Diet, menopause and risk of hormone-related cancers

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I hereby confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 1 entitled 'Background of study' incorporates the majority of a journal article:

> Dunneram YD, Greenwood DC, Cade JE. Diet, menopause and the risk of ovarian, endometrial and breast cancer. *Proceedings of the Nutrition Society*. 2019; **78**(3): 438-448.

YD designed and conducted literature search, critically evaluated the literature, interpreted results, won award for postgraduate competition, presented the paper at international conference, and wrote the manuscript. JEC and DCG critically revised the manuscript for important intellectual content.

Chapter 3 entitled 'Comparison between diets of pre- and post-menopausal women from the UK Women's Cohort Study' incorporates a small portion that has been published in the conference proceeding for the Nutrition Society Summer Meeting (11–14 July 2016, New technology in nutrition research and practice):

> Dunneram YD, Burley VJ, Cade JE, Greenwood DC. Dietary pattern by menopausal status in the UK Women's Cohort Study. *Proceedings of the Nutrition Society*. 2016; 75(OCE3).

YD did the data analysis and wrote the manuscript. All authors were involved in the study design, interpretation of findings, editing and approving the final draft.

Chapter 4 entitled 'Dietary intake and age at natural menopause: results from the UK Women's Cohort Study' is an exact copy of the journal article:

Dunneram YD, Greenwood DC, Burley VJ, Cade JE. Dietary intake and age at natural menopause: results from the UK Women's Cohort Study. *Journal of Epidemiology and Community Health*. 2018. **72**(8): 733-740.

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Chapter 5 entitled 'Dietary patterns and age at natural menopause in the UK Women's Cohort Study: A comparison between principal component analysis and reduced rank regression' incorporates a small portion that has been published in the conference proceeding for the Nutrition Society Summer Meeting (10–12 July 2018, Getting energy balance right) and the Society for Social Medicine:

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Dunneram YD, Greenwood DC, Cade JE. Dietary pattern associations with age at natural menopause in the UK Women's Cohort Study. *Journal of Epidemiology and Community Health*. 2018, **72**(Suppl 1) A19.

YD designed the study, conducted data analysis, interpreted results, and wrote the manuscript. JEC and DCG were also involved in the study design, interpretation of findings, editing and approving the final draft.

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YD, HFC and GDM designed the research and had primary responsibility for the final content. YD performed the statistical analysis, interpreted results and wrote the manuscript. JEC, DCG, ESM, NFW, EJB, TY, and DA contributed to the data. HFC,

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Chapter 7 entitled 'Diet and risk of breast, endometrial and ovarian cancer: UK Women's Cohort Study' is an exact copy of the journal article:

> Dunneram YD, Greenwood DC, Cade JE. Diet and risk of breast, endometrial and ovarian cancer: UK Women's Cohort Study. *British Journal of Nutrition*. 2018; **122**(5): 564-574.

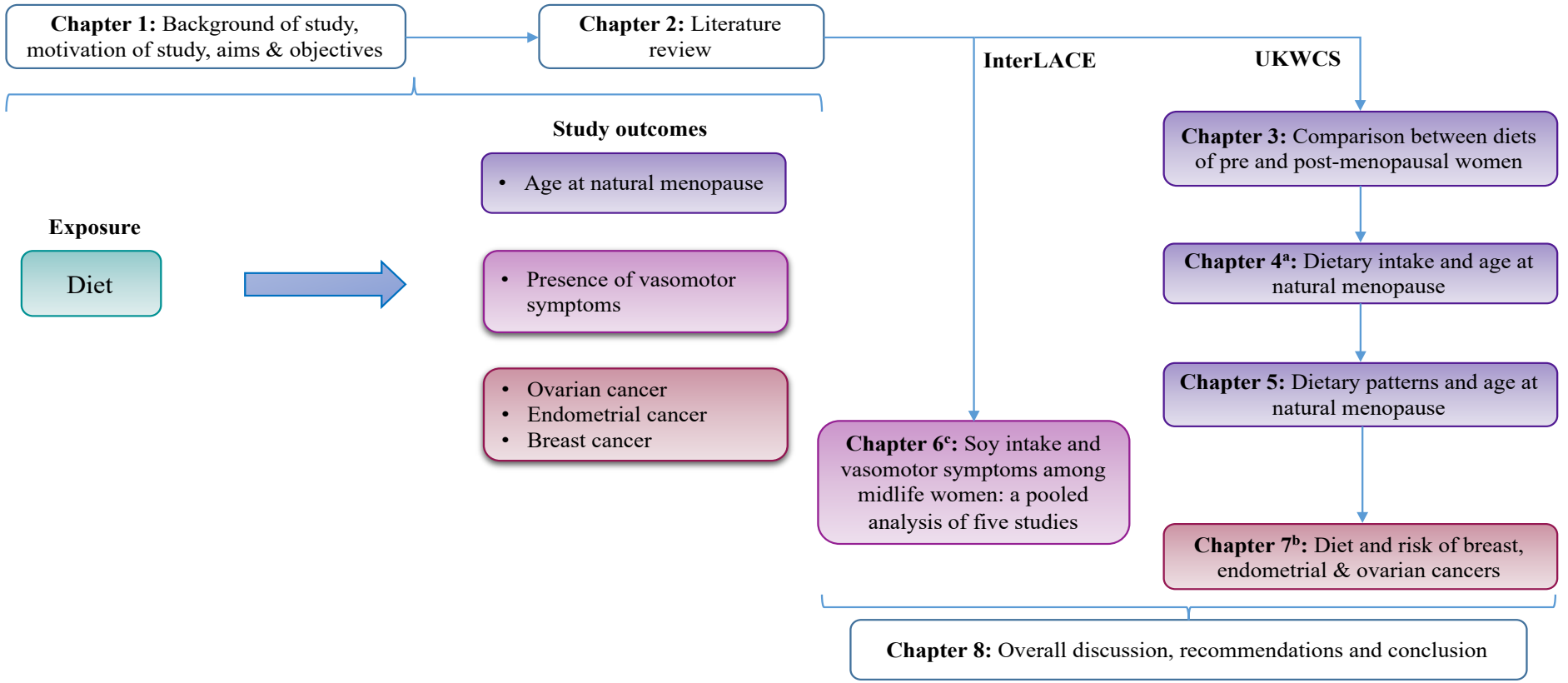
YD was responsible for data analysis and writing the manuscript. All authors were involved in the study design, interpretation of findings, editing and approving the final article.

Rationale for submitting the thesis in an alternative format

I currently have four published journal articles as outlined previously which are part of my doctoral degree at the University of Leeds. In addition, I have two papers in preparation. Thus, with the approval and encouragement of my supervisory team and as I fulfil the criteria for the alternative format under the guidelines of the School of Food Science and Nutrition, I have opted for submitting my thesis in the alternative format.

The thesis includes a background of the study area, which is followed by a review of literature. The next chapters include results section presented in a suitable format as in a peer-reviewed journal. The last section consists of an overall discussion section which provides a summary of the findings from the individual results chapters, drawing together the various outcomes of the work into a coherent synthesis, evaluation of the methods used and indicating directions for future work. Appendices have also been included to attach supplementary materials from the various publications as well as for the other chapters in order to provide additional details.

Thesis Structure



[a] Dunneram YD, Greenwood DC, Burley VJ, Cade JE. *Journal of Epidemiology and Community Health*. 2018;**72**(8):733-740.
[b] Dunneram YD, Greenwood DC, Cade JE. *British Journal of Nutrition*. 2018; **122**(5): 564-574.
[c] Dunneram YD, Chung HF, Cade JE, et al. *European Journal of Clinical Nutrition*. 2019.

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Abstract

Background: The timing of menopause can predict the duration of vasomotor menopausal symptoms (VMS), as well as the risk of hormone-related cancers such as ovarian, endometrial and breast cancer. Although evidence suggest an association between diet and the timing of menopause and its associated sequelae, current evidence are limited and conflicting. Thus, this thesis studied the associations between diet and age at natural menopause, the presence of VMS and the risk of hormone-related cancers.

Methods: Two of the largest and most complete datasets in the world were used to explore this topic: the UK Women's Cohort Study (UKWCS) and the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE).

Results: In the UKWCS, prospective analyses demonstrated that high intakes of oily fish and fresh legumes were associated with a delayed onset of menopause. Conversely, refined pasta and rice was associated with an earlier menopause. Specific dietary patterns were also linked to the onset of natural menopause. Furthermore, survival analyses demonstrated that intakes of processed meat and total meat were associated with a higher risk of breast and endometrial cancer. Higher intakes of tomatoes and dried fruits were inversely associated with breast and endometrial cancer respectively.

Using InterLACE consortium, a pooled analysis of three studies showed that soy product consumption was protective against the incidence of VMS.

Conclusion: This work has demonstrated, for the first time, how diet can play a role in influencing age at natural menopause in the UK. Further evidence for an association between diet and the presence of VMS and the risk of hormone-related cancers was provided. The complexity and cultural variations in diet suggest the need for further observational studies as well as randomized control trials to confirm whether specific dietary changes could modify the timing of natural menopause.

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List of Abbreviations

AICR	American Institute for Cancer Research
ALA	Alpha-linolenic acid
ALSWH	Australian Longitudinal Study on Women's Health
AMH	Anti-müllerian hormone
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
CVD	Cardiovascular diseases
DAG	Directed acyclic graph
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic Acid
DVS	Dietary variety score
EPA	Eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Oestrogen receptor
FA	Fatty acid
FAS	Fatty acid synthase
FFQ	Food frequency questionnaire
FMP	Final menstrual period
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GPAT	Glycerol-3-phosphate acyltransferase
HC	Hydroxycholestrol
Her2	Human epidermal growth factor receptor 2
HOW	Healthy Ageing of Women Study
HR	Hazard ratios
HRT	Hormone replacement therapy
HT	Hormone therapy
ICD	International Classification of Diseases
IGF	Insulin-like growth factor
InterLACE	International Collaboration for a Life course Approach to reproductive health and Chronic disease Events
JMWHS	Japanese Midlife Women's Health Study

LH	Luteinising hormone
MET	Metabolic equivalent
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NHSIC	National Health Service Information Centre
NIH-AARP	National Institutes of Health–American Association of Retired Persons
NLCS	Netherlands Cohort Study
NOS	Newcastle–Ottawa scale
OC	Oral contraceptive
PGE2	Prostaglandin E2
PLCO	Prostate, Lung, Colorectal, and Ovarian cancer screening trial
PPAR	Peroxisome proliferator-activated receptor
PR	Progesterone receptor
PCA	Principal component analysis
PUFA	Polyunsaturated fatty acid
RCTs	Randomised controlled trials
ROS	Reactive oxygen species
RRR	Reduced ranked regression & Relative risk ratio
SHBG	Sex-hormone binding globulin
SMWHS	Seattle Midlife Women's Health Study
SREBP-1c	Sterol regulatory element binding protein-1c
SSB	Sugar-sweetened beverage
TAG	Triacylglycerol
UK	United Kingdom
UKWCS	UK Women's Cohort Study
US	United States
VMS	Vasomotor menopausal symptoms
WCRF	World Cancer Research Fund
WHITEHALL	Whitehall II study
WHO	World Health Organisation

Chapter 1
Background of Study

Abstract

Menopause, the permanent cessation of the menstrual cycle, marks the end of a woman's reproductive lifespan. In addition to changes in sex hormone levels associated with menopause, its timing is another predictor of future health outcomes such as duration of the presence of vasomotor menopausal symptoms (VMS) and the risk of hormone-related cancers. With aging of the population, it is estimated that worldwide 1.2 billion women will be menopausal by the year 2030. Previously the effects of reproductive factors (e.g., parity, age at menarche, pregnancy) and socio-demographic factors on intermediate and long-term health outcomes of menopause have been widely documented. However, little is known about whether diet could have an impact on these. Therefore, we review current evidence on the associations of diet with age at menopause, the presence of VMS and the risk of hormone-related cancers such as ovarian, endometrial and breast cancer. Dietary factors could influence the lifespan of the ovaries and sex-hormones levels, hence the timing of natural menopause. Few studies reported an association between diet, in particular, soy consumption and a reduced risk of VMS. Sustained oestrogen exposure has been associated with a higher risk of hormone-related cancers, and thus high fat and meat diets have been linked with an increased risk of these cancers. However, to better understand the mechanistic pathways involved and to make stronger conclusions for these relationships, further studies investigating the associations of dietary intakes with menopause, the presence of VMS and the risk of hormone-related cancers are required.

1.1 Introduction

Menopause, the last menstrual period, marks the end of reproductive life in women. With aging of the population, it is estimated that worldwide 1.2 billion women will be menopausal by the year 2030 [1]. While menopause is inevitable, the age at which women reach menopause may vary depending on several factors such as geography and ethnicity. According to a meta-analysis of 36 studies (which included data from 35 countries), the overall mean age of natural menopause was 48.8 years (95% CI 48.3 to 49.2) with substantial geographic variation. For example, while the mean age of menopause in the United States (49.1y) and Asia (48.8y) were closest to the overall mean, it was higher in Europe (50.5y) and Australia (51.3y) and lower in Africa (48.4y), Latin America (47.2y) and the Middle East (47.4y) [2, 3].

Although heredity [4] may be a determinant of the timing of onset of natural menopause, several demographic, reproductive, and lifestyle factors seem to be important determinants of the timing of natural menopause [5]. Findings from a systematic review suggested ambiguous evidence for the association between educational level and age at menopause [6]. However, according to another systematic review and meta-analyses of studies across six continents which explored the effect of socioeconomic position and lifestyle factors on age at natural menopause, higher education and occupation level were associated with a later onset of natural menopause. In addition, smoking was associated with an earlier onset of menopause by approximately one year whereas relationships with physical activity and body mass index (BMI) were inconclusive [2]. Parity and oral contraceptive use have been associated with a later onset of natural menopause. Menstrual cycle characteristics such as cycle length and regularity are also strong predictors of onset [7-9]. As reported by Gold [10], along with BMI and physical activity, the relationship between diet and age at menopause is also inconclusive.

The menopausal transition is marked by alterations in bleeding patterns, hormone patterns, and physical and psychosocial characteristics. These hormonal fluctuations as a result of the neuroendocrine and reproductive endocrine interactions influence the risk of both intermediate and long term health outcomes associated with menopause [3]. One of the most common intermediate sequelae of the menopause transition, VMS, is defined as either the presence of hot flushes and/or night sweats. VMS is reported by 40-60% perimenopausal women and 8-80% postmenopausal women around the world [11]. The timing of onset of menopause can influence the length of the menopausal transition and hence the duration for the presence of VMS. Interestingly, the presence of VMS has also

been associated with an increased risk of cardiovascular disease (CVDs) [12]. Evidence also shows a link between an early onset of menopause and an increased risk of osteoporosis, CVDs, depression and mortality [10, 13]. On the other hand, a later age at menopause has been associated with a higher prevalence of hormone-related cancers such as breast, endometrial and ovarian cancers [10]. Previous studies have demonstrated a link between reproductive factors, socio-demographic factors and the presence of VMS as well as risk of hormone-related cancers [14-16]. However, its relationship with diet, a modifiable risk factor, has received less attention and current evidence of association is conflicting.

Therefore, this chapter gives an overview of the mechanistic pathway relating diet with age at natural menopause as well as elucidates the relationship between diet and VMS (an intermediate sequelae of menopause) in addition to the risk of hormone-dependent cancers such as breast, endometrial and ovarian cancers (long-term outcomes of menopause) supported by evidence from animal and human studies. In the next Chapter, a literature search is also conducted to include studies on the relationship between diet and onset of menopause and the presence of VMS as well as the risk of ovarian, endometrial and breast cancer.

1.2 Underlying physiology of menopause

At birth, the human ovaries contain approximately 1,000,000 primordial follicles [17]. This un-replenishable pool of follicles is further reduced to around 100,000 per ovary by the time of menarche. The fate of the remaining follicles is either to develop, reach maturity and then ovulate or degenerate by the process known as atresia [18]. At the perimenopausal transition stage, only about 100 to 1,000 follicles are left in each ovary and exhaustion of the follicle pool is accompanied by permanently elevated levels of pituitary gonadotropins and the progressive reduction in anti-müllerian hormone (AMH) which confirms ovarian senescence [19]. The hypoestrogenic changes taking place during the perimenopause (menopausal transition) are a result of the interactions taking place between the hypothalamic-pituitary axis and the reproductive endocrine axis marking this irreversible decline in ovarian responsiveness [3].

The menopausal transition is the shift from normal reproductive life to the last menstrual period and can last for up to 10–15 years [20]. According to the Staging of Reproductive Aging Workshop [21], it is divided into two stages: early and late (Figure 1.1). The early menopausal transition is marked by changes in menstrual cycle length and

is characterised by an increase in follicle-stimulating hormone (FSH) level, a decrease in AMH and inhibin B levels, while oestrogen level remains stable. The late transition is marked by oligomenorrhea (infrequent periods) and can last for 1–3 years on average. This stage is accompanied by an increase in anovulatory cycles and also significant fluctuations in hormonal levels. FSH level remains elevated while there is a consequent decrease in AMH and inhibin levels as well as oestrogen level. After the final menstrual period, ovarian ageing is marked by a decrease in the antral follicular count, and termination of ovulation and menstruation. In addition, there are further declines in AMH, inhibin, and oestradiol levels [22, 23]. Ovarian ageing is also accompanied by loss of responsiveness to FSH and luteinising hormone (LH), hence disrupting the negative feedback mechanism owing to the almost negligible inhibin level and the decline in oestrogen level. Consequently, the production of gonadotropin-releasing hormone (GnRH) is upregulated, stimulating the release of FSH and LH. Thus, during the initial years after menopause, the level of FSH peaks and gradually declines in the last postmenopausal stage [3]. These hormonal fluctuations as a result of the neuroendocrine and reproductive endocrine interactions consequently influence the risk of both intermediate (VMS) and long term health outcomes associated with menopause (risk of ovarian, endometrial and breast cancer) [3].

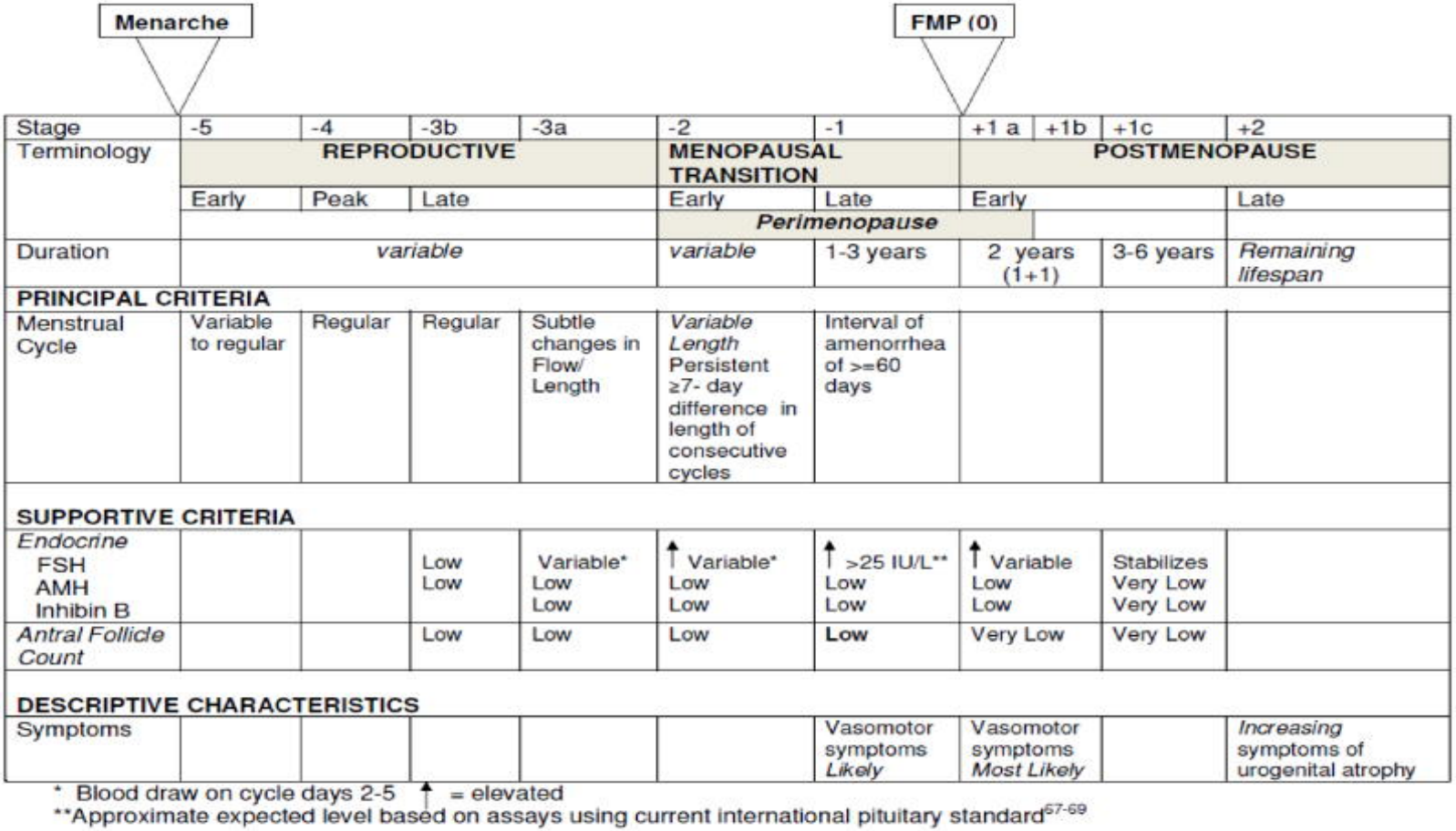

Figure 1.1 The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women

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1.3 Age at natural menopause

Natural menopause refers to the cessation of the menstrual cycle without any surgical procedures such as oophorectomy or ovarian failure as a result of chemotherapy or radiotherapy [3]. A premature menopause is one which is reached before the age of 40 years, an early menopause between 40-45 years and a late menopause is one after the age of 55 years [24, 25]. Depletion of the ovarian reserve and its responsiveness to pituitary gonadotropins governs the lifespan of the ovary and thus influence the onset of the timing of natural menopause [26]. Dietary factors and diet-related disorders can either enhance the lifetime of the ovaries by delaying follicular atresia or by maintaining sex-hormone levels involved in the feedback mechanisms of the menstrual cycle (Figure 1.2). However, the exact mechanisms still need to be elucidated. The association of age at natural menopause with chronic disease, ageing, and general health makes it an important subject of clinical and public interest [10].

Metabolic disorders such as diabetes could accelerate reproductive ageing by causing premature ovarian failure through several mechanisms. A recent study conducted in the Southern part of India demonstrated that an early menopause was more likely to be reported by diabetic women, 44.65 years in diabetic women while 48.2 years in non-diabetic women [27]. A similar relationship has been demonstrated in a study including women from 11 Latin American countries [28]. However, this association was only found in diabetic women under the age of 45 years. Furthermore, findings from the prospective Nurses' Health Study II demonstrated that a high vitamin D intake was associated with a lower risk of an early onset of menopause [29] which could be due to the fact that a high serum 25-dihydroxyvitamin D concentration could reduce the risk of diabetes as well as metabolic syndrome [30]. These findings thus indicate that the presence of type II diabetes, a diet-related disease could lead to an earlier onset of menopause.

Vegetarianism has also been linked to an earlier age at natural menopause [31]. Vegetarian diets are usually characterised by a high dietary fibre and low fat content particularly saturated fats. They tend to include more whole grains, vegetable protein sources such as legumes, nuts, and soy protein and exclude red meat. Dietary fibre may potentially interfere in the enterohepatic circulation of sex hormones, by modifying the metabolic pathway of oestrogens, leading to a decrease in oestrogen bioavailability [10, 32]. Karelis et al. [33] demonstrated that vegetarians had higher levels of sex-hormone binding globulin (SHBG), higher total fibre intake as well as lower levels of free

oestradiol, free testosterone, dehydroepiandrosterone sulphate, and a lower BMI. An intervention study also reported that an increase in fibre intake (20g/d) was significantly and independently associated with a decrease in serum bioavailable oestradiol and total oestradiol concentrations while no association was found between a reduced in fat intake and the hormone concentrations [34].

As opposed to the above findings which supported the association between vegetarianism and an earlier onset of menopause, intakes of green and yellow vegetables have been associated with a delayed onset of menopause [35]. Ovarian ageing is closely associated with increased levels of reactive oxygen species (ROS) which arises mainly due to an imbalance between ROS production and non-enzymatic antioxidant defences [36]. Oocyte maturation, ovulation, luteolysis, and follicle atresia are all affected by ROS [37]. Antioxidant properties of foods have been found to be positively associated with a reduced rate of follicular atresia. A recent *in vivo* study demonstrated a reduced atretic follicle count with use of resveratrol (a polyphenol found in the skin of red grapes and berries) [38]. These contradictory findings for the relationship between vegetarianism and intake of green and yellow vegetables with the onset of menopause could be because while one study investigated the associations with dietary patterns, the other considered the associations with individual food items. Moreover, differences in the participants' characteristics and distribution of age at natural menopause could further influence the findings. The confounders used in the analyses and large sample sizes could also explain the differences.

High consumptions of meat, fat, and protein have been positively associated with a delayed onset of menopause (please refer to Chapter 2, Table 2.2). Cholesterol, the starting product of steroidogenesis can be synthesised by de novo synthesis in the endocrine tissue (e.g., granulosa-lutein cells in the ovaries) from acetate, the end-product of fat oxidation [39]. Therefore, an excessive dietary fat intake can result in higher serum oestradiol levels. In addition, during the menopausal transition, significant changes occur in body composition. For instance, redistribution of body fat takes place such that there is an increase of total and central body fat, and also a redistribution of fat from lower body subcutaneous fat toward the abdominal region. This increase in adipose tissue becomes the main site for oestrogen production along with other hormones such as leptin, adiponectin, and resistin [40, 41]. Therefore, these endocrine changes taking place during the menopausal transition together with a high fat diet predisposes the woman to a later onset of menopause.

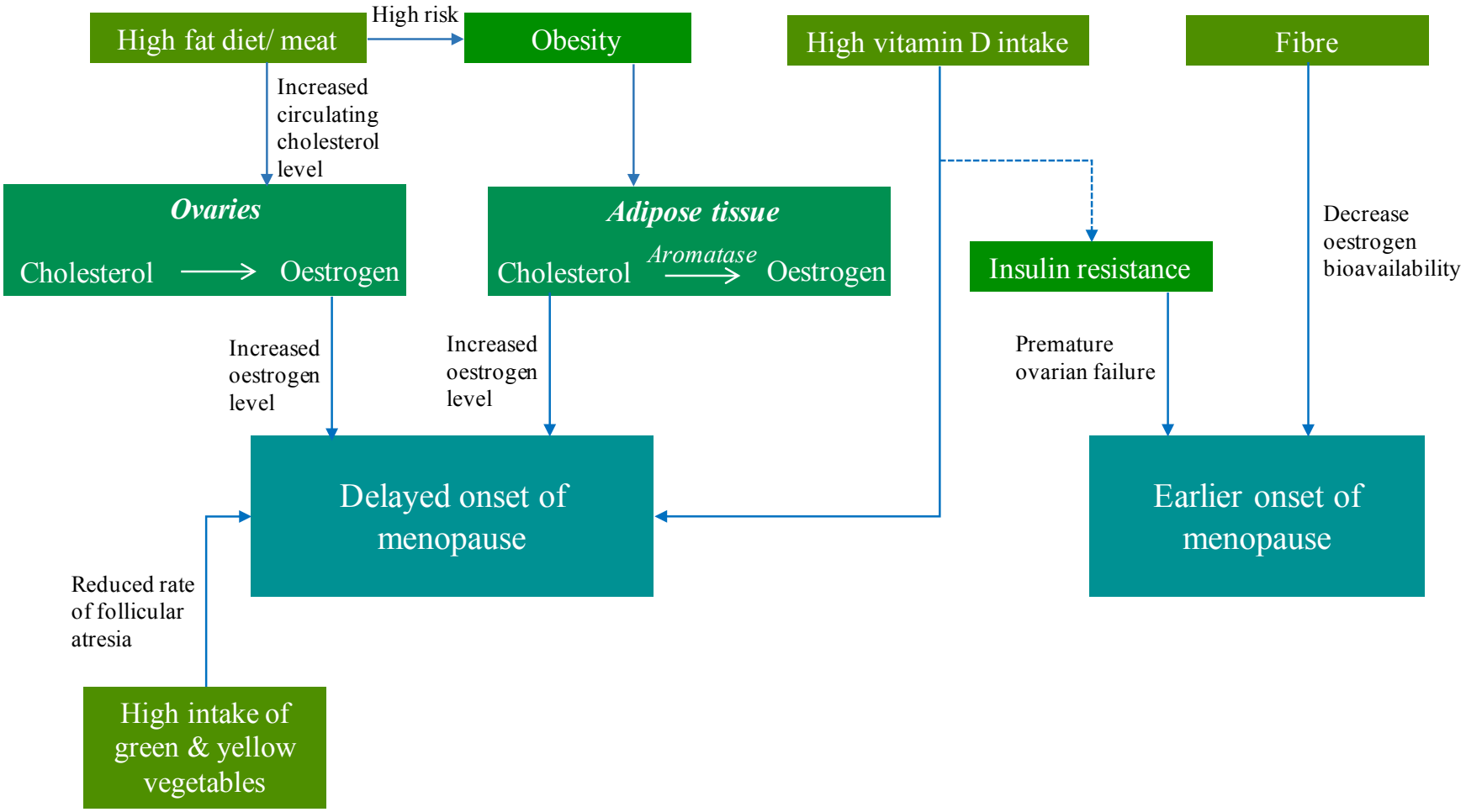

Figure 1.2 Potential mechanistic pathways though which diet can influence onset of natural menopause

1.4 Menopause and its associated sequelae

The timing of menopause could determine the duration of the presence of VMS which is mostly prevalent during the perimenopausal years as a consequence of lowered oestrogen levels. Previous randomised controlled trials (RCTs) have mainly focused on the study of phytoestrogen extracts and their influence on the presence of VMS. However, the study of foods consumed as part of the regular diet in relation to the presence of VMS has received less attention. The decline in oestrogen levels during the menopausal transition is postulated to be one of the causes for the presence of VMS. A low oestrogen level has been associated with narrowing of the thermoneutral zone between the core body temperatures, resulting in a lowered sweating threshold and hence a higher likelihood to experience hot flushes and night sweats. However, given that around 20% of premenopausal women also report hot flushes suggests that the decline in oestrogen levels is not the sole endocrine change causing VMS [42]. Dhanoya et al. [43] demonstrated that both AMH and FSH were associated with the presence of hot flushes while the level of oestradiol was not related with hot flushes.

Prolonged exposure to oestrogens as a consequence of a delayed menopause increases the risk of hormone-dependent cancers such as ovarian, endometrial and breast cancer as demonstrated previously by several epidemiological studies [44-46]. Other hormones such as progesterone may also be important. These hypotheses have been investigated in earlier published reviews [47-49]. Other factors such as diet, a modifiable risk factor may also explain the variation in oestrogen and other sex hormones levels [50-52]. Diet-related pathologies may also promote tumorigenesis while some components of the diet may be protective against these cancers. Therefore, the next sections explore the evidence for the hypothesis that diet is a major determinant for the presence of VMS and the risk of hormone-related cancers.

1.5 Presence of vasomotor symptoms

VMS such as hot flushes and night sweats are one of the most common symptoms experienced by women during the menopausal transition in particular during the premenopausal and early postmenopausal years. 54% of women reported experiencing hot flushes and night sweats in a cohort of 10,418 postmenopausal women in the UK [53]. According to a review of 66 papers across North America, Europe, East Asia, Southeast Asia, Australia, Latin America, South Asia, Middle East, and Africa, the prevalence of hot flushes ranged from 40-60% among perimenopausal women and 8-80% (median:

41.5%) among postmenopausal women. Regional patterns demonstrated a lower prevalence of hot flushes for postmenopausal East Asian women (16%) compared to Latin American (47%) and European (55%) women [11]. The median duration of these symptoms is 4 years but may persist as long as 15 years for some women [42]. Therefore, the presence of VMS influences the quality of life of menopausal women in terms of affecting their sleep quality, mood changes and cognitive function. The frequency and severity of VMS depend on several factors such as race/ethnicity, climate, obesity, health behaviours, lifestyle, social and demographic factors as well as diet [11, 54].

Evidence for a link between diet and presence of VMS arises from studies which have previously explored the associations between phytoestrogen extracts or phytoestrogen-rich foods and frequency or severity of VMS. A Cochrane review of 43 RCTs did not support the beneficial effects of phytoestrogen supplements for the reduction of the frequency or severity of VMS mainly due to the small size of the trials and also the high risk of bias while the same review stated the promising effect of genistein, a phytoestrogen found in soy [55]. A recent review further indicated the beneficial effect of isoflavones against hot flushes [56].

As mentioned previously, women tend to accumulate subcutaneous fat in the abdominal region during the menopausal transition which leads to endocrine changes in terms of higher circulating oestradiol level [40]. A prospective study of 6,040 women demonstrated that a Mediterranean-style diet and a fruit rich diet were both inversely associated with VMS. On the other hand, diets with high fat and sugar contents increased the risk of VMS [57]. This could imply that a healthier diet which prevents obesity could also be protective against VMS. The same study reported that even after adjusting for BMI, the same associations were observed. Therefore, the mechanism involved between diet and the presence of VMS remains unclear.

1.6 Hormone-related cancers: ovarian, endometrial and breast cancer

In this section, an overview of the epidemiology and the plausible mechanism of action of diet in relation to the ovarian, endometrial and breast cancer is provided.

1.6.1 Ovarian cancer

1.6.1.1 Incidence and mortality

Ovarian cancer is the sixth most common cancer among British women and the eighth most common cancer among women worldwide accounting to around 300,000 new

cases in 2018 [58, 59]. It is also ranked as the eighth cause of death from cancer among females. The highest incidence rates of ovarian cancer can be observed in the more developed regions, in particular, in Northern, Eastern and Central Europe while lower rates can be seen in Asian and African countries (Figure 1.3) [60, 61]. Variations in rates can also be observed by ethnicity within countries. For instance, in the United States incidence of ovarian cancer was reported to be higher among Non-Hispanic Whites, followed by Hispanics, Non-Hispanic Blacks, and lowest rates among Asian/Pacific Islanders [62].

1.6.1.2 Pathologic classification of ovarian cancer

Ovarian tumour, benign or malignant, may arise from one of three cell types namely epithelial cells, stromal cells, and germ cells, of which 90% of the malignant cancer are of epithelial origin [60]. The epithelial type is the most common among postmenopausal women while malignant tumours originating from the germ cells are more prevalent among younger women [63]. The epithelial ovarian cancer can further be classified into subtypes: serous, mucinous, endometrioid, clear cell and transitional cell [64].

1.6.1.3 Risk factors

It is well known that women with a family history of ovarian cancer are at a higher risk of the disease as compared to women without a family history [65, 66]. In addition, evidence shows that ovarian cancer in first-degree relatives increases the risk and an even higher risk among women with a first-degree relative who was diagnosed with ovarian cancer before the age of 50 years [67]. Mutations in the BRCA1 and BRCA 2 genes have been associated with familial ovarian cancer [65]. Jervis et al. [67] reported that 24% of epithelial ovarian cancer among women who had a first-degree relative diagnosed with ovarian cancer was due to the BRCA1 and BRCA2 mutations. Although mutations in these genes have been touted as the main risk factor for hereditary ovarian cancer, Adaniel and Kirchhoff [68] suggested that 10%-20% of this cancer is attributed to family history, and moreover only about 10% of the familial ovarian cancer is caused by mutations in the BRCA1 and BRCA2 genes.

In addition to a family history and genetic predisposition, risk factors of ovarian cancer include reproductive factors (Table 1.1) [69]. A higher risk of ovarian cancer with an early onset of menarche, later onset of menopause and nulliparity can be explained by the ‘incessant ovulation’ hypothesis which postulates that a higher number of ovulatory

cycles, increases the rate of cellular division which is consequently associated with a higher rate of repair of the surface epithelium after each ovulation, thus increasing the risk of spontaneous mutation [60]. While there is stronger evidence for the relationship between parity and reduced risk of ovarian cancer, the associations with age at menarche and age at menopause are less consistent [60]. According to a pooled analysis of 10 population-based case-control studies encompassing 906 ovarian cancer cases and 1,220 controls, the use of oestrogen-therapy only has been associated with an increased risk of serous and endometrioid ovarian cancer [70]. Ovarian cancer risk increases in an oestrogenic environment and this may further be enhanced by the use of oestrogen-therapy. The oestrogen-therapy could stimulate the growth of malignant cells and also increase the risk of transformation and proliferation of these cells [71]. On the other hand, a meta-analysis of oestrogen replacement therapy and risk of epithelial ovarian cancer did not report a significant association [72]. Unlike the use of hormone replacement therapy (HRT), the benefits of using oral contraceptives (OCs) on a reduced risk of ovarian cancer are well established [73-75].

Smoking, obesity, diet and other lifestyle factors have also been associated with the risk of ovarian cancer [69]. The association between smoking and risk of ovarian cancer differs by the histological subtype and also by smoking status. For instance, findings from a meta-analysis of 51 epidemiological studies concluded that current smokers had an increased risk of mucinous cancer as opposed to women who never smoked [76]. Moreover, current smoking was associated with a reduced risk of endometrioid and clear-cell ovarian cancer while no association was found with the serous type. Another meta-analysis also demonstrated an increased risk of mucinous ovarian cancer among current smokers, in addition to an increased risk of the serous type among former smokers [77]. Ovarian cancer risk has also been found to be higher among obese women, in particular, a significant association has been reported among obese premenopausal women [78]. Study of the association between BMI and different histologic subtypes demonstrated that a high BMI increased the risk of borderline serous, invasive endometrioid and invasive mucinous ovarian cancer [79]. While in a large pooled analysis including 8,309 cases and 12,612 controls demonstrated an increased risk of all epithelial ovarian cancer subtypes with physical inactivity [80], a review of epidemiological studies found an inconclusive association between physical activity and ovarian cancer risk [81]. Given that this cancer is usually diagnosed at the late stage when the survival rate is only 29%, reducing the risk through modifiable risk factors is recommended. One such risk factor is diet. However, the role of diet in the pathology of

ovarian cancer is not clearly understood [60]. In the next section (1.6.1.4), an attempt has been made to elucidate possible mechanisms between diet and the pathophysiology of ovarian cancer based on humans and animal studies.

Table 1.1 Risk factors for ovarian, endometrial and breast cancers

Factor	Ovarian	Endometrial	Breast
Family history	Increase [66]	Increase [82]	Increase [83]
Genetic alterations	Increase [67]	Increase [84]	Increase [85]
Reproductive and menstrual factors			
Late age at menarche	Decrease [69]	Decrease [69]	Decrease [83]
Late age at menopause	Increase [69]	Increase [69]	Increase [83]
Parity	Decrease [60]	Decrease [86]	Decrease [83]
Breastfeeding	Decrease [87]	Decrease [88]	Decrease [89]
Oral contraceptive use	Increase [70]	Decrease [90]	Increase [90]
Hormonal replacement therapy	Increase [91]	Increase [92]	Increase [93]
Lifestyle factors			
Smoking	Increase [76]	Decrease [94]	Increase [95]
Alcohol consumption	Increase [96]	Increase [97]	Increase [98]
Physical inactivity	Increase [80]	Increase [99]	Increase [100]
High BMI	Increase [78]	Increase [101]	Increase [102]
Socio-demographic factors			
High social class/ education/occupation level	Decrease [103]	Decrease [104]	Increase [105, 106]

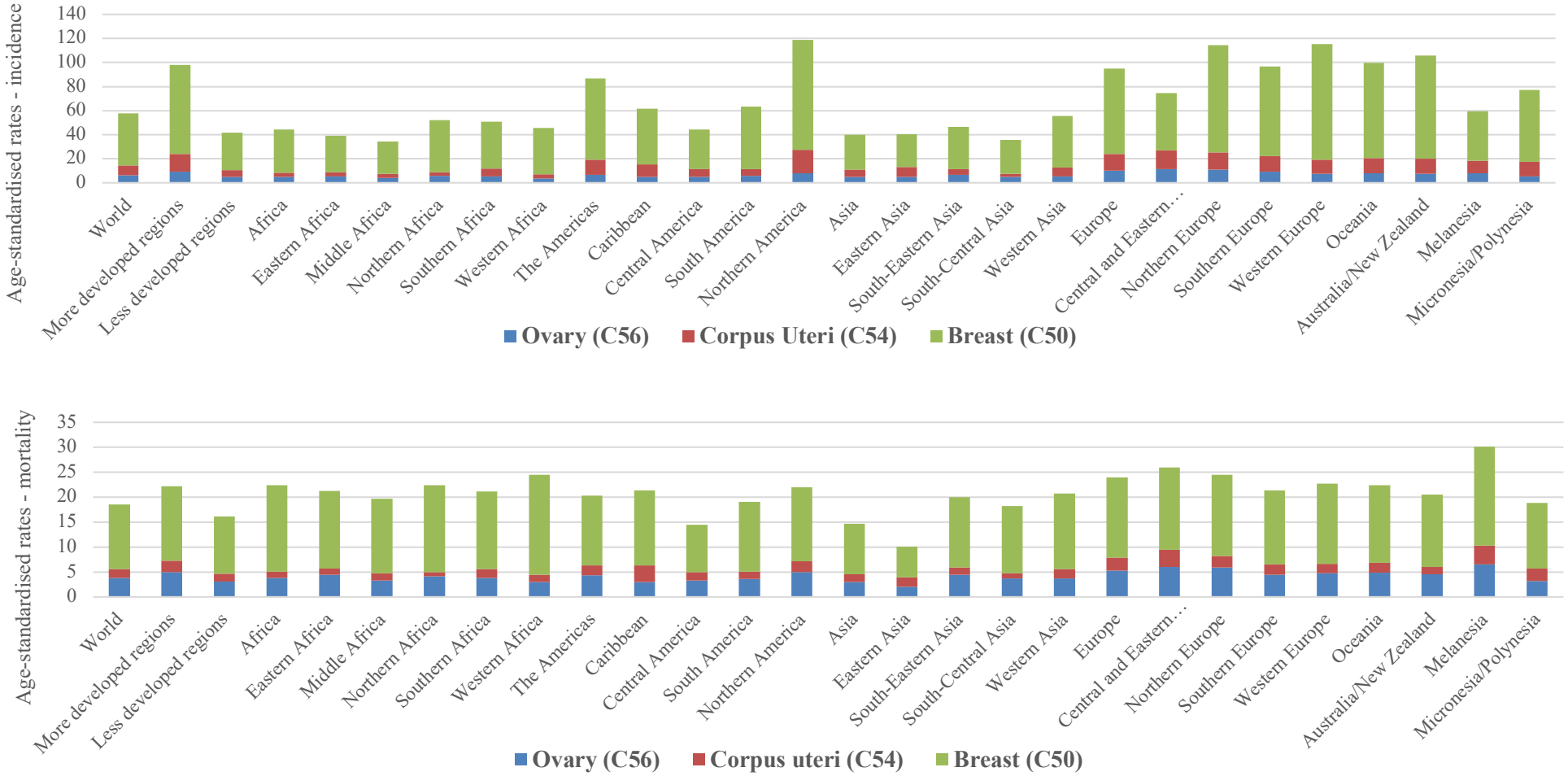

Figure 1.3 (A) Age-standardised rates for the incidence of ovarian, corpus uteri and breast cancer by region, (B) Age-standardised rates for the mortality of ovarian, corpus uteri and breast cancer by region, *Results are presented for these cancers as defined by the 10th edition of the International Classification of Diseases [Drawn from [61]]

1.6.1.4 Mechanism – diet and ovarian carcinogenesis

Women of reproductive age undergo cyclical cellular changes in their genital tract during the menstrual cycle [107]. During each cycle, several follicles containing an ovum undergo a maturation and selection process where ordinarily one of them is selected and released from the ovary during ovulation on or around the 14th day of the cycle [108]. The menstrual cycle is under the influence of various hormones namely GnRH, LH, FSH, oestrogen, and progesterone [109]. During ovulation, the surface of the ovary ruptures to release the ovum, following which the cells on the surface of the ovary, known as the epithelial cells, proliferate to close the breach under the influence of oestrogen. The improper proliferation of those cells can result in the formation of cysts or even cancers like surface epithelial tumours which are a subgroup among the diverse types of ovarian tumours [110].

Oestrogen and progesterone are steroid hormones synthesised from cholesterol [39]; individuals having a high-fat diet provide the substrate for excessive oestrogen synthesis which stimulates cell proliferation in the female genital tract. This can be supported by pooled estimates from a meta-analysis of 13 dietary fat intervention studies which showed that dietary fat reduction was related to a lowered serum oestradiol level [111]. Diets high in animal protein also contain xeno-oestrogens which have carcinogenic potential [112]. Leptin, another hormone secreted by the adipose tissue under the influence of factors like high lipid levels in the blood, has several effects on the body like producing a feeling of satiety, as well as stimulating the release of GnRH which in turn stimulates the release of LH and FSH [113]. High levels of LH may result in the immature release of the ovum and high levels of oestrogen secondary to high circulating cholesterol levels in the body (as a result of high saturated fat and energy intake). Consequently, this may result in improper re-epithelialisation of the ovaries. Chronic stimulation of ovaries in this way may predispose to development of abnormal growths which subsequently can undergo malignant transformation. Therefore, diets high in energy, animal fats or protein may promote the development of ovarian cancer.

According to the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study [114] which included 695 ovarian cancer cases recorded during an average of 9 years of follow-up, fat intake from animal sources was associated with an increased ovarian cancer risk. This can be further supported by a meta-analysis of 25 epidemiological studies (16 case-control studies and 9 cohort studies) [115]. An RCT including a total of 48,835 postmenopausal women followed up for an

average period of 8.1 years also demonstrated that a low-fat dietary pattern could potentially decrease ovarian cancer risk [116]. For the effect of dietary protein on risk of ovarian cancer, this has been demonstrated in a mice study [117]. A diet high plant protein was found to reduce the growth of the ovarian cancer cell line as compared to an animal-rich diet. However, evidence for the association between dietary protein types is inconclusive as demonstrated in a meta-analysis of observational studies [118] and a mice study. This could be because most of the included studies were among the North American population, thus restricting the findings to a specific population. In addition, the meta-analysis out of the 10 included studies, 8 were case-control studies which imply that potential recall bias of diet.

Omega-3 fatty acid, a polyunsaturated fatty acid (PUFA) can be obtained through dietary sources (flaxseeds, walnuts, canola oil, and oily fish) only. The n-3 family of PUFAs comprises alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). According to in vivo studies, EPA and DHA are precursors for anti-inflammatory lipid mediators [119]. Oestrogen has proliferative effects on oestrogen-sensitive tissues and thus could be involved in the pathogenesis of some hormone-dependent cancers such as ovarian cancer. Dietary n-3 PUFAs deter the promotion and progression stages of carcinogenesis through several mechanistic pathways. One of the mechanisms involves changes in oestrogen metabolism which could result in reduced oestrogen-stimulated cell growth [120, 121]. In addition, n-3 PUFAs can influence the regulation of two transcription factors; sterol regulatory element binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor alpha (PPAR alpha). SREBP-1c is involved in inducing a set of lipogenic enzymes in the liver and n-3 PUFAs can potentially inhibit the expression and processing of SREBP-1c and thus inhibits the de novo lipogenesis of fatty acids, making it an important consideration for the carcinogenesis. For instance, Merritt et al. [122] in a case-control study including 1,872 cases demonstrated that a higher intake of omega-3 might be protective for ovarian cancer, while a higher consumption of trans-fat was associated with an increased risk of ovarian cancer. However, the clinical effects of n-3 PUFAs do not solely rely on its concentration alone, but most importantly on the ratio of n-3 PUFAs to n-6 PUFAs in the cells [123]. This has been demonstrated in a study using a knockout mouse model whereby a dietary ratio of omega-6/omega-3 PUFA lower than five was effective in suppressing tumour growth and prolonging animal lifespan [124]. Findings from knockout mouse studies can be extrapolated to humans as humans and mice share many

genes [125]. Thus, a high intake of n-3 PUFAs relative to that of n-6 PUFAs may decrease endogenous oestrogen production and reduce the risk of ovarian cancer.

Prostaglandin E2 (PGE2), an arachidonic acid-derived eicosanoid (an n-6 PUFA found in meat and fish) stimulates the activity of aromatase P450, which converts 19-carbon steroids to oestrogens while on the other hand, PGE3 (derived from EPA metabolism), does not activate aromatase P450. Hence, an increased intake of EPA, which leads to increased production of PGE3 and decreased production of PGE2, is expected to decrease oestrogen production and thus reduce oestrogen-stimulated cell growth [120]. Thus, this further supports the mechanism that while n-3 PUFAs decrease the risk, intake of diet high in n-6 PUFAs such as a Western diet (rich in processed foods, high-fat foods, refined grains, high-sugar foods) could elevate the risk of ovarian cancer [126].

Along with hormonal control, diet can also interfere at the level of fatty acid (FA) and cholesterol biosynthesis and eventually affect sex steroid metabolism and thus the risk of ovarian cancer [127]. For instance, it has been found that feeding previously fasted animals a diet high in carbohydrate and low in fat content causes a dramatic induction of enzymes such as fatty acid synthase (FAS) and mitochondrial glycerol-3-phosphate acyltransferase (GPAT) which are the two critical enzymes involved in FA and triacylglycerol (TAG) synthesis. FAS catalyses the synthesis of long-chain fatty acids, primarily palmitate, using acetyl-CoA and malonyl-CoA as substrates and NADPH as the reducing equivalent while GPAT catalyses the first committed as well as the rate-limiting step in TAG and phospholipid biosynthesis [128].

Dietary variations are responsible for fluctuations in nutrient intake which can result in changes in circulating glucose, which in turn signal the secretion of hormones. For example, ingestion of a high-carbohydrate diet leads to a high circulating insulin level which consequently induces enzymes involved in FA and TAG synthesis, thus providing FA for membrane phospholipid biosynthesis in cancer cells [127-129]. The possible role of insulin resistance/hyperinsulinaemia has further been underpinned by an Italian case-control study including 1,031 women with incident epithelial ovarian cancer. The study showed that high dietary glycaemic index and glycaemic load were both associated with an increased ovarian cancer risk.

1.6.2 Endometrial cancer

1.6.2.1 Incidence and mortality

Endometrial cancer is the most common cancer of the uterine corpus. It is the most commonly diagnosed reproductive cancer especially in developed countries and its prevalence is on the rise mainly as a result of high obesity and metabolic syndrome rates in these countries [130]. Worldwide endometrial cancer is ranked as the sixth most common cancer among women with the highest prevalence in North America, and Europe, and the lowest rates observed in Africa [131]. In 2012, 320,000 new cases were diagnosed (4.8% of cancers among females) and 76,000 deaths were recorded (2.1% of deaths in women) around the world (Figure 1.3) [61]. Though only a small number of women are diagnosed with an advanced stage disease, death at this stage is more common. For instance, 5-year survival for the early stage of endometrial cancer is around 95% while for the advanced stage survival rate fluctuates between 25 to 79% [132]. In the UK, endometrial cancer stands fourth among the most common cancer in women [58]. Although endometrial cancer is more commonly prevalent among postmenopausal women (4 to 20 times higher in women aged 50 years or more), 14% of the cases are reportedly diagnosed among premenopausal women [133, 134].

1.6.2.2 Pathologic classification of endometrial cancer

Traditionally endometrial cancer has been classified as type I and type II tumours. Type I tumour is known as oestrogen-dependent cancer and is more prevalent among obese, hypertensive, diabetic, nulliparous or women who had a delayed onset of menopause (accounts for 80 to 85% of cases). On the other hand, the type II tumour is non-oestrogen dependent and is common among non-obese women (accounts for 10 to 15% of cases) [84]. According to the World Health Organisation (WHO) classification, endometrial cancer has several histological types namely, epithelial carcinomas (endometrioid, serous, clear cell, mucinous, squamous cell, transitional cell, small cell, and undifferentiated), mixed epithelial and mesenchymal tumours, or mesenchymal tumours, gestational trophoblastic diseases, and other malignant tumours [84, 135]. Out of these, the epithelial carcinoma is the most common with endometrioid subtype being the most prevalent, followed by the serous, and clear cell histological subtypes [135].

1.6.2.3 Risk factors

A family history of endometrial cancer among first- or second-degree relatives increases the risk of endometrial cancer [136, 137]. A family history of other cancers including hormone-related cancers has been less consistently associated with the risk of developing endometrial cancer [82, 138]. Familial endometrial cancer is related to germline mutations. For instance, type I endometrial cancer is attributed to mutations in PTEN, PIK3CA, KRAS, ARID1A, CTNNB1 as well as microsatellite instability; type 2 carcinomas are characterised by mutations in PIK3CA, P53, and PPP2R1A along with amplification in HER2 [84]. Moreover, epidemiological studies within multi-ethnic populations have demonstrated that Whites had a higher risk of endometrial cancer and African Americans and Latinas were at greater risk of developing the aggressive subtypes [139, 140].

The epidemiology of endometrial cancer and ovarian cancer overlaps in many ways [69]. Similar to ovarian cancer, established non-genetic risk factors for endometrial cancer encompass exposure to exogenous or endogenous oestrogens associated with nulliparity, early age at menarche, late-onset menopause as well as obesity (Table 1.1) [137]. Further supporting the 'unopposed oestrogen' hypothesis, breastfeeding in particular duration of breastfeeding has also been associated with a reduced risk of endometrial cancer. The suggested mechanisms include low oestrogen level during breastfeeding and reduced GnRH level which suppresses ovarian follicular growth [88, 141]. OC use has also been found to reduce endometrial cancer risk [90].

Furthermore, risk factors of endometrial cancer include diabetes (refer to section 1.6.2.4) and hypertension [142]. Although a recent systematic review and meta-analysis of case-control and cohort studies reported a strong association between hypertension and the risk of endometrial cancer [143], the plausible mechanism for this association remains unclear. It is speculated that cellular ageing and inhibition of apoptosis-related to hypertension [144] as well as medications used for the treatment of hypertension may increase the risk of endometrial cancer [145]. Factors such as smoking [94] and high physical activity level [99, 146] have been associated with a reduced endometrial cancer risk.

1.6.2.4 Mechanism – diet and endometrial carcinogenesis

As mentioned previously, the cells in the endometrium undergo cyclical cellular changes during the menstrual cycle. Hormones like oestrogen have a mitogenic effect on

the cells of the endometrium [147, 148]. Excessive exposure to oestrogen either exogenous or endogenous secondary to high-fat diet may cause increased proliferation of the endometrial cells. Cells proliferating at a faster rate are more prone to errors during DNA replication and the mutated cells can subsequently undergo malignant transformation, most commonly adenocarcinomas.

Endometrial cancer is a hormone-driven cancer, with approximately 80% of endometrial cancers potentially arising due to either an excess of oestrogen or a lack of progesterone. In the normal endometrium, the proliferative effects of oestrogen are normally countered by progesterone, but the absence of progesterone allows oestrogen to induce oncogenesis, an effect that is amplified in situations of excess oestrogen. One of the major emerging causes of the oestrogen/progesterone imbalance is obesity which is known to influence hormonal balance and level of growth factors [149, 150]. Evidence shows a positive link between increased dietary fat intake and obesity, thus associating fat intake to an increased risk of endometrial cancer [151].

Central obesity, characterised by high abdominal fatness is commonly observed among women during the menopausal years and is responsible for the increase in circulating free fatty acids and consequently promotes an increase in insulin resistance [152]. In addition, long-term consumption of high glycaemic index diet is another risk factor for obesity and insulin resistance and is also hypothesised to be involved in the pathogenesis of endometrial cancer [153]. Hyperinsulinaemia increases the risk of endometrial cancers mainly by the binding of insulin to insulin receptors on endometrial cells to stimulate the growth of endometrial stromal cells [147]. Hyperinsulinaemia may also increase the level of insulin-like growth factor (IGF) I and both may lead to an increased circulating level of oestrogen level and a decrease circulating level of sex hormone-binding globulin [154]. For instance, findings from the Women's Health Initiative study which included 88,107 postmenopausal women who were followed for over a mean of 11 years, reported that independently diabetes was modestly associated with an increased endometrial cancer risk. After adjusting for BMI, the risk of endometrial cancer was attenuated suggesting that this relationship could be explained by body weight [155]. Moreover, a similar association has been demonstrated in the Swedish Mammography Cohort, a prospective cohort of 36,773 women whereby diabetes was found to double the risk of endometrial cancer and diabetes in combination with obesity further increased the risk [156]. This mechanistic pathway is also backed by a recent systematic review and meta-analysis of 25 epidemiological studies [157].

1.6.3 Breast cancer

1.6.3.1 Incidence and mortality

Breast cancer is the most common cancer among women around the world (approximately 1.7 million cases diagnosed in 2012). It was also ranked as the fifth cause of death from cancer overall among women in 2012 [61]. In 2015, 31% of breast cancer cases were recorded among British women [58]. Similar to endometrial cancer, the prevalence of breast cancer is also increasing. The increasing rates have been seen in areas with previously low prevalence such Japan, China and eastern Europe due to obesity, diabetes and metabolic syndrome which suggest the nutritional link in the pathogenesis of breast cancer [158].

1.6.3.2 Pathologic classification of breast cancer

Histologically, breast cancer can be classified as *in situ* or invasive carcinoma. Invasive breast carcinoma which is the most common form is further classified as infiltrating ductal, invasive lobular, ductal/lobular, mucinous (colloid), tubular, medullary and papillary carcinomas [159]. Among these subtypes, the infiltrating ductal carcinoma is the most prevalent type of invasive breast carcinoma. The subtypes further incorporate molecular markers such as oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2) [160].

Molecular subtypes of breast cancer have also been identified using microarray-based gene expression analysis and unbiased hierarchical clustering. These include [160, 161]:

- Luminal subtype A (ER+ and/or PR+, HER2−)
- Luminal subtype B (ER+ and/or PR+, HER2+)
- Normal breast
- Her2-enriched (Her2+, ER−)
- Basal-like (ER−, PR−, Her2−)
- Claudin-low

1.6.3.3 Risk factors

Similar to ovarian and endometrial cancer, the aetiology of breast cancer is multifactorial. Breast cancer risk among women also has a link to family history such that having a first- or second-degree relative with breast cancer doubles the risk of a woman. However, a family history accounts for only 10% of breast cancer in women who have a

first-degree relative with this cancer. Similar to ovarian cancer, only around 5-10% of breast cancer cases are due to gene mutation [68, 83]. Germline mutations have been identified which include mutations in the genes BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11, which are high penetrant genes [85].

More prolonged exposure to oestrogen, regular ovulatory cycles and a high circulating oestrogen level have been associated with an increased breast cancer risk. Thus, an early age at menarche, late onset of menopause, and nulliparity are associated with a higher risk of breast cancer [83]. In addition, the use of exogenous hormones such as HRT and OC has also been linked to an increased risk of breast tumours [90, 93]. As reported by a systematic review of epidemiological studies [89], a higher cumulative duration of breastfeeding was protective against breast cancer risk as breastfeeding is associated with suppressed ovulation and thus a lower total number of ovulatory cycles. The protective effect has been found to be stronger among premenopausal women.

Other risk factors of breast cancer include lifestyle factors, for example, alcohol consumption, smoking, physical inactivity and a high BMI have been associated with an increased breast cancer risk (Table 1.1) [93]. As demonstrated in a large Norwegian prospective cohort study including 130,053 women aged 34-70 years, ever smokers (former or current) had a higher breast cancer risk as compared to never or passive smokers [95]. This is further supported by a review which suggests that long-term smoking was a risk factor for breast tumour and even worsens the disease [162]. Findings from the Women's Health Study which included 1,484 cases of breast cancer over an average of 10 years of follow-up showed that moderate alcohol consumption was related to an increased risk of the cancer, in particular, the ER+/PR+ subtypes [98]. Moreover, results from the E3N-EPIC cohort study demonstrated that total alcohol consumption was associated with an increased risk during the postmenopausal period and for the ER+/PR+ breast cancer subtypes [163].

1.6.3.4 Mechanism – diet and breast carcinogenesis

The pathogenesis of breast cancer is intricate and multifactorial. The aetiology of breast cancer could involve a similar hormonal pathogenesis as ovarian cancer [164]. Importantly, oestrogen influences the growth, differentiation, and functioning of the breast tissue. Aromatase, an enzyme found in the adipose tissues helps convert circulating cholesterol to oestradiol [165]. Due to the higher proportion of fat cells in breasts of older women, their level of oestradiol in the breast tissues mainly post menopause is likely to be higher than the circulating plasma level. The high oestradiol level in the breast tissues

can trigger differential effects on the oestrogen receptor expression which are found in those tissues, thus influencing the behaviour of cancer cells [166]. Stromal cells in the breast tissues can also support metastatic activity as they control not only the growth of normal breast epithelial cells but also that of neoplastic epithelial cells by secreting growth factors in response to the levels of endogenous hormones [167].

High cholesterol level, as a result of a high-fat diet has also been stated as a risk factor for breast cancer among women during the late peri-menopausal and post-menopausal state [168]. According to studies in mice [169, 170], oxysterol 27-hydroxycholestrol (27-HC), a metabolite of cholesterol synthesis has been identified in the pathogenesis of breast cancer. 27-HC could stimulate the growth of breast cancer cell lines by binding and activating ER in a similar way as oestradiol. There is also evidence that postmenopausal women experience an increase in their cholesterol level and thus its metabolite 27-HC which could help explain the increase in breast cancer risk among obese and hypercholesterolaemic women [171]. However, according to a recent nested case-control study from the EPIC-Heidelberg Cohort, including 530 invasive incident cases of breast cancer, a high level of 27-HC was associated with a reduced risk of breast cancer among postmenopausal women and no association was found among premenopausal women [172]. A reduced breast cancer risk was, in particular, observed among postmenopausal women not using hormone therapy (HT) as opposed to those using HT suggesting that this association may only be relevant in the case of low circulating oestrogen level. This disparity between the findings from animal studies and the nested case-control study could be explained by the fact that animal studies do not always translate to findings in epidemiological studies [173] as in this case it may be that the effect of 27-HC in conditions of varying oestrogen level have not been studied.

Moreover, a fat-rich diet and a high glycaemic index are positively correlated with insulin resistance [174, 175]. Insulin resistance, a significant factor in the pathogenesis of premenopausal breast cancer, is also involved in the aetiology of postmenopausal breast cancer. Insulin can bind to insulin receptors found on the epithelial cells of the breast. This insulin signalling can contribute to cancer through mitogenic activity mediated by the phosphatidylinositol-3 kinase and mitogen-activated protein kinase/Akt signalling pathways [176]. Insulin also has anti-apoptotic characteristics and thus promotes invasive tumour activity. Insulin resistance is also accompanied by high levels of proinflammatory cytokines and leptin as well as a decreased level of adiponectin which concomitantly lead to both ER+ and ER− breast cancer [177]. Moreover, insulin resistance is associated with

an increased oestrogen level as a result of enhanced aromatase activity and decreased production of SHBG [178, 179]. This mechanistic pathway has been supported by an Italian-nested case-control study which demonstrated that both pre- and post-menopausal women with hyperglycaemia had an increased risk of breast cancer [180].

In addition to the high circulating level of oestrogen as a result of obesity, the associated high levels of inflammatory markers, insulin-like growth factors and adipokines from the visceral fat also increase the risk of breast cancer among postmenopausal women [181]. While high circulating oestrogen level among premenopausal women can be a risk factor for breast cancer [182], some studies have demonstrated that obesity can be protective among premenopausal women. Obesity can lead to irregular ovarian cycles and hence lower circulating oestrogen levels. As demonstrated by a meta-analysis of prospective studies, waist circumference was associated with ER+ and PR+ breast cancers in postmenopausal women while in premenopausal women waist circumference was positively associated with ER-breast cancer [183]. This would suggest a lower likelihood of a hormonal pathogenesis for breast cancer among premenopausal women. Chronic inflammation, abnormally high levels of IGF and insulin resistance could instead explain premenopausal breast cancer [184].

1.6.4 Other protective effect of diet against the risk of hormone-dependent cancers

1.6.4.1 Vitamins

Vitamins like B6, B12, and folate are required for normal DNA repair mechanisms and proper DNA replication. Folate receptor alpha expression is correlated with stage and grade of ovarian cancer, suggesting this pathway may be relevant to ovarian carcinogenesis and progression [185]. Ascorbic acid, vitamin E and other trace elements like selenium having antioxidant properties help to protect from free radical injury and maintain normal cellular function. Vitamin C is recognised for its beneficial effect in cancer chemoprevention mainly as it has the potential to stimulate immune function, impede nitrosamine formation, minimise DNA damage and block the metabolic activation of carcinogens [186]. Vitamin A helps to control epithelisation of tissues and also has antioxidant properties to help protect from DNA damage [187]. Although these current theories support the likely role of these micronutrients in hormone-dependent cancers, prospective cohort studies as well as a meta-analysis of epidemiological studies, reported no association between dietary vitamins A, C or E and the risk of ovarian and

endometrial cancers [186, 188-190]. In addition, the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR) [152] reported an inconclusive association between nutrients such as vitamin A, C, E as well as folate and the incidence of ovarian, endometrial, breast cancers.

Moreover, a recent meta-analysis of cohort and case-control studies suggested that vitamin D intake was protective against premenopausal breast cancer [191]. A large cohort study including 68,567 postmenopausal women further demonstrated that women with a high intake of calcium, and vitamin D had a reduced risk of postmenopausal breast cancer [192]. Experimental studies have also suggested that vitamin D intake could reduce the stimulatory effect of androgen in human ovarian cancer cell lines and also reduce obesity-induced endometrial cancer [193, 194]. However, systematic reviews concluded that the evidence to support the association between vitamin D intake and endometrial and ovarian cancers are not consistent and robust, thus calling for further prospective studies. One of the limitations was that since most of the studies included in this systematic review were case-control studies, diet was thus measured only at 1-time period and was very prone to misreporting due to recall bias, therefore not accounting for diet change over time and vitamin D production through the skin [195, 196].

1.6.4.2 Flavonoids

Flavonoids, a group of heterogeneous polyphenols, have multiple health benefits. The main sources of flavonoids include fruits, vegetables, tea, and wine [197]. Flavonoids reportedly have several properties which contribute to the various health benefits including antioxidant, anti-mutagenic, and anti-proliferative properties. Among them, isoflavones and some flavones, flavanones, and flavanols also have oestrogenic or anti-oestrogenic activity, which makes these compounds of particular interest for modulation of reproductive cancer risks [198]. According to a large prospective cohort study including 171,940 US women, 723 of whom developed ovarian cancer over a period of 16–22y of follow-up, demonstrated inverse associations between flavonol and flavanone intakes and ovarian cancer risk [199]. Further supporting the chemoprotective role of the flavonol in ovarian cancer risk, two *in vitro* studies demonstrated that kaempferol induces apoptosis in ovarian cancer cells by regulating pro-apoptotic and anti-apoptotic protein expressions and by preventing angiogenesis in ovarian cancer cells [200, 201]. Furthermore, a meta-analysis of six cohorts and six case-control studies demonstrated that intakes of flavonols and flavones are protective against breast cancer, especially among

postmenopausal women [202], thus supporting the chemo-preventive role of fruits and vegetables in hormone-related cancers.

1.7 Diet – a determinant of the timing of menopause and its associated sequelae

Diet, the main exposure of this study, can broadly be defined as the consumption pattern of foods [203]. This thesis will specifically look at individual food group and nutrient intakes from the diet as well as consider dietary patterns (please refer to Chapter 8 for details on dietary patterns). Diet is a major modifiable risk factor of non-communicable diseases such as cardiovascular diseases and various cancers [204]. As explained in the sections above, diet can be linked with life-course experiences such as timing of the onset of menopause as well as with its associated immediate and longer-term health outcomes, for example, the presence of VMS and the risk of hormone-related cancers.

The National Institute for Health and Clinical Excellence's (NICE) conceptual framework which was developed for public health provide an account of its determinants and the interactions between them. It is based on six main principles as listed below [205]. This conceptual framework is also relevant to this thesis and has thus been adapted to demonstrate the link between various determinants and the timing of menopause as well as its associated sequalae (Figure 1.4). As elaborated in the previous sections of this chapter, alongside diet, smoking, high alcohol consumption and physical inactivity are also major risk factors of age at menopause and its associated sequelae (please refer to sections 1.1, 1.6.1.3, 1.6.2.3, 1.6.3.3). The timing of menopause and its associated sequalae, involves complex causal associations that link together diet and the physiology of obesity, environmental factors as well as individual behaviours.

Principles of the NICE conceptual framework:

1. Determinants of health and disease include social, economic, psychological and biomedical factors
2. The determinants causes individual-level diseases which lead to disease patterns in populations reflecting societal inequalities
3. The determinants work through distinguishable causal pathways
4. The causal pathways help both disease prevention and improvement
5. The causal pathways can also help in health promotion
6. The positive and negative causal pathways cross physical, biological, social, economic, political and psychological discipline boundaries

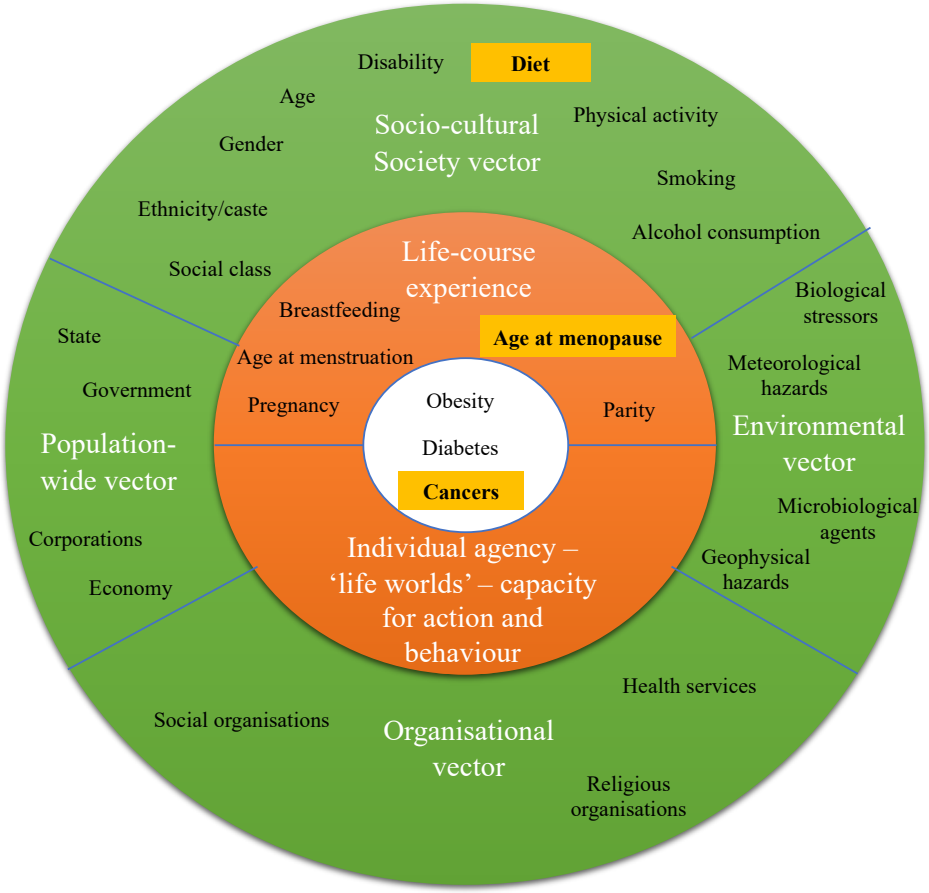

Figure 1.4 NICE's conceptual framework for public health guidance

According to the concept of this framework, the onset of menopause and its associated sequalae are dependent on causal mechanisms. These involve interactions between various determinants which are termed as vectors. There are four vectors of causation under this framework: population, environmental, organisational and the social vector. These vectors interact in different ways to influence life-course and life experiences (life worlds) leading to the health and disease outcomes [205]. The population vectors explain that elements such as the state, government, corporations, and the economy of the country influences health outcomes both positively and negatively. For instance, legislations and taxations such as the sugar levy on the soft drinks industry introduced in 2016 as part of a preventive strategy to reduce free sugars consumption and obesity in the UK [206], can directly affect food choices and hence the likelihood for obesity and consequently the timing of menopause, presence of VMS and hormone-related cancers. Secondly, the environmental vector suggests that microbiological agents, meteorological and geophysical hazards are also risk factors of health and diseases. The organisational vector which includes elements such as available health services could

interact with the environmental vector to also influence the timing of menopause [207]. Finally, the social vector consist of elements such as social class, gender, age, ethnicity/race, as well as lifestyle factors such as diet, alcohol consumption, smoking, physical activity. The social vector can influence life-course and life experiences both individually and synergistically [205]. This vector can also interact with the other vectors within the framework to influence the timing of menopause and the associated hormone-related cancers.

In addition, obesity has been strongly associated with insulin resistance and diabetes [208]. Both obesity and insulin resistance are also associated with the timing of menopause (please refer to section 1.3). As elaborated in section 1.4, the timing of menopause which is a life-course experience can consequently influence the presence of VMS as well as the risk of hormone-related cancers. Studies have also demonstrated that both obesity and diabetes are independently associated with the risk of cancers [209, 210]. According to the recent findings of the Global Burden of Disease study [211], type II diabetes and cancers are among the main diet-related causes of death across 195 countries. The authors reported that regardless of the socio-demographic characteristics (e.g. age, gender, area of residence) of people, diet is a major risk factor of non-communicable diseases as compared to other risk factors. Additionally, it was found that the number of deaths due to suboptimal diet was higher globally in comparison to the number of deaths associated with other risk factors such as smoking [211]. Therefore, this thesis focuses on the relationship between diet as the main exposure and the timing of the onset of natural menopause and its associated sequelae.

As shown in Figure 1.4, there are various factors which can be linked with the exposure (diet) and outcomes of interest (age at natural menopause, presence of VMS, risk of breast, ovarian and endometrial cancers) in this study. This is termed as confounding. It is crucial to control for these confounders in order to avoid spurious results [212]. Thus, using this conceptual framework, directed acyclic graphs (DAG) were constructed to identify potential confounders for each result chapter of this thesis (Chapters 3-7). The DAG will further be discussed in Chapter 8.

1.8 Research aims

1.8.1 Research Questions

- Is there an association between diet and age at natural menopause?
- Is there a relationship between diet and vasomotor menopausal symptoms?

- Is diet related to breast, endometrial and ovarian cancer risks?

1.8.2 Aims

- To elucidate the relationship between diet and onset of natural menopause
- To study the relationship between diet and the sequelae of menopause (VMS as well as hormone-related such as ovarian, endometrial and breast cancers)

1.8.3 Objectives

To address the aims of this study, the following objectives are proposed (Figure 1.5):

- To compare the diet of pre and post-menopausal women in the UK Women's Cohort Study (UKWCS)
- To investigate the relationship between diet (food groups and nutrient intake) and age at natural menopause in the UKWCS
- To investigate the relationship between dietary patterns and the age at onset of natural menopause in the UKWCS
- To examine the association between soy consumption and VMS in the International Collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) consortium
- To explore diet in relation to risk of breast, endometrial and ovarian cancers in the UKWCS
- To explore the interplay between diet, the risk of breast, endometrial, ovarian cancer and age at natural menopause in the UKWCS

1.8.4 Hypotheses

- An unhealthy diet (e.g., high fat, high meat consumption and low fruits and vegetables consumption) increases the risk of breast, endometrial and ovarian cancers.
- Diet is associated with the timing of onset of natural menopause. A healthy diet is associated with an earlier age at menopause while an unhealthy diet is associated with a later menopause.
- Frequent consumption of foods with high phytoestrogen content such as soy might be protective against VMS

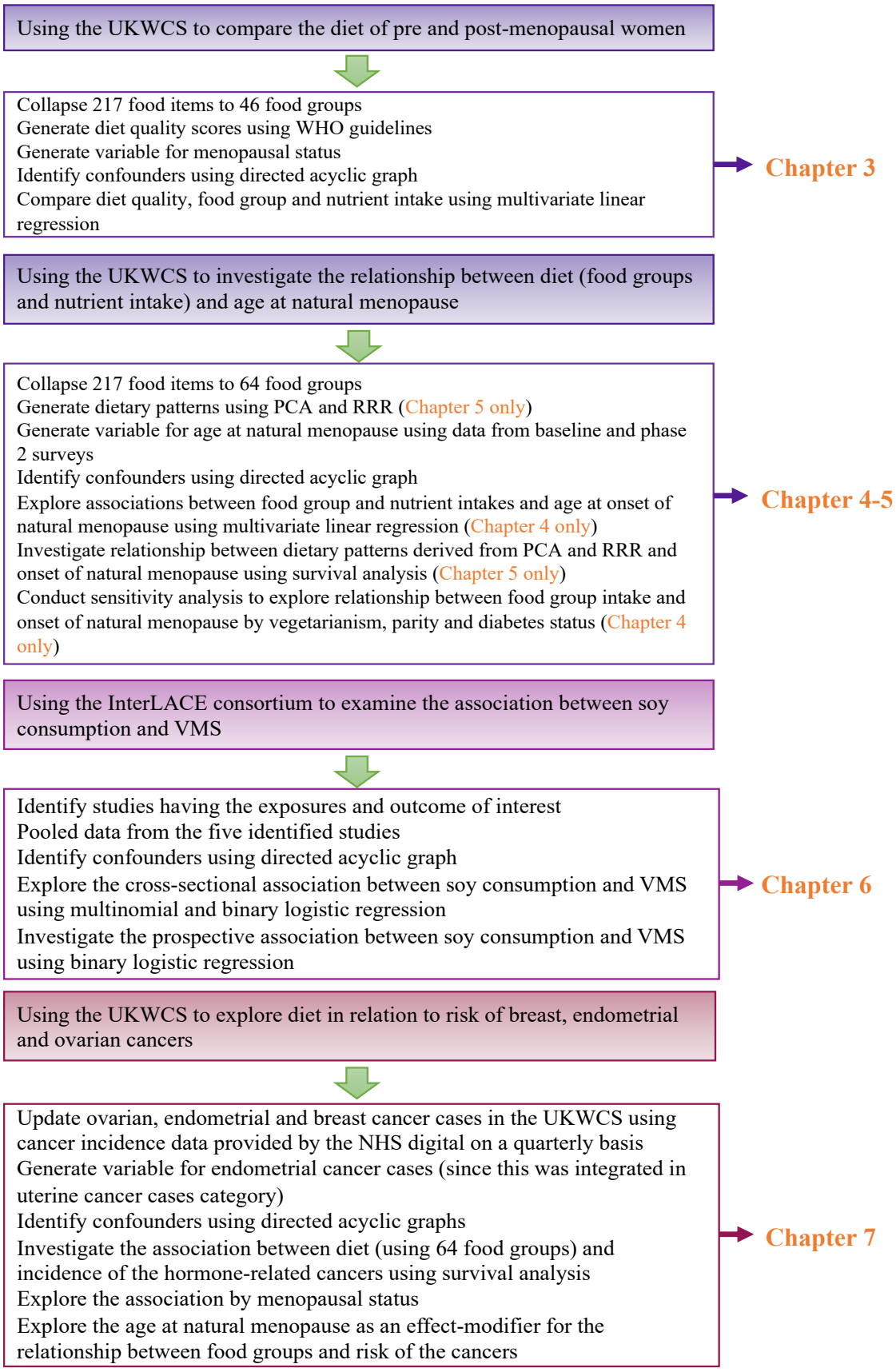

Figure 1.5 Research objectives and summarised methodology mapped onto result chapters

1.9 Summary

In summary, evidence shows that diets predisposing to obesity and insulin resistance are the main drivers of sex hormone fluctuations among both pre- and post-menopausal women. Fluctuations in oestrogen levels have been associated with the timing of the onset of natural menopause, the presence of VMS, and longer-term sequelae such as ovarian, endometrial and breast cancer. Studies have demonstrated that both the consumption of diets which are rich in fibre, fruits, and vegetables and, the consumption of less healthy diets, for example, those containing processed meats and rich in saturated fats can alter circulating levels of oestrogen and other sex hormones. Diet could consequently influence the timing of natural menopause and hence affect its associated sequelae. However, further evidence around the hypothesis that diet might influence the timing of menopause and the presence of VMS are required in observational trials, and use of metabolomics may be valuable in revealing mechanistic pathways. Additional observational studies may also clarify the association between diet and hormone-related cancers.

References

1. Hill, K. The demography of menopause. *Maturitas.* 1996, **23**(2), pp.113-127.
2. Schoenaker, D. et al. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International Journal of Epidemiology.* 2014, **43**(5), pp.1542-1562.
3. Davis, S.R. et al. Menopause. *Nature Reviews Disease Primers.* 2015, p.15004.
4. Voorhuis, M. et al. Human studies on genetics of the age at natural menopause: a systematic review. *Human Reproduction Update.* 2010, **16**(4), pp.364-377.
5. Gold, E.B. and Greendale, G.A. Chapter 6 - Epidemiology of Menopause: Demographics, Environmental Influences, and Ethnic and International Differences in the Menopausal Experience. In: Lobo, R.A. ed. *Treatment of the Postmenopausal Woman (Third Edition)*. St. Louis: Academic Press, 2007, pp.77-96.
6. Canavez, F.S. et al. The association between educational level and age at the menopause: a systematic review. *Archives of Gynecology and Obstetrics.* 2011, **283**(1), pp.83-90.
7. Gold, E.B. et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology.* 2001, **153**(9), pp.865-874.
8. Weinstein, M. et al. Timing of Menopause and Patterns of Menstrual Bleeding. *American Journal of Epidemiology.* 2003, **158**(8), pp.782-791.
9. Henderson, K.D. et al. Predictors of the Timing of Natural Menopause in the Multiethnic Cohort Study. *American Journal of Epidemiology.* 2008, **167**(11), pp.1287-1294.
10. Gold, E.B. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America.* 2011, **38**(3), pp.425-440.
11. Freeman, E.W. and Sherif, K. Prevalence of hot flushes and night sweats around the world: a systematic review. *Climacteric.* 2007, **10**(3), pp.197-214.
12. Pines, A. Vasomotor symptoms and cardiovascular disease risk. *Climacteric.* 2011, **14**(5), pp.535-536.
13. Schuit, E. et al. Association of menopausal characteristics and risk of coronary heart disease: a pan-European case–cohort analysis. *International Journal of Epidemiology*. 2019; dyz016.

14. Kaczmarek, M. The timing of natural menopause in Poland and associated factors. *Maturitas.* 2007, **57**(2), pp.139-153.

15. Kato, I. et al. Prospective Study of Factors Influencing the Onset of Natural Menopause. *Journal of Clinical Epidemiology.* 1998, **51**(12), pp.1271-1276.

16. Lawlor, D.A. et al. The association of socio-economic position across the life course and age at menopause: the British Women's Heart and Health Study. *BJOG : An International Journal of Obstetrics And Gynaecology.* 2003, **110**(12), pp.1078-1087.

17. Edmonds, D.K. and Dewhurst, J.S. *Dewhurst's textbook of obstetrics and gynaecology.* Malden, Mass: Blackwell Pub, 2006.

18. Sherwood, L. *Human physiology: from cells to systems.* St. Paul: West Publishing Company, 1993.

19. O'Connor, K.A. et al. Menstrual cycle variability and the perimenopause. *American Journal of Human Biology.* 2001, **13**(4), pp.465-478.

20. Morrison, J.H. et al. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. *The Journal of Neuroscience.* 2006, **26**(41), pp.10332-10348.

21. Harlow, S.D. et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause.* 2012, **19**(4), pp.387-395.

22. Burger, H.G. et al. Cycle and hormone changes during perimenopause: the key role of ovarian function. *Menopause.* 2008, **15**(4 Pt 1), pp.603-612.

23. Su, H.I. and Freeman, E.W. Hormone changes associated with the menopausal transition. *Minerva Ginecologica.* 2009, **61**(6), p.483.

24. Okeke, T.C. et al. Premature Menopause. *Annals of Medical and Health Sciences Research.* 2013, **3**(1), pp.90-95.

25. Faubion, S.S. et al. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric.* 2015, **18**(4), pp.483-491.

26. Sherman, S. Defining the menopausal transition. *American Journal of Medicine.* 2005, **118**(Suppl 12B), pp.3-7.

27. Sekhar, T.V.D.S. et al. Early Menopause in Type 2 Diabetes - A Study from a South Indian Tertiary Care Centre. *Journal of Clinical and Diagnostic Research.* 2015, **9**(10), p.OC08.

28. Monterrosa-Castro, A. et al. Type II diabetes mellitus and menopause: a multinational study. *Climacteric.* 2013, **16**(6), pp.663-672.

29. Purdue-Smithe, A.C. et al. Vitamin D and calcium intake and risk of early menopause. *The American Journal of Clinical Nutrition.* 2017, **105**(6), pp.1493-1501.

30. Parker, J. et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas.* 2010, **65**(3), pp.225-236.

31. Biela, U. [Determinants of the age at natural menopause]. *Przeglad Lekarski.* 2002, **59**(3), pp.165-169.

32. Bagga, D. et al. Effects of a very-low fat, high-fiber diet on serum hormones and menstrual function - implications for breast-cancer prevention. *Cancer.* 1995, **76**(12), pp.2491-2496.

33. Karelis, A.D. et al. Comparison of sex hormonal and metabolic profiles between omnivores and vegetarians in pre- and post-menopausal women. *British Journal of Nutrition.* 2010, **104**(2), pp.222-226.

34. Rock, C.L. et al. Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer. *Journal of Clinical Oncology.* 2004, **22**(12), pp.2379-2387.

35. Nagata, C. et al. Association of diet with the onset of menopause in Japanese women. *American Journal of Epidemiology.* 2000, **152**(9), pp.863-867.

36. Agarwal, A. et al. Role of oxidative stress in female reproduction. *Reproductive Biology and Endocrinology.* 2005, **3**, pp.28-28.

37. Ruder, E.H. et al. Oxidative stress and antioxidants: exposure and impact on female fertility. *Human Reproduction Update.* 2008, **14**(4), pp.345-357.

38. Ozcan, P. et al. Protective effect of resveratrol against oxidative damage to ovarian reserve in female Sprague-Dawley rats. *Reproductive Biomedicine Online.* 2015, **31**(3), pp.404-410.

39. Berg, J. et al. Important Derivatives of Cholesterol Include Bile Salts and Steroid Hormones. In: *Biochemistry*. 5th ed. New York: W H Freeman, 2002.

40. Zsakai, A. et al. Body fatness and endogenous sex hormones in the menopausal transition. *Maturitas.* 2016, **87**, pp.18-26.

41. Ho, S.C. et al. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. *International Journal of Obesity.* 2010, **34**(8), pp.1265-1274.

42. O'Neill, S. and Eden, J. The pathophysiology of menopausal symptoms. *Obstetrics, Gynaecology & Reproductive Medicine.* 2017, **27**(10), pp.303-310.

43. Dhanoya, T. et al. Hot flushes and reproductive hormone levels during the menopausal transition. *Maturitas.* 2016, **89**, pp.43-51.

44. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *The Lancet Oncology* 2012, **13**(11), pp.1141-1151.

45. Tavani, A. et al. Influence of menstrual and reproductive factors on ovarian cancer risk in women with and without family history of breast or ovarian cancer. *International Journal of Epidemiology.* 2000, **29**(5), pp.799-802.

46. Xu, W.H. et al. Menstrual and reproductive factors and endometrial cancer risk: Results from a population-based case-control study in urban Shanghai. *International Journal of Cancer.* 2004, **108**(4), pp.613-619.

47. Travis, R.C. and Key, T.J. Oestrogen exposure and breast cancer risk. *Breast Cancer Research.* 2003, **5**(5), pp.239-247.

48. Clemons, M. and Goss, P. Estrogen and the risk of breast cancer. *New England Journal of Medicine.* 2001, **344**(4), pp.276-285.

49. Mungenast, F. and Thalhammer, T. Estrogen biosynthesis and action in ovarian cancer. *Frontiers in Endocrinology.* 2014, **5**, p.192.

50. Wu, A.H. et al. Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. *Journal of the National Cancer Institute.* 1999, **91**(6), pp.529-534.

51. Nagata, C. et al. Fat Intake Is Associated with Serum Estrogen and Androgen Concentrations in Postmenopausal Japanese Women. *The Journal of Nutrition.* 2005, **135**(12), pp.2862-2865.

52. Gaskins, A.J. et al. Effect of daily fiber intake on reproductive function: the BioCycle Study. *The American Journal of Clinical Nutrition.* 2009, **90**(4), pp.1061-1069.

53. Hunter, M.S. et al. Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10,418 British women aged 54-65. *BJOG : An International Journal of Obstetrics and Gynaecology.* 2012, **119**(1), pp.40-50.

54. Thurston, R.C. and Joffe, H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstetrics and Gynecology Clinics of North America.* 2011, **38**(3), pp.489-501.

55. Lethaby, A. et al. Phytoestrogens for menopausal vasomotor symptoms. *The Cochrane Database of Systematic Reviews.* 2013, (12), p.Cd001395.

56. Schmidt, M. et al. Consensus: soy isoflavones as a first-line approach to the treatment of menopausal vasomotor complaints. *Gynecological Endocrinology.* 2016, **32**(6), pp.427-430.

57. Herber-Gast, G.C. and Mishra, G.D. Fruit, Mediterranean-style, and high-fat and -sugar diets are associated with the risk of night sweats and hot flushes in midlife: results from a prospective cohort study. *American Journal of Clinical Nutrition.* 2013, **97**(5), pp.1092-1099.

58. Cancer Research UK. *Cancer statistics by type*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type (accessed May 2018)

59. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available from: dietandcancerreport.org

60. Reid, B.M. et al. Epidemiology of ovarian cancer: a review. *Cancer Biology & Medicine.* 2017, **14**(1), pp.9-32.

61. Ferlay, J. et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer.* 2015, **136**(5), pp.E359-E386.

62. Torre, L.A. et al. Ovarian cancer statistics, 2018. *CA: A Cancer Journal for Clinicians.* 2018, **68**(4), pp.284-296.

63. Ana Fernández Montes, J.G.G., Miguel Nuñez Viejo, Miguel Alonso Bermejo, Susana Alonso Urrutia and Jesús García Mata. Epidemiology and Etiology of Ovarian Cancer. In: Farghaly, S.A. ed. *Ovarian Cancer - Basic Science Perspective*. IntechOpen, 2012, pp.1-16.

64. Chen, V.W. et al. Pathology and classification of ovarian tumors. *Cancer.* 2003, **97**(S10), pp.2631-2642.

65. Stratton, J.F. et al. A systematic review and meta-analysis of family history and risk of ovarian cancer. *British Journal of Obstetrics and Gynaecology.* 1998, **105**(5), pp.493-499.

66. Negri, E. et al. Family history of cancer and risk of ovarian cancer. *European Journal of Cancer.* 2003, **39**(4), pp.505-510.

67. Jervis, S. et al. Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants. *Journal of Medical Genetics.* 2014, **51**(2), pp.108-113.

68. Adaniel, C. and Kirchhoff, T. Introduction to epidemiology of breast and ovarian cancers. *Annals of Oncology.* 2013, **24**(suppl_8), pp.viii61-viii62.

69. Cramer, D.W. The epidemiology of endometrial and ovarian cancer. *Hematology/Oncology Clinics of North America.* 2012, **26**(1), pp.1-12.

70. Lee, A.W. et al. Association Between Menopausal Estrogen-Only Therapy and Ovarian Carcinoma Risk. *Obstetetrics & Gynecology.* 2016, **127**(5), pp.828-836.

71. Zhou, B. et al. Hormone replacement therapy and ovarian cancer risk: a meta-analysis. *Obstetetrics & Gynecology.* 2008, **108**(3), pp.641-651.

72. Coughlin, S.S. et al. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. *Journal of Clinical Epidemiology.* 2000, **53**(4), pp.367-375.

73. Iversen, L. et al. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. *American Journal of Obstetrics & Gynecology.* 2017, **216**(6), pp.580.e581-580.e589.

74. Cibula, D. et al. Hormonal contraception and risk of cancer. *Human Reproduction Update.* 2010, **16**(6), pp.631-650.

75. Iversen, L. et al. Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. *British Medical Journal.* 2018, **362**, p.k3609.

76. Collaborative Group on Epidemiological Studies of Ovarian, C. et al. Ovarian cancer and smoking: individual participant meta-analysis including 28,114 women with ovarian cancer from 51 epidemiological studies. *The Lancet Oncology.* 2012, **13**(9), pp.946-956.

77. Faber, M.T. et al. Cigarette smoking and risk of ovarian cancer: a pooled analysis of 21 case-control studies. *Cancer Causes & Control.* 2013, **24**(5), pp.989-1004.

78. Liu, D.-W. et al. The association between overweight, obesity and ovarian cancer: a meta-analysis. *Japanese Journal of Clinical Oncology.* 2015, **45**(12), pp.1107-1115.

79. Olsen, C.M. et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. *Endocrine-Related Cancer*. 2013, **20**(2), p.251.

80. Cannioto, R. et al. Chronic Recreational Physical Inactivity and Epithelial Ovarian Cancer Risk: Evidence from the Ovarian Cancer Association Consortium. *Cancer Epidemiol Biomarkers Prev.* 2016, **25**(7), pp.1114-1124.

81. Cannioto, R.A. and Moysich, K.B. Epithelial ovarian cancer and recreational physical activity: A review of the epidemiological literature and implications for exercise prescription. *Gynecologic Oncology.* 2015, **137**(3), pp.559-573.

82. Kazerouni, N. et al. Family history of breast cancer as a determinant of the risk of developing endometrial cancer: a nationwide cohort study. *Journal of Medical Genetics.* 2002, **39**(11), pp.826-832.

83. Henderson, I.C. *Breast Cancer: Fundamentals of Evidence-Based Disease Management* US: Oxford University Press, 2015.

84. Murali, R. et al. Classification of endometrial carcinoma: more than two types. *The Lancet Oncology.* 2014, **15**(7), pp.e268-e278.

85. Shiovitz, S. and Korde, L.A. Genetics of breast cancer: a topic in evolution. *Annals of Oncology.* 2015, **26**(7), pp.1291-1299.

86. Wu, Q.J. et al. Parity and endometrial cancer risk: a meta-analysis of epidemiological studies. *Scientific Reports.* 2015, **5**, p.14243.

87. Li, D.P. et al. Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pacific Journal of Cancer Prevention.* 2014, **15**(12), pp.4829-4837.

88. Wang, L. et al. Association between Breastfeeding and Endometrial Cancer Risk: Evidence from a Systematic Review and Meta-Analysis. *Nutrients.* 2015, **7**(7), pp.5697-5711.

89. Lipworth, L. et al. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature. *Journal of National Cancer Institute.* 2000, **92**(4), pp.302-312.

90. Gierisch, J.M. et al. Oral Contraceptive Use and Risk of Breast, Cervical, Colorectal, and Endometrial Cancers: A Systematic Review. *Cancer Epidemiology Biomarkers & Prevention.* 2013, **22**(11), pp.1931-1943.

91. Pearce, C.L. et al. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. *Cancer.* 2009, **115**(3), pp.531-539.

92. Beral, V. et al. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *The Lancet.* 2005, **365**(9470), pp.1543-1551.

93. Key, T.J. et al. Epidemiology of breast cancer. *The Lancet Oncology.* 2001, **2**(3), pp.133-140.

94. Zhou, B. et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. *American Journal of Medicine.* 2008, **121**(6), pp.501-508.e503.

95. Gram, I.T. et al. The fraction of breast cancer attributable to smoking: The Norwegian women and cancer study 1991-2012. *British Journal of Cancer.* 2016, **115**(5), pp.616-623.

96. La Vecchia, C. et al. Alcohol and epithelial ovarian cancer. *Journal of Clinical Epidemiology.* 1992, **45**(9), pp.1025-1030.

97. Setiawan, V.W. et al. Alcohol consumption and endometrial cancer risk: the multiethnic cohort. *International Journal of Cancer.* 2008, **122**(3), pp.634-638.

98. Zhang, S.M. et al. Alcohol Consumption and Breast Cancer Risk in the Women's Health Study. *American Journal of Epidemiology.* 2007, **165**(6), pp.667-676.

99. Voskuil, D.W. et al. Physical Activity and Endometrial Cancer Risk, a Systematic Review of Current Evidence. *Cancer Epidemiology Biomarkers & Prevention.* 2007, **16**(4), pp.639-648.

100. Loprinzi, P.D. et al. Physical activity and breast cancer risk. *Journal of Exercise Science & Fitness.* 2012, **10**(1), pp.1-7.

101. Onstad, M.A. et al. Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment. *Journal of Clinical Oncology.* 2016, **34**(35), pp.4225-4230.

102. Nattenmüller, C.J. et al. Obesity as risk factor for subtypes of breast cancer: results from a prospective cohort study. *BMC Cancer.* 2018, **18**(1), p.616.

103. Alberg, A.J. et al. Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study. *American Journal of Epidemiology.* 2016, **184**(4), pp.274-283.

104. Madison, T. et al. Endometrial cancer: socioeconomic status and racial/ethnic differences in stage at diagnosis, treatment, and survival. *American Journal of Public Health.* 2004, **94**(12), pp.2104-2111.

105. Hussain, S.K. et al. Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. *International Journal of Cancer.* 2008, **122**(1), pp.165-169.

106. Akinyemiju, T.F. et al. Socioeconomic status and incidence of breast cancer by hormone receptor subtype. *SpringerPlus.* 2015, **4**, pp.1-8.

107. Begum, S. and S, A. Study of immune profile during different phases of menstrual cycle. *International Journal of Biological and Medical Research.* 2012, **3**(1), pp.1407-1409.

108. Nair, A.R. and Taylor, H.S. The Mechanism of Menstruation. In: Santoro, N.F. and Neal-Perry, G. eds. *Amenorrhea: A Case-Based, Clinical Guide*. New York: Humana Press, 2010, pp.21-34.

109. Beshay, V.E. and Carr, B.R. Hypothalamic-Pituitary-Ovarian Axis and Control of the Menstrual Cycle. In: Falcone, T. and Hurd, W.W. eds. *Clinical Reproductive Medicine and Surgery: A Practical Guide*. 2 ed. New York: Springer, 2013, pp.31-42.

110. Lengyel, E. Ovarian cancer development and metastasis. *American Journal of Pathology.* 2010, **177**(3), pp.1053-1064.

111. Wu, A.H. et al. Meta-analysis: Dietary Fat Intake, Serum Estrogen Levels, and the Risk of Breast Cancer. *Journal of the National Cancer Institute.* 1999, **91**(6), pp.529-534.

112. Fucic, A. et al. Environmental exposure to xenoestrogens and oestrogen related cancers: Reproductive system, breast, lung, kidney, pancreas, and brain. *Environmental Health: A Global Access Science Source.* 2012, **11**(1), pp.S8-S8.

113. Ogura, K. et al. Effects of leptin on secretion of LH and FSH from primary cultured female rat pituitary cells. *European Journal of Endocrinology* 2001, **144**(6), pp.653-658.

114. Blank, M.M. et al. Dietary fat intake and risk of ovarian cancer in the NIH-AARP Diet and Health Study. *British Journal of Cancer.* 2012, **106**(3), pp.596-602.

115. Qiu, W. et al. Dietary fat intake and ovarian cancer risk: a meta-analysis of epidemiological studies. *Oncotarget.* 2016, **7**(24), pp.37390-37406.

116. Prentice, R.L. et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. *Journal of the National Cancer Institute.* 2007, **99**(20), pp.1534-1543.

117. Taha, A.A.A. et al. The effect of the type of dietary protein on the development of ovarian cancer. *Oncotarget.* 2018, **9**(35), pp.23987-23999.

118. Pang, Y. and Wang, W. Dietary protein intake and risk of ovarian cancer: evidence from a meta-analysis of observational studies. *Bioscience reports.* 2018, **38**(6), pp.1-7.

119. Azrad, M. et al. Current evidence linking polyunsaturated Fatty acids with cancer risk and progression. *Frontiers in Oncology.* 2013, **3**, p.224.

120. Larsson, S.C. et al. Dietary long-chain n− 3 fatty acids for the prevention of cancer: a review of potential mechanisms. *The American Journal of Clinical Nutrition.* 2004, **79**(6), pp.935-945.

121. Calder, P.C. Omega‐3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *British Journal of Clinical Pharmacology.* 2013, **75**(3), pp.645-662.

122. Merritt, M.A. et al. Dietary fat intake and risk of epithelial ovarian cancer by tumour histology. *British Journal of Cancer.* 2014, **110**(5), pp.1392-1401.

123. Hu, F. et al. *Lipid metabolism, metabolic syndrome, and cancer.* INTECH Open Access Publisher, 2013.

124. Berquin, I.M. et al. Modulation of prostate cancer genetic risk by omega-3 and omega-6 fatty acids. *Journal of Clinical Investigation.* 2007, **117**(7), pp.1866-1875.

125. Perlman, R.L. Mouse models of human disease: An evolutionary perspective. *Evolution, Medicine, and Public Health.* 2016, **2016**(1), pp.170-176.

126. Huerta-Yépez, S. et al. Role of diets rich in omega-3 and omega-6 in the development of cancer. *Boletín Médico del Hospital Infantil de México.* 2016, **73**(6), pp.446-456.

127. Wong, R.H.F. and Sul, H.S. Insulin signaling in fatty acid and fat synthesis: a transcriptional perspective. *Current Opinion in Pharmacology.* 2010, **10**(6), pp.684-691.

128. Sul, H.S. and Wang, D. Nutritional and hormonal regulation of enzymes in fat synthesis: Studies of fatty acid synthase and mitochondrial glycerol-3-phosphate acyltransferase gene transcription. *Annual Review of Nutrition.* 1998, **18**(1), pp.331-351.

129. Currie, E. et al. Cellular Fatty Acid Metabolism and Cancer. *Cell Metabolism.* 2013, **18**(2), pp.153-161.

130. Saso, S. et al. Endometrial cancer. *British Medical Journal.* 2011, **343**, p.d3954.

131. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. *Food, Nutrition, Physical Activity, and the Prevention of Endometrial Cancer*. 2013. Available from: https://www.wcrf.org/sites/default/files/Endometrial-Cancer-2013-Report.pdf

132. Weiss, J.M. et al. Risk Factors for the Incidence of Endometrial Cancer according to the Aggressiveness of Disease. *American Journal of Epidemiology.* 2006, **164**(1), pp.56-62.

133. I National Cancer Institute. *Endometrial Cancer Incidence Rising in the US and Worldwide*. 2017. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2017/endometrial-cancer-incidence-rising. [accessed October 2018]

134. Pellerin, G.P. and Finan, M.A. Endometrial cancer in women 45 years of age or younger: A clinicopathological analysis. *American Journal of Obstetrics & Gynecology.* 2005, **193**(5), pp.1640-1644.

135. Silverberg SG, K.R., Nogales F, Mutter GL, Kubik-Huch RA, Tavassoli FA. Epithelial tumours and related lesions. In: Tavassoli FA, D.P. ed. *World Health Organization classification of tumours: pathology and genetics—tumours of the breast and female genital organs*. Lyon: IARC Press, 2003, pp.217-232.

136. Win, A.K. et al. Family history and risk of endometrial cancer: a systematic review and meta-analysis. *Obstetrics and Gynecology.* 2015, **125**(1), pp.89-98.

137. Johnatty, S.E. et al. Family history of cancer predicts endometrial cancer risk independently of Lynch Syndrome: Implications for genetic counselling. *Gynecologic Oncology* 2017, **147**(2), pp.381-387.

138. Cook, L.S. et al. Endometrial cancer and a family history of cancer. *Gynecologic Oncology.* 2013, **130**(2), pp.334-339.

139. Cote, M.L. et al. The Growing Burden of Endometrial Cancer: A Major Racial Disparity Affecting Black Women. *Cancer Epidemiology Biomarkers & Prevention.* 2015, **24**(9), pp.1407-1415.

140. Setiawan, V.W. et al. Racial/Ethnic Differences in Endometrial Cancer Risk: The Multiethnic Cohort Study. *American Journal of Epidemiology.* 2006, **165**(3), pp.262-270.

141. Jordan, S.J. et al. Breastfeeding and Endometrial Cancer Risk: An Analysis From the Epidemiology of Endometrial Cancer Consortium. *Gynecologic Oncology.* 2017, **129**(6), pp.1059-1067.

142. Morice, P. et al. Endometrial cancer. *The Lancet.* 2016, **387**(10023), pp.1094-1108.

143. Aune, D. et al. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. *Scientific Reports.* 2017, **7**, p.44808.

144. Hamet, P. Cancer and hypertension: a potential for crosstalk? *Journal of Hypertension.* 1997, **15**(12 Pt 2), pp.1573-1577.

145. Bangalore, S. et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *The Lancet Oncology.* 2011, **12**(1), pp.65-82.

146. Du, M. et al. Physical activity and risk of endometrial adenocarcinoma in the Nurses' Health Study. *International Journal of Cancer.* 2014, **134**(11), pp.2707-2716.

147. Kaaks, R. et al. Obesity, endogenous hormones, and endometrial cancer risk: A synthetic review. *Cancer Epidemiology Biomarkers & Prevention.* 2002, **11**(12), pp.1531-1543.

148. Losordo, D.W. and Isner, J.M. Estrogen and Angiogenesis: A Review. *Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association.* 2001, **21**(1), pp.6-12.

149. Xu, W.H. et al. Effect of adiposity and fat distribution on endometrial cancer risk in Shanghai women. *American Journal of Epidemiology.* 2005, **161**(10), pp.939-947.

150. Carlson, M.J. et al. Catch it before it kills: progesterone, obesity, and the prevention of endometrial cancer. *Discovery Medicine.* 2012, **14**(76), pp.215-222.

151. Goodman, M.T. et al. Association of soy and fiber consumption with the risk of endometrial cancer. *American Journal of Epidemiology.* 1997, **146**(4), pp.294-306.

152. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. 2007. Available at: https://www.wcrf.org/sites/default/files/english.pdf

153. Mulholland, H.G. et al. Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis. *British Journal of Cancer.* 2008, **99**(3), pp.434-441.

154. Bosetti, C. et al. Metabolic syndrome and endometrial cancer risk. *Annals of Oncology.* 2010, **22**(4), pp.884-889.

155. Luo, J. et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. *British Journal of Cancer.* 2014, **111**, p.1432.

156. Friberg, E. et al. Diabetes and Risk of Endometrial Cancer: A Population-Based Prospective Cohort Study. *Cancer Epidemiology Biomarkers & Prevention.* 2007, **16**(2), pp.276-280.

157. Hernandez, A.V. et al. Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis. *European Journal of Cancer.* 2015, **51**(18), pp.2747-2758.

158. Shapira, N. The potential contribution of dietary factors to breast cancer prevention. *European Journal of Cancer Prevention.* 2017, **26**(5), pp.385-395.

159. Ellis IO, S.S., Sastre-Garau X, Bussolati G, Tavassoli FA, Eusebi V, Peterse JL, Mukai K, Tabár L, Jacquemier J, Cornelisse CJ, Sasco AJ, Kaaks R, Pisani P, Goldgar DE, Devilee P, Cleton-Jansen MJ, Børresen-Dale AL, van't Veer L, Sapino A. Invasive breast carcinoma. In: Tavassoli FA, D.P. ed. *Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. Lyon: IARC Press, 2003, pp.9-41.

160. Malhotra, G.K. et al. Histological, molecular and functional subtypes of breast cancers. *Cancer Biology & Therapy.* 2010, **10**(10), pp.955-960.

161. Anderson, K.N. et al. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Research and Treatment.* 2014, **144**(1), pp.1-10.

162. Kispert, S. and McHowat, J. Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. *Breast Cancer.* 2017, **9**, pp.127-132.

163. Fagherazzi, G. et al. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. *European Journal of Cancer Prevention.* 2015, **24**(3), pp.209-214.

164. Yoneda, A. et al. Breast and Ovarian Cancers: A Survey and Possible Roles for the Cell Surface Heparan Sulfate Proteoglycans. *Journal of Histochemistry and Cytochemistry.* 2012, **60**(1), pp.9-21.

165. Cleary, M.P. and Grossmann, M.E. Obesity and Breast Cancer: The Estrogen Connection. *Endocrinology.* 2009, **150**(6), pp.2537-2542.

166. Malara, N.M. et al. Ageing, hormonal behaviour and cyclin D1 in ductal breast carcinomas. *The Breast.* 2006, **15**(1), pp.81-89.

167. Bussard, K.M. et al. Tumor-associated stromal cells as key contributors to the tumor microenvironment. *Breast Cancer Research.* 2016, **18**(1), p.84.

168. Llaverias, G. et al. Role of Cholesterol in the Development and Progression of Breast Cancer. *The American Journal of Pathology.* 2011, **178**(1), pp.402-412.

169. Wu, Q. et al. 27-Hydroxycholesterol Promotes Cell-autonomous ER-positive Breast Cancer Growth. *Cell reports.* 2013, **5**(3), pp.637-645.

170. Baek, A.E. et al. The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. *Nature Communications.* 2017, **8**, p.864.

171. Derby, C.A. et al. Lipid Changes During the Menopause Transition in Relation to Age and WeightThe Study of Women's Health Across the Nation. *American Journal of Epidemiology.* 2009, **169**(11), pp.1352-1361.

172. Lu, D.-L. et al. Circulating 27-Hydroxycholesterol and Breast Cancer Risk: Results From the EPIC-Heidelberg Cohort. *Journal of the National Cancer Institute.* 2018, pp.djy115-djy115.

173. Bracken, M.B. Why animal studies are often poor predictors of human reactions to exposure. *Journal of the Royal Society of Medicine.* 2009, **102**(3), pp.120-122.

174. De Souza, C.T. et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology.* 2005, **146**(10), pp.4192-4199.

175. Willett, W. et al. Glycemic index, glycemic load, and risk of type 2 diabetes. *American Journal of Clinical Nutrition.* 2002, **76**(1), pp.274s-280s.

176. Orgel, E. and Mittelman, S.D. The Links Between Insulin Resistance, Diabetes, and Cancer. *Current Diabetes Reports.* 2013, **13**(2), pp.213-222.

177. Rose, D.P. et al. The Interactions of Obesity, Inflammation and Insulin Resistance in Breast Cancer. *Cancers.* 2015, **7**(4), pp.2147-2168.

178. Mukhopadhyay, K.D. et al. Aromatase Expression Increases the Survival and Malignancy of Estrogen Receptor Positive Breast Cancer Cells. *PLoS ONE.* 2015, **10**(4), p.e0121136.

179. Daka, B. et al. Inverse association between serum insulin and sex hormone-binding globulin in a population survey in Sweden. *Endocrine Connections.* 2013, **2**(1), pp.18-22.

180. Sieri, S. et al. Prospective study on the role of glucose metabolism in breast cancer occurrence. *International Journal of Cancer.* 2012, **130**(4), pp.921-929.

181. Howe, L.R. et al. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. *Clinical Cancer Research.* 2013, **19**(22), pp.6074-6083.

182. Key, T.J. et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *The Lancet Oncology.* 2013, **14**(10), pp.1009-1019.

183. Chen, G.-C. et al. Central obesity and risks of pre- and postmenopausal breast cancer: a dose–response meta-analysis of prospective studies. *Obesity Reviews.* 2016, **17**(11), pp.1167-1177.

184. Luque, R.M. et al. Breast cancer is associated to impaired glucose/insulin homeostasis in premenopausal obese/overweight patients. *Oncotarget.* 2017, **8**(46), pp.81462-81474.

185. Harris, H.R. et al. Folate, vitamin B 6, vitamin B 12, methionine and alcohol intake in relation to ovarian cancer risk. *International Journal of Cancer.* 2012, **131**(4), pp.E518-E529.

186. Bandera, E.V. et al. Antioxidant Vitamins and the Risk of Endometrial Cancer: A Dose–Response Meta-Analysis. *Cancer Causes & Control.* 2009, **20**(5), pp.699-711.

187. Donaldson, M.S. Nutrition and cancer: a review of the evidence for an anti-cancer diet. *Nutrition Journal.* 2004, **3**, p.19.

188. Navarro Silvera, S.A. et al. Carotenoid, vitamin A, vitamin C, and vitamin E intake and risk of ovarian cancer: A prospective cohort study. *Cancer Epidemiology Biomarkers & Prevention.* 2006, **15**(2), pp.395-397.

189. Thomson, C.A. et al. The Role of Antioxidants and Vitamin A in Ovarian Cancer: Results From the Women's Health Initiative. *Nutrition and Cancer.* 2008, **60**(6), pp.710-719.

190. Koushik, A. et al. Intake of vitamins A, C, and E and folate and the risk of ovarian cancer in a pooled analysis of 10 cohort studies. *Cancer Causes and Control.* 2015, **26**(9), pp.1315-1327.

191. Estébanez, N. et al. Vitamin D exposure and Risk of Breast Cancer: a meta-analysis. *Scientific Reports.* 2018, **8**(1), p.9039.

192. McCullough, M.L. et al. Dairy, Calcium, and Vitamin D Intake and Postmenopausal Breast Cancer Risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiology Biomarkers & Prevention.* 2005, **14**(12), pp.2898-2904.

193. Ahonen, M.H. et al. Androgen receptor and vitamin D receptor in human ovarian cancer: Growth stimulation and inhibition by ligands. *International Journal of Cancer.* 2000, **86**(1), pp.40-46.

194. Yu, W. et al. Dietary vitamin D exposure prevents obesity-induced increase in endometrial cancer in Pten+/- mice. *Cancer Prevention Research.* 2010, **3**(10), pp.1246-1258.

195. Cook, L.S. A systematic literature review of vitamin D and ovarian cancer. *American Journal of Obstetrics & Gynecology.* 2010, **203**(1), pp.70.e71-70.e78.

196. McCullough, M.L. et al. Vitamin D and calcium intake in relation to risk of endometrial cancer: A systematic review of the literature. *Preventive Medicine.* 2008, **46**(4), pp.298-302.

197. Romagnolo, D.F. and Selmin, O.I. Flavonoids and Cancer Prevention: A Review of the Evidence. *Journal of Nutrition in Gerontology and Geriatrics.* 2012, **31**(3), p.206.

198. Rossi, M. and La Vecchia, C. Flavonoids and the risk of ovarian cancer. *American Journal of Clinical Nutrition.* 2014, **100**(5), pp.1217-1219.

199. Cassidy, A. et al. Intake of dietary flavonoids and risk of epithelial ovarian cancer. *American Journal of Clinical Nutrition.* 2014, **100**(5), pp.1344-1351.

200. Luo, H. et al. Kaempferol induces apoptosis in ovarian cancer cells through activating p53 in the intrinsic pathway. *Food Chemistry.* 2011, **128**(2), pp.513-519.

201. Luo, H. et al. Kaempferol inhibits VEGF expression and in vitro angiogenesis through a novel ERK-NF kappa B-cMyc-p21 pathway. *Food Chemistry.* 2012, **130**(2), pp.321-328.

202. Hui, C. et al. Flavonoids, Flavonoid Subclasses and Breast Cancer Risk: A Meta-Analysis of Epidemiologic Studies. *PLoS ONE.* 2013, **8**(1), p.e54318.

203. Marijn Stok, F. et al. Dietary Behavior: An Interdisciplinary Conceptual Analysis and Taxonomy. *Frontiers in Psychology.* 2018, **9**(1689).

204. Hunter, D.J. and Reddy, K.S. Noncommunicable Diseases. *New England Journal of Medicine.* 2013, **369**(14), pp.1336-1343.

205. Kelly, M.P. et al. A conceptual framework for public health: NICE's emerging approach. *Public Health.* 2009, **123**(1), pp.e14-e20.

206. HM Revenue and Customs. Soft drinks industry levey: policy paper, 2016.

207. Golden, S.D. and Earp, J.A. Social ecological approaches to individuals and their contexts: twenty years of health education & behavior health promotion interventions. *Health Education & Behavior.* 2012, **39**(3), pp.364-372.

208. Al-Goblan, A.S. et al. Mechanism linking diabetes mellitus and obesity. *Diabetes, metabolic syndrome and obesity : targets and therapy.* 2014, **7**, pp.587-591.

209. Garg, S.K. et al. Diabetes and cancer: two diseases with obesity as a common risk factor. *Diabetes, Obesity & Metabolism.* 2014, **16**(2), pp.97-110.

210. Simone, V. et al. Obesity and Breast Cancer: Molecular Interconnections and Potential Clinical Applications. *The Oncologist.* 2016, **21**(4), pp.404-417.

211. Afshin, A. et al. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet.* 2019, **393**(10184), pp.1958-1972.

212. Pourhoseingholi, M.A. et al. How to control confounding effects by statistical analysis. *Gastroenterology and hepatology from bed to bench.* 2012, **5**(2), pp.79-83.

Chapter 2
Literature review

Abstract

Previously, one systematic review has been carried out which included studies having information on the associations between diet and the timing of menopause while no systematic review has been conducted in relation to the regular diet and the presence of VMS. Recently, the updated Continuous Update Project (CUP) report has been published, which systematically reviewed the relationships between diet and the risk of ovarian, endometrial and breast cancers. Therefore, in this chapter using PubMed, a search was conducted using relevant search strategies and inclusion criteria to update the current available literature. The search resulted to 13 pertinent studies for the association between diet and the onset of menopause, and 9 for diet and the presence of VMS. Moreover, 8 studies were considered for the relationship between diet and the risk of ovarian cancer, 13 for endometrial cancer risk and 28 for breast cancer risk. This literature search demonstrated that due to the methodological problems in the assessment tools used such as inconsistent adjustment of confounders across the studies, and the use of self-reported diet using food frequency questionnaires as well as insufficient follow-up time in each study, the findings for the associations between diet and the timing of menopause, presence of VMS as well as the risk of the hormone-related cancers remain inconclusive. The only exception was the relationship between alcohol intake and an increased risk of breast cancer which is in line with the CUP report. Thus, further observational studies are warranted to clarify these relationships.

2.1 Introduction

This section aims to provide a summary of key literature findings for the association between natural dietary components and age at menopause, the presence of VMS, as well as the risk of ovarian, endometrial and breast cancers. Given that only one systematic review has been conducted for the association between natural diet and age at menopause [1] and no systematic review was found which assessed the relationship between diet and the presence of VMS, this search included studies from 1946 until December 2018. Relevant studies have been summarised in Table 2.2 and Table 2.3.

As recently, the updated report of the Continuous Update Project (CUP) has been published [2] for the relationship between diet and risk of ovarian, endometrial and breast cancers, this search included studies post the end-point date of that systematic review as detailed in the section below. The report suggested limited/inconclusive results for the associations between a range of food items (e.g., vegetables, fruits, eggs, meat, poultry, cereals, etc.) and the risk of both ovarian and endometrial cancer. As for breast cancer, there was strong evidence that alcoholic drinks increase the risk. Consumption of non-starchy vegetables, dairy products, foods containing carotenoids and diet loaded with calcium are suggested to decrease breast cancer risk. However, association with other food items remain unresolved. Relevant studies identified through this search have been summarised in Table 2.5, Table 2.6 and Table 2.7. Given that these cancers have a strong hormonal pathogenesis; Table 2.4 summarises how menopausal status was used in the included studies. The aim of this literature review was to report primary research, that is, original research articles, relating to the main exposure (diet) and outcomes of interest for this thesis.

2.2 Methods

2.2.1 Search strategies

PubMed was the main search engine used to report evidence in this section, using the keywords or medical subject headings “age natural menopause”, “vasomotor symptoms”, “ovarian neoplasms”, “endometrial neoplasms”, “breast neoplasms” combined with “diet” (Appendix A). The papers were firstly screened by title and abstract to include the most relevant studies.

For evidence on the association between diet and onset of menopause as well as VMS, limits were set to include only humans, English, adult, female, and full texts to update the earlier review. Systematic reviews and meta-analyses were excluded to avoid the likelihood of having duplicate original research findings [3]. For evidence on diet and the hormone-related cancers, limits were also set to include only humans, English, adult, female, and full texts (Table 2.1). As the aim of this section was to report data post the latest systematic review recently published by the WCRF/AICR, studies with publication dates between January 1, 2013 to December 31, 2018 was included for ovarian and endometrial cancers, and May 1, 2015 to December 31, 2018 for studies on diet and breast cancer. To focus the findings on studies reporting evidence on the above outcomes and dietary exposures (natural diet), non-food containing exposures (e.g., acrylamide) and pharmacological exposures (e.g., supplements) were excluded. In addition, to include studies with less bias, such as recall of diet after the event, prospective studies and nested-case control studies were considered. Due to the limited number of studies on the association between natural diet and the onset of menopause as well as the presence of VMS, clinical trials, RCTs, case-control studies, and cross-sectional studies were also included. For the cancers, ≥200 cases were considered as having enough statistical power to observe any association [4]. However, given the small number of studies which explored the relationships between diet and the risks of breast, endometrial and ovarian cancers post the CUP report, studies with less than 200 cases were also considered.

Table 2.1 Search strategy - adapted from WCRF PubMed search strategy [5, 6]

Inclusion criteria
• Have to present results from an epidemiologic study of one of the following types: ❖ Randomized controlled trial ❖ Group randomized controlled trial (Community trial) ❖ Prospective cohort study ❖ Nested case-control study ❖ Case-cohort study • Must have as outcome of interest breast cancer (invasive) incidence or mortality in women • Have to present results on the relevant exposures • Published in English language • Included in Medline
Exclusion criteria
The articles to be excluded from the review: • Are out of the research topic • Do not report measure of relationship • The measure of relationship is only the mean difference of exposure • Are supplement to the main manuscript (e.g. Authors' Reply) • Are in-press • Are not in English language

2.2.2 Evaluation of study quality

The Newcastle–Ottawa scale (NOS) was used to assess the quality of the selected studies. The NOS is primarily used to determine the quality of case–control and cohort studies based on three parameters of quality: selection, comparability and exposure/outcome assessment [7]. The NOS allocates a maximum of four points for selection process, two points for comparability and three points for exposure or outcome of the study. The following scores was given to evaluate the quality of the studies: 0–3, 4–6, and 7–9 for low, moderate, and high quality studies, respectively (Appendix A). For cross-sectional studies, the NOS was adapted to assess the risk of bias [8]. Additionally, an adapted form of the Centre for Reviews and Dissemination (University of York) [9] was used to evaluate the risk of bias for RCTs [10].

2.3 Diet and timing of the onset of menopause

Thirteen publications that met the inclusion criteria were reviewed for this section. (Figure 2.1). These studies included analysis from eight prospective cohort studies, three cross-sectional studies, and one RCT (Table 2.2). Two big cohort studies were the Nurses' Health Study II and the Shanghai Women's Health Study. All studies had the onset of natural menopause as the outcome while two studies [11, 12] provided no information on the type of menopause (Table 2.2).

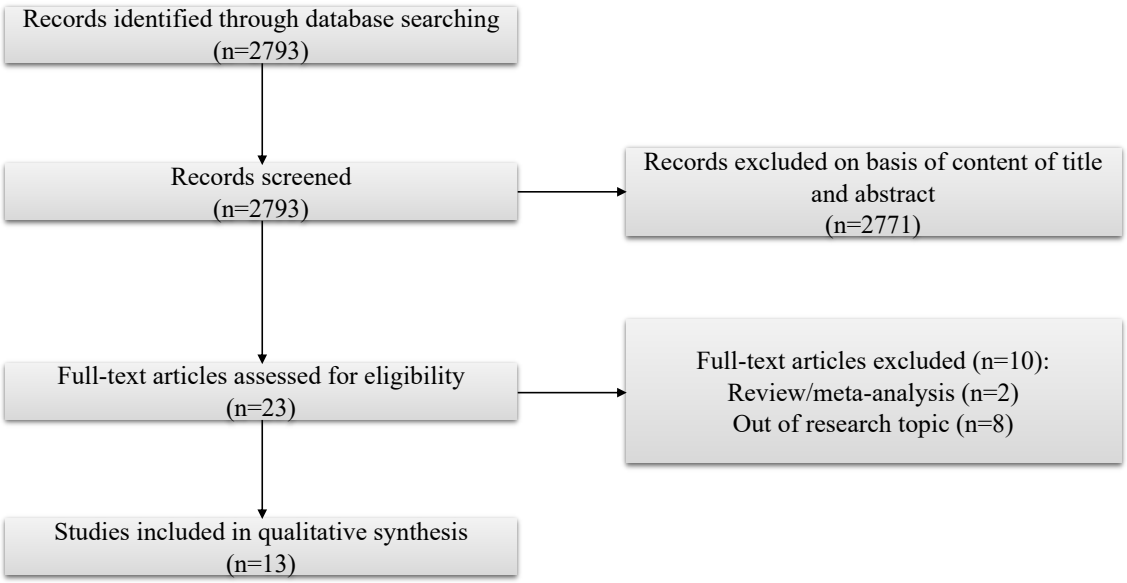

Figure 2.1 Flow diagram of selection process relating to diet and age at natural menopause

According to nine studies, foods such as meat, alcohol, dairy products, protein, and fat appeared to be associated with a delayed onset of menopause. On the other hand, few studies demonstrated no association between meat and alcohol consumption with the onset of natural menopause. For instance, in the cross-sectional study by Togerson et al. [11], meat was positively associated with the onset of menopause, but this could not be confirmed in their follow-up study. Findings on the association with carbohydrates, fruits and vegetables are conflicting. While Nagel et al. [13] and Wang et al. [14] demonstrated that consumption of fruits, and vegetables were related to an earlier onset of menopause, two prospective studies showed that these food items were associated with a later onset of menopause [15, 16]. In the EPIC-Heidelberg study [13], consumption of carbohydrates was associated with an earlier onset of menopause while in the Shanghai cohort [16], intake of carbohydrates was related with a later natural menopause. The only RCT [17] which investigated the influence of a dietary intervention on the timing of menopause demonstrated that this dietary intervention did not have any effect on the onset of menopause. This finding could be attributed to the selective nature of the study population such that the women included were at an increased risk of breast cancer and also had a median age at natural menopause of 54 years which is higher than that in prospective studies.

2.3.1 Discussion

These findings show that the relationship between diet and the onset of menopause remains unclear. Overall, the included prospective cohort studies were mostly of high quality based on the criteria of the NOS. On the other hand, the three included cross-sectional studies and the RCT were of poor methodological quality (Appendix A). The limited number of studies investigating this association and the quality of the included studies makes it difficult to confirm any relationship. In addition, the various definition of age at menopause used in the studies could also explain the differences in findings. For example, while some used the WHO's definition of menopause, that is, at least 12 consecutive months of amenorrhea [13, 16], and one study considered six months or more of amenorrhea [17]. Few studies relied on questions such as "Have you had your menopause" and "age of completion of menopause" [14, 18]. Two cross-sectional studies [11, 14] and one prospective study [12] did not adjust for potential confounders or no information was provided on the adjusted confounders, which may have introduced bias in an unpredictable direction. Most of the studies adjusted for key confounders such as

social class, physical activity, and smoking, as identified in Chapter 4. However, alcohol consumption which has also been associated with both diet [19] and onset of natural menopause [20] has not been controlled in some of the included studies.

Limitations of all the studies included potential recall bias for the dietary factors as these were assessed using self-reported FFQ in most studies except for the RCT which used a 3-day food diary to measure dietary intake of the participants. Weaknesses of FFQs has been elaborated in Chapter 8. In the Shanghai study [16], dietary intake was assessed at the start of the study which was after menopause had occurred, which questions the reliability of these findings. Furthermore, three of the studies were cross-sectional [11, 14, 21], thus are unable to understand dietary factors which precede the timing of menopause. However, the strengths of the studies include mainly the large sample sizes. The study in the Nurses' Health Study II also had a long follow-up time of 20 years whereby intakes of vitamin D and calcium were assessed five times. These studies also provide evidence from different populations such as Chinese, Japanese, Americans, Canadians, and Scottish. Yet, more studies investigating this relationship are required in particular in different countries. Thus, this will be explored in Chapters 4 and 5 of this thesis.

2.4 Diet and presence of vasomotor menopausal symptoms

The search from PubMed resulted to nine relevant studies (Figure 2.2), which included four RCTs, three prospective cohort studies, one case-control, and one surveillance study (Table 2.3). The cohort studies involved analysis from the Takayama Study (Japan), the Women's Health Across the Nation (US) and the Australian Longitudinal Study on Women's Health. The search also resulted to 15 RCTs which explored the influence of mainly soy isoflavones extracts on the presence of hot flushes. While some of the studies reported clinically significant associations, others found no evidence of an association.

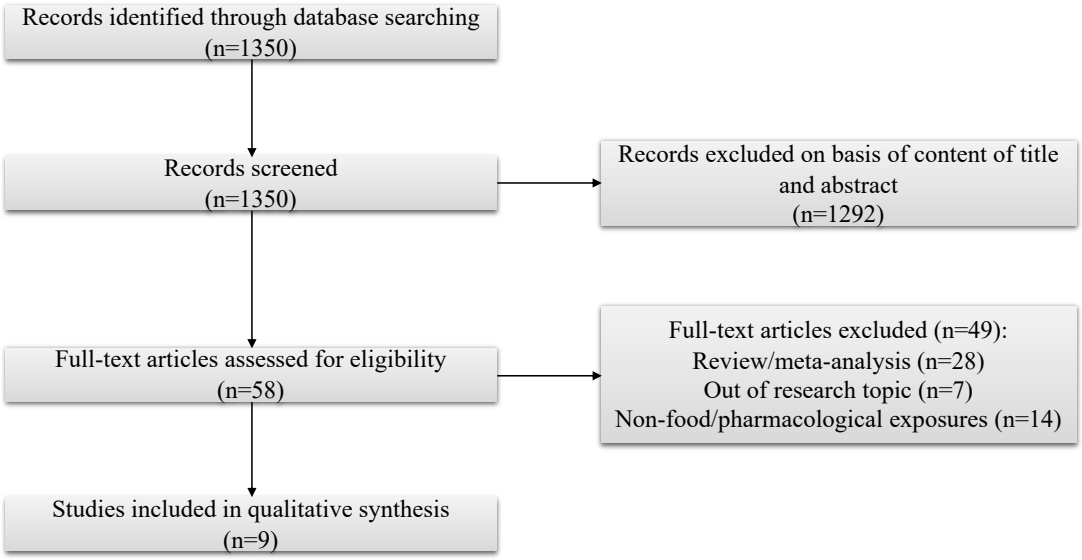

Figure 2.2 Flow diagram of selection process relating to diet and vasomotor menopausal symptoms

The dietary exposures considered across the studies were mainly soy products which are the most abundant source of isoflavones. According to the RCT among Australian postmenopausal women, a daily diet supplemented with soy flour significantly reduced hot flushes as compared to women who were consuming wheat flour [22]. Similarly, the prospective study among Japanese women demonstrated that a diet high in soy products, measured by both soy product intake and isoflavones content was inversely associated with hot flushes [23]. However, according to a more recent study among American women, none of the phytoestrogens (isoflavones, coumestrol, and lignans) intake appeared to be associated with hot flushes [24]. Another study among Japanese women enrolled at a hospital also did not suggest any association between dietary isoflavone intake from soy products and hot flushes [25].

Furthermore, flaxseed is the richest source of lignans. Three of the studies explored the effect of flaxseed on the presence of hot flushes [26-28]. All three RCTs found a reduction in the frequency of hot flushes among the intervention group, but the observed results were not significantly different from the placebo groups. Therefore, the effect of flaxseeds on hot flushes could not be demonstrated in these studies. Only one of the studies investigated the association between dietary patterns and VMS [29]. This prospective study among postmenopausal Australian women showed that consumption of a fruit rich diet or a Mediterranean diet was related to a decreased risk of reporting VMS.

2.4.1 Discussion

Overall, this search demonstrated that different study methods had been used to find the association between phytoestrogens and the presence of VMS. There were a limited number of studies considering the effect of natural dietary intake of phytoestrogens, in particular, the consumption of soy and soy products, one of the primarily sources of phytoestrogens has been explored in relation to the presence of VMS in only two prospective studies, indicating a gap in the literature. Therefore, this association will be further investigated in Chapter 6 using the InterLACE consortium.

The quality of the studies included were generally good. The three prospective studies and the case-control study yielded a score of 7 out of 9. Moreover, the methodological quality of two [26, 28] of the four RCTs was also satisfactory as they provided adequate amount of details on randomisation with suitable concealment of allocation. The inclusion criteria used were also reported as well as blinding of participants along with assessors were considered in these two studies which reduced the risk of bias. Moreover, strengths of the prospective studies were the use of validated FFQ for self-reported intakes and the quite long follow-up time. All three studies included premenopausal women at baseline and were followed through the menopausal transition, a period when the presence of VMS increases. Gold et al. [24] also included midlife women from four different racial/ethnic groups while the two other prospective studies were restricted to only one racial/ethnic group.

These studies also had limitations. One of the main weaknesses was that both the main exposure and outcome were self-reported which could have introduced potential bias in the studies. Yet, in the Australian Longitudinal Study [29] diet was measured at multiple time points which were an attempt to reduce this potential for bias. This was also the only study which examined the association between dietary patterns and the risk of VMS among middle-aged Australian women. Therefore, further studies in different populations are needed to confirm the observed findings. Furthermore, the RCT by Dodin et al. [26] did not include women with moderate and severe VMS due to the unwillingness of those participants and thus making the study's findings only relevant to women with mild symptoms. Three of the nine included studies did not report the confounders controlled for in the statistical analyses. The confounders adjusted for in the remaining studies were inconsistent which could explain the disparity in findings. Moreover, smoking status, an important confounder was considered in only two of the studies [29, 30].

Table 2.2 Evidence for the associations between diet and onset of menopause

Author, year	Study Design, sample size, duration	Intervention/exposure	Dietary assessment method	Adjusted confounders	Findings	
					Early	Late
Torgerson et al. 1994 [11]	Cross-sectional, n=2,074	Meat, alcohol	-	-	-	Meat Alcohol
Torgerson et al. 1997 [12]	Prospective, n=1,227	Meat, alcohol	-	-	-	Alcohol
Nagata et al. 1998 [21]	Cross-sectional, n=3,704	Total energy; macronutrients; cholesterol; calcium; crude fibre; vitamins A, C, D, E; carotene; soy product; retinol, coffee; alcohol	FFQ	Age, total energy intake	Soy products Coffee	Fat Cholesterol
Nagata et al. 2000 [15]	Prospective, n=1,130, 6 years	Energy, macronutrients, animal protein/fat, vegetable protein/fat, fat from fish, cholesterol, calcium, crude fibre, vitamin A, retinol, vitamin C, vitamin E, green and yellow vegetables, other vegetables, soy products	FFQ	Age, BMI, smoking, age at menarche	-	Green & yellow vegetable
Nagel et al. 2005 [13]	Prospective, n=5,568, 5.8 years	Macronutrients, alcohol, meat, dairy products, fish, vegetables, fruit, cereal products, fibre, soy products, sweets, added animal fat, added vegetable fat	FFQ	Age, education, OC use, HRT use, parity, BMI, breastfeeding, age at first pregnancy, smoking, alcohol intake, physical activity, total energy	Carbohydrate Vegetable Fibre Cereal products	Total fat Protein Meat
Martin et al. 2006 [17]	RCT, n=2,611	Low-fat high-carbohydrate diet	3-day food diary	Age, number of births, age at menarche, age at first child	-	-
Dorjgochoo et al. 2008 [16]	Prospective, n=33,054	Energy, macronutrients, vegetables, fruit, red meat, saturated fat, total soy, total fibre, tea, alcohol	FFQ	Age, education, occupation, age at menarche, number of live births, OC use, weight gain, smoking, physical activity, energy intake	-	Energy Fruits Protein Carbohydrate
Nagata et al. 2012 [31]	Prospective, n=3,115, 10 years	Energy, total fat, SFAs, PUFAs, MUFAs, long omega-3 FAs, dietary fibre, soy isoflavones, alcohol	FFQ	Age, BMI, smoking, parity, years of education, age at menarche, lifelong irregular menstrual cycle, physical activity	PUFA	-

Table 2.2 Continued

Author, year	Study Design, sample size	Intervention/exposure	Dietary assessment method	Adjusted confounders	Findings	
					Early	Late
Carwile et al. 2013 [18]	Prospective, n=46,059, 20 years	High-fat dairy, total low-fat dairy, skim milk, whole milk, dairy fat, dairy protein, calcium, vitamin D, lactose	FFQ	Energy, age at menarche, age at first birth, parity, physical activity, OC use, BMI, smoking, marital status, red meat and egg consumption	-	Low fat dairy Skim milk
Purdue-Smithe et al. 2017 [32]	Prospective, n=116,430, 20 years	Vitamin D, calcium intake from dairy and non-dairy sources	FFQ	age, smoking, BMI, age at menarche, parity, breast-feeding, physical activity, calories from vegetable protein, alcohol intake		Vitamin D from dairy sources Calcium from dairy sources
Boutot et al. 2017 [33]	Prospective, n=85,682, 20 years	Vegetable protein, animal protein, total protein, all meat, red meat, processed meat, chicken/turkey, seafood, eggs, soy/tofu, beans/lentils, peanuts, peas/lima beans, other nuts, peanut butter, pasta, dark bread, cold cereal	FFQ	smoking, BMI, age at menarche, breastfeeding, OC use, number of pregnancies ≥6 months, dairy protein, physical activity	-	Vegetable protein Pasta Dark bread Cold cereal
Wang et al. 2018 [14]	Cross-sectional, n=17,076	Meat, seafood, fresh eggs, soybean products, fresh fruits, dairy products, vitamins, minerals	FFQ	-	Seafood Fresh eggs Fresh fruits Vitamins	Meat
Purdue-Smithe et al. 2018 [34]	Prospective, n=116,429, 20 years	Low-fat dairy foods, high-fat dairy foods, total dairy	FFQ	age, smoking, BMI, age at menarche, parity, breast-feeding, kcal from vegetable protein, alcohol intake, current multivitamin use, vitamin D and calcium intake	-	Total dairy Low-fat dairy foods

Table 2.3 Evidence for the associations between diet and vasomotor menopausal symptoms

Author, year	Study design, sample size, duration	Age, menopausal status at baseline	Intervention/exposure	Dietary assessment method	Adjusted confounders	Findings
Murkies et al. 1995 [22]	RCT, n=58, 12 weeks	30-70 yrs, postmenopausal	Soy flour vs wheat flour	-	-	Soy flour: 40% reduction of hot flushes (p=<0.001) Wheat flour: 25% reduction of hot flushes (p=<0.001)
Nagata et al. 2001 [23]	Prospective, n=1,106, 6 years	35-54 yrs, premenopausal	Soy products	FFQ	Age, menopausal status	High vs low intake Soy products 0.47 (0.28–0.79) P_{trend}=0.005
Somekawa et al. 2001 [25]	Surveillance, n=478	44-80 yrs, postmenopausal	Dietary isoflavones in soy products	FFQ	-	No significant difference in hot flushes score between different isoflavones intake groups
Dodin et al. 2005 [26]	RCT, n=199, 12 months	45-65 yrs, peri- and post-menopausal	Flaxseed vs wheat germ placebo	3-day food diary	Age, weight, BMI	Significant reduction in hot flushes and night sweats with both flaxseed and wheat germ but no significant difference between groups
Schiling et al. 2005 [30]	Case-control, n=362 cases	45-54 years, pre- and peri-menopausal	Current alcohol consumer	Frequency questions	Age, smoking	Current alcohol use was associated with reduced risk of experiencing hot flushes (RR: 0.80, 95% CI: 0.71–0.91)
Lewis et al. 2006 [28]	RCT, n=87, 16 weeks	47-62 yrs, postmenopausal	Ground flaxseed muffins, soy flour muffins, wheat flour muffins	3-day food diary	BMI	No significant effect of hot flushes observed with neither dietary flaxseed or soy flour
Pruthi et al. 2012 [27]	RCT, n=188, 6 weeks	>18 yrs, postmenopausal	Flaxseed bar vs placebo	-	-	29% reduction in frequency of hot flushes in the flaxseed group vs 28% decrease in the placebo group. No significant difference between the groups
Gold et al. 2013 [24]	Prospective, n=3,303, 10 years	42-52 yrs, pre- and peri-menopausal	Dietary intakes of isoflavones, coumestrol, lignans, fibres	FFQ	Time varying oestrogen, day blood was drawn, age, menopause status, perceived stress, BMI, physical activity, education, marital status, number of premenstrual symptoms	High vs low intake Isoflavone 0.94 (0.69–1.27) P_{trend}=0.66 Coumestrol 0.93 (0.68–1.26) P_{trend}=0.67 Lignans 0.95 (0.70–1.29) P_{trend}=0.89 Fibre 1.40 (1.02–1.91) P_{trend}=0.08

Table 2.3 Continued

Author, year	Study design, sample size, duration	Age, menopausal status at baseline	Intervention/exposure	Dietary assessment method	Adjusted confounders	Findings
Herber-Gast et al. 2013 [29]	Prospective, n=6,040, 9 years	45-50 yrs, postmenopausal	Dietary patterns: 1) cooked vegetables, 2) fruit, 3) Mediterranean style, 4) meat and processed meat, 5) dairy, 6) high fat and sugar	FFQ	Time, age, education, occupation, marital status, BMI, physical activity, smoking, alcohol consumption, HT use, OC use, menopausal status, complementary and alternative medicine practitioners use, use of self-prescribed complementary and alternative medicine, total energy	High vs low intake Cooked vegetables 0.88 (0.77–1.01) P_{trend}=0.008 Fruit 0.81 (0.71–0.93) P_{trend}=0.001 Mediterranean style 0.80 (0.69–0.92) P_{trend}=<0.001 Meat and processed meat 1.03 (0.89–1.18) P_{trend}=1.00 Dairy 1.04 (0.92–1.19) P_{trend}=0.51 High fat and sugar 1.23 (1.05–1.44) P_{trend}=0.02

RCT: Randomised controlled trial

2.5 Diet and risk of ovarian cancer

This search resulted in eight studies which met the inclusion criteria (Figure 2.3). These included four prospective cohort studies, two nested case-control studies, one RCT and one pooled analysis of cohort studies (Table 2.5). The cohort studies included were the Nurses' Health Study (NHS), NHS II, Norwegian Women and Cancer Study, and the European Prospective Investigation into Cancer and Nutrition study (EPIC)/Netherlands Cohort Study (NLCS). The RCT was conducted among participants from the Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO). The two nested case-control studies involved participants from the Ovarian Cancer in Alberta and British Columbia Study and the African American Cancer Epidemiology Study.

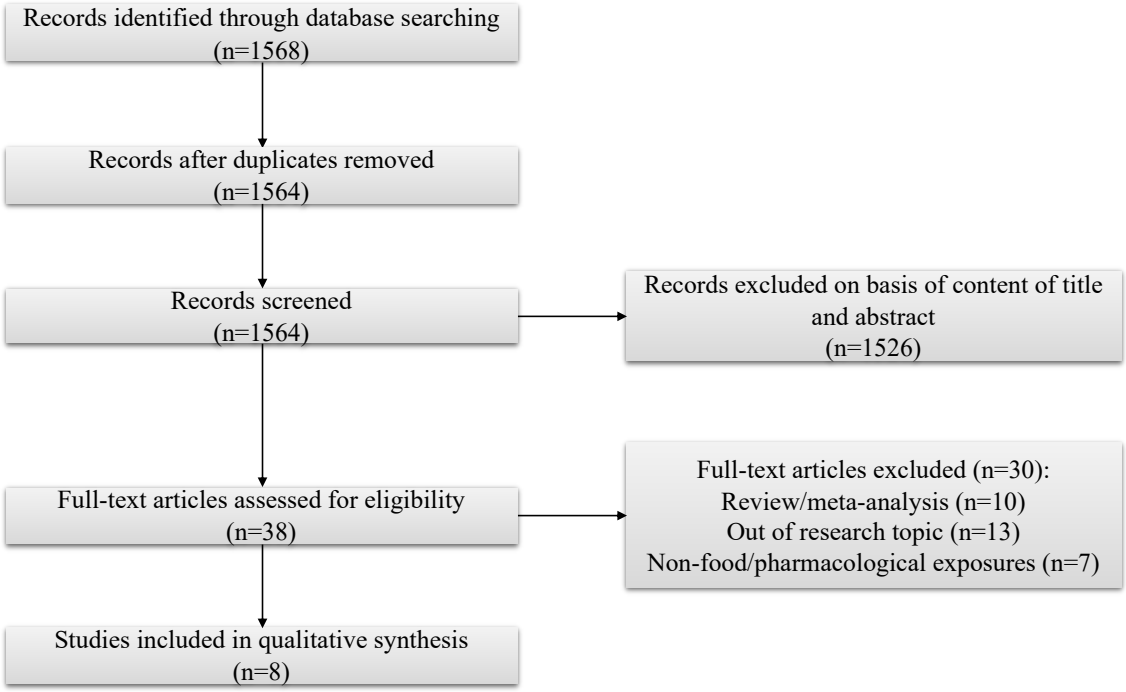

Figure 2.3 Flow diagram of selection process relating to diet and the risk of ovarian cancer

2.5.1 Dietary fat

Two studies evaluated the relationship between dietary fat intake and the risk of ovarian cancer. In the EPIC study [35] including 1,095 ovarian cancer cases demonstrated that in the multivariate model only PUFA was associated with an increased risk of cancer. No evidence of an association was found with consumption of total fat, animal or plant fat, saturated fat, cholesterol, monounsaturated fat, or fatty fish, and the risk of ovarian cancer. This study reported no significant associations between risk of serous and

endometrioid tumours in relation to the intake of total fat, fat subtypes and fat sources. In the pooled analysis including participants from the EPIC cohort as well as the NLCS, no association between intake of cholesterol and PUFA and ovarian cancer risk was reported [36]. However, the pooled estimate showed an increased risk of cancer with a high intake of saturated fat. Individual findings across the EPIC study population demonstrated that participants with a high intake of cholesterol, polyunsaturated fat, and saturated fat had a higher risk of epithelial ovarian cancer compared to those with a lower intake. In contrast, none of these four dietary components were found to be associated with the risk of ovarian cancer in the NLCS [36]. The differences observed between the individual findings from the EPIC and NLCS could be because the EPIC contributed to 1,095 cases while the NLCS contributed to only 383 cases. Differences in participants' characteristics could also be a determinant for the differences, given that women from the NLCS cohort were older and were all postmenopausal at enrolment.

2.5.2 Dairy products

Only two studies addressed the association between dairy consumption and the risk of ovarian cancer. Merritt et al. [37] demonstrated no evidence of an association between intake of total milk, dairy calcium, dairy fat, low-fat milk, and whole milk and ovarian cancer risk among all cancer cases, premenopausal cases or postmenopausal cases in the NHS. On the other hand, in a nested case-control study among African–American descent recruited into the African American Cancer Epidemiology Study, whole milk consumption was related to an increased risk while calcium intake was associated with a decreased risk of ovarian cancer [38]. This difference in results could mainly be because while the first study considered the cumulative average intake of the dairy products implying that dietary assessment was conducted at multiple time points, in the latter study diet was assessed only once. The case-control study was also prone to selection bias as compared to the prospective cohort study. Although these advantages of the NHS makes the study's findings more reliable, the generalisability of the results is debatable since the participants do not represent a random sample of U.S. women. Thus, the dietary and other lifestyle characteristics of the included women may not be compatible with the general population. Moreover, there could be racial/ethnic variations in the results since an association was observed in the African American Cancer Epidemiology Study as compared to the prospective study.

2.5.3 Coffee

Two studies also investigated the association between coffee consumption and the risk of ovarian cancer. In the Norwegian Women and Cancer Study which included 446 cancer cases reported no association between total coffee consumption and the risk of ovarian cancer when comparing the highest versus the lowest consumption group. Further analysis among never smokers also demonstrated no evidence of an association [39]. Similarly, according to the RCT including 162 postmenopausal cases of ovarian cancer no influence of coffee was found on the risk of ovarian cancer [40]. These findings are in line with a prospective cohort study and meta-analysis by Braem et al. [41] which also did not found any association between high coffee consumption and the risk of ovarian cancer.

2.5.4 Vitamins and wine

Only the study by Koushik et al. [42] reported the association between intake of vitamins A, C, and E and folate and the risk of ovarian cancer. This study pooled data from ten prospective cohort studies from North America and Europe accounting to a study population of 501,857 participants aged 27 to 93 years and included 1,973 ovarian cancer cases. The findings demonstrated no evidence of an association between dietary intake of these nutrients and ovarian cancer risk. However, higher vitamin intakes were associated with modestly higher risks of endometrioid tumours, but not with other histological types. Furthermore, the only study [43] reporting the relationship between wine intake and risk ovarian cancer found that total wine intake and red wine were both associated with a lowered risk of the overall cancer as well as with the serous histotype.

2.5.5 Discussion

Overall, most of the studies had sufficient cancer cases to explore the relationship between diet and ovarian cancer risk except for the RCT [40]. However, there was a limited number investigating this association of interest. While some of the studies considered the histological type of ovarian cancer, only one study presented the findings by menopausal status [37]. This search demonstrates the need for more observational studies to evaluate the role of diet in relation to ovarian cancer risk. Moreover, observational studies and pooled studies to assess associations by tumour subtype as well as RCTs of dietary exposures are warranted.

Overall, the included prospective cohort and case-control studies were of good quality as demonstrated by the NOS (Appendix A). However, the included RCT in this literature review was of poor methodological quality. The study provided insufficient information regarding randomisation, baseline characteristics of the intervention and control group, as well as details about reasons for withdrawal from the study were not given. Across all the included studies, important confounders such as education, smoking status, alcohol intake, age, menopausal status, and physical activity were included in the analyses but not all adjusted for the potentially important confounders. For instance, in the EPIC study [35], the authors argued that they excluded potential confounders such as smoking status, education level, duration of breastfeeding and physical activity as they did not modify the relative risk estimates by ≥10%. As demonstrated by previous studies, menopausal status can be independently associated with the risk of ovarian cancer, in particular, the risk increases post menopause [44, 45]. Although seven studies included both pre- and post-menopausal women at study entry (Table 2.4), only Merritt et al. [37] reported their findings stratified by menopausal status (pre vs post menopause). Therefore, observational studies exploring the risk of ovarian cancer in relation to diet by menopausal status are needed to confirm the findings. This association will be examined in Chapter 7 of this thesis.

The included studies had several limitations which led to no definite conclusions for the association between dietary factors and the risk of ovarian cancer. Firstly, most of the studies relied on self-reported FFQ for estimating dietary intake, leading to potential dietary misclassification and thus increasing the risk of misclassification bias. Interestingly in the EPIC study [35, 36], various dietary assessment methods such as FFQs, and food diaries were used as this cohort include participants from different European countries which could have led to a degree of systematic bias in the measurement of diet. However to counter the risk of distortions in the dietary measurement, standardised methods to calibrate the in-between country variations were applied [46]. Strengths of the included studies should also be acknowledged. These include the large sample sizes and thus greater statistical power to examine the associations with histological subtypes in some of the studies [35, 42, 43]. Yet they had limited power to examine the non-serous histologic subtypes such as the mucinous histotype. The studies also used various sources (e.g. participant self-report, medical records, cancer registry) to confirm the cancer diagnosis as well as the tumour stage and histological subtypes.

Table 2.4 Use of menopausal status in the included studies for the associations between diet and risk of ovarian, endometrial and breast cancers

Author, year	Cohort name	Dietary assessment method	Menopausal status at baseline		Results stratified by menopausal status	Menopausal status as a confounder
			Premenopausal	Postmenopausal		
Ovarian cancer						
Merritt et al. 2014 [37]	Nurses' Health Study (NHS) and NHSII	FFQ	X	X	X	X
Merritt et al. 2014 [35]	European Prospective Investigation into Cancer and Nutrition study	Dietary questionnaire, FFQ, food-diary	X	X		X
Hashibe et al. 2015 [40]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Diet history questionnaire		X		
Koushik et al. 2015 [42]	BCDDP, CPS II, IWHS, NLCS, NYSC, NYU, WHS, NHS (a), NHS (b), NHS II		X	X		X
Cook et al. 2016 [43]	Ovarian Cancer in Alberta and British Columbia Study	Frequency questionnaire	X	X		X
Lukic et al. 2016 [39]	Norwegian Women and Cancer Study	FFQ	X	X		X
Meritt et al. 2016 [36]	European Prospective Investigation into Cancer and Nutrition study/Netherlands Cohort Study	Dietary questionnaire, FFQ, food-diary	X	X		X
Qin et al. 2016 [38]	African American Cancer Epidemiology Study	FFQ	X	X		X
Endometrial cancer						
Arem et al. 2013 [47]	National Institutes of Health-AARP Diet and Health Study	FFQ		X		
Fedirko et al. 2013 [48]	European Prospective Investigation into Cancer	Dietary questionnaire	X	X	X	X
Inoue-Choi et al. 2013 [49]	Iowa Women's Health Study	FFQ		X		
Uccella et al. 2013 [50]	Iowa Women's Health Study	FFQ		X		
Brasky et al. 2014 [51]	Women's Health Initiative Observational Study and Clinical Trials	FFQ		X		
Coleman et al. 2014 [52]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Diet history questionnaire		X		
Gavrilyuk et al. 2014 [53]	Norwegian Women and Cancer Study	FFQ		X		
Je et al. 2014 [54]	Nurses' Health Study	FFQ	X	X	X	X

Table 2.4 Continued

Author, year	Cohort name	Dietary assessment method	Menopausal status at baseline		Results stratified by menopausal status	Menopausal status as a confounder
			Premenopausal	Postmenopausal		
Budhathoki et al. 2015 [55]	Japan Public Health Centre-based Prospective Study	FFQ	X	X		X
Canchola et al. 2015 [56]	California Teachers Study Cohort	FFQ	X	X		X
Yang et al. 2015 [57]	UK Million Women Study	FFQ	X	X		X
Hashibe et al. 2015 [40]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Diet history questionnaire		X		
Brasky et al. 2016 [58]	Black Women's Health Study	FFQ	X	X		
Breast cancer						
Farvid et al. 2015 [59]	Nurses' Health Study II	FFQ	X	X	X	X
Harris et al. 2015 [60]	Swedish Mammography Cohort	FFQ	X	X		X
Kiyabu et al. 2015 [61]	Japan Public Health Centre-based prospective study	FFQ	X	X		X
Romieu et al. 2015 [62]	European Prospective Investigation into Cancer and Nutrition	FFQ	X	X		X
Shin et al. 2015 [63]	Swedish Women's Lifestyle and Health study	FFQ	X	X		
Emaus et al. 2016 [64]	European Prospective Investigation into Cancer and Nutrition	Dietary questionnaire, FFQ, food-diary	X	X		X
Farvid et al. 2016 [65]	Nurses' Health Study II	FFQ	X	X	X	X
Farvid et al. 2016 [66]	Nurses' Health Study II	FFQ	X	X	X	X
Farvid et al. 2016 [67]	Nurses' Health Study II	FFQ	X	X	X	X
Gilsing et al. 2016 [68]	Netherlands Cohort Study—Meat Investigation Cohort	FFQ		X		
Harris et al. 2016 [69]	Nurses' Health Study II	FFQ	X	X	X	X
Hirko et al. 2016 [70]	Nurses' Health Study	FFQ	X	X		
Inoue-Choi et al. 2016 [71]	NIH-AARP Diet and Health Study	FFQ		X		
Jung et al. 2016 [72]	Pooled analysis of 20 cohort studies		-	-	-	-
Lukic et al. 2016 [39]	Norwegian Women and Cancer Study	FFQ	X	X		X

Table 2.4 Continued

Author, year	Cohort name	Dietary assessment method	Menopausal status at baseline		Results stratified by menopausal status	Menopausal status as a confounder
			Premenopausal	Postmenopausal		
Penniecook-Sawyers et al. 2016 [73]	Adventist Health Study-2	FFQ	X	X	X	X
Shin et al. 2016 [74]	Japan Public Health Centre-based Prospective Study	FFQ	X	X	X	X
Zhang et al. 2016 [75]	Nurses' Health Study, Nurses' Health Study II		X	X		
Ellingjord-Dale et al. 2017 [76]	Norwegian Breast Cancer Screening Program	Questionnaire	X	X		X
Kim et al. 2017 [77]	Nurses' Health Study II	FFQ	X	X		X
Kim et al. 2017 [78]	National Cancer Center, South Korea	FFQ	X	X	X	X
Kojima et al. 2017 [79]	Japan Collaborative Cohort Study	FFQ	X	X	X	
Makarem et al. 2017 [80]	Framingham Offspring cohort	FFQ	X	X		X
Narita et al. 2017 [81]	Japan Public Health Centre-based Prospective Study	FFQ	X	X	X	X
van den Brandt & Schulpen, 2017 [82]	Netherlands Cohort Study	FFQ		X		
Diallo et al. 2018 [83]	NutriNet-Santé cohort study	Web-based 24 h-dietary records	X	X	X	X
Fiolet et al. 2018 [84]	NutriNet-Santé cohort study	Web-based 24 h-dietary records	X	X	X	X

X=reported in the paper, BCDDP=Breast Cancer Detection Demonstration Project Follow-up Cohort, CPS II=Cancer Prevention Study II Nutrition Cohort, IWHS=Iowa Women's Health Study, NLCS =Netherland Cohort Study, NYSC = New York State Cohort, NYUWHS=New York University Women's Health Study, NHSa=Nurses' Health Study (a), NHSb=Nurses' Health Study (b), NHS II=Nurses' Health Study II

Table 2.5 Evidence for the relationship between diet and risk of ovarian cancer

Author, year	Study name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Merritt et al. 2014 [26]	Nurses' Health Study (NHS) and NHSII	Prospective cohort study N=164,599 Age: 25–55	28 yrs 764 cases (invasive & borderline)	Total caloric intake, number of pregnancies, parity, oral contraceptive pill use, menopausal status, tubal ligation, family history of ovarian cancer	>1 8oz glass/day vs <4 8oz glass/month Total milk 0.80 (0.57–1.13) P_{trend}=0.09 Low fat milk 0.76 (0.54–1.06) P_{trend}=0.05 0.74 (0.49–1.12) P_{trend}=0.13 0.77 (0.53–1.12) P_{trend}=0.14 Whole milk 1.29 (0.60–2.76) P_{trend}=0.33 1.06 (0.54–2.11) P_{trend}=0.93 0.83 (0.43–1.61) P_{trend}=0.43
Merritt et al. 2014 [27]	EPIC	Prospective cohort study N=325,007 Age: 25–70	Mean 11 yrs 1,095 cases	Ever use and duration of use of oral contraceptives, number of children, menopausal status at enrolment, total energy intake	High vs low intake Total fat 1.16 (0.96–1.40) P_{trend}=0.05 Plant fat 1.22 (0.98–1.52) P_{trend}=0.09 Animal fat 0.96 (0.80–1.15) P_{trend}=0.86 Saturated fat 1.17 (0.97–1.40) P_{trend}=0.15 Cholesterol 1.24 (0.97–1.58) P_{trend}=0.12 Monounsaturated fat 1.16 (0.93–1.44) P_{trend}=0.17 Polyunsaturated fat 1.22 (1.02–1.48) P_{trend}=0.02 Fatty fish 1.08 (0.89–1.31) P_{trend}=0.98
Hashibe et al. 2015 [31]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Randomized control trial N=50,563 Age: 55–74	10 yrs 162 cases	Age, sex, race, education, cigarette pack-years, alcohol drinking frequency	High vs low intake Coffee 1.17 (0.82–1.67) P_{trend}=0.398 Tea 0.87 (0.60–1.26)
Koushik et al. 2015 [32]	BCDDP, CPS II, IWHS, NLCS, NYSC, NYU, WHS, NHS (a), NHS (b), NHS II	Pooled analysis of cohort studies N=501,857 Age: 27-93	7-22 yrs 1,973 cases	Parity, oral contraceptive use, menopausal status, postmenopausal hormone use, age at menarche, BMI, physical activity, smoking status, total energy intake	High vs low intake Dietary vitamin A 1.03 (0.89–1.19) P_{trend}=0.51 Dietary vitamin C 0.97 (0.84–1.13) P_{trend}=0.40 Dietary vitamin E 0.95 (0.80–1.12) P_{trend}=0.24 Dietary folate 0.90 (0.7–1.05) P_{trend}=0.36
Cook et al. 2016 [33]	Ovarian Cancer in Alberta and British Columbia Study	Nested case-control study N=3,657 Age: 40->70	1,144 cases	Study site, age, oral contraceptive use, parity, current smoking, family history of ovarian or breast cancer	>2 times per month of wine All wine 0.72 (0.59–0.89) Red wine 0.59 (0.44–0.79)

Table 2.5 Continued

Author, year	Study name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Lukic et al. 2016 [30]	Norwegian Women and Cancer Study	Prospective cohort study N=104,080 Age: 30-70	6-8 yrs 762 cases	Smoking status, duration of education, BMI, physical activity level, alcohol consumption, area of residence, original hair color, number of moles larger than 5 mm, average number of sunburns per year, consumption of coffee brewed with two other methods	High vs low intake Total coffee 0.88 (0.67–1.14) P_{trend}=0.20 Filtered coffee 0.74 (0.53–1.02) P_{trend}=0.02 Instant coffee 1.45 (0.72–2.92) P_{trend}=0.39 Boiled coffee 0.87 (0.49–1.55) P_{trend}=0.72
Meritt et al. 2016 [28]	EPIC/Netherlands Cohort Study	Prospective cohort study N=327,220 Age: 25-70	Mean 11 yrs 1,478 cases	Total energy intake, oral contraceptive use, menopausal status, parity	Cholesterol 1.16 (0.8–1.51) PUFAs 0.97 (0.5–1.60) SFAs 1.21 (1.0–1.41) Bananas 0.94 (0.65–1.35)
Qin et al. 2016 [29]	African American Cancer Epidemiology Study	Nested case-control study N=1,146 Age: 20-79	490 cases	Age, region, total energy intake, education, parity, oral contraceptive use, menopausal status, tubal ligation, family history of breast/ovarian cancer, daylight hours spent outdoors in summer months, pigmentation, BMI, recreational physical activity	High vs low intake Total dairy 1.48 (0.95–2.28) P_{trend}=0.25 Milk 1.34 (0.87–2.05) P_{trend}=0.30 Whole milk 1.85 (1.05–3.27) P_{trend}=0.02 Low-fat milk 1.06 (0.66–1.70) P_{trend}=0.98 Cheese 1.25 (0.81–1.92) P_{trend}=0.34 Yoghurt 0.93 (0.67–1.28) P_{trend}=0.88

BCDDP=Breast Cancer Detection Demonstration Project Follow-up Cohort, CPS II=Cancer Prevention Study II Nutrition Cohort, IWHS=Iowa Women's Health Study, NLCS =Netherland Cohort Study, NYSC = New York State Cohort, NYUWHS=New York University Women's Health Study, NHSa=Nurses' Health Study (a), NHSb=Nurses' Health Study (b), NHS II=Nurses' Health Study II, EPIC = European Prospective Investigation into Cancer and Nutrition

2.6 Diet and risk endometrial cancer

Thirteen studies were identified through this search (Figure 2.4) after the latest CUP Report [2], 12 of which were prospective cohort studies and one RCT (Table 2.6). All the studies had over 200 endometrial cancer cases except for the Japanese study with 112 cases [55]. Six studies included both pre- and postmenopausal at the study entry while seven of the studies excluded premenopausal women (Table 2.4).

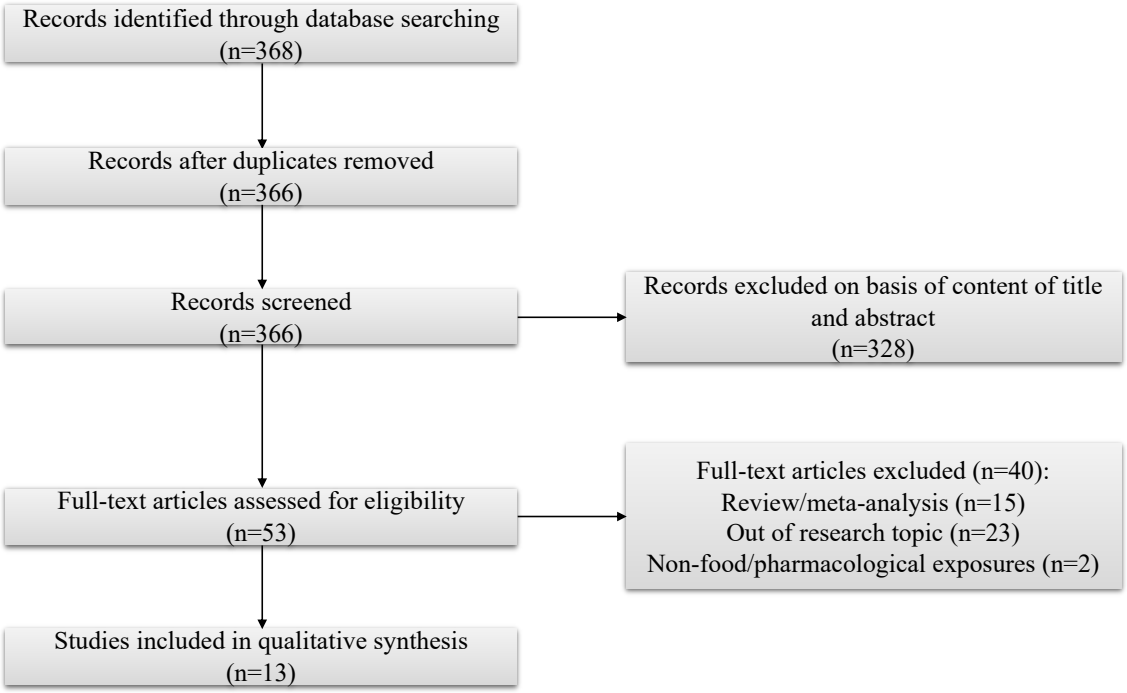

Figure 2.4 Flow diagram of selection process relating to diet and the risk of endometrial cancer

2.6.1 Fish

Three studies reported the association between consumption of fish and endometrial cancer risk. In a prospective study involving 111,356 participants aged 50-71 years and 1,486 endometrial cancer cases, no evidence of an association was found with high fish consumption [47]. Furthermore, Brasky et al. [58] demonstrated no effect on cancer risk with total fish, baked/boiled fish, tuna or fried fish consumption. On the other hand, findings from the Women's Health Initiative Observational Study and Clinical Trials which included 263 cancer cases, reported an increased risk of endometrial cancer with high consumption of total fish and baked/boiled fish as compared to women with low consumption [51]. No significant association was demonstrated with canned tuna, white fish, dark/oily fish, shellfish or fried fish. All three studies included US

women, but, one considered only African-American women [58] which could account for the observed differences in findings. In addition to other characteristic differences, the low number of cancer cases could also contribute to the differences in outcomes and the wide confidence intervals.

2.6.2 Alcohol

The relationship between alcohol consumption and the risk of endometrial cancer was explored in the EPIC study [48] and the NHS [54]. Findings from the EPIC study [48] showed no evidence of an association between alcohol consumption and the risk of endometrial cancer among all cancer cases, pre- or post-menopausal women. In contrast, the NHS [54] demonstrated that women who had light alcohol intake (approximately half drink per day) had a 22% reduced risk of cancer as compared to non-drinkers. However, when comparing high alcohol intake to light alcohol intake, the inverse association was attenuated after adjusting for potential confounders. The authors argued that although light alcohol consumption may have potential benefits against endometrial cancer, heavy intake may increase the risk. Moreover, consumption of beer, wine and liquor were not related to the risk of cancer in this study suggesting that the probable reduced risk cannot be ascribed to specific alcohol types. Limitations of this study were that drinkers were more likely to smoke and have a lower BMI. Although the authors adjusted for these factors, residual confounding could have still affected the estimates.

2.6.3 Coffee

The association between coffee consumption and the risk of endometrial cancer was evaluated in three prospective studies and one RCT. One of the prospective studies including 471 type I and 71 type II endometrial cancer cases among postmenopausal women demonstrated that caffeinated coffee was inversely associated with type I endometrial cancer [50]. Further analysis demonstrated that this reduced risk was observed only among obese postmenopausal women. The Norwegian Cancer Study also conducted among postmenopausal women, found that total coffee consumption decreased endometrial cancer risk among high coffee consumers as compared to low coffee consumers [53]. Similarly, in the RCT coffee consumption was associated with a 31% reduced risk of cancer (95% CI: 0.52, 0.91) [40]. However, findings from the UK Million Women Study which included 4,067 cases developed over an average follow-up of 9.3 years, showed no significant association between both tea and coffee consumption and the risk of endometrial cancer [57]. The number of cancer cases in the other three studies

as opposed to the UK Million Women Study could explain the differences in the observed findings. In addition, the study by Uccella et al. [50] stratified the outcomes by the type of endometrial cancer while the in the Norwegian study the risk of all cancer cases were explored in relation to coffee consumption [53].

2.6.4 Sugar-sweetened beverage

In a prospective study among postmenopausal women, Inoue-Choi [49] explored the relationship between sugar-sweetened beverage (SSB) and the risk of type I and II endometrial cancer. After 24 years of follow-up period, 506 type I and 89 type II incident endometrial cancer cases were identified. Consumption of SSB was associated with a 72% increased risk of type I cancer among high consumers in comparison to non-consumers. When consumption of SSB along with fruit juice was considered, there was a 38% higher risk of type I cancer among women in the highest quintile versus women in the lowest quintile. No association was observed for type II tumours given the small number of cases which reduced the statistical power for observing any possible association. In contrast, in the PLCO study Coleman et al. [52] reported that total sugar intake was protective against endometrial cancer risk. Likewise, total carbohydrate consumption and glycaemic load were inversely related to the cancer risk. These opposing findings could be due to the different and vast food sources (124 food items) that contributed to total sugar intake in the PLCO study while in the former study endometrial cancer risk was studied only in terms of SSB.

2.6.5 Others

Soy product consumption, given its high phytoestrogen content has also been explored in relation to endometrial cancer risk in a Japanese prospective study among postmenopausal women [55]. After an average follow-up time of 12.1 years, 112 women developed endometrial cancer. The findings of this study demonstrated no evidence of an association between soy product consumption and the risk of endometrial cancer. Furthermore, only one study investigated the relationship between dietary patterns and cancer risk. In this Californian teachers' cohort [56], no association was reported between plant-based, high protein/fat, high carbohydrates, ethnic or salad and wine patterns and risk of endometrial cancer.

2.6.6 Discussion

The studies included in this literature review explored the relationship between various food items, beverages and the risk of endometrial cancer. Two studies also considered the types of endometrial cancers and specific types of food sources (e.g. types of fish vs total fish) [51, 58]. Additional strengths of the studies include the prospective design, long duration of follow-up and most of the participants were retained at follow-up. The cancer cases were also unlikely to be biased as they were ascertained using primarily cancer registries as well as through medical records. Tumour stages and histological subtypes were confirmed by area hospitals, offices of pathologists, oncologists, and radiotherapists in relevant studies. Furthermore, most of the studies were also representative of the exposed cohort, thus increasing the generalisability of the findings. Using the NOS, out of the 14 prospective and case-control studies, nine were of high quality while four were of moderate quality and one was at high risk of bias (Appendix A).

However, limitations of these studies and the contrasting findings make any conclusion for the association between dietary factors and the risk of endometrial cancer difficult. Firstly, the small number of the types of endometrial cancer cases led to wide confidence intervals and also reduced statistical power to observe any association. Study of all cases versus the types of endometrial cancers could have also contributed to the observed disparities in findings. Moreover, dietary intake was assessed only at study entry, thus were unable to take into account changes in diet, in particular, over the long follow-up period. Additionally, only one study investigated the risk of endometrial cancer in relation to dietary patterns which indicates a gap in literature. The majority of included studies relied on self-reported FFQs for dietary assessment which is prone to dietary recall, as well as measurement errors. In particular, FFQ-derived nutrient data can be erratic. Moreover, none of the studies controlled for measurement errors in the analyses. Most of the studies controlled for key potential confounders such age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes. However, the studies also adjusted for intermediate variables, that is, one which is found on the causal pathway between the exposure and the outcome, which could have led to biased estimates [85]. Thus, these findings should be interpreted cautiously.

Table 2.6 Evidence for the relationship between diet and the risk of endometrial cancer

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Arem et al. 2013 [34]	National Institutes of Health-AARP Diet and Health Study	Prospective cohort study N=111,356 Age: 50–71	Mean 9.3 yrs 1,486 cases	Age, BMI, smoking status, total energy intake, other meat intake, age at menarche, age at first child's birth, parity, age at menopause, HT use, oral contraceptive use, diabetes, physical activity	High vs low intake Red meat 0.91 (0.77–1.08) P_{trend}=0.450 White meat 0.98 (0.83–1.17) P_{trend}=0.660 Processed meat 1.02 (0.86–1.21) P_{trend}=0.695 Fish 1.10 (0.93–1.29) P_{trend}=0.095
Fedirko et al. 2013 [35]	EPIC	Prospective cohort study N=301,051 Age: 20–85	Avg. 11 yrs 1,382 cases	Age at recruitment, physical activity level, smoking status and intensity, age at menopause and menopausal status, age at first menses, number of full-term pregnancies, BMI, hormone replacement therapy use, oral contraceptive use	High vs low intake Total alcohol 0.85 (0.61–1.18) P_{trend}=0.77* 0.82 (0.50–1.36) Ptrend=0.09** 0.70 (0.40–1.22) P_{trend}=0.55*** Wine 1.05 (0.82–1.35) P_{trend}=0.93* Beer 0.95 (0.72–1.24) P_{trend}=0.88* Liquor and spirits 1.11 (0.87–1.41) P_{trend}=0.71*
Inoue-Choi et al. 2013 [36]	Iowa Women's Health Study	Prospective cohort study N=23,039 Age: 55–69	24 yrs 592 cases	Age, smoking, physical activity, alcohol use, oestrogen use, age at menarche, age at menopause, number of live births, coffee intake	High vs low intake (Type I & Type II) Sugar-sweetened beverages 1.74 (1.27–2.38) P_{trend}=0.001 1.47 (0.69–3.12) P_{trend}=0.63 Fruit juice 1.18 (0.87–1.61) P_{trend}=0.09 1.06 (0.54–2.07) P_{trend}=0.73 Sugar-sweetened beverages + fruit juice 1.54 (1.12–2.12) P_{trend}=0.008; 1.17 (0.59–2.34) P_{trend}=0.62 Sugar-free beverages 0.80 (0.60–1.06) P_{trend}=0.35 0.87 (0.45–1.69) P_{trend}=0.97 Sweets/baked goods 1.08 (0.79–1.48) P_{trend}=0.40 0.58 (0.29–1.13) P_{trend}=0.19

Table 2.6 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Uccella et al. 2013 [37]	Iowa Women's Health Study	Prospective cohort study N=23,356 Age: 55–69	20 yrs 542 cases	Age, diabetes, duration of HT use, hypertension, age at menarche, age at menopause, quartiles of body mass index, waist-to-hip ratio, smoking status, pack years of smoking, total energy, alcohol use	High vs low intake (Type I & Type II) Total coffee 0.71 (0.51–0.99) P_{trend}=0.11 0.84 (0.33–2.12) P_{trend}=0.64 Caffeinated coffee 0.65 (0.47–0.89) P_{trend}=0.033 0.85 (0.37–1.93) P_{trend}=0.58 Decaffeinated coffee 0.76 (0.50–1.15) Pt_{rend}=0.53 1.08 (0.41–2.80) P_{trend}=0.93 Tea 0.95 (0.74–1.22) P_{trend}=0.55 1.26 (0.65–2.43) P_{trend}=0.46 Cola 1.08 (0.86–1.36) P_{trend}=0.55 1.42 (0.79–2.56) P_{trend}=0.16 Chocolate 0.94 (0.73–1.21) P_{trend}=0.47 1.79 (0.98–3.26) P_{trend}=0.085 Candy bars 0.96 (0.71–1.29) P_{trend}=0.76 1.71 (0.84–3.48) P_{trend}=0.087 Brownies 0.98 (0.68–1.40) P_{trend}=1.00 1.00 (0.38–2.58) P_{trend}=0.84
Brasky et al. 2014 [38]	Women's Health Initiative Observational Study and Clinical Trials	Prospective cohort study N=22,494 Age: 50–76	9 yrs 263 cases	Age, race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of oestrogen-only therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, total energy	High vs low intake Total Fish 2.28 (1.07–4.87) P_{trend}=0.010 Baked/boiled fish 1.72 (0.97–3.04) P_{trend}=0.015 Canned tuna/tuna casserole 1.26 (0.83–1.91) P_{trend}=0.195 White fish 1.33 (0.91–1.95) P_{trend}=0.109 Dark/oily fish 1.44 (0.96–2.17) P_{trend}=0.093 Shellfish, not fried 1.36 (0.86–2.15) P_{trend}=0.069 Fried fish/shellfish 0.89 (0.53–1.51) P_{trend}=0.890

Table 2.6 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Coleman et al. 2014 [39]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Prospective cohort study N=36,115 Age: 55–75	Median 9 yrs 386 cases	Age, BMI, age at menarche, age at menopause, race/ethnicity, oral contraceptive use, energy intake	High vs low intake Total carbohydrates 0.66 (0.49–0.90) P_{trend}=0.01 Starches 0.90 (0.67–1.19) P_{trend}=0.46 Total sugars 0.71 (0.52–0.96) P_{trend}=0.02 Fibre 1.13 (0.85–1.51) P_{trend}=0.53
Gavrilyuk et al. 2014 [40]	Norwegian Women and Cancer Study	Prospective cohort study N=97,926 Age: 30–70	Avg. 10.9 yrs 462 cases	Parity, smoking status, BMI, duration of OC and HRT use	High vs low intake Total coffee 0.52 (0.34–0.79) P_{trend}=0.003 Boiled coffee 0.45 (0.21–1.01) P_{trend}=0.07 Filtered coffee 0.55 (0.32–0.94) P_{trend}=0.07
Je et al. 2014 [41]	Nurses' Health Study	Prospective cohort study N=68,067 Age: 34–59	>30 yrs 794 cases	BMI, age at menopause, age at menarche, parity, age at last birth, duration of oral contraceptive use, postmenopausal hormone use, smoking status, physical activity, history of hypertension, total energy intake, coffee intake, other type of alcoholic beverages	High vs low intake Total alcohol intake 0.78 (0.49–1.25) P_{trend}=0.66* 0.64 (0.25–1.67) P_{trend}=0.45** 0.79 (0.58–1.08) P_{trend}=0.54*** Beer 0.35 (0.11–1.09) Pt_{rend}=0.08* Wine 1.00 (0.62–1.61) P_{trend}=0.49* Liquor 0.98 (0.64–1.51) P_{trend}=0.51*
Budhathoki et al. 2015 [42]	Japan Public Health Centre-based Prospective Study	Prospective cohort study N=49,121 Age: 45–74	Avg. 12.1 yrs 112 cases	Age, centre-area, BMI, physical activity, smoking, alcohol consumption, age at menarche, exogenous hormone use, number of deliveries, menopausal status and age at menopause, coffee intake, past history of diabetes mellitus and cancer	High vs low intake Soy food 1.11 (0.65–1.92) P_{trend}=0.63 Tofu 1.13 (0.65–1.93) P_{trend}=0.66 Miso soup 0.89 (0.50–1.60) P_{trend}=0.63

Table 2.6 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Canchola et al. 2015 [43]	California Teachers Study Cohort	Prospective cohort study N=75,093 Age: <85	Median 16.1 yrs 937 cases	Race and its interaction with time-dependent age, age at menarche, gravidity and age at last pregnancy and its interaction with time-dependent age, oral contraceptive use, physical activity, smoking status, height, caloric intake, the other four dietary patterns, BMI, menopausal status/hormone therapy use	High vs low score for dietary patterns Plant-based 0.91 (0.72–1.15) P_{trend}=0.68 High protein/fat 1.09 (0.84–1.42) P_{trend}=0.49 High carbohydrates 0.94 (0.69–1.28) P_{trend}=0.54 Ethnic 1.00 (0.81–1.23) P_{trend}=0.64 Salad and wine 1.23 (0.96–1.56) P_{trend}=0.23
Yang et al. 2015 [44]	UK Million Women Study	Prospective cohort study N=560,356 Age: 59 ± 5	Avg. 9.3 yrs 4,067 cases	Region, socioeconomic status, height, age at menarche, parity, duration of oral contraceptive use, age, menopausal status, duration of hormone therapy for menopause, BMI, smoking, alcohol consumption, strenuous exercise, tea consumption, other non-alcoholic fluid intake	High vs low intake Tea 1.01 (0.95–1.08) $P_{heterogeneity}$=0.6 Coffee 0.92 (0.82–1.03) $P_{heterogeneity}$=0.4
Hashibe et al. 2015 [31]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Randomized control trial N=32,392 Age: 55–74	10 yrs 254 cases	Age, sex, race, education, cigarette pack-years, alcohol drinking frequency	High vs low intake Coffee 0.69 (0.52–0.91) P_{trend}=0.009 Tea 1.24 (0.95–1.63)

Table 2.6 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Brasky et al. 2016 [45]	Black Women's Health Study	Prospective cohort study N=47,602 Age: 21–69	Median 18 yrs 282 cases	Age, time period, total energy intake, US region, education, BMI, physical activity, alcohol consumption, smoking, fruit consumption, vegetable consumption, age at menarche, age at menopause, parity, age at first birth, duration of combined hormone therapy, duration of oestrogen-alone hormone therapy, duration of oral contraceptive use, and diabetes	High vs low intake Total Fish 0.86 (0.56–1.31) P_{trend}=0.905 Baked/boiled fish 0.88 (0.58–1.34) P_{trend}=0.638 Tuna salad/tuna casserole 0.93 (0.61–1.40) P_{trend}=0.584 Fried fish/shellfish 1.08 (0.70–1.65) P_{trend}=0.436

* All cases, ** Premenopausal cases, *** Post-menopausal cases

2.7 Diet and risk of breast cancer

This search resulted to 28 prospective cohort studies (Figure 2.5, Table 2.7). All of the studies included both pre- and post-menopausal women at study baseline, except for one study which involved only postmenopausal women [82].

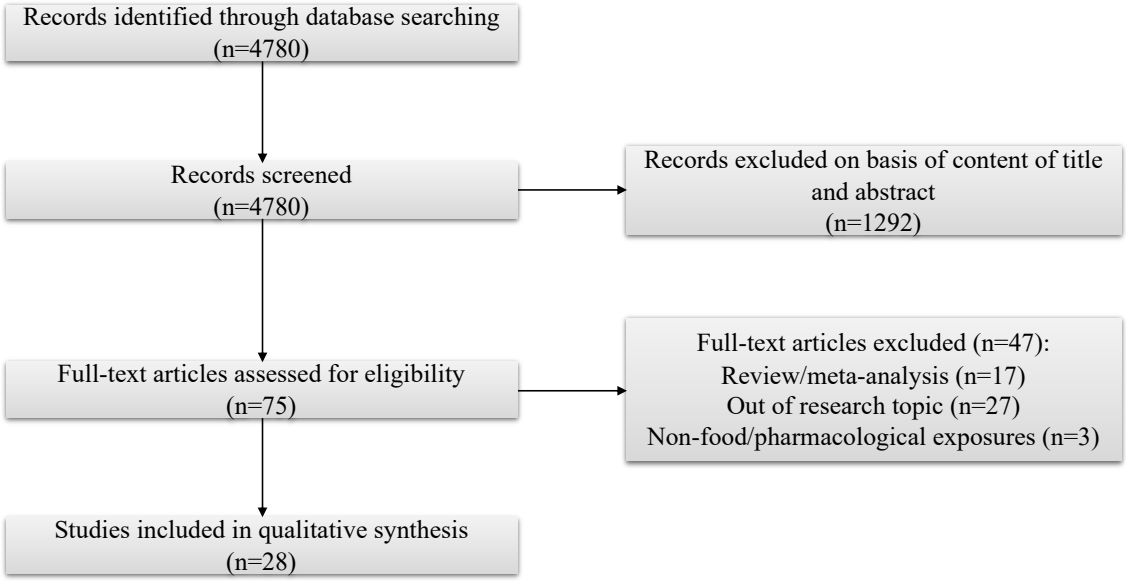

Figure 2.5 Flow diagram of selection process relating to diet and the risk of breast cancer

2.7.1 Alcohol

Six studies investigated the relationship between alcohol consumption and breast cancer risk. Findings from four studies reported an increased risk of breast cancer among high alcohol consumers. For instance, in a large EPIC study including 11,576 cases, alcohol intake was significantly associated with overall cancer cases [62]. Moreover, significant positive associations between alcohol intake and ER+/PR+, ER–/PR–, HER– and ER–/PR–HER– tumours were reported. Analysis of 2,760 cancer cases from the Nurses' Health Study [70] demonstrated that alcohol intake in particular increased the risk of luminal-A breast cancer. A similar association was reported by Ellingjord-Dale et al. [76]. These findings can further be supported by a pooled analysis of 20 prospective cohort studies which reported that alcohol intake was associated with all cancer cases as well as ER+ and ER– breast cancers [72]. On the other hand, findings from the Swedish study with 1,385 incident breast cancer demonstrated no association between alcohol intake and overall cancer cases as well as with the different tumour types [63]. Similarly, Kim et al. [77] reported no association between alcohol and breast cancer risk among high

alcohol consumers as compared to low consumers. These findings show clear evidence that high alcohol consumption could increase the risk for all breast cancer subtypes, supporting the CUP report findings [2].

2.7.2 Meat

In relation to meat intake, the NLCS with 312 breast cancer cases reported no relationship between intakes of red meat, beef, pork, chicken, processed meat and fish and the risk of breast cancer among postmenopausal women [68]. However, findings from the NIH-AARP Diet and Health Study [71] showed a 14% higher risk for localised breast cancer cases with higher intake of total processed meat. Moreover, total red meat consumption was associated with a 25% increased risk of the regional/distant types. The authors also reported a positive association between processed red meat intake and the risk of all breast cancer cases and in particular an increased risk of localised breast cancer. In a French prospective cohort study with 544 cases diagnosed over a median follow-up period of 4.1 years, an increased risk of breast cancer was demonstrated among high red meat consumers as well as red and processed meat consumers as compared to low consumers [83]. While two of the studies reported that red meat and processed meat were positively linked to breast cancer risk [71, 83], the NLCS reported a null association [68]. This is mainly due to the small number of cancer cases at the study end-point of the NLCS contributing to a reduced statistical power as compared to the two other prospective cohort studies which included a greater number of breast cancer cases. An additional strength of the French Cohort Study was the use of repeated 24h-dietary records based on a recent food composition database with over 3,300 food items. However, given that the study involved voluntary participants, this led to an overrepresentation of more health-conscious participants. Thus, caution should be taken when extrapolating these results.

2.7.3 Dietary patterns

Six studies were included that addressed the relationship between breast cancer risk and dietary patterns. In the NLCS—Meat Investigation Cohort [68] and the Adventist Health Study-2 [73], a vegetarian diet or low meat consumption did not reduce breast cancer risk when compared to meat eaters. Supporting these findings, two Japanese cohort studies also did not suggest an association between ‘prudent’ diet (high in vegetables, fruits, legumes, fish and poultry intakes) [74] or a ‘vegetable’ pattern [81] and breast cancer risk. On the other hand, according to the NHS which included 863 premenopausal and 614 postmenopausal breast cancer cases, a ‘prudent’ diet had a marginal inverse

(16%) association with premenopausal breast cancer and also lowered the risk of overall breast cancer [69]. In another cohort study including postmenopausal Dutch women [82], a 40% reduced risk of ER– was found with adherence to a Mediterranean diet.

In a Japanese centre-based prospective study which included 718 breast cancer cases, a 'Western' dietary pattern (high intake of bread, meat, processed meats, dairy products, soup, coffee, soft drinks, black tea, sauces, mayonnaise and dressing) was associated with an increased breast cancer risk among postmenopausal women [74]. An increased risk was also observed with ER+/PR+ tumours. In contrast, in another cohort study of Japanese pre- and post-menopausal women, an 'animal food pattern' which was highly loaded in meat, deep-fried foods, fried vegetables, fish paste, and salt-preserved fish, seemed to reduce the risk of breast cancer among premenopausal women [79]. While the former study used principal component analysis to derive dietary patterns, the latter study used factor analysis. Although these are different varieties of the same analysis, and thus have several similarities, they also have several differences [86]. Moreover, as both these analyses involve subjective decisions to determine dietary patterns; this could also explain the difference in findings. The 'animal' pattern was also highly loaded with fish and vegetables as compared to the 'Western' pattern.

2.7.4 Fruits, vegetables and fibre intake

In a study by Emaus et al. [64], compared to the lowest quintile, the highest quintile of total vegetable intake was associated with a 13% lower risk of breast cancer. There was no apparent association with fruits intake and also by hormone-receptor status. This study included 335,554 pre- and post-menopausal women and 10,197 cancer cases over a median 11.5-year period of follow-up. In another study by Farvid et al. [65], no association was found between breast cancer risk and total vegetable intake in either adolescence or early adulthood as well as with total fruit intake in early adulthood. However, total fruit intake during adolescence was significantly associated with a 25% lower risk of breast cancer among the highest intake compared to the lowest intake. Early adulthood consumption of fruits and vegetables rich in alpha-carotene was related with an 18% lower risk premenopausal breast cancer.

In the NHS [67] which involved 2,833 invasive breast cancer cases, total dietary fibre intake during both adolescence and early adulthood were associated with a lower risk of breast cancer among all women, and in particular among premenopausal women. Moreover, intakes of soluble and insoluble fibres were both associated with a lower

cancer risk. No evidence of an association was observed with the risk of breast cancer by hormone-receptor status. On the other hand, according to a Japanese centre-based prospective study, no associations were apparent between fibre intake and the risk of breast cancer [81]. Differences in the results were mainly because in the NHS fibre intake was determined from lifetime grain consumption and thus intake was assessed at multiple time-points while in the Japanese study diet was assessed only once. Moreover, in the Japanese study, the null association could be due to the small number of cases in the subtertile analysis.

2.7.5 Carbohydrates and glycaemic index

Farvid et al. [59] also examined the relationship between carbohydrate intake and breast cancer risk in the NHS. This study included 2,890 invasive cases diagnosed over a follow-up period of 20 years. The findings showed no evidence of an association between carbohydrate intake during both adolescence and early adulthood, and breast cancer risk. In addition, the authors reported no significant association between glycaemic index, glycaemic load, insulin load and insulin index scores, and breast cancer risk. Alternatively, findings from the Framingham Offspring Cohort Study [80] demonstrated that carbohydrate consumption in the highest compared to the lowest quintile was associated with a 41% lower breast cancer risk. Low glycaemic index foods were further associated with a lower risk. However, after adjustment for BMI and waist circumference, the relationship between total carbohydrates and breast cancer risk was mitigated, suggesting that these factors could explain the observation. In this Framingham Offspring cohort, participants with high carbohydrate intake also had lower BMI and waist circumference which could explain this inverse association while in the NHS, BMI was quite similar across the quintiles.

2.7.6 Soy products

The relationship between soy intake and breast cancer risk was investigated in two studies. According to findings from the Shanghai Women's Health Study [87] which involved 1,034 breast cancer cases, dietary soy protein intake in the highest versus the lowest quintile was significantly associated with a reduced risk for all breast cancer cases (22%) and also among premenopausal women (54%). Narita et al. [81] in contrast reported no association between fermented soy consumption and the risk of breast cancer.

2.7.7 Discussion

According to this search, except for alcohol, the relationship between other dietary factors and breast cancer risk remains unresolved given that some studies examined total intake while some considered specific foods (e.g., total vegetables vs green and yellow vegetables). Limitations of the included studies such as inconsistent adjustment for confounders could have also led to the differences in findings between the studies. In addition similar to the findings looking at the associations between diet and the risk of ovarian and endometrial cancers, in the included studies, only single time-point measurements of diet were evaluated, and thus were unable to account for changes in diet over time. Dietary changes over the life course may in particular be significant to cancer pathogenesis. For example, dietary habits during early years may lead to an earlier age at menarche while later diet in later life may be associated with a later onset of menopause which are both important risk factors of breast cancer. In addition to dietary changes during follow-up, measurement errors related to dietary assessment might have mitigated the association between diet and the risk of breast cancer. As explained in section 2.6.6, inconsistent adjustment of confounders across the different studies could have also led to contradictory findings.

Although the weaknesses of the included studies led to the inconsistent findings, strengths of the studies should also be acknowledged. These were the large sample size for most studies, a variety of dietary sources as the main exposure was explored and breast cancer risk was also stratified by menopausal status, intrinsic subtypes, and hormone-receptor status. However, three studies had less than 200 breast cancer cases which reduced the statistical power for observing any possible relationships [78-80]. Furthermore, the studies also lacked statistical power when breast cancer cases were stratified by menopausal or hormone-receptor status, which accounted for the wide confidence intervals. Another strength of the included studies was the use of validated FFQs for dietary assessment. The studies also had sufficient follow-up duration, retained the majority of participants at follow-up and were also representative of the exposed cohort which makes the results generalisable (Appendix A).

Table 2.7 Evidence for the association between diet and risk of breast cancer

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Farvid et al. 2015 [46]	Nurses' Health Study II	Prospective cohort study N=90,488 Age: 20–75	20 yrs 2,890 cases	Smoking, race, parity and age at first birth, height, BMI at age 18 years, weight gain since age 18, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, menopausal status, hormone use, age at menopause, adolescent alcohol intake, adult alcohol intake, adolescent energy intake	High vs low intake Carbohydrates 0.89 (0.79–1.00) $P_{trend}=0.07^{*}$ 0.87 (0.74–1.03) $P_{trend}=0.15^{**}$ 0.88 (0.72–1.09) $P_{trend}=0.56^{***}$
Harris et al. 2015 [47]	Swedish Mammography Cohort	Prospective cohort study N=37,004 Age: 39–76	15 yrs 1,603 cases	Age, energy intake, height, BMI, education, oral contraceptive use, hormone replacement therapy use, age at menarche, age at menopause, family history of breast cancer, history of benign breast disease, smoking status, physical activity, alcohol intake	High vs low intake Red meat 1.09 (0.91–1.31) $P_{trend}=0.76^{*}$ Legumes 0.96 (0.79–1.18) $P_{trend}=0.96^{*}$ Coffee 0.86 (0.72–1.04) $P_{trend}=0.16^{*}$ Whole grains 0.83 (0.69–1.00) $P_{trend}=0.04^{*}$
Hashibe et al. 2015 [31]	Prostate, Lung, Colorectal, and Ovarian cancer screening trial	Randomized control trial N=50,563 Age: 55–74	10 yrs 1,703 cases	Age, sex, race, education, cigarette pack-years, alcohol drinking frequency	High vs low intake Coffee 0.97 (0.87–1.08) $P_{trend}=0.638$ Tea 1.06 (0.95–1.18)
Kiyabu et al. 2015 [48]	Japan Public Health Centre-based prospective study	Centre-based prospective Study N= 38,234 Age: 45–74	Avg. 14.1 yrs 556 cases	Area, BMI, age at menarche, age at first birth, parity, menopausal age, menopausal status, use of exogenous female hormones, leisure-time physical activity, smoking status, alcohol intake, total energy-adjusted intake of isoflavones	High vs low intake Total fish 0.99 (0.77–1.28) $P_{trend}=0.79^{*}$ PUFA-rich fish 1.14 (0.88–1.48) $P_{trend}=0.50^{*}$

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Romieu et al. 2015 [49]	European Prospective Investigation into Cancer and Nutrition	Prospective cohort study N=334,850 Age: 35–70	Avg. 11 yrs 11,576 cases	Menopausal status, oral contraceptive, hormone replacement therapy, height, weight, interaction menopause and weight, smoking status, educational level, physical activity, age at first menses, age at first full term pregnancy, age at menopause, energy intake without alcohol intake	High vs low intake Alcohol 1.25 (1.17–1.35) P_{trend}= <0.001* 1.30 (1.15–1.48) P_{trend}=0.001 (ER+/PR+) 1.13 (0.88–1.43) P_{trend}=0.41 (ER+/PR–) 1.03 (0.57–1.86) P_{trend}=0.26 (ER–/PR+) 1.28 (1.01–1.61) P_{trend}=0.06 (ER–/PR–) 1.41 (1.17–1.68) P_{trend}=0.007 (HER2–) 0.97 (0.68–1.39) P_{trend}=0.83 (HER2+) 1.97 (1.23–3.16) P_{trend}=0.03 (ER–/PR–/HER2–)
Shin et al. 2015 [50]	Swedish Women's Lifestyle and Health study	Prospective cohort study N=45,233 Age: 30–49	1,385 cases	Educational attainment, history of breast cancer in mother and/or sister, smoking habits, age at menarche, parity, age at the first child birth, total breast feeding duration, oral contraceptive use	High vs low intake Alcohol 1.17 (0.90–1.53)* 1.11 (0.76–1.63) (ER+/PR+) 1.09 (0.53–2.25) (ER+/PR–) 1.04 (0.52–2.08) (ER–/PR–)
Baglia et al. 2016 [73]	Shanghai Women's Health Study	Prospective cohort study N=70,578 Age: 40–70	Median 13.2 yrs 1,034 cases	Age, body mass index, age at first live birth, physical activity, education, family history of breast cancer, season of recruitment, menopause (time-varying), total energy intake	High vs low intake Soy protein 0.78 (0.63–0.97) P_{trend}=0.007* 0.46 (0.29–0.74) P_{trend}=0.004** 0.90 (0.71–1.16) P_{trend}=0.15***
Emaus et al. 2016 [51]	European Prospective Investigation into Cancer and Nutrition	Prospective cohort study N=335,554 Age: 25–70	Median 11.5 yrs 10,197 cases	Energy intake, age at menarche, oral contraceptive use, age at first full-term pregnancy, menopausal status, hormone replacement therapy use, BMI, physical activity, smoking status and intensity, alcohol user, alcohol consumption, educational level	High vs low intake Total vegetables 0.87 (0.80–0.94) P_{trend}=<0.01* 0.90 (0.79–1.04) P_{trend}=0.13 (ER+/PR+) 0.81 (0.63–1.05) P_{trend}=0.07(ER+/PR–) 0.76 (0.58–0.98) P_{trend}=0.05 (ER–/PR–) Total fruit 0.99 (0.93–1.07) P_{trend}=0.86* 0.98 (0.86–1.10) P_{trend}=0.70 (ER+/PR+) 0.91 (0.73–1.14) P_{trend}=0.50 (ER+/PR–) 0.92 (0.73–1.16) P_{trend}=0.35 (ER–/PR–)

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Farvid et al. 2016 [52]	Nurses' Health Study II	Prospective cohort study N=97,813 Age: 27–44	22 yrs 3,235 cases	Race, family history of breast cancer, history of benign breast disease, smoking, height, BMI, weight change since age 18, age at menarche, parity, age at first birth, oral contraceptive use, alcohol intake, energy, hormone use, age at menopause, menopausal status	High vs low intake Fruit 0.96 (0.85–1.09) $P_{trend}=0.46^{*}$ 0.99 (0.84–1.17) $P_{trend}=0.94^{**}$ 0.91 (0.74–1.11) $P_{trend}=0.46^{***}$ Vegetables 0.97 (0.86–1.09) $P_{trend}=0.62^{*}$ 0.90 (0.76–1.06) $P_{trend}=0.67^{**}$ 0.97 (0.80–1.19) $P_{trend}=0.64^{***}$ Total fruit & vegetables 0.93 (0.82– 1.06) $P_{trend}=0.33^{*}$ 0.95 (0.80–1.12) $P_{trend}=0.87^{**}$ 0.97 (0.79–1.19) $P_{trend}=0.71^{***}$ Fruit juice 1.11 (0.99 –.25) $P_{trend}=0.13^{*}$ 1.12 (0.95–1.32) $P_{trend}=0.21^{**}$ 1.08 (0.89–1.30) $P_{trend}=0.68^{***}$
Farvid et al. 2016 [53]	Nurses' Health Study II	Prospective cohort study N=90,516 Age: 27–44	22 yrs 3,235 cases	Race, family history of breast cancer, history of benign breast disease, smoking, height, BMI, weight change since age 18, age at menarche, parity, age at first birth, oral contraceptive use, alcohol intake, energy, hormone use, age at menopause, menopausal status	High vs low intake Total whole-grain food 0.91 (0.81–1.02) $P_{trend}=0.11^{*}$ 0.88 (0.75–1.03) $P_{trend}=0.19^{**}$ 0.95 (0.78–1.16) $P_{trend}=0.45^{***}$ Total refined-grain food 0.89 (0.77–1.02) $P_{trend}=0.10^{*}$ 0.94 (0.78–1.14) $P_{trend}=0.57^{**}$ 0.86 (0.68–1.08) $P_{trend}=0.14^{***}$
Farvid et al. 2016 [54]	Nurses' Health Study II	Prospective cohort study N=90,534 Age: 27–44	20 yrs 2,833 cases	Race, family history of breast cancer, history of benign breast disease, smoking, height, BMI, weight change since age 18, age at menarche, Parity, age at first birth, oral contraceptive use, alcohol intake, energy, hormone use, age at menopause, menopausal status	High vs low intake Total fibre (early adulthood) 0.81 (0.72–0.91) $P_{trend}=0.002^{*}$ 0.77 (0.66–0.90) $P_{trend}=0.008^{**}$ 0.87 (0.70–1.07) $P_{trend}=0.29^{***}$ Total fibre (adolescence) 0.84 (0.70–1.01) $P_{trend}=0.04^{*}$ 0.76 (0.58–1.00) $P_{trend}=0.04^{**}$ 0.85 (0.64–1.13) $P_{trend}=0.16^{***}$

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Gilsing et al. 2016 [55]	Netherlands Cohort Study—Meat Investigation Cohort	Prospective cohort study N=11,082 Age: 55–69	Avg. 20.3 yrs 312 cases	Age, total energy intake, cigarette smoking, alcohol consumption, BMI, physical activity, level of education, family history of breast cancer, age menarche, age menopause, age first child, hormone replacement therapy, use of oral contraceptives, number of children	High vs low intake Total fresh meat 0.99 (0.74–1.34) $P_{trend}=0.76^{***}$ Fresh red meat 1.10 (0.82–1.48) $P_{trend}=0.97^{***}$ Beef 1.12 (0.82–1.51) $P_{trend}=0.15^{***}$ Pork 1.16 (0.85–1.58) $P_{trend}=0.77^{***}$ Minced meat 1.12 (0.81–1.54) $P_{trend}=0.59^{***}$ Chicken 0.93 (0.65–1.33) $P_{trend}=0.20^{***}$ Processed meat 1.31 (0.94–1.82) $P_{trend}=0.34^{***}$ Fish 1.18 (0.82–1.67) $P_{trend}=0.70^{***}$
Harris et al. 2016 [56]	Nurses' Health Study II	Prospective cohort study N=5,218 Age: 35–47	22 yrs 1,477 cases	Age, high-school total calories, height at age 18, age at menarche, BMI at age 18, physical activity in adolescence, family history of breast cancer, first birth/parity, oral contraceptive use, physical activity in adulthood, alcohol consumption, weight change since age 18, history of benign breast disease, menopausal status/age at menopause, hormone use	High vs low intake All cases Prudent 0.86 (0.73–1.02) $P_{trend}=0.04^{*}$ 0.86 (0.69–1.07) $P_{trend}=0.07$ (ER+/PR+) 0.85 (0.58–1.24) $P_{trend}=0.38$ (ER−/PR−) Western 0.99 (0.83–1.18) $P_{trend}=0.88^{*}$ 0.93 (0.74–1.18) $P_{trend}=0.73$(ER+/PR+) 0.94 (0.60–1.45) $P_{trend}=0.95$ (ER−/PR−) Fast food 0.99 (0.84–1.17) $P_{trend}=0.69^{*}$ 1.08 (0.87–1.35) $P_{trend}=0.80$ (ER+/PR+) 0.88 (0.57–1.35) $P_{trend}=0.48$ (ER−/PR−) Premenopausal cases Prudent 0.84 (0.67–1.04) $P_{trend}=0.07^{*}$ 0.84 (0.63–1.13) $P_{trend}=0.14$ (ER+/PR+) 0.82 (0.50–1.35) $P_{trend}=0.37$ (ER−/PR−) Western 1.03 (0.82–1.29) $P_{trend}=o.49^{*}$ 0.97 (0.71–1.32) $P_{trend}=0.85$ (ER+/PR+) 1.02 (0.57–1.81) $P_{trend}=0.60$ (ER−/PR−) Fast food 1.03 (0.83–1.29) $P_{trend}=0.71^{*}$ 1.17 (0.87–1.56) $P_{trend}=0.42$ (ER+/PR+) 0.85 (0.49–1.48) $P_{trend}=0.65$ (ER−/PR−)

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Hirko et al. 2016 [57]	Nurses' Health Study	Prospective cohort study N=105,972 Age: 30–55	2,760 cases	BMI, weight change since age 18, physical activity, parity/age at first birth, HRT, OC use, age at menarche, family history of breast cancer, benign breast disease diagnosis	High vs low intake Alcohol 1.24 (1.03–1.50) P_{trend}=0.001 (Luminal A) 1.08 (0.79–1.47) P_{trend}=0.21 (Luminal B) 1.63 (0.91–2.91) P_{trend}=0.20 (Her2) 0.66 (0.37–1.18) P_{trend}=0.08 (Basal-like) 0.54 (0.22–1.32) P_{trend}=0.45 (Unclassified)
Inoue-Choi et al. 2016 [58]	NIH-AARP Diet and Health Study	Prospective cohort study N=193,742 Age: 50–71	Avg. 9.4 yrs 9,305 cases	Age, race, BMI, height, education level, cigarette smoking, alcohol intake, physical activity, familial history of breast cancer, age at menarche, age at menopause, age at first live birth, number of live births, hormone use, oral contraceptive use, numbers of previous breast biopsy, total calorie intake, total fat intake, fibre intake, intake of other types of meat	High vs low intake Total meat 1.06 (0.99–1.13) P_{trend}=0.10* 1.00 (0.99–1.13) P_{trend}=0.83 (ER+/PR+) 0.87 (0.68– 1.11) P_{trend}=0.35 (ER−/PR−) Total processed meat 1.04 (0.97–1.12) P_{trend}=0.09* 0.96 (0.85–1.09) P_{trend}=0.94 (ER+/PR+) 1.01 (0.79–1.29) P_{trend}=0.91 (ER−/PR−) Total red meat 1.04 (0.97–1.13) P_{trend}=0.27* 0.97 (0.85–1.11) P_{trend}=0.59 (ER+/PR+) 0.95 (0.73–1.24) P_{trend}=0.47 (ER−/PR−) Fresh red meat 1.03 (0.96–1.11) P_{trend}=0.19* 1.04 (0.92–1.19) P_{trend}=0.50 (ER+/PR+) 1.03 (0.80–1.34) P_{trend}=0.93 (ER−/PR−) Processed red meat 1.09 (1.01–1.17) P_{trend}=0.05* 0.99 (0.87–1.13) P_{trend}=0.67 (ER+/PR+) 0.83 (0.64–1.09) P_{trend}=0.05 (ER−/PR−)
Jung et al. 2016 [59]	Pooled analysis of 20 cohort studies	Pooled analysis of cohort studies N=1,089273 Age: 18–104	6-18 yrs 37,191 cases	Ethnicity, education, BMI, height, physical activity, smoking, age at menarche, menopausal status, HRT, OC use, parity, age at first birth, family history, personal history of benign breast disease	High vs low intake Alcohol 1.32 (1.23–1.41) P_{trend}=<0.001* 1.35 (1.23–1.48) P_{trend}=<0.001 (ER+) 1.28 (1.10–1.49) P_{trend}=<0.001 (ER−) 1.36 (1.21–1.54) P_{trend}=<0.001 (PR+) 1.30 (1.16–1.46) P_{trend}=<0.001 (PR−)

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Lukic et al. 2016 [30]	Norwegian Women and Cancer Study	Prospective cohort study N=91,767 Age: 30–70	Avg. 13.1 yrs 9,675 cases	Menopausal status, smoking status, duration of education, BMI, physical activity level, alcohol consumption, parity, age at first birth, HRT, maternal history of breast cancer	High vs low intake Total coffee 0.87 (0.71–1.06) $P_{trend}=0.06^{*}$
Penniecook-Sawyers et al. 2016 [60]	Adventist Health Study-2	Prospective cohort study N=50,404 Age: 30–112	Mean 7.8 yrs 892 cases	Race, height, physical activity, family history of cancer, mammography in the last 2 years after age 42 years, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children, breastfeeding, educational level, smoking, alcohol, BMI	With reference to non-vegetarians Vegan 0.78 (0.58–1.05) $P_{trend}=0.09^{*}$ 0.77 (0.55–1.06) $P_{trend}=0.11^{***}$ 0.81 (0.38–1.70) $P_{trend}=0.58^{**}$ Lacto 1.05 (0.89–1.23) $P_{trend}=0.57^{*}$ 1.06 (0.89–1.26) $P_{trend}=0.53^{***}$ 0.96 (0.63–1.45) $P_{trend}=0.84^{**}$ Pesco 0.91 (0.71–1.17) $P_{trend}=0.48^{*}$ 0.85 (0.64–1.13) $P_{trend}=0.25^{***}$ 1.25 (0.75–2.10) $P_{trend}=0.40^{**}$ Semi 0.91 (0.67–1.23) $P_{trend}=0.52^{*}$ 0.73 (0.53–1.06) $P_{trend}=0.10^{***}$ 1.96 (1.12–3.43) $P_{trend}=0.019^{**}$ All vegetarians 0.97 (0.84–1.11) $P_{trend}=0.64^{*}$ 0.94 (0.80–1.09) $P_{trend}=0.40^{***}$ 1.12 (0.80–1.57) $P_{trend}=0.52^{**}$
Shin et al. 2016 [61]	Japan Public Health Centre-based Prospective Study	Prospective cohort study N=49,552 Age: 40–69	Avg. 14.6 yrs 718 cases	Age, public healthcare centre area, energy intake, BMI, smoking status, leisure-time physical activity, total physical activity, age at menarche, parity, menopause status, use of exogenous female hormones	High vs low intake Prudent 0.96 (0.75–1.23) $P_{trend}=0.93^{*}$ 0.83 (0.51–1.36) $P_{trend}=0.87^{**}$ 1.01 (077–1.34) $P_{trend}=0.70^{***}$ Westernised 1.32 (1.03–1.70) $P_{trend}=0.04^{*}$ 1.26 (0.81–1.96) $P_{trend}=0.59^{**}$ 1.29 (0.99–1.76) $P_{trend}=0.04^{***}$ Traditional 1.03 (0.80–1.32) $P_{trend}=0.69^{*}$ 1.22 (0.75–1.98) $P_{trend}=0.50^{**}$ 0.92 (0.69–1.23) $P_{trend}=0.24^{***}$

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Zhang et al. 2016 [62]	Nurses' Health Study, Nurses' Health Study II	Pooled analysis of cohort studies N=135,495 Age: 25–55	18-26 yrs 8,115 cases	Age, ethnicity, BMI, smoking status, physical activity, family history of cancer, multivitamin supplementation, total energy intake, consumption of fruit, vegetables, red meat, fish, nuts, whole grain, sugar-sweetened beverage, postmenopausal hormone use	High vs low intake Total rice 0.90 (0.70–1.16) P_{trend}=0.48*
Ellingjord-Dale et al. 2017 [63]	Norwegian Breast Cancer Screening Program	Nested case-control study N=344,348 Age: 50–69	4,402 cases	BMI, education, age at menarche, number of pregnancies, menopausal status, physical activity, smoking	High vs low intake Alcohol 1.14 (1.04–1.26) P_{trend}=0.01 (Luminal A-like) 1.05 (0.87–1.28) P_{trend}=0.46 (Luminal B-like HER2–) 1.23 (0.94–1.62) P_{trend}=0.14 (Luminal B-like HER2+) 0.68 (0.47–0.97) P_{trend}=0.03 (HER2+) 1.20 (0.93–1.57) P_{trend}=0.24 (Triple–)
Kim et al. 2017 [64]	Nurses' Health Study II	Prospective cohort study N=93,835 Age: 27–44	20 yrs 2,866 cases	Oral contraceptive use, the combination of parity and age at first birth, age at menarche, menopausal status, use of hormone therapy, BMI, personal history of benign breast disease, height, smoking status, red meat intake, folate intake	High vs low intake Alcohol 1.07(0.94–1.22) P_{trend}=0.39*

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Kim et al. 2017 [65]	National Cancer Center, South Korea	Prospective cohort study N=5,046 Age: >30	Mean 9.5 yrs 72 cases	Age, smoking status, education group, breast benign tumour history, BMI, family history of breast cancer, alcohol consumption, physical activity, age at menarche, parity, oral contraceptive use, hormone use and menopausal status, age at menopause	High vs low intake Cereals 0.95 (0.58–1.57)*; 1.15 (0.61–2.17)**; 0.53 (0.22–1.25)*** Salted vegetables & seafood 0.98 (0.61–1.58)*; 1.17 (0.65–2.09)**; 0.45 (0.18–1.14)*** Light-coloured vegetables 0.87 (0.54–1.38)*; 0.61 (0.35–1.09)**; 1.37 (0.55–3.39)*** Green-yellow vegetables 1.46 (0.91–2.33)*; 1.33 (0.75–2.36)**; 1.42 (0.62–3.30)*** Seaweed 1.06 (0.65–1.73)*; 0.76 (0.42–1.38)**; 1.73 (0.67–4.50)*** Fruit 1.22 (0.76–1.97)*; 1.23 (0.69–2.20)**; 1.22 (0.51–2.92)*** Grilled meat 1.77 (1.09–2.85)*; 1.36 (0.77–2.43**; 3.06 (1.31–7.15)*** Healthy protein foods 1.46 (0.91–2.34)*; 1.12 (0.63–2.00**; 2.28 (0.94–5.52)*** Dairy foods 1.32 (0.83–2.11)*; 1.20 (0.67–2.13)**; 1.56 (0.67–3.65)*** Bony fish 1.14 (0.71–1.83)*; 0.95 (0.53–1.69)**; 1.38 (0.55–3.46)*** Fried foods 1.19 (0.74–1.92)*; 1.00 (0.56–1.79)**; 1.78 (0.75–4.21)*** High-cholesterol foods 1.69 (1.01–2.82)*; 1.42 (0.75–2.67)**; 1.97 (0.81–4.80)*** Animal fat-rich foods 1.05 (0.64–1.71)*; 0.93 (0.52–1.67)**; 1.18 (0.47–2.99)*** Sweet foods 0.90 (0.56–1.45)*; 1.02 (0.56–1.86)**; 0.66 (0.27–1.57)*** Fast-foods 1.16 (0.70-1.90)*; 1.05 (0.58–1.89)**; 1.47 (0.58–3.71)*** Caffeinated drinks 0.90 (0.55-1.46)*; 1.07 (0.58–1.96)**; 0.56 (0.23–1.35)***

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
Kojima et al. 2017 [66]	Japan Collaborative Cohort Study	Prospective cohort study N=23,172 Age: 40–79	Median 16.9 yrs 119 cases	Age, area, tobacco smoking status, drinking status, family history of breast cancer, age at menarche, age at first birth, parity, energy intake, hormone therapy, daily walking, education, BMI	High vs low score Vegetable pattern 0.81 (0.35–1.89) $P_{trend}=0.61^{**}$ 0.93 (0.48–1.78) $P_{trend}=0.83^{***}$ Animal food pattern 0.42 (0.18–0.93) $P_{trend}=0.04^{**}$ 0.98 (0.48–1.99) $P_{trend}=0.83^{***}$ Dairy product pattern 1.20 (0.52–2.80) $P_{trend}=0.80^{**}$ 1.32 (0.70–2.49) $P_{trend}=0.19^{***}$
Makarem et al. 2017 [67]	Framingham Offspring cohort	Prospective cohort study N=3,184 Age: mean 54.4	Median 13.1 yrs 124 cases	Age, smoking, alcohol, energy, menopausal status, HRT, age at menopause, number of live births, BMI, waist circumference, height, pre-existing diabetes and CVD, antioxidant supplement use, education, physical activity	High vs low intake Carbohydrate 0.59 (0.36–0.97)*
Narita et al. 2017 [68]	Japan Public Health Centre-based Prospective Study	Prospective cohort study N=44,444 Age: 45–74	Avg. 14 yrs 681 cases	Age, area, BMI, age at menarche, age at first birth, parity, age at menopause, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, and total energy-adjusted intakes of fat, isoflavones, vitamin C, and carbohydrate	High vs low intake Total fibre 0.78 (0.55–1.09) $P_{trend}=0.15^{*}$ 0.62 (0.32–1.20) $P_{trend}=0.11^{**}$ 0.82 (0.56–1.22) $P_{trend}=0.48^{***}$ Soluble fibre 0.77 (0.55–1.06) $P_{trend}=0.20^{*}$ 0.82 (0.43–1.55) $Ptre_{nd}=0.47^{**}$ 0.74 (0.50–1.08) $P_{trend}=0.29^{***}$ Insoluble fibre 0.89 (0.64–1.24) $P_{trend}=0.47^{*}$ 1.02 (0.55–1.89) $P_{trend}=0.75^{**}$ 0.84 (0.57–1.24) $P_{trend}=0.51^{***}$ Fermented soybean 0.87 (0.69–1.10) $P_{trend}=0.68^{*}$ 0.84 (0.55–1.29) $P_{trend}=0.54^{**}$ 0.88 (0.66–1.16) $P_{trend}=0.92^{***}$ Rice 1.01 (0.78–1.31) $P_{trend}=0.75^{*}$ 1.44 (0.92–2.26) $P_{trend}=0.32^{**}$ 0.86 (0.63–1.17) $P_{trend}=0.34^{***}$

Table 2.7 Continued

Author, year	Cohort name	Study Design, sample size, Age	Follow-up & cancer incidence	Adjusted confounders	Relative risk/Hazards ratio/Odds ratio (95% CI)
van den Brandt & Schulpen, 2017 [69]	Netherlands Cohort Study	Prospective cohort study N=3,986 Age: 55–69	20.3 yrs 2,321 cases	Age, cigarette smoking, frequency, duration, height, BMI, physical activity, education level, family history of breast cancer in mother or sisters, history of benign breast disease, age at menarche, parity, age at first birth, age at menopause, oral contraceptive use, HRT, energy intake, alcohol intake	High vs low score Mediterranean diet 0.87 (0.72–1.06) P_{trend}=0.066* 0.87 (0.69–1.10) P_{trend}=0.101 (ER+) 0.60 (0.39–0.93) P_{trend}=0.032 (ER–) 0.90 (0.69–1.19) P_{trend}=0.378 (PR+) 0.72 (0.52–1.05) P_{trend}=0.047 (PR–) 0.91 (0.69–1.21) P_{trend}=0.400 (ER+PR+) 0.61 (0.36–1.01) P_{trend}=0.047 (ER–PR–)
Diallo et al. 2018 [70]	NutriNet-Santé cohort study	Prospective cohort study N=45,930 Age: 55–69	Median 4.1 yrs 544 cases	Age, sex, energy intake without alcohol, number of 24 h-dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, family history of cancers, lipids intake, fruits, vegetables, menopausal status, number of children	High vs low score Red meat 1.83 (1.33–2.51) P_{trend}=0.002* 2.04 (1.03–4.06) P_{trend}=0.4** 1.79 (1.26–2.55) P_{trend}=0.002*** Processed meat 1.05 (0.80–1.38) P_{trend}=0.4* 1.30 (0.79–2.15) P_{trend}=0.5** 0.95 (0.69–1.32) P_{trend}=0.7*** Red and processed meat 1.26 (0.93–1.71) P_{trend}=0.05* 1.05 (0.59–1.86) P_{trend}=0.8** 1.41 (0.99–2.01) P_{trend}=0.02***
Fiolet et al. 2018 [71]	NutriNet-Santé cohort study	Prospective cohort study N=81,420 Age: 18–73	Median 5 yrs 739 cases	Age, sex, energy intake without alcohol, number of 24 hour dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, family history of cancers, menopausal status, hormonal treatment for menopause, oral contraception, number of children, intakes of lipids, sodium, carbohydrates and Western dietary pattern	High vs low intake Ultra-processed food 1.13 (0.89–1.42) P_{trend}=0.2* 1.27 (0.88–1.83) P_{trend}=0.4** 1.38 (1.05–1.81) P_{trend}=0.02***

*All cases, **Premenopausal cases, ***Postmenopausal cases

2.8 Motivation for the research

Menopause is a natural phenomenon in a woman's life course and impacts the lives of women around the world. The current life expectancy of females in the UK is estimated to be 82.9 years [88], and the average age of menopause is 51 years [89]. British women are thus expected to spend around one-third of their life in the menopausal state. The timing for the onset of natural menopause is not the same for every woman. Several factors can influence its timing.

Genetic, behavioural, and environmental causes have been previously linked to the onset of natural menopause. Evidence shows that diet can also be linked to the timing of natural menopause (Table 2.2). However, very few studies have explored this association and have shown conflicting results, justifying the need for more prospective studies to elucidate the relationship between diet and the onset of natural menopause. Possible causes for these inconsistent results comprise disparities in methodology and socio-cultural differences among study populations. For instance, as mentioned in section 2.3, some studies have focussed on the analysis of individual foods and nutrients while others have considered food groups or total nutrient intake which makes drawing any conclusion impossible at present. As the study of single foods and nutrients are crucial in the understanding of the exact dietary factor associated with the onset of natural menopause, more observational studies looking these associations are warranted. This will be looked into in Chapter 4 of this thesis. Additionally, these inconsistent results, could also indicate that the relationship between all food groups referred in section 2.3 and the timing of onset of natural menopause deserves further research, especially oriented towards the analysis of dietary patterns rather than specific foods or nutrients. This is mainly because a group of different foods are eaten simultaneously rather than individually. Dietary patterns also account for the inter-relations as well as characterise the cumulative exposure to various food items [90]. Thus, the study of dietary patterns in addition to individual foods and nutrients in relation to the onset of menopause is equally essential. This will be explored in Chapter 5.

Furthermore, the age at which women reach menopause could also be a determinant for the duration of VMS. This subsequently has an impact on the quality of life of women which makes the study of possible ways to manage VMS important. As shown by this literature search, there is an indication that diet could modulate the frequency/severity of VMS. However, the limited number of observational study

investigating the relationship between the natural diet and the presence of VMS (Table 2.3), give ground to explore this association further. Therefore, the associations between diet and the presence of VMS will be investigated in Chapter 6.

The link between diet and cancer has been the interest of many during the recent years. However, many contradictory results have been published which explains the need for substantial evidence to show any association between diet and the risk of hormone-related cancers (ovarian, endometrial and breast cancer). According to previous studies, an association between timing of the onset of natural menopause and risk of the hormone-related cancers have also been reported. For instance, while an earlier menopause is linked to a higher risk of CVDs, osteoporosis and depression, it is also protective against some cancers such as breast, endometrial and ovarian cancer. Therefore, influencing the timing of natural menopause could potentially affect the risk of these cancers among mid-age women. Hence, these relationships will be further explored in Chapter 7 of this thesis.

Most of the studies (Table 2.5, Table 2.6, Table 2.7) investigating the association between diet and risk of ovarian, endometrial and breast cancer have adjusted for reproductive indicators but none have considered reproductive indicators as an effect modifier, that is, potentially having an effect on the causal pathway, between diet and risk of the gynaecological cancers. Even though studying the effect of age at natural menopause as a potential effect modifier would lead to loss of statistical power (as a result of sub-group analysis) [91], this could lead to some interesting findings. While some previous studies have stratified their findings by menopausal status, very few have considered a pre- or post-menopausal cancer. Given that premenopausal women have higher oestrogen levels than postmenopausal women; analyses will also be conducted by pre- and post-menopausal cancers to examine whether diet has a similar association between these two types of cancers (please refer to Chapter 7). As per our knowledge, this will be the first study to consider the influence of the relationship between diet and age at natural menopause on the incidence of ovarian, endometrial and breast cancer. This will also be the first study looking at the age of natural menopause and diet among women in the UK.

As explained in Chapter 1 using the NICE's conceptual framework (Figure 1.4, please refer to section 1.7), other than diet factors such as greater physical activity level and low or never smoking can be independently associated with the timing of natural menopause, the presence of VMS as well as the risks of ovarian, endometrial and breast cancers. Given that it is difficult to evaluate the extent to which other behaviours are

accurately controlled for in statistical models, it is impractical to attribute causality to the associations from observational studies. As demonstrated through this literature review, very few RCTs have investigated the outcome of interests of this thesis and the natural diet, which indicates the need for additional RCT evidence to determine causality as this study design is less prone to confounding bias. However, given the lengthy pathogenesis of the hormone-related cancers, as well as the prolonged process of menopause, trials of adequate follow-up time and sample sizes to observe any association, along with compliance of the participants, render RCTs costly and practically impossible to conduct. Thus, prospective studies become the most appropriate alternative to fill in the gap given that appropriate and consistent methodologies are used.

References

1. Moslehi, N. et al. Current Evidence on Associations of Nutritional Factors with Ovarian Reserve and Timing of Menopause: A Systematic Review. *Advances in Nutrition.* 2017, **8**(4), pp.597-612.
2. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. 2018. Available from: https://www.wcrf.org/sites/default/files/Summary-third-expert-report.pdf.
3. Daldrup-Link, H.E. Writing a review article - Are you making these mistakes? *Nanotheranostics.* 2018, **2**(2), pp.197-200.
4. Crane, T.E. et al. Dietary intake and ovarian cancer risk: A systematic review. *Cancer Epidemiology Biomarkers and Prevention.* 2014, **23**(2), pp.255-273.
5. Imperial College Team. *Continuous update of the epidemiological evidence on food, nutrition, physical activity and the risk of breast cancer*. Available from: https://www.wcrf.org/sites/default/files/breast-cancer-protocol.pdf
6. CUP Team and Imperial College London. *Continuous Update Project: epidemiological evidence on food, nutrition, physical activity and the risk of endometrial and ovarian cancers*. Available from: https://www.wcrf.org/sites/default/files/ovarian-cancer-protocol.pdf
7. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. 2011. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 12 August].
8. Hernandez, A.V. et al. Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis. *European Journal of Cancer.* 2015, **51**(18), pp.2747-2758.
9. Tacconelli, E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases.* 2010, **10**(4), pp.1-281.
10. Greenhalgh J. and Brown T. Quality assessment: Where do I begin? In: Boland A., Cherry M.G., Dickson R. (ed.) *Doing a systematic review - a student's guide*. 2nd ed. London: SAGE publications Ltd., 2017.

11. Torgerson, D.J. et al. Factors associated with onset of menopause in women aged 45–49. *Maturitas.* 1994, **19**(2), pp.83-92.
12. Torgerson, D.J. et al. Alcohol consumption and age of maternal menopause are associated with menopause onset. *Maturitas.* 1997, **26**(1), pp.21-25.
13. Nagel, G. et al. Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg. *Maturitas.* 2005, **52**(3-4), pp.337-347.
14. Wang, M. et al. Age at natural menopause and associated factors in adult women: Findings from the China Kadoorie Biobank study in Zhejiang rural area. *PLoS ONE.* 2018, **13**(4), p.e0195658.
15. Nagata, C. et al. Association of diet with the onset of menopause in Japanese women. *American Journal of Epidemiology.* 2000, **152**(9), pp.863-867.
16. Dorjgochoo, T. et al. Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. *Menopause.* 2008, **15**(5), pp.924-933.
17. Martin, L.J. et al. Intervention with a low-fat, high-carbohydrate diet does not influence the timing of menopause. *The American Journal of Clinical Nutrition.* 2006, **84**(4), pp.920-928.
18. Carwile, J.L. et al. Consumption of low-fat dairy products may delay natural menopause. *The Journal of Nutrition.* 2013, **143**(10), pp.1642-1650.
19. Kesse, E. et al. Do eating habits differ according to alcohol consumption? Results of a study of the French cohort of the European Prospective Investigation into Cancer and Nutrition (E3N-EPIC). *The American Journal of Clinical Nutrition.* 2001, **74**(3), pp.322-327.
20. Taneri, P.E. et al. Association of alcohol consumption with the onset of natural menopause: a systematic review and meta-analysis. *Human Reproduction Update.* 2016, **22**(4), pp.516-528.
21. Nagata, C. et al. Association of diet and other lifestyle with onset of menopause in Japanese women. *Maturitas.* 1998, **29**(2), pp.105-113.
22. Murkies, A.L. et al. Dietary flour supplementation decreases post-menopausal hot flushes: effect of soy and wheat. *Maturitas.* 1995, **21**(3), pp.189-195.
23. Nagata, C. et al. Soy product intake and hot flashes in Japanese women: results from a community-based prospective study. *American Journal of Epidemiology.* 2001, **153**(8), pp.790-793.

24. Gold, E.B. et al. Phytoestrogen and fiber intakes in relation to incident vasomotor symptoms: results from the Study of Women's Health Across the Nation. *Menopause.* 2013, **20**(3), pp.305-314.

25. Somekawa, Y. et al. Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. *Obstetrics and Gynecology.* 2001, **97**(1), pp.109-115.

26. Dodin, S. et al. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. *Journal of Clinical Endocrinology & Metabolism.* 2005, **90**(3), pp.1390-1397.

27. Pruthi, S. et al. A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause.* 2012, **19**(1), pp.48-53.

28. Lewis, J.E. et al. A randomized controlled trial of the effect of dietary soy and flaxseed muffins on quality of life and hot flashes during menopause. *Menopause.* 2006, **13**(4), pp.631-642.

29. Herber-Gast, G.C. and Mishra, G.D. Fruit, Mediterranean-style, and high-fat and -sugar diets are associated with the risk of night sweats and hot flushes in midlife: results from a prospective cohort study. *American Journal of Clinical Nutrition.* 2013, **97**(5), pp.1092-1099.

30. Schilling, C. et al. Current alcohol use is associated with a reduced risk of hot flashes in midlife women. *Alcohol and Alcoholism.* 2005, **40**(6), pp.563-568.

31. Nagata, C. et al. Associations of physical activity and diet with the onset of menopause in Japanese women. *Menopause.* 2012, **19**(1), pp.75-81.

32. Purdue-Smithe, A.C. et al. Vitamin D and calcium intake and risk of early menopause. *The American Journal of Clinical Nutrition.* 2017, **105**(6), pp.1493-1501.

33. Boutot, M.E. et al. Dietary Protein Intake and Early Menopause in the Nurses' Health Study II. *American Journal of Epidemiology.* 2017, pp.270-277.

34. Purdue-Smithe, A.C. et al. A Prospective Study of Dairy Food Intake and Early Menopause. *American Journal of Epidemiology.* 2018, pp.188-196.

35. Merritt, M.A. et al. Dietary fat intake and risk of epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiology.* 2014, **38**(5), pp.528-537.

36. Merritt, M.A. et al. Nutrient-wide association study of 57 foods/nutrients and epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition study and the Netherlands Cohort Study. *The American Journal of Clinical Nutrition.* 2016, **103**(1), pp.161-167.

37. Merritt, M.A. et al. Dairy food and nutrient intake in different life periods in relation to risk of ovarian cancer. *Cancer Causes and Control.* 2014, **25**(7), pp.795-808.

38. Qin, B. et al. Dairy, calcium, vitamin D and ovarian cancer risk in African-American women. *British Journal of Cancer.* 2016, **115**(9), pp.1122-1130.

39. Lukic, M. et al. Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study. *European Journal of Epidemiology.* 2016, **31**(9), pp.905-916.

40. Hashibe, M. et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. *British Journal of Cancer.* 2015, **113**(5), pp.809-816.

41. Braem, M.G. et al. Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. *American Journal of Clinical Nutrition.* 2012, **95**(5), pp.1172-1181.

42. Koushik, A. et al. Intake of vitamins A, C, and E and folate and the risk of ovarian cancer in a pooled analysis of 10 cohort studies. *Cancer Causes and Control.* 2015, **26**(9), pp.1315-1327.

43. Cook, L.S. et al. Adult lifetime alcohol consumption and invasive epithelial ovarian cancer risk in a population-based case-control study. *Gynecologic Oncology.* 2016, **140**(2), pp.277-284.

44. Beehler, G.P. et al. Risk of ovarian cancer associated with BMI varies by menopausal status. *Journal of Nutrition.* 2006, **136**(11), pp.2881-2886.

45. Shen, F. et al. The prevalence of malignant and borderline ovarian cancer in pre- and post-menopausal Chinese women. *Oncotarget.* 2017, **8**(46), pp.80589-80594.

46. Riboli, E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). *Annals of Oncology.* 1992, **3**(10), pp.783-791.

47. Arem, H. et al. A prospective investigation of fish, meat and cooking-related carcinogens with endometrial cancer incidence. *British Journal of Cancer.* 2013, **109**(3), pp.756-760.

48. Fedirko, V. et al. Alcohol drinking and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Annals of Epidemiology.* 2013, **23**(2), pp.93-98.

49. Inoue-Choi, M. et al. Sugar-sweetened beverage intake and the risk of type I and type II endometrial cancer among postmenopausal women. *Cancer Epidemiology, Biomarkers & Prevention.* 2013, **22**(12), pp.2384-2394.

50. Uccella, S. et al. Intake of coffee, caffeine and other methylxanthines and risk of Type I vs Type II endometrial cancer. *British Journal of Cancer.* 2013, **109**(7), pp.1908-1913.

51. Brasky, T.M. et al. Associations of long-chain ω-3 fatty acids and fish intake with endometrial cancer risk in the VITamins And Lifestyle cohort. *The American Journal of Clinical Nutrition.* 2014, **99**(3), pp.599-608.

52. Coleman, H.G. et al. Dietary carbohydrate intake, glycemic index, and glycemic load and endometrial cancer risk: A prospective cohort study. *American Journal of Epidemiology.* 2014, **179**(1), pp.75-84.

53. Gavrilyuk, O. et al. High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian women and cancer study: a population-based prospective study. *BMC Women's Health.* 2014, **14**, pp.1-10.

54. Je, Y. et al. Long-term alcohol intake and risk of endometrial cancer in the Nurses' Health Study, 1980-2010. *British Journal of Cancer.* 2014, **111**(1), pp.186-194.

55. Budhathoki, S. et al. Soy food and isoflavone intake and endometrial cancer risk: the Japan Public Health Center-based prospective study. *BJOG: An International Journal of Obstetrics and Gynaecology.* 2015, **122**(3), pp.304-311.

56. Canchola, A.J. et al. Dietary patterns and endometrial cancer risk in the California Teachers Study cohort. *Cancer Causes & Control.* 2015, **26**(4), pp.627-634.

57. Yang, T.O. et al. Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. *American Journal of Clinical Nutrition.* 2015, **101**(3), pp.570-578.

58. Brasky, T.M. et al. Associations of Dietary Long-Chain omega-3 Polyunsaturated Fatty Acids and Fish Consumption With Endometrial Cancer Risk in the Black Women's Health Study. *American Journal of Epidemiology.* 2016, **183**(3), pp.199-209.

59. Farvid, M.S. et al. Adolescent and Early Adulthood Dietary Carbohydrate Quantity and Quality in Relation to Breast Cancer Risk. *Cancer Epidemiology, Biomarkers & Prevention.* 2015, **24**(7), pp.1111-1120.

60. Harris, H.R. et al. An estrogen-associated dietary pattern and breast cancer risk in the Swedish Mammography Cohort. *International Journal of Cancer.* 2015, **137**(9), pp.2149-2154.

61. Kiyabu, G.Y. et al. Fish, n - 3 polyunsaturated fatty acids and n - 6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. *International Journal of Cancer.* 2015, **137**(12), pp.2915-2926.

62. Romieu, I. et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. *International Journal of Cancer.* 2015, **137**(8), pp.1921-1930.

63. Shin, A. et al. Alcohol consumption, body mass index and breast cancer risk by hormone receptor status: Women' Lifestyle and Health Study. *BMC Cancer.* 2015, **15**, p.881.

64. Emaus, M.J. et al. Vegetable and fruit consumption and the risk of hormone receptor-defined breast cancer in the EPIC cohort. *American Journal of Clinical Nutrition*. 2016, **103**(1), pp.168-177.

65. Farvid, M.S. et al. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. *British Medical Journal.* 2016, **353**, p.i2343.

66. Farvid, M.S. et al. Lifetime grain consumption and breast cancer risk. *Breast Cancer Research and Treatment.* 2016, **159**(2), pp.335-345.

67. Farvid, M.S. et al. Dietary Fiber Intake in Young Adults and Breast Cancer Risk. *Pediatrics.* 2016, **137**(3), p.e20151226.

68. Gilsing, A.M. et al. Vegetarianism, low meat consumption and the risk of lung, postmenopausal breast and prostate cancer in a population-based cohort study. *European Journal of Clinical Nutrition.* 2016, **70**(6), pp.723-729.

69. Harris, H.R. et al. Adolescent dietary patterns and premenopausal breast cancer incidence. *Carcinogenesis.* 2016, **37**(4), pp.376-384.

70. Hirko, K.A. et al. Alcohol consumption and risk of breast cancer by molecular subtype: Prospective analysis of the nurses' health study after 26 years of follow-up. *International Journal of Cancer.* 2016, **138**(5), pp.1094-1101.

71. Inoue-Choi, M. et al. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. *International Journal of Cancer.* 2016, **138**(7), pp.1609-1618.

72. Jung, S. et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *International Journal of Epidemiology.* 2016, **45**(3), pp.916-928.

73. Penniecook-Sawyers, J.A. et al. Vegetarian dietary patterns and the risk of breast cancer in a low-risk population. *British Journal of Nutrition.* 2016, **115**(10), pp.1790-1797.

74. Shin, S. et al. Dietary pattern and breast cancer risk in Japanese women: the Japan Public Health Center-based Prospective Study (JPHC Study). *British Journal of Nutrition.* 2016, **115**(10), pp.1769-1779.

75. Zhang, R. et al. Rice consumption and cancer incidence in US men and women. *International Journal of Cancer.* 2016, **138**(3), pp.555-564.

76. Ellingjord-Dale, M. et al. Alcohol, Physical Activity, Smoking, and Breast Cancer Subtypes in a Large, Nested Case-Control Study from the Norwegian Breast Cancer Screening Program. *Cancer Epidemiology, Biomarkers & Prevention.* 2017, **26**(12), pp.1736-1744.

77. Kim, H.J. et al. Alcohol Consumption and Breast Cancer Risk in Younger Women According to Family History of Breast Cancer and Folate Intake. *American Journal of Epidemiology.* 2017, **186**(5), pp.524-531.

78. Kim, J.H. et al. Dietary Factors and Female Breast Cancer Risk: A Prospective Cohort Study. *Nutrients.* 2017, **9**(12).

79. Kojima, R. et al. Dietary patterns and breast cancer risk in a prospective Japanese study. *Breast Cancer.* 2017, **24**(1), pp.152-160.

80. Makarem, N. et al. Carbohydrate nutrition and risk of adiposity-related cancers: results from the Framingham Offspring cohort (1991-2013). *British Journal of Nutrition.* 2017, **117**(11), pp.1603-1614.

81. Narita, S. et al. Dietary fiber intake and risk of breast cancer defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. *Cancer Causes & Control.* 2017, **28**(6), pp.569-578.

82. van den Brandt, P.A. and Schulpen, M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. *International Journal of Cancer.* 2017, **140**(10), pp.2220-2231.

83. Diallo, A. et al. Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Sante cohort study. *International Journal of Cancer.* 2018, **142**(2), pp.230-237.

84. Fiolet, T. et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. *British Medical Journal.* 2018, **360**, p.k322.

85. Schisterman, E.F. et al. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology (Cambridge, Mass.).* 2009, **20**(4), pp.488-495.

86. de Winter, J.C.F. and Dodou, D. Common Factor Analysis versus Principal Component Analysis: A Comparison of Loadings by Means of Simulations. *Communications in Statistics - Simulation and Computation.* 2016, **45**(1), pp.299-321.

87. Baglia, M.L. et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. *International Journal of Cancer.* 2016, **139**(4), pp.742-748.

88. Office for National Statistics. *Statistical bulletin: Adult smoking habits in Great Britain: 2014*. 2016. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2014 [accessed October 2018]

89. Sarri, G. et al. Diagnosis and management of menopause: summary of NICE guidance. *British Medical Journal.* 2015, **351**, pp.1-6.

90. Schulze, M.B. et al. Food based dietary patterns and chronic disease prevention. *British Medial Journal.* 2018, **361**, pp.1-6.

91. Glasser, S.P. *Essentials of clinical research.* Berlin: Springer, 2014.

Chapter 3
Comparison between diets of pre- and post-menopausal women from the UK Women's Cohort Study

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Abstract

Background: It is hypothesised that diet varies considerably according to menopausal status (pre or post). However, there is limited evidence describing the diet variability by menopausal status. This study thus aims to describe the diet of women in the UK Women's Cohort Study (UKWCS) at baseline by menopausal status.

Methods: Diet was measured using a 217-item food frequency questionnaire. Individual foods were collapsed into 64 food groups (g/day) according to culinary use, fat and fibre content. Overall dietary quality was assessed using the WHO Healthy Diet Index (HDI). Women were classified as premenopausal (≥1 menstrual period/year, using pills, pregnant; n=14,645) or naturally postmenopausal (no menstrual period during the last 12 months; n=17,813). Using data from 32,458 women, regression models adjusted for potential confounders were used to differentiate diet by menopausal status.

Results: In the adjusted model, postmenopausal women had higher intakes of protein, and fibre and lower intakes of saturated, polyunsaturated and monounsaturated fats than premenopausal women which were statistically significant. Postmenopausal women had a significantly higher consumption of low-fat dairy products, fish, meat, fruits, vegetables, soft drinks, and low-calorie soft drinks. Postmenopausal women also had significantly lower intakes of tea, alcohol, biscuits, refined pasta/rice compared to premenopausal women. Moreover, postmenopausal women had a higher HDI in comparison to premenopausal women (difference in mean=0.11, 99% CI: 0.02 to 0.20) after adjusting for age, total energy intake, smoking status, alcohol consumption, physical activity and social class.

Conclusion: These findings suggest that the diet of premenopausal women differs from that of postmenopausal women taking into account age and total energy intake. These differences suggest that pre-menopausal women may need to improve the quality of the diet, particularly regarding fruit and vegetable intake, to support maintenance of longer term health.

3.1 Introduction

Natural menopause is defined as the permanent cessation of menstruation as a result of ovarian ageing and signals the end of the reproductive potential. Several dynamic biological changes take place in the woman's body during the menopausal transition which can predict future health status [1]. Most commonly, intermediate effects of the menopausal transition which include a range of symptoms such as hot flushes, night sweats, mood changes, sleep disturbances, urogenital problems and sexual dysfunction affect several menopausal women [2, 3]. Further impacting the quality of life, menopause, in particular, the timing of menopause also contributes to later health outcomes in the postmenopausal years [4]. For instance, a later onset of menopause increases the risk of hormone-related cancers such as ovarian, endometrial and breast cancers. On the other hand, an earlier menopause is associated with a higher risk of cardiovascular diseases, osteoporosis and all-cause mortality [5].

The menopause transition period could thus be an opportunity for lifestyle changes among menopausal women. According to a 12-month intervention study which included 76 women, weight loss through a fat-reduced diet and a guided exercise program contributed to improved blood pressure, levels of triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, and glucose [6]. As previously evidenced, factors such as diet, physical inactivity [6], smoking [7] and alcohol consumption [8, 9] could increase the risk of certain health outcomes among postmenopausal women. Diet, in particular, may delay the appearance of risk factors and consequently predict a better overall health in this population group [6]. Having a healthy diet during the premenopausal years is equally crucial. As demonstrated in the Nurses' Health Study II which followed 88,804 women for 20 years, higher intake of animal fat during the premenopausal years was positively associated with incident breast cancer risk [10].

Therefore, this study aims to explore diet by menopausal status (pre vs post) among women who have experienced a natural menopause in the UK Women's Cohort Study (UKWCS).

3.2 Methods

3.2.1 Data collection

The UKWCS is a 20-year prospective study which aims to explore links between diet and chronic diseases, in particular, cancer [11, 12]. This study consists of 35,372 women (a 58% response rate) aged between 35 to 69 years, with a mean age of 52.3y (SD=9.4) at recruitment. The recruited participants were mainly from England, Scotland and Wales [13, 14]. Baseline data were collected between the years 1995 and 1998 via a postal questionnaire. Dietary assessment involved a detailed 217-item food frequency questionnaire (FFQ) which was derived from the FFQ based on the European Prospective Investigation into Cancer (EPIC) study [11, 12, 15]. Phase 2 data were collected on average 4 years later, between the years 1999 and 2002. Participants were required to complete a 4-day food diary as well as a 1-day activity and lifestyle questionnaire [12]. The UKWCS design allows the study of a range of dietary habits which is possible due to the large number of vegetarian participants (28% of the whole sample) as compared to other UK cohort studies [16-18].

For this cross-sectional analysis, the baseline dataset of the UKWCS was used whereby the mean age of the women was 48.8y (SD=5.8). The women were classified as being either premenopausal or postmenopausal (defined as no period in the last 12 months). To ensure that only participants who have had a natural menopause were considered as post-menopausal, the inclusion criteria were as follow: no period in the last 12 months; no hysterectomy; no bilateral oophorectomy; and excluded participants who were currently using pills and HRT. Women ≥40 and ≤65 years were considered to ensure that women who may have no menstruation due to other factors such as chemotherapy were excluded from the analysis. Women who were currently pregnant were excluded from the overall study. A sample of 32,458 participants was thus included for the final analyses.

3.2.2 Ethical approval

Ethical approval was obtained from 174 local ethics committees for this study [19]. Participants had consented to the use of information gathered at baseline, future phases, and cancer registries for research purposes provided that confidentiality was maintained. Moreover, the National Research Ethics Committee for Yorkshire and the Humber, Leeds East has recently taken on responsibility for the ongoing cohort [12].

3.2.3 Dietary assessment

Dietary assessment for the UKWCS involved a detailed 217-item food frequency questionnaire (FFQ) [12]. The 217 food items had 10 pre-coded classifications for the consumption frequency of the food items, ranging from 'never' to '6 or more times per day' [11]. Participants were asked to tick in the box to indicate the frequency of consumption for each food over the last 12 months. Any single missing items were assumed to have not been consumed [14].

In this study, the individual food items were initially collapsed into 64 food groups as shown in Table 3.1. These groupings were created based on the culinary uses, dietary fibre content or fat content. For example, starchy food items such as breads and breakfast cereals were grouped based on their fibre content, dairy products based on their fat content while fruits and vegetables were combined based on their culinary uses. Some individual food items were considered as it was inapt to integrate them into a specific food group (e.g., sauces, offal, oily fish, shellfish, bananas, tea, herbal tea, wines). Furthermore, all the vegetables were grouped under total vegetables, all fruits under total fruits and alcoholic drinks under alcohol. The individual food items were collapsed into food groups as it is unlikely that the participants consumed all the listed food items in the FFQ regularly but rather they may be likely to consume one or two food items from each food groups.

3.2.3.1 Nutrient intake

At baseline, the mean daily intake of vitamins such as vitamins C (mg), B1 (mg), B2 (mg), B6 (mg), B12 (µg), A (µg), D (µg) and E (mg) as well as minerals such as folate (µg), calcium (mg), non-haem iron (mg) and zinc (mg) had been previously estimated from the list of foods in the FFQ (described in 3.2.3) using SPSS syntax (SPSS Inc, Chicago, IL), which included nutrient values based on The Royal Society of Chemistry Food tables (version 5) [20]. Intake of haem iron was estimated using the percentage of haem iron present in meats, fish, and poultry available from the literature [21].

Table 3.1 Grouping of food items

Food Group	Food Items
Wholegrain products	Crispbread, Brown bread & rolls, Wholemeal bread & rolls ,
Refined grain products	White bread & rolls, Chapattis, Nan, paratha, Papadums, Tortillas, Pitta Bread, Cream crackers, cheese biscuits
Low fibre breakfast cereals	Cream crackers, cheese biscuits, Sugar coated cereals, Non-sugar coated cereals
High fibre breakfast cereals	Porridge, Readybrek , Muesli, All bran, bran flakes, Weetabix, shredded wheat
Plain Potatoes	Potatoes, Jacket potato
Potatoes with added fat	Chips, Roast potatoes, Potato salad
Refined pasta and rice	White pasta, Macaroni cheese, White rice
Wholegrain pasta and rice	Wholemeal pasta, Brown rice, Wild rice
Low fat dairy products	Low fat yoghurt, Diet yoghurt, Dairy desserts, Low-fat cheese, Cottage cheese, Milk puddings, Half fat milk, Fat free milk
High fat dairy products	Thick & creamy yoghurt, Greek yoghurt, Fromage frais/Crème fraiche, Single/sour cream, Double/clotted cream, Ice cream, Cheese, Cheese and onion pastie, Whole milk, Channel island milk, Dried milk
Butter and hard margarine	Butter, Block margarine
Margarine	Other soft margarine, Polyunsaturated margarine, Monounsaturated margarine
Low fat spreads	Low fat spread, Very low fat spread
High fat dressing	Mayonnaise, French type dressing
Low fat dressing	Low calorie salad cream
Soybean products	Soya cheese, Soya yoghurt, Soy milk
Textured vegetable protein	Textured vegetable protein
Pulses	Lentils, dals, Chick peas, chanas, Hummus, Baked beans, Mung beans & red kidney beans, Black eyed beans, Butter beans/broad beans
Eggs/eggs dishes	Boiled/poached egg, Omelette, scrambled egg, Fried egg, Quiche
Fish and fish dishes	Fish fingers/cakes, Fried fish in batter, White fish, Fish pie/fish lasagne, Fish roe
Oily fish	Oily fish
Shellfish	Shellfish
Red meat	Beef, Beef stew, Pork, Pork stew/casserole, Lamb, Lamb stew/casserole, Meat – lasagne/moussaka/ravioli
Poultry	Chicken/turkey, Breadcrumbed, Chicken/turkey in creamy sauce, curry
Processed meat	Bacon, Beefburger/hamburger, Ham, Corned beef, Sausages, Meat pizza, Pies/pasties/sausage rolls, Liver pate/sausage, salami
Offal	Offal
Total meat	Read meat, poultry, processed meat, offal

Table 3.1 Continued

Total vegetables	Vegetable dishes	Quorn, Vegetarian chilli, Mixed bean casserole, Stir-fry vegetables, Vegetable–lasagne/ moussaka/ ravioli, Vegetable pate, Vegetable pizza
	Allium	Leeks, Garlic
	Fresh legumes	Peas, mushy peas, mange-tout, Green beans
	Mediterranean vegetables	Sweetcorn, Courgettes, Olive, Aubergine, okra/ladies finger, Peppers
	Salad vegetables	Avocado, Lettuce, Cucumber, Celery, Coleslaw, Low calorie coleslaw
	Cruciferous vegetables	Broccoli, spring greens, kale, Cabbage, Cauliflower, Watercress, mustard & cress, Brussel sprouts
	Tomatoes	Tomatoes – raw/canned/sauce
	Mushrooms	Mushrooms
	Roots and tubers	Carrots, Parsnips, Turnip, Swedes, Beetroot
Total fruits	Stone fruits	Peaches, Plum, Mangoes, Nectarines, Apricots
	Deep orange/yellow fruits	Pineapple, Papaya, Melon
	Grapes	Grapes
	Citrus family fruits	Oranges, satsumas, grapefruit
	Rhubarb	Rhubarb
	Berries	Strawberries, Raspberries, Red currants/black currants, Kiwi fruit
	Bananas	Bananas
	Pomes	Apples, Pears
	Dried Fruits	Dates, Figs, Prunes, Mixed dried fruits, Currants, raisins, sultanas
Sauces		Sauces
Pickles/chutneys		Tomato ketchup, Pickles/chutney/pesto sauce
Soups		Packet soups, Other-vegetable soups, Other-Meat soups, Low calorie soups
Confectionery & spreads		Fruit bars, Chocolate snack bars, Mini chocolate snack bars, Boiled sweets, toffees, mints, Chocolate/chocolate & nut spread, Jam/marmalade, Honey
Nuts & Seeds		Peanuts/Pistachio nuts, Cashew nuts & almonds, Pecan nuts/ Walnuts, Sunflower seeds/ sesame seeds, Nut Pâté, Peanut butter, Peanuts/pistachio nuts, Mixed nuts and raisins
Savoury snacks		Crisps, Other fried snacks, Low fat or baked snacks, Bombay mix
Biscuits		Plain biscuits, Chocolate biscuits, Sandwich/cream biscuits
Cakes		Fruitcake, Sponge cake
Pastries and Puddings		Buns/pastries, Scones/pancakes/muffins/crumpets, Fruit pies, Sponge puddings
Tea		Tea
Herbal tea		Herbal tea
Coffee		Coffee – instant/ground, Coffee – decaffeinated
Other hot beverages		Cocoa, Horlicks, Ovaltine, Low calorie hot chocolate
Juices		Orange juice, Other – pure juices
Soft drinks		Fruit squash, Fizzy soft drinks
Low calorie/diet soft drinks		Low calorie/diet soft drinks
Alcohol		Wines
		Beer, Cider
		Port, sherry, liqueurs
		Spirits

3.2.3.2 Dietary quality

Dietary quality of pre and post-menopausal women were measured using the World Health Organisation (WHO) healthy diet indicator (HDI) scores which are based on the adherence of the WHO nutrition guidelines for the prevention of chronic diseases [22]. This dietary quality index has previously been used to assess the dietary quality of women in relation to their risk of breast cancer in the UKWCS, whereby the scoring method has been explicitly elaborated [23]. The HDI consist of 10 components: total fat, saturated fatty acids, polyunsaturated fatty acids, total carbohydrates, non-milk extrinsic sugars, non-starch polysaccharides, fruit and vegetables, protein, cholesterol, and salt [23]. A score of 1 was assigned if the recommended range for a component was met and a score of 0 was given if otherwise which tallied to a maximum score of 10 reflecting that the dietary recommendations/guidelines was met and a minimum score of 0 was assigned if the recommendations are not met (Table 3.2).

Table 3.2 Derivation of WHO Healthy Diet index [23]

	Indicator value	
	1	**0**
Total fat (% total E)	15-30	<15 or >30
Saturated fatty acids (% total E)	0-10	>10
Polyunsaturated fatty acids (% total E)	6-10	<6 or >10
Total carbohydrate (% total E)	55-75	<55 or >75
Non-milk extrinsic sugars (% total E)	0-10	>10
Non-starch polysaccharides (g)	>20	<20
Fruit and vegetables (g)	≥400	<400
Protein (% total E)	10-15	<10 or >15
Cholesterol (g)	<300	≥300
Salt (g)	<5	≥5

3.2.4 Statistical analysis

Descriptive statistics were used to explore the socio-demographic and reproductive history of the study population. Linear regression models were used to determine the relationships between menopausal status and the overall dietary quality, the food groups as well as nutrient intakes, first adjusting for age (years) and total energy intake (kcal/day) as a basic model (model 1). Total energy intake was included in the model in order to control for under and over-reporters. A directed acyclic graph (DAG) with menopausal status as the exposure (binary) and diet (continuous) as the outcome was used to establish the confounders (Figure 3.1). According to the minimally sufficient set of adjustments, a full model (model 2) adjusting for the confounders: smoking status

(current vs not current smoker), alcohol consumption (g/day), physical activity (MET-hours/week), and social class (routine and manual, intermediate, professional and managerial) in addition to model 1 was used. Ethnicity was also identified as a potential confounder, however, as the majority of participants in the UKWCS are White, ethnicity was not included in the model. For the associations between menopausal status and nutrient intakes, total energy intake was adjusted for the non-energy-containing nutrients such as the vitamins and minerals. Women were excluded if they had extremely high (>6000 kcal/day) or low (<500 kcal/day) energy intake) and energy from other macronutrients was adjusted for specific macronutrients. Assumptions for linear regression were checked by plotting the residuals against fitted values which showed a constant variance and a histogram demonstrated a normal distribution of the residuals. Stata version 15 was used for the analyses. A *p* value less than 0.01 was considered as statistically significant, to take account of multiple testing.

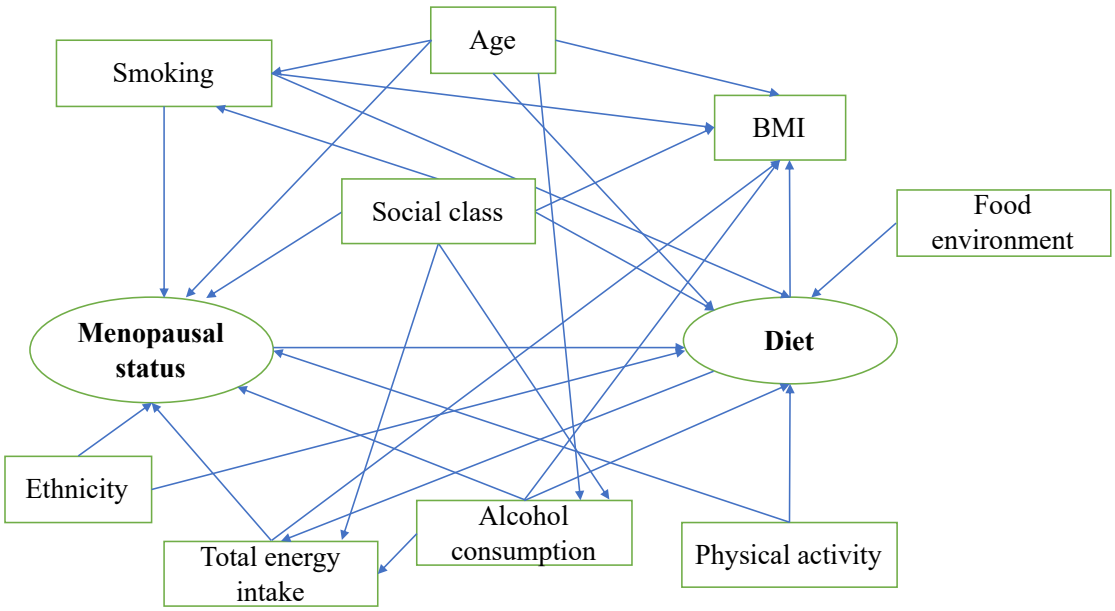

Figure 3.1 Directed Acyclic Graph to determine potential confounders

3.3 Results

3.3.1 Characteristics of participants

Pre-menopausal and post-menopausal women in this study had a mean age of 44.6 years (n = 14,645) and 59.1 years (n = 17,813) respectively (Table 3.3). The mean BMI of pre-menopausal women was at the borderline of the BMI cut-off value for normal weight (<25.0 kg/m^2) while the mean BMI for post-menopausal women was in the overweight category (≥25.0–30.0 kg/m^2). Compared to postmenopausal women, premenopausal women reported physical activity for a longer duration (14.3 mins/day vs 16.2 mins/day). Alcohol consumption was reportedly higher among premenopausal women (9.6 g/day) as compared to postmenopausal women (7.8 g/day). Overall, the majority of women in this study never smoked; 11.4% premenopausal and 10.3% postmenopausal women reported that they were current smokers. Furthermore, in this study population, the majority of women were married, educated and were mainly from the professional and managerial class.

Table 3.3 Characteristics of participants

Characteristics (mean/%, 95% CI)	**Premenopausal (n=14, 645)**	**Postmenopausal (n=17, 813)**
Age, years	44.6 (44.6 to 44.7)	59.1 (59.0 to 59.3)
BMI, kg/m²	23.8 (23.8 to 23.9)	25.0 (24.9 to 25.0)
Total energy intake, kcal	2293 (2281 to 2305)	2294 (2281 to 2306)
Physical activity, min/day	16.2 (15.7 to 16.6)	14.3 (13.8 to 14.8)
Alcohol consumption, g/day	9.6 (9.5 to 9.8)	7.8 (7.6 to 7.9)
Marital status (%)		
Married or living as married	78.1 (77.4 to 78.7)	71.8 (71.1 to 72.4)
Divorced	9.0 (8.5 to 9.4)	8.6 (8.2 to 9.0)
Widowed	1.3 (1.2 to 1.5)	11.1 (10.6 to 11.6)
Single	9.0 (8.6 to 9.5)	6.8 (6.4 to 7.2)
Separated	2.6 (2.4 to 2.9)	1.8 (1.6 to 2.0)
Education level (%)		
No formal record	7.6 (7.2 to 8.0)	26.0 (25.4 to 26.7)
O-level	31.7 (30.9 to 32.5)	29.6 (28.9 to 30.3)
A-level	25.7 (25.0 to 26.4)	23.7 (23.0 to 24.3)
Degree	35.0 (59.5 to 61.6)	39.5 (38.4 to 40.5)
Socioeconomic status (%)		
Professional/managerial	68.4 (67.6 to 69.2)	59.2 (58.4 to 59.9)
Intermediate	23.8 (23.1 to 24.5)	30.5 (29.8 to 31.2)
Routine and manual	7.8 (7.4 to 8.2)	10.3 (9.9 to 10.8)
Smoking status (%)		
Current	11.4 (10.9 to 11.9)	10.3 (9.9 to 10.8)
Former	29.3 (28.5 to 30.0)	31.8 (31.1 to 32.5)
Never smoked	59.3 (58.5 to 60.1)	57.9 (57.1 to 58.6)

3.3.2 Association between diet, nutrient intakes and menopausal status

The differences in food group and nutrient intakes comparing postmenopausal women against premenopausal women are shown in Table 3.3 and Table 3.4. After adjusting for all the potential confounders [age (years) and total energy intake (kcal/day), smoking status (current vs not current smoker), alcohol consumption (g/day), physical activity (MET-hours/week), and social class (routine and manual, intermediate, professional and managerial)], postmenopausal women had a significantly higher consumption of a range of foods including low-fat dairy products, oily fish, shellfish, fish and fish dishes, red meat, poultry, offal, total meat, total fruits, total vegetables, juices, soft drinks, and low-calorie soft drinks. Postmenopausal women also had significantly lower intakes of refined pasta and rice, margarine, high-fat salad dressings, sauces, textured vegetable protein, tea, alcohol, and biscuits compared to pre-menopausal women.

Furthermore, postmenopausal women had higher intakes of energy from protein, and fibre while lower intakes of saturated, polyunsaturated, and monounsaturated fats than pre-menopausal women which were statistically significant. Postmenopausal women also had higher intakes of the following vitamins: C, B2, B6, B12, A and D as well as folate, calcium, zinc, and iron. On the other hand, postmenopausal women reported a lower intake of vitamin E as compared to pre-menopausal women (Table 3.5).

Table 3.4 Comparison between diet of premenopausal and postmenopausal women

Daily intake of food groups (g)	Crude model		Model 1†		Model 2*	
	Post vs pre-menopausal‖		Post vs pre-menopausal‖		Post vs pre-menopausal‖	
	Difference in mean	99% CI	Difference in mean	99% CI	Difference in mean	99% CI
Total HDI score (out of 10)	-0.24	-0.30 to -0.19	0.06	-0.02 to 0.15	0.11	0.02 to 0.20
Starchy food sources						
Wholegrain products	2.94	1.02 to 4.85	-2.45	-5.23 to 0.33	-0.90	-3.84 to 2.05
Refined grain products	-5.45	-6.72 to -4.18	0.38	-1.50 to 2.26	-0.86	-2.82 to 1.11
Low fibre breakfast cereals	0.24	-0.15 to 0.63	0.28	-0.30 to 0.86	0.24	-0.37 to 0.86
High fibre breakfast cereals	9.77	7.98 to 11.6	0.01	-2.61 to 2.62	0.94	-1.82 to 3.69
Plain Potatoes	21.0	18.2 to 23.9	4.09	-0.00 to 8.19	3.79	-0.43 to 8.00
Potatoes with added fat	-1.83	-2.30 to -0.95	0.69	-0.59 to 1.96	-0.58	-1.77 to 0.61
Refined pasta and rice	-20.9	-22.6 to -19.3	-3.41	-5.81 to -1.02	-2.71	-5.21 to -0.22
Wholegrain pasta and rice	-8.17	-9.41 to -6.93	-0.26	-2.11 to 1.59	0.44	-1.44 to 2.33
Protein and fat food sources						
Low fat dairy products	9.17	7.03 to 11.3	7.77	4.63 to 10.9	7.18	3.87 to 10.5
High fat dairy products	1.61	0.03 to 3.19	2.57	0.32 to 4.81	2.13	-0.17 to 4.44
Butter and hard margarine	0.68	0.40 to 0.95	-0.36	-0.77 to 0.04	-0.38	-0.81 to 0.06
Margarine	-0.31	-0.57 to -0.56	-0.57	-0.95 to -0.19	-0.47	-0.88 to -0.06
Low fat spreads	-0.10	-0.29 to 0.09	0.05	-0.24 to 0.34	0.00	-0.31 to 0.31
High fat dressing	-0.82	-1.02 to -0.63	-0.56	-0.85 to -0.28	-0.47	-0.78 to -0.17
Low fat dressing	0.57	0.41 to 0.72	0.28	0.04 to 0.52	0.11	-0.15 to 0.36
Soybean products	-0.15	-0.48 to 0.18	-0.17	-0.68 to 0.33	-0.13	-0.62 to 0.35
Textured vegetable protein	-0.63	-0.72 to -0.54	-0.20	-0.34 to -0.07	-0.22	-0.36 to -0.08
Pulses	-7.89	-9.07 to -6.71	0.32	-1.36 to 2.00	-0.20	-1.98 to 1.59
Eggs/eggs dishes	3.08	2.48 to 3.68	0.57	-0.28 to 1.42	0.05	-0.80 to 0.91
Oily fish	1.54	1.18 to 1.91	0.72	0.17 to 1.26	0.88	0.29 to 1.47
Shellfish	-0.00	-0.15 to 0.14	0.28	0.07 to 0.49	0.26	0.08 to 0.44

Table 3.4 Continued

Daily intake of food groups (g)	Crude model		Model 1†		Model 2*	
	Post vs pre-menopausal‖		Post vs pre-menopausal‖		Post vs pre-menopausal‖	
	Difference in mean	99% CI	Difference in mean	99% CI	Difference in mean	99% CI
Fish and fish dishes	6.36	5.56 to 7.16	1.56	0.41 to 2.71	1.27	0.25 to 2.28
Red meat	10.9	9.70 to 12.2	3.86	2.08 to 5.64	2.73	0.97 to 4.49
Processed meat	3.15	2.71 to 3.58	1.12	0.48 to 1.76	0.59	-0.06 to 1.24
Poultry	2.33	1.73 to 2.93	1.55	0.66 to 2.44	1.01	0.08 to 1.93
Offal	0.92	0.82 to 1.03	0.25	0.09 to 0.40	0.19	0.03 to 0.36
Total meat	17.3	15.2 to 19.2	6.78	4.05 to 9.51	4.51	1.81 to 7.22
Fruits						
Stone fruits	-0.37	-0.92 to 0.18	0.58	-0.24 to 1.39	0.60	-0.16 to 1.37
Deep orange & yellow fruits	2.50	1.12 to 3.88	2.61	0.58 to 4.64	2.37	0.37 to 4.36
Grapes	5.91	4.44 to 7.38	2.57	0.38 to 4.76	2.61	0.36 to 4.85
Citrus family fruits	4.07	2.51 to 5.63	1.86	-0.46 to 4.18	2.50	0.06 to 4.93
Rhubarb	3.94	2.93 to 4.94	0.57	-0.91 to 2.05	0.73	-0.79 to 2.25
Berries	3.18	2.24 to 4.11	1.82	0.44 to 3.20	2.20	0.77 to 3.62
Bananas	2.19	0.58 to 3.81	0.80	-1.59 to 3.19	1.11	-1.38 to 3.60
Pomes	7.82	4.93 to 10.7	5.47	1.15 to 9.79	5.44	0.93 to 9.94
Dried Fruits	2.03	1.40 to 2.67	0.04	-0.87 to 0.95	0.45	-0.46 to 1.36
Total fruits	31.2	24.2 to 38.3	16.0	6.15 to 25.9	18.2	8.17 to 28.3
Vegetables						
Vegetable dishes	-26.7	-29.0 to -24.3	-3.41	-6.78 to -0.04	-2.61	-5.95 to 0.73
Allium	0.92	0.53 to 1.30	0.39	-0.18 to 0.96	0.50	-0.10 to 1.10
Fresh legumes	2.64	1.84 to 3.45	0.81	-0.36 to 1.98	0.81	-0.40 to 2.02
Mediterranean vegetables	-8.71	-9.63 to -7.79	-0.62	-1.95 to 0.71	-0.40	-1.78 to 0.97
Salad vegetables	-0.74	-1.47 to -0.02	0.47	-0.59 to 1.53	0.49	-0.62 to 1.60
Cruciferous vegetables	15.5	13.5 to 17.5	6.84	3.90 to 9.78	6.87	3.92 to 9.81
Tomatoes	1.02	-0.20 to 2.25	1.00	-0.82 to 2.82	0.92	-0.99 to 2.83
Mushrooms	-1.33	-1.61 to -1.06	0.10	-0.31 to 0.51	0.19	-0.24 to 0.61

Table 3.4 Continued

Daily intake of food groups (g)	Crude model		Model 1[†]		Model 2[*]	
	Post vs pre-menopausal[‖]		Post vs pre-menopausal[‖]		Post vs pre-menopausal[‖]	
	Difference in mean	99% CI	Difference in mean	99% CI	Difference in mean	99% CI
Roots and tubers	7.23	6.10 to 8.37	3.65	2.01 to 5.28	3.63	1.92 to 5.34
Total vegetables	4.58	0.98 to 10.1	11.7	4.14 to 19.3	13.9	6.01 to 21.7
Other food groups						
Sauces	-1.00	-1.29 to -0.72	-0.47	-0.88 to -0.05	-0.49	-0.92 to -0.06
Pickles/ chutneys	-0.87	-1.12 to -0.61	0.08	-0.29 to 0.46	-0.04	-0.43 to 0.35
Soups	11.9	10.1 to 13.6	2.07	-0.44 to 4.58	1.92	-0.31 to 4.14
Confectionary & spreads	-1.26	-2.52 to 0.00	-0.92	-2.62 to 0.79	-0.67	-2.49 to 1.16
Nuts & Seeds	-1.27	-1.77 to -0.77	-0.82	-1.54 to -0.10	-0.63	-1.33 to 0.08
Savoury snacks	-2.82	-3.07 to -2.58	-0.35	-0.71 to 0.00	-0.47	-0.85 to -0.09
Drinks and beverages						
Tea	30.3	15.6 to 45.0	-28.7	-50.88 to -6.52	-32.3	-56.3 to -8.34
Herbal tea	-26.2	-32.9 to -19.6	7.66	-2.38 to 17.7	9.60	-1.24 to 20.4
Coffee	-12.2	-22.3 to -2.19	8.47	-6.76 to 23.7	3.18	-13.3 to 19.6
Other hot beverages	1.10	0.68 to 1.52	0.72	0.09 to 1.34	0.60	-0.05 to 1.25
Juices	1.55	-2.04 to 5.13	6.06	0.75 to 11.4	7.47	1.78 to 13.2
Soft drinks	-0.56	-2.53 to 1.41	7.68	4.72 to 10.6	6.95	3.89 to 10.0
Low calorie/diet soft drinks	-10.2	-13.0 to -7.39	11.4	7.10 to 15.6	8.43	3.93 to 12.9
Alcohol[§]	-1.88	-2.17 to -1.58	-0.59	-1.03 to -0.14	-0.57	-1.05 to -0.10
Biscuits	-0.14	-0.57 to 0.30	-0.91	-1.54 to -0.29	-1.18	-1.84 to -0.51
Cakes	2.90	2.43 to 3.37	-0.08	-0.74 to 0.58	-0.13	-0.80 to 0.54
Pastries and Puddings	1.29	0.47 to 2.11	-0.76	-1.89 to 0.38	-0.85	-1.96 to 0.27

[‖]Pre-menopausal as reference group; [†]Model adjusted for age and total energy; [*]Model adjusted for model 1 in addition to smoking status, alcohol consumption, physical activity, and social class; [§]Not adjusted for alcohol consumption

Table 3.5 Comparison of nutrient intakes by menopausal status

	Unadjusted model		Model 1		Model 2	
	Post vs pre-menopausal[‖]		Post vs pre-menopausal[†‖]		Post vs pre-menopausal[†‖]	
Nutrients	Difference in nutrient intake	99% CI	Difference in nutrient intake	99% CI	Difference in nutrient intake	99% CI
Fibre (g)	0.45	0.13 to 0.76	0.30	-0.03 to 0.63	0.49	0.14 to 0.84
% energy from protein	0.85	0.77 to 0.93	0.03	0.00 to 0.07	0.04	0.00 to 0.08
% energy from carbohydrate	0.08	-0.10 to 0.25	0.01	-0.03 to 0.04	0.02	-0.02 to 0.05
% energy from fat	-0.81	-0.97 to -0.64	-0.01	-0.04 to 0.03	0.00	-0.04 to 0.04
Saturated fat (g)	0.02	-0.40 to 0.43	-0.66	-1.05 to -0.28	-0.76	-1.17 to -0.36
Polyunsaturated fat (g)	-1.10	-1.32 to -0.88	-0.39	-0.60 to -0.18	-0.36	-0.57 to -0.14
Monounsaturated fat (g)	-0.79	-1.15 to -0.43	-0.71	-0.99 to -0.44	-0.73	-1.01 to -0.45
Vitamin C (mg)	10.0	7.34 to 12.7	8.67	5.22 to 12.1	9.90	6.35 to 13.4
Vitamin B1 (mg)	-0.35	-0.43 to -0.28	0.01	-0.10 to 0.12	0.03	-0.08 to 0.15
Vitamin B2 (mg)	0.14	0.11 to 0.16	0.05	0.02 to 0.07	0.04	0.01 to 0.07
Vitamin B6 (mg)	0.14	0.11 to 0.17	0.07	0.04 to 0.09	0.07	0.04 to 0.09
Vitamin B12 (µg)	1.02	0.92 to 1.11	0.35	0.23 to 0.48	0.29	0.16 to 0.41
Folate (µg)	15.5	11.3 to 19.8	7.56	3.43 to 11.7	8.29	3.95 to 12.6
Vitamin A (µg)	153.7	136.8 to 171.5	37.7	15.5 to 60.0	34.9	11.4 to 58.4
Vitamin D (µg)	0.35	0.30 to 0.40	0.08	0.02 to 0.15	0.08	0.01 to 0.15
Vitamin E (mg)	10.5	10.3 to 10.8	-0.29	-0.42 to -0.15	-0.21	-0.35 to -0.07
Calcium (mg)	21.6	9.62 to 33.6	14.5	3.22 to 25.8	14.1	2.09 to 26.0
Iron (mg)	0.48	0.26 to 0.71	0.18	-0.06 to 0.43	0.33	0.07 to 0.59
Zinc (mg)	0.61	0.49 to 0.73	0.20	0.10 to 0.30	0.18	0.08 to 0.27
Haem iron (mg)	0.18	0.16 to 0.19	0.07	0.04 to 0.09	0.05	0.02 to 0.07
Non-haem iron (mg)	0.52	0.29 to 0.75	0.15	-0.11 to 0.40	0.32	0.05 to 0.59

[‖] Pre-menopausal as reference group; [†]Model adjusted for age and total energy; [*]Model adjusted for model 1 in addition to smoking status, alcohol consumption, physical activity, and social class

3.3.3 WHO Healthy Diet Index in relation to menopausal status

Table 3.6 demonstrates the percentage of women who met the recommended guidelines for the individual HDI components. Overall, a high number of women met the recommended guidelines for only 3 components: non-starch polysaccharides, fruit and vegetables and cholesterol. Interestingly, when comparing the component scores by menopausal status, a higher number of premenopausal women consumed the recommended percentage of energy intake from polyunsaturated fatty acids (45.5% vs 57.0%), protein (33.0% vs 46.3%) and cholesterol intake (68.8% vs 78.5%) as compared to postmenopausal women. Postmenopausal women were more likely to meet the recommended guidelines for the percentage of energy from total fat in comparison to premenopausal women (31.2% vs 25.2%). Furthermore, the association between menopausal status and the WHO HDI score is presented in Table 3.4. According to the crude model, postmenopausal women had a lower dietary quality score as compared to premenopausal women (difference in mean=-0.24, 99% CI: -0.30 to -0.19). However after adjusting for age and total energy intake (model 1), postmenopausal women demonstrated a higher dietary quality score as compared to premenopausal women. Additionally, after adjusting for all the potential confounders (model 2), a similar association was found (difference in mean=0.11, 99% CI: 0.02 to 0.20).

Table 3.6 HDI component scores (%) by menopausal status

	% cohort meeting guideline		
	Pre-menopausal	Post-menopausal	Total
Total fat (% total E)	25.2	31.2	28.5
Saturated fatty acids (% total E)	33.4	35.0	34.3
Polyunsaturated fatty acids (% total E)	57.0	45.5	50.7
Total carbohydrate (% total E)	24.3	26.5	25.5
Non-milk extrinsic sugars (% total E)	23.8	21.2	22.4
Non-starch polysaccharides (g)	67.1	68.2	67.7
Fruit and vegetables (g)	73.2	76.5	75.0
Protein (% total E)	46.3	33.0	39.0
Cholesterol (g)	78.5	68.8	73.2
Salt (g)	11.9	11.2	11.5

3.4 Discussion

3.4.1 Main findings

Findings from this study demonstrated that postmenopausal women had a slightly higher HDI score as compared to premenopausal women. In particular, postmenopausal

women had a significantly higher consumption of a healthier range of food items (e.g., fruits, vegetables, low-fat salad dressings, and fish) compared to premenopausal women accounting for the high fibre intake observed among postmenopausal women. In addition, postmenopausal women had a higher intake of the energy from protein a lower intake of fat (saturated, polyunsaturated and monounsaturated fats). Postmenopausal women also had higher intakes of vitamins C, B2, B6, B12, A and D as well as folate, calcium, zinc, and iron. The higher intake of fruits and vegetables by postmenopausal women (76.5% meeting the recommended guidelines) could explain the higher intake of the water soluble and fat soluble vitamins. Similarly, previous studies have demonstrated that compared to younger adults, older adults have more servings of fruits and vegetables [24, 25]. In particular, older women have been found to be more health conscious [26]. These findings suggest that in general postmenopausal women have a healthier dietary pattern compared to premenopausal women.

3.4.2 Comparison with previous studies

Comparisons with other studies are limited, as no studies have investigated the differences between the diets of pre- and post-menopausal women. The results of this study are in line with a prospective cohort study comparing the dietary pattern of young (25-30 years) and middle-aged women (50-55 years). Mishra et al. [27] reported that middle-aged women scored higher on cooked vegetables, fruit, reduced fat dairy and high-fat and sugar food patterns while they had a lower score on the Mediterranean-style and processed meat, meat and takeaway patterns. Furthermore, the comparison between dietary variety score (DVS) of young and older adults, showed that older adults had a higher DVS associated with higher vitamin C intake and lower consumption of saturated fats [28]. According to a review, the percentage of calories from total fat was found to decrease over time while percentage calories from protein was relatively stable (15% to 16%) and that from carbohydrates increased (38.4% to 44.5%) in the Baltimore Longitudinal Study of Aging study whereby nutrient intake of the study population was evaluated over three time point [26]. In line with our findings, results from the first phase of NHANES III study (1988–1991) demonstrated that even though the percentage of calories from fat dropped with age, the proportion of calories from protein was likely to be higher among older adults (>60y) than that of the younger age group [29]. In a cross-sectional study including both Spanish men and women aged 25-74 years, the authors likewise reported that intake of nutrients such as vitamin B1, vitamin B12, vitamin C, vitamin E, folate, potassium, iron, magnesium, copper, as well as dietary fibre intake and

healthy dietary habits (determined using a composite dietary score) were positively associated with age [30]. Additionally in a review study, Ruxton and Derbyshire [31] suggested that women in the age range of 50–64 years had a superior dietary quality as compared to women in other life phases, in particular, they consumed higher amount of fruit and vegetables, oily fish, fibre, and a lower amount of salt and alcohol which are in agreement with our study findings.

Interestingly, postmenopausal women were also found to have a higher consumption of meat, low- and high-fat dairy products as well as soft drinks and low-calorie soft drinks in comparison to premenopausal women. On the other hand, Bezerra et al. [32] reported that younger adults had a higher consumption of these food groups as compared to older adults. However, it must be noted that these results included food intake of men as well. Our findings showed that postmenopausal women had a traditional food pattern with higher intakes of fruits, vegetables, meat, and dairy products. This can be supported by the fact that views and perceptions associated with food culture, traditions and eating habits are established during early life and do not change to any great extent throughout life [33]. For instance, according to an intervention study, elderly Swedish participants requested traditional meals consisting of fish, meat, and vegetables [33].

3.4.3 Strengths and limitations

This is also to our knowledge the first study exploring the differences in the diet of pre- and post-menopausal women. Previously studies have mainly focused on the diet of women across individual life stages rather than comparing them [34, 35]. Others studies as reported in a systematic review by Wakimoto and Block [26], followed women from baseline until a specific period of time and demonstrated dietary changes over the course of time. However, these studies did not look at diet in relation to menopausal status.

Other strengths of this study include the large sample of women from the different parts of the UK, as well as the use of a validated FFQ designed for this study population. The 217-item FFQ had been previously validated on a sub-sample of 303 cohort subjects against a 4-day food diary as well as fasting blood measures of specific nutrients [12].The FFQ was additionally adapted for the high number of vegetarians included in the cohort [12]. Moreover in this study, 64 food group and nutrient intakes were explored in relation to menopausal status. Dietary quality of pre- and post-menopausal women was also

explored using the WHO HDI. A major advantage of the HDI is that as compared to other dietary quality indices, the HDI is appropriate for worldwide use and can be adapted for different cultures [36, 37].

Furthermore, a DAG was used to determine potential confounders. The DAG is based on a theoretical framework constructed using theoretical evidence to identify minimal sets of variables to be included in a statistical model to eliminate confounding bias as compared to other methods of identifying confounders are based on p-values [38]. Adjusting for potential confounders is to prevent biased estimates of exposure. Inclusion of variables that are associated with menopausal status (exposure), but unrelated to diet (outcome), can also lead to biased estimates as well as increase the variance when included in the statistical model [38]. Therefore, the use of the DAG helps to avoid under and over-adjustment, thus increasing the validity of our study. Yet, there might be possibility of residual confounding due to factors not measured in the study (e.g. food environment) which could lead to potential bias. The DAG can also be used to identify effect modifiers, that is, one which influences the magnitude of the association between menopausal status and diet. For example in this study, BMI could modify this association. However, this was not explored in this study.

Limitations of this study should also be acknowledged. Random measurement errors may be present which could mask the true relationships between menopausal status and diet [39]. For instance, there are several weaknesses of using FFQs for dietary assessment such as measurement errors due to unavailable foods in the list and imprecisions in consumption frequency and portion size estimations [40]. There is also a tendency to under and over-estimate consumption of certain food like fruits and vegetable intake [41]. Yet the use of an FFQ allows a better picture of diet over a long period of time as compared to other dietary assessment tools such as the 24-h recall and food diaries which record diet over a shorter period of time. The use of the FFQ is also an inexpensive method to assess diet of the thousands of women in the UKWCS and causes lower subject burden than the 24-h recall [40]. Some degree of random error could also have been included in the definition of menopausal status as this was determined using self-reported questions on the number of menstrual cycles in the last 12 months, which could be prone to recall bias and thus lead to potential misclassification of the menopausal status. Furthermore, systematic measurement error could be present as recruitment of participants for the UKWCS was based on a volunteer basis from a World Cancer Research Fund mailing list of previous questionnaire participants, which could to some

extent be prone to volunteer bias. Yet, an advantage of the UKWCS is that a wide range of dietary components have been explored which ensures adequate power and also reduces the effects of measurement error because of the number of dietary exposures considered for this study [42, 43].

Another weakness of this study is the cross-sectional nature of the study, suggesting that the observed relationships cannot imply causation. However, given that the findings from this study are consistent with previous longitudinal studies, shows the reliability of the study results. A better alternative to investigate the relationships between menopausal status and diet would have been to follow premenopausal women until they reach menopause and explore their dietary changes over that particular time frame.

3.4.4 Public health implications

It is well known that a healthy diet, in terms of adequate fibre, polyunsaturated fats, micronutrients intakes are primordial for women at all stages to maintain good health and to prevent future adverse health outcomes [31]. For instance, menopause causes redistribution of adipose tissue to the central area, increasing the risk of central obesity among postmenopausal women. Endocrine changes occurring during menopause also put women at a higher risk of hypertension [44], type II diabetes [45], cardiovascular diseases [46] and osteoporosis [47]. Findings from this study suggest that the diet of premenopausal women differs from that of postmenopausal women taking into account a range of potential confounders. Some of the differences observed may be due to an age cohort effect, but may also reflect improved adherence to dietary guidelines in postmenopausal women. Thus our findings suggest that pre-menopausal women may need to improve the quality of the diet, particularly regarding fruits, vegetables and micronutrient intakes, to support maintenance of longer term health.

References

1. Sherman, S. Defining the menopausal transition. *The American Journal of Medicine.* 2005, **118**(12), pp.3-7.
2. Grady, D. Management of Menopausal Symptoms. *New England Journal of Medicine.* 2006, **355**(22), pp.2338-2347.
3. Santoro, N. et al. Menopausal Symptoms and Their Management. *Endocrinology and Metabolism Clinics of North America.* 2015, **44**(3), pp.497-515.
4. Gold, E.B. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America.* 2011, **38**(3), pp.425-440.
5. Gold, E.B. et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology.* 2001, **153**(9), pp.865-874.
6. Deibert, P. et al. Effect of a weight loss intervention on anthropometric measures and metabolic risk factors in pre- versus postmenopausal women. *Nutrition Journal.* 2007, **6**(1), pp.1-7.
7. Sternfeld, B. et al. Relation of Demographic and Lifestyle Factors to Symptoms in a Multi-Racial/Ethnic Population of Women 40–55 Years of Age. *American Journal of Epidemiology.* 2000, **152**(5), pp.463-473.
8. Dam, M.K. et al. Five year change in alcohol intake and risk of breast cancer and coronary heart disease among postmenopausal women: prospective cohort study. *British Medical Journal.* 2016, **353**, pp.1-10.
9. Chen, W.Y. et al. Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk. *JAMA.* 2011, **306**(17), pp.1884-1890.
10. Farvid, M.S. et al. Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer. *Breast Cancer Research and Treatment.* 2014, **145**(1), pp.255-265.
11. Cade, J.E. et al. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutrition.* 2004, **7**(7), pp.871-878.
12. Cade, J.E. et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). *International Journal of Epidemiology.* 2015, **0**(0), pp.1-11.

13. Greenwood, D.C. et al. Seven unique food consumption patterns identified among women in the UK Women's Cohort Study. *European Journal of Clinical Nutrition.* 2000, **54**(4), pp.314-320.
14. Cade, J.E. et al. Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. *Nutrition and Cancer.* 2010, **62**(3), pp.300-306.
15. Cade, J.E. et al. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *International Journal of Epidemiology.* 2007, **36**(2), pp.431-438.
16. Key, T.J. et al. Vitamins, minerals, essential fatty acids and colorectal cancer risk in the United Kingdom Dietary Cohort Consortium. *International Journal of Cancer.* 2012, **131**(3), pp.E320-E325.
17. Threapleton, D.E. et al. Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study. *European Journal of Clinical Nutrition.* 2015, **69**(4), pp.467-474.
18. Taylor, E.F. et al. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *British Journal of Cancer.* 2007, **96**, pp.1139-1146.
19. Woodhouse, A. et al. The UK Women's Cohort Study: background and obtaining local ethical approval. *Proceedings of The Nutrition Society.* 1997, **56**(1A), p.64A.
20. Holland B, W.A., Unwin ID, Buss DH, Paul AA, Southgate DAT. *The composition of foods.* Cambridge, United Kingdom: The Royal Society of Chemistry and Ministry of Agriculture Fisheries and Food, 1991.
21. Cade, J.E. et al. Diet and genetic factors associated with iron status in middle-aged women. *The American journal of clinical nutrition.* 2005, **82**(4), pp.813-820.
22. WHO Technical Report Series (2003). *Diet, Nutrition and the Prevention of Chronic Diseases. Report of a Joint WHO/FAO Expert Consultation*. World Health Organization: Geneva.
23. Cade, J.E. et al. Does the Mediterranean dietary pattern or the Healthy Diet Index influence the risk of breast cancer in a large British cohort of women? *European Journal of Clinical Nutrition.* 2011, **65**, pp.920.
24. Nicklett, E.J. and Kadell, A.R. Fruit and vegetable intake among older adults: a scoping review. *Maturitas.* 2013, **75**(4), pp.305-312.
25. Lichtenstein, A.H. et al. Modified MyPyramid for older adults. *Journal of Nutrition.* 2008, **138**(1), pp.5-11.

26. Wakimoto, P. and Block, G. Dietary intake, dietary patterns, and changes with age: An epidemiological perspective. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences.* 2001, **56**(Supplement 2), pp.65-80.
27. Mishra, G.D. et al. Major dietary patterns of young and middle aged women: results from a prospective Australian cohort study. *European Journal of Clinical Nutrition.* 2010, **64**(10), pp.1125-1133.
28. Drewnowski, A. et al. The dietary variety score: Assessing diet quality in healthy young and older adults. *Journal of the American Dietetic Association.* 1997, **97**(3), pp.266-271.
29. Alaimo, K. et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. *Advance Data.* 1994, (258), pp.1-28.
30. Schröder, H. et al. Population dietary habits and physical activity modification with age. *European Journal of Clinical Nutrition.* 2004, **58**, pp.302.
31. Ruxton, C.H.S. and Derbyshire, E. Women's diet quality in the UK. *Nutrition Bulletin.* 2010, **35**(2), pp.126-137.
32. Bezerra, I.N. et al. Difference in adult food group intake by sex and age groups comparing Brazil and United States nationwide surveys. *Nutrition Journal.* 2014, **13**, pp.1-10.
33. Edfors, E. and Westergren, A. Home-Living Elderly People's Views on Food and Meals. *Journal of Aging Research.* 2012, **2012**, pp.1-9.
34. Derbyshire, E. et al. Habitual micronutrient intake during and after pregnancy in Caucasian Londoners. *Maternal & Child Nutrition.* 2009, **5**(1), pp.1-9.
35. Adamson, A.J. et al. Nutrition in advanced age: dietary assessment in the Newcastle 85+ study. *European Journal of Clinical Nutrition.* 2009, **63 Suppl 1**, pp.S6-18.
36. Jankovic, N. et al. Adherence to a healthy diet according to the World Health Organization guidelines and all-cause mortality in elderly adults from Europe and the United States. *American Journal of Epidemiology.* 2014, **180**(10), pp.978-988.
37. Jankovic, N. et al. WHO guidelines for a healthy diet and mortality from cardiovascular disease in European and American elderly: the CHANCES project. *American Journal of Clinical Nutrition.* 2015, **102**(4), pp.745-756.

38. Brookhart, M.A. et al. Confounding control in healthcare database research: challenges and potential approaches. *Medical care.* 2010, **48**(6 Suppl), pp.S114-S120.

39. Brakenhoff, T.B. et al. Random measurement error: Why worry? An example of cardiovascular risk factors. *PLoS ONE.* 2018, **13**(2), pp.e0192298-e0192298.

40. Ishihara, J. Challenges in Dietary Exposure Assessment in Epidemiology: Research Trends. *Journal of Nutritional Science and Vitaminology (Tokyo).* 2015, **61 Suppl**, pp.S33-35.

41. Cade, J. et al. Development, validation and utilisation of food-frequency questionnaires – a review. *Public Health Nutrition.* 2002, **5**(4), pp.567-587.

42. Schatzkin, A. et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *American Journal of Epidemiology.* 2001, **154**(12), pp.1119-1125.

43. White, E. et al. The effect of exposure variance and exposure measurement error on study sample size: implications for the design of epidemiologic studies. *J Clin Epidemiol.* 1994, **47**(8), pp.873-880.

44. Coylewright, M. et al. Menopause and Hypertension. *Hypertension.* 2008, **51**(4), pp.952-959.

45. Ren, Y. et al. Association of menopause and type 2 diabetes mellitus. *Menopause.* 2019, **26**(3), pp.325-330.

46. Dosi, R. et al. Cardiovascular disease and menopause. *Journal of clinical and diagnostic research : JCDR.* 2014, **8**(2), pp.62-64.

47. Ji, M.-X. and Yu, Q. Primary osteoporosis in postmenopausal women. *Chronic diseases and translational medicine.* 2015, **1**(1), pp.9-13.

Chapter 4

Dietary intake and age at natural menopause: results from the UK Women's Cohort Study

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***Erratum:** Menopause is an important phase in a woman's life indicating the end of the reproductive life span and is accompanied with a reduction in oestrogen level. [Introduction, line 2]

Abstract

Background: Age at natural menopause is a matter of concern for women of reproductive age as both an early or late menopause may have implications for health outcomes.

Methods: Study participants were women aged 40–65 years who had experienced a natural menopause from the UK Women's Cohort Study between baseline and first follow-up. Natural menopause was defined as the permanent cessation of menstrual periods for at least 12 consecutive months. A food frequency questionnaire was used to estimate diet at baseline. Reproductive history of participants was also recorded. Regression modelling, adjusting for confounders, was used to assess associations between diet and age at natural menopause.

Results: During the 4-year follow-up period, 914 women experienced a natural menopause. A high intake of oily fish and fresh legumes were associated with delayed onset of natural menopause by 3.3 years per portion/day (99% CI0.8 to 5.8) and 0.9 years per portion/day (99% CI 0.0 to 1.8), respectively. Refined pasta and rice was associated with earlier menopause (per portion/day: −1.5 years, 99% CI −2.8 to −0.2). A higher intake of vitamin B6 (per mg/day: 0.6 years, 99% CI 0.1 to 1.2) and zinc (per mg/day: 0.3 years, 99% CI −0.0 to 0.6) was also associated with later age at menopause. Stratification by age at baseline led to attenuated results.

Conclusion: Our results suggest that some food groups (oily fish, fresh legumes, refined pasta and rice) and specific nutrients are individually predictive of age at natural menopause.

4.1 Introduction

The average age of menopause in the UK is reported to be 51 years [1]. Menopause is an important phase in a woman's life indicating the end of the reproductive life span with reduction in oestrogen and increased progesterone levels [2, 3]. Several studies have documented an association between earlier age at natural menopause and lower bone density, osteoporosis, depression and premature death [4, 5]. Other studies have shown increased risk of cardiovascular and coronary diseases [[6, 7]. In contrast, a late menopause has been associated with a higher risk for breast, ovarian and endometrial cancers [8].

A number of causes have been postulated for the relationship between age at menopause and these health outcomes, such as genetic factors, behavioural and environmental exposures, socio-demographic factors, hormonal mechanisms and health-related factors [9]. Diet can also be an underlying factor [9]. Two large cohort studies have also hypothesised an association [10, 11] but reported conflicting findings.

The limited number of studies and contradictory results [10-12] in this area suggests the need for further cohort studies with detailed dietary intake measures to clarify this association. The aim of this analysis was to explore the associations between food groups and nutrient intake in a large cohort of British women with age at incident natural menopause. We hypothesised that intake of healthier food groups such as fruits and vegetables would be associated with an earlier menopause while a high consumption of meat and processed meat would delay the onset of menopause.

4.2 Methods

4.2.1 Study population

The UK Women's Cohort Study (UKWCS) is a large prospective study consisting of 35 372 women aged between 35 and 69 years. Recruited participants were from England, Scotland and Wales [13]. Baseline data were collected between the years 1995 and 1998 via postal questionnaire. Follow-up data were collected on average 4 years later, between the years 1999 and 2002 [13].

4.2.2 Study design and data collection

In total, 14 172 women who participated at both baseline and follow-up were considered for this study. Information was collected on demographic details, weight

history, physical activity, reproductive history (age at last period; number of periods in last 12 months; use of hormone replacement therapy (HRT)), anthropometric and other health-related factors at baseline as well as at follow-up. Participants who experienced a natural menopause at follow-up were identified through comparison of baseline and follow-up data. Natural menopause was defined as the permanent cessation of the menstrual periods for at least 12 consecutive months [2]. Menstruating women, that is, those having one or more menstrual period in the last 12 months at baseline and who became naturally postmenopausal at follow-up were included in the final analysis. Inclusion criteria also comprised never used HRT at baseline and currently not using HRT at follow-up (as HRT use may influence the bleeding pattern among premenopausal women [14]). Women who ever used HRT after reaching menopause at phase II were also included. Women who had bilateral oophorectomy and hysterectomy at baseline as well as pregnant women at baseline were excluded from the study. In addition, only women with an age at natural menopause between ≥40 and ≤65 years were included (as no menstruation before the age of 40 might be chemically induced or due to surgical procedures). In addition, participants with missing data on the main study outcome, age at natural menopause and confounders were also excluded from the study (Figure 4.1).

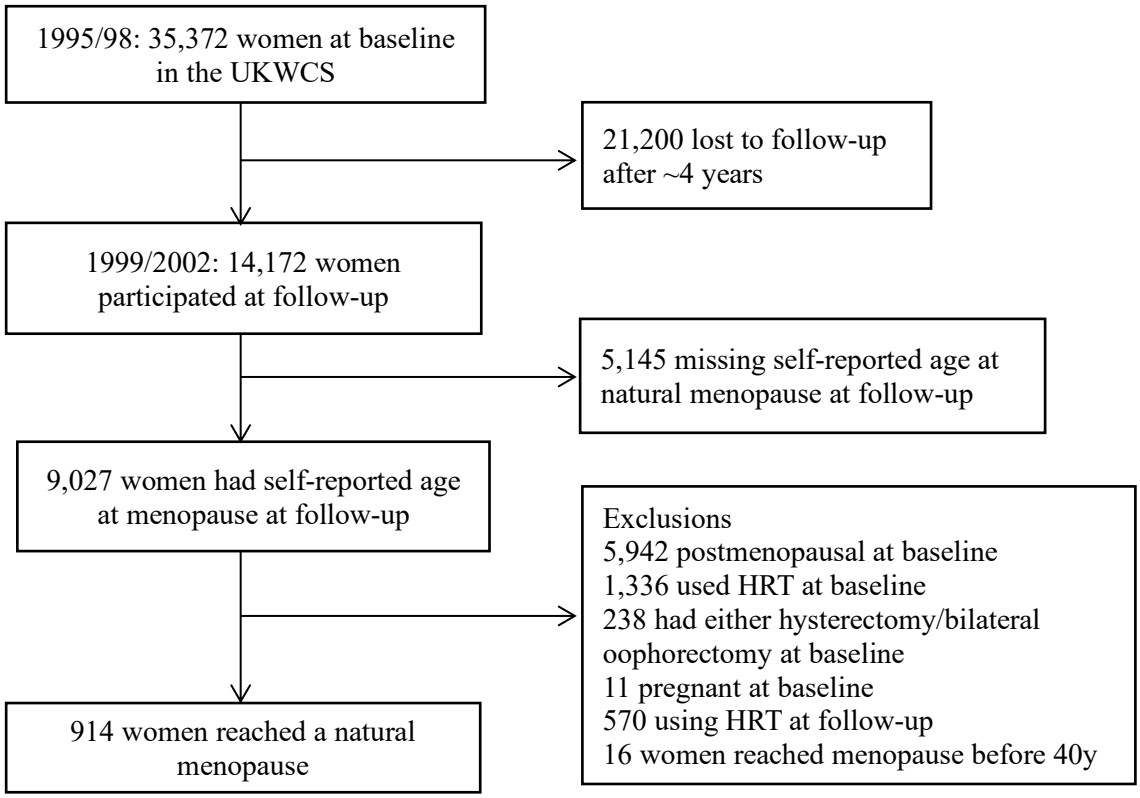

Figure 4.1 Flow diagram for participants' selection

4.2.3 Dietary assessment

Dietary assessment at baseline involved a detailed 217-item food frequency questionnaire (FFQ) derived from the FFQ which was validated on a subsample of 303 cohort subjects against a 4-day food diary as well as fasting blood measures of specific nutrients [13, 15, 16]. Using the different frequency categories of the FFQ, the number of daily portions for the 217 food items was defined. These were consequently converted into weight of each food consumed per day based on the Food Standards Agency portion sizes book [17]. For the current study, the individual food items were collated into food groups according to their culinary uses (e.g., Mediterranean vegetables, cruciferous vegetables, citrus family fruits) and nutrient profile (e.g., fat or fibre content) (Table B.1). In total, 15 food items were considered individually. Seven food items were considered individually due to their specific nutrient profile such as textured vegetable proteins, oily fish, shellfish, grapes, herbal tea, tea and wines, which have antioxidant properties and might separately affect age at natural menopause. The remaining eight food items (e.g., tomatoes, sauces, low calorie salad cream, etc.) were considered individually because they could not be collated under any of the other food groups. Furthermore, in order to have a better estimate for the difference in mean age at natural menopause across the different food groups, results were presented per portion size.

4.2.4 Covariate assessment

A directed acyclic graph (DAG) (Figure B.1) with diet (food groups) as the main exposure and age at natural menopause (continuous) as the outcome was generated to determine confounding variables. Based on available literature and data collected, potential confounding variables (age, parity, energy intake, body mass index (BMI), social class, age at first full-term pregnancy, age at menarche, smoking, alcohol consumption and physical activity) were included in the DAG. According to the minimal sufficiency set of adjustments, physical activity (MET-hours/week), smoking status (current vs not current smoker), alcohol consumption (g/day) and social class (routine and manual, intermediate, professional and managerial) were identified as confounders and were thus adjusted for in the regression models. For the associations between nutrient intake and age at natural menopause, total energy intake was also adjusted for the non-energy-containing nutrients (women were excluded if they had extremely high (>6000 kcal/day) or low (<500 kcal/day) energy intake) and energy from other macronutrients was adjusted for specific macronutrients.

4.2.5 Statistical analysis

Descriptive statistics were used to explore the socio-demographic and obstetric history of the women. Linear regression models were used to determine the relationships between the various food groups (continuous exposure in g/day) as well as nutrients (continuous exposure) and age at natural menopause (continuous outcome in years). In addition, because younger women at baseline have less chance of a later menopause we evaluated the associations by stratifying on age at baseline (≤50 vs >50 years). An estimate >0 was considered as a later age at natural menopause. Assumptions for linear regression were checked by plotting the residuals against fitted values which showed a constant variance and a histogram demonstrated a normal distribution of the residuals. Due to the differences in age at natural menopause by vegetarian status and parity as evidenced by previous studies [10, 18], sensitivity analysis exploring that relationship was undertaken stratified by vegetarian status and parity (nulliparous vs multiparous). Moreover, since presence of diabetes might influence both diet and age at natural menopause, we also adjusted for diabetes. To take account of multiple testing, the significance level was set at 1% with 99% CIs. All analyses were conducted using Stata V. 14.0 (StataCorp).

4.3 Results

4.3.1 Socio-demographic characteristics

Of the 1874 women who were premenopausal at baseline survey (and had self-reported age at natural menopause at follow-up), 914 had become postmenopausal at 4-year follow-up. Baseline characteristics of the participants are outlined in Table 4.1. The mean age at natural menopause at follow-up was 50.5 years (95% CI 50.3 to 50.8). Participants had a mean BMI of 23.9 kg/m2 (95% CI 23.6 to 24.1) and 9.6% were categorised as obese. Physical activity level was quite low among the participants with a mean of 15 min/day. This study also included 38% vegetarian participants. Most of the women were married, parous and of professional and managerial class. In this study, only 8% of women smoked and the mean alcohol consumption was 9 g/day (around one unit).

Table 4.1 Baseline characteristics of participants

Characteristics (mean/ %, 95% CI)	Age at natural menopause			
	40-48 years n=226	**49-51 years n=319**	**≥ 52 years n=369**	**Total n=914**
Age at baseline, y	45.4 (45.0 to 45.8)	49.0 (48.8 to 49.2)	52.1 (51.9 to 52.4)	49.4 (49.2 to 49.6)
Birth year, y	1950 (1950 to 1951)	1947 (1946 to 1947)	1944 (1943 to 1944)	1946 (1946 to 1946)
Body mass index, kg/m²	23.6 (23.0 to 24.1)	23.5 (23.1 to 23.9)	24.3 (23.8 to 24.7)	23.8 (23.6 to 24.1)
Obese, >30 kg/m² (%)	8.4 (5.4 to 12.8)	6.9 (4.6 to 10.3)	12.6 (9.5 to 16.4)	9.6 (7.8 to 11.7)
Physical activity, min/day	12.8 (10.2 to 15.4)	16.5 (13.6 to 19.4)	14.1 (11.8 to 16.3)	14.6 (13.1 to 16.1)
Vegetarian, (%)	45.7 (39.2 to 52.4)	44.2 (38.8 to 49.8)	33.0 (28.3 to 38.0)	40.0 (36.9 to 43.3)
Alcohol consumption, g/day	10.1 (8.4 to 11.8)	8.6 (7.5 to 9.7)	8.4 (7.4 to 9.4)	9.0 (8.2 to 9.6)
Smoking, (%)	10.2 (6.9 to 14.9)	8.0 (5.4 to 11.5)	5.0 (3.1 to 7.7)	7.3 (5.8 to 9.2)
Age at menarche, y	12.6 (12.4 to 12.8)	12.7 (12.5 to 12.8)	12.9 (12.7 to 13.1)	12.7 (12.6 to 12.8)
Age at first full term pregnancy, y	26.6 (25.8 to 27.5)	26.0 (25.4 to 26.5)	25.6 (25.1 to 26.0)	25.9 (25.6 to 26.3
Parous, (%)	68.6 (62.0 to 74.5)	77.1 (72.1 to 81.5)	84.3 (80.1 to 87.8)	78.0 (75.1 to 80.4)
Ever married, (%)	76.3 (70.3 to 81.5)	78.6 (73.7 to 82.8)	78.1 (73.5 to 82.0)	77.8 (75.0 to 81.1)
Degree level, (%)	36.7 (30.5 to 43.4)	37.5 (32.2 to 43.1)	26.1 (21.7 to 31.0)	32.8 (29.7 to 36.0)
Professional and managerial class, (%)	70.0 (63.6 to 75.6)	63.8 (58.3 to 68.9)	60.3 (55.1 to 65.2)	63.9 (60.7 to 67.0)

4.3.2 Association between food groups and age at natural menopause

An increase in portion size of refined pasta and rice as well as savoury snacks was associated with an earlier age at natural menopause by 1.8 years (99% CI −3.0 to −0.5) and 0.9 years (99% CI −1.7 to −0.1), respectively in the unadjusted model (Table 4.2). In the adjusted model, for each additional portion of oily fish and fresh legumes, age at menopause was increased by 3.3 years (99% CI 0.8 to 5.8) and 0.9 years (99% CI 0.0 to 1.8), respectively. On the other hand, a higher intake of refined pasta and rice (per portion/day: 1.5 years; 99% CI −2.8 to −0.2) was associated with an earlier menopause. Stratification by age at baseline led to reduced associations between the various food groups and age at natural menopause. The CIs were wider because of the smaller samples in these subgroups.

For the association between nutrients and age at natural menopause, a later age at natural menopause by approximately 0.6 years was found with a higher intake of vitamin B6 per mg (99% CI 0.1 to 1.2). Similarly, a higher intake of zinc was associated with a delayed age at natural menopause by 0.3 years per mg (99% CI −0.0 to 0.6) (Table 4.3). Stratification by age at baseline further demonstrated that a higher intake of carbohydrates was associated with an earlier age at natural menopause by 0.2 years (99% CI −0.4 to −0.0) among women 50 years or below.

Table 4.2 Estimates (overall and stratified on age at baseline) for the association between daily intake of the food groups/portion size (g) and age at natural menopause (years)

Age at baseline							≤50 years			>50 years		
Daily intake/ portion size	**Estimate[a]**	**99% CI**	***P***	**Estimate[b]**	**99% CI**	***P***	**Estimate[c]**	**99% CI**	***P***	**Estimate[d]**	**99% CI**	***P***
Starchy food sources												
Wholegrain products/ 33g	0.0	-0.1 to 0.2	0.491	0.0	-0.1 to 0.2	0.443	0.0	-0.2 to 0.1	0.559	0.1	-0.0 to 0.3	0.034
Refined grain products/ 51g	-0.0	-0.5 to 0.3	0.488	-0.2	-0.5 to 0.2	0.267	-0.1	-0.6 to 0.3	0.495	-0.3	-0.7 to 0.0	0.017
Low fibre breakfast cereals/ 40g	0.0	-1.0 to 1.0	0.920	-0.1	-1.1 to 1.0	0.888	-0.7	-1.8 to 0.4	0.109	0.5	-0.5 to 1.5	0.163
High fibre breakfast cereals/ 85g	0.2	-0.2 to 0.6	0.136	0.2	-0.3 to 0.7	0.273	0.1	-0.4 to 0.6	0.621	0.0	-0.4 to 0.5	0.915
Plain Potatoes/ 210g	0.4	-0.4 to 1.1	0.213	0.5	-0.3 to 1.2	0.114	-0.1	-1.0 to 0.9	0.868	-0.2	-0.8 to 0.5	0.516
Potatoes with added fat/ 127g	0.3	-1.1 to 1.8	0.566	0.1	-1.4 to 0.2	0.829	-0.1	-1.8 to 1.7	0.929	0.1	-1.4 to 1.6	0.843
Refined pasta and rice/ 210g	-1.8	-3.0 to -0.5	<0.001	-1.5	-2.8 to -0.2	0.003	-0.9	-2.3 to 0.5	0.101	0.8	-0.7 to 2.2	0.166
Wholegrain pasta and rice/ 197 g	0.4	-1.0 to 1.7	0.492	0.5	-0.9 to 2.0	0.309	0.0	-1.7 to 1.6	0.958	0.6	-0.7 to 1.9	0.243
Protein and fat food sources												
Low fat dairy products/ 80g	0.0	-0.1 to 0.1	0.043	0.0	-0.1 to 0.1	0.700	-0.1	-0.2 to 0.0	0.053	0.0	-0.1 to 0.1	0.835
High fat dairy products/ 75g	-0.1	-0.2 to 0.1	0.279	-0.2	-0.2 to 0.1	0.323	-0.1	-0.3 to 0.1	0.493	-0.1	-0.3 to 0.1	0.118
Butter and hard margarine/ 10g	0.1	-0.2 to 0.4	0.350	0.2	-0.2 to 0.5	0.228	0.1	-0.3 to 0.5	0.475	0.0	-0.3 to 0.3	0.838
Margarine/ 9g	-0.2	-0.4 to 0.1	0.103	-0.2	-0.5 to 0.1	0.101	-0.1	-0.4 to 0.2	0.636	0.0	-0.3 to 0.3	0.958
Low fat spreads/ 7g	0.1	-0.2 to 0.4	0.264	0.1	-0.2 to 0.4	0.538	0.1	-0.3 to 0.5	0.628	-0.1	-0.4 to 0.2	0.357
High fat dressing/ 23g	-0.1	-1.2 to 0.9	0.717	-0.0	-1.0 to 1.0	0.993	0.2	-1.0 to 1.3	0.708	0.0	1.0 to 1.1	0.932
Low fat dressing/ 30g	1.3	-0.8 to 3.4	0.116	0.8	-1.3 to 2.9	0.309	0.8	-1.6 to 3.1	0.401	-0.4	-2.5 to 1.7	0.596
Soybean products/ 62g	-0.0	-0.1 to 0.1	0.978	-0.0	-0.2 to 0.1	0.812	0.0	-0.1 to 0.2	0.392	-0.1	-0.3 to 0.1	0.136
Textured vegetable protein/ 130g	-4.2	-13.1 to 4.7	0.226	-3.6	-12.6 to 5.4	0.300	-2.9	-12.1 to 6.3	0.414	-2.7	-13.0 to 7.7	0.506
Pulses/ 91g	-0.4	-1.1 to 0.2	0.087	-0.3	-1.0 to 0.4	0.230	0.1	-0.7 to 0.8	0.760	-0.5	-1.1 to 0.2	0.065
Eggs/eggs dishes/ 88g	1.0	-0.4 to 2.4	0.070	0.6	-0.9 to 2.0	0.301	-0.4	-2.0 to 1.2	0.536	-0.5	1.9 to 0.9	0.358
Fish and fish dishes/ 140g	1.4	-0.6 to 3.4	0.068	1.2	-0.9 to 3.3	0.130	-1.0	-3.2 to 1.3	0.264	1.4	-0.7 to 3.6	0.085
Oily fish/ 90g	3.2	0.8 to 5.6	0.001	3.3	0.8 to 5.8	0.001	1.9	-1.2 to 4.9	0.118	0.9	-1.3 to 3.1	0.311
Shell fish/ 60g	1.7	-4.4 to 7.8	0.462	2.2	-4.1 to 8.5	0.361	-4.0	-11.5 to 3.5	0.165	1.7	4.1 to 7.6	0.438
Red meat/ 189g	1.9	0.3 to 3.5	0.003	1.5	-0.2 to 3.2	0.021	-0.2	-2.2 to 1.8	0.830	0.9	-0.6 to 2.5	0.123
Processed meat/ 74g	1.3	-0.4 to 3.0	0.042	1.0	-0.8 to 2.7	0.150	0.2	-1.8 to 2.2	0.830	0.4	-1.2 to 2.1	0.495
Poultry/ 143g	1.6	-0.6 to 3.8	0.063	1.4	-0.9 to 3.6	0.109	0.0	-2.4 to 2.4	0.993	1.2	-1.2 to 3.6	0.186
Offal/ 100g	6.9	-2.2 to 16.1	0.051	5.9	-3.5 to 15.2	0.104	-2.0	-14.4 to 10.4	0.675	-0.2	-8.1 to 7.7	0.948

Table 4.2 Continued

Age at baseline							≤50 years			>50 years		
Daily intake/ portion size	**Estimate[a]**	**99% CI**	***P***	**Estimate[b]**	**99% CI**	***P***	**Estimate[c]**	**99% CI**	***P***	**Estimate[d]**	**99% CI**	***P***
Vegetables												
Vegetable dishes/ 214g	-0.6	-1.3 to 0.2	0.069	-0.5	-1.3 to 0.3	0.102	-0.7	-1.7 to 0.2	0.055	-0.3	-1.0 to 0.5	0.341
Allium/ 39g	0.3	-0.5 to 1.2	0.322	0.5	-0.4 to 1.4	0.125	0.1	-1.0 to 1.1	0.814	-0.2	-1.1 to 0.6	0.478
Fresh legumes/ 75g	1.0	0.1 to 1.8	0.003	0.9	0.0 to 1.8	0.007	0.0	-0.9 to 1.0	0.896	0.4	-0.4 to 1.2	0.205
Mediterranean vegetables/ 60g	-0.0	-0.6 to 0.6	1.000	0.1	-0.5 to 0.6	0.730	0.1	-0.5 to 0.7	0.597	0.2	-0.4 to 0.8	0.363
Salad vegetables/ 43g	0.4	-0.0 to 0.8	0.021	0.4	-0.0 to 0.9	0.018	0.4	-0.1 to 0.8	0.036	0.2	-0.4 to 0.7	0.441
Cruciferous vegetables/ 75g	0.3	-0.0 to 0.6	0.017	0.3	-0.0 to 0.7	0.024	0.0	-0.3 to 0.4	0.845	0.0	-0.4 to 0.4	0.969
Tomatoes/ 83g	0.2	-0.4 to 0.8	0.352	0.0	-0.6 to 0.7	0.855	0.1	-0.6 to 0.8	0.765	0.0	-0.6 to 0.5	0.822
Mushrooms/ 34g	0.3	-0.8 to 1.5	0.431	0.3	-0.9 to 1.4	0.581	-0.3	-1.7 to 1.0	0.543	0.1	-1.1 to 1.2	0.860
Roots and tubers/ 66g	0.4	-0.1 to 1.0	0.032	0.4	-0.1 to 0.9	0.057	0.1	-0.5 to 0.7	0.715	0.4	-0.2 to 1.0	0.102
Fruits												
Stone fruits/ 49g	0.5	-0.2 to 1.3	0.058	0.4	-0.3 to 1.2	0.155	0.0	-0.7 to 0.8	0.884	0.3	-0.6 to 1.1	0.442
Deep orange & yellow fruits/ 118g	0.6	-0.1 to 1.3	0.036	0.5	-0.2 to 1.3	0.051	0.1	-0.6 to 0.9	0.669	0.5	-0.2 to 1.3	0.079
Grapes/ 100g	0.8	-0.1 to 1.6	0.022	0.7	-0.2 to 1.6	0.039	-0.3	-1.5 to 0.9	0.546	0.2	-0.5 to 0.9	0.428
Citrus family fruits/ 92g	0.3	-0.2 to 0.9	0.149	0.2	-0.3 to 0.8	0.316	-0.2	-0.8 to 0.5	0.542	-0.1	-0.6 to 0.5	0.799
Rhubarb/ 130g	0.8	-0.6 to 2.2	0.143	0.7	-0.7 to 2.1	0.181	0.7	-0.8 to 2.2	0.233	0.0	-1.4 to 1.3	0.937
Berries/ 48g	0.3	-0.2 to 0.8	0.151	0.2	-0.3 to 0.7	0.233	-0.1	-0.7 to 0.5	0.733	0.0	-0.5 to 0.4	0.839
Bananas/ 100g	0.1	-0.4 to 0.6	0.718	0.0	-0.5 to 0.6	0.893	-0.1	-0.8 to 0.6	0.668	-0.4	-0.9 to 0.2	0.073
Pomes/ 116g	0.1	-0.3 to 0.4	0.670	0.0	-0.3 to 0.4	0.805	0.0	-0.4 to 0.4	0.867	-0.1	-0.4 to 0.3	0.586
Dried Fruits/ 28g	0.4	-0.0 to 0.9	0.016	0.4	-0.0 to 0.9	0.017	0.4	-0.2 to 0.9	0.072	-0.1	-0.5 to 0.6	0.734
Other food groups												
Sauces/ 83g	0.4	-2.0 to 2.7	0.691	0.1	-2.3 to 2.5	0.910	-1.0	-4.0 to 1.9	0.357	-0.7	-2.9 to 1.6	0.441
Pickles/Chutneys/ 35g	-0.1	-1.4 to 1.2	0.822	-0.2	-1.5 to 1.1	0.743	0.0	-1.5 to 1.4	0.957	0.3	-1.1 to 1.6	0.601
Soups/ 163g	0.9	-0.2 to 2.0	0.035	0.9	-0.2 to 2.0	0.038	0.3	-1.1 to 1.7	0.587	0.4	-0.6 to 1.4	0.301
Confectionary & spreads/ 44g	0.0	-0.3 to 0.3	0.950	-0.0	-0.3 to 0.3	0.867	-0.1	-0.5 to 0.3	0.484	0.0	-0.3 to 0.3	0.891
Nuts and seeds/ 24g	0.1	-0.3 to 0.5	0.449	0.1	-0.2 to 0.5	0.421	0.1	-0.2 to 0.5	0.368	-0.1	-0.5 to 0.3	0.376
Savoury snacks/ 26g	-0.9	-1.7 to -0.1	0.006	-0.9	-1.8 to 0.1	0.017	-0.5	-1.5 to 0.5	0.196	-0.7	-1.6 to 0.3	0.075
Biscuits/ 15g	-0.1	-0.5 to 0.2	0.297	-0.2	-0.5 to 0.2	0.155	-0.2	-0.6 to 0.2	0.232	-0.2	-0.5 to 0.2	0.211
Cakes/ 66g	0.3	-1.1 to 1.6	0.592	-0.0	-1.6 to 1.5	0.934	-0.8	2.5 to 0.9	0.220	0.7	-0.8 to 2.3	0.226

Table 4.2 Continued

Age at baseline							≤50 years			>50 years		
Daily intake/ portion size	**Estimate[a]**	**99% CI**	***P***	**Estimate[b]**	**99% CI**	***P***	**Estimate[c]**	**99% CI**	***P***	**Estimate[d]**	**99% CI**	***P***
Pastries and Puddings/ 84g	-0.3	-1.4 to 0.7	0.402	-0.3	-1.5 to 0.8	0.413	-0.8	-2.1 to 0.5	0.121	-0.5	-1.6 to 0.5	0.182
Drinks and beverages												
Tea/ 260g	-0.1	-0.2 to 0.1	0.148	-0.1	-0.3 to 0.0	0.042	-0.1	-0.3 to 0.1	0.103	0.0	0.2 to 0.1	0.450
Herbal tea/ 260g	0.1	-0.3 to 0.4	0.648	0.1	-0.2 to 0.4	0.415	0.1	-0.2 to 0.5	0.298	0.0	-0.3 to 0.3	0.967
Coffee/ 190g	0.0	-0.1 to 0.2	0.470	0.1	-0.1 to 0.2	0.249	0.0	-0.2 to 0.2	0.842	0.0	-0.2 to 0.1	0.641
Other hot beverages/ 23g	0.1	-0.4 to 0.5	0.742	0.1	-0.4 to 0.6	0.650	0.0	-0.6 to 0.6	0.995	-0.2	-0.7 to 0.3	0.299
Juices/ 145g	0.2	-0.2 to 0.6	0.243	0.1	-0.3 to 0.6	0.400	0.0	-0.5 to 0.5	0.896	0.1	-0.3 to 0.5	0.448
Soft drinks/ 111g	-0.7	-1.5 to 0.1	0.022	-0.8	-1.6 to 0.1	0.016	-0.5	-1.3 to 0.3	0.085	0.0	-1.1 to 1.1	0.988
Low calorie/diet soft drinks/ 161g	-0.1	-0.7 to 0.4	0.516	-0.1	-0.7 to 0.5	0.566	-0.2	-1.0 to 0.5	0.431	-0.2	-0.7 to 0.3	0.333
Wines/ 1g	-0.2	-0.6 to 0.3	0.275	0.1	-0.5 to 0.8	0.563	0.1	-0.6 to 0.7	0.768	-0.3	-1.1 to 0.5	0.325
Beer and cider/ 1g	-0.5	-1.1 to 0.2	0.053	-0.5	-1.3 to 0.3	0.093	0.0	-0.7 to 0.7	0.871	-0.2	-1.7 to 1.3	0.690
Port, sherry, liqueurs/ 1g	0.9	-0.6 to 2.5	0.112	1.1	-0.5 to 2.7	0.068	1.1	-0.8 to 3.1	0.139	0.4	-1.0 to 1.8	0.420
Spirits/ 1g	-0.3	-1.1 to 0.4	0.215	-0.1	-1.0 to 0.7	0.686	-0.1	-0.9 to 0.7	0.668	0.4	-0.7 to 1.5	0.368

[a] Difference in age at natural menopause, unadjusted model (n=914)

[b] Difference in age at natural menopause, model adjusted for the following factors: Physical activity level, alcohol consumption, smoking, social class (n=838)

[c] Difference in age at natural menopause for those aged 50y or below in the fully adjusted model (n=477)

[d] Difference in age at natural menopause for those aged above 50y in the fully adjusted model (n=361)

Table 4.3 Estimates (overall and stratified on age at baseline) for the association between daily nutrient intake and age at natural menopause (years)

Age at baseline							≤50 years			>50 years		
Daily nutrient intake	**Estimate[a]**	**99% CI**	***P* value**	**Estimate[b]**	**99% CI**	***P* value**	**Estimate[c]**	**99% CI**	***P* value**	**Estimate[d]**	**99% CI**	***P* value**
Fibre (g)	0.0	-0.0 to 0.1	0.111	-0.0	-0.1 to 0.0	0.087	0.0	-0.0 to 0.1	0.161	0.0	-0.0 to 0.0	0.641
% energy from fats	0.0	-0.1 to 0.0	0.140	-0.1	-0.4 to 0.1	0.144	-0.2	-0.4 to 0.0	0.010	-0.1	-0.4 to 0.2	0.356
% energy from proteins	0.1	0.0 to 0.2	0.005	-0.0	-0.3 to 0.2	0.713	-0.3	-0.5 to 0.0	0.011	-0.0	-0.3 to 0.3	0.995
% energy from carbohydrates	0.0	-0.0 to 0.1	0.416	-0.1	-0.3 to 0.1	0.227	-0.2	-0.4 to -0.0	0.009	-0.1	-0.3 to 0.2	0.508
% energy from saturated fats	-0.1	-0.2 to 0.0	0.094	-0.1	-0.2 to 0.1	0.171	-0.1	-0.3 to 0.1	0.155	-0.0	-0.2 to 0.1	0.443
% energy from polyunsaturated fats	-0.1	-0.2 to 0.1	0.243	-0.0	-0.2 to 0.2	0.941	0.1	-0.2 to 0.3	0.485	0.0	-0.2 to 0.2	0.936
% energy from monounsaturated fats	0.0	-0.2 to 0.1	0.324	-0.1	-0.2 to 0.4	0.488	0.0	-0.3 to 0.4	0.795	0.0	-0.3 to 0.3	0.855
Vitamin C (mg)	0.0	0.0 to 0.1	0.010	0.0	-0.0 to 0.1	0.031	0.0	-0.0 to 0.1	0.329	0.0	-0.0 to 0.1	0.585
Vitamin B_1 (mg)	0.0	-0.2 to 0.1	0.271	-0.1	-0.2 to 0.0	0.110	-0.0	-0.2 to 0.1	0.396	-0.1	-0.2 to 0.0	0.130
Vitamin B_2 (mg)	0.3	-0.1 to 0.6	0.060	0.3	-0.2 to 0.9	0.105	-0.2	-0.9 to 0.4	0.306	0.0	-0.5 to 0.5	0.987
Vitamin B_6 (mg)	0.4	-0.0 to 0.7	0.014	0.6	0.1 to 1.2	0.005	0.0	-0.6 to 0.7	0.900	0.2	-0.4 to 0.8	0.508
Vitamin B_{12} (µg)	0.0	-0.0 to 0.0	0.198	0.0	-0.0 to 0.0	0.440	0.0	-0.0 to 0.0	0.848	0.0	-0.0 to 0.0	0.536
Folate (µg)	0.1	-0.0 to 0.2	0.038	0.2	-0.0 to 0.3	0.029	0.0	-0.2 to 0.2	0.805	0.1	-0.1 to 0.2	0.408
Vitamin D (µg)	0.4	-0.0 to 0.7	0.011	0.4	-0.0 to 0.8	0.017	0.2	-0.3 to 0.7	0.281	0.1	-0.3 to 0.5	0.519
Vitamin A (µg)	0.1	0.0 to 0.2	0.008	0.1	-0.0 to 0.2	0.020	0.0	-0.1 to 0.1	0.795	0.0	-0.1 to 0.1	0.675
Vitamin E (mg)	0.0	-0.1 to 0.1	0.516	-0.1	-0.1 to 0.0	0.145	0.0	-0.1 to 0.1	0.377	-0.0	-0.1 to 0.1	0.391
Calcium (mg)	0.0	-0.1 to 0.2	0.564	-0.0	-0.2 to 0.2	0.791	-0.2	-0.5 to 0.1	0.042	-0.1	-0.3 to 0.1	0.423
Iron (mg)	0.1	-0.0 to 0.2	0.085	0.1	-0.0 to 0.2	0.044	0.1	-0.1 to 0.2	0.244	0.0	-0.1 to 0.1	0.705
Zinc (mg)	0.2	-0.0 to 0.3	0.012	0.3	-0.0 to 0.6	0.007	-0.0	-0.4 to 0.3	0.725	0.2	-0.1 to 0.5	0.081

[a] Difference in age at natural menopause, unadjusted model (n=910)
[b] Difference in age at natural menopause, model adjusted for the following factors: Physical activity level, alcohol consumption, smoking, social class, total energy intake (n=838)
[c] Difference in age at natural menopause for those aged 50y or below in the fully adjusted model (n=477)
[d] Difference in age at natural menopause for those aged above 50y in the fully adjusted model (n=361)

4.3.3 Sensitivity analysis

Our findings demonstrated that non-vegetarians reach a natural menopause 0.8 years later compared with vegetarians (99% CI 0.2 to 1.4). Exploring associations for non-vegetarians alone showed they had an earlier age at natural menopause associated with an increased consumption of savoury snacks (per portion/day: −1.7 years, 99% CI −3.1 to −0.4) and soft drinks (per portion/day: −1.3 years, 99% CI −2.5 to −0.2) while an increase in intake of oily fish (per portion/day: 3.4 years, 99% CI 0.2 to 6.5) and fresh legumes (per portion/day: 1.4 years, 99% CI 0.2 to 2.7) were associated with a later onset of menopause (Table B.2).

Sensitivity analysis by parity demonstrated a difference for the association between the various food groups and age at natural menopause for nulliparous against the multiparous participants. In multiparous women, a later onset of age at natural menopause was found to be associated with an increased intake of oily fish (per portion/day: 3.3 years, 99% CI 0.3 to 6.3) and fresh legumes (per portion/day: 1.1 years, 99% CI 0.1 to 2.01) while an increase in intake of refined pasta and rice (per portion/day: −1.9 years, 99% CI −3.3 to −0.4) as well as savoury snacks (per portion/day: −1.0 years, 99% CI −2.1 to −0.0) was associated with an earlier age at natural menopause. For nulliparous women, a higher consumption of grapes (per portion/day: 2.5 years, 99% CI 0.0 to 4.9) and poultry (per portion/day: 5.2 years, 99 % CI 0.1 to 10.3) was found to be significantly associated with a later age at natural menopause (Table B.3).

Further adjusting the model by presence of diabetes demonstrated no changes in our results (Table B.4).

4.4 Discussion

This is the first study of women in the UK to report on food and nutrient intake in relation to age at incidence of natural menopause. Of 14 172 women who were followed up for approximately 4 years, 914 women went through a natural menopause. The mean age at natural menopause was 50.5 years with a median age of 51 years. We found that intakes of oily fish and fresh legumes were associated with later age at menopause and intake of refined pasta/rice was associated with an earlier menopause. Only a few previous studies have reported diet in relation to age at natural menopause with a limited number of food items/groups included [10, 12]. Previous research has mainly been

focused on the relationship between socio-demographic as well as lifestyle factors (education status, marital status, parity, etc.) and age at natural menopause [18-21].

Our results demonstrate that each additional increment in fresh legumes portion/day was associated with a later age at natural menopause by 0.9 years. Fresh legumes are a good source of antioxidants, which can partly explain this association. This has been supported by the biochemical and molecular analyses undertaken by Matamoros et al. [22]. Similarly, in a Japanese prospective study the antioxidant properties of green and yellow vegetables were postulated for the association between a higher intake of the green and yellow vegetables and a later age at natural menopause [12]. Oocyte maturation, ovulation, luteolysis and follicle atresia are affected by reactive oxygen species (ROS). Phenolic compounds, vitamins and carotenoids in vegetables counteract the ROS and may thus decrease the proportion of follicles undergoing follicular atresia [23, 24]. Further support of this theory from our findings was a later age at natural menopause with a high intake of vitamin B6 and zinc as both of these have antioxidant properties [23, 25]. Likewise, Stepaniack et al. [26] demonstrated an association between use of vitamin and mineral supplements and a later menopause.

Our findings demonstrate a later age at natural menopause by approximately 3 years for each additional portion/day of oily fish. However, in contrast to our findings, a recent review article as well as a 10-year follow-up study reported an earlier onset of menopause with high intake of polyunsaturated fats [27, 28]. Nagel et al. [10] reported no association between fish intake and age at natural menopause but it was not clear if oily fish was considered separately. Oily fish is a rich source of the omega-3 fatty acid which can potentially improve antioxidant capacity [29]. Therefore, in a similar way to the fresh legumes and vitamins described above, the antioxidant properties exerted by the oily fish intake could possibly offset ROS, therefore decreasing the proportion of follicles undergoing follicular atresia and delaying onset of natural menopause.

In the present study, increasing refined pasta and rice consumption was associated with an earlier age at natural menopause. The EPIC-Heidelberg study also reported a similar association [10]. High consumption of refined carbohydrates (classified as high glycaemic index foods) increases the risk of insulin resistance. Insulin resistance can lead to decreased sex hormone binding globulin levels (SHBG) as a result of the inhibitory effect of insulin on the SHBG production in the liver [30] as well as increased oestrogen levels [31]. High oestrogen levels cause release of the luteinising hormones which triggers ovulation, which might imply more cycles and rapid depletion of oocytes,

consequently leading to an earlier menopause [32]. This can be supported by a recent review study which reported that women with type II diabetes mellitus tend to have an earlier menopause although additional evidence is required to clarify this association [33].

Although we found that fresh legumes are associated with a later menopause, our study further demonstrated that women who were vegetarian had an earlier age at natural menopause compared with non-vegetarians. This finding is in line with other studies which also reported an earlier age at natural menopause among vegetarians [34, 35]. The vegetarian diet, which normally consists of high fibre and no animal fat-containing foods, may affect the levels of the luteinising hormone, follicle stimulating hormone and the length of the menstrual cycle [36]. Previous studies have demonstrated that high fibre and decreased fat intakes were both associated with a lower oestrogen level, which may account for the earlier age at natural menopause among vegetarians [37, 38]. However, caution should be taken in interpreting this finding as vegetarian status was self-reported in this study.

It is possible that results for younger women may differ from those for older women. This could result from different diets between younger and older women [39], and that younger women have less opportunity to report a later menopause. To explore this, stratifying on age at baseline showed reduced associations within each subgroup.

This is the first study looking prospectively at the relationship between diet and age at natural menopause in the UK. Strengths of this study include the investigation of the association between individual nutrients and a wide variety of food groups and age at natural menopause compared with similar few previous studies. Careful adjustment for likely confounders was also carried out in the regression modelling using the DAG. A limitation of this prospective cohort study is that diet was reported by the participants using an FFQ and may thus be subjected to recall bias. However, FFQ enables recording of a long-term diet, thus showing its cumulative influence on the outcome while food diaries/24-hour recall give only a snapshot of the diet. Our sample was also more health conscious given the high number of vegetarians in our sample population and more well-off participants than the general population as shown in the descriptive table (Table 4.1). However, our study still includes women from a range of different background which implies that findings of this study may be extrapolated to other countries.

Women with an earlier menopause spend more years deprived from the benefits of oestrogen compared with women who become menopausal around the normal

menopausal age range, which puts them at a greater risk of some future poor health outcomes such as osteoporosis and heart disease. On the other hand, women with a later onset of menopause are at greater risk of breast, endometrial and ovarian cancers. Our findings confirm that diet may be associated with the age at natural menopause. This may be relevant at a public health level since age at natural menopause may have implications on future health outcomes. Health practitioners might thus also need to take into account the diet of women when dealing with menopause-related issues.

In summary, our study is the first to demonstrate that diet is associated with age at natural menopause in a large cohort of British women. Intakes of oily fish and fresh legumes were found to be associated with a later onset of natural menopause while higher intake of refined pasta and rice was associated with younger age at natural menopause. The nutrients vitamin B6 and zinc were also found to be associated with a later age at natural menopause. Women who were vegetarian had an earlier age at natural menopause compared to non-vegetarians.

What is already known on this subject

Several factors including socio-demographic and reproductive factors are associated with age at natural menopause. Limited existing studies present conflicting evidence between diet and age at natural menopause.

What this study adds

This is the first study to our knowledge which demonstrated that dietary intake affected age at natural menopause in a prospective cohort of British women. This study shows that high intakes of oily fish, fresh legumes as well as vitamin B6 and zinc are associated with a later onset of natural menopause while a high consumption of refined pasta and rice is associated with an earlier age at natural menopause.

References

1. Sarri, G. et al. Guidelines Diagnosis and management of menopause: summary of NICE guidance. *British Medical Journal.* 2015, **351**, pp.1-6.
2. Schoenaker, D.A. et al. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International Journal of Epidemiology.* 2014, **43**(5), pp.1542-1562.
3. Pokoradi, A.J. et al. Factors associated with age of onset and type of menopause in a cohort of UK women. *American Journal of Obstetrics and Gynecology.* 2011, **205**(1), pp.34 e31-13.
4. Jung, S.J. et al. Menarche age, menopause age and other reproductive factors in association with post-menopausal onset depression: Results from Health Examinees Study (HEXA). *Journal of Affective Disorders.* 2015, **187**, pp.127-135.
5. Svejme, O. et al. Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. *BJOG : An International Journal of Obstetrics and Gynaecology.* 2012, **119**(7), pp.810-816.
6. Wellons, M. et al. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. *Menopause.* 2012, **19**(10), pp.1081-1087.
7. Appiah, D. et al. Association of Age at Menopause With Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis. *Journal of the American Heart Association.* 2016, **5**(8).
8. Gold, E.B. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America*. 2011, **38**(3), pp.425-440.
9. Gold, E.B. et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology.* 2001, **153**(9), pp.865-874.
10. Nagel, G. et al. Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg. *Maturitas.* 2005, **52**(3-4), pp.337-347.
11. Dorjgochoo, T. et al. Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. *Menopause.* 2008, **15**(5), pp.924-933.

12. Nagata, C. et al. Association of diet with the onset of menopause in Japanese women. *American Journal of Epidemiology.* 2000, **152**(9), pp.863-867.
13. Cade, J.E. et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). *International Journal of Epidemiology.* 2015, **0**(0), pp.1-11.
14. Feeley, K.M. and Wells, M. Hormone replacement therapy and the endometrium. *Journal of Clinical Pathology.* 2001, **54**(6), pp.435-440.
15. Cade, J.E. et al. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutrition.* 2004, **7**(7), pp.871-878.
16. Cade, J.E. et al. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *International Journal of Epidemiology.* 2007, **36**(2), pp.431-438.
17. Food Standards Agency. *Food Portion Sizes*. London: The Stationary office; 2002.
18. Kato, I. et al. Prospective Study of Factors Influencing the Onset of Natural Menopause. *Journal of Clinical Epidemiology.* 1998, **51**(12), pp.1271-1276.
19. Brambilla, D.J. and McKinlay, S.M. A prospective study of factors affecting age at menopause. *Journal of Clinical Epidemiology.* 1989, **42**(11), pp.1031-1039.
20. van Noord, P.A.H. et al. Age at Natural Menopause in a Population-Based Screening Cohort: The Role of Menarche, Fecundity, and Lifestyle Factors. *Fertility and Sterility.* 1997, **68**(1), pp.95-102.
21. Li, S. et al. Age at natural menopause in relation to all-cause and cause-specific mortality in a follow-up study of US black women. *Maturitas.* 2013, **75**(3), pp.246-252.
22. Matamoros, M.A. et al. Function of antioxidant enzymes and metabolites during maturation of pea fruits. *Journal of Experimental Botany.* 2010, **61**(1), pp.87-97.
23. Ebisch, I.M.W. et al. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. *Human Reproduction Update.* 2007, **13**(2), pp.163-174.
24. Ruder, E.H. et al. Oxidative stress and antioxidants: exposure and impact on female fertility. *Human Reproduction Update.* 2008, **14**(4), pp.345-357.
25. Cheng, S.B. et al. Vitamin B-6 Supplementation Could Mediate Antioxidant Capacity by Reducing Plasma Homocysteine Concentration in Patients with Hepatocellular Carcinoma after Tumor Resection. *BioMed Research International.* 2016, **2016**, pp.1-7.

26. Stepaniak, U. et al. Age at natural menopause in three Central and Eastern European urban populations: The HAPIEE study. *Maturitas.* 2013, **75**(1), pp.87-93.

27. Nagata, C. et al. Associations of physical activity and diet with the onset of menopause in Japanese women. *Menopause.* 2012, **19**(1), pp.75-81.

28. Sapre, S. and Thakur, R. Lifestyle and dietary factors determine age at natural menopause. *Journal of Midlife Health.* 2014, **5**(1), pp.3-5.

29. Kesavulu, M.M. et al. Effect of omega-3 fatty acids on lipid peroxidation and antioxidant enzyme status in type 2 diabetic patients. *Diabetes & Metabolism.* 2002, **28**(1), pp.20-26.

30. Daka, B. et al. Inverse association between serum insulin and sex hormone-binding globulin in a population survey in Sweden. *Endocrine Connections.* 2013, **2**(1), pp.18-22.

31. Yeung, E.H. et al. Longitudinal Study of Insulin Resistance and Sex Hormones over the Menstrual Cycle: The BioCycle Study. *The Journal of Clinical Endocrinology & Metabolism.* 2010, **95**(12), pp.5435-5442.

32. Woodard, T.L. and Bolcun-Filas, E. Prolonging Reproductive Life after Cancer: The Need for Fertoprotective Therapies. *Trends in Cancer.* 2016, **2**(5), pp.222-233.

33. Wellons, M.F. et al. Ovarian aging in women with diabetes: An overview. *Maturitas.* 2017, **96**, pp.109-113.

34. Biela, U. [Determinants of the age at natural menopause]. *Przeglad Lekarski.* 2001, **59**(3), pp.165-169.

35. Morris, D.H. et al. Body Mass Index, Exercise, and Other Lifestyle Factors in Relation to Age at Natural Menopause: Analyses From the Breakthrough Generations Study. *American Journal of Epidemiology.* 2012, **175**(10), pp.998-1005.

36. Hill, P.B. et al. Gonadotrophin release and meat consumption in vegetarian women. *The American Journal of Clinical Nutrition.* 1986, **43**(1), p.37.

37. Bagga, D. et al. Effects of a very-low fat, high-fiber diet on serum hormones and menstrual function - implications for breast-cancer prevention. *Cancer.* 1995, **76**(12), pp.2491-2496.

38. Wu, A.H. et al. Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. *Journal of the National Cancer Institute.* 1999, **91**(6), pp.529-534.

39. Mishra, G.D. et al. Major dietary patterns of young and middle aged women: results from a prospective Australian cohort study. *European Journal of Clinical Nutrition.* 2010, **64**(10), pp.1125-1133.

Chapter 5

Dietary patterns and age at natural menopause in the UK Women's Cohort Study: A comparison between principal component analysis and reduced rank regression

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Abstract

Background: Evidence linking diet and age at natural menopause is still sparse and inconsistent. This study aimed to investigate the prospective associations between dietary patterns derived from two different methods and age at natural menopause.

Methods: Menopausal status was reported at two time points 4 years apart in the UK Women's Cohort Study. Diet of participants was measured using a 217-item food frequency questionnaire at baseline. Principal component analysis (PCA) and reduced ranked regression (RRR) were used to derive dietary patterns for 13,916 women. Cox proportional hazards regressions were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for each pattern in relation to age at natural menopause, adjusting for potential confounders.

Results: Five patterns were identified from the PCA, which we labelled: 'vegetables and legumes', 'animal proteins', 'fruits', 'fats and sweets' and 'low-fat products'. Three patterns were derived from RRR: 'sweets, pastries and puddings', 'low-fat dairy and meat', and 'red meat and processed meat'. Women who scored higher on the 'animal proteins' pattern were 6% less likely to have gone through a natural menopause (HR: 0.94, 95% CI: 0.90 to 0.97) compared to those who scored lower. The 'red meat and processed meat' pattern also predicted a 7% higher risk for a later natural menopause (HR: 0.93, 95% CI: 0.87 to 1.00).

Conclusions: This is the first study investigating dietary patterns and age at natural menopause. Both PCA and RRR are useful in deriving dietary patterns which can influence the onset of natural menopause.

5.1 Introduction

The current life expectancy of females in the United Kingdom is estimated to be 82.9 years [1], and the average age of menopause is 51 years [2]. Women in the UK are therefore expected to spend around one-third of their life in the menopausal state. The timing of menopause influences future health outcomes of women, such that an early age at menopause increases the risk of bone fractures and cardiovascular diseases while an increased risk of breast, ovarian and endometrial cancer have been associated with a late onset of menopause [3]. Moreover, the type and severity of menopausal symptoms may also be influenced by the timing of menopause [4]. The onset of menopause is under the influence of several factors, potentially including diet. Contradictory results have been reported, and there is limited evidence on the link between diet and age at menopause [3, 5].

Lately, more emphasis has been placed on exploring dietary patterns rather than studying individual food or food groups in examining diet and disease relationships. The complex mechanisms, by which individual food items form part of the diet may influence a disease or a health outcome, make the study of dietary patterns important [6, 7]. Rather than eating foods and nutrients in isolation, individuals eat foods in various quantities, combinations, proportions and varieties. The study of dietary patterns thus take into account the cumulative effects of different aspects of the diet and also considers the interactions and synergies of the different food components which could influence health outcomes [8]. Additionally, the effects of single foods and nutrients could be too small to spot, but given that dietary patterns consider the cumulative effect of several foods and nutrients, this might be larger and easier to detect. Several different methods have been used to define dietary patterns including theoretical, empirical and hybrid methods [9].

Principal component analysis (PCA), one of the empirical methods, uses the correlation matrix of food intake variables to identify common patterns of food consumption within the data by accounting for the largest amount of variation in the diet [9, 10]. More recently, reduced rank regression (RRR), a hybrid method has been used to generate dietary patterns [11]. This technique identifies dietary patterns based on several nutrients or biomarkers that have been linked to the disease of interest [10]. The strength of PCA can be the limitation of RRR and vice versa. Principally, both methods use data reduction techniques to generate dietary patterns. PCA derived dietary patterns tend to

reflect the actual dietary behaviours of the population while RRR dietary patterns could be behaviourally irrelevant as the food components forming part of the patterns may not be consumed together [12]. As the definition suggests, dietary patterns derived from RRR are rather based on biologically relevant factors. Thus, comparing findings using both methods could provide useful insights for this study.

To date, mostly individual foods and food groups have been studied in relation to age at menopause [5, 13, 14]. Therefore, this study aims to compare dietary patterns derived by PCA and RRR and to investigate their associations prospectively with age at natural menopause. For RRR, selected response variables represent important risk factors of the timing of natural menopause. Factors such as age at menarche, body mass index (BMI) and total energy intake [3, 5, 13, 15] have all been associated with the timing of menopause. However, the conflicting findings make a definitive conclusion on the risk factors difficult. Therefore, the RRR derived dietary patterns should be considered as an initial hypothesis, rather than patterns with a confirmed association.

5.2 Methods

5.2.1 Study design and participants

14,172 women from the UKWCS [16] who participated at both baseline and follow-up were considered for this study. Women aged 35 years or more responded to self-administered questionnaires which asked about demographic details, weight history, physical activity, reproductive history, anthropometric, and other health-related factors. Age at natural menopause was defined as the age at the last menstrual period prior to permanent cessation of menstruation for 12 consecutive months [17]. To be considered naturally postmenopausal at follow-up, women had to be pre or peri-menopausal, that is, having one or more menstrual periods in the last 12 months, not pregnant and never used HRT at baseline as well as not using HRT at follow-up since these endogenous hormones may influence the bleeding pattern.

5.2.2 Dietary assessment

Diet was assessed using a validated 217-item food frequency questionnaire (FFQ) which was developed from the FFQ used in the European Prospective Investigation into Cancer (EPIC) study. Participants were asked to report their consumption frequency based on 10 pre-coded classifications of the frequency of consumption ranging from

'never' to '6 or more times per day' over the last 12 months. The reported frequency for each food item was then converted to daily intake [16].

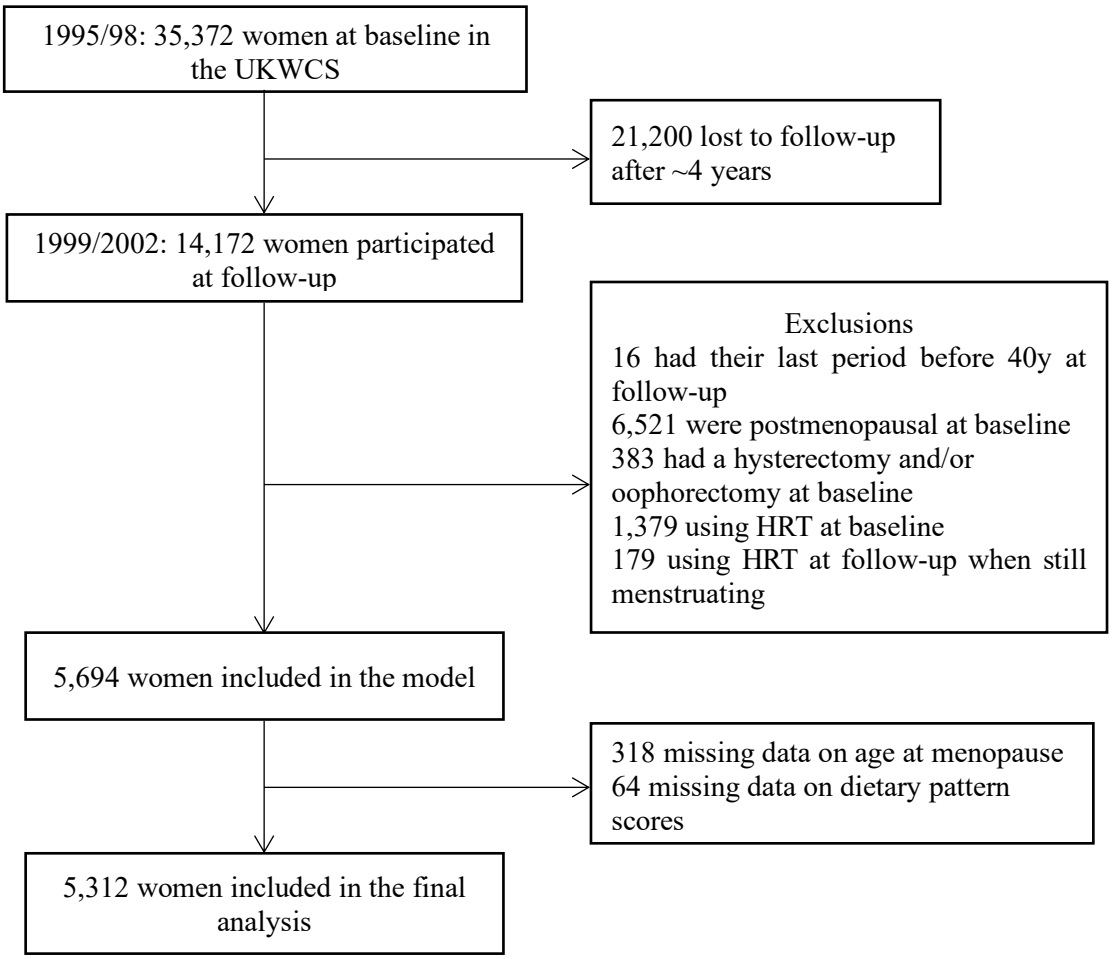

Figure 5.1 Flow diagram for participants' selection

5.2.3 Statistical analyses

Principal component analysis (PCA) and reduced rank regression (RRR) were used to derive dietary patterns. While the rank of the covariance matrix used for PCA corresponds to the number of foods/food groups, in the RRR method, the rank corresponds to the number of selected response variables. To ensure compatibility of the results from PCA and RRR, it is recommended to choose the minimum foods/food groups and response variables for both methods respectively [10]. Therefore, to simplify the complexity of our data, the 217 individual food items (in grams/day) were manually classified into 64 food groups according to the similarity of nutrient profiles or culinary usage of the foods. All 64 food groups were subsequently used to identify dietary patterns.

The number of factors retained was according to the combination of food group components with an eigenvalue >1.0 and examination of the breakpoint in the scree plot (Figure C.1), resulting in five factors retained for further analyses. The factors were rotated by an orthogonal transformation (Varimax option) to achieve a simpler structure with greater interpretability. Food groups with a factor loading ≥0.2 on a component were considered informative for interpretation of the dietary patterns. The Kaiser–Meyer–Olkin measure verified the sampling adequacy for the PCA, KMO = 0.82, which is considered as meritorious.

RRR was applied to derive dietary patterns predictive of age at natural menopause using Stata (StataCorp, version 14.0) in combination with the PLS option in SAS (version 9.3; SAS Institute). A directed acyclic graph (DAG) was used as the conceptual framework for the RRR (Figure C.2). Briefly, RRR determines linear combinations of predictor variables (e.g., food group intake) that explain as much as possible of the variation in the response variables (e.g., nutrients, biomarkers or risk factors), that are presumed to affect disease risk, in this case, age at natural menopause [10, 18]. The 64 food groups were entered as the predictor variables and the variables BMI, total energy intake and age at menarche were treated as response variables. The number of dietary patterns extracted using RRR analysis is determined by the number of response variables given that RRR aims to explain a high proportion of response variation [10], hence three dietary patterns were extracted. Factor scores were calculated for each of the derived patterns by summing the products of the observed consumption frequency and the factor loading for each of the significant food groups [9]. The groups that had a negative factor loading were also retained to maintain the complexity of eating habits.

Cox's proportional hazard models were fitted for each dietary pattern separately to identify the predictors of age at natural menopause using Stata (StataCorp, version 14.0). At follow-up, if the event was not a natural menopause, this was considered as censored. Age at phase 2 was considered as the time-scale variable for women who were still menstruating at follow-up while for those who were naturally postmenopausal at phase 2, their age of last natural period was used as the time variable [19]. Therefore, women who were postmenopausal, using HRT, had a hysterectomy or oophorectomy at baseline; using HRT at follow-up when still menstruating and those for whom age at natural menopause was either before the age of 40y (as this could be chemically induced) or after 65y were all excluded from the Cox's proportional hazard models (Figure 5.1).

Moreover, in this time-to-event model, women who were already postmenopausal at baseline were excluded as no information were available to infer whether they had a natural menopause. The proportional hazards assumption was tested graphically for all exposures and covariates in the model as well as using Schoenfeld residuals. The regression models were adjusted for potential confounding factors: physical activity (MET-hours/week), smoking status (current vs not current smoker), alcohol consumption (g/day) and social class (routine and manual, intermediate, professional and managerial) as identified by the DAG. Results of the regression models are expressed as hazard ratios (HR) and 95% CIs. A HR >1.00 represented a positive association with the incidence of a natural menopause with reference to the dietary pattern score per standard deviation.

5.3 Results

5.3.1 Principal component analysis

Using PCA, five dietary patterns were identified that together explained 16% of the variance in dietary intake as measured by the FFQ (Table 5.1). Factor 1 was characterised by high factor loadings for refined pasta and rice, pulses, and vegetables and was labelled 'vegetables and legumes'. Factor 2 was highly loaded for fish, shellfish, meat, poultry, and offal was labelled 'animal proteins'. Factor 3 which had high loadings of various fruits (e.g. stone fruits, citrus, etc.) was labelled 'fruits'. Factor 4 was labelled as 'fats and sweets' as it was characterised by high loadings for margarine, confectionaries and spreads, biscuits, cakes, pastries and puddings. Factor 5 (described as low-fat products) had positive factor loadings for low-fat dairy products, spreads, and dressings. Whilst these labels are subjective, they do describe the over-riding characteristics of the components, which form quite distinct components after rotation.

5.3.1.1 Participants' characteristics

Participants from the highest quintiles of the 'vegetables and legumes', 'animal proteins', and 'fats and sweets' dietary patterns were older at baseline compared to participants in the lowest quintiles. On the other hand, participants from the highest quintiles of the 'fruits' and 'low-fat products' dietary patterns were younger at baseline (Table 5.2). BMI of women from the highest quintile of the 'animal proteins' (25.5 ± 5.2 vs. 22.9 ± 3.6) and the 'low-calorie fats' (25.3 ± 5.6 vs 23.2 ± 3.7) patterns was higher as compared to women from the lowest quintile (Table 5.2).

Table 5.1 Factor loadings for food groups with a value >0.2 in varimax rotated principal components and for reduced rank regression*

	Principal component analysis (PCA)					**Reduced rank regression (RRR)**		
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 1	Factor 2	Factor 3
Potatoes with added fat	–	–	–	0.21	–	–	–	–
Refined pasta and rice	0.23	–	–	–	–	–	–	–
Wholegrain pasta and rice	–	–	–	–	–	–	–	-0.24
Low fat dairy products	–	–	–	–	0.45	–	0.20	–
High fat dairy products	–	–	–	–	-0.36	–	–	–
Butter and hard margarine	–	–	–	–	-0.33	–	–	–
Margarine	–	–	–	0.23	–	–	–	–
Low fat spreads	–	–	–	–	0.30	–	–	–
Low fat dressing	–	–	–	–	0.29	–	0.21	–
Fish and fish dishes	–	0.30	–	–	–	–	–	–
Shell fish	–	0.26	–	–	–	–	–	–
Pulses	0.22	–	–	–	–	–	–	–
Vegetable dishes	0.37	–	–	–	–	–	–	-0.31
Textured vegetable protein	0.21	-0.23	–	–	–	–	–	–
Allium	0.22	–	–	–	–	–	–	–
Fresh legumes	0.22	–	–	–	–	–	–	–
Mediterranean vegetables	0.36	–	–	–	–	–	–	–
Salad vegetables	0.23	–	–	–	–	–	–	–
Mushrooms	0.31	–	–	–	–	–	–	–
Stone fruits	–	–	0.36	–	–	–	–	–
Deep orange & yellow fruits	–	–	0.33	–	–	–	–	–
Grapes	–	–	0.22	–	–	–	–	–
Citrus family fruits	–	–	0.24	–	–	–	–	–
Rhubarb	–	–	0.24	–	–	–	–	–
Berries	–	–	0.35	–	–	–	–	–
Pomes	–	–	0.28	–	–	–	–	–
Confectionary & spreads	–	–	–	0.31	–	0.25	–	–
Nuts and seeds	–	–	–	–	-0.21	–	-0.24	–
Tea	–	–	–	0.21	–	–	–	–
Low calorie/diet soft drinks	–	–	–	–	–	–	0.34	–
Wines	–	–	–	-0.22	–	–	–	–
Biscuits	–	–	–	0.32	–	–	–	–
Cakes	–	–	–	0.37	–	–	–	–
Pastries and Puddings	–	–	–	0.37	–	0.22	–	–
Red meat	–	0.41	–	–	–	–	0.31	0.22
Processed meat	–	0.35	–	–	–	–	0.35	0.25
Poultry	–	0.37	–	–	–	–	0.27	–
Offal	–	0.25	–	–	–	–	–	–
Prop. VAR explained (%)	4.1	3.8	3.7	2.4	2.0	6.0	9.6	13.2
Cumul. VAR explained (%)	0.1	0.1	0.2	0.2	0.3	32.3	36.1	36.5

*Only food groups with factor loadings | ≥0.2| are displayed and listed in order for simplicity and ease of interpretation; PCA scores – Factor 1: Vegetables and legumes, Factor 2: Animal proteins, Factor 3: Fruits, Factor 4: Fats and sweets, Factor 5: Low-fat products; RRR score – Factor 1: Sweets, pastries and puddings, Factor 2: Low-fat dairy and meat, Factor 3: Red meat and processed meat

5.3.1.2 Association between dietary patterns and age at natural menopause

For dietary patterns derived by PCA, the unadjusted model demonstrated a 5% higher risk for a later natural menopause with the 'animal proteins' (95% CI: 0.91 to 0.98). On the other hand, the 'fruits' pattern was associated with a 5% higher risk for an earlier menopause (95% CI: 1.01 to 1.09). No evidence of an association was found between the 'vegetables and legumes', 'fats and sweets', and 'low-fat products' and age at natural menopause (Table 5.4). After adjusting for the potential confounders, the 'animal proteins' dietary pattern was still associated with a higher likelihood for a later age at natural menopause (HR: 0.94, 95% CI: 0.90 to 0.97).

5.3.2 Reduced ranked regression

For the RRR method, three dietary patterns were identified and allocated a subjective label. The three dietary patterns explained about 29% of the total variance in dietary intake. Factor 1: 'sweets, pastries and puddings', Factor 2: 'low-fat dairy and meat', Factor 3: 'red meat and processed meat' (Table 5.1). The first dietary pattern was characterised by high loadings for confectionaries and spreads as well as pastries and puddings. 'Low-fat dairy and meat' pattern had a high factor loading for low-fat dairy products, low-fat dressings, low calorie/diet soft drinks, red meat, processed meat, and poultry. 'Red meat and processed meat' pattern was characterised by high loadings for red meat and processed meat while negative loadings for wholegrain pasta and rice as well as vegetable dishes. Factor 3 explained the highest variation with 13.6% of the variation in the responses, and collectively they explain 36.5% of the variation in the responses.

5.3.2.1 Participants' characteristics

Participants from the highest quintiles of the three dietary patterns derived by RRR were older at baseline compared to women in the lowest quintiles of the dietary patterns' scores. In addition, these women were more likely to be parous and married as well as less likely to have a degree level and be in the professional and managerial class (Table 5.3). Women in the highest quintiles for the 'low-fat dairy and meat' (37% vs. 11%) and 'red meat and processed meat' (26% vs. 17%) patterns were more likely to be categorised as obese as compared to women in the lowest quintiles of these patterns.

Table 5.2 Characteristics of study participants

Characteristics of 13,916 women participating in the UK Women's cohort study for the lowest (Q1) and highest (Q5) quintiles of dietary patterns identified using principle component analysis at baseline

	Vegetables and legumes		**Animal proteins**		**Fruits**		**Fats and sweets**		**Low-calorie fats**	
Sample characteristics	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**
Age at baseline, y[a]	51.2 ± 9.1	52.6 ± 8.9	49.9 ± 8.5	54.0 ± 9.2	55.0 ± 8.9	49.4 ± 8.8	50.5 ± 8.4	55.3 ± 9.5	53.0 ± 9.5	52.0 ± 8.9
Body mass index, kg/m²	24.4 ± 4.3	24.0 ± 4.8	22.9 ± 3.6	25.5 ± 5.2	24.5 ± 5.4	23.7 ± 4.0	24.1 ± 4.6	24.1 ± 4.1	23.2 ± 3.7	25.3 ± 5.6
Obese, ≥30 kg/m² [*n* (%)]	264 (24)	212 (20)	117 (11)	360(33)	252 (23)	194 (18)	213 (20)	227 (21)	134 (12)	348 (32)
Physical activity, min/day	0.2 ± 0.5	0.3 ± 0.6	0.3 ± 0.5	0.2 ±0.5	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.2 ± 0.4	0.3 ± 0.6
Alcohol consumption, g/day	7.8 ± 10.6	8.6 ± 11.4	7.1 ± 9.5	9.0 ± 11.0	7.6 ± 9.8	9.1 ± 12.6	19.0 ± 15.4	3.1 ± 4.5	7.8 ± 9.6	8.3 ± 12.0
Smoking, [*n* (%)]	339 (29)	190 (16)	201 (17)	286 (25)	182 (16)	292 (25)	448 (39)	103 (9)	251 (22)	230 (20)
Parous, [*n* (%)]	1995 (19)	2069 (20)	1854 (18)	2230 (22)	1969 (19)	2099 (20)	1968 (19)	2075 (20)	2007 (19)	2110 (20)
Ever married, [*n* (%)]	1984 (19)	2137 (20)	1904 (18)	2283 (22)	2002 (19)	2173 (21)	2131 (20)	2054 (20)	2000 (19)	2187 (21)
Degree level, [*n* (%)]	631 (16)	828 (21)	1079 (27)	544 (14)	706 (18)	905 (23)	1010 (26)	548 (14)	978 (25)	542 (14)
Professional and managerial class, [*n* (%)]	1633 (18)	1914 (21)	2012 (22)	1570 (17)	1813 (20)	1830 (20)	1991 (22)	1644 (18)	1887 (21)	1701 (19)
Nutrient intake										
Fibre (g)	16.3 ± 5.2	39.0 ± 12.6	30.6 ± 11.9	26.1 ± 12.0	27.0 ± 12.2	30.0 ± 12.3	22.9 ± 11.5	32.4 ± 11.9	27.0 ± 12.5	29.4 ± 12.1
% energy from fats	32.7 ± 5.8	31.5 ± 5.9	30.7 ± 6.3	34.6 ± 4.7	28.1 ± 5.4	35.5 ± 5.0	34.1 ± 5.8	30.6 ± 5.5	36.0 ± 5.6	29.4 ± 5.1
% energy from proteins	15.6 ± 2.7	14.7 ± 2.5	13.7 ± 2.0	16.3 ± 2.6	16.6 ± 3.0	13.6 ± 1.9	15.2 ± 2.7	14.8 ± 2.3	13.6 ± 2.2	16.9 ± 2.6
% energy from carbohydrates	48.9 ± 6.6	51.8 ± 6.5	53.3 ± 6.6	47.0 ± 5.5	52.7 ± 7.1	48.9 ± 5.4	44.6 ± 5.9	54.1 ± 5.3	48.2 ± 6.8	51.4 ± 5.9
Vitamin C (mg)	97.4 ± 35.9	281.4 ± 121.1	191.9 ± 101.5	181.6 ± 112.5	209.5 ± 120.6	176.7 ± 94.5	170.2 ± 110.6	195.5 ± 99.8	186.9 ± 118.3	186.9 ± 95.5
Vitamin B_1 (mg)	2.0 ± 1.2	4.6 ± 3.6	4.5 ± 4.0	2.7 ± 1.3	2.5 ± 1.6	4.6 ± 3.8	2.8 ± 2.7	3.7 ± 2.7	3.0 ± 2.3	3.9 ± 3.3
Vitamin B_2 (mg)	2.0 ± 0.7	3.1 ± 1.1	2.4 ± 0.9	3.0 ± 1.0	2.4 ± 0.9	2.8 ± 1.0	2.2 ± 0.9	3.1 ± 0.9	2.5 ± 0.9	3.0 ± 0.9
Vitamin B_6 (mg)	2.1 ± 0.6	3.7 ± 1.2	2.6 ± 1.0	3.3 ± 1.2	2.8 ± 1.1	3.1 ± 1.1	2.6 ± 1.3	3.3 ± 1.0	2.7 ± 1.1	3.2 ± 1.1
Vitamin B_{12} (μg)	117.0 ± 300.1	289.6 ± 566.6	237.2 ± 475.9	172.6 ± 356.4	231.4 ± 481.3	186.4 ± 416.5	86.6 ± 226.1	370.5 ± 651.9	183.7 ± 409.1	269.4 ± 560.2
Folate (μg)	288.9 ± 77.5	564.7 ± 181.7	424.5 ± 156.9	454.3 ± 172.5	395.4 ± 158.4	478.0 ± 172.2	375.1 ± 167.4	483.9 ± 155.9	411.4 ± 157.7	465.5 ± 166.7
Vitamin D (μg)	2.6 ± 1.3	3.8 ± 2.6	2.1 ± 1.3	4.4 ± 2.1	3.0 ± 2.1	3.7 ± 2.1	2.9 ± 2.1	4.0 ± 2.0	2.9 ± 1.7	4.0 ± 2.5

Table 5.2 Continued

	Vegetables and legumes		Animal proteins		Fruits		Fats and sweets		Low-calorie fats	
Sample characteristics	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**
Vitamin A (μg)	901.1 ± 427.9	1684.0 ± 754.8	1091.4 ± 512.3	1700.4 ± 785.8	1237.8 ± 704.8	1416.5 ± 641.2	1292.0 ± 717.9	1380.0 ± 630.1	1367.4 ± 657.2	1371.1 ± 685.1
Vitamin E (mg)	6.8 ± 2.9	14.1 ± 5.5	11.4 ± 5.2	10.8 ± 5.0	8.4 ± 4.1	13.5 ± 5.5	9.5 ± 4.9	12.0 ± 5.1	11.2 ± 5.2	10.0 ± 4.8
Calcium (mg)	945.4 ± 307.3	1421.0 ± 498.3	1074.4 ± 428.9	1324.7 ± 436.2	1084.3 ± 399.5	1367.2 ± 465.7	1014.8 ± 417.6	1411.3 ± 418.9	1133.6 ± 424.4	1359.4 ± 432.0
Iron (mg)	13.4 ± 5.4	24.8 ± 8.9	19.3 ± 7.9	20.6 ± 8.5	18.1 ± 8.2	21.3 ± 8.3	17.1 ± 7.6	22.4 ± 9.0	18.9 ± 8.3	20.7 ± 8.6
Zinc (mg)	8.9 ± 2.7	14.3 ± 5.7	10.5 ± 3.8	14.5 ± 5.4	10.8 ± 4.9	13.1 ± 4.6	10.8 ± 5.4	13.3 ± 3.9	11.6 ± 5.3	12.9 ± 4.3

[a]mean ± SD (all such values)

Table 5.3 Characteristics of study participants

Characteristics of 13,916 women participating in the UK Women's cohort study for the lowest (Q1) and highest (Q5) quintiles of dietary patterns identified using reduced ranked regression at baseline

	Sweets, pastries and puddings		**Low-fat dairy and meat**		**Red meat and processed meat**	
Sample characteristics	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**
Age at baseline, y [a]	51.3 ± 8.8	53.1 ± 9.2	51.3 ± 9.2	52.8 ± 8.8	50.7 ± 8.4	53.7 ± 9.4
Body mass index, kg/m²	24.0 ± 4.2	24.4 ± 4.9	22.9 ± 3.6	25.7 ± 5.7	23.8 ± 4.6	24.5 ± 4.4
Obese, ≥30 kg/m² [*n* (%)]	221 (20)	256 (23)	115 (11)	403 (37)	188 (17)	278 (26)
Physical activity, min/day	0.2 ± 0.5	0.3 ± 0.6	0.3 ± 0.4	0.3 ± 0.6	0.3 ± 0.5	0.2 ± 0.5
Alcohol consumption, g/day	9.7 ± 12.5	7.4 ± 8.6	7.4 ± 9.7	7.8 ± 9.7	7.7 ± 11.1	8.6 ± 11.2
Smoking, [*n* (%)]	354 (31)	177 (15)	186 (16)	314 (27)	165 (14)	339 (29)
Parous, [*n* (%)]	1854 (18)	2135 (21)	1890 (18)	2195 (21)	1988 (19.3)	2105 (20)
Ever married, [*n* (%)]	1900 (18)	2177 (21)	1903 (18)	2212 (21)	2044 (20)	2125 (20)
Degree level, [*n* (%)]	820 (21)	735 (19)	1078 (27)	520 (13)	957 (24)	605 (15)
Professional and managerial class, [*n* (%)]	1797 (20)	1830 (20)	1966 (22)	1647 (18)	1987 (22)	1618 (18)
Nutrient intake						
Fibre (g)	17.1 ± 5.5	38.4 ± 13.1	29.1 ± 12.6	25.5 ± 11.3	36.3 ± 13.4	19.8 ± 7.7
% energy from fats	32.4 ± 6.2	31.5 ± 5.5	33.2 ± 6.1	31.2 ± 5.2	30.1 ± 5.7	35.4 ± 5.1
% energy from proteins	15.2 ± 2.8	15.1 ± 2.5	13.4 ± 2.0	16.9 ± 2.6	14.6 ± 2.4	15.3 ± 2.6
% energy from carbohydrates	48.5 ± 7.3	52.0 ± 5.9	51.2 ± 6.7	49.8 ± 5.9	53.4 ± 6.0	46.7 ± 6.2
Vitamin C (mg)	109.7 ± 43.7	267.8 ± 126.8	188.6 ± 105.0	176.2 ± 107.2	246.7 ± 127.7	134.4 ± 67.3
Vitamin B_1 (mg)	2.0 ± 1.5	4.7 ± 3.6	3.7 ± 3.4	2.9 ± 2.0	4.9 ± 4.1	2.2 ± 1.1
Vitamin B_2 (mg)	1.7 ± 0.5	3.4 ± 1.0	2.3 ± 0.9	3.0 ± 0.9	3.0 ± 1.0	2.3 ± 0.8
Vitamin B_6 (mg)	1.9 ± 0.5	3.9 ± 1.2	2.6 ± 1.0	3.1 ± 1.1	3.3 ± 1.2	2.6 ± 0.9
Vitamin B_{12} (µg)	102.5 ± 284.0	323.4 ± 606.0	251.4 ± 504.8	189.6 ± 394.9	278.8 ± 522.9	139.3 ± 325.1
Folate (µg)	273.0 ± 68.8	582.3 ± 173.2	417.1 ± 164.3	433.3 ± 161.6	517.0 ± 185.9	350.8 ± 126.0
Vitamin D (µg)	2.2 ± 1.2	4.2 ± 2.5	2.7 ± 2.0	3.8 ± 2.0	3.2 ± 2.5	3.3 ± 1.6

Table 5.3 Continued

	Sweets, pastries and puddings		Low-fat dairy and meat		Red meat and processed meat	
Sample characteristics	**Q1**	**Q5**	**Q1**	**Q5**	**Q1**	**Q5**
Vitamin A (μg)	864.7 ± 404.7	1731.3 ± 763.8	1205.4 ± 597.6	1367.7 ± 699.7	1431.2 ± 713.4	1274.6 ± 643.4
Vitamin E (mg)	6.9 ± 3.0	13.9 ± 5.5	11.7 ± 5.5	9.5 ± 4.4	12.8 ± 5.6	8.6 ± 3.9
Calcium (mg)	785.9 ± 234.3	1594.0 ± 437.9	1016.3 ± 436.3	1378.2 ± 404.5	1372.3 ± 495.8	1031.5 ± 370.6
Iron (mg)	13.0 ± 4.8	25.6 ± 9.1	19.0 ± 8.2	19.3 ± 8.2	23.0 ± 8.7	15.9 ± 6.5
Zinc (mg)	7.9 ± 2.2	15.6 ± 5.4	10.6 ± 4.1	13.0 ± 5.3	13.0 ± 5.4	11.0 ± 3.9

[a]mean ± SD (all such values)

5.3.2.2 Association between dietary patterns and age at natural menopause

In the unadjusted model, no evidence of an association was found between the dietary patterns derived from the RRR and age at menopause (Table 5.4). After adjusting for the potential confounders, smoking status, education level, social class, and physical activity level, the 'red meat and processed meat' pattern was associated with a 7% higher risk for a later menopause (95% CI: 0.87 to 1.00), while no evidence of an association was found with the 'sweets, pastries and puddings' and 'low-fat dairy and meat' patterns and age of natural menopause.

Table 5.4 Adjusted and unadjusted hazard ratios (HR) for age at natural menopause and corresponding 95% confidence intervals (CI)

	Crude[a]			Model 1[b]		
Dietary patterns	HR	95% CI	*P*	HR	95% CI	*P*
Principal component analysis						
Vegetables and legumes	0.99	0.96 to 1.01	0.34	1.00	0.97 to 1.03	0.92
Animal proteins	0.95	0.91 to 0.98	<0.01	0.94	0.90 to 0.97	<0.01
Fruits	1.05	1.01 to 1.09	0.02	1.04	0.99 to 1.08	0.12
Fats and sweets	1.00	0.95 to 1.05	0.94	1.00	0.94 to 1.07	0.98
Low-calorie fats	0.99	0.95 to 1.04	0.77	0.97	0.92 to 1.03	0.30
Reduced ranked regression						
Sweets, pastries and puddings	0.95	0.89 to 1.01	0.12	0.96	0.88 to 1.04	0.28
Low-fat dairy and meat	0.96	0.89 to 1.02	0.17	0.97	0.90 to 1.04	0.38
Red meat and processed meat	0.95	0.89 to 1.01	0.11	0.93	0.87 to 1.00	0.05

[a] Unadjusted model (n=5,312)
[b] Model adjusted for covariates: smoking status, education level, social class, physical activity level (n=4,920)

5.3.3 Correlation between dietary patterns derived from principal component analysis and reduced rank regression

The 'vegetables and legumes' dietary pattern was strongly and positively correlated with the 'sweets, pastries and puddings' dietary pattern while it was negatively correlated with the 'red meat and processed meat' dietary pattern (Table 5.5). The 'animal proteins' dietary pattern derived from PCA was positively correlated with the 'low-fat dairy and meat' and 'red meat and processed meat dietary patterns. The low-fat products' had a strong positive correlation with the 'low-fat dairy and meat' dietary pattern. It conversely had a weak negative correlation with the 'red meat and processed meat'.

Table 5.5 Correlation between dietary patterns derived from principal component analysis and reduced rank regression (n=13,916)

Reduced ranked regression	Sweets, pastries and puddings		Low-fat dairy and meat		Red meat and processed meat	
	r	95% CI	*r*	95% CI	*r*	95% CI
Principal component analysis						
Vegetables and legumes	0.79	0.78 to 0.79	-0.13	-0.15 to -0.11	-0.66	-0.67 to -0.66
Animal proteins	0.27	0.26 to 0.29	0.59	0.58 to 0.60	0.46	0.45 to 0.48
Fruits	0.19	0.18 to 0.21	-0.13	-0.14 to -0.11	0.03	0.02 to 0.05
Fats and sweets	0.31	0.29 to 0.32	0.08	0.06 to 0.09	-0.10	-0.12 to -0.09
Low-calorie fats	0.08	0.06 to 0.09	0.51	0.50 to 0.52	-0.28	-0.29 to -0.26

5.4 Discussion

The objective of this study was to find the associations between dietary patterns derived from PCA and RRR and the likelihood of becoming menopausal during the follow-up period of the UKWCS. We identified five dietary patterns using PCA while three patterns were derived using RRR. Dietary patterns generated from this study are in line with studies that looked at dietary patterns and health outcomes among postmenopausal women [6, 20].

Given that the aims of the two methods differ such that PCA derived patterns usually reflect the dietary behaviours in the population while RRR derived patterns are based on the risk factors of the health outcome, different dietary patterns can be expected in the same study sample. Nevertheless, in this study dietary patterns generated from the two methods were quite similar and were correlated. In line with this study, Sauvageot et al. [21] also reported similar findings. For instance, we found that the ‘animal proteins’ pattern was moderately correlated with the RRR-patterns ‘low-fat dairy and meat’ and the ‘red meat and processed meat’. The PCA-pattern ‘fats and sweets’ was moderately correlated with the ‘sweets, pastries and puddings’ pattern derived from RRR. Moreover, the ‘vegetables and legumes’ pattern was positively correlated with the ‘sweets, pastries and puddings’ pattern and negatively correlated with the ‘red meat and processed meat’ pattern both derived from RRR.

Comparing the relationship between dietary patterns and the chance of experiencing a menopause, we found that the ‘animal proteins’ derived from PCA and the ‘red meat and processed meat’ derived from RRR patterns were found to be associated with a higher chance of experiencing a later menopause. As no previous study has

specifically investigated dietary patterns in relation to the timing of natural menopause direct comparison with other studies is impossible. Our recent findings for the association between food groups and the timing of onset of natural menopause demonstrated that a higher consumption of oily fish and fresh legumes were both associated with a later onset of menopause while a higher intake of refined pasta and rice was linked to an earlier onset of menopause [22]. Interestingly, these food items did not form part of any of the dietary patterns as they contributed to eigenvalues below 0.2 implying that they did not explain as large an amount of variance as compared to the other food items [23]. Yet our previous findings [22] are in line with the current results such that the intake of an extra portion of fish, red meat and processed meat resulted in a positive estimate, indicating a later onset of menopause. The use of different analytical methods, multiple linear regression and survival analysis, could have accounted for the observed disparities. While the previous analysis was restricted to 914 women who experienced a natural menopause at follow-up, this study was rather based on the whole cohort. The fact that not all of them will have achieved menopause at the time of follow-up was considered here as these participants contribute to crucial data that they quitted at a certain amount of time without having reached a menopause is itself informative.

In line with the few studies which have evaluated the association between food groups or individual food items and age at natural menopause, a later onset of menopause has been demonstrated with the consumption of meat [13, 24, 25]. On the other hand, according to a recent study including women from the Nurses' Health Study II, a higher risk of an earlier menopause was reported with each 1 serving per day of red meat and no evidence of an association was demonstrated between animal protein intake and an early menopause [26]. The main disparity in findings is because meat consumption was explored individually rather than as part of a dietary pattern. Additionally, the Nurses' Health Study II consisted of much younger women at the study entry (25-42 years) to investigate the risk of an early menopause, while women in the UKWCS were older at baseline and we explored the association between overall risk of menopause and diet rather than the early menopause.

Some components in red meat such as haem iron, heterocyclic amines in cooked meat and exogenous hormone residues are potentially oestrogenic [27]. Thus, the consumption of red and processed meats could lead to a higher circulating oestrogen level and contribute to the feedback mechanisms of the menstrual cycle. Supporting this

hypothesis, a randomised controlled trial among 272 premenopausal women demonstrated that serum levels of oestrone and oestradiol were higher among non-vegetarians as compared to with minimal meat intake (vegetarians and pescatarians) [28]. Moreover, according to a cross-sectional study among women in the Nurses' Health Study, a 'Western' dietary pattern which was highly loaded with intakes of red and processed meats, refined grains, sweets, and desserts was associated with a higher level of oestradiol [29]. On the other hand, a traditional Mediterranean diet, that is, a low intake of animal fats and proteins and higher intake of vegetables and fruits was associated with a reduced endogenous level of oestrogen [30]. Furthermore, in our study, the 'animal proteins' pattern was positively correlated with the RRR-derived 'red meat and processed meat' pattern. The 'red meat and processed meat' pattern was also negatively correlated with the 'vegetables and legumes' pattern generated from PCA.

According to a systematic review, premature ovarian failure is characterised by amenorrhea, hypergonadotropinaemia as well as oestrogen deficiency [31]. Moreover, studies have indicated that an increased level of follicle stimulating hormones (FSH) at the start of the menstrual cycle could mean an earlier reproductive ageing. Oestrogen and FSH levels are related; higher oestrogen levels have been associated with a reduced level of FSH which possibly led to delayed or skipped ovulations [32-34]. Consequently, it is plausible that by sustaining the hormonal feedback loop and by preventing or delaying the ovum from undergoing ovulation, a higher oestrogen level could put off the onset of menopause. However, the exact mechanism for the association between oestrogen level and the timing of menopause still need to be elucidated.

Our study has some potential limitations. These include the use of an FFQ to estimate dietary intake, and self-reported age at natural menopause which are both prone to recall bias and measurement errors. However, the FFQ used in this study has been previously validated against biomarkers [16]. Moreover, some volunteer bias may be likely as recruitment of participants for the UKWCS was based on a volunteer basis from a World Cancer Research Fund mailing list of previous questionnaire participants. The RRR method is limited due to the data-driven approaches, including that the identified dietary patterns are specific to the population under study. This issue can be partly sorted by validating the method in other populations [35]. Therefore, caution should be applied when extrapolating these findings in different study populations. In addition, both RRR and PCA have several weaknesses owing to the subjective choices for determining the

variable scale, the number of variables and factors as well as interpretation of the dietary patterns [36]. Although an explicit method was used to determine the potential confounders in this study, residual confounding due to unmeasured factors (e.g. environmental factors such as the location of habitation) in the UKWCS may still be present. Another limitation is the applicability of the findings to the general UK population and other countries, as the UKWCS consisted of a larger number of vegetarians which could refers to a more 'health-conscious' sample. Yet this cohort in addition to being able to explore healthy diets, also included women with other dietary habits such as meat-eaters and fish-eaters and participants who were came from different socio-demographic backgrounds.

The main strength of our study is that it is the first ever study prospectively investigating dietary patterns with age at natural menopause in a large cohort. This study also benefits from including two different methods, PCA and RRR, to study dietary patterns in relation to the incidence of being naturally menopausal by providing a broader overview of this association in this cohort of postmenopausal British women. Additionally, in this study age at phase 2 was considered as the time-scale variable for women who were still menstruating at follow-up instead of time on study. Thiébaut and Bénichou [19], for instance, demonstrated that the use of time-on-study instead of age as the time-scale for Cox's regression analysis of epidemiological cohort studies could lead to bias. Using age as the time-scale led to flexible control of the effects of age and avoid the need to include age as a confounder in the regression model. Moreover, this method provides a more meaningful basis to explore the risk of becoming menopausal fluctuates over time [37].

5.5 Public health implications

This study demonstrated that a diet rich in animal proteins as well as red and processed meats could delay the onset of menopause. These dietary patterns were negatively correlated with the 'vegetables and legumes' pattern. To our knowledge, this is the first study demonstrating a link between dietary patterns and age at natural menopause. Both PCA and RRR are useful in deriving dietary patterns which can influence the onset of natural menopause. However further observational studies, especially, in different populations must be conducted to confirmed these results. As such it may be too premature to base public health messages on our findings. Yet, these results

will contribute to an improved understanding of the timing of natural menopause in relation to diet, which may also have implications associated with longer-term health outcomes in post-menopausal women. As demonstrated by our recent study [38] and previous studies [3], a late menopause increases the risk of ovarian, endometrial and breast cancers. Therefore, as part of preventive strategies, women with a family history of late menopause or these hormone-related cancers should be advised to limit or avoid the consumption of animal proteins, in particular, red meats and processed meats. It would not be advisable for women who are at a high risk of an early menopause such as those with a family history of early menopause [39], those who are nulliparous or have had an early menarche to consume these meats to delay their onset of menopause given the adverse health risks associated with consumption of red and processed meats. This is also in line with the latest Lancet EAT report [40] which supports the need to reduce the consumption of red meat and highly processed foods and to increase the consumption of fruits, vegetables and legumes as part of the aim to achieve dietary changes from current diets to healthy diets which would enhance human health and lead to a reduction in the number of yearly deaths.

References

1. Office for National Statistics. Statistical bulletin - National life tables, UK: 2014 to 2016. 2017. Available from: https://www.gov.uk/government/statistics/national-life-tables-uk-2014-to-2016 [accessed 18 January 2018].
2. Sarri, G. et al. Diagnosis and management of menopause: summary of NICE guidance. *BMJ : British Medical Journal.* 2015, **351**, pp.1-6.
3. Gold, E.B. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America.* 2011, **38**(3), pp.425-440.
4. Pokoradi, A.J. et al. Factors associated with age of onset and type of menopause in a cohort of UK women. *American Journal of Obstetrics and Gynecology.* 2011, **205**(1), pp. 34.e1-34.e13.
5. Dorjgochoo, T. et al. Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. *Menopause.* 2008, **15**(5), pp.924-933.
6. de Franca, N.A. et al. Dietary patterns and bone mineral density in Brazilian postmenopausal women with osteoporosis: a cross-sectional study. *European Journal of Clinical Nutrition.* 2016, **70**(1), pp.85-90.
7. Waijers, P.M. et al. A critical review of predefined diet quality scores. *British Journal of Nutrition.* 2007, **97**(2), pp.219-231.
8. Schulze, M.B. et al. Food based dietary patterns and chronic disease prevention. *British Medical Journal.* 2018, **361**, pp.1-6.
9. Thorpe, M.G. et al. A comparison of the dietary patterns derived by principal component analysis and cluster analysis in older Australians. *International Journal of Behavioral Nutrition and Physical Activity.* 2016, **13**(1), pp.1-14.
10. Hoffmann, K. et al. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. *American Journal of Epidemiology.* 2004, **159**(10), pp.935-944.
11. Michels, K.B. and Schulze, M.B. Can dietary patterns help us detect diet-disease associations? *Nutrition Research Reviews.* 2005, **18**(2), pp.241-248.

12. Batis, C. et al. Using both principal component analysis and reduced rank regression to study dietary patterns and diabetes in Chinese adults. *Public Health Nutrition.* 2016, **19**(2), pp.195-203.
13. Nagel, G. et al. Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg. *Maturitas.* 2005, **52**(3-4), pp.337-347.
14. Sapre, S. and Thakur, R. Lifestyle and dietary factors determine age at natural menopause. *Journal of Midlife Health.* 2014, **5**(1), pp.3-5.
15. Ceylan, B. and Özerdoğan, N. Factors affecting age of onset of menopause and determination of quality of life in menopause. *Turkish Journal of Obstetrics and Gynecology.* 2015, **12**(1), pp.43-49.
16. Cade, J.E. et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). *International Journal of Epidemiology.* 2017, **46**(2), pp.1-11.
17. Nagata, C. et al. Association of diet with the onset of menopause in Japanese women. *American Journal of Epidemiology.* 2000, **152**(9), pp.863-867.
18. Jankovic, N. et al. Stability of dietary patterns assessed with reduced rank regression; the Zutphen Elderly Study. *Nutrition Journal.* 2014, **13**, p.30.
19. Thiebaut, A.C. and Benichou, J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Statistics in Medicine.* 2004, **23**(24), pp.3803-3820.
20. Vrieling, A. et al. Dietary patterns and survival in German postmenopausal breast cancer survivors. *British Journal of Cancer.* 2013, **108**(1), pp.188-192.
21. Sauvageot, N. et al. Association of Empirically Derived Dietary Patterns with Cardiovascular Risk Factors: A Comparison of PCA and RRR Methods. *PLoS ONE.* 2016, **11**(8), pp.1-6.
22. Dunneram, Y. et al. Dietary intake and age at natural menopause: results from the UK Women's Cohort Study. *Journal of Epidemiology and Community Health.* 2018, **72**(8), pp.733-740.
23. Bakolis, I. *The use of dietary patterns empirically derived from Principal Components Analysis and alternative strategies to identify associations between diet and disease.* Doctor of Philosophy thesis, Imperial College London, 2013.
24. Torgerson, D.J. et al. Factors associated with onset of menopause in women aged 45–49. *Maturitas.* 1994, **19**(2), pp.83-92.

25. Wang, M. et al. Age at natural menopause and associated factors in adult women: Findings from the China Kadoorie Biobank study in Zhejiang rural area. *PLoS ONE.* 2018, **13**(4), pp.1-13.

26. Boutot, M.E. et al. Dietary Protein Intake and Early Menopause in the Nurses' Health Study II. *American Journal of Epidemiology.* 2018, **187**(2), pp.270-277.

27. Cho, E. et al. Red Meat Intake and Risk of Breast Cancer Among Premenopausal Women. *Archives of Internal Medicine.* 2006, **166**(20), pp.2253-2259.

28. Harmon, B.E. et al. Oestrogen levels in serum and urine of premenopausal women eating low and high amounts of meat. *Public Health Nutrition.* 2014, **17**(9), pp.2087-2093.

29. Fung, T.T. et al. Dietary patterns, the Alternate Healthy Eating Index and plasma sex hormone concentrations in postmenopausal women. *International Journal of Cancer.* 2007, **121**(4), pp.803-809.

30. Carruba, G. et al. A traditional Mediterranean diet decreases endogenous estrogens in healthy postmenopausal women. *Nutrition and Cancer.* 2006, **56**(2), pp.253-259.

31. Nippita, T.A. and Baber, R.J. Premature ovarian failure: a review. *Climacteric.* 2007, **10**(1), pp.11-22.

32. Ahmed Ebbiary, N.A. et al. Hypothalamic-pituitary ageing: progressive increase in FSH and LH concentrations throughout the reproductive life in regularly menstruating women. *Clinical Endocrinology.* 1994, **41**(2), pp.199-206.

33. Sherman, B.M. et al. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. *Journal of Clinical Endocrinology & Metabolism.* 1976, **42**(4), pp.629-636.

34. Klein, N.A. et al. Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. *Journal of Clinical Endocrinology & Metabolism.* 1996, **81**(3), pp.1038-1045.

35. Jacobs, S. et al. Dietary Patterns Derived by Reduced Rank Regression Are Inversely Associated with Type 2 Diabetes Risk across 5 Ethnic Groups in the Multiethnic Cohort. *Current Developments in Nutrition.* 2017, **1**(5).

36. Newby, P.K. and Tucker, K.L. Empirically derived eating patterns using factor or cluster analysis: A review. *Nutrition Reviews.* 2004, **62**(5), pp.177-203.

37. Griffin, B.A. et al. Use of alternative time scales in Cox proportional hazard models: implications for time-varying environmental exposures. *Statistics in Medicine.* 2012, **31**(27), pp.3320-3327.

38. Dunneram, Y. et al. Diet and risk of breast, endometrial and ovarian cancer: UK Women's Cohort Study. *British Journal of Nutrition.* 2018, pp.1-24.

39. Mishra, G.D. et al. EMAS position statement: Predictors of premature and early natural menopause. *Maturitas.* 2019, **123**, pp.82-88.

40. Willett, W. et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet.* 2019, **393**(10170), pp.447-492.

Chapter 6

Soy intake and vasomotor menopausal symptoms among midlife women: a pooled analysis of five studies from the InterLACE consortium

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Abstract

Background/Objectives: Phytoestrogen rich-foods such as soy may be associated with less frequent/severe vasomotor menopausal symptoms (VMS), although evidence is limited. We thus investigated the associations between the consumption of soy products and soy milk and the frequency/severity of VMS.

Subjects/Methods: We pooled data from 19,351 middle-aged women from five observational studies in Australia, UK, USA, and Japan that contribute to the International Collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE). Information on soy consumption, VMS and covariates were collected by self-report. We included 11,006 women who had complete data on soy consumption, VMS and covariates at baseline for the cross-sectional analysis. For the prospective analysis, 4522 women who were free of VMS at baseline and had complete data on VMS at follow-up were considered. Multinomial logistic regression and binary logistic regression models were used.

Results: No statistically significant evidence of an association was found between soy products (relative risk ratio (RRR): 0.92, 95% CI: 0.76–1.11) or soy milk (RRR: 1.24, 95% CI: 0.93–1.65) and the likelihood of reporting frequent or severe VMS cross-sectionally. Prospective results indicated that frequent consumption of soy products (odds ratio (OR): 0.63, 95% CI: 0.45–0.89) but not soy milk (OR: 1.11, 95% CI: 0.85–1.45) was associated with lower likelihood of reporting subsequent VMS, after adjustment for socio-demographic and reproductive factors.

Conclusions: These are the first ever findings from pooled observational data of association between consumption of soy products and VMS.

6.1 Introduction

Menopause, a natural event marking the end of the reproductive life of women, is often accompanied by menopausal symptoms. Vasomotor menopausal symptoms (VMS), including hot flushes and night sweats, are the most common symptoms which arise as a consequence of a decline in endogenous oestrogen levels, in particular during the perimenopausal and early postmenopausal phases [1, 2]. The frequency and severity of VMS usually, decrease over time, but this varies by individual with symptoms subsiding after a year for some or persisting for over 30 years in others [3]. The frequency/severity of VMS has been linked to various chronic diseases, including cardiovascular disease, osteoporosis and cognitive decline [4, 5].

Phytoestrogen rich-foods such as soy have been associated with less frequent and less severe menopausal symptoms, although evidence is limited [6, 7]. Epidemiological studies which investigated the association between soy intake and the frequency/severity of VMS also demonstrated conflicting results [8, 9]. Moreover, according to a review of 43 randomised controlled trials (RCTs) [1], the positive effect of phytoestrogen supplements on the frequency/severity of hot flushes and night sweats in peri- or postmenopausal women is still inconclusive given the small sample size and potential high risk of bias of the included trials. However, the same review suggested that the effect of genistein (a soy derived isoflavone) was promising [1].

While dietary intake of phytoestrogens is usually, in the form of soy bean, soy bean curd, tofu, tempeh, soy milk and other soy products, most studies have investigated the effects of soy supplements and extracts [10-12]. This study thus sought to elucidate the cross-sectional and prospective associations between soy intake and VMS among peri and postmenopausal women across five studies contributing to the International Collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) consortium.

6.2 Subjects and methods

6.2.1 Ethical approval

Written consent was obtained from all participants. All the cohort studies included in the InterLACE consortium have been previously granted ethical approval by the respective ethical committees [13].

6.2.2 Study participants

The InterLACE consortium includes individual data from ten countries. It involves around 230,000 participants from 20 observational studies with data on women's health (12 of which provided longitudinal data). Further detailed information on InterLACE has been published elsewhere [13, 14]. For the current study, five studies that had information on soy intake (the exposure) and hot flushes and/or night sweats (the outcome) were included: Australian Longitudinal Study on Women's Health (ALSWH) [15], Healthy Ageing of Women Study (HOW)—Australia, Whitehall II study (WHITEHALL)—UK [16], Seattle Midlife Women's Health Study (SMWHS) [17] and Japanese Midlife Women's Health Study (JMWHS) [18] (Table D.1). For the cross-sectional analysis, data from 11,006 women who reported VMS (either frequency or severity), consumption frequency of soy products and soy milk and had complete information on confounders (listed below) were included in the analysis. The prospective analysis included data from three studies (ALSWH, HOW and WHITEHALL) (n = 10,082). Excluding 5560 women who reported VMS at baseline and those with missing data on VMS, menopausal status and use of hormone therapy at follow-up, 4522 women were considered for the prospective analysis (Figure D.1).

6.2.3 Main outcome and exposure variables

VMS was defined as the presence of hot flushes and/ or night sweats. Response options for the frequency of hot flushes and night sweats (over the last 12 months) were 'never, rarely, sometimes, and often' in ALSWH. For the other four studies, the severity of VMS over a shorter period was recorded; HOW, WHITEHALL and JMWHS considered the current severity of VMS, while SMWHS considered the severity of VMS in the last 1–3 months. For example, in HOW and JMWHS the response options for the extent of symptoms were 'not at all, a little, quite a bit, and extremely' and for WHITEHALL the response options were 'not at all, a little, somewhat, and a lot'. The degree of severity was harmonised as 'never, mild, moderate and severe' over a shorter period of time. Since the frequency of VMS was assessed in ALSWH and severity in the remaining four studies, results were presented separately. VMS were further coded dichotomously as 'absent' (never and rarely if reporting frequency; never and mild if reporting severity) and 'present' (sometimes and often if reporting frequency; moderate and severe if reporting severity) for the study-specific and prospective analysis.

Soy products such as tofu, soy beans, tempeh, and soy milk were commonly reported in the five studies. The soy products were combined based on their phytoestrogen contents. Thus, tofu, soy beans, tempeh and soy flour having a high phytoestrogen content were grouped under the soy products category, while soy milk was considered separately [19, 20]

In ALSWH, there were ten consumption frequency options: 'never, less than once per month, 1–3 times per month, 1 time per week, 2 times per week, 3–4 times per week, 5–6 times per week, 1 time per day, 2 times per day and 3 or more times per day'. In the WHITEHALL study, nine consumption frequency options were provided; five in SMWHS and four response categories in HOW and JMWHS. Therefore, for this study, studies having more than four categories were collapsed into four frequency categories: 'never/rarely', 'monthly', 'weekly' and 'daily'. They were further coded dichotomously as 'less frequent' (never/rarely and monthly) and 'frequent' (weekly and daily) given the small number of observations for 'weekly' and 'daily' intake for the prospective analysis.

6.2.4 Covariates

Categorical variables in the InterLACE study were collapsed into the simplest categories possible so as to include data from as many studies as possible [13]. For example, education level was collated into three categories as ≤10 years, 11–12 years and >12 years. Smoking status was grouped as never smokers, past smokers and current smokers. Based on gynaecological surgery and menstrual bleeding patterns, menopausal status was collated into five categories to include (1) hysterectomy/oophorectomy, (2) unknown due to hormone use (menopausal hormone therapy or oral contraceptive hormones before reaching menopause), (3) premenopause (regular menstruation in the last 3 and 12 months), (4) perimenopause (menses in the past 3 months and changes/irregularity in menstrual patterns in the past 12 months; or no menses in the previous 3 months but menses in the preceding 11 months) and (5) natural postmenopause (amenorrhoea for at least 12 months). Current use of menopausal hormone therapy (e.g., oestrogen) was categorised as yes and no.

Table 6.1 Baseline characteristics of participants

Characteristics	Overall	ALSWH	HOW	WHITEHALL	SMWHS	JMWHS
n	**11,006**	**7,373**	**563**	**2,146**	**174**	**750**
Race/ethnicity						
Caucasian-Australian/New Zealand	6323 (57.5)	5853 (79.4)	470 (83.5)	0 (0.0)	0 (0.0)	0 (0.0)
Caucasian-European	3163 (28.7)	1207 (16.4)	65 (11.6)	1891 (88.1)	0 (0.0)	0 (0.0)
Caucasian-American/Canadian	202 (1.8)	54 (0.7)	0 (0.0)	0 (0.0)	148 (85.1)	0 (0.0)
Japanese	756 (6.9)	6 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	750 (100.0)
Chinese & other Asians	166 (1.5)	144 (2.0)	7 (1.2)	0 (0.0)	15 (8.6)	0 (0.0)
Others	396 (3.6)	109 (1.5)	21 (3.7)	255 (11.9)	11 (6.3)	0 (0.0)
Birth year (n=11,002)						
<1940	856 (7.8)	N/A	N/A	855 (39.8)	1 (0.6)	N/A
1940-1949	7354 (66.8)	5410 (73.4)	475 (85.0)	1034 (48.2)	81 (46.6)	354 (47.2)
≥1950	2792 (25.4)	1963 (26.6)	84 (15.0)	257 (12.0)	92 (52.9)	396 (52.8)
Education level						
≤10 years	5096 (46.3)	3568 (48.4)	286 (50.8)	1171 (54.6)	0 (0.0)	71 (9.5)
11-12 years	2177 (19.8)	1269 (17.2)	92 (16.3)	345 (16.1)	24 (13.8)	447 (59.6)
>12 years	3733 (33.9)	2536 (34.4)	185 (32.9)	630 (29.4)	150 (86.2)	232 (30.9)
Marital status (n=10,225)						
Married	7927 (77.5)	6028 (82.0)	427 (76.3)	1357 (63.3)	115 (66.1)	N/A
Separated/divorced/widowed	1597 (15.6)	1099 (15.0)	106 (18.9)	340 (15.9)	52 (29.9)	N/A
Single	701 (6.9)	221 (3.0)	27 (4.8)	446 (20.8)	7 (4.0)	N/A

Table 6.1 Continued

Characteristics	Overall	ALSWH	HOW	WHITEHALL	SMWHS	JMWHS
n	**11,006**	**7,373**	**563**	**2,146**	**174**	**750**
Body mass index (n=10,425)						
Normal weight (<25 kg/m²)	5071 (48.6)	3048 (43.9)	233 (43.3)	1068 (52.7)	90 (51.7)	632 (85.8)
Overweight (25-29.9 kg/m²)	3259 (31.3)	2297 (33.1)	165 (30.7)	654 (32.3)	47 (27.0)	96 (13.0)
Obese (≥30 kg/m²)	2095 (20.1)	1604 (23.1)	140 (26.0)	305 (15.1)	37 (21.3)	9 (1.2)
Smoking status						
Never	6707 (60.9)	4505 (61.1)	356 (63.2)	1108 (51.6)	89 (51.2)	649 (86.5)
Past smoker	2704 (24.6)	1782 (24.2)	158 (28.1)	667 (31.1)	67 (38.5)	30 (4.0)
Current smoker	1595 (14.5)	1086 (14.7)	49 (8.7)	371 (17.3)	18 (10.3)	71 (9.5)
Menopausal status						
Hysterectomy/oophorectomy	2598 (23.6)	2001 (27.1)	165 (29.3)	344 (16.0)	6 (3.5)	82 (10.9)
Unknown due to hormone use	1721 (15.6)	1346 (18.3)	46 (8.2)	265 (12.4)	47 (27.0)	17 (2.3)
Premenopause	1315 (12.0)	636 (8.6)	22 (3.9)	463 (21.6)	44 (25.3)	150 (20.0)
Perimenopause	2090 (19.0)	1484 (20.1)	76 (13.5)	390 (18.2)	53 (30.5)	87 (11.6)
Natural menopause	3282 (29.8)	1906 (25.9)	254 (45.1)	684 (31.9)	24 (13.8)	414 (55.2)
Current use of menopausal hormone therapy						
No	8085 (73.5)	5043 (68.4)	369 (65.5)	1813 (84.5)	134 (77.0)	726 (96.8)
Yes	2921 (26.5)	2330 (31.6)	194 (34.50	333 (15.5)	40 (23.0)	24 (3.2)
Frequency or severity of hot flushes						
Never	4443 (40.4)	2249 (30.5)	323 (57.4)	1344 (62.6)	118 (67.8)	409 (54.5)
Rarely or mild	2009 (18.3)	1183 (16.1)	160 (28.4)	388 (18.1)	29 (16.7)	249 (33.2)
Sometimes or moderate	2608 (23.7)	2241 (30.4)	59 (10.5)	233 (10.9)	15 (8.6)	60 (8.0)
Often or severe	1946 (17.7)	1700 (23.1)	21 (3.73)	181 (8.4)	12 (6.9)	32 (4.3)

Table 6.1 Continued

Characteristics	Overall	ALSWH	HOW	WHITEHALL	SMWHS	JMWHS
n	**11,006**	**7,373**	**563**	**2,146**	**174**	**750**
Frequency or severity of night sweats						
Never	5510 (50.1)	2996 (40.6)	358 (63.6)	1458 (67.9)	137 (78.7)	561 (74.8)
Rarely or mild	1813 (16.5)	1157 (15.7)	136 (24.2)	339 (15.8)	22 (12.6)	159 (21.2)
Sometimes or moderate	2183 (19.8)	1914 (26.0)	52 (9.2)	190 (8.9)	5 (2.9)	22 (2.9)
Often or severe	1500 (13.6)	1306 (17.7)	17 (3.0)	159 (7.4)	10 (5.8)	8 (1.1)
Frequency or severity of vasomotor symptoms[a]						
Never	4049 (36.8)	2034 (27.6)	285 (50.6)	1251 (58.3)	112 (64.4)	367 (48.9)
Rarely or mild	2099 (19.1)	1212 (16.4)	184 (32.7)	388 (18.1)	31 (17.8)	284 (37.9)
Sometimes or moderate	2728 (24.8)	2312 (31.4)	66 (11.7)	269 (12.5)	15 (8.6)	66 (8.8)
Often or severe	2130 (19.4)	1815 (24.6)	28 (5.0)	238 (11.1)	16 (9.2)	33 (4.4)
Consumption frequency of soy products						
Never/rarely	9239 (84.0)	6590 (89.4)	475 (84.4)	2047 (95.4)	127 (73.0)	0 (0.0)
Monthly	491 (4.5)	357 (4.8)	50 (8.9)	62 (2.9)	0 (0.0)	22 (2.9)
Weekly	820 (7.5)	357 (4.8)	34 (6.0)	35 (1.6)	36 (20.7)	358 (47.7)
Daily	456 (4.1)	69 (0.9)	4 (0.7)	2 (0.1)	11 (6.3)	370 (49.3)
Consumption frequency of soy milk (n=10,954)						
Never/rarely	9860 (90.0)	6634 (90.0)	460 (85.2)	2103 (98.2)	147 (84.5)	516 (70.8)
Monthly	156 (1.4)	29 (0.4)	21 (3.9)	17 (0.8)	0 (0.0)	89 (12.2)
Weekly	237 (2.2)	110 (1.5)	11 (2.0)	19 (0.9)	13 (7.5)	84 (11.5)
Daily	701 (6.4)	596 (8.1)	48 (8.9)	3 (0.1)	14 (8.1)	40 (5.5)

Data are presented as n (%); N/A – not applicable

[a] Vasomotor menopausal symptoms were defined as having hot flushes, night sweats, or both

6.2.5 Statistical analysis

As the result of different assessments (frequency or severity) and different recall periods (in the past 12 months or in a more recent period) for VMS, studies were grouped as: (1) frequency of VMS in the past 12 months (ALSWH) and (2) severity of VMS over a shorter time period (HOW, WHITEHALL, SMWHS and JMWHS). The associations between soy consumption and VMS were first examined separately for the two different designs, followed by the overall estimates.

Multinomial logistic regression models with four categories of outcome for VMS (never, rarely/mild, sometimes/moderate and often/severe) were used to investigate the cross-sectional associations between frequency of consumption of soy products and soy milk with frequency/severity of VMS at baseline. The VMS category 'never' was used as the reference group for the outcome, and the soy consumption category 'never' was used as the reference group for the exposure. Relative risk ratios (RRR) and 95% confidence intervals (CI) were estimated. According to the minimally sufficient set of adjustments, smoking status, education level, menopausal status and race/ethnicity were identified as confounders using a directed acyclic graph (DAG) (Figure D.2) and were adjusted for in the regression models. However, race/ethnicity was not included in the model as participants from ALSWH (96.5%), HOW (95.1%), WHITEHALL (88.1%) and SMWHS (88.1%) were mainly Caucasians, and in JMWHS all the participants were Japanese. Concurrent menopausal hormone therapy use was included in the model given its potential effect on the frequency/severity of VMS [21]. The models were thus adjusted for menopausal status and concurrent menopausal hormone therapy use (model 1) and additionally adjusted for other potential covariates including education level and smoking status (model 2). 'Study' was included as a fixed effect to account for differences in levels of VMS between studies and as a stratification variable to account for correlation of individuals within studies.

Due to small numbers of participants in the four categories of exposure and outcome in individual studies, dichotomised soy consumption (frequent and less frequent) and dichotomised VMS (presence and absence) were used for the study-specific and prospective analyses. To examine between-study heterogeneity in the effect size estimates, study-specific logistic regression and random-effects meta-analysis were used with the estimates adjusted for all the covariates in model 2.

For the prospective analysis based on three studies (ALSWH, HOW and WHITEHALL), logistic regression models with the binary outcome for VMS (presence and absence) were fitted, adjusted for all the covariates in model 2. In addition, a sensitivity analysis was conducted to investigate the association between soy consumption and subsequent risk of VMS at follow-up with all the women included (n = 10,082), but adjusting for their baseline VMS, given that a large proportion of women were excluded in the prospective analysis due to the presence of VMS at baseline. Analyses were performed using STATA 14 (StataCorp LP, College Station, TX). All statistical tests were two sided.

6.3 Results

A total of 11,006 women reported their consumption frequency of soy and VMS, and also had complete data on the covariates. The median age of the women at baseline was 52 years (interquartile range: 51–54) (Table D.1). Table 6.1 shows the baseline characteristics of the participants in each study. The majority of the participants were Caucasians-Australians/New-Zealanders (57.5%), had 10 years or less of education (46.3%), and never smoked (60.9%). Nearly, 30% of the women were naturally postmenopausal, and 26.5% were currently using menopausal hormone therapy. Across HOW, WHITEHALL, SMWHS and JMWHS which measured the severity of VMS, WHITEHALL had the highest percentage of women who reported ‘severe’ VMS (11.1%), while JMWHS (Japanese) had the lowest percentage (4.4%). In the ALSWH study, 24.6% reported ‘often’ for the frequency of VMS. In this predominantly Caucasian population, 80–90% of the women reported that they never consumed soy products or soy milk. Across the individual studies, JMWHS had the largest percentage of women who reported ‘daily’ and ‘weekly’ soy product consumption (49.3% and 47.7%, respectively) (Table 6.1). Comparing baseline characteristics of women included in the prospective analysis and those excluded due to loss to follow-up, the excluded women were less educated and more likely to be obese and current smokers at baseline. They were more likely to be postmenopausal and less likely to report frequent/severe VMS compared to women with complete follow-up data (Table D.2).

Table 6.2 Cross-sectional association of soy products and soy milk consumption frequency with the frequency/severity of vasomotor menopausal symptoms at baseline

		VMS (hot flushes and night sweats) (%)				Model 1[a] RRR (95% CI)				Model 2[b] RRR (95% CI)		
Soy consumption frequency	n	Never	Rarely/ mild	Sometimes/ moderate	Often/ severe	Never	Rarely/ mild	Sometimes/ moderate	Often/ severe	Rarely/ mild	Sometimes/ moderate	Often/ severe
Soy products												
ALSWH[c] ***(n=7,373)***												
Never/rarely	6590	27.3	16.6	31.4	24.8	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	357	29.1	14.9	29.4	26.6	Reference	0.81 (0.58 to 1.14)	0.84 (0.63 to 1.11)	0.96 (0.71 to 1.29)	0.80 (0.57 to 1.13)	0.85 (0.64 to 1.13)	1.03 (0.76 to 1.38)
Weekly	357	31.9	14.6	33.1	20.5	Reference	0.72 (0.52 to 1.02)	0.85 (0.65 to 1.11)	0.66 (0.49 to 0.90)	0.71 (0.51 to 1.00)	0.86 (0.66 to 1.13)	0.73 (0.53 to 0.99)
Daily	69	29.0	20.3	33.3	17.4	Reference	1.13 (0.57 to 2.26)	0.97 (0.52 to 1.79)	0.64 (0.31 to 1.33)	1.11 (0.56 to 2.21)	0.98 (0.53 to 1.81)	0.69 (0.33 to 1.43)
HOW, WHITEHALL, SMWHS, JMWHS[c] ***(n=3,633)***												
Never/rarely	2649	57.3	20.7	12.1	9.9	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	134	53.0	24.6	11.9	10.5	Reference	0.97 (0.63 to 1.51)	1.08 (0.60 to 1.93)	1.45 (0.76 to 2.70)	1.02 (0.65 to 1.59)	1.23 (0.68 to 2.21)	1.70 (0.90 to 3.21)
Weekly	463	52.3	31.3	11.5	5.0	Reference	1.01 (0.65 to 1.56)	1.22 (0.71 to 2.09)	0.86 (0.42 to 1.75)	1.05 (0.68 to 1.63)	1.35 (0.79 to 2.31)	0.95 (0.46 to 1.95)
Daily	387	47.3	41.6	6.7	4.4	Reference	1.33 (0.81 to 2.19)	0.77 (0.38 to 1.55)	0.86 (0.37 to 2.02)	1.41 (0.86 to 2.32)	0.89 (0.44 to 1.80)	1.00 (0.43 to 2.34)
OVERALL ***(n=11,006)***												
Never/rarely	9239	35.9	17.8	25.8	20.5	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	491	35.6	17.5	24.6	22.2	Reference	0.85 (0.65 to 1.12)	0.89 (0.69 to 1.14)	1.03 (0.79 to 1.35)	0.87 (0.66 to 1.13)	0.93 (0.72 to 1.20)	1.14 (0.88 to 1.49)
Weekly	820	43.4	24.0	20.9	11.7	Reference	0.81 (0.63 to 1.05)	0.95 (0.75 to 1.20)	0.70 (0.53 to 0.93)	0.85 (0.66 to 1.09)	1.03 (0.81 to 1.30)	0.82 (0.62 to 1.09)
Daily	456	44.5	38.4	10.8	6.4	Reference	1.11 (0.79 to 1.56)	0.77 (0.51 to 1.16)	0.65 (0.40 to 1.05)	1.18 (0.85 to 1.65)	0.85 (0.57 to 1.28)	0.78 (0.49 to 1.24)

Table 6.2 Continued

Soy consumption frequency	n	VMS (hot flushes and night sweats) (%) Never	Rarely/ mild	Sometimes/ moderate	Often/ severe	Model 1[a] RRR (95% CI) Never	Rarely/ mild	Sometimes/ moderate	Often/ severe	Model 2[b] RRR (95% CI) Rarely/ mild	Sometimes/ moderate	Often/ severe
Soy milk												
ALSWH ***(n=7,369)***												
Never/rarely	6634	27.9	16.5	31.3	24.3	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	29	34.5	13.8	41.4	10.3	Reference	0.68 (0.21 to 2.17)	1.05 (0.45 to 2.48)	0.34 (0.09 to 1.25)	0.69 (0.21 to 2.20)	1.08 (0.46 to 2.54)	0.37 (0.10 to 1.38)
Weekly	110	22.7	19.1	35.5	22.7	Reference	1.41 (0.79 to 2.54)	1.38 (0.83 to 2.32)	1.17 (0.66 to 2.08)	1.42 (0.79 to 2.56)	1.41 (0.84 to 2.36)	1.27 (0.71 to 2.26)
Daily	596	24.7	15.3	30.7	29.4	Reference	1.02 (0.78 to 1.34)	1.08 (0.86 to 1.36)	1.33 (1.05 to 1.68)	1.03 (0.78 to 1.35)	1.09 (0.87 to 1.37)	1.39 (1.10 to 1.77)
HOW, WHITEHALL, SMWHS, JMWHS[c] ***(n=3,585)***												
Never/rarely	3226	56.9	22.6	11.6	8.8	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	127	40.9	40.9	11.8	6.3	Reference	1.74 (1.14 to 2.66)	1.73 (0.92 to 3.25)	1.80 (0.80 to 4.06)	1.78 (1.17 to 2.72)	1.84 (0.98 to 3.45)	1.89 (0.82 to 4.34)
Weekly	127	50.4	35.4	7.9	6.3	Reference	1.21 (0.79 to 1.83)	0.87 (0.43 to 1.77)	1.27 (0.57 to 2.82)	1.22 (0.80 to 1.86)	0.90 (0.44 to 1.82)	1.33 (0.60 to 2.94)
Daily	105	39.1	39.1	11.4	10.5	Reference	1.76 (1.10 to 2.82)	1.52 (0.77 to 3.01)	2.85 (1.35 to 6.03)	1.80 (1.13 to 2.87)	1.64 (0.83 to 3.23)	3.09 (1.47 to 6.50)
OVERALL ***(n=10,954)***												
Never/rarely	9860	37.4	18.5	24.9	19.2	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Monthly	156	39.7	35.9	17.3	7.1	Reference	1.50 (1.02 to 2.20)	1.64 (0.99 to 2.73)	1.04 (0.50 to 2.13)	1.51 (1.03 to 2.22)	1.68 (1.01 to 2.77)	1.09 (0.53 to 2.25)
Weekly	237	37.6	27.9	20.7	13.9	Reference	1.26 (0.90 to 1.76)	1.17 (0.80 to 1.72)	1.09 (0.70 to 1.70)	1.28 (0.91 to 1.79)	1.20 (0.82 to 1.76)	1.18 (0.76 to 0.84)
Daily	701	26.8	18.8	27.8	26.5	Reference	1.18 (0.93 to 1.49)	1.16 (0.93 to 1.45)	1.46 (1.16 to 1.84)	1.20 (0.95 to 1.51)	1.20 (0.96 to 1.50)	1.56 (1.24 to 1.96)

Multinomial logistic regression models were used to estimate relative risk ratios (RRR) and 95% confidence intervals (95% CI); [a] Model 1 was adjusted for menopausal status and current use of menopausal hormone therapy; [b] Model 2 was adjusted model 1 along with other covariates including smoking status, and education level; [c] Results for ALSWH and other four studies were presented separately due to the different assessments (frequency or severity) and different recall periods (in the past 12 months for ALSWH and in a shorter period for the other four studies) for VMS used across the studies

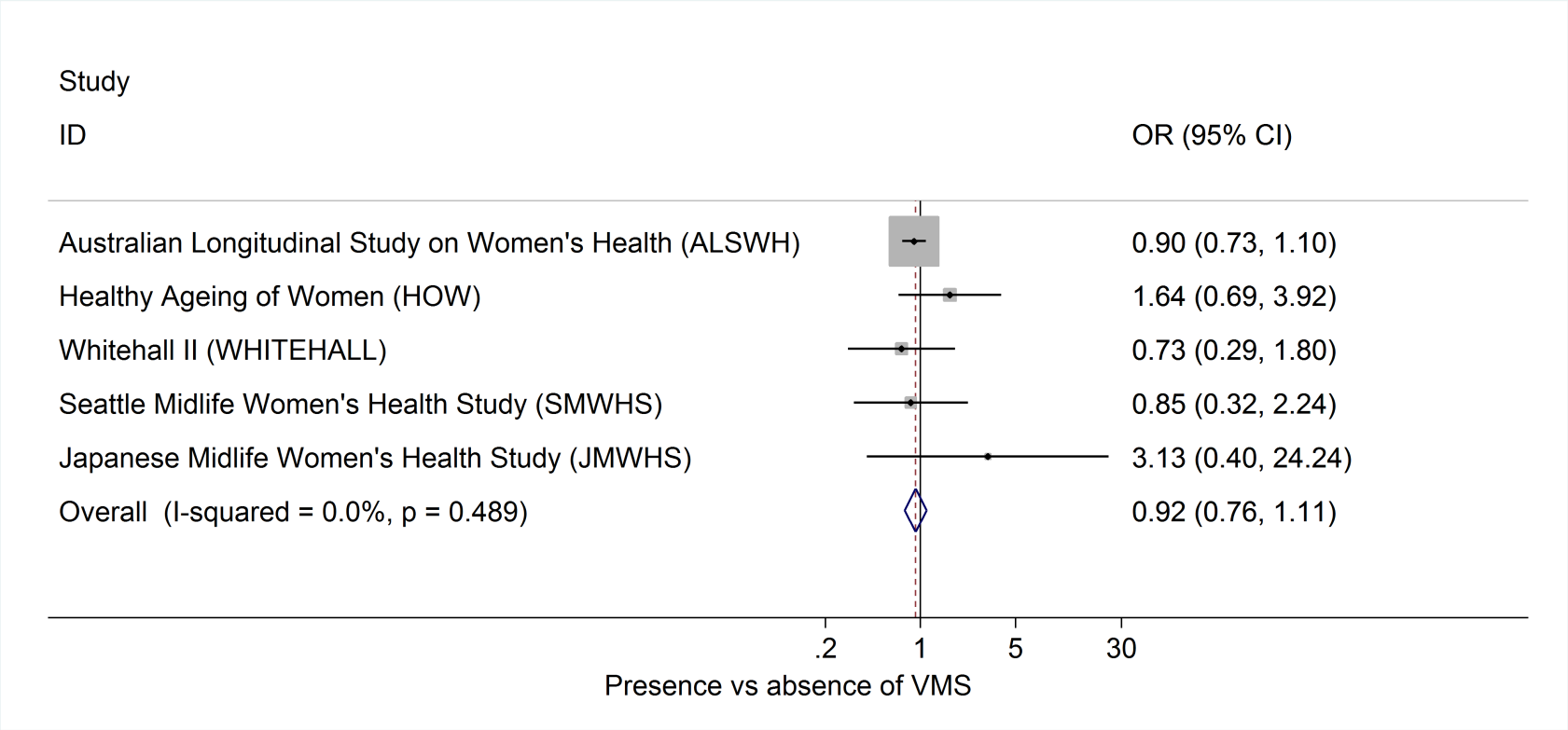

Figure 6.1 Forest plot of study-specific effect estimates of the cross-sectional association between consumption frequency of soy products and the presence of vasomotor menopausal symptoms at baseline.

Soy product consumption was coded dichotomously as 'frequent' (weekly and daily) and 'less frequent' (never/rarely and monthly) and vasomotor symptoms as 'present" (sometimes and often if reporting frequency; moderate and severe if reporting severity) and 'absent' (never and rarely if reporting frequency; never and mild if reporting severity) given the small number of observations in each study. Odds ratios (ORs) a presented on a log scale. Effect estimates were adjusted for menopausal status, current use of menopausal hormone therapy, education level, and smoking status. VMS: Vasomotor menopausal symptoms

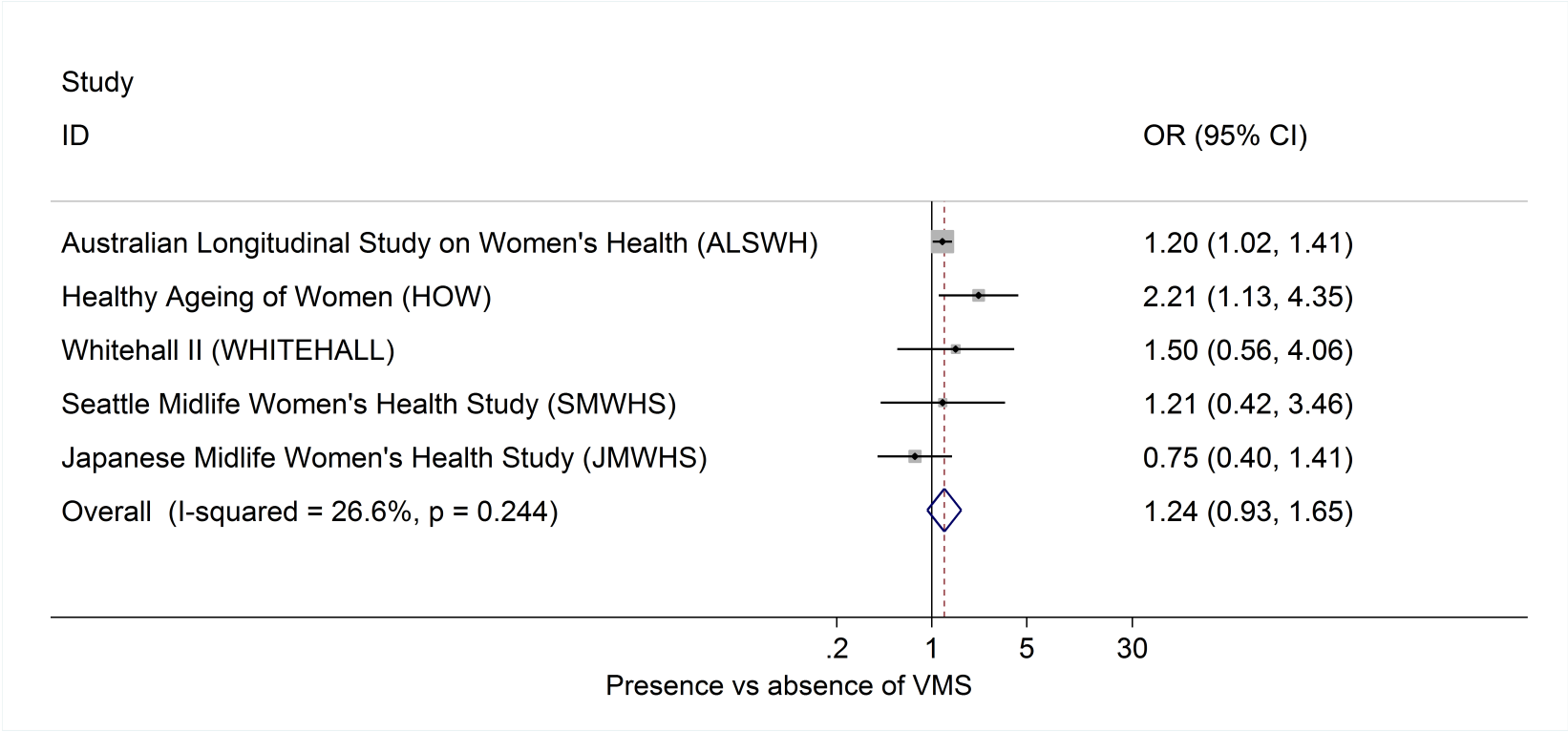

Figure 6.2 Forest plot of study-specific effect estimates of the cross-sectional association between consumption frequency of soy milk and the presence of vasomotor menopausal symptoms at baseline.

Soy milk consumption was coded dichotomously as 'frequent' (weekly and daily) and 'less frequent' (never/rarely and monthly) and vasomotor symptoms as 'present" (sometimes and often if reporting frequency; moderate and severe if reporting severity) and 'absent' (never and rarely if reporting frequency; never and mild if reporting severity) given the small number of observations in each study. Odds ratios (ORs) a presented on a log scale. Effect estimates were adjusted for menopausal status, current use of menopausal hormone therapy, education level, and smoking status. VMS: Vasomotor menopausal symptoms.

For the cross-sectional analysis, women with ‘weekly’ and ‘daily’ consumption of soy products were less likely to report frequent/severe VMS compared to those with ‘never/rarely’ consumption (11.7% vs. 20.5% and 6.4% vs. 20.5%, respectively) (Table 6.2). However, after adjusting for covariates and study differences, no clear evidence of an association was found between soy product consumption and the degree of VMS. Similarly, there was no clear evidence of an association observed for ALSWH or the other four studies. For soy milk consumption, women with a daily consumption were more likely to report frequent/severe VMS compared to women who reported ‘never/rarely’ consumption (RRR: 1.56, 95% CI: 1.24–1.96). A similar pattern for ‘daily’ consumption and risk of frequent/severe VMS was observed in ALSWH (RRR: 1.39, 95% CI: 1.10–1.77) and the other four studies (RRR: 3.09, 95% CI: 1.47–6.50).

When using dichotomised exposure and outcome variables for the study-specific analysis, the pooled estimate of association between frequent soy product consumption and the presence of VMS was 0.92 (95% CI: 0.76–1.11), with no statistically significant heterogeneity between studies, test for heterogeneity: P = 0.49, I2 = 0% (Figure 6.1). For the association between frequent consumption of soy milk and the presence of VMS, the pooled OR estimate was 1.24 (95% CI: 0.93–1.65) with no statistically significant heterogeneity between the studies (test for heterogeneity: P = 0.24, I2 = 26.6%) (Figure 6.2).

For the prospective analysis, the overall estimates suggest that women who had frequent soy product consumption were less likely to report the incidence of VMS at follow-up (OR: 0.63, 95% CI: 0.45–0.89) (Table 6.3). A consistent pattern was observed in ALSWH (OR: 0.63, 95% CI: 0.44–0.90) and the other four studies (OR: 0.60, 95% CI: 0.18–1.97). There was no clear evidence of an association between frequent consumption of soy milk and incident VMS at follow-up (OR: 1.11, 95% CI: 0.85–1.45). The sensitivity analysis with all the women included demonstrated a similar or weaker association between soy consumption and subsequent VMS, even after adjusting for baseline VMS (Table 6.4).

Table 6.3 Prospective association of soy product and soy milk consumption frequency with the presence of vasomotor menopausal symptoms at the follow-up survey

Soy consumption	n	VMS[a] (%)	Crude OR (95% CI)	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)
Soy products					
ALSWH *(n=2,852)*					
Less frequent[d]	2688	35.5	Reference	Reference	Reference
Frequent	164	26.2	0.65 (0.45 to 0.92)	0.63 (0.44 to 0.91)	0.63 (0.44 to 0.90)
HOW, WHITEHALL *(n=,1670)*					
Less frequent	1625	12.4	Reference	Reference	Reference
Frequent	45	6.7	0.56 (0.17 to 1.85)	0.58 (0.18 to 1.91)	0.60 (0.18 to 1.97)
OVERALL *(n=4,522)*					
Less frequent	4313	26.8	Reference	Reference	Reference
Frequent	209	22.0	0.64 (0.45 to 0.90)	0.63 (0.45 to 1.88)	0.63 (0.45 to 0.89)
Soy milk					
ALSWH *(n=2,849)*					
Less frequent	2608	34.9	Reference	Reference	Reference
Frequent	241	35.7	1.04 (0.79 to 1.37)	1.05 (0.79 to 1.38)	1.04 (0.79 to 1.38)
HOW, WHITEHALL *(n=1,655)*					
Less frequent	1614	12.2	Reference	Reference	Reference
Frequent	41	17.1	2.01 (0.85 to 4.78)	2.08 (0.86 to 4.99)	2.18 (0.91 to 5.23)
OVERALL *(n=4,504)*					
Less frequent	4222	26.2	Reference	Reference	Reference
Frequent	282	33.0	1.09 (0.84 to 1.43)	1.10 (0.84 to 1.43)	1.11 (0.85 to 1.45)

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI).
[a] VMS was defined as "presence of VMS" for 'never' and 'rarely/mild' VMS and "absence of VMS" for 'sometimes/moderate' and 'often/severe' VMS
[b] Model 1 was adjusted for menopausal status and current use of menopausal hormone therapy at follow-up
[c] Model 2 was adjusted for model 1 along with other covariates including smoking status, and education level
[d] Soy consumption frequency was defined as "frequent" for 'daily' and 'weekly' consumption and "less frequent" for 'monthly' and 'never/rarely' consumption

Table 6.4 Sensitivity analysis for the prospective association between soy consumption and likelihood of reporting vasomotor symptoms at follow-up

Soy consumption	n	VMS[a] (%)	Crude OR (95% CI)	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)	Model 3[d] OR (95% CI)
Soy products						
ALSWH *(n=6,603)*						
Less frequent[e]	6235	54.8	Reference	Reference	Reference	Reference
Frequent	368	48.6	0.78 (0.63 to 0.96)	0.76 (0.62 to 0.94)	0.79 (0.64 to 0.98)	0.79 (0.63 to 1.00)
HOW, WHITEHALL *(n=2,251)*						
Less frequent	2194	21.4	Reference	Reference	Reference	Reference
Frequent	57	19.3	1.05 (0.54 to 2.07)	0.99 (0.50 to 1.97)	1.05 (0.53 to 2.08)	1.04 (0.54 to 1.99)
OVERALL *(n=8,854)*						
Less frequent	8429	46.1	Reference	Reference	Reference	Reference
Frequent	425	44.7	0.80 (0.65 to 0.98)	0.78 (0.63 to 0.96)	0.81 (0.66 to 1.00)	0.81 (0.65 to 1.01)
Soy milk						
ALSWH *(n=6,599)*						
Less frequent	5970	54.1	Reference	Reference	Reference	Reference
Frequent	629	57.6	1.15 (0.97 to 1.36)	1.15 (0.97 to 1.36)	1.17 (0.99 to 1.38)	1.06 (0.89 to 1.27)
HOW, WHITEHALL *(n=2,233)*						
Less frequent	2175	21.2	Reference	Reference	Reference	Reference
Frequent	58	31.0	2.63 (1.43 to 4.84)	2.44 (1.29 to 4.60)	2.65 (1.40 to 5.00)	2.10 (1.07 to 4.13)
OVERALL *(n=8,832)*						
Less frequent	8145	45.3	Reference	Reference	Reference	Reference
Frequent	687	55.3	1.21 (1.03 to 1.43)	1.20 (1.01 to 1.41)	1.22 (1.04 to 1.44)	1.10 (0.92 to 1.32)

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI); [a] VMS was defined as "presence of VMS" for 'never' and 'rarely/mild' VMS and "absence of VMS" for 'sometimes/moderate' and 'often/severe' VMS; [b] Model 1 was adjusted for menopausal status and current use of menopausal hormone therapy at follow-up; [c] Model 2 was adjusted for model 1 along with other covariates including smoking status and education level; [d] Model 3 was adjusted for model 2 along with baseline VMS; [e] Soy consumption frequency was defined as "frequent" for 'daily' and 'weekly' consumption and "less frequent" for 'monthly' and 'never/rarely' consumption

6.4 Discussion

This pooled study demonstrated no clear evidence of an association between consumption frequency of soy products and VMS in the cross-sectional analysis. However, in the prospective analysis, women with frequent consumption of soy products were less likely to report subsequent VMS. Furthermore, there was no evidence of an association between consumption of soy milk and frequency/severity of VMS both cross-sectionally (Figure 6.1 and Figure 6.2) and prospectively (Table 6.3).

Our prospective analysis showed an association between frequent consumption of soy products and decreased odds of VMS at follow-up, though this was attenuated when baseline VMS was taken into account. Similarly, a Japanese community-based study in which women were followed for 6 years found that soy products intake alleviated hot flushes [9]. Several RCTs have investigated the association between some type of substance containing dietary soy (e.g., soy extract in capsule or tablet form, soy powder or soy protein added to diets) and its effect on hot flushes. While some demonstrated a reduction in the frequency/severity of hot flushes [10, 22-24], others have shown contradictory findings [25, 26]. According to a review study, the dose of genistein, in particular, was associated with a reduction of the symptoms rather than total isoflavone [27]. The oestrogen-like properties of soy food due to the isoflavones content have been linked to the protective effect on VMS. A decrease in the number of ovarian follicles and consequent fall in oestrogen level could be the underlying hormonal aetiology of VMS [28, 29]. However, the effect of phytoestrogens in reducing VMS remains unclear [30]. One of the possible mechanisms of action is the structural similarity of isoflavones to that of oestradiol could confer oestrogenic or anti-oestrogenic effects depending on the circulating oestrogen level by binding to oestrogen receptors [31, 32]. The relative decline in oestrogen level leads to higher circulating norepinephrine levels and an upregulation of serotonin receptors which mediate hot flushes in menopausal women. By binding to oestrogen receptors, isoflavones help to restore the oestrogen level, and causes subsequent changes in norepinephrine and serotonin levels, thus reducing the propensity of hot flushes [33].

Our pooled data did not show a clear association between soy milk consumption and frequency/severity of VMS. The source of dietary isoflavones may also contribute to the observed effect since processing methods tend to alter the phytoestrogen contents of

soy products [34]. For instance, the total isoflavone content in soy beans (103 mg per 100 g), tempeh (18 mg per 100 g) and tofu (27 mg per 100 g) is much higher than that in soy milk (3 mg per 100 g) [20]. The overall low-consumption frequency of soy milk among the participants and its low isoflavone content could possibly explain this finding.

The main drawback of our study is the variation in assessments used by the different studies. Soy consumption was measured as frequency, with no information on quantities. Moreover, for the consumption of soy milk, the cross-sectional nature of some of the studies and lack of evidence of a significant association from the prospective analysis, mean that we cannot confirm a temporal relationship between soy milk consumption and VMS. There also might be possibility of residual confounding, e.g., by factors not measured in the studies. One weakness of data harmonisation is the collapsing of the variables of interest into the simplest level of detail in order to incorporate information from as many studies as possible, leading to loss of statistical power as well as potential misclassification of the degree of VMS and frequency of soy consumption. For instance, studies like ALSWH and WHITEHALL had ten and nine frequency options respectively for consumption of soy that were collapsed to four categories for this analysis. In addition, the frequency of VMS was reported in ALSWH over a longer period of time (12 months), and the other four studies recorded the severity of VMS over a shorter period that limited our ability to pool data. Despite these limitations the pooled results showed considerable homogeneity as shown in the forest plots and the low values for the statistic I^2.

Furthermore, our study had several strengths that ranged from the inclusion of a large number of women across different geographic regions and cultures that allowed greater generalisability of the results. This is also, to our knowledge, the first pooled study consisting of women's health studies from four different countries examining an association between soy products and soy milk with frequency/severity of VMS. We also included women who had a hysterectomy, oophorectomy, and/or were currently using hormones that could provide a better estimate of the prevalence of VMS. In addition, the individual data available in the InterLACE enabled harmonisation of the variables of interest using common definitions, coding and cut points not normally possible with meta-analyses of published results. Harmonisation of the data further reduces the between-study heterogeneity. A consistent approach to confounder adjustment was used

for the regression models along with careful selection of the confounders using a DAG, thus reducing the probability of the results being affected by uncontrolled confounders.

While menopause is an inevitable phenomenon in a woman's life cycle, the frequency and severity of VMS show marked variations [35]. VMS are reported by around 75% of postmenopausal women globally, with a minority reporting severe symptoms [36, 37]. Findings from this study provide some evidence that frequent consumption of soy products (e.g., soy beans, tofu and tempeh) as part of the usual diet may be associated with a reduced risk of subsequent VMS. However, frequent consumption of soy milk did not appear to be associated with subsequent VMS. As justified by potential mechanisms in previous studies, our findings could prompt RCTs testing the effects of dietary soy intake in particular on VMS as opposed to earlier RCTs which have mainly considered the effects of soy extracts and supplements.

References

1. Lethaby, A. et al. Phytoestrogens for menopausal vasomotor symptoms. *The Cochrane Database of Systematic Reviews.* 2013, (12), p.Cd001395.
2. Gold, E.B. et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *American Journal of Public Health.* 2006, **96**(7), pp.1226-1235.
3. Rapkin, A.J. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. *American Journal of Obstetrics and Gynecology.* 2007, **196**(2), pp.97-106.
4. Pines, A. Vasomotor symptoms and cardiovascular disease risk. *Climacteric.* 2011, **14**(5), pp.535-536.
5. Biglia, N. et al. Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases? *Climacteric.* 2017, **20**(4), pp.306-312.
6. Levis, S. and Griebeler, M.L. The role of soy foods in the treatment of menopausal symptoms. *Journal of Nutrition.* 2010, **140**(12), pp.2318s-2321s.
7. Baber, R. Phytoestrogens and post reproductive health. *Maturitas.* 2010, **66**(4), pp.344-349.
8. Sievert, L.L. et al. Vasomotor symptoms among Japanese-American and European-American women living in Hilo, Hawaii. *Menopause.* 2007, **14**(2), pp.261-269.
9. Nagata, C. et al. Soy product intake and hot flashes in Japanese women: results from a community-based prospective study. *American Journal of Epidemiology.* 2001, **153**(8), pp.790-793.
10. Carmignani, L.O. et al. The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial. *Maturitas.* 2010, **67**(3), pp.262-269.
11. Khaodhiar, L. et al. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. *Menopause.* 2008, **15**(1), pp.125-132.

12. Ye, Y.B. et al. Soy germ isoflavones improve menopausal symptoms but have no effect on blood lipids in early postmenopausal Chinese women: a randomized placebo-controlled trial. *Menopause.* 2012, **19**(7), pp.791-798.
13. Mishra, G.D. et al. The InterLACE study: Design, data harmonization and characteristics across 20 studies on women's health. *Maturitas.* 2016, **92**, pp.176-185.
14. Mishra, G.D. et al. InterLACE: A New International Collaboration for a Life Course Approach to Women's Reproductive Health and Chronic Disease Events. *Maturitas.* 2013, **74**(3), pp.235-240.
15. Lee, C. et al. Cohort Profile: the Australian Longitudinal Study on Women's Health. *International Journal of Epidemiology.* 2005, **34**(5), pp.987-991.
16. Marmot, M. and Brunner, E. Cohort Profile: the Whitehall II study. *International Journal of Epidemiology.* 2005, **34**(2), pp.251-256.
17. Mitchell, E.S. and Woods, N.F. Cognitive symptoms during the menopausal transition and early postmenopause. *Climacteric.* 2011, **14**(2), pp.252-261.
18. Anderson, D. et al. Menopause in Australia and Japan: effects of country of residence on menopausal status and menopausal symptoms. *Climacteric.* 2004, **7**(2), pp.165-174.
19. Bhagwat S, Haytowitz DB, Holden JM. *USDA Database for the Isoflavone Content of Selected Foods, Release 2.0*. U.S. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory, 2008.
20. Thompson, L.U. et al. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. *Nutrition and Cancer.* 2006, **54**(2), pp.184-201.
21. Stuenkel, C.A. et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2015, **100**(11), pp.3975-4011.
22. Welty, F.K. et al. The association between soy nut consumption and decreased menopausal symptoms. *Journal of Women's Health.* 2007, **16**(3), pp.361-369.
23. Cheng, G. et al. Isoflavone treatment for acute menopausal symptoms. *Menopause.* 2007, **14**(3 Pt 1), pp.468-473.
24. Nahas, E.A. et al. Efficacy and safety of a soy isoflavone extract in postmenopausal women: a randomized, double-blind, and placebo-controlled study. *Maturitas.* 2007, **58**(3), pp.249-258.

25. Burke, G.L. et al. Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. *Menopause.* 2003, **10**(2), pp.147-153.
26. Penotti, M. et al. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertility and Sterility.* 2003, **79**(5), pp.1112-1117.
27. Williamson-Hughes, P.S. et al. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. *Menopause-The Journal of The North American Menopause Society.* 2006, **13**(5), pp.831-839.
28. Sturdee, D.W. The menopausal hot flush—Anything new? *Maturitas.* 2008, **60**(1), pp.42-49.
29. Pachman, D.R. et al. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. *International Journal of Women's Health.* 2010, **2**, pp.123-135.
30. Moreira, A.C. et al. Phytoestrogens as alternative hormone replacement therapy in menopause: What is real, what is unknown. *The Journal of Steroid Biochemistry and Molecular Biology.* 2014, **143**, pp.61-71.
31. Rietjens, I. et al. The potential health effects of dietary phytoestrogens. *British Journal of Pharmacology.* 2017, **174**(11), pp.1263-1280.
32. Kuiper, G.G. et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology.* 1998, **139**(10), pp.4252-4263.
33. Morrow, P.K.H. et al. Hot Flashes: A Review of Pathophysiology and Treatment Modalities. *Oncologist.* 2011, **16**(11), pp.1658-1664.
34. Setchell, K.D.R. and Cole, S.J. Variations in Isoflavone Levels in Soy Foods and Soy Protein Isolates and Issues Related to Isoflavone Databases and Food Labeling. *Journal of Agricultural and Food Chemistry.* 2003, **51**(14), pp.4146-4155.
35. Luoto, R. Hot flushes and quality of life during menopause. *BMC Women's Health.* 2009, **9**(1), p.13.
36. Monteleone, P. et al. Symptoms of menopause - global prevalence, physiology and implications. *Nature Reviews Endocrinology*. 2018, **14**(4), pp.199-215.

37. Woods, N.F. and Mitchell, E.S. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. T*he American Journal of Medicine.* 2005, **118**(Suppl 12B), pp.14-24.

Chapter 7

Diet and risk of breast, endometrial and ovarian cancer: UK Women's Cohort Study

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Abstract

Objectives: This study aimed to investigate the association between diet and the risk of breast, endometrial and ovarian cancer in the UK Women's Cohort Study.

Methods: A total of 35 372 women aged 35–69 years were enrolled between 1995 and 1998 and completed a validated 217-item FFQ. The individual foods were collapsed into sixty-four main food groups and compared using Cox proportional models, adjusting for potential confounders. Hazard ratio (HR) estimates are presented per portion increase in food items.

Results: After approximately 18 years of follow-up, there were 1822, 294 and 285 cases of breast, endometrial and ovarian cancer, respectively. A high consumption of processed meat and total meat was associated with an increased risk of breast and endometrial cancer. High intake of tomatoes (HR 0.87, 99% CI 0.75 to 1.00) and dried fruits (HR 0.60, 99% CI 0.37 to 0.97) was associated with a reduced risk of breast and endometrial cancer, respectively. Mushroom intake was associated with a higher risk of ovarian cancer (HR 1.57, 99% CI 1.09 to 2.26). Subgroup analysis by pre- or postmenopausal cancer further demonstrated an association between processed meat intake and both postmenopausal breast cancer and endometrial cancer. Intake of dried fruits was associated with a reduced risk of postmenopausal endometrial cancer (HR 0.55, 99% CI 0.31 to 0.98).

Conclusion: Our findings suggest that while some foods may trigger the risk of these cancers, some foods may also be protective; supporting the call for further randomised controlled trials of dietary interventions to reduce the risk of cancer among pre- and postmenopausal women.

7.1 Introduction

In the UK, breast cancer is the most commonly diagnosed cancer among women accounting for almost one-third of all female cancers. Endometrial and ovarian cancers are the next most frequently diagnosed hormone-related cancers among British women [1]. These cancers are all age dependent and commonly diagnosed postmenopausally [2]. The mechanisms involved in the pathogenesis of these cancers are not completely elucidated. Reproductive and hormonal risk factors such as an early age at menarche, late age at menopause, lack of oral contraceptive use, lack of tubal ligation, postmenopausal hormone therapy, nulliparity, all contribute to the lifetime oestrogen exposure [3, 4] as well as a family history have been consistently associated with these reproductive cancers [5]. Moreover, smoking has also been associated with an increased risk of breast and ovarian cancers while it reduces the risk of endometrial cancer [6, 7]. In addition, evidence from observational studies has indicated that obesity-related metabolic disorders such as diabetes and the metabolic syndrome can be linked to the aetiology of these cancers [8]. These metabolic disorders are partly outcomes of poor dietary quality [9].

In addition to being one of the triggering factors in the development of obesity, diet also potentially influences the endogenous hormonal milieu, thereby increasing the risk of these hormone-related cancers [10]. As demonstrated in previous studies, dietary changes have been linked to changes in menstrual cycle length, circulating sex hormone-binding globulin levels and also oestradiol levels [11-14]. Even though studies have shown that diet may be related to the risk of breast, endometrial and ovarian cancer, the specific dietary components involved in the aetiology of these cancers remain unclear. For instance, according to the recent World Cancer Research Fund/American Institute for Cancer Research report [15], there was strong evidence that alcohol consumption increases both the risk of pre- and postmenopausal breast cancers. In addition, there was suggestive evidence demonstrating that a high consumption of non-starchy vegetables, foods sources of carotenoids, dairy products and Ca-rich diets were associated with a decreased risk of breast cancer. On the other hand, the link between other foods and risk of breast cancer remains limited and inconclusive. Likewise, the relationship between diet and endometrial as well as ovarian cancer was sparse and conflicting. Therefore, using data from the UK Women's Cohort Study (UKWCS), this study aims to investigate the associations between food intake and the risk of breast, endometrial and ovarian cancer.

The aetiology of these cancers also differs by whether the cancer is pre- or postmenopausal. While evidence suggests a link between endogenous oestrogens and risk of these cancers among postmenopausal women, there is only weak evidence supporting this relationship among premenopausal women [16, 17]. In addition, the menstrual cycle variations in circulating sex hormone levels make deciphering the aetiology behind premenopausal breast, endometrial and ovarian cancer risk a challenge [18]. This study thus also seeks to look into the relationship between diet and risk of the hormone-dependent cancers by menopausal status.

7.2 Methods

7.2.1 Study design, study population and ethical approval

At baseline, the UKWCS involved 35 372 women across England, Wales and Scotland who responded to a postal questionnaire between 1995 and 1998. The recruitment process has been detailed elsewhere [19]. Recruited women were aged between 35 and 69 years. Dietary data, lifestyle as well as health-related data were collected at baseline. Approximately 4 years later, further diet, lifestyle and health-related data were collected between the years 1999 and 2002 (40.1% response), which formed the follow-up cohort. Reproductive history including menopausal status was also collected at study baseline and follow-up. At its initiation in 1993, ethical approval was obtained from 174 local research ethics committees (Research Ethics Committee reference number: 15/YH/0027).

7.2.2 Dietary assessment

A detailed validated [20] 217-food item FFQ was used to assess the dietary intake of the participants over a period of 12 months. Daily intake of each food item (g/d) was determined using the frequency categories to estimate the portion size. Using a standard portion size, these were then converted into weights. According to the recent World Cancer Research Fund report, one of the identified critical areas of research included better characterisation of diet [15] and their cancer prevention recommendations [21] suggests consumption of a fibre-rich diet, limiting consumption of foods high in fat, starches or sugars as well as limiting consumption of red and processed meat. Therefore, in this study, the individual food items were collapsed into sixty-four food groups based on their fibre and fat contents, the type of meat or according to their culinary uses. Details on grouping of the foods have been described previously [22]. The standard portion sizes

were estimated by calculating the average portion size of the individual food items within the food group as per the Food Standards Agency [23].

7.2.3 Case definition

Incident cases of invasive breast carcinomas, endometrial and ovarian cancers were identified through linkage to the National Health Service Central Register [24]. The International Classification of Diseases 9 and 10 were used to code incident cancer cases. Participants were followed from study entry till diagnosis of the breast cancer (International Classification of Diseases (ICD)-9 code 174 or ICD-10 code C50), endometrial cancer (ICD-9 code 182 or ICD-10 code C54.1 or C54.9), ovarian cancer (ICD-9 code 183 or ICD-10 code C56), date of death or until the censor date (1 April 2016) whichever came first.

7.2.4 Statistical analysis

Descriptive statistics were used to describe lifestyle characteristics of participants for breast, endometrial and ovarian cancer separately as well as for women without any incident case of a malignant cancer. Cox proportional hazards regression was used to provide hazard ratios (HR) and 99% CI to account for potential multiple testing of breast, endometrial and ovarian cancers in relation to diet. For ease of interpretation, the HRs were presented per standard portion size of the food group per day. The proportional hazards assumption was tested graphically as well as using the Cox–Snell residuals for all terms in the model. Time in the study was used as the time variable calculated from the date of questionnaire receipt until either death or censor date.

Risk factors for cancer previously identified in the literature were considered to build a directed acyclic graph. A parsimonious age-adjusted model was firstly used to estimate the association between each individual food groups and risk of the cancers in separate models (model 1). According to the minimal sufficiency set of adjustments, the final models for risk of breast and ovarian cancer were adjusted for age (years), physical activity (h/d) [25], ethanol intake (g/d) [26], smoking status (never, current or former smoker) [27], cumulative duration of breast-feeding (weeks) [28-30], menopausal status (pre- or post-menopausal) [2], and socio-economic status (professional/managerial, intermediate or routine and manual) [31] (model 2). For risk of endometrial cancer, history of diabetes [32] and hypertension [33] were also included in model 2. Participants with incomplete data on these variables were excluded.

Subgroup analyses by pre-menopausal cancer and postmenopausal cancer were also performed. A premenopausal cancer was defined as an incident case diagnosed before the last menstrual period, while a postmenopausal cancer case was one diagnosed either at or after the last menstrual period. For premenopausal cancer, cases contributed to person-time from age at baseline until the diagnosis of the event. If the participant did not have a premenopausal cancer, the age until last menstrual period was considered as the time variable instead. Women who were already postmenopausal at study entry were excluded from the model (adjusted for model 2). For postmenopausal cancer, cases contributed to person-time from age at last menstrual period until the diagnosis of the event. Women who were incident cases of premenopausal cancer and those who were still premenopausal at censor date were excluded from the model (adjusted for model 2).

Age at natural menopause was further explored as an effect modifier for the foods that were significantly associated with the risk of the cancers. Previous studies have also demonstrated an increased risk of these cancers with a later age at natural menopause due to longer exposure to oestrogen [34]. Age at last period was self-reported at both baseline and phase 2. This variable was grouped as having a menopause either between 40 and 49 years (n=10 505) or 50 and 65 years (n=6295). To include only postmenopausal women with a natural menopause, those who had a hysterectomy or bilateral oophorectomy as well as those who reported current or ever use of hormone replacement therapy (HRT) before their last period were excluded from the analyses. In addition, women who had their last period before the age of 40 years were also excluded as this could be due to other treatments or surgical procedures that could not be ascertained in this study. All statistical analyses were conducted using Stata version 15 statistical software.

Sensitivity analysis was also conducted using model 2, further adjusting for both family history of any cancer and family history of breast cancer in the first-degree relatives to estimate the association between food groups and the risk of breast cancer. To estimate the association of the risk of endometrial cancer, family history of endometrial cancer was included in the model, and for the risk of ovarian cancer, a family history of ovarian cancer and breast cancer was adjusted for in addition to model 2. Sensitivity analyses also involved adjusting for total energy intake (kJ/d) to account for under- and over-reporters (model 3). Adjustments were also made for current HRT use [35, 36], use of oral contraceptive pills and parity [37, 38] (model 4) in addition to model 3 as these are known risk factors for breast, endometrial and ovarian cancers.

7.3 Results

7.3.1 Baseline characteristics according to cancer type

Of the 35 372 women at baseline, 695 women who were not flagged on the National Health Services (NHS) digital, 2340 women reporting history of any previous malignant cancer at baseline (except for non-melanoma of the skin) and women who were diagnosed with breast (n=68), endometrial (n=7) and ovarian (n=12) cancer within 1 year of baseline were excluded. After the exclusions, 32 228 women were eligible for the breast cancer analysis, 32 289 for the endometrial cancer analysis and 32 284 for the ovarian cancer analysis.

Baseline characteristics of the participants according to cancer type are summarised in Table 7.1. After approximately 18 years of follow-up, there were 1822 incident cases of breast cancer, 294 and 285 incident cases of endometrial and ovarian cancer, respectively. Women with endometrial and ovarian cancer were on average overweight at baseline with a BMI of 27.3 and 25.1 kg/m^2, respectively, while women with breast cancer were borderline overweight (24.8 kg/m^2) and women without any cancer had a normal weight (24.4 kg/m^2). Women with endometrial cancer were less likely to be current smokers and had lower ethanol intake in comparison to those with breast and ovarian cancer as well as those without any cancer. A majority of women with incident breast cancer were current users of HRT at baseline (58.3%). Women without any cancer had an earlier natural menopause (mean=47.5 years) as compared with women with breast, endometrial and ovarian cancer. Around 42-46% of women with breast, endometrial and ovarian cancer had a family history of any cancer at baseline as compared with 38.4% for the non-cancer cases. Total energy intake and fibre intake was quite similar between the cancer cases and non-cancer cases.

Table 7.1 Baseline characteristics according to cancer type from the UKWCS

Characteristics	Breast cancer cases n= 1,822	Endometrial cancer cases n= 294	Ovarian cancer cases n=285	No cancer n=28,929
Demographic characteristics				
Age (years), mean (SD)	53.2 (9.0)	54.1 (8.3)	55.7 (9.0)	51.7 (9.3)
BMI (kg/m^2), mean (SD)	24.8 (4.3)	27.3 (6.3)	25.1 (4.5)	24.4 (4.2)
Professional/managerial SES, n (%)	1,105 (62.1)	182 (63.4)	171 (61.3)	18262 (63.6)
Medical history				
Family history of any cancer, n (%)	755 (43.7)	127 (46.0)	112 (42.6)	10577 (38.4)
Family history of breast cancer, n (%)	172 (10.0)	23 (8.3)	25 (9.5)	2145 (7.8)
Family history of endometrial cancer, n (%)	17 (1.0)	6 (2.2)	1 (0.4)	274 (1.00)
Family history of ovarian cancer, n (%)	15 (0.9)	6 (2.2)	6 (2.3)	284 (1.0)
Lifestyle characteristics				
Current smoker, n (%)	185 (10.4)	24 (8.4)	40 (14.3)	3093 (10.9)
Physical activity, mean (SD)	0.25 (0.55)	0.24 (0.44)	0.19 (0.34)	0.26 (0.49)
Reproductive history				
Current hormone replacement therapy use, n (%)	433 (58.3)	61 (51.7)	69 (53.1)	5309 (53.2)
Parous, n (%)	1370 (78.1)	227 (79.9)	214 (78.7)	21443 (79.3)
Postmenopausal, n (%)	1,003 (55.5)	160 (54.6)	189 (66.3)	13892 (50.1)
Age last natural menopause, mean (SD)	48.1 (4.5)	50.0 (4.4)	49.1 (3.4)	47.3 (4.5)
Energy and food intake				
Total energy intake (kcal/day), mean (SD)	2291 (783)	2222 (715)	2260 (694)	2291 (793)
Fibre intake (g/day), mean(SD)	25.5 (11.2)	24.2 (10.3)	25.4 (10.1)	25.6 (10.9)
Ethanol (g/day), mean(SD)	9.1 (10.1)	7.5 (8.7)	9.3 (11.4)	8.7 (10.4)
Total vegetable intake (g/day), mean(SD)	314.7 (208.7)	305.0 (174.7)	322.8 (190.6)	317.7 (191.6)
Total fruit intake (g/day), mean(SD)	319.1 (225.5)	292.4 (198.3)	307.2 (207.7)	316.1 (243.3)
Total meat intake (g/day), mean(SD)	69.1 (61.2)	72.5 (59.5)	66.3 (69.3)	64.5 (63.5)

7.3.2 Diet and risk of breast, endometrial and ovarian cancer

For the association between food intake and risk of breast cancer, in both the age-adjusted model and fully adjusted model, a standard portion of 83 g of tomato consumption was associated with a significant risk reduction (HR 0.87, 99% CI 0.75 to 0.999). In the fully adjusted model, a standard portion of both processed meat and total meat intake was associated with higher risk of breast cancer, 36 and 17%, respectively (HR 1.36, 99% CI 1.02 to 1.81; HR 1.17, 99% CI 1.00 to 1.36) (Table 7.2). According to the subgroup analysis by pre- and postmenopausal breast cancer, consumption of tomatoes reduced the risk of postmenopausal breast cancer but not premenopausal breast cancer. Consumption of processed meat and total meat were both associated with a significant higher risk of postmenopausal breast cancer only. In addition, intake of 15 g of biscuits per day was associated with a 17% higher risk of premenopausal breast cancer (Table 7.3).

Similarly, an increased risk of endometrial cancer was observed in the fully adjusted model with consumption of a standard portion of processed and total meat per d (HR 2.19, 99% CI 1.34 to 3.60; HR 1.53, 99% CI 1.04 to 2.24). Consumptions of 28 g of dried fruits per day and 85 g of high breakfast cereals were associated with a 40 and 26% reduced risk of endometrial cancer, respectively (HR 0.60, 99% CI 0.37 to 0.97; HR 0.74, 99% CI 0.55 to 0.998) (Table 7.2). In the subgroup analysis, a standard portion of processed meat per d was associated with a higher risk of postmenopausal endometrial cancer. Consumption of dried fruits was associated with a significant reduced risk of only postmenopausal endometrial cancer (HR 0.55, 99% CI 0.31 to0.98), while a higher intake of low-energy/-diet soft drinks was positively associated with the risk of postmenopausal endometrial cancer (HR 1.27; 99% CI 1.00 to 1.61). For ovarian cancer, 34 g of mushroom intake per day was associated with a significantly higher risk (HR 1.57, 99% 1.09 to 2.26). Furthermore, it was found that a higher mushroom intake was associated with an increased risk of postmenopausal ovarian cancer. A higher consumption of citrus fruits and total fruits was associated with an 87 and 37% reduced risk of premenopausal ovarian cancer, respectively.

Table 7.2 Hazard ratios (99% confidence intervals) of breast, endometrial and ovarian cancer by food groups

Daily intake/ standard portion size	Breast Cancer Cases				Endometrial cancer cases				Ovarian cancer cases			
	Model 1 n=1796/32,228 [a]		Model 2 n=1625/29,183 [b]		Model 1 n=285/32,289 [a]		Model 2 n=238/27,338 [c]		Model 1 n=274/32,284 [a]		Model 2 n=251/29,229 [b]	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Starchy food sources												
Wholegrain products/ 33g	0.99	0.96 to 1.02	0.99	0.96 to 1.03	0.95	0.88 to 1.03	0.92	0.84 to 1.01	1.02	0.94 to 1.10	1.00	0.93 to 1.09
Refined grain products/ 51g	1.03	0.96 to 1.10	1.03	0.95 to 1.11	1.11	0.95 to 1.30	1.15	0.98 to 1.35	1.04	0.87 to 1.24	1.02	0.84 to 1.24
Low fibre breakfast cereals/ 40g	1.00	0.83 to 1.20	1.04	0.85 to 1.26	0.83	0.50 to 1.37	0.76	0.43 to 1.37	1.16	0.76 to 1.75	1.08	0.67 to 1.74
High fibre breakfast cereals/ 85g	1.00	0.92 to 1.08	1.01	0.92 to 1.10	0.82	0.64 to 1.06	0.74	0.55 to 0.998	0.89	0.70 to 1.13	0.89	0.69 to 1.15
Plain Potatoes/ 210g	0.93	0.81 to 1.06	0.94	0.81 to 1.09	0.92	0.66 to 1.30	0.94	0.64 to 1.38	0.79	0.54 to 1.15	0.83	0.56 to 1.23
Potatoes with added fat/ 127g	1.13	0.94 to 1.37	1.28	0.96 to 1.71	1.28	0.97 to 1.68	1.90	1.00 to 3.60	0.78	0.35 to 1.70	0.80	0.35 to 1.84
Refined pasta and rice/ 210g	0.99	0.78 to 1.25	0.94	0.72 to 1.22	0.99	0.55 to 1.78	1.05	0.54 to 2.05	0.69	0.34 to 1.42	0.73	0.34 to 1.54
Wholegrain pasta and rice/ 197 g	1.07	0.82 to 1.40	1.14	0.84 to 1.55	0.72	0.31 to 1.67	0.60	0.23 to 1.60	0.58	0.23 to 1.49	0.70	0.27 to 1.83
Protein and fat food sources												
Low fat dairy products/ 118g	1.01	0.98 to 1.03	1.01	0.98 to 1.03	1.04	0.98 to 1.10	1.03	0.97 to 1.10	0.95	0.90 to 1.02	0.95	0.89 to 1.02
High fat dairy products/ 93g	1.00	0.97 to 1.03	1.00	0.97 to 1.04	0.96	0.88 to 1.04	0.98	0.90 to 1.07	1.05	0.98 to 1.12	1.06	0.99 to 1.13
Butter and hard margarine/ 10g	0.99	0.93 to 1.06	0.98	0.92 to 1.05	0.98	0.83 to 1.16	1.00	0.83 to 1.20	0.92	0.76 to 1.10	0.86	0.69 to 1.06
Margarine/ 9g	0.97	0.91 to 1.03	0.99	0.92 to 1.05	0.95	0.81 to 1.12	0.93	0.77 to 1.11	1.06	0.91 to 1.22	1.03	0.88 to 1.21
Low fat spreads/ 7g	1.03	0.96 to 1.09	1.03	0.96 to 1.10	1.02	0.87 to 1.19	0.98	0.82 to 1.17	0.94	0.79 to 1.13	0.95	0.78 to 1.15
High fat dressing/ 23g	1.00	0.81 to 1.23	0.98	0.78 to 1.22	0.72	0.39 to 1.32	0.77	0.40 to 1.50	0.92	0.53 to 1.61	0.72	0.38 to 1.38
Low fat dressing/ 30g	0.98	0.70 to 1.36	1.02	0.72 to 1.45	0.88	0.37 to 2.08	0.86	0.32 to 2.29	1.02	0.46 to 2.30	1.09	0.47 to 2.54
Soybean products/ 62g	0.97	0.90 to 1.04	0.97	0.90 to 1.05	0.98	0.82 to 1.17	0.98	0.81 to 1.19	0.94	0.75 to 1.16	0.93	0.73 to 1.19
Textured vegetable protein/ 130g	0.44	0.03 to 6.93	0.16	0.01 to 3.50	-	-	-	-	-	-	-	-
Pulses/ 91g	1.00	0.87 to 1.14	1.03	0.89 to 1.19	0.87	0.60 to 1.28	0.81	0.52 to 1.25	1.08	0.79 to 1.48	1.17	0.83 to 1.64
Eggs/eggs dishes/ 88g	0.99	0.76 to 1.27	0.98	0.73 to 1.31	1.29	0.82 to 2.02	1.63	0.88 to 2.99	1.21	0.74 to 1.96	1.21	0.62 to 2.37
Fish and fish dishes/ 140g	1.04	0.76 to 1.43	1.01	0.68 to 1.51	0.90	0.36 to 2.24	0.96	0.34 to 2.71	0.99	0.43 to 2.24	0.86	0.30 to 2.43
Oily fish/ 90g	0.98	0.64 to 1.50	0.98	0.62 to 1.54	0.45	0.12 to 1.68	0.52	0.13 to 2.13	1.06	0.39 to 2.89	1.06	0.36 to 3.14
Shell fish/ 60g	1.17	0.66 to 2.07	1.44	0.56 to 3.70	0.52	0.04 to 6.83	0.72	0.04 to 11.69	0.85	0.11 to 6.65	0.65	0.04 to 10.06
Red meat/ 189g	1.20	0.97 to 1.49	1.28	0.95 to 1.72	1.33	0.87 to 2.02	1.90	0.92 to 3.94	0.91	0.45 to 1.88	0.85	0.38 to 1.92

Table 7.2 Continued

Daily intake/ standard portion size	Breast Cancer Cases				Endometrial cancer cases				Ovarian cancer cases			
	Model 1 n=1796/32,228 [a]		Model 2 n=1625/29,183 [b]		Model 1 n=285/32,289 [a]		Model 2 n=238/27,338 [c]		Model 1 n=274/32,284 [a]		Model 2 n=251/29,229 [b]	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Processed meat/ 74g	1.34	1.03 to 1.73	1.36	1.02 to 1.81	1.81	1.16 to 2.83	2.19	1.34 to 3.60	1.22	0.62 to 2.42	1.27	0.60 to 2.69
Poultry/ 143g	1.30	0.90 to 1.87	1.32	0.86 to 2.03	1.35	0.55 to 3.32	1.76	0.60 to 5.18	0.63	0.19 to 2.07	0.62	0.17 to 2.21
Offal/ 100g	2.19	0.44 to 10.89	2.27	0.41 to 12.55	2.70	0.05 to 138.5	-	-	0.10	0.00 to 12.00	0.07	0.00 to 12.00
Total meat/ 150g	1.12	1.01 to 1.24	1.17	1.00 to 1.36	1.19	0.98 to 1.45	1.53	1.04 to 2.24	0.94	0.65 to 1.37	0.92	0.61 to 1.39
Vegetables												
Vegetable dishes/ 214g	0.97	0.82 to 1.14	0.91	0.75 to 1.10	0.74	0.45 to 1.22	0.67	0.38 to 1.19	1.02	0.70 to 1.49	1.03	0.64 to 1.67
Allium/ 39g	0.98	0.82 to 1.17	0.99	0.82 to 1.20	1.02	0.67 to 1.57	0.97	0.58 to 1.61	0.81	0.49 to 1.33	0.77	0.44 to 1.33
Fresh legumes/ 75g	1.01	0.86 to 1.18	0.96	0.80 to 1.15	1.12	0.80 to 1.56	1.14	0.75 to 1.72	1.03	0.71 to 1.51	1.08	0.73 to 1.60
Mediterranean vegetables/ 60g	0.98	0.87 to 1.10	0.96	0.84 to 1.09	0.98	0.73 to 1.32	0.85	0.58 to 1.23	1.17	0.93 to 1.47	1.18	0.90 to 1.56
Salad vegetables/ 43g	0.97	0.87 to 1.08	0.97	0.87 to 1.09	0.84	0.62 to 1.12	0.84	0.61 to 1.17	0.98	0.76 to 1.28	0.99	0.74 to 1.32
Cruciferous vegetables/ 75g	1.01	0.95 to 1.07	0.99	0.91 to 1.06	0.94	0.78 to 1.14	0.94	0.76 to 1.16	1.01	0.87 to 1.18	1.04	0.88 to 1.24
Tomatoes/ 83g	0.88	0.77 to 1.00	0.87	0.75 to 0.999	0.81	0.57 to 1.15	0.77	0.52 to 1.16	0.94	0.69 to 1.29	0.97	0.70 to 1.35
Mushrooms/ 34g	0.98	0.79 to 1.22	0.96	0.76 to 1.22	1.19	0.77 to 1.85	1.29	0.78 to 2.12	1.40	0.98 to 1.99	1.57	1.09 to 2.26
Roots and tubers/ 66g	0.94	0.83 to 1.05	0.94	0.83 to 1.06	0.96	0.74 to 1.25	0.90	0.66 to 1.25	1.06	0.83 to 1.34	1.12	0.88 to 1.43
Total vegetables/150g	0.98	0.94 to 1.03	0.97	0.91 to 1.02	0.95	0.84 to 1.09	0.93	0.80 to 1.08	1.02	0.91 to 1.14	1.04	0.92 to 1.18
Fruits												
Stone fruits/ 49g	1.00	0.96 to 1.04	1.03	0.86 to 1.23	0.84	0.49 to 1.42	0.94	0.55 to 1.62	0.63	0.32 to 1.22	0.66	0.32 to 1.33
Deep orange & yellow fruits/ 118g	1.03	0.90 to 1.18	1.08	0.92 to 1.26	0.67	0.39 to 1.15	0.75	0.42 to 1.32	0.97	0.65 to 1.44	0.98	0.62 to 1.54
Grapes/ 100g	0.98	0.86 to 1.11	0.96	0.84 to 1.10	0.92	0.66 to 1.29	0.91	0.61 to 1.34	0.84	0.57 to 1.23	0.91	0.62 to 1.32
Citrus family fruits/ 92g	1.03	0.93 to 1.14	1.02	0.92 to 1.14	0.81	0.60 to 1.11	0.77	0.54 to 1.10	0.85	0.63 to 1.15	0.88	0.64 to 1.21
Rhubarb/ 130g	0.96	0.76 to 1.22	0.93	0.71 to 1.24	0.59	0.24 to 1.45	0.74	0.30 to 1.82	1.04	0.61 to 1.77	1.07	0.57 to 2.00
Berries/ 48g	1.02	0.93 to 1.11	1.03	0.94 to 1.14	0.85	0.62 to 1.15	0.85	0.60 to 1.21	0.84	0.61 to 1.15	0.82	0.57 to 1.17
Bananas/ 100g	1.04	0.94 to 1.158	1.07	0.95 to 1.19	0.87	0.65 to 1.18	0.88	0.63 to 1.22	1.10	0.85 to 1.42	1.21	0.92 to 1.59
Pomes/ 116g	0.97	0.90 to 1.04	0.98	0.91 to 1.06	0.97	0.80 to 1.16	0.92	0.75 to 1.15	0.91	0.74 to 1.11	0.97	0.79 to 1.19
Total fruits/150g	1.00	0.96 to 1.04	1.01	0.97 to 1.05	0.91	0.81 to 1.02	0.90	0.79 to 1.03	0.95	0.85 to 1.06	0.98	0.88 to 1.10
Dried Fruits/ 28g	1.03	0.96 to 1.11	1.04	0.98 to 1.13	0.67	0.46 to 0.99	0.60	0.37 to 0.97	1.02	0.86 to 1.22	1.06	0.89 to 1.26

Table 7.2 Continued

Daily intake/ standard portion size	Breast Cancer Cases				Endometrial cancer cases				Ovarian cancer cases			
	Model 1 n=1796/32,228 [a]		Model 2 n=1625/29,183 [b]		Model 1 n=285/32,289 [a]		Model 2 n=238/27,338 [c]		Model 1 n=274/32,284 [a]		Model 2 n=251/29,229 [b]	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Other food groups												
Sauces/ 83g	1.05	0.63 to 1.74	1.07	0.62 to 1.87	1.46	0.48 to 3.40	1.29	0.31 to 5.37	1.48	0.49 to 4.49	1.78	0.48 to 6.65
Pickles/Chutneys/ 35g	0.90	0.70 to 1.17	0.89	0.68 to 1.18	1.16	0.68 to 1.97	0.96	0.49 to 1.91	0.72	0.35 to 1.48	0.65	0.29 to 1.44
Soups/ 163g	0.98	0.82 to 1.18	0.98	0.79 to 1.22	0.93	0.57 to 1.51	0.90	0.50 to 1.61	0.95	0.60 to 1.50	1.03	0.62 to 1.70
Confectionary & spreads/ 44g	0.98	0.92 to 1.04	0.99	0.92 to 1.05	0.94	0.79 to 1.12	0.88	0.71 to 1.09	0.98	0.83 to 1.15	0.96	0.81 to 1.15
Nuts and seeds/ 24g	1.01	0.93 to 1.10	1.03	0.94 to 1.13	1.03	0.85 to 1.25	0.77	0.53 to 1.13	1.02	0.83 to 1.25	1.02	0.80 to 1.30
Savoury snacks/ 26g	1.05	0.87 to 1.26	1.06	0.87 to 1.29	1.21	0.79 to 1.85	1.12	0.68 to 1.86	1.05	0.63 to 1.73	1.06	0.63 to 1.81
Biscuits/ 15g	1.00	0.94 to 1.06	1.01	0.94 to 1.08	0.97	0.83 to 1.14	0.97	0.81 to 1.17	0.95	0.80 to 1.13	0.95	0.80 to 1.15
Cakes/ 66g	0.89	0.68 to 1.16	0.88	0.65 to 1.19	0.85	0.43 to 1.68	0.84	0.38 to 1.87	1.01	0.55 to 1.83	0.95	0.47 to 1.92
Pastries and Puddings/ 84g	1.05	0.89 to 1.24	1.12	0.92 to 1.36	0.85	0.51 to 1.43	1.00	0.58 to 1.73	0.78	0.45 to 1.35	0.71	0.37 to 1.34
Drinks and beverages												
Tea/ 260g	0.98	0.95 to 1.02	0.98	0.95 to 1.02	1.04	0.96 to 1.12	1.02	0.93 to 1.11	0.98	0.91 to 1.07	0.98	0.90 to 1.07
Herbal tea/ 260g	0.97	0.90 to 1.04	0.99	0.91 to 1.06	0.96	0.80 to 1.16	0.89	0.71 to 1.12	0.94	0.77 to 1.15	0.93	0.75 to 1.16
Coffee/ 190g	1.01	0.98 to 1.04	1.01	0.97 to 1.04	1.03	0.95 to 1.12	1.03	0.94 to 1.13	1.04	0.96 to 1.13	1.04	0.95 to 1.13
Other hot beverages/ 23g	1.02	0.92 to 1.12	1.03	0.93 to 1.14	1.03	0.81 to 1.31	1.01	0.77 to 1.33	0.99	0.77 to 1.28	1.04	0.80 to 1.35
Juices/ 145g	1.00	0.93 to 1.07	1.01	0.93 to 1.08	0.97	0.80 to 1.16	0.95	0.76 to 1.17	0.95	0.78 to 1.15	0.97	0.79 to 1.18
Soft drinks/ 111g	1.00	0.89 to 1.10	1.00	0.90 to 1.12	1.05	0.83 to 1.33	1.00	0.74 to 1.34	1.03	0.80 to 1.33	1.02	0.78 to 1.33
Low calorie/diet soft drinks/ 161g	1.01	0.91 to 1.12	1.03	0.93 to 1.14	1.10	0.87 to 1.38	1.03	0.79 to 1.35	0.96	0.72 to 1.28	0.98	0.73 to 1.31
Wines/ glass*	1.03	0.94 to 1.12	1.03	0.94 to 1.13	0.90	0.70 to 1.14	0.90	0.69 to1.17	1.06	0.86 to 1.32	1.06	0.85 to 1.32
Beer and cider/ half pint*	1.09	0.93 to 1.28	1.10	0.93 to 1.29	1.13	0.77 to 1.68	0.81	0.42 to 1.56	1.11	0.71 to 1.72	1.10	0.72 to 1.69
Port, sherry, liqueurs/ glass*	0.97	0.75 to 1.26	0.98	0.74 to 1.29	0.93	0.47 to 1.82	1.11	0.57 to 2.17	1.17	0.72 to 1.92	1.20	0.74 to 1.95
Spirits/ measure*	1.11	0.97 to 1.27	1.10	0.95 to 1.27	0.51	0.25 to 1.02	0.54	0.26 to 1.12	1.27	0.97 to 1.67	1.26	0.96 to 1.66

[a] Model 1: adjusted for age; [b] Model 2: adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status; [c] Model 2 (endometrial cancer): adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes and history of hypertension; * not adjusted for ethanol intake

Table 7.3 Associations between various food groups and risk of breast, endometrial and ovarian cancer by incidence of premenopausal and postmenopausal cancer cases

Daily intake/ standard portion size	Breast Cancer Cases[a]				Endometrial Cancer Cases[b]				Ovarian Cancer Cases[a]			
	Premenopausal n=291/3,178		Postmenopausal n=1,030/23,806		Premenopausal n=35/3,024		Postmenopausal n=175/24,118		Premenopausal n=44/3,030		Postmenopausal n=163/24,115	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Starchy food sources												
Wholegrain products/ 33g	1.01	0.93 to 1.10	0.98	0.94 to 1.02	1.21	0.84 to 1.76	0.91	0.81 to 1.01	1.21	0.94 to 1.56	1.01	0.91 to 1.12
Refined grain products/ 51g	0.99	0.83 to 1.18	1.06	0.97 to 1.16	1.06	0.55 to 2.03	1.16	0.95 to 1.42	1.31	0.90 to 1.91	0.84	0.63 to 1.13
Low fibre breakfast cereals/ 40g	0.90	0.60 to 1.34	1.02	0.80 to 1.30	0.29	0.06 to 1.50	0.75	0.38 to 1.50	0.68	0.17 to 2.80	1.02	0.55 to 1.86
High fibre breakfast cereals/ 85g	1.06	0.87 to 1.29	1.00	0.90 to 1.12	1.34	0.41 to 4.42	0.86	0.62 to 1.17	1.28	0.63 to 2.58	0.86	0.62 to 1.19
Plain Potatoes/ 210g	0.98	0.61 to 1.56	0.95	0.79 to 1.14	0.58	0.09 to 3.69	0.98	0.63 to 1.51	0.97	0.27 to 3.47	0.86	0.53 to 1.40
Potatoes with added fat/ 127g	1.05	0.49 to 2.27	1.31	0.90 to 1.91	0.33	0.03 to 3.29	1.96	0.89 to 4.31	9.87	0.87 to 111.5	0.54	0.17 to 1.70
Refined pasta and rice/ 210g	1.10	0.60 to 2.01	1.00	0.71 to 1.40	1.04	0.13 to 8.14	1.28	0.62 to 2.63	2.91	0.37 to 22.9	0.72	0.28 to 1.88
Wholegrain pasta and rice/ 197 g	1.15	0.49 to 2.70	1.29	0.88 to 1.88	4.90	0.51 to 47.3	0.44	0.12 to 1.56	0.06	0.00 to 3.08	1.32	0.51 to 3.42
Protein and fat food sources												
Low fat dairy products/ 118g	1.03	0.97 to 1.10	1.02	0.99 to 1.05	0.96	0.81 to 1.14	1.04	0.97 to 1.12	1.02	0.85 to 1.22	0.96	0.89 to 1.04
High fat dairy products/ 93g	1.00	0.93 to 1.08	1.00	0.96 to 1.04	0.94	0.73 to 1.20	0.93	0.82 to 1.05	1.05	0.89 to 1.23	1.04	0.95 to 1.13
Butter and hard margarine/ 10g	1.00	0.82 to 1.21	0.99	0.91 to 1.09	1.04	0.50 to 2.17	1.02	0.83 to 1.26	0.90	0.57 to 1.43	0.76	0.57 to 1.03
Margarine/ 9g	1.08	0.91 to 1.28	0.98	0.90 to 1.06	0.75	0.42 to 1.33	0.93	0.75 to 1.15	1.06	0.67 to 1.68	1.08	0.90 to 1.31
Low fat spreads/ 7g	1.03	0.90 to 1.18	0.98	0.90 to 1.07	1.15	0.64 to 2.06	0.98	0.80 to 1.21	1.46	0.84 to 2.55	0.94	0.74 to 1.19
High fat dressing/ 23g	1.39	0.69 to 2.82	1.00	0.76 to 1.33	0.25	0.01 to 4.55	0.84	0.40 to 1.78	0.34	0.05 to 2.49	0.99	0.48 to 2.02
Low fat dressing/ 30g	1.06	0.41 to 2.71	0.99	0.64 to 1.53	0.64	0.02 to 24.3	0.87	0.29 to 2.62	3.31	0.06 to 175.2	1.26	0.49 to 3.23
Soybean products/ 62g	0.90	0.69 to 1.17	0.99	0.90 to 1.08	0.84	0.42 to 1.65	1.02	0.84 to 1.25	-	-	0.91	0.66 to 1.25
Textured vegetable protein/ 130g	-	-	0.04	0.00 to 2.55	-	-	-	-	-	-	-	-
Pulses/ 91g	1.04	0.71 to 1.53	1.06	0.88 to 1.27	0.82	0.23 to 2.90	0.90	0.55 to 1.48	1.31	0.44 to 3.89	1.28	0.84 to 1.94
Eggs/eggs dishes/ 88g	0.92	0.44 to 1.95	0.94	0.65 to 1.37	1.18	0.07 to 18.4	1.64	0.84 to 3.21	0.70	0.14 to 3.64	0.86	0.33 to 2.22
Fish and fish dishes/ 140g	0.84	0.29 to 2.38	1.01	0.61 to 1.67	1.88	0.07 to 51.3	0.81	0.23 to 2.91	0.56	0.01 to 31.7	1.04	0.30 to 3.58
Oily fish/ 90g	0.46	0.11 to 1.81	0.93	0.52 to 1.63	0.46	0.00 to 104.8	0.27	0.04 to 1.64	0.21	0.01 to 6.52	0.95	0.24 to 3.82
Shell fish/ 60g	0.83	0.04 to 17.7	2.06	0.64 to 6.61	-	-	0.25	0.01 to 11.5	-	-	1.39	0.06 to 33.7
Red meat/ 189g	0.91	0.40 to 2.05	1.37	0.94 to 1.98	0.44	0.04 to 5.37	1.86	0.80 to 4.30	2.55	0.66 to 9.77	0.62	0.21 to 1.80

Table 7.3 Continued

Daily intake/ standard portion size	Breast Cancer Cases[a]				Endometrial Cancer Cases[b]				Ovarian Cancer Cases[a]			
	Premenopausal n=291/3,178		Postmenopausal n=1,030/23,806		Premenopausal n=35/3,024		Postmenopausal n=175/24,118		Premenopausal n=44/3,030		Postmenopausal n=163/24,115	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Processed meat/ 74g	1.36	0.66 to 2.80	1.50	1.01 to 2.22	0.65	0.03 to 12.1	3.05	1.34 to 6.91	2.13	0.84 to 5.40	0.71	0.23 to 2.18
Poultry/ 143g	1.08	0.33 to 3.55	1.33	0.78 to 2.28	-	-	1.29	0.35 to 4.81	-	-	0.54	0.11 to 2.66
Offal/ 100g	-	-	3.67	0.49 to 27.2	-	-	-	-	-	-	0.05	0.00 to 30.6
Total meat/ 150g	1.03	0.69 to 1.56	1.22	1.00 to 1.47	0.94	0.27 to 3.26	1.50	0.95 to 2.35	1.67	0.89 to 3.13	0.75	0.44 to 1.29
Vegetables												
Vegetable dishes/ 214g	1.00	0.60 to 1.67	1.00	0.79 to 1.27	1.73	0.39 to 7.72	0.77	0.40 to 1.48	0.36	0.08 to 1.70	1.23	0.72 to 2.10
Allium/ 39g	0.81	0.46 to 1.42	1.12	0.91 to 1.37	1.28	0.33 to 5.03	0.95	0.53 to 1.72	0.32	0.08 to 1.33	0.96	0.53 to 1.74
Fresh legumes/ 75g	0.87	0.49 to 1.56	1.09	0.89 to 1.33	1.91	0.39 to 9.24	1.23	0.79 to 1.90	0.54	0.12 to 2.40	1.21	0.78 to 1.87
Mediterranean vegetables/ 60g	0.98	0.65 to 1.50	1.04	0.89 to 1.22	1.24	0.51 to 3.00	0.93	0.61 to 1.42	0.54	0.21 to 1.35	1.23	0.88 to 1.72
Salad vegetables/ 43g	0.99	0.68 to 1.44	1.04	0.91 to 1.20	1.34	0.37 to 4.87	0.88	0.61 to 1.28	0.61	0.28 to 1.31	1.00	0.70 to 1.43
Cruciferous vegetables/ 75g	0.94	0.74 to 1.20	1.03	0.94 to 1.12	1.09	0.46 to 2.60	0.97	0.77 to 1.23	1.06	0.58 to 1.93	1.10	0.93 to 1.30
Tomatoes/ 83g	0.96	0.62 to 1.48	0.88	0.74 to 1.04	1.85	0.61 to 5.62	0.76	0.48 to 1.22	1.16	0.54 to 2.49	0.91	0.59 to 1.39
Mushrooms/ 34g	0.94	0.51 to 1.75	1.03	0.77 to 1.38	2.13	0.26 to 14.7	1.24	0.66 to 2.31	0.29	0.06 to 1.43	1.84	1.21 to 2.79
Roots and tubers/ 66g	0.86	0.60 to 1.22	0.98	0.85 to 1.12	0.69	0.20 to 2.38	0.97	0.69 to 1.37	0.64	0.26 to 1.60	1.20	0.94 to 1.53
Total vegetables/150g	0.94	0.79 to 1.13	1.01	0.94 to 1.08	1.18	0.71 to 1.96	0.96	0.81 to 1.14	0.82	0.58 to 1.18	1.09	0.95 to 1.25
Fruits												
Stone fruits/ 49g	0.60	0.31 to 1.16	1.13	0.97 to 1.33	8.93	0.38 to 207.5	1.11	0.72 to 1.70	0.14	0.01 to 3.50	0.98	0.52 to 1.87
Deep orange & yellow fruits/ 118g	0.70	0.44 to 1.11	1.12	0.93 to 1.35	0.65	0.15 to 2.90	0.78	0.41 to 1.49	0.09	0.01 to 1.07	1.20	0.79 to 1.81
Grapes/ 100g	0.91	0.64 to 1.29	0.95	0.80 to 1.13	1.11	0.20 to 6.05	0.93	0.60 to 1.42	1.08	0.21 to 5.62	1.04	0.73 to 1.49
Citrus family fruits/ 92g	1.02	0.76 to 1.37	1.06	0.93 to 1.21	0.89	0.16 to 4.97	0.85	0.58 to 1.25	0.13	0.02 to 0.81	1.06	0.76 to 1.48
Rhubarb/ 130g	0.80	0.29 to 2.17	0.93	0.64 to 1.33	0.26	0.01 to 11.2	0.83	0.31 to 2.21	0.47	0.06 to 3.88	1.19	0.59 to 2.38
Berries/ 48g	0.87	0.68 to 1.14	1.06	0.95 to 1.18	1.46	0.30 to 7.13	0.89	0.61 to 1.29	0.71	0.37 to 1.36	0.88	0.59 to 1.31
Bananas/ 100g	0.94	0.72 to 1.24	1.09	0.94 to 1.25	0.65	0.24 to 1.81	0.96	0.67 to 1.39	0.44	0.15 to 1.31	1.32	0.97 to 1.80
Pomes/ 116g	0.90	0.71 to 1.14	0.99	0.90 to 1.09	1.25	0.60 to 2.61	0.93	0.73 to 1.19	0.62	0.24 to 1.61	1.03	0.82 to 1.30
Total fruits/150g	0.94	0.84 to 1.05	1.02	0.97 to 1.07	0.97	0.64 to 1.47	0.93	0.80 to 1.08	0.63	0.40 to 0.99	1.06	0.94 to 1.19
Dried Fruits/ 28g	1.06	0.96 to 1.16	1.04	0.94 to 1.15	0.99	0.25 to 3.93	0.55	0.31 to 0.98	0.35	0.04 to 2.86	1.14	0.99 to 1.31

Table 7.3 Continued

Daily intake/ standard portion size	Breast Cancer Cases[a]				Endometrial Cancer Cases[b]				Ovarian Cancer Cases[a]			
	Premenopausal n=291/3,178		Postmenopausal n=1,030/23,806		Premenopausal n=35/3,024		Postmenopausal n=175/24,118		Premenopausal n=44/3,030		Postmenopausal n=163/24,115	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Other food groups												
Sauces/ 83g	2.52	0.38 to 16.7	1.30	0.66 to 2.58	-	-	1.91	0.40 to 9.12	8.89	0.37 to 215.9	1.28	0.22 to 7.49
Pickles/Chutneys/ 35g	1.35	0.79 to 2.30	0.85	0.60 to 1.22	2.31	0.23 to 22.9	1.01	0.46 to 2.21	2.35	0.18 to 30.5	0.68	0.25 to 1.82
Soups/ 163g	0.87	0.41 to 1.83	1.08	0.84 to 1.38	-	-	1.00	0.54 to 1.85	1.01	0.32 to 3.17	1.05	0.57 to 1.91
Confectionary & spreads/ 44g	0.95	0.84 to 1.08	1.00	0.92 to 1.09	0.89	0.51 to 1.55	0.93	0.74 to 1.17	0.89	0.55 to 1.45	0.99	0.80 to 1.23
Nuts and seeds/ 24g	1.03	0.90 to 1.18	1.04	0.92 to 1.16	1.13	0.54 to 2.36	0.70	0.43 to 1.14	0.39	0.10 to 1.51	1.02	0.76 to 1.38
Savoury snacks/ 26g	0.85	0.47 to 1.52	1.06	0.82 to 1.38	1.64	0.25 to 10.8	1.31	0.75 to 2.27	1.01	0.19 to 5.34	1.24	0.67 to 2.28
Biscuits/ 15g	1.17	1.00 to 1.38	1.00	0.93 to 1.09	0.93	0.45 to 1.93	1.01	0.84 to 1.23	1.40	0.75 to 2.60	0.93	0.74 to 1.18
Cakes/ 66g	0.83	0.45 to 1.52	0.84	0.57 to 1.22	0.06	0.00 to 1.82	0.95	0.41 to 2.21	0.24	0.01 to 5.17	1.06	0.48 to 2.37
Pastries and Puddings/ 84g	1.47	0.98 to 2.19	1.08	0.83 to 1.39	0.26	0.01 to 4.75	1.16	0.64 to 2.11	1.12	0.06 to 22.0	0.76	0.35 to 1.61
Drinks and beverages												
Tea/ 260g	0.98	0.90 to 1.06	0.99	0.95 to 1.03	1.14	0.84 to 1.55	1.02	0.92 to 1.13	0.98	0.77 to 1.24	0.94	0.84 to 1.04
Herbal tea/ 260g	1.06	0.87 to 1.29	1.00	0.91 to 1.09	1.49	0.71 to 3.11	0.89	0.68 to 1.16	0.76	0.34 to 1.72	0.96	0.74 to 1.25
Coffee/ 190g	1.03	0.95 to 1.11	1.01	0.97 to 1.06	1.03	0.76 to 1.39	1.01	0.91 to 1.13	1.16	0.87 to 1.54	1.07	0.96 to 1.19
Other hot beverages/ 23g	1.02	0.79 to 1.31	1.01	0.89 to 1.15	0.25	0.04 to 1.47	1.05	0.79 to 1.42	1.18	0.54 to 2.58	1.08	0.80 to 1.46
Juices/ 145g	0.89	0.72 to 1.10	0.99	0.90 to 1.09	1.09	0.51 to 2.33	0.96	0.76 to 1.23	0.65	0.31 to 1.35	1.02	0.81 to 1.29
Soft drinks/ 111g	1.04	0.87 to 1.23	1.03	0.90 to 1.19	0.98	0.36 to 2.67	1.15	0.88 to 1.50	1.52	0.80 to 2.88	1.09	0.80 to 1.48
Low calorie/diet soft drinks/ 161g	1.00	0.78 to 1.29	1.03	0.90 to 1.18	0.34	0.05 to 2.18	1.27	1.00 to 1.61	1.70	0.64 to 4.50	1.01	0.70 to 1.45
Wines/ glass*	0.98	0.81 to 1.18	1.03	0.92 to 1.15	1.24	0.40 to 3.79	0.85	0.61 to 1.18	0.89	0.50 to 1.59	1.01	0.75 to 1.36
Beer and cider/ half pint*	1.09	0.65 to 1.83	1.15	0.94 to 1.42	4.11	0.44 to 38.4	1.26	0.81 to 1.97	1.81	0.93 to 3.53	1.05	0.56 to 1.97
Port, sherry, liqueurs/ glass*	1.23	0.59 to 2.60	1.01	0.73 to 1.39	-	-	0.95	0.42 to 2.15	0.58	0.16 to 2.14	1.31	0.77 to 2.21
Spirits/ measure*	1.07	0.80 to 1.43	1.05	0.87 to 1.28	0.76	0.01 to 76.3	0.49	0.20 to 1.21	1.21	0.51 to 2.86	1.12	0.74 to 1.71

[a] Fully adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status; [b] Fully adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes and history of hypertension; * not adjusted for ethanol intake

After further adjustment for family history of the respective cancers, similar results were obtained to those reported above (Table E.1). In addition, a significantly higher risk of breast and endometrial cancer was observed with frequent consumption of a standard portion of potatoes with added fat (i.e. chips/roast potatoes). The associations between diet and the risk of breast, endometrial and ovarian cancer after further adjustments for total energy intake and current HRT use, oral contraceptive use and parity were also in agreement with the study's main associations (Table E.2). We also found that the risk of breast, endometrial and ovarian cancer significantly increased with an increase in age at natural menopause (Table E.3). Subgroup analysis by age at natural menopause demonstrated that the diet of women with either an earlier or later age at natural menopause did not change the risk of the cancers (Table E.4).

7.4 Discussion

In this prospective investigation of the consumption of food groups in relation to the risk of breast, endometrial and ovarian cancers, we consistently found that consumption of processed meat and total meat was associated with a significantly higher risk of breast and endometrial cancer. In addition, frequent consumption of a standard portion of tomatoes and dried fruits were associated with a reduced risk of breast and endometrial cancer, respectively. A higher consumption of mushrooms was found to be weakly associated with a higher risk of ovarian cancer. Subgroup analysis showed similar associations between these food items and cancer risk, when differentiating between a pre- and postmenopausal cancer as well as when further adjustments for family history of cancer, total energy intake, current HRT use, oral contraceptive use and parity were accounted for in the different models.

Previous studies have also reported an increased risk of breast and endometrial cancer with a higher consumption of processed meat and total meat. According to the recent UK Biobank cohort study [39], a 6% higher risk of breast cancer was reported in relation to processed meat consumption. Similar to our results, they also found only a significant increased risk of postmenopausal breast cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) [40] and NutriNet-Santé [41] prospective cohort studies have also reported an increased risk of breast cancer associated with the consumption of processed meat. Our findings are further supported by a prospective randomised control trial conducted over a period of 8 years [42]. Studies investigating the association between processed meat and the risk of endometrial cancer are limited and

conflicting. While a case–control study [43] including 274 participants with endometrial cancer found that intake of processed meats such as boiled ham, salami and sausages and canned meat was associated with an increased risk of endometrial cancer, findings from a cohort study, the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study [44] including 1486 incident cases reported no evidence of an association. Another cancer multi-site study from the NIH-AARP Diet and Health Study also reported no association between processed meat consumption and risk of both breast and endometrial cancer [45].

The underlying mechanisms for the pathogenesis of breast cancer are heterogeneous. High levels of nitrates, nitrites and amines, which are precursors of N-nitroso compounds, added in processed meat to enhance its colour and flavour have been consistently reported to be one of the causes of carcinogenicity [46]. In addition, cooking especially at high temperatures (e.g. frying, grilling or barbecuing) can lead to the formation of heterocyclic aromatic amines, which are also potent mutagens and carcinogens [47]. The N-nitro compounds, heterocyclic amines along with other compounds (haem Fe, saturated fat and oestradiol), present in meats can directly cause DNA damage and have been associated with mammary tumour development as demonstrated in both animal and human studies [46, 48]. We also found that processed meat consumption was positively associated with postmenopausal breast cancer though not for premenopausal breast cancer. Disparities could be due to differing oestrogen metabolism pathways between the two groups. These results could suggest that processed meat influences breast cancer risk by interacting with oestrogen metabolism in scenarios where the levels of circulating oestrogens are lower [20].

Endometrial cancer is a hormone-driven cancer, with approximately 80% potentially arising due to either an excess of oestrogen or a lack of progesterone. In the normal endometrium, the proliferative effects of oestrogen are normally countered by progesterone but in the absence of progesterone, oestrogen can induce oncogenesis, an effect that is amplified in situations of excess oestrogen [49]. In addition to being a source of N-nitroso compounds, processed meat is also rich in cholesterol, which can be converted into androgens and oestrogens through varying metabolic pathways [50].

Our study further demonstrated that consumption of a standard portion of tomatoes per d was associated with a reduced risk of breast cancer. The protective association was mainly observed among women with postmenopausal breast cancer. Lycopene, a carotenoid widely available in tomatoes, has a very high antioxidant potential

and can thus protect the DNA from damage. In a large pooled analysis which included more than 3000 breast cancer cases, Eliassen et al. [51] also found an inverse association between lycopene and risk of breast cancer. The anti-proliferative effect of lycopene has also been demonstrated in mammary cancer cell lines by its inhibitory effect on insulin-like growth factor-I-stimulated cell multiplying [52, 53]. The observed inverse association could also be due to the high flavonol content of tomatoes which also confers enhanced antioxidant capacity.

Consumption of dried fruits and high-fibre breakfast cereals such as porridge, muesli and bran flakes were inversely associated with risk of endometrial cancer, in particularly among women who were incident cases of postmenopausal endometrial cancer. Dried fruits reportedly have a higher total phenolic content, flavonoids and total antioxidant capacity compared with fresh fruits, making dried fruits a potential candidate of a chemopreventive food [54, 55]. Previous studies have similarly reported an inverse association between wholegrain cereal consumption and endometrial cancer [56, 57]. Dietary fibre has been found to interact with the metabolism of oestrogen, causing a reduced bioavailability of the hormone [58]. High-fibre cereals and dried fruits are also good sources of dietary lignans. Lignans, a type of phyto-oestrogens are plant compounds having structural similarity to 17-oestrodiol. They can lower endogenous oestrogen levels by potentially binding to oestrogen receptors [59], hence reducing the risk of endometrial cancer.

Contrary to a previous case–control study undertaken in Chinese women, which demonstrated an inverse association between white button mushrooms and risk of ovarian cancer [60], our findings showed weak evidence of an increased risk in relation to the consumption of a standard portion of mushrooms per day. Furthermore according to a study among Korean women, high mushroom intake was reportedly associated with a lower risk of breast cancer among premenopausal women and a stronger association was reported among premenopausal women with oestrogen-receptor-positive and progesterone-receptor-positive tumours [61]. However, in this study we do not have this level of detail in terms of types of mushroom consumption and breast cancer by hormone receptor type. This difference could also be attributed to the fact that Chinese cohorts most commonly consume fresh mushrooms, while in Europe the use of canned mushrooms is more widespread. In addition, in the UK, there is no other evidence suggesting that mushrooms can increase or decrease the risk of cancer [62].

Strengths of this study include the prospective study design, a long follow-up time and large sample size. This is also the first study in the UK looking at multiple food groups in relation to the risk of breast, endometrial and ovarian cancers. We were also able to study the associations with specific types of meat, cereal products (wholegrain or refined) and dairy products (high fat or low fat). We adjusted for a wide range of confounders including sociodemographic and lifestyle using a consistent method (directed acyclic graph). However, as in any observational study, residual confounding is still possible. A limitation of our study was the inability to determine whether the associations varied according to the hormone receptor status of tumours, due to the lack of these data at present in this cohort. The UKWCS will soon be expanding to include additional details on the tumour types. Moreover, the use of an FFQ for dietary assessment could also be prone to low accuracy due to recall bias. However, the FFQ is a useful tool in providing a snapshot of the dietary habit over a longer period of time. Regression dilution might also be an issue, given participants' diets may have changed over time, potentially introducing further measurement error. This study also does not take into account the use of pesticides which is also a potential carcinogen influencing cancer risk in women. Our sample was also more health conscious, given the high number of vegetarians in our sample population and more well-off participants than the general population. However, our study still included women from a range of different backgrounds, which implies that findings of this study may be extrapolated to other countries.

Primary prevention of cancer is important and a matter of consideration in public health. While factors such as parity, age at onset of natural menopause and family history are well established to have a link with the risk of breast, endometrial and ovarian cancer, they are non-modifiable risk factors. However, diet which has been shown to either increase or decrease the risk of carcinogenesis makes focus on diet an interesting opportunity in cancer prevention.

To summarise, this study suggests a link between specific foods: processed meat, total meat, tomatoes, dried fruits and wholegrain products and the risk of breast as well as endometrial cancer while a relationship between diet and risk of ovarian cancer is less evident. These findings support the call for further randomised controlled trials of dietary interventions to reduce the risk of these hormone-related cancers among pre- and postmenopausal women.

References

1. Office for National Statistics. *Statistical bulletin: Cancer registration statistics, England: 2016*. 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/final2016 (accessed May 2018)
2. Cancer Research UK. *Cancer statistics by type*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type (accessed May 2018)
3. Kelsey, J.L. et al. Reproductive factors and breast cancer. *Epidemiologic Reviews.* 1993, **15**(1), pp.36-47.
4. McPherson, C.P. et al. Reproductive factors and risk of endometrial cancer: The Iowa Women's Health study. *American Journal of Epidemiology.* 1996, **143**(12), pp.1195-1202.
5. Hunn, J. and Rodriguez, G.C. Ovarian cancer: etiology, risk factors, and epidemiology. *Clinical Obstetrics and Gynecology.* 2012, **55**(1), pp.3-23.
6. Cramer, D.W. The epidemiology of endometrial and ovarian cancer. *Hematology/Oncology Clinics of North America.* 2012, **26**(1), pp.1-12.
7. Jones, M.E. et al. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Research.* 2017, **19**(1), p.118.
8. Gallagher, E.J. and LeRoith, D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. *Diabetes Care.* 2013, **36**(Suppl 2), pp.S233-239.
9. de Oliveira, E.P. et al. Dietary factors associated with metabolic syndrome in Brazilian adults. *Nutrition Journal.* 2012, **11**(1), p.13.
10. Henderson, B.E. and Feigelson, H.S. Hormonal carcinogenesis. *Carcinogenesis.* 2000, **21**(3), pp.427-433.
11. Thomas, H.V. et al. Oestradiol and sex hormone-binding globulin in premenopausal and post-menopausal meat-eaters, vegetarians and vegans. *British Journal of Cancer.* 1999, **80**, p.1470.
12. Barnard, N.D. et al. Diet and sex-hormone binding globulin, dysmenorrhea, and premenstrual symptoms. *Obstetrics and Gynecology.* 2000, **95**(2), pp.245-250.

13. Gann, P.H. et al. The effects of a low-fat/high-fiber diet on sex hormone levels and menstrual cycling in premenopausal women: a 12-month randomized trial (the diet and hormone study). *Cancer.* 2003, **98**(9), pp.1870-1879.

14. Boyd, N.F. et al. Effects of a low-fat high-carbohydrate diet on plasma sex hormones in premenopausal women: results from a randomized controlled trial. Canadian Diet and Breast Cancer Prevention Study Group. *British Journal of Cancer.* 1997, **76**(1), pp.127-135.

15. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available from: dietandcancerreport.org

16. Samavat, H. and Kurzer, M.S. Estrogen metabolism and breast cancer. *Cancer Letters.* 2015, **356**(2, Part A), pp.231-243.

17. Allen, N.E. et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocrine-Related Cancer.* 2008, **15**(2), pp.485-497.

18. Lukanova, A. and Kaaks, R. Endogenous Hormones and Ovarian Cancer: Epidemiology and Current Hypotheses. *Cancer Epidemiology, Biomarkers & Prevention.* 2005, **14**(1), pp.98-107.

19. Cade, J.E. et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). *International Journal of Epidemiology.* 2015, **0**(0), pp.1-11.

20. Taylor, E.F. et al. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *British Journal of Cancer.* 2007, **96**, pp.1139-1146.

21. World Cancer Research Fund/American Institute for Cancer Research. *Changes since the 2007 Second Expert Report: Important shifts in emphasis*. 2018. Available from: https://www.wcrf.org/dietandcancer/changes-since-2007-second-expert-report (accessed June 2018).

22. Dunneram, Y. et al. Dietary intake and age at natural menopause: results from the UK Women's Cohort Study. *Journal of Epidemiology and Community Health.* 2018, **72**(8), pp.733-740.

23. Food Standards Agency. *Food Portion Sizes.* London: The Stationary office. 2002.

24. Cade, J.E. et al. Does the Mediterranean dietary pattern or the Healthy Diet Index influence the risk of breast cancer in a large British cohort of women? *European Journal of Clinical Nutrition.* 2011, **65**(8), pp.920-928.

25. Clague, J. and Bernstein, L. Physical activity and cancer. *Current Oncology Reports.* 2012, **14**(6), pp.550-558.

26. Bagnardi, V. et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British Journal of Cancer.* 2015, **112**(3), pp.580-593.

27. Stockwell, H.G. and Lyman, G.H. Cigarette smoking and the risk of female reproductive cancer. *American Journal of Obstetrics & Gynecology.* 1987, **157**(1), pp.35-40.

28. Wang, L. et al. Association between Breastfeeding and Endometrial Cancer Risk: Evidence from a Systematic Review and Meta-Analysis. *Nutrients.* 2015, **7**(7), pp.5697-5711.

29. Zhan, B. et al. Breastfeeding and the incidence of endometrial cancer: A meta-analysis. *Oncotarget.* 2015, **6**(35), pp.38398-38409.

30. Su, D. et al. Ovarian cancer risk is reduced by prolonged lactation: a case-control study in southern China. *The American Journal of Clinical Nutrition.* 2013, **97**(2), pp.354-359.

31. Liu, L. et al. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). *Cancer Causes & Control.* 1998, **9**(4), pp.369-380.

32. Friberg, E. et al. Diabetes and Risk of Endometrial Cancer: A Population-Based Prospective Cohort Study. *Cancer Epidemiology Biomarkers & Prevention*. 2007, **16**(2), pp.276-280.

33. Aune, D. et al. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. *Scientific Reports.* 2017, **7**, p.44808.

34. Persson, I. Estrogens in the causation of breast, endometrial and ovarian cancers - evidence and hypotheses from epidemiological findings. *The Journal of Steroid Biochemistry and Molecular Biology.* 2000, **74**(5), pp.357-364.

35. Simin, J. et al. Menopausal hormone therapy and cancer risk: An overestimated risk? *European Journal of Cancer.* 2017, **84**, pp.60-68.

36. Beral, V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003, **362**(9382), pp.419-427.

37. Salazar-Martinez, E. et al. Reproductive Factors of Ovarian and Endometrial Cancer Risk in a High Fertility Population in Mexico. *Cancer Research.* 1999, **59**(15), pp.3658-3662.

38. Tsilidis, K.K. et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *British Journal of Cancer.* 2011, **105**(9), pp.1436-1442.

39. Anderson, J.J. et al. Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis. *European Journal of Cancer.* 2018, **90**, pp.73-82.

40. Pala, V. et al. Meat, eggs, dairy products, and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *The American Journal of Clinical Nutrition.* 2009, **90**(3), pp.602-612.

41. Fiolet, T. et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *British Medical Journal.* 2018, **360**, pp.1-11.

42. Pouchieu, C. et al. Prospective association between red and processed meat intakes and breast cancer risk: modulation by an antioxidant supplementation in the SU.VI.MAX randomized controlled trial. *International Journal of Epidemiology.* 2014, **43**(5), pp.1583-1592.

43. Fabio, L. et al. Dietary factors and the risk of endometrial cancer. *Cancer.* 1993, **71**(11), pp.3575-3581.

44. Arem, H. et al. A prospective investigation of fish, meat and cooking-related carcinogens with endometrial cancer incidence. *British Journal of Cancer.* 2013, **109**(3), pp.756-760.

45. Cross, A.J. et al. A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Medicine.* 2007, **4**(12), p.e325.

46. Inoue-Choi, M. et al. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. *International Journal of Cancer.* 2016, **138**(7), pp.1609-1618.

47. Zheng, W. et al. Well-Done Meat Intake and the Risk of Breast Cancer. *JNCI: Journal of the National Cancer Institute.* 1998, **90**(22), pp.1724-1729.

48. Nagao, M. et al. Dietary carcinogens and mammary carcinogenesis. Induction of rat mammary carcinomas by administration of heterocyclic amines in cooked foods. *Cancer.* 1994, **74**(3 Suppl), pp.1063-1069.

49. Carlson, M.J. et al. Catch it before it kills: progesterone, obesity, and the prevention of endometrial cancer. *Discovery Medicine.* 2012, **14**(76), pp.215-222.
50. Bremer, A.A. and Miller, W.L. Chapter 13 - Regulation of Steroidogenesis A2 - Ulloa-Aguirre, Alfredo. In: Conn, P.M. ed. *Cellular Endocrinology in Health and Disease*. Boston: Academic Press, 2014, pp.207-227.
51. Eliassen, A.H. et al. Circulating Carotenoids and Risk of Breast Cancer: Pooled Analysis of Eight Prospective Studies. *Journal of the National Cancer Institute.* 2012, **104**(24), pp.1905-1916.
52. Levy, J. et al. Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. *Nutrition and Cancer.* 1995, **24**(3), pp.257-266.
53. Karas, M. et al. Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. *Nutrition and Cancer.* 2000, **36**(1), pp.101-111.
54. Lutz, M. et al. Phenolic content and antioxidant capacity in fresh and dry fruits and vegetables grown in Chile. *CyTA - Journal of Food.* 2015, **13**(4), pp.541-547.
55. Capanoglu, E. Investigating the Antioxidant Potential of Turkish Dried Fruits. *International Journal of Food Properties.* 2014, **17**(3), pp.690-702.
56. Goodman, M.T. et al. Association of soy and fiber consumption with the risk of endometrial cancer. *American Journal of Epidemiology.* 1997, **146**(4), pp.294-306.
57. Bidoli, E. et al. Fiber intake and endometrial cancer risk. *Acta Oncologica.* 2010, **49**(4), pp.441-446.
58. Sowers, M.R. et al. Selected Diet and Lifestyle Factors Are Associated with Estrogen Metabolites in a Multiracial/Ethnic Population of Women. *The Journal of Nutrition.* 2006, **136**(6), pp.1588-1595.
59. Kuiper, G.G.J.M. et al. Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor β. *Endocrinology.* 1998, **139**(10), pp.4252-4263.
60. Lee, A.H. et al. Mushroom intake and risk of epithelial ovarian cancer in southern Chinese women. *International Journal of Gynecological Cancer.* 2013, **23**(8), pp.1400-1405.
61. Shin, A. et al. Dietary mushroom intake and the risk of breast cancer based on hormone receptor status. *Nutrition and Cancer.* 2010, **62**(4), pp.476-483.

62. Cancer Research UK. *Mushrooms in cancer treatment.* 2015 [Online]. Available from: http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/complementary-alternative-therapies/individual-therapies/mushrooms-in-cancer-treatment [accessed 20 June 2018]

Chapter 8
Overall discussion

Diet is one of the major modifiable factors that may influence sex hormone levels, the risk of obesity and insulin resistance which subsequently may affect the timing of onset of natural menopause. Eventually, the timing of menopause may also influence the duration of the presence of VMS and also the risk of hormone-related cancers such as breast, ovarian and endometrial cancers. However, as documented in Chapter 1 and Chapter 2, there are several gaps in the literature regarding the inter-relationship between diet, age at menopause and its associated sequelae. For instance, only a limited number of studies have explored the association between diet and the onset of natural menopause. The evidence is also inconsistent across the observational studies, thus leading to inconclusive findings. In addition, as concluded by a systematic review [1], intake of the phytoestrogen genistein which is found in soy products could influence the presence of VMS. However, very few studies have investigated the association between the natural diet and the presence of VMS. Chapter 1 summarises the effect of dietary components on the risk of breast, ovarian and endometrial cancers; while some dietary factors may be protective against these hormone-related cancers, some increase the risk. Yet, the relationship between diet and these cancers is also inconsistent within observational studies except for the strong link between alcohol consumption and the high possibility of breast cancer (Chapter 2).

Therefore, in this thesis, the relationships between diet and the timing of onset of natural menopause as well as the relationships between diet and sequelae of menopause such as the presence of VMS and the risk of ovarian, endometrial and breast cancers have been thoroughly examined. The analyses presented in this thesis have used data from the UKWCS and the InterLACE consortium. The research questions and objectives of this thesis, outlined in Chapter 2 have been met. In this chapter, a summary of the findings from this thesis has been presented. The results have also been compared and contrasted with findings across the different chapters of this thesis as well as with previous studies. Moreover, a critique of the methods used has also been included while summarising the findings. Furthermore, an evaluation of the strengths and limitations of the thesis,

followed by recommendations for future studies, public health messages and finally a conclusion have been provided.

8.1 Novel findings from this thesis

- The first study to compare the diet of premenopausal and naturally postmenopausal women in the UK (Chapter 3).
- The first study in the UK to explore the association between various dietary components as well as dietary patterns and the timing of the onset of natural menopause (Chapter 4 and Chapter 5).
- Provided novel information by pooling data from five different observational studies across countries on the relationship between soy consumption and frequency/severity of VMS (Chapter 6).
- Provided additional evidence for the association between diet and the risk of ovarian, endometrial and breast cancers in the UK (Chapter 7).

8.2 Summary discussion

8.2.1 Diet and age at natural menopause

The first research question of this thesis, the association between diet and timing of the onset of natural menopause was estimated using linear regression as well as survival analysis which are presented in Chapter 4 and Chapter 5 respectively.

In a sample of 914 women who experienced a natural menopause after 4 years of follow-up, intake of an additional portion of oily fish was associated with a delayed onset of menopause by 3.3 years (at 1% level). Similarly, an extra portion of fresh legumes (e.g., peas, mushy peas, mange-tout, and green beans) was associated with a later menopause by approximately a year. On the other hand, our findings showed that a higher intake of refined pasta and rice was related to an earlier onset of menopause. Moreover, being vegetarian was also associated with an earlier onset of menopause. No evidence of an association was found between the other food groups and timing of the onset of natural menopause. Furthermore, when stratification by age at baseline was conducted, this led to reduced associations and wider confidence intervals due to the smaller samples in the subgroups. Only the consumption of refined grain products was found to be associated with an earlier onset of menopause by 0.3 years per portion among women who were aged above 50 years at study recruitment period which was borderline significant.

Traditionally, the relationship between diet and the event (e.g., health outcomes) have explored the effect of single foods. However, the study of dietary patterns has been recommended by several authors given that foods are less commonly consumed individually or as isolated foods, they rather form part of a more elaborate meal. Although the study of individual food components is useful in identifying the single foods associated with the timing of onset of natural menopause, this approach does not consider the fact that the foods eaten may be highly correlated [2]. Therefore, it is equally crucial to investigate the relationship between dietary patterns and age at menopause. The work in Chapter 4 is thus extended in Chapter 5 to derive dietary patterns from the 64 food groups using two methods namely PCA and RRR. Five dietary patterns were derived from the PCA method while three patterns were generated using the RRR method. Interestingly, food items such as oily fish, fresh legumes and refined grains and cereals which were found to be significantly associated with age at natural menopause in Chapter 4, did not form part of any of the dietary patterns as they contributed to eigenvalues below 0.2 implying that they did not explain as large an amount of variance as compared to the other food items [3].

In the analyses including 5,312 participants, after adjusting for the potential confounders, women who scored higher on the 'animal proteins' pattern (derived from PCA; highly loaded with fish, shellfish, meat, poultry and offal) were 6% less likely to have gone through the menopause compared to those who scored lower. The 'red meat and processed meat' pattern (derived from RRR) predicted a 7% higher risk for a later menopause. Findings from Chapter 4 are in line with these results which demonstrated that intake of individual food items such as an extra portion of fish, red meat and processed meat resulted in a positive estimate, indicating a later onset of menopause.

8.2.1.1 Findings in context of previous research

As shown by the literature search in Chapter 2 (Table 2.2), only 13 studies have explored the relationship between diet and the timing of menopause. The exposure of interest across the observational studies includes various types of single foods while one RCT explored the effect of a dietary intervention (low-fat, high-carbohydrate diet) [4] on age at menopause.

In contrast to our findings, no study reported an association between the intake of oily fish and a delayed onset of menopause. Out of two studies which investigated the association between seafood and age at menopause, a cross-sectional study reported an

early onset of menopause [5] while a prospective study of 85,682 premenopausal women at baseline demonstrated no evidence of an association [6]. Similarly, Nagel et al. [7] reported that consumption of fish was not related with the timing of onset of menopause. The main disparity between our findings and previous evidence is that the authors did not consider specific types of fish. One probable mechanism for the observed finding in our study is that oily fish being a rich source of omega-3 fatty acid could exert antioxidant properties and potentially offset ROS. Subsequently, the ovarian follicles are protected against atresia, thus delaying the onset of menopause. This can be supported by an intervention study whereby 37 women (15 obese and 12 normal-weight) with regular menses were given omega-3 fatty acid supplementation for one month. The omega-3 supplementation resulted in an improvement in the levels of pro-inflammatory cytokines among obese women while a reduction in FSH level was observed among normal-weight women, implying the possibility that omega-3 fatty acids could delay ovarian aging [8]. However, in a prospective study including 3,115 premenopausal Japanese women followed up for 10 years, intake of omega-3 fatty acids was not found to be associated with the onset of menopause [9]. The main reason for the disparity between the findings of these two studies is the study design. While the exposure diet was measured retrospectively using an FFQ in the Japanese study, omega-3 fatty acid supplementation was given to the women in the intervention study. In addition, study participants in the prospective study were substantially older at baseline with a mean age of 43.0 years while in the intervention study the women were aged between 28 to 34 years.

Nagata et al. [10] prospectively assessed the relationship between specific foods and the likelihood of menopause over 6 years among 1,130 Japanese women. Although the authors did not directly look at the consumption of fresh legumes, they reported a relationship between a later onset of menopause and the intake of green and yellow vegetables. These findings can be supported by biological mechanisms as described in Chapter 1 (section 1.3), suggesting that high antioxidant potential of these food items could help prevent degradation of ovarian follicles and hence delay the onset of menopause. In addition, our study also found that a higher intake of vitamin B6 and zinc, both of which have antioxidant properties, were also linked with a delayed onset of menopause (Chapter 4).

On the other hand, our findings showed that a higher intake of refined pasta and rice was related to an earlier onset of menopause, in line with the EPIC-Heidelberg study [7]. Previous evidence has suggested that a high consumption of refined carbohydrates

may be associated with a higher risk of insulin resistance [11-13]. In a longitudinal cohort study, Sowers et al. [14] reported that insulin resistance was associated with an earlier onset of menopause irrespective of a link between insulin resistance and levels of AMH and inhibin B. In line with this study, Isik et al. [15] demonstrated that in comparison to healthy women, women with type II diabetes had a lower ovarian reserve. These findings could be explained by observations in animal models which showed that in a hyperglycaemic-hyperinsulinaemic condition, there was a reduction in ovarian steroid hormone production and release, anovulation, and also accelerated follicular atresia [16, 17]. Although evidence suggests that insulin resistance (section 1.3) could lead to premature ovarian failure and thus an earlier natural menopause, findings from this thesis further demonstrated that irrespective of being diabetic at the study baseline, an additional portion of refined pasta and rice was still associated with an earlier menopause.

With regard to dietary patterns, as evidenced in Chapter 2 (Table 2.2) there are no previous studies which have explored their association with the onset of natural menopause, thus making comparison impossible. Our findings can be supported by a few previous studies which also reported a later onset of menopause with the consumption of meat, although meat consumption was explored individually rather than as part of a dietary pattern [5, 7, 18]. On the other hand, Boutot et al. [6] reported a higher risk of an earlier menopause with each 1 serving per day of red meat among women in the Nurses' Health Study II. The authors also did not found an association between high levels of animal protein intake and an early menopause. The Nurses' Health Study II consisted of much younger women at the study entry (25-42 years) to investigate the risk of an early menopause, while women in the UKWCS and the previous studies were older at baseline, and these studies also considered the association between overall risk of menopause and diet rather than the early menopause as the outcome.

8.2.1.2 Evaluation of methods used

8.2.1.2.1 Study design

The UKWCS data has been used in Chapters 3, 4, and 5 of this thesis. The aim of the UKWCS is to investigate links between diet and health, in particular, cancer. Women recruited from a WCRF mailing list of approximately 500,000 responders formed part of the UKWCS. In order to be able to explore differences in health due to diet, this cohort selected participants from three main groups of dietary patterns: vegetarian, eating fish (not meat) and meat-eaters [19]. This cohort consisted of 35,372 women (a 58% response

rate) aged between 35 to 69 years at study baseline. Baseline data was collected between the years 1995 to 1998 via postal questionnaire. This included an extensive lifestyle questionnaire and a 217-item FFQ (please refer to section 8.2.1.2.3). Phase 2 data was collected four years later, and included 14,172 women (40.1% response rate). In addition to a further lifestyle questionnaire, the participants had to complete a 4-day food diary, and 1-day activity diary [20]. Using participants details such as their National Health Service (NHS) number, full name and date of birth where possible, all the women were flagged to the National Health Service Information Centre (NHSIC) to have updates on cancer incidence and death, to which all women agreed to [19].

8.2.1.2.2 Assessment of age at natural menopause

As discussed in Chapter 2, various definitions of age at menopause have been used in previous studies which have looked at the association between diet and the timing of natural menopause. In this thesis, age at natural menopause was assigned based on the WHO definition which states that the last menstrual bleeding followed by at least 12 months of amenorrhea as some women may have regular bleeding still after 6 months of amenorrhea. Based on answers to the question: 'If no natural menstrual periods in the last 12 months, how old were you when you had your last natural menstrual period?' age at menopause was defined as the age at the final menstrual period. In order to ensure that premenopausal women at baseline became postmenopausal at follow-up, the baseline question: 'How many natural menstrual periods have you had in the last 12 months?' was used (Please refer to Chapter 4 for more details on the inclusion and exclusion criteria used to ensure a natural menopause). If data on age at last natural period was missing, the year of last menstruation (if provided) and birth year were used to estimate the age at menopause.

8.2.1.2.3 Dietary assessment: Food Frequency Questionnaire

As described in Chapters 3-5, the 217-item FFQ was adapted from the EPIC-Oxford Cohort [21] and tailored for the large number of vegetarians in the UKWCS. These alterations were based on a pilot study conducted in a sample of vegetarian women whereby they had to complete food diaries. Further vegetable composite dishes and portion size estimates were included in the FFQ based on the results of this pilot study. The FFQ required participants to report their dietary intake over the last 12 months, using one of ten response categories ranging from "Never" to "More than 6+ portions a day". Using the different frequency categories, the number of daily portions for the 217 food

items was defined. These were consequently converted into weight of each food consumed per day based on the Food Standards Agency portion sizes book [22]. For the purpose of this study, the 217 food items were collapsed into 64 food groups (refer to Chapters 3 and 4).

The mean daily intake of vitamins such as vitamins C (mg), B1 (mg), B2 (mg), B6 (mg), B12 (µg), A (µg), D (µg) and E (mg) as well as minerals such as folate (µg), calcium (mg), non-haem iron (mg) and zinc (mg) had been previously estimated from the 217 food items based on The Royal Society of Chemistry Food tables (version 5) [23]. Average energy, macronutrient and micronutrient intakes were computed by multiplying the consumption frequency for each food with the estimated portion size.

8.2.1.2.4 Dietary patterns

Various methods exist that can be used to derive dietary patterns. *A priori* methods based on dietary guideline knowledge can be used to generate diet quality scores or statistical methods based on data-reduction techniques which are known as the *a posteriori* methods can also be used [24]. Data driven dietary patterns are used in Chapter 5 of this thesis. Using the 64 food groups derived from the FFQ (refer to Chapters 3 and 4 for more details), dietary patterns were generated using two methods: PCA and RRR.

PCA is the most commonly used dimension-reduction technique to generate dietary patterns [25] and has good reproducibility across studies as demonstrated in a review of 65 studies [26]. PCA was conducted using Stata. Firstly, the data were reduced by forming linear combinations of the original observed variables. The correlated variables are then grouped together which identifies any underlying dimensions in the data. Factor loadings are generated which are coefficients defining these linear combination and the correlations of each food item with that component [27]. Secondly, a scree plot [28] was used which plots the eigenvalues against each component (in order of highest to lowest). The number of factors retained was according to the combination of food group components with an eigenvalue >1.0 and examination of the breakpoint in the scree plot, resulting in five factors retained for further analyses. The eigenvalue is defined as the amount of variance that is explained by a given component [29]. Thirdly, varimax rotation [30] was applied which redistributes the explained variance for the individual components, so as to obtain the simplest factor structure. This helps to increase the number of larger and smaller loadings. Finally, factor scores were produced for each participants for each of the dietary patterns identified. A higher score reflected closer

adherence to the particular dietary pattern. As PCA mainly aims to construct uncorrelated linear combinations of food intakes to provide as many variations in food intake as possible, it is usually helpful in reproducing dietary patterns which reflect dietary behaviours of a population. However, these may not be linked to the outcome of interest.

The more recently introduced RRR by Hoffman et al. [31], is also an *a posteriori* method which generates dietary patterns based on biological risk factors or nutrients relevant to the health outcome. RRR determines linear combinations of predictor variables (e.g., food group intake) that explain as much as possible of the variation in the response variables (e.g., nutrients, biomarkers or risk factors), that are presumed to affect disease risk [31, 32]. The DAG used in Chapter 5 describes the conceptual framework for RRR in this thesis. In this analysis similar to PCA, the 64 food items were used as predictor variables and age at menarche, BMI and total energy intake were the response variables. RRR was applied to derive dietary patterns predictive of age at natural menopause using Stata in combination with the PLS option in SAS. Dietary patterns that accounted for the maximum variation in the response variables were identified. Factor loadings are generated which were used to identify food items which formed part of the dietary patterns. Eventually, a factor score for the identified dietary pattern was produced for each participant similar to PCA. But unlike PCA, RRR derived dietary patterns may not reflect the patterns observed in the population. Interestingly though, findings from Chapter 5 demonstrated that the 'animal proteins' pattern derived from PCA was positively and moderately correlated with the 'red meat and processed meat' pattern derived from RRR, suggesting that the RRR derived dietary patterns were also behaviourally meaningful. Thus, findings from this thesis provide quite strong evidence that a higher consumption of a diet highly loaded with red meat and processed meat are associated with a delayed onset of natural menopause.

8.2.1.2.5 Statistical analyses

The use of different analytical methods to investigate the association between age at natural menopause and food groups as well as dietary patterns, multiple linear regression and survival analysis respectively could have accounted for the differences in results found in Chapter 4 and Chapter 5. The aim of using multiple linear regression was to explore the age of natural menopause as a continuous variable in relation to the consumption of a standard portion of the various food groups. The analyses were restricted to just 914 women who experienced a natural menopause at follow-up. This

ensured that women who may be too young to have gone through a menopause were excluded, thus preventing under-estimation of the age at natural menopause. A limitation of this analysis could be multiple testing of the food groups which could have led to spurious significant associations by chance. However, this was accounted for by setting the significance level at 99%. Although the pros of multiple regression models include better prediction from multiple predictors and can avoid 'picking' a specific single predictor, results should be interpreted with caution as the significant associations do not necessarily indicate causal effects [33].

In order to include more information and observations, in subsequent research based on the whole cohort, survival analysis approach was used, with age at menopause right censored to take into account the fact that not all of them will have achieved menopause at the time of follow-up. While these may appear to be cases of missing data as the time-to-event is not actually observed, these participants contribute to crucial information that they quitted at a certain amount of time without having reached a menopause is itself informative. This ability to handle censored observations is an advantage of survival analysis over linear regression analysis which ignores this aspect [34]. The use of the time-to-event analytic approach has also been suggested as a better way to explore the risk of being naturally postmenopausal [35]. While the multiple regression model gave mean estimates of age at natural menopause, the survival analysis provided the risk estimates of being naturally postmenopausal.

8.2.2 Diet and vasomotor menopausal symptoms

In relation to the presence of VMS, the pooled analysis of five studies forming part of the InterLACE consortium resulted in a null observation with the consumption of soy products (soy bean, soy bean curd, tofu, tempeh) cross-sectionally. Similarly, no evidence of an association was found with the intake of soy milk. Across the individual studies, no evidence of an association was found between soy products and presence of VMS for the cross-sectional analysis (Chapter 6). The odds ratio for the ALSWH, WHITEHALL and SMWHS studies were prone to a negative estimate, as opposed to the HOW and JMWHS studies. The opposing direction for the odds ratio obtained for JMWHS could reflect the frequent consumption of soy products and lower frequency/severity of VMS in this Japanese cohort. The exposure, that is, soy consumption and the outcome which was the severity of VMS were measured in a similar way in both HOW and JMWHS. In addition, HOW included only 5% of women reporting

severe VMS which is comparable to JMWHS (4.4%). Although the Japanese data is quite different from the other studies, this study did not affect the overall analysis to a large extent as demonstrated through the pooled-analysis; JMWHS contributed to only 0.84% of the overall analysis.

When assessed prospectively, the pooled analysis demonstrated that soy product consumption was protective against the incidence of VMS. Comparing frequent consumption of soy products versus less frequent consumption, lower odds for reporting the presence of VMS was observed across ALSWH, HOW and WHITEHALL studies. On the other hand, for the relationship between soy milk consumption and presence of VMS at follow-up, across all three studies, higher odds for reporting the presence of VMS were observed. As elaborated in Chapter 6, this could be due to reverse causality. As women in these studies were mainly Caucasians, soy milk consumption could be the most commonly consumed dietary phytoestrogen source and used by the women to try to prevent VMS (Chapter 6).

8.2.2.1 Findings in context of previous research

Our findings regarding the inverse association between soy product consumption and incidence of VMS are in line with a Japanese community-based study also reported a negative association between total soy product consumption and hot flushes after a follow-up period of 6 years [36]. According to a systematic review of 43 RCTs, there was no conclusive evidence for an association between dietary soy or soy extracts and the frequency or severity of hot flushes. However, genistein extract, a phytoestrogen found in soy products appeared to reduce the number of hot flushes among postmenopausal women reporting these symptoms [1].

Isoflavones, abundantly found in soy and soy products are the most common phytoestrogen with the effects of genistein and daidzein being mainly investigated. Due to a similarity in the molecular structure of phytoestrogens to that of oestradiol, they can as well bind to ERs to produce either oestrogenic or anti-oestrogenic activities depending on the circulating level of oestrogen. The reduced oestrogen level during the menopausal transition causes a decrease in endorphin concentration in the hypothalamus which leads to an increased level of the neurotransmitters norepinephrine and serotonin [37, 38]. Consequently, the thermoregulatory threshold is lowered which produce excessive heat loss. Thus in this condition of low circulating oestrogen level, by binding to ERs

phytoestrogens could offset those biologic effects and reduce the frequency or severity of VMS.

8.2.2.2 Evaluation of methods used

8.2.2.2.1 Study design

The InterLACE study was established in 2012 with the aim to understand women's reproductive health in relation to chronic disease risk, specifically diabetes and cardiovascular diseases [39]. It includes data from 20 studies, more specifically from nine national cohorts namely Denmark, Japan, Sweden, Norway, UK, USA, Lebanon, Spain and Australia. In addition, it comprises of state-based studies from specific places such as San Francisco, Seattle, Hawaii, among others which make up the remaining 11 studies. In particular, the InterLACE dataset pooled data from approximately 230,000 participants mainly from existing observational studies having data on women's health [40]. Ethical clearance for each study had been approved at initiation of the individual studies.

The individual studies were thus requested for the relevant data in the form of a list of variables, survey questionnaires, data dictionaries/formats, and protocols, according to the study's aim. Data regarding socio-demographic and lifestyle factors (e.g. age, marital status, BMI, etc.), female reproductive characteristics (e.g. number of pregnancies, menopausal status, VMS, etc.), and chronic disease outcomes were provided [40].

Twelve of the observational studies were longitudinal and some had data collected at different waves. In this thesis, one of the objective was to investigate the association between soy consumption and the presence of VMS (Chapter 1). Therefore, five studies which had information on the exposure and outcome of interest were used. The appropriate waves had to be identified as the baseline and follow-up cohort for the ALSWH, HOW, WHITEHALL, and JMWHS studies (Table D.1). Prior to data harmonisation, the individual datasets were checked for outliers and discrepancies, and if required, the data providers were probed in order to resolve the issue. Using specific coding instructions developed by the interlace team, the variables were harmonised to generate new variables. Data harmonisation for the whole dataset has been described elsewhere. Please refer to Chapter 6 (sections 6.2.3 and 6.2.4) for more details on data harmonisation for the exposure and outcome of interest as well as covariates used in this thesis.

8.2.2.2.2 Assessment of exposure and outcome

Please refer to Chapter 6, section 6.2.3 whereby the assessments of soy consumption and the presence of VMS have been detailed.

8.2.2.2.3 Data harmonisation and statistical analysis

The pooled analysis allowed the investigation of soy consumption in relation to the presence of VMS in this thesis which would not be otherwise possible in the single studies due to the low sample size. The pooled analysis, in addition, enabled examination of the consistency across the studies. Availability of raw data from the individual studies also made re-analysis feasible by considering specific inclusion criteria for all the studies and a standardised definition of the variables of interest.

In order to make findings across the five individual studies comparable, data harmonisation was conducted prior to the pooling analyses. Details on harmonisation of the variables of interests and the covariates are provided in Chapter 6. Data harmonisation is the collapsing of the variables of interest into the simplest level of detail in order to incorporate information from as many studies as possible. However, this can potentially lead to loss of statistical power as well as potential misclassification of the degree of VMS and frequency of soy consumption. For instance, studies like ALSWH and WHITEHALL had ten and nine frequency options respectively for consumption frequency of soy that were collapsed to four categories for this analysis. Similarly, for the frequency/severity of VMS, the variable was collapsed to include four categories. To include as much information as possible for both the consumption frequency of soy products and frequency/severity of VMS across the five individual studies, for the cross-sectional analyses, multiple logistic regression was used. However, to make the pooled analysis of the cross-sectional data more interpretable, the variables were further dichotomised as consumption of soy products: ‘yes or no’, and presence of VMS: ‘presence or absence’.

Likewise, for the prospective analysis across the three individual studies (ALSWH, HOW, WHITEHALL) as well as for the pooled estimate, as the frequency of soy consumption was still quite low across the different categories of frequency/severity of VMS, the dichotomised variables had to be used. Although harmonising the variables led to a reduced number of categories (the smallest common denominator) implying that the amount of information is also diminished, it is a simple way to maximise the number of studies being analysed [41].

Various sources of heterogeneity such as differences in study populations, information available on the potential confounders, data collection, and validation methods as well as dietary assessment methods are possible when pooling data from the five observational studies of the InterLACE consortium [42]. To account for the different levels of VMS in different populations, 'study' was included in the model as a stratification variable to account for correlation of individuals within studies. This ensured that the modelling results of the five individual studies for the cross-sectional analyses align with the forest plots that are also based on estimates from the individual studies. Furthermore, the Stata 'svy' command was used to identify strata defined by 'study' in order to improve standard error estimates.

For the pooled analysis, the random effect model was used. This model includes variation between the five studies, thus accounting for heterogeneity between the effects of the studies. The model assumes that the different studies have their own true effects and that these effects are randomly positioned about a central value [43]. With this model, the confidence intervals tend to be wider implying that caution needs to be taken when interpreting the summary effects [44]. Additionally, to reduce heterogeneity and allow for more precise estimation of effect, covariates such as smoking status, education level, menopausal status, representing individual features of the studies were also included in the random effects model [44].

8.2.3 Diet and the risk of ovarian, endometrial and breast cancer

As stated in Chapter 1, a later onset of menopause has been linked to an increased risk of hormone-related cancers such as ovarian, endometrial and breast cancer. Similar findings have been demonstrated in Chapter 7. Longer exposure to the hormone oestrogen has been postulated as one of the pathways through which a delayed onset of menopause increases the risk of these cancers. After around 18 years of follow-up in the UKWCS, the overall results from individual food items demonstrated that a high intake of processed meat and total meat (which included red meat, poultry, offal, and processed meat) were associated with an increased risk of both breast and endometrial cancer. Moreover, unexpectedly a higher consumption of mushroom was linked to an increased risk of ovarian cancer. On the other hand, a higher intake of tomatoes and dried fruits were protective against breast and endometrial cancer risk respectively. To investigate whether age at natural menopause could influence the observed associations, subgroup analysis

by age at menopause was conducted. However, the diet of women with either an earlier or a later natural menopause did not seem to change the risk of cancers.

The aetiology and pathogenesis of these hormone-related cancers when diagnosed premenopausally and when diagnosed postmenopausally are not the same (section 1.6.3.4). For instance, additional findings from Chapter 7 demonstrated that an increased risk of postmenopausal breast cancer was associated with processed meat and total meat consumption while postmenopausal breast cancer risk was reduced with consumption of tomatoes. As for postmenopausal endometrial cancer, intakes of processed meat and low calorie/diet soft drinks were related with a higher risk. Consumption of dried fruits was in particular protective against postmenopausal endometrial cancer. Furthermore, an increased risk of ovarian cancer was linked with high mushroom consumption. However, the findings for endometrial and ovarian cancer risk by menopausal status in this thesis are less reliable given the relatively small number of cases which contributed to the wide confidence intervals.

8.2.3.1 Findings in context of previous research

As demonstrated by the literature search in Chapter 2, no study explored the association between diet and ovarian cancer risk by menopausal status; two studies stratified their findings by menopausal status for endometrial cancer risk [45, 46]; and for breast cancer risk, out of 28 studies, 12 studies conducted analyses by menopausal status. Yet out of the 12 studies, only three studies [47-49] stratified the cancer analyses by menopausal status by conducting survival models defined as women contributing person-time from baseline until their age at menopause or the event for the premenopausal model and the postmenopausal model from their age at menopause until the event. On the other hand, in the remaining nine studies [50-58], menopausal status was instead evaluated as an effect modifier by stratifying the outcomes by menopausal status. Stratification analysis is based on a non-parametric approach. It not only leads to fewer participants in the individual strata but also makes estimation of the main association less precise and less reliable [59]. Therefore, the way stratification by menopausal status has been conducted could additionally account for the disparities in findings between the studies included in Chapter 2.

In line with these outcomes, previous findings from the UKWCS which investigated the association between meat consumption and risk of breast cancer also reported positive associations between total meat and processed meat intake and

postmenopausal breast cancer risk. That analysis also found a positive association between total meat and non-processed meat and incident risk of premenopausal breast cancer [60] whereas in this thesis no such relationships with premenopausal breast cancer risk were demonstrated. The main disparity for the findings could be due to the fact that in the previous study, pre- and post-menopausal breast cancer risk were not treated as a time-to-event variable as compared to analyses in this thesis. Instead, the survival model was stratified by menopausal status at baseline.

Although the recent CUP findings [61] and four out of six studies published since the WCRF/AICR systematic review (Chapter 2) have reported a strong evidence for the association between the consumption of alcoholic drinks and an increased risk of breast cancer, findings from this thesis did not provide any evidence of an association between alcohol consumption and breast cancer risk. Differences in findings could mainly be due to the larger number of breast cancer cases in those studies. Another potential explanation is that alcohol consumption in this study population was quite low (9.1g/day among women with breast cancer). Thus, in this thesis, the relationship with high alcohol consumption could not be investigated due to low study power. As demonstrated in a recent pooled analysis of 20 prospective studies, although a positive linear trend was observed with any amount of alcohol consumption, for <30g/day of alcohol intake the association was modest [62]. In addition, according to the large EPIC study which included 11,576 breast cancer cases, the risk of breast cancer was found to increase by 6%, 12% and 25% with the consumption of 5-15 g/day, 15-30 g/day and >30 g/day of alcohol, respectively [63]. Furthermore, the relationship between alcohol and risk of breast cancer could also vary by hormone receptor status [62-65]. However, this could not be investigated in this thesis due to the lack of this data. The UKWCS will soon be expanding to include additional details on the tumour types through linkage to Public Health England data.

8.2.3.2 Evaluation of methods used

8.2.3.2.1 Updating Breast, Endometrial and Ovarian Cancer Cases in the UKWCS

As mentioned in section 8.2.1.2.1, at baseline women in the UKWCS agreed to provide their NHS details which was flagged to the NHSIC. The NHSIC could thus provide updates on cancer incidence and death data on a quarterly basis. These data are subsequently applied to the UKWCS Microsoft Access database by the Nutritional Epidemiology Group (NEG) Database Manager. These information are then updated into

Stata by linking the data to the UKWCS participants' identification codes. This process is conducted through a series of steps which had been developed previously (Appendix F). As the latest cancer database included data until September 2015, that is, lagging behind by approximately three years, the database was updated by me so as to increase the sample size for cancer incidence.

8.2.3.2.2 Study design and dietary assessment

Please refer to sections 8.2.1.2.1 and 8.2.1.2.3 for description of the study design and dietary assessment.

A post hoc sample size calculation demonstrated that after nearly 18 years of follow-up, for ovarian cancer cases, there was approximately 80% power to detect a relative risk of around 1.4 (two-tailed $p<0.05$) comparing early versus late age at menopause, dichotomising age at natural menopause at the median age, or more than 90% power for a relative risk of 1.5. A similar power was found for endometrial cancer. This represents reasonable power for what are rare outcomes. Analysing the exposure as a continuous variable provided even more power. For breast cancer, there was 95% power to detect a relative risk of 1.2, which represents excellent power for this outcome.

8.2.3.2.3 Time-to-event analysis

Time-to-event analysis also known as survival analysis is one which rely on fixed time periods in comparison to other forms of analysis. The Kaplan-Meier plot which involves the use of life tables and drawing of survival curves to make comparison between two or more groups, and the log-rank test which is used to test for any significant differences between the groups are the commonly used techniques [66]. However, these are nonparametric methods, that is, distributions are estimated directly from the data without any model assumptions.

On the other hand, the Cox proportional hazard model is a semiparametric method whereby distributions are modelled as a function of an unspecified baseline distribution and a set of unknown parameters. Additionally in comparison to the two other methods, the Cox proportional hazard model makes it possible to adjust for confounding [67]. Therefore, this survival analysis method was used to explore the associations between diet and the risk of ovarian, endometrial and breast cancers in the UKWCS (Chapter 7). The analyses measured the time from FFQ completion date at study baseline to the incidence of hormone-related cancers or the date the participant was lost to follow-up or,

for women who did not develop breast cancer, which was the censor date (as described in section 7.2.3). The time-to-event analysis is also able to deal with recruitment which occurred at different time points in the study.

In the Cox proportional hazard regression model, it is imperative to check the assumption of proportional hazards [66]. The cumulative survivor functions were plotted to ensure that they do not cross which indicated that the assumptions of proportional hazards have been met. [68]. In addition to the graphical method, the Cox-Snell residuals test was used as an objective approach to evaluate the goodness of fit of the model. An important criterion for a good model fit is that the residuals should have a standard exponential distribution with hazard function equal to one [69].

8.2.4 Assessment of potential confounders by Directed Acyclic Graphs

Systematic errors are reduced through randomisation of participants in intervention or control groups in RCTs. However, in observational studies, no such allocation of participants is conducted [70]. It is important to control for confounders in such studies to reduce bias and make valid causal inferences from observational studies as confounders tend to mask the real effect of the exposure [71]. The most common method to address this issue is to adjust for the confounders in statistical models. Data-driven methods such as forward or backward stepwise regression are commonly used to identify potential confounders. The criteria used to identify the confounders is usually based on the magnitude of p-values. However, the causal relations between the exposure and outcome are not often accounted for through these methods [70].

Recently, directed acyclic graphs (DAGs) which are visual representations of causal assumptions have been increasingly used to identify confounders [72]. The DAG is called a directed graph as variables in the graph are connected through a series of arrows illustrating causal relationships between them along a timeline. It is termed as acyclic as the causes always precede their effects, thus, none of the paths in the graph would form a closed loop. Covariates included in the DAG and the direction of the arrows are based on a priori knowledge [71]. As explained in Chapter 1 (section 1.7), covariates included in the DAGs used Chapters 3-7 are based on a conceptual framework constructed using theoretical evidence to identify minimal sets of variables to be included in the statistical models [38] (Figures B.1, C.2, D.2, E.1, E.2).

The casual relationship is termed as the causal path in the DAG and is the assumed association between the exposure and outcome. A backdoor path is an alternative path

through which the exposure can lead to the outcome. The presence of at least one open backdoor path between exposure and outcome is known as confounding [73]. For example, smoking is a confounder for the association between diet (exposure) and age at natural menopause (outcome) as it leaves the backdoor path open, that is, there is an arrow starting with an arrowhead towards the exposure and the outcome (diet←smoking→age at menopause). In order to control for confounding, the confounder has to be removed from the pathway such that the backdoor path blocked. The DAG provides an illustration of the potential causal mechanisms under study, as such when the graph includes all appropriate variables and their causal relationships, confounding can be identified through explicit assumptions [71]. Confounders that had a considerable proportion of missing observations were not considered when constructing the DAG (e.g. education level and occupational status), mainly if other closely related variables were available (e.g. socio-economic status).

In addition to confounding, the DAG also helps to identify mediation and collider bias. Mediators and colliders may also appear as causal relationships in the DAG. For instance, the mediator (diet→BMI→age at menopause) leave the indirect causal path open. However, adjusting for mediators (e.g. BMI) would attenuate the effect of diet as this is not a true confounder, thus will restrict the ability to observe any relationship between the exposure and outcome [71]. As mediators lie on the causal pathway and could be involved in the mechanism of the outcome, in Chapter 7, age at menopause identified as a mediator has been further explored using effect modification analysis. Furthermore, adjusting for colliders could introduce collider bias in the analysis. A collider is also found on the causal pathway but is caused by both the exposure and the outcome. It naturally closes backdoor path, therefore adjusting for the collider would introduce bias by opening the backdoor path [73]. This further demonstrates the advantages of using a DAG.

Therefore, the use of the DAG does not only help to ascertain confounding but is also valuable to avoid under and over-adjustment, thus increasing the validity of our study. Since these criteria could be prone to subjective decisions, and using the DAG could be cumbersome in particular in epidemiological studies which involves a large number of variables, in this thesis, the web application DAGitty which offers a simple interface has been used to identify the minimum sets of confounders [74].

8.3 Critical evaluation of study strengths

8.3.1 Prospective design

Prospective cohort studies are valuable in determining associations between exposures and health outcomes in the field of epidemiology. However, compared to RCTs, these studies are considered to provide weaker evidence. Yet, prospective cohort studies can postulate direct information on the sequence of events, which can eventually be used in RCTs to explain causality. Thus, these studies play a key role in evidence-based medicine [75]. The UKWCS dietary data was collected prior to development of any of the outcomes of interest of this thesis, thus, the possibility of recall bias and reverse causality are unlikely as compared to case control study designs. Since participants were not recruited based on this research's outcomes, the probability of selection bias is also eliminated.

8.3.2 Novel findings

Firstly, this thesis provides an overview of the diet of pre- and post-menopausal women in the UKWCS which to our knowledge is the first to explore this association. The study investigating the association between various food and nutrient intakes and the timing of natural menopause is also the first among British women. As mentioned in Chapter 1, previously several studies have looked into the association between socio-demographic factors such as smoking, socioeconomic status, ethnicity as well as reproductive factors (e.g. parity, age at first pregnancy) and the onset of natural menopause. Although evidence indicated a link between diet and the timing of natural menopause, very few studies have investigated this association and existing findings are also contradictory. There have been only few studies in the past exploring this association possibly because diet is difficult to measure, and also there are few large enough follow up studies on women of the right age which could look at this. It was thus interesting to observe that specific foods and nutrients were linked with the timing of natural menopause in this study (Chapter 4).

Given that these foods are eaten as part of a diet, the effect of other food items may either counteract or enhance the individual associations observed in this study [76]. For example, although fresh legumes appeared to delay menopause, a self-reported vegetarian diet was associated with an earlier onset of natural menopause (Chapter 4). As a 217-item FFQ was used in the UKWCS to assess diet, this also allowed the generation

of dietary patterns derived from a variety of food items. Therefore, the association between dietary patterns and the timing of natural menopause was also explored. This is in addition the first prospective cohort study looking at this relationship.

Another uniqueness of this thesis involves the pooled analysis from five different studies of the InterLACE consortium which demonstrated an association between frequent soy product consumption and reduced odds of reporting incident VMS (Chapter 6). To our knowledge, this is the first pooled study which investigated both the cross-sectional and prospective associations between soy consumption and presence of VMS. This study described the presence of VMS, consumption of soy products from the natural diet and further explored their association which has the advantage to represent this pattern for participants from five different studies, in particular from four different countries (Australia, UK, USA, and Japan). Given that a protective effect of soy product consumption was demonstrated with the incidence of VMS among women from two countries namely Australia and UK, this study's finding can be generalised to the Caucasian women from other countries as well.

8.3.3 Dietary patterns

Traditionally, nutritional epidemiology involved the study of nutrients and single food components in relation to health. However, the study of these isolated single components may not provide a realistic picture of the actual diet of people [77]. Moreover, the disease burden associated to nutrition has now shifted. Instead of undernutrition and nutrient related deficiencies which used to be prevalent, nowadays non-communicable diseases have taken the lead in high income countries as well as low and middle income countries [78]. These are associated with the multiple interactions of various food items rather than single components, which make the study of dietary patterns of utmost importance. Dietary patterns are able to represent the cumulative and interactive effects of various components of the diet. Thus, public health recommendations based on dietary patterns are more easily translated. Nevertheless, it is quite likely that any observed associations between dietary patterns and the onset of menopause in this study could be due to the single components rather than the overall dietary pattern [79]. Therefore, the strength of this thesis is that both single components and dietary patterns were considered which allowed a better understanding of the influence of diet on the timing of menopause.

Another forte of this study was the application and the comparison of two *a posteriori* techniques to generate dietary patterns, PCA and RRR. In comparison to *a priori* techniques which are based on dietary recommendations, these *a posteriori* methods are not based on prior knowledge but instead they are based only on the data, making them more easily reproducible and comparable [79]. Although the aims of PCA and RRR vary, findings from this thesis demonstrated that their results complement each other and thus both methods provided important insights for predicting the risk of being naturally menopausal in relation to dietary patterns. Moreover, as demonstrated by Jankovic et al. [80], another strength of the dietary patterns as measured by RRR is that they are reasonably stable over a period of five years and in this thesis, the age at natural menopause was assessed approximately 4 years at follow-up after diet was evaluated. Thus, RRR is suitable to derive dietary patterns based on long-term dietary exposure for nutritional epidemiological studies, with one dietary assessment at baseline.

8.3.4 Assessment of age at menopause

As elaborated by Cramer [35], several methodological concerns may arise when predicting the outcome of interest, age at natural menopause. This study has assigned a natural menopause based on the WHO definition which states that the last menstrual bleeding followed by at least 12 months of amenorrhea as some women may have regular bleeding still after 6 months of amenorrhea. In addition, as HRT may cause the return of regular menstrual bleeding, in this study women who reported using HRT prior to menopause were excluded. The memory of the age at last menstruation may be prone to recall bias. However in this thesis, as the included premenopausal participants were aged between 45 to 53 years at baseline (Chapter 4) and the average age at natural menopause was 50.5 years (95% CI: 50.3 to 50.8), the recall period has been shorter and thus the variable age at menopause may have been more accurately provided by the women at the follow-up and may be less prone to bias. Additionally, both the primary exposure (diet) and age at natural menopause were used as continuous data which helped to retain as much information and providing enough statistical power to observe any possible associations [81].

8.3.5 Assessment of confounding

A further strength of this thesis was the use of DAGs to determine potential confounders for the analyses. If not identified and adjusted for, a confounder could lead to distortion of the interpretation by masking the true relationship between two variables

[82]. The use of DAG can be considered superior to logistic regression techniques including all likely confounders which have been used in previous studies as the latter is based on significant *p*-values while the former is based on stronger theoretical evidence. In addition as suggested by Shrier and Platt [83], other advantages of the DAG are that only a subset of confounders are used which are associated with both the exposure and health outcome of interest and because this led to the use of fewer confounders in the model, the statistical efficiency of the analysis is increased. Yet, the use of the DAG may be limited by the absence of unmeasured confounders when constructing the graph. However, as the UKWCS included a wide range of factors which have been assessed such as socio-economic, family history, medical history, and reproductive history, an attempt to include all likely confounders when composing the DAGs have been made. Moreover, the inclusion of participants with a wide range of exposure to different diet in the UKWCS also decreased bias related to measurement error.

8.3.6 Cancer data

As mentioned in section 8.2.3.2.1, incident cases of invasive breast carcinomas, endometrial and ovarian cancers were identified through linkage to the NHSIC to which all women consented at the start of the study. Thus loss to follow was minimal. However, if any woman was no longer a resident of the UK and had not communicated this to the Nutritional Epidemiology Group, this would be interpreted as having not developed breast cancer.

Other strengths of using the cancer linkage were greater reliability of the data as compared to self-reported data, lower participant burden and the use of ICD codes for the diagnoses of the hormone-related cancers improves the consistency of the data. Yet, it should be acknowledged that despite quarterly updates from the NHSIC, there is some lag time in receiving notification of cancer incidence.

Additionally in the cancer analysis (refer to Chapter 7), in order to ensure that dietary information was collected before diagnosis of the cancers, women reporting history of any previous malignant cancer at baseline (except for non-melanoma of the skin) and women who were diagnosed with breast, endometrial and ovarian cancer within 1 year of baseline were excluded. Thus, any potential measurement error associated with dietary assessment would have been non-differential between the cases and non-cases and would led to weakening of the true relationships instead of causing any overestimation.

8.4 Critical evaluation of potential limitations

8.4.1 Dietary data

There are several weaknesses of using FFQs for dietary assessment. These include potential recall bias leading to low accuracy of dietary information, restricted to information on only the food items listed in the FFQ and reporting can also be subjective [86, 87]. Measurement errors associated with the FFQ are also likely in this research due to unavailable foods in the list and imprecisions in consumption frequency and portion size estimations [84]. The under and over-estimate consumption of certain food like fruits and vegetable intake are also likely [85]. The FFQ also does not account for variability of portion sizes over different eating occasions. Additionally, nutrient estimation might be biased by imprecision in the portion sizes used and errors inherent to the FFQ [86]. Yet it must be acknowledged that the use of an FFQ allows a better picture of diet over a long period of time as compared to other dietary assessment tools such as the 24-h recall and food diaries which record diet over a shorter period of time. Moreover, the use of the FFQ in an inexpensive method to assess diet of the thousands of women in the UKWCS and causes lower subject burden as compared to the 24-h recall [84]. The FFQ used in the UKWCS was also validated on a subsample of 303 cohort subjects against a 4-day food diary as well as fasting blood measures of specific nutrients. It was also tailored for the large number of vegetarians [19].

The UKWCS dietary data was collected in between 1995-1998. It is very likely that the diet of women today are different as compared to women in the 90s. Therefore, another weakness of the dietary assessment was that only a single-point evaluation was conducted rather that repeated measures which would have accounted for the dietary changes over time.

8.4.2 Dietary patterns

Although a quite elaborate FFQ was used in the UKWCS to assess women's diet, it was still a closed list of foods and, therefore, cannot fully capture in detail an individual's diet. The dietary patterns derived using the FFQ in Chapter 5 might not give an accurate picture of the participants' dietary patterns.

Furthermore, the two empirically-based dietary pattern methods, PCA and RRR used for the analyses in Chapter 5, have their own set of limitations for dietary pattern analysis. Several subjective decisions are required for both methods that can influence

the final interpretation such as collapsing of the various food items into food groups, the format of the input variable, the factor loading cut-off value, and the labelling of the dietary patterns. In an attempt to reduce subjectivity, the food items from the FFQ were grouped based on WCRF recommendations for cancer prevention [61]. Dietary patterns may also be a proxy measure for other variables which can be associated with age at natural menopause as they may be a constituent of a larger pattern of healthy or unhealthy habits. However, after controlling for potential confounders, both dietary patterns derived from PCA and RRR were still significantly associated with the onset of natural menopause.

In this thesis, RRR explained less variability as compared to PCA. This is because the RRR derived dietary patterns are based on the variation of the response variables. As the RRR technique is contingent on the *a priori* hypothesis through the set of response variables, this method thus allows the generation of dietary patterns based on biologically important intermediate variables. However, the key consideration is to include response variables that are likely predictive or important risk factors of the health outcome of interest, though this may not always be possible as in the case of this thesis [87]. This is because only a limited number of studies has previously explored age at natural menopause and its risk factors, thus, there are no strong evidence regarding its risk factors yet. In this study an attempt has been made to consider risk factors which have quite consistently been associated with the timing of menopause. Therefore, the RRR derived dietary patterns should be considered as an initial hypothesis, rather than patterns with a confirmed association. Another concern is that RRR is unlikely to generate dietary patterns that are linked to most or all potential pathways through which diet can influence the age at onset of natural menopause. In addition, it is important that the response variables have been investigated in relation to the health outcome in the same population [88].

8.4.3 Generalisability

A common limitation of the UKWCS results is that as there was a larger sample of vegetarians and thus more health conscious women in the cohort, as compared to the general UK population. Moreover, the under-representation of unhealthy dietary behaviours could have led to weakened observed relationships or may have caused null observations. Sensitivity analyses involving weighting of the results to the proportion of vegetarians in the UK population could have been conducted in this thesis to overcome

this [19]. However, as demonstrated by a previous study using the UKWCS, the results remained unchanged after weighting for vegetarians [60]. Given that participants in the UKWCS came from a range of different backgrounds as demonstrated in Chapters 3,4 and 7, findings of this study could be extrapolated to the general population.

In addition, as the derived dietary patterns were based on the available data, the findings of this thesis cannot be extrapolated to other countries. In particular, findings for dietary patterns derived using RRR have rarely been replicated across other populations [79].

8.4.4 Data pooling

Whilst pooling data from individual studies are beneficial in terms of increasing the study power, especially if the sample size is not big enough to explore the relationship between the exposure and outcome in the individual studies, weaknesses of pooling data should be acknowledged. One drawback could be that errors attributed to the study design of the single studies are multiplied [43]. Furthermore, as mentioned in section 6.4, there are several sources of heterogeneity when pooling data from the five observational studies of the InterLACE consortium [42]. However, in this study, heterogeneity between the studies was not significant (please refer to Chapter 6). In addition, the I^2 values for both the pooled estimates for the cross-sectional association between the presence of VMS and frequent consumption of soy products (0%) as well as soy milk (26.6%) were quite low. As suggested by Higgins et al. [64], the I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance is a better approach of quantifying heterogeneity [42, 89]. Moreover, the use of the random effect model for the pooled analysis has a disadvantage in terms of potential undue weight given to the studies with small sample size, thereby highlighting evidence that may be weak [44]. In addition to the limitations discussed in Chapter 6, as with all longitudinal studies retention of participants is an issue [40]. However, in order to account for this, a sensitivity analysis was carried out to investigate the association between soy consumption and subsequent risk of VMS at follow-up with all the women included adjusting for their baseline presence/absence of VMS.

8.4.5 Potential for biases

Although adjustments were made for potential confounders which were identified using an explicit method, the possibility of residual confounding due to unmeasured

covariates or imprecision in the measure of included covariates as in any other observational study is still likely in this thesis. As demonstrated using the conceptual framework (Figure 1.4) in Chapter 1, other than dietary components, there are various other factors which could influence the pathophysiology of the onset of menopause, and consequently the presence of VMS and the risk of the hormone-related cancers. However, not all the factors were not available in the UKWCS dataset. For instance, models used in this thesis did not control for environmental factors such as area of residence and genetic factors which could have contributed to residual confounding.

Moreover as mentioned previously, measurement errors arising due to inaccuracy or imprecision of the FFQ, single measurement of diet over a long period of time in particular when investigated in relation to cancer incidence could have led to substantial for potential biases in this research. However, the inclusion of participants with a wide range of dietary exposure in the UKWCS (e.g. vegetarians, fish-eaters and meat-eaters) [19] and the adequate sample sizes (please refer to section 8.2.3.2.2) decreased the risk of bias related to measurement error.

8.4.6 Others

Finally, as dietary data was measured prior to the assessment of age at menopause, the analyses from Chapter 4 and Chapter 5 could not be repeated in the InterLACE consortium. Racial/ethnic variation for the association between soy products and VMS could also not be analysed in this thesis given that the included studies had a quite high distribution of Caucasians and only one study had data on Japanese women.

8.5 Recommendations for future work

8.5.1 In the UKWCS

Besides dietary factors, endocrine disruptors such as bisphenol A, phthalates, parabens, pesticides among others have also been suggested to influence the onset of natural menopause, in particular, they can lead to ovarian senescence and thus an earlier menopause [90]. Therefore, as canned foods could be a source of bisphenol A [91], the link between the proportion of canned foods consumed could also be investigated among women in the UKWCS. Furthermore, in order to include more participants in the analyses survival regression models could also be used when studying the association between individual foods and age at menopause.

Using the UKWCS, interesting extensions could be exploring the relationship between specific nutrients, dietary patterns and the risk of ovarian, endometrial and breast cancers. Dietary patterns generated through different techniques both *a priori* and *a posteriori* to make comparisons between the findings. Given the limitations of FFQs, the use of other self-reported instruments such as food diaries and 24-hour recall have been preferred over FFQs [92]. At Phase 2 of UKWCS, 12, 453 participants also completed a 4-day food diary [19] which could be ideal for studying the association between portion sizes of various foods and the risk of the hormone-related cancers. In addition, given that previous studies indicate that cooking methods could be linked to the risk of hormone-related cancers [93, 94], this aspect could also be investigated in the future.

8.5.2 In the InterLACE consortium

The InterLACE consortium is currently trying to accrue by including more cohort studies which have women's health data especially from countries which are not part of the consortium yet. As evidenced by Melby et al. [95], both biological and cultural differences contribute to the symptoms experienced by women during the menopausal transition. Previously, a high prevalence of VMS has been reported in Western countries while a lower prevalence rate has been recorded in Asian countries and in India, no VMS was reported by some groups [96]. Given that cross-cultural factors may influence the way frequency and severity of VMS are reported in Asian countries, additional data from other countries would allow consideration of this cross-cultural variation and also the interaction between culture and biology of VMS. The inclusion of more dietary data in particular assessed prior to the evaluation of reproductive health and chronic diseases would be a further asset of the consortium. This would allow the study of other food items besides soy products in relation to VMS. For instance, as demonstrated by Herber-Gast [97], the consumption of diets highly loaded with cooked vegetables and fruits were protective against VMS while a diet rich in fat and sugars increased the risk of VMS. Therefore, the study of such dietary aspects using the InterLACE consortium would lead to a better understanding of VMS in relation to diet. In addition, phytoestrogen contents from the soy products could be estimated to explore whether total phytoestrogen or specific phytoestrogens such as isoflavones, lignans, daidzein, genistein or coumestrol may have any association with the frequency or severity of VMS. Earlier studies have mainly investigated the influence of specific phytoestrogens in relation to the frequency or severity of VMS (Chapter 2, Table 2.3) but a pooled analysis is yet to be explored.

Previous studies using data from the InterLACE consortium have investigated the associations between several exposures such as early menarche, nulliparity [98], BMI [99], smoking [100], and age at natural menopause. However, age at natural menopause in relation to diet has not yet been explored. Therefore, the acquisition of more dietary data would allow pooled analysis of this association, leading to results that may prompt interventions to study the same further and consequently lead to clinically relevant outcomes. Using the InterLACE consortium would also allow the study of the cross-cultural variation in the association between diet and age at natural menopause.

8.5.3 Other studies

As discussed in this chapter, further prospective cohort studies are required for exploring the association between diet and age at onset of natural menopause. Similar to the distribution of VMS, age at menopause may also be influenced by cross-cultural differences. Previously, most studies investigating this association have been conducted among Japanese and American women. However, more studies are warranted to observe the pattern in other Asian, European and African countries. More studies are also required in racially diverse populations. As explained in Chapter 2, due to the numerous methodological concerns for predicting age at menopause, comparing findings for the association between dietary aspects and age at menopause is quite difficult. Therefore, using a standard definition of age at menopause in future studies could help resolve this issue. Moreover, as there are no pathological tests which can be carried out to determine the age at natural menopause, researchers would have to rely on participants' memory. As suggested by Cramer [35], ideally following premenopausal women in their late 30's for 15 to 20 years whereby menopausal status is queried at several points might be helpful to determine their age at last menstrual bleeding. As the menopausal transition is associated with several hormonal changes, weight gain, menopausal symptoms, changing menstrual patterns, women tend to alter their diet (Chapter 3) and other lifestyle behaviours. Thus, assessing dietary habits at various time points would also be beneficial to study diet at which age point reflects the age at natural menopause. However, as this would be a quite time consuming and costly process, studying perimenopausal women aged between 45 to 54 years might be an alternative [35]. Another approach could be using new technology to contact people (e.g., email, social media), and measure diet which are much cheaper than it used to be. Furthermore, considering age at natural menopause as a continuous variable would help provide more information as compared

to dichotomising the variable into early and late menopause. Future prospective studies including more premenopausal women at the study baseline may lead to more women undergoing menopause at follow-up, thus providing greater statistical power to study this association. The compilation of studies scrutinising this relationship would subsequently lead to more meta-analyses and systematic reviews on this subject.

Besides racial and ethnic differences, future studies might also consider the role of genetic factors which would help throw light on the possible mechanisms behind any observed associations between diet and age at natural menopause. As elaborated in Chapter 1, a high oestrogen level could delay the onset of menopause while premature ovarian aging may be associated with an earlier onset of menopause. However, to confirm these proposed mechanisms, clinical trials, especially with long follow-up period examining the effect of dietary interventions on markers of ovarian ageing such AMH and follicle count and subsequently the timing of menopause, would also be meaningful. The association between dietary changes and plasma level of oestrogen would be equally of relevance to understand the underlying endocrinology.

Kroenke et al. [101] demonstrated that weight loss which was achieved through a dietary intervention which consisted of reducing fat and increasing fruit, vegetable and fibre intake led to a reduction or elimination of VMS over a period of one year. This study indicates the possible influence of dietary intervention of the presence of VMS. Thus, other than RCTs investigating the effect of phytoestrogens from specific phytoestrogen-rich food sources, the effect of additional dietary intervention on the presence of VMS should be investigated. Furthermore, as reporting of VMS may also be subjective among overweight or obese women due to social or psychological factors [102], dietary interventions targeting women with different BMI ranges can be conducted. Interventions in these specific groups of women may support health practitioners when counselling menopausal women. The RCTs may also be beneficial in detecting the time point when any dietary change might influence the timing of menopause and also the amount of the food required to observe any change.

Evidence from population-based studies of women as well as findings from this thesis increasingly points to the inter-related nature of reproductive health (age at natural menopause and VMS), lifestyle (diet), and chronic disease risk (ovarian, endometrial and breast cancers). Previous studies have also demonstrated a link between diet and the onset of the timing of menarche [103] and also a higher risk of hormone-related cancers have been found with an earlier onset of menarche [104-106]. Thus, future cohort studies which

have dietary data measured before both age at menarche and age at natural menopause as well as have cancer-related data, can explore this inter-relationship by developing life course models. Future work in this area will highlight the importance of examining the timing of exposures, such as during critical periods in early life, and the temporal order of exposures. These models will help policymakers in terms of identifying the appropriate type of intervention and the time point at which an intervention is required [107].

8.6 Public health messages and implications

Age at natural menopause varies according to regions, countries and ethnic groups [108, 109] in addition to other factors as explained in Chapter 1 (section 1.1). The age at which women go through the menopause is of public health concern as an earlier menopause is linked to a higher risk of cardiovascular diseases, osteoporosis, and fracture, and depression, while a delayed onset of menopause is associated with a higher likelihood of hormone-related cancers such breast, endometrial and ovarian cancers [110]. In addition to the health concerns, an earlier menopause can also have a detrimental impact on the quality of life of a woman, influence fertility and consequently have an influence on society. The timing of menopause can determine the duration a woman is in the perimenopausal state and thus affect the duration of VMS. Therefore, influencing the timing of natural menopause could potentially modify the risk of health outcomes among middle-aged women. Given that both an early and a late menopause are related to adverse health effects, targeting the mean age of menopause which ranges between 46 to 52 years would be ideal [111]. Diet is one of the modifiable behavioural risk factors for both the timing of menopause and its associated sequelae as demonstrated in this thesis.

At present, the British Nutrition Foundation [112] recommends a healthy balanced diet which includes high intakes fruits and vegetables, starchy foods, and is low in sugar, salt and saturated fats for women of all ages. As menopausal women are at risk of menopausal symptoms and other health risks such as osteoporosis and cardiovascular diseases (CVD), based on recommendations by the National Health Services UK for the prevention of CVD, osteoporosis, and guidelines for a healthy lifestyle, the British Nutrition Foundation in addition has put forward the following guidelines for this group of women [112]. These include intake of:

- 700 mg of calcium per day
- 10 μg of vitamin D per day
- unsaturated fats rather than saturated fats

- fish especially oily fish once or twice per week
- less than 6 g of salt per day
- wholegrain and high fibre foods
- dietary sources of isoflavones and lignans
- < 14 units of alcohol per week

Findings from this thesis are in line with these recommended guidelines. Additionally, the results of this thesis suggest that it can be regarded as safe to encourage women to consume oily fish and fresh legumes to avoid an early onset of menopause as these food items have not been found to be associated with the ovarian, endometrial and breast cancer risks (please refer to Chapters 4 and 7). As showed in Chapter 6, the consumption of soy products such as tofu, tempeh, soy beans, and soy flour are protective against the incidence of VMS and thus women are recommended to also consume these sources of isoflavones.

As mentioned before, a late menopause is associated with a higher risk of hormone-related cancers such as breast, ovarian and endometrial cancers (Chapter 7). Furthermore as demonstrated in Chapter 7, high intakes of red and processed meats were associated with a higher risk of breast and endometrial cancers, in particular, postmenopausal breast and endometrial cancer risks. Therefore, as part of preventive strategies, women with a family history of late menopause or these hormone-related cancers should be advised to limit or avoid the consumption of animal proteins, in particular, red meats and processed meats. It would not be advisable for women who are at a high risk of an early menopause such as those with a family history of early menopause [113], those who are nulliparous or have had an early menarche to consume these meats to delay their onset of menopause given the adverse health risks associated with consumption of red and processed meats. This is also in line with the recommendations by the WCRF for cancer prevention [61] and the latest Lancet EAT report [114] which supports the need to reduce the consumption of red meat and highly processed foods and to increase the consumption of fruits, vegetables and legumes as part of the aim to achieve dietary changes from current diets to healthy diets and improve human health as well as reduce the number of mortality. Alternatively it is recommended to consume other protein sources such as from plants, including soy foods, other legumes, and nuts, fish and modest consumption of poultry and eggs [114]. According to the report, unhealthy diets poses a greater risk to non-communicable diseases and hence mortality

and morbidity as compared to alcohol, drug and tobacco use combined. The commission advocates for healthy diets as food production also has adverse impacts on environmental changes by contributing at various levels (e.g. climate change, biodiversity loss, etc.). Therefore adoption of a plant-based diet, which would imply significantly cutting down on the intake of particularly red meat rather consuming a vegan diet would help towards achieving this goal. The report also recommends cutting down the intake of refined starches which conforms with the findings of this thesis.

However, given that more studies are required in this area, and that both an early or a late menopause are associated with adverse health outcomes it would be premature at this stage to make universal dietary recommendations based on our findings alone. This study could yet be beneficial for health practitioners when counselling women who are in their late 30s or early 40s, in particular, those who may already be at risk or have a family history of certain complications related to menopause. As more evidence unfolds in the future, health practitioners might also need to consider the specific disease risk of the women in addition to her unique family history to stipulate dietary advice regarding the timing of menopause. At this point, a balanced diet based on the consumption of oily fish, high fibre foods, and reduced consumption of refined cereals and grain products can be suggested. As for the amount of these food items and at what point they should be consumed, would have to be investigated in the future.

8.7 Conclusions

8.7.1 What was already known on this topic

Diet is associated with the timing of onset of natural menopause. However, previously a limited number of studies have investigated this association and findings are also conflicting. Diet is also linked to immediate and longer-term sequelae of menopause such as the presence of VMS and risk of hormone-related cancers (e.g. ovarian, endometrial and breast cancer). A later onset of menopause is associated with an increased risk of ovarian, endometrial and breast cancers. Except for the high risk of breast cancer associated with consumption of high amounts of alcohol, there is inconclusive and limited findings for the relationship between diet and ovarian, endometrial and breast cancers.

There is evidence that multiple and complex factors determine the timing of natural menopause as well as the presence of VMS and the risk of breast, ovarian and

endometrial cancers. According to the NICE's conceptual framework (Figure 1.4), diet is one of the determinants in the social vector category which influences the timing of menopause and its associated sequalae. Various factors can shape dietary choices and patterns, hence influencing the timing of menopause and the associated health outcomes as well as they can have both synergistic and independent effects on the health sequels. However, as per a recent report [115], diet is a major risk factor of cancers as compared to other risk factors. Therefore, diet was studied in relation to the timing of the onset of natural menopause and its associated sequalae using the UKWCS and the InterLACE consortium.

8.7.2 What this work adds

There are various factors which can be linked with the exposure (diet) and outcomes of interest (age at natural menopause, presence of VMS, risk of breast, ovarian and endometrial cancers) of this thesis (Figure 1.4). Thus, in order to avoid spurious results, DAGs were constructed based on the conceptual framework to identify potential confounders for each result chapter in this thesis (Chapters 3-7).

In particular, it was demonstrated that high intakes of individual foods such as oily fish, fresh legumes and nutrients such as vitamin B6 and zinc are associated with a later onset of menopause while a high consumption of refined pasta and rice is linked to an earlier onset of menopause in the UKWCS. To complement the findings on the association between individual foods and the onset of natural menopause and to take into account that people consume meals which are complex interactions between various foods and nutrients which may be interactive, dietary patterns using PCA and RRR techniques were further investigated in relation to this outcome. It was showed that diets which are highly loaded with red meat and processed meat may also increase the risk of a later natural menopause.

Furthermore, this study conducted the first pooled analysis which included five observational studies from the InterLACE consortium to assess the associations between intake of soy products and the presence of VMS. Frequent consumption of soy products (e.g., soy beans, tofu, tempeh) as part of the usual diet may be associated with a reduced risk of subsequent VMS as opposed to soy milk consumption. Additionally in the UKWCS, it was also demonstrated that high intakes of red meats and processed meats are associated with a higher risk of breast and endometrial cancers. These associations are especially significant for postmenopausal breast and endometrial cancer risks as

determined using time-to-event analyses. Tomato and dried fruits consumption were related with a reduced risk of breast and endometrial cancer respectively. In this thesis, no significant associations were found in the case of the risk of ovarian cancer. Although timing of natural menopause has been found to increase the risk of hormone-related cancers, effect modification analyses showed that it did not influence the association between diet and risk of the cancers.

Given that the study of the timing of natural menopause in relation to dietary factors is still fledgling, findings from this thesis makes a significant contribution to this field. This thesis also adds to the existing evidence for the associations between diet and the presence of VMS as well as the risk of breast, ovarian and endometrial cancers. Thus, diet remains an important factor which is related to the female reproductive health. Further observational studies among different populations as well as clinical trials are mandated to contribute to this area of women's health. Yet, even though additional evidence on the relationships between diet and the timing of menopause were known, it would be complicated to make collective recommendations as each woman has a unique family history and particular health risks. Health practitioners would therefore need to consider these criteria prior to making dietary recommendations.

References

1. Lethaby, A. et al. Phytoestrogens for menopausal vasomotor symptoms. *The Cochrane Database of Systematic Reviews.* 2013, (12), p.Cd001395.
2. Sauvageot, N. et al. Association of Empirically Derived Dietary Patterns with Cardiovascular Risk Factors: A Comparison of PCA and RRR Methods. *PLoS ONE.* 2016, **11**(8), p.e0161298.
3. Bakolis, I. *The use of dietary patterns empirically derived from Principal Components Analysis and alternative strategies to identify associations between diet and disease.* Doctor of Philosophy thesis, Imperial College London, 2013.
4. Martin, L.J. et al. Intervention with a low-fat, high-carbohydrate diet does not influence the timing of menopause. *The American Journal of Clinical Nutrition.* 2006, **84**(4), pp.920-928.
5. Wang, M. et al. Age at natural menopause and associated factors in adult women: Findings from the China Kadoorie Biobank study in Zhejiang rural area. *PLoS ONE.* 2018, **13**(4), p.e0195658.
6. Boutot, M.E. et al. Dietary Protein Intake and Early Menopause in the Nurses' Health Study II. *American Journal of Epidemiology.* 2018, **187**(2), pp.270-277.
7. Nagel, G. et al. Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg. *Maturitas.* 2005, **52**(3-4), pp.337-347.
8. Al-Safi, Z.A. et al. Omega-3 Fatty Acid Supplementation Lowers Serum FSH in Normal Weight But Not Obese Women. *The Journal of Clinical Endocrinology and Metabolism.* 2016, **101**(1), pp.324-333.
9. Nagata, C. et al. Associations of physical activity and diet with the onset of menopause in Japanese women. *Menopause.* 2012, **19**(1), pp.75-81.
10. Nagata, C. et al. Association of diet with the onset of menopause in Japanese women. *American Journal of Epidemiology.* 2000, **152**(9), pp.863-867.
11. Ford, E.S. et al. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *The American Journal of Clinical Nutrition.* 2004, **79**(5), pp.774-779.
12. Jenkins, D.J. et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *The American Journal of Clinical Nutrition.* 1981, **34**(3), pp.362-366.

13. Miller, J.C. Importance of glycemic index in diabetes. *The American Journal of Clinical Nutrition.* 1994, **59**(3 Suppl), pp.747s-752s.
14. Sowers, M.R. et al. Relating smoking, obesity, insulin resistance, and ovarian biomarker changes to the final menstrual period. *Annals of the New York Academy of Sciences.* 2010, **1204**, pp.95-103.
15. Isik, S. et al. Evaluation of ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with type 2 diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism.* 2012, **97**(1), pp.261-269.
16. Garris, D.R. Effects of progressive hyperglycemia on ovarian structure and function in the spontaneously diabetic Chinese hamster. *The Anatomical Record..* 1984, **210**(3), pp.485-489.
17. Garris, D.R. and Garris, B.L. Diabetes (db/db) mutation-induced ovarian involution: progressive hypercytolipidemia. *Experimental Biology and Medicine.* 2003, **228**(9), pp.1040-1050.
18. Torgerson, D.J. et al. Factors associated with onset of menopause in women aged 45–49. *Maturitas.* 1994, **19**(2), pp.83-92.
19. Cade, J.E. et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). *International Journal of Epidemiology.* 2017, **46**(2), pp.e11-e11.
20. Cade, J.E. et al. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutrition.* 2004, **7**(7), pp.871-878.
21. Riboli, E. and Kaaks, R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *International Journal of Epidemiology.* 1997, **26 (**Suppl 1), pp.S6-14.
22. Food Standards Agency. Food Portion Sizes. London: The Stationary office; 2002.
23. Holland B, W.A., Unwin ID, Buss DH, Paul AA, Southgate DAT. *The composition of foods.* Cambridge, United Kingdom: The Royal Society of Chemistry and Ministry of Agriculture Fisheries and Food, 1991.
24. Kant, A.K. Dietary patterns and health outcomes. *Journal of the American Dietetic Association.* 2004, **104**(4), pp.615-635.
25. Ocke, M.C. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. *Proceedings of the Nutrition Society.* 2013, **72**(2), pp.191-199.

26. Newby, P.K. and Tucker, K.L. Empirically derived eating patterns using factor or cluster analysis: a review. *Nutrition Reviews.* 2004, **62**(5), pp.177-203.
27. Northstone, K. et al. Dietary patterns in pregnancy and associations with socio-demographic and lifestyle factors. *European Journal of Clinical Nutrition.* 2008, **62**(4), pp.471-479.
28. Cattell, R.B. The Scree Test For The Number Of Factors. *Multivariate Behavioral Research.* 1966, **1**(2), pp.245-276.
29. Julie Armstrong, A.S., Wendy L Wrieden, Yvonne Brogan, Karen L Barton. *Deriving and interpreting dietary patterns in the Scottish diet: Further analysis of the Scottish health survey and expenditure and food survey.* Scotland: Food Standards, 2009.
30. Kline, P. *An easy guide to factor analysis.* Routledge, 2014.
31. Hoffmann, K. et al. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. *American Journal of Epidemiology.* 2004, **159**(10), pp.935-944.
32. Jankovic, N. et al. Stability of dietary patterns assessed with reduced rank regression; the Zutphen Elderly Study. *Nutrition Journal.* 2014, **13**, p.30.
33. Bender, R. Introduction to the use of regression models in epidemiology. *Methods in Molecular Biology.* 2009, **471**, pp.179-195.
34. George, B. et al. Survival analysis and regression models. *Journal of Nuclear Cardiology.* 2014, **21**(4), pp.686-694.
35. Cramer, D.W. and Xu, H. Predicting age at menopause. *Maturitas.* 1996, **23**(3), pp.319-326.
36. Nagata, C. et al. Soy product intake and hot flashes in Japanese women: results from a community-based prospective study. *American Journal of Epidemiology.* 2001, **153**(8), pp.790-793.
37. Freedman, R.R. Physiology of hot flashes. *American Journal of Human Biology.* 2001, **13**(4), pp.453-464.
38. Moreira, A.C. et al. Phytoestrogens as alternative hormone replacement therapy in menopause: What is real, what is unknown. *The Journal of Steroid Biochemistry and Molecular Biology.* 2014, **143**, pp.61-71.
39. Mishra, G.D. et al. InterLACE: A new international collaboration for a life course approach to women's reproductive health and chronic disease events. *Maturitas.* 2013, **74**(3), pp.235-240.

40. Mishra, G.D. et al. The InterLACE study: Design, data harmonization and characteristics across 20 studies on women's health. *Maturitas.* 2016, **92**, pp.176-185.

41. Qi, W. et al. Application of data pooling to longitudinal studies of early post-traumatic stress disorder (PTSD): the International Consortium to Predict PTSD (ICPP) project. *European Journal of Psychotraumatology.* 2018, **9**(1), p.1476442.

42. Friedenreich, C.M. Commentary: Improving pooled analyses in epidemiology. *International Journal of Epidemiology.* 2002, **31**(1), pp.86-87.

43. Blettner, M. et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *International Journal of Epidemiology.* 1999, **28**(1), pp.1-9.

44. Friedenreich, C.M. Methods for Pooled Analyses of Epidemiologic Studies. *Epidemiology.* 1993, **4**(4), pp.295-302.

45. Fedirko, V. et al. Alcohol drinking and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Annals of Epidemiology.* 2013, **23**(2), pp.93-98.

46. Je, Y. et al. Long-term alcohol intake and risk of endometrial cancer in the Nurses' Health Study, 1980-2010. *British Journal of Cancer.* 2014, **111**(1), pp.186-194.

47. Farvid, M.S. et al. Adolescent and Early Adulthood Dietary Carbohydrate Quantity and Quality in Relation to Breast Cancer Risk. *Cancer Epidemiology, Biomarkers & Prevention.* 2015, **24**(7), pp.1111-1120.

48. Diallo, A. et al. Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Sante cohort study. *International Journal of Cancer.* 2018, **142**(2), pp.230-237.

49. Fiolet, T. et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. *British Medical Journal.* 2018, **360**, p.k322.

50. Baglia, M.L. et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. *International Journal of Cancer.* 2016, **139**(4), pp.742-748.

51. Farvid, M.S. et al. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. *British Medical Journal.* 2016, **353**, p.i2343.

52. Farvid, M.S. et al. Lifetime grain consumption and breast cancer risk. *Breast Cancer Research and Treatment.* 2016, **159**(2), pp.335-345.

53. Farvid, M.S. et al. Dietary Fiber Intake in Young Adults and Breast Cancer Risk. *Pediatrics.* 2016, **137**(3), p.e20151226.

54. Kim, J.H. et al. Dietary Factors and Female Breast Cancer Risk: A Prospective Cohort Study. *Nutrients.* 2017, **9**(12).

55. Kojima, R. et al. Dietary patterns and breast cancer risk in a prospective Japanese study. *Breast Cancer.* 2017, **24**(1), pp.152-160.

56. Narita, S. et al. Dietary fiber intake and risk of breast cancer defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. *Cancer Causes & Control.* 2017, **28**(6), pp.569-578.

57. Penniecook-Sawyers, J.A. et al. Vegetarian dietary patterns and the risk of breast cancer in a low-risk population. *British Journal of Nutrition.* 2016, **115**(10), pp.1790-1797.

58. Shin, S. et al. Dietary pattern and breast cancer risk in Japanese women: the Japan Public Health Center-based Prospective Study (JPHC Study). *British Journal of Nutrition.* 2016, **115**(10), pp.1769-1779.

59. Ughade, S. Statistical modeling in epidemiologic research: Some basic concepts. *Clinical Epidemiology and Global Health.* 2013, **1**(1), pp.32-36.

60. Taylor, E.F. et al. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *British Journal of Cancer.* 2007, **96**, pp.1139-1146.

61. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. 2018. Available from: https://www.wcrf.org/sites/default/files/Summary-third-expert-report.pdf

62. Jung, S. et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *International Journal of Epidemiology.* 2016, **45**(3), pp.916-928.

63. Romieu, I. et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. *International Journal of Cancer.* 2015, **137**(8), pp.1921-1930.

64. Hirko, K.A. et al. Alcohol consumption and risk of breast cancer by molecular subtype: Prospective analysis of the nurses' health study after 26 years of follow-up. *International Journal of Cancer.* 2016, **138**(5), pp.1094-1101.

65. Ellingjord-Dale, M. et al. Alcohol, Physical Activity, Smoking, and Breast Cancer Subtypes in a Large, Nested Case-Control Study from the Norwegian Breast

Cancer Screening Program. *Epidemiology, Biomarkers & Prevention.* 2017, **26**(12), pp.1736-1744.

66. Flynn, R. Survival analysis. *Journal of Clinical Nursing.* 2012, **21**(19pt20), pp.2789-2797.
67. Korn, E.L. et al. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *American Journal of Epidemiology.* 1997, **145**(1), pp.72-80.
68. Bland, M. *An introduction to medical statistics.* Oxford University Press (UK), 2015.
69. Ansin, E. *An evaluation of the Cox-Snell residuals*. Master thesis, Uppsala Universitet, 2015.
70. Cook, J.A. and Ranstam, J. Statistical models and confounding adjustment. *The British Journal of Surgery.* 2017, **104**(6), pp.786-787.
71. Suttorp, M.M. et al. Graphical presentation of confounding in directed acyclic graphs. *Nephrology Dialysis Transplantation.* 2014, **30**(9), pp.1418-1423.
72. Greenland, S. et al. Causal diagrams for epidemiologic research. *Epidemiology.* 1999, **10**(1), pp.37-48.
73. Lederer, D.J. et al. Control of Confounding and Reporting of Results in Causal Inference Studies. Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Annals of the American Thoracic Society.* 2019, **16**(1), pp.22-28.
74. Textor, J. et al. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *International Journal of Epidemiology.* 2016, **45**(6), pp.1887-1894.
75. Bennett, D.A. Review of analytical methods for prospective cohort studies using time to event data: single studies and implications for meta-analysis. *Statistical Methods in Medical Research.* 2003, **12**(4), pp.297-319.
76. Tapsell, L.C. et al. Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines. *Advances in nutrition.* 2016, **7**(3), pp.445-454.
77. Cespedes, E.M. and Hu, F.B. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. *The American Journal of Clinical Nutrition.* 2015, **101**(5), pp.899-900.

78. Tapsell, L.C. et al. Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines. *Advances in Nutrition.* 2016, **7**(3), pp.445-454.

79. Schulze, M.B. et al. Food based dietary patterns and chronic disease prevention. *British Medical Journal.* 2018, **361**, p.k2396.

80. Jankovic, N. et al. Stability of dietary patterns assessed with reduced rank regression; the Zutphen Elderly Study. *Nutrition Journal.* 2014, **13**(1), p.30.

81. Altman, D.G. and Royston, P. The cost of dichotomising continuous variables. *British Medical Journal.* 2006, **332**(7549), pp.1080-1080.

82. Williams, T.C. et al. Directed acyclic graphs: a tool for causal studies in paediatrics. *Pediatric Research.* 2018, **84**(4), pp.487-493.

83. Shrier, I. and Platt, R.W. Reducing bias through directed acyclic graphs. *BMC Medical Research Methodology.* 2008, **8**(1), p.70.

84. Ishihara, J. Challenges in Dietary Exposure Assessment in Epidemiology: Research Trends. *Journal of Nutritional Sciences and Vitaminology.* 2015, **61** Suppl, pp.S33-35.

85. Cade, J. et al. Development, validation and utilisation of food-frequency questionnaires – a review. *Public Health Nutrition.* 2002, **5**(4), pp.567-587.

86. Gazan, R. et al. Structural Validation of a French Food Frequency Questionnaire of 94 Items. *Frontiers in Nutrition.* 2017, **4**(62).

87. Michels, K.B. and Schulze, M.B. Can dietary patterns help us detect diet-disease associations? *Nutrition Research Reviews.* 2005, **18**(2), pp.241-248.

88. Schulze, M.B. and Hoffmann, K. Methodological approaches to study dietary patterns in relation to risk of coronary heart disease and stroke. *British Journal of Nutrition.* 2006, **95**(5), pp.860-869.

89. Higgins, J.P.T. et al. Measuring inconsistency in meta-analyses. *British Medical Journal.* 2003, **327**(7414), pp.557-560.

90. Rattan, S. et al. Exposure to endocrine disruptors during adulthood: consequences for female fertility. *The Journal of Endocrinology.* 2017, **233**(3), pp.R109-R129.

91. Hartle, J.C. et al. The consumption of canned food and beverages and urinary Bisphenol A concentrations in NHANES 2003-2008. *Environmental Research.* 2016, **150**, pp.375-382.

92. Freedman, L.S. et al. Dealing with dietary measurement error in nutritional cohort studies. *Journal of the National Cancer Institute.* 2011, **103**(14), pp.1086-1092.

93. Boldo, E. et al. Meat intake, methods and degrees of cooking and breast cancer risk in the MCC-Spain study. *Maturitas.* 2018, **110**, pp.62-70.

94. Xu, W.H. et al. Animal food intake and cooking methods in relation to endometrial cancer risk in Shanghai. *British Journal of Cancer.* 2006, **95**(11), pp.1586-1592.

95. Lock, M. et al. Culture and symptom reporting at menopause. *Human Reproduction Update.* 2005, **11**(5), pp.495-512.

96. Obermeyer, C.M. Menopause across cultures: a review of the evidence. *Menopause.* 2000, **7**(3), pp.184-192.

97. Herber-Gast, G.-C.M. and Mishra, G.D. Fruit, Mediterranean-style, and high-fat and -sugar diets are associated with the risk of night sweats and hot flushes in midlife: results from a prospective cohort study. *The American Journal of Clinical Nutrition.* 2013, **97**(5), pp.1092-1099.

98. Mishra, G.D. et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Human Reproduction.* 2017, **32**(3), pp.679-686.

99. Zhu, D. et al. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. *European Journal of Epidemiology.* 2018, **33**(8), pp.699-710.

100. Zhu, D. et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS Medicine.* 2018, **15**(11), p.e1002704.

101. Kroenke, C.H. et al. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause.* 2012, **19**(9), pp.980-988.

102. Li, C. et al. Background factors influencing somatic and psychological symptoms in middle-age women with different hormonal status. A population-based study of Swedish women. *Maturitas.* 2005, **52**(3-4), pp.306-318.

103. Yermachenko, A. and Dvornyk, V. Nongenetic Determinants of Age at Menarche: A Systematic Review. *BioMed Research International.* 2014, **2014**, p.14.

104. Gong, T.T. et al. Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. *International Journal of Cancer.* 2013, **132**(12), pp.2894-2900.

105. Gong, T.T. et al. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. *Scientific Reports.* 2015, **5**, pp.14051-14051.

106. Collaborative Group on Hormonal Factors in Breast, C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *The Lancet Oncology.* 2012, **13**(11), pp.1141-1151.

107. Mishra, G.D. et al. A life course approach to reproductive health: Theory and methods. *Maturitas.* 2010, **65**(2), pp.92-97.

108. Morabia, A. et al. International Variability in Ages at Menarche, First Livebirth, and Menopause. *American Journal of Epidemiology.* 1998, **148**(12), pp.1195-1205.

109. Thomas, F. et al. International variability of ages at menarche and menopause: patterns and main determinants. *Human Biology.* 2001, **73**(2), pp.271-290.

110. Gold, E.B. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America.* 2011, **38**(3), pp.425-440.

111. Schoenaker, D. et al. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International Journal of Epidemiology.* 2014, **43**(5), pp.1542-1562.

112. British Nutrition Foundation. Healthy eating and the menopause. 2016. Available from: https://www.nutrition.org.uk/healthyliving/lifestages/menopause.html [accessed February 2019]

113. Mishra, G.D. et al. EMAS position statement: Predictors of premature and early natural menopause. *Maturitas.* 2019, **123**, pp.82-88.

114. Willett, W. et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *The Lancet.* 2019, **393**(10170), pp.447-492.

115. Afshin, A. et al. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet.* 2019, **393**(10184), pp.1958-1972.

Appendix A

Chapter 2 supplementary materials

Search strategy - adapted from the WCRF PubMed search strategy

Research question 1: Is diet related to the risk of breast, endometrial and ovarian cancer?

a) Searching for all studies relating to breast cancer (1st May 2015 – current):

#**1** Breast Neoplasms [MeSH Terms]

#**2** Breast AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*)

#**3** mammary AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*)

#**4** #**1** OR #**2** OR #**3**

b) Searching for all studies relating to food:

#**5** vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#**6** vitamins[MeSH Terms]

#**7** fibre[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR cholesterol[tiab] OR diet*protein*[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#**8** dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR dietary fats [MeSH Terms] OR dietary lipids [MeSH Terms]

#**9** diet therapy[MeSH Terms] OR nutrition[MeSH Terms] OR Food Habits[MeSH Terms] OR Micronutrients[MeSH Terms]

#**10** fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#**11** food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab]

OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR Potato*[tiab] OR Cabbage*[tiab] OR Brassica[tiab] OR Cruciferous[tiab] OR Radish[tiab] OR Carrot*[tiab] OR Lettuce*[tiab] OR Spinach[tiab] OR Onion*[tiab] OR Tomato*[tiab] OR Soybean[tiab]

#**12** food and beverages[MeSH Terms]

#**13** diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR Lactose[tiab] OR Galactose[tiab] OR Cheese[tiab] OR Sausage[tiab] OR Ham[tiab]

#**14** diet therapy [MeSH Terms] OR nutrition[MeSH Terms]

#**15** #**5** OR #**6** OR #**7** OR #**8** OR #**9** OR #**10** OR #**11** OR #**12** OR #**13** OR #**14**

b) Combining searches on breast cancer and searches on all studies relating to food:

#**16** #**4** AND #**15**

c) Searching for all studies relating to endometrial cancer (1st January 2013 – current):

#**17** endometrial neoplasm [MeSH]

#**18** malign* [tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab]

#**19** endometr* [tiab] OR corpus uteri [tiab] OR uterine [tiab]

#**20** #18 AND #19

#**21** #17 AND #20

d) Combining searches on endometrial cancer and searches on all studies relating to food:

#**22** #**21** AND #**15**

e) Searching for all studies relating to ovarian cancer (1st January 2013 – current):

#**23** Ovarian Neoplasms [MeSH]

#**24** Ovar* AND (cancer* OR carcinoma* OR neoplasm* OR tumor* OR tumour* OR adenocarcinoma* Or Endometrioid carcinoma* OR cystoadenoma* OR cystoadenocarcinoma* OR adenoma*)

#**25** Androblastom* OR arrhenoblastoma* OR sertoli leydig OR Brenner OR granulosa cell tumor* OR granulosa cell tumour* OR luteoma* OR luteinoma*

#**26** #23 OR #24 OR #25

f) Combining searches on ovarian cancer and searches on all studies relating to food:

#**27** #**26** AND #**15**

Research question 2: Is diet related to the timing of natural menopause?

a) Searching for all studies relating to age at natural menopause (1946 to current):

#**25** Age natural menopause [MeSH term]

#**26** Natural menopause AND (age OR onset OR timing OR occurrence)

#**27** Menopause AND (early OR earlier OR late OR later OR premature)

#**28** Menstrual period AND (final OR last)

#**29** **#25** OR #**26** OR #**27** OR #**28**

b) Combining searches on natural menopause and searches on all studies relating to food:

#**29** AND #**15**

Research question 3: Is soy consumption related to the presence of vasomotor menopausal symptoms?

a) Searching for all studies relating to vasomotor symptoms (1946 to current):

#**30** Vasomotor symptoms [MeSH term]

#**31** Vasomotor symptoms AND (hot flushes OR hot flashes OR night sweats OR climacteric symptoms OR menopausal symptoms)

#**32** #**30** AND #**31**

b) Searching for all studies relating to diet (1946 to current):

#**33** AND #**15**

Table A.1 Study Quality assessment using Newcastle-Ottawa scale for cohort studies*

Study, Year	Selection				Comparability of cohorts (matched for)	Outcome			Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at baseline		Assessment of outcome	Sufficient follow-up duration	Adequate follow-up	
Diet and age at natural menopause									
Torgerson et al. 1997 [12]	-	-	-	★	-	-	★	★	3
Nagata et al. 2000 [15]	★	★	-	★	★★ (social class, smoking)	-	★	★	7
Nagel et al. 2005 [13]	★	★	-	★	★★ (smoking, alcohol intake)	-	★	★	7
Dorjgochoo et al. 2008 16]	-	-	★	★	★★ (education, smoking)	-	-	-	4
Nagata et al. 2012 [31]	★	★	★	★	★★ (smoking, education)	-	★	★	8
Carwile et al. 2013 [18]	★	★	-	-	★★ (smoking, physical activity)	-	★	★	6
Purdue-Smithe et al. 2017 [32]	★	★	-	★	★★ (smoking, physical activity)	-	★	★	7
Boutot et al. 2017 [33]	★	★	-	★	★★ (smoking, physical activity)	-	★	★	7
Purdue-Smithe et al. 2018 [34]	★	★	-	★	★★ (smoking, alcohol intake)	-	★	★	7
Diet and presence of VMS									
Nagata et al. 2001 [23]	★	★	-	★	★★ (age, menopausal status)	-	★	★	7
Gold et al. 2013 [24]	★	★	-	★	★★ (age, menopausal status)	-	★	★	7
Herber-Gast et al. 2013 [29]	★	★	-	★	★★ (age, menopausal status)	-	★	★	7
Diet and the risk of ovarian cancer									
Merritt et al. 2014 [37]	★	★	-	★	★ (menopausal status)	★	★	★	7
Merritt et al. 2014 [35]	★	★	★	★	★ (menopausal status)	★	★	★	8
Lukic et al. 2016 [39]	★	★	-	★	★★(smoking, alcohol consumption)	★	-	★	7
Meritt et al. 2016 [36]	★	★	★	★	★ (menopausal status)	★	★	★	8
Diet and the risk of endometrial cancer									
Arem et al. 2013 [47]	★	★	-	★	★★ (smoking, diabetes)	★	-	★	7
Fedirko et al. 2013 [48]	★	★	★	★	★★ (smoking, physical activity)	★	★	★	9
Inoue-Choi et al. 2013 [49]	★	★	-	★	★★ (smoking, alcohol intake)	★	★	★	8
Uccella et al. 2013 [50]	★	★	-	★	★★ (smoking, diabetes)	★	★	★	7
Brasky et al. 2014 [51]	★	★	-	★	★★ (education, smoking)	★	-	-	6
Coleman et al. 2014 [52]	-	-	-	★	★★ (age, ethnicity)	-	-	-	3

Table A.1 Continued

Study, Year	Selection				Comparability of cohorts (matched for)	Outcome			Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at baseline		Assessment of outcome	Sufficient follow-up duration	Adequate follow-up	
Gavrilyuk et al. 2014 [53]	★	★	-	★	★ (smoking)	★	-	★	6
Je et al. 2014 [54]	★	★	-	★	★★ (smoking, physical activity)	★	★	-	7
Budhathoki et al. 2015 [55]	★	-	-	★	★★ (smoking, alcohol intake)	★	-	★	6
Canchola et al. 2015 [56]	★	-	-	★	★★ (smoking, ethnicity)	★	★	★	7
Yang et al. 2015 [57]	-	-	-	★	★★ (smoking, alcohol intake)	★	-	★	5
Brasky et al. 2016 [58]	★	★	-	★	★★ (smoking, alcohol intake)	★	★	-	7
Diet and the risk of breast cancer									
Farvid et al. 2015 [59]	★	★	-	★	★★ (smoking, menopausal status)	★	★	-	7
Harris et al. 2015 [60]	★	★	-	★	★★ (smoking, alcohol intake)	★	★	★	8
Kiyabu et al. 2015 [61]	★	-	-	★	★★ (smoking, physical activity)	★	★	★	7
Romieu et al. 2015 [62]	★	★	-	★	★★ (smoking, physical activity)	★	★	★	8
Shin et al. 2015 [63]	★	-	-	★	★★ (smoking, breastfeeding)	★	-	★	6
Baglia et al. 2016 [87]	★	-	-	★	★★ (physical activity, menopause status)	★	★	-	6
Emaus et al. 2016 [64]	★	★	★	★	★★ (smoking, menopause status)	★	★	★	9
Farvid et al. 2016 [65]	★	★	-	★	★★ (smoking, alcohol intake)	★	★	★	8
Farvid et al. 2016 [66]	★	★	-	★	★★ (smoking, alcohol intake)	★	★	★	8
Farvid et al. 2016 [67]	★	★	-	★	★★ (smoking, menopause status)	★	★	★	8
Gilsing et al. 2016 [68]	★	★	-	★	★★ (physical activity, alcohol intake)	★	★	-	7
Harris et al. 2016 [69]	★	★	-	★	★★ (physical activity, alcohol intake)	★	★	-	7
Hirko et al. 2016 [70]	★	★	-	★	★ (physical activity)	★	★	★	7
Inoue-Choi et al. 2016 [71]	★	★	-	★	★★ (smoking, alcohol intake)	★	-	★	7
Penniecook-Sawyers et al. 2016 [73]	★	★	-	★	★★ (physical activity, smoking)	★	-	★	7
Shin et al. 2016 [74]	★	-	-	★	★★ (physical activity, smoking)	★	★	★	7
Kim et al. 2017 [77]	★	★	-	★	★★ (menopausal status, smoking)	★	★	★	8
Kim et al. 2017 [78]	★	-	-	★	★★ (menopausal status, smoking)	★	-	-	5
Kojima et al. 2017 [79]	★	★	-	★	★★ (age, smoking)	★	★	★	8
Makarem et al. 2017 [80]	★	-	-	★	★★ (age, smoking)	★	-	★	6

Table A.1 Continued

Study, Year	Selection				Comparability of cohorts (matched for)	Outcome			Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at baseline		Assessment of outcome	Sufficient follow-up duration	Adequate follow-up	
Narita et al. 2017 [81]	★	★	-	★	★★ (smoking, alcohol consumption)	★	-	★	7
van den Brandt & Schulpen, 2017 [82]	★	★	-	★	★★ (age, alcohol intake)	★	★	★	8
Diallo et al. 2018 [83]	★	★	-	★	★★ (age, alcohol intake)	★	-	★	7
Fiolet et al. 2018 [84]	★	★	-	★	★★ (age, alcohol intake)	★	-	★	7

*Please refer to Chapter 2 for the references

Table A.2 Study Quality assessment using Newcastle-Ottawa scale for case-control studies*

Study, Year	Selection				Comparability of cases and controls (matched for)	Exposure			Total Score
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Diet and presence of VMS									
Schiling et al. 2005 [30]	★	★	-	★	★★ (age, smoking)	★	★	-	7
Diet and the risk of ovarian cancer									
Cook et al. 2016 [43]	★	★	★	★	★★ (smoking, alcohol consumption)	★	★	-	8
Qin et al. 2016 [38]	★	★	★	★	★★ (menopausal status, education)	★	★	-	8
Diet and risk of breast cancer									
Ellingjord-Dale et al. 2017 [76]	★	★	★	★	★★ (education, smoking)	★	★	-	8

*Please refer to Chapter 2 for the references

Table A.3 Study Quality assessment using adapted Newcastle-Ottawa scale for cross-sectional studies*

Study, Year	Selection				Comparability of outcome groups (matched for)	Outcome		Total score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure		Assessment of outcome	Appropriate statistical test	
Diet and age at natural menopause								
Torgerson et al. 1994 [11]	-	★	-	-		-	★	2
Nagata et al. 1998 [21]	★	-	-	★	-	★	★	4
Wang et al. 2018 [14]	★	-	-	★	-	★	★	4
Diet and the presence of VMS								
Somekawa et al. 2001 [25]	-	-	-	★	-	★	★	3

*Please refer to Chapter 2 for the references

Table A.4 Quality assessment for randomised controlled trials*

Study, Year	Randomisation			Baseline comparability		Eligibility		Blinding				Withdrawals			Other outcomes
	Truly random	Allocation concealment	Number stated	Presented	Achieved	Inclusion criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	Intention to treat	
Diet and age at natural menopause															
Martin et al. 2006 [17]	✓	✓	✓	✓	✓	✓	NS	NS	NS	NS	NS	×	NS	×	×
Diet and the presence of VMS															
Murkies et al. 1995 [22]	NS	✓	✓	NS	NS	✓	NS	✓	✓	✓	NS	✓	×	×	×
Dodin et al. 2005 [26]	✓	✓	✓	✓	✓	✓	NS	✓	✓	✓	NS	✓	✓	✓	×
Lewis et al. 2006 [28]	✓	✓	✓	✓	✓	✓	NS	✓	✓	✓	NS	✓	✓	✓	
Pruthi et al. 2012 [27]	✓	NS	✓	✓	✓	✓	NS	×	×	✓	✓	✓	NS	×	×
Diet and the risk of ovarian, endometrial and breast cancers															
Hashibe et al. 2015 [40]	✓	NS	✓	×	NA	✓	NS	×	×	✓	NS	NS	NS	×	×

✓ Yes (item adequately addressed); × no (item not adequately assessed); ✓× partially (item partially addressed); NS (not stated); NA (not applicable); *Please refer to Chapter 2 for the references

Appendix B

Chapter 4 supplementary materials

Table B.1 Grouping of individual food items into 64 food groups

Food Group	Food Items
Wholegrain products	Crispbread, Brown bread & rolls, Wholemeal bread & rolls ,
Refined grain products	White bread & rolls, Chapattis, Nan, paratha, Papadums, Tortillas, Pitta Bread, Cream crackers, cheese biscuits
Low fibre breakfast cereals	Cream crackers, cheese biscuits, Sugar coated cereals, Non-sugar coated cereals
High fibre breakfast cereals	Porridge, Readybrek , Muesli, All bran, bran flakes, Weetabix, shredded wheat
Plain Potatoes	Potatoes, Jacket potato
Potatoes with added fat	Chips, Roast potatoes, Potato salad
Refined pasta and rice	White pasta, Macaroni cheese, White rice
Wholegrain pasta and rice	Wholemeal pasta, Brown rice, Wild rice
Low fat dairy products	Low fat yoghurt, Diet yoghurt, Dairy desserts, Low-fat cheese, Cottage cheese, Milk puddings, Half fat milk, Fat free milk
High fat dairy products	Thick & creamy yoghurt, Greek yoghurt, Fromage frais/Crème fraiche, Single/sour cream, Double/clotted cream, Ice cream, Cheese, Cheese and onion pastie, Whole milk, Channel island milk, Dried milk
Butter and hard margarine	Butter, Block margarine
Margarine	Other soft margarine, Polyunsaturated margarine, Monounsaturated margarine
Low fat spreads	Low fat spread, Very low fat spread
High fat dressing	Mayonnaise, French type dressing
Low fat dressing	Low calorie salad cream
Soybean products	Soya cheese, Soya yoghurt, Soy milk
Textured vegetable protein	Textured vegetable protein
Pulses	Lentils, dals, Chick peas, chanas, Hummus, Baked beans, Mung beans & red kidney beans, Black eyed beans, Butter beans/broad beans
Eggs/eggs dishes	Boiled/poached egg, Omelette, scrambled egg, Fried egg, Quiche
Fish and fish dishes	Fish fingers/cakes, Fried fish in batter, White fish, Fish pie/fish lasagne, Fish roe
Oily fish	Oily fish
Shellfish	Shellfish
Red meat	Beef, Beef stew, Pork, Pork stew/casserole, Lamb, Lamb stew/casserole, Meat – lasagne/moussaka/ravioli
Poultry	Chicken/turkey, Breadcrumbed, Chicken/turkey in creamy sauce, curry
Processed meat	Bacon, Beefburger/hamburger, Ham, Corned beef, Sausages, Meat pizza, Pies/pasties/sausage rolls, Liver pate/sausage, salami
Offal	Offal
Vegetable dishes	Quorn, Vegetarian chilli, Mixed bean casserole, Stir-fry vegetables, Vegetable – lasagne/moussaka/ravioli, Vegetable pate, Vegetable pizza
Allium	Leeks, Garlic
Fresh legumes	Peas, mushy peas, mange-tout, Green beans
Mediterranean vegetables	Sweetcorn, Courgettes, Olive, Aubergine, okra/ladies finger, Peppers
Salad vegetables	Avocado, Lettuce, Cucumber, Celery, Coleslaw, Low calorie coleslaw

Table B.1 Continued

Food Group	Food Items
Cruciferous vegetables	Broccoli, spring greens, kale, Cabbage, Cauliflower, Watercress, mustard & cress, Brussel sprouts
Tomatoes	Tomatoes – raw/canned/sauce
Mushrooms	Mushrooms
Roots and tubers	Carrots, Parsnips, Turnip, Swedes, Beetroot
Stone fruits	Peaches, Plum, Mangoes, Nectarines, Apricots
Deep orange/yellow fruits	Pineapple, Papaya, Melon
Grapes	Grapes
Citrus family fruits	Oranges, satsumas, grapefruit
Rhubarb	Rhubarb
Berries	Strawberries, Raspberries, Red currants/black currants, Kiwi fruit
Bananas	Bananas
Pomes	Apples, Pears
Dried Fruits	Dates, Figs, Prunes, Mixed dried fruits, Currants, raisins, sultanas
Sauces	Sauces
Pickles/chutneys	Tomato ketchup, Pickles/chutney/pesto sauce
Soups	Packet soups, Other-vegetable soups, Other-Meat soups, Low calorie soups
Confectionery & spreads	Fruit bars, Chocolate snack bars, Mini chocolate snack bars, Boiled sweets, toffees, mints, Chocolate/chocolate & nut spread, Jam/marmalade, Honey
Nuts & Seeds	Peanuts/Pistachio nuts, Cashew nuts & almonds, Pecan nuts/ Walnuts, Sunflower seeds/ sesame seeds, Nut Pâté, Peanut butter, Peanuts/pistachio nuts, Mixed nuts and raisins
Savoury snacks	Crisps, Other fried snacks, Low fat or baked snacks, Bombay mix
Biscuits	Plain biscuits, Chocolate biscuits, Sandwich/cream biscuits
Cakes	Fruitcake, Sponge cake
Pastries and Puddings	Buns/pastries, Scones/pancakes/muffins/crumpets, Fruit pies, Sponge puddings
Tea	Tea
Herbal tea	Herbal tea
Coffee	Coffee – instant/ground, Coffee – decaffeinated
Other hot beverages	Cocoa, Horlicks, Ovaltine, Low calorie hot chocolate
Juices	Orange juice, Other – pure juices
Soft drinks	Fruit squash, Fizzy soft drinks
Low calorie/diet soft drinks	Low calorie/diet soft drinks
Wines	Wines
Beer and cider	Beer, Cider
Port, sherry, liqueurs	Port, sherry, liqueurs
Spirits	Spirits

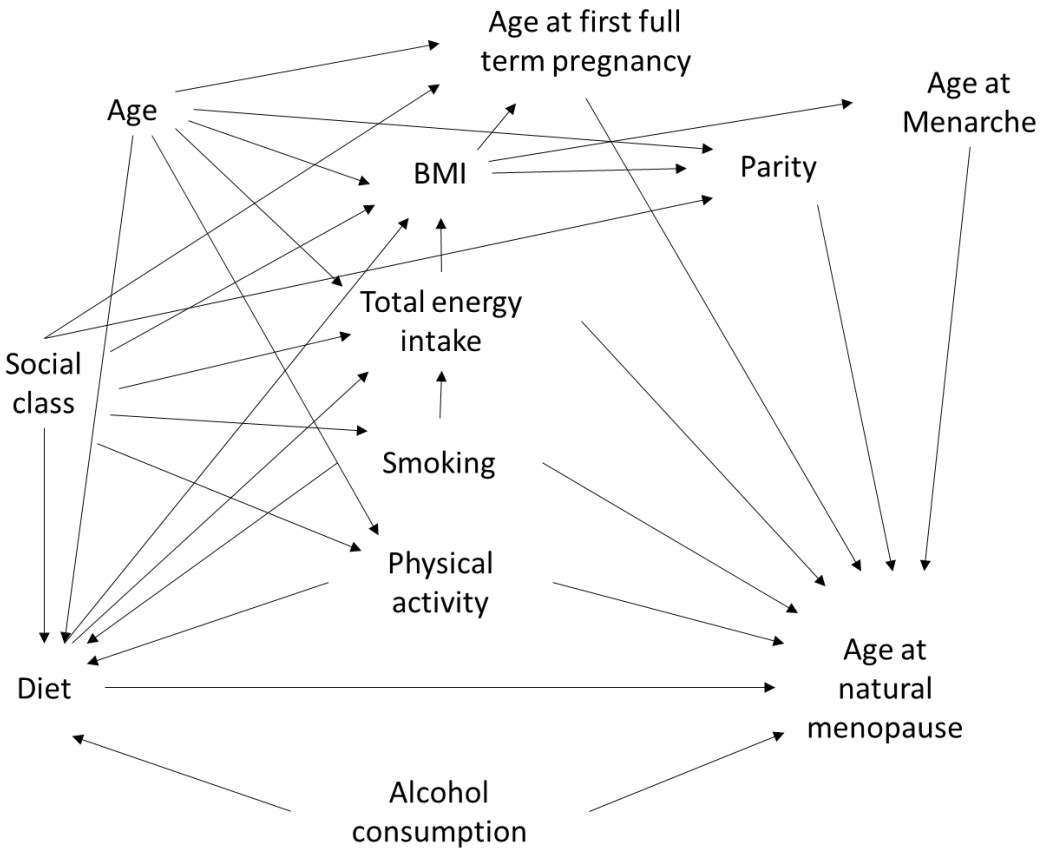


Figure B.1 Directed acrylic graph – for assessment of covariates

Table B.2 Sensitivity analysis of daily food groups intake/portion size and age at natural menopause by vegetarian status, fully adjusted model

Daily intake/ portion size	Vegetarians (n=323)			Non-vegetarians (n=501)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Starchy foods						
Wholegrain products/ 33g	0.0	-0.2 to 0.3	0.589	0.1	-0.0 to 0.3	0.219
Refined grain products/ 51g	-0.1	-0.7 to 0.5	0.665	-0.2	-0.7 to 0.3	0.300
Low fibre breakfast cereals/ 40g	0.0	-1.7 to 1.8	0.945	-0.1	-1.3 to 1.1	0.829
High fibre breakfast cereals/ 85g	0.1	-0.6 to 0.8	0.755	0.4	-0.2 to 1.0	0.108
Plain Potatoes/ 210g	0.5	-0.6 to 1.6	0.260	0.6	-0.4 to 1.6	0.140
Potatoes with added fat/ 127g	-0.2	-3.0 to 2.6	0.828	-0.3	-2.3 to 1.6	0.651
Refined pasta and rice/ 210g	-1.4	-3.3 to 0.5	0.057	-1.6	-3.4 to 0.3	0.031
Wholegrain pasta and rice/ 197 g	0.9	-1.1 to 2.8	0.237	0.9	-1.2 to 3.0	0.256
Protein and fat food sources						
Low fat dairy products/ 80g	-0.1	-0.2 to 0.1	0.171	0.1	-0.0 to 0.2	0.228
High fat dairy products/ 75g	0.0	-0.2 to 0.3	0.656	-0.2	-0.4 to 0.1	0.074
Butter and hard margarine/ 10g	0.0	-0.6 to 0.5	0.852	0.3	-0.2 to 0.7	0.103
Margarine/ 9g	-0.1	-0.5 to 0.3	0.379	-0.1	-0.5 to 0.3	0.675
Low fat spreads/ 7g	0.2	-0.4 to 0.8	0.320	0.0	-0.4 to 0.3	0.749
High fat dressing/ 23g	0.0	-1.5 to 1.5	0.979	0.1	-1.4 to 1.6	0.870
Low fat dressing/ 30g	0.9	-2.5 to 4.3	0.475	1.2	-1.5 to 3.9	0.262
Soybean products/ 62g	0.0	-0.1 to 0.2	0.436	-0.1	-0.4 to 0.3	0.630
Textured vegetable protein/ 130g	1.1	-8.8 to 10.9	0.782	-9.9	-43.0 to 23.2	0.440
Pulses/ 91g	0.1	-0.9 to 1.0	0.885	-0.2	-1.3 to 0.9	0.653
Eggs/eggs dishes/ 88g	0.1	-1.8 to 2.1	0.865	1.1	-1.0 to 3.1	0.187
Fish and fish dishes/ 140g	-1.5	-4.7 to 1.7	0.227	1.8	-1.3 to 5.0	0.132
Oily fish/ 90g	0.7	-4.0 to 5.3	0.713	3.4	0.2 to 6.5	0.005
Shell fish/ 60g	-1.8	-12.7 to 9.0	0.663	2.3	-5.9 to 10.4	0.476
Red meat/ 189g	12.5	-136.4 to 161.4	0.828	0.7	-1.5 to 2.9	0.400
Processed meat/ 74g	-4.2	-23.1 to 14.7	0.566	-0.3	-2.5 to 2.0	0.743
Poultry/ 143g	7.4	-3.1 to 17.8	0.069	-0.6	-3.4 to 2.3	0.607

Table B.2 Continued

Daily intake/ portion size	Vegetarians (n=323)			Non-vegetarians (n=501)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Offal/ 100g	.	.	.	1.8	-8.5 to 12.1	0.647
Vegetables						
Vegetable dishes/ 214g	0.0	-1.2 to 1.1	0.924	-0.3	-1.7 to 1.1	0.593
Allium/ 39g	0.6	-0.7 to 1.9	0.219	0.5	-0.8 to 1.8	0.282
Fresh legumes/ 75g	0.3	-1.0 to 1.5	0.556	1.4	0.2 to 2.7	0.003
Mediterranean vegetables/ 60g	0.0	-0.8 to 0.8	0.904	0.4	-0.6 to 1.3	0.314
Salad vegetables/ 43g	0.3	-0.3 to 1.0	0.210	0.7	0.0 to 1.3	0.009
Cruciferous vegetables/ 75g	0.3	-0.2 to 0.8	0.143	0.4	-0.1 to 0.9	0.051
Tomatoes/ 83g	-0.3	-1.1 to 0.5	0.313	0.8	-0.2 to 1.8	0.043
Mushrooms/ 34g	0.1	-1.5 to 1.8	0.831	0.5	-1.2 to 2.2	0.424
Roots and tubers/ 66g	0.2	-0.5 to 0.9	0.550	0.8	-0.1 to 1.7	0.016
Fruits						
Stone fruits/ 49g	0.2	-0.7 to 1.1	0.604	1.0	0.5 to 2.5	0.083
Deep orange & yellow fruits/ 118g	0.5	-0.4 to 1.4	0.139	0.7	-0.6 to 2.0	0.189
Grapes/ 100g	0.6	-0.5 to 1.7	0.175	0.9	-0.6 to 2.3	0.117
Citrus family fruits/ 92g	0.3	-0.5 to 1.1	0.363	0.1	-0.7 to 1.0	0.651
Rhubarb/ 130g	-0.1	-2.0 to 1.8	0.862	1.5	-0.5 to 3.5	0.056
Berries/ 48g	0.2	-0.5 to 0.8	0.514	0.5	-0.4 to 1.3	0.157
Bananas/ 100g	0.0	-0.8 to 0.8	0.980	0.1	-0.6 to 0.9	0.662
Pomes/ 116g	0.0	-0.5 to 0.5	0.865	0.1	-0.3 to 0.6	0.451
Dried Fruits/ 28g	0.2	-0.5 to 0.9	0.371	0.5	-0.1 to 1.2	0.025
Other food groups						
Sauces/ 83g	0.1	-3.6 to 3.8	0.936	0.2	-3.1 to 3.5	0.888
Pickles/Chutneys/ 35g	-0.6	-2.4 to 1.3	0.429	0.2	-1.7 to 2.1	0.827
Soups/ 163g	1.3	-0.5 to 3.2	0.065	0.7	-0.7 to 2.1	0.222
Confectionary & spreads/ 44g	-0.1	-0.6 to 0.3	0.455	0.1	-0.4 to 0.6	0.690
Nuts and seeds/ 24g	0.2	-0.26 to 0.6	0.279	0.2	-0.5 to 0.9	0.476

Table B.2 Continued

Daily intake/ portion size	Vegetarians (n=323)			Non-vegetarians (n=501)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Savoury snacks/ 26g	0.1	-1.2 to 1.4	0.863	-1.7	-3.1 to -0.4	0.001
Biscuits/ 15g	-0.1	-0.7 to 0.5	0.567	-0.3	-0.7 to 0.2	0.130
Cakes/ 66g	-1.2	-3.4 to 1.1	0.183	0.7	-1.4 to 2.8	0.389
Pastries and Puddings/ 84g	-0.1	-1.7 to 1.5	0.912	-0.8	-2.3 to 0.8	0.190
Drinks and beverages						
Tea/ 260g	-0.1	-0.3 to 0.2	0.567	-0.2	-0.4 to 0.0	0.045
Herbal tea/ 260g	0.1	-0.4 to 5.8	0.533	0.3	-0.2 to 0.7	0.151
Coffee/ 190g	0.0	-0.3 to 0.2	0.767	0.1	-0.1 to 0.3	0.162
Other hot beverages/ 23g	0.0	-0.6 to 0.6	0.975	0.4	-0.5 to 1.2	0.272
Juices/ 145g	-0.2	-0.9 to 0.5	0.489	0.3	-0.3 to 0.8	0.219
Soft drinks/ 111g	-0.2	-1.4 to 0.1	0.674	-1.3	-2.5 to -0.2	0.003
Low calorie/diet soft drinks/ 161g	0.1	-0.8 to 0.9	0.812	-0.4	-1.3 to 0.6	0.301
Wines/ 1g	0.4	-0.6 to 1.3	0.360	0.0	-0.9 to 0.8	0.882
Beer and cider/ 1g	-0.6	-1.8 to 0.6	0.191	-0.3	-1.4 to 0.8	0.449
Port, sherry, liqueurs/ 1g	1.6	-1.0 to 4.3	0.112	0.7	-1.2 to 2.7	0.346
Spirits/ 1g	0.1	-1.1 to 1.2	0.887	-0.4	-1.6 to 0.7	0.345

Table B.3 Sensitivity analysis of daily food groups intake/portion size and age at natural menopause by parity, fully adjusted model

Daily intake/ portion size	Nulliparous (n=179)			Multiparous (n=645)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Starchy foods						
Wholegrain products/ 33g	0.0	-0.3 to 0.3	0.899	0.1	-0.1 to 0.2	0.344
Refined grain products/ 51g	0.0	-0.9 to 0.9	0.939	-0.3	-0.7 to 0.2	0.119
Low fibre breakfast cereals/ 40g	-0.4	-2.8 to 2.0	0.643	-0.1	-1.3 to 1.0	0.769
High fibre breakfast cereals/ 85g	0.1	-0.9 to 1.0	0.890	0.2	-0.4 to 0.7	0.366
Plain Potatoes/ 210g	0.4	-1.0 to 1.7	0.501	0.4	-0.5 to 1.3	0.202
Potatoes with added fat/ 127g	0.1	-3.9 to 4.1	0.948	-0.3	-2.1 to 1.4	0.637
Refined pasta and rice/ 210g	-2.0	-5.6 to 1.6	0.157	-1.9	-3.3 to -0.4	0.001
Wholegrain pasta and rice/ 197 g	1.0	-2.0 to 4.0	0.388	0.5	-1.1 to 2.1	0.448
Protein and fat food sources						
Low fat dairy products/ 80g	0.0	-0.3 to 0.2	0.575	0.0	-0.1 to 0.1	0.722
High fat dairy products/ 75g	0.1	-0.3 to 0.5	0.654	-0.1	-0.3 to 0.1	0.227
Butter and hard margarine/ 10g	0.0	-0.7 to 0.6	0.862	0.2	-0.2 to 0.6	0.120
Margarine/ 9g	-0.1	-0.7 to 0.5	0.677	-0.2	-0.6 to 0.1	0.061
Low fat spreads/ 7g	0.2	-0.8 to 1.2	0.682	0.0	-0.3 to 0.4	0.969
High fat dressing/ 23g	-0.1	-2.1 to 1.8	0.862	-0.1	-1.4 to 1.2	0.830
Low fat dressing/ 30g	-0.2	-4.4 to 4.0	0.900	1.1	-1.4 to 3.5	0.266
Soybean products/ 62g	0.0	-0.3 to 0.2	0.690	0.0	-0.2 to 0.2	0.900
Textured vegetable protein/ 130g	-12.6	-39.7 to 14.6	0.230	-3.1	-12.8 to 6.5	0.400
Pulses/ 91g	-0.6	-1.9 to 0.8	0.290	-0.3	-1.1 to 0.5	0.298
Eggs/eggs dishes/ 88g	1.8	-1.5 to 5.1	0.167	0.1	-1.5 to 1.7	0.829
Fish and fish dishes/ 140g	3.9	-1.5 to 9.3	0.064	0.4	-1.9 to 2.7	0.628
Oily fish/ 90g	3.2	-1.0 to 7.4	0.046	3.3	0.3 to 6.3	0.005
Shell fish/ 60g	7.6	-10.0 to 25.1	0.262	0.5	-6.4 to 7.4	0.847
Red meat/ 189g	3.0	-1.3 to 7.3	0.073	1.1	-0.8 to 3.0	0.150
Processed meat/ 74g	1.6	-2.8 to 6.1	0.341	0.6	-1.4 to 2.5	0.435
Poultry/ 143g	5.2	0.1 to 10.3	0.008	0.2	-2.4 to 2.7	0.869

Table B.3 Continued

Daily intake/ portion size	Nulliparous (n=179)			Multiparous (n=645)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Offal/ 100g	13.3	-10.5 to 37.0	0.148	4.7	-5.6 to 14.9	0.242
Vegetables						
Vegetable dishes/ 214g	-1.4	-3.1 to 0.4	0.047	-0.4	-1.4 to 0.5	0.236
Allium/ 39g	-0.1	-2.0 to 1.9	0.942	0.6	-0.5 to 1.7	0.135
Fresh legumes/ 75g	-0.1	-1.9 to 1.7	0.872	1.1	0.1 to 2.1	0.006
Mediterranean vegetables/ 60g	-0.3	-1.5 to 0.9	0.501	0.0	-0.7 to 0.7	0.938
Salad vegetables/ 43g	0.2	-0.7 to 1.1	0.522	0.4	-0.1 to 1.0	0.032
Cruciferous vegetables/ 75g	0.1	-0.9 to 1.0	0.874	0.4	-0.1 to 0.8	0.023
Tomatoes/ 83g	-0.4	-1.7 to 0.8	0.351	0.2	-0.5 to 0.9	0.507
Mushrooms/ 34g	-1.4	-4.5 to 1.7	0.234	0.4	-0.9 to 1.7	0.471
Roots and tubers/ 66g	0.3	-1.0 to 1.6	0.567	0.4	-0.2 to 1.1	0.086
Fruits						
Stone fruits/ 49g	0.4	-2.0 to 2.7	0.695	0.3	-0.5 to 1.1	0.316
Deep orange & yellow fruits/ 118g	0.0	-2.0 to 1.9	0.978	0.6	-0.2 to 1.4	0.057
Grapes/ 100g	2.5	0.1 to 4.9	0.008	0.4	-0.5 to 1.4	0.248
Citrus family fruits/ 92g	0.0	-1.1 to 1.1	0.976	0.2	-0.5 to 0.9	0.481
Rhubarb/ 130g	1.0	-2.6 to 4.5	0.475	0.7	-0.9 to 2.2	0.256
Berries/ 48g	0.4	-1.2 to 1.9	0.538	0.2	-0.4 to 0.7	0.404
Bananas/ 100g	0.0	-1.0 to 1.0	0.989	0.0	-0.6 to 0.7	0.890
Pomes/ 116g	0.2	-0.5 to 0.9	0.456	0.0	-0.4 to 0.4	0.856
Dried Fruits/ 28g	0.2	-0.7 to 1.2	0.478	0.4	-0.1 to 1.0	0.029
Other food groups						
Sauces/ 83g	-0.9	-6.3 to 4.5	0.673	0.1	-2.7 to 2.8	0.963
Pickles/Chutneys/ 35g	-1.0	-3.6 to 1.6	0.324	-0.1	-1.6 to 1.4	0.869
Soups/ 163g	1.0	-1.6 to 3.5	0.316	0.8	-0.5 to 2.1	0.108
Confectionary & spreads/ 44g	0.1	-0.5 to 0.7	0.684	-0.1	-0.4 to 0.3	0.716
Nuts and seeds/ 24g	0.2	-0.9 to 1.3	0.580	0.1	-0.3 to 0.5	0.499

Table B.3 Continued

Daily intake/ portion size	Nulliparous (n=179)			Multiparous (n=645)		
	Difference in age at natural menopause (y)	99% CI	*P* value	Difference in age at natural menopause (y)	99% CI	*P* value
Savoury snacks/ 26g	0.0	-2.1 to 2.2	0.964	-1.1	-2.1 to -0.0	0.009
Biscuits/ 15g	-0.2	-0.9 to 0.5	0.491	-0.2	-0.6 to 0.2	0.141
Cakes/ 66g	-0.7	-3.5 to 2.2	0.533	0.2	-1.7 to 2.0	0.793
Pastries and Puddings/ 84g	-0.5	-3.7 to 2.6	0.650	-0.5	-1.7 to 0.7	0.271
Drinks and beverages						
Tea/ 260g	-0.2	-0.5 to 0.1	0.052	-0.1	-0.3 to 0.1	0.161
Herbal tea/ 260g	0.4	-0.2 to 0.9	0.066	0.0	-0.4 to 0.4	0.868
Coffee/ 190g	0.0	-0.4 to 0.3	0.800	0.1	-0.1 to 0.3	0.214
Other hot beverages/ 23g	-0.3	-1.4 to 0.7	0.393	0.3	-0.3 to 0.9	0.145
Juices/ 145g	0.0	-1.0 to 1.0	0.992	0.1	-0.4 to 0.6	0.522
Soft drinks/ 111g	-1.2	-2.7 to 0.3	0.032	-0.6	-1.6 to 0.4	0.098
Low calorie/diet soft drinks/ 161g	-0.6	-2.1 to 0.9	0.273	-0.1	-0.8 to 0.6	0.759
Wines/ 1g	0.7	-0.2 to 1.7	0.033	-0.3	-1.2 to 0.5	0.332
Beer and cider/ 1g	-0.5	-1.6 to 0.6	0.274	-0.4	-1.5 to 0.6	0.277
Port, sherry, liqueurs/ 1g	2.3	-0.8 to 5.3	0.052	0.6	-1.3 to 2.4	0.408
Spirits/ 1g	0.3	-1.8 to 2.4	0.722	-0.3	-1.2 to 0.6	0.399

Table B.4 Sensitivity analysis of daily food groups intake/portion size and age at natural menopause by presence of diabetes at baseline, fully adjusted model

Daily intake/ portion size	Difference in age at natural menopause[a]	99% CI	*P* value
Starchy food sources			
Wholegrain products/ 33g	0.1	-0.1 to 0.2	0.272
Refined grain products/ 51g	-0.1	-0.5 to 0.2	0.347
Low fibre breakfast cereals/ 40g	0.0	-1.0 to 1.0	0.944
High fibre breakfast cereals/ 85g	0.2	-0.3 to 0.6	0.338
Plain Potatoes/ 210g	0.6	-0.2 to 1.3	0.046
Potatoes with added fat/ 127g	-0.1	-1.7 to 1.6	0.923
Refined pasta and rice/ 210g	-1.6	-2.9 to -0.2	0.003
Wholegrain pasta and rice/ 197 g	0.4	-1.0 to 1.8	0.483
Protein and fat food sources			
Low fat dairy products/ 80g	0.0	-0.1 to 0.1	0.642
High fat dairy products/ 75g	-0.1	-0.3 to 0.1	0.212
Butter and hard margarine/ 10g	0.1	0.2 to 0.5	0.283
Margarine/ 9g	-0.1	-0.4 to 0.1	0.196
Low fat spreads/ 7g	0.1	-0.2 to 0.4	0.320
High fat dressing/ 23g	-0.1	-1.2 to 0.9	0.724
Low fat dressing/ 30g	1.0	-1.2 to 3.2	0.255
Soybean products/ 62g	0.0	-0.2 to 0.1	0.791
Textured vegetable protein/ 130g	-4.2	-13.2 to 4.7	0.225
Pulses/ 91g	-0.3	-1.0 to 0.3	0.192
Eggs/eggs dishes/ 88g	0.5	-0.9 to 2.0	0.338
Fish and fish dishes/ 140g	1.2	-0.9 to 3.3	0.148
Oily fish/ 90g	3.0	0.5 to 5.5	0.002
Shell fish/ 60g	0.6	6.0 to 7.2	0.818
Red meat/ 189g	1.3	-0.4 to 3.1	0.044
Processed meat/ 74g	1.2	-0.6 to 3.0	0.093
Poultry/ 143g	1.9	-0.6 to 4.4	0.047
Offal/ 100g	6.6	-2.8 to 16.0	0.071
Vegetables			
Vegetable dishes/ 214g	-0.6	-1.4 to 0.2	0.054
Allium/ 39g	0.5	0.5 to 1.4	0.196
Fresh legumes/ 75g	0.9	0.0 to 1.8	0.007
Mediterranean vegetables/ 60g	0.0	-0.6 to 0.6	0.991
Salad vegetables/ 43g	0.3	-0.1 to 0.8	0.057
Cruciferous vegetables/ 75g	0.3	-0.1 to 0.6	0.047
Tomatoes/ 83g	0.0	-0.6 to 0.6	0.985
Mushrooms/ 34g	0.2	-1.0 to 1.4	0.672
Roots and tubers/ 66g	0.3	-0.2 to 0.9	0.111
Fruits			
Stone fruits/ 49g	0.2	-0.5 to 1.0	0.425
Deep orange & yellow fruits/ 118g	0.5	-0.2 to 1.2	0.088
Grapes/ 100g	0.6	-0.2 to 1.5	0.065
Citrus family fruits/ 92g	0.2	-0.4 to 0.7	0.443
Rhubarb/ 130g	0.8	-0.6 to 2.1	0.149
Berries/ 48g	0.2	-0.3 to 0.7	0.293
Bananas/ 100g	0.1	-0.5 to 0.6	0.736
Pomes/ 116g	0.0	-0.3 to 0.4	0.846
Dried Fruits/ 28g	0.3	-0.1 to 0.8	0.051
Other food groups			
Sauces/ 83g	-0.2	-2.7 to 2.2	0.831

Table B.4 Continued

Daily intake/ portion size	Difference in age at natural menopause[a]	99% CI	*P* value
Pickles/Chutneys/ 35g	-0.3	-1.6 to 1.1	0.622
Soups/ 163g	0.7	-0.4 to 1.9	0.096
Confectionary & spreads/ 44g	0.0	-0.3 to 0.3	0.889
Nuts and seeds/ 24g	0.1	-0.3 to 0.4	0.643
Savoury snacks/ 26g	-0.8	-1.8 to 0.1	0.020
Biscuits/ 15g	-0.2	-0.5 to 0.2	0.214
Cakes/ 66g	-0.3	-2.0 to 1.2	0.569
Pastries and Puddings/ 84g	-0.5	-1.6 to 0.6	0.263
Drinks and beverages			
Tea/ 260g	-0.1	-0.3 to 0.1	0.100
Herbal tea/ 260g	0.1	-0.2 to 0.5	0.243
Coffee/ 190g	0.1	-0.1 to 0.2	0.301
Other hot beverages/ 23g	0.1	-0.4 to 0.6	0.763
Juices/ 145g	0.1	-0.3 to 0.5	0.547
Soft drinks/ 111g	-0.8	-1.6 to 0.0	0.015
Low calorie/diet soft drinks/ 161g	-0.1	-0.7 to 0.5	0.760
Wines/ 1g	0.1	-0.5 to 0.8	0.573
Beer and cider/ 1g	-0.4	-1.2 to 0.3	0.126
Port, sherry, liqueurs/ 1g	1.0	-0.5 to 2.6	0.086
Spirits/ 1g	-0.1	-1.0 to 0.7	0.673

[a] Model adjusted for the following factors: physical activity level, alcohol consumption, smoking, social class, presence of diabetes at baseline

Appendix C

Chapter 5 supplementary materials

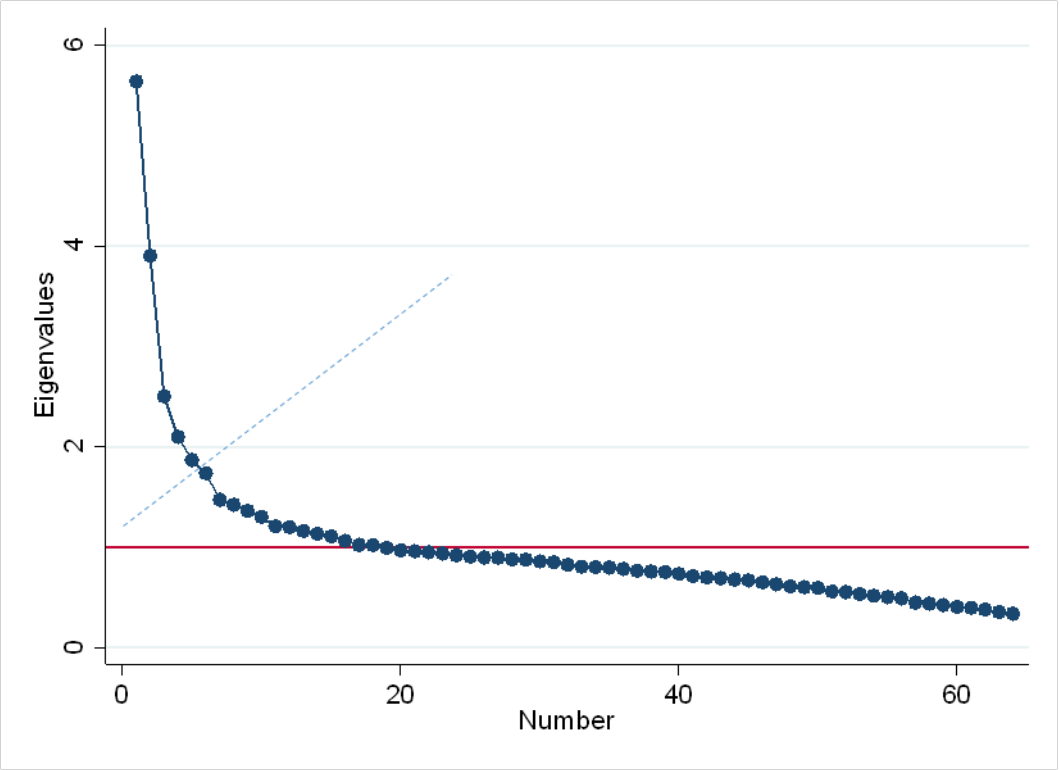


Figure C.1 Scree plot of eigenvalues after principal component analysis

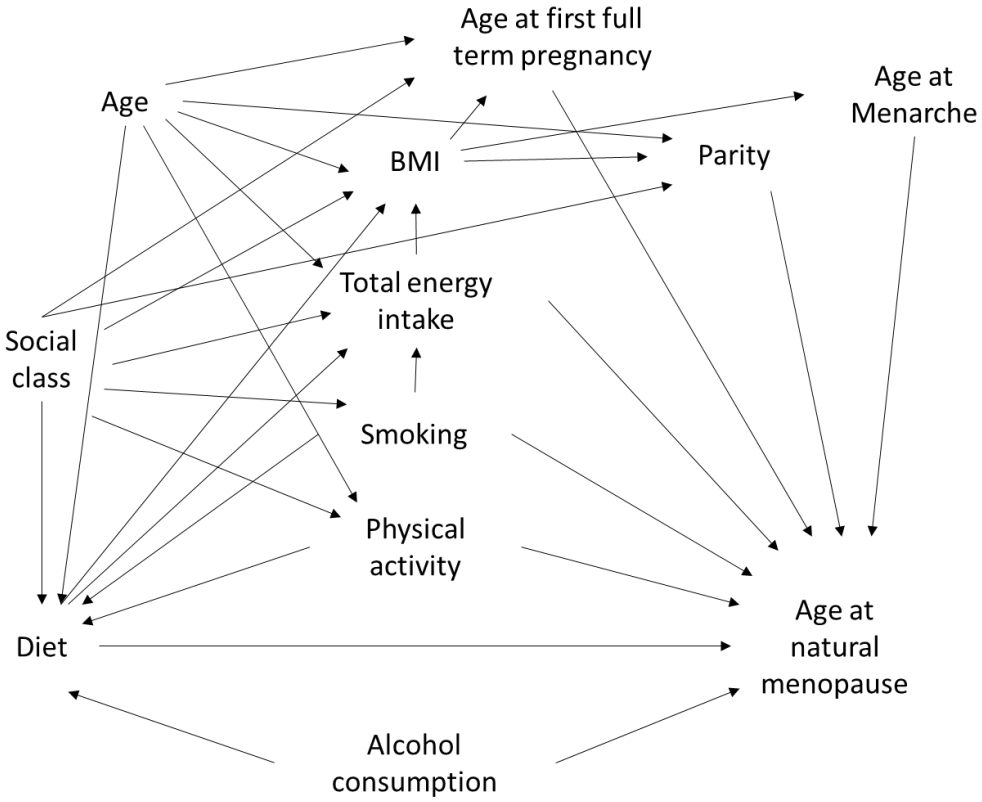


Figure C.2 Directed Acyclic Graph

Appendix D

Chapter 6 supplementary materials

Table D.1 Baseline characteristics of individual studies in the InterLACE consortium included in this study

Study	Country	Survey (year) selected for baseline	n	Age at baseline Median (Q1, Q3)	Survey (year) selected for follow-up
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	Survey 3 (2001)	7,373	52 (51, 54)	Survey 4 (2004)
Healthy Ageing of Women Study (HOW)	Australia	Survey 1 (2001)	563	54 (52, 56)	Survey 2 (2006)
Whitehall II study (WHITEHALL)	UK	Survey 3 (1991-94)	2,146	50 (45, 56)	Survey 4 (1995-96)
Seattle Midlife Women's Health Study (SMWHS)	USA	Survey in year 2000	174	50 (46, 53)	N/A
Japanese Midlife Women's Health Study (JMWHS)	Japan	Survey 1 (2002)	750	N/A*	N/A
Overall			11,006	52 (51, 54)†	

Abbreviations: N/A – not applicable; Q1 – 25th percentile; Q3 – 75th percentile

*JMWHS provided age by category only (≤55 and >55 years), and 47% of women were aged more than 55 years (age range: 45-60 years)

†Median age at baseline was based on four studies (ALSWH, HOW, WHITEHALL, SMWHS) with data on age as a continuous variable

Table D.2 Baseline characteristics of participants included and excluded for the prospective analysis

	Participants with complete data on VMS at follow-up (n=8,854)		Participants lost to follow-up (n=1,228)		
	n	**%**	**n**	**%**	***p***
Race/ethnicity					
Caucasian-Australian/New Zealand	5571	62.9	752	61.2	<0.01
Caucasian-European	2812	31.8	351	28.6	
Caucasian-American/Canadian	46	0.5	8	0.7	
Japanese	5	0.1	1	0.1	
Chinese & other Asians	112	1.3	39	3.2	
Others	308	3.5	77	6.3	
Birth year					
<1940	763	8.6	92	7.5	0.22
1940-1949	6054	68.4	865	70.7	
≥1950	2037	23.0	267	21.8	
Education level					
≤10 years	4369	49.3	656	53.4	<0.01
11-12 years	1484	16.8	222	18.1	
>12 years	3001	33.9	350	28.5	
Marital status					
Married	6917	78.3	895	73.4	<0.01
Separated/divorced/widowed	1299	14.7	246	20.2	
Single	616	7.0	78	6.4	
Body mass index					
Normal weight (<25 kg/m²)	3860	46.1	489	42.8	0.02
Overweight (25-29.9 kg/m²)	2742	32.8	374	32.8	
Obese (≥30 kg/m²)	1770	21.1	279	24.4	
Smoking status					
Never	5299	59.9	670	54.6	<0.01
Past smoker	2303	26.0	304	24.8	
Current smoker	1252	14.1	254	20.7	
Menopausal status					
Hysterectomy/oophorectomy	2183	24.7	327	26.6	<0.01
Unknown due to hormone use	1475	16.7	182	14.8	
Premenopause	996	11.3	125	10.2	
Perimenopause	1759	19.9	191	15.6	
Natural menopause	2441	27.6	403	32.8	
Current use of menopausal hormone therapy					
No	6371	72.0	854	69.5	0.08
Yes	2483	28.0	374	30.5	

Table D.2 Continued

	Participants with complete data on VMS at follow-up (n=8,854)		Participants lost to follow-up (n=1,228)		
	n	**%**	**n**	**%**	***p***
Frequency or severity of hot flushes					
Never	3407	38.5	509	41.5	<0.01
Rarely or mild	1484	16.8	247	20.1	
Sometimes or moderate	2265	25.6	268	21.8	
Often or severe	1698	19.2	204	16.6	
Frequency or severity of night sweats					
Never	4194	47.4	618	50.3	0.05
Rarely or mild	1421	16.1	211	17.2	
Sometimes or moderate	1922	21.7	234	19.1	
Often or severe	1317	14.9	165	13.4	
Frequency or severity of vasomotor symptoms[a]					
Never	3108	35.1	462	37.6	<0.01
Rarely or mild	1525	17.2	259	21.1	
Sometimes or moderate	2369	26.8	278	22.6	
Often or severe	1852	20.9	229	18.7	
Consumption frequency of soy products					
Never/rarely	8031	90.7	1081	88.0	0.01
Monthly	398	4.5	71	5.8	
Weekly	357	4.0	69	5.6	
Daily	68	0.8	7	0.6	
Consumption frequency of soy milk					
Never/rarely	8094	91.6	1103	90.5	0.01
Monthly	51	0.6	16	1.3	
Weekly	117	1.3	23	1.9	
Daily	570	6.5	77	6.3	

[a] Vasomotor menopausal symptoms were defined as having either hot flushes and/or night sweats

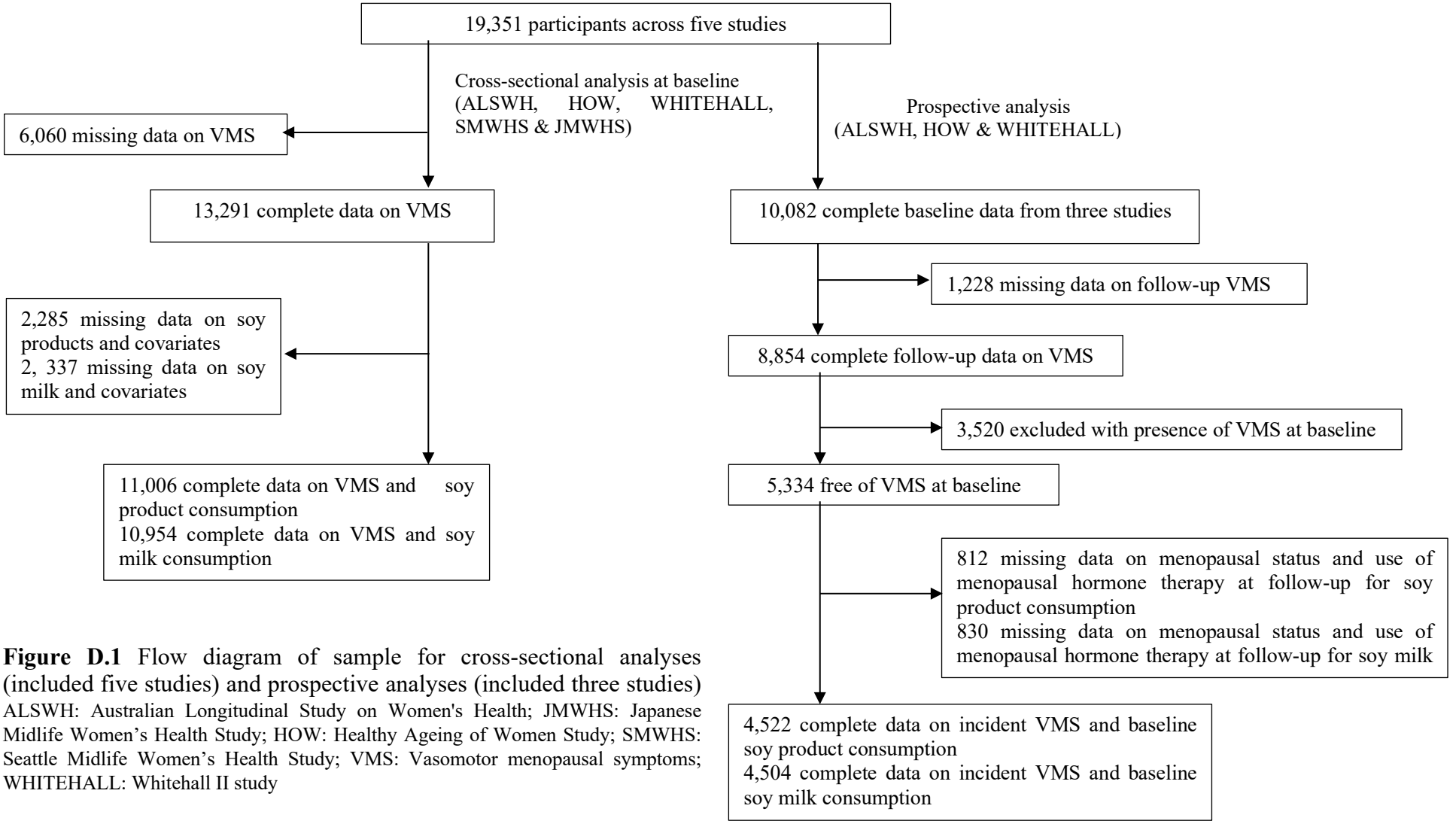


Figure D.1 Flow diagram of sample for cross-sectional analyses (included five studies) and prospective analyses (included three studies)
ALSWH: Australian Longitudinal Study on Women's Health; JMWHS: Japanese Midlife Women's Health Study; HOW: Healthy Ageing of Women Study; SMWHS: Seattle Midlife Women's Health Study; VMS: Vasomotor menopausal symptoms; WHITEHALL: Whitehall II study

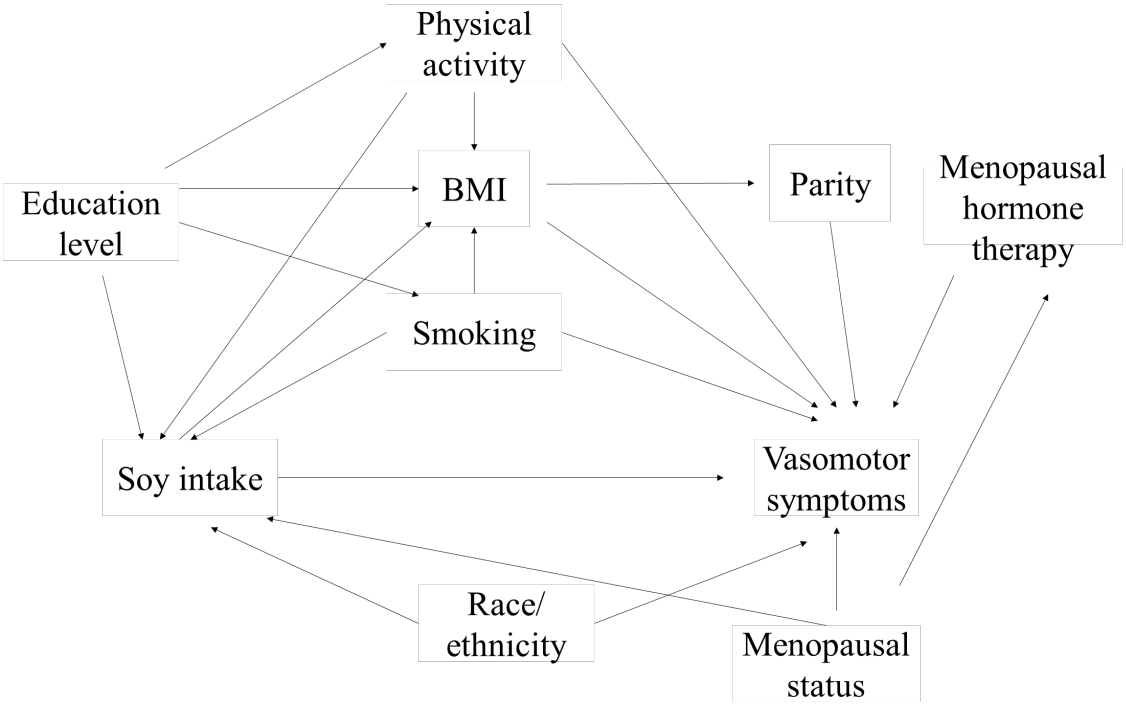


Figure D.2 Directed Acyclic Graph

Appendix E

Chapter 7 supplementary materials

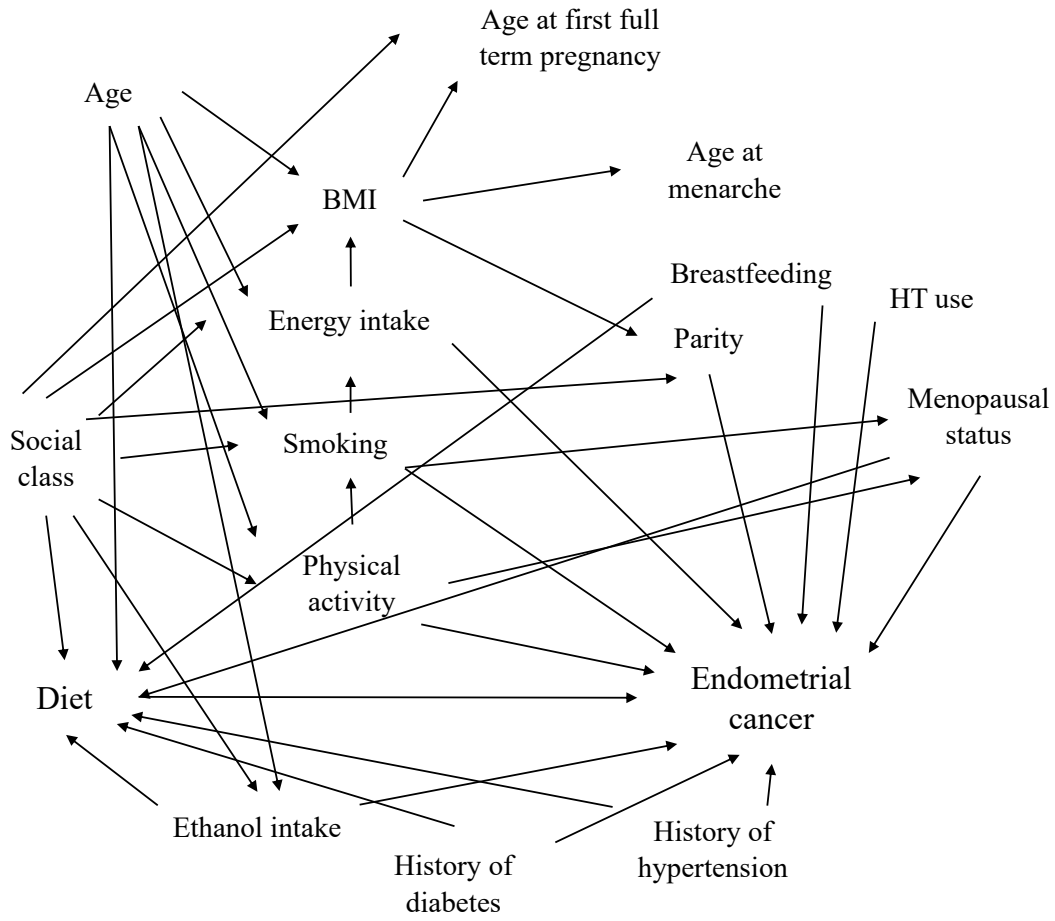


Figure E.1 Directed acyclic graph to determine potential confounders for the association between diet and the risk of endometrial cancer

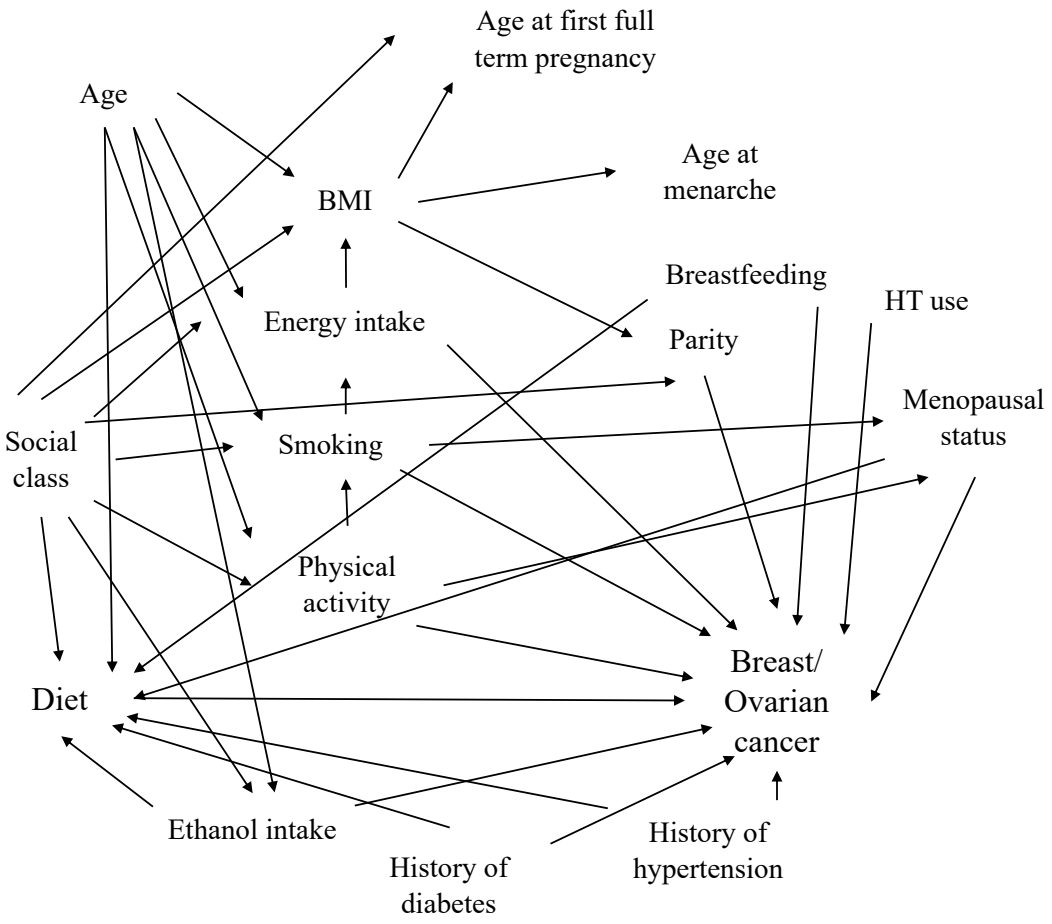


Figure E.2 Directed acyclic graph to determine potential confounders for the association between diet and the risk of breast and ovarian cancers

Table E.1 Hazard ratios for the association between diet and risk of breast, endometrial and ovarian cancer further adjusted for family history of cancer in first-degree relatives

	Breast cancer[a]		**Endometrial cancer[b]**		**Ovarian cancer[c]**	
Cancer cases	1,535/27,427		223/25,755		231/27,490	
Daily intake/ standard portion size	HR	99% CI	HR	99% CI	HR	99% CI
Starchy food sources						
Wholegrain products/ 33g	1.00	0.97 to 1.03	0.94	0.85 to 1.03	1.01	0.93 to 1.10
Refined grain products/ 51g	1.03	0.96 to 1.12	1.13	0.94 to 1.34	1.04	0.85 to 1.26
Low fibre breakfast cereals/ 40g	1.07	0.88 to 1.30	0.80	0.44 to 1.45	1.16	0.71 to 1.90
High fibre breakfast cereals/ 85g	1.00	0.91 to 1.09	0.74	0.54 to 1.01	0.85	0.64 to 1.13
Plain Potatoes/ 210g	0.95	0.82 to 1.11	0.97	0.66 to 1.43	0.80	0.52 to 1.22
Potatoes with added fat/ 127g	1.33	1.00 to 1.78	1.93	1.00 to 3.72	0.85	0.36 to 1.99
Refined pasta and rice/ 210g	0.93	0.71 to 1.23	1.07	0.53 to 2.15	0.81	0.38 to 1.73
Wholegrain pasta and rice/ 197 g	1.16	0.84 to 1.59	0.53	0.18 to 1.53	0.68	0.25 to 1.88
Protein and fat food sources						
Low fat dairy products/ 118g	1.01	0.98 to 1.04	1.02	0.96 to 1.09	0.95	0.89 to 1.02
High fat dairy products/ 93g	1.01	0.97 to 1.04	0.99	0.90 to 1.08	1.06	0.99 to 1.14
Butter and hard margarine/ 10g	0.99	0.92 to 1.06	0.99	0.82 to 1.20	0.87	0.70 to 1.07
Margarine/ 9g	0.99	0.92 to 1.06	0.92	0.76 to 1.11	1.02	0.86 to 1.21
Low fat spreads/ 7g	1.04	0.97 to 1.11	0.99	0.83 to 1.19	0.98	0.81 to 1.19
High fat dressing/ 23g	0.99	0.79 to 1.24	0.80	0.41 to 1.57	0.77	0.40 to 1.50
Low fat dressing/ 30g	1.03	0.72 to 1.48	0.93	0.35 to 2.50	0.98	0.38 to 2.47
Soybean products/ 62g	0.97	0.89 to 1.05	0.99	0.82 to 1.21	0.95	0.75 to 1.20
Textured vegetable protein/ 130g	0.14	0.01 to 3.42	-	-	-	-
Pulses/ 91g	1.03	0.89 to 1.20	0.83	0.53 to 1.30	1.15	0.80 to 1.66
Eggs/eggs dishes/ 88g	1.00	0.74 to 1.36	1.83	0.97 to 3.45	1.22	0.60 to 2.48
Fish and fish dishes/ 140g	1.01	0.67 to 1.52	0.92	0.32 to 2.63	0.63	0.20 to 2.01
Oily fish/ 90g	1.01	0.64 to 1.60	0.53	0.12 to 2.27	1.01	0.31 to 3.26
Shell fish/ 60g	1.47	0.56 to 3.86	0.86	0.05 to 14.19	0.60	0.03 to 10.73
Red meat/ 189g	1.28	0.94 to 1.74	1.88	0.88 to 3.99	0.90	0.39 to 2.08
Processed meat/ 74g	1.42	1.07 to 1.88	2.18	1.29 to 3.70	1.34	0.63 to 2.86
Poultry/ 143g	1.36	0.88 to 2.12	1.66	0.54 to 5.10	0.50	0.13 to 1.93
Offal/ 100g	2.07	0.36 to 12.0	-	-	0.16	0.00 to 25.9
Total meat/ 150g	1.18	1.00 to 1.38	1.51	1.01 to 2.24	0.92	0.60 to 1.42
Vegetables						
Vegetable dishes/ 214g	0.90	0.73 to 1.10	0.72	0.40 to 1.29	0.99	0.59 to 1.66
Allium/ 39g	0.99	0.81 to 1.20	1.00	0.60 to 1.67	0.67	0.37 to 1.23
Fresh legumes/ 75g	0.97	0.80 to 1.16	1.14	0.74 to 1.75	1.10	0.73 to 1.64
Mediterranean vegetables/ 60g	0.95	0.83 to 1.09	0.83	0.56 to 1.22	1.22	0.93 to 1.60
Salad vegetables/ 43g	0.98	0.87 to 1.10	0.85	0.60 to 1.19	0.97	0.71 to 1.31
Cruciferous vegetables/ 75g	0.99	0.91 to 1.07	0.96	0.77 to 1.19	1.03	0.86 to 1.24
Tomatoes/ 83g	0.85	0.73 to 0.99	0.79	0.52 to 1.19	0.98	0.70 to 1.37
Mushrooms/ 34g	0.97	0.77 to 1.24	1.34	0.81 to 2.19	1.60	1.09 to 2.34
Roots and tubers/ 66g	0.95	0.84 to 1.07	0.93	0.68 to 1.29	1.13	0.88 to 1.44
Total vegetables/150g	0.97	0.91 to 1.02	0.94	0.81 to 1.10	1.04	0.92 to 1.19
Fruits						
Stone fruits/ 49g	1.03	0.86 to 1.24	0.98	0.57 to 1.68	0.65	0.31 to 1.37
Deep orange & yellow fruits/ 118g	1.11	0.95 to 1.30	0.80	0.45 to 1.42	0.93	0.56 to 1.54
Grapes/ 100g	0.97	0.85 to 1.12	0.89	0.59 to 1.34	0.93	0.63 to 1.36

Table E.1 Continued

	Breast cancer[a]		Endometrial cancer[b]		Ovarian cancer[c]	
Cancer cases	1,535/27,427		223/25,755		231/27,490	
Daily intake/ standard portion size	HR	99% CI	HR	99% CI	HR	99% CI
Citrus family fruits/ 92g	1.03	0.92 to 1.15	0.76	0.53 to 1.11	0.87	0.62 to 1.21
Rhubarb/ 130g	0.92	0.69 to 1.23	0.67	0.25 to 1.79	1.07	0.57 to 2.02
Berries/ 48g	1.03	0.93 to 1.13	0.86	0.61 to 1.23	0.84	0.59 to 1.20
Bananas/ 100g	1.08	0.96 to 1.21	0.84	0.60 to 1.19	1.17	0.87 to 1.56
Pomes/ 116g	0.98	0.91 to 1.06	0.90	0.72 to 1.13	0.94	0.76 to 1.17
Total fruits/150g	1.01	0.97 to 1.06	0.89	0.77 to 1.02	0.97	0.86 to 1.10
Dried Fruits/ 28g	1.05	0.97 to 1.14	0.58	0.35 to 0.97	1.05	0.87 to 1.27
Other food groups						
Sauces/ 83g	1.09	0.62 to 1.92	1.22	0.28 to 5.35	1.48	0.36 to 6.13
Pickles/Chutneys/ 35g	0.91	0.68 to 1.20	0.93	0.45 to 1.91	0.71	0.32 to 1.60
Soups/ 163g	1.00	0.80 to 1.25	0.86	0.46 to 1.59	1.00	0.59 to 1.73
Confectionary & spreads/ 44g	0.98	0.92 to 1.06	0.90	0.73 to 1.11	0.95	0.78 to 1.15
Nuts and seeds/ 24g	1.04	0.94 to 1.14	0.79	0.54 to 1.16	1.05	0.83 to 1.33
Savoury snacks/ 26g	1.07	0.87 to 1.31	1.17	0.70 to 1.94	1.06	0.61 to 1.84
Biscuits/ 15g	1.00	0.93 to 1.07	0.99	0.83 to 1.19	0.92	0.75 to 1.13
Cakes/ 66g	0.86	0.63 to 1.17	0.81	0.35 to 1.87	0.97	0.47 to 1.98
Pastries and Puddings/ 84g	1.14	0.94 to 1.39	1.01	0.57 to 1.77	0.75	0.39 to 1.44
Drinks and beverages						
Tea/ 260g	0.98	0.95 to 1.02	1.02	0.94 to 1.12	0.99	0.91 to 1.09
Herbal tea/ 260g	0.99	0.92 to 1.07	0.86	0.67 to 1.10	0.96	0.77 to 1.19
Coffee/ 190g	1.01	0.97 to 1.05	1.02	0.93 to 1.12	1.03	0.94 to 1.13
Other hot beverages/ 23g	1.02	0.92 to 1.14	1.06	0.81 to 1.38	1.05	0.81 to 1.37
Juices/ 145g	1.01	0.93 to 1.09	0.97	0.78 to 1.20	0.96	0.78 to 1.19
Soft drinks/ 111g	1.00	0.89 to 1.12	1.02	0.77 to 1.37	1.04	0.80 to 1.36
Low calorie/diet soft drinks/ 161g	1.02	0.91 to 1.13	1.03	0.78 to 1.36	0.97	0.71 to 1.31
Wines/ glass[*]	1.03	0.94 to 1.13	0.93	0.71 to 1.22	1.04	0.83 to 1.32
Beer and cider/ half pint[*]	1.11	0.95 to 1.31	0.87	0.47 to 1.63	1.13	0.74 to 1.72
Port, sherry, liqueurs/ glass[*]	0.99	0.75 to 1.31	1.14	0.58 to 2.23	1.22	0.75 to 1.99
Spirits/ measure[*]	1.10	0.95 to 1.28	0.55	0.26 to 1.16	1.23	0.91 to 1.65

[a] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, family history of any cancer and family history of breast cancer; a Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, diabetes, hypertension, and family history of endometrial cancer; a Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, family history of breast cancer and family history of ovarian cancer; [*] not adjusted for ethanol intake

Table E.2 Hazard ratios for the association between diet and risk of breast, endometrial and ovarian cancer further adjusted for total energy intake and reproductive factors

	Breast cancer cases				Endometrial cancer cases				Ovarian cancer cases			
Daily intake/	n=1796/32,228[a]		n=1625/29,183[b]		n=238/27,335[c]		n=86/9,227[d]		n=251/29,226[a]		n=251/29,229[b]	
standard portion size	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Starchy food sources												
Wholegrain products/ 33g	0.99	0.96 to 1.02	0.95	0.90 to 1.01	0.93	0.84 to 1.03	0.94	0.80 to 1.11	1.01	0.93 to 1.11	1.01	0.88 to 1.15
Refined grain products/ 51g	1.02	0.95 to 1.11	1.03	0.91 to 1.17	1.19	1.01 to 1.41	1.16	0.84 to 1.59	1.04	0.85 to 1.27	1.02	0.75 to 1.39
Low fibre breakfast cereals/ 40g	1.03	0.84 to 1.25	0.92	0.66 to 1.29	0.80	0.45 to 1.44	0.80	0.30 to 2.14	1.11	0.68 to 1.80	1.02	0.48 to 2.14
High fibre breakfast cereals/ 85g	1.00	0.91 to 1.10	1.05	0.93 to 1.18	0.76	0.56 to 1.04	0.91	0.59 to 1.41	0.90	0.69 to 1.18	0.99	0.71 to 1.38
Plain Potatoes/ 210g	0.92	0.79 to 1.08	0.95	0.75 to 1.20	1.03	0.69 to 1.53	1.15	0.65 to 2.06	0.85	0.56 to 1.29	0.98	0.56 to 1.71
Potatoes with added fat/ 127g	1.27	0.95 to 1.72	1.18	0.73 to 1.90	2.21	1.16 to 4.20	2.27	0.89 to 5.80	0.84	0.36 to 1.98	0.67	0.17 to 2.64
Refined pasta and rice/ 210g	0.92	0.70 to 1.20	1.08	0.72 to 1.64	1.18	0.61 to 2.31	0.56	0.13 to 2.42	0.76	0.35 to 1.64	0.95	0.31 to 2.92
Wholegrain pasta and rice/ 197 g	1.13	0.82 to 1.55	1.15	0.70 to 1.92	0.66	0.25 to 1.79	0.78	0.16 to 3.92	0.73	0.28 to 1.93	0.75	0.17 to 3.21
Protein and fat food sources												
Low fat dairy products/ 118g	1.01	0.98 to 1.03	0.99	0.95 to 1.03	1.05	0.98 to 1.12	1.05	0.94 to 1.17	0.96	0.89 to 1.02	0.92	0.83 to 1.02
High fat dairy products/ 93g	1.00	0.97 to 1.04	1.01	0.96 to 1.07	0.99	0.91 to 1.09	1.00	0.86 to 1.16	1.07	1.00 to 1.14	1.09	0.98 to 1.21
Butter and hard margarine/ 10g	0.98	0.91 to 1.05	0.96	0.85 to 1.08	1.03	0.85 to 1.24	1.11	0.83 to 1.49	0.87	0.70 to 1.07	0.83	0.59 to 1.16
Margarine/ 9g	0.98	0.92 to 1.05	0.96	0.85 to 1.07	0.95	0.79 to 1.15	0.98	0.71 to 1.35	1.05	0.89 to 1.24	1.06	0.82 to 1.38
Low fat spreads/ 7g	1.02	0.96 to 1.09	0.99	0.88 to 1.10	0.99	0.82 to 1.19	0.94	0.67 to 1.31	0.95	0.79 to 1.16	0.96	0.72 to 1.29
High fat dressing/ 23g	0.96	0.77 to 1.21	1.00	0.69 to 1.45	0.84	0.43 to 1.65	0.53	0.14 to 2.04	0.74	0.38 to 1.44	0.95	0.37 to 2.44
Low fat dressing/ 30g	1.01	0.71 to 1.44	0.60	0.31 to 1.16	0.92	0.34 to 2.46	0.48	0.07 to 3.38	1.12	0.48 to 2.63	0.94	0.23 to 3.86
Soybean products/ 62g	0.97	0.90 to 1.05	0.98	0.85 to 1.14	0.98	0.81 to 1.19	1.04	0.75 to 1.45	0.93	0.73 to 1.19	0.90	0.56 to 1.45
Textured vegetable protein/ 130g	0.14	0.01 to 3.19	0.02	0.00 to 8.20	0.00	0.00 to 45.3	-	-	-	-	-	-
Pulses/ 91g	1.02	0.87 to 1.18	1.11	0.87 to 1.41	0.87	0.55 to 1.36	1.06	0.52 to 2.17	1.23	0.86 to 1.75	1.72	1.07 to 2.77
Eggs/eggs dishes/ 88g	0.95	0.69 to 1.30	1.27	0.82 to 1.98	2.00	1.08 to 3.69	2.17	0.86 to 5.43	1.34	0.67 to 2.69	1.28	0.46 to 3.60
Fish and fish dishes/ 140g	0.99	0.65 to 1.49	1.07	0.55 to 2.08	1.13	0.41 to 3.16	0.73	0.10 to 5.18	0.92	0.32 to 2.67	2.64	0.73 to 9.57
Oily fish/ 90g	0.97	0.61 to 1.53	1.18	0.66 to 2.11	0.59	0.14 to 2.42	0.77	0.09 to 6.37	1.11	0.38 to 3.24	1.09	0.26 to 4.57
Shell fish/ 60g	1.41	0.55 to 3.64	1.42	0.34 to 5.97	0.85	0.05 to 13.9	0.11	0.00 to 40.4	0.71	0.05 to 10.95	0.63	0.01 to 34.0
Red meat/ 189g	1.27	0.93 to 1.73	1.22	0.76 to 1.97	2.28	1.07 to 4.87	2.00	0.56 to 7.12	0.90	0.39 to 2.07	1.21	0.38 to 3.86
Processed meat/ 74g	1.36	1.01 to 1.82	1.45	0.87 to 2.43	2.47	1.53 to 3.98	5.01	1.50 to 16.7	1.37	0.64 to 2.93	1.42	0.40 to 5.10

Table E.2 Continued

Daily intake/ standard portion size	Breast cancer cases				Endometrial cancer cases				Ovarian cancer cases			
	n=1796/32,228[a]		n=1625/29,183[b]		n=238/27,335[c]		n=86/9,227[d]		n=251/29,226[a]		n=251/29,229[b]	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Poultry/ 143g	1.30	0.84 to 2.02	1.07	0.53 to 2.16	2.04	0.69 to 6.02	0.73	0.09 to 6.13	0.66	0.18 to 2.37	0.35	0.04 to 2.77
Offal/ 100g	2.18	0.39 to 12.2	2.79	0.22 to 35.2	-	-	-	-	0.08	0.00 to 14.05	-	-
Total meat/ 150g	1.17	1.00 to 1.37	1.14	0.88 to 1.47	1.74	1.16 to 2.62	1.57	0.77 to 3.20	0.95	0.61 to 1.46	0.98	0.51 to 1.88
Vegetables												
Vegetable dishes/ 214g	0.89	0.73 to 1.09	0.86	0.62 to 1.19	0.72	0.40 to 1.31	0.77	0.28 to 2.07	1.08	0.66 to 1.78	0.82	0.35 to 1.91
Allium/ 39g	0.98	0.81 to 1.20	0.95	0.69 to 1.31	1.04	0.62 to 1.72	0.86	0.34 to 2.17	0.78	0.45 to 1.37	0.87	0.39 to 1.92
Fresh legumes/ 75g	0.94	0.78 to 1.14	0.87	0.64 to 1.19	1.23	0.82 to 1.85	1.04	0.48 to 2.28	1.12	0.75 to 1.67	1.52	1.02 to 2.24
Mediterranean vegetables/ 60g	0.95	0.83 to 1.09	1.00	0.81 to 1.24	0.89	0.61 to 1.31	0.79	0.39 to 1.57	1.23	0.92 to 1.63	1.12	0.68 to 1.86
Salad vegetables/ 43g	0.96	0.86 to 1.08	0.93	0.76 to 1.13	0.88	0.63 to 1.24	0.83	0.46 to 1.48	1.01	0.75 to 1.36	1.22	0.82 to 1.82
Cruciferous vegetables/ 75g	0.98	0.91 to 1.06	1.01	0.90 to 1.14	0.97	0.78 to 1.20	0.93	0.65 to 1.34	1.06	0.89 to 1.26	1.16	0.92 to 1.46
Tomatoes/ 83g	0.86	0.74 to 0.99	0.86	0.69 to 1.08	0.81	0.54 to 1.21	0.63	0.30 to 1.34	0.99	0.71 to 1.38	1.05	0.65 to 1.68
Mushrooms/ 34g	0.95	0.75 to 1.21	0.98	0.68 to 1.42	1.39	0.86 to 2.25	1.29	0.54 to 3.08	1.62	1.13 to 2.32	1.66	0.99 to 2.79
Roots and tubers/ 66g	0.93	0.82 to 1.05	0.88	0.72 to 1.09	0.96	0.69 to 1.32	1.09	0.72 to 1.66	1.15	0.91 to 1.47	1.30	1.06 to 1.59
Total vegetables/150g	0.95	0.90 to 1.01	0.96	0.87 to 1.05	0.96	0.81 to 1.13	0.93	0.70 to 1.23	1.07	0.94 to 1.22	1.14	0.97 to 1.34
Fruits												
Stone fruits/ 49g	1.02	0.85 to 1.23	1.02	0.75 to 1.40	1.00	0.59 to 1.70	1.30	0.61 to 2.74	0.67	0.33 to 1.37	0.57	0.18 to 1.74
Deep orange & yellow fruits/ 118g	1.07	0.92 to 1.26	1.07	0.83 to 1.37	0.79	0.45 to 1.40	0.97	0.43 to 2.19	1.00	0.64 to 1.59	0.85	0.39 to 1.84
Grapes/ 100g	0.95	0.83 to 1.10	0.96	0.77 to 1.19	0.96	0.64 to 1.39	0.67	0.28 to 1.64	0.93	0.63 to 1.35	0.73	0.35 to 1.50
Citrus family fruits/ 92g	1.02	0.91 to 1.14	0.97	0.81 to 1.17	0.79	0.55 to 1.13	0.94	0.56 to 1.60	0.89	0.65 to 1.23	0.84	0.50 to 1.40
Rhubarb/ 130g	0.92	0.69 to 1.23	0.87	0.54 to 1.40	0.82	0.34 to 1.99	0.76	0.17 to 3.49	1.11	0.60 to 2.05	0.95	0.31 to 2.88
Berries/ 48g	1.03	0.94 to 1.13	1.00	0.85 to 1.18	0.88	0.62 to 1.25	0.78	0.40 to 1.52	0.83	0.58 to 1.19	0.78	0.44 to 1.39
Bananas/ 100g	1.06	0.95 to 1.19	0.99	0.82 to 1.21	0.92	0.66 to 1.28	0.84	0.47 to 1.52	1.25	0.95 to 1.64	1.39	0.95 to 2.02
Pomes/ 116g	0.97	0.90 to 1.06	0.97	0.85 to 1.10	0.95	0.76 to 1.17	0.83	0.55 to 1.25	0.98	0.80 to 1.21	0.98	0.71 to 1.35
Total fruits/150g	1.01	0.96 to 1.05	0.99	0.92 to 1.07	0.92	0.80 to 1.05	0.88	0.69 to 1.13	1.00	0.88 to 1.12	0.97	0.80 to 1.17
Dried Fruits/ 28g	1.05	0.96 to 1.13	1.11	0.98 to 1.26	0.62	0.39 to 1.01	0.78	0.40 to 1.49	1.07	0.90 to 1.28	0.97	0.65 to 1.46
Other food groups												
Sauces/ 83g	1.04	0.59 to 1.84	1.81	0.79 to 4.16	1.65	0.39 to 6.97	0.79	0.05 to 12.8	2.03	0.53 to 7.77	6.23	1.33 to 29.2

Table E.2 Continued

Daily intake/ standard portion size	Breast cancer cases				Endometrial cancer cases				Ovarian cancer cases			
	n=1796/32,228[a]		n=1625/29,183[b]		n=238/27,335[c]		n=86/9,227[d]		n=251/29,226[a]		n=251/29,229[b]	
	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
Pickles/Chutneys/ 35g	0.87	0.65 to 1.16	0.85	0.52 to 1.40	1.09	0.55 to 2.17	0.70	0.16 to 3.15	0.67	0.30 to 1.53	0.73	0.20 to 2.60
Soups/ 163g	0.97	0.78 to 1.21	0.98	0.71 to 1.36	0.98	0.54 to 1.76	1.11	0.49 to 2.53	1.07	0.64 to 1.78	0.89	0.39 to 2.00
Confectionary & spreads/ 44g	0.97	0.90 to 1.05	0.98	0.87 to 1.12	0.92	0.73 to 1.16	0.94	0.63 to 1.39	0.99	0.81 to 1.20	0.83	0.58 to 1.21
Nuts and seeds/ 24g	1.03	0.93 to 1.13	1.02	0.86 to 1.21	0.81	0.55 to 1.19	0.89	0.48 to 1.66	1.05	0.82 to 1.34	1.10	0.77 to 1.58
Savoury snacks/ 26g	1.05	0.85 to 1.29	1.06	0.74 to 1.51	1.23	0.74 to 2.04	1.18	0.44 to 3.18	1.11	0.65 to 1.90	0.97	0.39 to 2.46
Biscuits/ 15g	1.00	0.94 to 1.08	1.04	0.93 to 1.16	1.02	0.84 to 1.23	1.16	0.89 to 1.53	0.97	0.80 to 1.18	0.99	0.75 to 1.32
Cakes/ 66g	0.84	0.61 to 1.16	1.03	0.64 to 1.66	1.00	0.44 to 2.28	1.34	0.43 to 4.14	1.03	0.50 to 2.14	0.95	0.30 to 3.02
Pastries and Puddings/ 84g	1.12	0.90 to 1.38	1.27	0.90 to 1.80	1.18	0.67 to 2.11	1.21	0.43 to 3.39	0.73	0.37 to 1.44	0.78	0.28 to 2.18
Tea/ 260g	0.98	0.95 to 1.01	1.01	0.96 to 1.07	1.02	0.94 to 1.12	0.99	0.86 to 1.14	0.99	0.91 to 1.07	0.98	0.86 to 1.11
Herbal tea/ 260g	0.98	0.91 to 1.06	0.97	0.86 to 1.11	0.90	0.72 to 1.12	0.80	0.51 to 1.26	0.94	0.75 to 1.16	0.92	0.65 to 1.30
Coffee/ 190g	1.01	0.97 to 1.04	1.00	0.94 to 1.05	1.03	0.95 to 1.13	1.05	0.90 to 1.21	1.04	0.96 to 1.14	1.02	0.90 to 1.17
Other hot beverages/ 23g	1.03	0.93 to 1.14	0.96	0.80 to 1.14	1.04	0.79 to 1.36	1.00	0.62 to 1.61	1.05	0.81 to 1.37	1.02	0.68 to 1.52
Juices/ 145g	1.00	0.93 to 1.08	0.94	0.83 to 1.08	0.98	0.78 to 1.21	0.89	0.60 to 1.33	0.98	0.80 to 1.20	0.94	0.68 to 1.31
Soft drinks/ 111g	1.00	0.89 to 1.12	1.00	0.84 to 1.19	1.03	0.77 to 1.37	0.76	0.36 to 1.60	1.03	0.79 to 1.35	1.07	0.74 to 1.54
Low calorie/diet soft drinks/ 161g	1.03	0.93 to 1.14	1.03	0.88 to 1.21	1.04	0.79 to 1.36	1.00	0.60 to 1.66	0.98	0.73 to 1.31	1.01	0.65 to 1.56
Wines/ glass*	0.95	0.83 to 1.09	1.06	0.92 to 1.21	0.90	0.69 to 1.17	0.83	0.51 to 1.34	1.06	0.85 to 1.32	1.10	0.80 to 1.50
Beer and cider/ half pint*	1.04	0.87 to 1.25	1.13	0.85 to 1.51	0.83	0.44 to 1.60	1.34	0.67 to 2.71	1.12	0.73 to 1.71	1.11	0.53 to 2.31
Port, sherry, liqueurs/ glass*	0.92	0.69 to 1.23	1.09	0.76 to 1.54	1.14	0.59 to 2.20	1.02	0.33 to 3.16	1.21	0.75 to 1.96	0.74	0.23 to 2.43
Spirits/ measure*	1.06	0.90 to 1.24	1.18	0.98 to 1.43	0.54	0.26 to 1.13	0.57	0.19 to 1.73	1.26	0.96 to 1.65	1.24	0.85 to 1.82

[a] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status and total energy intake (excluding participants with a total energy intake below 500 kcal and above 6000 kcal); [b] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, total energy intake, current use of HRT, oral contraceptive use, and parity; [c] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes, history of hypertension, and total energy intake (excluding participants with a total energy intake below 500 kcal and above 6000 kcal); [d] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes, history of hypertension, total energy intake, current use of HRT, oral contraceptive use, and parity; * not adjusted for ethanol intake

Table E.3 Hazard ratios for the association between age at natural menopause and risk of breast, endometrial and ovarian cancer

	Breast cancer				Endometrial cancer				Ovarian cancer			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age at natural menopause†	1.04	1.03 to 1.06	1.03	1.01 to 1.06	1.15	1.11 to 1.19	1.15	1.09 to 1.22	1.08	1.04 to 1.13	1.09	1.02 to 1.16

*Model adjusted for age, BMI, physical activity, smoking, ethanol intake, total energy intake, social class, parity, age at menarche, and age at first full term pregnancy

† Excluded women who had a hysterectomy or bilateral oophorectomy, those who reported current or ever use of HRT prior to their last period as well as women who had their last period before the age of 40 years and after 65 years

Table E.4 Subgroup analysis by age at last natural menopause for the association between diet and risk of breast, endometrial and ovarian cancer

		Age at last natural menopause*				
		40-49 years		50-65 years		
Daily intake/ standard portion size	**Breast cancer[a]**	HR	99% CI	HR	99% CI	Overall *P-value*[†]
Tomatoes/ 83g	766/14,058	0.96	0.75 to 1.24	0.82	0.59 to 1.15	0.327
Processed meat/ 74g	716/13,239	1.31	0.72 to 2.40	1.56	0.77 to 3.14	0.632
Total meat/ 150g	766/14,058	1.06	0.79 to 1.42	1.37	0.97 to 1.94	0.135
	Endometrial cancer[b]					
Dried Fruits/ 28g	134/14,083	0.50	0.16 to 1.52	0.52	0.21 to 1.27	0.938
Processed meat/ 74g	134/13,262	2.79	0.70 to 11.1	3.16	0.91 to 11.0	0.859
Total meat/ 150g	134/14,083	2.12	1.09 to 4.12	1.41	0.69 to 2.88	0.276
	Ovarian cancer[a]					
Mushrooms/ 34g	112/14,081	1.98	1.03 to 3.85	1.85	0.99 to 3.45	0.834

[a] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status; [b] Model adjusted for age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status, history of diabetes and history of hypertension; [*] Excluded women who had a hysterectomy or bilateral oophorectomy, those who reported current or ever use of HRT prior to their last period as well as women who had their last period before the age of 40 years and after 65 years; [†] *P-value* for the difference between the two age group

Appendix F

Chapter 8 supplementary materials

Protocol & log file to import death and cancer registry data to the cohort Access database

Template document, red areas mark where document should be filled in.

Date data received/ data period: [_____]

Note: there are a couple of duplicate ids :

36145 and 22248 (same name, address , NHS number and dob)

36215 and 24855 (same name, address and dob (NHS number fields blank))

(The ones to keep are 22248 (has a cancer incident) and 24855 (has a 4 day diary)).

If a cancer or mortality incident occurs for 36145 or 36215 then they should be recorded against their duplicate. 36145 and 36215 have been put in a duplicate table 'COHORT – duplicates'. There are others in this table, but shouldn't be an issue since they don't have any completed questionnaires/diary data.

*** ensure all ICD codes are input with capital letters (the Stata script used in the survival calcs will not pick them up otherwise) ***

1) **Open database**

Use database: S:\Faculty-of-Medicine-and-Health\Research-Projects\UK womens cohort study\UKWCS\Access database\Cohort97_new.mdb

Press [Database window] to open table and query list

2) **Check MR511 files (English and Welsh):**
   a. Save csv files as xls files.
   b. Remove 'Cancelled cancer' (usually indicated in column H) entries out of 'cancer and deaths' and create a separate file of cancelled cancers.
   c. Delete deaths out of 'cancer and deaths'.xls file.
   d. Add in headings for both cancer and death files and cancelled cancers from 'cen data\ MR511 headings.xlsx'. Headings are based on document : MRIS File Formats 01Dec2011.pdf.
   e. In both cancer and death files, ensure event date is in format dd/mm/yyyy (ensures when Access table created the field is created as a date field). Can use formula: =MID(E2,7,2)&"/"&MID(E2,5,2)&"/"&MID(E2,1,4)
   f. check in excel 'MR number' is populated and numeric

g. Inspect for cancer type being blank – it will fail to import. (set it to say 0, then import and when on cancer table set back to blank. (Next time this happens need to see why it fails to import))

3) IMPORT DATA (English and Welsh):

a. Open [frmUpdateDeathsCancer]
b. Click 'Import Excel data from ONS'
c. Select the file MR511*date*.xls (from cen data folder) [import deaths first (more columns)]. Process deaths to step j) below, then repeat from this step, but *append* cancers.
d. Ensure header row selected [NEXT], select no primary key, [NEXT]...
e. Import to table: call the file same name as from cen data MR511_*MM_YYYY*
f. [Finish] The English death and cancer info is now in a table you just created called MR511_*MM_YYYY.* Check for import errors.
g. Change format of 'Event date' to Date/Time with a format of 'short date'.
h. Open your new file MR511date to check import numbers

Type of data	Number of rows from original check of excel file	Number of rows in this imported file	Notes if numbers don't match up- explain discrepancy	Your name	Date of action
Deaths					
Misc deaths					
Cancers					

i. Check your new file for duplicate records (a single record for each occurrence of) :-

Member Number (MR Member Number)
Death or Cancer (Ev Type)
Cancer Date (Event date)
Cancer Site (Registration Number or Cancer Site)
Cancer Type (Entry number or Cancer type)
Cancerfields (Cancerfields)

Type of data	Number duplicates	IDs	Duplicate data deleted from import file?	Number to import after removal of dups/ errors	Your name	Date of action
Deaths						
Cancers						

4) UPDATE DATA (English and Welsh):

a. Open the 'Cancer Details' table and 'Death_flagging' table. Record the row count in both,

'Cancer Details' : [_____]

'Death_flagging' : [_____]

b. Open [frmUpdateDeathsCancer]
c. Select the table you just imported and checked, which is free of any duplicates
d. Click 'update cancer information' *(note #of records appending to check they all imported-fill in below table 3)*
e. Click 'update death information' *(note how many records it will append-fill in below table 3)*
f. Click 'update multiple underlying causes' (click ok to the many messages that pop up)
g. The deaths go to 'death_flagging' table. Open this table up, sort by date added. Check: are the new ones there –are all the important fields occupied in the same way as the records previously added? fill in below table 3
h. Cancers go to 'cancer details' table. Open table, check has import worked? Fill in table 3

Table 3: Check that the numbers imported match expected

	Number expected to import from table above	Number the append said would be added	Notes to explain any missing	Look in death_ flagging table for # added in this period	Look in cancer details table for # added in this period	Notes to explain any missing	Your name & date
Death					/		
Cancer				/			

5) **Scottish** registry **deaths** (paper format)
    a. Open up COHORT table to identify participant ID number using date of birth and name.
    Paper format:
        Update word document of Scottish deaths with Case numbers (highlighted to stand out).
    Excel format:
        Combine all Scottish Excel death files into one Excel file

        Add in headings from 'cen data\ MR511 headings.xlsx'.
        Create a new column and update with Case numbers.
        Process as below, but using column heading to identify correct ICD codes
    b. Open 'death_flagging_form'
    c. Press 'add new record' :
        i. Type **Case number** into 'Subject ID' and fill in **date of death**. Then select 'pending pencil' icon so that the record is updated and the name and DOB appear. Ensure name and DOB match the certificate [if ICD codes appear already check if this certificate is just a duplicate]
        ii. Select yourself from the **enter id** dropdown list on the left and check ICD version says 10
        iii. Fill in **NHS number** (found at the bottom of the form) if this is absent in our records (new format is a 9 digit all numerical code, old format includes letters and numbers)
        iv. ICD10 code for underlying cause (often in bold) must be entered into 'original underlying cause' blue box
        v. If nothing is listed as a secondary underlying cause (II) then copy all remaining ICD10 cause of death codes into the green box, remembering to enter numbers 1, 2, 3, 4, etc into the first column of this green table for each code you enter
        vi. If there are conditions under primary and secondary underlying causes (I(a, b, c, d) and II) then use the ICD10 code book (or http://apps.who.int/classifications/icd10/browse/2010/en#/C80 - if 4 digits may need to insert a full stop before last digit) to identify those that are secondary and these must be entered into the red box, put the rest into the green. Again, remember to manually add numbers in the first column for each ICD code you enter.
        vii. Note that the primary original code (often in bold) may also appear as a primary underlying cause-it is ok to enter this twice if that is how it is presented on the form.

viii. Enter location of file containing death certificate info in the field : 'Death certificate doc'.

Death certificates entered?	Your name	Date	Notes- were any duplicates found?

6) *Fixing secondary underlying cause ICD codes for deaths & multiples* (English and Welsh)

*[*During the automated import, the secondary codes cannot be separated from multiple underlying cause codes (the ICD codes come mixed and the description for the secondary code is free text). You must view the text in the secondary field and column to the right from the excel doc and identify the correct ICD codes to match to this]:

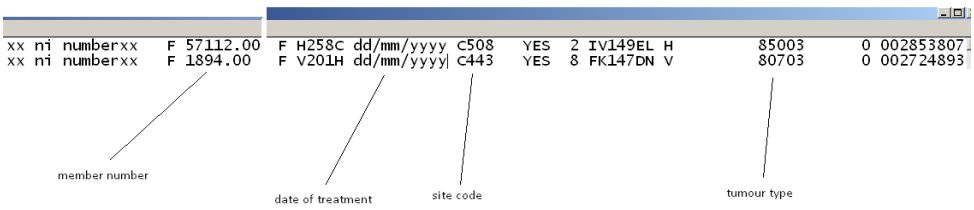
a. Open the excel file of English and Welsh deaths. Copy the data onto a new tab and cut out the cancer data and all records where there is no text in the columns labelled Cause of Death text II and the one to the right of this. So you just have the data for the IDs where there is some text in these columns.
b. Open 'death_flagging_form': On this form the ICD10 codes from the multiples list are matched to their proper description at the bottom of the form. Note that the codes with three characters don't appear in the grey box at the bottom-use the ICD10 codebook to look these up.
c. Using the free text descriptions from the excel doc identify those multiple codes to move into the red box-as they actually relate to secondary underlying causes and not multiples. Add them to the red box, remembering to number the lines 1, 2, 3 etc and then cut the lines from the green box.

	Your name	Date
Secondary underlying codes sorted out?		

7) **Scottish** registry **cancers** (paper format)/electronic

<u>New format text files</u>

a. Open the text files in notepad.
b. Merge into one text document (one line may have more than one entry – these need separating onto separate line)
c. Replace tabs with a single space, then make align by inserting further spaces



d. Paste the information into Excel (use fixed length delimiting) – Excel allows you to pick where the field delimiters are.
e. In Excel format the information so that it matches the layout on the 'Cancer details' table.
f. Check that the UKWCS id provided in the files matches to the correct woman using the COHORT table .
g. Open the 'Cancer Details' table in the Cohort97New database
h. Check that the new cancer does not already exist (ID, Cancer site, cancer data and cancer type all match)
i. If the Cancer Type is blank, use the literal 'unknown'
j. On a new line, populate the ID, Cancer site, cancer date and cancer type field with the new cancer details (by pasting from Excel)
k. Add a note to include the month of the Scottish Cancer update provided and that this was manually added and by whom. E.g. Dec 2009 Scottish cancer manually added MM

<u>Old format text files</u>

a. Print the cancer records
b. Some of the women in these files will need to be matched to obtain their ID number, using the COHORT table from COHORTtbl database.
c. Check that the new cancer does not already exist (ID, Cancer site, cancer date and cancer type all match)
d. On a new line, populate the ID, Cancer site, cancer data and cancer type field with the new cancer details.
e. Add a note to include the month of the Scottish Cancer update provided and that this was manually added and by whom. E.g. Dec 2009_Scottish cancer_Manually added MM

8) **Cancelled cancers**:

a. Note : if receive a cancelled cancer before we receive the cancer notification, still put the cancelled details on the 'Cancer details' table in Access (that way we will not later add in the cancer when we receive it and miss out the fact it has been cancelled).

b. Open the new cancelled cancer file.
c. Copy the cancelled cancers into the Cancelled cancers tab in the log file :
<N:\Faculty-of-Medicine-and-Health\LIGHT\Nutr-Epi\FOOD\COHORT\cen data\LOG FILE Death and cancer import to access.xlsx>
d. Open the 'Cancer details' table in Access.
e. Locate the cancer entry to be cancelled (match on Member No., Cancer date, Cancer site, Cancer type)
f. Populate the 'cancelled date' field with the 1st day of the month that the update relates to.
g. Update the 'notes' field to record when the cancer was cancelled and who performed the cancellation e.g. MR511_09_2014 would be '-cancelled NH 07.01.2014'

9) **Other documents to process ?**
a. Other documents may be present in the folder eg a pdf document containing surname change or a 'flag status change sheet' or an 'event sheet'. These need reviewing and actioning. If there has been a name change, this can be recorded in the notes field in the Cohort table. Also 'Exit to NI', 'Embark', 'Re-entry' are also recorded in the comments field.

10) **Complete the LOG file**

11) EXPORT DATA [Export] on frmUpdateDeathsCancer
a. Output death and cancers in excel format to send to Darren Greenwood

	Export done?	Sent to Darren?	Your name and date
Cancers			
Deaths			

12) To finish:

Once have added deaths, cancers, cancelled cancers and Scottish data from the data folder- update the **LOG FILE** <N:\Faculty-of-Medicine-and-Health\LIGHT\Nutr-Epi\FOOD\COHORT\cen data\LOG FILE Death and cancer import to access.xlsx> in the cohort/cen data file

13) CHECKS

Table 1: Numbers log file (initial count and final check of the import)

BEFORE					**AFTER**		
List all files located within this cen data time period [_____]	**Data type**	**Row count/ record# using summary page info and counting rows**	**Notes**	**Name of person doing data count initially & date**	**Number of rows from this file now in access**	**Notes for any for any IDs not in access**	**Name of person doing data count to check import**