	1.65 (0.0622)	1.60 (0.0599)	1.62 (0.0624)	1.76 (0.0681)	1.80 (0.0673)	1.74 (0.0645)	1.76 (0.0674)
Weight (kg), Mean (SD)	59.5 (5.71)	64.7 (5.32)	67.8 (5.54)	80.2 (12.8)	71.6 (6.77)	78.5 (6.14)	80.3 (6.50)	94.0 (12.8)
Waist circumference (cm) , Mean (SD)	72.4 (4.33)	83.5 (3.46)	76.1 (2.72)	93.2 (10.1)	84.7 (5.23)	96.2 (2.34)	89.4 (3.27)	104 (8.79)
Body Mass index (kg/m²) Mean (SD)	22.4 (1.56)	23.7 (1.03)	26.4 (1.23)	30.5 (4.54)	23.1 (1.40)	24.2 (0.757)	26.7 (1.30)	30.3 (3.72)
Smoking								
Never	41,4329 (63.4%)	10,330 (57.5%)	10,223 (64.1%)	64,897 (58.5%)	22,597 (57.1%)	2,088 (47.9%)	17,648 (55.1%)	45,570 (45.6%)
Previous	18,487 (28.3%)	5,903 (32.9%)	46,69 (29.3%)	36,914 (33.3%)	11,596 (29.3%)	1,565 (35.9%)	10,997 (34.4%)	43,270 (43.3%)
Current	5,480 (8.4%)	1,725 (9.6%)	1,062 (6.7%)	9,140 (8.2%)	5,396 (13.6%)	707 (16.2%)	3,368 (10.5%)	11,041 (11.1%)
Alcohol intake								
Daily or almost daily	12,633 (19.3%)	3,818 (21.3%)	2,226 (14.0%)	14,912 (13.4%)	10,543 (26.6%)	1,350 (31.0%)	7,512 (23.5%)	24,787 (24.8%)
3-4 times a week	16,051 (24.5%)	4,240 (23.6%)	3,525 (22.1%)	20,458 (18.4%)	10,633 (26.9%)	1,116 (25.6%)	9,191 (28.7%)	26,134 (26.2%)
Once or twice a week	17,175 (26.3%)	4,604 (25.6%)	4,641 (29.1%)	28,892 (26.0%)	9,798 (24.7%)	1,002 (23.0%)	8,859 (27.7%)	2,6531 (26.6%)
1-3 times a month	7,586 (11.6%)	1,942 (10.8%)	2,146 (13.5%)	15,868 (14.3%)	3,364 (8.5%)	313 (7.2%)	2,781 (8.7%)	9,201 (9.2%)
Special occasions only	7,185 (11.0%)	2,005 (11.2%)	2,125 (13.3%)	19,275 (17.4%)	2,712 (6.9%)	280 (6.4%)	2,013 (6.3%)	7,171 (7.2%)
Never	4,766 (7.3%)	1,349 (7.5%)	1,291 (8.1%)	11,547 (10.4%)	2,539 (6.4%)	299 (6.9%)	1,657 (5.2%)	6,058 (6.1%)
Sedentary time (hours/day), Mean (SD)	4.25 (1.84)	4.49 (1.89)	4.64 (1.88)	4.99 (2.08)	4.79 (2.23)	5.21 (2.31)	5.28 (2.28)	5.86 (2.50)
Physical activity (MET-min/day, Mean (SD)	1.52 (1.33)	1.63 (1.50)	1.58 (1.40)	1.93 (1.82)	1.66 (1.42)	1.87 (1.73)	1.64 (1.35)	1.95 (1.73)
Diet score, Mean (SD)	4.85 (1.55)	4.72 (1.54)	4.81 (1.52)	4.58 (1.54)	4.27 (1.68)	4.03 (1.63)	4.23 (1.62)	3.92 (1.58)
Baseline diabetes								
No	64,873 (99.2%)	17,633 (98.2%)	15,783 (98.9%)	105,047 (94.7%)	38,553 (97.4%)	4,124 (94.6%)	30,912 (96.6%)	90,299 (90.4%)
Yes	523 (0.8%)	325 (1.8%)	171 (1.1%)	5904 (5.3%)	1035 (2.6%)	236 (5.4%)	1101 (3.4%)	9582 (9.6%)
Baseline hypertension								
No	57,675 (88.2%)	14,699 (81.9%)	13,337 (83.6%)	76,338 (68.8%)	33,248 (84.0%)	3,298 (75.6%)	24,647 (77.0%)	62,114 (62.2%)
Yes	7723 (11.8%)	3259 (18.1%)	2617 (16.4%)	34617 (31.2%)	6341 (16.0%)	1062 (24.4%)	7366 (23.0%)	37772 (37.8%)
Baseline CVD								
No	56,510 (86.4%)	14,287 (79.6%)	12,950 (81.2%)	73,109 (65.9%)	31,844 (80.4%)	3,100 (71.1%)	23,440 (73.2%)	57,513 (57.6%)
Yes	8,816 (13.5%)	3,643 (20.3%)	2,983 (18.7%)	37,655 (33.9%)	7,694 (19.4%)	1,252 (28.7%)	8,537 (26.7%)	42,255 (42.3%)
Missing	72 (0.1%)	28 (0.2%)	21 (0.1%)	191 (0.2%)	51 (0.1%)	8 (0.2%)	36 (0.1%)	118 (0.1%)
Baseline longstanding illness								
No	51,481 (78.7%)	13,195 (73.5%)	12,188 (76.4%)	70,756 (63.8%)	28,768 (72.7%)	2,727 (62.5%)	23,167 (72.4%)	5,9761 (59.8%)
Yes	12,773 (19.5%)	43,93 (24.5%)	3,476 (21.8%)	37,259 (33.6%)	10,159 (25.7%)	1,560 (35.8%)	8,322 (26.0%)	38,125 (38.2%)
Missing	1,142 (1.7%)	370 (2.1%)	290 (1.8%)	2,936 (2.6%)	661 (1.7%)	73 (1.7%)	524 (1.6%)	1,995 (2.0%)
Baseline multimorbidity								
no illness	31,831 (48.7%)	7,268 (40.5%)	6,873 (43.1%)	32,729 (29.5%)	19,275 (48.7%)	1,586 (36.4%)	14,334 (44.8%)	30,414 (30.5%)
1+ illness	33,565 (51.3%)	10,690 (59.5%)	9,081 (56.9%)	78,222 (70.5%)	20,313 (51.3%)	2,774 (63.6%)	17,679 (55.2%)	69,467 (69.5%)

Data are presented as number of participants and their percentage (%) unless otherwise specified. Data available for 386,101.

Cancer risk by combined categories of body mass index and waist circumference

There were no interactions found between general and central obesity after correcting for multiple testing ratios of HRs and interaction p-values as shown in Supplementary Table 2.

Compared with men who had normal weight and WC, men who were overweight and centrally obese had a higher risk of incidence of cancer at three sites: stomach (HR: 1.75, 95% CI, 1.33, 2.32), kidney (HR: 1.45, 95% CI, 1.17, 1.81), and colorectal (HR: 1.31, 95% CI, 1.17, 1.47) cancer. Overweight men who were not centrally obese were not at higher risk of any incident cancers (Table 5-2). The associations with kidney (HR: 1.75, 95% CI, 1.14, 2.71) and colorectal (HR: 1.27, 95% CI, 1.02, 1.58) cancer mortality had a similar magnitude of association but became non-significant after adjusting for multiple testing. Overweight men who were not centrally obese had a higher risk of brain cancer mortality (HR: 1.79, 95% CI, 1.25, 2.75) compared with people with normal BMI and WC (Supplementary Table 3).

The results for women are presented in Table 5-3. Women who were overweight and centrally obese were at higher risk of cancer incidence overall (HR: 1.07, 95% CI, 1.03, 1.10) and at four sites (endometrial, uterine, kidney and breast cancer) compared with women with normal BMI and WC. The hazard ratio was greatest for endometrial cancer (HR: 2.48, 95% CI, 2.06, 2.98) followed by uterine (HR: 2.23, 95% CI, 1.89, 2.64), then kidney (HR: 1.84, 95% CI, 1.37, 2.46) and finally breast (HR: 1.24, 95% CI, 1.16, 1.32) cancer. Interestingly, women with normal weight and central obesity were also at higher risk of breast cancer (HR: 1.21, 95% CI, 1.10, 1.33) compared with those with normal BMI and WC. No other associations were significant for other categories and cancers (Table 5-3). For mortality, only endometrial

cancer was significantly associated with women being overweight and centrally overweight or obese (HR: 3.28, 95% CI, 1.77, 6.07) (Supplementary Table 4).

People who were either overweight or obese people as well as having central obesity were at higher risk of endometrial, uterine, kidney, colorectal, breast and all-cause cancers while those who were obese and centrally obese were also at increased risk of stomach and liver cancer (Supplementary Table 5)

Table 5-2: Association of BMI and WC categories with cancer incidence in men.

	Normal weight (18.5 – 24.9 kg/m²)					Overweight (≥25 kg/m²)					
	Without central obesity		With central obesity			Without central obesity			With central obesity		
Cancer site	**Total/Event**	**HR**	**Total/Event**	**HR (95% CI)**	**P adj**	**Total/Event**	**HR (95% CI)**	**P adj**	**Total/Event**	**HR (95% CI)**	**P adj**
All-cause	38,893/4,411	1.00 (Ref.)	4,251/663	1.11 (1.02; 1.20)	0.306	31,562/3,496	1.02 (0.97; 1.06)	1.000	97,898/13,478	1.05 (1.02; 1.09)	0.051
Bladder	39,550/235	1.00 (Ref.)	4,352/28	0.79 (0.54; 1.17)	1.000	31,991/192	1.06 (0.87; 1.28)	1.000	99,744/825	1.13 (0.97; 1.31)	1.000
Brain	39,570/65	1.00 (Ref.)	4,359/12	1.53 (0.82; 2.83)	1.000	32,004/77	1.54 (1.11; 2.15)	0.208	99,846/187	1.12 (0.84; 1.50)	1.000
Colorectal	39,517/378	1.00 (Ref.)	4,348/49	0.94 (0.70; 1.27)	1.000	31,967/296	1.02 (0.87; 1.18)	1.000	99,619/1,410	**1.31 (1.17; 1.47)**	**<0.001**
Kidney	39,573/102	1.00 (Ref.)	4,358/19	1.31 (0.80; 2.13)	1.000	32,001/83	1.03 (0.77; 1.38)	1.000	99,826/464	**1.45 (1.17; 1.81)**	**0.016**
Leukemia	39,568/115	1.00 (Ref.)	4,359/13	0.83 (0.46; 1.47)	1.000	32,006/90	1.02 (0.78; 1.35)	1.000	99,840/386	1.20 (0.97; 1.48)	1.000
Liver	39,581/49	1.00 (Ref.)	4,360/8	1.01 (0.48; 2.13)	1.000	32,008/33	0.87 (0.56; 1.35)	1.000	99,858/277	1.51 (1.11; 2.06)	0.139
Lung	22,589/38	1.00 (Ref.)	2,086/3	0.64 (0.20; 2.09)	1.000	17,645/32	1.13 (0.70; 1.81)	1.000	45,559/93	0.99 (0.67; 1.47)	1.000
Lymphatic	39,530/335	1.00 (Ref.)	4,356/49	1.08 (0.80; 1.46)	1.000	31,980/264	1.03 (0.87; 1.21)	1.000	99,744/1,086	1.16 (1.02; 1.31)	0.342
Melanoma	39,562/158	1.00 (Ref.)	4,356/19	0.96 (0.60; 1.55)	1.000	31,997/146	1.18 (0.94; 1.48)	1.000	99,813/549	1.32 (1.10; 1.58)	0.051
Multiple Myeloma	39,578/72	1.00 (Ref.)	4,360/8	0.84 (0.41; 1.75)	1.000	32,004/64	1.17 (0.83; 1.64)	1.000	99,851/226	1.18 (0.90; 1.56)	1.000
Non-Hodgkin	39,562/162	1.00 (Ref.)	4,358/27	1.23 (0.82; 1.85)	1.000	31,997/124	1.00 (0.79; 1.26)	1.000	99,815/484	1.06 (0.88; 1.27)	1.000
Esophagus	22,594/27	1.00 (Ref.)	2,086/2	0.62 (0.15; 2.62)	1.000	17,646/21	1.04 (0.59; 1.85)	1.000	45,552/106	1.60 (1.03; 2.48)	0.466
Oral	22,591/36	1.00 (Ref.)	2,088/6	1.58 (0.66; 3.76)	1.000	17,642/31	1.09 (0.67; 1.77)	1.000	45,557/78	0.90 (0.60; 1.37)	1.000
Pancreas	39,580/99	1.00 (Ref.)	4,360/15	1.04 (0.60; 1.79)	1.000	32,008/80	1.03 (0.77; 1.39)	1.000	99,840/362	1.17 (0.93; 1.47)	1.000
Stomach	39,578/61	1.00 (Ref.)	4,358/14	1.59 (0.89; 2.84)	1.000	32,003/60	1.27 (0.89; 1.81)	1.000	99,834/327	**1.75 (1.33; 2.32)**	**0.002**
Thyroid	39,583/11	1.00 (Ref.)	4,360/2	1.55 (0.34; 7.01)	1.000	32,013/16	1.83 (0.85; 3.96)	1.000	99,874/41	1.36 (0.68; 2.69)	1.000
Prostate	39,429/1,319	1.00 (Ref.)	4,331/205	1.16 (1.00; 1.35)	0.910	31,901/1,079	1.07 (0.98; 1.16)	1.000	99,448/3,679	1.02 (0.95; 1.09)	1.000
Testis	39,585/13	1.00 (Ref.)	4,360/1	0.78 (0.10; 6.01)	1.000	32,008/14	1.33 (0.62; 2.83)	1.000	99,876/36	1.18 (0.61; 2.27)	1.000

Data are presented in hazard ratio with 95% confidence intervals. The reference group was men with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, smoking, sedentary behavior and physical activity. Central obesity (≥94 cm men). Significant results in bold.

Table 5-3: Association of BMI and WC categories with cancer incidence in women.

	Normal weight (18.5 – 24.9 kg/m²)					Overweight (≥25 kg/m²)					
	Without central obesity		With central obesity			Without central obesity			With central obesity		
Cancer site	**Total/Event**	**HR**	**Total/Event**	**HR (95% CI)**	**P adj**	**Total/Event**	**HR (95% CI)**	**P adj**	**Total/Event**	**HR (95% CI)**	**P adj**
All-cause	64,473/5,547	1.00 (Ref.)	17,654/1,816	1.05 (1.00; 1.11)	1.000	15,729/1,330	0.96 (0.90; 1.01)	1.000	109,065/11,448	**1.07 (1.03; 1.10)**	**0.003**
Bladder	65,381/103	1.00 (Ref.)	17,954/29	0.81 (0.53; 1.22)	1.000	15,948/31	1.16 (0.78; 1.74)	1.000	110,912/245	1.06 (0.83; 1.35)	1.000
Brain	65,386/61	1.00 (Ref.)	17,955/28	1.49 (0.95; 2.33)	1.000	15,954/23	1.50 (0.92; 2.42)	1.000	110,928/145	1.24 (0.90; 1.69)	1.000
Colorectal	65,328/444	1.00 (Ref.)	17,933/154	1.08 (0.90; 1.30)	1.000	15,933/117	1.05 (0.85; 1.28)	1.000	110,800/1,015	1.15 (1.02; 1.29)	0.363
Kidney	65,388/59	1.00 (Ref.)	17,954/30	1.52 (0.98; 2.37)	1.000	15,950/25	1.60 (1.00; 2.55)	1.000	110,916/248	**1.84 (1.37; 2.46)**	**0.001**
Leukemia	65,380/104	1.00 (Ref.)	17,958/36	1.03 (0.70; 1.51)	1.000	15,952/22	0.81 (0.51; 1.29)	1.000	110,929/241	1.07 (0.84; 1.36)	1.000
Liver	65,386/57	1.00 (Ref.)	17,955/20	1.03 (0.62; 1.72)	1.000	15,953/11	0.73 (0.38; 1.39)	1.000	110,939/153	1.14 (0.83; 1.56)	1.000
Lung	41,420/77	1.00 (Ref.)	10,327/29	1.27 (0.82; 1.94)	1.000	10,220/25	1.24 (0.79; 1.96)	1.000	64,881/158	1.06 (0.79; 1.40)	1.000
Lymphatic	65,340/375	1.00 (Ref.)	17,943/115	0.94 (0.76; 1.16)	1.000	15,947/80	0.83 (0.65; 1.05)	1.000	110,860/818	1.03 (0.91; 1.17)	1.000
Melanoma	65,351/266	1.00 (Ref.)	17,949/69	0.91 (0.70; 1.19)	1.000	15,941/61	0.92 (0.70; 1.22)	1.000	110,884/420	0.92 (0.78; 1.08)	1.000
Multiple Myeloma	65,386/74	1.00 (Ref.)	17,954/19	0.80 (0.48; 1.32)	1.000	15,953/17	0.90 (0.53; 1.53)	1.000	110,938/190	1.23 (0.92; 1.62)	1.000
Non-Hodgkin	65,366/187	1.00 (Ref.)	17,948/54	0.90 (0.66; 1.22)	1.000	15,950/41	0.85 (0.61; 1.19)	1.000	110,894/388	1.00 (0.83; 1.20)	1.000
Esophagus	41,424/29	1.00 (Ref.)	10,329/7	0.79 (0.35; 1.81)	1.000	10,223/5	0.63 (0.24; 1.63)	1.000	64,893/68	1.12 (0.71; 1.77)	1.000
Oral	41,424/40	1.00 (Ref.)	10,330/7	0.67 (0.30; 1.50)	1.000	10,222/9	0.92 (0.45; 1.90)	1.000	64,892/54	0.85 (0.55; 1.30)	1.000
Pancreas	65,383/110	1.00 (Ref.)	17,957/30	0.79 (0.53; 1.18)	1.000	15,951/35	1.25 (0.85; 1.82)	1.000	110,917/265	1.10 (0.87; 1.39)	1.000
Stomach	65,390/50	1.00 (Ref.)	17,955/14	0.82 (0.45; 1.48)	1.000	15,953/12	0.91 (0.48; 1.71)	1.000	110,939/122	1.00 (0.71; 1.41)	1.000
Thyroid	65,387/46	1.00 (Ref.)	17,954/11	0.85 (0.44; 1.64)	1.000	15,950/5	0.43 (0.17; 1.08)	1.000	110,932/117	1.29 (0.90; 1.84)	1.000
Breast	65,087/1,598	1.00 (Ref.)	17,861/552	**1.21 (1.10; 1.33)**	**0.003**	15,866/392	1.01 (0.91; 1.13)	1.000	110,324/3,409	**1.24 (1.16; 1.32)**	**<0.001**
Endometrium	65,376/147	1.00 (Ref.)	17,945/55	1.25 (0.92; 1.70)	1.000	15,947/58	1.60 (1.18; 2.16)	0.061	110,848/685	**2.48 (2.06; 2.98)**	**<0.001**
Ovary	65,358/226	1.00 (Ref.)	17,945/55	0.79 (0.58; 1.06)	1.000	15,945/48	0.84 (0.61; 1.14)	1.000	110,879/436	0.99 (0.84; 1.18)	1.000
Uterine	65,368/180	1.00 (Ref.)	17,941/56	1.05 (0.78; 1.41)	1.000	15,946/64	1.44 (1.08; 1.91)	0.279	110,829/750	**2.23 (1.89; 2.64)**	**<0.001**

Data are presented in hazard ratio with 95% confidence intervals. The reference group was women with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, smoking, sedentary behavior and physical activity. Central obesity (≥80 cm women). Significant results in bold.

Table 5-4: Association BMI and WC categories breast, endometrial, ovary and uterine cancer by menopausal status

			Premenopausal			Postmenopausal			
	General obesity	**Central obesity**	**Total/Event**	**HR 95% CI**	**P value**	**Total/Event**	**HR 95% CI**	**P value**	**P interaction**
Breast	Normal weight	No	12,087/261	1.00 (Ref.)		24,846/614	1.00 (Ref.)		**0.020**
		Yes	2,408/75	**1.42 (1.10; 1.84)**	**0.007**	8,379/244	1.15 (0.99; 1.33)	0.067	
	Overweight and obese	No	2,664/63	1.12 (0.85; 1.48)	0.419	6,459/161	1.03 (0.87; 1.23)	0.742	
		Yes	13,584/318	1.12 (0.94; 1.33)	0.189	49,545/1,600	**1.32 (1.20; 1.46)**	**<0.001**	
Endometrial	Normal weight	No	12,128/18	1.00 (Ref.)		24,960/71	1.00 (Ref.)		0.105
		Yes	2,417/5	1.26 (0.46; 3.41)	0.651	8,422/27	1.10 (0.70; 1.71)	0.687	
	Overweight and obese	No	2,673/5	1.17 (0.43; 3.18)	0.753	6,494/33	**1.73 (1.14; 2.62)**	**0.010**	
		Yes	13,622/41	1.57 (0.87; 2.81)	0.133	49,803/381	**2.46 (1.89; 3.19)**	**<0.001**	
Ovary	Normal weight	No	12,126/16	1.00 (Ref.)		24,956/103	1.00 (Ref.)		0.105
		Yes	2,417/3	0.83 (0.24; 2.89)	0.769	8,421/29	0.79 (0.52; 1.19)	0.255	
	Overweight and obese	No	2,674/4	1.10 (0.36; 3.30)	0.871	6,490/30	1.08 (0.72; 1.63)	0.706	
		Yes	13,626/34	1.68 (0.90; 3.16)	0.104	49,821/215	0.98 (0.76; 1.25)	0.840	
Uterine	Normal weight	No	12,124/21	1.00 (Ref.)		24,957/84	1.00 (Ref.)		0.248
		Yes	2,415/5	1.09 (0.41; 2.91)	0.858	8,421/27	0.93 (0.60; 1.43)	0.728	
	Overweight and obese	No	2,673/5	1.05 (0.39; 2.80)	0.923	6,493/34	**1.50 (1.01; 2.24)**	**0.046**	
		Yes	13,620/52	**1.77 (1.04; 3.03)**	**0.036**	49,796/415	**2.27 (1.78; 2.89)**	**<0.001**	

Data are presented in hazard ratio with 95% confidence intervals. Cox proportional hazard were done. The reference group was women with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, smoking, sedentary behavior, physical activity, age menarche, first and last live birth and hormonal replacement. Normal weight (BMI 18.5 – 24.9 kg/m2), Overweight (BMI ≥25 kg/m2), Central obesity (≥80 women). Significant results in bold.

Sensitivity analyses

The associations among women differed by menopausal status (Table 5-4). Among premenopausal women, the association with breast cancer was stronger in those who had normal weight and central obesity whereas, among postmenopausal women, the association was stronger in those who were both overweight and centrally obese ($P_{interaction}$=0.02). For endometrial and uterine cancers, the associations were generally stronger among postmenopausal women even though the interactions were not significant.

When participants with baseline morbidity were excluded, being overweight with central obesity was associated with endometrial, uterine, breast and all-cause cancer (Supplementary Table 6). Finally, when the analyses were restricted to only those with white ethnicity, the results were largely similar to the main findings (Supplementary Table 7).

5.5 Discussion

This study provided novel evidence regarding the risk of cancer associated with different combinations of general and central adiposity. Overweight people with central obesity had higher risk of developing cancer at several sites. People with both general and central obesity had higher risk of six cancers than people with only one type of obesity, and even higher risk than those with neither. Some of the associations differed between men and women and, among the latter, the associations with breast cancer were moderated by menopausal status.

Our findings corroborated previous evidence, including the WCRF Obesity and Cancer 2018 Report, and meta-analysis of prospective cohort studies, which supported the association between BMI and cancer at several sites (Fang et al., 2018, Wei et al., 2018, Renehan et al., 2008). In our study, adiposity (assessed using BMI and WC) was associated with a higher risk of kidney, colorectal,

postmenopausal breast, endometrial and uterine cancers. Our findings were also consistent with recent Mendelian randomization (MR) studies that suggested high BMI may be causally related to several site-specific cancers (Gao et al., 2016, Thrift et al., 2015, Vithayathil et al., 2020, Guo et al., 2018). Furthermore, our epidemiological evidence of associations with other cancers, such as stomach cancer, is supported by previous MR studies (Kubo and Corley, 2006, Vithayathil et al., 2020).

There is convincing evidence (Johnson et al., 2013) that adiposity is associated with an increased risk of colorectal cancer, derived mainly through BMI measured in prospective cohorts (Johnson et al., 2013, Kubo and Corley, 2006, Lee et al., 2018, Guo et al., 2016) and in MR studies (Jarvis et al., 2016, Thrift et al., 2015, Vithayathil et al., 2020). However, this association is stronger in men than women (Kim and Giovannucci, 2017). Different hypotheses have been proposed for these sex differences. It has been suggested that, adult weight gain in men may be a more important risk factor for colorectal cancer (Song et al., 2016), whereas early life obesity in women may be more important (Zhang et al., 2015). One plausible mechanism behind these associations may be hormonal differences which warrants further investigation (Terry et al., 2001).

We found that the association between general adiposity combined with central adiposity and higher risk of breast cancer was mainly driven by postmenopausal women. This is consistent with previous evidence from prospective cohort studies that have shown an association between BMI and postmenopausal breast cancer (Renehan et al., 2008, Benn et al., 2016, Guo et al., 2018). Sun Y et al. showed, using data from the Women's Health Initiative, that postmenopausal women who had normal weight but central obesity had a similar risk of all-cause cancer incidence and mortality as women who were overweight (Sun et al., 2019). In our study this association were stronger in premenopausal women but

not for postmenopausal and only for breast cancer (Table 5-4).

People who were overweight but not centrally obese had a higher risk of brain cancer mortality. This was consistent with a previous metanalysis showing an association between BMI and brain cancer (Fang et al., 2018). Previous meta-analyses showed an inverse association between obesity and lung cancer overall (Shen et al., 2017, Yang et al., 2013), but a positive association among never smokers (Zhu and Zhang, 2018). Our analyses were restricted to never smokers because of anticipation of effect modification and the strong risk of a negative association in current and former smokers being due to reverse causation.

The mechanism underlying the association between adiposity and cancer could be related to adiposity induced inflammation (Deng et al., 2016, Iyengar et al., 2016), and the resultant increase in circulating adipokines, cytokines, and chemokines (MacDougald and Burant, 2007). These create a tumor microenvironment, which is critical in the initiation and progression of cancer (Deng et al., 2016). Adiposity may also generate systemic metabolic dysregulation - increased insulin, dyslipidemia, glycemia, oxidative stress, and insulin growth factor-1 (Deng et al., 2016, Iyengar et al., 2016, Rose et al., 2015) - which have been associated with cancer, especially the latter (Giovannucci, 2003, Gunter et al., 2009, Key et al., 2010, Murphy et al., 2019). Central adiposity appears to have an important role in this association. Barberio et al. (Barberio et al., 2019) reported a stronger association for WC than BMI even though BMI was still a significant predictor of cancer (Renehan et al., 2008). Therefore, both measures should contribute to the prediction of several cancers. BMI and WC are easily and cheaply measured, even in clinical practice, and use of both in combination may enhance the prediction of cancer.

Limitations

This study is not free from limitations. UK Biobank is not representative of the

general population in terms of lifestyle and therefore, we should be cautious in generalizing summary statistics (Collins, 2012). However, relative risks can be generalized and were consistent with a more representative population cohort (Batty et al., 2020). Measurements were collected from all participants, by trained staff rather than self-report, but only on one occasion. However, it is unlikely that anthropometric measurements will have changed markedly over a mean follow-up period of 9 years. Among over 20,000 UK Biobank participants who had longitudinal BMI measurements, the intra-correlation coefficients for BMI were 92.6% (95% CI 92.4%-92.8%) and 89.8% (95% CI 89.6%-90.0%) for 4.4- and 8.5-years follow-up respectively. Reverse causation is a potential limitation of cohort studies. However, to minimize this risk, we performed landmark analyses excluding all participants with prevalent cancer or cancer diagnosed within the first 2-years of follow up. We did not have sufficient statistical power to conduct subgroup analyses for non-white people, which may have different association patterns. Moreover, recent evidence from MR studies has reported causal links between BMI and several cancer sites, consistent with our results, and Barberio et al. showed that WC was a stronger predictor, which we also reported for some cancer sites (Vithayathil et al., 2020, Barberio et al., 2019). Last, but not least, causality cannot be confirmed in any observational study and residual confounding may occur because of the omission of some covariates, such as the dosage of smoking.

5.6 Conclusion

Our findings provide evidence that combining information on general obesity, based on BMI, with central obesity, based on WC, identifies people at higher risk of several cancers. Their combination could provide a useful marker for targeting cancer prevention in clinical practice.

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5.8 Additional File Chapter 5

Supplementary Table 1: Characteristic by sex

	Women	Men	Overall
n	210,259 (54.5%)	175,842 (45.5%)	386,101
Age			
Mean (SD)	56.1 (8.03)	56.5 (8.22)	56.2 (8.12)
Townsend deprivation index			
Lower	71,491 (34.0%)	60,352 (34.3%)	131,843 (34.1%)
Middle	71,660 (34.1%)	58,381 (33.2%)	130,041 (33.7%)
Higher	67,108 (31.9%)	57,109 (32.5%)	124,217 (32.2%)
Height (m)			
Mean (SD)	1.63 (0.0629)	1.76 (0.0682)	1.69 (0.0928)
Weight (Kg)			
Mean (SD)	71.5 (13.9)	86.1 (14.2)	78.2 (15.8)
Waist (cm)			
Mean (SD)	84.6 (12.3)	96.9 (11.2)	90.2 (13.3)
Body Mass index (kg/m2)			
Mean (SD)	27.1 (5.09)	27.9 (4.19)	27.4 (4.72)
Smoking			
Never	126,882 (60.3%)	87,904 (50.0%)	214,786 (55.6%)
Previous	65,976 (31.4%)	67,431 (38.3%)	13,3407 (34.6%)
Current	17,407 (8.3%)	20,513 (11.7%)	37,920 (9.8%)
Alcohol intake			
Daily or almost daily	33,589 (16.0%)	44,192 (25.1%)	77,781 (20.1%)
3-4 times a week	44,274 (21.1%)	47,074 (26.8%)	91,348 (23.7%)
Once or twice a week	55,312 (26.3%)	46,190 (26.3%)	101,502 (26.3%)
1-3 times a month	27,542 (13.1%)	15,659 (8.9%)	43,201 (11.2%)
Special occasions only	30,589 (14.5%)	12,176 (6.9%)	42,765 (11.1%)
Never	18,953 (9.0%)	10,551 (6.0%)	29,504 (7.6%)
Sedentary time			
Mean (SD)	4.69 (2.00)	5.50 (2.44)	5.06 (2.25)
Physical activity			
Mean (SD)	1.75 (1.64)	1.83 (1.61)	1.79 (1.62)
Diet score			
Mean (SD)	4.69 (1.55)	4.06 (1.62)	4.40 (1.61)
Diabetes diagnostic			
No	203,336 (96.7%)	163,888 (93.2%)	367,224 (95.1%)
Yes	6,923 (3.3%)	11,954 (6.8%)	18,877 (4.9%)
Longstanding illness			
No	147,620 (70.2%)	114,423 (65.1%)	262,043 (67.9%)
Yes	57,901 (27.5%)	58,166 (33.1%)	116,067 (30.1%)
Missing	4,738 (2.3%)	3,253 (1.8%)	7,991 (2.1%)
Multimorbidity			
no illness	78,701 (37.4%)	65,609 (37.3%)	14,4310 (37.4%)
1+ illness	131558 (62.6%)	110233 (62.7%)	241791 (62.6%)

Data are presented as number of participants and their percentage (%) unless otherwise specified. Data available for 386,101.

Supplementary Table 2: Interaction Body mass index obese with waist circumference

		Incident Cancer			Cancer mortality		
Cancer sites	**Total**	**Events**	**RHR 95% CI**	**P adj**	**Deaths**	**RHR 95% CI**	**P adj**
All-cause	379525	42189	1.00 (1.00; 1.00)	1.000	9826	1.00 (1.00; 1.01)	1.000
Bladder	385832	1688	1.00 (0.99; 1.01)	1.000	267	1.00 (0.97; 1.02)	1.000
Brain	386002	598	0.99 (0.97; 1.00)	1.000	499	0.98 (0.96; 1.00)	0.380
Colorectal	385445	3863	1.00 (1.00; 1.01)	1.000	1020	1.01 (1.00; 1.02)	1.000
Kidney	385966	1030	0.99 (0.98; 1.01)	1.000	282	0.98 (0.96; 1.00)	1.000
Leukemia	385992	1007	1.00 (0.99; 1.01)	1.000	354	0.99 (0.97; 1.02)	1.000
Liver	386040	608	1.02 (1.00; 1.03)	0.447	383	1.02 (1.00; 1.04)	0.327
Lung	214727	455	1.00 (0.98; 1.02)	1.000	217	1.01 (0.98; 1.04)	1.000
Lymphatic	385700	3122	1.00 (0.99; 1.01)	1.000	926	1.00 (0.98; 1.01)	1.000
Melanoma	385853	1688	1.00 (0.99; 1.01)	1.000	159	1.00 (0.97; 1.04)	1.000
Multiple Myeloma	386024	670	0.99 (0.97; 1.01)	1.000	187	1.00 (0.97; 1.03)	1.000
Non-Hodgkin	385890	1467	1.00 (0.99; 1.02)	1.000	364	0.99 (0.97; 1.01)	1.000
Esophagus	214747	265	1.01 (0.98; 1.03)	1.000	139	1.02 (0.99; 1.05)	1.000
Oral	214746	261	1.02 (0.99; 1.05)	1.000	41	1.01 (0.95; 1.08)	1.000
Pancreas	385996	996	1.00 (0.99; 1.02)	1.000	802	1.01 (0.99; 1.02)	1.000
Stomach	386010	660	1.00 (0.99; 1.02)	1.000	268	1.02 (1.00; 1.05)	1.000
Thyroid	386053	249	0.99 (0.96; 1.01)	1.000	15	0.93 (0.83; 1.05)	1.000
Prostate	175109	6282	0.99 (0.99; 1.00)	1.000	552	0.98 (0.96; 1.01)	1.000
Testis	175829	64	0.96 (0.89; 1.03)	1.000	0	NA	
Breast	209138	5951	0.99 (0.98; 1.00)	0.015	426	1.00 (0.98; 1.02)	1.000
Ovary	210127	765	1.00 (0.99; 1.02)	1.000	341	1.03 (1.01; 1.06)	0.327
Uterine	210084	1050	1.01 (1.00; 1.03)	0.875	171	1.01 (0.98; 1.04)	1.000
Endometrium	210116	945	1.01 (1.00; 1.02)	1.000	112	0.99 (0.96; 1.03)	1.000

Data are presented in ratio hazard ratio with 95% confidence intervals. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, smoking, sedentary behavior and physical activity. Body mass index as binary variable (BMI <30 and ≥ 30 kg/m^2) and waist circumference as continuous variable.

Supplementary Table 3: Association BMI and WC categories with cancer mortality in men.

	Normal weight (18.5 – 24.9 kg/m^2)					Overweight (≥25 kg/m^2)					
	Without central obesity		With central obesity			Without central obesity			With central obesity		
Cancer site	**Event**	**HR**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**
All-cause	39,505/1,032	1.00 (Ref.)	4,346/172	1.11 (0.94; 1.30)	1.000	31,977/738	0.92 (0.84; 1.01)	1.000	99,635/3,604	1.09 (1.02; 1.17)	0.258
Bladder	39,585/46	1.00 (Ref.)	4,360/6	0.83 (0.36; 1.96)	1.000	32,013/17	0.48 (0.28; 0.84)	0.173	99,880/139	0.94 (0.67; 1.33)	1.000
Brain	39,577/51	1.00 (Ref.)	4,359/11	1.77 (0.92; 3.40)	1.000	32,010/71	**1.79 (1.25; 2.57)**	**0.029**	99,862/159	1.19 (0.86; 1.65)	1.000
Colorectal	39,581/110	1.00 (Ref.)	4,360/10	0.67 (0.35; 1.29)	1.000	32,012/78	0.91 (0.68; 1.22)	1.000	99,858/394	1.27 (1.02; 1.58)	0.497
Kidney	39,585/25	1.00 (Ref.)	4,360/3	0.80 (0.24; 2.64)	1.000	32,011/23	1.16 (0.66; 2.05)	1.000	99,876/145	1.75 (1.14; 2.71)	0.203
Leukemia	39,586/39	1.00 (Ref.)	4,360/6	1.00 (0.42; 2.36)	1.000	32,013/33	1.06 (0.67; 1.69)	1.000	99,869/154	1.22 (0.85; 1.75)	1.000
Liver	39,584/35	1.00 (Ref.)	4,360/5	0.88 (0.34; 2.24)	1.000	32,013/17	0.61 (0.34; 1.09)	1.000	99,871/177	1.31 (0.90; 1.89)	1.000
Lung	22,596/25	1.00 (Ref.)	2,087/2	0.63 (0.15; 2.66)	1.000	17,647/13	0.67 (0.34; 1.32)	1.000	45,566/47	0.76 (0.46; 1.26)	1.000
Lymphatic	39,580/106	1.00 (Ref.)	4,359/14	0.89 (0.51; 1.55)	1.000	32,009/81	0.99 (0.74; 1.33)	1.000	99,856/357	1.11 (0.89; 1.38)	1.000
Melanoma	39,586/20	1.00 (Ref.)	4,360/2	0.78 (0.18; 3.34)	1.000	32,013/18	1.14 (0.60; 2.17)	1.000	99,878/57	1.05 (0.62; 1.78)	1.000
Multiple Myeloma	39,587/25	1.00 (Ref.)	4,360/2	0.60 (0.14; 2.52)	1.000	32,012/11	0.62 (0.31; 1.27)	1.000	99,877/67	1.13 (0.70; 1.82)	1.000
Non-Hodgkin	39,583/41	1.00 (Ref.)	4,359/6	0.98 (0.42; 2.32)	1.000	32,010/37	1.18 (0.76; 1.84)	1.000	99,874/124	0.97 (0.67; 1.39)	1.000
Esophagus	22,596/13	1.00 (Ref.)	2,088/2	1.23 (0.28; 5.46)	1.000	17,648/8	0.80 (0.33; 1.95)	1.000	45,567/63	1.80 (0.97; 3.35)	0.918
Oral	22,597/7	1.00 (Ref.)	2,088/1	1.33 (0.16; 10.89)	1.000	17,648/5	0.89 (0.28; 2.82)	1.000	45,569/15	0.77 (0.30; 1.99)	1.000
Pancreas	39,583/79	1.00 (Ref.)	4,360/11	0.97 (0.51; 1.82)	1.000	32,009/58	0.92 (0.66; 1.30)	1.000	99,851/299	1.20 (0.93; 1.54)	1.000
Prostate	39,585/114	1.00 (Ref.)	4,359/18	1.07 (0.65; 1.75)	1.000	32,012/73	0.85 (0.63; 1.14)	1.000	99,872/347	1.05 (0.84; 1.30)	1.000
Stomach	39,584/30	1.00 (Ref.)	4,360/2	0.47 (0.11; 1.95)	1.000	32,009/24	1.04 (0.61; 1.79)	1.000	99,871/124	1.34 (0.89; 2.02)	1.000

Data are presented in hazard ratio with 95% confidence intervals. The reference group was people with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, sedentary behavior and physical activity. Central obesity (≥94 cm men). Significant results in red.

Supplementary Table 4: Association BMI and WC categories with cancer mortality in women

	Normal weight (18.5 – 24.9 kg/m^2)					Overweight (≥25 kg/m^2)					
	Without central obesity		With central obesity			Without central obesity			With central obesity		
Cancer site	**Event**	**HR**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**
All-cause	65,341/1,106	1.00 (Ref.)	17,926/352	0.93 (0.83; 1.05)	1.000	15,943/267	0.93 (0.82; 1.07)	1.000	110,809/2,555	1.02 (0.95; 1.10)	1.000
Bladder	65,396/7	1.00 (Ref.)	17,958/4	1.60 (0.47; 5.50)	1.000	15,952/5	2.77 (0.88; 8.76)	1.000	110,948/43	2.47 (1.09; 5.61)	0.601
Colorectal	65,392/114	1.00 (Ref.)	17,956/42	1.13 (0.79; 1.61)	1.000	15,953/28	0.97 (0.64; 1.47)	1.000	110,942/244	1.04 (0.82; 1.31)	1.000
Kidney	65,394/15	1.00 (Ref.)	17,957/9	1.71 (0.75; 3.91)	1.000	15,953/6	1.47 (0.57; 3.81)	1.000	110,947/56	1.53 (0.85; 2.76)	1.000
Leukemia	65,391/29	1.00 (Ref.)	17,958/7	0.70 (0.31; 1.60)	1.000	15,954/6	0.80 (0.33; 1.92)	1.000	110,944/80	1.25 (0.80; 1.95)	1.000
Liver	65,392/33	1.00 (Ref.)	17,955/15	1.31 (0.71; 2.42)	1.000	15,953/7	0.78 (0.34; 1.77)	1.000	110,945/94	1.15 (0.76; 1.74)	1.000
Lung	41,427/41	1.00 (Ref.)	10,329/10	0.85 (0.43; 1.70)	1.000	10,223/12	1.17 (0.61; 2.23)	1.000	64,893/67	0.97 (0.65; 1.46)	1.000
Lymphatic	65,389/91	1.00 (Ref.)	17,956/28	0.90 (0.59; 1.38)	1.000	15,954/14	0.59 (0.33; 1.03)	1.000	110,940/235	1.16 (0.90; 1.50)	1.000
Melanoma	65,396/22	1.00 (Ref.)	17,958/2	0.30 (0.07; 1.27)	1.000	15,953/7	1.25 (0.53; 2.93)	1.000	110,951/31	0.76 (0.43; 1.35)	1.000
Multiple Myeloma	65,396/17	1.00 (Ref.)	17,957/6	1.02 (0.40; 2.59)	1.000	15,954/6	1.39 (0.55; 3.54)	1.000	110,950/53	1.41 (0.80; 2.49)	1.000
Non-Hodgkin	65,395/41	1.00 (Ref.)	17,957/14	1.03 (0.56; 1.89)	1.000	15,954/1	0.09 (0.01; 0.66)	0.410	110,948/100	1.10 (0.75; 1.61)	1.000
Esophagus	41,429/16	1.00 (Ref.)	10,330/5	0.96 (0.35; 2.63)	1.000	10,223/1	0.22 (0.03; 1.68)	1.000	64,896/31	0.82 (0.43; 1.56)	1.000
Oral	41,428/5	1.00 (Ref.)	10,330/1	0.72 (0.08; 6.22)	1.000	10,223/0	0.00 (0.00; 0.00)	1.000	64,897/7	0.78 (0.23; 2.62)	1.000
Pancreas	65,390/89	1.00 (Ref.)	17,958/25	0.80 (0.51; 1.25)	1.000	15,953/30	1.28 (0.85; 1.94)	1.000	110,933/211	1.04 (0.80; 1.35)	1.000
Stomach	65,394/23	1.00 (Ref.)	17,958/8	1.07 (0.48; 2.40)	1.000	15,954/4	0.65 (0.22; 1.89)	1.000	110,947/53	1.03 (0.62; 1.71)	1.000
Thyroid	65,395/1	1.00 (Ref.)	17,958/0	0.00 (0.00; 0.00)	1.000	15,954/0	0.00 (0.00; 0.00)	1.000	110,949/5	1.58 (0.17; 14.52)	1.000
Breast	65,395/123	1.00 (Ref.)	17,956/37	1.02 (0.70; 1.47)	1.000	15,953/24	0.79 (0.51; 1.22)	1.000	110,944/242	1.04 (0.83; 1.31)	1.000
Endometrium	65,396/12	1.00 (Ref.)	17,958/8	1.97 (0.80; 4.83)	1.000	15,954/5	1.59 (0.56; 4.52)	1.000	110,949/87	**3.28 (1.77; 6.07)**	**0.004**
Ovary	65,394/115	1.00 (Ref.)	17,958/17	0.46 (0.28; 0.77)	0.069	15,954/25	0.85 (0.55; 1.31)	1.000	110,942/184	0.80 (0.62; 1.02)	1.000
Uterine	65,396/29	1.00 (Ref.)	17,957/13	1.37 (0.71; 2.64)	1.000	15,953/9	1.19 (0.56; 2.53)	1.000	110,948/120	1.91 (1.25; 2.90)	0.055

Data are presented in hazard ratio with 95% confidence intervals. The reference group was people with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, sedentary behavior and physical activity. Central obesity (≥80 cm women). Significant results in red.

Supplementary Table 5: Association of BMI (normal weight, overweight and obese) and WC categories with cancer mortality in men and women

	Normal weight (18.5 – 24.9 kg/m^2)				**Overweight (≥25 – 29.9 kg/m^2)**				**Obese (≥30 kg/m^2)**	
	Without central obesity		**With central obesity**		**Without central obesity**		**With central obesity**		**With central obesity**	
Cancer site	**Event**	**HR**	**Event**	**HR (95% CI)**	**Event**	**HR (95% CI)**	**Event**	**HR (95% CI)**	**Event**	**HR (95% CI)**
All-cause	104,931/338	1.00 (Ref.)	22,306/57	1.06 (1.01; 1.10)	47,021/216	0.99 (0.95; 1.02)	118,191/571	**1.05 (1.02; 1.08)**	92,465/499	**1.06 (1.03; 1.09)**
Bladder	104,956/126	1.00 (Ref.)	22,314/40	0.80 (0.60; 1.06)	47,042/96	1.05 (0.89; 1.25)	118,254/198	1.05 (0.92; 1.21)	92,520/134	1.21 (1.05; 1.40)
Brain	104,845/822	1.00 (Ref.)	22,281/203	1.47 (1.03; 2.11)	46,983/408	1.52 (1.16; 2.00)	118,039/1,357	1.22 (0.97; 1.54)	92,380/1,068	1.10 (0.85; 1.42)
Colorectal	104,980/13	1.00 (Ref.)	22,318/5	1.05 (0.90; 1.23)	47,047/2	1.01 (0.89; 1.14)	118,285/35	**1.21 (1.11; 1.32)**	92,540/38	**1.27 (1.16; 1.40)**
Kidney	104,948/219	1.00 (Ref.)	22,317/49	1.36 (0.99; 1.88)	47,040/112	1.11 (0.86; 1.43)	118,252/351	**1.46 (1.21; 1.77)**	92,517/276	**1.80 (1.48; 2.18)**
Leukemia	104,967/106	1.00 (Ref.)	22,315/28	0.98 (0.72; 1.34)	47,044/44	0.98 (0.77; 1.23)	118,274/191	1.12 (0.94; 1.33)	92,523/239	1.17 (0.97; 1.41)
Liver	64,009/115	1.00 (Ref.)	12,413/32	1.06 (0.70; 1.62)	27,327/57	0.78 (0.55; 1.11)	62,616/146	1.11 (0.87; 1.41)	47,824/105	**1.58 (1.24; 2.01)**
Lung	104,870/710	1.00 (Ref.)	22,299/164	1.15 (0.77; 1.70)	47,009/343	1.19 (0.86; 1.64)	118,161/1,043	1.06 (0.83; 1.36)	92,443/861	0.99 (0.74; 1.31)
Lymphatic	104,913/424	1.00 (Ref.)	22,305/88	0.99 (0.83; 1.17)	47,020/203	0.97 (0.85; 1.10)	118,212/553	1.06 (0.96; 1.17)	92,485/416	1.15 (1.03; 1.27)
Melanoma	104,964/146	1.00 (Ref.)	22,314/27	0.95 (0.75; 1.20)	47,039/80	1.01 (0.85; 1.19)	118,267/226	1.06 (0.93; 1.20)	92,522/190	1.11 (0.96; 1.28)
Multiple Myeloma	104,928/349	1.00 (Ref.)	22,306/81	0.80 (0.53; 1.21)	47,029/165	1.11 (0.84; 1.47)	118,220/486	1.16 (0.93; 1.43)	92,489/386	1.30 (1.03; 1.63)
Non-Hodgkin	64,018/56	1.00 (Ref.)	12,415/9	0.99 (0.78; 1.26)	27,331/26	0.96 (0.79; 1.16)	62,616/89	1.01 (0.88; 1.16)	47,829/85	1.04 (0.90; 1.22)
Esophagus	64,015/76	1.00 (Ref.)	12,418/13	0.80 (0.40; 1.63)	27,326/40	0.88 (0.55; 1.41)	62,618/76	1.24 (0.88; 1.75)	47,831/56	1.51 (1.05; 2.16)
Oral	104,963/209	1.00 (Ref.)	22,317/45	0.94 (0.52; 1.69)	47,041/114	1.02 (0.69; 1.51)	118,249/333	0.89 (0.64; 1.23)	92,508/294	0.83 (0.57; 1.20)
Pancreas	104,968/111	1.00 (Ref.)	22,313/28	0.86 (0.63; 1.20)	47,038/71	1.09 (0.87; 1.37)	118,257/219	1.08 (0.91; 1.29)	92,516/230	1.23 (1.02; 1.49)
Stomach	104,970/57	1.00 (Ref.)	22,314/13	1.18 (0.78; 1.79)	47,045/21	1.10 (0.82; 1.49)	118,274/80	1.28 (1.01; 1.61)	92,532/78	**1.66 (1.31; 2.11)**
Thyroid	104,931/338	1.00 (Ref.)	22,306/57	0.93 (0.51; 1.71)	47,021/216	1.01 (0.61; 1.67)	118,191/571	1.25 (0.88; 1.77)	92,465/499	1.41 (0.98; 2.03)
Prostate	39,429/1,1319	1.00 (Ref.)	4,331/205	1.16 (1.00; 1.34)	31,242/1,062	1.07 (0.98; 1.16)	55,724/2,260	1.07 (1.00; 1.15)	43,724/1,419	0.93 (0.86; 1.01)
Testis	39,585/13	1.00 (Ref.)	4,360/1	0.78 (0.10; 6.00)	31,348/14	1.35 (0.63; 2.89)	55,993/21	1.24 (0.61; 2.50)	43,883/15	1.09 (0.50; 2.38)
Breast	65,087/1598	1.00 (Ref.)	17,861/552	**1.21 (1.10; 1.33)**	15,610/388	1.02 (0.91; 1.14)	61,951/1,898	**1.21 (1.13; 1.30)**	48,373/1,511	**1.27 (1.18; 1.37)**
Endometrium	65,376/147	1.00 (Ref.)	17,945/55	1.26 (0.92; 1.72)	15,689/56	1.59 (1.17; 2.16)	62,260/260	**1.72 (1.40; 2.12)**	48,588/425	**3.74 (3.07; 4.55)**
Ovary	65,358/226	1.00 (Ref.)	17,945/55	0.79 (0.58; 1.06)	15,688/46	0.81 (0.59; 1.12)	62,263/244	0.98 (0.82; 1.18)	48,616/192	1.01 (0.82; 1.24)
Uterine	65,368/180	1.00 (Ref.)	17,941/56	1.05 (0.78; 1.42)	15,688/62	1.44 (1.07; 1.92)	62,249/292	**1.59 (1.32; 1.92)**	48,580/458	**3.29 (2.74; 3.95)**
Prostate	39,429/1,319	1.00 (Ref.)	4,331/205	1.16 (1.00; 1.34)	31,242/1,062	1.07 (0.98; 1.16)	55,724/2,260	1.07 (1.00; 1.15)	43,724/1,419	0.93 (0.86; 1.01)
Testis	39,585/13	1.00 (Ref.)	4,360/1	0.78 (0.10; 6.00)	31,348/14	1.35 (0.63; 2.89)	55,993/21	1.24 (0.61; 2.50)	43,883/15	1.09 (0.50; 2.38)

Data are presented in hazard ratio with 95% confidence intervals. The reference group was people with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, sedentary behavior and physical activity. Central obesity (≥94 cm Men, ≥80 cm women). Significant results in red.

Supplementary Table 6: Association BMI and WC categories with cancer incidence in men and women without comorbidities.

	Normal weight (18.5 – 24.9 kg/m²)					**Overweight (≥25 kg/m²)**					
	Without central obesity		**With central obesity**			**Without central obesity**			**With central obesity**		
Cancer site	**Event**	**HR**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**
All-cause	50,463/4,216	1.00 (Ref.)	8,718/886	1.09 (1.02; 1.18)	0.353	20,967/1,756	0.98 (0.92; 1.03)	1.000	62,285/6,160	**1.07 (1.03; 1.12)**	**0.018**
Bladder	51,091/132	1.00 (Ref.)	8,850/19	0.85 (0.52; 1.38)	1.000	21,201/78	1.11 (0.84; 1.48)	1.000	63,111/216	1.02 (0.82; 1.28)	1.000
Brain	51,096/55	1.00 (Ref.)	8,852/17	1.90 (1.09; 3.29)	0.473	21,203/33	1.26 (0.81; 1.95)	1.000	63,130/112	1.50 (1.08; 2.09)	0.318
Colorectal	51,053/350	1.00 (Ref.)	8,843/66	0.97 (0.75; 1.27)	1.000	21,184/173	1.11 (0.93; 1.34)	1.000	63,054/598	1.20 (1.05; 1.37)	0.202
Kidney	51,099/66	1.00 (Ref.)	8,850/15	1.32 (0.75; 2.32)	1.000	21,204/33	1.01 (0.66; 1.54)	1.000	63,125/144	1.47 (1.09; 1.98)	0.246
Leukemia	51,093/91	1.00 (Ref.)	8,854/16	1.01 (0.59; 1.73)	1.000	21,203/41	0.90 (0.62; 1.31)	1.000	63,125/151	1.11 (0.85; 1.45)	1.000
Liver	51,098/39	1.00 (Ref.)	8,853/9	1.05 (0.50; 2.17)	1.000	21,205/12	0.72 (0.38; 1.39)	1.000	63,141/60	1.00 (0.66; 1.50)	1.000
Lung	32,725/51	1.00 (Ref.)	5,146/12	1.14 (0.61; 2.15)	1.000	13,067/19	1.04 (0.61; 1.78)	1.000	35,892/59	0.93 (0.63; 1.37)	1.000
Lymphatic	51,059/314	1.00 (Ref.)	8,847/55	0.96 (0.72; 1.28)	1.000	21,191/128	0.89 (0.72; 1.09)	1.000	63,091/452	1.01 (0.88; 1.18)	1.000
Melanoma	51,079/207	1.00 (Ref.)	8,848/30	0.83 (0.57; 1.22)	1.000	21,194/77	0.85 (0.65; 1.11)	1.000	63,107/269	1.01 (0.84; 1.22)	1.000
Multiple Myeloma	51,098/75	1.00 (Ref.)	8,853/11	0.85 (0.45; 1.61)	1.000	21,203/33	0.93 (0.61; 1.41)	1.000	63,135/94	0.91 (0.67; 1.24)	1.000
Non-Hodgkin	51,083/151	1.00 (Ref.)	8,849/27	0.95 (0.63; 1.44)	1.000	21,200/57	0.86 (0.63; 1.17)	1.000	63,116/211	1.00 (0.81; 1.24)	1.000
Esophagus	32,728/23	1.00 (Ref.)	5,146/4	1.07 (0.37; 3.14)	1.000	13,067/5	0.44 (0.17; 1.18)	1.000	35,895/33	1.07 (0.62; 1.85)	1.000
Oral	32,728/37	1.00 (Ref.)	5,148/6	1.04 (0.44; 2.49)	1.000	13,067/19	1.13 (0.64; 2.00)	1.000	35,892/37	0.80 (0.50; 1.28)	1.000
Pancreas	51,098/73	1.00 (Ref.)	8,854/13	0.90 (0.50; 1.63)	1.000	21,203/39	1.20 (0.81; 1.78)	1.000	63,129/128	1.19 (0.89; 1.60)	1.000
Stomach	51,100/40	1.00 (Ref.)	8,851/4	0.60 (0.21; 1.68)	1.000	21,205/25	1.18 (0.71; 1.95)	1.000	63,131/97	1.51 (1.04; 2.19)	0.582
Prostate	19,213/575	1.00 (Ref.)	1,582/68	1.14 (0.88; 1.47)	<0.0001	14,304/398	1.05 (1.92; 1.19)	0.490	30,328/954	1.03 (0.92; 1.114)	0.620
Testis	19,273/6	1.00 (Ref.)	1586/0	NA		14,330/5	1.06 (0.32; 3.05)	1.000	30,413/14	1.57 (0.59; 4.18)	1.000
Thyroid	51,100/22	1.00 (Ref.)	8,851/7	1.65 (0.70; 3.89)	1.000	21,206/7	0.96 (0.41; 2.29)	1.000	63,139/39	1.51 (0.88; 2.58)	1.000
Breast	31,690/771	1.00 (Ref.)	7,225/223	**1.20 (1.03; 1.40)**	**0.019**	6,828/166	1.00 (0.85; 1.19)	1.000	32,567/988	**1.21 (1.10; 1.33)**	**<0.0001**
Endometrium	31,821/64	1.00 (Ref.)	7,266/22	1.39 (0.86; 2.26)	0.258	6,871/26	**1.88 (1.19; 2.98)**	**0.007**	32,708/165	**2.36 (1.76; 3.17)**	**<0.0001**
Ovary	31,813/93	1.00 (Ref.)	7,263/26	1.08 (0.70;1.67)	1.000	6,871/15	0.72 (0.41; 1.24)	0.229	32,710/128	1.19 (0.90; 1.57)	1.000
Uterine	31,818/80	1.00 (Ref.)	7,266/22	1.12 (0.70; 1.80)	1.000	6,871/31	**1.79 (1.18; 2.72)**	**0.006**	32,700/182	**2.09 (1.59; 2.73)**	**<0.0001**

Data are presented in hazard ratio with 95% confidence intervals. The reference group was people with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, diet score, sedentary behavior and physical activity. Central obesity (≥94 cm Men, ≥80 cm women). Significant results in red.

Supplementary Table 7: Association of BMI and WC categories with cancer incidence in incidence in men and women of white ethnic background.

	Normal weight (18.5 – 24.9 kg/m^2)					Overweight (≥25 kg/m^2)					
	Without central obesity		With central obesity			Without central obesity			With central obesity		
Cancer site	**Event**	**HR**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**	**Event**	**HR (95% CI)**	**P adj**
All-cause	98,558/9686	1.00 (Ref.)	20,788/2406	1.06 (1.01; 1.11)	0.291	44,616/4662	0.98 (0.95; 1.01)	1.000	196,103/24193	**1.05 (1.03; 1.08)**	**0.001**
Bladder	100,076/331	1.00 (Ref.)	21,172/54	0.78 (0.58; 1.04)	1.000	45,242/217	1.05 (0.89; 1.25)	1.000	199,695/1037	1.10 (0.97; 1.25)	1.000
Brain	100,101/124	1.00 (Ref.)	21,180/40	1.51 (1.05; 2.16)	0.523	45,262/98	1.56 (1.19; 2.04)	0.280	199,811/323	1.16 (0.94; 1.44)	1.000
Colorectal	99,992/798	1.00 (Ref.)	21,151/195	1.05 (0.89; 1.23)	1.000	45,206/399	1.00 (0.88; 1.13)	1.000	199,463/2356	**1.23 (1.13; 1.34)**	**<0.0001**
Kidney	100,105/156	1.00 (Ref.)	21,178/46	1.32 (0.95; 1.83)	1.000	45,254/106	1.19 (0.93; 1.53)	1.000	199,781/692	**1.59 (1.33; 1.90)**	**<0.0001**
Leukemia	100,093/213	1.00 (Ref.)	21,183/47	0.97 (0.70; 1.33)	1.000	45,261/110	0.97 (0.77; 1.22)	1.000	199,806/605	1.13 (0.96; 1.33)	1.000
Liver	100,113/103	1.00 (Ref.)	21,181/27	1.05 (0.69; 1.61)	1.000	45,264/37	0.66 (0.45; 0.97)	0.679	199,836/418	1.30 (1.04; 1.63)	0.322
Lung	60,659/110	1.00 (Ref.)	11,569/29	1.11 (0.73; 1.67)	1.000	26,085/54	1.16 (0.83; 1.62)	1.000	102,669/229	1.00 (0.79; 1.27)	1.000
Lymphatic	100,017/685	1.00 (Ref.)	21,165/160	1.01 (0.85; 1.20)	1.000	45,233/328	0.94 (0.82; 1.08)	1.000	199,651/1836	1.09 (1.00; 1.20)	0.811
Melanoma	100,057/420	1.00 (Ref.)	21,171/88	0.96 (0.76; 1.21)	1.000	45,242/207	1.02 (0.86; 1.21)	1.000	199,734/964	1.08 (0.96; 1.22)	1.000
Multiple Myeloma	100,109/143	1.00 (Ref.)	21,180/27	0.83 (0.55; 1.25)	1.000	45,261/74	1.03 (0.78; 1.37)	1.000	199,829/387	1.15 (0.94; 1.40)	1.000
Non-Hodgkin	100,073/333	1.00 (Ref.)	21,172/79	1.02 (0.79; 1.30)	1.000	45,252/157	0.94 (0.78; 1.14)	1.000	199,751/854	1.05 (0.92; 1.20)	1.000
Esophagus	60,667/55	1.00 (Ref.)	11,571/9	0.82 (0.40; 1.66)	1.000	26,089/25	0.85 (0.53; 1.37)	1.000	102,671/169	1.33 (0.97; 1.82)	0.957
Oral	60,664/73	1.00 (Ref.)	11,574/12	0.92 (0.50; 1.71)	1.000	26,084/37	0.99 (0.66; 1.47)	1.000	102,676/125	0.87 (0.64; 1.18)	1.000
Pancreas	100,108/198	1.00 (Ref.)	21,183/43	0.88 (0.63; 1.22)	1.000	45,262/111	1.10 (0.87; 1.39)	1.000	199,796/606	1.17 (0.99; 1.38)	0.920
Stomach	100,112/107	1.00 (Ref.)	21,179/27	1.18 (0.77; 1.80)	1.000	45,259/66	1.04 (0.77; 1.42)	1.000	199,811/433	**1.43 (1.15; 1.78)**	**0.022**
Prostate	37,205/1257	1.00 (Ref.)	4,094/202	1.20 (1.04; 1.40)	0.106	29,966/1024	1.06 (0.98; 1.16)	0.144	95,109/3563	**1.16 (1.08; 1.24)**	**<0.0001**
Testis	37,347/12	1.00 (Ref.)	4,121/2	0.83 (0.18; 3.71)	1.000	29,966/13	2.28 (1.04; 5.02)	0.809	95,109/36	1.47 (0.75; 2.90)	1.000
Thyroid	100,115/53	1.00 (Ref.)	21,181/11	0.86 (0.45; 1.64)	1.000	45,267/20	1.01 (0.60; 1.71)	1.000	199,847/150	1.36 (0.98; 1.89)	0.920
Breast	62,475/1551	1.00 (Ref.)	16,971/527	**1.19 (1.08; 1.32)**	**0.005**	15,212/385	1.02 (0.91; 1.14)	0.737	103,727/3296	**1.24 (1.17; 1.32)**	**0.015**
Endometrium	62,758/142	1.00 (Ref.)	17,050/53	1.26 (0.91; 1.72)	0.152	15,292/56	**1.59 (1.16; 2.16)**	**0.004**	104,237/645	**2.45 (2.03; 2.95)**	**<0.0001**
Ovary	62,745/219	1.00 (Ref.)	17,051/52	0.78 (0.57; 1.05)	1.000	15,290/47	0.85 (0.62; 1.16)	0.305	104,265/417	1.01 (0.85; 1.20)	1.000
Uterine	62,750/173	1.00 (Ref.)	17,047/54	1.06 (0.78; 1.44)	0.649	15,291/61	**1.42 (1.06; 1.90)**	**0.019**	104,218/702	**2.20 (1.85; 2.62)**	**<0.0001**

Data are presented in hazard ratio with 95% confidence intervals. Cox proportional hazard were done. The reference group was men with normal BMI and normal WC. Analyses were adjusted for age, education, deprivation, ethnicity, comorbidity, diet score, smoking, sedentary behavior and physical activity. Central obesity (≥94 cm Men, ≥80 cm women). Significant results in red.

Chapter 6. Absolute and relative grip strength as predictors of cancer: Prospective cohort study of 445,552 participants in UK Biobank

6.1 Abstract

Background: Reduced muscular strength, as measured by absolute grip strength, has been associated with increased risk of some site-specific cancers. The ability of grip strength to predict other diseases may be affected by whether it is expressed in absolute or relative terms, but the evidence for cancer is scarce. This study compared the associations of absolute and relative grip strength with all-cause and 15 site-specific cancers.

Methods: A prospective cohort study was undertaken using data from the UK Biobank. The exposure variable was grip strength, in absolute form (kg) and relative to weight, body mass index (BMI), height and body fat mass (BFM). The outcome was incident cancer; at 15 sites and overall. Cox proportional hazard models were performed to study the associations.

Results: This study included 445,552 participants, where 53.8% of the participants were women, with a mean (SD) age of 56.3 (8.11) years. During a median of 8.8-year follow-up period, 48,886 (11.0 %) patients were diagnosed with cancer. After adjusting for sociodemographic and lifestyle factors, as well as multiple testing, absolute grip strength was inversely and linearly associated with endometrial (HR: 0.74, 95% CI: 0.69; 0.79, p value <0.001), gallbladder (HR: 0.81, 95% CI: 0.72; 0.92, p value = 0.001), liver (HR: 0.86, 95% CI: 0.79; 0.93, p value <0.001), kidney (HR: 0.93, 95% CI: 0.88; 0.99), and breast (HR: 0.93, 95% CI: 0.91; 0.96 p value = 0.031), as well as all-cause cancer (HR: 0.97, 95% CI: 0.95; 0.98, p value <0.001). Eight cancer sites were inversely associated with HGS relative to weight and BMI: endometrium, liver, gallbladder, kidney, oesophagus, pancreas, colorectal, and breast cancer, and all-cause cancer. Compared with absolute grip strength, grip strength relative to BFM had better discriminatory power for head and neck and breast cancer. Grip strength relative

to BMI was marginally better than absolute grip strength in predicting stomach cancer.

Conclusions: Grip strength was associated with risk of several site-specific cancers and all-cause cancer. Head and neck and breast cancers might be better predicted by relative grip strength.

6.2 Introduction:

There were 19.3 million new cancer cases in 2020 (International Agency for Research on Cancer, 2021) and, by 2040, this number is expected to increase to 27.5 million (GLOBOCAN, 2018). To alleviate the burden of cancer, several public health guidelines have been developed. The current physical activity guidelines include recommendations that aim to increase and maintain muscular strength across the life span (Rock et al., 2020).

One of the most common muscle strength markers, in clinical and research settings, is handgrip strength (HGS) as it correlates well with overall strength (Wu et al., 2017, Buckner et al., 2019). HGS is a simple, non-invasive and low-cost method, that has been associated with several chronic diseases and all-cause mortality across different age groups (Ho et al., 2019, Welsh et al., 2020, Yeung et al., 2019). HGS has been associated with a range of health outcomes such as all-cause mortality, cardiovascular diseases and some site-specific cancers (colorectal, lung, and breast) as well as all-cause cancer (Buckner et al., 2019, Celis-Morales et al., 2017, Ntuk et al., 2017, Welsh et al., 2020). However, evidence regarding the association of grip strength with cancer has been mainly restricted to absolute HGS, with limited and conflicting evidence available for site-specific cancers (Celis-Morales et al., 2018, Wu et al., 2017, Garcia-Hermoso et al., 2018).

A meta-analysis published in 2018, which included 309,413 participants and 9,787 cases, found no association between HGS and overall cancer mortality. However, the categorisation of strength and adjustment for covariates was heterogeneous between studies, and there was no differentiation between sites of cancer (Garcia-Hermoso et al., 2018). The Prospective Urban Rural Epidemiology (PURE) study, which included data from 139,691 participants

across 17 countries, reported that absolute HGS (per 5 kg reduction in HGS) was associated with increased overall cancer risk, especially in participants from high-income countries (Leong et al., 2015). Some previous studies in UK Biobank reported associations of absolute HGS with all-cause cancer, colorectal, lung, and breast cancer incidence and mortality (Celis-Morales et al., 2018). Whilst similar results were reported by Yates et al., the authors concluded that the association between absolute HGS and all-cause cancer mortality was less consistent than other diseases (Yates et al., 2017). Individual study findings have also been inconsistent across cancer sites (Wu et al., 2017, Yates et al., 2017, Garcia-Hermoso et al., 2018). Hence, Wu Y. et al., in a meta-analysis that included 42 studies, did not find an association between HGS and overall cancer (HR: 0.89, 95% confidence interval (CI): 0.66-1.20) (Wu et al., 2017).
Studies have shown that relative HGS might be a better indicator for muscle weakness (Alley et al., 2014), as well as more predictive of cardiometabolic diseases (Churilla et al., 2020). Because of these, there is yet a consensus on how HGS should be used in clinical practice (Roberts et al., 2011). To our knowledge, all existing studies on HGS and cancer expressed HGS in absolute terms. The aims of this study, therefore, were to investigate the associations of HGS, expressed 1) in absolute terms (kilograms) and 2) relative to anthropometric variables, with 15 cancer sites and all-cause cancer and to compare risk prediction scores of HGS when differentially expressed.

6.3 Methods

Study design

Between April 2007 and December 2010, UK Biobank recruited ~502,000 participants, aged 37–73 years from the general population (Collins, 2012).

Participants attended 1 of 22 assessment centres across England, Wales, and Scotland (Sudlow et al., 2015), where they completed a touch-screen questionnaire, had physical measurements taken and provided biological samples, as described in detail elsewhere (Sudlow et al., 2015, Palmer, 2007). In this prospective population-based study, 15 site-specific cancers and all-cause cancer incidence (fatal/non-fatal) were the outcomes, HGS was the exposure variables; and socio-demographic factors (age, ethnicity, area socioeconomic deprivation index), smoking status, sedentary behaviour, physical activity, height, diet (red and processes meat, oily fish and alcohol) and multimorbidity were covariates. After excluding participants with cancer at baseline (n=41,406), and with missing data for the exposure and covariates (n=15,534), our sample was restricted to the 445,552 participants who had full data available.

Procedure:

Hospital admissions were identified via record linkage to Health Episode Statistics records for England (01 June 2020) and Wales (31 March 2017) and to Scottish Morbidity Records for Scotland (31 March 2017). The International Classification of Diseases, 10th revision (ICD-10) was used to define the following 15 cancers: all cancers (C00-C97, D37, D48), and oral (C00-C14), oesophageal (C15), stomach (C16), colorectal (C18, C19, and C20), liver (C22), gallbladder (C23), pancreatic (C25), lung (C34), kidney (C64-C65), bladder (C67), breast (C50), endometrial (C54), cervical (C53), ovarian (C56), and prostate (C61) cancer. Of these, 10 cancer sites were used for men and women; one site was specific to men (prostate) and four to women (breast, endometrium, cervix and ovary). Potential confounders were identified a priori based on established relationships with cancer and muscular strength. Area-based socioeconomic status was derived from postcode of residence, using the Townsend score (Townsend P et al., 1988). Age at baseline was calculated from date of birth and

date of baseline assessment. Medical history (physician diagnosis of depression, stroke, angina, heart attack, hypertension, cancer, diabetes, or long-standing illness), ethnicity, smoking status (never, former, or current smoker) and female reproductive factors were collected from the self-completed, baseline questionnaire. Dietary intake was collected via a food frequency questionnaire, with participants asked how many portions of red meat, processed meat, and fish they generally ate. Total time spent in discretionary sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Anthropometric measurements, height and weight were obtained during the baseline assessment by trained clinic staff using standard operating procedures and regularly calibrated equipment. Body fat was measured using the Tanita BC-418 MA body composition analyser (fat mass divided by the total body mass). Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk)

Exposures:

HGS was assessed using a Jamar J00105 hydraulic hand dynamometer (Patterson Medical, Sutton-in-Ashfield, UK), and the mean of the right and left hand values, expressed as kg, was used in the analysis, as reported elsewhere (Arnold et al., 2010, Celis-Morales et al., 2017). Five representations of HGS were analysed: (1) absolute HGS in kg, (2) HGS divided by height, (3) HGS divided by weight, (4) HGS divided by BMI, (5) HGS divided by body fat mass (BFM) in kg. All these variables were standardised using sex-specific mean and standard deviation of the whole sample ([X – Mean] ÷ SD).

Statistical analyses

Continuous variables were summarised using mean and standard deviation, and categorical variables using frequencies and percentages. Non-linear associations between HGS and cancer sites were visually explored using multivariable

penalised cubic splines in Cox-proportional hazard models (Eisen et al., 2004). Penalised spline is a technique that balances data fit and smoothness (Eilers and Marx, 1996). Spline curvature is penalised by the integrated second derivative. Knots were selected based on generalised cross-validation and were equally spaced across the range of the exposure variable. The results were reported as hazard ratios together with 95% confidence intervals (CIs). Analyses were adjusted for baseline age (at time of hand grip assessment), sex, ethnicity, Townsend deprivation index, height, smoking status, dietary intake (alcohol, red meat, oily fish, and processed meat), sedentary behaviour, physical activity, comorbidities (longstanding illness, diabetes, hypertension, cardiovascular disease (CVD), cancer, and depression), as well as height when it was not included in the exposure. Additional covariates were added for breast, cervical, endometrial, and ovarian cancer: hormonal replacement (yes/no), contraceptive use (yes/no) and age at menarche. Finally, because of potentially inflated type-I errors due to multiple tests, we provided the adjusted p-values (denoted as P_{adj}) using Holm's method controlling family-wise error rate (ETH Zurich).

We calculated Harrell's C-index (which estimates the probability of concordance between observed and predicted responses) to compare the discriminatory power of HGS markers (Harrell et al., 1996). The proportional hazard assumption was checked by tests based on Schöenfeld residuals. All analyses were performed using R Statistical Software version 3.6.2 with the package survival. Statistical significance was set at $\alpha < 0.05$.

Patient involvement

No patients were involved in setting the research question or the outcome measures.

6.4 Results

Characteristics of the study population

445,552 participants were included in the analysis. The median follow-up period was 8.8 years [IQR 7.9—9.6]. During the follow-up period, 48,886 (11.0%) people developed cancer. Table 6-1 presents the characteristics of the study population. In summary, 53.8% of the cohort were women, the mean (SD) age was 56.3 (8.11) years, and the majority were white. People with lower HGS had a higher mean weight and waist circumference than those with moderate and higher strength, as well as a higher prevalence of obesity. No substantial differences were observed in lifestyle variables. However, more people in the lower strength group had been diagnosed with diabetes and hypertension and they had a higher multimorbidity count compared with people in the moderate and higher strength groups.

Table 6-1: Baseline characteristics by tertials of grip strength

	Lower HGS	Moderate HGS	Higher HGS	Overall
Sociodemographic				
N (%)	145,337 (32.6%)	152,701 (34.3%)	147,514 (33.1%)	445,552
Age Mean (SD)	58.6 (7.58)	56.7 (7.91)	53.4 (7.97)	56.3 (8.11)
Sex				
Females	79,127 (54.4%)	79,917 (52.3%)	80,794 (54.8%)	239,838 (53.8%)
Males	66,210 (45.6%)	72,784 (47.7%)	66,720 (45.2%)	205,714 (46.2%)
Townsend deprivation index				
Lower	43,016 (29.6%)	53,120 (34.8%)	54,111 (36.7%)	150,247 (33.7%)
Middle	47,056 (32.4%)	51,784 (33.9%)	50,158 (34.0%)	148,998 (33.4%)
Higher	55,265 (38.0%)	47,797 (31.3%)	43,245 (29.3%)	146,307 (32.8%)
Ethnicity				
White	135,052 (92.9%)	145,503 (95.3%)	140,908 (95.5%)	421,463 (94.6%)
Mixed	2,420 (1.7%)	2,081 (1.4%)	2,175 (1.5%)	6,676 (1.5%)
South Asian	4,881 (3.4%)	2,430 (1.6%)	1,521 (1.0%)	8,832 (2.0%)
Black	2,593 (1.8%)	2,240 (1.5%)	2,333 (1.6%)	7,166 (1.6%)
Chinese	391 (0.3%)	447 (0.3%)	577 (0.4%)	1,415 (0.3%)
Anthropometric				
Height (m)	1.7 (0.09)	1.7 (0.09)	1.7 (0.10)	1.7 (0.09)
Weight (Kg)	81.4 (15.58)	77.8 (14.45)	75.2 (17.04)	78.1 (15.92)
Waist (cm)	94.8 (12.86)	90.1 (12.28)	85.9 (13.69)	90.2 (13.44)
Body fat percentage (%)	4.2 (9.55)	31.3 (8.15)	28.5 (6.75)	31.3 (8.54)
Body Mass index (kg/m2)	29.2 (5.43)	27.2 (4.07)	25.8 (4.07)	27.4 (4.77)
BMI (kg/m2)				
Underweight	443 (0.3%)	365 (0.2%)	1,424 (1.0%)	2,232 (0.5%)
Normal	30,431 (20.9%)	47,183 (30.9%)	67,814 (46.0%)	145,428 (32.6%)
Overweight	59,897 (41.2%)	72,249 (47.3%)	57,704 (39.1%)	189,850 (42.6%)
Obese	54,566 (37.5%)	32,904 (21.5%)	20,572 (13.9%)	108,042 (24.2%)
Lifestyle				
Smoking				
Never	78,642 (54.1%)	83,729 (54.8%)	83,776 (56.8%)	246,147 (55.2%)
Previous	51,866 (35.7%)	53,281 (34.9%)	47,681 (32.3%)	152,828 (34.3%)
Current	14,829 (10.2%)	15,691 (10.3%)	16,057 (10.9%)	46,577 (10.5%)
Alcohol intake				
Daily or almost daily	26,001 (17.9%)	32,400 (21.2%)	32,484 (22.0%)	90,885 (20.4%)

3-4 times a week	28,923 (19.9%)	36,618 (24.0%)	38,577 (26.2%)	104,118 (23.4%)
Once or twice a week	36,448 (25.1%)	39,956 (26.2%)	39,216 (26.6%)	115,620 (25.9%)
1-3 times a month	17,093 (11.8%)	16,848 (11.0%)	15,851 (10.7%)	49,792 (11.2%)
Special occasions only	21,104 (14.5%)	16,138 (10.6%)	13,119 (8.9%)	50,361 (11.3%)
Never	15,768 (10.8%)	10,741 (7.0%)	8,267 (5.6%)	34,776 (7.8%)
Fruit and vegetable intake (portion/day)	2.0 (0.83)	2.0 (0.83)	2.0 (0.83)	2.0 (0.83)
Red meat (portion/week)	2.1 (1.49)	2.1 (1.43)	2.1 (1.42)	2.1 (1.45)
Processed meat (portion/week)	1.9 (1.06)	1.9 (1.06)	1.8 (1.07)	1.9 (1.06)
Oily fish (portion/week)	1.6 (0.95)	1.6 (0.92)	1.6 (0.91)	1.6 (0.93)
Sedentary time (h/day)	5.2 (2.36)	5.0 (2.24)	4.9 (2.23)	5.0 (2.28)
Physical activity (h/day)	2.1 (1.94)	1.8 (1.59)	1.7 (1.43)	1.8 (1.67)
Health				
Diabetes diagnostic				
No	133,364 (91.8%)	146,313 (95.8%)	144,063 (97.7%)	423,740 (95.1%)
Yes	11,973 (8.2%)	6,388 (4.2%)	3,451 (2.3%)	21,812 (4.9%)
Hypertension diagnostic				
No	95,572 (65.8%)	113,819 (74.5%)	119,971 (81.3%)	329,362 (73.9%)
Yes	49,765 (34.2%)	38,882 (25.5%)	27,543 (18.7%)	116,190 (26.1%)
Multimorbidty				
No illness	40,045 (27.6%)	57,711 (37.8%)	68,780 (46.6%)	166,536 (37.4%)
1+ illness	105,292 (72.4%)	94,990 (62.2%)	78,734 (53.4%)	279,016 (62.6%)

Data are shown in n (%) and Mean (SD): SD: Standard deviation, Data available 445,552.

Absolute HGS *and incident cancers*

Absolute HGS was inversely associated with five cancer sites: endometrium (HR: 0.74, 95% CI: 0.69; 0.79, p value <0.001), gallbladder (HR: 0.81, 95% CI: 0.72; 0.92, p value = 0.001), liver (HR: 0.86, 95% CI: 0.79; 0.93, p value <0.001), kidney (HR: 0.93, 95% CI: 0.88; 0.99, p value = 0.031), and breast (HR: 0.94, 95% CI: 0.91; 0.96, p value <0.001), as well as all-cause cancer (HR: 0.97, 95% CI: 0.95; 0.98, p value <0.001) (Figure 6-1 and Table S1). There was no strong evidence to suggest nonlinear associations (Figure S2).

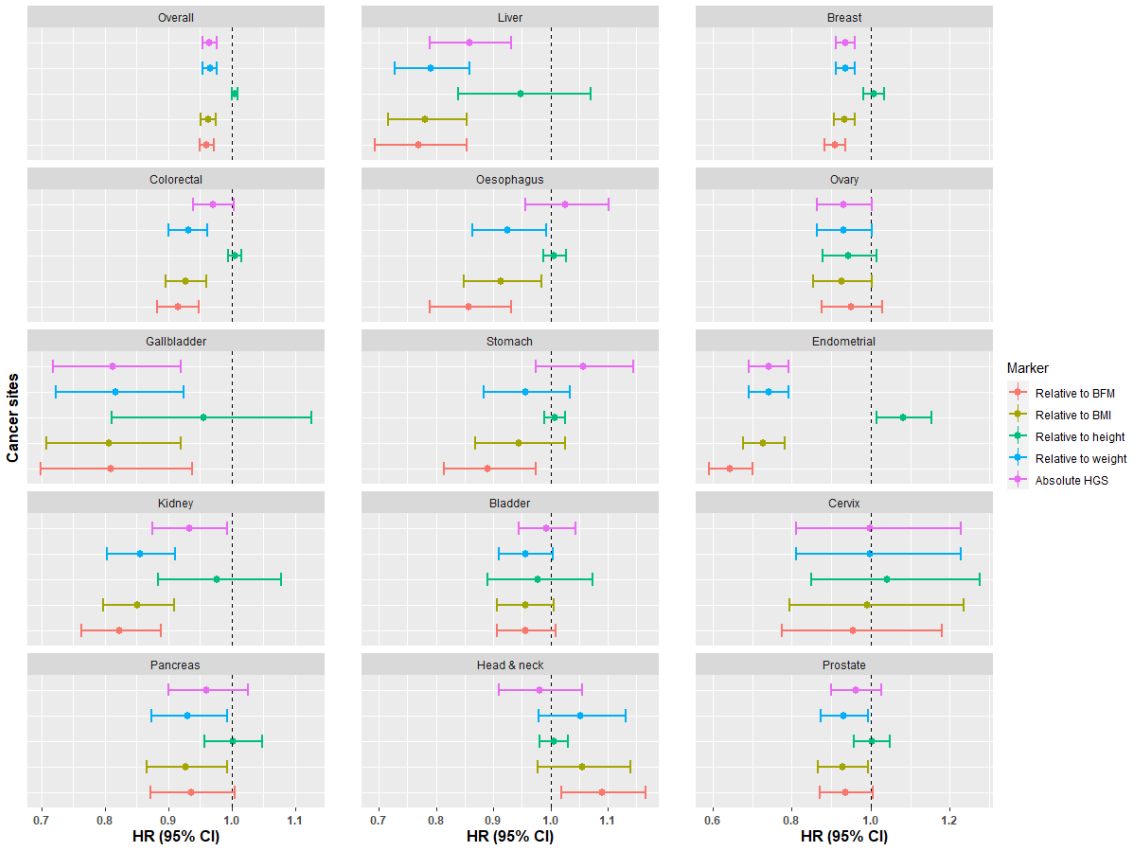

Figure 6-1: Association between relative grip strength and cancer incidence for 15 cancer.

Relative HGS *and incident cancers*

Eight cancer sites were inversely associated with HGS relative to weight and BMI: endometrium, liver, gallbladder, kidney, oesophagus, pancreas, colorectal, and breast cancer, and all-cause cancer. The majority of these associations were

linear (Table S1, Figure S2 and S3). The association patterns were similar for HGS relative to BFM, except that the association with stomach cancer was significant and with pancreatic cancer was not (Table S1 and Figure S5). HGS relative to height was inversely associated with only endometrial and lung cancer, as well as overall cancer (Table S1 and Figure S4). Prostate cancer was positively associated with almost all HGS markers (Figure 1 and Table S1) and head and neck cancer were positively associated with HGS relative to BFM.

C-index

Table 6-2 shows the Harrell's C-indices for prediction of overall and site-specific cancers. There were no significant differences in C-indices between HGS expressed in absolute and relative terms for most cancer sites. However, HGS relative to BFM was better than absolute HGS in predicting head and neck and breast cancer. Also, HGS relative to BMI was better than absolute HGS at predicting stomach cancer.

Table 6-2: C-indices of absolute and relative HGS in predicting cancer incidence.

	Absolute HGS (95% CI)	Relative HGS (95% CI)	Difference (95% CI)	p-value
Handgrip to weight				
Overall	0.6506 (0.6478; 0.6533)	0.6515 (0.6487; 0.6543)	-0.0009 (-0.0013; -0.0006)	**<0.001**
Head and neck	0.6774 (0.6580; 0.6959)	0.6753 (0.6558; 0.6943)	0.0020 (0.0001; 0.0039)	**0.035**
Oesophagus	0.7686 (0.7539; 0.7828)	0.7687 (0.7540; 0.7827)	-0.0001 (-0.0016; 0.0015)	0.945
Bladder	0.7742 (0.7642; 0.7840)	0.7741 (0.7641; 0.7839)	0.0001 (-0.0004; 0.0006)	0.742
Colorectal	0.6691 (0.6613; 0.6767)	0.6686 (0.6609; 0.6763)	0.0004 (-0.0005; 0.0013)	0.384
Gallbladder	0.6743 (0.6450; 0.7023)	0.6770 (0.6476; 0.7050)	-0.0026 (-0.0063; 0.0010)	0.154
Kidney	0.7111 (0.6973; 0.7243)	0.7091 (0.6953; 0.7226)	0.0019 (-0.0006; 0.0045)	0.135
Pancreas	0.6979 (0.6837; 0.7116)	0.6979 (0.6837; 0.7117)	0.0000 (-0.0016; 0.0016)	0.984
Stomach	0.7369 (0.7195; 0.7533)	0.7375 (0.7200; 0.7542)	-0.0006 (-0.0025; 0.0013)	0.552
Lung	0.8209 (0.8135; 0.8281)	0.8212 (0.8138; 0.8284)	-0.0003 (-0.0006; -0.0001)	**0.003**
Prostate	0.6809 (0.6757; 0.6861)	0.6807 (0.6755; 0.6859)	0.0002 (-0.0002; 0.0005)	0.332
Breast	0.5470 (0.5401; 0.5539)	0.5552 (0.5483; 0.5620)	-0.0082 (-0.0121; -0.0043)	**<0.001**
Endometrium	0.6497 (0.6339; 0.6653)	0.6497 (0.6338; 0.6652)	0.0001 (-0.0003; 0.0004)	0.761
Handgrip to height				
Overall	0.6502 (0.6475; 0.6530)	0.6515 (0.6487; 0.6543)	-0.0013 (-0.0016; -0.0009)	**<0.001**

Head and neck	0.6765 (0.6571; 0.6953)	0.6753 (0.6558; 0.6943)	0.0012 (0.0001; 0.0023)	**0.039**
Oesophagus	0.7686 (0.7539; 0.7826)	0.7687 (0.7540; 0.7827)	-0.0001 (-0.0005; 0.0003)	0.549
Bladder	0.7740 (0.7639; 0.7838)	0.7741 (0.7641; 0.7839)	-0.0001 (-0.0006; 0.0003)	0.517
Colorectal	0.6680 (0.6602; 0.6756)	0.6686 (0.6609; 0.6763)	-0.0007 (-0.0015; 0.0001)	0.104
Gallbladder	0.6678 (0.6384; 0.6961)	0.6770 (0.6476; 0.7050)	-0.0091 (-0.0170; -0.0013)	**0.023**
Kidney	0.7079 (0.6940; 0.7214)	0.7091 (0.6953; 0.7226)	-0.0013 (-0.0034; 0.0009)	0.250
Pancreas	0.5438 (0.5370; 0.5506)	0.5552 (0.5483; 0.5620)	-0.0114 (-0.0160; -0.0067)	**<0.001**
Stomach	0.6805 (0.6753; 0.6857)	0.6807 (0.6755; 0.6859)	-0.0002 (-0.0006; 0.0002)	0.284
Lung	0.7332 (0.7149; 0.7509)	0.7356 (0.7174; 0.7531)	-0.0024 (-0.0054; 0.0006)	0.111
Prostate	0.6970 (0.6829; 0.7109)	0.6979 (0.6837; 0.7117)	-0.0009 (-0.0024; 0.0007)	0.284
Breast	0.6319 (0.6163; 0.6470)	0.6497 (0.6338; 0.6652)	-0.0177 (-0.0293; -0.0062)	**0.003**
Endometrium	0.8212 (0.8138; 0.8283)	0.8212 (0.8138; 0.8284)	-0.0001 (-0.0003; 0.0002)	0.655
Handgrip to BMI				
Overall	0.6503 (0.6475; 0.6531)	0.6515 (0.6487; 0.6543)	-0.0012 (-0.0016; -0.0009)	**<0.001**
Head and neck	0.6774 (0.6580; 0.6959)	0.6753 (0.6558; 0.6943)	0.0020 (0.0002; 0.0039)	**0.033**
Oesophagus	0.7687 (0.7540; 0.7829)	0.7687 (0.7540; 0.7827)	0.0000 (-0.0016; 0.0015)	0.986
Bladder	0.7741 (0.7640; 0.7839)	0.7741 (0.7641; 0.7839)	0.0000 (-0.0006; 0.0005)	0.860
Colorectal	0.6686 (0.6608; 0.6762)	0.6686 (0.6609; 0.6763)	-0.0001 (-0.0010; 0.0009)	0.867

Gallbladder	0.6730 (0.6436; 0.7011)	0.6770 (0.6476; 0.7050)	-0.0040 (-0.0088; 0.0008)	0.102
Kidney	0.7099 (0.6961; 0.7232)	0.7091 (0.6953; 0.7226)	0.0008 (-0.0019; 0.0035)	0.572
Pancreas	0.5446 (0.5377; 0.5514)	0.5552 (0.5483; 0.5620)	-0.0106 (-0.0150; -0.0062)	**<0.001**
Stomach	0.6810 (0.6758; 0.6862)	0.6807 (0.6755; 0.6859)	0.0003 (0.0000; 0.0006)	**0.046**
Lung	0.7367 (0.7184; 0.7545)	0.7356 (0.7174; 0.7531)	0.0011 (-0.0021; 0.0043)	0.501
Prostate	0.6975 (0.6833; 0.7112)	0.6979 (0.6837; 0.7117)	-0.0004 (-0.0021; 0.0013)	0.619
Breast	0.6482 (0.6323; 0.6638)	0.6497 (0.6338; 0.6652)	-0.0015 (-0.0040; 0.0010)	0.232
Endometrium	0.8209 (0.8135; 0.8281)	0.8212 (0.8138; 0.8284)	-0.0003 (-0.0005; -0.0001)	**0.003**
Handgrip to BFM				
Overall	0.6506 (0.6478; 0.6533)	0.6515 (0.6487; 0.6543)	-0.0009 (-0.0013; -0.0006)	**<0.001**
Head and neck	0.6783 (0.6589; 0.6968)	0.6753 (0.6558; 0.6943)	0.0030 (0.0003; 0.0057)	**0.031**
Oesophagus	0.7692 (0.7545; 0.7837)	0.7687 (0.7540; 0.7827)	0.0006 (-0.0018; 0.0029)	0.638
Bladder	0.7742 (0.7641; 0.7839)	0.7741 (0.7641; 0.7839)	0.0000 (-0.0005; 0.0005)	0.947
Colorectal	0.6692 (0.6614; 0.6769)	0.6686 (0.6609; 0.6763)	0.0005 (-0.0006; 0.0017)	0.338
Gallbladder	0.6724 (0.6429; 0.7007)	0.6770 (0.6476; 0.7050)	-0.0046 (-0.0108; 0.0017)	0.152
Kidney	0.7113 (0.6976; 0.7244)	0.7091 (0.6953; 0.7226)	0.0022 (-0.0012; 0.0056)	0.201
Pancreas	0.5503 (0.5434; 0.5572)	0.5552 (0.5483; 0.5620)	-0.0049 (-0.0089; -0.0008)	**0.019**
Stomach	0.6809 (0.6757; 0.6861)	0.6807 (0.6755; 0.6859)	0.0002 (-0.0002; 0.0006)	0.408

Lung	0.7362 (0.7177; 0.7546)	0.7356 (0.7174; 0.7531)	0.0006 (-0.0032; 0.0044)	0.771
Prostate	0.6975 (0.6834; 0.7112)	0.6979 (0.6837; 0.7117)	-0.0004 (-0.0021; 0.0013)	0.667
Breast	0.6617 (0.6455; 0.6783)	0.6497 (0.6338; 0.6652)	0.0120 (0.0077; 0.0164)	**<0.001**
Endometrium	0.8208 (0.8134; 0.8281)	0.8212 (0.8138; 0.8284)	-0.0004 (-0.0007; -0.0001)	**0.004**

6.5 Discussions

This paper reports the associations between HGS, in absolute and relative terms, and incident site-specific and all-cause cancer and explores the relative performance of these emerging risk markers in cancer risk prediction. Eight cancer sites were inversely associated with strength relative to weight, BMI, and BFM. Meanwhile, five cancer sites were inversely associated with absolute HGS. HGS expressed in relative terms modestly improved the prediction of head and neck, stomach, and breast cancer.

Comparisons with other studies

The association patterns shown in this study are generally consistent with previous studies. HGS (per 5-kg decreases) was previously associated with lung, breast and colorectal cancer (Celis-Morales et al., 2018). In our study, both absolute and relative HGS, apart from HGS relative to height, were associated with breast cancer. Only relative HGS was associated with colorectal cancer and, whilst absolute HGS was associated with incident lung cancer in the partially adjusted models, it was not in the fully adjusted model including comorbidities. To date, all studies have focused on absolute HGS, with equivocal results with most evidence relating to all-cause cancer (Celis-Morales et al., 2018, Leong et al., 2015). Gale et al., found a 19% decrease in overall cancer risk per 1-SD increase of HGS (Gale et al., 2007), but García-Hermoso et al. did not find the same association for cancer mortality (HR: 0.97, 95% CI, 0.92-1.02) (Garcia-Hermoso et al., 2018). A previous large-scale study, showed a positive association between HGS and cancer mortality, but only in high-income countries (Leong et al., 2015), consistent with our finding that, in the UK population, absolute and relative HGS were associated with lower risk of all-cause cancer.

HGS has been suggested as a good risk marker for other diseases, such as CVD, irrespective of which HGS marker is used (Ho et al., 2019). HGS is a cheap and easy measure to incorporate into clinical practice (Yeung et al., 2018). In our study, absolute HGS was a predictor of five site-specific cancers as well as all-cause cancer. Better prediction for some site-specific cancers was achieved by using relative HGS. Further studies should explore the clinical utility of using absolute and relative HGS in the prevention and early detection of cancers.

The main finding of the current study was that when comparing numerous different ways to express HGS - absolute and relative to height, weight, BMI, and BFM - relative HGS only showed a modestly improvement in prediction of two groups of cancers. These findings could have important public health implications in terms of the operationalisation of HGS in predicting cancer risk (Ho et al., 2019). This study demonstrates that the most basic form of reporting grip strength, namely in absolute units (kg), is largely sufficient for predicting cancer outcomes in clinical practice and further adjust might not be needed.

Limitations of this study

UK Biobank is not representative of the general population in terms of deprivation and lifestyle (Collins, 2012, Sudlow et al., 2015). However, effect size estimates were generally consistent with population representative cohorts (Batty et al., 2020). As in all observational studies, residual confounding is possible, and association may not imply causation. Nonetheless, we minimised the risk of reverse causation using a two-year landmark analysis. Even though UK Biobank has large sample size, there were small numbers of events for some site-specific cancers which, therefore, might be underpowered.

6.6 Conclusion

HGS was associated with a higher risk of several cancer sites and all-cause

cancer. HGS expressed in relative terms modestly improved the prediction of head and neck and breast cancers. Therefore, expressing grips strength in it most simple unit (kg) appears adequate for predicting cancer outcomes.

6.7 References Chapter 6

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6.8 Additional File Chapter 6

Table S1: Association between HGS z-scores and cancer incidence

		Absolute HGS		**Relative to weight**		**Relative to height**		**Relative to BMI**		**Relative to BFM**	
Cancer	Total/events	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Overall	437,170/37,085	0.97 (0.95; 0.98)	<0.001	0.97 (0.95; 0.98)	<0.001	1.00 (1.00; 1.01)	0.013	0.96 (0.95; 0.97)	<0.001	0.96 (0.95; 0.97)	<0.001
Head & neck	442,799/848	0.98 (0.91; 1.06)	0.597	1.05 (0.98; 1.13)	0.172	1.01 (0.98; 1.03)	0.679	1.06 (0.98; 1.14)	0.164	1.09 (1.02; 1.17)	0.013
Oesophagus	442,778/954	1.03 (0.96; 1.10)	0.478	0.93 (0.86; 0.99)	0.029	1.01 (0.99; 1.03)	0.532	0.91 (0.85; 0.98)	0.017	0.86 (0.79; 0.93)	<0.001
Liver	442,849/695	0.86 (0.79; 0.93)	<0.001	0.79 (0.73; 0.86)	<0.001	0.95 (0.84; 1.07)	0.380	0.78 (0.72; 0.85)	<0.001	0.77 (0.69; 0.85)	<0.001
Stomach	442,819/757	1.06 (0.97; 1.14)	0.181	0.96 (0.88; 1.03)	0.253	1.01 (0.99; 1.02)	0.461	0.94 (0.87; 1.03)	0.174	0.89 (0.81; 0.97)	0.011
Pancreas	442,796/1,154	0.96 (0.90; 1.03)	0.229	0.93 (0.87; 0.99)	0.030	1.00 (0.96; 1.05)	0.950	0.93 (0.87; 0.99)	0.030	0.94 (0.87; 1.01)	0.070
Lung	442,497/3,345	0.97 (0.93; 1.01)	0.092	1.01 (0.97; 1.05)	0.671	0.93 (0.89; 0.98)	0.007	1.00 (0.97; 1.04)	0.837	1.02 (0.98; 1.06)	0.240
Gallbladder	442,885/316	0.81 (0.72; 0.92)	0.001	0.82 (0.72; 0.92)	0.001	0.96 (0.81; 1.13)	0.588	0.81 (0.71; 0.92)	0.001	0.81 (0.70; 0.94)	0.005
Bladder	442,608/1,984	0.99 (0.94; 1.04)	0.768	0.96 (0.91; 1.00)	0.068	0.98 (0.89; 1.07)	0.631	0.96 (0.91; 1.01)	0.084	0.96 (0.91; 1.01)	0.105
Kidney	442,765/1,201	0.93 (0.88; 0.99)	0.031	0.86 (0.80; 0.91)	<0.001	0.98 (0.88; 1.08)	0.633	0.85 (0.80; 0.91)	<0.001	0.82 (0.76; 0.89)	<0.001
Colorectal	442,160/4,457	0.97 (0.94; 1.00)	0.081	0.93 (0.90; 0.96)	<0.001	1.00 (0.99; 1.02)	0.403	0.93 (0.90; 0.96)	<0.001	0.91 (0.88; 0.95)	<0.001
Prostate	203,050/7,327	1.03 (1.01; 1.06)	0.012	1.04 (1.02; 1.07)	0.001	1.00 (0.97; 1.03)	0.883	1.05 (1.02; 1.07)	0.001	1.04 (1.01; 1.06)	0.007
Breast	237,735/6,776	0.94 (0.91; 0.96)	<0.001	0.94 (0.91; 0.96)	<0.001	1.01 (0.98; 1.03)	0.629	0.93 (0.91; 0.96)	<0.001	0.91 (0.88; 0.93)	<0.001
Ovary	238,853/870	0.93 (0.86; 1.00)	0.062	0.93 (0.86; 1.00)	0.062	0.94 (0.88; 1.01)	0.112	0.93 (0.85; 1.00)	0.058	0.95 (0.88; 1.03)	0.199
Endometrium	238,841/1,092	0.74 (0.69; 0.79)	<0.001	0.74 (0.69; 0.79)	<0.001	1.08 (1.01; 1.15)	0.016	0.73 (0.68; 0.78)	<0.001	0.64 (0.59; 0.70)	<0.001
Cervix	238,988/108	1.00 (0.81; 1.23)	0.982	1.00 (0.81; 1.23)	0.982	1.04 (0.85; 1.28)	0.704	0.99 (0.79; 1.23)	0.934	0.96 (0.77; 1.18)	0.672

Data are presented in hazard ratio with 95% confidence intervals. Model was adjusted for age, sex, deprivation and ethnicity, height (except in HGS height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking and sedentary behaviour and comorbidity. Breast, cervix, endometrium and ovary also for age menarche, hormonal replacement use and contraceptive use. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass. In red and bold significant results after multiple testing.

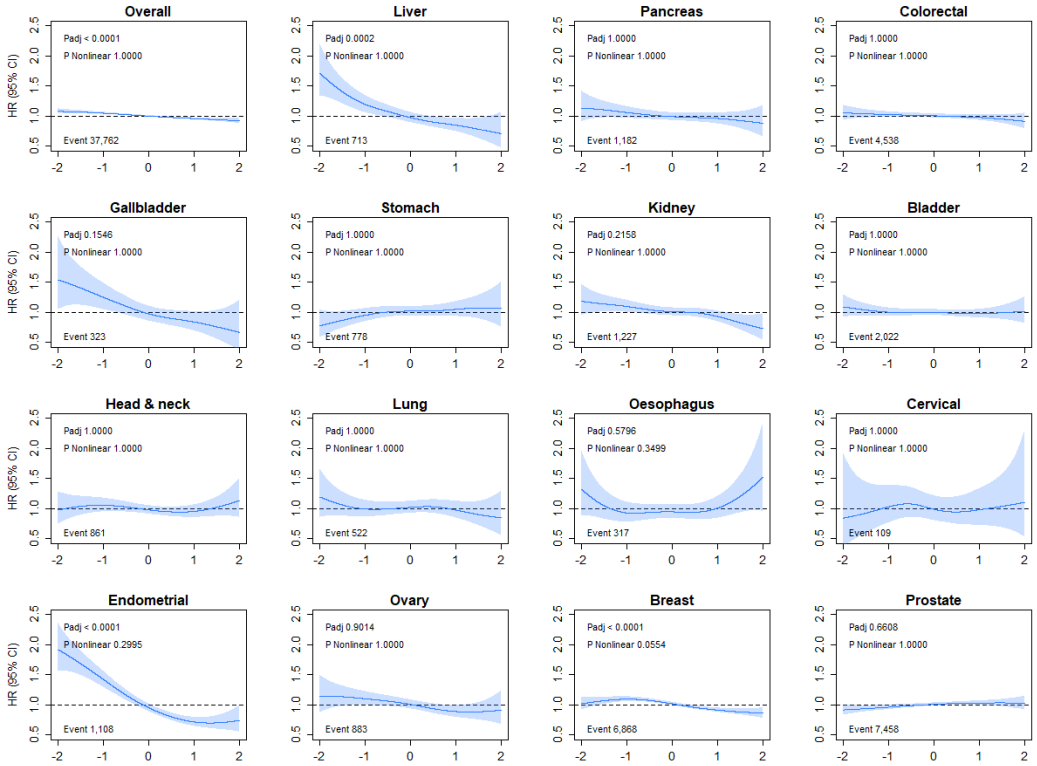

Figure S1: Association between absolute HGS and cancer incidence

Data are presented in hazard ratio with 95% confidence intervals. Analyses were adjusted for age, sex, deprivation, ethnicity, height (except in HGS relative to height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking, sedentary behaviour and comorbidity. For breast, cervix, endometrium, and ovary cancer also hormonal replacement (yes/no), contraceptive use (yes/no) and age menarche. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass.

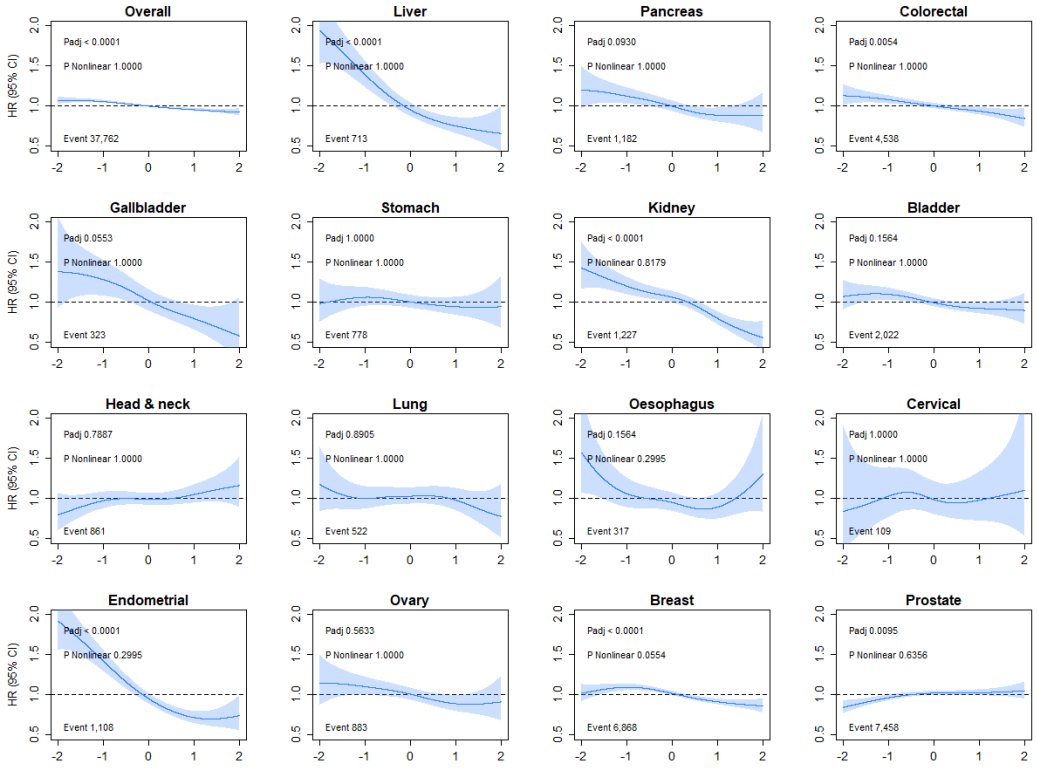

Figure S2: Association between HGS relative to body weight and cancer incidence Data are presented in hazard ratio with 95% confidence intervals. Analyses were adjusted for age, sex, deprivation, ethnicity, height (except in HGS height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking, sedentary behaviour and comorbidity. For breast, cervix, endometrium, and ovary cancer also hormonal replacement (yes/no), contraceptive use (yes/no) and age menarche. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass.

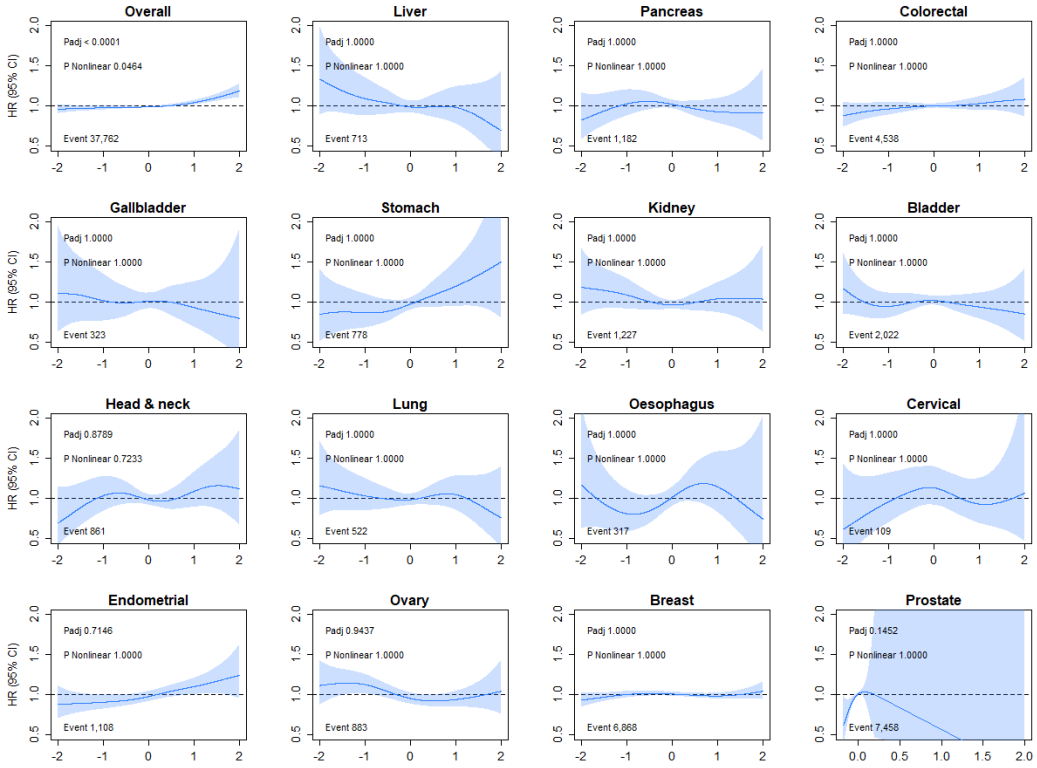

Figure S3: Association between HGS relative to height and cancer incidence

Data are presented in hazard ratio with 95% confidence intervals. Analyses were adjusted for age, sex, deprivation, ethnicity, height (except in HGS height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking, sedentary behaviour and comorbidity. For breast, cervix, endometrium, and ovary cancer also hormonal replacement (yes/no), contraceptive use (yes/no) and age menarche. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass.

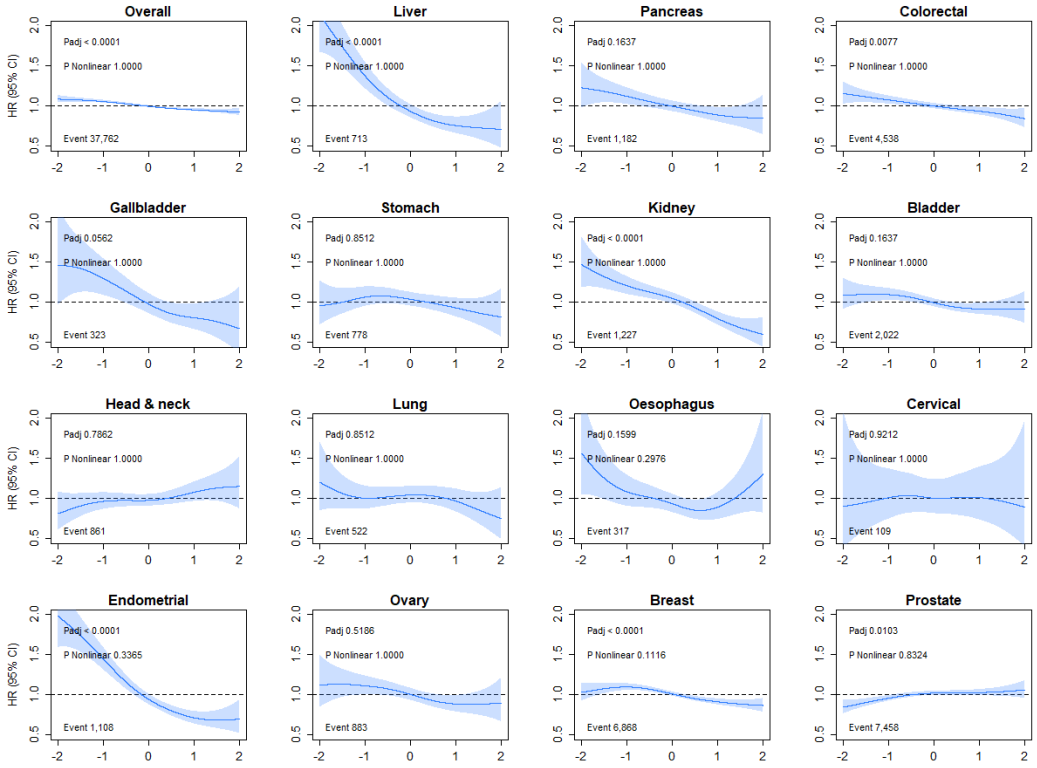

Figure S4: Association between HGS relative to body mass index and cancer incidence Data are presented in hazard ratio with 95% confidence intervals. Analyses were adjusted for age, sex, deprivation, ethnicity, height (except in HGS height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking, sedentary behaviour and comorbidity. For breast, cervix, endometrium, and ovary cancer also hormonal replacement (yes/no), contraceptive use (yes/no) and age menarche. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass.

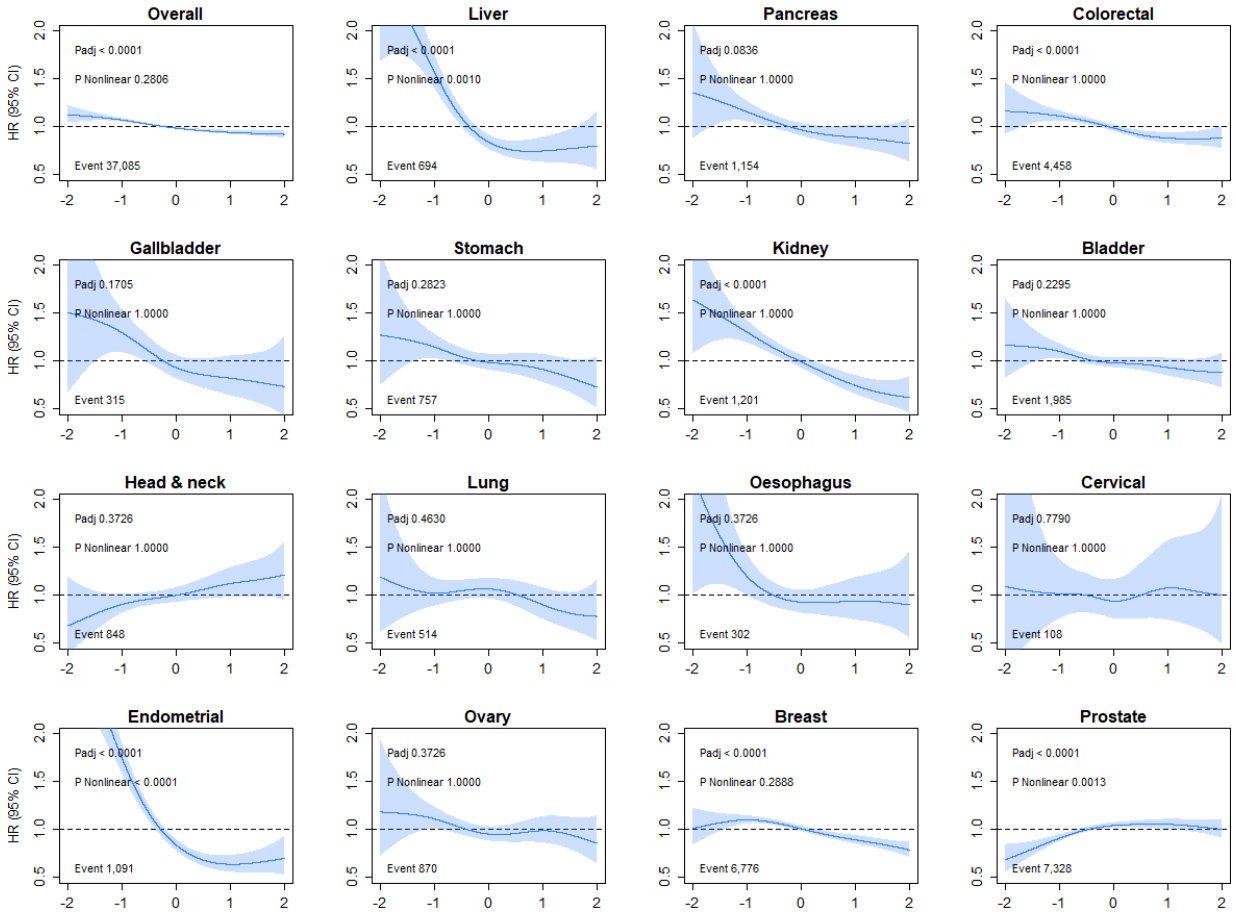

Figure S5: Association between HGS relative to body fat mass and cancer incidence Data are presented in hazard ratio with 95% confidence intervals. Analyses were adjusted for age, sex, deprivation, ethnicity, height (except in HGS height), diet (red & process meat, fruits & vegetables, oily fish & alcohol), smoking, sedentary behaviour and comorbidity. For breast, cervix, endometrium, and ovary cancer also hormonal replacement (yes/no), contraceptive use (yes/no) and age menarche. All P-values were corrected for multiple testing by using the Holm's method. HGS: hand grip strength, BMI: body mass index, BMF: body fat mass, FFM: free fat mass.

Chapter 7 Discussion

7.1 Summary of key findings

Lifestyle factors play an important role in the risk of cancer. Through this thesis, three aspects of the associations between lifestyle and cancer were investigated: diet, adiposity and physical activity, and grip strength.

In Chapter 3 the association of meat, vegetarian, pescatarian and fish-poultry diets with the risk of 19 cancer sites and all cancer was studied (Parra-Soto et al., 2022a). My analysis of the UK Biobank data found that vegetarians had a lower risk of all cancer than meat-eaters. Pescatarians also had a lower risk of colorectal cancer than meat-eaters. My meta-analysis, which included 10 studies with 1,180,523 participants, supported the findings of my UK Biobank study, with vegetarians having a lower risk of all cancer and fish-eaters having a lower risk of colorectal cancer compared to meat-eaters. The findings support the potential benefits of plant-based diets for cancer prevention but note that further trial-based research is needed such as long-term changes in dietary habits, and degree of vegetarianism, to confirm these findings.

Chapter 4 contains two papers that I have published. In the first study, I investigated the association between six adiposity-related markers and the incidence and mortality of 24 different cancers (Parra-Soto et al., 2021a). The study found that higher levels of all six adiposity-related markers were associated with a higher risk of developing and dying from cancer. Specifically, the study found that BMI was positively associated with the incidence of and mortality from 10 out of the 24 cancer types studied, with the strongest associations observed for breast, colon, and prostate cancer.

The study also found that waist circumference, hip circumference, and waist-to-hip ratio were positively associated with the incidence and mortality from several cancer types, including cancers of the liver, lung, and pancreas.

The third study included in Chapter 5, aimed to investigate the combined association of general and central obesity with the incidence of and mortality from cancers in 22 different sites (Parra-Soto et al., 2021). Both general obesity (defined as BMI ≥30 kg/m^2) and central obesity (defined as waist circumference >90 cm for men and >84 cm for women) were independently associated with a higher risk of developing and dying from all cancer. Specifically, the study found that the combined presence of general and central obesity was associated with a higher risk of developing and dying from several cancer types, including colorectal, liver, and pancreatic cancers. My study also found that the association between obesity and cancer risk varied by sex and cancer site. My findings highlight the importance of maintaining a healthy weight and body composition for cancer prevention and the importance of addressing both general and central obesity for cancer prevention.

In Chapter 6, I investigated absolute and relative grip strength as predictors of cancer in a prospective cohort study of 445 552 participants in UK Biobank, (Parra-Soto et al., 2022). My study aimed to investigate whether grip strength, measured using a handgrip dynamometer, was associated with the risk of developing cancer. The study found that both absolute and relative grip strength were inversely associated with the risk

of developing all cancer. Specifically, a one standard deviation increase in absolute grip strength was associated with a 3% lower risk of developing all cancer (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.95 to 0.98). Similarly, a one standard deviation increase in relative grip strength was associated with a 4% lower risk of developing all cancer (HR 0.96, 95% CI 0.95 to 0.97). The association between grip strength and cancer risk was consistent across different cancer types and across different subgroups of participants. Grip strength may be a simple and inexpensive way to identify individuals at higher risk of developing cancer at whom preventative interventions could be targeted.

7.2 Comparison with existing evidence

7.2.1 Vegetarian diet and cancer

Vegetarian diets are increasing in popularity in the UK and worldwide. Recent evidence suggests that vegetarians have a lower risk of cancers, but evidence is conflictive and still restricted to limited numbers of cancers. (DeClercq et al., 2022, Gupta et al., 2022, Watling et al., 2022).

In a previous study of 472,377 UK Biobank participants, Watling et al. (Watling et al., 2022) reported that vegetarians had a lower risk of all cancers, prostate cancer and postmenopausal breast cancer, and pescatarians had a lower risk of all cancers than regular meat eaters. Although these results are similar to the findings reported in this thesis, Watling et al, use a different meat eater classification therefore some of the difference on risk estimates reported in their study compared to this thesis could be attributable to this. Watling et al., defined regular and low meat eaters as those who consumed processed, red (beef, pork, lamb) meat or poultry >5 or ≤5 times a week, respectively. They reported that

low meat eaters had a lower risk of colorectal cancer compared to regular meat eaters, while the study presented in this thesis did not stratify meat eaters on low and high. Despite these differences in the methodology, both studies shows that vegetarian diets could be associated to a lower risk of specific types of cancer. However, as this is observational-based evidence future studies are needed with longer follow up or based on new epidemiological techniques such as Mendelian Randomization to prove causality (Weller, 2022).

My findings from analysing UK Biobank data suggested that prostate cancer had one of the strongest associations with a vegetarian diet. In a recent publication, Loeb et al., analysed data on 47,239 men from the Health Professionals Follow-Up prospective cohort study followed from 1986 to 2014. Their findings suggested that greater consumption of nutritious plant-based meals was associated with a lower risk of prostate cancer, with the effect being strongest in men over 65 years of age (Loeb et al., 2022). Similar conclusions were drawn by Gupta et al. in their systematic review which included 32 observational studies. For incident prostate cancer, most of the observational published papers included showed either a lower risk or no significant association, meanwhile, intervention studies showed favourable results (Gupta et al., 2022). Future research address inconsistencies in dietary assessment methods and the evidence gap that currently exists for hitherto underrepresented groups, such as diverse racial and ethnic backgrounds, and should include intervention studies (DeClercq et al., 2022).

7.2.2 Adiposity and cancer

My findings demonstrated that BMI or WC - both simple and cheaper methods - can predict cancer risk as well as BF%, which is a more complex and expensive measurement. Yet, for some cancer sites, especially to a clinical practice other markers are shown better prediction for this disease. BMI is an easy measure to calculate, is recognised by the general population and is also easily measured compared between different populations (Nuttall, 2015). However, BMI is an inadequate measurement of body fat percentage. Furthermore, importantly, BMI does not reflect the amount of fat located in different body sites (Nuttall, 2015). In a recent, multi-national study, six anthropometric measurements were positively associated with the incidence of 17 different cancers and overall cancer (Sedlmeier et al., 2022). Meanwhile, a previous study using data from UK Biobank described the associations of body shape phenotypes, using A Body Shape Index (ABSI) and Hip index, “apple” phenotype was positively associated with colon cancer (Christakoudi et al., 2021). Although there are several methods to predict cancer risk, BMI might practical to use because of the reason mentioned above.

Associations demonstrated in observational studies do not necessarily imply causation. Most sophisticated methods, such as Mendelian randomisation (MR) are often employed (Fang et al., 2022, Ahmed et al., 2021). In addition, more MR studies are needed to explore the effect of obesity at different timepoints (Fang et al., 2022).

7.2.3 Grip strength and cancer

The latest American Physical Activity guidelines included muscle strengthening activity as part of their recommendation (U.S. Department of Health and Human Services, 2018), highlighting the

importance of a healthy muscle mass. Even if there are more sophisticated methods to evaluate muscle mass, HGS has been showed as a good marker for different health outcomes (Bohannon, 2015, Celis-Morales et al., 2018, Ho et al., 2019).

Prior to my analyses, the existing articles presented contradictory evidence, because most of them used grip strength in isolation (Celis-Morales et al., 2018, Leong et al., 2015, Wu et al., 2017). Recent evidence has shown a clear association between grip strength relative to BMI and all cause of mortality (López-Bueno et al., 2022). Xie et al. found that relative HGS has an optimal value in predicting the short- and long-term survival of cancer patients, especially for lung cancer (Xie et al., 2022). No further evidence has been published until now. Ho et al. showed that changing the way grip strength was expressed had no effect on its ability to predict all-cause death (Ho et al., 2019). Future research should confirm if this is also true of cancer outcomes.

7.2.4 Possible Mechanisms

Associations observed in epidemiologically studies are not necessarily causal. However, causal associations between diet, adiposity and grip strength and cancer are biologically plausible via a number of possible underlying mechanisms.

In relation to diet, nutrient composition is a possible explanation. Vegetarian diets contain a diverse of nutrients such as fibre, vitamins, minerals, and antioxidants which play essential roles in maintaining cellular health, modulating immune responses, and protecting against oxidative stress, which are linked to cancer development (Liu et al., 2022; Luskczki

et al., 2023). An alternative mechanism could be the anti-inflammatory effects of healthy diets. Consuming dietary patterns rich in nutrients sourced from plants rather than animals has been proven to reduce markers of chronic inflammation, including CRP, IL-6, and fibrinogen (Craddock, et al., 2019; Menzel et al., 2020).

In relation to adiposity, a number of mechanisms are possible. Adipose tissue, in particular visceral fat, is metabolically active and releases inflammatory cytokines. Metabolic dysfunction and adipokines play a role in numerous metabolic and physiological signalling pathways, such as regulating insulin signalling, glucose uptake, fatty acid oxidation, and other energy-producing and metabolic processes, and these may contribute to cancer development (Kawai et al., 2020). Higher levels of circulating insulin, linked to insulin resistance, may promote the growth of cancer cell. This mechanism is particularly relevant for cancers that are influenced by insulin, such as colorectal cancer (Chiefari et al., 2021).

A possible mechanism underpinning the association between grip strength and cancer is the importance of the muscle mass for general health; maintenance of muscle mass relates to better metabolic health, insulin sensitivity, and overall physical function (Paquin et al., 2021). Also, muscle tissue plays a role in the modulation of hormones, including insulin and growth factors. Improved insulin sensitivity and hormonal balance due to regular muscle-strengthening activities may also influence cancer risk (Ahmad et al., 2020).

7.3 Implications of findings for research and practice

Over the past few decades, the incidence of cancer in the UK has been progressively rising (Cancer Research UK, 2022), mostly as a result of an aging population and lifestyle factors like smoking, alcohol consumption, and obesity (World Cancer Research Fund/American Institute for Cancer Research, 2018). The latest lifestyle and cancer prevention recommendations published by WCRF/AIRC included maintaining a healthy body weight, limiting intake of red and processed meats, and being physical active (World Cancer Research Fund/American Institute for Cancer Research, 2018). Recently, Shams-White and colleagues published a scoring system to assess extent of adherence to the 2018 WCRF/AICR recommendations intended for use worldwide (Shams-White et al., 2019). Lifestyle factors play an important role in cancer incidence and mortality (Brown et al., 2018, Collaborators, 2022). However, these cannot be studied in isolation.

Our population is becoming older, which increase the risk of cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018). However most evidence regarding the importance to have a good muscular structure to have a healthy longevity (Carrick-Ranson et al., 2022) A review by Lavie et al showed that physical activity and fitness seem be more important than adiposity (Lavie et al., 2022). In the same line, resistance exercise has been describe one of the key intervention to prevent sarcopenia (which include low muscle mass as one of the key factors), as well as increase protein intake (Coletta and Phillips, 2023). The evidence regarding the beneficial effects of exercise in a healthy longevity is

increasing (Carapeto and Aguayo-Mazzucato, 2021). Therefore, having healthy population should be a key to reduce the risk of cancer and other chronic diseases.

The first paper included have several implications. First, people who follow a vegetarian diet has lower risk for overall and colorectal cancer. Second, this study suggests that dietary factor may play a role in cancer prevention, and finally, these results are consistent with the current recommendations to reduce the red and processed meat consumption, increase the intake of fruits, vegetables, whole grains and fibre.

Chapter 4 and 5, showed the association of adiposity and cancer risk. Both papers suggest that obesity is a major risk for cancer. Therefore, interventions to reduced general and central obesity could be particularly effective to reduce the burden of cancer. People with overweight and obesity should be targeting for preventing cancer.

Finally in chapter 6 was showed that grip strength may be a useful marker for cancer risk. Therefore, interventions to improve grip strength could reduce the risk of cancer, being grip strength a modifiable risk for cancer. Which could include in the clinical practice as a simple a cheaper measure for cancer prevention. For individuals following vegetarian or pescatarian diets, or people with overweight and lower grip strength, the relative risk provides insight into the proportional reduction or increase in the likelihood of developing cancer. However, if the risk of a certain cancer is low, a relative reduction may not result in a substantial decrease in the actual number of cases.

This thesis adds to the evidence available to both individuals and policymakers that modifiable lifestyle risk factors, such as diet and

adiposity, are associated with overall risk of cancer and a wide range of individual cancers. Providing this information to individuals can motivate them to try and modify their lifestyles. However, other stakeholders such as policymakers, industry and employers also need to play a role in modifying the obesogenic environment to support individuals to make and maintain these changes.

7.4 Strengths and limitations

The utilization of UK Biobank offers the unique chance to test my research hypotheses in a sizable and well-characterized population cohort study of middle-aged and older persons, as it has been emphasized in each of my publications included in this thesis. Furthermore, UK Biobank has data on a wide range of potential confounders and cancer sites as outcomes, especially for the most common cancers. Additionally, most of the exposures selected for my thesis were well measured. For instance, muscle strength was objectively measured using grip strength and weight, height, WC, and BF% were measured by trained staff using standard protocols. In all the studies I conducted two-year landmark analyses to reduce the risk of reverse causation.

However, this thesis is not exempt from limitations. In spite of use of landmark analysis and adjustment for known potential confounders, further limitations may exist due to the observational nature of the research. Firstly, the UK Biobank cohort is not representative of the overall UK population in terms of lifestyle and sociodemographic factors (Fry et al., 2017). Therefore, whilst effect size estimates may be generalisable to the general population, summary measures, such as incidence and prevalence, and population attributable fractions, may not be. Furthermore, the self-

reported nature of dietary intake data may have introduced recall and misclassification biases, thus warranting cautious interpretation of the results. Baseline UK Biobank data were used to define the exposure variables, but all of the exposures measured could have changed over time. Therefore, future studies should record and analyse serial measurements over time. Absolute risk is the incidence of cancer in the exposed or not exposed groups. Absolute risk increase or reduction is the difference between these and is informative regarding the effect or benefit of the exposure in the study population (assuming causality); i.e. the incidence of admissions or deaths that is due to or avoided by the exposure. The disadvantage of measuring absolute risk increase or reduction is that it is dependent on the baseline incidence of the disease in a given population and therefore limits the generalizability of the study findings. In contrast, relative risk is the ratio of cancer incidence in the exposed and not exposed groups and is more generalizable to other populations with different baseline incidence.

In this thesis, I studied diet, adiposity and grip strength adjusting these for other lifestyle factors such as alcohol consumption, smoking, sleep and physical activity. it is important to consider the weight of each of these factors and how these changes through life, we were not able to measure. Most evidence is needed to know how these changes could impact the risk of cancer and how the combination of this one could increase or decrease our risk.

More evidence in this line could improve our understanding that how the combination of different lifestyle factors affects the cancer risk and mortality.

The ultimate aim is more effective cancer preventive interventions resulting in a meaningful reduction in cancer risk on a population level. As with clinical interventions, prevention strategies can include precision prevention; also known as precision public health. This requires a thorough understanding of the specific risk factors association with specific outcomes, the magnitude of their contribution and the extent to which these vary between individuals. My thesis provides the first step in comprehensively investigating how three modifiable risk factors are associated with an extensive range of cancer outcomes. Future research should explore how the contribution of these risk factors varies by population sub-group, so that interventions to modify these risk factors can be targeted at those individuals who are most at risk and who can benefit most.

7.5 Final conclusions

Through this thesis, I was able to investigate three different lifestyle-related factors and their associations with sites of cancer. My findings support the potential benefits of plant-based diets for cancer prevention, highlight the importance of maintaining a healthy weight and body composition, and addressing both general and central obesity for cancer prevention. They also suggest that grip strength may be a simple and inexpensive way to identify individuals with higher risk of cancer.

Overall, these four papers provide important insights into lifestyle factors that may impact cancer risk, and highlight the importance of maintaining a healthy diet, maintaining muscle strength, and maintaining a healthy body weight for cancer prevention.

7.6 References Discussion

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