Pinpointing the Association between Obesity and Cancer Risk

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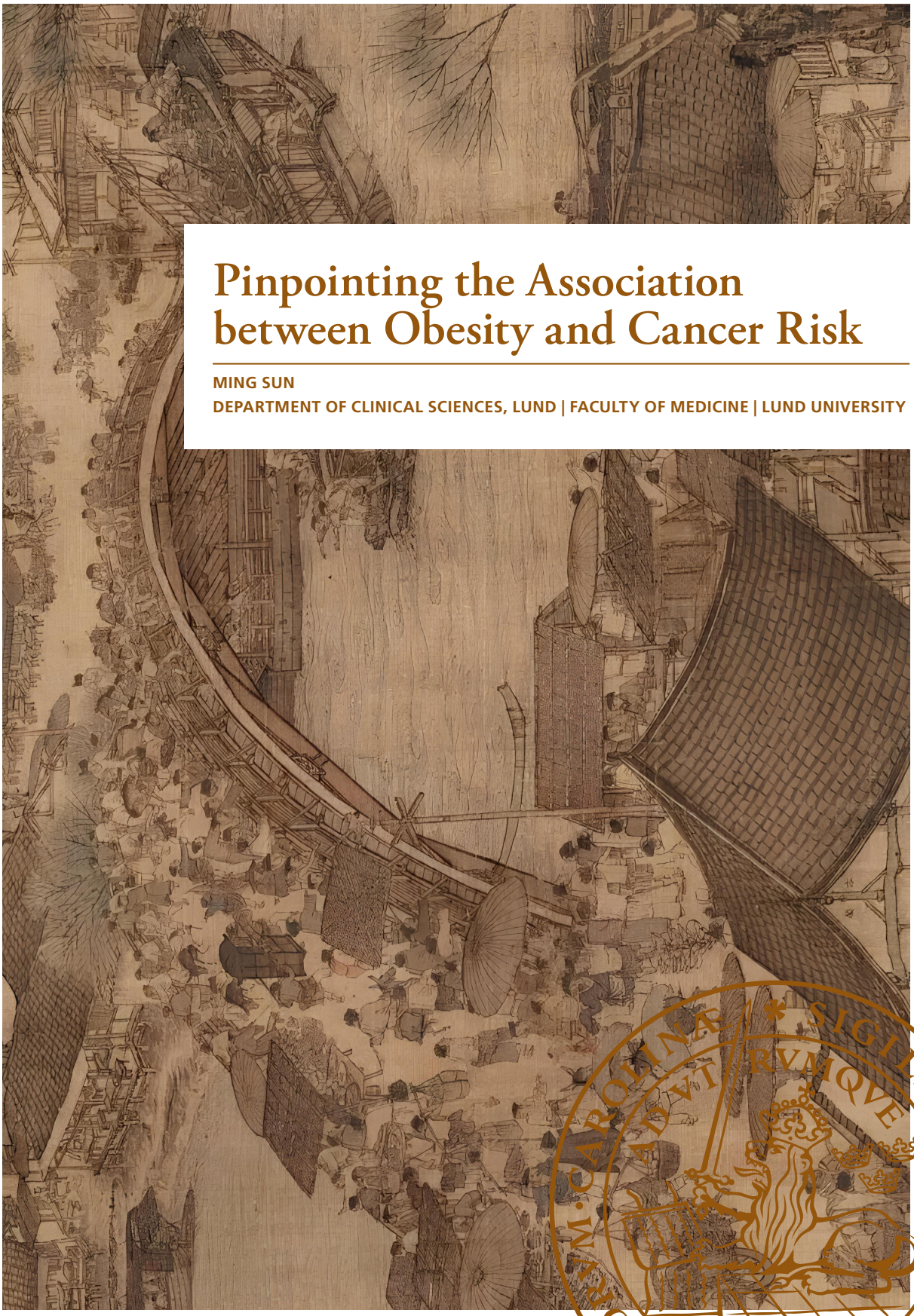

Pinpointing the Association between Obesity and Cancer Risk

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Ming Sun

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UNIVERSITY

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Abstract:

Obesity is an increasingly prevalent health burden worldwide and has been linked to an increased risk of cancer. Body mass index (BMI) has been associated with 13 cancers with sufficient evidence, but there is little evidence regarding rarer cancers and cancer subtypes. Moreover, the interactions between obesity and other factors are largely unknown. This thesis aimed to identify further potential obesity-related cancers using BMI, and to contrast waist circumference (WC) and BMI regarding the risk of such cancers. Another aim was to investigate BMI in combination and interaction with metabolic aberrations and leisure-time physical activity (PA) in relation to obesity-related cancer risk.

This thesis comprises four papers which were all based on large, pooled cohort studies from Sweden or northern Europe. Individuals in the study population were matched with data from national cancer registers to identify cancer diagnoses. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by multivariable-adjusted Cox regression models with attained age as the underlying time metric. Multiplicative and additive interaction were also assessed.

We identified 15 cancers in men and 16 in women (18 altogether) as potential obesity-related cancers in addition to the 13 already established types (Paper I). The HR (95% CI) per 5 kg/m^2 higher BMI was 1.17 (1.15-1.20) in men and 1.13 (1.11-1.15) in women for potential obesity-related cancers overall. The magnitudes of the associations were largely comparable to those of the already established obesity-related cancers. For WC, positive associations were found for nearly all obesity-related cancers (Paper II). Compared to BMI, WC was a slightly stronger risk factor for obesity-related cancers in men (HR 1.19 vs.1.25), but not in women (HR 1.13 vs.1.13). WC residuals were more strongly associated with obesity-related cancer risk in men than women (HR, 1.09, 95% CI 1.06-1.12 vs.1.03, 1.02-1.05). Metabolically unhealthy obesity was associated with an increased risk of any obesity-related cancer (men: HR 1.91, 95% CI 1.74-2.09; women 1.43, 1.35-1.51) and several separate cancers (Paper III). Metabolically healthy obesity showed a higher relative risk for any obesity-related cancer and some of the separate cancers, though the relationships were weaker. Positive additive interactions between BMI and metabolic health status were found for the risk of obesity-related and rectal cancer among men and endometrial cancer among women. This study highlights the importance of the type of metabolic obesity phenotype when assessing obesity-related cancer risk. High leisure-time PA was associated with a 7% (95% CI 4%-10%) lower risk of any obesity-related cancer compared to low PA, with similar associations amongst individuals with a low and a high BMI (6% and 7%), and was associated with decreased risks of renal cell and colon cancer (Paper IV). There were no interactions between PA and BMI on cancer risk. This study suggests a reduced risk of obesity-related cancer through leisure-time PA in both individuals with normal-weight and overweight. In summary, keeping a normal weight or metabolically healthy status, or reducing weight through measures such as engaging in PA, can help reduce the risk of many cancers.

Key words: obesity, body mass index, waist circumference, metabolic status, physical activity, cancer, obesity-related cancer, risk

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I cannot choose the best, the best chooses me.

— Rabindranath Tagore

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List of papers

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I. **Sun M**, da Silva M, Bjørge T, Fritz J, Mboya IB, Jerkeman M, Stattin P, Wahlström J, Michaëlsson K, van Guelpen B, Magnusson PKE, Sandin S, Yin W, Lagerros YT, Ye W, Nwaru BI, Kankaanranta H, Lönnberg L, Chabok A, Isaksson K, Pedersen NL, Elmståhl S, Lind L, Hedman L, Häggström C, Stocks T. Body mass index and risk of over 100 cancer forms and subtypes in 4.1 million individuals in Sweden: the Obesity and Disease Development Sweden (ODDS) pooled cohort study. Lancet Reg Health Eur. 2024;45:101034.

II. **Sun M**, Häggström C, da Silva M, Mboya I.B, Trolle Lagerros Y, Michaëlsson K, Sandin S, Leppert J, Hägg S, Elmståhl S, Magnusson P.K.E, Wood A, Stocks T*, Fritz J*. Comparing waist circumference with body mass index on obesity-related cancer risk: a pooled Swedish study. Manuscript. *Equal contribution.

III. **Sun M**, Fritz J, Häggström C, Bjørge T, Nagel G, Manjer J, Engeland A, Zitt E, van Guelpen B, Stattin P, Ulmer H, Stocks T. Metabolically (un)healthy obesity and risk of obesity-related cancers: a pooled study. J Natl Cancer Inst. 2023;115(4):456-467.

IV. **Sun M**, Bjørge T, Teleka S, Engeland A, Wennberg P, Häggström C, Stocks T. Interaction of leisure-time physical activity with body mass index on the risk of obesity-related cancers: a pooled study. Int J Cancer. 2022;151(6):859-868.

Papers not included in this thesis

I. da Silva M, Fritz J, Mboya IB, **Sun M**, Wahlström J, van Guelpen B, Michaëlsson K, Magnusson PKE, Melander O, Sandin S, Yin W, Trolle Lagerros Y, Nwaru B, Leppert J, Chabok A, Pedersen NL, Elmståhl S, Isaksson K, Ingvar C, Hedman L, Backman H, Häggström C, Stocks T. Cohort profile: The Obesity and Disease Development Sweden (ODDS) study, a pooled cohort. BMJ Open. 2024;14(7):e084836.

II. Mboya IB, Fritz J, da Silva M, **Sun M**, Wahlström J, Magnusson PKE, Sandin S, Yin W, Söderberg S, Pedersen NL, Lagerros YT, Nwaru BI, Kankaanranta H, Chabok A, Leppert J, Backman H, Hedman L, Isaksson K, Michaëlsson K, Häggström C, Stocks T. Time trends of the association of body mass index with mortality in 3.5 million young Swedish adults. Ann Epidemiol. 2024;97:23-32.

Thesis at a glance

Paper and cohort	Aims	Methods	Main results
I ODDS	To identify further potential obesity-related cancers and cancer subtypes and to quantify the association between BMI and all potential obesity-related cancers relative to that of all established ones.	We calculated HRs for the association between BMI in categories (<25/30 kg/m^2) and per 5 kg/m^2 higher BMI in relation to the risk of 122 cancers and cancer subtypes, grouped by topography and morphology in 4,142,349 individuals using Cox regression models. Potential sex interactions and the heterogeneity of HR between cancer subtypes were considered when identifying potential obesity-related cancers.	We identified 15 cancers in men and 16 in women (18 altogether) as potential obesity-related cancers. The magnitudes of the associations for potential obesity-related cancers were largely comparable to those of the already established obesity-related cancers.
II ODDS	To contrast WC and BMI on the risk of obesity-related cancers overall and for specific sites, and to determine whether WC provides additional risk information beyond that already included in BMI.	We calculated HRs for WC and BMI on obesity-related cancer risk among 339,190 individuals using Cox regression models. The WC residual calculated from WC regressed on BMI was included in the Cox model alongside BMI to quantify the additional risk information that WC provides beyond BMI.	Compared to BMI, WC was a slightly stronger risk factor for obesity-related cancers in men, but not in women. WC residuals were associated with obesity-related cancer risk and the association was stronger in men than in women.
III Me-Can	To investigate the association of metabolic status in combination and interaction with BMI, in relation to the risk of obesity-related cancer overall and for specific sites.	We investigated BMI (18.5-24.9, 25-29.9, ≥30 kg/m^2) jointly and in interaction with metabolic health status, assessed using a metabolic score comprising mid-BP, plasma glucose, and triglycerides, in relation to obesity-related cancer risk among 797,193 individuals using the Cox regression model.	Metabolically unhealthy obesity was associated with higher risks of obesity-related cancers, while metabolically healthy obesity also posed a risk, albeit with weaker associations. Additive interactions were found for obesity-related and rectal cancer among men and endometrial cancer in women.
IV Parts of Me-Can & MDCS	To investigate the association of leisure-time PA, its combination with BMI, and its interaction with BMI, in relation to the risk of obesity-related cancers overall and for specific sites.	We examined the association of leisure-time PA (high/low) and its combination with BMI, (<25/≥25 kg/m^2) on obesity-related cancer risk in 570,021 individuals using Cox regression models. Multiplicative and additive. interactions between PA and BMI on obesity-related cancer risk were assessed.	Moderate to hard leisure-time PA was associated with lower risk of obesity-related cancer overall. No interaction with BMI was found although higher PA together with low-to-normal weight was associated with the lowes risk.

Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; BP, blood pressure; PA, physical activity. ODDS, Obesity and Disease Development Sweden; Me-Can, Metabolic Syndrome and Cancer Project; MDCS, Malmö Diet and Cancer Study.

Popular scientific summary

Obesity is a major global health problem, and most people know that it increases the risk of conditions such as cardiovascular disease and diabetes. However, what is less known is that obesity is also linked to an increased risk of developing cancer. But does it affect all cancers in the same way? This thesis aimed to find out more about how obesity, body size measurements, and metabolic health affect cancer risk, and how exercise can reduce the risk of cancer. Another focus was on rarer cancers and cancer subtypes.

We know that being overweight or obese can cause common cancers, such as breast, colorectal, and endometrial cancers. However, this study, which looked at data from large populations over many years, found that obesity could be linked to many cancers in men and women. These include some rarer cancers, such as cancers of the endocrine organs and haematological malignancies. If future studies show that all these cancers are found to be related to obesity, obesity-related cancers could account for up to 40% of all cancers in Sweden. In another study, we show that waist circumference may be a stronger risk factor for obesity-related cancers in men. While BMI gives a general idea of body fat, waist circumference focuses more on abdominal fat.

The thesis did not just look at overall weight, but also at how metabolic health, assessed as a combination of blood pressure, blood lipids and blood sugar, affects cancer risk. Metabolic health refers to how well the body manages, for example, blood sugar and cholesterol. Some people are considered 'metabolically healthy' even if they are overweight, while others may have conditions like high blood pressure – signs of 'metabolically unhealthy' obesity. This study found that metabolically unhealthy obesity is a big cancer risk. People with this condition were much more likely to develop cancers such as colorectal, pancreatic, liver, and kidney cancers. Even people with metabolically healthy obesity – who do not have any metabolic problems such as high blood pressure, glucose, and triglycerides – had a higher risk of certain cancers, but this risk was not as high as in those with metabolic problems. Metabolic health is therefore an important factor in cancer risk.

Given the multiple risk factors of obesity-related cancers that people are exposed to, it is important to know how we can reduce this risk. This study highlights the importance of physical activity. People who regularly took part in leisure-time physical activity – such as walking, jogging, or swimming – had about a 7% lower risk of obesity-related cancers. This protective effect did not just apply to people of normal weight, but also to those who were overweight or obese. This means that staying active can lower the cancer risk, no matter the person’s weight.

This study shows the harm caused by overweight and obesity. Even if a person is overweight, maintaining metabolic health with, for example, healthy blood pressure and blood sugar, can reduce the risk of obesity-related cancers. Regular physical

activity is also important. This does not mean marathon running to benefit; regular moderate activity such as walking or swimming can significantly reduce the risk of cancer. Importantly, this protection works regardless of whether the person is of a healthy weight or obese. Improving metabolic health and maintaining an active lifestyle can make a big difference, and these lifestyles can help reduce the risks of developing many types of cancer.

Abbreviations

AIC	Akaike information criterion
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DBP	Diastolic blood pressure
HDL	High-density lipoprotein
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IQR	Interquartile range
MAR	Missing at random
Me-Can	Metabolic Syndrome and Cancer Project
MET	Metabolic equivalent of task
MI	Multiple imputation
ODDS	Obesity and Disease Development Sweden
PA	Physical activity
PH	Proportional hazards
RDR	Regression dilution ratio
RERI	Relative excess risk due to interaction
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
WC	Waist circumference
WCRF	World Cancer Research Fund

Background

Obesity

Definition of obesity

Obesity is a chronic complex condition defined as an excessive accumulation of body fat that may impair health. The most common measurement used to assess obesity is body mass index (BMI) – an individual's weight in kilograms divided by the square of height in meters (kg/m²). According to the classification made by the World Health Organization (WHO), an adult with a BMI 30 kg/m² or above has obesity, while one with a BMI 25 kg/m² or above, and less than 30 kg/m² is classified as overweight[1]. In some Asia-Pacific countries, classifications with lower cutoffs are used[2]. Obesity can be caused by many factors, including excess food intake and positive energy balance, physical inactivity, psychological factors, sleep deprivation, as well as genetics and family history.

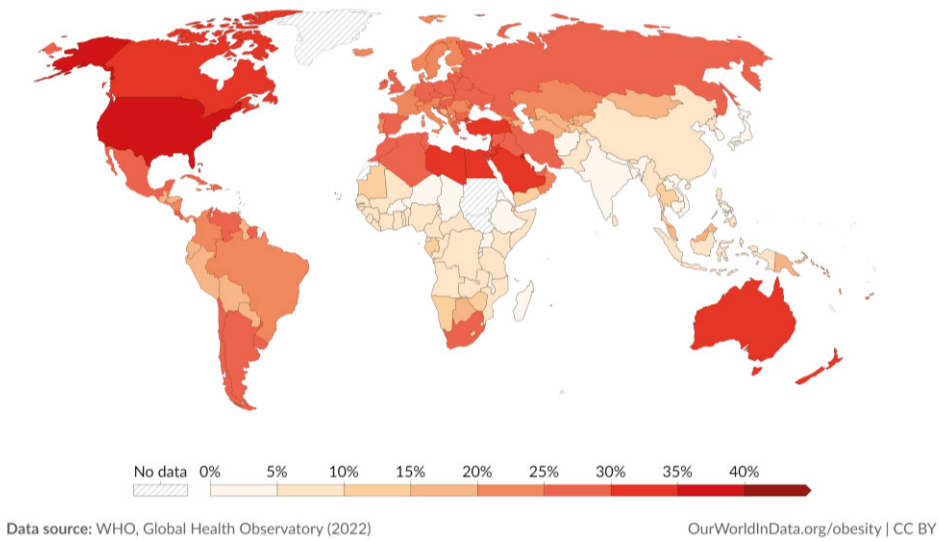


Figure 1. Prevalence of obesity in adults, 2016, adapted from OurWorldInData.org/obesity.

Epidemiology of obesity

Obesity is an increasingly prevalent health burden worldwide (Figure 1). From 1990 to 2022, the prevalence of obesity in adults increased in 188 countries (94%) for women and in all except one country for men[3]. The age-standardised prevalence increased from 3.2% (interquartile range [IQR] = 2.4-4.1) in 1975 to 14.0% (IQR = 13.4-14.6) in 2022 in men, and from 6.4% (IQR = 5.1-7.8) to 18.5% (IQR = 17.9-19.1) in women[3,4]. This proportion is expected to rise to 23% and 27% for men and women respectively by 2035[5]. In 2022, about 16% adults lived with obesity, and 43% were living with overweight.

In addition to sex, the prevalence and trend largely differ across the regions and levels of economic development. The Americas, Europe, and Eastern Mediterranean are the regions with the highest prevalence of obesity (Figure 2). By 2035, obesity prevalence in low to lower middle-income countries is expected to rise faster in both men and women, although the prevalence is still relatively low by then compared with upper-middle to high-income countries[5]. In 2021, more than three million deaths were attributed to obesity, ranking sixth of all risk factors. There was a 34% increase in disability-adjusted life-years due to high BMI from 2010 to 2019[6]. By 2035, on current trends, overweight and obesity are estimated to cost over USD 4 trillion, nearly 3% of current global gross domestic product (GDP)[5].

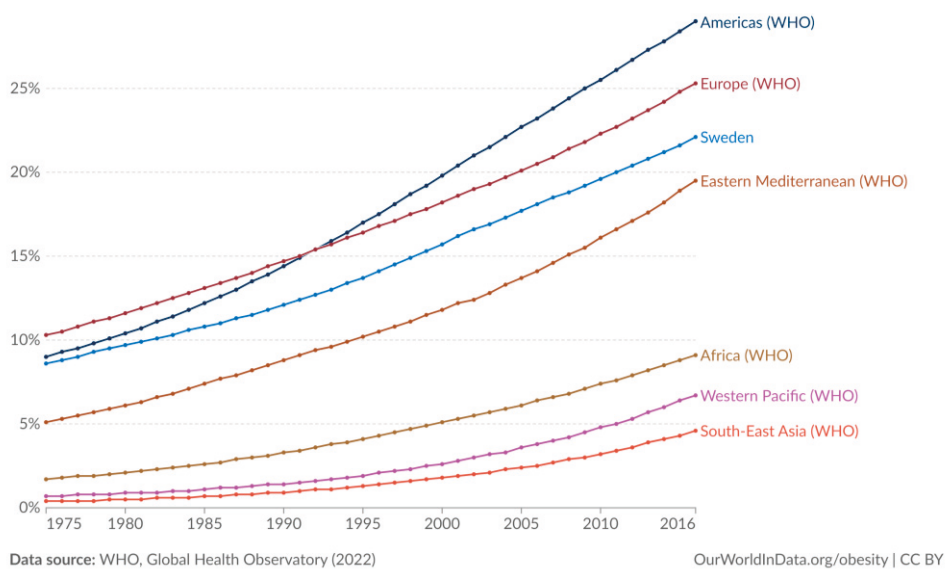


Figure 2. Prevalence of obesity in adults. 1975-2016, adapted from OurWorldInData.org/obesity

In Sweden, the prevalence of obesity has risen over recent decades, in line with the global trend, and is at a high level in relation to the rest of the world[7,8]. According to the Swedish National Board of Health and Welfare, the prevalence of obesity in adults increased from 11% to 15% from 2004 to 2020, and obesity is more prevalent in the northern regions compared to the southern parts. In 2016, the cost for obesity was EUR 2.7 billion, mainly due to production loss caused by premature death (28%) and permanent sick leave (37%). Only 18% of the cost was used in the health and social care sectors[9].

Obesity indicators

BMI is a widely used indicator of adiposity as it is simple and cheap to measure. However, BMI only reflects a comparison of weight and height rather than the distribution of fat mass and lean mass, especially for people with low muscle and high body fat content and people with increased body fat and normal BMI. The degree of correlation between BMI and measures of adiposity depends on multiple factors such as sex and age. A study showed that BMI reflected percentage body fat better in women than men (0.80 vs. 0.77)[10]. Women have relatively more fat mass compared to men. These correlation coefficients tend to decrease with increasing age in both men and women[11,12]. One explanation is that BMI may overestimate obesity in older adults due to a loss of physiological height[13]. Moreover, the gain in fat mass and loss of lean mass in older people is not correctly reflected through BMI, so BMI is a suboptimal marker for percentage body fat in older people[14].

Waist circumference (WC), measured midway between the lower rib margin and the iliac crest or at the umbilical level, is a frequently used indicator as a proxy for central obesity. Central obesity refers to the excessive accumulation of fat especially in the abdominal region, also known as abdominal fat, which can be further categorised into visceral fat and subcutaneous fat. Although WC is strongly correlated with BMI (Pearson correlation ~0.90), WC captures more specifically abdominal fat mass, which is more metabolically active. It has been suggested to better discriminate risks associated with obesity for different diseases.

Investigation into the correlation between obesity indicators showed that the strength of the correlation depends on multiple factors, such as sex and age. A study showed that BMI correlated slightly more strongly with WC in women than in men (Pearson correlation 0.91 vs. 0.88). This can be partly explained by differences in fat distribution patterns, with men tending to have a greater prevalence of abdominal adiposity than women[10].

Studies also investigated the correlation between obesity indicators and obesity-related biomarkers, such as insulin, C-reactive protein, triglycerides, cholesterol, and glucose[10,15]. In comparison to other obesity indicators such as percentage body fat, BMI and WC reflected obesity-related metabolic risk better. Among these

biomarkers, insulin was most correlated with BMI and WC. WC appears to be a better predictor compared to BMI[16,17], but the correlation coefficients were comparable[10]. However, because of the complexity of measuring WC due to the heterogeneity of anatomical measurement sites, the reproducibility of WC measurements is considerably lower than that of BMI, which limits the estimation of health risk at an individual level.

Diverse obesity phenotypes

Obesity is a heterogeneous condition. In addition to general obesity, which is defined using BMI, there are more other distinct obesity phenotypes and classifications that differ in fat distribution, cause of obesity, and subsequent health consequences. The risk of disease varies between individuals with the same BMI, as it does not differentiate between body composition, body fat distribution, and adipocyte function. As a result, the concept of central obesity has emerged, characterised by an excessive accumulation of fat around the abdomen. This has also led to the concept of different body composition phenotypes that incorporate both BMI and metabolic health[18,19], which was often referred to as metabolically healthy/unhealthy obesity in recent studies, i.e., obesity with or without metabolic aberrations. Sarcopenic obesity, an obesity phenotype common in elderly, is a combination of two conditions, sarcopenia and obesity, characterised by a concurrent decline in muscle mass and function, along with increased adipose tissue[20]. The risk of sarcopenic obesity increases with age owing to sedentary lifestyles in older populations.

Health implications of obesity

Obesity develops when energy intake exceeds energy expenditure from metabolic and physical activity (PA). Excessive or abnormal accumulation of adipose tissue may cause metabolic, inflammatory, and immunologic alterations through multiple pathways affecting deoxyribonucleic acid repair, gene function, and cell mutation rate, leading to increased risk for many diseases. Obesity is a serious threat to public health, accounting for a large proportion of the global burden of non-communicable diseases. Obesity is associated with premature mortality from type II diabetes, cardiovascular disease, hypertension, and certain cancers. Conditions that are not inflammatory but are caused by mechanical stress due to increased weight, such as osteoarthritis and sleep apnoea[21,22], also affect quality of life. Recent studies have reported an association between obesity and infectious diseases, particularly viral infections[23,24].

Metabolic risk factors

The metabolic risk factors generally refer to raised blood pressure (BP), impaired fasting glucose, low high-density lipoprotein (HDL) cholesterol levels, high triglycerides level, as well as overweight/obesity, which are established risk factors of cardiovascular diseases. An increasing number of studies have investigated the association between these factors and other non-communicable diseases, including eye conditions, dementia, and cancer.

BP is the pressure of circulating blood against the walls of blood vessels. Hypertension, or elevated BP is defined as systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg according to the European Society of Hypertension[25]. High BP is classified as primary (essential) hypertension which is due to genetic factors and lifestyle such as excess salt, excess body weight, smoking, physical inactivity, and alcohol use. Primary hypertension accounts for 90-95% of hypertension cases. Secondary hypertension is due to other diseases or the use of certain medications[26]. Hypertension is a major risk factor cardiovascular disease such as stroke and coronary artery disease, vision loss, chronic kidney disease, and dementia, and is a major cause of premature death[27-29].

Glucose is the primary source of energy for cells in the human body. When too much glucose circulates in the blood plasma, it can result in hyperglycaemia. This condition occurs when the body either produces insufficient insulin or fails to use it effectively. Hyperglycaemia commonly occurs in people with diabetes[30]. In type I diabetes, the body produces insufficient insulin. In type II diabetes, the body fails to use insulin effectively, which is called insulin resistance. Long-term hyperglycaemia can lead to health problems that affect the eyes, kidneys, nerves and cardiovascular system.

Triglycerides are the main constituents of body fat in humans. They are also present in the blood to enable the bidirectional transference of adipose fat and blood glucose from the liver[31]. Hypertriglyceridemia is positively associated with obesity and insulin resistance[32], and increases the risk of atherosclerosis and other cardiovascular diseases. Lifestyle changes, including reduced intake of sugar, refined carbohydrates, and alcohol, and doing exercise, along with medication, are vital to managing hypertriglyceridemia.

Cholesterol is a type of lipid with many functions. Low-density lipoprotein (LDL) cholesterol makes up the majority of the body's cholesterol. Excess LDL cholesterol can build up on the walls of blood vessels, leading to heart disease and stroke. HDL cholesterol can absorb cholesterol in the blood and carry it back to the liver. Therefore, a higher level of HDL cholesterol can lower the risk for heart disease and stroke.

Rather than treating these metabolic risk factors as a single risk factor, some studies investigated them as a component of the metabolic syndrome. This is commonly a cluster of at least three of the following five conditions: obesity, high BP, high glucose, high serum triglycerides, and low serum HDL, which is defined differently by WHO[33] and the National Cholesterol Education Program Adult Treatment Panel III (ATP III)[34]. Studies have shown that metabolic syndrome defined by either the WHO or ATP III is positively associated with the risk of kidney disease[35], diabetes[36], and cardiovascular disease morbidity and mortality[37,38].

Physical activity

PA is defined as any physical movement produced by skeletal muscles that requires the expenditure of energy[39]. PA can be classified into household, transportation, occupational, and leisure-time PA according to the activity performed, or according to the intensity. Metabolic equivalents that describe intensity as oxygen uptake relative to a person's resting metabolic rate are commonly used to measure PA. PA affects several body systems, including endocrine, immune, and metabolic processes. As well as increasing oxygen uptake and improving cardiovascular function, engaging in PA can increase muscle strength and mass. The WHO recommends at least 150-300 minutes of moderate-intensity PA or 75-150 minutes of vigorous-intensity PA a week to reduce the risk of chronic non-communicable diseases[40].

Overall, PA is beneficial for reducing the risk of a range of chronic diseases, including cardiovascular diseases, type II diabetes, and hypertension[41-43]. Numerous studies have demonstrated that individuals who engage in regular PA have lower risk of these conditions compared with those who are inactive. Mendelian randomisation studies also support this association[44]. Furthermore, a higher level of PA has been shown to reduce the risk of all-cause mortality[45]. The protective effect of PA is more pronounced in reducing the risk of death from cardiovascular diseases, which are among the leading causes of mortality worldwide[46,47]. Engaging in at least 150 minutes of moderate-intensity PA per week has been linked to a significant decrease in the risk of chronic diseases and premature death. An increasing number of studies also reported the association between PA and lower risk of mental disorders[48,49].

Despite evidence of the benefits of PA, the association between PA and disease risk is not consistent across all populations. Differences in sex[50,51], PA domains[47,50,52,53], baseline health status[54,55], and even seasonal variations[45] influence the association. A recent study suggests that women derived greater gains than men regarding all-cause and cardiovascular mortality risk reduction from equivalent amounts of PA[51], potentially due to hormonal differences and varying patterns of fat distribution.

While the beneficial effect of leisure-time PA has been widely documented[56,57], the association between occupational PA and health-related outcomes is inconsistent. Both favourable and unfavourable associations were found for mortality and risk of cardiovascular disease, cancer, and mental health, which may be due to confounding such as by socioeconomic status, and type, intensity, and environment of PA at work[58-61]. Otherwise, occupational PA is characterised by low intensity and long duration, heavy lifting or static postures, and insufficient recovery time might be the potential underlying mechanisms between occupational PA and increased risks of various diseases[62]. The type of PA that achieves the greatest reductions in risk remains to be determined.

Cancer

Epidemiology of cancer

Cancer is one of the leading causes of death globally. Every sixth death (16.8%) and every fourth (22.8%) non-communicable disease-related death worldwide is due to cancer. In 2022, there were 9.7 million deaths from cancer, 70% of which occurred in low- and middle-income countries[63,64]. There were almost 20 million new cancer cases in 2022, and the number is estimated to increase by 77% and reach 35 million by 2050. Europe has a disproportionately high burden of both cancer incidence and cancer mortality (Figure 3). With less than 10% of the global population, Europe accounts for one-fifth of global cancer cases (22.4%) and cancer deaths (20.4%). Breast cancer was the most common cancer in women, followed by lung and colorectal cancer. In men, lung cancer was the most commonly diagnosed cancer in 2022, followed by prostate and colorectal cancer. Cancer has been a major societal, public health, and economic problem in the 21st century. The global economic cost of cancers from 2020 to 2050 was estimated to be more than USD 25 trillion[65].

In Sweden, cancer affects one out of three persons, with around 78,000 new cancer cases in 2022 and 63,000 deaths from cancer in 2020[66]. The highest number of new cases were diagnosed among those aged 65 years and above. The most common cancers are breast cancer in women and prostate cancer in men. From 2040, as many as 100,000 people are expected to develop cancer each year, and the costs are estimated to increase from SEK 34 billion in 2016 to around SEK 70 billion annually[67].

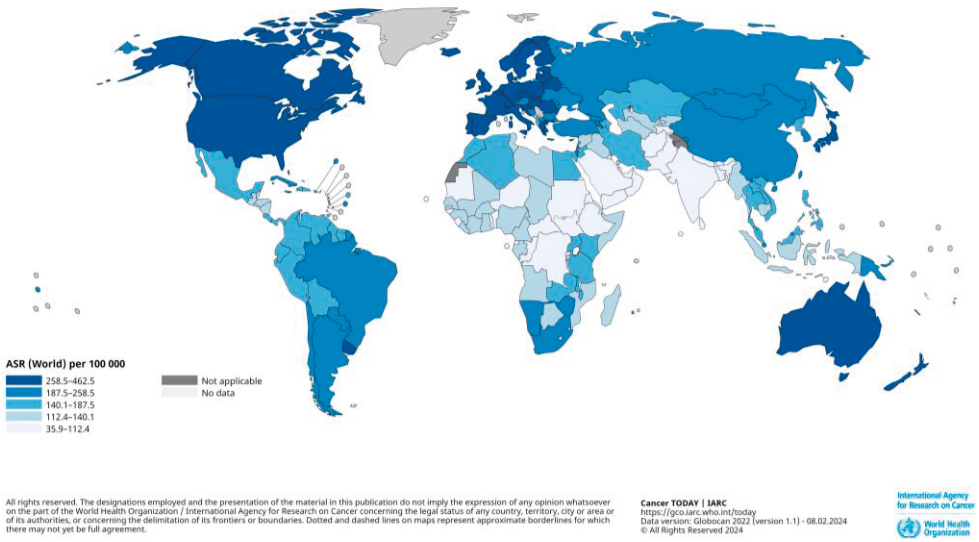


Figure 3. Age-standardised rates of cancer per 100,000 person-year in 2022, adapted from Cancer TODAY|IARC.

Risk factors for cancer

Various factors contribute to the development of cancer. Genetics plays a crucial role in certain cancers. A first-degree family history of cancer is related to a two to three times elevated risk of developing the same cancer[68]. Several risk loci have been identified for many common cancers, including cancers of the colorectum, breast, ovarian, prostate, and melanoma[69-71]. Advancing age is the most important risk factor for cancer overall and for many individual cancer forms. The median age of a cancer diagnosis is 66 years, but several cancers are more common in younger people, such as bone cancer, nervous system cancers, and haematological malignancies. Male sex is a risk factor for most cancers although it remains largely unexplained. A study showed that this disparity remained even after adjustment for a wide range of risk behaviours and carcinogenic exposures[72]. The results suggested the potential role of sex-related biological mechanisms in this relationship, such as differences in sex-steroid hormones, and genetic and epigenetic mechanisms.

Apart from these nonmodifiable factors mentioned above, some are modifiable risk factors such as lifestyle and environmental factors (Figure 4). Smoking contributes to approximately 30% of all cancers in the developed countries, causing over 90% of lung cancers, but also a high proportion of many other cancers, such as cancers of the mouth, oesophagus, stomach, colon, kidney, and bladder[73]. Not only cigarette, but also cigar, pipe, and smokeless tobacco use increases the risk of cancer. Alcoholic drinks have been associated with cancers of the mouth, oesophagus,

stomach, colorectal, breast, and liver[74]. Alcoholic drinks, regardless of the type of alcoholic drink consumed, can cause various cancers because ethanol contained in all alcohol is a carcinogenic compound. In addition to alcohol, diet-related factors including red meat, processed meat, and salt-preserved foods are convincing or probably associated with increased risks of colorectal and gastric cancer according to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report[74]. At least seven viruses have been causally associated with cancer risk, including Epstein-Barr virus, hepatitis B virus, human papillomavirus virus, human T-cell lymphotropic virus, hepatitis C virus, Kaposi's sarcoma herpes virus, and Merkel cell polyomavirus[75].

Figure 4. Major established modifiable cancer risk factors, adapted from IARC/WHO. https://cancerpreventioneurope.iarc.fr/preventable-cancers/

Obesity-related cancer

High BMI was the third leading risk factor for cancer death worldwide after smoking and alcohol use among 34 environmental and occupational, behavioural, and metabolic risk factors, according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2019[76]. The report from the International Agency for Research on Cancer (IARC) in 2016 established the association between excess body fatness and 13 cancers with sufficient evidence, including cancers of the oesophagus

(adenocarcinoma), stomach (cardia), colorectum, liver, gallbladder, pancreas, breast (postmenopausal), endometrium, ovary, meningioma, thyroid, multiple myeloma, and renal cell carcinoma[77]. An umbrella review in 2017 based on 204 meta-analyses confirmed most of these as obesity-related cancers[78]. The WCRF/AICR report has also supported the association between obesity and risk of mouth, pharynx and larynx cancers and prostate cancer (advanced) with probable evidence[79]. Of these obesity-related cancers, supported by strong epidemiological evidence, the causal relationship with cancers of the oesophagus (adenocarcinoma), stomach (cardia), colorectum, liver, gallbladder, pancreas, endometrium, ovary, and kidney, have been further strengthened by Mendelian randomisation studies[80,81].

In addition to BMI, other adiposity indicators have also been found to be associated with several cancers. The umbrella review showed a positive association between waist-to-hip ratio and risk of endometrial cancer with strong evidence. In addition, colon and pancreatic cancer were positively associated with waist-to-hip ratio and WC with suggestive evidence. Several large studies reported findings for more cancer types. A Spanish study involving 3.4 million adults showed positive associations between WC and risks of cancers of the colorectum, breast (postmenopausal), and endometrium[82]. A study based on the UK biobank reported that, in addition to BMI, at least one of the adiposity markers of WC, waist-to-height ratio, waist-to-hip ratio, hip circumference, and body fat percentage was associated with a higher risk of cancers of the stomach (cardia), colorectum, liver, gallbladder, kidney, breast (postmenopausal), and endometrium[83].

Besides these cancers with sufficient evidence, more cancers have been suggested to be probably related to obesity but with limited evidence or inconsistent findings. The IARC report concluded that there was limited or inadequate evidence that excess body fatness increases the risk of cancers of the breast (male), prostate (fatal), diffuse large B-cell lymphoma, oesophagus (squamous-cell carcinoma), stomach (non-cardia), extrahepatic bile duct, lung, skin, testis, bladder, and brain[77]. The umbrella review also suggested leukaemia, non-Hodgkin's lymphoma, and malignant melanoma (in men) to be potentially obesity-related with weak evidence[78]. Taken together, the inconclusive evidence on obesity and the risk of many cancers remains, as they are either rare or only weakly associated with BMI. More studies are needed with a large number of cases and a detailed cancer categorisation to provide evidence of these associations. Also, systematic reviews and meta-analysis studies on the relationship between cancer and obesity need to be updated, as numerous studies involving more cancer types have been published in recent years.

Multiple mechanisms have been hypothesised to underlie the link between obesity and cancer, involving chronic low-grade inflammation, insulin resistance, hormonal changes, and altered immune response[84-86]. Chronic inflammation in individuals with obesity produces pro-inflammatory cytokines that create an environment conducive to cancer development. Insulin resistance leads to elevated levels of insulin and IGF-1, which stimulates cell proliferation and reduces apoptosis,

favouring cancer growth. Obesity also impairs immune function and increases oxidative stress, leading to DNA damage.

The most common obesity-related cancers, and those with highest risk in obesity

Colorectal cancer, also known as bowel cancer, is the most common obesity-related cancer in men. It is the development of cancer from the colon or rectum and is primarily adenocarcinoma (95%). Of all cancers, colorectal cancer has the third highest incidence worldwide, with over 1.9 million new cases in 2020[64]. It is less common in women than men. Sweden has one of the highest incidences of colorectal cancer worldwide. The incidence over the past few decades has continuously increased, while the mortality rate has fallen slightly[87]. Ageing, male sex, height, hereditary factors, and environmental factors (e.g., smoking, alcohol, and diet) are established risk factors. Obesity has been associated with a 30% increased risk of colorectal cancer compared to normal weight with sufficient evidence according to the IARC report, and it is more pronounced in men than in women. The umbrella review in 2017 concluded with strong evidence that colon and rectal cancer only among men are obesity-related cancers. This gender difference might be explained by sex differences in age of onset of obesity, prevalence, and age of onset of metabolic syndrome, or a protective effect of oestrogen[88,89]. When stratified by anatomical sites, colon cancer has been reported to have a stronger association with obesity compared to rectal cancer according to the WCRF/AICR report in 2017[90]. For colon cancer, there is no difference between proximal and distal cancer[90]. A non-linear dose-response relationship has been observed as the increased risk appeared to be greater when BMI was above 27 kg/m^2.

Breast cancer, of which 99% of cases occur in women, is the most common obesity-related cancer and also the most common cancer among women worldwide, with 2.3 million new cases in 2020[63]. The incidence rates vary widely according to region. Breast cancer is the fifth most common cause of death from cancer in women, with an estimated 685,000 deaths in 2020, while survival rates are steadily increasing[91]. Female sex, hormone level, specific genes (e.g., BRCA, PTEN, and TP53), and lifestyle factors (alcohol and smoking) are established risk factors. The association between high BMI and breast cancer in women has been investigated in many studies, but there is some discordance between the findings in terms of menopause status, geographical location, and age at obesity onset. Postmenopausal breast cancer has been established to be associated with obesity with a 10-12% increase per 5 kg/m^2 higher BMI[77,79]. The biological mechanism underlying this association is that, in postmenopausal women, oestrogen is produced in excess adipose tissue rather than by the ovaries, resulting in a multiplication of the oestrogen hormone in the blood, which may increase the probability of breast cancer[92]. Some studies showed a decreased risk of premenopausal breast cancer among individuals with obesity, but most of these studies were based on European and American women.

Studies among Asian or Oceanian women reported no or an opposite association[93-95].

Endometrial cancer makes up the majority of corpus uteri and is the cancer with the strongest association with obesity. It occurs most frequently during perimenopause and arises from the epithelial lining of the uterine cavity. Endometrial cancer is the sixth most common cancer among women worldwide. There were 420,000 new cases in 2022, thereby accounting for around 5% of all new cancers in women and its incidence is rising globally[63]. Endometrial cancer is mainly a disease of high-income areas, especially North America and Central and Eastern Europe. The main risk factor is exposure to endogenous and exogenous oestrogens[96]. Obesity is a convincing risk factor of endometrial cancer according to the WCRF/AICR report. Approximately 40% of cases are thought to be attributable to obesity. According to the WCRF/AICR report, obesity is more strongly associated with the development of endometrial cancer than any other cancer type, with an increase of 50% per 5 kg/m^2 higher BMI[79]. Women with obesity have a six-fold higher risk of developing endometrial cancer compared to those of normal weight[77]. The mechanisms through which obesity influences endometrial cancer include excess oestrogen exposure, insulin resistance, and pro-inflammatory state[97]. Type I endometrial cancer is the most common type, which primarily made up by endometrioid adenocarcinomas. Type II endometrial cancer includes uterine serous carcinomas and clear cell carcinomas, and is not linked to excess oestrogen. Fewer studies have investigated the association between obesity and endometrial cancer risk stratified by cancer subtypes. The pronounced risk for type I rather than type II tumours reported by a Norwegian study has not been confirmed[98].

Oesophageal adenocarcinoma is one of the two main subtypes of oesophageal cancer and is one of the cancers with the strongest association with obesity. Oesophageal cancer ranks as the eleventh most common cancer and the seventh leading cause of cancer-related deaths globally[63]. It is more prevalent in men than women. There are two primary subtypes of oesophageal cancer, adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma, raising from the epithelial cells lining the oesophagus, is common in Eastern Asia and Eastern and Southern Africa, where it accounts for approximately 90% of oesophageal cancer cases[63,99]. However, the incidence has declined in many regions, likely due to the reduced prevalence of two main risk factors, tobacco smoking and alcohol consumption[100]. Other risk factors include intake of red meat[101], consumption of very hot beverages[102], and genetics[103]. Adenocarcinoma arises from glandular cells present in the lower third of the oesophagus and is more prevalent in developed continents like Europe, North America, and Australia[63,99]. Obesity and gastroesophageal reflux are well-established risk factors of adenocarcinoma. According to the WCRF/AICR report, per 5 kg/m^2 higher BMI was associated with a 48% increased risk of developing oesophageal adenocarcinoma[79]. A marked increase of incidence has been observed, potentially due to more reflux and obesity[104]. In contrast, studies

have shown no or negative association between obesity and risk of squamous cell carcinoma, which could be partly explained by residual confounding from smoking.

Metabolic risk factors and cancer risk

Several metabolic risk factors have been shown to be associated with certain cancers. High blood pressure was observed to be related to risk of renal cell carcinoma, colorectal cancer, and breast cancer in meta-analyses[105-107]. Studies assessing the association between high blood pressure and most cancers are inconsistent[108,109]. Mendelian randomisation studies only observed a causal association for renal cell carcinoma[110,111]. Diabetes has been associated with an increased risk of cancer[112,113]. A meta-analysis based on 32 million individuals quantified the robustness of the observational associations to unmeasured confounding and suggested a causal association between type II diabetes and an increased risk of liver, pancreatic, and endometrial cancer[114]. Some studies showed a differential association by sex, which might be explained by different proportions of specific cancers in the populations[115,116]. As the obligatory precursor of steroid hormones that are involved in tumour promotion as well as tumour death, cholesterol has been suggested to be associated with cancer risk[117]. Several epidemiologic studies suggested associations between risk of several cancers and blood cholesterol level[118]. However, results of epidemiologic studies are contradictory and were not supported by meta-analyses and Mendelian randomisation studies[119-123]. Studies on triglyceride levels and the risk of cancer are few, and findings are inconsistent. A pooled cohort study observed an increased risk of cancers of the colon, respiratory tract, kidney, melanoma, thyroid, and cervix for the top quintile versus the bottom quintile of triglycerides[124].

Apart from metabolic factors individually, metabolic syndrome comprising of several metabolic factors has been shown to be associated with an increased risk of obesity-related cancers, such as pancreatic, breast (postmenopausal), liver, colorectal, endometrial, and renal cell cancer[125-128]. Since obesity is often accompanied by metabolic aberrations, data on the additional contribution of metabolic aberrations beyond the effect of obesity on obesity-related cancers is lacking. Obesity with metabolic aberration is known as metabolically unhealthy obesity. Metabolically unhealthy obesity has been extensively investigated in the cardiovascular field, but studies regarding cancer are limited. Some individuals with obesity have few or no elevated metabolic risk factors. These individuals with so-called metabolically healthy overweight/obesity have normal glucose tolerance, lipid levels and BP as well as less ectopic fat than the more typical individuals with metabolically unhealthy overweight/obesity[129,130]. Whether they are protected from obesity-related cancers is unknown. A meta-analysis published in 2020 investigated the relationship between metabolically healthy obesity and cancer risk based on only seven studies of different cancer forms[131]. However, the very existence of metabolically healthy obesity has been questioned, as it has been suggested to

commonly be a transitional state to metabolically unhealthy obesity[130]. Moreover, the potential interaction between body size and metabolic health status on cancer risk remains unclear.

PA and cancer risk

PA is reported to decrease the risk of cancer, but the association with risk of most individual cancers remains inconclusive[74]. The WCRF/AICR report compiled over 500 observational epidemiologic studies and evaluated the association between PA and cancer incidence. There is strong evidence that being physically active is associated with lower risk of cancers of the colon, breast (postmenopausal), and endometrium. Studies have also shown potential associations with kidney and liver cancer[74,132-135], which are both obesity-related cancers. The evidence for associations between PA and other cancers remains insufficient. The dose-response relationship between PA level and cancer risk remains inconclusive due to inconsistencies in the methods used to measure and categorise levels of PA in epidemiological studies.

Apart from PA helping to maintain a healthy body weight, which is a critical factor in cancer prevention, the biological mechanisms underlying this protective effect include improved immune function, modulation of inflammation, and enhanced insulin sensitivity[136]. PA and weight regulation are determinants of energy balance. Physical inactivity could contribute to energy imbalance, which may be linked to cancer through oxidative stress, DNA repair, and telomere length[137]. Maintaining an optimal level of energy balance can help reduce systemic and adipose tissue inflammation and angiogenesis, alter endogenous hormone metabolism, and improve insulin sensitivity, which are strongly hypothesised to be biological mechanisms in the development of cancer[138]. These potential mechanisms indicate the potential for interaction of PA and obesity, i.e. a risk or relative risk increase or reduction that only occurs in the existence of both factors.

Aims

Overall aim

The overall aim of this thesis was to investigate the association between BMI and WC and cancer risk, and the associations between BMI and its combination and interaction with metabolic factors and physical activity on risk of obesity-related cancers.

Specific aims

Paper I: To identify further potential obesity-related cancers and cancer subtypes and to quantify the association between BMI and all potential obesity-related cancers relative to that of all established ones.

Paper II: To contrast the associations between WC and the risk of obesity-related cancers overall and for specific sites, with those of BMI, and to determine whether WC provides additional risk information beyond that already included in BMI.

Paper III: To investigate the association of metabolically unhealthy and healthy normal weight, overweight, and obesity with the risk of obesity-related cancer overall and for specific sites; to investigate multiplicative or additive interactions between BMI and metabolic health status on obesity-related cancer risk.

Paper IV: To investigate the association of leisure-time PA and its combined association and multiplicative and additive interaction with BMI, in relation to the risk of obesity-related cancers overall and for specific sites.

Methods

Study populations

Several pooled cohorts were used for the studies. In Papers I and II, we used the Obesity and Disease Development Sweden (ODDS) study. In Paper III, we used the Metabolic Syndrome and Cancer (Me-Can) 2.0 study. In Paper IV, we pooled three Norwegian cohorts (Oslo Study 1, Norwegian Counties Study [NCS] and the Age 40-Programme [40-y]) and two Swedish cohorts (Västerbotten Intervention Project [VIP] and Malmö Diet and Cancer Study [MDCS]).

The Obesity and Disease Development Sweden (ODDS) study

The ODDS study was initiated for the purpose of forming a large, pooled cohort in Sweden to investigate the association of anthropometric measures with the risk of morbidity and mortality[139]. ODDS is a pooling of large Swedish cohorts and national registers with individual-level information on height, weight, and WC, once or more between 1963 and 2020. The ODDS study includes 4,295,859 individuals with 7,733,901 weight assessments, with a minimum age of 17 years. The Swedish Military Conscription Register (1,771,429 men with 1,779,681 weight assessments) and the Medical Birth Register (1,855,606 women with 3,208,127 weight assessments), which are both nationwide, are the two largest cohorts comprising the majority (85%) of the study population. The coverage in the Military Conscription Register of the Swedish male birth cohorts of 1951-1988 (corresponding to conscription 1969-2006) is 90%. The completeness of the weight assessment was at least 95% until 2000. The Medical Birth Register records approximately 98% of all births in Sweden. The remaining other cohorts in ODDS are either local (e.g., Malmö cohorts), regional (e.g., Northern Sweden Health and Disease Study [NSHDS]), or national (e.g., Construction Workers Cohort [CWC], and Swedish Twin Registry), commonly used in epidemiological research (972,974 individuals with 2,225,946 weight assessments).

The Metabolic Syndrome and Cancer (Me-Can) project

The Me-Can was initiated for the purpose of creating a large, pooled cohort to investigate the association between metabolic syndrome factors and cancer risk[140]. Me-Can 2.0 is a follow-up project from Me-Can 1.0, combining data from six population-based cohorts from three countries: Sweden (Västerbotten Intervention Project [VIP] and Malmö Preventive Project [MPP]), Norway (Oslo Study I, Norwegian Counties Study [NCS] and the Age 40-Programme [40-y]), and Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]). All cohorts include information obtained from one or more health examinations conducted between 1972 and 2014, and information on smoking habits from questionnaires. Me-Can 2.0 includes 843,531 individuals (Figure 5).

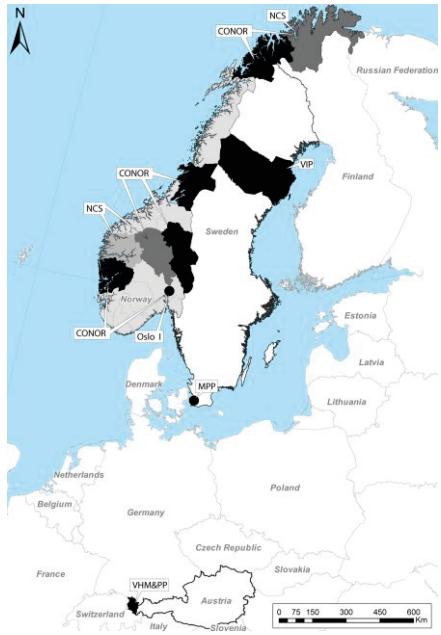


Figure 5. Map with location of subcohorts included in Me-Can. Copyright © Stocks et al, 2009

The Oslo Study 1

The Oslo Study I was initiated with the aim of preventing and investigating the epidemiology of cardiovascular diseases[141]. Baseline information about nearly 18,000 men living in Oslo was collected during 1972-1973, most of whom were aged 40-49 years, and a few were aged 20-39 years. Attendance rate was around 60%. The follow-up examination was conducted in 2000.

The Norwegian Counties Study (NCS)

The NCS was established in order to screen for cardiovascular disease in the Norwegian counties[142]. In Finnmark, Sogn og Fjordane and Oppland, all residents aged 35-49 years, and a random sample aged 20-34 were invited to participate the screening in three time periods: 1974-1978, 1977-1983 and 1985-1988. The NCS includes around 93,000 individuals. Attendance rate in these counties was 78-90%.

The Age 40-Programme

The Age 40-Programme was performed between 1985 and 1999, and covered all counties in Norway by 1993[143]. All residents aged 40-42 were invited to a health examination with the aim of performing epidemiological research and monitoring risk factors of cardiovascular diseases. The examinations during the period 1994-

1999 were used as the baseline in Me-Can studies. Approximately 140,000 individuals were included, with an attendance rate of 62% during this period.

The Västerbotten Intervention Project (VIP)

The VIP is an ongoing study that started in 1985, aiming at preventing diabetes and cardiovascular disease in the north of Sweden[144]. All residents in Västerbotten county were invited to undergo a health examination and donate a blood sample at ages 40, 50 and 60 years (and 30 years until 1996). Approximately 124,200 individuals had participated by 2020, with an attendance rate of 48-67%[145].

The Malmö Preventive Project (MPP)

The MPP is a screening programme conducted in Malmö located in the south of Sweden aiming at preventive intervention on cardiovascular disease, alcohol abuse, and breast cancer during the period 1974-1992[146]. All middle-aged residents (aged 32-51 years) born between 1921 and 1949 were invited to attend a comprehensive risk factor screening. A total of 33,346 individuals finished the baseline screening. Attendance rate over the years was 71%.

The Vorarlberg Health Monitoring and Prevention Programme (VHM&PP)

The VHM&PP is a risk factor surveillance programme running since 1985 for the purpose of preventing chronic diseases and health promotion[147]. All adult residents in Vorarlberg, the westernmost province of Austria, were invited to perform a health examination. Data from 1985-2003 involving approximately 176,000 participants are included in Me-Can, with an attendance rate of 66% on average over the years.

The Malmö Diet and Cancer Study (MDCS)

The MDCS was initiated on 1 January, 1991, primarily aiming to investigate the association of diet with the development of certain cancers[148]. All residents in Malmö born between 1926 and 1945 were invited in the form of both passive and active recruitment. In total, 30,446 individuals were eligible to participate. Attendance rate over the baseline years was 40.8%[149].

Assessment of exposures

Body mass index

In Papers I and II, weight and height were either objectively measured or self-reported through a questionnaire. In Papers III and IV, weight and height were measured for participants wearing light indoor clothes and no shoes. Recalled

weights were excluded. BMI was calculated by dividing weight in kilograms by the square of height in metres (kg/m^2). In Paper I, BMI was analysed per 5 kg/m^2 and in categories (underweight [< 18.5 kg/m^2], normal weight [18.5-24.9 kg/m^2], overweight [25-29.9 kg/m^2], and obesity [≥ 30 kg/m^2]). In Paper II, per standard deviation (SD) higher BMI and sex-specific BMI quintiles were used in the analysis. In Paper III, individuals with underweight (< 18.5 kg/m^2) were excluded. BMI was analysed using three categories: normal weight (< 25 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥ 30 kg/m^2). In Paper IV, BMI was categorised into two groups (low BMI [25 kg/m^2] and high BMI [≥ 25 kg/m^2]).

Waist circumference

In ODDS, WC was either measured on-site at a test centre by a trained nurse or self-reported via a questionnaire. Questionnaires in some cohorts included a picture or text instructions on how to measure WC, and some also included a tape measure. WC was commonly measured midway between the lower rib margin and the iliac crest or around the umbilical level. The standardised WC within sex strata and WC sex-specific quintiles were used in the analyses.

Blood pressure, glucose, and triglycerides

In Me-Can 2.0, BP, glucose, and triglycerides were measured on-site, but the methods of assessment differed between cohorts. BP in the Norwegian and Austrian cohorts was measured in a sitting position but was measured in a supine position in the Swedish cohorts. Mercury sphygmomanometers were used in all cohorts except for the Age 40 programme, where automatic devices were used. Glucose and triglycerides were measured in a non-fasting state in the Norwegian cohorts. In the MPP, VHM&PP, and VIP, fasting was requested since the beginning, 1988, and 1992, respectively. Glucose was measured in serum in the Norwegian cohorts, in plasma in the VHM&PP and the VIP, and in whole blood in the MPP. Triglycerides were measured in serum in all cohorts. In the analysis, a metabolic score was calculated as the sum of Z-transformed levels of mid-blood pressure [(systolic blood pressure + diastolic blood pressure)/2], glucose, and triglycerides[126]. Mid-blood pressure was used as it has been shown to best predict cardiovascular mortality among blood pressure indices[150,151]. Glucose and triglycerides were log-transformed prior to Z-transformation due to their skewed distributions. Z-transformation was performed by (level - mean)/SD within strata of cohort and sex, and within fasting time (< 4h, 4-< 8h, and ≥ 8h) for glucose and triglycerides. The top tertile of the metabolic score was defined as metabolically unhealthy.

Leisure-time physical activity

In Paper IV, leisure-time PA was assessed with closed-ended question/-s in written questionnaire form in all cohorts. In the Norwegian cohorts, the usual level of leisure-time PA during the year preceding the survey was indicated by selecting one of the four given categories. In VIP, participants were asked to indicate their frequency of exercise aimed at increasing their fitness level or well-being during the last three months by selecting one of five given categories. In MDCS, the indicator of PA level is a score calculated as the sum of the number of minutes per week on 17 leisure-time PA types separately for the four seasons multiplied by the metabolic equivalent of task (MET) value assigned to each activity. The original categories used in each cohort and the categories used in Paper III are shown in Table 1. Due to the different assessments of PA between cohorts and the consequent difficulty in harmonising absolute PA levels between cohorts, in the pooled cohort we used a similar percentile cut point for all cohorts to categorise PA levels as low or high.

Table 1. Cohort-specific definitions and levels for leisure-time physical activity categorisation

Cohort	Norwegian cohorts	VIP	MDCS
Cohort-specific definition	During the year preceding the survey, the usual level of PA in leisure time	The frequency of exercising in changed outfit with the purpose to increase fitness level or wellbeing during the last three months	MET units were multiplied by the sum of the number of minutes per week on 17 leisure-time PA types for the four seasons
Low PA (reference) (Sedentary to light exercise)	1) Reading, watching TV or any other sedentary activity 2) Walking, cycling, or other activity, for at least four hours a week	1) Never 2) Once in a while 3) 1-2 times/week	< 2,692 MET-min/week (below 80th percentile of continuous PA variable)
High PA (Moderate to hard exercise)	3) Light sports, heavy gardening (at least four hours per week) 4) Regular, hard exercise, or participating in competitive sports several times a week	4) 2-3 times/week 5) >3 times/week	≥ 2,692 MET-min/week (above 80th percentile of continuous PA variable)

Abbreviations: PA, physical activity; VIP, Västerbotten Intervention Programme; MDCS, Malmö Diet and Cancer Study; MET, Metabolic equivalent of task.

Assessment of covariates

In Papers I and II, only year and quarter of a year of the birth date were retrieved from the Total Population Register[152] due to Swedish legislation protecting individual integrity. The month and day were imputed using day 15 and the middle month of the quarter, e.g. February for the first quarter. Sex, country of birth, and marital status were also retrieved from the Total Population Register. We retrieved

information on education level, total income per year, and main source of income from the Longitudinal integrated database for health insurance and labour market studies (LISA)[153] and from the Population and housing censuses (for early years, 1960-70). Smoking habits were self-reported and obtained from some of the included cohorts. In total, 828,763 individuals have at least one weight assessment with never/former/current smoking information available, and the proportion is larger for individuals with WC assessments (330,775 individuals). In Papers III and IV, demographic and socioeconomic status, including sex, date of birth, and smoking status and smoking dosage (among current smokers) were obtained from the self-administered questionnaire. In the analysis, smoking status and smoking dosage were integrated into one variable.

Follow-up and outcome assessment

Cancer diagnoses were identified through linkage with the respective national cancer register in Norway[154], Sweden[155], and Austria[156]. Death was retrieved from each national cause of death register[157-159]. Emigration was captured from the population registers in Norway and Sweden.

In Papers I and II, the International Classification of Diseases (ICD) codes, WHO/HS/CANC/24.1 (Swedish PAD codes), and ICD-O/2 and -O/3 codes (Swedish SNOMED codes) were used to classify cancers. Follow-up for linkages ended on 31 December 2019. In Paper I, first-incident primary cancers with at least 100 cases diagnosed during follow-up were included as outcomes. Finally, 122 cancers categorised according to topography and morphology were investigated. In Paper II, first-incident primary obesity-related cancers with at least 100 cases were investigated. Established obesity-related cancers were defined as those concluded with sufficient evidence of being obesity-related by the IARC group[77], including cancers of the oesophagus (adenocarcinoma), stomach (cardia), colon, rectum/anus, liver/intrahepatic bile ducts, gallbladder/biliary tract, pancreas, breast (postmenopausal), endometrium, ovary, renal cell, and multiple myeloma. Potential obesity-related cancers were defined as cancers associated with BMI in Paper I, including cancers of the oral cavity, nasal and paranasal sinuses, stomach (gastrointestinal stromal tumours), small intestine, biliary tract, pancreatic islets, adrenal glands, parathyroid gland, pituitary gland, connective tissue, lymphoid neoplasms, and myeloid neoplasms for both men and women, and also included cancers of the head and neck (adenocarcinoma), penis, and malignant melanoma for men, and cancers of the head and neck (squamous-cell carcinoma), nodular melanoma, vulva, and cervix (adenocarcinoma) for women.

In Papers III and IV, obesity-related cancers were defined as those concluded with strong or highly suggestive evidence of being related to obesity in an umbrella

review by Kyrgiou et al in 2017[160], including cancers of the oesophagus (adenocarcinoma), stomach (cardia), colon, rectum/anus, liver/intrahepatic bile ducts, gallbladder/biliary tract, pancreas, breast (postmenopausal), endometrium, ovary, renal cell, and multiple myeloma. Each cancer was analysed separately if the number of cases was more than 400. Cancers with fewer than 400 cases each were grouped as "other" obesity-related cancers. Follow-up for linkages ended on 31 December 2012, in Norway, on 31 December 2014, in Austria, on 31 December 2014, for the VIP and MPP, and on 31 December 2019, for the MDCS.

Selection

Missing data on main exposures

All observations with missing information on the main exposures were excluded. In Papers I-IV, missing data on BMI were excluded. Observations with missing WC in Paper II, missing blood pressure, glucose (except from the NCS and 40-y cohorts), triglycerides or fasting status in Paper III, and missing PA in Paper IV were also excluded. In Paper I, observations with recalled weight were excluded, due to the lower accuracy of retrospective recall of body weight.

Extreme values

An extreme value, also known as outlier, could be truly extreme due to natural variability, or erroneous due to measurement or recording error. They may not be representative of the population being studied. The presence of extreme values might skew the result, hamper model performance, or lead to conclusions that are not relevant to the general population. Removing extreme values can help improve the overall accuracy and robustness of the model. Therefore, in Papers I-IV, extreme values of weight (<35 or >250 kg), height (<100 or >250 cm), or BMI (<15 or >60 kg/m^2) were excluded. In Paper II, extreme values on WC (<40 or >160 cm) were also excluded. The proportion of extreme values was low for all variables (<1%).

Prevalent cancers

We excluded observations with a cancer diagnosis before the weight assessment. In Papers I and II, all primary malignant cancers, and a limited number of potentially harmful cancers of borderline or malignant potential or benign (e.g. of the ovaries, central nervous system, endocrine and haematological malignancies) and in situ urothelial cancers, were included, in accordance with the Swedish National Board of Health and Welfare.

In Papers I-IV, we selected the first observation as baseline examination. In Paper I, the first observation with information on smoking status (if available) was selected as baseline examination.

Statistical analysis

Cox proportional hazards regression

We used Cox regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) with attained age as the underlying time metric and counting person-years at risk from baseline until the diagnosis of a cancer, censoring at date of another cancer, death, emigration, or until the end of follow-up, whichever came first. The overview of adjustments and strata variables for each study are shown in Table 2. The calendar year of birth was stratified in Papers I-III to account for the variation across the study population and the change in cancer incidence between calendar years.

In Paper II, in addition to investigating the association between WC and cancer risk, the additional contribution of WC as a cancer risk factor beyond BMI was investigated using the WC residual calculated from WC regressed on BMI. The WC residuals alongside BMI were included in the Cox model. Tertiles of BMI and WC within each BMI tertile of the population were also created to calculate HRs of BMI and WC tertiles within BMI tertiles. If the HRs for WC tertiles within BMI population tertiles are larger than that of BMI tertiles within BMI population tertiles, this suggests that WC provides additional risk information beyond BMI.

The proportional hazards (PH) assumption of the Cox models for the primary exposures and covariates was tested using Schoenfield residuals statistics combined with log-log survival curves. When a covariate violated the PH assumption, it was added as a stratum in the model, but it did not materially change the effect estimates in all cases, so in the end it was not retained as stratum in the models. In Paper I, BMI appeared to violate the PH assumption for some cancers. Flexible parametric survival models were used to investigate the association between per 5 kg/m^2 higher BMI and cancer risk as a function of attained age for these cancers.

Table 2. Overview of adjustment and strata for studies in this thesis.

Paper	Exposure	Outcome	Adjustment	Strata
I	BMI	Cancers	Baseline age (continuous), weight assessment from the Medical Birth Register (yes/no), mode of weight and height assessment (measured/self-reported), marital status, education level, and birth country	Sex, calendar year of birth (<1950, 1950-59, 1960-69, 1970-79, ≥1980)
II	WC	Obesity-related cancers	Baseline age (continuous), mode of WC assessment (measured/self-reported), height (continuous), smoking in three categories (never smoker, ex-smoker, current smoker), cohort, marital status, education level, birth country, income level, and main source of income	Sex, calendar year of birth (<1940, 1940-49, 1950-59, 1960-69, ≥1970)
III	Metabolic health status & BMI	Obesity-related cancers	Sex, baseline age (continuous), smoking in six categories (never smoker, ex-smoker, current smoker with <20 pack-years, current smoker with ≥20 pack-years, current smoker with pack-years missing, and smoking status missing)	Cohort, calendar year of birth (<1931, 1931-38, 1939-46, 1947-54, ≥1955).
IV	PA & BMI	Obesity-related cancers	Sex, baseline age (continuous), cohort, calendar year of birth (<1931, 1931-38, 1939-46, 1947-54, ≥1955), smoking in seven categories (never smoker, ex-smoker, current smoker by tertile of pack-years, smokers with pack-years missing, and smoking status missing)	-

Restricted cubic spline

Restricted cubic spline analysis with Cox model was used to visualise the shape of the association with cancer risk across the BMI range or WC range in Papers I and II. The same adjustments and strata were fitted as described in Table 2. Restricted cubic splines with knots placed at Harrell's recommended percentiles were fitted[161]. In Paper I, the reference BMI for these plots (with HR fixed as 1.0) was 22.5 kg/m². For each cancer, models with three, four, five, six, and seven knots were fitted, and the Akaike Information Criterion (AIC) was calculated; the number of knots resulting in the minimum AIC were then chosen. In Paper II, the reference WC for these plots (with HR fixed to 1.0) was 0 and models with four knots were fitted. Non-linearity was assessed by testing the null hypothesis of equal spline coefficients using the post-estimation Wald test.

Cumulative incidence estimation

Cumulative incidence in epidemiology refers to the proportion of a specific population experiencing an event or developing a disease over a period of time. It measures the absolute risk of disease and is, therefore, a good complement to HR, which measures relative risk. In Papers I, III, and IV, we calculated sex-specific cumulative incidence across age using competing risk analysis[162,163]. Age was used as the time metric and death as the competing event. This model was also used to calculate the absolute risks and CIs at age 80 years.

Interaction analysis

Interaction refers to a scenario where the combined effect of two exposures on a health outcome differs from what would be expected based on their individual effects, indicating that the exposures act together in a dependent manner. There are two scales for assessing interaction, multiplicative and additive. Interaction on a multiplicative scale means that the combined relative risk is larger (or smaller) than the product of the individual effects, which can be calculated using risk ratio. Interaction on an additive scale means that the combined absolute risk of two exposures is larger (or smaller) than the sum of the individual effects of the two exposures, which can be calculated using risk difference. Additive interaction is often the more relevant public health measure, as assessing additive interaction can help identify the subgroups in which the intervention or treatment is likely to have the largest effect, i.e., would be the most beneficial. The choice of a measure of interaction depends on the goal or the motivation for the analysis. VanderWeele also recommends that, in general, either the presence or absence of additive or multiplicative interaction may be of interest, so it is suggested to evaluate both of them[164].

In all papers, multiplicative interaction was tested by the Wald test of the respective product term in the Cox model. *P* values for interactions were reported. In Papers III and IV, additive interactions between PA and BMI and metabolic health status and BMI in relation to obesity-related cancer risk were assessed using relative excess risk due to interaction (RERI). The RERI was based on adjusted HRs representing relative risks (RRs) in the formula: RR11 - RR10 - RR01 + 1, denoting individuals in the low BMI-high PA/obesity-metabolic unhealthy group (RR11), low BMI-low PA/obesity-metabolic healthy group (RR10), high BMI-high PA/normal weight-metabolic unhealthy group (RR01) and high BMI-low PA/ normal weight-metabolic healthy group (1, reference group). CIs were calculated using the delta method[165].

Regression dilution ratio

HRs might be diluted by intra-personal variability due to physiological changes and random measurement error, which is referred to as "regression dilution bias" due to the propensity of values that are extreme on a single measure to be less extreme upon a repetition[166]. For BMI, the regression dilution ratio (RDR) is usually small due to the small random measurement error. The RDR of WC is relatively large because of the complexity of measuring WC and larger variability in WC itself due to the effects of food, faeces, and flatus[167]. In Paper II, for the analysis that compares HRs of cancer risks between BMI and WC, we corrected the HRs by using the method based on RDRs as described by Wood *et al.*, based on all available repeated measurements[168]. RDRs for WC and BMI were calculated for men and women separately and combined using the user-written function "rdrcalc" (see https://www.phpc.cam.ac.uk/ceu/erfc/programmes/). The HRs were corrected with the equation $HR_{correct} = \exp(\log[HR_{original}]/RDR)$.

Strategies for managing missing data

Missing indicator method

The missing indicator method, which treat missing values in covariates as an additional category (or value) in the analytical model, has been proposed for etiologic studies[169]. For covariates including education level, birth country, and marital status in Paper I, education level, income level, and main source of income in Paper II, and smoking status in Papers II-IV, the missing indicator method was applied.

Multiple imputation

Multiple imputation (MI) is a statistical technique to use the distribution of the observed data to estimate a set of plausible values for the missing data[170,171]. Multiple datasets are created and then analysed individually but identically to obtain a set of parameter estimates. These estimates are then combined to obtain the overall estimates, variances, and CIs through Rubin's Rules. MI is usually implemented under missing at random mechanisms (MAR – the probability of data being missing does not depend on unobserved data, conditional on the observed data).

In Paper III, around 300,000 women had no information on glucose levels, and nearly 90% of these were from the 40-y cohort and the remaining 10% were from the NCS cohort. The reason for missingness in these Norwegian cohorts was that glucose was not measured during certain years, i.e. MAR was assumed. Glucose is one of three components of the metabolic score and the information on the other two components is virtually complete. Excluding all women with missing glucose levels may introduce selection bias. Therefore, we performed the MI imputation approach to impute glucose level of individuals in the 40-y and the NCS cohorts.

We used multivariate normal regression with ten imputations to obtain imputed glucose levels in the 40-y and the NCS cohorts. Besides covariates used in the Cox model (see Table 2), obesity-related cancer diagnosis[171], fasting status, and diabetes were also included as predictors in the model.

All statistical analysis was conducted on Stata 16, 17, and 18 (StataCorp LLC, College Station, TX, USA).

Ethical considerations

This thesis is based on already established cohorts and registry data, with all protocols approved by the relevant Ethical Review Authority. Since studies of this thesis are based on information on individuals, some of which is sensitive (e.g. health data and country of birth), secure handling of data is crucial. Participants may fear potential reidentification, particularly in studies involving rare diseases, and may experience anxiety about the exposure of their health information. This concern is reasonable, as cohort individuals can be linked to national registers through the unique personal identity number of inhabitants of the corresponding countries of the cohorts. However, Me-Can data were anonymised after linkage to the registers, i.e. no link to personal identity numbers was available to researchers, making re-identification of individuals difficult. Data in the MDCS and ODDS were pseudonymised, with the key to personal identity numbers available only to the central database manager of the MDCS, and to Statistics Sweden, respectively. In ODDS, information only on the birth year and quarter of the year further hampers the possibility to reidentify individuals.

Written informed consent was only collected at initiation of some of the included cohorts, such as the MDCS. Other cohorts, including the large Military Conscription Register and the Medical Birth Register, lack informed consent as they were not formed for the purpose of research. Some of the cohorts, such as the Construction Workers Cohort, have regularly published notices in relevant media to participants of the cohort, informing them that they have the right to withdraw from the cohort at any time.

The potential scientific knowledge gained by studies of this thesis has been assessed by the researchers and review authorities to outweigh ethical concerns such as missing informed consent and the small integrity risks for the individual. Studies using the Me-Can cohort (Papers III and IV) were approved by ethics committees in Norway (Regional Committee for Medical and Health Research Ethics, no 2012/2271/REC South-East), Sweden (EPN Umeå, no 2012-354-31M and no 2015-7-32M), and Austria (Ethics Committee of the Province of Vorarlberg, no 2006-6/2). Paper IV, which also included the MDCS, was approved by the ethics

committee in Lund (EPN Lund, no 2014/830). The ODDS study (Papers I and II) was approved by the Swedish Ethical Review Authority (no: 2020-03846).

Results

Paper I

Body mass index and risk of cancers

A total of 4,142,349 individuals, 2,013,200 women and 2,129,149 men, with a mean baseline age of 31 (SD = 9.7) and 23 (SD = 11.8) years, were involved in the study. Women had a mean BMI of 24.0 kg/m^2 (SD = 4.2), with a prevalence of obesity of 9% (n = 176,650); the corresponding values for men were 22.5 kg/m^2 (SD = 3.3) and 3% (n = 69,385). After a median follow-up of 24 years (IQR = 13.8-34.7), 332,501 cancer cases, 139,685 in women and 192,816 in men, had been recorded.

A decision algorithm, including the presence of a sex-interaction and/or cancer heterogeneity, was used to define a cancer as potentially obesity related (Figure 6). Associations with an increased risk for either obesity (BMI ≥30 kg/m^2) vs. normal weight (BMI 18.5-24.9 kg/m^2) or per 5 kg/m^2 higher BMI at a two-sided α-level of 0.05 were considered a "potential obesity-related cancer".

HRs of potential obesity-related cancers for obesity vs. normal weight and per 5 kg/m^2 higher BMI are shown in Table 3. These were cancers of the oral cavity, nasal and paranasal sinuses, stomach (gastrointestinal stromal tumours), small intestine, biliary tract, pancreatic islets, adrenal glands, parathyroid gland, pituitary gland, connective tissue, lymphoid neoplasms, and myeloid neoplasms for both men and women, and also included cancers of the head and neck (adenocarcinoma), penis, and malignant melanoma for men, and cancers of the head and neck (squamous-cell carcinoma), nodular melanoma, vulva, and cervix (adenocarcinoma) for women. Sex interactions were observed for cancers of the lip, tongue, head and neck (adenocarcinoma and squamous-cell carcinoma), connective tissue, malignant melanoma, and lymphoid neoplasms. Among potential obesity-related cancers with at least 250 cases, non-linear associations with BMI were found for cancers of the biliary tract, vulva, pituitary gland, and malignant melanoma.

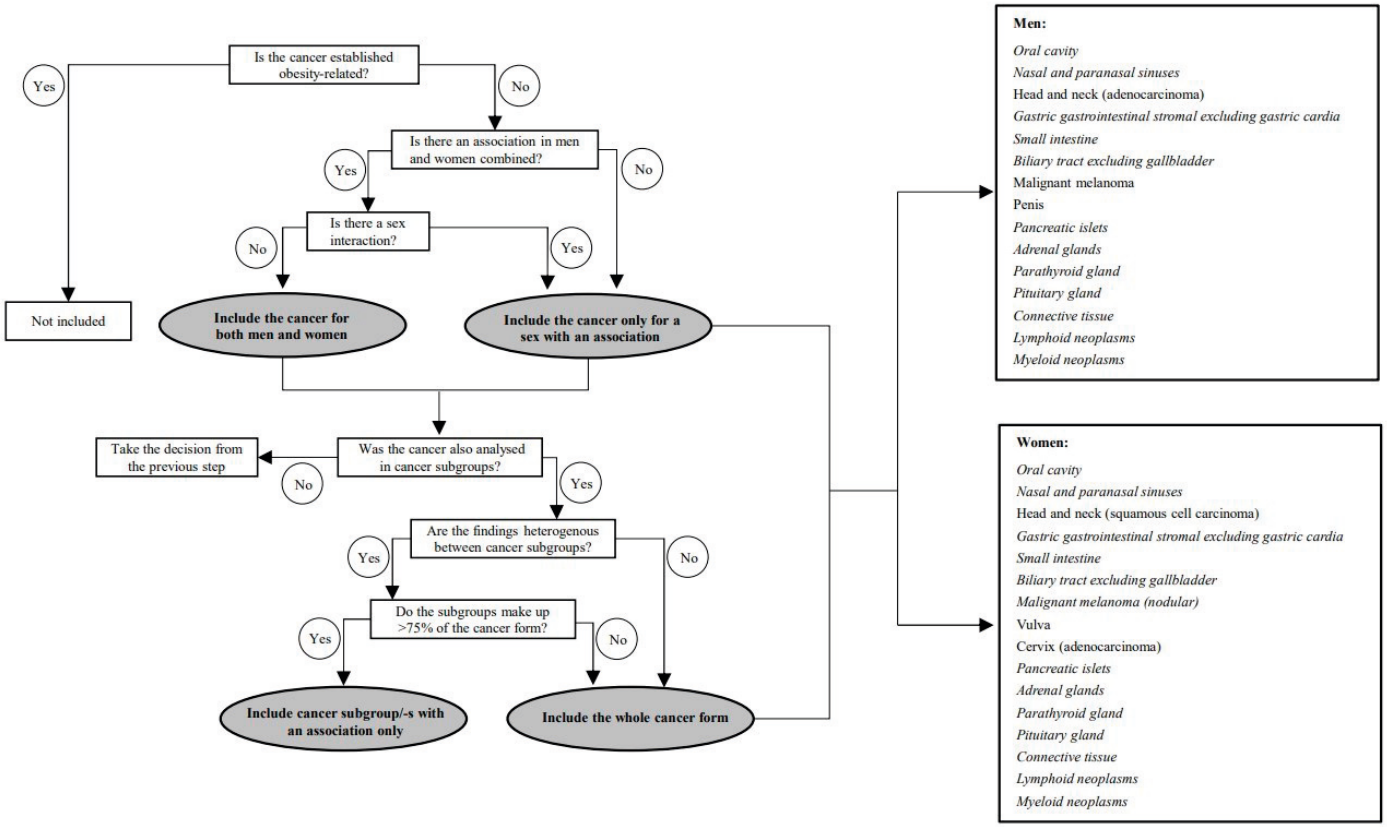


Figure 6. Flow-chart for decision making of inclusion of a cancer as potentially obesity related. A two-sided α-level of 0.05 for an increased cancer risk in obesity vs. normal weight or per 5 kg/m^2 higher body mass index was used to indicate a cancer as obesity related. In a final step amongst cancers in grey-shaded circles, any remaining cancer subtypes overlapping with an established obesity-related cancer, e.g. gastric-cardia and gallbladder cancer, were excluded. Potential obesity-related cancers are listed for men and women separately on the right side, with cancers included for both men and women in italics.

Table 3. Hazard ratios (95% confidence intervals) of potential obesity-related cancers, and subtypes of established obesity-related cancers associated with body mass index in this study (*in italics*), according to body mass index and sex[1]

	All			Men		Women	
Cancer category	No. at risk /cases	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]
Head and neck							
Oral cavity[4]	4,142,349/2,688	1.11 (0.94-1.32)	1.06 (1.00-1.12)	1.06 (0.85-1.33)	1.03 (0.96-1.11)	1.20 (0.92-1.57)	1.11 (1.01-1.21)
Lip	4,142,349/760	1.17 (0.87-1.57)	1.13 (1.01-1.25)[5]	1.22 (0.88-1.71)	1.17 (1.03-1.32)	NA[3]	1.06 (0.86-1.31)
Tongue	4,142,349/925	1.45 (1.09-1.91)[5]	1.14 (1.04-1.26)	1.29 (0.86-1.92)	1.09 (0.96-1.25)	1.66 (1.12-2.46)	1.19 (1.04-1.37)
Nasal and paranasal sinuses	4,142,349/431	1.55 (1.06-2.26)	1.16 (1.01-1.33)	1.75 (1.07-2.86)	1.19 (1.00-1.43)	NA[3]	1.12 (0.90-1.39)
Adenocarcinoma	4,042,179/208	NA[3]	1.26 (1.04-1.52)[5]	NA[3]	1.53 (1.18-1.98)	NA[3]	NA[3]
Squamous-cell carcinoma	4,142,349/6,410	0.96 (0.85-1.08)[5]	0.96 (0.93-1.00)[5]	0.86 (0.74-1.01)	0.92 (0.88-0.96)	1.21 (0.99-1.49)	1.08 (1.01-1.16)
Gastric							
Gastrointestinal stromal	4,142,349/227	NA[3]	1.29 (1.08-1.55)	NA[3]	1.19 (0.90-1.59)	NA[3]	NA[3]
Small intestine[4]	4,142,349/1,431	1.55 (1.25-1.93)	1.26 (1.17-1.35)	1.62 (1.20-2.19)	1.32 (1.19-1.45)	1.42 (1.03-1.95)	1.18 (1.05-1.32)
Duodenum	4,142,349/291	1.04 (0.60-1.83)	1.16 (0.98-1.38)	NA[3]	1.31 (1.05-1.64)	NA[3]	0.99 (0.76-1.30)
Ileum	4,092,313/348	2.35 (1.59-3.47)	1.39 (1.21-1.60)	NA[3]	1.37 (1.11-1.68)	NA[3]	1.41 (1.17-1.71)
Neuroendocrine	4,142,349/778	2.04 (1.56-2.68)	1.39 (1.26-1.52)	1.94 (1.31-2.86)	1.38 (1.20-1.57)	2.05 (1.41-2.98)	1.38 (1.20-1.59)
Colon[4]							
Proximal	4,142,349/9,542	1.33 (1.23-1.45)[5]	1.15 (1.11-1.18)[5]	1.51 (1.35-1.69)	1.20 (1.15-1.25)	1.19 (1.06-1.33)	1.10 (1.06-1.15)
Distal	4,142,349/7,253	1.43 (1.30-1.57)[5]	1.16 (1.13-1.20)[5]	1.65 (1.46-1.87)	1.26 (1.20-1.31)	1.21 (1.05-1.39)	1.07 (1.01-1.12)
Adenocarcinoma	4,142,349/16,801	1.38 (1.30-1.46)[5]	1.16 (1.13-1.18)[5]	1.60 (1.47-1.74)	1.24 (1.20-1.27)	1.17 (1.07-1.28)	1.08 (1.05-1.12)
Neuroendocrine	4,142,349/774	1.53 (1.14-2.06)	1.15 (1.05-1.27)	1.04 (0.58-1.87)	1.07 (0.92-1.26)	1.80 (1.27-2.55)	1.21 (1.07-1.37)
Rectum/anus	4,142,349/11,644	1.19 (1.10-1.29)[5]	1.08 (1.06-1.12)[5]	1.26 (1.14-1.40)	1.11 (1.07-1.15)	1.10 (0.97-1.24)	1.05 (1.01-1.10)
Adenocarcinoma	4,142,349/10,519	1.20 (1.10-1.30)	1.09 (1.06-1.13)	1.28 (1.16-1.43)	1.11 (1.07-1.16)	1.07 (0.94-1.23)	1.07 (1.02-1.12)
Biliary tract[2]	4,142,349/2,002	1.48 (1.26-1.74)	1.24 (1.16-1.31)	1.28 (0.98-1.67)	1.19 (1.08-1.31)	1.61 (1.31-1.98)	1.26 (1.16-1.36)
Extrahepatic bile ducts	4,142,349/589	1.49 (1.07-2.08)	1.25 (1.11-1.41)	1.11 (0.69-1.80)	1.19 (1.02-1.39)	NA[3]	1.33 (1.12-1.59)
Malignant melanoma[6]	4,142,349/22,167	0.96 (0.89-1.02)[5]	1.05 (1.03-1.07)[5]	1.15 (1.04-1.28)	1.15 (1.11-1.18)	0.84 (0.77-0.92)	0.97 (0.95-1.00)
Acral lentiginous	4,042,179/310	1.04 (0.64-1.70)	1.08 (0.93-1.27)	NA[3]	1.29 (1.01-1.67)	NA[3]	0.97 (0.80-1.19)
Superficial spreading	4,042,179/12,855	0.91 (0.83-1.00)[5]	1.04 (1.02-1.07)[5]	1.09 (0.94-1.27)	1.15 (1.10-1.20)	0.83 (0.74-0.92)	0.97 (0.94-1.01)
Nodular	4,042,179/2,281	1.09 (0.89-1.33)	1.10 (1.04-1.17)	1.00 (0.75-1.35)	1.13 (1.03-1.23)	1.17 (0.90-1.53)	1.08 (0.99-1.18)
Vulva	-	-	-	-	-	2.43 (1.88-3.14)	1.42 (1.29-1.55)
Cervix							
Adenocarcinoma						1.34 (1.08-1.65)	1.10 (1.02-1.19)
Endometrium[4]							
Type I	-	-	-	-	-	3.35 (2.99-3.76)	1.68 (1.61-1.74)
Type II	-	-	-	-	-	-	1.54 (1.30-1.83)

(Continued)

Cancer category	All			Men		Women	
	No. at risk /cases	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]	Obesity vs. normal weight[1]	Per 5 kg/m^2 higher BMI[1]
Penis	-	-	-	3.07 (2.28-4.14)	1.54 (1.38-1.73)	-	-
Renal cell[4]							
Clear cell	3,837,868/2,962	2.39 (2.07-2.76)	1.53 (1.46-1.61)	2.39 (1.96-2.90)	1.54 (1.45-1.64)	2.38 (1.92-2.97)	1.52 (1.41-1.64)
Papillary	4,042,179/466	1.56 (1.02-2.40)	1.25 (1.09-1.43)	1.20 (0.66-2.17)	1.19 (1.00-1.41)	NA[3]	NA[3]
Chromophobe	3,837,868/282	2.06 (1.31-3.24)	1.31 (1.12-1.54)	NA[3]	1.40 (1.11-1.77)	NA[3]	1.24 (1.00-1.54)
Endocrine organs	4,142,349/11,224	1.34 (1.24-1.45)	1.14 (1.11-1.17)[5]	1.52 (1.31-1.77)	1.21 (1.16-1.27)	1.28 (1.18-1.40)	1.11 (1.08-1.15)
Pancreatic islets	4,142,349/480	1.36 (0.90-2.05)	1.20 (1.06-1.37)	1.65 (0.90-3.00)	1.40 (1.18-1.66)	NA[3]	1.03 (0.86-1.25)
Thyroid[4]							
Papillary	4,042,179/2,809	1.24 (1.07-1.43)	1.08 (1.03-1.14)[5]	2.16 (1.56-2.99)	1.21 (1.08-1.36)	1.12 (0.95-1.31)	1.06 (1.00-1.12)
Follicular	4,042,179/408	1.20 (0.81-1.78)	1.17 (1.03-1.32)	NA[3]	1.30 (0.98-1.74)	1.25 (0.83-1.91)	1.15 (1.00-1.32)
Adrenal glands	4,142,349/479	1.50 (1.03-2.17)	1.18 (1.04-1.33)	NA[3]	1.13 (0.92-1.40)	NA[3]	1.19 (1.02-1.40)
Parathyroid gland	4,142,349/3,144	1.41 (1.23-1.62)	1.16 (1.11-1.22)	1.40 (1.02-1.93)	1.21 (1.09-1.33)	1.40 (1.20-1.63)	1.15 (1.09-1.21)
Pituitary gland	4,142,349/2,936	1.57 (1.35-1.83)	1.19 (1.13-1.25)	1.63 (1.27-2.09)	1.25 (1.16-1.35)	1.54 (1.27-1.86)	1.16 (1.08-1.24)
Connective tissue	4,142,349/2,029	1.34 (1.11-1.62)	1.20 (1.13-1.28)[5]	1.59 (1.23-2.04)	1.28 (1.17-1.38)	1.10 (0.82-1.47)	1.11 (1.01-1.23)
Lymphoid neoplasms[4]	4,142,349/16,018	1.22 (1.14-1.31)	1.11 (1.09-1.14)[5]	1.30 (1.19-1.43)	1.14 (1.11-1.18)	1.12 (1.01-1.25)	1.08 (1.04-1.12)
Hodgkin lymphoma[4]	4,142,349/2,239	1.38 (1.13-1.67)	1.18 (1.11-1.25)	1.52 (1.18-1.96)	1.20 (1.12-1.29)	1.23 (0.91-1.66)	1.15 (1.04-1.26)
Mixed cellularity	4,042,179/237	NA[3]	1.30 (1.10-1.54)	NA[3]	1.33 (1.08-1.63)	NA[3]	NA[3]
Nodular lymphocyte	4,042,179/166	NA[3]	1.72 (1.45-2.03)	NA[3]	1.53 (1.21-1.94)	NA[3]	NA[3]
Acute lymphocytic leukaemia	4,142,349/539	1.61 (1.13-2.29)	1.18 (1.05-1.33)	1.69 (1.04-2.75)	1.20 (1.03-1.40)	NA[3]	1.17 (0.97-1.41)
Chronic lymphocytic leukaemia	4,142,349/2,854	1.05 (0.89-1.24)	1.06 (1.00-1.12)	1.13 (0.93-1.39)	1.08 (1.01-1.16)	0.90 (0.66-1.21)	1.01 (0.91-1.12)
Diffuse large B-cell	4,042,179/2,775	1.53 (1.31-1.79)	1.23 (1.17-1.30)	1.70 (1.37-2.10)	1.29 (1.20-1.39)	1.37 (1.08-1.72)	1.16 (1.07-1.26)
Follicular	4,042,179/1,931	1.15 (0.94-1.41)	1.09 (1.02-1.16)	1.42 (1.07-1.90)	1.14 (1.03-1.25)	0.98 (0.74-1.30)	1.04 (0.95-1.14)
Myeloid neoplasm[4]	4,142,349/4,784	1.41 (1.26-1.59)	1.15 (1.10-1.20)	1.44 (1.22-1.70)	1.16 (1.09-1.22)	1.39 (1.17-1.64)	1.14 (1.07-1.21)
Acute myeloid leukaemia	4,142,349/1,498	1.24 (1.00-1.54)	1.13 (1.05-1.22)	1.36 (1.02-1.81)	1.14 (1.03-1.27)	1.13 (0.83-1.56)	1.12 (1.01-1.25)
Chronic myeloid leukaemia	4,142,349/1,002	1.47 (1.13-1.92)	1.17 (1.07-1.28)	1.42 (0.97-2.08)	1.16 (1.03-1.31)	1.55 (1.06-2.27)	1.19 (1.04-1.36)

Abbreviations: NW, normal weight; BMI, body mass index.

[1] Hazard ratios from Cox regression models with age as time scale, adjusted for baseline age (continuous), weight assessment from the Medical Birth Register (yes/no), mode of weight assessment, mode of height assessment, marital status, education level, and birth country, and stratified by sex (in analysis of men and women combined) and calendar year of birth.

[2] Gallbladder cancer, which is established obesity-related, is a subtypes of biliary tract cancer and makes up around half of biliary tract cancer.

[3] The number of cancer cases was considered too low for analysis (<250 cases for categorical body mass index and <100 cases for per 5 kg/m^2).

[4] The heterogeneity of hazard ratios per 5 kg/m^2 higher BMI between cancer subtypes was calculated using the Lunn and McNeil duplication method, separately in men and women whenever a sex-interaction was identified. P=0.0039 for the groups of gastric-adenocarcinoma, gastric-neuroendocrine, and

gastric-gastrointestinal stromal; P=0.0045 for the groups of small intestine-adenocarcinoma, small intestine-neuroendocrine, and small intestine-gastrointestinal stromal; P=0.00030 for cervix-adenocarcinoma vs. cervix-squamous-cell carcinoma; P=0.0019 for the groups of renal cell-clear cell, renal cell-papillary, and renal cell-chromophobe; P<0.0001 for the groups of Hodgkin-nodular sclerosis, Hodgkin-mixed cellularity, and Hodgkin-nodular lymphocyte; P<0.0001 for the groups of Hodgkin lymphoma, acute lymphocytic leukaemia, chronic lymphocytic leukaemia, diffuse large B-cell lymphoma, follicular lymphoma, and T-cell/natural killer-cell lymphoma in men. No heterogeneity was found between other cancer subtypes.

[5] $P_{sex\text{-}interaction}<0.05$, calculated by adding a product term of sex and BMI in categories or per 5 kg/m^2 higher BMI in the Cox model using Wald test.

[6] Hazard ratios for malignant melanoma and its subtypes were also calculated additionally adjusted for height (continuous) – a strong risk factor and commonly adjusted for in studies of BMI and malignant melanoma risk. The associations did not change, for example, HRs (95% CI) per 5 kg/m^2 higher BMI for malignant melanoma, melanoma-superficial spreading, and melanoma-nodular were 1.06 (1.04-1.08), 1.06 (1.03-1.08), and 1.11 (1.05-1.18), respectively.

When combining all potential obesity-related cancers, the HR per 5 kg/m^2 higher BMI was 1.13 (95% CI 1.11-1.15) in women and 1.17 (95% CI 1.15-1.19) in men (Figure 7). In comparison, the association with all established obesity-related cancers was slightly stronger in men (HR 1.24, 95% CI 1.22-1.26), but of similar effect size in women (HR 1.12, 95% CI 1.11-1.13). The absolute risk of all potential and established obesity-related cancers combined by age 80 was 16.3% (16.1%-16.5%) for normal weight and 18.7% (18.1%-19.1%) for obesity in women. The corresponding risks were 12.0% (11.9%-12.2%) and 14.2% (13.8%-14.6%) in men.

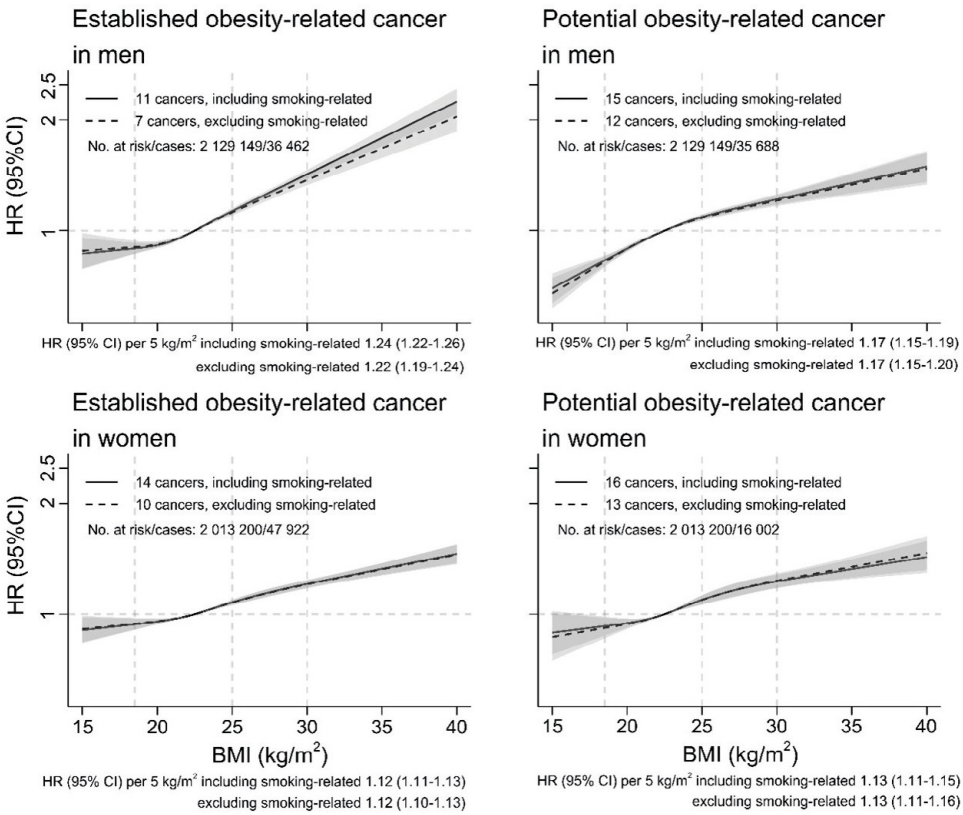


Figure 7. Hazard ratios of established obesity-related cancers and potential obesity-related cancers according to BMI allowing for non-linear associations, with 95% confidence intervals. The reference BMI was 22.5 kg/m^2. Restricted cubic splines for BMI with knots placed at Harrell's recommended percentiles of BMI were fitted adjusting for baseline age (continuous), weight assessment from Medical Birth Register, mode of weight assessment, mode of height assessment, marital status, education level, and birth country, and stratified by calendar year of birth. Smoking-related cancers include cancers of the oral cavity, nasal and paranasal sinuses, head and neck (adenocarcinoma), and head and neck (squamous cell carcinoma), oesophagus (adenocarcinoma), stomach-cardia, liver/intrahepatic bile ducts, and pancreas. HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Paper II

Waist circumference and risk of obesity-related cancers

A total of 339,190 individuals, 196,756 women and 142,434 men, with a mean baseline age of 50 (SD = 13.1) and 53 (SD = 12.4) years, were eligible for analysis. The mean WC in women was 82.3 cm and in men 95.5 cm. After a median follow-up of 14 years (IQR = 8.0-22.5), 18,185 established obesity-related cancers, 13,703 in women and 4,482 in men, and 6,893 potential obesity-related cancers, 3,091 in women and 3,802 in men, had been recorded.

The associations of WC and BMI quintiles, and per SD higher WC and BMI with risks of obesity-related cancers combined in men and women separately are shown in Table 4. The results of WC and BMI quintiles revealed an approximately linear increase in the risk of obesity-related cancers for both variables. When WC and BMI were analysed as continuous variables, a 1-SD increase in WC was associated with a 25% higher risk of developing established obesity-related cancers (HR 1.25, 95% CI 1.21-1.30) among men, which was stronger than for BMI, which had an HR of 1.19 (95% CI 1.15-1.23) per 1-SD increase, although the 95% CIs overlapped. Among women, the associations of WC and BMI were weaker and of comparable size (WC: HR 1.13, 95% CI 1.11-1.16; BMI: HR 1.13, 95% CI 1.11-1.15). A similar pattern but weaker association were found for all established and potential obesity-related cancers combined.

Residual analyses showed that WC residuals remained associated with the risk of obesity-related cancer in men (HR 1.09, 95% CI 1.06-1.12) in models adjusted for BMI, and this association was notably weaker in women (HR 1.03, 95% CI 1.02-1.05) (Figure 8). For specific sites, results were generally consistent with these findings. The risk of developing established obesity-related cancer increased gradually across WC tertiles within BMI tertiles, among both men and women (Figure 8). The risk for BMI subgroup-tertiles within BMI tertiles also increased gradually as expected, due to the inherent gradient within BMI categories. In men, the increase in risk was more pronounced for WC tertiles than for BMI tertiles; all point estimates for the eight HRs for WC tertile within BMI tertile combinations were higher than those for BMI subgroup-tertile within BMI tertile combinations, although the 95% CIs overlapped. Specifically, the HR for the highest WC tertile within highest BMI tertile was 1.91 (95% CI 1.66-2.20), whereas the HR for the highest BMI subgroup-tertile within the highest BMI group was 1.58 (95% CI 1.39-1.80). In women, HRs for WC tertiles within BMI tertiles were comparable to HRs for BMI subgroup-tertiles within BMI tertiles, even for the highest combination (WC-BMI: HR 1.43, 95% CI 1.33-1.55; BMI-BMI: HR 1.46, 95% CI 1.35-1.57).

When comparing the risks for per SD higher WC within BMI quintiles and per SD higher BMI within WC quintiles, associations were observed between continuous

WC and higher risks of established obesity-related cancers among men except for the second lowest quintile; however, continuous BMI and higher risk was only found within the highest quintile of WC (Figure 8). Among women, both per SD higher WC within BMI quintiles and per SD higher BMI within WC quintiles exhibited weak and similarly sized associations with cancer risk.

Table 4. Hazard ratios (95% confidence interval) of all established obesity-related cancers and all established and potential obesity-related cancers combined according to BMI and WC quintiles.

		All established obesity-related cancers		All established and potential obesity-related cancers	
	Median (Range)	No. at risk/cases	HR (95% CI)[1]	No. at risk/cases	HR (95% CI)[1]
Men					
WC quintiles					
Q1	83.0 (40.0-86.5)	27,105/554	Reference	27,105/1,101	Reference
Q2	89.0 (86.7-91.5)	25,642/727	1.16 (1.04-1.30)	25,642/1,360	1.09 (1.04-1.14)
Q3	94.0 (91.6-97.0)	34,383/1,118	1.27 (1.14-1.40)	34,383/2,113	1.17 (1.11-1.22)
Q4	100.0 (97.1-103.2)	26,640/965	1.40 (1.26-1.56)	26,640/1,782	1.19 (1.13-1.25)
Q5	109.0 (103.3-160.0)	28,664/1,118	1.67 (1.51-1.86)	28,664/1,928	1.31 (1.25-1.38)
P for trend/χ2			<0.01/220.09		<0.01/281.83
WC continuous (per SD incr.)[2]		142,434/4,482	1.25 (1.21-1.30)	142,434/8,284	1.18 (1.16-1.22)
BMI quintiles					
Q1	22.1 (15.0-23.2)	28,588/766	Reference	28,588/1,479	Reference
Q2	24.2 (23.3-25.0)	28,391/840	1.05 (0.95-1.16)	28,391/1,576	1.11 (1.04-1.17)
Q3	25.8 (25.1-26.6)	28,516/890	1.11 (1.01-1.22)	28,516/1,696	1.18 (1.11-1.24)
Q4	27.7 (26.7-28.8)	28,453/1,000	1.29 (1.17-1.41)	28,453/1,844	1.23 (1.16-1.30)
Q5	30.9 (28.9-60.0)	28,486/986	1.48 (1.35-1.63)	28,486/1,689	1.35 (1.28-1.43)
P for trend/χ2			<0.01/226.37		<0.01/259.23
BMI continuous (per SD incr.)[2]		142,434/4,482	1.19 (1.15-1.23)	142,434/8,284	1.14 (1.12-1.18)
Women					
WC quintiles					
Q1	70.0 (40.0-73.0)	46,406/2,880	Reference	46,406/3,561	Reference
Q2	76.0 (73.1-78.0)	38,788/2,577	1.04 (0.99-1.10)	38,788/3,158	1.04 (0.99-1.09)
Q3	81.0 (78.1-83.0)	33,802/2,447	1.16 (1.06-1.18)	33,802/2,979	1.10 (1.05-1.16)
Q4	87.0 (83.1-91.0)	39,450/2,967	1.16 (1.10-1.22)	39,450/3,640	1.15 (1.10-1.21)
Q5	98.0 (91.1-160.0)	38,310/2,832	1.29 (1.22-1.36)	38,310/3,456	1.27 (1.21-1.34)
P for trend/χ2			<0.01/306.77		<0.01/345.67
WC continuous (per SD incr.)[2]		196,756/13,703	1.13 (1.11-1.16)	196,756/16,794	1.12(1.10-1.15)
BMI quintiles					
Q1	20.3 (15.0-21.5)	39,392/2,063	Reference	39,392/2,567	Reference
Q2	22.4 (21.6-23.2)	39,365/2,541	1.03 (0.96-1.10)	39,365/3,136	1.10 (1.05-1.16)
Q3	24.1 (23.3-25.1)	39,487/2,884	1.11 (1.03-1.18)	39,487/3,524	1.16 (1.10-1.22)
Q4	26.3 (25.2-27.9)	39,180/3,084	1.24 (1.16-1.33)	39,180/3,761	1.21 (1.15-1.27)
Q5	30.5 (28.0-60.0)	39,332/3,131	1.34 (1.25-1.44)	39,332/3,806	1.33 (1.26-1.40)
P for trend/χ2			<0.01/265.86		<0.01/318.64
BMI continuous (per SD incr.)[2]		196,756/13,703	1.13 (1.11-1.15)	196,756/16,794	1.12(1.09-1.14)

Abbreviations: WC, waist circumference; BMI, body mass index; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

[1] Hazard ratios were calculated by use of Cox regression using age as time scale, stratified by calendar year of birth (<1940, 1940-1949, 1950-1959, 1960-1969, ≥1970), and adjusted for baseline age (continuous), smoking status, cohort, marital status, education level, birth country, income level, and main source of income. We additionally adjusted for mode of waist circumference assessment and height (continuous) for the analysis of waist circumference, and mode of weight and height assessment for the analysis of body mass index.

[2] HRs were corrected for regression dilution ratios of body mass index or waist circumference (men, BMI: 0.92, WC: 0.78; women, BMI: 0.95, WC: 0.83).

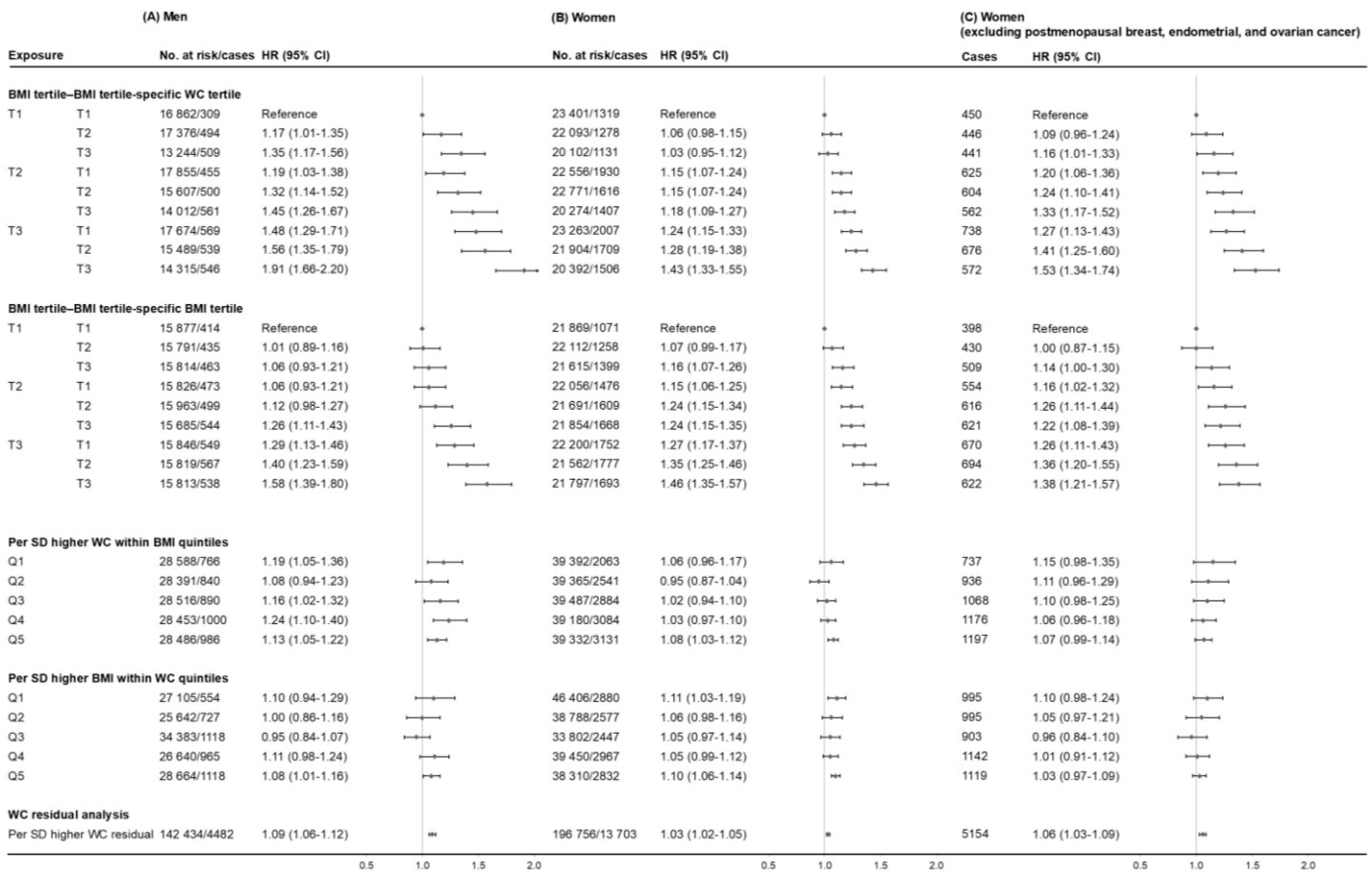


Figure 8. Hazard ratios (95% confidence interval) of all established obesity-related cancers combined associated with body mass index and waist circumference within body mass index and waist circumference tertiles and quintiles in men (A) and women (B) separately. HR, hazard ratio; CI, confidence interval; SD, standard deviation; WC, waist circumference; BMI, body mass index.

Paper III

Metabolic health status and body mass index and risk of obesity-related cancers

A total of 797,193 individuals, 397,082 women and 400,111 men, with a mean baseline age of 43 years (SD = 9.1) were eligible for analysis. Obesity represented 10% (n = 81,423) and metabolically unhealthy represented 35% (n = 276,489) of all individuals. Metabolically healthy normal weight and metabolically unhealthy obesity were prevalent in 42% (n = 334,924) and 7% (n = 54,238) of the population, respectively. After an average follow-up of 20 years (SD = 7.8), 23,630 established obesity-related cancer cases (16,114 in women, 7,516 in men) had been recorded.

Sex-specific HRs for combinations of metabolic health status and BMI of all established obesity-related cancers combined are shown in Figure 9. Compared to metabolically healthy normal weight, the HR for all established obesity-related cancers combined in metabolically unhealthy obesity was 1.91 (95% CI 1.74-2.09) in men and 1.43 (95% CI 1.35-1.51) in women ($P_{\text{sex-interaction}} = 0.001$).

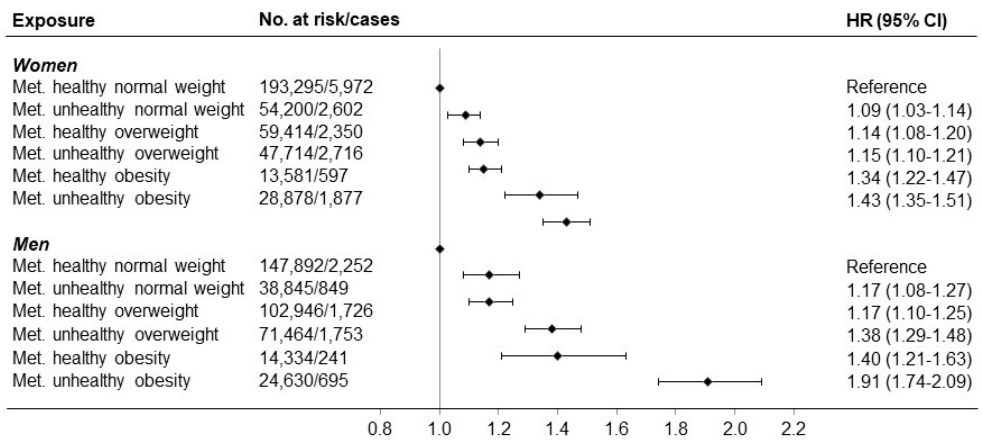


Figure 9. Hazard ratios (95% confidence interval) of all obesity-related cancers in 797,193 women and men according to combinations of metabolic health status and body mass index. Hazard ratios were calculated by use of Cox regression using age as timescale, adjusted for sex, baseline age, and smoking status and pack-years and stratified by cohort and date of birth. Normal weight: 18.5 < BMI < 25 kg/m^2; overweight: 25 < BMI < 30 kg/m^2; obesity: BMI < 30 kg/m^2; metabolically healthy: middle and lowest tertile of metabolic score; metabolically unhealthy: top tertile of metabolic score. Metabolic score composes equal weight from mid-blood pressure, glucose, and triglycerides. BMI, body mass index; CI, confidence interval; HR, hazard ratio; Met., metabolically

Figure 10 shows HRs of separate cancers for combinations of metabolic health status and BMI. Higher risks in metabolically unhealthy obesity relative to metabolically healthy normal weight were found for all separate obesity-related cancers, except multiple myeloma and, in women, postmenopausal breast, and ovarian cancer. The strongest effect estimates of metabolically unhealthy obesity were found for endometrial cancer (HR 3.00, 95% CI 2.65-3.39), liver cancer (HR 2.74, 95% CI 2.13-3.53), "other" obesity-related cancers comprising oesophageal adenocarcinoma and gastric-cardia cancer (HR 2.56, 95% CI 1.97-3.32), and renal cell cancer (HR 2.55, 95% CI 2.18-2.98). A sex interaction was observed for colon cancer and multiple myeloma ($P_{\text{sex-interaction}} = 0.003$ and 0.01, respectively). For colon cancer, metabolically unhealthy obesity conveyed a higher risk in men (HR 1.67, 95% CI 1.42-1.96) than in women (HR 1.18, 95% CI 1.00-1.39). No differential risk with metabolically unhealthy obesity was observed in women and men for multiple myeloma (HR 0.83, 95% CI 0.57-1.20; HR 0.98, 95% CI 0.66-1.46).

Regarding metabolically healthy obesity and overweight, increased risks of all established obesity-related cancers combined were observed for both men and women relative to metabolically healthy normal weight (Figure 9). For separate cancers, metabolically healthy obesity or overweight were associated with an increased risk of cancers of the colon, endometrium, gallbladder, liver, and renal cell carcinoma (Figure 10).

A positive, additive interaction between metabolic health status and BMI (normal weight/obesity) was observed regarding the risk of all established obesity-related cancers combined among men ($P = 0.02$), rectal cancer among men ($P = 0.04$), and endometrial cancer among women ($P = 0.07$). When BMI was categorised into normal weight vs. overweight and obesity, the P value of interaction for endometrial cancer was reduced to 0.01. The absolute risk from age 35 to 85 of all established obesity-related cancers combined among men and women separately, rectal cancer among men, and endometrial cancer among women are shown in Figure 11. The additive interactions were also reflected in the absolute risk curves, where the risk difference between individuals with metabolically healthy and metabolically unhealthy was larger among individuals with obesity than normal weight. No multiplicative interactions were observed.

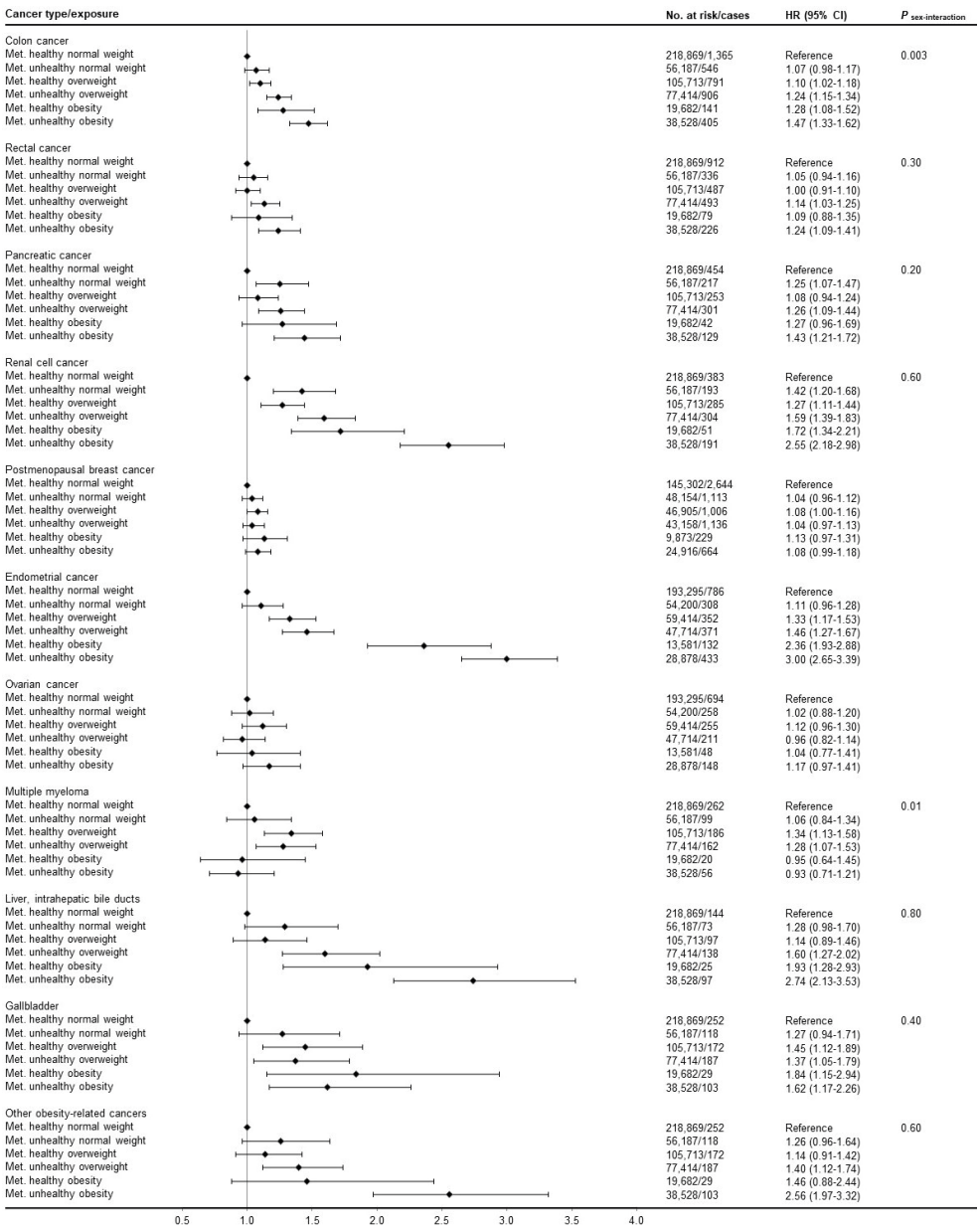
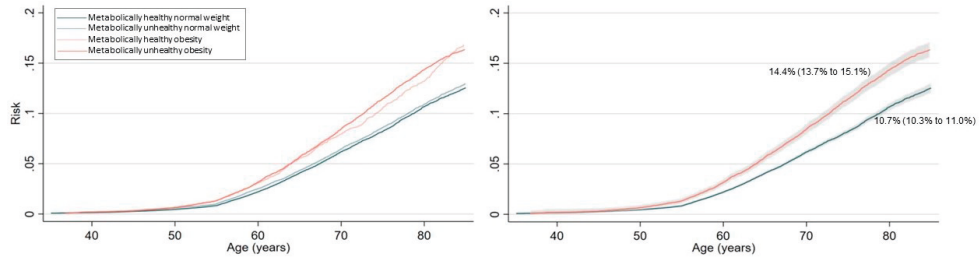
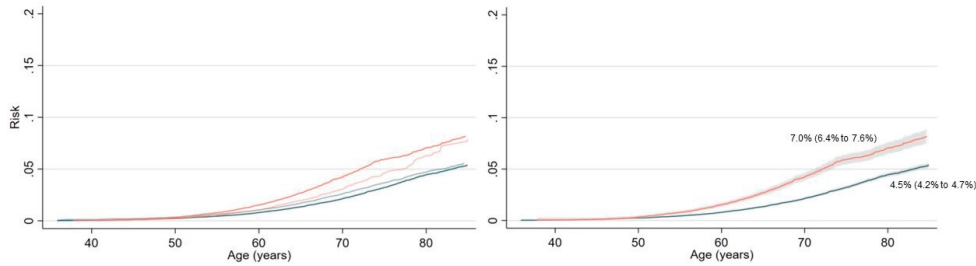


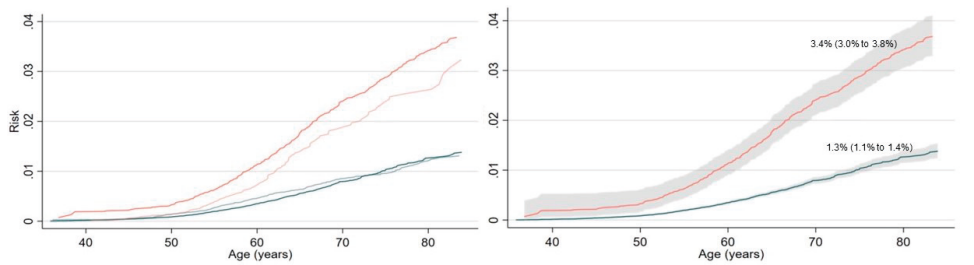
Figure 10. Hazard ratios (95% confidence interval) of obesity-related cancers for specific sites in 797,193 women and men according to combinations of metabolic health status and body mass index. Other obesity-related cancers include oesophageal adenocarcinoma and stomach-cardia cancer. BMI, body mass index; CI, confidence interval; HR, hazard ratio; Met., metabolically



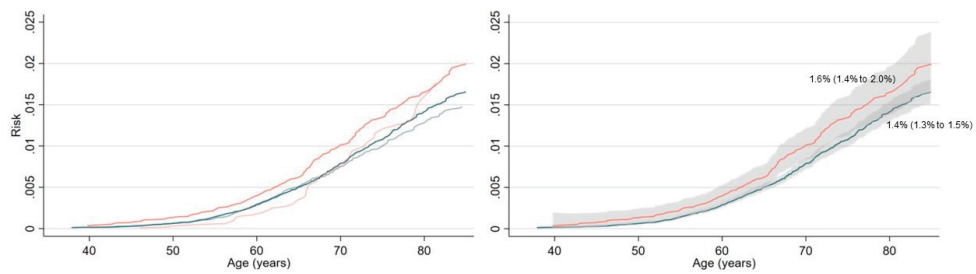
(A) All established obesity-related cancers (women), No. cases = 16,114



(B) All established obesity-related cancers (men), No. cases = 7,516



(C) Endometrial cancer, No. cases = 2,382



(D) Rectal cancer (men), No. cases = 2,196

Figure 11. Risk of all obesity-related cancers among women (A), all obesity-related cancers among men (B), endometrial cancer (C), rectal cancer among men (D) among 397,082 women and 400,111 men according to combinations of metabolic health status and body mass index. Shaded areas are 95% confidence bands. BMI, body mass index

Paper IV

Leisure-time physical activity and body mass index and risk of obesity-related cancers

A total of 570,021 individuals (284,928 women, 285,093 men) with a mean baseline age of 43 years (SD = 7.5) were involved in the study. Approximately 13% of women and 26% of men were categorised into the moderate to hard PA group, and 63% of women and 46% of men had a low-to-normal BMI. A total of 19,074 individuals (12,075 in women, 6,999 in men) were diagnosed with established obesity-related cancers after a follow-up of 20 years (SD = 8.0) on average.

Compared to individuals with sedentary to light leisure-time PA, individuals with moderate to hard PA showed a lower risk of all established obesity-related cancers combined (HR 0.93, 95% CI 0.90-0.96), colon cancer (HR 0.91, 95% CI 0.84-0.98), and renal cell cancer (HR 0.79, 95% CI 0.69-0.91) (Table 5). These associations slightly attenuated after additionally adjusting for BMI. No sex interaction was observed.

Figure 12 shows HRs for the combination of leisure-time PA and BMI for all established obesity-related cancers combined and separate cancers. Compared to individuals with overweight or obesity and low PA, individuals with low-to-normal weight and high PA had a lower risk of all established obesity-related cancers combined (HR 0.76, 95% CI 0.72-0.80). For separate cancers, individuals with low-to-normal weight and high PA had a lower risk of colon cancer, pancreatic cancer, endometrial cancer, renal cell carcinoma, multiple myeloma, and the combination of "other" obesity-related cancers composed of oesophageal adenocarcinoma, stomach-cardia cancer, liver cancer and gallbladder cancer. The strongest effect size was found for endometrial cancer (HR 0.53, 95% CI 0.43-0.65), renal cell carcinoma (HR 0.59, 95% CI 0.49-0.73), and "other" obesity-related cancers (HR 0.66, 95% CI 0.54-0.82). For all obesity-related cancers combined, endometrial cancer, multiple myeloma and "other" obesity-related cancers, the inverse associations appeared to be driven more by BMI than PA. No additive or multiplicative interactions were found between PA and BMI. No sex interactions were observed.

Table 5. Hazard ratio (95% confidence interval) of established obesity-related cancers by level of leisure-time physical activity.

Cancer type	Level of leisure time PA[1]	No. at risk/ cases	HR (95% CI)[2] Not BMI-adjusted	HR (95% CI)[3] BMI-adjusted	$P_{sex-interaction}$[4]
All established obesity-related cancers	All				0.67
	Low PA	460,382/16,127	Reference	Reference	
	High PA	109,639/2,947	0.93 (0.90-0.96)	0.94 (0.91-0.98)	
	Women				
	Low PA	248,433/10,696	Reference	Reference	
	High PA	36,495/1,379	0.93 (0.88-0.98)	0.95 (0.90-1.01)	
	Men				
	Low PA	211,949/5,431	Reference	Reference	
	High PA	73,144/1,568	0.92 (0.87-0.97)	0.94 (0.89-1.00)	
Colon cancer	All				0.67
	Low PA	460,382/3,841	Reference	Reference	
	High PA	109,639/779	0.91 (0.84-0.98)	0.92 (0.85-1.00)	
	Women				
	Low PA	248,433/1,974	Reference	Reference	
	High PA	36,495/249	0.94 (0.82-1.07)	0.95 (0.84-1.09)	
	Men				
	Low PA	211,949/1,867	Reference	Reference	
	High PA	73,144/530	0.89 (0.80-0.98)	0.91 (0.83-1.00)	
Rectal cancer	All				0.39
	Low PA	460,382/2,336	Reference	Reference	
	High PA	109,639/513	0.93 (0.84-1.02)	0.93 (0.85-1.03)	
	Women				
	Low PA	248,433/1,045	Reference	Reference	
	High PA	36,495/141	0.99 (0.83-1.19)	1.01 (0.84-1.20)	
	Men				
	Low PA	211,949/1,291	Reference	Reference	
	High PA	73,144/372	0.91 (0.81-1.03)	0.92 (0.82-1.04)	
Pancreatic cancer	All				0.92
	Low PA	460,382/1,168	Reference	Reference	
	High PA	109,639/221	0.89 (0.77-1.03)	0.90 (0.78-1.04)	
	Women				
	Low PA	248,433/560	Reference	Reference	
	High PA	36,495/65	0.89 (0.69-1.15)	0.90 (0.70-1.17)	
	Men				
	Low PA	211,949/608	Reference	Reference	
	High PA	73,144/156	0.88 (0.74-1.06)	0.89 (0.74-1.06)	
Postmenopausal breast cancer	Women				
	Low PA	171,989/3,180	Reference	Reference	
	High PA	22,272/467	0.99 (0.89-1.09)	0.99 (0.90-1.09)	
Endometrial cancer	Women				
	Low PA	248,433/1,689	Reference	Reference	
	High PA	36,495/201	0.88 (0.76-1.02)	0.95 (0.82-1.10)	
Ovarian cancer	Women				
	Low PA	248,433/1,144	Reference	Reference	
	High PA	36,495/155	1.02 (0.86-1.21)	1.03 (0.87-1.21)	

(Continued)

Cancer type	Level of leisure time PA[1]	No. at risk/ cases	HR (95% CI)[2] Not BMI-adjusted	HR (95% CI)[3] BMI-adjusted	P $_{sex-interaction}$[4]
Renal cell cancer	All				0.11
	Low PA	460,382/1,189	Reference	Reference	
	High PA	109,639/237	0.79 (0.69-0.91)	0.82 (0.71-0.95)	
	Women				
	Low PA	248,433/450	Reference	Reference	
	High PA	36,495/37	0.63 (0.45-0.89)	0.66 (0.47-0.93)	
	Men				
	Low PA	211,949/739	Reference	Reference	
	High PA	73,144/200	0.84 (0.72-0.98)	0.87 (0.74-1.02)	
Multiple myeloma	All				0.05
	Low PA	460,382/666	Reference	Reference	
	High PA	109,639/168	1.03 (0.87-1.23)	1.05 (0.88-1.25)	
	Women				
	Low PA	248,433/301	Reference	Reference	
	High PA	36,495/32	0.77 (0.53-1.11)	0.77 (0.53-1.11)	
	Men				
	Low PA	211,949/365	Reference	Reference	
	High PA	73,144/136	1.16 (0.95-1.42)	1.19 (0.97-1.45)	
Other obesity-related cancers[5]	All				0.07
	Low PA	460,382/955	Reference	Reference	
	High PA	109,639/216	0.95 (0.82-1.11)	0.99 (0.85-1.15)	
	Women				
	Low PA	248,433/373	Reference	Reference	
	High PA	36,495/37	0.73 (0.52-1.03)	0.76 (0.54-1.07)	
	Men				
	Low PA	211,949/582	Reference	Reference	
	High PA	73,144/179	1.03 (0.87-1.22)	1.08 (0.91-1.28)	

Abbreviations: HR, hazard ratio; CI, confidence interval; PA, physical activity.

[1] Low PA: sedentary to light PA, High PA: moderate to hard PA.

[2] Hazard ratios from Cox regression models with age as time scale, adjusted for sex, cohort, baseline age, date of birth in 5 categories (before 1931, 1931-1938, 1939-1946, 1947-1954, 1955 and later), and smoking status and intensity in 7 categories.

[3] Hazard ratios from Cox regression models with age as time scale, adjusted for sex, cohort, baseline age, date of birth in 5 categories (before 1931, 1931-1938, 1939-1946, 1947-1954, 1955 and later), smoking status and intensity in 7 categories, and BMI (continuous).

[4] The *P*-value for sex-interaction was based on Wald statistics of the product terms of sex and leisure-time physical activity in the Cox regression model.

[5] Other obesity-related cancers include oesophageal adenocarcinoma, stomach cardia, liver/intrahepatic bile ducts, and gallbladder/biliary tract cancer.

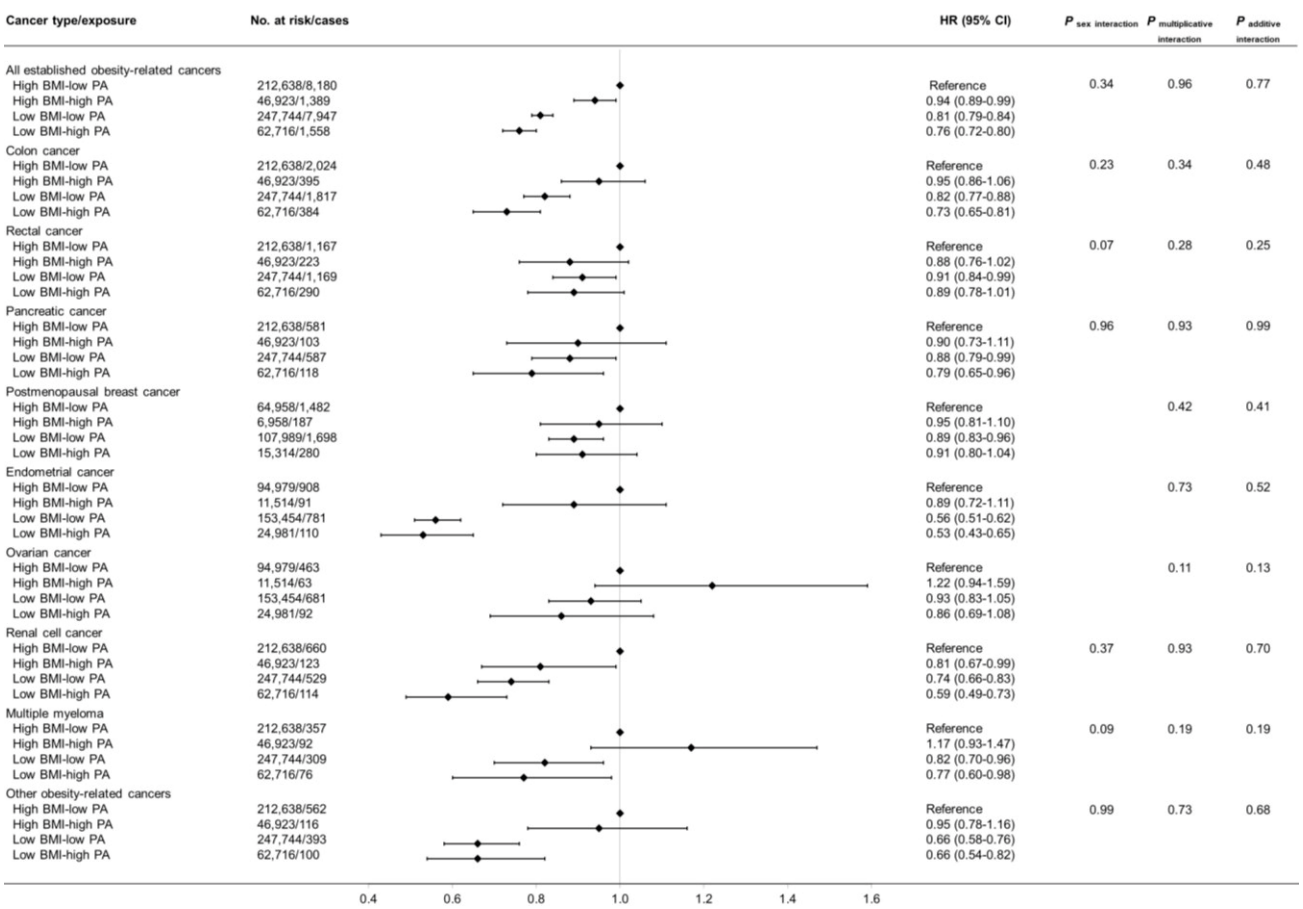


Figure 12. Hazard ratios (95% confidence interval) of obesity-related cancers, single and combined according to combinations of leisure-time physical activity and body mass index level. Multiplicative interactions of PA and BMI, and a three-way interaction of PA, BMI, and sex, were tested by the Wald test of the respective product term in the model. BMI, body mass index; CI, confidence interval; HR, hazard ratio; PA, physical activity.

Discussion

Main findings

This thesis further strengthens the evidence of already established obesity-related cancers, presents the evidence for positive associations between BMI and some cancers that are potentially related to obesity but for which there is insufficient evidence, and suggests additional cancers, most of which are rare, to be potentially obesity related. Furthermore, we found that, in men, WC is a slightly stronger risk factor for obesity-related cancers compared to BMI, and WC offers additional risk information beyond that provided by BMI alone. In women, however, the associations of WC and BMI with cancer risk were similar in magnitude, and WC provided little additional risk information beyond BMI. Obesity together with metabolically unhealthy status (metabolically unhealthy obesity), based on a score for blood pressure, plasma triglycerides, and glucose, conveyed the highest risk of any obesity-related cancer compared with other combinations. Obesity remained a risk factor even in a healthy metabolic status (metabolically healthy obesity), although the associations were weakened. We also found that compared to sedentary to light leisure-time PA, moderate to hard leisure-time PA was associated with a lower risk of all obesity-related, colon, and renal cell cancer. A low-to-normal range of BMI combined with higher level PA was associated with a further reduced cancer risk.

Observational studies on obesity and cancer risk using BMI as adiposity indicator have confirmed 13 cancers as obesity related; however, this conclusion was made based on studies mostly focusing on more common site-specific cancers[82,172]. The evidence for the relationship between obesity and risk of many cancers is inconclusive, as they are either rare or weakly associated with BMI. In this thesis, based on the dataset with 4.1 million individuals and more than 300,000 incident cancer cases, we investigated the association between BMI and the risk of 122 cancers and cancer subtypes, grouped by topography and morphology. Our findings are consistent with current evidence on established obesity-related cancers, and we also suggest that some of the associations are driven by specific cancer subtypes, such as clear cell carcinoma for renal cell cancer and papillary carcinoma for thyroid cancer. Our results support the association between BMI and a range of cancers reported by the IARC, the WCRF, or an umbrella review from 2017 to have a potential association with obesity, but with insufficient evidence[77-79]. These include

cancers of the oral cavity, cervix (adenocarcinoma only), extrahepatic bile duct, and malignant melanoma (men only). We also provide evidence for a positive association between BMI and haematological malignancies, for which diffuse large B-cell lymphoma, other lymphoid neoplasms, and myeloid neoplasms (the IARC report used non-Hodgkin lymphoma and leukaemia instead, but the included subtypes largely overlap) have previously been reported to be associated with obesity separately, and multiple myeloma is an already established obesity-related cancer. This association is also supported by a biological mechanism where adipocytes may modify the bone marrow microenvironment and provide substances that could enhance the growth and survival of tumour cells[173]. In haematological malignancies, as in several other cancers, there are other potential mechanisms linking obesity and cancer, including insulin resistance, insulin-like growth factors, and systemic inflammation[85].

We found positive associations between BMI and risk for several cancers for which there was little or no evidence from previous studies. These include cancers of the small intestine, stomach (gastrointestinal stromal tumours), vulva, penis, some endocrine organs, and connective tissue. The strongest association was observed with penile cancer, where the risk was found to be twice as high in men with obesity compared to those of normal weight. It has been suggested that this link may be influenced by factors such as poor hygiene and difficulty with self-examination in individuals with severe obesity[174]. A variety of rare malignant endocrine neoplasms, including cancers of the pancreatic islets, adrenal glands, parathyroid gland, and pituitary gland, were found to have a positive association with BMI. Since these organs secrete hormones, it is biologically plausible that excess weight leads to hormonal changes that promote cancer development. However, further epidemiological and experimental studies are needed to confirm this association.

BMI has been widely used in observational studies; however, the accuracy of BMI has been questioned because it does not distinguish between muscle mass and fat mass. It is suggested that the use of other indicators could provide information on fat distribution. WC is a simple and cost-effective anthropometric measure that reflects abdominal fat accumulation[175,176]. However, in contrast to BMI, the effects of WC on specific cancers remain less investigated. A study based on 3.5 million Spanish adults reported comparable estimates of cancer risk associated with adiposity and overlapping CIs using BMI and WC[82], which are largely in line with our findings. However, although the 95% CIs for HRs per SD often overlapped, we found that HRs for WC were generally slightly higher than those for BMI, with point estimates being higher for WC in 12 out of 17 analysed cancers for men and 16 out of 22 analysed cancers for women, similar to Barberio et al.[177]. One plausible explanation for the differences between results for WC compared to BMI in our study, as compared to that of other studies, is the higher intra-personal variability of WC compared to BMI due to greater random measurement error, which we, but not others, accounted. The availability of repeated measurements allowed us to correct

HRs for RDR. And due to the greater RDR of WC compared with BMI, the HRs for WC strengthened relatively more. For example, for established obesity-related cancers in men, the RDR-corrected HRs were 1.19 for BMI and 1.25 for WC, whereas the uncorrected values would have been 1.17 and 1.19, respectively, thereby closer together.

Central obesity, as measured by WC, reflects accumulation of fat around abdominal organs, which are metabolically more active and associated with adverse health outcomes such as insulin resistance, inflammation, and dyslipidaemia[84,178,179]. As a result, individuals with similar BMI may have different cancer risks due to variations in fat distribution. It is assumed that a high WC poses a greater risk than a high BMI. Our results support this, suggesting that WC appears to provide additional risk information beyond that conveyed by BMI, particularly in men compared with women. A plausible explanation is that men tend to store fat viscerally, while women typically accumulate more subcutaneous fat[180]. Consequently, WC is a more accurate measure of visceral fat in men, potentially making it a stronger risk factor for cancer risk. This may explain why WC adds risk information beyond BMI in men but not in women. The difference in how WC and BMI relate to cancer risk between men and women underscores the complexity of the impact of obesity on cancer development.

Another way to improve risk stratification of BMI, rather than using a different adiposity marker, could be to combine BMI with metabolic risk markers. Obesity combined with metabolic aberration in the metabolic syndrome or in summary scores has been consistently linked to an increased risk of several obesity-related cancers[125,126,128,181-187]. Evidence about the added contribution of metabolic aberrations beyond the effect of obesity on cancer risk is limited. One large European study showed that metabolically unhealthy obesity was associated with an increased risk for ten (nine obesity-related) out of 22 cancers[188]. In our study, the highest relative risks were found for endometrial, liver, and renal cell cancer, with both obesity and metabolic aberrations contributing to the elevated risks. We found no association between metabolically unhealthy obesity and multiple myeloma and ovarian cancer risk, consistent with the European study. It is worth noting that while different definitions of metabolically unhealthy were used – a metabolic score in our study, and the ATP III definition in the other study – similar findings were observed. Despite variations in definitions across studies, they all include components of hypertension, dyslipidaemia, and hyperglycaemia. These may jointly capture the aetiology linking metabolically unhealthy with cancer irrespective of the exact components and cut-points used, as has been suggested in relation to all-cause and cardiovascular mortality[189,190].

Because individuals with metabolically healthy obesity typically show no evidence of insulin resistance, inflammation, or ectopic lipid deposition[129,130] – factors hypothesised to promote the development of cancer – there has been growing interest in whether metabolically healthy obesity is linked to an increased risk of

obesity-related cancers. Our study found that individuals with metabolically healthy obesity had an approximately 30% higher risk of developing any obesity-related cancer compared with individuals with metabolically healthy normal weight. The European study and a meta-analysis reported the association between metabolically healthy obesity and increased risk of several obesity-related cancers[125,188]. The associations for endometrial and kidney (renal cell) cancer are supported by our study. Moreover, we observed an increased risk of colon cancer in men with metabolically healthy obesity.

This thesis also systematically examined the interaction between BMI and metabolic health status in relation to the risk of several cancers. We observed positive interactions on the additive scale in relation to any obesity-related and rectal cancer among men, as well as for endometrial cancer in women. These findings suggest that obesity together with metabolic aberrations increase the risk of these cancers more than would be expected from the sum of their individual parts.

While excess weight heightens the likelihood of developing cancer, regular PA could help reduce the risk. The role of leisure-time PA on reducing risk of some cancers, including colon, postmenopausal breast, and endometrial cancer, has been supported by strong evidence[74]. An association for kidney cancer has been suggested by accumulating evidence[133,191], which is also confirmed by our results. Our results did not confirm the association between PA and risk of postmenopausal breast and endometrial cancer; however, previous studies have shown heterogeneous results and modest effect sizes for postmenopausal breast cancer[90]. These observed heterogeneous findings between studies are potentially affected by different assessments and cut-points for PA. For example, for cancers where light exercise has been shown to reduce risk[90], the association could not have been captured in our study due to the higher PA cut-point.

Some potential biological mechanisms underlying the link between obesity, PA, and cancer risk have been suggested. For example, obesity and physical inactivity contribute to energy imbalance, which may be linked to cancer through oxidative stress, DNA repair, and telomere length[137]. Maintaining an optimal level of energy balance, determined by PA and weight regulation, can reduce systemic and adipose tissue inflammation and angiogenesis, alter endogenous hormone metabolism and adipokine levels, and improve insulin sensitivity, which are strongly hypothesised biological mechanisms in the development of cancer[136,138]. These shared pathways also suggest the possibility for interaction between PA and obesity on cancer risk. However, our study found no evidence of multiplicative or additive interaction, which is consistent with findings from a Danish study[192]. The modest association between PA and cancer risk in our study may explain why no interaction with BMI was found. For all obesity-related cancers, BMI appeared to be a stronger factor in the joint association with PA on risk than was PA, which was also observed for some separate cancers, especially endometrial cancer. However, the strength of these associations and the individual contribution of PA and BMI are highly

dependent on the cut-points chosen, as discussed above, and on the specific markers used to measure PA and adiposity.

Given the prevalence of obesity, and its association with increased cancer risk, prevention of obesity is particularly important. Several guidelines have been published on the management of body weight in adults. The primary method of prevention is lifestyle modification, including healthy diet habits and increased activity. Besides prevention, lifestyle therapy is also the cornerstone of obesity treatment. In addition, lifestyle therapy combined with pharmacotherapy and metabolic and bariatric surgery might result in greater and more sustained weight loss. A few approved medications for the long-term treatment of obesity have been used widely, including liraglutide, naltrexone/bupropion, orlistat, and semaglutide. These medications work by reducing appetite and consequently energy intake, or by preventing food from becoming a useful source of calories by inducing early excretion[193]. However, the long-term consequence of these medications on obesity treatment and risk of other diseases is unknown. Bariatric surgery is a treatment for individuals with obesity class III which is defined as a BMI greater than 40, or a BMI more than 35 with obesity-associated comorbidity. The typical patients can expect to regain some weight over time, usually starting from the second postoperative year. The studies on the long-term durability of weight loss of bariatric surgery reported inconsistent results[194]. A systematic review of studies with 10-year follow-up showed that the mean percentage excess weight loss for whichever procedure is 50-60%[195]. It is worth noting that the risk of many chronic diseases, including cancer, diabetes, hypertension, osteoarthritis, and sleep apnoea has been shown to be reduced after bariatric surgery in people with obesity[194].

Methodological considerations

Study design

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations. Observational studies are the most common design in epidemiology. In an observational study, the strength of the relationship between an exposure and disease variable is assessed through observation. Observational studies include cross-sectional studies, cohort studies, and case-control studies. In this thesis, all four papers were conducted using a cohort design. In a cohort study, an outcome or disease-free study population is first identified by the exposure and followed over time until the disease or outcome of interest occurs. Therefore, in all papers, we measured the exposure (BMI, WC, metabolic risk factors, and level of PA) before the occurrence of cancers. In Me-Can, follow-up consequently starts one year after the baseline examination to reduce

the possibility of reverse causation. In ODDS, less than 1% of individuals have less than one year of follow-up.

In this thesis, all four papers were conducted using survival analysis, a statistical procedure to investigate the outcome of interest over time until an event occurs. The Cox proportional hazards model was used to calculate the hazards. The choice of time scale is an important aspect of survival analysis. There are two choices of time scale for a Cox regression model, which are time-on-study, and age. Using age as the time scale is an indirect way to adjust for an age effect[196]. In this thesis, we used age as the time scale and controlled for birth cohort effects that can be achieved by stratifying the model on the birth cohort. One study also proposed that the use of time-on-study as the time scale will nevertheless yield approximately unbiased proportional hazard regression coefficients[197]. Clarifying the purpose of the study is crucial for choosing a method.

Bias

Selection bias

Selection bias is a systematic error caused by the difference between characteristics of the study population and the population not involved in the research. It may occur when the participants have intrinsically distinct characteristics from the target population of the study, resulting in a biased sample, called self-selection bias or volunteer bias. Studies have shown that volunteers tend to come from a higher social standing than from a lower socio-economic background. One consequence of volunteer bias is that it undermines the external validity of a test (i.e., the ability of the test results to generalise to the rest of the population). In Me-Can, the attendance rates of all cohorts are 60-90%. The ODDS study consists of many cohorts. Representativeness of the background population for the two largest cohorts in the study, the Medical Birth Register and the Swedish Military Conscription Register, is high. Therefore, the effect of volunteer bias is limited. Attrition bias (loss to follow-up) is another common type of selection bias, which is a situation in which the subjects lose contact, resulting in missing data. Loss to follow-up may reduce the internal validity of the study. All cohorts used in this thesis were linked to the Cancer Register and Cause of Death Register which capture more than 95% of cancer diagnoses and death. This minimised the possibility of attrition bias in all papers.

Information bias

Information bias refers to bias occurring when key study variables are incorrectly measured or classified, also known as observation bias and misclassification. Reporting bias refers to a systematic error caused by research subjects intentionally exaggerating or understating certain information during the information collection

process. For example, when reporting weight, research subjects who have overweight or obesity may tend to underreport their weight or WC, while subjects who are underweight tend to overreport. In Papers I and II, the proportions of self-reported weight measurement are 6% and 39%, respectively, which may introduce the possibility of reporting bias. However, studies showed that measured and self-reported weight measurement had good agreement, with a Kappa statistic above 0.9[198,199]. In Papers III and IV, all weight and height measurements were measured. In Paper IV, the level of PA was self-reported. Previous studies suggested that there was moderate agreement between self-reported and measured levels of PA among adults[200,201]. Male sex and individuals with lower BMI tend to overestimate their PA level which can lead to misclassification[200,202]. Since participants were asked to indicate their usual level of PA during the year preceding the survey, this can also cause recall bias, a systematic error caused by differences in the accuracy or completeness of the recollections retrieved. In addition, measurement of WC may also introduce detection bias due to heterogeneity in the anatomical measurement site.

Confounding

Confounding occurs in the calculation of association between exposure and outcome caused by one or more potential confounders. Confounder refers to factors associated with both the exposure and outcome, but not factors in the causal chain (mediator). An imbalanced distribution of confounders in comparison groups of the exposure causes confounding. Measures to reduce the effect of potential confounding include matching, randomisation, stratification, and measuring the known confounders and including them as covariates in multivariable analysis. In this thesis, confounding was controlled by including known confounders as covariates and strata in the models. In all papers, we adjusted or stratified for common confounders, including age, sex, and birth cohort. Smoking, a strong risk factor of many cancers, was adjusted for in the main analysis in Paper II-IV, and in the sensitivity analysis in Paper I.

Despite controlling for confounders in the analysis, distortion remains, which is called residual confounding. In observational studies, common causes for residual confounding include lack of detailed information on known confounders and no information on potential confounders. In Papers I and II, we had no information on the intensity of smoking for current smokers. Nevertheless, very few of the established and potential obesity-related cancers have a strong association with smoking. In all papers, information on potentially important cancer-specific confounders was incomplete, such as lifestyle (e.g., diet, alcohol, and PA), reproductive factors (e.g., parity and age at first birth), virus infection history (e.g., human papillomavirus and Epstein-Barr virus), and medication use, and were therefore not adjusted for. Failure to adjust for these factors or inadequate

adjustment could result in residual confounding. In Paper I, we applied the E-value method to assess the robustness of observed associations in the presence of residual confounding. For a larger E-value, it is less likely that an unmeasured confounder could fully explain the observed association with obesity[203].

Type I and type II errors and statistical power

We used hypothesis testing to determine whether there was enough evidence in sample data to draw conclusions about the population. There are two types of error in hypothesis testing, type I error and type II error. A type I error, also known as a false-positive error, occurs when we erroneously state that the study found significant differences when there was actually no difference. A type II error or a false-negative error, occurs when the null hypothesis is incorrectly assumed to be true, i.e., concludes that a relationship does not exist when it actually does. When too many outcomes are investigated in a study, the potential of false positive findings increases, as in Paper I. Therefore, in addition to the results of statistical analysis from epidemiological studies, evidence from experimental studies and reliable biological mechanisms should be considered together when drawing a conclusion. A type II error usually occurs when the sample size is small. In this thesis, we set lower limits on the number of cases for outcomes. Only outcomes that reached the corresponding lower limits were analysed. Ensuring adequate sample size is one way to reduce type error, which can also increase the statistical power. For interaction analysis, according to the study by statistician Andrew Gelman, interactions require a minimum of four times the sample size to estimate a main effect, or 16 times greater to have adequate power[204]. The studies involving interactions in this thesis still does not meet this requirement, which may lead to false-negative results. However, to reduce this risk, we had a lower limit of number of cases to be analysed.

Strengths and limitations

There are several strengths across the four papers. Firstly, linking individuals to national registers using unique personal identity numbers ensures high completeness and reduces attrition bias. The linkage to national cancer registers allows the investigation with detailed cancer categorisation, especially for Paper I. In addition, the large sample size and long follow-up give our investigation high statistical power and enable the investigation of rarer cancer forms.

The studies of this thesis have several limitations. Firstly, all studies used single baseline measurements of height, weight, WC, metabolic factors, and PA level. All PA information and parts of the body size measurements were self-reported. This

may lead to both random and systematic misclassification, potentially causing diluted or biased results. In Paper II, we partially accounted for this as we corrected the HR for WC that might be diluted by intra-personal variability due to physiological changes and random measurement error using the RDR method. In Paper III, the once-only measurement could not account for the long-term changes, such as the transition from metabolically healthy to unhealthy obesity. Information on potentially important cancer-specific confounders was incomplete as previously discussed, and therefore not adjusted. Finally, the investigation of multiple cancers increases the potential of type I error, i.e., false positive findings.

Public health implication

The findings of this thesis have important public health implications. With the increasing prevalence of obesity worldwide, understanding its relationship with cancer is crucial for the development of targeted prevention programmes. The proportion of obesity-related cancers increased from 25% to 40% in our study population when the potential obesity-related cancers we identified were added to the established obesity-related cancers, suggesting a greater burden of obesity than previously recognised. The findings highlight the importance of comprehensive cancer prevention strategies that go beyond disease management and instead emphasise early control of obesity. Furthermore, WC was found to have a stronger association with obesity-related cancer risk than BMI in men, suggesting that monitoring abdominal fat may be a more effective strategy for assessing cancer risk, especially in men.

Early weight control intervention in individuals with metabolically healthy obesity is likely to be most effective in reducing the burden of obesity-related cancers. Targeting metabolic aberration among men and women with obesity could be effective in reducing the number of any obesity-related cancers in men and of endometrial cancer in women. Thus, public health measures should focus not only on reducing overall body weight, but also on improving metabolic health through lifestyle changes such as diet, exercise, and medical interventions. The protective role of leisure-time PA is also notable. The findings suggest that promoting regular moderate to hard leisure-time PA as a preventive measure to reduce the risk of these cancers, regardless of body weight, emphasizes the importance of promoting PA as a cancer-preventive measure for all individuals, not just those at risk of obesity.

Overall, public health efforts should consider multifaceted interventions targeting obesity, metabolic health, and PA to reduce the burden of obesity-related cancers. Public health interventions should also consider implementing recommendations based on sex differences and metabolic phenotypes to maximize their effectiveness.

Conclusion

In this thesis, we aimed to investigate the association between obesity and cancer risk by using BMI and WC as obesity indicators. We also aimed to investigate the association between obesity in combination with metabolic aberrations and leisure-time PA and risk of obesity-related cancers.

Paper I

We identified 15 cancers in men and 16 in women (18 altogether), most of which are rare, as potential obesity-related cancers. Importantly, the magnitudes of the associations were largely comparable to those of the already established obesity-related cancers. We also provide evidence of specific cancer subtypes driving some associations with BMI.

Paper II

Compared to BMI, WC is a slightly stronger risk factor for obesity-related cancers in men, but not in women. WC appears to provide additional risk information beyond that conveyed by BMI in men.

Paper III

Metabolically unhealthy obesity was associated with higher risks of any obesity-related cancer and with several specific cancers. For some cancers, obesity without metabolic aberrations remained a risk factor, albeit with a weaker association compared to metabolically unhealthy obesity. Furthermore, positive additive interactions were found between BMI and metabolic health status in relation to any obesity-related and rectal cancer among men and endometrial cancer in women. In general, these findings suggest that both obesity and metabolic aberrations are useful targets for prevention.

Paper IV

Moderate to hard leisure-time PA can help reduce the risk of obesity-related cancer, as well as colon and renal cell cancer. No interaction was found although higher PA together with low-to-normal weight was associated with a further reduced cancer risk.

Future perspectives

The results of this thesis not only confirm existing evidence but also provide new insights, underscoring the importance of continued research in this field. Despite these advancements, the field remains far from fully understood, and many critical questions remain that need to be addressed.

1. The identification of potential obesity-related cancers in this thesis should be considered exploratory. Replication of these findings in future studies, validated through updated systematic reviews, is necessary, especially for rarer cancers.
2. Metabolically healthy obesity was observed to be associated with high risk of several obesity-related cancers, although inconsistent results have also been reported. Moreover, the existence of metabolically healthy obesity has been questioned, as it has been suggested to commonly be a transitional state to metabolically unhealthy obesity. It remains unclear how metabolic health status changes over time across BMI groups and how such dynamic metabolic changes affects cancer risk. Future research should investigate the impact of this transition on cancer risk.
3. This thesis relied on single baseline measurements of BMI and WC. Future research using more precise and repeated measures of adiposity could further clarify the relationship between body fat distribution and cancer risk.

In addition to the epidemiological evidence from observational studies, it is crucial to explore the underlying biological mechanisms that may drive these associations. Understanding the biological pathways and processes involved can provide a more comprehensive explanation for the observed relationships and help determine whether these associations are causal.

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