Adiposity and Smoking in Relation to Risk of Endometrial Cancer

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2020



This thesis is submitted for the degree of Doctor of Philosophy

for my parents

Acknowledgements

I would like to express my deepest gratitude to my supervisors, Professor Naomi Allen and Dr Siân Sweetland, for their incredible support throughout my DPhil programme. I learned a lot from their thoughtful guidance and feedback and appreciate their contributions to making me a better researcher. I want to thank Dr Thomas Littlejohns for his support with STATA coding and the UK Biobank analyses. I also wish to thank all the participants and staff of the UK Biobank and the Million Women Study, whose data I had the privilege to use. I am grateful to the Nuffield Department of Population Health for the generous financial support. I would also like to thank my colleagues and friends including Yvonne, Sarasvati and Debbie for their thoughtful advice and support over the past 4 years. Lastly, I want to thank my family (parents, sisters, husband, children, in-laws) for their constant prayers, support and encouragement. I especially thank my husband, Ayo, for standing by me through the good and bad times.

Statement of contribution to work

The research presented in chapters 4 to 6 of this thesis is original work that I carried out during my DPhil at the Nuffield Department of Population Health. With guidance from my supervisors, I wrote the analysis plan, conducted all statistical analyses, produced all relevant tables and figures and drafted the text. To produce some of the figures, I used the R package ‘Jasper’ developed by Matthew Arnold. Part of the work presented in chapter 4 was previously published in the International Journal of Cancer 2020 as “Body size, body composition and endometrial cancer risk among postmenopausal women in UK Biobank” of which I am first author (abstract in appendix 1).

Abstract

The associations of adiposity and smoking with endometrial cancer risk, although well established, are not fully understood. Most previous studies have relied on relatively crude measures of exposures and were not large enough to examine reliably these associations by population characteristics and tumour subtypes. This thesis aims to characterise in unprecedented detail the associations of both adiposity and smoking with endometrial cancer risk.

The analyses were performed using data from UK Biobank and the Million Women Study. Adjusted hazard ratios (HRs) for the associations of different measures of adiposity and smoking with endometrial cancer risk were estimated using Cox regression models.

Analyses involving 135,110 postmenopausal women in UK Biobank demonstrated that body mass index (BMI) and more specific indices of overall adiposity obtained from bioimpedance analysis (such as fat mass) were broadly similar in their associations with endometrial cancer risk (HR per 1-SD BMI = 1.71, 95%CI 1.61-1.82; fat mass = 1.73,1.63-1.85). These associations were mediated, in part, by inflammation and alterations in free testosterone levels. Central adiposity was associated with a small increase in risk of endometrial cancer independently of BMI (HR per 1-SD waist to hip ratio = 1.13, 1.01-1.26). Data from up to 674,971 postmenopausal women in the Million Women Study showed that the risk associated with adiposity was more pronounced in never and past HRT users than current users. The association between adiposity and risk was significantly stronger for type I than type II tumours. Analyses involving up to 195,446 UK Biobank women and 743,114 Million Women Study participants demonstrated that current and past smoking reduced the risk of endometrial cancer by 27% and 11%, respectively, compared with never smoking. The risk reduction was dose-dependent, consistent across tumour subtypes and persisted for more than 20 years after smoking cessation.

These results suggest that both overall and central adiposity contribute to endometrial cancer risk and provide support for the hypothesis that adiposity influences endometrial cancer risk through pathways involving sex hormones and inflammation. The findings also indicate that smoking confers long-term protection against endometrial cancer risk and highlight the need for further research to elucidate the mechanisms underlying the reduced risk of endometrial cancer among smokers.

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List of abbreviations

BMI – Body mass index

CI – Confidence interval

CRP – C-reactive protein

HbA1c – glycated haemoglobin

HR– Hazard ratio

HRT – Hormone replacement therapy

ICD – International Classification of Diseases

IGF-1 – Insulin-like growth factor

NHS – National Health Service

SD – Standard deviation

SHBG – Sex hormone binding globulin

WHO – World Health Organization

Chapter 1: Introduction

Summary

Adiposity is an important public health problem and a major modifiable risk factor for endometrial cancer. Although several studies have examined the association between adiposity and endometrial cancer risk, questions remain about the mechanisms underlying this association and whether, and to what extent, the association varies with different indicators/aspects of adiposity, population characteristics and tumour subtypes. In contrast to adiposity, smoking reduces the risk of developing endometrial cancer. This inverse association between smoking and endometrial cancer risk has been known for decades, but the evidence as to whether, and to what extent, risk varies with different smoking characteristics, in different population subgroups or by tumour subtypes, remain unclear. This thesis aims to examine in greater detail than previously possible the associations of both adiposity and smoking with endometrial cancer risk in order to enhance our understanding of these associations, which could, in turn, help guide public health advice.

1.1. Background

Endometrial cancer—the cancer of the lining of the uterus—is the sixth most common cancer among women worldwide, with about 382,000 new cases diagnosed in 2018.[1] In developed countries, it is the most frequently diagnosed gynaecological cancer.[2,3] The established risk factors for endometrial cancer include adiposity, hormone replacement therapy (HRT) use and reproductive factors such as early menarche and late menopause.[4] Adiposity is of particular interest because it accounts for a substantial proportion of all endometrial cancer cases.[5] For instance, in the UK, 34% of all endometrial cancer cases are attributable to overweight and obesity.[6] Adiposity is also of interest because it is a modifiable factor—women who are overweight or obese can achieve a healthy weight through lifestyle modification and clinical management.[7]

In many parts of the world, the proportion of women who are either overweight or obese is high and increasing.[8–13] Recent estimates from England and the USA indicate that at least 60% of women are overweight or obese.[14,15] Because adiposity affects such a large proportion of women, a better understanding of its association with endometrial cancer risk is vital in order to improve prevention strategies for endometrial cancer.

Several studies have examined the association between adiposity and endometrial cancer risk.[16–39] For practical reasons, most of these studies used body mass index (BMI) as a proxy for overall adiposity.[16] However, BMI may not accurately capture the true relationship between overall adiposity and endometrial cancer risk because of its inability to differentiate fat from fat-free

mass.[40,41] Bioimpedance analysis, an alternative technique for body composition assessment in large-scale epidemiological studies, yields separate estimates for fat and fat-free mass and may better describe overall adiposity in relation to endometrial cancer risk.[42] However, very little is known about the associations of bioimpedance-derived indices of adiposity with risk,[30] and it is unclear whether they are better indicators of adiposity-related risk of endometrial cancer than BMI.

The relationship between body fat distribution and endometrial cancer risk is also unclear. It is well known that the pattern of body fat distribution is a key determinant of adiposity-related health risks.[43–47] Fat accumulation in the upper body or trunk region (central adiposity) has been shown to increase the risk of diabetes, cardiovascular diseases and some cancers, independently of overall adiposity.[48–50] However, studies that have examined the association between central adiposity, typically assessed using waist circumference and waist to hip ratio, and endometrial cancer risk have yielded mixed results, with some reporting positive associations[16,25,38] and others null associations.[18,29,36,37,51] These inconsistencies in epidemiological findings may be due in part to methodological issues such as low statistical power to detect modest associations; use of self-reported measures of central adiposity, which are subject to reporting bias; and use of a single measurement of central adiposity, which is subject to measurement error that may obscure the true association, should one exist.[52]

The mechanisms underlying the relationship between adiposity and endometrial cancer risk have not been fully elucidated. Proposed biological pathways

include alterations in levels of sex hormones, insulin resistance and chronic inflammation.[53,54] Because previous studies often lack data on biomarkers associated with these pathways, limited data exist regarding the extent to which potential mediating factors explain the association between adiposity and endometrial cancer risk.

It has been suggested that the pathways through which adiposity influences endometrial cancer risk differ before and after menopause.[53] Low progesterone levels due to increased anovulation is believed to be the primary mechanism underlying the association before menopause, whereas increased oestrogen bioavailability resulting from aromatisation of androgen in the adipose tissue is thought to be the main underlying mechanism after menopause.[53] Despite these important mechanistic differences, many studies examining adiposity in relation to endometrial cancer risk have not distinguished between endometrial cancers diagnosed before and after menopause, thereby complicating interpretation of findings.

The literature on the association between adiposity and endometrial cancer risk in important population subgroups is limited. Factors that influence endometrial cancer risk such as use of HRT and smoking are potential modifiers of the association of adiposity with endometrial cancer risk, but few studies are large enough to reliably quantify the risk of endometrial cancer associated with adiposity by levels of these factors.

There is also limited data on the association of adiposity with the risk of different subtypes of endometrial cancer. Endometrial cancers can be broadly

classified into type I and type II tumours, and these two subtypes are thought to differ with respect to aetiology and clinical outcomes.[55] While the association of adiposity with type I tumours is well established, uncertainty remains regarding whether adiposity influences the development of type II tumours. Notable limitations of previous cohort studies assessing associations with type II tumours include a relatively small number of type II endometrial cancers and inclusion of some type I tumours in the type II category.[21,23,56]

In contrast to adiposity, evidence suggests that smoking reduces the risk of developing endometrial cancer.[20,57–62] This puzzling inverse association between smoking and endometrial cancer risk has been known for decades, but its biological basis remains unclear. The predominant hypothesis is that smoking lowers endometrial cancer risk through its antiestrogenic effects,[63] although most epidemiological studies evaluating circulating levels of endogenous oestrogen by smoking status have not found evidence of lower oestrogen levels in smokers compared with non-smokers.[64–77]

It is unclear if the relationship between smoking and endometrial cancer risk varies by smoking characteristics such as number of cigarettes smoked per day, duration of smoking, age at smoking initiation and time since smoking cessation. The few cohort studies that have examined quantitative measures of smoking in relation to endometrial cancer risk found no evidence of dose-response associations with number of cigarettes smoked per day, duration of smoking or age at smoking initiation.[58–60,78,79] However, most of these studies were relatively small and hence had limited statistical power to detect modest associations.

Few studies have examined the relationship between smoking and endometrial cancer risk according to tumour subtypes,[58] and uncertainty remains regarding whether, and to what extent, smoking affects the risk of type I and type II tumours. Further, there is limited data on the association between smoking and endometrial cancer risk in important population subgroups such as those defined by menopausal status, BMI and other characteristics that influence endometrial carcinogenesis. Previous studies were not sufficiently large to allow for reliable estimation of the association by these characteristics. Quantifying potential variation in the association of smoking with endometrial cancer risk by these characteristics is important because it could provide valuable insights into the mechanisms underlying this well-established inverse association between smoking and endometrial cancer risk.

1.2. Research aims

The overall aim of this thesis is to characterise in unprecedented detail the associations of adiposity and smoking with the risk of endometrial cancer. Specifically, this thesis will:

1. Evaluate the associations of different measures of body size and body composition with the risk of endometrial cancer according to menopausal status and compare the associations of bioimpedance-derived measures of fat to those of traditional adiposity metrics.
2. Assess whether central adiposity is associated with endometrial cancer risk independently of overall adiposity.

3. Evaluate the extent to which some potential mediating factors such as inflammation and sex hormones account for the relationship between adiposity and endometrial cancer risk.
4. Robustly quantify the association between adiposity and endometrial cancer risk in important population subgroups and by tumour subtypes.
5. Examine the associations of different measures of smoking with the risk of endometrial cancer and robustly assess whether the relationship between smoking and endometrial cancer differs by population characteristics and tumour subtypes.

1.3. Significance of study

The findings of this thesis will contribute to our understanding of which aspects of body size and composition are most relevant to endometrial carcinogenesis. It may also provide information on the best indicator of adiposity to use in assessing this risk in epidemiological studies. The investigations of the association of adiposity with endometrial cancer risk in different population subgroups could help to improve identification of high-risk groups, who may benefit from targeted intervention. Analysis of association by tumour subtypes and by levels of other risk factors could yield further insights into the mechanisms linking adiposity with the risk of endometrial cancer.

Although the inverse association between smoking and endometrial cancer is unlikely to be of direct benefit to primary preventative measures for endometrial cancer, detailed analyses of the association by smoking characteristics, population characteristics and tumour subtypes could shed more light on the

mechanism underlying this relationship and enhance our understanding of endometrial cancer aetiology.

1.4. Structure of thesis

Chapter 2 reviews the literature on the epidemiology of endometrial cancer including evidence on the apparent “well-known” relationships of adiposity and smoking with the risk of endometrial cancer. Chapter 3 describes the cohorts used in these investigations, UK Biobank and the Million Women Study, and the main methods used in the analyses. Chapter 4 reports on the associations of a wide range of indices of body size and composition (height, weight, BMI, body fat percentage, fat mass, waist circumference, hip circumference, waist to hip ratio, waist to height ratio, trunk fat percentage and fat-free mass) with the risk of endometrial cancer in the UK Biobank. It also explores the extent to which selected biomarkers explain the association between adiposity and endometrial cancer risk. Chapter 5 reports on the association of adiposity with endometrial cancer risk in different population subgroups and by tumour subtypes in the Million Women Study. Chapter 6 reports on the associations of different measures of smoking with the risk of endometrial cancer in both the UK Biobank and the Million Women Study. Chapter 7 summarises the findings of this thesis, discusses the overall strengths and limitations, and provides suggestions for future work.

Chapter 2: Overview of endometrial cancer

Summary

Endometrial cancer is the sixth most common cancer in women worldwide, with about 382,000 new cases diagnosed in 2018. Over the past few decades, several countries have observed an increase in the incidence of endometrial cancer. This is attributed in part to changes in the prevalence of risk/protective factors for endometrial cancer. Adiposity and smoking are two important factors known to influence endometrial cancer risk. While adiposity increases risk, smoking lowers endometrial cancer risk. Although numerous studies have examined the associations of adiposity and smoking with endometrial cancer risk, important gaps remain in our understanding of how these relationships vary with measures of exposure, population characteristics and tumour subtypes. Other factors that are associated with endometrial cancer development include age, HRT use, oral contraceptive use, age at menarche, age at menopause, parity, diabetes and physical activity.

2.1. Endometrial cancer: classification, diagnosis and treatment

More than 90% of cancers occurring in the body of the uterus (uterine cancers) are endometrial cancers.[80] Traditionally, endometrial cancers are classified into two groups—type I and type II tumours.[55] Type I tumours, which account for the majority of cases (70-80% of endometrial cancers), are mostly low-grade tumours of endometroid histology.[81] They arise from unopposed oestrogen stimulation of the endometrium via atypical hyperplasia and generally have a good prognosis.[82] At the molecular level, type I tumours are characterised by mutations in PTEN, KRAS and β-catenin genes, and presence of microsatellite instability.[83,84] By contrast, type II tumours are high-grade tumours typically of serous or clear cell histology.[81] They often develop in the atrophic endometrium of older women and have an aggressive clinical course.[85] The traditional view is that type II tumours are not associated with oestrogen exposure,[81,85] although recent epidemiological studies suggest that oestrogen might play a role in the development of these tumours.[86,87] Type II tumours are associated with mutations in P53 genes and overexpression of Her2/neu oncogenes.[83,84,88,89]

Although this classification system has no value in informing patient management, it provides a framework for understanding endometrial carcinogenesis.[90] The classification used to guide therapy is based on histopathological characteristics (e.g. endometrioid, serous and clear cell) and grade.[91]

Most endometrial cancers are diagnosed in postmenopausal women, with age at diagnosis usually between 50 and 70 years.[92] Patients typically present with abnormal vaginal bleeding[93,94] and diagnosis is established through histopathological examinations of endometrial tissue sample.[95] The primary treatment for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy.[94–97] Women diagnosed with more advanced diseases may require chemotherapy or radiation therapy.[94]

2.2. Descriptive epidemiology of endometrial cancer

Cancer registries often report incidence and mortality data for all uterine cancers rather than for endometrial cancer separately. Therefore, rates for uterine cancers will be used as a proxy for that of endometrial cancer in this section.

2.2.1. Incidence and mortality in the UK

Uterine cancer is the fourth most common cancer in UK women, with about 9,400 new cases diagnosed annually.[80] The age-standardised incidence rate (European standard population) in 2016 was 29.6 per 100,000 females. The lifetime risk of being diagnosed with endometrial cancer is about 3% in UK women.[80]

Since the 1990s, the incidence of uterine cancer has been rising in the UK. Between 1993-1995 and 2015-2017, age-standardised incidence rates increased by 55% from an average of 18.8 per 100,000 females to 29.1 per 100,000 females.[80] The greatest increase was in women aged 70-79 years,

with an 88% increase in the incidence rate during this time-period. These trends reflect the combined effects of changes in the prevalence of risk factors, improvements in diagnosis and data recording.[80]

Approximately 3% of all cancer deaths in UK women are due to uterine cancer. Over the past decade, mortality rates increased by 23% from an average of 5.7 per 100,000 women in 2005-2007 to 7.0 per 100,000 females in 2015-2017.[80]

2.2.2. International patterns

Worldwide, uterine cancer is the sixth most common cancer in women, with an estimated 382,069 new cases diagnosed in 2018.[1] Incidence rates vary substantially across the world (figure 2-1). The highest rates are seen in more developed regions, with Australia, Northern America and many parts of Europe having age-standardised incidence rates (World standard population) of 14.0-20.5 per 100,000 females in 2018.[98] The lowest rates are observed in South-Central Asia and Africa (<4.0 per 100,000 females).[98] This international variation in rates suggests that environmental factors play a role in the development of uterine cancer. This is clear from migrant studies showing that migration from countries with low incidence rates to those with high rates results in greater risk.[99,100]

Temporal trends in uterine cancer incidence also vary by geographical location.[101] In general, incidence rates of uterine cancers are either increasing or stabilising over time, although there is evidence of decline in some countries (for example in Austria and Sweden).[101]

The estimated mortality rate for uterine cancer worldwide in 2018 was 1.8 per 100,000 females.[1] Compared with incidence, mortality rates are somewhat less variable across the world, with rates ranging from 0.7 per 100,000 females in Northern Africa to 4.7 per 100,000 females in Polynesia.[98]

2.3. Factors affecting endometrial cancer risk

2.3.1. Adiposity

Adiposity—the abnormal or excessive accumulation of fat that may impair health[102]—is a major public health problem worldwide. Various measurements exist for assessing adiposity (discussed later). In adults, the most commonly used measure is the body mass index (BMI). The World Health Organization (WHO) defines a BMI of 25.0-<30 kg/m^2 as overweight and a BMI of 30.0 kg/m^2 or higher as obese.[103] Based on this definition, more than 1.9 billion adults worldwide are currently considered to be either overweight or obese.[103] The proportion of overweight or obese adults varies substantially across the world, with the highest rates in North America and Europe; the lowest rates are seen in Sub-Saharan Africa and Asia (figure 2-2). In England, 63% of adults are classed as either overweight or obese.[14] The proportion of overweight or obese adults increases with age, with the highest rates in men aged 55-64 years (82%) and women aged 65-74 years (70%).[14]

Since the 1970s, mean BMI has been rising globally. Between 1975 and 2014, age-standardised mean BMI increased from 21.7 kg/m^2 to 24.2 kg/m^2

in men, and from 22.1 kg/m^{2}to 24.4 kg/m^2 in women.[9] The rate of change varied substantially by geographical region ranging from 0.2 kg/m^2 per decade in Central and Southwestern Europe to more than 1 kg/m^2 per decade in Polynesia, Southeast Asia and Latin America.[9]

Adiposity is a leading risk factor for cardiovascular diseases, type II diabetes mellitus and several cancers including endometrial cancer and postmenopausal breast cancer.[44,104] Some of the health risks associated with adiposity are due to the pattern of fat distribution. Accumulation of fat in the central region (abdomen and trunk) is thought to be more strongly related to cardiovascular disease and type II diabetes than fat accumulation in the lower extremities (gynoid adiposity).[46]

2.3.1.1. Assessment of overall adiposity

BMI

The measure recommended in international guidelines for assessing overall adiposity in adults is the BMI, which is calculated by dividing weight in kilograms by the square of height in metres.[102,105] BMI is based on the assumption that variations in body weight between individuals with the same height are due to body fat.[106] BMI shows high correlation with body fat measured by reference methods such as underwater weighing.[107] Its simplicity and low cost make it ideal for use in routine clinical practice and population settings.[108] However, there are limitations to using BMI in assessing adiposity. Weight, which is the numerator in the calculation of BMI, does not differentiate between fat and fat-free mass.[40,108] BMI is also an

unreliable measure of adiposity in older women, particularly postmenopausal women, because of reductions in muscle mass and height, and an increase in fat mass that occurs with ageing.[108–111] Furthermore, many epidemiological studies use self-reported height and weight to calculate BMI. This may incorporate measurement error into the calculation of BMI as people tend to underreport weight and overreport height.[112–115] However, validation studies have generally shown high correlations between self-reported and measured weight and height ($r > 0.90$).[116–118] Absolute weight has been used to estimate adiposity in some studies, but this does not take into account differences in weight due to height.

Fat mass and body fat percentage

Fat mass is the absolute amount of body fat and body fat percentage is the amount of fat mass relative to overall body mass (fat and fat-free mass).[119] Several methods can be used to estimate these body components. Traditional approaches such as underwater weighing and isotope dilution, and imaging techniques such as magnetic resonance imaging (MRI), computer tomography scan (CT scan) and dual energy x-ray absorptiometry (DEXA) yield accurate estimates and are used as reference methods. However, they are not used in most large-scale epidemiological settings because of their lack of portability, high cost and technical complexity.[120]

Bioimpedance analysis is a simple, quick and relatively inexpensive method that is increasingly used to quantify body composition in epidemiological studies.[121] It is based on the principle that electrical current moves quickly

through fat-free mass than through fat mass.[122] It measures the resistance of the body to a small alternating current (typically 50 kHz)[120,123] and uses this resistance (or impedance) value in a prediction equation to estimate various body components.[122] The prediction equation usually includes height, age and sex, and describes the statistical relationship between impedance readings and body composition measured by a reference method for a calibration population; hence, prediction equations are often population specific.[124] The validity of bioimpedance-derived measurements of body composition is influenced by sex, age, hydration status, disease state, race and ethnicity.[125]

2.3.1.2. Assessment of body fat distribution

Imaging techniques and bioimpedance analysis

MRI and CT scans are considered to be the most accurate techniques for estimating regional body fat.[43] These methods can be used to quantify total abdominal fat and more importantly to quantify fat in the subcutaneous and visceral depots.[43,120] Visceral fat is believed to be the key determinant of the metabolic disturbances associated with central adiposity.[126,127] DEXA is another technique that is used to quantify fat in different body regions; however, it cannot accurately distinguish between subcutaneous and visceral fat.[120] Some bioimpedance technologies can be used to estimate body fat in different body segments; however, like DEXA, they are unable to discriminate between subcutaneous and visceral fat.[128]

Waist circumference, waist to hip ratio and waist to height ratio

Waist circumference, hip circumference and waist to hip ratio are indirect measures commonly used to assess body fat distribution in epidemiological studies. Hip circumference reflects adiposity in the lower body while waist circumference and waist to hip ratio are typically used as indicators of central adiposity. Although both waist circumference and waist to hip ratio correlate strongly with abdominal fat measured by CT and MRI[129,130] and are associated with many chronic diseases such as cardiovascular diseases and diabetes independently of overall fatness,[43,48] they reflect different aspects of central adiposity.

Waist circumference estimates the crude amount of abdominal fat[46] while waist to hip ratio—calculated by dividing waist circumference by hip circumference—measures the relative amount of upper versus lower body adiposity.[43] Because waist to hip ratio does not quantify the amount of abdominal fat, two individuals, one normal weight and one morbidly obese, can have similar waist to hip ratio but differ markedly in their amount of abdominal fat.[46] Waist to hip ratio is also difficult to interpret biologically because it is influenced by variations in bone, muscle, subcutaneous and visceral fat.[119] While a change in waist circumference is likely to reflect a change in abdominal fat, a change in waist to hip ratio may reflect several possibilities including changes in abdominal fat, muscle or bone mass.[46] Another disadvantage when using waist to hip ratio as a measure of central adiposity is that it may not change with weight loss, as weight loss tends to lower both waist and hip circumferences.[43,131]

Waist to height ratio, calculated by dividing waist circumference (cm) by height (cm) is another indirect measure that is used to assess central adiposity in epidemiological studies. Waist to height ratio takes into account differences in stature as shorter people have been shown to have a higher risk of metabolic abnormalities than tall people for any given level of waist circumference.[132]

2.3.1.3. Epidemiological studies on adiposity and endometrial cancer risk

Overall adiposity

Epidemiological studies in a variety of populations have consistently observed an increased risk of endometrial cancer with increasing overall adiposity.[16–18,21–30,32–34,37–39,133–147] The most commonly used measure of overall adiposity in these studies is the BMI. Table 2-1 summarises the risk estimates from cohort studies reporting on the association of BMI with endometrial cancer risk. The largest study, a cohort of more than 2.8 million UK women, found a 62% increase in the risk of endometrial cancer for each 5 kg/m^2 increase in BMI.[34] A meta-analysis of 30 prospective studies involving 6.44 million participants and 22,320 endometrial cancers estimated that endometrial cancer risk increased by 54% for each 5 kg/m^2 increase in BMI.[16] The positive association between BMI and endometrial cancer risk has been confirmed in at least four Mendelian randomisation studies, suggesting that this association is causal.[148–151]

The increased risk of endometrial cancer with increasing BMI is evident for both premenopausal and postmenopausal women,[16,34] although some studies have suggested that the magnitude of association may vary by menopausal status.[26,33] A study using data from Nurses' Health Study I and II cohorts found a stronger association in premenopausal women compared with postmenopausal women.[33] In contrast, a previous analysis in the Million Women Study reported a stronger association in postmenopausal never users of HRT compared with premenopausal women.[26]

Among postmenopausal women, studies have consistently observed a variation in the effect of BMI by HRT use.[16,21,152] In the meta-analysis mentioned previously, the risk estimates per 5 kg/m^2 increase in BMI for never and ever HRT users were 1.65 (1.33-2.05) and 1.10 (1.06-1.14), respectively.[16] Data regarding whether the association of BMI with endometrial cancer risk varies by recency of use or type of HRT used are sparse. There is also limited data on how other population characteristics affect the association between adiposity and endometrial cancer risk.

Studies that have evaluated the association between BMI and endometrial cancer risk by tumour subtypes suggest that the association is stronger for type I than type II tumours.[21,23,56,86] A study including over 1 million Norwegian women found a 9% (HR = 1.09, 95%CI: 1.09-1.10) and 6% (HR = 1.06, 95%CI: 1.05-1.08) increase in risk of type I and type II tumours, respectively, for each 1 kg/m^2 increase in BMI.[23] In a pooled analysis of 10 cohort and 14 case-control studies, each 2 kg/m^2 increase in BMI increased the risk of type I and type II tumours by 20% (HR = 1.20, 95%CI: 1.19-1.21)

and 12% (HR = 1.12, 95%CI: 1.09-1.14, $P_{heterogeneity}$ <0.0001), respectively.[86] However, some of these previous studies included high grade type I tumours in the type II category, which may lead to bias in the risk estimates for type II tumours.[21,23]

Absolute weight is another frequently used index of adiposity in studies relating overall adiposity to the risk of endometrial cancer. In a meta-analysis of 8 cohort studies, each 5 kg increase in weight was found to increase the risk of endometrial cancer by 18%.[16] As with BMI, the risk associated with weight was more pronounced in never HRT users than ever users.[25]

As previously mentioned, both weight and BMI are imperfect measures of adiposity and have been criticised for their inability to distinguish between fat and fat-free mass.[153] Body fat percentage and fat mass are more precise measures of adiposity than BMI or weight. However, there is limited data on the associations of these measures with risk. In the China Kadoorie Biobank, endometrial cancer risk increased by 58% for each standard deviation increase in body fat percentage measured by bioimpedance analysis.[30] A comparable value was not provided for BMI in that study; therefore, it is unclear if body fat percentage was more strongly related to endometrial cancer risk than BMI.

Body fat distribution

The pattern of body fat distribution is an important determinant of many chronic diseases.[46,154] Central adiposity is more strongly associated with metabolic abnormalities than gynoid adiposity.[43,46] Several prospective

studies have reported on the association of central adiposity with the risk of endometrial cancer.[18,25,29,30,38,140,147,155–158] The majority of these studies used waist circumference and/or waist to hip ratio as the indicator of central adiposity, but some studies also explored associations with waist to height ratio and hip circumference. The largest study, a Korean cohort including more than 10 million women and 9,726 endometrial cancers, found a positive association between central adiposity, as reflected by waist circumference, and risk of endometrial cancer in both premenopausal and postmenopausal women.[155] These associations, however, disappeared after adjustment for BMI, suggesting that waist circumference is not an independent predictor of endometrial cancer risk.[155] Consistent with this finding, three other cohorts also reported null associations between waist circumference and endometrial cancer risk after adjusting for BMI.[18,147,157] In contrast, a recent analysis in the Women's Health Initiative found a strong positive association between waist circumference and endometrial cancer risk independently of BMI.[158] Three other prospective studies and a meta-analysis also reported a strong positive association between waist circumference and risk of endometrial cancer after adjusting for BMI.[16,25,38,159]

Most of the previous cohorts examining waist to hip ratio in relation to endometrial cancer risk found no evidence of an association after accounting for BMI.[25,29,157,159] Results from a recent Mendelian randomisation study also do not support an association between waist to hip ratio and endometrial cancer risk.[148] In contrast, epidemiological data from the California Teachers' study showed a positive association between waist to hip ratio and risk of

type I endometrial cancer independently of BMI among postmenopausal never HRT users.[38]

Waist to height ratio was associated with endometrial cancer risk independently of BMI in the California Teacher's study[38] but not in the Black Women's Study.[147] Studies that have evaluated the independent effect of hip circumference, an indicator of gynoid adiposity, have generally reported null associations after adjusting for BMI.[25,147,157]

2.3.1.4. Biological mechanisms linking adiposity to endometrial cancer risk

Several mechanisms may link adiposity with endometrial cancer risk. The ones that are the most understood involve alterations in sex hormones, insulin resistance/hyperinsulinaemia and chronic low-grade inflammation (figure 2-3). The predominant hypothesis relates to alterations in sex hormones. In postmenopausal women, oestrogen biosynthesis occurs primarily in the adipose tissue through conversion of androgen to oestrogen by aromatase.[160–162] Hence, women with a greater amount of adipose tissue tend to have higher circulating levels of oestrogen.[163] Obese individuals also have low levels of sex hormone binding globulin (SHBG), which leads to greater oestrogen bioavailability.[53] Oestrogen promotes endometrial carcinogenesis by stimulating proliferation of endometrial cells.[53,164]

In premenopausal women, adiposity does not increase circulating levels of oestrogen, as levels are governed by hormones, such as follicle-stimulating hormones and luteinising hormones, that regulate the menstrual cycle.[165,166]

Instead, the main mechanism through which adiposity influences endometrial cancer risk in premenopausal women is through low progesterone levels, resulting from chronic anovulation.[53] Because progesterone counteracts the proliferative effect of oestrogen, a low progesterone level in premenopausal women leads to unopposed oestrogen activity in the endometrium, which may result in malignancy (figure 2-3).

Adiposity may also influence endometrial risk through pathways involving insulin resistance and hyperinsulinaemia. Adiposity, particularly visceral adiposity, is associated with increased release of free fatty acids and tumour necrosis factor alpha (TNF-α) as well as decreased production of adiponectin, which leads to insulin resistance and hyperinsulinaemia.[167] Insulin has mitogenic properties and has been shown to stimulate proliferation of endometrial stromal cells in experimental studies.[168,169] Insulin can also affect endometrial cancer risk indirectly by lowering SHBG levels leading to increased bioavailability of oestrogen.[53] Insulin also reduces hepatic production of insulin-like growth factor binding proteins resulting in an increase in bioavailability of insulin-like growth factor 1 (IGF-1), which has strong mitogenic and antiapoptotic effects (figure 2-3).[170,171]

Chronic low-grade inflammation is another mechanism that may link adiposity with endometrial carcinogenesis. Obesity is considered to be a low-grade inflammatory state and is associated with increased production of pro-inflammatory cytokines such as TNF and interleukin-6 (IL-6) as well as decreased production of anti-inflammatory adipokines such as adiponectin.[172–175] Inflammation may influence carcinogenesis by generating

free radicals, which in turn can damage DNA and induce cell proliferation.[176] Chronic inflammation can also activate transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to inhibition of apoptosis and cell cycle arrest.[176,177] Some of the mechanisms through which adiposity may influence endometrial cancer risk will be explored in chapter 4.

2.3.2. Cigarette smoking

Cigarette smoke is a complex mixture of over 7,000 chemicals, including more than 60 carcinogens.[178,179] Smoking is associated with an increased risk of cardiovascular disease, chronic obstructive pulmonary disease and cancers of the lung, liver, oral cavity, oesophagus, pancreas, bladder and kidney.[178,180] In addition, it is a major cause of mortality—about 8 million people die each year from diseases caused by smoking.[179]

In 2016, the age-standardised prevalence rate of current smoking in people aged 15 years or over worldwide was 20%.[181] The age-standardised prevalence rate was lower in women (6.2%) compared with men (33.7%).[181] The prevalence of smoking varies substantially across world regions. Among females, the highest age-standardised prevalence rates are observed in European regions (20.7%) while the lowest rates are seen in Africa and Eastern Mediterranean regions (2.2%).[181] Since the beginning of the twenty-first century, the prevalence rates of smoking have been decreasing in many populations. Between 2005 and 2015, prevalence rates among females

decreased by 0.38% to 0.22% annually.[181] This trend is expected to continue during 2015-2025 (figure 2-4).

2.3.2.1. Epidemiological studies on smoking and endometrial cancer risk

Several case-control and cohort studies have reported on the association of smoking with endometrial cancer risk.[7,135–156] Most of these studies examined associations with crude measures of smoking (ever, current, past, never smoking), but some also explored associations with quantitative smoking metrics such as number of cigarettes smoked per day, duration of smoking and age at smoking initiation.[58–60,79,141,182] The majority of these studies found a reduced risk of endometrial cancer among current smokers.[20,58–60,62,79,140,183–197] Table 2-2 shows the risk estimates associated with current and past smoking, compared with never smoking, in published cohort studies. The largest of these cohorts included 324,704 Norwegian women and reported a 33% lower risk of endometrial cancer in current smokers compared with never smokers.[23] A meta-analysis of 7 cohort and 16 case-control studies reported a 26% and 37% lower risk of endometrial cancer for current smokers (compared with never smokers) in cohort and case-control studies, respectively.[57]

It is unclear whether the association between smoking and endometrial cancer risk differs by quantitative characteristics of smoking such as the number of cigarettes smoked per day, smoking duration and age at smoking initiation. Prospective studies that have investigated these measures in

relation to endometrial cancer risk have generally not found any evidence of a dose-response association.[58–60,79,141,182]

A reduced risk of endometrial cancer has also been reported among past smokers in some studies.[58,60,62,196,198] In many of these studies, the magnitude of risk reduction in past smokers was smaller compared with that of current smokers, suggesting that the effect of smoking on endometrial cancer risk is attenuated after smoking cessation.[58,62,196,198] However, it is uncertain how long the protective effect of smoking lasts after cessation.[58–62,78,79]

In studies that stratified the association of smoking with endometrial cancer risk by menopausal status, the inverse association between smoking and risk appeared to be restricted to postmenopausal women.[57–59,188,194,199,200] The effect of smoking on endometrial cancer risk in premenopausal women is less clear, with studies reporting positive,[59,199] inverse,[190] or null associations.[57,58,187,188,192,194] It is also unclear whether other characteristics of the study population modify the association between smoking and endometrial cancer risk. Three case-control studies reported that body weight modified the association between smoking and endometrial cancer risk, with a stronger inverse association among women with a higher body weight.[61,187,191] However, prospective studies that have investigated effect modification by BMI did not find evidence of heterogeneity in the association by BMI.[58–60]

The evidence relating smoking to the risk of different subtypes of endometrial cancer is limited, as most studies examined association with the risk of endometrial cancer overall. Data from the NIH-AARP Diet and Health Study suggest that smoking reduces the risk of both type I and type II tumours to a similar extent.[58] A pooled analysis of 23 studies, which also includes data from the NIH-AARP Study, showed that the risk reductions for type I and type II tumours were similar in magnitude.[86] Compared with never smokers, current smokers had a 36% reduction in the risk of type I tumours (HR =0.64, 95%CI: 0.60-0.70) and a 40% reduction in the risk of type II tumours (HR = 0.60, 95%CI: 0.46-0.77; $P_{heterogeneity}$ = 0.79).[86]

2.3.2.2. Biological mechanisms linking smoking with endometrial cancer risk

The mechanism underlying a reduced risk of endometrial cancer among smokers is unclear. Compared with non-smokers, women who smoke tend to have an earlier menopause and an increased risk of osteoporosis, both of which are conditions associated with oestrogen deficiency.[63,201] These observations have led to the hypothesis that smoking reduces endometrial cancer risk through an antiestrogenic effect. The exact mechanism for this antiestrogenic effect of smoking is not clear but may involve alterations in oestrogen metabolism. It has been suggested that smoking shifts the metabolism of oestrogen in favour of the 2-hydroxylation pathways leading to increased production of 2-hydroxyoestrogens and 2-methoxyoestrogens.[202–205] These metabolites have virtually no oestrogenic activity and are rapidly cleared from the circulation.[202,206] The antiestrogenic effect of smoking may

also be mediated by a decrease in oestrogen biosynthesis.[207] Experimental studies showing that components of cigarette smoke such as nicotine and cotinine inhibit conversion of androstenedione to oestrogen in vitro provide support for this hypothesis.[208–210] However, most epidemiological studies that have evaluated endogenous oestrogen levels by smoking status in premenopausal and postmenopausal women did not find evidence of lower oestrogen levels in smokers compared with non-smokers.[64–77]

Smoking could also affect endometrial cancer risk by increasing the expression of homeobox A10 and progesterone receptors, which drive differentiation of endometrial cells.[211] Another mechanism is through its relationship with established risk factors for endometrial cancer such as adiposity.[63] Smokers tend to have lower levels of adiposity,[212–215] which could lead to a reduced risk of endometrial cancer in postmenopausal women because of decreased oestrogen biosynthesis in the adipose tissue. However, BMI did not fully explain the association between smoking and endometrial cancer risk in studies that have adjusted for BMI,[20,58,60–62,78,79] suggesting that other pathways are involved.

2.3.3. Other factors that affect endometrial cancer risk

2.3.3.1. Family history and genetic susceptibility

Although most endometrial cancers occur sporadically, about 2-5% of cases are due to genetic susceptibility.[216] Women with a first-degree relative diagnosed with endometrial cancer or colorectal cancer have been shown to have a higher risk of developing endometrial cancer.[217] Lynch syndrome or

hereditary non-polyposis colorectal cancer (an autosomal dominant inherited cancer susceptibility syndrome caused by germline mutation in one of the DNA mismatch repair genes including MLH1, MSH2, MSH6 or PMS2) predisposes carriers to multiple malignancies including endometrial cancer.[218–221] Women with Lynch syndrome have a 40-60% lifetime risk of developing endometrial cancer.[222]

2.3.3.2. Age

Endometrial cancer is rare before age 40 years. Only 4% of incident cases worldwide were reported in women under the age of 40 years.[98] In the UK, the incidence rate of endometrial cancer (per 100,000 females) between 2014-2016 was 2.8 among women aged 35 to 39 years and 7.6 among those aged 40 to 44 years.[80] Incidence rises steeply from ages 45-49 years (14.4 per 100,000 females) and peaks at ages 75-79 years (97.3 per 100,000 females) before declining in the older age groups (figure 2-5).[80]

2.3.3.3. Endogenous hormones

Steroid hormones, particularly oestrogen and progesterone, play a critical role in the development of most endometrial cancers. The predominant theory explaining endometrial carcinogenesis, “the unopposed oestrogen hypothesis”, proposes that oestrogen not adequately opposed by progesterone stimulates endometrial cell proliferation, increasing the likelihood of genetic errors which may lead to malignancy.[53,164] Consistent with this hypothesis, several studies have reported an increased risk of endometrial cancer with increasing circulating levels of endogenous

oestrogen.[223–225] For example, in the EPIC cohort, postmenopausal women in the highest third of serum oestradiol had a 2.1-fold higher risk of endometrial cancer compared with those in the lowest third.[224] Data from the Women's Health Initiative Observation Study showed that the association was stronger for type I tumours than type II tumours, suggesting a greater influence of oestrogen on the development of type I tumours.[225]

Higher circulating levels of androgens have also been associated with an increased risk of endometrial cancer in postmenopausal women.[223,224,226,227] However, it is unclear if this association is mediated by their conversion to oestrogens in peripheral tissue.

2.3.3.4. Exogenous hormones

Menopausal HRT

Use of oestrogen-only replacement therapy is an established risk factor for endometrial cancer. Women who use oestrogen-only replacement therapy have a 2- to 5- fold higher risk of endometrial cancer compared with never users of HRT.[38,56,87,137,228–233] Risk increases with increasing duration of use and remains elevated for up to 10 years after stopping use.[87,229,234,235] To minimise this risk in women with a uterus, progestin, which opposes oestrogen-driven proliferation in the endometrium, is routinely added to oestrogen in HRT.[236] This type of HRT is referred to as combined HRT. Some studies have also found an increased risk of endometrial cancer among users of combined HRT.[229,232,233,235] The increase in risk appears to be limited to users of sequential HRT regimen (oestrogen with progestin

added for less than 15 days).[233,235,237] In contrast, use of continuous HRT (oestrogen with progestin added daily) has been associated with a lower risk of endometrial cancer,[232,233,235,237] supporting the hypothesis that progesterone counteracts the adverse effects of oestrogen on the endometrium. The association between HRT and endometrial cancer risk is largely confined to type I tumours,[56] although findings from a recent study suggest that HRT use may also influence the risk of type II tumours.[87]

Adiposity, which is associated with high circulating levels of endogenous oestrogen, is known to modify the effect of HRT (both oestrogen-only and combined HRT) on endometrial cancer risk.[232,237] Such effect modification strongly suggests that both HRT and adiposity influence risk through similar sex hormone pathways.

Oral contraceptive use

Oral contraceptive use has consistently been associated with a reduced risk of endometrial cancer.[238–241] An individual participant meta-analysis involving 27,276 women with endometrial cancer and 115,743 women without endometrial cancer found a 31% lower risk of endometrial cancer among ever users of oral contraceptives compared with never users.[238] The risk reduction was greater among long-term users and persisted for at least 20 years after cessation of use.[238] Oral contraceptive use has been shown to be similarly associated with the risk of type I and type II tumours.[56,86,238] The protective effect of oral contraceptive use on endometrial cancer risk is thought to be mediated by the progestin component of the pill.[236,242]

2.3.3.5. Reproductive factors

Early menarche and late menopause are established risk factors for endometrial cancer.[56,140,240,243–247] Both factors are thought to influence risk by increasing lifetime exposure of the endometrium to oestrogen. Parity has been associated with a reduced risk of endometrial cancer in numerous studies.[86,240,247–249] An umbrella review of the literature found a 40% lower risk of endometrial cancer among parous women compared to nulliparous women.[248] Among parous women, studies have reported stronger risk reduction with increasing number of births.[86,240,247–249] One meta-analysis reported a 14% decrease in risk for each additional live births.[250] The biological mechanism underlying the protective effect of parity is unclear but may include decreased lifetime exposure to oestrogen and shedding of pre-malignant/malignant cells during delivery.[4] The associations of parity, early menarche and late menopause with endometrial cancer risk are similar for type I and type II tumours.[56,86]

2.3.3.6. Medical conditions

There is evidence that diabetes is an independent risk factor for endometrial cancer.[20,86,248,251–258] A recent meta-analysis of 22 studies found a 72% higher risk of endometrial cancer in women with diabetes compared with those without diabetes.[259] This association remained after accounting for BMI and other important confounders.[259] Plausible biological mechanisms for this association include hyperinsulinaemia and chronic inflammation.[176] Hyperinsulinaemia may promote endometrial carcinogenesis by stimulating

endometrial cell proliferation[169] or indirectly by elevating levels of free IGF-1 and oestrogen.[53,260] The association of diabetes with risk of endometrial cancer is similar for type I and type II tumours.[56,86] Polycystic ovarian syndrome (which is associated with obesity and low progesterone levels) and hypertension are other conditions that have been linked with endometrial cancer development but evidence for these are inconsistent.[140,141,147,253,261–269]

2.3.3.7. Physical activity

Several studies have reported an inverse association between physical activity and endometrial cancer risk.[270–279] A recent meta-analysis of 33 studies reported a 20% lower risk of endometrial cancer in women in the highest category of physical activity compared with those in the lowest category.[272] The reduction in risk was observed for a broad range of physical activities including walking, recreational and occupational activities.[272] Some studies have reported a stronger risk reduction in obese women compared with lean women.[272,275,278,279] Physical activity is hypothesised to lower endometrial cancer risk by decreasing exposure to oestrogen. Data from studies showing an inverse association between physical activity and serum levels of oestrogen support this hypothesis.[280–284]

2.3.3.8. Height and fat-free mass

Height has also been associated with an increased risk of endometrial cancer in several studies.[16,23,35,139,142,285–290] A meta-analysis of 13 cohort studies found that each 10 cm increase in height increased the risk of

endometrial cancer by 15%.[16] Results from a Mendelian randomisation analysis in UK Biobank also support a positive association between height and risk.[291] The biological explanation for a relationship between height and endometrial cancer risk is unclear. Height is thought to reflect early life exposures such as nutrition and insulin-like growth factors that influence both height and cancer risk.[290,292,293]

There is limited data on the association of fat-free mass (also referred to as lean mass) with the risk of endometrial cancer. A prospective study reported that each 5 kg increase in fat-free mass increases the risk of endometrial cancer by 4%.[141] It is unclear if this association reflects confounding by other factors as the study did not adjust for many potential confounders including BMI, which is associated with both fat-free mass and endometrial cancer risk.

2.4. Conclusion

The incidence of endometrial cancer is rising in many countries. Adiposity and smoking are two important factors known to influence endometrial cancer risk. While adiposity increases risk, smoking lowers endometrial cancer risk. Although several studies have reported on the associations of adiposity and smoking with endometrial cancer risk, questions remain about whether, or to what extent, risk varies with different aspects/indicators of exposure and whether risk varies by tumour subtype or by levels of other risk factors. To address these questions, this thesis examines the associations of both smoking and adiposity with endometrial cancer risk within the UK

Biobank and the Million Women Study cohorts. The next chapter describes both cohorts in more detail.

Table 2-1: Relative risk estimates and confidence intervals from cohort studies reporting on the association of BMI (kg/m^2) with endometrial cancer risk

First author, year	Cohort	Country	Age at recruitment (years), range, mean or median	Population size/number of cases	Description of BMI categories or BMI unit (kg/m^2)	Relative risk (CIs)
Bjorge 2019[294]	Me-can project 2.0	Six European countries	19-85	111,832 / 730	Per 1-unit	1.10 (1.07-1.13)
Kawachi 2019[144]	Japanese women	Japan	40-69	53,651 / 180	≥30 vs 23-24.9	2.37 (1.20-4.66)
Wang 2019[30]	China Kadoorie Biobank	China	Mean age: 51.5	~290,000 / 275	Per 5-unit	2.01 (1.72-2.35)
da Silva 2018[145]	The Norwegian Women and Cancer (NOWAC) study	Norway	30-70	128,314 / 1,057	Per 5-unit	1.51 (1.42-1.60)
Sponholtz 2016[147]	The Black Women's Health Study	USA	21-69	47,557 / 235	≥30 vs <25	1.88 (1.27-2.78)
Horn-Ross 2016[286]	California Teachers study	USA	Median age Non-HRT users: 46 Median age Current HRT users: 56	88,142 / 887	≥30 vs <25, Non- HRT users ≥25 vs <25, current HRT users	2.67 (2.04-3.50) 1.00 (0.74-1.35)
Liu 2016[29]	Chinese women	China	40-70	68,253 / 234	Per 5-unit	1.98 (1.67-2.35)
Alford 2015[295]	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	USA	55-74	23,485 / 77	Obese vs normal weight	2.25 (1.37-3.70)
Kabat 2015[158]	Women's Health Initiative	USA	50-70	143,901 / 1,157	Quintile 5 vs Quintile 1	2.32 (1.93-2.80)
Dougan 2015[33]	Nurses' Health Study I & II	USA	25 – 55	152,645 / 757	≥35 vs <25, premenopausal ≥35 vs <25, postmenopausal	4.43 (2.68-7.34) 3.97 (3.06-5.14)

First author, year	Cohort	Country	Age at recruitment (years), range, mean or median	Population size/number of cases	Description of BMI categories or BMI unit (kg/m^2)	Relative risk (CIs)
Bhaskaran, 2014[34]	UK Clinical Practice Research Databank	UK	Median age: 37.9	2,864,658 / 2,758	Per 5-unit	1.62 (1.56-1.69)
Weiderpass 2014[35]	Swedish Women's Lifestyle and Health (WLH) cohort	Sweden	30-49	42,270 / 144 type 1 cancers	Per 5-unit	1.42 (1.22-1.66)
Wu 2014[36]	Community Breast Cancer Screening Programme	Taiwan	30-65	11,258 / 38	≥27 vs <27	1.08 (0.48-2.41)
Park 2010[39]	The Multiethnic Cohort Study	USA	45-75	50,376 / 463	>30 vs <25	3.54 (2.70-4.63)
Bjorge 2010[296]	Me-Can Study	Austria, Norway and Sweden	Mean age:44	287,320 / 917	Per 1-SD increase	1.39 (1.31-1.47)
Conroy 2009[18]	Women's Health study	USA	≥ 45	32,642 / 264	≥30 vs <22.5	2.49 (1.73-3.59)
McCullough 2008[21]	CPS-II Nutrition Cohort	USA	Median age: 62	33,436 / 318	≥35 vs 22.5-<25.0	4.70 (3.12-7.07)
Epstein 2009[19]	Swedish women	Sweden	25-64	17,822 / 166	>29 vs <25	3.5 (2.2-5.4)
Lindemann 2008[20]	The HUNT Study	Norway	20-101	36,761 / 222	≥40 vs 20-24	6.36 (3.08-13.16)
Song 2008[22]	Korean women	Korea	Mean age: 55.9	170,481 / 112	Per 1-unit	1.13 (1.07-1.20)
Reeves 2007[26]	Million Women Study	UK	50-64	~1 million /2,657	Per 10-unit	2.89 (2.62-3.18)
Chang 2007[24]	NIH-AARP Diet and Health Cohort	USA	50-71	103,882 / 677	30.0 vs <25.0	3.03 (2.50-3.68)
Friedenreich 2007[25]	EPIC cohort	10 Western European countries	Mean age: 50.2	223,008 / 567	Per 1-unit	1.06 (1.04-1.08)
Lundqvist 2007[134]	Swedish and Finnish Twin data	Sweden and Finland	Median age younger cohort: 29 Median age Older cohort: 56	Younger cohort 43,328 / 134 Older cohort 24,821 / 180	Per 1-unit, younger cohort Per 1-unit, older cohort	1.09 (1.04-1.14) 1.11 (1.06- 1.15)

First author, year	Cohort	Country	Age at recruitment (years), range, mean or median	Population size/number of cases	Description of BMI categories or BMI unit (kg/m^2)	Relative risk (CIs)
Bjorge 2006[23]	Norwegian women	Norway	20-74	1,038,018 / 9,227	≥ 30 vs <18.5-24.9	2.51 (2.38-2.66)
Lukanova 2006[135]	Northern Sweden Health and Disease Cohort	Sweden	Mean age: 46.1	35,362 /115 cases	≥30 vs 18.5-24.9	2.93 (1.85-4.61)
Kuriyama 2005[136]	Japanese women	Japan	≥40	15,054 / 22	≥30 vs 18.5-24.9	4.04 (1.14-14.36)
Lacey 2005[137]	Breast Cancer Detection Demonstration Project	USA	Mean age: 57.2	30,379 / 541	≥35 vs 18.5-24.9	2.5 (0.7-3.7)
Rapp 2005[138]	The Vorarlberg Health Monitoring and Promotion Program Cohort	Austria	35-54	78,484 / 175	≥35 vs 18.5-24.9	3.93 (2.45-6.56)
Silvera 2005[297]	The Canadian National Breast Screening Study	Canada	40-59	34,391 / 426	>30 vs <25	3.40 (2.68-4.33)
Schouten 2004[139]	The Netherlands Cohort Study on Diet and Cancer	Netherlands	55-69	2,589 subcohort / 226	Per 1-unit	1.13 (1.08-1.18)
Furberg 2003[263]	Norwegian cohort	Norway	Mean age: 44.7	24,460 / 130	≥30 vs <25	2.57 (1.61-4.10)
Folsom 2000[298]	The Iowa Women's Health Study	USA	55-69	31,702 / 298	Quintile 5 vs Quintile 1	4.6 (3.1-6.8)
de Waard 1996[142]	Women from the breast cancer screening programme	Netherlands	40-64	900 subcohort / 147 cases	≥29 vs <25, premenopausal ≥29 vs <25, postmenopausal	1.6 * 1.9*
Tornberg 1994[143]	Swedish women	Sweden	Mean age: 48	47,003 / 271	Per 1-unit	1.24 (1.16-1.34)

- CIs were not provided in the publication.

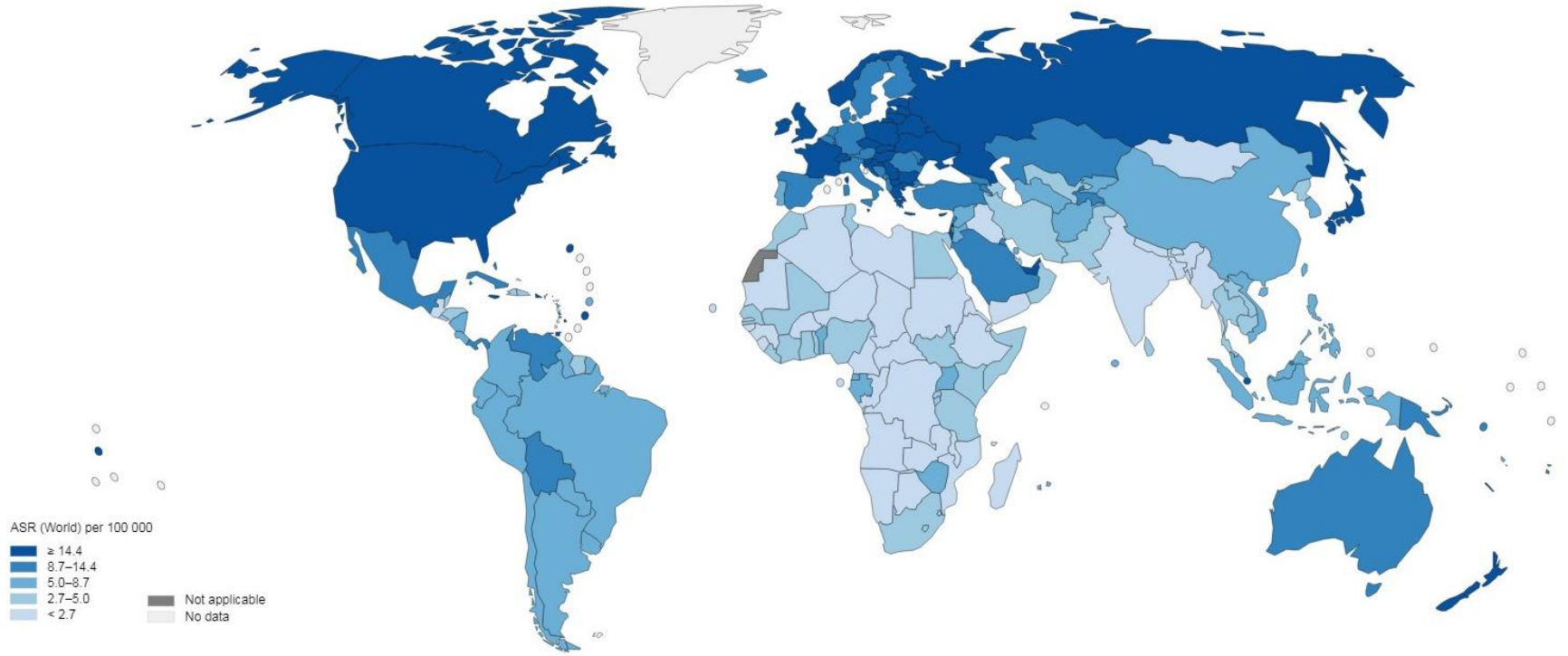
Results from the publication with the largest number of cases were included for cohorts with several publications.
Risk estimates from analyses based on continuous measures are presented for studies reporting risk estimates for both continuous and categorical analyses.

Table 2-2: Relative risk estimates and confidence intervals associated with current or past vs never smoking in previous cohort studies

First author, year	Cohort	Country	Age at recruitment (years), Range or Mean	Population/cases	Current vs never HR (95%CI)	Past vs never HR (95%CI)
Viner 2019[299]	Alberta's Tomorrow Project (ATP)	Canada	35 – 69	16,581 / 110	0.59 (0.32-1.09)	0.56 (0.36-0.86)
Felix 2014[58]	NIH-AARP Diet and Health cohort	USA	50-71	110,304 / 1,476	0.65 (0.55-0.78)	0.89 (0.80-1.00)
Weiderpass 2014[35]	Swedish Women's Lifestyle and Health (WLH) cohort	Sweden	30-49	42,270 / 144 type I cases	0.90 (0.59-1.35)	0.91 (0.61-1.36)
Blakely 2013[195]	New Zealand census-cancer registry cohorts	New Zealand	25+	-	0.67 (0.56-0.79)	-
Lindemann 2008[20]	The HUNT Study	Norway	20+	36,761 / 222	0.55 (0.35-0.86)	1.06 (0.71-1.61)
Setiawan 2007[300]	Multiethnic Cohort Study	USA	45-75	46,933 / 321	0.72 (0.48-1.08)	1.16 (0.91-1.47)
Loerbroks 2007[78]	The Netherlands Cohort Study	Netherlands	55-69	2,229 subcohort / 280 cases	0.59 (0.40-0.88)	0.83 (0.58-1.20)
Al-zoughool 2007[59]	European Prospective Investigation into Cancer and Nutrition (EPIC) cohort	10 European countries	19.9-58.0	*Premenopausal* 115,915 / 126	*Premenopausal* 1.79 (1.13-2.70)	*Premenopausal* 0.78 (0.46-2.78)
			27.8-98.5	*Postmenopausal* 133,578 / 493	*Postmenopausal* 0.78 (0.59-1.03)	*Postmenopausal* 0.88 (0.70-1.11)
Bjorge 2006[23]	Norwegian women	Norway	20-74 years	324,704 /242	0.67 (0.47-0.97)	1.05 (0.73-1.51)
Viswanathan 2005[60]	Nurses' Health Study	USA	30-55	96,704 / 702	0.72 (0.57-0.90)	0.73 (0.62-0.87)
Folsom 2003[140]	The Iowa Women's Health Study	USA	55-69	23,335 / 415	0.53 (0.37-0.75)	0.84 (0.64-1.08)
Terry 2002[79]	Canadian National Breast Screening Study	Canada	40-59	70,591 / 403	0.83 (0.63-1.09)	0.99 (0.78-1.25)

First author, year	Cohort	Country	Age at recruitment (years), Range or Mean	Population/cases	Current vs never HR (95%CI)	Past vs never HR (95%CI)
Terry 1999[249]	Swedish Twin Registry	Sweden	Mean age: 56.2 years	11,659 / 133	*1-10 cigarettes / day* 1.20 (0.60-2.30) *11+ cigarettes/day* 0.50 (0.10-2.00)	0.70 (0.30-2.00)
Tulinius 1997[141]	Icelandic cardiovascular risk factors study	Iceland	Mean age: 50.5	11,580 / 98	*1-14 cigarettes/day* 0.53 (0.29-0.96) *15-24 cigarettes/day* 0.54 (0.27-1.10) *25+ cigarettes/day* 0.91 (0.22-3.75)	0.72 (0.40-1.32)
Nordlund 1997[182]	Random sample of women drawn from the Swedish population registry	Sweden	18-69 years	26,032 / 248	0.81 (0.55-1.18)	1.02 (0.52-2.01)
Engeland 1996[301]	Norwegian parts of the Migrant Study	Norway	33-72 years	14,269 / 140	1.1 (0.7-1.6)	1.20 (0.60-2.20)

Results from the publication with the largest number of cases were included for cohorts with several publications.



Source: GLOBOCAN, 2018

Figure 2-1: Estimated age-standardised incidence rates of uterine cancer in 2018

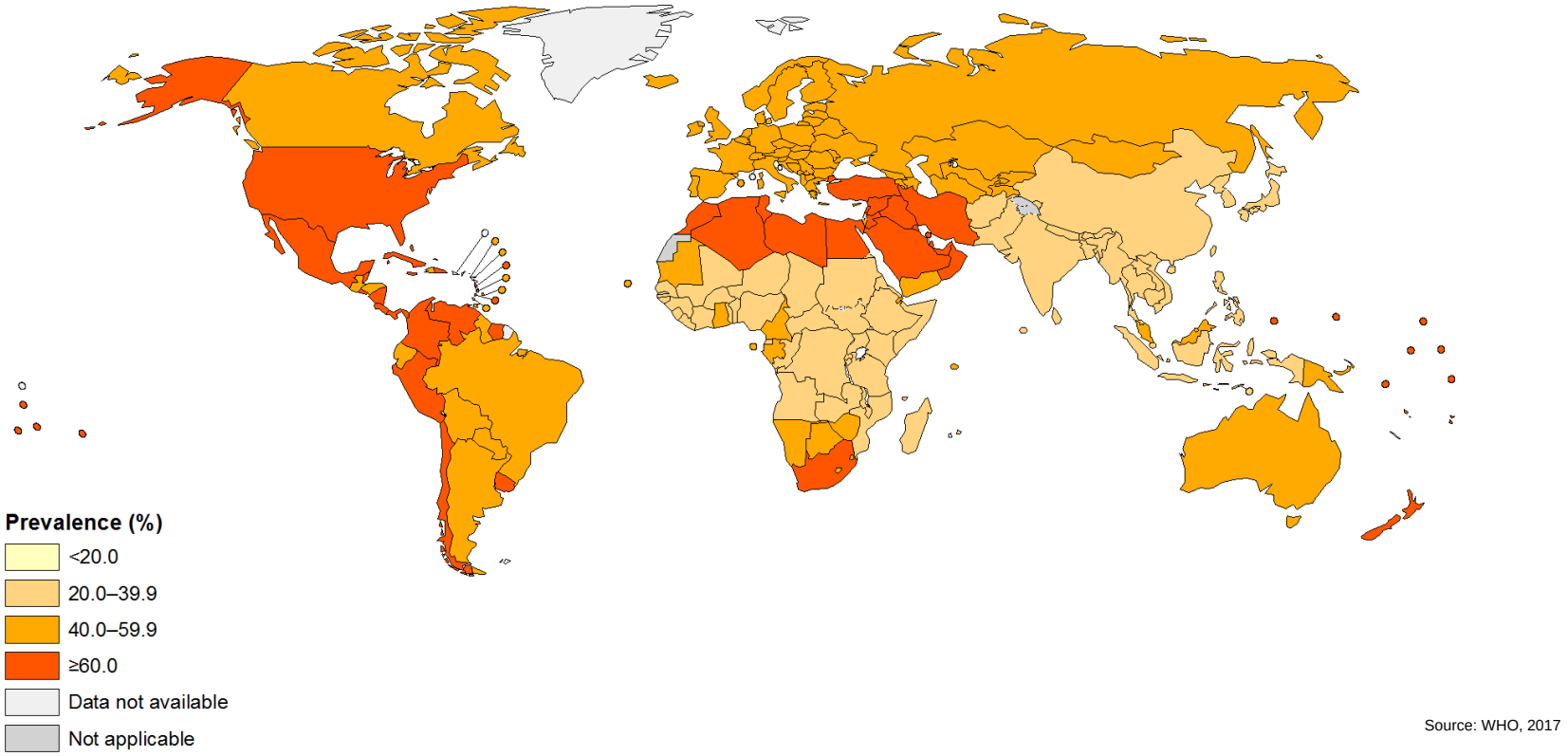


Figure 2-2: Estimated age-standardised prevalence rates of overweight/obesity (BMI ≥25 kg/m^2) among females, aged 18 years or over in 2016

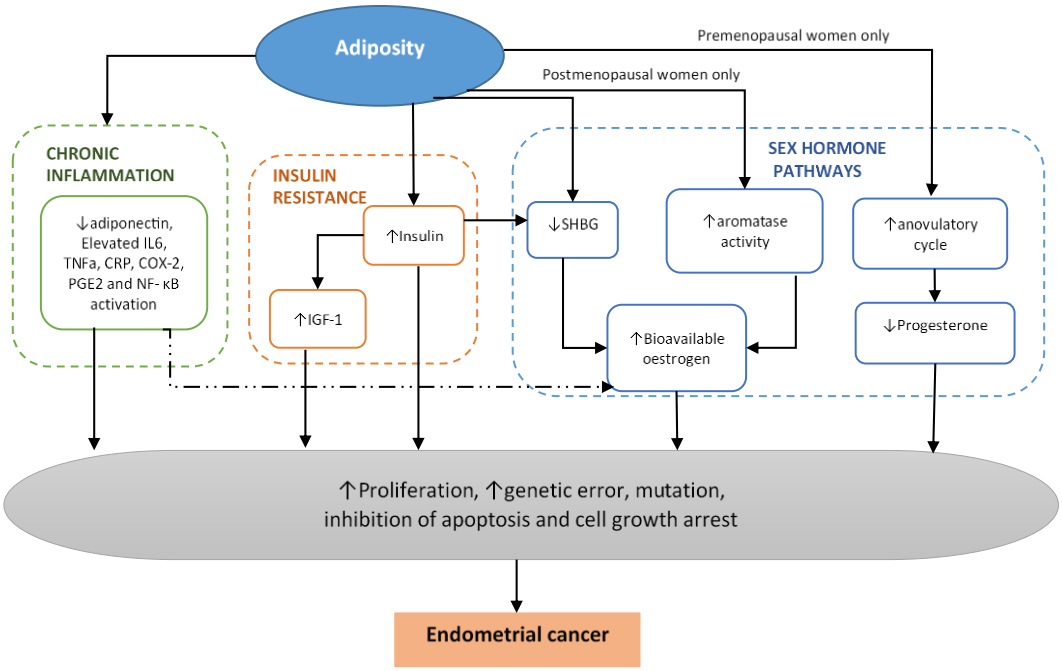
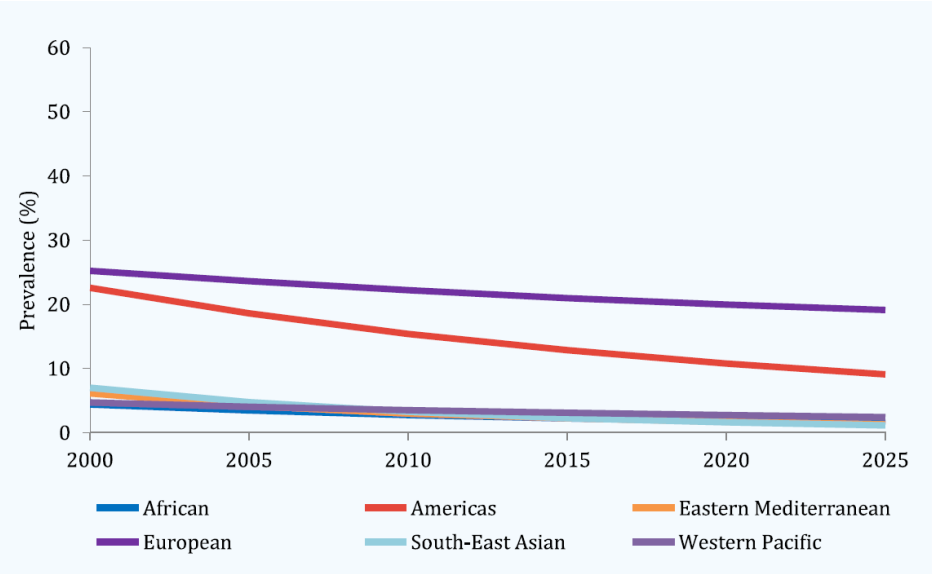
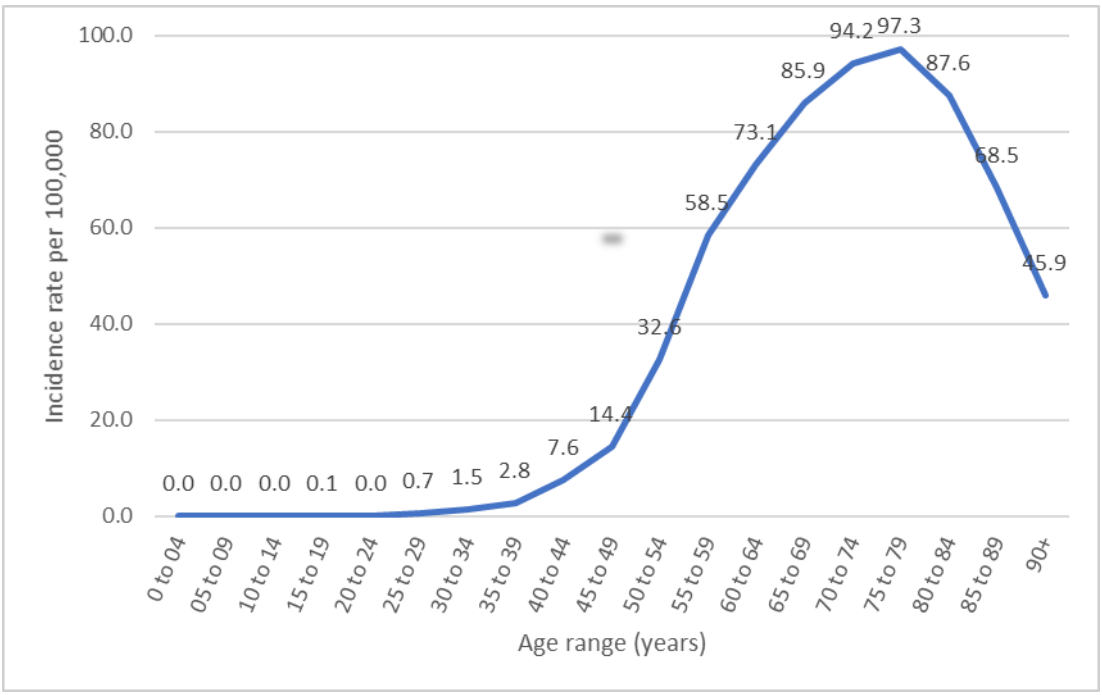


Figure 2-3: Mechanisms linking adiposity with endometrial cancer development



Source: WHO, 2018

Figure 2-4: Age-standardised fitted and projected global rates of prevalence of smoking in females aged ≥15 years by WHO region, 2000–2025



Source: Cancer Research UK, 2019

Figure 2-5: Age-specific incidence rates for uterine cancer in the UK, 2014-2016

Chapter 3: Overall study design and methods

Summary

The two cohorts used in this thesis, UK Biobank and the Million Women Study, are both ongoing prospective studies in the UK. Each cohort collected data on demographics, lifestyle, reproductive and medical factors from all participants at recruitment. Participants were followed for various health outcomes through electronic data linkage with a variety of National Health Service (NHS) databases. Cox regression models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of the exposures of interest with endometrial cancer risk.

3.1. UK Biobank

UK Biobank was established by the Medical Research Council and the Wellcome Trust to facilitate detailed investigation of the environmental and genetic determinants of a wide range of diseases of middle and old age.[302] It consists of approximately 500,000 participants recruited from the general population in England, Scotland and Wales between 2006 and 2010. UK Biobank holds extensive data on a wide range of exposures including lifestyle, reproductive factors, medical history, physical measures and genetic data. Follow-up is ongoing via electronic data linkage with a variety of NHS administrative databases in England, Scotland and Wales. The study was approved by the NHS North West Centre for Research Ethics Committee (Ref: 11/NW/0382), and all participants provided informed consent for health-related research that is in the public interest.

3.1.1. Recruitment

Postal invitations were sent to 9,238,453 individuals registered with the NHS who were aged between 40 and 69 years and lived within approximately 25 miles of 22 assessment centres across England, Scotland and Wales.[303] A total of 503,317 individuals consented to participate and attended an assessment centre between 2006 and 2010.[303]

3.1.2. Data collection

At the assessment centre, participants completed questionnaires requesting information on their lifestyle, environment and medical history. They also

underwent a range of physical assessments including measurement of body size and composition, and provided blood, urine and saliva samples for subsequent analyses. In a subset of the cohort (approximately 20,000 individuals), repeat assessment of all baseline measures were performed approximately 5 years after recruitment.

3.1.2.1. Baseline questionnaires and assessment of smoking status

UK Biobank questionnaires were administered using the computerised direct data entry system. The advantages of this method over traditional paper questionnaires include automated coding, internal consistency checks and immediate access. The majority of information was collected by means of a self-administered touch-screen questionnaire, which took approximately 50 minutes to complete. The touch-screen questionnaire was designed such that participants were only asked questions that are relevant to them (for example, detailed smoking habits were only requested from smokers, see appendix 2). The broad topic areas assessed by the UK Biobank questionnaires include socio-demographics and occupation, lifestyle, early life exposures and medical history. Information that was not readily collected via the touch-screen questionnaire, for example those that required detailed questioning, were collected via a computer-assisted personal interview (CAPI) that lasted about 10 minutes.

Smoking information in UK Biobank

Participants were asked “Do you smoke now?” with options including “Yes on most or all days, only occasionally, no, prefer not to answer”. All participants, except those who indicated “Yes on most or all days”, were asked how often they smoked in the past, with possible answers being “smoked on most or all days, smoked occasionally, just tried once or twice, I have never smoked and prefer not to answer”. Participants who reported they smoked occasionally in the past or tried once or twice were further asked if they had smoked a total of at least 100 times in their lifetime. Those who reported they smoked on most or all days at baseline or in the past were asked to provide information on the age they started smoking, the average number of cigarettes they smoked daily and the age at last smoke (past smokers only).

Current smokers were defined as women who had smoked at least 100 times in their lifetime and who indicated that they still smoke at the time of baseline assessment. Past smokers were defined as women who had smoked at least 100 times in their lifetime but quit smoking before baseline assessment. Women who indicated that they were past smokers but whose age at stopping was the same as their age at baseline assessment were considered to be current smokers. Never smokers were defined as women who had never smoked or who had smoked less than 100 times in their lifetime (figure 3-1).

Duration of smoking was defined as the difference between age at baseline (or age at last smoke for past smokers) and the age at starting smoking.

Time since smoking cessation for past smokers was the difference between age at baseline and age at last smoke.

3.1.2.2. Measurement of body size and composition

Trained personnel collected data on body size and composition. Height was measured to the nearest 0.1 centimetres (cm) using a Seca 240 cm height measure, with participants standing barefoot and with the head positioned in the Frankfort plane. Weight was measured using the Tanita BC-418MA segmental body composition analyser. Body mass index (BMI) was calculated as weight in kilogram (kg) divided by the square of height in metres (m). Waist and hip circumferences were measured using a Seca 200 cm tape. Waist circumference was measured at the narrowest part of the trunk or at the level of the umbilicus at the end of a normal expiration, while hip circumference was measured at the widest part of the buttocks.

Body composition was determined using the bioimpedance technique (the principle underlying this technique is described in section 2.3.1.1). Bioimpedance analysis involves passing a small electric current through the body and measuring the resistance or impedance of body tissues to this current.[122] From the impedance readings, measurements of various body fractions can be calculated using appropriate prediction equations. The prediction equations relate impedance readings to body composition parameters measured by a reference technique in a specific population; hence, prediction equations tend to be population specific.[124]

The Tanita BC-418MA segmental body composition analyser was used to measure impedance in UK Biobank. This device consists of eight electrodes and can provide body composition readings for the whole body and for different body segments such as right arm, left arm, trunk, right leg and left leg. The eight electrodes are located on the analyser's platform and on its two handgrips. The measurement process required participants to stand barefoot on the analyser's platform with both feet in contact with the electrodes on the platform while grasping the handgrips. A low voltage current passing through the body via these electrodes was used to generate the impedance readings. All measurements were performed according to the manufacturer's instructions. Fat mass, fat-free mass and body fat percentage for the whole body and for different body segments were estimated from the readings using equations built into the Tanita BC-418MA analyser. The in-built body composition prediction equations have not been released by the manufacturers. However, for this thesis, it was assumed that the formulae had been derived from a population with similar characteristics to the UK Biobank study population. The data captured by the analyser were transmitted directly into the assessment centre software (i.e. without the need for manual data entry).

3.1.2.3. Measurement of biomarkers

During the baseline visit, about 45 ml of blood were collected from each participant. These samples were processed and cryopreserved within 24 hours of collection at the central processing laboratory. At a later date, the samples were retrieved and assayed for several biomarkers including

glucose, glycated haemoglobin (HbA1c), insulin-like growth factor-1 (IGF-1), C-reactive protein (CRP), albumin, testosterone and sex hormone binding globulin (SHBG).

Serum glucose was measured by an enzymatic test using a fully automated system (Beckman Coulter AU5800 Analyser). HbA1c was assayed by a High-Performance Liquid Chromatography (HPLC) technique using Bio-Rad Laboratories Analyser. IGF-1 was measured by a chemiluminescent immunoassay one step sandwich method using the Diasorin Liaison XL Analyser. CRP was assayed by an immuno-turbidometric method and albumin by a colourimetric test using the Beckman Coulter AU5800 Analyser. Serum concentrations of testosterone and SHBG were measured by a chemiluminescent assay (competitive binding method for testosterone and one step method for SHBG) using the Beckman Coulter DXI 800 Analyser.

Internal quality control samples, containing known high, medium and low concentrations of each biomarker, were run before and after each batch of participant samples. The coefficients of variation for each assay over the project period and other details about the assay procedures are available on UK Biobank's webpage "https:// biobank.ndph.ox.ac.uk /showcase/showcase /docs/serum_biochemistry.pdf".

3.1.2.4. Repeat assessment visits

About 20,000 UK Biobank participants who lived within a 35-mile radius of the UK Biobank Co-ordinating Centre in Stockport, underwent a repeat of the baseline assessment visit between August 2012 and June 2013 (4-5 years

after the baseline visit). The objective of this reassessment was to enable correction of the association between a risk factor and an outcome of interest for regression dilution bias (discussed later in section 3.4.3).

3.1.3. Follow-up of participants and endometrial cancer ascertainment

During the baseline assessment visit, permission was obtained from all participants to access all their past and future medical and health-related records. Participants were linked to NHS health administrative databases for deaths, cancers and hospital admissions using their NHS number (or Community Health Index Number for those in Scotland) and other unique identifiers. Incident cancers during follow-up were identified through the cancer registry data obtained from NHS Digital (for participants in England and Wales) and National Records of Scotland, NHS Central Register (for participants in Scotland). Endometrial cancer in this study was defined using the International Classification of Diseases edition 10 (ICD-10) code for cancer of the corpus uteri:C54. This code includes endometrial cancer and other cancers arising in the uterus such as uterine sarcoma.

3.1.4. Research in this thesis undertaken using the UK Biobank dataset

In chapter 4, data from this cohort were used to assess the associations of different measures of body size and body composition with endometrial cancer risk. In chapter 6, data from this cohort were used to investigate the associations of different measures of smoking with endometrial cancer risk.

3.2. The Million Women Study

The Million Women Study was originally established to investigate the association between different types of HRT and breast cancer risk.[304] It consists of approximately 1.3 million women recruited through the National Health Service Breast Cancer Screening Programme (NHSBSP) between 1996 and 2001.[305] The Million Women Study was approved by the Oxford and Anglia Multi-Centre Research Ethics Committee, and all participants provided written consent to follow-up.

3.2.1. Recruitment and data collection

Recruitment into the Million Women Study took place between 1996 and 2001. At that time, the NHSBSP routinely invited women aged 50-64 years for mammographic screening every 3 years. In 66 of the screening centres across England and Scotland, the Million Women Study recruitment questionnaire was included in the screening invitation letter. Approximately 1.3 million women returned completed questionnaires and were enrolled in the study. This is about one in four women born between 1935 and 1950.[305]

The recruitment questionnaire included questions on lifestyle, reproductive and medical histories (appendix 3). Every 3-5 years, participants were sent a resurvey questionnaire to update information on these exposures and to request data on additional exposures. The first resurvey (approximately 3 years after recruitment) questionnaire was completed by about 800,000 participants; the second resurvey (approximately 8 years after recruitment)

questionnaire by around 680,000 participants; and the third resurvey (approximately 12 years after recruitment) questionnaire by approximately 590,000 participants.

3.2.1.1. Smoking information in the Million Women Study

In the recruitment questionnaire, smoking was assessed by asking participants “About how many cigarettes do you smoke per day now?” with options including none, <5, 5-9, 10-14, 15-19, 20-24, 25 or more. Participants were also asked whether they were ex-smokers. This information was jointly used to classify participants as never, past or current smokers. Current smokers were women who indicated that they were not ex-smokers and who provided data on the number of cigarettes they smoked per day. Past smokers were women who indicated that they were ex-smokers. Never smokers were women who reported that they were not ex-smokers and who indicated ‘none’ when asked about the number of cigarettes smoked per day now.

Information on timing of smoking (age at smoking initiation and age at smoking cessation) was first obtained during the first resurvey. Participants who indicated that they were ever smokers were asked to provide information on their age when they first started smoking regularly, the number of cigarettes smoked on average each day and the age when smoking stopped (if past smoker).

3.2.1.2. Body size measures in the Million Women Study

Participants reported their weight and height in the recruitment questionnaire. BMI was calculated as weight (kg) divided by the square of height (m). Data on waist and hip circumferences were first reported during the first resurvey. Waist to hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm). Waist to height ratio was calculated by dividing waist circumference (cm) at first resurvey by height (cm) as reported at recruitment.

3.2.2. Follow-up of participants and endometrial cancer ascertainment

The records of study participants were linked electronically to NHS health administrative databases for cancer registrations, deaths and hospital admissions using their unique NHS numbers and other personal identifiers. These databases provided information on the date of registration of each event with diagnoses coded to the 9th and 10th revisions of the WHO International Classification of Diseases (ICD-9 and ICD-10). Endometrial cancer was defined in the same way as for UK Biobank (section 3.1.3).

3.2.3. Research in this thesis undertaken using the Million Women Study dataset

The large size of this cohort allowed for more detailed investigation of the associations of adiposity and smoking with endometrial cancer risk. In chapter 5, data from the recruitment cohort, i.e. women enrolled in the study, were used to assess the associations of BMI with endometrial cancer risk in

important subgroups of the population and by tumour subtypes. Data from the subset of the cohort that participated in the first resurvey, when information on waist and hip circumferences was first reported, were used to investigate the associations between central adiposity measures and endometrial cancer risk. In chapter 6, data from the recruitment cohort were used for the analysis of the association of smoking status with endometrial cancer risk overall and by tumour subtypes. Data from women who participated in the first resurvey, when information on timing of smoking was first collected, were used to assess the associations of quantitative measures of smoking with endometrial cancer risk.

3.3. Variables used in this thesis

The following variables were explored as potential confounders or effect modifiers in this thesis: menopausal status, age, deprivation score, UK region, age at menarche, parity, age at menopause, oral contraceptive use, HRT use, physical activity and diabetes. These variables were considered as potential confounders for analyses in both cohorts and the definitions were standardised as much as possible. The definitions used for these variables are shown in table 3-1.

In both cohorts, premenopausal women were never HRT users who were younger than age 55 years at baseline and who indicated that their periods had not stopped. Women were considered to be postmenopausal if they had a history of bilateral oophorectomy at baseline (self-reported or from hospital admissions records), or if they indicated that they had had menopause in the

baseline questionnaire, or if they were aged 55 years or over at baseline. Coding of procedures in the hospital admissions records was based on the Office of Populations Censuses and Surveys Classification of Interventions and Procedures, Version 4 (OPCS-4), and bilateral oophorectomy was defined as OPCS-4 codes “Q221” and “Q223”.

Current HRT users in both cohorts were women who, at baseline, indicated that they were still using HRT. In the Million Women Study, current HRT users were further categorised by the type of HRT recently used (oestrogen only, oestrogen plus progestogen, tibolone and others). Parity was defined as the number of live births in UK Biobank and as the number of full-term pregnancies in the Million Women Study.

In both cohorts, age at menarche was the age at first period and age at menopause was the age when periods stopped (or age at bilateral oophorectomy for women who reported bilateral oophorectomy). Ever users of oral contraceptives were women who reported use of oral contraceptives. These women were further categorised according to the duration of use, calculated as the difference between age at last use (or age at baseline for current users) and age at first use.

The questions used to assess physical activity differed between the cohorts. In the Million Women Study, women were asked to provide information on the frequency of strenuous exercise (number of days per week). In UK Biobank, physical activity was assessed using an adapted version of the short form of International Physical Activity Questionnaires (IPAQ) that

requested data on the number of days per week and minutes per day of walking, moderate and vigorous physical activities. The IPAQ scoring protocol available on the website “https:// www.scribd.com /document /92677948/IPAQ-Scoring” was used to process these data and classify women into low, moderate, and high physical activity categories.

Women were considered to have a history of diabetes if they self-reported diabetes or if they indicated that they were being treated for diabetes. UK region refers to the region where each participant attended baseline assessment in UK Biobank (10 regions) and the cancer registry region at the time of recruitment in the Million Women Study (10 regions).

3.4. Overview of statistical methods

3.4.1. General exclusions

At the time of analysis, data were available for 273,402 women in UK Biobank and 1,364,308 women in the Million Women Study (of whom 866,526 participated in the first resurvey). In both cohorts, participants were excluded from all analyses if, at baseline, they: (i) self-reported hysterectomy or had a hospital admission record of hysterectomy (OPCS-4 codes “Q07, “Q08” and “R251”); (ii) had missing information on hysterectomy; (iii) had prevalent cancer other than non-melanoma skin cancer (ICD-10 code: C44); (iv) had unknown menopausal status; or (v) were lost to NHS follow-up (figures 3-2, 3-3 and 3-4). Other study-specific exclusions are described in the respective chapters.

3.4.2. Analyses of associations between exposures of interest and endometrial cancer risk

The statistical methods used to investigate the associations of adiposity and smoking with endometrial cancer risk were as similar as possible across the studies to enable comparisons to be made. Because of known differences in the associations and/or biological effects of adiposity and smoking on endometrial cancer risk by menopausal status (see sections 2.3.1.4 and 2.3.2.1), all analyses were carried out separately in premenopausal and postmenopausal women. Cox proportional hazard models, with time in study as the underlying metric, were used to examine the associations between the baseline values of the exposures of interest and endometrial cancer risk. Participants in both cohorts contributed person-time from baseline (date of baseline assessment in UK Biobank, date depends on exposure of interest in the Million Women Study—see table 3-2) to the end of follow-up or until they were censored due to any invasive cancer (other than non-melanoma skin cancer, ICD-10: C44), hysterectomy (from hospital admissions records) or death, whichever came first. Premenopausal women were also censored at age 55 years in order to assess associations with endometrial cancers diagnosed during the premenopausal years.

All models were stratified by year of birth and year of data collection. Potential confounders included age, UK region, deprivation score, age at menarche, parity, oral contraceptive use/duration, diabetes, physical activity, smoking status (for analyses of body size and composition), BMI (for analyses of smoking measures), HRT use/type and age at menopause.

3.4.3. Measurement error and regression dilution ratios for the different measures of body size and body composition

The association between a risk factor and an outcome of interest may be underestimated in analysis that uses a single measurement of the risk factor because of regression dilution bias arising from random measurement error and/or within person variability in the levels of the risk factor over time.[306] In this thesis, these sources of bias are collectively referred to as measurement error. Different adiposity measures are associated with different degrees of measurement error,[307] and this may complicate comparisons across measures as those with greater measurement errors are likely to have their associations with disease risk underestimated to a greater degree.

In chapters 4 and 5, the risk estimates for the associations between baseline values of adiposity measures and endometrial cancer risk were corrected for regression dilution bias in order to obtain risk estimates for the associations of usual levels of adiposity measures with endometrial cancer risk. For analyses using categories of adiposity measures, this was done by plotting the hazard ratios (HRs) and 95% confidence intervals (CIs) for the baseline category against the repeat assessment mean values within the same categories.[308]

For analyses based on continuous measures, the regression dilution ratio (RDR)—a measure of the extent of measurement error associated with a risk factor—for the adiposity measure was calculated; then the log HR and standard error were multiplied by the reciprocal of the RDR.[308,309] The RDRs

for the different measures of adiposity were estimated using the Rosner's approach, which involves regressing the repeat measurements of the variable against the baseline values using data from individuals with replicate measurements.[309] In UK Biobank, data from women who participated in the repeat assessment resurvey carried out approximately 4-5 years after the baseline visit were used to calculate the RDRs. In the Million Women Study, data from women who participated in the second resurvey (approximately 8 years after recruitment) were used because the measurements were obtained at a period that is approximately equivalent to the midpoint of the follow-up period for analyses in this cohort.

The RDRs for adiposity measures and other body size/composition variables assessed among postmenopausal women in each cohort are shown in table 3-3. A value closer to 1 implies smaller measurement error and a value closer to 0 indicates greater measurement error. The RDRs for BMI, waist circumference, hip circumference, waist to hip ratio and waist to height ratio in UK Biobank were similar to those of the Million Women Study. BMI had a higher RDR (RDR = 0.94 in both cohorts) than other measures of adiposity indicating that the reproducibility of BMI is superior to that of other measures. Waist to hip ratio (RDR = 0.63 in UK Biobank) was less reproducible compared to waist circumference (RDR = 0.87 in UK Biobank) and other measures of adiposity, indicating that the degree of underestimation of the strength of association with disease risk is likely to be greater for waist to hip ratio than for waist circumference or any of the other adiposity measures in analyses using baseline measurements only.

3.5. Baseline characteristics of participants

The baseline characteristics of women included in the UK Biobank analyses (n = 196,074) and in analyses based on the recruitment cohort of the Million Women Study (n = 789,964) after the general exclusions (described in section 3.4.1 and presented in figures 3-2 and 3-3) are shown in table 3-4. The mean (SD) ages at recruitment were 55.7 (8.2) years in UK Biobank and 57.7 (4.7) years in the Million Women Study. The proportion of premenopausal women was higher in UK Biobank (29.8%) than the Million Women Study (8.9%; figure 3-4). More women were overweight or obese in UK Biobank (57.6%) compared with the Million Women Study (49.7%). UK Biobank participants were less likely to be current smokers but were more likely to be nulliparous and ever users of oral contraceptives or HRT compared with their counterparts in the Million Women Study (table 3-4).

3.6. Cross-sectional correlates of adiposity and smoking

As reviewed in chapter 2, the mechanism underlying the known inverse association between smoking and endometrial cancer risk is not well understood (section 2.3.2.2). A better understanding of correlates of cigarette smoking may shed light on how smoking influences endometrial cancer risk. It may also help to identify potential confounders of the association of smoking with endometrial cancer risk. As part of the preliminary analyses, multivariable-logistic models were used to examine the association of current smoking (compared with never smoking) with demographic and endometrial cancer risk factors in both the UK Biobank and the Million Women Study.

The cross-sectional associations of adiposity, as reflected by BMI, with known risk factors for endometrial cancer were also investigated by regressing BMI on each of these factors. Because smoking has different associations with overall and central adiposity,[310] the relationships between smoking and different adiposity measures were further assessed in multivariable-adjusted linear regression models, with each adiposity measures as the dependent variable. To facilitate comparison across measures, each adiposity measure was standardised to have a mean of 0 and a standard deviation of 1.

3.6.1. Association of current smoking with demographic and known endometrial cancer risk factors among postmenopausal women

Table 3-5 shows the odds ratios for the association of current smoking with various endometrial cancer risk factors among postmenopausal women in both cohorts. Overall, older women at baseline were less likely to be current smokers compared with those who were aged less than 50 years at baseline. Women who live in more deprived areas were more likely to be current smokers compared to those who live in the least deprived areas. Ever users of oral contraceptives were more likely to be current smokers compared with never users. Current and past users of HRT were also more likely to be current smokers compared with never users. Overweight or obese women were less likely to be current smokers compared with normal weight women. In contrast, underweight women were more likely to be current smokers compared to those of normal weight. Age at menopause was also associated with current smoking. Women who had menopause at later ages were less

likely to be current smokers compared to those who had menopause before age 49 years. Women in the higher categories of physical activity were less likely to be current smokers compared to those in the lowest category of physical activity (table 3-5).

3.6.2. Association of BMI with demographic and known endometrial cancer risk factors among postmenopausal women

In both cohorts, women who lived in more deprived areas at baseline had higher values of BMI compared with those living in the least deprived areas (table 3-6). Women who had menarche at later ages had lower values of BMI compared to those who had menarche before age 13 years. Parous women had higher values of BMI compared with nulliparous women. Users of oral contraceptives had lower BMI values compared with never users. Furthermore, current users of HRT had lower values of BMI compared with never users. Participants with a history of diabetes had higher values of BMI compared with those without a history of diabetes (table 3-6).

3.6.3. Association of different indices of adiposity with current smoking among postmenopausal women

Overall, current smokers had lower values of all overall adiposity measures (BMI, weight, body fat percentage and fat mass) than never smokers (table 3-7). However, they had higher values of waist to hip ratio than never smokers. Current smokers in UK Biobank had higher values of waist circumference and waist to height ratio than never smokers. In contrast,

those in the Million Women Study, had lower values of these variables compared with never smokers.

3.7. Conclusion

This chapter describes the methods used to establish the UK Biobank and the Million Women study, as well as the definitions of the variables used in this thesis. Chapters 4 to 6 report on the three studies conducted in this thesis using these datasets.

Table 3-1: Definitions of some variables used in this thesis

Variables	UK Biobank	Million Women Study
Body mass index	Weight in kilograms divided by the square of height in metres. Weight and height were measured by trained personnel in UK Biobank.	Defined in the same way as for UK Biobank. However, weight and height were self-reported in the Million Women Study.
Smoking status	**Never smokers:** women who had smoked less than 100 times in their lifetime. **Past smokers:** women who reported that they had smoked at least 100 times in their lifetime but quit before baseline assessment. **Current smokers**: women who had smoked at least 100 times in their lifetime and who indicated that they smoked daily or occasionally at baseline. Past smokers whose age at last smoke was the same as their baseline age were considered to be current smokers.	**Never smokers:** women who indicated that they were not ex-smokers and who reported none when asked about the number of cigarettes smoked per day. **Past smokers:** women who indicated that they were ex-smokers in the recruitment questionnaire. **Current smokers:** women who indicated that they were not ex-smokers and who provided data on the number of cigarettes smoked per day.
Menopausal status	**Premenopausal:** Never HRT users who were younger than 55 years at baseline and who indicated that their periods had not stopped. **Postmenopausal:** women who had a history of bilateral oophorectomy; or who self-reported menopause in the baseline questionnaire; or who were aged 55 years old or over at baseline. (Women were considered to have a history of bilateral oophorectomy if they either self-reported bilateral oophorectomy at recruitment or had hospital admissions record of bilateral oophorectomy [OPCS-4 codes: Q221 or Q223]).	Same as UK Biobank.
Parity	Number of live births	Number of full-term pregnancies

Variables	UK Biobank	Million Women Study
Hormone replacement therapy	**Never users**: women who, at baseline, reported that they had never used HRT. **Past users**: women who, at baseline, reported that they were past HRT users. **Current users**: women who, at baseline, indicated that they were still using HRT.	Same as UK Biobank. Current HRT users were further categorised by the type of most recent HRT used (oestrogen only, oestrogen plus progestogen, tibolone and others).
Age at menarche	Age when periods started	Same as UK Biobank
Age at menopause	Age when periods stopped or age at bilateral oophorectomy	Age when periods stopped
Oral contraceptive use	**Ever users**: women who reported use of oral contraceptives. Ever users provided further information on the age at first and last use, which was used to calculate duration of use. **Never users**: women who reported that they had never used oral contraceptives.	Same as UK Biobank
Physical activity	Based on the short IPAQ questionnaire. Participants reported the number of days per week and minutes per day of walking, moderate and vigorous physical activities. This information was processed using the IPAQ scoring protocols and participants were categorised into low, moderate and high activity groups.	Number of days of strenuous exercise per week
Diabetes status	**Yes** - Women who self-reported a history of diabetes during the brief computer-assisted interview. **No**- Women who did not report a history of diabetes at baseline	**Yes** - Women who either self-reported diabetes or indicated that they were receiving treated for diabetes. **No**- Women with no history of diabetes at baseline.

Variables	UK Biobank	Million Women Study
UK region	Ten UK regions where participants underwent baseline assessment	Ten regions of cancer registries at the time of recruitment
Deprivation score	This was based on Townsend deprivation index derived from each participant's postcode at recruitment.	Same as UK Biobank

Table 3-2: Baseline for analyses in the Million Women Study

Main exposure of interest	Baseline
BMI (kg/m^2) Smoking status	Date of completing the recruitment questionnaire OR 1 April 1997 for the small proportion of women in England (<5%) recruited into the study before hospital admissions records began.
Waist circumference (cm) Hip circumference (cm) Waist to hip ratio Waist to height ratio Number of cigarettes smoked per day Duration of smoking (years) Age at smoking initiation (years) Time since smoking cessation (years)	Date of completing the first resurvey questionnaire

Table 3-3: Regression dilution ratios for body size and composition measures among postmenopausal women in UK Biobank and the Million Women Study

	RDRs	
Body size/ composition variables	**UK Biobank**	**Million Women Study**
Height (cm)	0.98	-
Overall adiposity measures		
BMI (kg/m^2)	0.94	0.94
Weight (kg)	0.93	-
Body fat (%)	0.87	-
Fat mass (kg)	0.91	-
Central adiposity		
Waist circumference (cm)	0.87	0.86
Hip circumference (cm)	0.89	0.87
Waist to hip ratio	0.63	0.69
Waist to height ratio	0.88	0.86
Trunk fat (%)	0.83	-
Fat-free mass (kg)	0.91	-

RDRs for body size/composition measures in UK Biobank were calculated using data from 5,495 postmenopausal women with repeat measurements for all variables.
RDR for BMI in the Million Women Study was calculated using data from postmenopausal women with data on BMI both at recruitment and second resurvey (n = 362,836).
RDRs for waist circumference, hip circumference, waist to hip ratio and waist to height ratio were calculated using data from postmenopausal women who had data on these measures both at first and second resurvey (n = 182,843).

Table 3-4: Baseline characteristics of women in UK Biobank and the Million Women Study

Characteristics	UK Biobank (n = 196,074)	Million women Study (n=789,964)
Age at baseline (years), n (%)		
<50	52,412 (26.7)	18,696 (2.4)
50-<55	29,108 (14.9)	228,757 (29.0)
55 -<60	37,663 (19.2)	276,751 (35.0)
60 -<65	45,501 (23.2)	233, 839 (29.6)
≥65	31,390 (16.0)	31,921 (4.0)
Mean age at baseline, mean (SD)	*55.7 (8.2)*	*57.7 (4.7)*
BMI (kg/m^2)		
<18.5 (underweight)	1,431 (0.7)	7,903 (1.0)
18.5 -<25.0 (normal weight)	78,283 (39.9)	349,022 (44.2)
25.0-<30.0 (overweight)	70,383 (35.9)	264,313 (33.5)
≥30.0 (obese)	42,598 (21.7)	127,654 (16.2)
Missing	3,379 (1.7)	41,072 (5.1)
Mean (SD) BMI (kg/m^2) at baseline	*26.8 (5.1)*	*26.1 (4.6)*
Smoking status, n (%)		
Never	120,538 (61.5)	388,741 (49.2)
Past	58,273 (29.7)	207,874 (26.3)
Current	16,635 (8.5)	146,499 (18.6)
Missing	628 (0.3)	46,850 (5.9)
Menopausal status at baseline		
Premenopausal	58,377 (29.8)	70,229 (8.9)
Postmenopausal	137,697 (70.2)	719,735 (91.1)
Parity		
Nulliparous	38,929 (19.9)	92,011 (11.6)
1	26,563 (13.5)	101,416 (12.8)
2	85,118 (43.4)	329,899 (41.8)
≥3	45,312 (23.1)	263,695 (33.4)
Missing	152 (0.1)	2,943 (0.4)
Mean (SD) number of children (parous women only)	*2.2 (0.9)*	*2.4 (1.1)*
HRT (postmenopausal women)		
Never	76,913 (55.9)	417,039 (57.9)
Ever	60,422 (44.2)	295,171 (41.0)
Current	*50,668*	*126,828*
Past	*9,751*	*168,343*
Unknown	*3*	-
Missing	362 (<0.1)	7,525 (1.1)
Age at menarche (years)		
<13	72,135 (36.8)	282,454 (35.7)
13 -<15	85,798 (43.8)	354,943 (44.9)
≥15	32,141 (16.4)	138,682 (17.6)
Missing	6,000 (3.0)	13,885 (1.8)
Mean (SD) age at menarche	*13.0 (1.6)*	*13.1 (1.6)*

Characteristics	UK Biobank (n = 196,074)	Million women Study (n=789,964)
Age at menopause (years)		
<49	34,172 (24.8)	216,138 (30.0)
49-<52	37,985 (27.6)	224,194 (31.2)
52-<55	33,417 (24.3)	152,742 (21.2)
≥55	20,449 (14.8)	51,908 (7.2)
Missing	11,674 (8.5)	74,753 (10.4)
Mean (SD) age at menopause	*50.3 (4.5)*	*49.4 (4.2)*
Oral contraceptive use		
Never	36,134 (18.4)	349,231 (44.2)
Ever	159,477 (81.3)	434,171 (55.0)
Duration of use		
0-<5	*36,134*	*171,336*
5-<10	*35,109*	*114,039*
10-<15	*30,247*	*82,009*
≥15	*40,825*	*47,405*
Unknown	*17,162*	*19,382*
Missing	463 (0.3)	6,562 (0.8)
Physical activity		
Low	19,428 (9.9)	-
Moderate	69,466 (35.4)	-
High	57,543 (29.4)	-
Missing	49,637 (25.3)	
Frequency of strenuous exercise (number of days per week)		
Rare/never		373,023 (47.2)
<1	-	228, 236 (28.9)
≥1	-	159,022 (20.1)
Missing	-	29,683 (3.8)
Diabetes status, n (%)		
No	190,035 (96.9)	767,266 (97.1)
Yes	6,039 (3.1)	22,484 (2.9)
Missing	-	214 (<0.1)

Table 3-5: Association of current smoking with demographic and endometrial cancer risk factors among postmenopausal women in UK Biobank and the Million Women Study

Characteristics	Odds ratio (95%CIs) for current smoking			
	Number of women	UK Biobank	Number of women	Million Women Study
Age (years)				
<50	3,044	Referent	5,156	Referent
50-54	13,710	0.90 (0.82-1.01)	119,436	0.94 (0.89-1.00)
55-59	25,784	0.74 (0.67-0.82)	186,272	0.80 (0.75-0.85)
60-<65	29,668	0.70 (0.63-0.78)	155,779	0.59 (0.55-0.63)
≥65	20,560	0.59 (0.53-0.66)	20,220	0.34 (0.32-0.37)
P for trend	*92,766*	*0.88 (0.86-0.90)*	*486,863*	*0.94 (0.95-0.96)*
Deprivation score (Quintiles)				
1 (least deprived)	20,130	Referent	97,766	Referent
2	19,646	1.14 (1.06-1.22)	96,945	1.26 (1.23-1.29)
3	18,772	1.48 (1.38-1.60)	95,493	1.53 (1.50-1.57)
4	17,691	2.18 (2.03-2.34)	96,617	2.04 (2.00-2.09)
5 (most deprived)	16,428	4.13 (3.85-4.43)	96,456	3.32 (3.25-3.39)
Missing	99	1.42 (0.73-2.76)	3,586	1.53 (1.41-1.66)
Age at menarche (years)				
<13	35,086	Referent	173,240	Referent
13-<15	39,681	0.99 (0.95-1.04)	219,373	0.93 (0.92-0.94)
≥15	14,974	1.17 (1.10-1.24)	85,871	1.12 (1.10-1.14)
Missing	3,025	0.94 (0.83-2.76)	8,379	1.06 (1.01-1.12)
Parity				
Nulliparous	16,104	Referent	57,873	Referent
1	11,315	1.39 (1.29-1.49)	61,267	1.37 (1.33-1.41)
2	42,060	0.94 (0.88-0.99)	200,342	1.11 (1.09-1.14)
≥3	23,201	1.18 (1.10-1.26)	165,719	1.45 (1.41-1.48)
Missing	86	1.19 (0.64-2.24)	1,662	1.85 (1.67-2.06)
Oral contraceptive use				
Never	22,023	Referent	230,607	Referent
0-<5	18,121	1.31 (1.22-1.41)	100,305	1.25 (1.23-1.28)
5-<10	16,028	1.62 (1.51- 1.74)	64,910	1.39 (1.36-1.42)
10-<15	12,443	1.74 (1.61-1.87)	47,781	1.56 (1.53-1.60)
≥15	14,822	1.84 (1.71-1.98)	27,861	1.51 (1.46-1.55)
Ever users, missing duration	247	1.06 (0.70-1.58)	11,542	1.35 (1.29-1.40)
Missing	9,082	1.55 (1.42-1.68)	3,857	1.66 (1.55-1.78)

Characteristics	Odds ratio (95%CIs) for current smoking			
	Number of women	UK Biobank	Number of women	Million Women Study
HRT use				
Never	54,618	Referent	289,678	Referent
Past	31,785	1.44 (1.38-1.52)	82,249	1.12 (1.10-1.14)
Current	6,102	1.45 (1.34-1.57)	110,282	1.04 (1.03-1.06)
Missing	261	0.96 (0.66-1.40)	4,653	1.33 (1.25-1.42)
Age at menopause (years)				
<49	22,914	Referent	147,043	Referent
49-<52	25,804	0.73 (0.69-0.77)	152,363	0.64 (0.63-0.65)
52-<55	22,643	0.59 (0.56-0.63)	103,297	0.44 (0.43-0.45)
≥55	13,621	0.51 (0.47-0.55)	35,572	0.33 (0.32-0.34)
Missing	7,784	0.62 (0.57-0.67)	47,958	0.74 (0.73-0.76)
BMI (kg/m^2) categories				
Underweight	782	1.89 (1.57-2.27)	5,839	1.90 (1.79-2.01)
Normal weight	36,030	Referent	223,157	Referent
Overweight	34,362	0.94 (0.90-0.99)	160,568	0.81 (0.79-0.82)
Obese	19,951	0.76 (0.72-0.81)	72,562	0.61 (0.59-0.62)
Missing	1,641	1.00 (0.86-1.16)	24,737	0.94 (0.91-0.97)
Diabetes status				
No	89,395	Referent	473,584	Referent
Yes	3,371	1.00 (0.89-1.11)	13,161	0.93 (0.89-0.97)
Missing	-	-	118	1.43 (0.95-2.16)
Physical activity				
Low	8,562	Referent	-	-
Moderate	31,941	0.75 (0.69-0.80)	-	-
High	26,039	0.69 (0.54-0.75)	-	-
Missing	26,224	0.94 (0.87-1.01)	-	-
Frequency of strenuous activity				
Rarely/never	-	-	234,225	Referent
<1	-	-	140,186	0.57 (0.56-0.58)
≥1	-	-	94,464	0.59 (0.58-0.60)
Missing	-	-	17,988	1.41 (1.37-1.46)

Premenopausal women, past smokers and women with missing smoking status were excluded from these analyses.
Models were adjusted for UK regions and the other variables in the tables. Number of women included in UK Biobank analyses = 92,766. Number of women in the Million Women Study analyses = 486,863.

Table 3-6: Differences in BMI by demographics and endometrial cancer risk factors among postmenopausal women in UK Biobank and the Million Women Study

Characteristics	Differences in BMI associated with different factors			
	Number of women	UK Biobank	Number of women	Million Women Study
Age (years)				
<50	3,982	Referent	6,677	Referent
50-54	18,799	0.12 (-0.05, 0.29)	160,695	0.13 (0.02, 0.24)
55-59	37,063	0.10 (-0.06, 0.27)	262,818	0.15 (0.04, 0.26)
60-<65	44,731	0.14 (-0.02, 0.31)	221,164	0.10 (-0.01, 0.21)
≥65	30,685	0.07 (-0.10, 0.23)	30,249	-0.49 (-0.61, -0.37)
Per unit increase	135,260	-0.00 (-0.01, 0.02)		-0.01 (-0.02, -0.01)
Smoking status				
Never	80,388	Referent	332, 487	Referent
Past	43,687	0.49 (0.43, 0.54)	180,992	0.54 (0.52, 0.57)
Current	10,693	-0.57 (-0.67, -0.48)	129,122	-0.95 (-0.98, -0.92)
Missing	492	0.69 (0.26, 1.11)	39,002	0.34 (0.29, 0.38)
Deprivation score				
1 (least deprived)	28,120	Referent	136,533	Referent
2	28,138	0.20 (0.12, 0.28)	136,192	0.25 (0.22, 0.28)
3	27,566	0.45 (0.37, 0.53)	135,064	0.43 (0.40, 0.47)
4	26,488	0.81 (0.73, 0.89)	135,852	0.75 (0.72, 0.79)
5 (most deprived)	24,812	1.55 (1.47, 1.64)	132,991	1.23 (1.20, 1.27)
Missing	136	1.02 (0.22, 1.82)	4,971	0.54 (0.41, 0.66)
Age at menarche (years)				
<13	50,797	Referent	242,328	Referent
13-<15	58,448	-1.11 (-1.17, -1.05)	307,173	-1.07 (-1.09, -1.04)
≥15	21,928	-1.49 (-1.57, -1.42)	120,832	-1.57 (-1.60, -1.54)
Missing	4,087	-1.01 (-1.17, -0.86)	11,270	-0.76 (-0.84, -0.68)
Parity				
Nulliparous	22,920	Referent	80,617	Referent
1	17,145	0.36 (0.27, 0.46)	87,888	0.23 (0.19, 0.27)
2	61,382	0.31 (0.23, 0.38)	281,673	0.30 (0.27, 0.34)
≥3	33,701	0.72 (0.64, 0.81)	229,024	0.89 (0.86, 0.93)
Missing	112	0.26 (-0.63, 1.15)	2,401	0.44 (0.26, 0.62)
Oral contraceptive use / duration of use (years)				
Never	29,031	Referent	314,195	Referent
0-<5	26,444	-0.18 (-0.26, -0.10)	142,597	-0.16 (-0.19, -0.13)
5-<10	24,146	-0.27 (-0.35, -0.18)	93,746	-0.26 (-0.30, -0.23)
10-<15	19,268	-0.29 (-0.38, -0.20)	69,830	-0.39 (-0.43, -0.36)
≥15	22,562	-0.37 (-0.46, -0.28)	40,092	-0.50 (-0.55, -0.46)
Ever users, missing duration	308	-0.74 (-1.28, -0.20)	15,623	0.13 (0.06, 0.20)
Missing	13,501	-0.30 (-0.40, -0.20)	5,520	0.14 (0.03, 0.26)

Characteristics	Differences in BMI associated with different factors			
	Number of women	UK Biobank	Number of women	Million Women Study
HRT use				
Never	75,536	Referent	393,615	Referent
Past	49,763	-0.02 (-0.08, 0.04)	120,550	0.01 (-0.02, 0.04)
Current	9,606	-1.00 (-1.10, -0.89)	160,806	-0.83 (-0.85, -0.80)
Missing	359	0.21 (-0.29, 0.72)	6,632	-0.10 (-0.21, 0.00)
Age at menopause (years)				
<49	33,488	Referent	204,029	Referent
49-<52	37,376	-0.22 (-0.29, 0.15)	213,038	0.07 (0.04, 0.09)
52-<55	32,859	-0.05 (-0.13, 0.02)	145,832	0.30 (0.27, 0.33)
≥55	20,108	0.43 (0.34, 0.52)	49,239	0.76 (0.72, 0.81)
Missing	11,429	0.08 (-0.02, 0.19)	69,464	0.32 (0.28, 0.36)
Diabetes status				
No	130,351	Referent	661,734	Referent
Yes	4,909	4.61 (4.47, 4.75)	19,676	3.39 (3.33-3.45)
Missing		-	193	0.60 (-0.03, 1.22)
Physical activity				
Low	12,510	Referent	-	-
Moderate	46,751	-1.50 (-1.59, -1.41)	-	-
High	38,798	-2.18 (-2.28, -2.09)	-	-
Missing	37,201	-0.91 (-1.01, -0.81)	-	-
Frequency of strenuous activity				
Rarely/never		-	323,166	Referent
<1		-	196,187	-0.84 (-0.86, -0.81)
≥2		-	138,091	-1.43 (-1.46, -1.41)
Missing		-	24,159	-0.48 (-0.54, -0.43)

Premenopausal women, women with missing BMI and women with BMI <16 or >60 kg/m^2 were excluded from these analyses.
Number of women included in the UK Biobank analyses = 135,260.
Number of women in the Million Women Study analyses = 681,603.
Models were adjusted for UK regions and for other variables in the table.

Table 3-7: Differences in standardised values of adiposity measures associated with current vs never smoking

Adiposity measure	Differences in standardised values of adiposity measures in current vs never smokers	
	UK Biobank	Million Women Study
Overall adiposity		
BMI (kg/m^2)	-0.11 (-0.13, -0.09)	-0.20 (-0.21, -0.19)
Weight (kg)	-0.10 (-0.12, -0.08)	-
Body fat (%)	-0.12 (-0.14, -0.10)	-
Fat mass (kg)	-0.11 (-0.13, -0.09)	-
Central adiposity		
Waist circumference (cm)	0.04 (0.02, 0.06)	-0.16 (-0.17, -0.15)
Hip circumference (cm)	-0.17 (-0.19, -0.15)	-0.30 (-0.31, -0.29)
Waist to hip ratio	0.26 (0.24, 0.28)	0.04 (0.03, 0.05)
Waist to height ratio	0.03 (0.01, 0.05)	-0.16 (-0.17, -0.15)
Trunk fat (%)	-0.13 (-0.15, -0.11)	-

In UK Biobank, 135,151 postmenopausal women were included in these analyses.
In the Million Women Study, 681,603 postmenopausal women were included in the analysis of cross-sectional association of smoking with BMI, 343,484 postmenopausal women who participated in the first resurvey were included in the analyses of cross-sectional associations of central adiposity measures with smoking.
Models were adjusted for age, oral contraceptive use, diabetes, physical activity, deprivation score, parity, age at menarche, UK region, age at menopause and HRT use.
To obtain the values in the original scale of adiposity measures, differences have to be multiplied by standard deviation of the respective adiposity measures.
In UK Biobank, SDs were 5.0 kg/m2 for BMI, 13.5 kg for weight, 6.7 for body fat percentage, 9.7 kg for fat mass, 12.3 cm for waist circumference, 10.1 cm for hip circumference, 0.07 for waist to hip ratio, 0.08 for waist to height ratio, 7.6 for trunk fat percentage, 4.8 kg for fat-free mass and 6.2 cm for height.
In the Million Women Study, SDs were 4.6 kg/m^2 for BMI, 9.3 cm for waist circumference, 7.5 cm for hip circumference, 0.06 for waist to hip ratio and 0.06 for waist to height ratio.

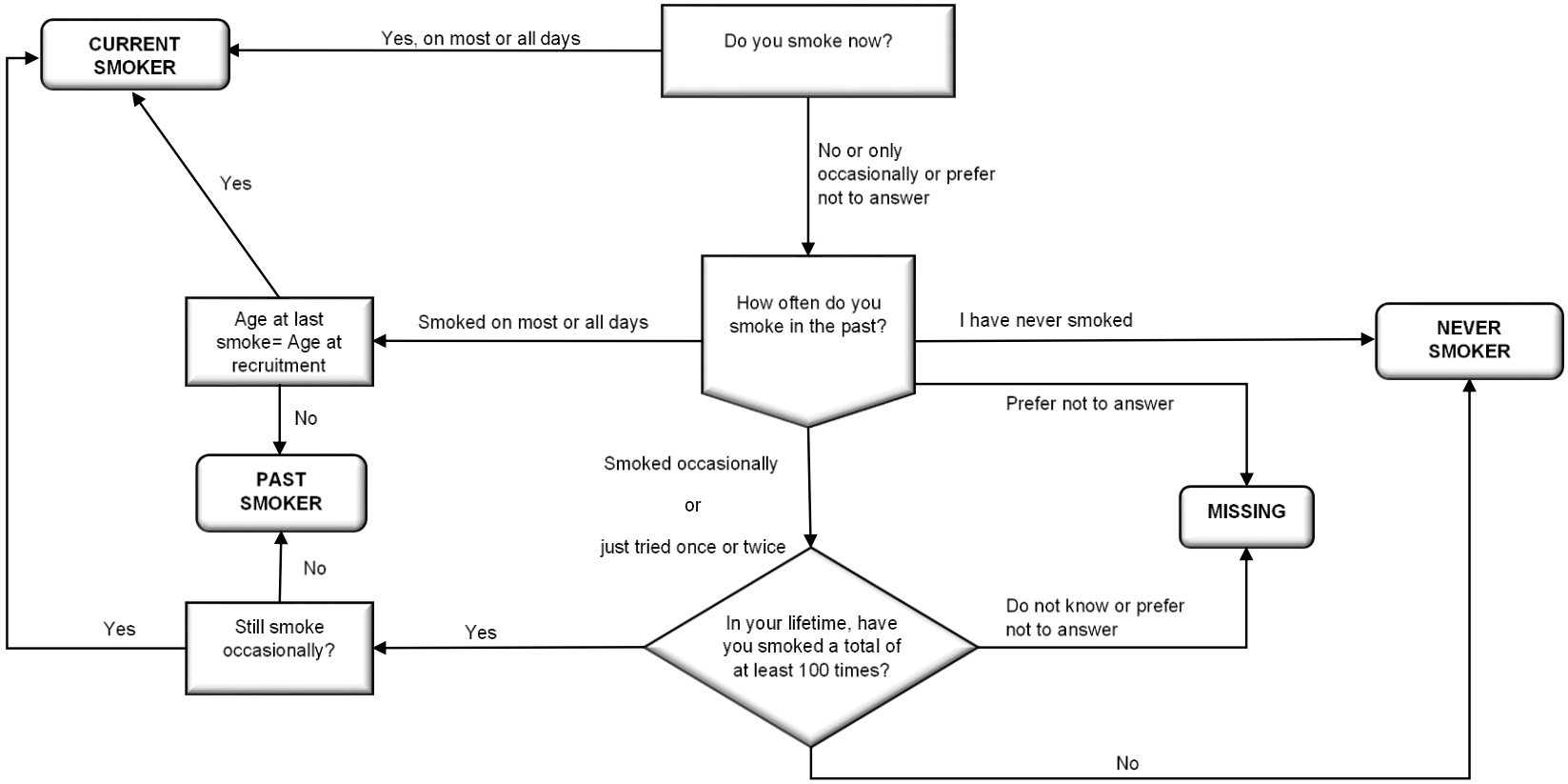


Figure 3-1: Algorithm for defining smoking status in UK Biobank

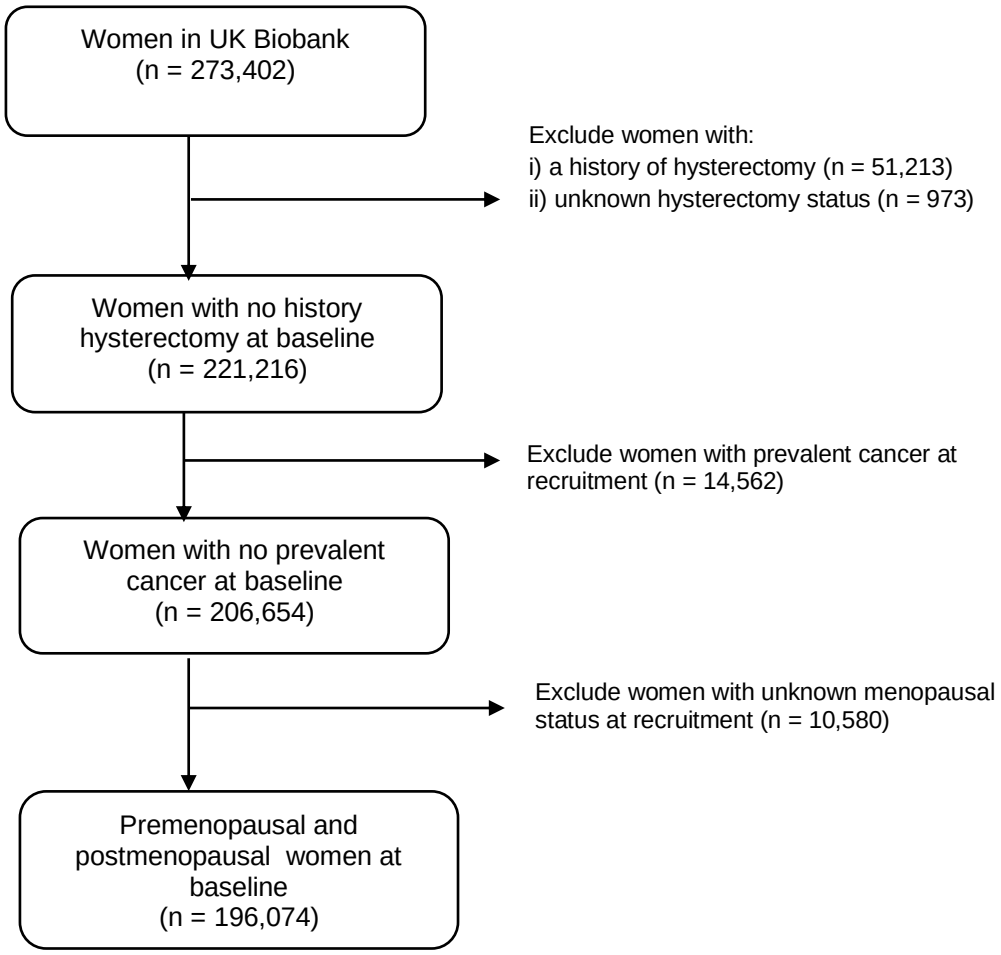


Figure 3-2: General exclusions in UK Biobank

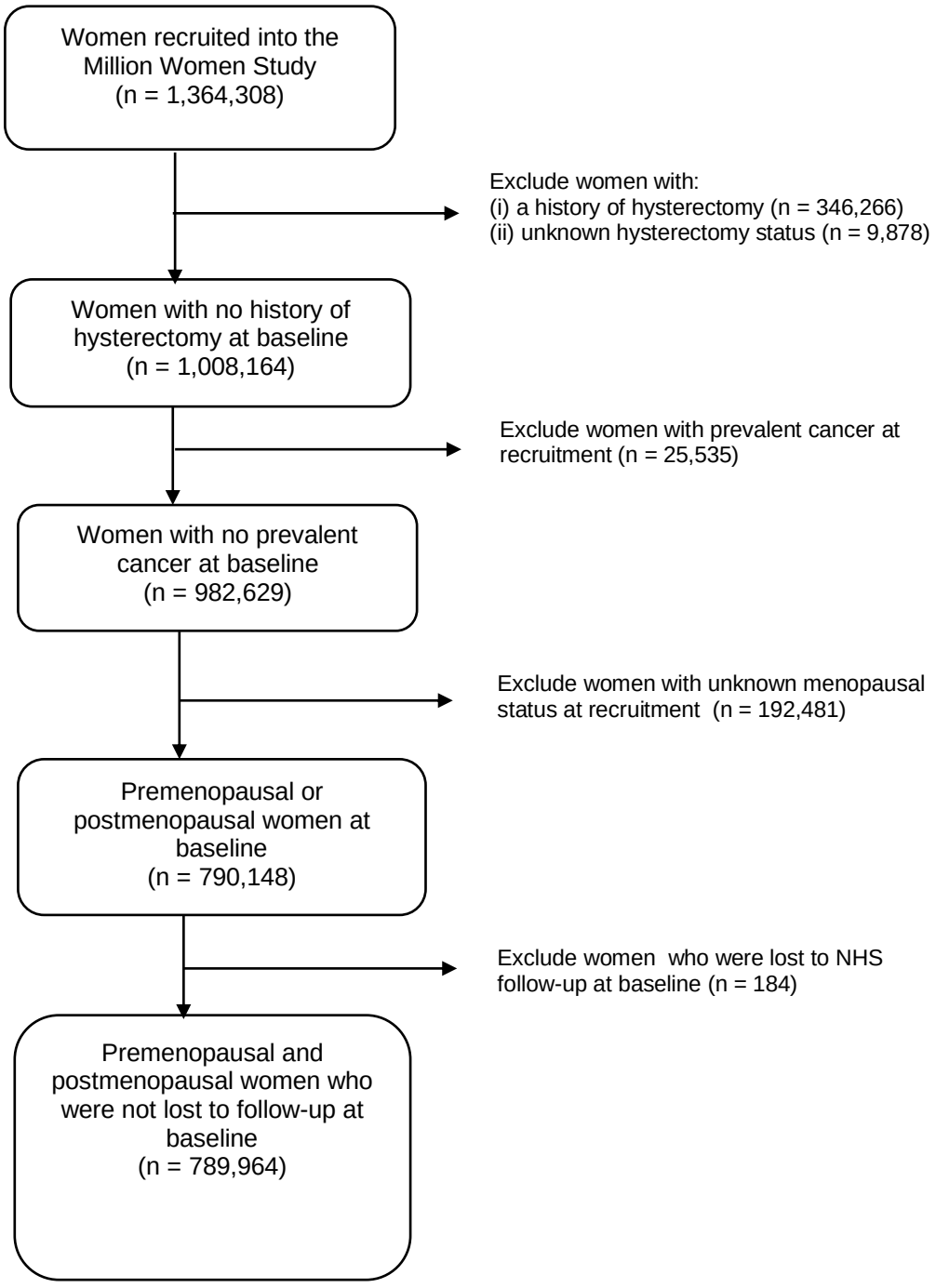


Figure 3-3: General exclusions in analyses based on the recruitment cohort of the Million Women Study

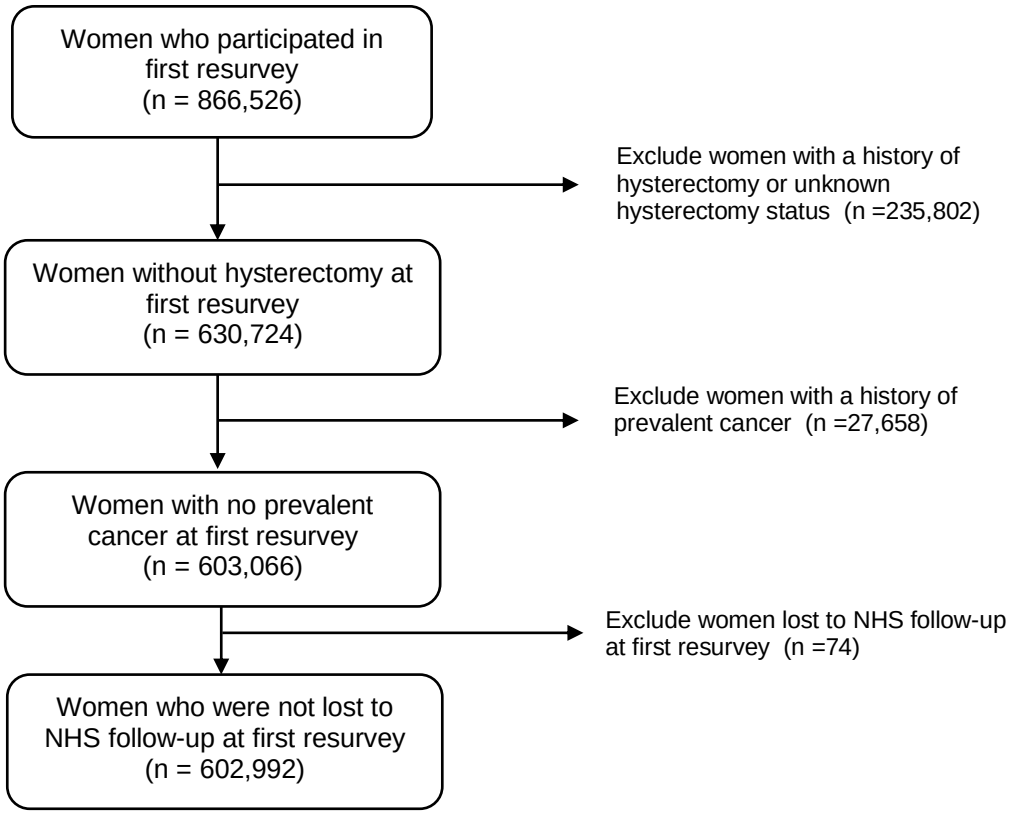


Figure 3-4: General exclusions in analyses from first resurvey in the Million Women Study

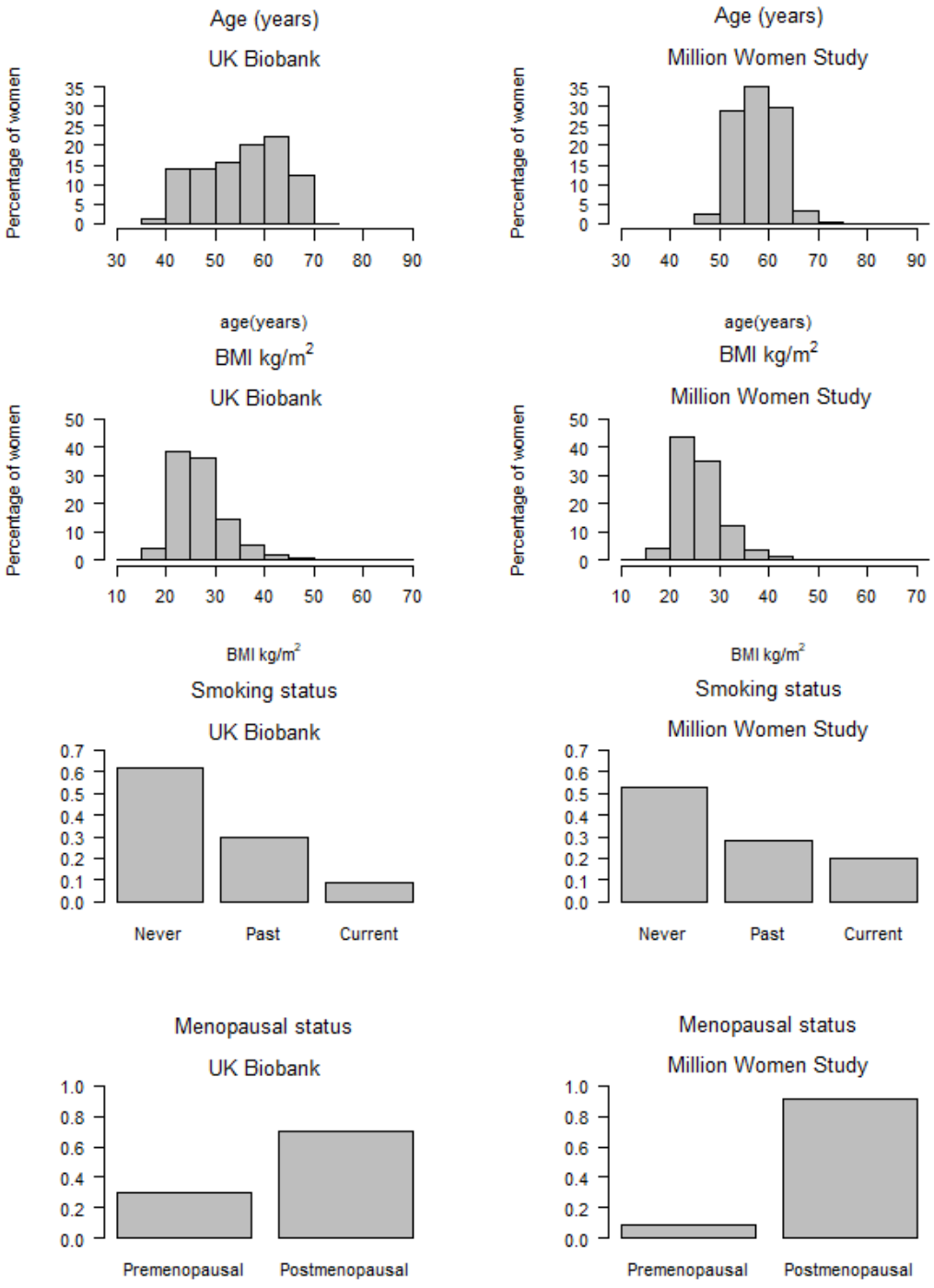


Figure 3-5: Distribution of age, BMI, smoking and menopausal status in UK Biobank and the Million Women Study

Chapter 4: Associations of body size and body composition measures with endometrial cancer risk

Summary

The association between adiposity and endometrial cancer risk is well established. However, uncertainty remains regarding whether more specific indices of adiposity (body fat percentage and fat mass) are better indicators of risk than body mass index (BMI) and whether central adiposity contributes to risk independently of overall adiposity. The current study examines the associations of different indices of body size and body composition with endometrial cancer risk using data from UK Biobank. Hazard ratios (HRs) and 95% confidence intervals (CIs) for endometrial cancer associated with different measures of body size and composition were estimated using Cox regression models. The effects of adjustment for potential mediating factors on the associations with adiposity measures were also assessed. Among 135,110 postmenopausal women, 706 incident endometrial cancers were diagnosed during a mean follow-up of 6.8 years. Endometrial cancer risk increased with increasing adiposity, regardless of index used. The magnitude of association with BMI ($HR_{per\ 1\text{-}SD\ increment}$ = 1.71, 95%CI: 1.61-1.82) was broadly comparable to those of body fat percentage ($HR_{per\ 1\text{-}SD\ increment}$ = 1.92; 95%CI: 1.75-2.11) and fat mass ($HR_{per\ 1\text{-}SD\ increment}$ = 1.73, 95%CI: 1.63-1.85) derived from bioimpedance analysis. The associations with central adiposity measures were attenuated after adjustment for BMI, although waist circumference and waist to hip ratio remained modestly associated with risk

($HR_{\text{per 1-SD increment in waist circumference}}$ = 1.08, 95%CI: 1.00-1.17; $HR_{\text{per 1-SD increment in waist to hip ratio}}$ = 1.13, 95%CI: 1.01-1.26). Adjustment for C-reactive protein (CRP) or calculated free testosterone slightly attenuated the associations of BMI and other overall adiposity measures with risk, suggesting that inflammation and alterations in free testosterone levels may explain in part the association of overall adiposity with endometrial cancer risk. In summary, body fat percentage and fat mass derived from bioimpedance analysis are not better indicators of endometrial cancer risk than BMI. Central adiposity, as reflected by waist circumference and waist to hip ratio, may be associated with endometrial cancer risk independently of BMI.

4.1. Introduction

Body mass index (BMI) is the most often used index of adiposity in studies assessing the well-known positive association between overall adiposity and endometrial cancer risk.[16,17,26,28,31,32,34,146,311] However, BMI may not accurately reflect adiposity-related risk of endometrial cancer because of its inability to distinguish fat from fat-free mass.[40] Bioimpedance analysis, a more recent technique for body composition assessment, yields more specific indices of adiposity (such as body fat percentage and fat mass, see section 2.3.1.1).[312] Limited data exist on the relationship between measures of fat obtained from bioimpedance analysis and endometrial cancer risk, and it is not known whether these measures are better indicators of risk than BMI.

The role of body fat distribution, particularly central adiposity, in endometrial cancer development is unclear. Studies that have examined indirect measures of central adiposity, such as waist circumference and waist to hip ratio, in relation to endometrial cancer risk have reported either positive[16,25,38] or null associations[18,29,36,37,51,157] after accounting for BMI. These inconsistencies in epidemiological findings may be due in part to methodological issues such as: use of self-reported anthropometric data, which may lead to misclassification of fat distribution patterns; failure to account for regression dilution bias, which may obscure true associations between a risk factor and disease; and limited statistical power to detect modest associations.

The mechanisms underlying the association of adiposity with endometrial cancer risk are not well understood. Proposed pathways include alterations in levels of endogenous hormones, hyperinsulinaemia/insulin resistance and inflammation.[53,313–315] Because previous prospective studies often lack measurement of biomarkers, it is unclear how much of the association of adiposity with endometrial cancer risk is accounted for by potential mediating factors associated with these pathways.

In addition to adiposity, other indices of body size and composition may also influence endometrial cancer risk. Height, a marker of early life and nutritional factors, has been associated with the risk of endometrial cancer in some studies[23,287–290] but not others.[25,39,134,147,316,317] One prospective study reported an increased risk of endometrial cancer with higher fat-free mass; however, it is unclear whether this association was independent of BMI.[141]

The current study examines the associations of different measures of body size and body composition with the risk of endometrial cancer in a large population-based cohort. The specific objectives are:

(i) To assess whether more specific indices of overall adiposity (body fat percentage and fat mass) obtained from bioimpedance analysis are more strongly related to endometrial cancer risk than traditional adiposity metrics (BMI and weight).
(ii) To examine whether central adiposity (assessed by waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage) is associated with endometrial cancer risk independently of BMI.

(iii) To assess the extent to which various hormonal and metabolic biomarkers, namely albumin, glucose, glycated haemoglobin (HbA1c), insulin-like growth factor 1 (IGF-1), C-reactive protein (CRP), testosterone and free-testosterone, explain the associations of overall and central adiposity with endometrial cancer risk.

(iv) To investigate whether height and fat-free mass are determinants of endometrial cancer risk.

4.2. Methods

4.2.1. Analytical cohort

Of the 196,074 UK Biobank women eligible for inclusion in this analysis (see section 3.4.1 and figure 3.2), 3,610 women were excluded because they had missing data on body size/composition and another 60 women were excluded because they had extreme values of BMI (<16 or >60 kg/m^2) (figure 4-1).

4.2.2. Exposure assessment

The methods used for the measurements of body size and body composition variables in UK Biobank have been described in detail in chapter 3 (section 3.1.2.2). Height, weight, waist circumference and hip circumference were measured by trained personnel according to standard protocols. Body composition was measured by bioimpedance analysis using the Tanita BC-418MA segmental body composition analyser. BMI was calculated as weight (kg) divided by the square of height (m). Waist to hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm), and waist to

height ratio was calculated as waist circumference (cm) divided by height (cm).

4.2.3. Assessment of covariates

Data on age, menopausal status, oral contraceptive use, parity, age at menarche, age at menopause, menopausal HRT use, smoking status, physical activity and diabetes were derived from the baseline questionnaire (see section 3.3 for definitions of these variables). Albumin, glucose, HbA1c, IGF-1, CRP and testosterone were measured from blood samples collected at recruitment (see section 3.1.2.3). Serum concentrations of free testosterone were calculated from testosterone and SHBG using an equation derived from the law of mass action.[318–320]

4.2.4. Outcome ascertainment

Participants were followed for incident cancers through record linkage with the NHS Central Registers (see section 3.1.3). The cancer registers provided information on the date of cancer diagnosis, site and histology. The site of cancer was coded using the International Classification of Diseases and related Health Problems tenth revision (ICD-10). Incident endometrial cancer was defined as ICD-10 code C54.

4.2.5. Statistical analyses

All analyses were performed separately for premenopausal and postmenopausal women. Age-adjusted Pearson's partial correlation coefficients were used to assess the relationships between body size and

body composition variables, and to evaluate the relationships between indices of adiposity and the biomarkers of interest.

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for endometrial cancer associated with each body size/composition variable were estimated using Cox regression models, with time in study as the underlying time metric. Women contributed person-time to these analyses from the date of baseline assessment to the end of follow-up for this analysis (31 October 2015 for participants in Scotland and 31 March 2016 for participants in England and Wales) or until they were censored due to any invasive cancer (except non-melanoma skin cancer, ICD-10 code: C44), hysterectomy or death, whichever came first. For analyses in premenopausal women, participants only contributed person-time up to the day they turned 55 years and were censored thereafter.

Each body size/composition variable was categorised into quartiles of the baseline distribution in the study population. HRs were estimated for each quartile, with the lowest quartile as the referent category. To allow for valid comparisons between any two groups even if neither is the referent category, group-specific confidence intervals (gsCIs) for the HRs were calculated and presented in tables and figures.[321] However, conventional 95%CIs are provided in the texts when comparison is made between two categories. Tests for trend were performed by assigning repeat assessment median values (an estimate of the usual long-term value within each category) to ordinal categories and modelling these values as a continuous variable. To

account for measurement error, the HRs based on baseline quartiles were plotted against the repeat assessment mean values within each category.[308]

Hazard ratios for endometrial cancer corresponding to one standard deviation (1-SD) increment in each measure were also estimated to facilitate comparison across adiposity measures. To correct for regression dilution bias and obtain risk estimates for the association between usual levels of each body size/composition variable and endometrial cancer risk, the log HR per 1-SD increment in each measure and the corresponding standard error were multiplied by the reciprocal of the relevant regression dilution ratio (see section 3.4.3).[309]

To assess whether the variation in endometrial cancer risk explained by adiposity varies with the measure used, the likelihood ratio χ^2 statistics for the Cox models estimating HR per 1-SD increment in the different adiposity measures were compared.[322] All models were stratified by year of birth ($\leq$1940, 1941-1945, 1946-1950, 1951-1955, 1956-1960, 1961-1965, $\geq$1966) and year of recruitment ($\leq$2007, 2008, 2009, 2010) and adjusted for age (continuous), quintiles of Townsend deprivation score and UK regions (10 regions). Additional adjustments were made for duration of oral contraceptive use (never, 0-<5, 5-<10, 10-<15, $\geq$15 years), physical activity (low, moderate, high), parity (0, 1, 2, $\geq$3), age at menarche (<13, 13-<15, $\geq$15 years) diabetes status (no, yes) and smoking status (never, past and current). Models for postmenopausal women were additionally adjusted for age at menopause (<49, 49-<52, 52-<55, $\geq$55 years) and HRT status (never, past, current). For each covariate, missing values were assigned to a separate category.

Models for central adiposity measures and fat-free mass were further adjusted for BMI using the residual method in order to assess the independent associations of these exposures with risk.[323] For this analysis, residuals for each central adiposity measure (or fat-free mass) were computed from a linear regression of that variable on BMI. These residuals (categorised into quartiles or standardised to 1-SD units) were examined in relation to endometrial cancer risk in multivariable Cox models, which were further adjusted for BMI. The association of fat-free mass with risk was also adjusted for fat mass instead of BMI. However, other impedance measures were not adjusted for each other because of their high correlations (tables 4-2 and 4-3).

To assess the extent to which selected biomarkers might account for the association between adiposity and endometrial cancer risk, HRs for endometrial cancer per 1-SD increment in each adiposity measure were estimated with and without adjustment for each biomarker. To facilitate comparison between the HRs (adjusted and unadjusted for biomarker), the analysis for each biomarker was limited to women with data on the relevant biomarker. All biomarkers were log-transformed to normalise their distributions and modelled as a continuous variable.

Several sensitivity analyses were performed. First, the association of each body size/composition variable with type I endometrial cancer risk was examined because of previous studies suggesting differences in the associations of adiposity measures with endometrial cancer risk by tumour subtypes.[56,86] For this analysis, women who developed type II tumours or

other types of endometrial cancer were censored at the date of diagnosis. There were too few cases of type II endometrial cancers (n = 79) to allow for any meaningful analyses of associations with this subtype in this cohort. Second, analyses in postmenopausal women were repeated after restricting the dataset to never HRT users, since HRT use is known to attenuate the relationship between adiposity and endometrial cancer risk (section 2.3.3.4).[152] Third, associations of central adiposity measures and fat-free mass with endometrial cancer risk were adjusted for BMI using the standard method i.e. with BMI (continuous) included as a covariate in models evaluating the association of central adiposity measures with risk. Finally, standard WHO categories were used for BMI (<25.0, 25.0-<30.0, 30.0-<35.0, ≥35.0 kg/m^2), waist circumference (<80, 80-88, ≥88 cm) and waist to hip ratio (<0.85, ≥0.85) to enable comparison with other study populations.

The proportional hazard assumption for each of the Cox model was tested using log-log plots and tests based on Schoenfeld residuals. All analyses were performed using STATA version 15.0.

4.3. Results

4.3.1. Baseline characteristics

After all exclusions (figure 4-1), 57,294 premenopausal women and 135,110 postmenopausal women were included in the analyses, with mean (SD) ages at baseline of 45.8 (3.6) years and 59.9 (5.4) years, respectively. The baseline characteristics of participants according to menopausal status and quartiles of BMI are shown in table 4-1. For both premenopausal and

postmenopausal women, those in the highest quartile of BMI were more likely to have an earlier age at menarche and to report a history of diabetes compared with those in the lowest quartile. For postmenopausal women, those in the highest quartile of BMI were less likely to be nulliparous, ever users of oral contraceptives or current smokers compared with those in the lowest quartile. With the exception of height, the mean values of all body size and body composition measures increased in parallel with increasing BMI (table 4-1).

During a mean follow-up of 6.1 years per woman, 57 incident cases of endometrial cancer were identified among premenopausal women, with a mean (SD) age at diagnosis of 51.2 (3.3) years. Among postmenopausal women, 706 incident endometrial cancers were identified during a mean follow-up of 6.8 years per woman, with a mean age at diagnosis of 65.5 (5.3) years.

4.3.2. Correlations between measures

The age-adjusted partial correlation coefficients between the various body size and composition measures in premenopausal and postmenopausal women are shown in table 4-2 and table 4-3, respectively. In both premenopausal and postmenopausal women, all adiposity measures were correlated with each other. BMI was highly correlated with body fat percentage ($r \geq 0.85$) and fat mass ($r = 0.94$), suggesting that these measures are not providing information that differs substantially from BMI. All central adiposity measures were positively correlated with each other and with measures of overall adiposity ($r > 0.40$). Fat-free mass was correlated to

varying degree with all measures of adiposity (r >0.25). Height was not correlated with body fat percentage (r <0.05), waist circumference (r <0.06) and waist to hip ratio (r <-0.10) but showed weak correlations with other measures of adiposity (tables 4-2 and 4-3).

As expected, the residuals for central adiposity measures and fat-free mass used in models assessing the independent associations of these measures with risk were not correlated with BMI (table 4-4). Age-adjusted partial correlation coefficients for the relationships between adiposity measures and serum biomarkers among postmenopausal women are shown in table 4-5. In general, adiposity measures showed positive correlations with glucose, HbA1c, CRP and calculated free testosterone, but negative correlations with IGF-1 and albumin.

4.3.3. Associations with premenopausal endometrial cancer

Table 4-6 shows the associations of overall adiposity measures and height with the risk of premenopausal endometrial cancer (i.e. endometrial cancer diagnosed before age 55 years). The associations of measures of central adiposity and fat-free mass with premenopausal endometrial cancer risk are shown in table 4-7. There was no association between any measure of adiposity and premenopausal endometrial cancer risk, although this was based on a small number of incident endometrial cancers (n = 57). Height and fat-free mass were also not associated with endometrial cancer risk in these women (tables 4-6 and 4-7).

4.3.4. Associations with postmenopausal endometrial cancer

4.3.4.1. Overall adiposity and height

Table 4-8 and figure 4-2 show the associations of overall adiposity indices and height with endometrial cancer risk in postmenopausal women. All measures of overall adiposity (BMI, weight, body fat percentage and fat mass) were positively associated with endometrial cancer risk in an approximately linear fashion (P_{trend} <0.0001). After adjusting for all important confounders (detailed in section 4.2.5), the HRs (95%CIs) for endometrial cancer associated with the highest vs lowest quartiles of BMI, weight, body fat percentage and fat mass were 3.45 (2.71-4.40), 3.73 (2.92-4.76), 3.70 (2.87-4.77) and 4.03 (3.12-5.20), respectively.

The HRs (95%CIs) per 1-SD increment in these measures were broadly comparable, being 1.71 (1.61-1.82), 1.70 (1.60-1.81), 1.92 (1.75-2.11) and 1.73 (1.63-1.85) for BMI, weight, body fat percentage and fat mass, respectively. However, in terms of χ^2 statistics, BMI appeared to be the most informative marker (χ^2 statistics for models with BMI, weight, body fat percentage and fat mass were 509, 499, 456 and 501, respectively). Height was not associated with endometrial cancer risk among postmenopausal women in this study (P_{trend} >0.50, table 4-8).

4.3.4.2. Central adiposity measures and fat-free mass

All central adiposity measures (waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage) showed strong positive associations with endometrial cancer risk among postmenopausal women (P_{trend} <0.0001;

table 4-9 and figure 4-3). In models adjusted for all confounders (except BMI), the HRs (95%CIs) for endometrial cancer associated with the highest vs lowest quartiles of waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage were 3.67 (2.90-4.66), 2.23 (1.78-2.80), 3.43 (2.73-4.30) and 3.24 (2.53-4.14), respectively. The HRs (95%CIs) per 1-SD increment in waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage were broadly comparable to those of overall adiposity measures (table 4-7). However, in terms of χ^2 statistics, these measures were not as informative as BMI (χ^2 statistics values varied from 321 for the model with waist to hip ratio to 477 for the model with waist circumference).

Further adjustment for BMI (using the residual method) attenuated the associations of all central adiposity measures with endometrial cancer risk, although a small positive association remained for waist circumference (HR=1.08, 95%CI: 1.00-1.17) and waist to hip ratio (HR=1.13, 95%CI: 1.01-1.26), suggesting that these measures may contribute to risk independently of BMI (table 4-9). In contrast, adjustment for central adiposity measures had a relatively small effect on the risk estimates for the association between BMI and endometrial cancer risk (table 4-10).

Hip circumference and fat-free mass were also positively associated with endometrial cancer risk among postmenopausal women, with multivariable-adjusted HRs (95%CIs) of 2.89 (2.31-3.63) and 2.70 (2.16-3.37), respectively, for those in the highest quartile compared with those in the lowest quartile of these measures (P_{trend} <0.0001, table 4-9). However, these associations were completely attenuated after further adjustment for BMI

(P_{trend} >0.20; table 4-9). Adjustment of the association between fat-free mass and endometrial cancer for fat mass (instead of BMI) produced similar results to that of BMI-adjusted models (P_{trend} = 0.24, appendix 4).

4.3.4.3. Effects of adjustment for selected biomarkers

The effects of adjustment for various biomarkers on the associations of overall and central adiposity measures with risk are shown in table 4-11 and table 4-12. The number of women included in the analyses varied between biomarkers; therefore, the HRs associated with a 1-SD increment in each adiposity measure varied according to which biomarker was examined. Adjustment for CRP or calculated free testosterone resulted in a slight reduction in the HRs associated with overall adiposity measures. For example, the HRs (95%CIs) for endometrial cancer per 1-SD increment in BMI were 1.72 (1.60-1.84) and 1.63 (1.51-1.77) before and after adjustment for CRP; and 1.73 (1.61-1.86) and 1.61 (1.49-1.74) before and after adjustment for calculated free testosterone (table 4-11). Adjustment for glucose, HbA1c, IGF-1 or albumin did not appreciably alter the associations of overall adiposity measures with endometrial cancer risk (table 4-11). The BMI-adjusted HRs associated with a 1-SD increment in central adiposity measures were not meaningfully altered after further adjustment for each biomarker (table 4-12).

4.3.4.4. Sensitivity analyses

The majority of incident endometrial cancers in this cohort were type I tumours (79%). In sensitivity analyses restricted to outcomes of this subtype

(n = 558), the associations of adiposity measures with risk were slightly strengthened, although the overall pattern of associations remained unchanged (table 4-13). Similarly, restricting the analysis to postmenopausal never HRT users (n = 75,448) did not alter the overall pattern of the associations (table 4-14). Results from analysis that used the standard method to adjust for BMI did not differ substantially from that of the main analysis (table 4-15). Table 4-16 shows the results for analyses using standard WHO categories of BMI, waist circumference and waist to hip ratio. Compared with women with BMI values below 25 kg/m^2, those with a BMI of 25-<30 kg/m^2, 30-<35 kg/m^2 and $\geq$35 kg/m^2 had HRs (95%CIs) of 1.64 (1.33-2.02), 2.46 (1.95-3.11) and 5.92 (4.68-7.49), respectively. In models adjusted for BMI, compared with women with a waist circumference of 80 cm or less, those with a waist circumference of 88 cm or higher had a HR (95%CI) of 1.37 (1.05-1.74) (table 4-16).

4.4. Discussion

In the current study, BMI, bioimpedance-derived indices of fat and central adiposity measures showed comparable positive associations with postmenopausal endometrial cancer risk. The associations with central adiposity measures were substantially attenuated after adjustment for BMI, although waist circumference and waist to hip ratio remained modestly associated with risk. Adjustment for CRP or calculated free testosterone slightly attenuated the associations of overall adiposity measures with postmenopausal endometrial cancer risk.

To my knowledge, this is the first study to compare anthropometric and bioimpedance-derived measures of adiposity in relation to endometrial cancer risk in premenopausal and postmenopausal women separately. There was no relationship between any index of adiposity and endometrial cancer risk in premenopausal women. This lack of association is most likely due to limited statistical power resulting from a small number of incident premenopausal endometrial cancers, as previous research has shown that adiposity also increases the risk of developing premenopausal endometrial cancer.[16,248] By contrast, among postmenopausal women, endometrial cancer risk clearly increased with increasing adiposity, regardless of which adiposity measure was used. The magnitude of association with BMI was not materially different from those of body fat percentage and fat mass, which are considered to be more precise indices of overall adiposity. These results suggest that bioimpedance analysis has no advantage over BMI when it comes to assessing endometrial cancer risk. As bioimpedance analysis is more expensive and cumbersome to use in large population studies, these findings provide support for the continued use of BMI in epidemiology studies assessing endometrial cancer risk.

There was no relationship between fat-free mass and endometrial cancer risk in this study. This finding suggests that fat mass is the aspect of body composition that is most relevant to endometrial carcinogenesis. Height was also not associated with endometrial cancer risk in this cohort which is consistent with results from some studies[25,39,134,147,316,317] but not others.[23,287–290]

Evidence regarding the independent effect of central adiposity on endometrial cancer risk is conflicting. In the current study, central adiposity, as measured by waist circumference and waist to hip ratio, slightly increased the risk of postmenopausal endometrial cancer independently of BMI. This agrees with results from the California Teachers' Study, which found a positive association with both waist circumference and waist to hip ratio among postmenopausal never HRT users after adjustment for BMI.[38] In contrast, the Nurses' Health Study reported null associations with both measures after adjusting for BMI.[157] The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and a meta-analysis published in 2015 observed a positive association, that was independent of BMI, for waist circumference but not waist to hip ratio.[16,25] The only study, to my knowledge, which explored associations with waist to hip ratio using Mendelian randomisation analysis, found no evidence to support an association between waist to hip ratio and endometrial cancer risk.[148]

The association between adiposity and postmenopausal endometrial cancer risk is largely attributed to an increase in oestrogen bioavailability, resulting in part from a greater conversion of androstenedione to oestrogen in the adipose tissue and a decrease in SHBG levels.[53] Consistent with this, studies have shown that the association between BMI and endometrial cancer risk is partly attenuated after adjustment for oestradiol.[224,315] Oestrogen promotes endometrial carcinogenesis by stimulating endometrial cell proliferation.[53] Hyperinsulinaemia/insulin resistance may also link adiposity with endometrial cancer risk.[53] Insulin could influence endometrial

carcinogenesis directly through its mitogenic effects or indirectly by increasing bioavailability of IGF-1.[53] Another mechanism that could explain the relationship between adiposity and endometrial cancer risk is inflammation.[314] Adiposity leads to increased release of inflammatory factors such as CRP and decreased production of anti-inflammatory cytokines such as adiponectin.[176] Inflammation may induce endometrial carcinogenesis through increased cell proliferation, DNA damage and inhibition of apoptosis.[176]

To better understand the pathways through which overall and central adiposity affect endometrial cancer development, the associations between measures of adiposity and postmenopausal endometrial cancer risk were further adjusted for some biomarkers that are associated with the proposed biological pathways. Adjustment for CRP resulted in a slight reduction in the HRs associated with overall adiposity measures, which is consistent with the notion that inflammation partly mediates the association between overall adiposity and endometrial cancer risk.[176,313,314] Adjustment for calculated free testosterone resulted in a similar reduction in the risk estimates for overall adiposity measures, suggesting that alterations in levels of free testosterone may also account for some of the association between overall adiposity and endometrial cancer risk. There was no material difference in the risk estimates following adjustment for HbA1c, glucose, albumin, IGF-1 and testosterone, suggesting that these factors do not mediate the association of adiposity with endometrial cancer risk.

The strengths of this study include its large size, prospective design and breadth of data available on body composition. To my knowledge, it is the first prospective study to report on the associations of bioimpedance-derived fat mass, fat-free mass and trunk fat percentage with the risk of endometrial cancer. All body size and body composition variables were measured rather than self-reported, thereby minimising potential for differential misclassification known to be associated with self-reported measures, particularly shown for body weight and height.[115] Repeat measures available in a subset of the cohort allowed for assessment of the extent of measurement error (quantified by RDR) associated with each body measure and the correction of risk estimates for regression dilution bias. With the exception of waist to hip ratio, the RDRs for the body size/composition indices were small indicating that these measures did not change substantially over a 5-year period. Availability of data on biomarkers allowed for exploration of potential mediating factors of the association of adiposity with endometrial cancer risk.

Several limitations of this study need to be acknowledged. First, analyses in premenopausal women were limited by a small number of incident endometrial cancers occurring before the menopause. Second, although bioimpedance analysis is a valid technique for estimating body fat and body composition,[324] certain factors including hydration status of participants and presence of medical conditions that impact on fluid and electrolyte balance, which are difficult to assess in large-scale epidemiological settings, could affect the accuracy of body composition parameters.[121] Third, the small

number of incident type II endometrial cancers in this study precluded analyses of the associations of all exposures of interest with the risk of this subtype. Fourth, HRT use is known to attenuate the associations of adiposity with endometrial cancer risk in postmenopausal women and may bias the risk estimates for the associations. However, in analyses restricted to postmenopausal women who have never used HRT, the overall pattern of the association did not materially change, indicating that inclusion of ever HRT users in the analyses did not unduly influence the findings. Lastly, most postmenopausal women in this cohort lacked measurements of circulating oestradiol; therefore, it was not possible to assess the effect of adjustment for oestrogen on the associations of adiposity measures with endometrial cancer risk.

4.5. Conclusion

Body fat percentage and fat mass derived from bioimpedance analysis are not better indicators of endometrial cancer risk than BMI. Central adiposity, as reflected by waist circumference and waist to hip ratio, may contribute to endometrial cancer risk independently of overall adiposity. Inflammation and alterations in free testosterone levels may account for some of the association between overall adiposity and endometrial cancer risk.

Table 4-1: Baseline characteristics of the study population by menopausal status and quartiles of BMI

Characteristics	Premenopausal women (n =57,294)				Postmenopausal women (n = 135,110)			
	BMI (kg/m^2) in quartiles							
	1	2	3	4	1	2	3	4
Number of women	14,552	14,187	14,412	14,143	34,033	34,043	33,953	33,081
BMI (kg/m^2), range	<22.8	22.8-<25.3	25.3-<29.0	>29.0	<23.6	23.6-<26.2	26.2-<29.7	>29.7
Age at recruitment (years), mean (SD)	45.5 (3.5)	45.8 (3.5)	45.9 (3.6)	46.0 (3.6)	59.4 (5.5)	60.0 (5.4)	60.4 (5.3)	60.1 (5.4)
Age at menarche (years), mean (SD)	13.4 (1.5)	13.2 (1.5)	13.0 (1.6)	12.7 (1.6)	13.2 (1.6)	13.1 (1.6)	12.9 (1.6)	12.7 (1.6)
Age at menopause (years), mean (SD)	-	-	-	-	50.1 (4.3)	50.4 (4.3)	50.4 (4.5)	50.3 (4.7)
Nulliparous, n (%)	4,119 (28.3)	3,565 (25.1)	3,514 (24.4)	3,955 (28.0)	6,959 (20.5)	5,515 (16.2)	5,085 (15.0)	5,328 (16.1)
Ever users of HRT, n (%)	-	-	-	-	14,518 (42.7)	15,341 (45.1)	15,457 (45.5)	13,994 (42.3)
Ever users of oral contraceptives, n (%)	12,870 (88.4)	12,734 (89.8)	12,889 (89.4)	12,415 (87.8)	27,298 (80.2)	27,017 (79.4)	26,361 (77.6)	25,137 (76.0)
Current smokers, n (%)	1,444 (9.9)	1,317 (9.3)	1,405 (9.8)	1,437 (10.2)	3,038 (8.9)	2,650 (7.8)	2,620 (7.7)	2,372 (7.2)
Had a history of diabetes, n (%)	79 (0.5)	99 (0.7)	184 (1.3)	568 (4.0)	376 (1.1)	549 (1.6)	1,060 (3.1)	2,910 (8.8)
Body size and composition								
Height (cm), mean (SD)	165.0 (6.3)	164.4 (6.3)	163.8 (6.3)	163.2 (6.3)	163.1 (6.2)	162.2 (6.2)	161.6 (6.1)	160.8 (6.2)
Weight (kg), mean (SD)	57.6 (5.3)	64.8 (5.2)	72.2 (6.2)	89.9 (13.6)	57.8 (5.6)	65.4 (5.3)	72.5 (6.0)	87.8 (12.1)
Body fat (%), mean (SD)	26.7 (4.4)	32.0 (3.5)	36.5 (3.4)	43.2 (4.2)	29.4 (4.6)	35.0 (3.4)	38.9 (3.2)	44.4 (3.9)
Fat mass (kg), mean (SD)	15.5 (3.5)	20.8 (3.3)	26.5 (4.0)	39.3 (9.4)	17.1 (3.8)	23.0 (3.4)	28.3 (3.9)	39.3 (8.4)
Waist circumference (cm), mean (SD)	70.9 (5.2)	76.8 (5.4)	83.4 (6.2)	97.6 (10.7)	72.9 (5.8)	80.0 (5.9)	86.9 (6.5)	99.7 (10.2)
Hip circumference (cm), mean (SD)	93.2 (4.6)	98.3 (4.4)	103.2 (4.8)	115.3 (10.0)	93.8 (4.7)	99.3 (4.5)	104.3 (4.9)	115.5 (9.5)
Waist to hip ratio, mean (SD)	0.76 (0.05)	0.78 (0.06)	0.81 (0.06)	0.85 (0.07)	0.78 (0.06)	0.81 (0.06)	0.83 (0.06)	0.86 (0.07)
Waist to height ratio, mean (SD)	0.43 (0.03)	0.47 (0.03)	0.51 (0.04)	0.60 (0.07)	0.45 (0.04)	0.49 (0.04)	0.54 (0.04)	0.62 (0.06)
Percent trunk fat (%), mean (SD)	23.6 (5.7)	29.5 (4.9)	34.3 (4.7)	40.9 (5.2)	26.6 (5.9)	32.6 (4.7)	36.7 (4.5)	42.0 (5.0)
Fat-free mass (kg), mean (SD)	42.1 (3.4)	44.0 (3.4)	45.8 (3.6)	50.6 (5.3)	40.7 (3.3)	42.5 (3.4)	44.3 (3.6)	48.6 (5.0)

SD = standard deviation

Table 4-2: Age-adjusted partial correlation coefficients for the relationship between body size and body composition variables in premenopausal women (n = 57,294)

Body size/composition measures	Height (cm)	Weight (kg)	BMI (kg/m^2)	Body fat (%)	Fat mass (kg)	Waist circumference (cm)	Hip circumference (cm)	Waist to hip ratio	Waist to height ratio	Trunk fat (%)	Fat-free mass (kg)
Height (cm)	1.00										
Weight (cm)	0.27	1.00									
BMI (kg/m^2)	-0.10	0.93	1.00								
Body fat (%)	0.03	0.85	0.87	1.00							
Fat mass (kg)	0.15	0.97	0.94	0.93	1.00						
Waist circumference (cm)	0.05	0.87	0.89	0.83	0.89	1.00					
Hip circumference (cm)	0.14	0.92	0.90	0.83	0.92	0.84	1.00				
Waist to hip ratio	-0.09	0.43	0.47	0.46	0.45	0.75	0.28	1.00			
Waist to height ratio	-0.21	0.78	0.89	0.80	0.83	0.97	0.78	0.75	1.00		
Trunk fat (%)	0.15	0.81	0.78	0.98	0.90	0.77	0.79	0.42	0.72	1.00	
Fat-free mass (kg)	0.48	0.87	0.71	0.50	0.72	0.67	0.74	0.29	0.54	0.47	1.00

Table 4-3: Age-adjusted partial correlation coefficients for the relationship between body size and body composition variables in postmenopausal women (n = 135,110)

Body size/composition measures	Height (cm)	Weight (kg)	BMI (kg/m^2)	Body fat (%)	Fat mass (kg)	Waist circumference (cm)	Hip circumference (cm)	Waist to hip ratio	Waist to height ratio	Trunk fat (%)	Fat-free mass (kg)
Height (cm)	1.00										
Weight (cm)	0.27	1.00									
BMI (kg/m^2)	-0.12	0.92	1.00								
Body fat (%)	0.01	0.83	0.85	1.00							
Fat mass (kg)	0.14	0.97	0.94	0.93	1.00						
Waist circumference (cm)	0.03	0.86	0.87	0.81	0.88	1.00					
Hip circumference (cm)	0.12	0.91	0.89	0.81	0.91	0.82	1.00				
Waist to hip ratio	-0.08	0.41	0.45	0.44	0.43	0.74	0.24	1.00			
Waist to height ratio	-0.22	0.77	0.88	0.78	0.82	0.96	0.77	0.74	1.00		
Trunk fat (%)	0.13	0.78	0.75	0.98	0.88	0.74	0.76	0.39	0.69	1.00	
Fat-free mass (kg)	0.48	0.86	0.69	0.45	0.70	0.65	0.71	0.28	0.51	0.40	1.00

Table 4-4: Age-adjusted partial correlation coefficients between residuals of central adiposity measures and BMI

Variable (residuals)	BMI (kg/m^2)	
	Premenopausal	Postmenopausal
Waist circumference (cm)	-0.0013	-0.0023
Hip circumference (cm)	0.0022	0.0011
Waist to hip ratio	-0.0026	-0.0029
Waist to height ratio	-0.0030	-0.0043
Trunk fat (%)	-0.0008	-0.0016
Fat-free mass (kg)	0.0034	0.0045

Residuals for each central adiposity measure (or fat-free mass) were computed from a linear regression of that variable on BMI.

Table 4-5: Age-adjusted partial correlation coefficients between adiposity measures and selected biomarkers among postmenopausal women with data on the respective biomarkers

	Albumin (n = 115,194)	Glucose (n = 115,081)	HbA1c (n = 125,595)	IGF-1 (n = 125,749)	CRP (n = 126,252)	Testosterone (n = 104,447)	Calculated free testosterone (n = 94,943)
Weight (kg)	-0.19	0.14	0.21	-0.12	0.44	0.10	0.31
BMI (kg/m^2)	-0.20	0.15	0.24	-0.15	0.49	0.11	0.34
Body fat (%)	-0.14	0.12	0.18	-0.13	0.49	0.10	0.32
Fat mass (kg)	-0.18	0.14	0.21	-0.14	0.48	0.11	0.32
Waist circumference (cm)	-0.17	0.17	0.27	-0.14	0.48	0.09	0.34
Hip circumference (cm)	-0.20	0.11	0.17	-0.13	0.42	0.10	0.28
Waist to hip ratio	-0.06	0.15	0.24	-0.08	0.32	0.04	0.25
Waist to height ratio	-0.17	0.17	0.27	-0.15	0.49	0.09	0.34
Trunk fat (%)	-0.12	0.10	0.14	-0.12	0.45	0.09	0.28

Table 4-6: Hazard ratios for endometrial cancer associated with height and overall adiposity measures among premenopausal women

Body size/composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)
Height (cm) in quartiles					
1	125.0-<160.1	157.0	18	1.00 (0.63-1.59)	1.00 (0.63-1.60)
2	160.1-< 164.1	162.0	15	0.94 (0.57-1.56)	0.98 (0.59-1.63)
3	164.1-<168.1	166.0	13	0.85 (0.49-1.47)	0.88 (0.51-1.51)
4	168.1-199.0	171.0	11	0.74 (0.41-1.33)	0.74 (0.41-1.35)
P for trend				0.41	0.98
HR (95%CI) per 1-SD increment				0.89 (0.68-1.16)	0.90 (0.68-1.17)
Weight (kg) in quartiles					
1	35.3-< 61.0	57.4	16	1.00 (0.61-1.63)	1.00 (0.61-1.64)
2	16.0-<68.3	64.9	11	0.69 (0.38-1.25)	0.71 (0.39-1.29)
3	68.3-<78.1	72.8	12	0.76 (0.43-1.34)	0.73 (0.42-1.29)
4	78.1-170.8	86.8	18	1.17 (0.74-1.87)	0.95 (0.58-1.55)
P for trend				0.46	0.86
HR (95%CI) per 1-SD increment				1.27 (0.99-1.62)	1.12 (0.87-1.44)
BMI (kg/m^2) in quartiles					
1	16.0-<23.4	21.5	14	1.00 (0.59-1.69)	1.00 (0.59-1.71)
2	23.4-<26.0	24.1	14	1.02 (0.60-1.72)	1.07 (0.63-1.80)
3	26.0-<29.5	27.2	9	0.65 (0.34-1.26)	0.65 (0.34-1.24)
4	29.5-59.9	32.2	20	1.52 (0.98-2.37)	1.23 (0.76-1.98)
P for trend				0.24	0.87
HR (95%CI) per 1-SD increment				1.33 (1.05-1.68)	1.17 (0.92-1.49)
Body fat (%) in quartiles					
1	8.8-<29.7	27.5	17	1.00 (0.62-1.61)	1.00 (0.61-1.63)
2	29.7-<34.6	33.4	12	0.71 (0.40-1.25)	0.73 (0.41-1.29)
3	34.6-<39.6	37.8	9	0.55 (0.29-1.07)	0.54 (0.28-1.03)
4	39.6-69.3	43.8	19	1.17 (0.74-1.85)	0.92 (0.57-1.49)
P for trend				0.72	0.46
HR (95%CI) per 1-SD increment				1.15 (0.84-1.56)	1.01 (0.75-1.37)
Fat mass (kg) in quartiles					
1	5.0-<18.2	16.1	18	1.00 (0.62-1.60)	1.00 (0.62-1.60)
2	18.2-<23.5	21.6	9	0.51 (0.26-0.99)	0.51 (0.27-0.99)
3	23.5-<30.7	27.5	12	0.67 (0.38-1.17)	0.67 (0.38-1.17)
4	30.7-109.8	38.0	18	0.84 (0.51-1.37)	0.84 (0.51-1.37)
P for trend				0.55	0.53
HR (95%CI) per 1-SD increment				1.24 (0.96-1.60)	1.09 (0.84-1.41)

Minimally adjusted models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score and UK region.
Multivariable- adjusted models include all the variables defined above, plus smoking status, physical activity, duration of oral contraceptive use, age at menarche and diabetes status.
Standard deviations for the anthropometric/body composition measures were as follows: 6.3 cm for height, 14.6 kg for weight, 5.2 for BMI, 7.2% for body fat percentage and 10.5 kg for fat mass.
Each HR (95%CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and standard error by the relevant regression dilution ratio (RDR). The RDRs for height, weight, BMI, body fat percentage and fat mass were 0.98, 0.94, 0.94, 0.86 and 0.92, respectively.

Table 4-7: Hazard ratios for endometrial cancer associated with central adiposity measures and fat-free mass among premenopausal women

Body size/composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	Further adjusted for BMI HR (95%gsCI)
Waist circumference (cm) in quartiles						
1	41.4-<73.1	72.0	17	1.00 (0.62-1.61)	1.00 (0.61-1.63)	1.00 (0.64-1.57)
2	73.1-<80.1	79.0	14	0.84 (0.50-1.43)	0.87 (0.51-1.46)	0.55 (0.30-1.03)
3	80.1-<89.1	86.0	8	0.52 (0.26-1.04)	0.52 (0.26-1.04)	0.95 (0.59-1.53)
4	89.1-163.0	98.0	18	1.24 (0.78-1.98)	1.01 (0.61-1.66)	0.51 (0.27-0.96)
P for trend				0.57	0.90	0.22
HR (95%CI) per 1-SD increment				1.23 (0.93-1.62)	1.08 (0.82-1.44)	0.84 (0.63-1.12)
Hip circumference (cm) in quartiles						
1	71.0-<95.1	93.0	16	1.00 (0.61-1.64)	1.00 (0.61-1.65)	1.00 (0.63-1.58)
2	95.1-<101.1	99.0	15	0.83 (0.50-1.38)	0.84 (0.51-1.40)	0.64 (0.37-1.14)
3	101.1-<107.1	104.0	7	0.50 (0.24-1.06)	0.47 (0.22-0.98)	0.74 (0.44-1.26)
4	107.1-174.0	114.0	19	1.24 (0.79-1.96)	0.97 (0.60-1.57)	0.58 (0.33-1.03)
P for trend				0.48	0.68	0.19
HR (95%CI) per 1-SD increment				1.24 (0.96-1.60)	1.08 (0.83-1.41)	0.84 (0.64-1.10)
Waist to hip ratio in quartiles						
1	0.45-< 0.76	0.76	17	1.00 (0.62-1.61)	1.00 (0.62-1.63)	1.00 (0.62-1.62)
2	0.76-<0.80	0.80	12	0.79 (0.45-1.40)	0.82 (0.47-1.45)	0.73 (0.41-1.33)
3	0.80-<0.85	0.83	16	1.03 (0.63-1.68)	1.07 (0.66-1.75)	1.02 (0.61-1.69)
4	0.85-1.39	0.87	12	0.81 (0.46-1.44)	0.74 (0.41-1.34)	0.91 (0.53-1.56)
P for trend				0.73	0.84	0.99
HR (95%CI) per 1-SD increment				1.12 (0.74-1.70)	1.06 (0.70-1.61)	0.94 (0.62-1.42)
Waist to height ratio in quartiles						
1	0.25-<0.45	0.44	15	1.00 (0.60-1.66)	1.00 (0.60-1.68)	1.00 (0.60-1.67)
2	0.45-<0.50	0.48	17	0.97 (0.61-1.57)	1.03 (0.64-1.66)	1.27 (0.79-2.06)
3	0.50-<0.55	0.53	7	0.57 (0.27-1.19)	0.58 (0.28-1.21)	0.97 (0.56-1.66)
4	0.55-0.99	0.60	18	1.28 (0.80-2.05)	1.05 (0.64-1.74)	0.81 (0.45-1.44)
P for trend				0.57	0.67	0.47
HR (95%CI) per 1-SD increment				1.26 (0.96-1.65)	1.11 (0.84-1.46)	0.89 (0.67-1.18)

Body size/composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	Further adjusted for BMI HR (95%gsCI)
Trunk fat (%) in quartiles						
1	2.0-< 26.6	24.0	17	1.00 (0.62-1.61)	1.00 (0.61-1.63)	1.00 (0.63-1.58)
2	26.6-<32.2	30.8	11	0.67 (0.37-1.20)	0.68 (0.37-1.22)	1.04 (0.66-1.63)
3	32.2-<37.8	35.5	15	0.90 (0.54-1.49)	0.83 (0.50-1.37)	0.58 (0.31-1.08)
4	37.8-75.0	41.8	14	0.87 (0.51-1.48)	0.67 (0.38-1.15)	0.48 (0.25-0.93)
P for trend				0.82	0.48	0.03
HR (95%CI) per 1-SD increment				1.12 (0.81-1.54)	0.99 (0.72-1.36)	0.79 (0.59-1.06)
Fat-free mass (kg) in quartiles						
1	27.9-<42.2	39.8	13	1.00 (0.58-1.72)	1.00 (0.58-1.73)	1.00 (0.61-1.65)
2	42.2-<45.1	43.2	12	0.94 (0.53-1.65)	0.94 (0.54-1.67)	0.80 (0.45-1.40)
3	45.1-<48.4	45.9	12	0.96 (0.54-1.69)	0.93 (0.53-1.64)	0.82 (0.46-1.45)
4	48.4-79.4	50.2	20	1.61 (0.80-3.24)	1.38 (0.88-2.18)	1.12 (0.69-1.81)
P for trend				0.15	0.56	0.75
HR (95%CI) per 1-SD increment				1.31 (1.01-1.70)	1.19 (0.92-1.54)	1.08 (0.82-1.42)

Minimally adjusted models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score and UK region.
Multivariable-adjusted models include all the variables defined above, plus smoking status, physical activity, duration of oral contraceptive use, age at menarche and diabetes status.
Standard deviations for the anthropometric/body composition measures were as follows: 12.3 cm for waist circumference, 10.4 cm for hip circumference, 0.07 for waist to hip ratio, 0.08 for waist to height ratio and 8.2% for trunk fat percentage and 5.1 kg for fat-free mass.
Each HR (95%CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and standard error by the regression dilution ratio (RDR). The RDRs for waist circumference, hip circumference, waist to hip ratio, waist to height ratio, trunk fat percentage and fat-free mass were 0.88, 0.91, 0.63, 0.89, 0.83 and 0.92, respectively.
The residual method was used to adjust for BMI.

Table 4-8: Hazard ratios for endometrial cancer associated with height and overall adiposity measures among postmenopausal women

Body size/ composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	χ^2 for multivariable adjusted model
Height (cm) in quartiles						
1	121.0-<158.1	155.0	205	1.00 (0.87-1.15)	1.00 (0.87-1.15)	
2	158.1-<162.1	160.0	199	1.17 (1.02-1.35)	1.20 (1.04-1.38)	
3	162.1-<166.0	164.0	148	0.97 (0.83-1.14)	1.01 (0.86-1.18)	
4	166.0-199.0	169.0	154	1.07 (0.91-1.25)	1.11 (0.95-1.31)	
P for trend				0.86	0.56	
HR (95%CI) per 1-SD increment				1.02 (0.95-1.10)	1.04 (0.96-1.12)	264
Weight (kg) in quartiles						
1	35.3-<61.5	56.7	83	1.00 (0.81-1.24)	1.00 (0.81-1.24)	
2	61.5-<68.7	64.8	114	1.37 (1.14-1.65)	1.36 (1.14-1.64)	
3	68.7-<77.8	71.9	175	2.12 (1.83-2.46)	2.06 (1.77-2.38)	
4	77.8-169.5	84.6	334	4.09 (3.67-4.56)	3.73 (3.32-4.18)	
P for trend				<0.0001	<0.0001	
HR (95%CI) per 1-SD increment				1.77 (1.67-1.88)	1.70 (1.60-1.81)	499
BMI (kg/m^2) in quartiles						
1	16.0-<23.6	22.0	88	1.00 (0.81-1.23)	1.00 (0.81-1.24)	
2	23.6-<26.2	24.8	117	1.30 (1.08-1.56)	1.29 (1.08-1.55)	
3	26.2-<29.7	27.7	165	1.80 (1.55-2.10)	1.75 (1.50-2.04)	
4	29.7-59.9	32.5	336	3.81 (3.41-4.24)	3.45 (3.07-3.88)	
P for trend				<0.0001	<0.0001	
HR (95%CI) per 1-SD increment				1.77 (1.67-1.87)	1.71 (1.61-1.82)	509

Body size/ composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	χ^2 for multivariable adjusted model
Body fat (%) in quartiles						
1	10.1-32.6	30.1	79	1.00 (0.80-1.25)	1.00 (0.80-1.25)	
2	32.6-<37.2	35.5	123	1.49 (1.25-1.78)	1.50 (1.25-1.78)	
3	37.2-<41.6	39.5	184	2.25 (1.95-2.60)	2.22 (1.92-2.57)	
4	41.6-69.8	44.3	320	3.97 (3.56-4.44)	3.70 (3.29-4.16)	
P for trend				<0.0001	<0.0001	
HR (95%CI) per 1-SD increment				2.00 (1.83-2.20)	1.92 (1.75-2.11)	456
Fat mass (kg) in quartiles						
1	5.0-<20.2	17.2	75	1.00 (0.80-1.25)	1.00 (0.80-1.26)	
2	20.2-<25.4	23.0	108	1.41 (1.17-1.70)	1.41 (1.17-1.70)	
3	25.4-<32.0	28.1	191	2.48 (2.15-2.85)	2.43 (2.11-2.80)	
4	32.0-97.4	37.0	332	4.36 (3.91-4.86)	4.03 (3.59-4.52)	
P for trend				<0.0001	<0.0001	
HR (95%CI) per 1-SD increment				1.80 (1.69-1.91)	1.73 (1.63-1.85)	501

Minimally adjusted models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score and UK region.
Multivariable- adjusted models include all the variables defined above, plus use of HRT, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status.
Standard deviations for the anthropometric/body composition measures were as follows: 6.2 cm for height, 13.5 kg for weight, 5.0 for BMI, 6.7% for body fat percentage and 9.7 kg for fat mass.
Each HR (95%CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and standard error by the relevant regression dilution ratio (RDR). The RDRs for height, weight, BMI, body fat percentage and fat mass were 0.98, 0.93, 0.94, 0.87 and 0.91, respectively.
Likelihood ratio χ^2 statistics for the basic model (i.e. model with all covariate but no body size/composition measure) = 263.

Table 4-9: Hazard ratios for endometrial cancer associated with central adiposity measures and fat-free mass among postmenopausal women

Body size/ composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	Further adjusted for BMI HR (95%gsCI)	χ^2 for Multivariable-adjusted model	χ^2 for BMI-adjusted model
Waist circumference (cm) in quartiles								
1	46.0-<76.1	74.0	93	1.00 (0.82-1.23)	1.00 (0.81-1.23)	1.00 (0.86-1.16)		
2	76.1-<83.1	82.0	108	1.30 (1.08-1.57)	1.32 (1.09-1.59)	0.84 (0.70-1.00)		
3	83.1-<92.1	89.0	172	1.95 (1.68-2.26)	1.95 (1.68-2.26)	1.26 (1.09-1.45)		
4	92.1-166.0	100.0	333	3.93 (3.53-4.39)	3.67 (3.27-4.13)	1.21 (1.06-1.39)		
P for trend				<0.0001	<0.0001	0.005		
HR (95%CI) per 1-SD increment				1.87 (1.74-2.01)	1.80 (1.67-1.94)	1.08 (1.00-1.17)	477	513
Hip circumference (cm) in quartiles								
1	62.0-<96.1	94.0	105	1.00 (0.83-1.21)	1.00 (0.82-1.21)	1.00 (0.87-1.15)		
2	96.1-<102.1	100.0	130	1.15 (0.97-1.37)	1.14 (0.96-1.35)	0.93 (0.79-1.09)		
3	102.1-<108.1	105.0	154	1.74 (1.49-2.04)	1.68 (1.44-1.97)	0.97 (0.83-1.14)		
4	108.1-179.0	114.0	317	3.23 (2.89-3.61)	2.89 (2.58-3.25)	0.99 (0.85-1.14)		
P for trend				<0.0001	<0.0001	0.985		
HR (95%CI) per 1-SD increment				1.74 (1.64-1.85)	1.66 (1.56-1.78)	1.00 (0.93-1.08)	461	509
Waist to hip ratio in quartiles								
1	0.48-<0.78	0.77	121	1.00 (0.84-1.20)	1.00 (0.83-1.20)	1.00 (0.86-1.16)		
2	0.78-<0.83	0.82	171	1.32 (1.14-1.54)	1.35 (1.16-1.57)	0.96 (0.81-1.13)		
3	0.83-<0.88	0.85	169	1.52 (1.31-1.77)	1.54 (1.32-1.79)	1.15 (0.99-1.33)		
4	0.88-1.56	0.89	245	2.37 (2.09-2.69)	2.23 (1.96-2.55)	1.22 (1.06-1.41)		
P for trend				<0.0001	<0.0001	0.021		
HR (95%CI) per 1-SD increment				1.66 (1.48-1.85)	1.57(1.40-1.76)	1.13 (1.01-1.26)	321	513
Waist to height ratio in quartiles								
1	0.29-<0.48	0.46	106	1.00 (0.83-1.21)	1.00 (0.82-1.21)	1.00 (0.86-1.16)		
2	0.48-<0.52	0.51	95	1.21 (0.99-1.48)	1.22 (1.00-1.49)	1.11 (0.95-1.29)		
3	0.52-<0.58	0.55	176	1.75 (1.51-2.03)	1.76 (1.52-2.03)	0.99 (0.85-1.16)		
4	0.58-1.03	0.63	329	3.69 (3.30-4.12)	3.42 (3.04-3.86)	1.15 (1.00-1.32)		
P for trend				<0.0001	<0.0001	0.342		

Body size/ composition measures	Range at recruitment	Median at resurvey	Number of cases	Minimally adjusted HR (95%gsCI)	Multivariable-adjusted HR (95%gsCI)	Further adjusted for BMI HR (95%gsCI)	χ^2 for Multivariable-adjusted model	χ^2 for BMI-adjusted model
HR (95%CI) per 1-SD increment				1.83 (1.71-1.97)	1.76 (1.64-1.90)	1.03 (0.95-1.11)	463	509
Trunk fat (%) in quartiles								
1	3.0-<29.7	26.8	85	1.00 (0.81-1.24)	1.00 (0.81-1.24)	1.00 (0.86-1.17)		
2	20.7-<34.9	33.1	121	1.39 (1.16-1.66)	1.38 (1.16-1.65)	1.07 (0.92-1.24)		
3	34.9-<39.7	37.2	200	2.33 (2.03-2.68)	2.29 (1.99-2.63)	1.10 (0.94-1.28)		
4	39.7-75.6	42.1	300	3.47 (3.09-3.89)	3.24 (2.88-3.65)	1.21 (1.04-1.41)		
P for trend				<0.0001	<0.0001	0.087		
HR (95%CI) per 1-SD increment				1.87 (1.70-2.05)	1.79 (1.63-1.97)	1.06 (0.97-1.16)	405	510
Fat-free mass (kg) in quartiles								
1	26.2-<40.7	38.5	110	1.00 (0.83-1.21)	1.00 (0.83-1.21)	1.00 (0.86-1.16)		
2	40.7-<43.5	41.4	123	1.17 (0.98-1.39)	1.16 (0.97-1.39)	1.03 (0.88-1.20)		
3	43.5-<46.7	44.2	170	1.65 (1.42-1.91)	1.59 (1.37-1.85)	1.06 (0.91-1.24)		
4	46.7-81.7	48.0	303	3.02 (2.70-3.39)	2.70 (2.40-3.04)	1.12 (0.97-1.30)		
P for trend				<0.0001	<0.0001	0.258		
HR (95%CI) per 1-SD increment				1.68 (1.57-1.79)	1.58 (1.48-1.69)	1.06 (0.98-1.14)	417	511

Minimally adjusted models stratified by year of birth and year of recruitment and adjusted for age, deprivation score and region.
Multivariable-adjusted models include all the variables defined above, plus use of HRT, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status.
Standard deviations for the anthropometric/body composition measures were as follows: 12.3 cm for waist circumference, 10.1 cm for hip circumference, 0.07 for waist to hip ratio, 0.08 for waist to height ratio and 7.6% for trunk fat percentage and 4.8 kg for fat-free mass.
Each HR (95%CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and standard error by the corresponding regression dilution ratio (RDR). The RDRs for waist circumference, hip circumference, waist to hip ratio, waist to height ratio, trunk fat percentage and fat-free mass were 0.87, 0.89, 0.63, 0.88, 0.83 and 0.91, respectively.
Likelihood ratio χ^2 statistics for the basic model (i.e. model with all covariate but no body size/composition measure) = 263.
The residual method was used to adjust for BMI.

Table 4-10: Hazard ratios for endometrial cancer per 1-SD increment in BMI adjusted for central adiposity measures and fat-free mass

Body size/ composition measures	**HR (95%CI) per 1-SD increment in BMI**
BMI (kg/m^2) alone	1.71 (1.61-1.82)
Adjusted separately for:	
Waist circumference (cm)	1.51 (1.33-1.73)
Hip circumference (cm)	1.72 (1.48-2.00)
Waist to hip ratio	1.67 (1.56-1.79)
Waist to height ratio	1.63 (1.42-1.88)
Trunk fat (%)	1.64 (1.50-1.79)
Fat-free mass (kg)	1.62 (1.47-1.78)

Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, parity, use of HRT, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status. The standard method was used to adjust for central adiposity measures or fat-free mass.

Table 4-11: Hazard ratios for endometrial cancer per 1-SD increment in overall adiposity measures before and after adjustment for selected biomarkers

Biomarkers	HR (95%CI) per 1-SD increment			
	BMI (kg/m^2)	Weight (kg)	Body fat (%)	Fat mass (kg)
Albumin (n = 115,194, cases = 611)				
Multivariable-adjusted model	1.72 (1.61-1.84)	1.72 (1.60-1.84)	1.94 (1.75-2.14)	1.75 (1.63-1.88)
+ Albumin (g/L)	1.71 (1.60-1.83)	1.71 (1.59-1.83)	1.91 (1.72-2.11)	1.74 (1.62-1.87)
Glucose (n = 115,081, cases = 610)				
Multivariable-adjusted model	1.72 (1.61-1.84)	1.72 (1.61-1.84)	1.94 (1.75-2.15)	1.75 (1.64-1.88)
+ Glucose (mmol/L)	1.72 (1.61-1.84)	1.72 (1.61-1.84)	1.94 (1.76-2.15)	1.76 (1.64-1.88)
HbA1c (n =125,595, cases = 653)				
Multivariable-adjusted model	1.71 (1.60-1.82)	1.68 (1.58-1.80)	1.91 (1.73-2.10)	1.72 (1.61-1.84)
+ HbA1c (mmol/mol)	1.69 (1.58-1.81)	1.67 (1.56-1.78)	1.88 (1.70-2.07)	1.70 (1.59-1.82)
IGF-1 (n = 125,749, cases = 655)				
Multivariable-adjusted model	1.72 (1.61-1.83)	1.71 (1.60-1.82)	1.94 (1.76-2.14)	1.74 (1.63-1.86)
+ IGF-1 (nmol/L)	1.71 (1.60-1.83)	1.70 (1.59-1.81)	1.92 (1.74-2.12)	1.73 (1.62-1.86)
CRP (n = 126,252, cases = 658)				
Multivariable-adjusted model	1.72 (1.61-1.83)	1.71 (1.60-1.82)	1.95 (1.77-2.15)	1.74 (1.63-1.87)
+ CRP (mg/L)	1.61 (1.50-1.74)	1.59 (1.48-1.71)	1.75 (1.57-1.96)	1.63 (1.51-1.76)
Testosterone (n = 104,447, cases = 573)				
Multivariable-adjusted model	1.73 (1.61-1.85)	1.72 (1.60-1.84)	2.02 (1.82-2.25)	1.76 (1.64-1.89)
+ Testosterone (nmol/L)	1.69 (1.58-1.82)	1.69 (1.57-1.81)	1.97 (1.77-2.19)	1.72 (1.60-1.85)
Calculated free testosterone (n = 94,943, cases = 528)				
Multivariable-adjusted model	1.73 (1.61-1.86)	1.73 (1.61-1.86)	2.00 (1.79-2.23)	1.76 (1.64-1.90)
+ Calculated free testosterone (nmol/L)	1.61 (1.49-1.74)	1.61 (1.49-1.74)	1.80 (1.61-2.02)	1.64 (1.51-1.77)

Table 4-12: Hazard ratios for endometrial cancer per 1-SD increment in central adiposity measures before and after adjustment for selected biomarkers

Biomarkers	HR (95%CI) per 1-SD increment				
	Waist circumference (cm)	Hip circumference (cm)	Waist to hip ratio	Waist to height ratio	Trunk fat (%)
Albumin (n = 115,194, cases = 611)					
Multivariable-adjusted model	1.82 (1.68-1.98)	1.66 (1.55-1.78)	1.63 (1.44-1.84)	1.79 (1.65-1.94)	1.80 (1.62-2.00)
+ BMI	1.10 (1.02-1.20)	0.98 (0.91-1.07)	1.17 (1.04-1.32)	1.05 (0.96-1.14)	1.06 (0.97-1.17)
+ Albumin (g/L)	1.10 (1.02-1.20)	0.98 (0.91-1.06)	1.18 (1.04-1.32)	1.05 (0.96-1.14)	1.06 (0.97-1.17)
Glucose (n = 115,081, cases = 610)					
Multivariable-adjusted model	1.82 (1.68-1.98)	1.66 (1.55-1.79)	1.63 (1.44-1.83)	1.79 (1.65-1.94)	1.80 (1.62-2.00)
+ BMI	1.11 (1.02-1.20)	0.99 (0.91-1.07)	1.17 (1.04-1.32)	1.05 (0.96-1.14)	1.06 (0.97-1.17)
+ Glucose (mmol/L)	1.11 (1.02-1.20)	0.99 (0.91-1.07)	1.18 (1.04-1.33)	1.05 (0.96-1.14)	1.06 (0.97-1.17)
HbA1c (n =125,595, cases = 653)					
Multivariable-adjusted model	1.78 (1.64-1.92)	1.66 (1.55-1.78)	1.53 (1.36-1.72)	1.76 (1.62-1.90)	1.77 (1.60-1.96)
+ BMI	1.07 (0.98-1.16)	1.00 (0.93-1.09)	1.10 (0.98-1.24)	1.03 (0.95-1.11)	1.05 (0.96-1.15)
+ HbA1C (mmol/mol)	1.06 (0.98-1.15)	1.01 (0.93-1.09)	1.09 (0.97-1.23)	1.02 (0.94-1.11)	1.06 (0.96-1.15)
IGF-1 (n = 125,749, cases = 655)					
Multivariable-adjusted model	1.81 (1.67-1.96)	1.66 (1.55-1.78)	1.60 (1.42-1.79)	1.78 (1.64-1.92)	1.81 (1.64-2.00)
+ BMI	1.09 (1.01-1.18)	0.99 (0.92-1.07)	1.15 (1.03-1.29)	1.04 (0.96-1.13)	1.07 (0.98-1.18)
+ IGF-1 (nmol/L)	1.09 (1.01-1.18)	0.99 (0.92-1.07)	1.15 (1.02-1.29)	1.04 (0.96-1.12)	1.07 (0.98-1.17)
CRP (n = 126,252, cases = 658)					
Multivariable-adjusted model	1.81 (1.67-1.96)	1.66 (1.55-1.78)	1.60 (1.42-1.80)	1.78 (1.64-1.92)	1.82 (1.64-2.01)
+ BMI	1.09 (1.01-1.18)	0.99 (0.92-1.07)	1.15 (1.03-1.29)	1.04 (0.96-1.13)	1.08 (0.99-1.13)
+ CRP (mg/L)	1.09 (1.01-1.17)	0.99 (0.92-1.07)	1.13 (1.01-1.27)	1.02 (0.94-1.11)	1.05 (0.96-1.15)

Biomarkers	HR (95%CI) per 1-SD increment				
	Waist circumference (cm)	Hip circumference (cm)	Waist to hip ratio	Waist to height ratio	Trunk fat (%)
Testosterone (n = 104,447, cases = 573)					
Multivariable-adjusted model	1.83 (1.68-1.99)	1.65 (1.54-1.78)	1.67 (1.47-1.90)	1.80 (1.65-1.95)	1.87 (1.68-2.09)
+ BMI	1.10 (1.01-1.20)	0.96 (0.88-1.04)	1.20 (1.06-1.36)	1.05 (0.96-1.14)	1.10 (1.00-1.22)
+ Testosterone (nmol/L)	1.10 (1.01-1.20)	0.96 (0.88-1.04)	1.20 (1.06-1.36)	1.05 (0.96-1.14)	1.10 (1.00-1.21)
Calculated free testosterone (n = 94,943, cases = 528)					
Multivariable-adjusted model	1.84 (1.69-2.01)	1.65 (1.53-1.78)	1.69 (1.48-1.92)	1.80 (1.65-1.96)	1.85 (1.65-2.07)
+ BMI	1.11 (1.01-1.21)	0.96 (0.88-1.04)	1.21 (1.07-1.38)	1.04 (0.95-1.14)	1.08 (0.98-1.20)
+ Calculated free testosterone (nmol/L)	1.08 (0.98-1.18)	0.97 (0.89-1.05)	1.15 (1.01-1.31)	1.02 (0.93-1.11)	1.06 (0.96-1.17)

Table 4-13: Hazard ratios for type I endometrial cancer per 1-SD increment in various measures of body size and composition in postmenopausal women

Body size/composition measures	HR per 1-SD (95%CI) increment	
	Multivariable adjusted	Further adjusted for BMI
Height (cm)	1.05 (0.95-1.13)	-
Weight (kg)	1.76 (1.64-1.89)	-
BMI (kg/m^2)	1.77 (1.66-1.90)	-
Body fat (%)	2.01 (1.81-2.24)	-
Fat mass (kg)	1.79 (1.66-1.92)	-
Waist circumference (cm)	1.87 (1.72-2.03)	1.08 (0.99-1.18)
Hip circumference (cm)	1.72 (1.60-1.85)	0.99 (0.91-1.08)
Waist to hip ratio	1.61 (1.42-1.82)	1.14 (1.00-1.29)
Waist to height ratio	1.83 (1.69-1.99)	1.02 (0.94-1.12)
Trunk fat (%)	1.85 (1.66-2.06)	1.05 (0.95-1.16)
Fat-free mass (kg)	1.65 (1.53-1.78)	1.09 (1.00-1.18)

Number of incident type I endometrial cancer = 558.
Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, use of HRT, parity, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status.
The residual method was used to adjust for BMI.

Table 4-14: Hazard ratios for endometrial cancer per 1-SD increment in different measures of body size and composition among postmenopausal never HRT users

Body size/ composition measures	HR (95%CI) per 1-SD increment	
	Multivariable- adjusted	Further adjusted for BMI
Height (cm)	1.05 (0.94-1.16)	-
Weight (kg)	1.75 (1.62-1.90)	-
BMI (kg/m^2)	1.76 (1.62-1.90)	-
Body fat (%)	2.09 (1.84-2.36)	-
Fat mass (kg)	1.79 (1.65-1.95)	-
Waist circumference (cm)	1.88 (1.71-2.07)	1.11 (1.01-1.23)
Hip circumference (cm)	1.69 (1.56-1.84)	0.97 (0.88-1.07)
Waist to hip ratio	1.71 (1.47-1.99)	1.21 (1.04-1.39)
Waist to height ratio	1.85 (1.68-2.04)	1.06 (0.95-1.17)
Trunk fat (%)	1.91 (1.68-2.17)	1.09 (0.97-1.22)
Fat-free mass (kg)	1.61 (1.48-1.76)	1.05 (0.95-1.16)

Number of postmenopausal never HRT users= 75,448 (cases = 397).
Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, parity, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status.
The residual method was used to adjust for BMI.

Table 4-15: Hazard ratios for endometrial cancer per 1-SD increment in central adiposity measures and fat-free mass adjusted for BMI using the standard or residual method

Body size/ composition measures	Multivariable-adjusted HR (95%CI) per 1-SD increment	
	Standard method	Residual method
Waist circumference (cm)	1.18 (1.01-1.38)	1.08 (1.00-1.17)
Hip circumference (cm)	1.00 (0.85-1.17)	1.00 (0.93-1.08)
Waist to hip ratio	1.15 (1.01-1.30)	1.13 (1.01-1.26)
Waist to height ratio	1.06 (0.90-1.26)	1.03 (0.95-1.11)
Trunk fat (%)	1.10 (0.96-1.24)	1.06 (0.97-1.16)
Fat-free mass (kg)	1.08 (0.98-1.20)	1.07 (0.99-1.15)

Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, parity, use of HRT, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche, diabetes status and BMI.
Standard method: Models including central adiposity measure as the main exposure of interest adjusted for BMI
Residual method: residuals of the central adiposity measure of interest obtained from linear regression of the that measure on BMI were modelled as the main exposure of interest in the Cox model and additionally adjusted for BMI.

Table 4-16: Hazard ratios for endometrial cancer associated with WHO categories for BMI, waist circumference and waist to hip ratio in postmenopausal women

Adiposity measures	Number of cases	Multivariable- adjusted model HR (95%gsCI)	Further adjusted for BMI HR (95%gsCI)
BMI (kg/m^2)			
<25	141	1.00 (0.84-1.19)	-
25-<30	239	1.64 (1.44-1.86)	-
30-<35	149	2.46 (2.10-2.89)	-
≥35	177	5.92 (5.05-6.94)	-
P for trend		<0.0001	
Waist circumference (cm)			
<80	134	1.00 (0.84-1.19)	1.00 (0.83-1.21)
80-<88	141	1.48 (1.26-1.75)	1.13 (0.97-1.30)
≥ 88	431	2.99 (2.70-3.31)	1.37 (1.15-1.60)
P for trend		<0.0001	0.015
Waist to hip ratio[2]			
<0.85	366	Referent	Referent
≥0.85	340	1.58 (1.38-1.84)	1.10 (0.93-1.29)

Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, use of HRT, parity, smoking status, physical activity, age at menopause, duration of oral contraceptive use, age at menarche and diabetes status.

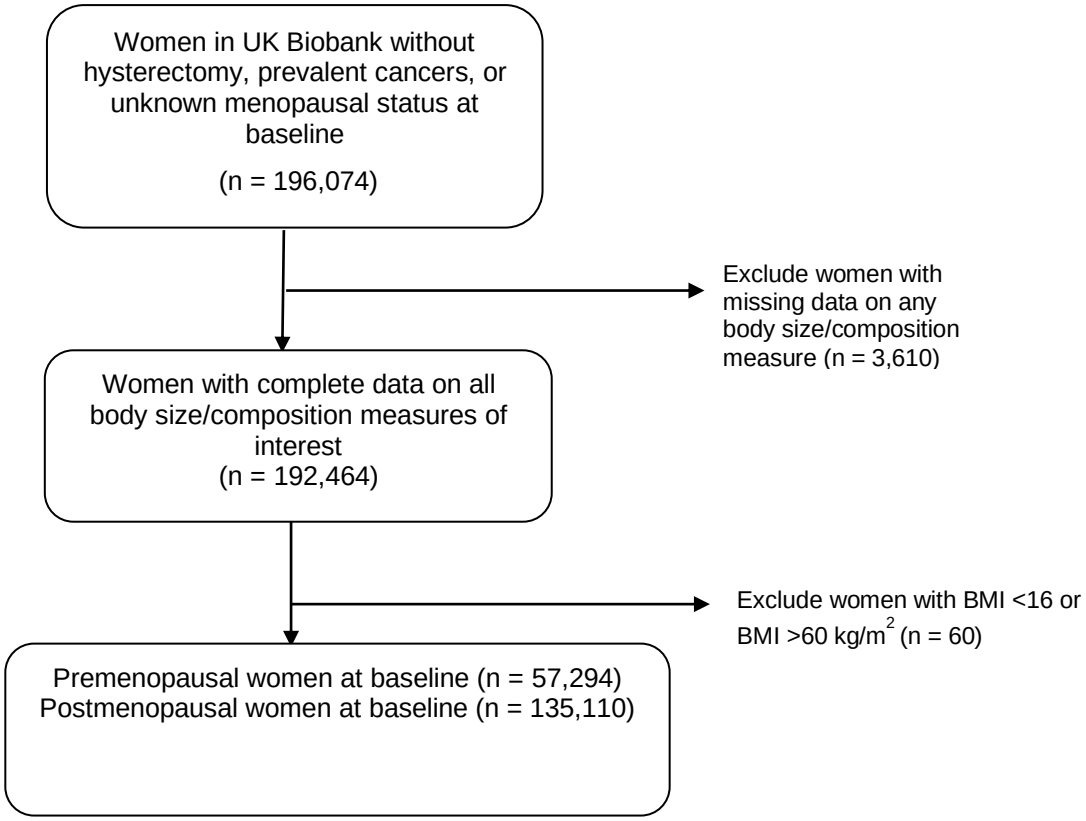


Figure 4-1: Flowchart for inclusion of participants in analyses

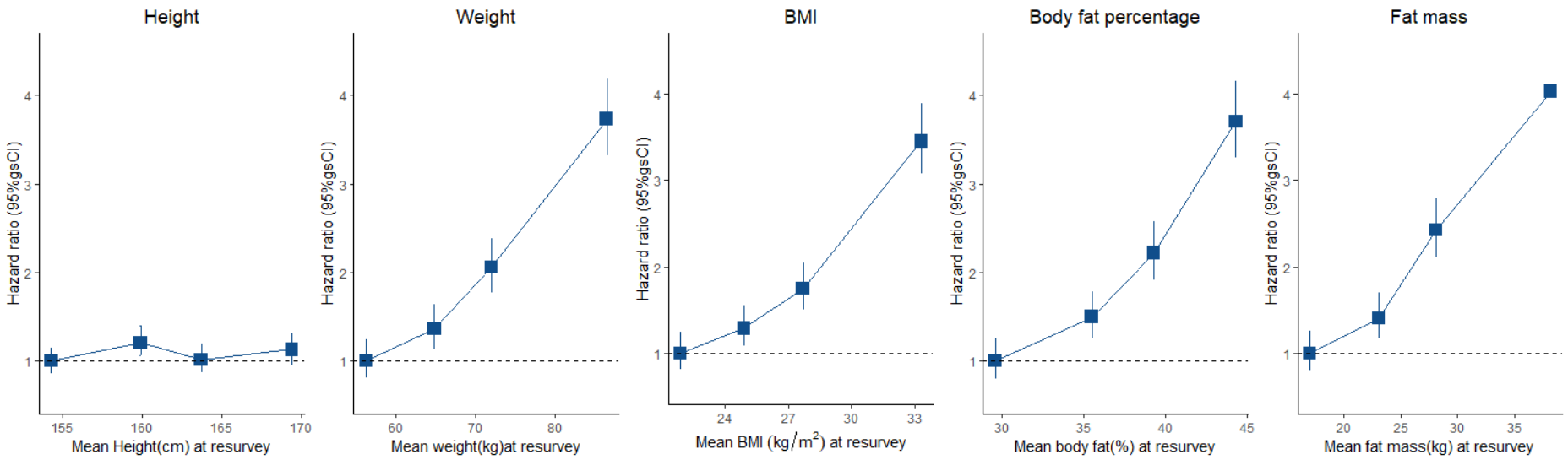


Figure 4-2: Hazard ratios for endometrial cancer by quartiles of height and overall adiposity measures in postmenopausal women

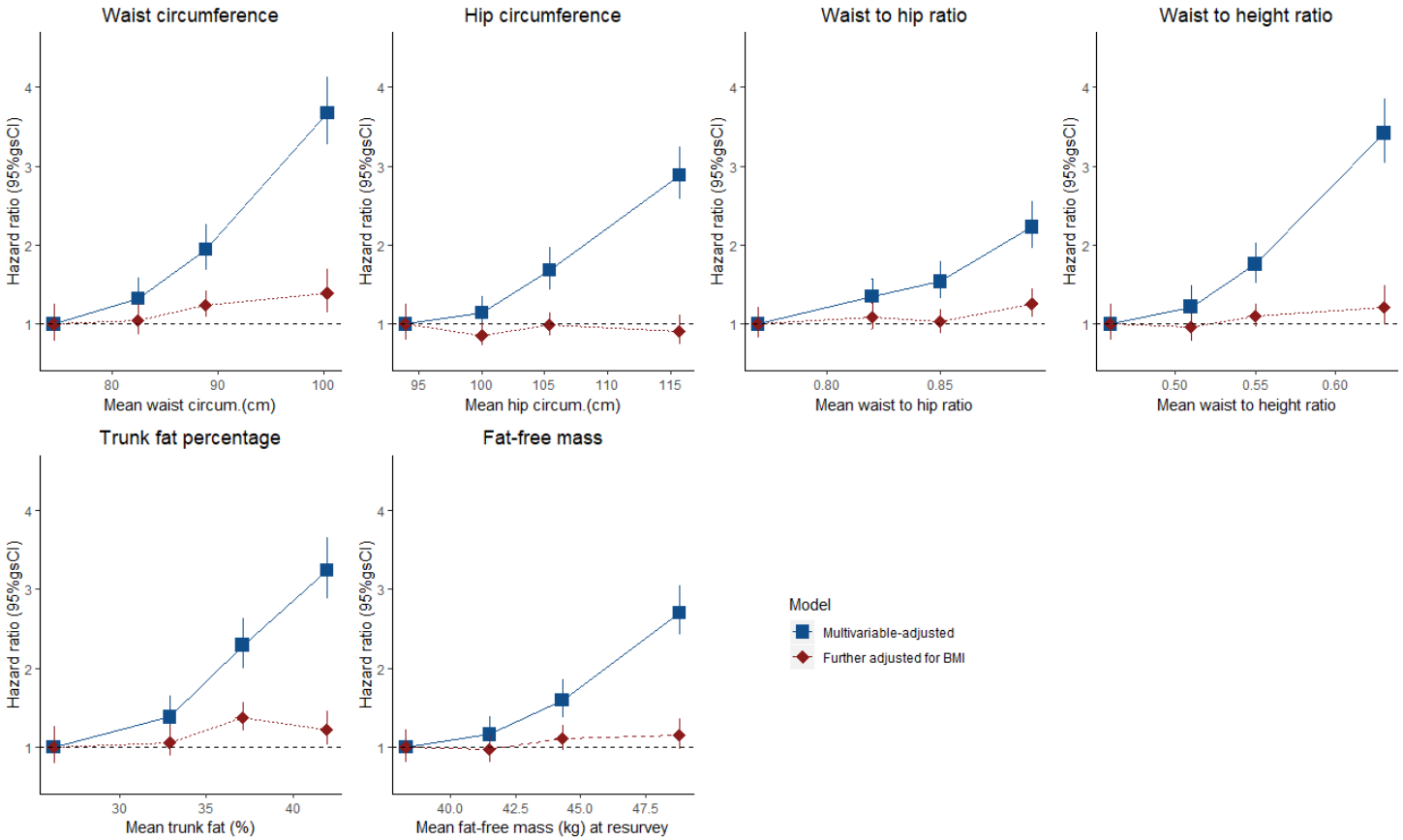


Figure 4-3: Hazard ratios for endometrial cancer by quartiles of central adiposity measures and fat-free mass in postmenopausal women

Chapter 5: Association of adiposity with endometrial cancer risk in important population subgroups

Summary

Limited evidence is available regarding the association of adiposity with endometrial cancer risk in important population subgroups such as HRT users, and the extent to which adiposity affects the risk of different subtypes of endometrial cancer is unclear. Using data from the Million Women Study cohort, this study examines in unprecedented detail the association of BMI with endometrial cancer risk. In a subset of the cohort, the risk associated with central adiposity was also explored. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of adiposity measures with endometrial cancer risk were estimated using Cox regression models. Among 674,971 postmenopausal women, 9,660 incident endometrial cancers were diagnosed during a mean follow-up time of 16.3 years per woman. The risk associated with a higher BMI varied considerably by HRT status, with stronger associations in never ($HR_{per\ 5\ kg/m2\ increment\ in\ BMI}$ = 1.78, 95%CI: 1.74-1.82) and past HRT users ($HR_{per\ 5\ kg/m2\ increment\ in\ BMI}$ = 1.72, 95%CI: 1.64-1.80) compared with current users ($HR_{per\ 5\ kg/m2\ increment\ in\ BMI}$ = 1.20, 95%CI: 1.07-1.36). The association between BMI and endometrial cancer risk did not differ by the type of HRT used or by the time since last use of HRT. Among postmenopausal never HRT users, there were suggestions of differences in the magnitude of association of BMI with risk by oral contraceptive use, parity, diabetes and time since menopause

($P_{heterogeneity}$ <0.05). The positive association between BMI and endometrial cancer risk was significantly stronger for type I ($HR_{per\ 5\ kg/m2\ increment\ in\ BMI}$ = 1.84, 95%CI: 1.79-1.88) than type II tumours ($HR_{per\ 5\ kg/m2\ increment\ BMI}$ = 1.46, 95%CI:1.35-1.58; $P_{heterogeneity}$ <0.0001). Central adiposity was independently associated with endometrial cancer risk, especially among women with BMI values below 25 kg/m^2. In conclusion, these findings provide support for the hypothesis that overall adiposity influences endometrial cancer risk through its oestrogenic effects.

5.1. Introduction

Previous research has established that HRT use modifies the association between adiposity and endometrial cancer risk, and that the association is attenuated in ever HRT users compared with never users.[16,21,24,25,33,152] However, it is unclear whether the effect of HRT on the risk associated with adiposity differs by the type of HRT used or the recency of use. Owing to limited sample size and insufficient information on HRT use, most previous studies were unable to assess the association between adiposity and endometrial cancer risk by levels of these characteristics. Examining the relationship between adiposity and endometrial cancer risk by type of HRT used and recency of use is important because it could provide useful insights into the mechanism through which adiposity and HRT interact with each other to influence endometrial cancer risk.

It is possible that other characteristics that affect endometrial cancer risk, such as oral contraceptive use and parity, also modify the relationship between adiposity and endometrial cancer risk.[325] However, data on the association of adiposity with endometrial cancer risk in subgroups defined by these characteristics are sparse.

Furthermore, there is limited evidence on the association of adiposity with the risk of different subtypes of endometrial cancer. While the association between adiposity and risk of oestrogen-dependent type I tumours is well established,[86,326] uncertainty remains regarding whether, and to what extent, adiposity influences the risk of type II tumours, which are thought to be

unrelated to oestrogen exposure[21,23,56,86,326] Notable limitations of previous studies assessing associations with type II tumours include a relatively small number of type II tumours and/or inclusion of some type I tumours in the type II category.[21,23,56,144]

The objective of this study is to robustly examine the association of adiposity, as measured by BMI, with endometrial cancer risk in important population subgroups and by tumour subtypes using data from the Million Women Study. In addition, because the previous analyses in UK Biobank (chapter 4) found a modest association between central adiposity and endometrial cancer risk independently of BMI, the associations of central adiposity measures with risk were also examined in this study in an attempt to replicate findings from UK Biobank and to further assess these associations in greater detail.

5.2. Methods

5.2.1. Analytical cohorts

Analyses relating to BMI and endometrial cancer risk were based on data from the recruitment cohort (i.e. women recruited into the Million Women Study). The characteristics of these women have been described in chapter 3 (section 3.4.1). Of the 789,964 women eligible for inclusion in this analysis, 41,072 women were excluded because they had missing BMI, 733 women were excluded because they had extreme values of BMI (<16 or >60 kg/m^2) and another 6,632 women were excluded because they had missing information on HRT status (figure 5-1).

Analyses relating to central adiposity measures (waist circumference, hip circumference, waist to hip ratio and waist to height ratio) and endometrial cancer risk were restricted to women who participated in the first resurvey when data on waist and hip circumferences were first reported. Similar exclusion criteria to that of the recruitment cohort were applied to this subcohort (section 3.4.1 and figure 3-4). In addition, premenopausal women (n = 46,926), women who reported ever use of HRT or who had missing HRT status (n = 265,088), those with missing data on waist circumference, hip circumference or height (n = 114,960) and those with extreme values of BMI ((<16 or >60 kg/m^2; n = 140)) were further excluded from these analyses (figure 5-2).

5.2.2. Assessment of adiposity measures

Height and weight were self-reported at recruitment. BMI was calculated as weight (kg) divided by the square of height (m). Weight was also self-reported during the first resurvey, which enabled recalculation of BMI for use in analyses relating to central adiposity measures. Waist and hip circumferences were first reported during the first resurvey. Waist to hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm). Waist to height ratio was calculated as waist circumference (cm) divided by height (cm).

5.2.3. Assessment of covariates

For all analyses, data on Townsend deprivation score, year of birth, age at menarche, duration of oral contraceptive use, frequency of strenuous

exercise and number of full-term pregnancies were taken from the recruitment questionnaire (see section 3.3 for definitions of these variables). For analyses in which BMI is the main exposure of interest, data on age at baseline, smoking status, use of HRT, menopausal status and diabetes were obtained from the recruitment questionnaire. For analyses relating to central adiposity measures, data on these covariates were obtained from the first resurvey questionnaire.

5.2.4. Outcome ascertainment

Incident cancers were identified through record linkage with the NHS cancer registries. Endometrial cancer was defined as ICD-10 C54. Tumour subtypes were defined using the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3). Type I endometrial cancers included ICD-O-3 codes: 8140, 8260, 8380-8382, 8480, 8481 and 8570 while type II endometrial cancers were defined as ICD-O-3 codes 8041, 8050, 8070, 8071, 8310, 8323, 8441, 8460, 8461 and 8560. Uterine sarcomas were defined as ICD-O-3 codes 8800, 8802, 8850, 8890, 8930 and 8933 while ICD-O-3 codes 8950, 8951 and 8980 were classified as Malignant Mixed Mullerian tumours (MMMTs).

5.2.5. Statistical analyses

Cox proportional hazard models, with time in study as the underlying time variable, were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association of BMI with endometrial cancer risk in premenopausal women; for postmenopausal women, this relationship

was examined according to HRT use (current, past and never). Women contributed person-time to these analyses from baseline (see table 3-2 for baseline dates for various analyses in the Million Women Study) until the earliest of the following events: diagnosis of any invasive cancer (except non-melanoma skin cancer, ICD-10: C44), hysterectomy, death, emigration or other loss to follow-up event, or end of follow-up (31 December 2016 for participants in Scotland, 31 December 2017 for all other participants). Premenopausal women contributed person-time up to the day they turned 55 years old and were censored thereafter.

For analyses in postmenopausal women, BMI was categorised as follows: <22.5, 22.5-<25.0 (referent), 25.0-<27.5, 27.5-<30.0, 30.0-<35.0 and ≥35.0 kg/m^2. Cut-points corresponding to WHO categories of underweight/normal weight (<25 kg/m^2; referent), overweight (25.0-<30.0 kg/m^2), class I obese (30.0-<35.0 kg/m^2) and class II/III obese (≥35.0 kg/m^2) were also used. Owing to the very small number of premenopausal women, BMI was assessed as ≥25.0 versus <25.0 kg/m^2. Tests for trend (postmenopausal women only) were performed by assigning repeat assessment median values from the second resurvey (conducted approximately 8 years after recruitment) to the baseline categories and modelling these values as a continuous variable. HRs and 95%CIs for endometrial cancer per 5 kg/m^2 increment in BMI were also calculated.

All models were stratified by year of birth (≤1930, in single years from 1931 to 1949, ≥1950) and year of data collection (in single years) and adjusted for age at baseline (continuous), deprivation score (quintiles of Townsend

deprivation index) and regions of cancer registry (10 regions at recruitment). The effect of further adjustment for age at menarche (<13, 13-<15, ≥15 years), duration of oral contraceptive use (never, 0-<5, 5-<10, 10-<15, ≥15 years), number of full-term pregnancies (0, 1, 2, ≥3), diabetes status (yes, no), frequency of strenuous exercise (never, <1, ≥1 day per week), smoking status (never, past and current) and, among postmenopausal women, age at menopause (<49, 49-<52, 52-<55, ≥55 years) were also examined. For each covariate, missing values were assigned to a separate category.

Where comparison is made between any two groups even if neither is the referent category, group-specific confidence intervals (gsCIs) for the HRs were calculated and presented in tables and figures;[321] however, conventional 95% CIs are given in the text. To account for measurement error, the HRs (95%CIs) for endometrial cancer based on baseline categories of BMI were plotted against the repeat assessment mean values (from the second resurvey) within the same category.[308] HRs (95%CIs) for endometrial cancer based on continuous measures were corrected for regression dilution bias by multiplying the log HRs and standard errors by the reciprocal of the regression dilution ratio for BMI (0.94) derived by regressing repeat measurements of BMI from second resurvey against the baseline values (see section 3.4.3). The proportional hazard assumption for each of the Cox models was assessed using log-log plots and tests based on Schoenfeld residuals.

5.2.5.1. Further analyses in postmenopausal current and past HRT users

For all analyses in current HRT users, participants were censored after a maximum follow-up of 5 years because many current HRT users at recruitment stopped using HRT during follow-up. This shortened follow-up time allowed for evaluation of the association of BMI with endometrial cancer risk when the potential for misclassification of HRT status was smaller. Additional analyses were carried out in current HRT users to assess whether the association of BMI with endometrial cancer risk differed by the type of HRT used (oestrogen only, oestrogen plus progestogen, tibolone and others). In past HRT users, further analyses were performed to assess whether the association of BMI with risk varied by the time since last use of HRT reported at baseline (<1, 1-<5, 5-<10, ≥10 years).

5.2.5.2. Further analyses in postmenopausal never HRT users

To eliminate any residual confounding by HRT use, further analyses, including those that assessed the association of BMI with endometrial cancer risk according to levels of other population characteristics and by tumour subtypes, were restricted to postmenopausal never HRT users only. These analyses are described below.

Shape of association

To characterise the shape of the association of BMI with endometrial cancer risk, BMI categories were defined as multiples of 2.5 kg/m^2 i.e. <22.5, 22.5-

<25.0 (referent), 25.0-<27.5, 27.5-<30.0, 30.0-<32.5, 32.5-<35.0, 35.0-<37.5, 37.5-<40.0 and ≥40.0 kg/m^2. HRs and 95% gsCIs for these categories were calculated and plotted against the repeat assessment mean values within each category in order to account for regression dilution bias.[308] Potential non-linearity in the association of BMI with risk was assessed using restricted cubic splines[327] with four knots positioned at the 5th, 35th, 65th and 95th percentiles of BMI distribution corresponding to BMI values of 20.3, 24.1, 27.2 and 35.6 kg/m^2, respectively.

Association by other population characteristics

Subgroup analyses were conducted according to age at study entry (<60, ≥60 years), number of full-term pregnancies (0, ≥1), age at menarche (<13, ≥13 years), oral contraceptive use (never, ever), diabetes (yes, no), smoking status (never, past, current), frequency of strenuous exercise (≤1, >1 days per week) and time since menopause (<10, 10-<20 and ≥20 years before baseline assessment). Potential variation between strata was assessed using chi square tests of heterogeneity.

Analysis by tumour subtypes

To evaluate the association of BMI with endometrial cancer risk by tumour subtypes, separate Cox models were fitted for each tumour subtype while censoring the other subtypes at the date of diagnosis. Test for heterogeneity between subtypes were conducted using the competing risk approach described by Lunn and McNeil.[328] Briefly, a separate observation for each subject was created for each event type (type I and type II), and a Cox model

that included an interaction between the event type and all covariates was fitted allowing for estimation of separate association for each subtype in the same model. A second model which assumes the same association for both subtypes was fitted by excluding the interaction term between event type and BMI. Likelihood ratio tests compared models which assumed different association for each subtype to the one that assumed the same association.

5.2.5.3. Sensitivity analyses

The main analyses in postmenopausal women were based on the assumption that women maintained their baseline HRT status throughout the follow-up period. However, many women who stated that they were currently using HRT at baseline stopped use over time. For example, among women who participated in the second resurvey (on average, 7.8 years after recruitment), 83% of women who were current HRT users at recruitment indicated they were past users at second resurvey. To minimise bias due to misclassification of HRT status, the main analyses censored current HRT users after a follow-up duration of 5 years. Sensitivity analyses that examined the impact of incremental increase in follow-up period (6, 7 and 8 years) on the risk estimates in current HRT users were performed in order to assess whether the association is significantly different for a longer follow-up period.

Because the proportion of women who started using HRT during follow-up was relatively small (among women who were participants in the second resurvey, 1.7% of women who were never users at baseline and 2% of past

users at baseline indicated that they were current HRT users at second resurvey), the main analyses censored these women at the end of the full follow-up period (see section 5.2.5). Sensitivity analyses that examined the risk associated with BMI in never and past HRT users when follow-up was censored at 5 years were also performed in order to assess whether the association is different for a shorter follow-up period, when the potential for misclassification was smaller.

To account for changes in BMI over time, among postmenopausal never HRT users, BMI was modelled as a time-varying exposure, using data from the first, second and third resurveys (conducted, on average, 3.3 years, 7.8 years and 12.5 years, respectively, after recruitment) to update BMI during follow-up. Women with missing information on BMI at each resurvey were put in a separate category. Finally, among postmenopausal never HRT users, the potential effect of reverse causation (i.e. early symptoms of diseases influencing BMI) on the association of BMI with endometrial cancer risk was assessed by excluding the first 5 years of follow-up.

5.2.5.4. Associations of central adiposity measures with endometrial cancer risk

Cox regression models were used to estimate HRs and corresponding 95%CIs for the associations of waist circumference, hip circumference, waist to hip ratio and waist to height ratio with endometrial cancer risk among women who were postmenopausal never HRT users at first resurvey (n = 175,846). All central adiposity measures were categorised into thirds of their

distributions in this subcohort and HRs for endometrial cancer were estimated for each category with the lowest third as the reference group. HRs and 95%CIs for endometrial cancer per 1-SD unit increment in each measure were also estimated.

Models were adjusted for the same covariates as those in the analysis of the association of BMI with endometrial cancer risk (see section 5.2.5). As mentioned earlier, data on covariates used in these analyses were taken from the recruitment questionnaire, with the exception of diabetes, smoking status, age and year of data collection, which were based on data collected at first resurvey. To assess the independent associations of central adiposity measures with risk, the effect of additional adjustment for BMI (calculated using updated weight from first resurvey) modelled as a continuous measure was also examined.

To further assess the independent associations of central adiposity measures, the association of each measure with endometrial cancer risk was evaluated within standard categories of BMI (<25, 25-<30, $\geq$30 kg/m^2). Additional analyses were performed to assess whether the relationship between central adiposity and risk differed by tumour subtypes (type I and type II tumours). The methods used were the same as those in the analyses of the association of BMI with risk of different subtypes of endometrial cancer risk (section 5.2.5.2).

All statistical analyses were conducted using STATA version 15.0.

5.3. Results

After all exclusions as shown in figure 5-1, a total of 741,527 women (91% postmenopausal), with a mean (SD) age at baseline of 57.6 (4.7) years were included in the analyses of BMI and endometrial cancer risk. The characteristics of participants according to baseline categories of BMI are presented in table 5-1. Compared with women in the lowest category of BMI (<25 kg/m^2), those with a higher BMI were more likely to have a history of diabetes and to live in the most deprived areas. They were more likely to report an earlier age at menarche and were less likely to be current smokers, or ever users of oral contraceptives or HRT (table 5-1).

5.3.1. BMI and endometrial cancer risk in premenopausal women

Among 66,556 premenopausal women included in this analysis (mean age at baseline = 51.2 years), 60 endometrial cancers were diagnosed among women who were considered to be of premenopausal age (mean age at diagnosis = 53.3 years) during a mean follow-up of 3.7 years per woman. Overall, there was no association between BMI and endometrial cancer risk in either minimally- or multivariable-adjusted model (multivariable-adjusted $HR_{BMI \geq 25 \text{ vs } < 25 \text{ kg/m2}}$ =1.19, 95%CI: 0.70-2.01; table 5-2). Due to limited statistical power, no further analyses were performed in premenopausal women.

5.3.2. BMI and endometrial cancer risk by HRT status in postmenopausal women

Of the 674,971 postmenopausal women included in this analysis, 58.3% were never HRT users at recruitment, 17.9% were past users and 23.8% were current users. During a mean follow-up of 16.3 years per woman, 9,660 endometrial cancers were diagnosed, with a mean age at diagnosis of 68.8 (SD=6.4) years.

Table 5-3 and figure 5-3 show the HRs (95%gsCIs) for the association of BMI with endometrial cancer risk according to HRT status at recruitment. Because results did not differ substantially between minimally- and multivariable-adjusted models, only results from multivariable-adjusted models are presented. The effect of adjustment for each confounder among postmenopausal never HRT users is discussed later (section 5.3.2.2).

As expected, the risk associated with BMI differed substantially by HRT status ($P_{heterogeneity}$ <0.0001), with the strongest association in never HRT users. After correcting for regression dilution bias, the HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were 1.78 (1.74-1.82) among never HRT users, 1.72 (1.64-1.80) among past users and 1.20 (1.07-1.36) among current users (table 5-3).

5.3.2.1. Association by type of HRT used and time since last used of HRT

Among current HRT users, the association between BMI and endometrial cancer risk did not differ significantly by the type of HRT used ($P_{heterogeneity}$ = 0.8), suggesting that type of HRT does not modify the risk associated with adiposity. The HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were 1.34 (0.80-2.24) among users of oestrogen-only therapy; 1.21 (1.04-1.40) among users of combined oestrogen and progestogen therapy; 1.24 (1.12-1.37) among users of tibolone; and 1.72 (0.85-3.48) among users of other menopausal HRT subtypes (table 5-4).

Among past users, no significant difference in the association by time since last use of HRT was apparent; the HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI among women who stopped using HRT <1, 1-<5, 5-<10 and $\geq$10 years before baseline were 1.76 (1.54-2.02), 1.77 (1.66-1.89), 1.72 (1.57-1.88) and 1.75 (1.51-2.03), respectively ($P_{heterogeneity}$ = 0.97; table 5-5). Hence, the effect of HRT on adiposity-related risk of endometrial cancer appears to wear off quickly (i.e. within 1 year) after use ceased.

5.3.2.2. Further analyses in never HRT users

As mentioned previously, further analyses including analyses that evaluated the association between BMI and endometrial cancer risk by other population characteristics were restricted to postmenopausal never HRT users to eliminate any residual confounding by HRT.

Shape of association

Among postmenopausal never HRT users, BMI showed an approximately linear association with endometrial cancer risk (figure 5-4). Although the test for non-linearity was statistically significant in the restricted cubic spline model, the association appeared approximately linear in the plot (figure 5-5).

Effect of adjustment for various confounders

The effect of adjustment for potential confounders on the association of BMI with endometrial cancer risk among postmenopausal never HRT users is shown in table 5-6. Overall, the risk estimate from the model that was adjusted for all confounders (i.e. age at menarche, number of full-term pregnancies, duration of oral contraceptive use, age at menopause, frequency of strenuous exercise, diabetes status and smoking status) was not substantially different from that of the model stratified by year of birth and year of data collection, and adjusted for age, deprivation score and region only, although duration of oral contraceptive use, age at menarche and age at menopause appeared to attenuate the associations the most when each covariate was added independently (table 5-6).

Subgroup analyses

Figure 5-6 shows the association between BMI and endometrial cancer risk according to baseline levels of selected population characteristics. The association between BMI and endometrial cancer risk did not differ by age at baseline, age at menarche, smoking status or frequency of strenuous

exercise. However, there were statistically significant differences in the association by oral contraceptive use and by parity (figure 5-6). The HR for endometrial cancer per 5 kg/m^2 increment in BMI appeared to be slightly stronger among ever users of oral contraceptives (HR =1.89, 95%CI:1.83-1.96) than never users (HR =1.73, 95%CI:1.68-1.78; $P_{heterogeneity}$ <0.0001), and among parous (HR =1.80, 95%CI:1.76-1.84) compared with nulliparous women (HR =1.66, 95%CI:1.57-1.76; $P_{heterogeneity}$ = 0.01). There were also suggestions of differences in the association by diabetes and time since menopause (P <0.05; figure 5-6).

To assess the differences in association by oral contraceptive use and parity in more detail, the association between BMI and endometrial cancer risk was additionally examined by the duration of oral contraceptive use (<5, 5-<10, ≥10 years) and by the number of full-term pregnancies (1, 2, ≥3). Among ever users of oral contraceptives, the HRs for endometrial cancer per 5 kg/m^2 increment in BMI for women who used the pill for <5, 5-<10 and ≥ 10 years were 1.83 (1.74-1.92), 1.95 (1.82-2.10) and 2.04 (1.88-2.22), respectively ($P_{heterogeneity}$ = 0.06). Among parous women, the HRs for endometrial cancer per 5 kg/m^2 increment in BMI were 1.85 (1.75-1.96), 1.82 (1.76-1.89) and 1.78 (1.72-1.85) for women who had 1, 2 and ≥3 full term pregnancies, respectively ($P_{heterogeneity}$ = 0.48).

Association by tumour subtypes

Table 5-7 shows the association between BMI and risk of different subtypes of endometrial cancer. Of the 5,659 incident endometrial cancers identified

among postmenopausal never HRT users, 4,663 were type I tumours, 572 were type II tumours, 66 were uterine sarcomas, 243 were MMMTs and 115 were unclassified. BMI was positively associated with both type I and type II tumours, although the association was significantly stronger for type I ($HR_{\text{per 5 kg/m2 increment in BMI}}$ = 1.84, 95%CI: 1.79-1.88) than type II tumours ($HR_{\text{per 5 kg/m2 increment BMI}}$ = 1.46, 95%CI:1.35-1.58; $P_{heterogeneity}$ <0.001). BMI was also positively associated with the risk of uterine sarcomas, MMMTs and unclassified subtypes (P_{trend} <0.0001 for each subtype, table 5-7). The association between BMI and specific histological subtypes of type I (endometroid and adenocarcinoma NOS) and type II endometrial cancers (serous and clear cell carcinoma) are shown in appendix 5a.

5.3.2.3. Sensitivity analyses

In the main analyses, postmenopausal current HRT users were censored after 5 years of follow-up in order to minimise misclassification bias due to women stopping HRT use over time. However, because of the short follow-up time, the number of incident cases of endometrial cancer was relatively small (n = 385). In sensitivity analyses that assessed the effect of including incrementally longer follow-up (by censoring women after a follow-up duration of 6, 7 and 8 years), the risk estimates for the association of BMI with risk were not substantially different from that of the main analyses (table 5-8), suggesting that the weaker association between BMI and endometrial cancer risk among current HRT users in this study is not due to the shorter follow-up time.

Because the potential for misclassification of HRT status was smaller among never and past HRT users, these women were censored at the end of the full follow-up period rather than after 5 years of follow-up. However, sensitivity analyses were also performed that examined the association of BMI with endometrial cancer risk when these women were censored after 5 years of follow-up. Results from these analyses were not substantially different from that of the main analyses, suggesting that changes in HRT status that may occur during longer periods of follow-up had minimal impact on these risk estimates (table 5-9).

Results from the sensitivity analysis that modelled BMI as a time-varying variable among postmenopausal never HRT users were not materially different from that of the main analyses, suggesting that changes in BMI over time did not significantly affect the risk estimates (table 5-10). Also, results from sensitivity analyses that excluded the first five years of follow-up in order to assess the effect of potential reverse causation did not differ substantially from that of the main analyses (table 5-10).

5.3.3. Central adiposity and endometrial cancer risk among postmenopausal never HRT users at first resurvey

A total of 175,846 postmenopausal never HRT users at first resurvey were included in the analyses of central adiposity measures and endometrial cancer risk. During a mean follow-up of 14.1 years per woman, 1,913 endometrial cancers were identified, with a mean age at diagnosis of 69.3 (SD=6.3) years. BMI at first resurvey was highly correlated with waist

circumference, hip circumference and waist to height ratio in this subcohort (r >0.65) but showed weaker correlation with waist to hip ratio (r = 0.30; table 5-11).

In multivariable-adjusted models that did not include BMI, all measures of central adiposity demonstrated a strong positive association with endometrial cancer risk (P_{trend} <0.0001; table 5-12). The HRs (95%CIs) for endometrial cancer per 1-SD increment in waist circumference, hip circumference, waist to hip ratio and waist to height ratio were 1.60 (1.53-1.68), 1.69 (1.61-1.77), 1.30 (1.22-1.38) and 1.58 (1.51-1.65), respectively. These multivariable-adjusted risk estimates were not substantially different from those of models stratified by year of birth and year of data collection and adjusted for age, UK region and deprivation score only (table 5-13). After further adjustment for BMI, the associations of all central adiposity measures with endometrial cancer risk were attenuated, although waist and hip circumference remained significantly associated with endometrial cancer risk ($HR_{\text{per 1-SD increment in waist circumference}}$= 1.08, 95%CI: 1.03-1.13; $HR_{\text{1-SD increment in hip circumference}}$ = 1.09, 95%CI: 1.04-1.14; table 5-12).

When these associations were stratified by BMI group, statistically significant associations were only found for women with BMI values below 25 kg/m^2. There was no significant association between central adiposity measures and endometrial cancer risk in women with BMI values of 25.0-<30.0 kg/m^2 or $\geq$30.0 kg/m^2 (table 5-14). For instance, the HR (95%CIs) for endometrial cancer per 1-SD (9.4 cm) increment in waist circumference for women with BMI values below 25 kg/m^2 was 1.23 (1.10-1.37), but for women with BMI

values of 25.0-<30.0 kg/m^2 and ≥30.0 kg/m^2, the corresponding HRs were 0.98 (0.91-1.06) and 1.05 (0.97-1.13), respectively (table 5-14).

Table 5-15 shows the associations of measures of central adiposity with endometrial cancer risk by tumour subtypes. In multivariable-adjusted models that did not include BMI, the associations of all measures of central adiposity with risk were significantly stronger for type I than type II tumours. For example, the HRs (95%CIs) for endometrial cancer per 1-SD increment in waist circumference were 1.66 (1.58-1.75) for type I tumours and 1.30 (1.11-1.52) for type II tumours. Additional adjustment for BMI attenuated the associations of all central adiposity measures with the risk of both type I and type II tumours. Further, no heterogeneity in the association of central adiposity with endometrial cancer risk by tumour subtypes was apparent in BMI-adjusted multivariable models (table 5-15).

5.4. Discussion

In this large cohort, HRT modified the association of adiposity with endometrial cancer risk such that each 5 kg/m^2 increment in BMI increased the risk of developing endometrial cancer by 78%, 72% and 20% among never, past and current HRT users, respectively. However, the risk associated with a higher BMI did not differ significantly by the type of HRT used among current HRT users or by the time since last use of HRT in past users. Among postmenopausal never HRT users, BMI demonstrated an approximately linear association with risk. There were suggestions of heterogeneity in the association by oral contraceptive use, parity, time since

menopause and diabetes. The risk associated with BMI was significantly stronger for type I than type II tumours. Central adiposity was associated with endometrial cancer risk independently of overall adiposity in women with BMI values below 25 kg/m^2.

5.4.1. BMI and endometrial cancer risk

Previous studies have shown that the association between adiposity and endometrial cancer risk is attenuated in ever HRT users compared with never users.[16,21,24,33,152] The large size of this cohort allowed for reliable estimation of the risk associated with adiposity in current and past HRT users separately. The results suggest that the association between adiposity and endometrial cancer risk is attenuated only in current HRT users. The magnitude of association between adiposity and endometrial cancer risk in past HRT users, regardless of time since last used, was broadly comparable to that of never HRT users, suggesting that the attenuating effect of HRT wears off quickly once HRT use ceased. To my knowledge, only one other study, involving a relatively small number of endometrial cancers (n = 677), has assessed the prospective association of BMI with endometrial cancer risk in current and past HRT users separately.[24] In that study, the risk associated with adiposity appeared to be stronger in past HRT users ($HR_{BMI\ >30\ vs\ <25\ kg/m2}$ =2.53, 95%CI: 1.21-5.30) than current users ($HR_{BMI\ >30\ vs\ <25\ kg/m2}$ =1.44, 95%CI: 1.00-2.05), although the risk estimates were not significantly different. The study, however, did not examine the association between BMI and endometrial cancer risk by the time since last HRT use.[24]

In the current analysis, there was no heterogeneity in the association of BMI with endometrial cancer risk by the type of HRT used (oestrogen-only, oestrogen plus progestogen, tibolone). This implies that a common, predominantly oestrogenic, mechanism underlies the attenuating effect of HRT on the association. Indeed, the pattern of variation in the association by HRT use is in line with the hypothesis that adiposity increases endometrial cancer risk through its oestrogenic effects.[53] As reviewed in chapter 2, after menopause, oestrogen is derived mainly from aromatisation of androgen to oestrone in the adipose tissue.[161] Thus, in postmenopausal women, a higher BMI is associated with a higher level of circulating oestrogen.[76,281,329] Oestrogen through oestrogen receptors signals endometrial cell proliferation which could lead to malignancy.[53] Current HRT users have substantially higher levels of oestrogen compared with women who do not use HRT.[330] In the excess oestrogen environment of these women, the impact of adipose tissue-derived oestrogen on carcinogenesis may be less pronounced possibly because of receptor saturation. When women stop using HRT, levels of oestrogen quickly return to baseline levels i.e. to the levels of never users,[331] which may explain the similar association of BMI with endometrial cancer risk in past and never HRT users.

The increase in risk of endometrial cancer with increasing adiposity was continuous throughout the range of BMI observed in postmenopausal never HRT users i.e. there was no evidence of a threshold effect. This is consistent with results from several large epidemiological studies[16,17,34] and

emphasises the importance of keeping weight as low as possible in order to minimise the risk of developing endometrial cancer.

There were significant differences in the magnitude of association of BMI with endometrial cancer risk by oral contraceptive use and parity, with more pronounced associations among ever users of oral contraceptives than never users, and among parous women compared with nulliparous women. To my knowledge, no previous prospective study has reported such effect modification by oral contraceptive use or parity. There were also suggestions of heterogeneity in the association of BMI with risk by diabetes and by time since menopause. It is unclear whether these results reflect true differences in the biological effects of BMI by these characteristics or whether they are due to a play of chance given the number of tests conducted. Additional studies are needed to confirm or refute these findings.

In this study, the association between adiposity and endometrial cancer risk was stronger for oestrogen-dependent type I tumours than type II tumours. This is consistent with results from previous studies[21,23,56,86] and provides additional support for the hypothesis that BMI influences endometrial carcinogenesis through its oestrogenic effects. The positive association with type II tumours, which are thought to be unrelated to oestrogen exposure, is also noteworthy, as it implies that other (i.e. non-oestrogenic) mechanisms might also mediate the association of adiposity with endometrial cancer risk. Plausible biological mechanisms include insulin resistance and chronic low-grade inflammation.[313,315] An alternative explanation for the association with type II tumours is that the oestrogenic effect of BMI may also have an impact

on the development of type II endometrial cancer, implying that type II tumours, at least to some extent, may be caused by oestrogen-driven proliferation.[86] This latter hypothesis is supported by studies showing that factors which modulate oestrogen levels such as oral contraceptive use, age at menarche and age at menopause also affect the risk of type II endometrial cancers.[56,86] Future studies should clarify the mechanisms through which adiposity influences the risk of type II endometrial cancer.

5.4.2. Central adiposity and endometrial cancer risk

The current data suggest that central adiposity contributes to endometrial cancer risk independently of BMI. This is consistent with results from the UK Biobank (see appendix 5b for comparable risk estimates) and adds to evidence for a role of central adiposity in endometrial carcinogenesis. However, the effect of central adiposity on risk in this study appeared to be limited to women with BMI values below 25 kg/m^2. As far as I am aware, this is the first study to examine the association between central adiposity and endometrial cancer risk by BMI level. A possible explanation for this finding might be that visceral adiposity influences endometrial carcinogenesis though a metabolic pathway which is different from that of overall adiposity and which may be less pronounced in overweight or obese women as hormonal mechanisms of carcinogenesis may predominate. It is also possible that this finding is due to chance. Further research is needed to establish whether the effect of central adiposity on endometrial cancer risk differs by BMI level.

5.4.3. Strengths and limitations

The strengths of this study include its prospective design, the large number of incident endometrial cancers and availability of data on a variety of covariates which allowed for an unprecedented in-depth analysis of the prospective association of BMI with endometrial cancer risk in different population subgroups and by tumour subtypes. Updated information on adiposity measures available for some participants enabled correction of risk estimates for regression dilution bias due to measurement error.

A major limitation of this study is the reliance on self-reported anthropometric measures, which is subject to inaccurate reporting. However, self-reported anthropometric measures have been shown to be valid in this cohort.[118] The Pearson's correlation coefficients between self-reported and measured values of BMI, waist and hip circumference in a subset of this cohort were 0.95, 0.71 and 0.82, respectively.[118] Despite the large size of the Million Women Study, this study lacked sufficient statistical power to examine the association between BMI and endometrial cancer risk in premenopausal women, owing to the recruitment strategy of the cohort that invited women aged 50-64 years to join as part of their breast cancer screening visit. Information on covariates was based on data collected at one point in time. This may lead to bias in risk estimates for variables which are likely to change during periods of follow-up.

5.5. Conclusion

The association between BMI and postmenopausal endometrial cancer risk was significantly stronger in past HRT users than current HRT users, suggesting that the attenuating effect of HRT on the risk associated with adiposity wears off once use ceased. BMI was more strongly related to the risk of type I than type II tumours consistent with the hypothesis that BMI influences endometrial carcinogenesis through its oestrogenic effects. Central adiposity was associated with an increased risk of endometrial cancer independently of BMI among women with BMI values below 25 kg/m^2, adding to evidence for a role of central adiposity in endometrial carcinogenesis. Future studies should investigate possible variations in the effect of BMI on endometrial cancer risk by oral contraceptive use, parity, diabetes and time since menopause, and the mechanisms underlying the association of BMI and central adiposity measures with endometrial cancer risk.

Table 5-1: Baseline characteristics of women included in analysis assessing the association of BMI with endometrial cancer risk

Characteristics	**All women**	**BMI categories (kg/m^2)**			
		<25.0	**25.0 - <30.0**	**30.0 -<35.0**	**≥35.0**
Number of women	741,527	353,365	261,835	89,547	36,780
BMI (kg/m^2), mean (SD)	26.1 (4.6)	22.6 (1.7)	27.1 (1.4)	32.0 (1.4)	38.8 (3.7)
Age at recruitment (years), mean (SD)	57.6 (4.7)	57.4 (4.8)	57.9 (4.7)	57.9 (4.6)	57.3 (4.5)
Most deprived, n (%)	141,540 (19.1)	57,638 (16.3)	51,000 (19.5)	21,743 (24.3)	11,159 (30.3)
Age at menarche (years), mean (SD)	13.1 (1.6)	13.2 (1.6)	13.0 (1.6)	12.7 (1.6)	12.5 (1.6)
Nulliparous, n (%)	87,707 (11.7)	45,445 (12.9)	27.481 (10.5)	9,527 (10.6)	4,254 (11.6)
Ever users of oral contraceptives, n (%)	409,734 (55.3)	203,653 (57.6)	141,183 (53.9)	46,316 (51.7)	18,582 (50.5)
Current smokers, n (%)	135,701 (18.3)	72,450 (20.5)	44,753 (17.1)	13,551 (15.1)	4,947 (13.5)
Had a history of diabetes, n (%)	20,515 (2.8)	4,505 (1.3)	6,843 (2.6)	5,195 (5.8)	3,972 (10.8)
Postmenopausal, n (%)	674,971 (91.0)	320,092 (90.1)	239,995 (91.7)	81,804 (91.4)	33,080 (89.9)
Age at menopause (years), mean (SD)	49.4 (4.2)	49.3 (4.1)	49.5 (4.2)	49.6 (4.4)	49.6 (4.5)
Ever users of HRT at recruitment, n (%)	281,356 (41.7)	140,740 (44.0)	99,361 (41.4)	30,748 (37.6)	10,507 (31.8)

SD = Standard deviation

Table 5-2: Hazard ratios for endometrial cancer associated with BMI in premenopausal women

BMI (kg/m^2) categories	Number of women/ cases	Minimally adjusted HR (95%CI)	Multivariable- adjusted HR (95%CI)
<25.0	33,273 / 26	Referent	Referent
≥25.0	33,283 / 34	1.35 (0.81-2.27)	1.19 (0.70-2.01)

Minimally adjusted models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score and region.
Multivariable-adjusted models included all the variables defined above and, number of full-term pregnancies, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise per week and diabetes status.

Table 5-3: Hazard ratios for endometrial cancer associated with BMI in postmenopausal women according to HRT status at recruitment

BMI (kg/m^2) categories	Never HRT users at recruitment		Past HRT users at recruitment		Current HRT users at recruitment[1]	
	Number of women/cases	Multivariable-adjusted HR (95%gsCI)	Number of women/cases	Multivariable-adjusted HR (95%gsCI)	Number of women/cases	Multivariable-adjusted HR (95%gsCI)
<22.5	75,413 / 408	0.68 (0.62-0.75)	21,131 / 145	0.75 (0.63-0.88)	38,658 / 73	0.81 (0.64-1.02)
22.5-<25.0	103,939 / 854	1.00 (0.93-1.07)	32,461 / 308	1.00 (0.89-1.12)	48,490 / 115	1.00 (0.83-1.20)
25.0-<27.5	85,607 / 988	1.39 (1.31-1.48)	27,670/ 337	1.26 (1.13-1.40)	34,590 / 86	1.05 (0.85-1.30)
27.5-<30.0	55,027 / 933	2.02 (1.90-2.16)	17,926 / 313	1.78 (1.59-1.99)	19,175 / 48	1.06 (0.80-1.41)
30.0-<35.0	51,056 / 1,343	3.13 (2.96-3.30)	15,697 / 388	2.50 (2.27-2.77)	15,051 / 45	1.28 (0.96-1.72)
≥35.0	22,573 / 1,133	6.05 (5.70-6.44)	5,665 / 255	4.67 (4.11-5.31)	4,842 / 18	1.68 (1.05-2.69)
P for trend		<0.0001		<0.0001		0.002
HR (95%CI) per 5 kg/m^2 increment in BMI	393,615 / 5,659	1.78 (1.74-1.82)	120,550 / 1,746	1.72 (1.64-1.80)	160,806 / 385	1.20 (1.07-1.36)

[1]Current HRT were censored after a maximum follow-up of 5 years.
Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).

Table 5-4: Hazard ratios for endometrial cancer associated with BMI in postmenopausal current HRT users by type of HRT used at recruitment

BMI (kg/m^2) categories	Type of HRT used								All current users	
	Oestrogen only		Oestrogen + progesterone		Tibolone		Others			
	Number of women/ cases	Multivariable-adjusted HR (95%gsCI)	Number of women/cases	Multivariable-adjusted HR (95%gsCI)	Number of women/ cases	Multivariable-adjusted HR (95%gsCI)	Number of women/ cases	Multivariable-adjusted HR (95%gsCI)	Number of women/ cases	Multivariable-adjusted HR (95%gsCI)
<25.0	3,738 / 13	1.00 (0.55-1.81)	71,614/ 132	1.00 (0.84-1.20)	9,253 / 36	1.00 (0.71-1.40)	2,543 / 7	1.00 (0.33-3.00)	87,148 / 188	1.00 (0.86-1.16)
25.0-<30.0	2,287 / 11	1.20 (0.64-2.25)	42,735/ 90	1.17 (0.96-1.44)	7,110 / 30	1.02 (0.71-1.46)	1,633 / 3	0.64 (0.11-3.64)	53,765 / 134	1.15 (0.97-1.36)
≥30.0	824 / 3	1.12 (0.34-3.71)	15,479/ 41	1.56 (1.14-2.13)	2,856 / 15	1.32 (0.78-2.23)	734 / 4	4.87 (1.00-23.83)	19,893 / 63	1.50 (1.16-1.93)
P for trend		0.770		0.016		0.421		0.148		0.008
HR (95%CI) per 5 kg/m^2 increment in BMI	6,849 / 27	1.34 (0.80-2.24)	129,828 / 263	1.21 (1.04-1.40)	19,219 / 81	1.24 (1.12-1.37)	4910 / 14	1.72 (0.85-3.48)	160,806 / 385	1.20 (1.07-1.36)

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
Women were censored after a maximum follow-up of 5 years.
HRs (95%CI) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).
P for heterogeneity across all four categories = 0.80.

Table 5-5: Hazard ratios for endometrial cancer associated with BMI in postmenopausal past users according to time since last use of HRT reported at recruitment

BMI (kg/m^2) categories	Time since last HRT use reported at baseline								All past users	
	<1 year		1-<5 years		5-<10years		≥10years			
	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)
<25.0	57	1.00 (0.76-1.31)	207	1.00 (0.87-1.15)	108	1.00 (0.82-1.22)	43	1.00 (0.73-1.37)	453	1.00 (0.91-1.10)
25.0-<30.0	80	1.81 (1.45-2.25)	303	1.70 (1.52-1.91)	166	1.69 (1.45-1.96)	50	1.17 (0.88-1.55)	650	1.62 (1.50-1.75)
30.0-<35.0	43	3.17 (2.34-4.28)	176	2.80 (2.42-3.25)	89	2.56 (2.08-3.15)	43	2.71 (2.00-3.68)	388	2.76 (2.50-3.05)
≥35.0	26	5.81 (3.89-8.68)	124	5.82 (4.84-6.98)	63	5.12 (3.95-6.63)	28	4.99 (3.36-7.41)	255	5.14 (4.53-5.84)
P for trend		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
HR (95%CI) per 5 kg/m^2 increment in BMI	206	1.76 (1.54-2.02)	810	1.77 (1.66-1.89)	426	1.72 (1.57-1.88)	164	1.75 (1.51-2.03)	1,746	1.72 (1.64-1.80)

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).
Test for heterogeneity in HR per 5 kg/m^2 increment in BMI across categories of time since last use: $x^2 = 0.26$, $p = 0.97$.

Table 5-6: Hazard ratios for endometrial cancer associated with a 5 kg/m^2 increment in BMI among postmenopausal never HRT users (n = 393,615) adjusted for different confounders

	HR (95% CI) per 5 kg/m^2 increment in BMI
Stratified by year of birth and year of recruitment and adjusted for age (years), UK region and deprivation score	1.85 (1.81-1.89)
Adjusted independently for:	
Age at menarche (years)	1.83 (1.79-1.87)
Number of full-term pregnancies	1.86 (1.82-1.90)
Duration of oral contraceptive use (years)	1.83 (1.80-1.87)
Age at menopause (years)	1.83 (1.79-1.86)
Frequency of strenuous exercise	1.84 (1.81-1.88)
Diabetes status	1.85 (1.81-1.88)
Smoking status	1.84 (1.81-1.88)
Adjusted for all covariates	1.78 (1.74-1.82)

Table 5-7: Hazard ratios for endometrial cancer associated with BMI in postmenopausal never HRT users by tumour subtypes

BMI (kg/m^2) categories	Tumour subtypes										All subtypes	
	Type I		Type II		Uterine Sarcoma		MMMT		Others			
	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)
<25.0	977	1.00 (0.94-1.07)	171	1.00 (0.85-1.17)	16	1.00 (0.60-1.67)	68	1.00 (0.78-1.28)	30	1.00 (0.69-1.46)	1,262	1.00 (0.94-1.06)
25.0-<30.0	1,569	1.99 (1.89-2.09)	200	1.43 (1.25-1.64)	25	1.92 (1.30-2.83)	90	1.70 (1.38-2.09)	37	1.57 (1.14-2.17)	1,921	1.88 (1.80-1.97)
30.0-<35.0	1,115	3.83 (3.61-4.06)	129	2.54 (2.14-3.01)	16	3.27 (2.00-5.33)	58	3.05 (2.36-3.94)	25	2.95 (2.00-4.36)	1,343	3.58 (3.39-3.78)
≥35.0	1,002	7.85 (7.36-8.37)	72	3.30 (2.60-4.18)	9	4.19 (2.14-8.19)	27	3.36 (2.28-4.94)	23	6.25 (4.08-9.57)	1,133	6.92 (6.51-7.35)
P for trend		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
HR (95%CI) per 5 kg/m^2 increment in BMI	4,663	1.84 (1.79-1.88)	572	1.46 (1.35-1.58)	66	1.63 (1.32-2.01)	243	1.50 (1.33-1.68)	115	1.69 (1.45-1.97)	5,659	1.78 (1.74-1.82)

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).
Test for heterogeneity between type I and type II tumours (p <0.0001).

Table 5-8: Hazard ratios for endometrial cancer associated with BMI in postmenopausal current HRT users by duration of follow-up

BMI (kg/m^2) categories	Maximum duration of follow-up							
	5 years		6years		7years		8 years	
	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)
<22.5	73	0.81 (0.64-1.02)	83	0.78 (0.62-0.97)	101	0.79 (0.65-0.96)	121	0.80 (0.67-0.97)
22.5-<25.0	115	1.00 (0.83-1.20)	137	1.00 (0.84-1.19)	165	1.00 (0.86-1.17)	195	1.00 (0.87-1.15)
25.0-<27.5	86	1.05 (0.85-1.30)	103	1.05 (0.87-1.28)	120	1.02 (0.85-1.22)	141	1.01 (0.85-1.19)
27.5-<30.0	48	1.06 (0.80-1.41)	60	1.12 (0.87-1.44)	79	1.22 (0.98-1.52)	93	1.20(0.98-1.47)
30.0-<35.0	45	1.28 (0.96-1.72)	55	1.32 (1.01-1.72)	69	1.37 (1.08-1.74)	84	1.38 (1.12-1.72)
≥35.0	18	1.68 (1.05-2.69)	21	1.67 (1.08-2.58)	26	1.70 (1.15-2.51)	37	1.99 (1.44-2.76)
P for trend		0.002		<0.0001		<0.0001		<0.0001
HR (95%CI) per 5 kg/m^2 increment in BMI	385	1.20 (1.07-1.36)	459	1.23 (1.10-1.37)	560	1.24 (1.12-1.37)	671	1.26 (1.16-1.38)

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status. HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).

Table 5-9: Hazard ratios for endometrial cancer associated with BMI in postmenopausal never and past HRT in analyses that censored participants after 5 years of follow-up

BMI (kg/m^2) categories	Never HRT users		Past HRT users	
	Number of cases	Multivariable adjusted HR (95%gsCI)	Number of cases	Multivariable adjusted HR (95%gsCI)
<22.5	75,413 / 87	0.82 (0.67-1.02)	21,131 / 25	0.68 (0.45-1.01)
22.5-<25.0	103,939 / 152	1.00 (0.85-1.17)	32,461 / 58	1.00 (0.77-1.30)
25.0-<27.5	85,607 / 178	1.37 (1.18-1.59)	27,670/ 54	1.06 (0.81-1.39)
27.5-<30.0	55,027 / 148	1.72 (1.47-2.02)	17,926 / 50	1.50 (1.14-1.98)
30.0-<35.0	51,056 / 221	2.65 (2.32-3.03)	15,697 /61	2.07 (1.61-2.67)
≥35.0	22,573 / 214	5.62 (4.88-6.48)	5,665 / 34	3.14 (2.22-4.46)
P for trend		<0.0001		<0.0001
HR (95%CI) per 5 kg/m^2 increment in BMI	393,615 / 1.000	1.71 (1.63-1.80)	120,550 / 282	1.58 (1.41-1.77)

Models were stratified by year of birth and year of recruitment and adjusted for age at recruitment, deprivation score, region, number of full- term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).

Table 5-10: Hazard ratios for endometrial cancer associated with BMI in postmenopausal never HRT users in sensitivity analyses that modelled BMI as a time dependent covariate and in analyses that excluded the first five years of follow-up

BMI (kg/m^2) categories	Baseline BMI, follow-up from recruitment		BMI as a time-varying exposure, follow-up from recruitment		Baseline BMI, exclude first five years of follow-up	
	Number of women/ cases	Multivariable-adjusted HR (95%CI)	Number of women/ cases	Multivariable-adjusted HR (95%CI)	Number of women/ cases	Multivariable-adjusted HR (95%CI)
<22.5	75,413 / 408	0.68 (0.62-0.75)	69,509 / 401	0.75 (0.68-0.83)	71,235 / 299	0.65 (0.58-0.72)
22.5 -< 25.0	103,939 / 854	1.00 (0.93-1.07)	87,342 / 706	1.00 (0.93-1.08)	98,236 / 659	1.00 (0.93-1.08)
25.0 - <27.5	85,607 / 988	1.39 (1.31-1.48)	83,564 / 948	1.44 (1.35-1.53)	80,584 / 774	1.42 (1.33-1.53)
27.5 -<30.0	55,027 / 933	2.02 (1.90-2.16)	56,764 / 888	2.01 (1.89-2.15)	51,531 / 743	2.12 (1.97-2.28)
30.0 -<35.0	51,056 / 1,343	3.13 (2.96-3.30)	52,726 / 1,280	3.11 (2.94-3.28)	47,588 / 1,080	3.33 (3.14-3.54)
≥35.0	22,573 / 1,133	6.06 (5.70-6.44)	22,730 / 1,114	6.29 (5.92-6.69)	20,687 / 881	6.33 (5.90-6.78)
Missing BMI at last questionnaire			*15,321 / 322*	*2.90 (2.60-3.24)*		
HR (95%CI) per 5 kg/m^2 increment in BMI	393,615 / 5,659	1.78 (1.74 - 1.82)	393,615 / 5,337	1.74 (1.70 - 1.77)	369,861 / 4,436	1.81 (1.77-1.85)

Multivariable-adjusted models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).

Table 5-11: Age-adjusted partial correlation coefficients between adiposity measures among 175,846 postmenopausal never HRT users at first resurvey

Adiposity measures	BMI	Waist circumference (cm)	Hip circumference (cm)	Waist to hip ratio
BMI (kg/m^2)	1.00			
Waist circumference (cm)	0.67	1.00		
Hip circumference (cm)	0.75	0.74	1.00	
Waist to hip ratio	0.30	0.79	0.18	1.00
Waist to height ratio	0.72	0.94	0.67	0.77

Table 5-12: Hazard ratios for endometrial cancer associated with central adiposity measures among 175,846 postmenopausal never HRT users at first resurvey

Tertiles of adiposity measures	Number of women/cases	Multivariable-adjusted HR (95%gsCI)	Further adjusted[1] for BMI HR (95%gsCI)
Waist circumference (cm)			
<74.0	69,510 / 440	1.00 (0.91-1.10)	1.00 (0.92-1.08)
74.0-<84.0	65,465 / 701	1.64 (1.53-1.77)	1.08 (1.00-1.18)
≥84.0	40,871 / 772	2.88 (2.68-3.10)	1.12 (1.04-1.21)
P for trend		<0.0001	0.05
HR per 1-SD (9.4 cm) increment		1.60 (1.53-1.68)	1.08 (1.03-1.13)
Hip circumference (cm)			
<99.0	77,107 / 481	1.00 (0.91-1.10)	1.00 (0.92-1.08)
99.0-<104.0	43,814 / 436	1.52 (1.38-1.67)	1.01 (0.93-1.10)
≥104.0	54,925 / 996	2.69 (2.52-2.87)	1.13 (1.05-1.21)
P for trend		<0.0001	0.03
HR per 1-SD (7.6 cm) increment		1.69 (1.61-1.77)	1.09 (1.04-1.14)
Waist to hip ratio			
<0.74	69, 709 / 588	1.00 (0.92-1.08)	1.00 (0.93-1.08)
0.74-<0.79	52,629 / 567	1.27 (1.17-1.38)	1.00 (0.92-1.09)
≥0.79	53508 / 758	1.68 (1.57-1.81)	1.07 (1.00-1.16)
P for trend		<0.0001	0.20
HR per 1-SD (0.06) increment		1.31 (1.23-1.40)	1.06 (0.99-.1.12)
Waist to height ratio			
<0.45	64,345 / 409	1.00 (0.91-1.10)	1.00 (0.93-1.08)
0.45-<0.50	57,907 / 574	1.52 (1.40-1.65)	0.98 (0.90-1.07)
≥0.50	53,594 / 930	2.63 (2.46-2.82)	1.07 (0.99-1.15)
P for trend		<0.0001	0.23
HR per 1-SD (0.06) increment		1.58 (1.51-1.65)	1.03 (0.98-1.07)

[1] Adjusted for BMI using the residual method described in chapter 4 (section 4.2.5)
Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs for endometrial cancer per 1-SD increase in central adiposity measures were corrected for regression dilution ratios. The RDRs for waist circumference, hip circumference and waist to hip ratio were 0.86, 0.87, 0.69 and 0.86, respectively.

Table 5-13: Hazard ratios for endometrial cancer associated with central adiposity measures among 175,846 postmenopausal never HRT users at first resurvey adjusted for various confounders

	HR (95%CI) per 1-SD increment			
	Waist circumference (cm)	**Hip circumference (cm)**	**Waist to hip ratio**	**Waist to height ratio**
Stratified by year of birth and year of recruitment and adjusted for age, UK region and deprivation score	1.66 (1.58-1.74)	1.76 (1.68-1.84)	1.33 (1.26-1.42)	1.63 (1.56-1.71)
Adjusted independently for:				
Age at menarche (years)	1.64 (1.56-1.71)	1.73 (1.65-1.81)	1.33 (1.25-1.41)	1.61 (1.54-1.68)
Number of full-term pregnancies	1.66 (1.59-1.74)	1.76 (1.68-1.84)	1.34 (1.26-1.43)	1.64 (1.57-1.72)
Duration of oral contraceptive use (years)	1.65 (1.57-1.73)	1.74 (1.67-1.83)	1.33 (1.25-1.42)	1.62 (1.55-1.70)
Age at menopause (years)	1.64 (1.57-1.72)	1.74 (1.66-1.82)	1.33 (1.25-1.41)	1.62 (1.55-1.70)
Frequency of strenuous exercise	1.65 (1.57-1.73)	1.75 (1.67-1.83)	1.33 (1.25-1.41)	1.62 (1.55-1.70)
Diabetes status	1.65 (1.57-1.73)	1.75 (1.67-1.83)	1.32 (1.24-1.40)	1.63 (1.55-1.70)
Smoking status	1.66 (1.58-1.74)	1.75 (1.67-1.83)	1.34 (1.26-1.43)	1.63 (1.56-1.71)
Adjusted for all covariates	1.60 (1.53-1.68)	1.69 (1.61-1.77)	1.31 (1.23-1.40)	1.58 (1.51-1.65)

Table 5-14: Hazard ratios for endometrial cancer associated with central adiposity measures according to BMI group among 175,846 postmenopausal never HRT users at first resurvey

Adiposity measures	**HR (95%CI) per 1-SD increment**			
	BMI <25 kg/m^2 (n = 94,278, cases = 570)	**BMI 25-<30 kg/m^2 (n=62,655, cases = 809)**	**BMI ≥30 kg/m^2 (n= 18,913, cases = 534)**	**P for heterogeneity**
Waist circumference (cm)	1.23 (1.10-1.37)	0.98 (0.91-1.06)	1.05 (0.97-1.13)	<0.01
Hip circumference (cm)	1.11 (1.00-1.23)	1.06 (0.95-1.20)	1.06 (0.99-1.15)	0.75
Waist to hip ratio	1.22 (1.07-1.38)	0.95 (0.86-1.04)	1.03 (0.93-1.14)	<0.01
Waist to height ratio	1.16 (1.03-1.30)	0.93 (0.87-1.01)	1.01 (0.94-1.08)	<0.01

Multivariable-adjusted models were stratified by year of birth and year of recruitment and adjusted for age at recruitment, deprivation score, region, number of full- term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise, diabetes status and BMI.
HR per 1-SD higher baseline values of waist circumference, hip circumference, waist to hip ratio and waist to height ratio are shown in this table. One SD in waist circumference, hip circumference, waist to hip ratio and waist to height ratio correspond to 9.4cm, 7.6cm, 0.06 and 0.06 increment, respectively.
HRs (95%CIs) for endometrial cancer per 1-SD increase in central adiposity measures were corrected for regression dilution ratios. The RDRs for waist circumference, hip circumference and waist to hip ratio were 0.86, 0.87, 0.69 and 0.86, respectively.

Table 5-15: Hazard ratios for endometrial cancer associated with central adiposity measures by tumour subtypes among 175,846 postmenopausal never HRT users at first resurvey

Adiposity measures	HR (95%CI) per 1-SD increment in central adiposity measures				
	Type I tumours (n= 1,569)		Type II tumours (n = 199)		
	Multivariable adjusted	Further adjusted for BMI[1]	Multivariable adjusted	Further adjusted for BMI[1]	P for heterogeneity models with BMI
Waist circumference (cm)	1.66 (1.58-1.75)	1.09 (1.04-1.14)	1.30 (1.11-1.52)	1.04 (0.89-1.21)	0.56
Hip circumference (cm)	1.76 (1.67-1.85)	1.10 (1.04 -1.15)	1.35 (1.16-1.57)	1.06 (0.91-1.24)	0.53
Waist to hip ratio	1.32 (1.24-1.41)	1.06 (0.99-1.13)	1.15 (0.96-1.39)	1.01 (0.83-1.23)	0.75
Waist to height ratio	1.65 (1.56-1.73)	1.01 (0.94-1.08)	1.26 (1.08-1.48)	0.98 (0.84-1.14)	0.59

[1] Adjusted for BMI using the residual method
Multivariable-adjusted models were stratified by year of birth and year of recruitment and adjusted for age at recruitment, deprivation score, region, number of full- term pregnancies, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
Standard deviation increases in waist circumference, hip circumference, waist to hip ratio and waist to height ratio were 9.4cm, 7.6cm, 0.06 and 0.06, respectively.
HR per 1-SD increase corrected for regression dilution ratios. The RDRs for waist circumference, hip circumference and waist to hip ratio were 0.86, 0.87, 0.69 and 0.86 respectively.

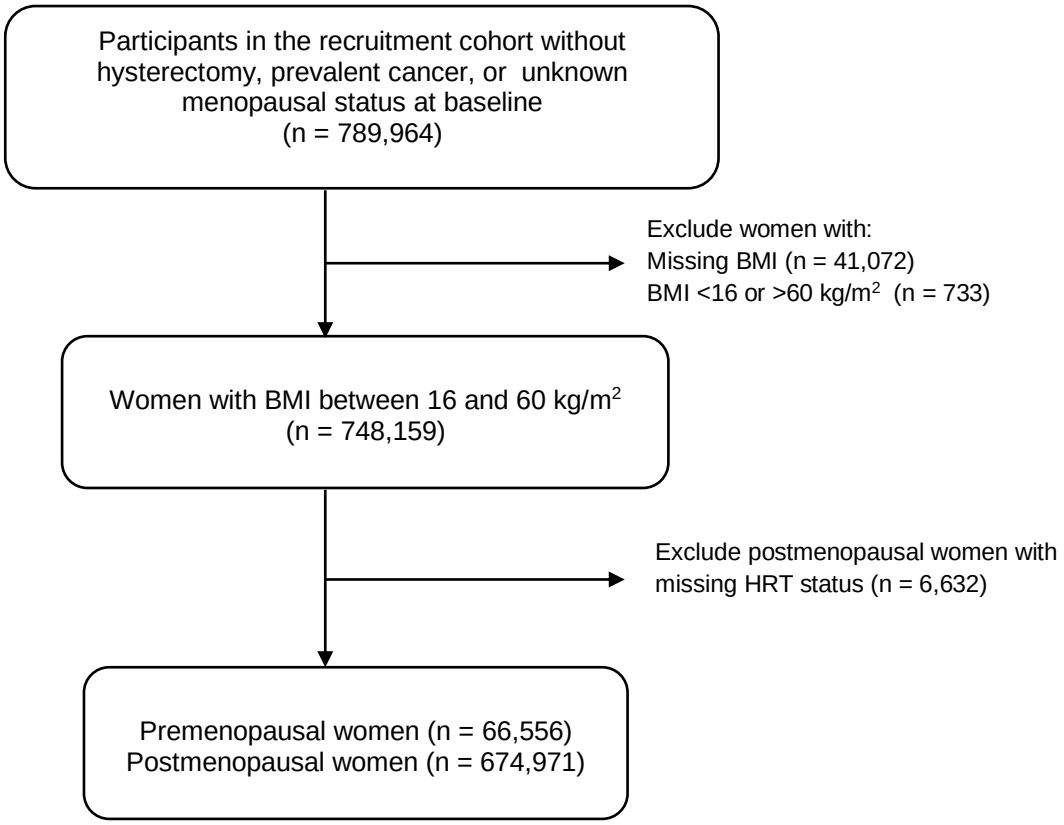


Figure 5-1: Flowchart for inclusion of participants in analyses assessing the association of BMI with endometrial cancer risk

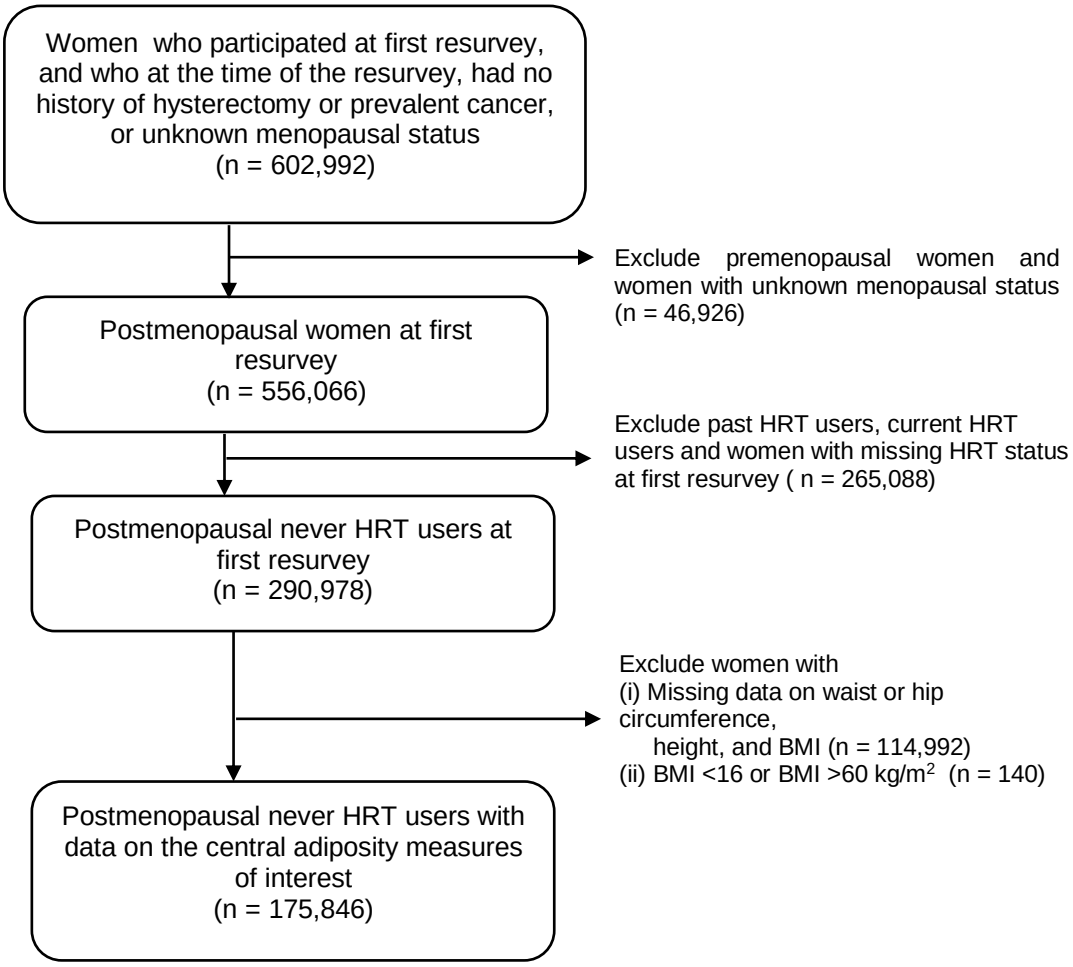


Figure 5-2: Flowchart for inclusion of participants in analyses assessing the associations of central adiposity measures with endometrial cancer risk

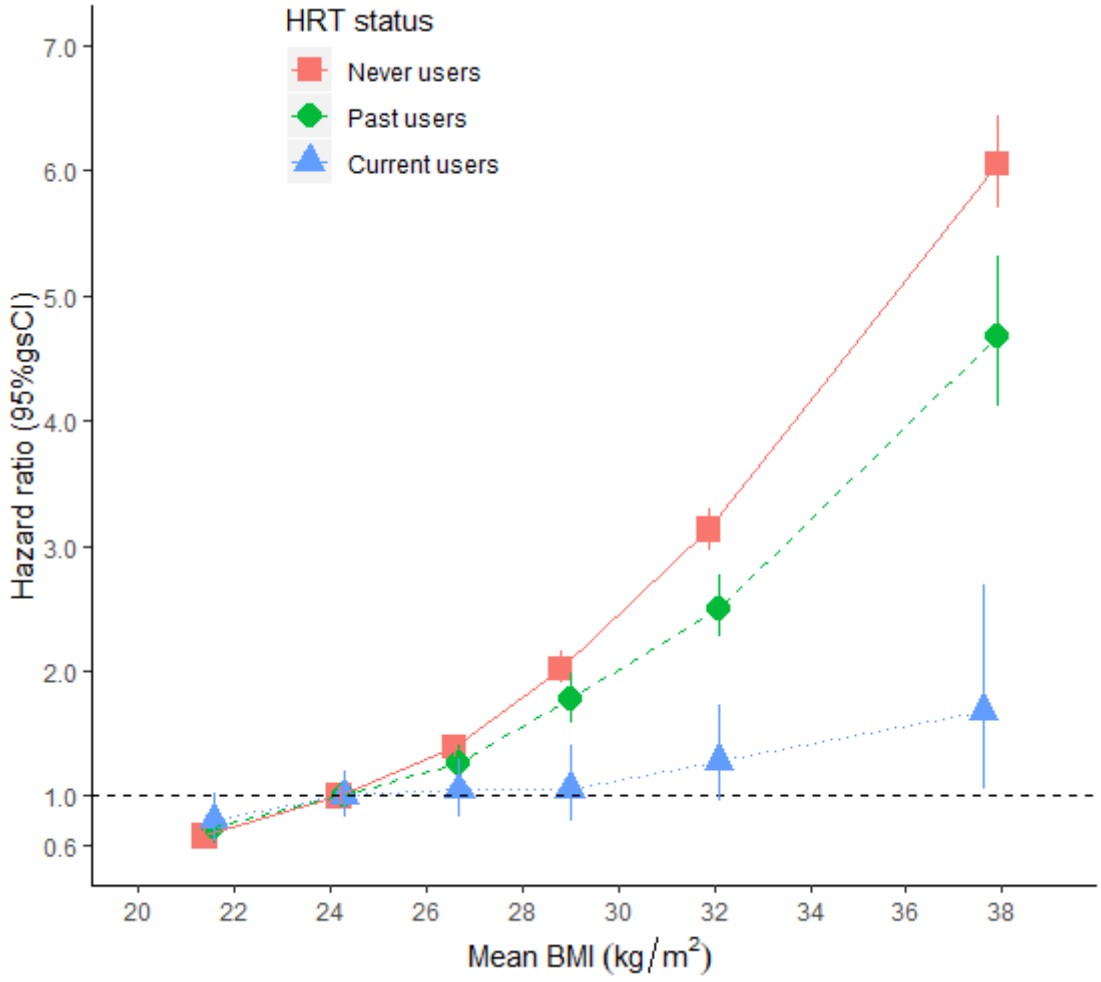


Figure 5-3: Hazard ratios (95%gsCIs) for endometrial cancer associated with BMI categories in postmenopausal women according to HRT status at baseline

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise per week and diabetes status.

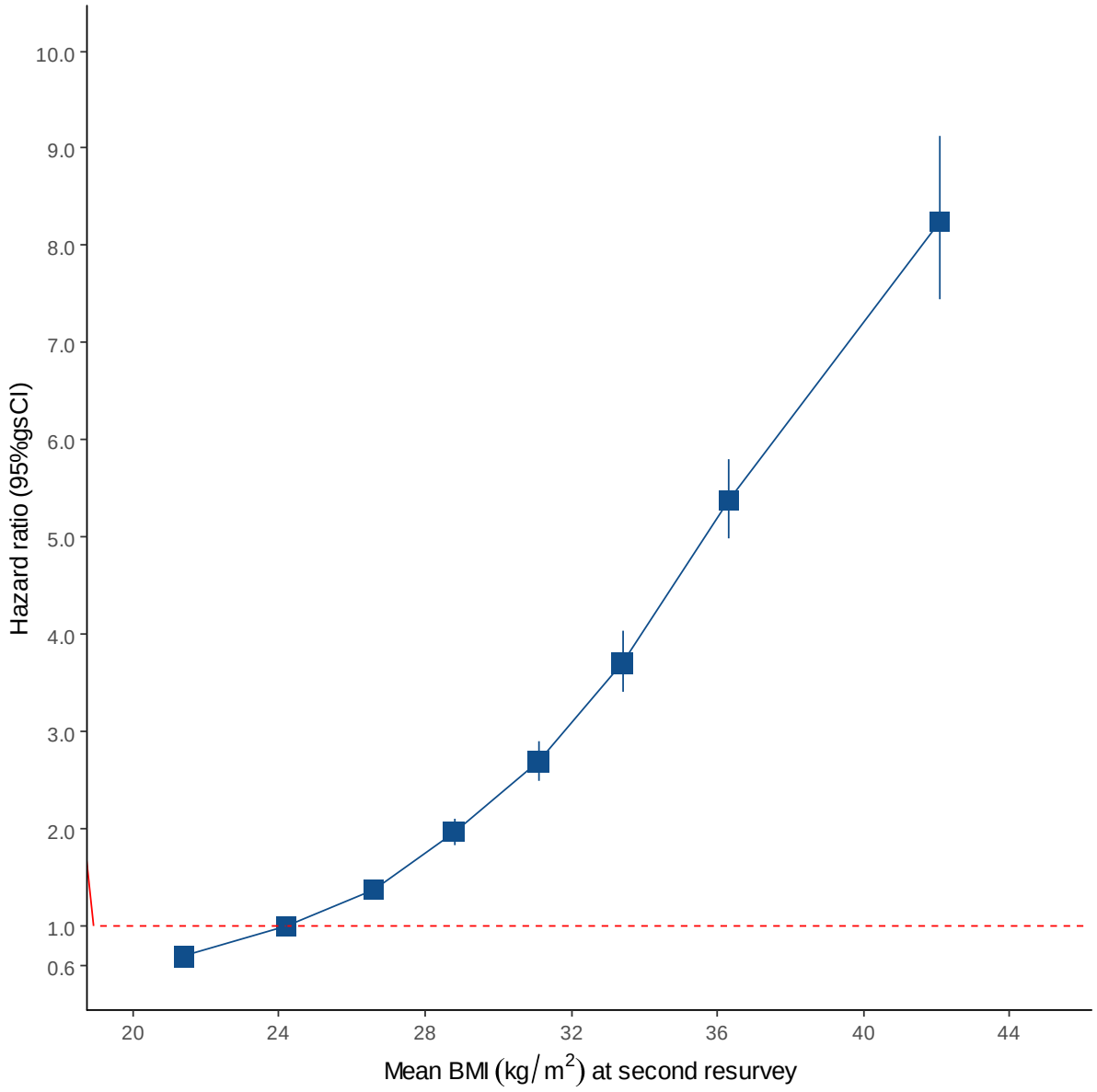


Figure 5-4: Hazard ratios (95%gsCIs) for endometrial cancer associated with BMI categories in postmenopausal never HRT users

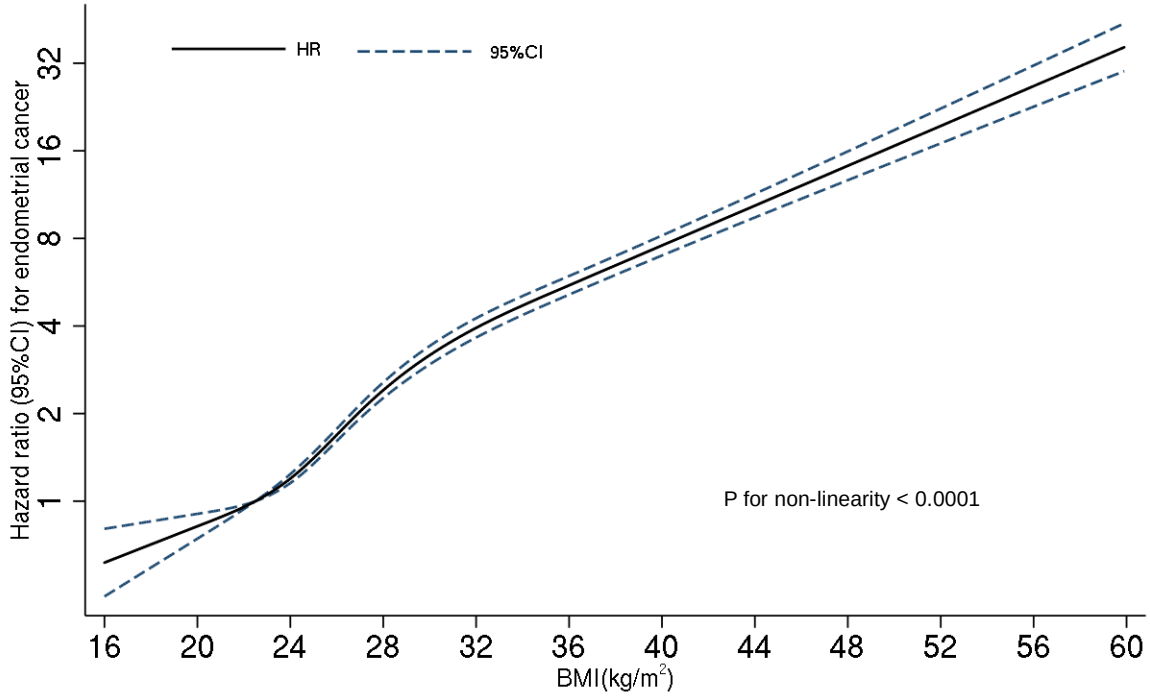
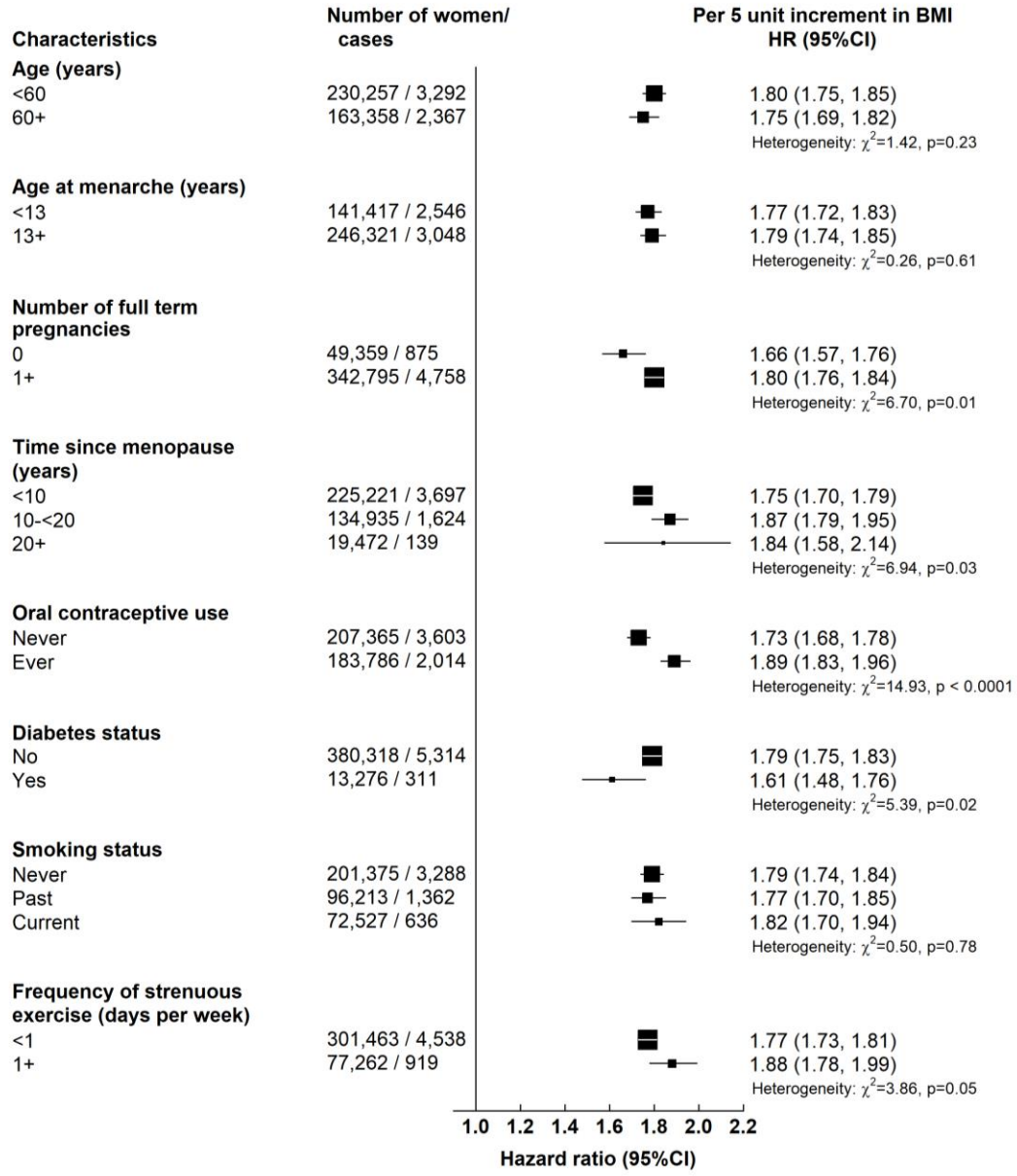


Figure 5-5: Hazard ratios for endometrial cancer associated with BMI (modelled as a restricted cubic spline) in postmenopausal never HRT users



Note: '+' used instead of '≥' because the software used to generate the figure does not recognize '≥'

Figure 5-6: Hazard ratios for endometrial cancer associated with BMI according to participants' characteristics at baseline

Chapter 6: Association between smoking and endometrial cancer risk

Summary

The inverse association between smoking and endometrial cancer risk is well-established; however, uncertainty remains regarding whether and to what extent this association varies with different smoking characteristics, population characteristics or tumour subtypes. This study examines in detail the association of smoking with endometrial cancer risk using data from 195,446 UK Biobank women and 743,114 Million Women Study participants. Adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the associations of various measures of smoking with endometrial cancer risk were estimated using Cox regression models. As expected, in postmenopausal women, the risk of developing endometrial cancer was lower in current (HR = 0.73, 95%CI: 0.69-0.78) and past smokers (HR = 0.89, 95%CI: 0.85-0.93) compared with never smokers. There were significant dose-response associations with number of cigarettes smoked per day and age at smoking initiation among current smokers in the Million Women Study (P_{trend} <0.05), with stronger risk reductions among women who smoked more cigarettes per day and among those who started smoking at younger ages. The risk reduction persisted for more than 20 years after smoking cessation and was consistent across tumour subtypes. Overall, these findings suggest that smoking confers long-lasting protection against the risk of endometrial cancer, regardless of subtype.

6.1. Introduction

Several epidemiological studies have examined the association between smoking and endometrial cancer risk.[57–62,184,187,188,192,194,198,199,299] In general, findings from these studies suggest that current smoking and, to a lesser extent, past smoking reduce the risk of endometrial cancer. This effect of smoking appears to be confined to postmenopausal women.[91,175,179,180,189,32] Evidence regarding the association of smoking with endometrial cancer risk in premenopausal women is inconsistent, with studies reporting positive,[59,199] inverse[190] or null associations.[57,58]

It is unclear if the relationship between smoking and endometrial cancer risk differs by smoking characteristics such as number of cigarettes smoked per day, duration of smoking, age at smoking initiation and time since smoking cessation. Previous cohorts were unable to reliably evaluate associations with these smoking characteristics because most of them had a relatively small sample size and hence limited statistical power.[58–60,78,79]

The relationship between smoking and endometrial cancer risk in important population subgroups, such as HRT users and obese women, is also unclear. Further, there is limited data on the association of smoking with the risk of different subtypes of endometrial cancer. Most previous studies were unable to quantify the association in important population groups or by tumour characteristics because they lacked sufficient sample size or endometrial cancer cases.

Although the inverse association between smoking and endometrial cancer risk is unlikely to be of direct benefit to primary preventative measures, a better understanding of whether and how this relationship varies with different population characteristics or tumour subtypes may provide useful insights into the mechanisms underlying the reduced risk of endometrial cancer among smokers.

Using data from two of the largest UK cohorts, UK Biobank and the Million Women Study, the current study examines in detail the association of smoking with the risk of endometrial cancer. Specifically, the study evaluates the association between different measures of smoking and endometrial cancer risk overall. It also examines the relationship between smoking and endometrial cancer risk in different population subgroups and by tumour subtypes.

6.2. Methods

6.2.1. Analytical cohorts

All analyses in UK Biobank were based on data from the full cohort. Of the 196,074 UK Biobank women eligible for inclusion in these analyses (see section 3.4.1 and figure 3-2), 628 women were excluded because they had missing smoking status (figure 6-1).

In the Million Women Study, analyses relating to smoking status and endometrial cancer risk were based on data from the recruitment cohort. Of the 789,964 women eligible for inclusion in these analyses (see section 3.4.1

and figure 3-3), 46,850 women were excluded because they had missing smoking status (figure 6-2). Analyses relating to quantitative smoking metrics and endometrial cancer risk were restricted to women who participated in the first resurvey as this was when data on timing of smoking were first collected. Of the 602,992 women eligible for inclusion in these analyses, 46,926 women were excluded because they were premenopausal or had unknown menopausal status, and another 10,823 women were excluded because they had missing data on smoking status at that resurvey (figure 6-3).

6.2.2. Assessment of smoking

The questions used to assess smoking status in both cohorts have been described in chapter 3 (section 3.1.2.1 and section 3.2.1.1). In UK Biobank, current smokers were defined as women who reported that they smoked at baseline and who had smoked at least 100 times in their lifetime. Past smokers were women who had smoked at least 100 times in their lifetime but stopped smoking before baseline assessment. Women who indicated that they were past smokers but whose age at stopping was the same as their age at baseline assessment were classified as current smokers. Never smokers were women who indicated that they had never smoked or who had smoked less than 100 times in their lifetime. Current and past smokers, who smoked on most or all days, further provided information on the average number of cigarettes they smoked per day, age at smoking initiation and age at last smoke. Smoking duration was calculated as the difference between the age at smoking initiation and the age at baseline or age at last smoke (for

past smokers). Time since smoking cessation for past smokers was calculated by subtracting age at last smoke from the age at baseline.

In the Million Women Study, participants were classified as current, past or never smokers based on their responses to the questions “About how many cigarettes do you smoke on average each day, now?” and “Are you an ex-smoker?” in the recruitment questionnaire. Because information on temporal measures of smoking (age at smoking initiation and age at last smoke) were not available at recruitment, data from the first resurvey questionnaire, administered approximately 3 years after recruitment, were used for analyses relating to all quantitative measures of smoking. Here, participants who indicated they were current or past smokers were asked to report the average number of cigarettes they smoked per day, age at smoking initiation and age when smoking stopped (past smokers only). Duration of smoking and time since smoking cessation were defined in the same way as for UK Biobank.

For analyses in UK Biobank, quantitative smoking metrics were dichotomised as follows: number of cigarettes smoked per day (<20, ≥20), smoking duration (<20, ≥20 years), age at smoking initiation (<18, ≥18 years) and time since smoking cessation (<20, ≥20 years). Because of the larger size of the Million Women Study cohort, these exposures were categorised into finer groups as follows: number of cigarettes smoked per day (<10, 10-<20, ≥20), smoking duration (<20, 20-<40, ≥40 years), age at smoking initiation (<18, 18-<25, ≥25 years) and time since smoking cessation (<10, 10-<20, 20-<30, ≥30 years).

6.2.3. Outcome ascertainment

Participants in both cohorts were followed for incident cancers and deaths through record linkage with the NHS Central registers (through NHS Digital). The cancer registers provided information on the date of cancer diagnosis, site, histology, and behaviour. The site of cancer was coded using the International Statistical Classification of Diseases and related Health Problems tenth revision (ICD-10). Endometrial cancer was defined as ICD-10 code C54. Tumour subtypes were defined using the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3). Type I endometrial cancer was defined as ICD-O-3 codes: 8140, 8260, 8380-8382, 8480, 8481 and 8570, while type II endometrial cancers included ICD-O-3 codes 8041, 8050, 8070, 8071, 8310, 8323, 8441, 8460, 8461 and 8560. Uterine sarcomas were defined as ICD-O-3 codes 8800, 8802, 8850, 8890, 8930 and 8933 while ICD-O-3 codes 8950, 8951 and 8980 were classified as Malignant Mixed Mullerian tumours (MMMTs).

6.2.4. Statistical analyses

6.2.4.1. Analyses involving participants in both cohorts

All analyses were conducted separately for each cohort because of difficulty in harmonising all the exposures of interest and potential confounding variables. Person-time for each participant was calculated from baseline (date of baseline assessment in UK Biobank, date depends on the exposure of interest in the Million Women Study—see table 3-2) to the earliest of the following events: any invasive cancer except non-melanoma skin cancer,

hysterectomy (from hospital admissions records), death, age 55 years (for analyses in premenopausal women only) or end of follow-up (31 October 2015 for UK Biobank participants in Scotland; 31 March 2016 for UK Biobank participants in England and Wales; 31 December 2016 for Million Women Study participants in Scotland; and 31 December 2017 for all other participants in the Million Women Study).

Cox regression models, with time in study as the underlying time variable, were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the associations of different smoking measures with endometrial cancer risk. Overall HRs and 95%CIs for the association of smoking status with endometrial cancer risk across both studies were calculated using a fixed-effect meta-analysis with each study result weighted by the inverse of the within-study error variance. In all analyses, never smokers were the referent category. For analyses assessing associations with quantitative measures of smoking (Million Women Study cohort only), tests for linear trend across categories of each smoking exposure (see section 6.2.2) were performed by assigning median values to ordinal categories and modelling these values as a continuous variable.

All models were stratified by year of birth (5-year categories in UK Biobank, single years in the Million Women Study) and year of data collection (single years); and adjusted for age (continuous), Townsend deprivation score (fifths, based on distribution in each cohort) and region (UK region in UK Biobank, cancer registry region at recruitment in the Million Women Study). The effects of additional adjustment for BMI (<20.0, 20.0-<22.5, 22.5-<25.0,

25.0-<27.5, 27.5-<30.0, 30.0-<32.5, 32.5-<35.0, ≥35.0 kg/m^2), duration of oral contraceptive use (never users, 0-<5, 5-<10, 10-<15, ≥15 years), age at menarche (<13, 13-<15, ≥15 years), diabetes status (no, yes), physical activity (UK Biobank only: low, moderate or high), frequency of strenuous exercise (Million Women Study only: none, <1, ≥1 days per week) were also examined. Models for postmenopausal women were further adjusted for age at menopause (<49, 49-<52, 52-<55, ≥55 years), HRT status in UK Biobank (never, past or current) or type of HRT used in Million Women Study (never, past, oestrogen only, oestrogen plus progesterone, tibolone, others) and an interaction term for BMI and HRT. For analyses relating to quantitative measures of smoking in the Million Women Study, which were based on smoking data collected at first resurvey, data on BMI, HRT, year of data collection and diabetes were taken from the first resurvey questionnaire. Missing values for each covariate were assigned to a separate category.

Where comparison is made between more than two exposure groups, group-specific confidence intervals (gsCIs) were calculated and presented in figures or tables, as these allow comparison to be made between two exposure groups even if neither is the reference group; however, conventional 95%CIs are provided in the text. The proportional hazard assumption for each model was tested using log-log plots and tests based on Schoenfeld residuals.

6.2.4.2. Further analyses in the Million Women Study

Owing to the large size of the Million Women Study cohort, additional analyses could be performed that were not possible in UK Biobank. These include: (i) analyses that assessed the independent effects of quantitative smoking metrics, (ii) analyses of associations by tumour subtypes, and (iii) analyses of associations in important population subgroups.

Assessment of independent effects of quantitative smoking measures

In an attempt to separate the effect of smoking duration from those of number of cigarettes smoked per day, age at smoking initiation and time since smoking cessation, smoking duration was cross classified separately with the number of cigarettes smoked per day and age at smoking initiation among current smokers, and with time since smoking cessation among past smokers; HRs and 95%gsCIs were estimated for each of the joint categories with never smokers as the referent category.

Associations by tumour subtypes

For analyses by tumour subtypes, separate Cox models were fitted for each tumour subtype while censoring other subtypes at the date of diagnosis. Test for heterogeneity between subtypes (type I and type II tumours) were conducted using the competing risk approach described by Lunn and McNeil (see section 5.2.5.2).[328] Likelihood ratio tests were used to compare models which assume different associations for each subtype to the one that assumed the same association.

Associations by population characteristics

Subgroup analyses were performed according to age at recruitment (<60, ≥60 years), BMI (<25, 25-<30, ≥30 kg/m^2), age at menarche (<13, ≥13 years), number of full-term pregnancies (0, ≥1), oral contraceptive use (never, ever), use of HRT (never, ever), diabetes status (no, yes), frequency of strenuous exercise (≤1, >1 days per week) and time since menopause (<10, 10-<20, ≥20 years before baseline assessment). Potential heterogeneity between strata was assessed using chi squared (χ^2) tests.

Sensitivity analyses

The main analyses were based on the assumption that women maintained the same smoking status throughout follow-up. However, during long periods of follow-up, it is likely that some current smokers may give up smoking and probably a smaller number of past or never smokers may initiate smoking. This could lead to exposure misclassification that may bias the risk estimates. To assess the effect of misclassification of exposure on risk estimates, three sensitivity analyses were performed among postmenopausal women in the Million Women Study. First, the duration of follow-up for each woman was restricted to a maximum of 5 years, to allow for estimation of risk when the potential for misclassification was smaller. Second, smoking status was modelled as a time-varying exposure using data from the first, second and third resurvey (conducted, on average, 3.3 years, 7.8 years and 12.5 years, respectively, after recruitment) to update smoking status. Third, the analysis of smoking status and endometrial cancer

risk was restricted to women who maintained the same smoking status at both recruitment and the last questionnaire before the end of follow-up. The last questionnaire was the recruitment questionnaire for 28.5% of women, the first resurvey questionnaire for 16.8% of women, the second resurvey questionnaire for 16.3% of women and the third resurvey questionnaire for 38.4% of women.

All statistical analyses were conducted using STATA software version 15.0.

6.3. Results

6.3.1. Baseline characteristics

After all exclusions, 195,446 UK Biobank women (70.2% postmenopausal) and 743,114 Million Women Study participants (91.1% postmenopausal) were included in the analysis of smoking status and endometrial cancer risk (figure 6-1 and figure 6-2). The mean (SD) ages at baseline were 55.4 (8.1) years in UK Biobank and 57.6 (4.7) years in the Million Women Study. Approximately 8.9% of UK Biobank participants and 19.7% of Million Women Study participants were current smokers at baseline. Table 6-1 shows the characteristics of study participants according to baseline smoking status. Compared with never smokers, current smokers in both cohorts were younger, had an earlier age at menopause and were more likely to be ever users of oral contraceptives and HRT.

During a mean follow-up of 6.9 years per woman in UK Biobank, 58 premenopausal women and 732 postmenopausal women were diagnosed

with endometrial cancer. The mean (SD) ages at diagnosis were 51.1 (3.5) years for premenopausal women and 65.5 (5.3) years for postmenopausal women. During a mean follow-up of 16.3 years per woman in the Million Women Study, 59 premenopausal women and 9,684 postmenopausal women were diagnosed with endometrial cancers, with mean (SD) ages at diagnosis of 53.2 (1.1) years and 68.8 (6.4) years, respectively.

6.3.2. Smoking status and endometrial cancer risk by menopausal status

Table 6-2 shows the cohort-specific and overall (meta-analysis estimate) HRs for the association of smoking status with endometrial cancer risk in premenopausal and postmenopausal women. Smoking was not significantly associated with the risk of endometrial cancer among premenopausal women in either cohort. Compared with never smokers, the overall HRs (95%CIs) for current and past smokers, were 1.07 (0.53-2.03) and 1.08 (0.71-1.67), respectively, in multivariable-adjusted analyses, although this was based on 117 premenopausal endometrial cancer cases in total (table 6-2).

In contrast, there was an inverse association between smoking and endometrial cancer risk among postmenopausal women in both cohorts. In minimally adjusted analyses (i.e. stratified by years of birth and recruitment, and adjusted for age, UK region and deprivation score), the overall HRs (95%CIs) for current and past smokers, compared with never smokers, were 0.60 (0.56-0.63) and 0.89 (0.85-0.93), respectively. Adjustment for other

covariates attenuated the association in current smokers but not past smokers (Overall $HR_{current\ vs\ never}$ = 0.73, 95%CI: 0.69-0.78; Overall $HR_{past\ vs\ never}$ = 0.89, 95%CI: 0.85-0.93). This attenuation in risk for current smokers appeared to be mainly driven by BMI and age at menopause (table 6-3).

6.3.3. Quantitative smoking metrics and endometrial cancer risk

This section presents results for the associations of different quantitative measures of smoking with risk in postmenopausal women. Due to limited statistical power, the associations between quantitative smoking measures and risk were not examined in premenopausal women.

6.3.3.1. UK Biobank

Owing to the relatively small number of smokers in UK Biobank, quantitative measures of smoking were dichotomised for this analysis (see section 6.2.2). The HRs (95%CIs) for endometrial cancer associated with smoking <20 and ≥20 cigarettes per day among current smokers were 0.62 (0.39-0.98) and 0.69 (0.38-1.26), respectively (table 6-4). The HRs (95%CIs) associated with smoking duration <20 and ≥20 years among current smokers were 2.37 (0.59-9.55) and 0.61 (0.42-0.90), respectively. Current smokers who started smoking before age 18 years and those who initiated smoking at age 18 years or over had HRs (95%CIs) of 0.52 (0.29-0.92) and 0.77 (0.48-1.23), respectively (table 6-4). These results, however, were based on a very small number of incident endometrial cancers among current smokers (n = 30).

6.3.3.2. Million Women Study

As mentioned previously, quantitative measures of smoking were only available from the first re-survey of the Million Women Study. As such this analytical cohort consists of 545,243 women (see figures 6-3), of whom 7,115 were diagnosed with endometrial cancer during a mean follow-up of 13.8 years per woman. At the beginning of follow-up for these analyses (date of first resurvey), 12.9% of women were current smokers (compared to 19.7% at recruitment) and 32.8% were past smokers. On average, current smokers had smoked for 40.1 (SD=6.6) years, with the vast majority (98.5%) reporting having smoked for 20 or more years. Approximately 89% of current smokers started smoking before age 25 years. Past smokers, on average, had smoked for 19.9 (SD=12.0) years and stopped smoking 21.7 (SD = 11.7) years before the first resurvey. The HRs for endometrial cancer associated with current (HR =0.72, 95%CI: 0.66-0.79) and past smoking (HR=0.91, 95%CI: 0.86-0.95) in this subcohort were similar to those of the recruitment cohort.

Figure 6-4 shows the multivariable-adjusted HRs for the association of various quantitative smoking metrics with endometrial cancer risk. Among current smokers, increasing number of cigarettes smoked per day and earlier age at smoking initiation were associated with a reduction in risk of endometrial cancer in a dose-response manner (P_{trend} <0.05). Compared with never smokers, women who smoked <10, 10-<20 and $\geq$20 cigarettes per day had HRs (95%CIs) of 0.92 (0.77-1.10), 0.68 (0.60-0.78) and 0.66 (0.57-0.77), respectively. The HRs (95%CIs) for women who started smoking

at ages ≥ 25, 18-<25 and <18 years were 1.01 (0.83-1.24), 0.69 (0.60-0.78) and 0.67 (0.58-0.76), respectively (figure 6-4). Endometrial cancer risk among current smokers also appeared to decrease with increasing duration of smoking, although the test for trend was not statistically significant (P_{trend} = 0.086). Compared with never smokers, women who smoked for <20, 20-<40 and ≥40 years had HRs (95%CIs) of 1.16 (0.70-1.93), 0.73 (0.64-0.83) and 0.70 (0.62-0.78), respectively (figure 6-4).

In analyses that cross classified smoking duration with number of cigarettes smoked per day in order to assess their independent effects, no clear pattern of association was observed for smoking duration within strata of number of cigarettes smoked per day, and vice versa, although this analysis was limited by sparse data in some strata (table 6-5). Results from the analysis that cross-classified smoking duration and age at smoking initiation were not very informative because of lack of data in some strata (table 6-6).

Among past smokers, the risk of endometrial cancer decreased with increasing duration of smoking (P_{trend} = 0.037). Compared with never smokers, the HRs for women who smoked for <20, 20-<40 and ≥40 years were 0.94 (0.89-1.00), 0.88 (0.83-0.94) and 0.75 (0.62-0.91), respectively (figure 6-4). Endometrial cancer risk among past smokers did not vary significantly by the number of cigarettes smoked per day or age at smoking initiation (P_{trend} >0.1; figure 6-4).

The risk of endometrial cancer among past smokers also varied by the time since smoking cessation (P_{trend} = 0.047). The magnitude of risk reduction

was strongest among women who recently quit smoking but diminished over time (figure 6-5). However, risk remained low compared to that of never smokers even 20-<30 years after cessation (HR = 0.89, 95%CI: 0.82-0.97), and only approached levels comparable to that of never smokers after 30 years since cessation (HR=0.97, 95%CI: 0.90-1.06; figure 6-5).

Since women who quit smoking more recently in this cohort were more likely to have smoked for longer (the median durations of smoking among women who quit <10, 10-<20, 20-<30 and ≥30 years previously were 36, 26, 16 and 7 years, respectively), time since smoking cessation was cross-classified with smoking duration among past smokers in order to assess their independent effects. Results from this analysis did not reveal a clear pattern of association for either of these variables (table 6-7).

6.3.4. Further analyses in the Million Women Study

6.3.4.1. Associations by tumour subtypes

The association between smoking status and endometrial cancer risk did not differ significantly between type I and II tumours (table 6-8). Compared with never smokers, current smokers had a 28% reduction in the risk of type I tumours (HR = 0.72, 95%CI: 0.67-0.77) and a 21% reduction in the risk of type II tumours (HR=0.79, 95%CI: 0.65-0.96; $P_{heterogeneity}$ >0.80). Smoking was not significantly associated with the risk of uterine sarcomas, MMMTs and other uterine cancers (table 6-8). The associations of smoking with specific histological subtypes of type I (endometroid, adenocarcinoma NOS)

and type II tumours (serous and clear cell carcinoma) are shown in appendix 6.

6.3.4.2. Associations by population characteristics

Figure 6-6 shows the HRs for endometrial cancer associated with current smoking, compared with never smoking, in various population subgroups. The association between current smoking and endometrial cancer risk did not differ by age at recruitment, BMI, age at menarche, number of full-term pregnancies, time since menopause, diabetes status and frequency of strenuous exercise ($P_{heterogeneity}$ >0.10, figure 6-6). However, there were significant differences in the magnitude of association by oral contraceptive use. The risk reduction associated with current smoking was stronger among never users of oral contraceptives (HR= 0.68, 95%CI: 0.62-0.74) compared with ever users (HR=0.81, 95%CI: 0.74-0.89; $P_{heterogeneity}$ = 0.007).

6.3.4.3. Sensitivity analyses

Because smoking status at recruitment may not accurately reflect smoking status during follow-up, three sensitivity analyses were conducted in the Million Women Study cohort (table 6-9). In the first analysis, follow-up time for each woman was restricted to a maximum of 5 years. Here the HRs (95%CIs) for endometrial cancer associated with current and past smokers were 0.78 (0.68-0.89) and 0.89 (0.81-0.89), respectively.

In the second analysis, smoking status was modelled as a time-varying exposure in order to account for changes in smoking status over time.

Current and past smokers in this analysis had HRs (95%CIs) of 0.69 (0.65-0.74) and 0.88 (0.85-0.92), respectively. Some women had missing information on smoking status at the last questionnaire (n = 8,726) and were classified into a separate category. The risk estimate for these women was 0.90 (0.74-1.10).

The third sensitivity analysis examined the association between smoking status and endometrial cancer in women who maintained the same smoking status both at recruitment and at the last questionnaire before the end of follow-up for each woman. The HRs (95%CIs) for current and past smokers in this analysis were 0.77 (0.72-0.83) and 0.88 (0.84-0.91), respectively (table 6-9). The results from all three sensitivity analyses were similar to the main results, suggesting that changes in smoking status that occur during follow-up had a very little effect on the risk estimates for current and past smokers.

6.4. Discussion

The main findings of this study were that: (i) both current and past smoking reduced the risk of developing endometrial cancer in postmenopausal women; (ii) the risk reduction in current smokers varied in a dose-response manner with the number of cigarettes smoked per day and age at smoking initiation, with stronger risk reduction among women who smoked more cigarettes per day and among those who started smoking at younger ages; (iii) the risk reduction associated with smoking persisted for 20-<30 years after smoking cessation; (iv) the inverse association between smoking and

endometrial cancer risk was similar for type I and type II tumours; and (v) the reduction in endometrial cancer risk associated with current smoking was slightly stronger in never users of oral contraceptives compared with ever users.

This is by far the largest study to examine the association between smoking and endometrial cancer risk (see table 2-2). These results confirm previous reports of an inverse association between smoking and postmenopausal endometrial cancer risk and enhance our knowledge of this relationship.[57–59,188,192] Importantly, dose-response associations were observed with the number of cigarettes smoked per day and age at smoking initiation in current smokers, suggesting that this relationship is probably causal. Previous prospective studies did not find dose-response associations with either number of cigarettes smoked per day or age at smoking initiation, possibly because they lacked sufficient statistical power to detect modest associations.[58–60,78,79]

In addition to number of cigarettes smoked per day and age at smoking initiation, smoking duration and time since smoking cessation also appeared to influence endometrial cancer risk in this study. However, these quantitative metrics are known to correlate strongly with each other such that the effect of one is difficult to separate from the effect of the other.[332] Thus, the relative importance of each of these aspects of smoking in endometrial cancer development remains an open question.

A key finding from this study is that the reduction in risk of endometrial cancer associated with smoking persists for decades after smoking cessation. As far as I am aware, no previous study has reported on this long-term effect of smoking. This finding implies that the biological changes induced by smoking continue to have an impact on endometrial cancer risk many years after exposure stops. Since smoking has been suggested to reduce endometrial cancer risk through antiestrogenic mechanisms (see section 2.3.2.2), it is plausible that this long-term effect reflects the impact of a reduced lifetime exposure to oestrogen. Epidemiological evidence supports the notion that factors which decrease cumulative lifetime exposure to oestrogen (such as oral contraceptive use, late menarche and early menopause) confer long-lasting protection on endometrial cancer risk.[63]

The association between smoking and endometrial cancer was similar for type I and type II tumours in the current analysis, which is consistent with results from previous studies.[56,58,86] This suggests that smoking influences endometrial cancer risk through pathways shared by both subtypes. Given that type II tumours are generally not thought to be associated with oestrogen exposure, this finding implies that non-oestrogenic pathways may link smoking with endometrial cancer. An alternative explanation is that smoking influences endometrial cancer risk through antiestrogenic mechanisms and that type II tumours are, to some extent, associated with oestrogen exposure.[86] This latter hypothesis is supported by findings from studies showing that factors which modulate oestrogen exposure such as BMI, oral contraceptive use and age at menopause influence the

development of type II tumours.[86] More research is needed to clarify the mechanisms underlying the association of smoking with endometrial cancer risk, particularly with risk of type II tumours, as this can provide an insight into the aetiology of this tumour subtype.

The association between current smoking and endometrial cancer risk was consistent across levels of characteristics such as BMI and HRT use in line with results from previous cohorts.[58–60,79] Interestingly, oral contraceptive use appeared to modify the association, with a stronger risk reduction in never users of oral contraceptives compared with ever users. This finding has not been reported in any study and may be due to chance given the number of tests conducted. Alternatively, it might reflect a diminished effect of smoking on endometrial cancer risk among women who benefit from a protective effect of oral contraceptive use. More research is needed to verify this finding.

There was no relationship between smoking and risk of endometrial cancer diagnosed in premenopausal women. This finding is consistent with results from some studies[57,58,188] but not others.[59,199] The lack of association between smoking and endometrial cancer risk among premenopausal women in the current study may also be due to chance given the small number of incident cases (less than 60 in each cohort).

The mechanism underlying a reduced risk of endometrial cancer among smokers is not clearly understood. The predominant hypothesis is that smoking decreases endometrial cancer risk through its antiestrogenic

effects. Possible mechanisms for this antiestrogenic effect of smoking include reduced oestrogen biosynthesis[207] and increased 2-hydroxylation of oestrogen leading to the formation of metabolites with minimal oestrogen activity.[203,204] Smoking may also increase endometrial cancer risk by increasing expression of homeobox A10 and progesterone receptor, which drive endometrial differentiation.[211]

The strengths of this study include its large size and prospective design. The association between smoking and endometrial cancer risk was examined in two well-characterised cohorts with information on potential confounders, both of which found a lower risk of endometrial cancer in past and current smokers even after adjustment for important confounders such as BMI and age at menopause, which are strongly associated with both endometrial cancer[16,17,333] and smoking.[212,334,335] The large number of women and incident endometrial cancers in the Million Women Study cohort provided sufficient statistical power to detect modest associations with relatively high precision in various subgroups of women and by tumour subtypes.

Several limitations of this study need to be acknowledged. First, the UK Biobank and the Million Women Study had some overlap in study population (approximately 40,000 women are participants in both studies); therefore, there may have been an overlap in cases and results. Second, smoking data were based on self-report and may be subject to misreporting. Third, all analyses were based on smoking information collected at one point in time and may be subject to misclassification during long periods of follow-up. However, results from the various sensitivity analyses carried out in the

Million Women Study including analyses that used information on smoking habits collected during follow-up suggest that changes in smoking exposure that may occur over time did not significantly impact on the risk estimates. Fourth, the small numbers of smokers and incident endometrial cancers in the UK Biobank prevented detailed assessment of the effect of smoking on endometrial cancer risk in the cohort. Fifth, nearly all current smokers in both cohorts had smoked for more than 20 years, precluding analysis of the association in short-term smokers. Sixth, despite the large size of the Million Women Study cohort, investigations of the independent effects of quantitative measures of smoking exposure were limited by sparse data in some of the categories because of the high correlation between these smoking metrics. Seventh, the small number of premenopausal women limited analysis of the association of smoking with premenopausal endometrial cancer risk. Finally, given the observational design of this study, it is possible that the inverse association between smoking and endometrial cancer is due to unmeasured confounding. However, the consistent report of a lower risk in different populations despite adjustment for confounding variables and the dose-response relationship with different metrics of smoking in this study, make this association more plausible.

6.5. Conclusion

The current study supports a protective, dose-dependent effect of smoking on endometrial cancer. This protective effect of smoking was consistent across tumour subtypes and lasted for decades after smoking cessation. Future studies should elucidate the biological mechanisms underlying this

association. In addition, studies should also explore the differences in association by oral contraceptive use to determine whether they are due to chance or whether they represent true biological differences in effect.

Table 6-1: Baseline characteristics of participants according to smoking status in UK Biobank and the Million Women Study

	UK Biobank			Million Women Study		
Characteristics	**Never (n = 120,538)**	**Past (n = 57,449)**	**Current (n = 17,459)**	**Never (n = 388,741)**	**Past (n = 207,874)**	**Current (n = 146,499)**
Age (years), mean (SD)	55.4 (8.2)	57.0 (7.9)	53.9 (8.1)	57.8 (4.8)	57.8 (4.8)	56.9 (4.4)
Postmenopausal, n (%)	81,838 (67.9)	43,883 (76.4)	11,465 (65.7)	349,073 (89.8)	189,793 (91.3)	137,790 (94.1)
Age at menarche (years), mean (SD)	13.0 (1.6)	13.0 (1.6)	13.1 (1.7)	13.0 (1.6)	13.1 (1.6)	13.1 (1.7)
Age at menopause (years), mean (SD)	50.5 (4.4)	50.3 (4.5)	49.0 (4.8)	49.9 (4.0)	49.3 (4.2)	48.1 (4.4)
Nulliparous, n (%)	24,508 (20.3)	10,498 (18.3)	3,843 (22.0)	48,179 (12.4))	24,102 (11.6)	14,705 (10.0)
Ever users of HRT, n (%)	32,661 (27.1)	22,024 (38.3)	5,503 (31.5)	137,370 (35.3)	88,605 (42.6)	59,372 (40.5)
Ever users of oral contraceptives, n (%)	94,927 (78.8)	49,069 (85.4)	15,009 (86.0)	200,221 (51.5)	123,204 (59.3)	88,472 (60.4)
BMI (kg/m^2), mean (SD)	26.7 (5.1)	27.2 (5.2)	26.6 (5.2)	26.1 (4.6)	26.6 (4.8)	25.4 (4.5)
Had a history of diabetes, n (%)	3,606 (3.0)	1,851 (3.2)	547 (3.1)	10,208 (2.6)	6,845 (3.3)	3,750 (2.6)
Smoking variables[1]						
Smoking duration (years), mean (SD)		20.7 (11.2)	35.7 (9.5)		19.5 (11.9)	39.8 (6.6)
Number of cigarettes smoked per day, mean (SD)		16.5 (8.3)	13.8 (7.4)		13.1 (9.2)	15.1 (7.3)
Age at smoking initiation (years), mean (SD)		17.8 (3.7)	18.3 (5.7)		18.8 (4.4)	19.1 (5.4)
Time since smoking cessation (years), mean (SD)		18.8 (11.3)			21.6 (11.3)	

SD = Standard deviation

[1]Data on quantitative measures of smoking in the Million Women Study were taken from the first resurvey questionnaire

Table 6-2: Hazard ratios for endometrial cancer by smoking status in premenopausal and postmenopausal women according to study cohort

	Premenopausal women			Postmenopausal women		
Smoking status	**Number of women / cases**	**Minimally adjusted HR (95%gsCI)**	**Multivariable-adjusted HR (95%gsCI)**	**Number of women/cases**	**Minimally adjusted HR (95%gsCI)**	**Multivariable-adjusted HR (95%gsCI)**
UK Biobank						
Never	38,700 / 42	1.00 (0.73-1.36)	1.00 (0.73-1.37)	81,838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)
Past	13,566 / 14	0.96 (0.57-1.62)	1.01 (0.60-1.71)	43,883 / 271	0.83 (0.73-0.95)	0.84 (0.74-0.96)
Current	5,994 / 2	0.33 (0.08-1.33)	0.36 (0.09-1.43)	11,465 / 35	0.54 (0.39-0.76)	0.65 (0.47-0.91)
Million Women Study						
Never	39,668 / 33	1.00 (0.71-1.41)	1.00 (0.71-1.41)	349,073 / 5,752	1.00 (0.97-1.03)	1.00 (0.97-1.03)
Past	18,081 / 16	1.04 (0.64-1.69)	1.16 (0.71-1.90)	189,793 / 2,718	0.89 (0.86-0.93)	0.89 (0.86-0.93)
Current	8,709 / 10	1.31 (0.70-2.47)	1.41 (0.75-2.66)	137,790 / 1,214	0.60 (0.56-0.63)	0.74 (0.70-0.78)
Meta-analysis						
Never	78,368 / 75	Referent	Referent	430,911 / 6,223	Referent	Referent
Past	31,647 / 30	1.00 (0.65-1.53)	1.08 (0.71-1.67)	233,676 / 2,989	0.89 (0.85-0.93)	0.89 (0.85-0.93)
Current	14,703 / 12	0.99 (0.52-1.89)	1.07 (0.56-2.03)	149,255 / 1,249	0.60 (0.56-0.63)	0.73 (0.69-0.78)

Minimally adjusted models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score and UK region.
Multivariable-adjusted models include all the variables defined above, plus BMI, duration of oral contraceptive use, age at menarche, parity, physical activity and diabetes status. Models for postmenopausal women were further adjusted for age at menopause, HRT status and interaction term for BMI and HRT status.
[1] Conventional 95%CI are presented for meta-analysis

Table 6-3: Hazard ratios for endometrial cancer associated with current vs never smoking after adjustment for various confounders

Variables	**HR (95%CI) for current vs never smokers)**	
	UK Biobank	**Million Women Study**
Stratified by year of birth and year of data collection, and adjusted for age, UK region and deprivation score	0.54 (0.38-0.77)	0.60 (0.57 - 0.64)
Adjustment independently for:		
BMI (kg/m^2)	0.58 (0.42-0.81)	0.66 (0.63-0.88)
Age at menopause (years)	0.58 (0.41-0.82)	0.65 (0.61-0.69)
HRT use / type[1]	0.55 (0.39-0.78)	0.60 (0.56-0.64)
Parity[2]	0.54 (0.38-0.77)	0.60 (0.57-0.64)
Duration of oral contraceptive use (years)	0.57 (0.40-0.80)	0.62 (0.59-0.66)
Age at menarche (years)	0.58 (0.41-0.82)	0.60 (0.57-0.64)
Physical activity[3]	0.54 (0.38-0.76)	0.58 (0.55-0.62)
Diabetes status	0.55 (0.39-0.76)	0.60 (0.57-0.63)
Adjusted for all covariates	**0.65 (0.46-0.92)**	**0.74 (0.70 - 0.78)**

[1]HRT status (current, past or never) in UK Biobank, type of HRT currently used in Million Women Study (never, past, oestrogen only, oestrogen + progestogen, tibolone, others)
[2] number of full-term pregnancies in Million Women Study
[3] Frequency of strenuous exercise per week in Million Women Study

Table 6-4: Hazard ratios for endometrial cancer associated with quantitative smoking metrics among postmenopausal women in UK Biobank

Smoking measures	Past smokers			Current smokers		
	Number of women / cases	Minimally adjusted HR (95%gsCI)	Multivariable adjusted HR (95%gsCI)	Number of women / cases	Minimally adjusted HR (95%gsCI)	Multivariable adjusted HR (95%gsCI)
Number of cigarettes smoked per day						
Never smokers	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)
<20	14,754 / 86	0.97 (0.78-1.20)	1.05 (0.85-1.30)	6,850 / 19	0.49 (0.31-0.77)	0.62 (0.40-0.97)
≥20	13,277 / 59	0.74 (0.56-0.97)	0.68 (0.52-0.88)	3,127 / 11	0.64 (0.35-1.15)	0.69 (0.38-1.25)
Smoking duration						
Never smokers	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)
<20 years	13, 106 / 59	0.79 (0.61-1.02)	0.82 (0.63-1.06)	205 / 2	2.20 (0.55-8.83)	2.37 (0.59-9.52)
≥20 years	14,909 / 87	0.93 (0.75-1.15)	0.90 (0.73 -1.12)	9,774 / 28	0.51 (0.35-0.74)	0.61 (0.42-0.89)
Age at smoking initiation						
Never smokers	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)
≥18 years	14,110 / 83	0.95 (0.77-1.18)	0.95 (0.76-1.18)	4,796 / 18	0.65 (0.41-1.02)	0.77 (0.48-1.22)
<18 years	14,038 / 63	0.76 (0.60-0.98)	0.77 (0.60-0.99)	5,183 / 12	0.43 (0.24-0.75)	0.52 (0.29-0.91)
Time since smoking cessation						
Never smokers	81, 838 / 471	1.00 (0.91-1.10)	1.00 (0.91-1.10)	-	-	-
≥20 years	15,660 / 78	0.82 (0.66-1.03)	0.85 (0.68-1.06)	-	-	-
<20 years	12,523 / 69	0.92 (0.73-1.17)	0.90 (0.71-1.14)	-	-	-

Minimally adjusted models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score and UK region.
Multivariable-adjusted models include all the variables defined above, plus BMI, duration of oral contraceptive use, menopause status/ age at menopause, age at menarche, parity, HRT use, interaction term for BMI and HRT, physical activity and diabetes status.

Table 6-5: Hazard ratios for endometrial cancer by smoking duration and number of cigarettes smoked per day among postmenopausal current smokers in the Million Women Study

		Number of cigarettes smoked per day		
Smoking duration	**Current smokers**	**<10**	**10-<20**	**≥20**
<20 years				
Multivariable-adjusted HR (95%gsCI)	1.16 (0.70-1.92)	1.80 (0.90-3.60)	1.06 (0.48-2.36)	0.39 (0.05-2.76)
Number of women	1,001	376	435	176
Number of cases	15	8	6	1
Median smoking duration (years)	14.6	13.5	14.9	16.6
Median cigarettes per day	10	5	10	20
20-<40 years				
Multivariable-adjusted HR (95%gsCI)	0.72 (0.64-0.82)	0.91 (0.69-1.18)	0.72 (0.60-0.87)	0.64 (0.51-0.80)
Number of women	31,279	5,549	14,337	11,078
Number of cases	244	54	107	79
Median smoking duration (years)	36.9	36.4	36.8	37.1
Median cigarettes per day	15	5	12	20
≥40 years				
Multivariable-adjusted HR (95%gsCI)	0.70 (0.62-0.78)	0.92 (0.72-1.17)	0.63 (0.53-0.76)	0.68 (0.56-0.82)
Number of women	37,687	6,156	16,901	14,369
Number of cases	293	65	116	110
Median smoking duration (years)	43.8	44.1	43.9	43.6
Median cigarettes per day	15	5	14	20

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, HRT status, interaction term between BMI and HRT status, physical activity and diabetes status. Never smokers (n= 295,728, cases=4,269) were the referent category.

Table 6-6: Hazard ratios for endometrial cancer by smoking duration and age at smoking initiation among postmenopausal current smokers in the Million Women Study

		Age at smoking initiation (years)		
Smoking duration	**Current smokers**	**≥25**	**18-<25**	**<18**
<20 years				
Multivariable-adjusted HR (95%gsCI)	1.16 (0.70-1.92)	1.16 (0.70-1.92)	-	-
Number of women	1,001	1001	-	-
Number of cases	15	15	-	-
Median smoking duration (years)	14.6	14.6	-	-
Median age at smoking initiation (years)	45	45	-	-
20-<40 years				
Multivariable-adjusted HR (95%gsCI)	0.73 (0.64-0.83)	0.99 (0.79-1.25)	0.67 (0.56-0.80)	0.59 (0.44-0.78)
Number of women	31,279	6,361	16,522	8,396
Number of cases	244	76	119	49
Median smoking duration (years)	36.9	30.9	36.5	38.5
Median age at smoking initiation (years)	20	29	20	16
≥40 years				
Multivariable-adjusted HR (95%gsCI)	0.70(0.62-0.78)	0.92 (0.38-2.23)	0.70 (0.58-0.85)	0.69 (0.59-0.80)
Number of women	37,687	515	14,017	23,155
Number of cases	293	5	110	178
Median smoking duration (years)	43.8	41.5	43.5	44.1
Median age at smoking initiation (years)	16	25	19	16

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, HRT status, interaction term between BMI and HRT status, physical activity and diabetes status. Never smokers (n= 295,728, cases=4,269) were the referent category.

Table 6-7: Hazard ratios for endometrial cancer by smoking duration and time since smoking cessation among postmenopausal past smokers in the Million Women Study

		Time since cessation		
Smoking duration (years)	**Past smokers**	**<20 years**	**20 -<30 years**	**≥30 years**
<20				
Multivariable-adjusted HR (95%gsCI)	0.94 (0.89-1.00)	1.03 (0.84-1.27)	0.88 (0.79-0.98)	0.97 (0.89-1.05)
Number of women	88,039	6,823	35,170	46,046
Number of cases	1,144	98	423	623
Median smoking duration (years)	10	16	13	7
Median time since cessation	30.4	16.8	26	34.7
20-<30				
Multivariable-adjusted HR (95%gsCI)	0.88 (0.81-0.96)	0.85 (0.76-0.96)	0.92 (0.79-1.07)	1.23 (0.70-2.17)
Number of women	39,885	25,469	13,620	796
Number of cases	520	317	191	12
Median smoking duration (years)	24	25	22	21
Median time since cessation	17.6	14.9	22.8	31.8
≥30				
Multivariable-adjusted HR (95%gsCI)	0.84 (0.77 -0.92)	0.84 (0.77-0.93)	0.64 (0.30-1.34)	-
Number of women	42,672	41,737	908	27
Number of cases	510	503	7	0
Median smoking duration (years)	35	36	31	31
Median time since cessation	7.3	7.1	21.6	31.2

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, HRT status, interaction term between BMI and HRT status, physical activity and diabetes status. Never smokers (n= 295,728, cases=4,269) were the referent category.

Table 6-8: Hazard ratios for different subtypes of endometrial cancer by smoking status among postmenopausal women in the Million Women Study

Smoking status	Type I		Type II		Uterine sarcoma		MMMTs		Others	
	Cases	Multivariable-adjusted HR (95%gsCI)	Cases	Multivariable-adjusted HR (95%gsCI)	Cases	Multivariable-adjusted HR (95%gsCI)	Cases	Multivariable-adjusted HR (95%gsCI)	Cases	Multivariable-adjusted HR (95%gsCI)
Never	4,699	1.00 (0.97-1.03)	595	1.00 (0.92-1.09)	76	1.00 (0.79-1.26)	257	1.00 (0.88-1.14)	125	1.00 (0.83-1.20)
Past	2,230	0.90 (0.86-0.93)	279	0.90 (0.80-1.01)	37	0.93 (0.67-1.28)	112	0.84 (0.70-1.01)	60	0.88 (0.68-1.13)
Current	962	0.72 (0.68-0.77)	137	0.79 (0.67-0.94)	21	0.85 (0.55-1.32)	61	0.82 (0.63-1.06)	33	0.84 (0.59-1.20)

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, type of HRT, interaction term for BMI and HRT type, physical activity and diabetes status.
Test for heterogeneity between type I and type II tumours among current smokers: p = 0.44.
Test for heterogeneity between type I and type II tumours among past smokers: p = 0.95.

Table 6-9: Hazard ratios endometrial cancer by smoking status in various sensitivity analyses performed among postmenopausal women in the Million Women Study

Smoking status	Number of women / cases	Baseline smoking status, full follow-up period HR (95%gsCI)	Number of women / cases	Baseline smoking status, first five years of follow-up only	Number of women/ cases	Smoking status modelled as a time-varying exposure HR (95%gsCI)	Number of women / cases	Women with same smoking status at recruitment and at last questionnaire HR (95%gsCI)
Never	349,073 / 5,752	1.00 (0.97-1.03)	349,073 / 983	1.00 (0.94-1.07)	331,767 / 5,650	1.00 (0.97-1.03)	326,604 / 5,450	1.00 (0.97-1.03)
Past	189,793 / 2,718	0.89 (0.86-0.93)	189,793 / 464	0.89 (0.81-0.98)	222,048 / 3,001	0.88 (0.85-0.92)	177,436 / 2,528	0.88 (0.84-0.91)
Current	137,790 / 1,214	0.74 (0.70-0.78)	137,790 / 221	0.78 (0.68-0.89)	104,431 / 934	0.69 (0.65-0.74)	100,408 / 892	0.77 (0.72- 0.83)
Missing smoking status at last questionnaire					8,726 / 99	0.90 (0.74 - 1.10)		

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, type of HRT, interaction term for BMI and HRT type, physical activity and diabetes status.

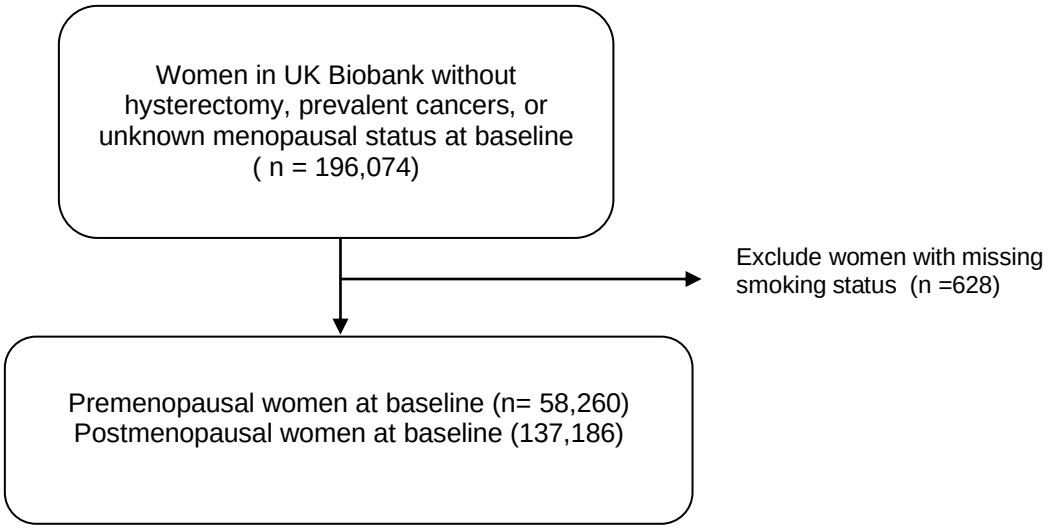


Figure 6-1: Flowchart for inclusion of participants in all analyses in UK Biobank

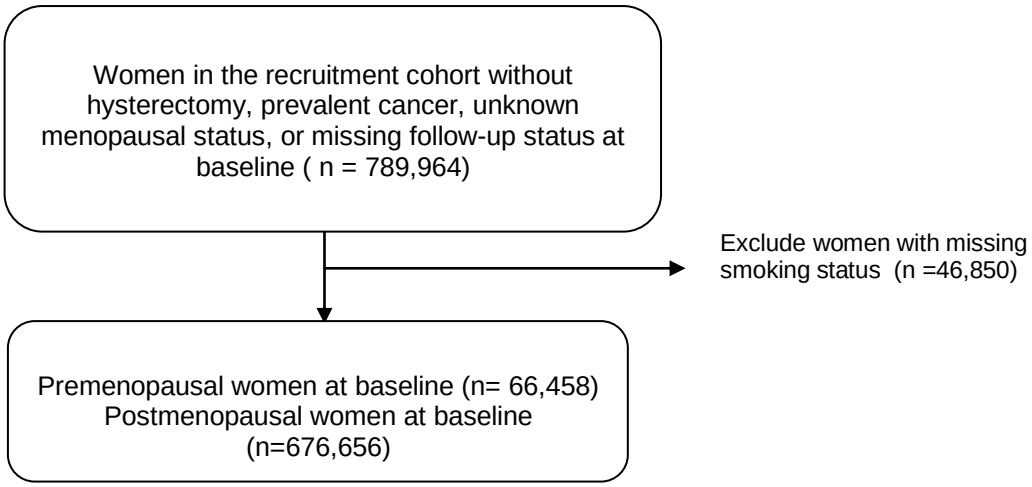


Figure 6-2: Flowchart for inclusion of participants in analyses relating to smoking status in the Million Women Study

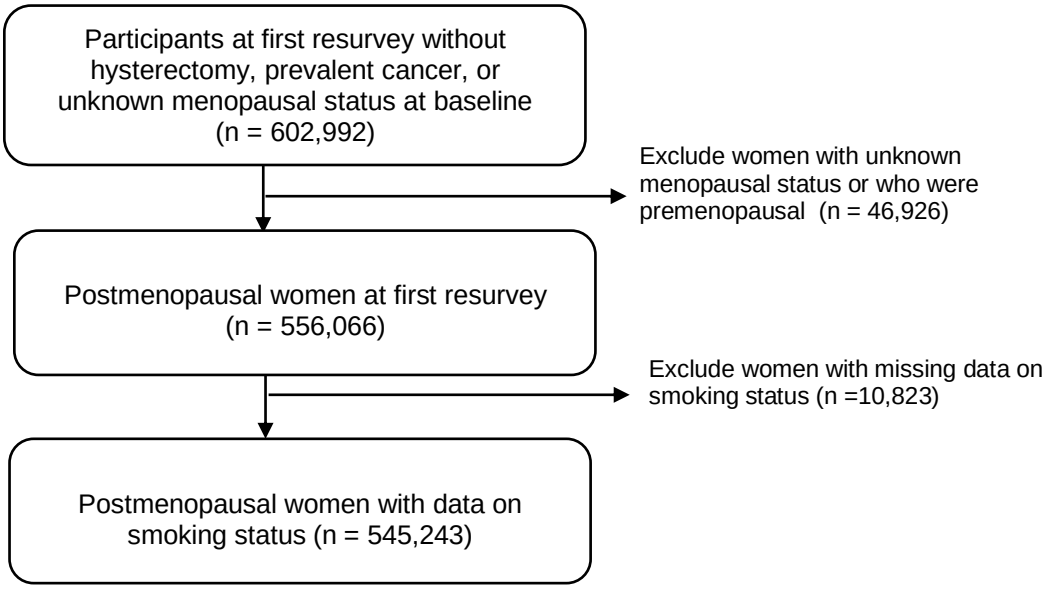
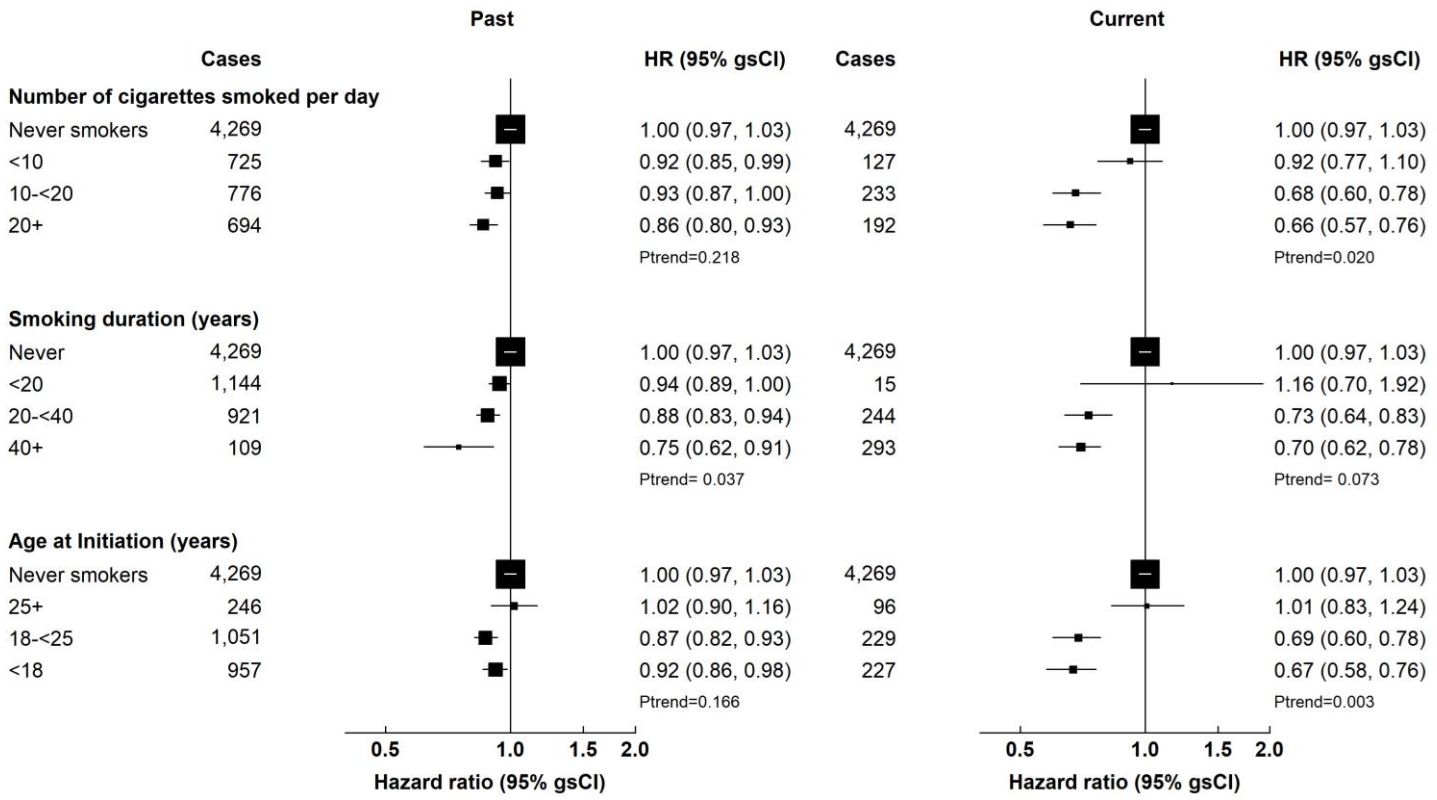
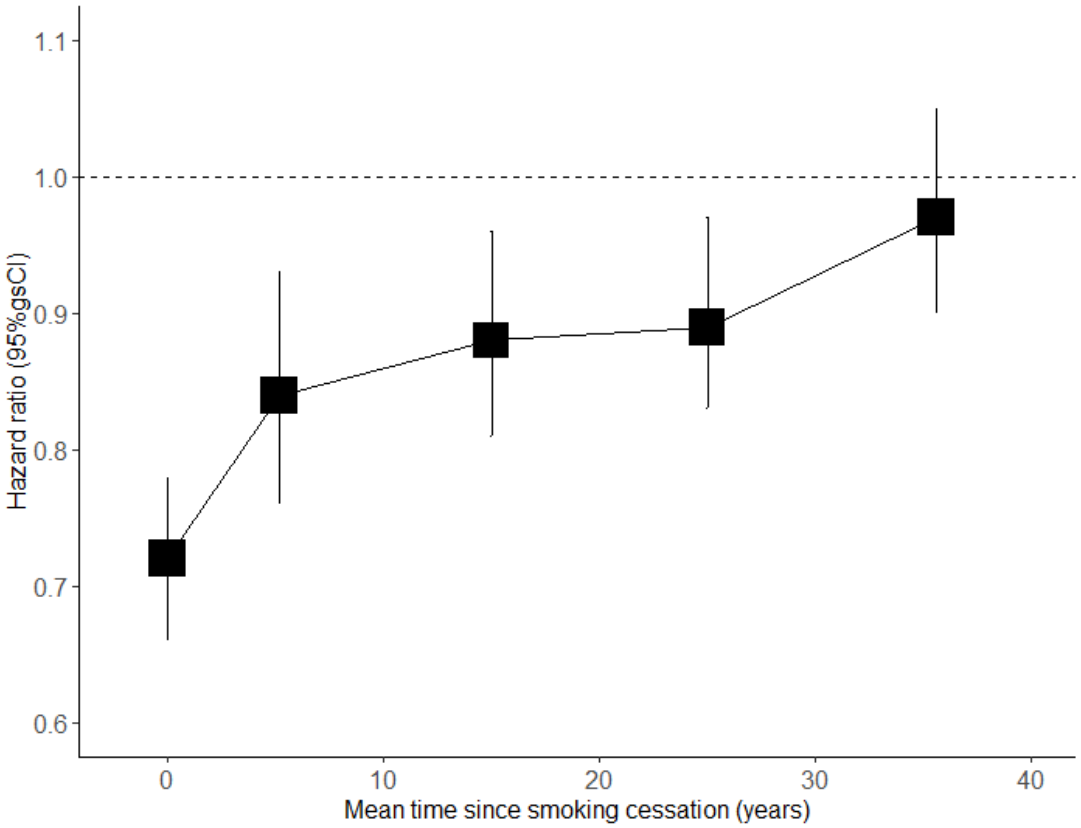


Figure 6-3: Flowchart for inclusion of participants in analyses of associations with quantitative smoking metrics in the Million Women Study



Note: '+' used instead of '≥' because the software used to generate the figure does not recognize '≥'

Figure 6-4: Hazard ratios for endometrial cancer by categories of various quantitative smoking metrics among postmenopausal women in the Million Women Study

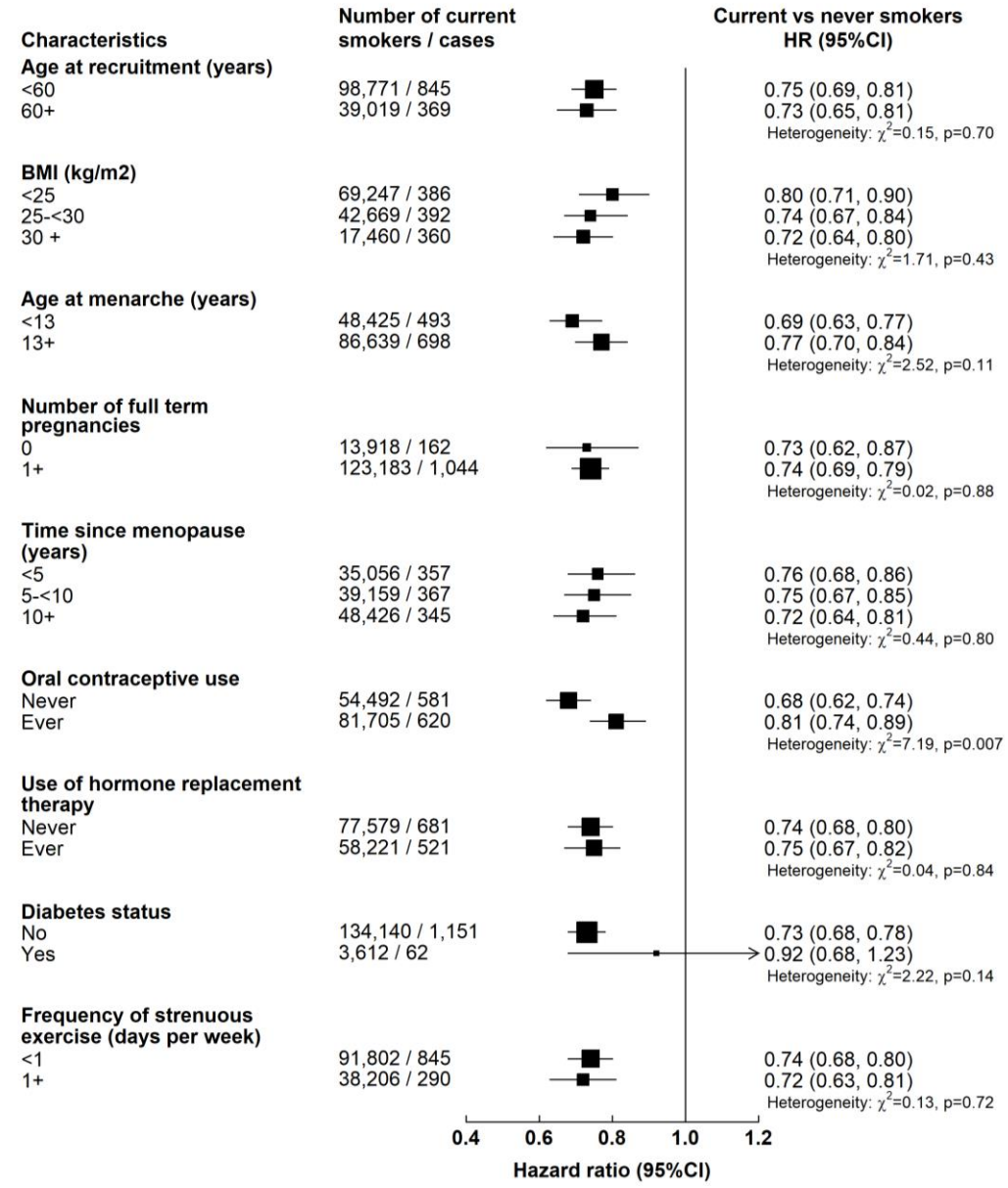


TSSC	Current	<10 years	10-<20 years	20-<30 years	≥30years
Mean tssc	0	5.2 years ago	15.0 years ago	25.0 years ago	35.6 years ago
Cases	558	395	532	628	643
HR(95%gsCI)	0.72 (0.66-0.78)	0.84 (0.76-0.93)	0.88 (0.81-0.96)	0.89 (0.83-0.97)	0.97 (0.90-1.05)
Median duration	40.4 years	36years	26years	16years	7 years

TSSC is time since smoking cessation

Model was stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, menopause status/ age at menopause, age at menarche, parity, type of HRT, interaction term between BMI and HRT type, physical activity and diabetes status.

Figure 6-5: Hazard ratios for endometrial cancer by time since smoking cessation among postmenopausal past smokers in the Million Women Study



Note: '+' used instead of '≥' because the software used to generate the figure does not recognize '≥'

Figure 6-6: Hazard ratios for the association of current vs never smoking with endometrial cancer risk according to selected baseline characteristics among postmenopausal women in the Million Women Study

Chapter 7: General discussions

7.1. Introduction

This thesis used data from the UK Biobank and the Million Women Study to examine in unprecedented detail the well-established associations of adiposity and smoking with endometrial cancer risk. Specifically, the thesis: (i) evaluated whether bioimpedance-derived measures of adiposity are better indicators of endometrial cancer risk than traditional adiposity indices; (ii) examined whether central adiposity is associated with endometrial cancer risk independently of overall adiposity; (iii) assessed the extent to which selected biomarkers explain the association of adiposity with risk; (iv) quantified potential variations in the association of adiposity with endometrial cancer risk by population characteristics and tumour subtypes; and (v) evaluated the association between smoking and endometrial cancer risk by smoking characteristics, population characteristics and tumour subtypes. This chapter summarises the key findings, their implications and recommendations for future research.

7.2. Key findings and their implications

7.2.1. Adiposity and endometrial cancer risk (chapters 4 and 5)

Much of the research on the association of adiposity with endometrial cancer risk has been done using BMI, which reflects both fat and fat-free mass. The

analysis involving 135,110 postmenopausal women in the UK Biobank contributed novel information regarding the association of adiposity as assessed by bioimpedance analysis with endometrial cancer risk (chapter 4). The results demonstrated that bioimpedance-derived body fat percentage and fat mass are not materially different from BMI in their associations with endometrial cancer risk (section 4.3.4), indicating that BMI is as good as bioimpedance-derived measures of fat when it comes to assessing endometrial cancer risk. As bioimpedance analysis is more cumbersome to use in large epidemiological studies, these results provide support for the continued use of BMI in epidemiological studies assessing adiposity-related risk of endometrial cancer.

An important unresolved question in the aetiology of endometrial cancer is whether central adiposity contributes to endometrial cancer risk independently of overall adiposity. In both the UK Biobank (section 4.3.4.2) and the Million Women Study cohorts (section 5.3.3), central adiposity, as reflected by waist circumference and waist to hip ratio, slightly increased the risk of postmenopausal endometrial cancer independently of BMI. These findings add to evidence that central adiposity is an independent risk factor for endometrial cancer and highlight the need to take into account both overall and central adiposity when assessing endometrial cancer risk due to adiposity.

Several mechanisms have been proposed to explain the relationship between adiposity and endometrial cancer risk. These include alterations in levels of endogenous hormones, inflammation and insulin resistance.[53,313] Consistent with the notion that inflammation might explain some of the association between adiposity and endometrial cancer risk, this thesis found a slight reduction in the risk of endometrial cancer associated with overall adiposity measures after adjustment for CRP (section 4.3.4.3). For instance, the HR per 1-SD increment in BMI reduced from 1.72 (1.60-1.84) to 1.63 (1.51-1.77) after adjustment for CRP (section 4.3.4.3).

Adjustment for free testosterone also had a similar attenuating effect on the association (HRs per 1-SD increment in BMI before and after adjustment for free testosterone were 1.73 and 1.61, respectively), suggesting that alterations in free testosterone may explain in part the relationship between overall adiposity and endometrial cancer risk (section 4.3.4.3). Since androgens are the precursors of oestrogen,[160] it is possible that free testosterone only acts as a marker of oestrogen bioavailability here.

Analyses examining the association of adiposity with endometrial cancer risk by population characteristics and tumour subtypes are important because they could provide valuable insight into the mechanisms underlying this association. In chapter 5, data from up to 674,971 postmenopausal women in the Million Women Study were used to assess the relationship between adiposity, measured by BMI, and endometrial cancer risk by levels of various

characteristics. The results demonstrated that the risk associated with adiposity was substantially attenuated in current HRT users ($HR_{\text{per 5 kg/m2 increment in BMI in all current users}}$= 1.20, 95%CI: 1.07-1.36), irrespective of the type of HRT used, and that the attenuating effect of HRT on the association wore off rapidly once use ceased ($HR_{\text{per 5 kg/m2 increment in BMI}}$ = 1.76, 95%CI: 1.54-2.02 for women who stopped using HRT less than one year before baseline assessment; section 5.4.1). These findings are consistent with the notion that sex hormones, predominantly oestrogen, are in the causal pathway between adiposity and postmenopausal endometrial cancer development.[53]

With respect to tumour subtypes, stronger positive associations were observed with type I tumours than type II tumours (section 5.3.2.2). Type I tumours are associated with oestrogen exposure, whereas type II tumours are thought to arise through pathways that are unrelated to oestrogen.[55,81] Thus, the stronger association with type I tumours provides support for the notion that BMI influences endometrial cancer risk largely through oestrogenic pathways.

The association between BMI and type II tumours is also noteworthy as it implies that non-oestrogenic mechanisms may also link adiposity with endometrial cancer risk. Plausible mechanisms include chronic inflammation and insulin resistance. Owing to lack of data on biomarkers in the Million Women Study cohort, it was not possible to assess how much of the association of BMI with type II tumours is accounted for by these

mechanisms. However, the fact that adjustment for diabetes (which is characterised by insulin resistance) had little effect on the association between BMI and endometrial cancer risk (section 5.3.2.2) suggests that insulin resistance is unlikely to explain much of the effect of adiposity on endometrial cancer risk. An alternative explanation for the association with type II tumours is that the oestrogenic effect of adiposity also affects the development of type II endometrial cancer. Further research is needed to determine whether oestrogen explains the association between BMI and type II tumours.

7.2.2. Smoking and endometrial cancer risk (chapter 6)

The existing literature on the inverse association between smoking and endometrial cancer fulfils many of the classical criteria for causal inference in epidemiology including strength of association, consistency across studies, temporality and biological plausibility.[336] The research undertaken in this thesis further strengthens evidence for an inverse association between smoking and endometrial cancer by showing dose-response associations with several quantitative smoking metrics including number of cigarettes smoked per day and age at smoking initiation among current smokers (P_{trend} <0.05; section 6.3.3.2). Such dose-response relationships have not been reported in previous prospective studies.

This thesis also contributed novel information regarding how long the risk reduction associated with smoking lasts when women stop smoking.

Endometrial cancer risk in past smokers remained low compared to that of never smokers for more than 20 years after smoking cessation (HR = 0.89, 95%CI: 0.82-0.97) and risk only returned to levels comparable to that of never smokers after 30 years since smoking cessation (section 6.3.3.2). This finding suggests that the biological changes induced by smoking have long-lasting impact on endometrial cancer risk. Since smoking is thought to influence endometrial cancer risk through antiestrogenic mechanisms, it is plausible that this finding reflects the impact of prolonged periods of oestrogen deprivation.[173] [173,218]

With regard to tumour subtypes, smoking was similarly associated with the risk of both type I and type II tumours (section 6.3.4.1). As type II tumours are generally not thought to be associated with oestrogen exposure, this finding conflicts with the hypothesis that smoking reduces endometrial cancer risk via antiestrogenic mechanisms. A possible explanation for this might be that the effect of smoking on endometrial cancer development is not mediated by antiestrogenic mechanisms. An alternative explanation is that the antiestrogenic effects of smoking may also have an impact on the development of type II tumours, suggesting that oestrogen may play a role in the development of type II tumours. This latter hypothesis appears to be credible given that both adiposity and smoking—which are hypothesised to affect endometrial cancer risk through pathways involving oestrogen—showed significant associations with type II tumours in this thesis. Results from recent epidemiological studies showing that factors which modulate

oestrogen exposure, such as HRT, oral contraceptive use, early menarche and age at menopause, are associated with risk of type II tumours also support this hypothesis.[56,57,124] These observations raise questions about the validity of the dualistic view of endometrial carcinogenesis and highlight the need for research to clarify the extent to which oestrogen plays a role in the development of type II endometrial cancer.

7.2.3. Public health implications

Adiposity is potentially modifiable, whereas most of the other established risk factors (such as age, age at menarche, age at menopause and Lynch syndrome) for endometrial cancer are not. The works of this thesis add to evidence for a causal role of overall adiposity in endometrial carcinogenesis and provide support for the notion that central adiposity might contribute to risk independently of overall adiposity. Given the high levels of adiposity in many populations and the substantial contribution of adiposity to endometrial cancer incidence (34% of endometrial cancers in the UK are attributable to adiposity),[6] these findings underscore the importance of controlling adiposity for endometrial cancer prevention.

As evident from the dose-response analysis, the risk of developing endometrial cancer was not confined to postmenopausal women who had a BMI value above a specific threshold (chapters 4 and 5). Risk increased linearly with increasing BMI even within the normal weight category (i.e. BMI less than 25 kg/m^2). This finding suggests that public health strategies that

aim to shift the whole distribution of BMI in the population towards lower values could result in a substantial reduction in endometrial cancer incidence.

Although the results of this thesis suggest that smoking confers long-term protection against endometrial cancer risk, there is no basis for considering smoking as a preventative measure for endometrial cancer given its well-known adverse effect on health. However, further exploration of the mechanism underlying the inverse association between smoking and endometrial cancer risk could potentially lead to the identification of modifiable pathways for endometrial cancer prevention and treatment.

7.3. Methodological considerations

The research undertaken in this thesis has many strengths including the prospective design, the use of data from two large well-established cohorts, with a vast amount of information recorded in each and virtually complete follow-up of participants. Repeat measurements for all exposures of interest were available for subsets of participants in both cohorts allowing for assessment of the impact of changes in exposure over time and correction of risk estimates for regression dilution bias. Body composition in UK Biobank was assessed using traditional anthropometric indices and bioimpedance analysis, allowing for investigation of more precise indices of adiposity with endometrial cancer risk. The large sample size of the Million Women Study and the large number of incident endometrial cancers in the cohort allowed

for robust estimation of the associations of adiposity and smoking with endometrial cancer risk in important population subgroups as well as by tumour subtypes.

Several limitations of the UK Biobank and Million Women Study data need to be considered. First, participants in both cohorts were 40 years or older and were predominantly of European origin. Therefore, the findings of this thesis may not be generalisable to younger populations (although endometrial cancers are rare in younger women) and to those of other racial or ethnic backgrounds. Second, because of the relatively small number of premenopausal women, this thesis was unable to reliably examine the associations of adiposity and smoking with the risk of premenopausal endometrial cancers. Third, central adiposity was assessed using indirect anthropometric indicators such as waist circumference and trunk fat percentage. These measures cannot distinguish between subcutaneous and visceral fat, which are thought to have different health impacts. Fourth, despite the large sample size of the Million Women Study cohort, numbers were limited in some stratified analyses such as analyses that investigated the associations between adiposity and endometrial cancer risk by the type of HRT used. Fifth, the large number of subgroup analyses performed could lead to the finding of statistically significant associations by chance. These analyses were not corrected for multiple testing because of the exploratory nature; therefore, the results of the subgroup analyses should be interpreted with caution. Sixth, information on smoking history including number of

cigarettes smoked per day were self-reported in both cohorts and is therefore subject to information and reporting bias. Quantitative measures such as smoking duration are particularly subject to information bias and may not reflect cumulative duration of smoking as many smokers cease and resume smoking repeatedly over time.[178] Seventh, tumour subtypes classification were based on cancer registry data which may be subject to some degree of misclassification as cancer registries rely on multiple pathology laboratories that use different assays. Lastly, given the observational design, the possibility of residual or unmeasured confounding cannot be excluded despite adjusting for all known confounders.

7.4. Recommendations for further work

There are a number of gaps in our knowledge of the associations of adiposity and smoking with endometrial cancer risk that follow from this thesis which would benefit from further research. These gaps are detailed below.

7.4.1. Central adiposity and endometrial cancer risk

Although the findings of this thesis suggest that central adiposity, as reflected by waist circumference and waist to hip ratio, is associated with endometrial cancer risk independently of BMI, the possibility remains that this association is due to residual confounding by BMI. The relationship between central adiposity and endometrial cancer risk could be further investigated using the Mendelian randomisation approach, a method that allows causal inferences

to be made within observational studies.[337] Because Mendelian randomisation uses genetic variants as markers for an exposure of interest, it is less susceptible to confounding than traditional observational studies.[337,338] To my knowledge, only one study has used this method to assess the association between waist to hip ratio and endometrial cancer risk, and the study found no evidence of an association with waist to hip ratio, which is contrary to the results presented here.[148] As far as I am aware, no study has employed this method to assess the association of waist circumference with endometrial cancer risk. Because UK Biobank has genetic data for all participants, this resource could be used to perform Mendelian randomisation analysis that will enhance our understanding of the associations of waist circumference and waist to hip ratio with endometrial cancer risk.

Another area for possible research is to examine more accurate measures of visceral adiposity—the key determinants of the health-risk associated with central adiposity—in relation to endometrial cancer risk. MRI and CT scans can be used to precisely quantify the amount of fat in the visceral fat depot.[43] The use of these techniques is largely limited to small research settings; however, the UK Biobank is performing full-body MRI scans in a large subset of the cohort (approximately 100,000 over the coming years).[339] Various research groups are processing the MRI images to produce image-derived phenotypes related to body composition.[340] These data, when available,

could significantly advance our understanding of the relationship between visceral adiposity and endometrial cancer risk.

The research conducted in this thesis is relevant for understanding disease aetiology rather than providing information on the utility of central adiposity measures in endometrial cancer risk prediction. More research is needed to determine whether waist circumference or waist to hip ratio provide additional information on risk beyond BMI and other risk factors for improved risk prediction at the population level.

7.4.2. Further analysis of association of smoking with risk

In this thesis, it was not possible to distinguish the effect of smoking intensity (assessed by number of cigarettes smoked per day) from those of smoking duration or age at smoking initiation because of correlation between these exposures. As there are genetic instruments for smoking intensity,[341,342] future studies should consider using Mendelian randomisation approach to examine the role of smoking intensity in endometrial cancer development. Such analysis could be performed using genetic data available in the UK Biobank.

7.4.3. Associations of smoking and adiposity with endometrial cancer risk in various population subgroups

Due to the cohorts recruiting mostly postmenopausal women, it was not possible to robustly assess the associations of adiposity and smoking with

endometrial cancer risk in premenopausal women. Prospective studies that specifically recruit younger women are needed to analyse in detail the associations of both adiposity and smoking with endometrial cancer risk in premenopausal women.

In this thesis, there was evidence of heterogeneity in the association of BMI with postmenopausal endometrial cancer risk by parity, oral contraceptive use, timing of menopause and diabetes (section 5.3.2.2). Given the number of multiple tests performed in the subgroup analyses, it is possible that these findings are due to chance. Future studies should verify or refute these findings in order to enhance our understanding of these associations. Research is also needed to verify possible effect modification of the association of smoking with endometrial cancer risk by oral contraceptive use (section 6.3.4.2).

7.4.4. Biological mechanisms linking adiposity and smoking with endometrial cancer risk

Further studies are needed to elucidate the mechanisms underlying the associations of both adiposity and smoking with the risk of endometrial cancer. In particular, mechanistic research is needed to determine whether and to what extent oestrogen mediates the associations of both adiposity and smoking with the risk of type II endometrial cancer. Such research could enhance our understanding of the aetiology of this rare tumour subtype and

provide clues to modifiable pathways for endometrial cancer prevention and treatment.

7.5. Conclusion

BMI and bioimpedance-derived measures of overall adiposity showed broadly similar positive associations with endometrial cancer risk in postmenopausal women, indicating that bioimpedance analysis is not better than BMI for assessing endometrial cancer risk. Central adiposity, as reflected by waist circumference or waist to hip ratio, was modestly associated with endometrial cancer risk independently of BMI, indicating that central adiposity may be a determinant of endometrial cancer risk. The association between BMI and endometrial cancer risk was stronger in never and past HRT users than current users and was greater for type I than type II tumours. These findings are consistent with the notion that adiposity affects endometrial cancer risk largely through oestrogenic mechanisms. Smoking was associated with a reduced risk of endometrial cancer. The risk reduction was evident for type I and type II tumours and lasted for decades after smoking cessation. Future studies should elucidate the mechanisms underlying this inverse association between smoking and endometrial cancer risk.

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Appendix 1: Abstract for journal article based on the work presented in chapter 4

Received: 20 January 2020 | Revised: 7 April 2020 | Accepted: 17 April 2020

DOI: 10.1002/ijc.33023



CANCER EPIDEMIOLOGY

IJC

Body size, body composition and endometrial cancer risk among postmenopausal women in UK Biobank

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Abstract

Previous studies on the association of adiposity with endometrial cancer risk have mostly used body mass index (BMI) as the main exposure of interest. Whether more precise measures of body fat, such as body fat percentage and fat mass estimated by bioimpedance analyses, are better indicators of risk than BMI is unknown. The role of central adiposity and fat-free mass in endometrial cancer development remains unclear. We used Cox regression models to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations of various measures of body size/composition with the risk of endometrial cancer among 135 110 postmenopausal women enrolled in UK Biobank. During a mean follow up of 6.8 years, 706 endometrial cancers were diagnosed, with a mean age at diagnosis of 65.5 years. The HRs (95% CIs) for endometrial cancer per 1 SD increase in BMI, body fat percentage and fat mass were broadly comparable, being 1.71 (1.61-1.82), 1.92 (1.75-2.11) and 1.73 (1.63-1.85), respectively. There was an indication of positive association between central adiposity, as reflected by waist circumference ($HR_{per\ 1\text{-}SD\ increase}$ = 1.08, 95% CI: 1.00-1.17) and waist to hip ratio ($HR_{per\ 1\text{-}SD\ increase}$ = 1.13, 95% CI: 1.01-1.26), and endometrial cancer risk after accounting for BMI. Fat-free mass was not an independent predictor of risk in this cohort. These findings suggest that body fat percentage and fat mass are not better indicators of endometrial cancer risk than BMI. Further studies are needed to establish whether central adiposity contributes to risk beyond overall adiposity.

KEYWORDS

bioimpedance, BMI, body composition, endometrial cancer

Appendix 2: UK Biobank questionnaire showing questions used to assess some variables of interest in the thesis

Appendix 2A: Questions used to assess smoking status in the UK Biobank questionnaire

Q. No	Stem	Responses	Action Branches
S1	Do you smoke tobacco now?	Select one from - 01 Yes, on most or all days - 02 Only occasionally - 00 No - DA Prefer not to answer	If no or only occasionally or DA go to S2 If yes go to S3
S2	In the past, how often have you smoked tobacco?	Select one from - 01 Smoked on most or all days - 02 Smoked occasionally - 03 Just tried once or twice - 04 I have never smoked - DA Prefer not to answer	If smoked on most or all days go to S6 If never smoked or DA go to S11 Otherwise go to S2A
S2A	In your lifetime, have you smoked a total of at least 100 times?	Select one from - YE Yes - NO No - UN Do not know - DA Prefer not to answer	Go to S11

Appendix 2B: Questions used to assess age at smoking initiation and number of cigarettes smoked per day in current smokers

Q. No	Stem	Responses	Action Branches
S3	How old were you when you first started smoking on most days?	Enter age OR UN Do not know OR DA Prefer not to answer	Go to S4
S4	What type of tobacco do you mainly smoke?	Select one from - 01 Manufactured cigarettes - 02 Hand-rolled cigarettes - 03 Cigars or pipes - NN None of the above - DA Prefer not to answer	If manufactured or hand-rolled go to S4A If none of the above or DA go to S5 If cigars or pipes go toS4AA
S4A	About how many cigarettes do you smoke on average each day? (Include hand rolled cigarettes if smoked).	Enter number OR FR Less than one a day OR UN Do not know OR DA Prefer not to answer	Go to S4B

Appendix 2C: Questions used to assess age at smoking initiation, number of cigarettes smoked per day and time since smoking cessation in past smokers

Q. No	Stem	Responses	Action Branches
S6	How old were you when you first started smoking on most days?	Enter age OR UN Do not know OR DA Prefer not to answer	Go to S7
S7	What type of tobacco did you usually smoke?	Select one from - 01 Manufactured cigarettes - 02 Hand-rolled cigarettes - 03 Cigars or pipes - NN None of the above - DA Prefer not to answer	Go to S7A If none of the above or DA or cigars or pipes go to S8
S7A	About how many cigarettes did you smoke on average each day? (Include hand rolled cigarettes if smoked).	Enter number OR FR Less than one a day OR UN Do not know	Go to S8
S8	How old were you when you last smoked on most days?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to S9

Appendix 2D: Questions used to assess age at menarche, menopause, age at menopause and parity in UK Biobank

WOMEN ONLY QUESTIONS

Q. No	Stem	Responses	Action Branches
FH1	How old were you when your periods started?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to FH2
FH2	Have you had your menopause (periods stopped)?	Select one from - YE Yes - NO No - 02 Not sure – had a hysterectomy - 03 Not sure – other reason - DA Prefer not to answer	If yes go to FH2A If no go to FH2B If not sure had a hysterectomy go to FH3 If not sure other reason or DA go to FH2D
FH2A	How old were you when your periods stopped?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to FH3
FH3	How many children have you given birth to? (please include live births only)	Enter number OR DA Prefer not to answer	If 0 or DA go to FH4 Otherwise go to FH3A

Appendix 2E: Questions used to assess oral contraceptive use and hormone replacement therapy in UK Biobank

Q. No	Stem	Responses	Action Branches
FH5	Have you ever taken the contraceptive pill? (include the 'mini-pill')	Select from - YE Yes - NO No - UN Do not know	If yes go to FH5A If no go to FH6 If do not know or DA go to FH6
FH5A	About how old were you when you first went on the contraceptive pill?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to FH5B
FH5B	How old were you when you last used the contraceptive pill?	Enter number OR UN Do not know OR -11 Still taking the pill OR DA Prefer not to answer	Go to FH6
FH6	Have you ever used hormone replacement therapy (HRT)?	Select from - YE Yes - NO No - UN Do not know	If yes go to FH6A If no or do not know or DA go to FH9 unless FH2=02, then go to FH9A.
FH6B	How old were you when you last used HRT?'	Enter number OR UN Do not know OR -11 Still taking HRT OR DA Prefer not to answer	If FH2=02 go to FH9A Otherwise Go to FH9

Appendix 2F: Questions used to assess physical activity in UK Biobank

Q. No	Stem	Responses / Categorical Label	Action Branches
INTRO2	Next are some questions about your day to day activities. We know it may be difficult to answer some of these questions exactly but an approximate answer is better than none. The first few questions ask about the time you have spent being physically active in the last 4 weeks. To answer these questions, think about all the activities that you do at work, as part of your house work, to get from place to place and in your leisure time. Please touch 'next' to continue.	Only one selection - Next	Go to WP1
WP1	In a typical WEEK, on how many days did you walk for at least 10 minutes at a time? (include walking that you do at work, travelling to and from work, and for sport or leisure)	Enter number OR UN Do not know OR NA Unable to walk OR DA Prefer not to answer	If 'unable to walk' or DNK or 0 or DA go to WP2 Otherwise go to WP1A
WP1A	How many minutes did you usually spend walking on a typical DAY?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to WP2

Appendix 2F continued: Questions used to assess physical activity continued

Q. No	Stem	Responses / Categorical Label	Action Branches
WP2	In a typical WEEK, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace? (do not include walking)	Enter number OR UN Do not know OR DA Prefer not to answer	If do not know or 0 or DA Go to WP3 Otherwise go to WP2A
WP2A	How many minutes did you usually spend doing moderate activities on a typical DAY?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to WP3

WP3	In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (these are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)	Enter number
		OR
		UN Do not know
		OR
		DA Prefer not to answer
			If >0 go to WP3A
			If (0 or DA or UN) & (WP1=unable to walk), go to WP11
			If (0 or DA or UN) & (WP1=/unable to walk), go to WP4

WP3A	How many minutes did you usually spend doing vigorous activities on a typical DAY?	Enter number OR UN Do not know OR DA Prefer not to answer	Go to WP4 unless WP1=unable to walk then go to WP4B1

Appendix 3: Million Women Study recruitment questionnaire

THE MILLION WOMEN STUDY

A national survey of women invited for breast screening

We need one million women to help us in research that will benefit women all over the world.

Would you become one of these special women?

More and more women are taking hormone replacement therapy (HRT) so it is vital that we find out as much as possible about its benefits and any possible side effects. We have a unique opportunity through the NHS Breast Screening Programme to learn about the way different types of HRT and other lifestyle factors affect a woman's health, particularly her breasts. Britain is the only country in the world that can carry out this study because it is the only one with the combination of a large population and a comprehensive national breast screening programme.

The NHS Breast Screening Programme, the Imperial Cancer Research Fund and the Medical Research Council have joined together to organise The Million Women Study. If one million women answer this questionnaire over the next three years we could have some of the answers to our most important questions about HRT within five years or so.

We would be very grateful if you could set aside some time to answer these questions. It should not take more than 10-15 minutes. You do not have to answer this questionnaire and if you decide not to you will still have your screening done in the normal way.

Please answer every question and do not leave blanks as all the information that you give us is very useful. If you are not sure about exact dates or ages an approximate answer is better than none. If you have any questions you can ring us on freephone **0800 262 872.**

Even if you are not taking HRT it is just as important that you fill in the questionnaire.

Please bring this questionnaire to your breast screening appointment

To help us read your answers please write as clearly as possible and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) ☒ ☐ ☐

OR put numbers in the appropriate box e.g. *23rd April 1946* 2 3 / 0 4 / 4 6 age 4 4 years

SAMPLE

GENERAL QUESTIONS ABOUT YOU

1. What is your date of birth? *(please put day/month/year)*
   ☐☐ / ☐☐ / ☐☐

2. How old are you? ☐☐ years

3. How tall are you? *(please give to the nearest inch)*
   ☐ feet ☐☐ inches

4. About how much do you weigh?
   ☐☐ stone ☐☐ lbs

5. How old were you when you finished full time schooling? *(please cross one box)*
   - ☐ did not go to school
   - ☐ 13 or younger
   - ☐ 14
   - ☐ 15
   - ☐ 16
   - ☐ 17 or older

6. What qualification(s) do you have from school, college or the equivalent?
   (please put a cross in the most appropriate box(es))
   - ☐ clerical or commercial qualifications *(eg secretarial, hairdressing etc)*
   - ☐ nursing or teaching
   - ☐ "O" level *(or equivalent)*
   - ☐ "A" level *(or equivalent)*
   - ☐ college/university degree *(or equivalent)*
   - ☐ none of these

7. About how many cigarettes do you smoke on average *each day*, now? *(please cross one box)*
   - ☐ none
   - ☐ less than 5
   - ☐ 5-9
   - ☐ 10-14
   - ☐ 15-19
   - ☐ 20-24
   - ☐ 25 or more

8. Are you an ex-smoker? ☐ No ☐ Yes

9. About how much wine, beer or spirits do you drink on average *each week*? *(please cross one box for each type)*

Wine (glasses per week)	Lager/Cider/Beer (half pints per week)	Spirits (tots per week)
☐ none	☐ none	☐ none
☐ less than 1	☐ less than1	☐ less than1
☐ 1-3	☐ 1-3	☐ 1-3
☐ 4-6	☐ 4-6	☐ 4-6
☐ 7-10	☐ 7-10	☐ 7-10
☐ 11-15	☐ 11-15	☐ 11-15
☐ 16-20	☐ 16-20	☐ 16-20
☐ 21+	☐ 21+	☐ 21+

If you drink wine is it
- ☐ mostly red
- ☐ mostly white
- ☐ about the same amount of red and white?

10. How often do you do *any* exercise?

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

11. How often do you do *strenuous* exercise?
(that is, enough to cause sweating or a fast heart beat.)

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

QUESTIONS ABOUT YOU AND YOUR FAMILY

12. Have you ever had any children? ☐ No ☐ Yes
- if No, please go on to question 15

13. How many children have you had? ☐☐
(please include stillbirths; it is not necessary to include miscarriages)

14. When was each child born, and for how many months did you breastfeed each child, if at all?

	DATE OF BIRTH (If you had twins or triplets please repeat the same date for each child) day / month / year	BREASTFEEDING (Months that you breastfed each child; put "0" if you did not breastfeed that child at all; put "1" if you breastfed for a month or less)
1st child	☐☐ / ☐☐ / ☐☐	☐☐ months
2nd child	☐☐ / ☐☐ / ☐☐	☐☐ months
3rd child	☐☐ / ☐☐ / ☐☐	☐☐ months
4th child	☐☐ / ☐☐ / ☐☐	☐☐ months
5th child	☐☐ / ☐☐ / ☐☐	☐☐ months
6th child	☐☐ / ☐☐ / ☐☐	☐☐ months
7th child	☐☐ / ☐☐ / ☐☐	☐☐ months
8th child	☐☐ / ☐☐ / ☐☐	☐☐ months
9th child	☐☐ / ☐☐ / ☐☐	☐☐ months
10th child	☐☐ / ☐☐ / ☐☐	☐☐ months

15. Have you ever been for breast screening before?

- ☐ No
- ☐ Yes- If Yes, about how many years ago was your last screen? ☐☐ years ago

16. Have you ever had a breast lump removed or any operations on your breast(s)?

- ☐ No
- ☐ Yes- If Yes, how old were you? ☐☐ years

(If you have had more than one operation please write your age at the first operation)

17. Have you ever had breast cancer diagnosed?

- ☐ No
- ☐ Yes- If Yes, how old were you when the cancer was first diagnosed? ☐☐ years

18. Has your mother ever had breast cancer diagnosed?

- ☐ No ☐ Don't know
- ☐ Yes- If Yes, how old was she when the cancer was first diagnosed? ☐☐ years

19. How many sisters do you have? ☐☐ sisters
(put "0" if you do not have any sisters, please include any sisters who have died)

20. Have any of your sisters ever had breast cancer diagnosed?

- ☐ No/No sisters ☐ Don't know
- ☐ Yes- If Yes, how old were they when the cancer was first diagnosed?

1st sister ☐☐ years 2nd sister ☐☐ years

QUESTIONS ABOUT YOUR HEALTH

21. Have you ever had any other cancer?
☐ Yes ☐ No

Please describe

22. Have you EVER had:
(please cross "Yes" or "No" for each condition)

High blood pressure - when pregnant	☐ Yes	☐ No
High blood pressure - when not pregnant	☐ Yes	☐ No
Heart disease *(eg heart attack/angina)*	☐ Yes	☐ No
Stroke	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Blood clot *(thrombosis)*	☐ Yes	☐ No

23. Are you NOW being treated for:

High blood pressure *(hypertension)*	☐ Yes	☐ No
Heart disease	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Varicose veins	☐ Yes	☐ No
Clotting problems	☐ Yes	☐ No
Asthma	☐ Yes	☐ No
Rheumatoid arthritis	☐ Yes	☐ No
Osteoarthritis	☐ Yes	☐ No
Thyroid problems	☐ Yes	☐ No
Osteoporosis	☐ Yes	☐ No
Depression/Anxiety	☐ Yes	☐ No

SAMPLE

24. Are you *NOW* being treated for any other *serious* illness?
☐ Yes ☐ No

Please describe this illness

Please describe the treatment

QUESTIONS ABOUT PAST OPERATIONS

25. Have you had a hysterectomy?
☐ No
☐ Yes- If Yes, how old were you? ☐☐ years

26. Have you had BOTH ovaries removed?
☐ No ☐ Not sure
☐ Yes- If Yes, how old were you? ☐☐ years

27. Have you been sterilised *(had your tubes tied)*?
☐ No
☐ Yes- If Yes, how old were you? ☐☐ years

QUESTIONS ABOUT YOUR USE OF THE PILL

28. Have you ever used the pill *(oral contraceptive)*?
☐ Yes
☐ No - *if No, please go to question 32*

29. About how old were you when you *first went on* the pill? ☐☐ years

30. About how old were you when you *last came off* the pill? ☐☐ years

31. For how many years *in total* did you take the pill?
☐☐ years
(Add together the years and months when you actually took the pill -do not count the years and months when you were not taking it. Please write "0" if you used the pill for less than a year in total)

QUESTIONS ABOUT YOUR USE OF HORMONE REPLACEMENT THERAPY (HRT)

32. Have you ever used hormone replacement therapy (HRT)? ☐ No - *if No - please go to question 39*
☐ Yes

33. How old were you when you *first started* using HRT?
☐☐ years

34. Had your periods stopped before you started using HRT? *(Cross "Yes" if you had a hysterectomy before starting HRT)*
☐ No
☐ Yes - if Yes, how old were you when your periods stopped? ☐☐ years

35. For about how many years *in total* have you used HRT? ☐☐ years
(Add together the years and months when you used HRT - do not count the years and months when you were not using HRT. Please write "0" if you used HRT for less than a year in total)

36. Are you *now* using HRT?
☐ Yes
☐ No - if No, how old were you when you last used HRT? ☐☐ years

37. What is the name of the most RECENT HRT you have used?

☐ Prempak C 0.625mg	☐ Premarin 0.625mg
☐ Prempak C 1.25mg	☐ Premarin 1.25mg
☐ Tridestra	☐ Evorel 25mcg/50mcg
☐ Trisequens	☐ Evorel 75mcg/100mcg
☐ Trisequens Forte	☐ Progynova 1mg
☐ Cycloprogynova 1mg	☐ Progynova 2mg
☐ Cycloprogynova 2mg	☐ Estraderm 25mcg
☐ Estrapak	☐ Estraderm 50mcg
☐ Estracombi	☐ Estraderm 100mcg
☐ Climaval 1mg	☐ Zumenon 1mg
☐ Climaval 2mg	☐ Zumenon 2mg
☐ Premique Cycle	☐ Ethinyloestradiol
☐ Premique	☐ Micronor
☐ Nuvelle	☐ Provera
☐ Kliofem	☐ Duphaston
☐ Livial	

☐ Do not know ☐ Implants ☐ Oestrogel

Other *(please write here)*

38. For how many years in total did you use the most *recent* type of HRT? ☐☐ years
(Please write "0" if you used this recent HRT for less than a year in total)

SAMPLE

QUESTIONS ABOUT YOUR PERIODS

39. About how old were you when your periods started? ☐☐ years

40. Have your periods NOW stopped?

Cross "Yes"-if you are not having periods now, either because of your menopause, after a hysterectomy or after stopping HRT.
Cross "No"- if you are still having regular periods now, even if they are because you are taking HRT.
Cross "Irregular"-if your periods have been irregular and you think it might be because of the menopause.

☐ **Yes**- If **Yes**, how old were you when they **stopped?** ☐☐ years

☐ **No**

☐ **Irregular**

FINAL SECTION

41. So that we can find out about your health in the future we may need to contact you again or look at your screening or medical records. We would be grateful if you gave us permission to contact you again or to use information from those records. **We guarantee that all information obtained will be treated with absolute confidentiality and used for medical research only.** Of course, you do not have to give permission. Your response to this request will not affect your screening or the treatment you receive in any way.

If you give permission, please sign here and print your name, address and other details in the section below. Please print in BLOCK CAPITALS as clearly as possible.

Signature: ☐ today's date: ☐☐ ☐☐ ☐☐

Surname: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Given name(s): ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

House number and street: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

District: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

County: ☐☐☐☐☐☐☐☐☐☐ Postcode: ☐☐☐☐☐☐☐☐

Surname at birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town of birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

NHS (National Health Service)Number: ☐☐☐☐☐☐☐☐☐☐
(The number on your medical card)

Breast Screening Number: ☐☐☐☐☐☐☐☐☐☐
(This is in the top left hand corner of your screening invitation letter and starts with the letters LGL)

SAMPLE

Please bring this questionnaire to your breast screening appointment

If you would like to post this questionnaire back to us, please send it to:
THE MILLION WOMEN STUDY CO-ORDINATING CENTRE
ICRF-CEU, GIBSON BUILDING,
RADCLIFFE INFIRMARY,
OXFORD OX2 6HE

FREEPHONE: 0800 262 872

Breast Screening Unit
Linton House
Thirlestaine Road
Cheltenham
GL53 7AS

LGL ☐

THANK YOU VERY MUCH FOR YOUR HELP

Appendix 4: Supplementary table to chapter 4

Effect of adjustment for fat mass instead of BMI on the association between fat-free mass and endometrial cancer risk

Quartiles of fat-free mass	Number of cases	Multivariable-adjusted HR (95%gsCI)
< 40.7	110	1.00 (0.82-1.23)
40.7-<43.5	123	0.96 (0.80-1.14)
43.5-<46.7	170	1.09 (0.95-1.26)
≥ 46.7	303	1.13 (0.96-1.34)
P for trend		0.237
HR per 1-SD increase		1.08 (0.97-1.20)

Appendix 5: Supplementary tables to chapter 5

Appendix 5a: Hazard ratios for endometrial cancer associated with BMI in postmenopausal never HRT users by histological subtypes

BMI categories	Endometroid		Adenocarcinoma NOS		Serous/papillary serous		Clear cell carcinoma	
	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)	Number of cases	Multivariable-adjusted HR (95%gsCI)
<25.0	720	1.00 (0.93-1.08)	228	1.00 (0.87-1.14)	113	1.00 (0.82-1.21)	33	1.00 (0.70-1.43)
25.0-<30.0	1,198	2.07 (1.95-2.19)	333	1.80 (1.62-2.01)	139	1.49 (1.26-1.76)	39	1.45 (1.06-1.98)
30.0-<35.0	848	3.98 (3.72-4.26)	243	3.54 (3.12-4.01)	85	2.51 (2.03-3.10)	32	3.15 (2.23-4.46)
≥35.0	760	8.19 (7.60-8.82)	219	7.16 (6.24-8.22)	50	3.48 (2.62-4.62)	16	3.48 (2.10-5.77)
P for trend		<0.0001		<0.0001		<0.0001		<0.0001
HR (95%CI) per 5 kg/m^2 increment in BMI	3,526	1.85 (1.80-1.90)	1,023	1.81 (1.73-1.91)	387	1.44 (1.31-1.58)	120	1.60 (1.37-1.87)

Models were stratified by year of birth and year of recruitment and adjusted for age at baseline, deprivation score, region, number of full-term pregnancies, age at menopause, duration of oral contraceptive use, age at menarche, smoking status, frequency of strenuous exercise and diabetes status.
HRs (95%CIs) for endometrial cancer per 5 kg/m^2 increment in BMI were corrected for regression dilution bias by dividing the log hazard ratio and standard error by the regression dilution ratio for BMI (0.94).
Histological subtypes were defined using the following ICD-O-3 codes:
Endometroid – 8380, 8381 and 8382
Adenocarcinoma NOS – 8140
Serous/papillary serous – 8441, 8460, 8461
Clear cell carcinoma – 8310

Appendix 5b: Association of BMI and central adiposity measures with endometrial cancer risk among postmenopausal never HRT users in the UK Biobank and the Million Women Study

Body size/ composition measures	UK Biobank		Million Women Study	
	Multivariable- adjusted HR (95%CI)	Further adjusted for BMI[1] HR (95%CI)	Multivariable- adjusted HR (95%CI)	Further adjusted for BMI[1] HR (95%CI)
BMI (per 5 kg/m^2)	1.72 (1.60-1.86)	-	1.78 (1.74-1.82)	-
Central adiposity measures[2]				
Waist circumference (per 10 cm increase)	1.65 (1.53-1.79)	1.19 (1.01-1.41)	1.65 (1.57-1.73)	1.12 (1.05-1.19)
Hip circumference (per 10 cm increase)	1.66 (1.53-1.80)	0.94 (0.77-1.16)	1.98 (1.87-2.11)	1.19 (1.08-1.30)
Waist to hip ratio (per 0.1-unit increase)	2.14 (1.73-2.66)	1.35 (1.07-1.70)	1.54 (1.40-1.70)	1.10 (0.99-1.21)
Waist to height ratio (per 0.1-unit increase)	2.16 (1.91-2.44)	1.16 (0.88-1.52)	2.16 (2.00-2.34)	1.06 (0.95-1.19)

[1] Adjusted for BMI using the standard method i.e. BMI as a covariate.
[2] Data on central adiposity measures in the Million Women Study were taken from the first resurvey questionnaire
Number of women included in UK Biobank analyses n = 75,448 (cases = 397).
Number of women included in the analysis of the association of BMI with endometrial cancer risk in the Million Women Study n = 393,615 (cases = 5,659).
Number of women included in the analysis of the association between central adiposity measures and endometrial cancer risk in the Million Women Study n = 175,846 (cases = 1,913).

Appendix 6: Supplementary table to Chapter 6

Hazard ratios for different subtypes of endometrial cancer by smoking status among postmenopausal women in the Million Women Study

	Endometroid		Adenocarcinoma NOS		Serous/papillary serous		Clear cell carcinoma	
Smoking status	**Number of cases**	**Multivariable-adjusted HR (95%gsCI)**	**Number of cases**	**Multivariable-adjusted HR (95%gsCI)**	**Number of cases**	**Multivariable-adjusted HR (95%gsCI)**	**Number of cases**	**Multivariable-adjusted HR (95%gsCI)**
Never	3,543	1.00 (0.97-1.03)	1,026	1.00 (0.94-1.07)	419	1.00 (0.90-1.10)	100	1.00 (0.82-1.23)
Past	1,683	0.89 (0.85-0.94)	493	0.91 (0.84-1.00)	177	0.81 (0.70-0.94)	64	1.23 (0.96-1.57)
Current	729	0.73 (0.67-0.78)	217	0.74 (0.65-0.85)	91	0.77 (0.62-0.95)	26	0.86 (0.58-1.28)

Models were stratified by year of birth and year of recruitment and adjusted for age, deprivation score, UK region, BMI, duration of oral contraceptive use, age at menopause, age at menarche, parity, type of HRT, interaction term for BMI and HRT type, physical activity and diabetes status.
Histological subtypes were defined using the following ICD-O-3 codes:
Endometroid adenocarcinoma – 8380, 8381 and 8382
Adenocarcinoma NOS – 8140
Serous/papillary serous – 8441, 8460, 8461
Clear cell carcinoma – 8310