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Diet and Menopause

PhD Thesis submitted by

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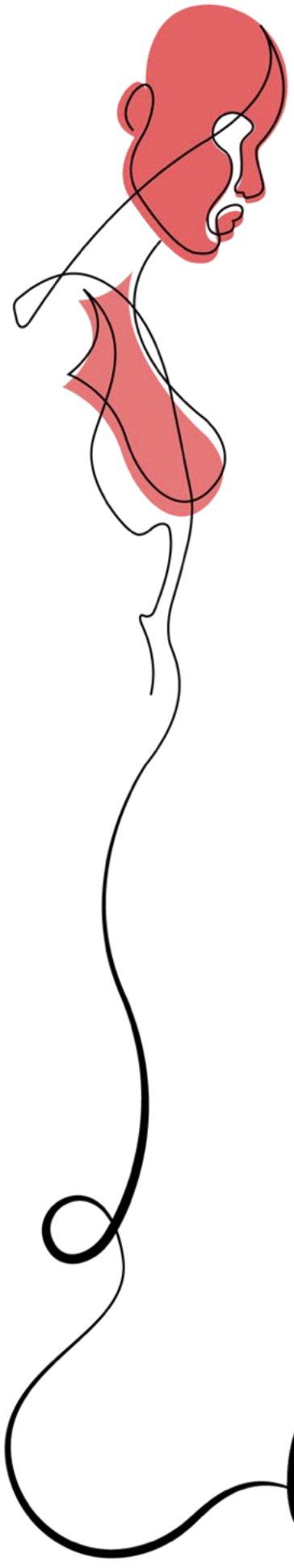

Challenges understanding the association between diet and menopause

PhD Thesis

female health

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ABSTRACT

Background: Menopause occurs naturally between the ages of 40 and 60, with 80–90% of women experiencing menopause between ages 45 and 55. Menopausal transition is associated with a drastic drop in oestrogen, an increase in iron concentrations, the appearance of menopausal symptoms, and an increase in the incidence and mortality rates for cardiovascular disease (CVD). Early menopause (at age 45 or younger) is associated with increased risk of type 2 diabetes (T2D), CVDs, bone fractures, mood disorders, and decline in cognitive functions. Conversely, late menopause (at age 55 or older) is associated with an increased risk of ovarian, endometrial, and breast cancer. Understanding modifiable risk factors affecting the age at which menopause occurs may have implications not only for family planning, but also for menopause-related diseases.

Aims: I analyse the role diet has on natural menopause onset. In my first article, I evaluate the association between menopausal status and changes in dietary intake among adult women in Switzerland. In the second article, I systematically review and evaluate published research on the associations between diet and the onset of natural menopause (ONM). In the third and fourth articles, by using data from large population-based cohorts, I investigate the association of plant-based diet index (PDI) and dietary iron intake with incidence of early natural menopause.

Methods: For the first article, I used data from women enrolled in the first and the second follow-up visits of the CoLaus study—a population-based cohort study in Lausanne, Switzerland. I included women with available data on dietary intake and information on menopause status from two visits in my analysis. I used multivariable and linear models and linear mixed models adjusted for potential confounders to cross-sectionally and longitudinally investigate the association between menopause status and dietary intake. To summarize the evidence on the association between diet and ONM, I used a systematic review and meta-analysis in the second article. In articles 3 and 4, I used data from premenopausal women enrolled in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts—population-based cohorts in the United States. I conducted a Cox proportional hazard model to assess the association of PDI in quintiles with incidence of early natural menopause in NHS and NHSII separately and fixed-effect model to pool the results from both cohorts (article 3). I conducted the same analyses to assess the association of dietary iron intake with incidence of early natural menopause (article 4). Dietary intake was assessed using the food-frequency questionnaire (FFQ), while menopause status and ONM was self-reported for all studies.

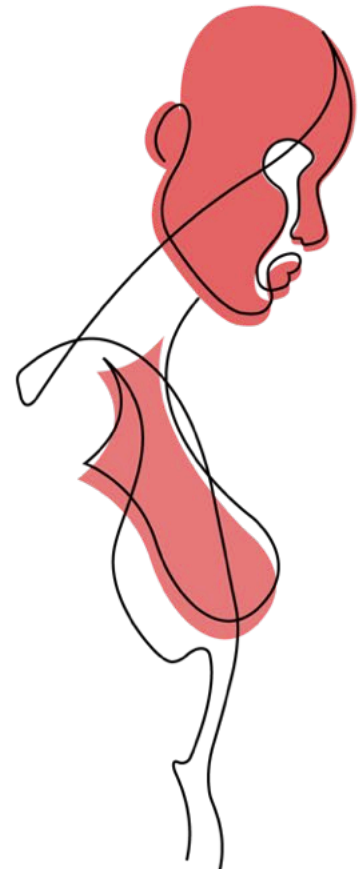
Results: These studies' results are presented in 4 articles. In article 1, I included 1,641 women and showed no association of menopause status with total energy intake (TEI), dietary intake, and adherence to the Swiss dietary recommendations, neither cross-sectionally nor longitudinally. Article 2 shows that among the investigated food groups, higher intake of green and yellow vegetables was associated with early age of ONM, while high intakes of some dairy products, such as low-fat, skim milk, and low intake of alcohol were associated with a later onset. I observed no consistent association between

macronutrient and micronutrient intake and ONM, although a vegetarian diet was more associated with early ONM. After adjustment for potential confounders, article 3 shows no observed association between PDI and the incidence of early natural menopause in either cohort or when pooling the results from both cohorts. Article 4 shows high intake of iron heme was strongly associated with higher risk to experience early natural menopause among the NHSII cohort. Yet, an association was found between iron non-heme and higher risk of early natural menopause in NHS only in fully adjusted models.

Conclusion: I contribute to scientific knowledge by recognizing the current gaps regarding the role of diet on ONM and by providing new knowledge about components of diet, such as dietary iron intake, that may impact ONM. Despite menopause being associated with elevated risks of T2D and CVD and adhering to a healthy diet during this critical phase of women's life could help reduce these risks, my research shows that women do not change their diets during menopause transition or when they are in menopause. Also, to be easily understood by a wide range of professionals and the public, I suggest writing dietary guidelines and scientific findings related to menopause in plain language.

ABBREVIATIONS

AMH	Anti-Müllerian hormone
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CMD	Cardiometabolic disease
CVD	Cardiovascular disease
DHEA	Dehydroepiandrosterone
E2	Oestradiol
FFQ	Food-frequency questionnaire
FMP	Final menstrual period
FSH	Follicle-stimulating hormone
GSM	Genitourinary syndrome of menopause
hPDI	Healthy plant-based diet index
HR	Hazard ratio
HRT	Hormone replacement therapy
MUFA	Monounsaturated fatty acid
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
NOS	Nine-star Newcastle-Ottawa Scale
ONM	Onset of natural menopause
OR	Odds ratio
PDI	Plant-based diet index
PMO	Postmenopausal osteoporosis
POI	Premature ovarian insufficiency
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
TEI	Total energy intake
T2D	Type 2 diabetes
uPDI	Unhealthy plant-based diet index
WHO	World Health Organization
WMD	Weighted mean difference



1. Introduction

"Replace fear of the unknown with curiosity."

Danny Gokey

female health

1. INTRODUCTION

1.1. Menopause

1.1.1. What is menopause?

The World Health Organization (WHO) defines menopause as 'the permanent cessation of menstruating resulting from the loss of ovarian follicular activity' and absence of menstruation (amenorrhoea) over a period of 12 months [1]. On average, the cessation of reproductive function occurs naturally between the ages of 50 and 52, with 80-90% of women having their final menstrual period (FMP) between ages 45 and 55 [2]. Up to 10% of women may experience early menopause (<45 years old) naturally, non-naturally due to medical treatment (chemotherapy and radiation), or due to the removal of both ovaries (bilateral oophorectomy) prior to natural menopause, the latter two known as surgical menopause [2].

The variation in age of ONM could be due to different geographic areas, ethnic backgrounds, and genetic and non-genetic factors [3]. Geographic region has been found to explain 68.5% of the observed heterogeneity in mean age of menopause range. As reported in **Figure 1**, among countries in Africa, Latin America, Asia (except for several East Asian countries, such as Japan and Korea), and the Middle East, age at menopause onset was generally earlier compared to countries in Europe, Australia, and the United States; variations in age at natural menopause are reported also within the same geographical region [4].

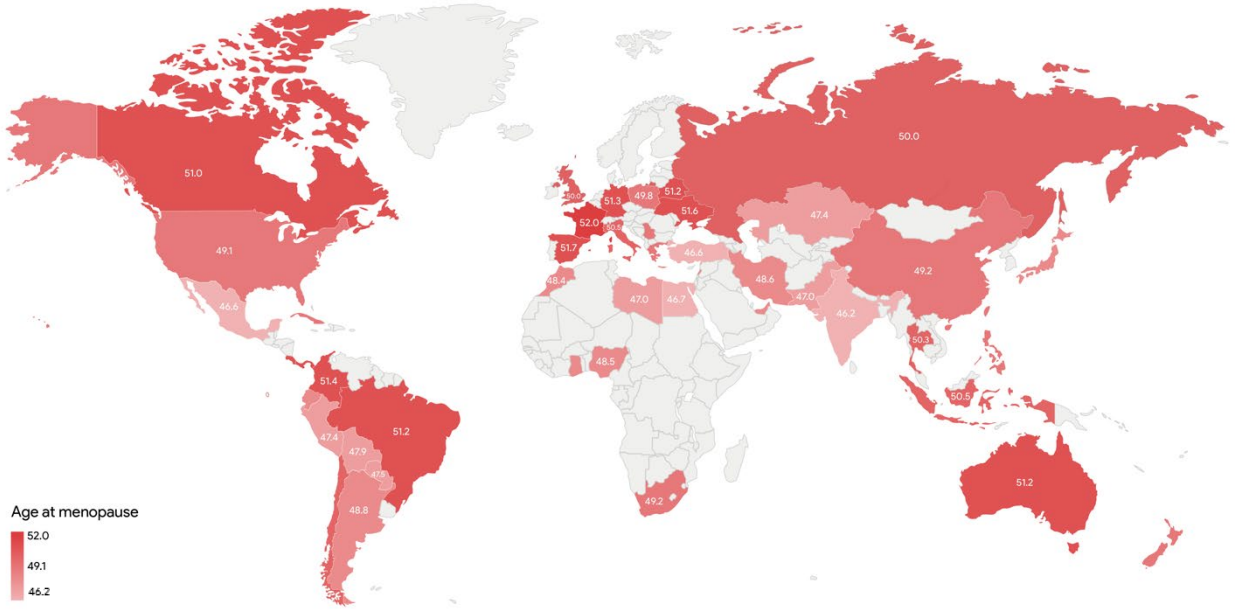


Figure 1. Variation in menopause timing according to geographic region. Adapted from Laisk et al. [5]

Few studies assessed racial/ethnic variability in age at menopause onset and of studies that have, findings have been inconsistent, mainly due to conflating two terms in the literature: race (denoting a person's physical appearance) and ethnicity (including a broader concept of similarities in cultural heritage, social practice, traditions, language, and geopolitical factors) [6]. Socioeconomic factors are also related to menopause timing; in general, studies showed lower education and lower socioeconomic levels to be associated with earlier age at ONM [7]. Other factors identified linked to menopausal age can be categorized into lifestyle factors and life history, such as early menarche and nulliparity which are associated with early age at menopause [8,9], while increasing parity is associated with later age at menopause [10,11]. Among lifestyle factors, smoking has a strong association with earlier age at menopause, while a weaker association has been found with lower body mass index (BMI) and earlier age at menopause [12,13]. In the last decade, lifestyle factors expanded to diet with few studies reporting controversial but existing associations with ONM.

1.1.2. Physiological mechanisms

During foetal life, women[1] receive a maximum quota of oocytes. In the first half of foetal development, the ovaries contain around 6–7 million oocytes [14]. At birth, the ovarian reserve decreases to 1–2 million oocytes and at menarche, the rate decreases to 300,000–400,000 [15]. During the fertility period, the continued decline in quantity and quality of oocytes will cause a drastic drop below 1,000 at the time of menopause, as reported in **Figure 2** [16].

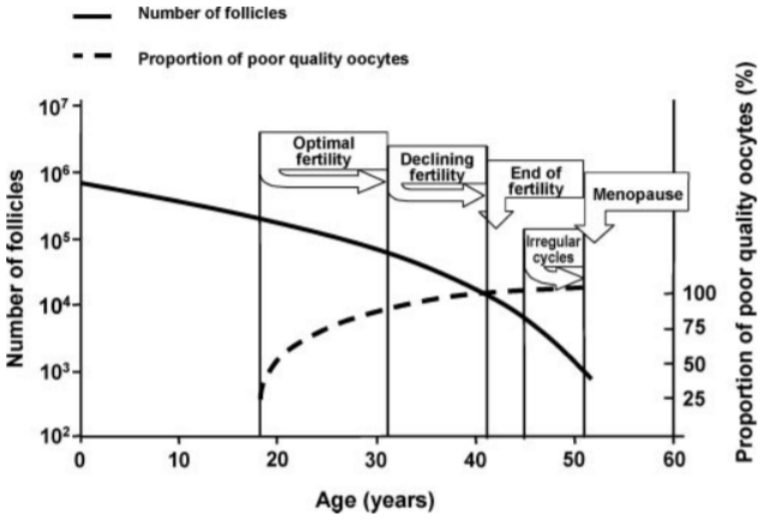


Figure 2. Representation of the number of primordial follicles present in the ovaries and quality of oocytes in relation to female age. Adapted from Broekmans et al. [14]

[1] For ease of read, I use "women" to signify all those born biological women, although they may not identify as women.

Several sources reported that fertility gradually decreases from the age of 30 years onward, even though the physiological process is still unnoticed [17,18]. During the fertility period, the menstrual cycle has a mean length of 28 days, but the regularity of the menstrual cycle is gradually lost and cycles become shorter due to a shorter duration of the follicular phase. Then, cycles may become lengthened with delayed initiation of dominant follicle growth or anovulatory bleeding [19,20]. Later, cycle length will vary and cycles may be skipped due to prolonged absence of recruitable follicles. The complete loss of cyclic ovarian follicular activity is defined by 12 consecutive months of amenorrhea. Within the first year after menopause, a residual follicular activity may still be present due to a small number of oocytes left; however, the number is too low to sustain a regular menstrual cycle [21].

The hormonal changes of the transition are complex, variable, and unpredictable. The menopause transition is characterized by wide variability in follicle-stimulating hormone (FSH), oestrogen, inhibin B, androgens, and Anti-Müllerian hormone (AMH) in the blood [22]. When follicle numbers reach a presumably critically low level, inhibin B secretion declines. FSH levels generally remain in the reproductive age range when regular ovulatory cycles continue, and the levels rise when cycles are no longer normal [23]. The gradual decline in ovarian oestrogen production in the years prior to the complete cessation of menstruation is largely related to the number of remaining primordial follicles; during menopause a dramatic decline in plasma oestradiol (E2) level occurs and the postmenopausal ovary will cease to contribute to E2 levels in blood [24], even though the pituitary gland continues to produce FSH throughout life [22]. Menopausal oestrogen deprivation plays a role in the aetiology of many symptoms and health conditions such as osteoporosis, CVD, and urogenital atrophy; currently the mechanisms underlying ovarian senescence are not yet fully understood [25].

1.1.3. Early, normal, and late menopause

A homogeneous classification of menopausal status (**Table 1**) based on physiologic phenotypes is fundamental for comparing, generalizing, integrating, and spreading findings, as well for promoting public health and improving and guiding future research [2]. *Natural menopause* is determined by the completion of '12 consecutive months of amenorrhea resulting from the loss of ovarian follicular activity' and occurs naturally for most women between the ages of 50 and 52 [2,28]. *Menopausal transition* defines the period before the FMP when irregularity in the menstrual cycle usually increases, while *perimenopause* should include the period immediately before menopause and the first year after menopause. *Premenopause* is often used ambiguously either to refer to the 1 or 2 years before menopause or the entire reproductive period before menopause; WHO recommends the term enclose the entire reproductive period before the FMP. Last, *post-menopause* is defined as the period dating from the FMP, regardless of induced or spontaneous menopause [26].

	Premenopause				Perimenopause				
STAGE	**REPRODUCTIVE**				**TRANSITION TO THE MENOPAUSE**			**POSTMENOPAUSE**	
Phase	Early	Peak	Late		Early	Late	Menopause	Early	Late
Duration	Variable	Variable	Variable	Variable	Variable	1-3 years	1 year	1 year	3-6 years	Till the end of life

Table 1. Classification of the reproductive phases of the woman with approximate duration. Adapted from García-Ríos et al. [27]

Approximately 10% of the menstruating population enter menopause before age 45—a condition termed *early menopause* [29]. About 1% of women enter menopause before age 40 and 0.1% of women before age 30—a condition termed premature ovarian insufficiency (POI) [30]. Emerging evidence suggests that early menopause and POI may be due a variety of possible causes, including genetic factors [31], autoimmune disease, iatrogenic conditions, infections [14], and other modifiable lifestyle factors, such as diet [32,33]. Both early menopause and POI are associated with increased risk of T2D, CVD, bone fractures, mood disorders, and decline in cognitive functions. Conversely, *late menopause* occurs after age 55, and it is associated with increased risks of ovarian, endometrial, and breast cancer [34].

Menopausal transition is characterized by hormonal changes, in particular hormones such as E2, FSH, inhibin B, androgens, and AMH are involved in this delicate phase. To predict ovarian aging, recommendations favour using AMH; AMH is the most consistent and reliable predictive marker of impending menopause; serum levels of AMH were found to be less than the detectable limit (0.08 ng/mL) for 3 years before menopause. This finding suggests that menopause occurs within 3 years among women with serum levels of AMH below the limit who experience irregular menstruation [35].

1.2. Adverse metabolic outcomes following menopause

1.2.1. Menopausal symptoms

Menopause and associated biological changes have a negative impact on the general health and quality of life as well as the wellbeing of middle-aged women [36]. The most frequently annoying menopausal symptoms among pre- and postmenopausal women are joint and muscular discomforts, depressive mood, hot flushes, night sweats, decreased libido, urogenital complaints, and higher central and intra-abdominal fat accumulation [36].

Menopausal symptoms and their time of occurrence vary widely. For some women, symptoms occur before the actual cessation of menses; for other women, symptoms coincide with menopause; and for some others, symptoms do not appear until several years later. Although around 60–80% of women experience menopausal symptoms, there is also a group of women who do not experience these symptoms [37]. The prevalence and severity of menopausal symptoms differ by geographic region and may vary due to factors such as lifestyle, social status, body composition, and psychological status [38]. Within

geographic variation, culture, religious beliefs, and ethnicity may play a role in the way women perceive menopause symptoms, as well as the rate and severity of the symptoms. For example, urogenital and sexual issues are not discussed openly in some Asian cultures, such as Chinese and Indian, and these issues might get translated into somatic and psychological symptoms. In addition, women in those cultures might believe those symptoms are a part of ageing [39]. Furthermore, in tropical countries hot flushes from hot weather effects or as symptom of menopause might be indistinguishable. Different perceptions or approaches affect reporting of menopausal symptoms and consequent variation in prevalence.

1.2.2. Cardiometabolic diseases

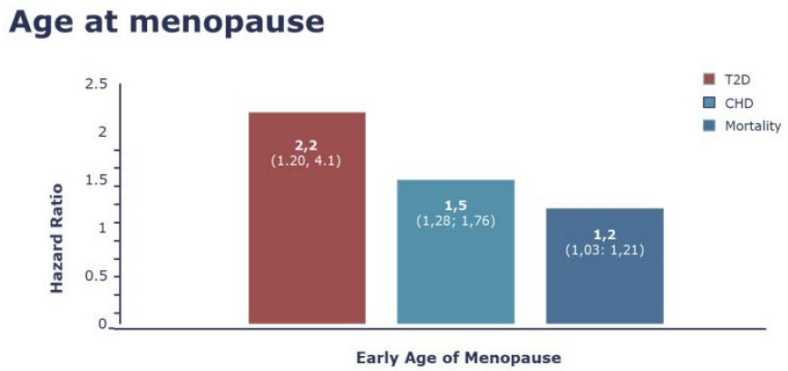


Figure 3. Representation of the risk of T2D, coronary heart disease (CHD), and overall mortality among women with early age of menopause. Adapted from Muka et al. [40]

Among women with early menopause, overall mortality and morbidity are mainly due to cardiometabolic diseases (CMD), including T2D and CVD (Figure 3), and their associated factors, such as hypertension, dyslipidaemia, insulin resistance, and obesity [41]. At a young age, CMD prevalence is higher among men than women, but this gap disappears with aging, particularly after menopause [42,43]. Women in post-menopause face more cardiovascular events than women in pre-menopause at the same age [44]; during menopausal transition women increase blood lipids, fasting glucose, blood pressure, and abdominal fat—all CMD risk factors [45]. In addition, psychological and somatic-vegetative symptoms, such as sleep disturbances, depression, and anxiety, have been linked with adverse cardiometabolic profile [46,47].

Even ONM is considered a predictor of cardiometabolic health. For instance, early ONM is associated with long-term health consequences, including T2D, CVD, and overall mortality. Data confirmed that premature menopause or early menopause, induced by bilateral oophorectomy, accompany increased risk for CVD [48]. Currently, data used to determine the association between menopause and CVD risk are mainly based on traditional risk factors; decline in E2 levels coincide with increased CVD and T2D and recent studies show oestrogen can have beneficial cardiometabolic effects among younger women but harmful effects in older women [49,50]. The impact of E2 and androgens on women's health remains debatable and further studies are needed [51]. Indeed, the impact of other

androgens, such as serum dehydroepiandrosterone (DHEA) and testosterone, on the association between menopause and CMD risk could be more complex than we expect and depend on several hormonal pathways, as reported in **Figure 4**.

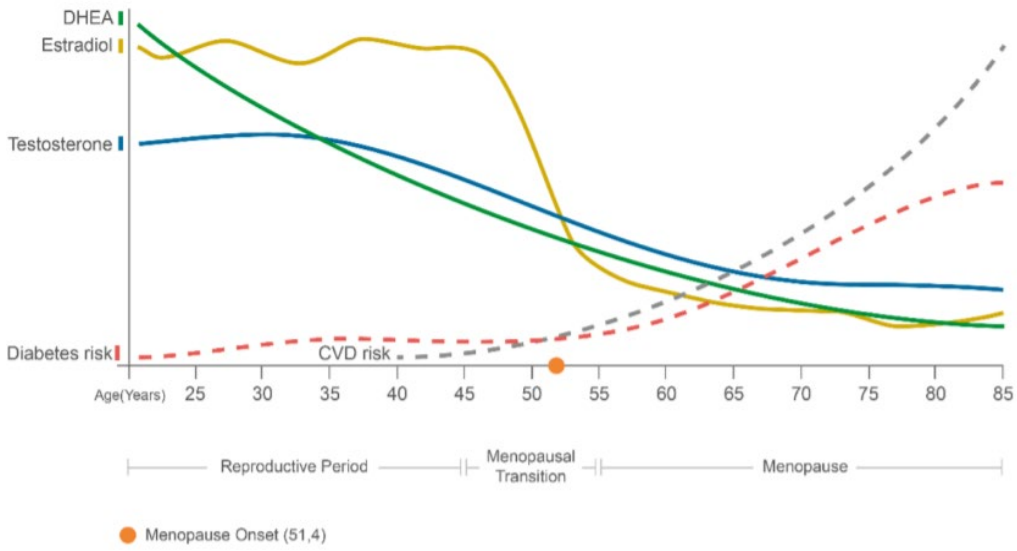


Figure 4. Age-related variations in serum sex hormones and cardiometabolic risk in women. Adapted from Roa-Díaz et al. [45]

In conclusion, the mechanisms underlying menopause transition and CMD associations are not well understood; and novel pathways, such as iron metabolism, the role of environmental factors, and the possible role of DNA damage response mechanisms, may explain the association of menopause and CMD [45].

1.2.3. Non-cardiometabolic outcomes

1.2.3.1. Osteoporosis

Oestrogen is the major hormonal regulator of bone metabolism among women and men and bone is a strong oestrogen-dependent tissue. Oestrogen plays a major role in the acquisition and maintenance of bone mineral content; inhibits osteoclastic differentiation, and maintains bone formation activity [52]. Postmenopausal osteoporosis (PMO) is a frequent clinical condition, which affects nearly 1 in 3 women after age 50; it is characterized by structural deterioration of bone tissue, leading to increased bone fragility and thus higher risk of fracture in postmenopausal women. PMO is due to the deficiency of oestrogen production, maximal within the first 2–3 years after menopause transition, which causes an imbalance in the bone remodelling process where resorption/formation skewed more towards resorption and consequent bone loss. It causes high morbidity and severe health complications, such as increased frailty, functional limitations, loss of independence, and mortality [53,54]. However, there are large individual variations in the bone mineral content of each woman at menopause; such variations are not fully elucidated. For instance, early onset of menopause, the nature of menopause (natural/surgical), and smoking seem to be associated with rapid bone loss [55,56],

whereas overweight, obesity, and later age of menopause may be associated with slower postmenopausal bone loss [57]. Yet, genetic determinants may contribute to inter-individual differences in the impact of oestrogen deficiency on bone [58,59]. Even though the current PMO therapy has many unwanted side effects and even increases the possibility of tumorigenesis [53], hormone replacement therapy (HRT) prevents bone loss and significantly reduces the risk of fracture at all bone sites by 20–40%. Also, the individual benefit-risk balance of HRT is dependent on individual risk profiles, as well as the type of oestrogens and progestogens or doses and routes of administration. In conclusion, in the absence of contraindication, use of HRT should be considered the first option for the maintenance of bone health among those women where specific bone active medications are not warranted [54].

1.2.3.2. Mood disorders and sexual function

The existence of an association between depression and menopause has been the focus of clinical and scientific debates for years due to the heterogeneity of studies, lack of use of standardized tools or instruments necessary to characterize psychiatric symptoms, and lack of proper characterization of menopausal staging. Nowadays, ongoing efforts to improve those aspects are changing this scenario [60]. Several studies have confirmed that the menopausal transition constitutes a window of vulnerability to depressive symptoms with higher risk of depressive symptoms mostly in perimenopause and menopause [61-64]. Fluctuations in E2 and FSH levels, history of premenstrual complaints, poor sleep, and employment status were found to be individual contributors to the increased risk of depression [65].

The menopausal transition is also associated with an increased frequency of sleep disturbances, and insomnia represents one of the most reported symptoms by menopausal women. Different predisposing factors, such as hormonal changes, vasomotor symptoms (hot flashes and night sweats), pain, and other circadian modifications, may favour its occurrence; thus, insomnia treatment implies a careful evaluation of psychological and somatic symptoms [66].

Since 2014, the genitourinary syndrome of menopause (GSM) has been introduced as a new term to incorporate conditions such as vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy. Most of these symptoms can be attributed to the lack of oestrogen that mostly characterizes the menopausal period. The hypoestrogenic state leads to vaginal dryness, dyspareunia (genital pain), and reduced lubrication with a consequence of great impact on sexual life and quality of life of affected women [67]. The first treatment for women with mild to moderate GSM symptoms consists of non-hormonal therapies, such as lubricants and moisturizers that act immediately and provide temporary relief. Hormonal therapy with local oestrogen products is considered the ‘gold-standard’ and it is an option for the treatment of moderate to severe GSM symptoms. Recent approaches consist of using selective oestrogen receptor modulators or laser technologies, which restore the tropism in the lower genitourinary tract, but further research is needed [67].

The physiological and psychological effects of menopause are largely mediated by oestrogen but occur simultaneously with interpersonal, sociocultural, and psychological factors [68].

1.2.3.3. Neurological outcomes

A recent study shows that human menopause is a dynamic neurological transition that significantly impacts brain structure, connectivity, and metabolic profile during midlife endocrine aging of the female brain [69]. Observational studies have suggested that early and prolonged loss of ovarian E2 (premature menopause) leads to a doubled lifetime risk for dementia and a fivefold increased risk of mortality from neurological disorders, yet some controversy remains related to cerebral ischemia and Alzheimer's disease [70]. Understanding the biological mechanisms behind menopause is complicated but emerging evidence shows that oestrogens are a key influence on immune and inflammatory processes; even oestrogen receptor-beta regulates an important component of the innate immune response involved in regulation of neuronal mitochondrial function, the inflammasome [71]. The role of oestrogen on neurological diseases is far from understood; however, novel research is changing this current scenario.

1.2.3.4. Cancer

Generally, cancer arises when dividing cells undergo mutations and these genetically damaged cells become susceptible to unrestrained division. Thus, female hormones and other hormones that affect growth are potential risk factors for cancer, such as breast, ovarian, and endometrial. In contrast, factors that induce differentiation are likely to reduce the risk of cancer [72]. Even though the mechanisms are still equivocal, later menopausal age is associated with an increased risk of breast, ovarian, and endometrial cancer [72,73]. Several hypotheses have been formulated; one hypothesis suggests that high levels of oestrogen may increase the probability of DNA damage, such as mitotic activity, DNA replication, and somatic mutations [74,75]. People with a later menopause have higher hormone levels and longer time exposure to oestrogens. Another hypothesis suggests that anovulatory cycles, common among people having later menopause, is associated with progesterone deficiency, which may also contribute to cancer risk [76]. In conclusion, menopause and increasing age may be factors associated with cancer and rise more in mid age [77].

1.3. Diet and other factors associated with onset of menopause

1.3.1. Non-dietary factors associated with menopause

Multiple factors, including hormonal and environmental exposures, socioeconomic status, and stress throughout a woman's life course, interact to influence menopause onset and menopause-related pathways, including the evaluation of the genetic role on menopause onset [78]. In **Table 2**, I summarize the association between multiple factors and ONM.

FACTORS	ONSET OF MENOPAUSE
GENETIC	-> It contribuites to ~ 50% of the variation in age at menopause; few gentic variants identified
MARITAL STATUS	-> Married and widowed women may experience later menopause
AGE AT MENARCHE	-> Uncertain association
PARITY	-> Increasing pregnancies and age at last birth may be associated with later menopause
EDUCATION LEVEL & SOCIAL CLASS	-> Higher education and better social class may be associated with later menopause
OBESITY	-> Lower BMI may be associated with earlier menopause, while high BMI with later menopause
SMOKING STATUS	-> Smokers may be associated with earlier menopause
ALCOHOL	-> Low and moderate alcohol intake may be associated with later menopause
MACRO/MICRONUTRIENTS	-> Incosistent results
DIETARY PATTERN	-> Vegetarian diet may be associated with earlier menopause

Table 2. Association between dietary and non-dietary factors and ONM.

1.3.1.1. Genetic

Menopause is a highly heritable condition. Genetic variants contribute to ~50% of the variation in age at menopause [79]. Genome-wide linkage studies have associated a limited number of genetic variants with menopause, mostly correlated with POI [80,81]. However, the results are conflicting because many of these studies suffer from methodological issues, the results are generally not replicated in different independent samples, and most of these studies are underpowered. Recent genome-wide association studies (GWAS) have identified several genes involved in DNA repair, maintenance, and immune function associated with menopause and POI [82,83]. In conclusion, data seem to indicate that fertility, age at menopause, and longevity are interlinked through common genetic factors involved mostly in DNA repair and maintenance [82,83]. If these systems fail, cell death and accelerated aging occur with upcoming onset of menopause.

1.3.1.2. Marital status, age of menarche, and parity

Several studies reported that married and widowed women experience later menopause when compared with single and divorced women. The effect of marriage on age at menopause may be due to behavioural factors that alter the internal hormonal or chemical environment, such as sexual activity, parity, or smoking habits. [84,85]. Yet, unmarried women experience more severe symptoms at menopause when compared with those who are married; the probable reason for this is that married women have better social relationships and family support [86,87]. Nowadays, the association between age at

menarche and age at menopause remains uncertain. Some studies report that women with early menarche experience early menopause; other studies report that early menarche is associated with late menopause or there is no association [86,87]. The duration of the reproductive period may be an indicator of cumulative exposure to oestrogens and progestogens [88] even though menopause is mainly about the aging of eggs and what causes them to age more quickly. Increasing the number of pregnancies and childbirths, or the age of the last pregnancy, can also lead to late menopause onset; potential explanations for these findings include increased oestrogen and progesterone secretion due to longer uterine and ovarian activity and breastfeeding [89,90].

1.3.1.3. Education and socioeconomic status

Women with more education experience older menopausal ages; one study reported that mean age of natural menopause among primary educated women was 45.7 years, while graduate education and above was 47.2 ±4.4 years [84]. In addition, better social class (e.g., financial position) was found associated with better health status and later menopause (high vs. low occupation level; Weighted Mean Difference [WMD], 0.76; 95% Confidence Interval [CI], 0.44–1.09); this association could be explained by better nutritional status, reproductive choices, stress, and access to better health and medical care [4,91]. People who had a low economic situation in childhood experienced earlier age at menopause, probably due to an increase in smoking in adulthood [92,93].

1.3.1.4. Lifestyle: obesity and smoking

Studies indicate that there is an association between lifestyle and ONM; lower BMI has been found to be associated with earlier onset of menopause, while high BMI has been found to be associated with later menopause. A meta-analysis reported women with overweight have a lower likelihood of experiencing early menopause [Hazard Ratio (HR), 0.93; 95% CI, 0.91–0.96; $P < 0.001$] compared with women at ideal weight. This association was markedly confirmed even among women with obesity, after adjusting for smoking (HR, 0.85; 95% CI, 0.81–0.90; $P < 0.001$) [94]. Several studies have endogenous oestrogen levels and women with higher BMI have higher levels of E2 and oestrogen in their bodies, leading to delayed menopause [95].

Smoking influences the age of menopause and smokers experience menopause at an earlier age. Some studies reported that smoking is the most important cause of early menopause [96]. A meta-analysis confirmed this association; they analysed two groups of women according to their data on menopause (dichotomous and continuous studies). Women who smoked were significantly associated with early ONM in both dichotomous (Odds Ratio [OR], 0.74; 95% CI, 0.60–0.91; $P < 0.01$) and continuous studies (OR, 1.12; 95% CI, 1.80 to 0.44; $P = 0.04$) when compared with non-smokers [97].

1.3.2. Current evidence on diet and menopause onset: the role of food, micro-/macronutrients, and dietary patterns

1.3.2.1. Food, micro-/macronutrients intake and menopause onset

Diet has been implicated in menopause onset, yet the findings in the literature are inconsistent. In some studies [98,99], high fruit intake showed to be associated with later onset of menopause, while other studies found no association [100-103]. When focused on markers of menopause, high fruit intake was inversely associated with annual reduction in AMH, suggesting prolonging reproductive life [104]. The micronutrient β-cryptoxanthin—a common carotenoid mainly found in fruit—is associated with later onset of menopause [99], suggesting its role in prolonging reproductive life.

Different findings obtained regarding the association between vegetable intake and menopause onset may depend on the type of vegetable being consumed. For instance, green and yellow vegetable intake could be associated with earlier natural menopause and the antioxidative mechanism may explain this association [105]; the antioxidant activity of carotenoids may be related to menopausal transition due to their impact on FSH secretion [106]. In recent years, there has been an increasing trend of consuming vegetarian diets; however, their role on menopause onset is still unclear. Due to activating/inhibiting oestrogen receptors, high phytoestrogen intake, rich in vegetable food, could affect menopause onset—these compounds may inhibit oestrogen action even though the risks or benefits of estrogenic or antioestrogenic effects highly depend on targeted tissue, timing, and level of exposure [107]. Evidence has been inconsistent regarding phytoestrogen-rich foods such as soy/tofu, beans, and legumes and menopause onset [108,109].

Some dairy products may be associated with onset of menopause; low-fat dairy-food intake, such as skim milk and yogurt, may reduce the risk of early natural menopause up to 17% [108,109]. Similarly, dairy protein and dairy fat were associated with a late natural menopause [110]. In addition, total dairy, milk, and fermented dairy products seem to reduce the rate of AMH decline, prolonging reproductive life [104]. In conclusion, higher dietary intakes of calcium from dairy sources, free galactose, and lactose are also associated with both lower annual reduction in AMH and the odds of its rapid decline [104,111].

1.3.2.2. Alcohol intake and menopause onset

The association between alcohol consumption and menopause onset is not fully understood [112]. Several studies reported low and moderate alcohol intake might be associated with late onset of menopause [33] due to a rise in circulating oestrogen levels, induced by alcohol [12,113]. However, studies exploring possible associations between alcohol intake and oestrogen metabolism are limited [114]. Among specific beverages, evidence of lower early menopause risk was confined to consumption of white wine,

potentially red wine, and liquor, but not to beer [115]. In addition, these findings should be read within the context of the complex association of alcohol with menopause-related health conditions. Although low to moderate alcohol consumption has been linked to a reduced risk of CVD and T2D [116,117], an association has been reported between high alcohol intake and risk of breast cancer among premenopausal women [118].

1.3.2.3. Dietary patterns and menopause onset

Traditionally, nutrition research has focused on single nutrients or specific foods, although, except for supplements, individuals do not consume nutrients or foods in isolation. Recent epidemiological studies have shifted to dietary pattern analysis, which describes the overall diet. Dietary patterns have several advantages, such as limiting potential confounding by other features of diet, assessing the cumulative effects of foods, and allowing for interactions, assessing the food combination and variety, as well as the frequency and quantity with which they are habitually consumed [103]. One study reported a dietary pattern characterized by high animal-based protein intake to be associated with late natural menopause [103], yet other studies failed to show any impact. A vegetarian diet seems to be associated with early natural menopause onset [100,119] due to its anti-atherogenic activity and ability to impact oestrogen levels; better atherogenic profiles have been suggested to slow depletion of the follicle pool [120].

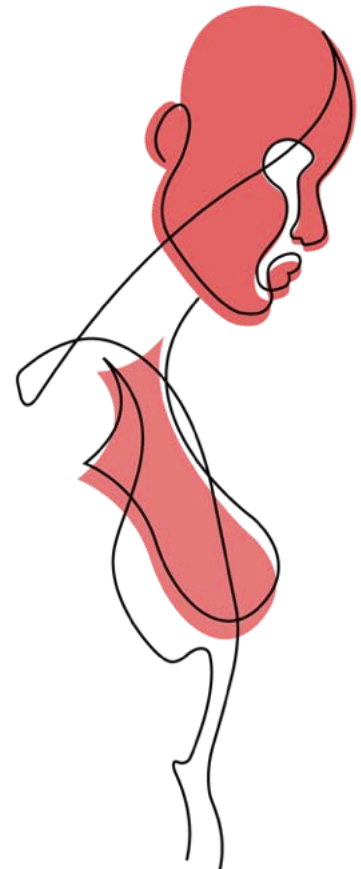
1.3.3. Closing the gaps on impact of diet on menopause onset

In the last decade, more attention has been given to diet as risk factor to determine timing of menopause and mostly about the biological and physiological processes behind menopause. Particularly, long life after menopause is a relatively recent phenomenon, resulting from the progress of medicine and better lifestyle, which have succeeded in prolonging life; in fact, women now spend one-third of their lifetime in menopause. In parallel, novel studies have been conducted to treat the wide range of climacteric symptoms affecting women before and after menopause [121].

Despite the progresses made in this field, there is no comprehensive review of the literature on diet and menopause or a critical evaluation of the evidence. Most evidence comes from poor quality studies, not well-defined menopause outcomes, and not well-defined food item or food group exposures, which can explain the inconsistent evidence. For instance, soy, such as whole food tofu and soybeans or processed versions like soy protein powders and soy-based veggie burgers, has been studied. Processed and unprocessed food have a different composition in terms of bioavailable nutrient; thus, different responses on the body [122]. In addition, considering menopause is related with several health outcomes, changing diet during menopause can help reduce the burden of menopause-related diseases. Yet, to date, there are no prospective studies evaluating whether menopause can impact women's diet (or vice versa). Further, since PDI has been linked to lower risks of several diseases and is environmentally friendly, PDI has become

popular. However, the impact of PDI on reproductive health remains under investigated. Within PDI, iron remains an important dietary element with impact on multiple health outcomes, such as cardiovascular risk, T2D, metabolic syndrome, oxidative stress, and menopause symptoms [123,124]. To my knowledge, there is no study in the literature investigating the association between dietary iron intake and menopause onset.

Understanding whether specific dietary factors might be associated with menopause onset could lead to new approaches reducing unhealthy dietary habits and adverse outcomes related to early/late natural menopause, and diet may be an alternative treatment for hot flushes and other symptoms that accompany menopause [125].



2. Aims

"Curiosity is the engine of achievement."

Sir Ken Robinson

female health

2. GENERAL AIMS

In this PhD thesis, I add to understandings about the impact of diet on menopause onset. To achieve this, in article 1 I evaluate the association between menopausal status and changes in dietary intake among adult women in Lausanne, Switzerland. Adherence to a healthy diet may contribute to maintaining adequate health throughout the menopausal transition. In article 2, I evaluate the currently published evidence on associations between diet and ONM. In article 3, I evaluate the association of PDI with early natural menopause in the NHS and NHSII. Additionally, using the same cohorts, in article 4 I investigate the association between dietary iron intake and early natural menopause.

2.1. Specific aims

2.1.1. Article 1. Menopausal transition is not associated with dietary change in Swiss women

Adherence to a healthy diet could contribute to maintaining adequate health throughout the menopausal transition, yet data are scarce. Therefore, I 1) studied the changes in dietary intake among women before and after menopause using data from the CoLaus cohort study. I cross-sectionally compared the dietary intake between pre and postmenopausal women, and then whether the change in menopausal status was prospectively associated with 5 years changes in dietary intake compared with women who remained premenopausal during the follow-up or were postmenopausal across the study period and 2) assessed whether menopausal status was associated with adherence to dietary Swiss recommendations (**Supplementary material 1**) as published in 2021 by Grisotto et al.

2.1.2. Article 2. Dietary factors and onset of natural menopause: a systematic review and meta-analysis

I conducted a systematic appraisal of the literature on how diet can influence the ONM. Understanding factors that can influence the timing of natural menopause has emerged as an important and relevant public health topic in reducing adverse outcomes related to early or late natural menopause; however, the evidence is inconsistent. Therefore, I 1) systematically reviewed prospective studies investigating the association between diet and timing of natural menopause; 2) meta-analysed studies exploring the association between alcohol intake (consumers vs. non-consumers, lowest vs. highest) and natural menopause onset as published in 2022 by Grisotto et al.

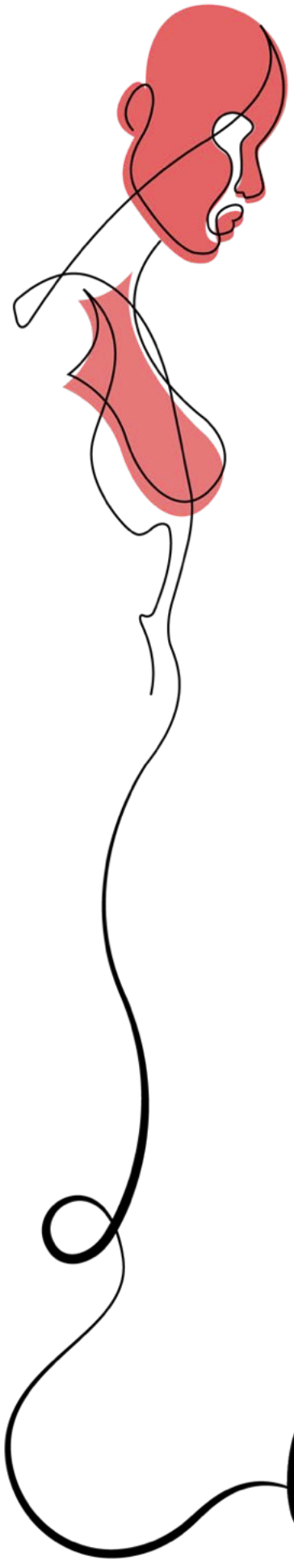
2.1.3. Article 3. Association of plant-based diet and early onset of natural menopause

For health promotion and disease prevention related to early natural menopause, it is important to understand whether PDI (**Supplementary material 2**) can affect timing of the

menopausal transition. Therefore, I 1) prospectively investigated the association between plant-based diet and incidence of early natural menopause among women enrolled in the NHS and NHSII and 2) investigated the association between healthy plant-based diet index (hPDI) (**Supplementary material 2**) and unhealthy plant-based diet index (uPDI) (**Supplementary material 2**) and early natural menopause as published in 2022 by Grisotto et al.

2.1.4. Article 4. Association of dietary iron intake and early onset of natural menopause: a prospective study

Iron storage increases by two- to threefold from before to after menopause. Epidemiological studies have reported an association between high iron stores and increased adverse outcomes such as CVD, metabolic syndrome, and osteoporosis, yet no studies have investigated whether dietary iron intake is associated with incidence of early natural menopause. Therefore, I 1) prospectively investigated the associations of iron heme, iron non-heme, and supplemental iron with the incidence of early natural menopause among women in the NHS and NHSII. This paper has not been published yet.



3. Results

"It's not interesting to achieve; the ways of achievement are interesting."

Krzysztof Kieslowski

female health

3. RESULTS

3.1. Article 1. Menopausal transition is not associated with dietary change in Swiss women

Menopausal transition is not associated with dietary change in Swiss women

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Original article. Published in *The Journal of Nutrition, 2021*
Contribution: I participated in the conceptualization of study. I consulted the Swiss Food Pyramid. I performed the analysis, made the figure and tables, and wrote the first draft of the manuscript. After that, I incorporated co-authors' and reviewers' comments.

The Journal of Nutrition
Nutritional Epidemiology

Menopausal Transition Is Not Associated with Dietary Change in Swiss Women

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ABSTRACT

Background: Adherence to a healthy diet could contribute to maintaining adequate health throughout the menopausal transition, but data are scarce.

Objective: We evaluated the association between menopausal status and changes in dietary intake in Swiss adult women.

Methods: Cross-sectional ($n = 2439$) and prospective analyses ($n = 1656$) were conducted between 2009 and 2012 (first follow-up) among women (mean age ± SD, 58.2 ± 10.5 y) living in Lausanne, Switzerland. In both visits, dietary intake was assessed using a validated FFQ, and menopausal status was classified based on the presence or absence of menstruations. Multivariable linear and logistic regression models were used to investigate the cross-sectional association of menopausal status (postmenopausal compared with premenopausal) at the first follow-up with food intake and dietary recommendations. To examine whether menopausal status (premenopausal as reference group, menopausal transition, and postmenopausal) during 5 y of follow-up was associated with longitudinal changes in diet, including adherence to dietary Swiss recommendations, we applied multivariable linear and logistic mixed models adjusted for several covariates.

Results: At the first follow-up, postmenopausal women consumed less ($P < 0.002$) meat [median (IQR) 57.2 (35–86.2) compared with 62.5 (41.2–95.2) g/d], pasta [61.8 (37.5–89.2) compared with 85 (57.8–128) g/d], and added sugar [0.1 (0–4) compared with 0.7 (0–8) g/d] and more dairy products [126 (65.4–214) compared with 109 (64.5–182) g/d] and fruit [217 (115–390) compared with 174 (83.2–319) g/d] than premenopausal women. However, linear regression analysis adjusted for potential confounding factors showed no independent (cross-sectional) associations of menopausal status with total energy intake (TEI) and individual macro- or micronutrient intakes. In the prospective analysis, compared with women who remained premenopausal during follow-up ($n = 244$), no differences were found in changes in TEI, dietary intakes, or adherence to the Swiss dietary recommendations in women transitioning from premenopausal to postmenopausal ($n = 229$) and who remained postmenopausal ($n = 1168$).

Conclusion: The menopausal transition is not associated with changes in dietary habits among Swiss women. *J Nutr* 2021;0:1–8.

Keywords: menopause transition, dietary recommendation, dietary habits, Switzerland, cross-sectional, population-based study

Introduction

Menopause marks the end of a physiologic process, after which women face a drastic drop in estrogen concentrations, an increase in iron concentrations, appearance of menopausal symptoms, and an increase in the incidence and mortality rates for cardiovascular disease (CVD) (1, 2). Menopausal transition is associated with adverse changes in sleep and mood (3), body composition as weight gain and accumulation of central body fat (4), a shift toward a more atherogenic lipid profile and impairment of glucose homeostasis, and higher depression, all important risk factors for CVD and overall mortality (5–7). Numerous postmenopausal women also live with type 2 diabetes (T2D), which confers a greater risk of CVD in women compared with men (8–10). Furthermore, the menopausal transition has an adverse impact on overall musculoskeletal

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health, including osteoporosis, osteoarthritis, and sarcopenia (11).

As a preventive approach, balanced nutrition and correct dietary changes during the menopausal transition could have substantial positive effects on cardiometabolic risk, musculoskeletal health, and psychological health. To date, there are few studies examining changes in dietary intake during the menopausal transition (12), with inconsistent results and with smaller sample sizes (i.e., <1000 participants). Some studies report no change and some a decrease in total energy intake (TEI) and carbohydrates (13, 14). For health promotion and disease prevention in women transitioning in menopause, it is important to understand whether dietary changes occur. Furthermore, examining possible changes in dietary intake during menopause can also provide more information on whether the observed adverse metabolic changes during menopause can be attributed to dietary changes.

Therefore, we studied the changes in dietary intake in women before and after menopause using data from the CoLaus study. We compared cross-sectionally the dietary intake between pre- and postmenopausal women, and then we examined whether the change in menopausal status was prospectively associated with 5-y changes in dietary intake compared with women who remained premenopausal during the follow-up or were postmenopausal across the study period.

Methods

Study population

The study was carried out within the framework of CoLaus study, a population-based cohort study conducted in Lausanne, Switzerland. The details of the study have been reported elsewhere (15). Briefly, the baseline study was conducted between June 2003 and May 2006 and included 6733 participants, of whom 5064 attended the first follow-up, April 2009 and September 2012. The second follow-up included 4750 participants and was conducted between May 2014 and March 2017. During each visit, information on medical conditions, use of medications, and lifestyle was collected, and each participant was extensively evaluated regarding cardiovascular risk factors, and blood characterization was performed.

Ethical statement

The institutional Ethics Committee of the University of Lausanne, which afterward became the Ethics Commission of Canton Vaud (www.cer-vd.ch), approved the baseline CoLaus study (reference 16/03, decisions of January 13, 2003, and February 10, 2003). The approval was renewed for the first (reference 33/09, decision of February 23, 2009) and the second (reference 26/14, decision of March 11, 2014). The study was performed in agreement with the Declaration of Helsinki and its former amendments, as well as in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Selection criteria

The present study used data from the first and the second follow-up visits of the CoLaus study. A total of 2707 women were included in the first follow-up of CoLaus. Of these, 46 were excluded because there was no information on their menopause status and 222 women were excluded due to no information on dietary intake, leaving 2439 women for the cross-sectional analysis (**Figure 1**). Among them, 271 did not participate in the second follow-up visit of the study, and a further 527 women were excluded because there was no information on menopause status (n = 57), menopause status was unreliable (women reporting being postmenopausal at the first follow-up and premenopausal at the second follow-up; n = 15), or dietary intake was not known (n = 455), leaving 1641 women for the prospective analysis (Figure 1).

Menopause status

Women participating in the study were asked whether they were still having menses. Women reporting "no" were classified as postmenopausal and as premenopausal if they answered "yes." Based on the self-reported menopausal status at the first and second follow-up visits, women were classified as being *1*) *premenopausal-premenopausal* if they remained premenopausal, *2*) *premenopausal-postmenopausal* if they changed their status, *3*) and otherwise as *postmenopausal-postmenopausal*.

Dietary assessment

Dietary intake of 4 wk prior to the interview was assessed using a self-administered, semiquantitative FFQ that also included portion size (16). This FFQ has been validated among 626 volunteers from the Geneve population (16, 17). The FFQ consisted of 97 different food items accounting for >90% of the intake of calories, proteins, fats, carbohydrates, alcohol, cholesterol, vitamin D, and retinol and 85% of fiber, carotene, and iron. For each item, consumption frequencies ranging from "less than once during the last 4 weeks" to "2 or more times per day" were provided, and the participants indicated the average serving size (smaller, equal, or bigger) compared with a reference size. To calculate nutrient intakes, frequency of intake was multiplied by the nutrient composition of the specified portion size. Nutrient estimates were based on the French CIQUAL food composition table. Two values of TEI were computed: one including alcohol consumption, the other not. Carbohydrates (total and subtypes such as disaccharides), proteins (total, plant and animal derived), and fats (total, SFAs, MUFAs, and PUFAs) were expressed as a percentage of TEI (alcohol excluded). All food items were reported in g/d. Participants were further dichotomized based on whether they adhered to dietary guidelines recommendations of the Swiss Society of Nutrition, including *1*) 2 and 3 portions of fruits and vegetables per day, *2*) <3 portions of meat per week, *3*) >1 portion of fish per week, and *4*) 3 portions of dairy products per day (milk, yogurt, hard and soft cheese) (18). For each food item recommendation (fruits, vegetables, meat, fish, dairy products), a binary variable (1 = yes, 0 = no) was computed, classifying participants on whether they adhered to the recommendation per item. We also further divided participants into adhering to 3 or more recommendations.

Covariates

On the basis of biological plausibility and previous literature, we selected the potential confounding factors, namely, age, marital status, education level, BMI (in kg/m^2), history of CVD and diabetes, serum lipids, and antihypertensive, hypolipidemic, and antidiabetic treatments (19, 20).

Sociodemographic and lifestyle data were collected by self-administered questionnaires. Sociodemographic data included age, marital status (married, divorced, single, or widowed), and education level (university education, high school, apprenticeship, and mandatory

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468, and 33CS30-148401).

The study participants of CoLaus have not provided consent to publicly share the individual-level data underlying this study. Information related to data access is available to qualified, interested researchers at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/. All responses to data-sharing requests must comply with the ethical and legal constraints of Switzerland.

Author disclosures: The authors report no conflicts of interest.

Supplemental Tables 1–10 are available from "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com.jn/.

PM-V and TM contributed equally to this work.

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Abbreviations used: CVD, cardiovascular disease; FSH, follicle-stimulating hormone; TEI, total energy intake; T2D, type 2 diabetes.

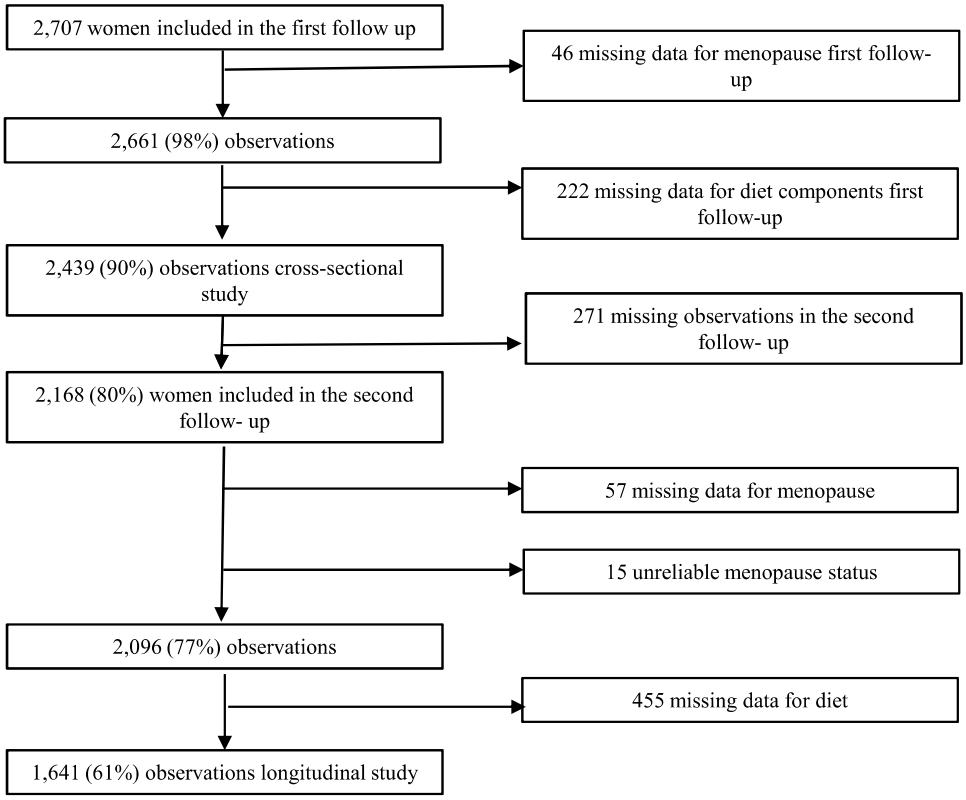

FIGURE 1 Selection of participants for the present study.

education). Health characteristics included BMI calculated and categorized in 3 groups (normal, 18.5 to <25; overweight, 25 to <30; and obese, ≥30) based on the WHO recommendations (21). CVD was defined as a history of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty. T2D mellitus was diagnosed if fasting serum glucose concentration was ≥7 mmol/L or if the participants used glucose-lowering medication. Participants also indicated whether they used antihypertensive medications or lipid-lowering medications.

Statistical analysis

Statistical analyses were performed using Stata version 15.1 for Windows (StataCorp). Continuous variables were reported as mean ± SD if normally distributed and as median and IQR if not normally distributed; categorical variables were presented as numbers and percentages. The normality of continuous variables was checked using a histogram and the Shapiro–Wilk test.

Cross-sectional analysis

We compared the sociodemographic, diet, and other lifestyle variables between pre- and postmenopausal women included in the cross-sectional analysis, using the Student *t* test, Wilcoxon rank-sum test, and χ^2 test, as appropriate. Age and multivariable-adjusted linear and logistic regression models were performed to examine whether menopause status (premenopausal compared with postmenopausal) was cross-sectionally associated with TEI, food intake, and dietary recommendations. Factors for multivariable analyses were selected based on current knowledge and literature, and they were adjusted for age, education level, civil status, BMI, prevalent CVD and diabetes, and use of medications, including lipid-lowering medications and antihypertensive treatment.

Longitudinal analysis

We used repeated-measures analysis to analyze dietary changes during the follow-up among *1*) women who transitioned from premenopausal to menopausal, as well as among women who remained *2*) premenopausal or *3*) postmenopausal. To examine whether changing menopausal status during the follow-up was independently associated with changes in TEI and dietary intake, we performed a linear mixed model with random effects of menopausal categories: *1*) premenopausal during the follow-up (as reference), *2*) women who transitioned to menopause, and *3*) women who were postmenopausal during the all study periods. The models were adjusted for age, education level, civil status, BMI, prevalent CVD and diabetes, and use of medications, including lipid-lowering medications and antihypertensive treatment. Similarly, to investigate whether menopause status would affect changes over time in adherence with the dietary guidelines, we applied mixed-effects logistic regression .

Sensitivity analysis

As a sensitivity analysis, to investigate the possibility of selection bias, we examined whether there were differences in sociodemographic characteristics between included and excluded women from the cross-sectional analysis by using χ^2 or Student *t* test. Because some of the dietary variables were not normally distributed, we also reran the main linear regression and linear mixed analyses using natural log-transformed values, and for longitudinal analysis, we also did a sensitivity analysis applying a generalized linear mixed model, which does not require the response variable to be normally distributed. To explore the impact of BMI, we stratified the main cross-sectional and longitudinal analyses by BMI categories [normal (<25) compared with overweight/obese (≥25)]. To evaluate a possible overadjustment for age or the impact of TEI without alcohol, we ran a sensitivity analysis excluding age as a covariate and using TEI without alcohol as a variable instead of TEI with alcohol. Because physical activity and weight changes during menopausal transition could be related to diet (22), in the longitudinal analysis, we included BMI at both visits as a covariate and also baseline physical activity (expressed as total time min/d). To examine the impact of dietary supplements, we ran the main analyses *1*) adjusting for supplement use (vitamins and minerals, calcium and vitamin D) or *2*) excluding women reporting dietary supplements.

TABLE 1 Demographic and clinical characteristics of women at the first and second follow-ups (after 5 y) of the CoLaus study[1]

Characteristic	First follow-up	Second follow-up
Sample size	$n = 2439$	$n = 1656$
Age, y	58.2 ± 10.5	62.9 ± 9.9
BMI	25.5 ± 4.9	25.7 ± 4.9
BMI category,[2] *n* (%)		
Normal	1284 (53.1)	832 (50.3)
Overweight	753 (31.1)	550 (33.2)
Obese	383 (15.8)	272 (16.4)
Waist circumference, cm	87.4 ± 12.8	86.3 ± 12.6
Smoking status, *n* (%)		
Former	826 (33.9)	593 (36.7)
Never	1126 (46.3)	752 (46.6)
Current	482 (19.8)	269 (16.7)
Educational level, *n* (%)		
University education	443 (18.2)	322 (19.4)
High school	659 (27)	477 (28.8)
Apprenticeship	881 (36.1)	618 (37.3)
Mandatory education	455 (18.7)	239 (14.4)
Marital status, *n* (%)		
Single	413 (16.9)	288 (17.4)
Married/cohabitating	1207 (49.5)	774 (46.7)
Divorced	593 (24.3)	410 (24.8)
Widowed	226 (9.3)	182 (11)
Menopause status, *n* (%)		
Premenopause	677 (27.8)	254 (15.3)
Postmenopause	1762 (72.2)	1397 (84.4)
History of CVD, *n* (%)		
Yes	76 (3.1)	78 (4.7)
No	2363 (96.9)	1578 (95.3)
History of diabetes, *n* (%)		
Yes	137 (5.6)	94 (5.7)
No	2295 (94.4)	1562 (94.3)
Serum lipids, mmol/L		
HDL cholesterol	1.8 ± 0.4	1.8 ± 0.4
LDL cholesterol	3.4 ± 0.9	3.2 ± 0.9
Triglycerides	1.2 ± 0.6	1.2 ± 0.8
Treatments, *n* (%)		
Antihypertensive	584 (23.9)	474 (28.6)
Hypolipidemic	371 (15.2)	272 (16.4)
Antidiabetic	69 (2.8)	73 (4.4)

[1]Values are mean ± SD unless otherwise indicated. CVD, cardiovascular disease.
[2]BMI (in kg/m^2) categories: normal, 18.5 to <25; overweight, 25 to <30; and obese, ≥30.

In addition, we explored whether menopause status in the cross-sectional and longitudinal analyses was associated with supplement intake. An additional sensitivity analysis was performed censoring the nutrition data at the 0.5 and 99.5 percentiles to account for the influence of outliers.

To account for multiple testing, we applied a conservative Bonferroni-corrected $P < 0.002$ [0.05 divided by the number of diet variables ($n = 30$)].

Results

Sample characteristics

The characteristics of the study sample of women included in the cross-sectional and longitudinal analyses are shown in Table 1. After 5 y, women reported higher use of antidiabetic medications and were less frequently current smokers.

Cross-sectional analysis: Menopausal status and dietary intake at first follow-up

Compared with premenopausal women, postmenopausal women were older, had higher BMI, and had more prevalent CVD and T2D (**Supplemental Table 1**). No differences were found in TEI between nonmenopausal and menopausal women (mean ± SD; 1686 ± 638 compared with 1633 ± 649 kcal/d). Compared with premenopausal women, postmenopausal women reported consuming less meat, pasta, added sugar, polysaccharides, MUFAs, and cholesterol but more dairy products, fruits, monosaccharides, and retinol (**Supplemental Table 2**). However, the multivariable linear regression analysis showed no association between menopause status, TEI, and the intake of micro- and macronutrients (Table 2). With no adjustments for potential confounding factors, compared with premenopausal women, postmenopausal women showed higher adherence to the dietary guidelines on fruit intake [*n* (%) 809 (33.2) compared with 253 (19.4)] and meat intake [769 (31.5) compared with 248 (10.2)], but no difference was found between the 2 women-groups for other dietary components (Supplemental Table 2). The multivariable logistic regression analysis showed no association between menopause status and adherence to Swiss dietary guidelines related to intake of fruits or for vegetables, meat, or dairy products (Table 2).

Longitudinal analysis: Changes in menopausal status and changes in dietary intake

During the follow-up, there were 244 women who remained premenopausal, and 229 women transitioned from premenopausal to menopause; the rest ($n = 1168$) were postmenopausal women at both first and second follow-up. TEI and dietary intake according to different menopausal status at the first follow-up and after 5 y are summarized in **Supplemental Table 3**.

For the women remaining premenopausal during follow-up, there was an increase in intakes of total fat and MUFAs and a decrease in intakes of pastries, pasta, added sugar, total carbohydrates, and monosaccharides. Premenopausal women transitioning to menopause, during the follow-up, consumed less milk and pasta and more MUFAs, whereas no differences were found for the other dietary components. Menopausal women from the first to second follow-up showed a reduction in intakes of milk, bread and cereals, pasta, vegetable proteins, total carbohydrates, monosaccharides, polysaccharides, and fiber but increases in fish, total fat, SFAs, MUFAs, cholesterol, and vitamins (Supplemental Table 3). The multivariable linear mixed-model analysis showed that, compared with women remaining premenopausal during the follow-up, women transitioning to menopause or being postmenopausal had no significant differences in changes in dietary intake over 5 y ($P < 0.002$). Similarly, women transitioning to menopause or being postmenopausal, compared with women remaining premenopausal during the follow-up, showed no differences in changes in adherence to Swiss dietary guidelines (18) (Table 3).

Sensitivity analysis

Supplemental Table 4 summarizes the characteristics of women included in the final cross-sectional analysis ($n = 2439$) and of those excluded ($n = 268$). Compared with women included in the cross-sectional analysis, excluded women were less frequently married and single and more divorced or widowed, had a lower education level, and mostly were current smokers with a higher prevalence of history of diabetes. Stratification analyses by BMI categories did not show a

TABLE 2 Multivariable cross-sectional association between menopausal status (postmenopausal compared with premenopausal women) and dietary intake at the first follow-up of the CoLaus study[1]

Characteristic	β or OR (95% CI)[4]	*P* value
Sample size	$n = 2439$	
Total energy, kcal/d	−36.6 (−116, 43.1)	0.37
Daily intake, animal products, g/d		
Meat	9.4 (0.6, 18.1)	0.04
Fish	−0.06 (−4.8, 4.7)	0.98
Milk	−9.9 (−22.4, 2.5)	0.12
Dairy products	0.2 (−18.9, 19.3)	0.98
Daily intake, other foods, g/d		
Bread and cereals	−3.7 (−11.8, 4.3)	0.36
Pastries	0.09 (−2.2, 2.1)	0.80
Pasta	−9.8 (−16.8, −2.7)	0.01
Added sugar	−0.4 (−1.3, 0.5)	0.41
Vegetable oils	0.3 (−0.6, 1.2)	0.58
Fruits	13.7 (−18.8, 46.2)	0.41
Vegetables	−0.2 (−17.8, 17.4)	0.98
Dietary intake (% of TEI)		
Total proteins	0.4 (−0.02, 0.8)	0.06
Vegetable proteins	−0.1 (−0.2, 0.05)	0.17
Animal proteins	0.5 (0.03, 1)	0.04
Total carbohydrate	−0.8 (−1.9, 0.4)	0.18
Monosaccharides	0.5 (−0.6, 1.6)	0.36
Polysaccharides	−1.2 (−2.2, −0.3)	0.01
Total fat	−0.1 (−0.9, 0.8)	0.88
SFAs	−0.2 (−0.6, 0.2)	0.39
MUFAs	0.04 (−0.4, 0.5)	0.85
PUFAs	0.05 (−0.1, 0.2)	0.63
Daily nutrient intake per day		
Alcohol, g	5.6 (−3.8, 15.1)	0.24
Fiber, g	−0.04 (−1.2, 1.1)	0.95
Cholesterol, mg	0.2 (−17.4, 17.9)	0.98
Calcium, mg	−18.2 (−81.2, 44.8)	0.57
Iron, mg	0.04 (−0.5, 0.5)	0.88
Retinol, μg	13 (−76.3, 102)	0.78
Carotene, μg	−14.7 (−447, 417)	0.95
Vitamin D, μg	0.2 (−0.1, 0.4)	0.30
Adherence to dietary guidelines		
Fruits	1.0 (0.7, 1.2)	0.70
Vegetables	1.2 (0.8, 1.9)	0.35
Meat[2]	0.9 (0.7, 1.2)	0.66
Fish[3]	1.1 (0.8, 1.4)	0.64
Dairy products	0.9 (0.6, 1.2)	0.46
Guidelines adherence score		
At least 3 recommendations	1.0 (0.7, 1.4)	0.84

[1]Values are coefficients β (95% CI) for each food item and OR (95% CI) for dietary guidelines [18], comparing postmenopausal to nonmenopausal women. TEI, total energy intake.
[2]Included poultry.
[3]Included fresh and fried/baked fish.
[4]Obtained from linear or logistic regression models adjusted for age, BMI, education level, civil status, prevalent cardiovascular and diabetes, and use of antihypertensive and hypolipidemic treatments have been applied

role of BMI in the cross-sectional (**Supplemental Table 5**) and longitudinal (**Supplemental Table 6**) associations between menopause status and dietary intake. Restricting the analyses to nutrition data within 0.5 and 99.5 percentiles and using natural log-transformed values of dietary variables yielded similar results to the main analyses (data not shown). Also, applying generalized linear mixed models (**Supplemental Table 7**) did not significantly change the main results. Unlike the results reported in the main analyses, by removing age as a covariate, we found in the cross-sectional analysis that menopause status was associated with pasta, added sugar, and adherence to fruit dietary recommendations ($P < 0.002$) (**Supplemental Table 8**), whereas in the longitudinal analysis, postmenopausal women, compared with postmenopausal women after 5 y, significantly reported higher intakes of dairy products and fruits, lower intake of pasta, and higher adherence to fruit and meat dietary recommendations ($P < 0.002$) (**Supplemental Table 9**). Performing the longitudinal analysis with adjustment for BMI at 2 time points and also for baseline physical activity (**Supplemental Table 10**) or using TEI without alcohol did not

TABLE 3 Multivariable longitudinal association between menopausal categories (premenopausal as reference group, menopausal transition, and postmenopausal) and dietary intake in the first and second follow-up (after 5 y) of the CoLaus study[1]

	Pre-postmenopause		Post-postmenopause	
Characteristic	β or OR (95% CI)[4]	*P* value	β or OR (95% CI)[4]	*P* value
Sample size	$n = 229$		$n = 1168$	
Total energy, kcal/d	−36.6 (−136, 62.7)	0.47	−34.8 (−136, 66.3)	0.50
Daily intake, animal products, g/d				
Meat	−1.4 (−10, 7.2)	0.74	5.1 (−3.6, 13.9)	0.25
Fish	−0.7 (−5.5, 4.0)	0.76	0.9 (−3.9, 5.7)	0.72
Milk	−6.8 (−21.9, 8.2)	0.38	−9.6 (−24.9, 5.8)	0.22
Dairy products	−1.8 (−23.7, 20.1)	0.87	4.9 (−17.4, 27.2)	0.67
Daily intake, other foods, g/d				
Bread and cereals	3.2 (−6.9, 13.3)	0.54	−1.4 (−11.6, 8.9)	0.79
Pastries	−1.8 (−5.4, 1.8)	0.34	0.1 (−3.6, 3.8)	0.94
Pasta	−3.8 (−12.8, 5.2)	0.41	−10.6 (−20.8, −2.5)	0.01
Added sugar	−0.9 (−2.0, 0.2)	0.11	−0.7 (−1.8, 0.4)	0.20
Vegetable oils	0.4 (−0.7, 1.6)	0.44	0.6 (−0.6, 1.7)	0.34
Fruits	4.8 (−34, 43.5)	0.81	20.2 (−19.3, 59.6)	0.32
Vegetables	−3 (−22.6, 16.6)	0.76	2.4 (−17.5, 22.3)	0.81
Dietary intake, % of TEI				
Total proteins	−0.1 (−0.6, 0.4)	0.65	0.4 (−0.1, 0.9)	0.16
Vegetable proteins	0.1 (−0.1, 0.3)	0.33	−0.04 (−0.2, 0.1)	0.63
Animal proteins	−0.2 (−0.8, 0.4)	0.47	0.4 (−0.2, 1)	0.15
Total carbohydrates	0.01 (−1.4, 1.4)	0.99	−0.8 (−2.2, 0.6)	0.28
Monosaccharides	−0.5 (−1.8, 0.8)	0.42	0.02 (−1.3, 1.3)	0.97
Polysaccharides	0.5 (−0.6, 1.7)	0.38	−0.8 (−2.0, 0.4)	0.20
Total fat	0.1 (−0.9, 1.2)	0.81	0.1 (−1, 1.1)	0.90
SFAs	−0.2 (−0.7, 0.3)	0.42	−0.3 (−0.8, 0.2)	0.26
MUFAs	0.3 (−0.3, 0.9)	0.33	0.2 (−0.3, 0.8)	0.41
PUFAs	0.1 (−0.1, 0.3)	0.49	0.1 (−0.1, 0.3)	0.21
Daily nutrient intake per day				
Alcohol, g	−1.5 (−13.1, 10)	0.79	2.1 (−9.7, 13.9)	0.73
Fiber, g	0.3 (−1.0, 1.7)	0.63	0.3 (−1.1, 1.7)	0.68
Cholesterol, mg	−7.1 (−28.5, 14.2)	0.51	−7.4 (−29.2, 14.3)	0.50
Calcium, mg	−48 (−122, 26)	0.20	−16.2 (−91.5, 59.1)	0.67
Iron, mg	−0.1 (−0.7, 0.5)	0.68	−0.1 (−0.7, 0.5)	0.78
Retinol, μg	−41 (−129, 46.7)	0.36	−9.2 (−98.5, 80.1)	0.84
Carotene, μg	−254 (−786, 278)	0.35	−195 (−737, 346)	0.48
Vitamin D, μg	−0.2 (−0.4, 0.1)	0.31	0.1 (−0.2, 0.4)	0.62
Adherence to dietary guidelines				
Fruits	−0.1 (−0.6, 0.4)	0.75	−0.1 (−0.6, 0.4)	0.64
Vegetables	0.1 (−0.5, 0.8)	0.70	0.1 (−0.5, 0.8)	0.69
Meat[2]	0.4 (−0.1, 0.9)	0.15	0.2 (−0.3, 0.7)	0.48
Fish[3]	0.1 (−0.5, 0.7)	0.75	0.2 (−0.3, 0.8)	0.43
Dairy products	−0.3 (−2, 1.4)	0.70	−0.3 (−1.9, 1.3)	0.68
Guidelines adherence score				
At least 3 recommendations	0.2 (−0.3, 0.7)	0.41	0.1 (−0.4, 0.6)	0.72

[1] Values are coefficients β (95% CI) for each food item and OR (95% CI) for dietary guidelines [18], between menopausal categories, with women being premenopausal at both first and second follow-ups as reference category. TEI, total energy intake.
[2] Included poultry.
[3] Included fresh and fried/baked fish.
[4] Obtained from linear or logistic mixed-effect models adjusted for age, BMI, civil status, prevalent cardiovascular and diabetes, and use of hypertensive and hypolipidemic treatments have been applied.

materially change the results (data not shown). Also, the cross-sectional and longitudinal analyses adjusted for supplement use (vitamins and minerals, calcium and vitamin D) or excluding women reporting dietary supplements did not materially change the results. Finally, menopause status was not associated with supplement intake at baseline or with changes in supplement intake during the 5 y of follow-up (data not shown).

Discussion

To our knowledge, this is the first large study to comprehensively investigate the associations of menopause status and transition to menopause with dietary changes. We observed that among adult Swiss women, there are changes in diet over time, but these changes are independent of the level and changes in menopause status.

In our study, menopause per se was not a period of marked changes in TEI and dietary intake even after stratification by BMI. This is in line with a study of 898 women that reported that nutrient intakes over a period of 5 to 6 y were similar across menopausal status, with menopause not being independently associated with changes in diet (12). Also, a small study of 94 women showed no role of menopausal status on any of macronutrients investigated during 5 y of follow-up, except for an increase in carbohydrate intake in the menopausal transition group compared with women being postmenopausal for over 12 mo. However, in the later study, the premenopausal women and women transitioning into menopause were grouped together, making the interpretation of the results challenging (13).

Cross-sectional analysis

In the cross-sectional analysis, postmenopausal women consumed more fruits and retinol but less meat, pasta, and added sugar compared with nonmenopausal women. Adherence to dietary guidelines was higher in postmenopausal women. A possible explanation for these differences could be that postmenopausal women, as they age, could have a higher health awareness due to a higher number of diagnosed conditions, as well as a higher purchasing power. This is also supported by our results that, after adjusting for cardiovascular risk factors and chronic conditions, showed no differences between pre- and postmenopausal women on all food items. Also, after removing age as a covariate from the analyses, some of these results remained significant.

Longitudinal analysis

In the prospective analysis, the menopause transition was not associated with changes in TEI and diet, except for a decrease in milk consumption and pasta. The decrease in milk and pasta consumption over a period of 5 y was also observed in premenopausal and postmenopausal women, albeit the decline in milk intake was nonsignificant in premenopausal women. This suggests that the decrease in milk and pasta intake might not be due to the changes in menopause status but could be related to other factors. For instance, the decrease in milk consumption could be due to increased awareness of lactose intolerance and/or due to the large availability in the past years of plant-based types of milk in the market. Many marketing campaigns advertise the use of different types of milk deriving from soya, coconut, almond, rice, and so on rather than cow and other animals, which were constituting the milk component included in our analyses.

Considering age and menopause are correlated, it is difficult to understand the contribution of each of the 2 factors in affecting dietary changes. Removing age from our analyses, postmenopausal women at the first follow-up, compared with postmenopausal women after 5 y, showed higher intakes of dairy products and fruits, lower intake of pasta, and higher adherence to fruit and meat dietary recommendations but not other dietary factors considered in the current study. Future research is needed to understand the independent effects of menopause and age (Supplemental Tables 8 and 9).

Menopause, cardiometabolic changes, and diet

While women undergo menopause, they experience various symptoms, including hot flashes, night sweats, depression, irritability, and anxiety, which might increase the risk of CVD and hamper quality of life. The decline in estrogen concentrations and accumulation of iron during menopause can negatively affect metabolism, potentially leading to weight gain and repercussions on cholesterol levels and carbohydrate digestion (23). In addition, the hormonal changes during menopause can lead to decreased bone density and adverse metabolic changes, which can, in turn, increase the risk of fractures (24) and overall mortality. These adverse metabolic changes in menopause, including weight gain, can also be due to adverse changes in dietary intake in women transitioning into menopause or due to increases in energy intake because of increased appetite (13, 25). Future research is needed to explore dietary factors that could counteract the adverse metabolic changes women experience after menopause and improve women's overall health.

Public health implications

Healthier eating habits (e.g., more vegetables and fruits) and specific educational campaigns throughout women's lives could be important in maintaining optimal health and reducing the development of several medical complications during the menopausal years. Yet, there is little research examining the effect of changes in diet during menopausal transition on metabolic changes and cardiovascular health. Future studies should examine which dietary components or dietary patterns are associated with better health during menopausal transition and whether the identified dietary components/patterns have beneficial and long-term effects in women.

Study limitations

This study has several limitations. First, the food questionnaire is based on self-reported data, with the possibility of inaccurate reporting and recall bias. Although FFQs can be used to estimate TEI, the overall TEI would be a less accurate estimate, and therefore our results on TEI should be interpreted with caution (26). The food questionnaire also is focused on a limited number of food items (97 overall), and some food groups were missing.

We had no information on type of carotene intakes but only on total intake of carotene, and therefore, we cannot exclude the possibility that women may have changed the consumption of different types of carotenoids. Also, FFQs may not be very sensitive in detecting dietary changes, despite studies demonstrating that FFQs, compared with 24-h dietary recalls, have greater reproducibility in detecting differences in self-reported dietary intake over time (27). Furthermore, our study included only the population of Lausanne and Caucasian women, and it might not be generalized for all Swiss people, other populations, and other ethnicities. A misclassification of menopause status might be due to self-reported data and missing information regarding the absence of menstruations in the past 12 mo. Also, because the diet in the longitudinal analysis was assessed prospectively, the subjective measure of menopause would probably lead to nondifferential misclassification with respect to the outcome and would therefore bias estimates toward the null. Yet, when exploring the women reporting the age of menopause, 100% of them had reported no menses, suggesting that the misclassification is unlikely to have happened. Future studies with better definition of menopause status are needed to replicate our findings. For instance, self-reported menopause status should capture the lack of menstruations in the past 12 mo. Also, use of biomarkers as follicle-stimulating hormone (FSH) is helpful if the diagnosis is in doubt in women with suspected premature ovarian failure, but concentrations of FSH do not predict when the last menstrual period will occur. Measurement of thyroid-stimulating hormone and prolactin is

also useful in investigating menstrual irregularity (28). Finally, some differences have been reported between included and excluded women regarding smoking status, educational level, marital status, history of diabetes, and antidiabetic treatment, and therefore, the possibility of selection bias cannot be excluded.

Conclusion

In this Swiss population-based study, menopause per se was not associated with changes in TEI and dietary habits or with changes in adherence to dietary guidelines.

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The authors' contributions were as follows—TM: conceived and supervised the study; GG, PM-V, and TM: designed the study; GG, PFR, MG, LB, AB, PM-V, OHF, and TM: participated in data acquisition, collection, analysis, or interpretation; GG and PFR: performed the statistical analyses; GG and TM: drafted the manuscript; PFR, MG, LB, AB, PM-V, and OHF: critically revised the manuscript for intellectual content; and all authors: approved the final version of the manuscript.

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Contents

Supplementary Table 1. Demographic and clinical characteristics of women at the first follow-up of the CoLaus study[1]

	Premenopausal	**Postmenopausal**
Sample size	*n* = 677	*n* = 1,762
Age (years)	46.4 ± 3.8	62.7 ± 8.5
BMI (kg/m²)	24.8 ± 4.8	25.8 ± 4.9
BMI category[2], *n* (%)		
Normal	423 (62.8)	861 (49.3)
Overweight	168 (24.9)	585 (33.5)
Obese	83 (12.3)	300 (17.2)
Waist circumference (cm)	84 ± 11.9	88.7 ± 12.9
Smoking status, *n* (%)		
Former	219 (32.4)	607 (34.5)
Never	309 (45.7)	817 (46.5)
Current	148 (21.9)	334 (19)
Educational level (%)		
University education	181 (26.7)	262 (14.9)
High school	198 (29.2)	461 (26.2)
Apprenticeship	199 (29.4)	682 (38.7)
Mandatory education	99 (14.6)	356 (20.2)
Marital status (%)		
Single	156 (23)	257 (14.6)
Married/cohabitating	360 (53.2)	847 (48.1)
Divorced	157 (23.2)	436 (24.7)
Widowed	4 (0.6)	222 (12.6)
History of CVD (%)		
Yes	6 (0.9)	70 (3.4)
No	671 (99.1)	1692 (96)
History of diabetes (%)		
Yes	9 (1.3)	128 (7.3)
No	666 (98.7)	1629 (92.7)
Serum lipids, mmol/L		
HDL cholesterol	1.8 ± 0.4	1.8 ± 0.4
LDL cholesterol	3.2 ± 0.8	3.6 ± 0.9

Triglycerides	1 ± 0.6	1.2 ± 0.6
Treatments (%)		
Antihypertensive	59 (8.7)	525 (29.8)
Hypolipidemic	16 (2.4)	355 (20.2)
Antidiabetic	4 (0.6)	65 (3.7)

[1]Values are mean ± SD unless otherwise indicated.

[2]BMI categories: normal 18.5 to < 25 kg/m^2, overweight 25 to < 30 kg/m^2, obese ≥ 30 kg/m^2.

Supplementary Table 2. Dietary intake characteristics in postmenopausal and non-menopausal women at the first follow-up of the CoLaus study[1]

	Premenopausal	**Postmenopausal**	***P* value**
Sample size	*n* = 677	*n* = 1,762	
Total energy (kcal/d)	1686 ± 638	1633 ± 649	0.07
Daily intake, animal products (g/day)			
Meat [a]	62.5 [41.2 - 95.2]	57.2 [35 - 86.2]	**0.001**
Fish [a]	31.2 [16.6 - 50.9]	29.5 [16.2 - 48.2]	0.24
Milk [a]	30 [0 - 90]	29.6 [0 - 75]	0.04
Dairy products [a]	109 [64.5 - 182]	126 [65 - 214]	**0.001**
Daily intake, other foods (g/day)			
Bread and cereals [a]	67.7 [41.2 - 104]	75 [41.4 - 123]	0.24
Pastries [a]	16.9 [8.6 - 30.4]	16.3 [7.8 - 29.5]	0.46
Pasta [a]	85 [57.8 - 128]	61.8 [37.5 - 89.2]	**0.001**
Added sugar [a]	0.7 [0 - 8]	0.1 [0 - 4]	**0.001**
Vegetable oils [a]	7 [3.5 - 10.5]	7 [3.5 - 10.5]	0.28
Fruits [a]	174 [83.2 - 319]	217 [115 - 390]	**0.001**
Vegetables [a]	172 [118 - 239]	169 [115 - 244]	0.44
Dietary intake (% of TEI)			
Total proteins	15.6 ± 3.5	15.5 ± 3.6	0.35
Vegetable proteins	4.8 ± 1.2	4.7 ± 1.2	0.80
Animal proteins	10.9 ± 3.8	10.7 ± 4.0	0.45
Total carbohydrate	46.8 ± 8.5	47.1 ± 9.3	0.43
Monosaccharides	23.7 ± 8.2	25.1 ± 8.9	**0.001**
Polysaccharides	22.9 ± 7.7	21.9 ± 7.8	0.003
Total fat	35.1 ± 6.8	34.4 ± 7.1	0.04
SFAs	12.5 ± 3.2	12.4 ± 3.4	0.74
MUFAs	14.5 ± 3.8	13.9 ± 3.8	**0.001**
PUFAs	5.0 ± 1.5	4.9 ± 1.6	0.50
Alcohol (g/day) [a]	20.2 [3.4 - 49.6]	19.8 [0 - 55.2]	0.37
Fibre (g) [a]	13.3 [9.5 - 19.6]	14.3 [9.9 - 20.5]	0.02
Cholesterol (mg)	283 ± 139	265 ± 144	0.005
Ca (mg)	942 ± 474	980 ± 518	0.10
Fe (mg)	9.8 ± 4.0	9.7 ± 4.2	0.33
Retinol (µg) [a]	281 [180 - 463]	326 [204 - 585]	**0.001**

Carotene (mg) [a]	3.5 [2.4 - 5.5]	3.3 [2.3 - 5]	0.03
Vitamin D (µg) [a]	2.1 [1.2 - 3.3]	2.1 [1.2 - 3.0]	0.18
Adherence to dietary guidelines (%)			
Fruits	253 (10.4)	809 (33.2)	**0.001**
Vegetables	57 (2.3)	167 (6.8)	0.42
Meat [b]	249 (10.2)	773 (31.7)	**0.001**
Fish [c]	506 (20.8)	1,304 (53.5)	0.71
Dairy products	88 (3.6)	260 (10.7)	0.26
Guidelines adherence score			
At least 3 recommendations	137 (5.6)	470 (19.3)	**0.001**

[1]Values are mean ± SD and statistical analysis conducted for each food item by student's t-test. [a] Values are expressed as median [IQR] and statistical analysis conducted for each item by Wilcoxon rank-sum test. Compliance with dietary guidelines [18] and compliance score are number of subjects (percentage) and statistical analysis conducted for each item by chi-square test. [b] Included poultry; [c] Included fresh and fried/baked fish. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

Supplementary Table 3. Dietary intake characteristics between premenopausal, menopausal transition and postmenopausal women at the first and second follow-up (after 5 years) of the CoLaus study[1]

	Premenopausal *n* = 224			**Premenopausal - Postmenopausal** *n* = 229			**Postmenopausal** *n* = 1,168		
	First follow-up	Second follow-up	*P* value	First follow-up	Second follow-up	*P* value	First follow-up	Second follow-up	*P* value
Total energy (kcal/d)	1677 ± 601	1598 ± 559	0.04	1675 ± 578	1584 ± 574	0.02	1677 ± 648	1646 ± 649	0.10
Daily intake, animal products (g/day)									
Meat [a]	67.1 [43.9 - 97.4]	67.2 [41.4 - 98.4]	0.65	61.1 [40.6 - 95.2]	56.5 [36.3 - 91.2]	0.01	59.1 [36.3 - 87]	57.1 [35.3 - 87.7]	0.31
Fish [a]	31.2 [17.7 - 50.9]	34 [17.7 - 53.7]	0.45	30.8 [17.1 - 49.6]	33.5 [18 - 52.3]	0.43	30.9 [17.8 - 47.4]	32.1 [17.8 - 52.7]	0.002
Milk [a]	30 [0 - 105]	15 [0 - 75]	0.01	20.1 [0 - 80.4]	13.4 [0 - 75]	**0.001**	30 [0 - 75]	15 [0 - 75]	**0.001**
Dairy products [a]	112 [64.8 - 183]	94 [54.4 - 168]	0.06	111 [73.2 - 181]	104 [60 - 180]	0.20	127 [70 - 21]	128 [71.9 - 213]	0.18
Daily intake, other foods (g/day)									
Bread and cereals [a]	66.1 [39.9 - 102]	58.8 [35.8 - 94.6]	0.12	71.4 [45.5 - 105]	67.1 [34.2 - 102]	0.02	75 [43.4 - 125]	66.6 [38.1 - 107]	**0.001**
Pastries [a]	19.6 [10.7 - 31.8]	16.1 [7.8 - 28.8]	**0.001**	15.4 [7 - 31.8]	15.4 [7.8 - 7]	0.18	18.2 [9.5 - 30.8]	17.4 [8.9 - 29.3]	0.03
Pasta [a]	89.7 [60.3 - 142]	83.5 [51.2 - 125]	0.002	85.4 [58 - 127]	70.7 [45.5 - 97.8]	0.002	65.1 [41.6 - 90.5]	60.7 [35.7 - 87.9]	**0.001**
Added sugar [a]	0.7 [0 - 8]	0.4 [0 - 4]	**0.001**	0.4 [0 - 4]	0.3 [0 - 4]	0.96	0.3 [0 - 4]	0.3 [0 - 4]	0.85
Vegetable oils [a]	7 [3.6 - 10]	7 [3.5 - 10.2]	0.55	7 [3.5 - 10.4]	7 [3.5 - 10]	0.63	7 [3.5 - 10.5]	7 [3.5 - 10.5]	0.17
Fruits [a]	175 [90.1 - 318]	166 [93.9 - 305]	0.73	179 [94.5 - 339]	191 [99.3 - 335]	0.47	224 [123 - 393]	219 [121 - 376]	0.18
Vegetables [a]	172 [122 - 240]	171 [119 - 250]	0.71	169 [119 - 234]	169 [119 - 244]	0.66	172 [119 - 244]	170 [117 - 246]	0.77

Dietary intake (% of TEI)									
Total proteins	15.8 ± 3.7	16 ± 3.6	0.40	15.6 ± 3	15.6 ± 3.5	0.85	15.4 ± 3.4	15.6 ± 3.4	0.18
Vegetable proteins	4.7 ± 1.2	4.7 ± 1.2	0.48	4.9 ± 1.1	4.7 ± 1.2	0.14	4.8 ± 1.2	4.6 ± 1.2	**0.001**
Animal proteins	11.1 ± 4.1	11.4 ± 4.1	0.35	10.7 ± 3.4	10.9 ± 3.9	0.52	10.6 ± 3.8	10.9 ± 3.8	0.03
Total carbohydrate	46.9 ± 8.3	44.4 ± 9.2	**0.001**	46.9 ± 8.4	45.2 ± 8.8	0.02	47.2 ± 8.9	45.6 ± 9	**0.001**
Monosaccharides	24.2 ± 8	22.5 ± 8.3	**0.001**	23.2 ± 8.1	23.1 ± 8.3	0.86	25.1 ± 8.2	24.3 ± 8.3	0.002
Polysaccharides	22.6 ± 7.9	21.8 ± 7.9	0.15	23.5 ± 7.3	22 ± 7.8	0.02	22 ± 7.6	21.2 ± 7.4	**0.001**
Total fat	34.8 ± 6.5	36.9 ± 7.4	**0.001**	35.1 ± 7.2	36.5 ± 7	0.02	34.5 ± 6.8	35.9 ± 6.9	**0.001**
SFAs	12.6 ± 3.2	12.8 ± 3.2	0.46	12.5 ± 3.4	12.7 ± 3.2	0.57	12.5 ± 3.3	12.9 ± 3.3	**0.001**
MUFAs	14.3 ± 3.4	15.8 ± 4.4	**0.001**	14.5 ± 4	15.6 ± 4.1	**0.001**	14 ± 3.8	14.8 ± 4	**0.001**
PUFAs	4.8 ± 1.3	5 ± 1.5	0.05	4.9 ± 1.5	5 ± 1.4	0.72	4.8 ± 1.5	5 ± 1.5	0.04
Alcohol (g/day) [a]	19.9 [3.8 - 50.8]	21.1 [6.4 - 46.2]	0.41	24.4 [8.2 - 50]	24.3 [8.3 - 59]	0.07	19.8 [3.3 - 54.6]	19.8 [3.3-57.5)	0.30
Fibre (g) [a]	13 [9.9 - 19.6]	12.2 [9.1 - 18.4]	0.32	13.7 [9.9 - 19.9]	13.3 [9.3 - 19]	0.05	14.5 [10.2 - 21.1]	14 [9.6 - 20.3]	**0.001**
Cholesterol (mg)	282 ± 133	285 ± 131	0.75	279 ± 122	276 ± 128	0.75	267 ± 140	284 ± 147	**0.001**
Ca (mg)	964 ± 433	893 ± 444	0.01	921 ± 435	894 ± 470	0.45	999 ± 520	976 ± 479	0.15
Fe (mg)	9.7 ± 3.8	9.4 ± 3.3	0.22	9.9 ± 3.6	9.3 ± 3.6	0.01	9.9 ± 4	9.6 ± 3.8	0.01
Retinol (µg) [a]	282 [174 - 462]	264 [165 - 375]	0.08	288 [189 - 449]	263 [179 - 411]	0.05	331 [211 - 591]	332 [211 - 584]	0.91
Carotene (mg) [a]	3.4 [2.4 - 5.4]	3.5 [2.4 - 5.9]	0.57	3.5 [2.5 - 5.5]	3.6 [2.2 - 5.5]	0.84	3.4 [2.4 - 5]	3.4 [2.3 - 5.4]	0.98
Vitamin D (µg) [a]	2.2 [1.3 - 3.4]	2.4 [1.5 - 3.6]	0.12	2.1 [1.3 - 3.3]	2.2 [1.2 - 3.3]	0.82	2.1 [1.3 - 3.1]	2.3 [1.4 - 3.5]	**0.001**
Adherence to dietary guidelines (%)									

Fruits	86 (35.2)	92 (37.7)	**0.001**	93 (40.6)	85 (37.1)	**0.001**	533 (45.6)	556 (47.6)	**0.001**
Vegetables	19 (7.8)	21 (8.6)	**0.001**	21 (9.2)	17 (7.4)	0.002	99 (8.5)	95 (8.1)	**0.001**
Meat [b]	84 (34.4)	82 (33.6)	**0.001**	98 (42.8)	85 (37.1)	**0.001**	511 (43.8)	491 (42)	**0.001**
Fish [c]	185 (75.8)	185 (75.8)	**0.001**	179 (78.2)	172 (75.1)	**0.001**	890 (76.2)	895 (76.3)	**0.001**
Dairy products	29 (11.9)	30 (12.3)	**0.001**	26 (11.3)	23 (10)	**0.001**	174 (14.9)	166 (14.2)	**0.001**
Guidelines adherence score									
At least 3 recommendations	42 (17.2)	49 (20.1)	**0.001**	51 (22.3)	37 (16.2)	**0.001**	312 (26.7)	311 (26.6)	**0.001**

[1]Values are mean ± SD and statistical analysis conducted for each item by paired t-test. [a] Values are expressed as median [IQR] and statistical analysis conducted for each item by Wilcoxon matched-pairs signed-ranks test. Compliance with dietary guidelines [18] and compliance score are number of subjects (percentage) and statistical analysis conducted for each item by chi-square test. [b] Included poultry; [c] Included fresh and fried/baked fish. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acid.

Supplementary Table 4. Demographic and clinical characteristics of included and excluded women at the first follow-up of the CoLaus study[1]

	Included	**Excluded**	***P* value**
Sample size	*n* = 2,439	*n* = 268	
Age (years)	58.2 ± 10.5	58.8 ± 10.9	0.39
BMI (kg/m²)	25.5 ± 4.9	25.8± 5.3	0.35
BMI category[2], *n* (%)			
Normal	1284 (53.1)	131 (51.8)	0.81
Overweight	753 (31.1)	78 (30.8)	
Obese	383 (15.8)	44 (17.4)	
Waist circumference (cm)	87.4 ± 12.8	89.2 ± 12.2	0.03
Smoking status, n (%)			
Former	826 (33.9)	62 (26.5)	0.003
Never	1126 (46.3)	105 (44.9)	
Current	482 (19.8)	67 (28.6)	
Educational level (%)			
University education	443 (18.2)	30 (11.2)	**0.001**
High school	659 (27.0)	73 (27.2)	
Apprenticeship	881 (36.1)	72 (26.9)	
Mandatory education	455 (18.7)	93 (34.7)	
Marital status (%)			
Single	413 (16.9)	34 (12.7)	**0.001**
Married/cohabitating	1207 (49.5)	105 (39.2)	
Divorced	593 (24.3)	72 (26.9)	
Widowed	226 (9.3)	28 (10.4)	
Menopause status (%)			
Pre menopause	677 (27.8)	49 (22.1)	0.07
Post menopause	1762 (72.2)	173 (77.9)	
History of CVD (%)	76 (3.1)	11 (4.1)	0.38
History of diabetes (%)	137 (5.6)	31 (11.7)	**0.001**
Serum lipids, mmol/L			
HDL cholesterol	1.8 ± 0.4	1.8 ± 0.5	0.02
LDL cholesterol	3.4 ± 0.9	3.3 ± 0.9	0.05
Triglycerides	1.2 ± 0.6	1.2 ± 0.8	0.07
Treatments (%)			

Antihypertensive	584 (23.9)	77 (28.7)	0.08
Hypolipidemic	371 (15.2)	40 (14.9)	0.90
Antidiabetic	69 (2.8)	18 (6.7)	**0.001**

[1]Values are mean ± SD unless otherwise indicated. Statistical comparisons between postmenopausal and non-menopausal women performed using chi-square or Student's t-test.

[2]BMI categories: normal 18.5 to < 25 kg/m^2, overweight 25 to < 30 kg/m^2, obese ≥ 30 kg/m^2.

Supplementary Table 5. Multivariable cross-sectional association between menopausal status (postmenopausal versus premenopausal women) and dietary intake at the first follow-up of the CoLaus study stratified by BMI[1]

	BMI[2] < 25 kg/m²		**BMI[2] ≥ 25 kg/m²**	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Total energy (kcal/d)	-86.3 (-182 ; 9)	0.08	25 (-110 ; 160)	0.72
Daily intake, animal products (g/day)				
Meat	4.3 (-4.2 ; 12.8)	0.32	15.7 (-1 ; 32.4)	0.07
Fish	-0.7 (-5.9 ; 4.5)	0.78	-0.2 (-8.8 ; 8.4)	0.96
Milk	-17.7 (-34.9 ; -0.5)	0.04	-0.1 (-18.5 ; 18.2)	0.99
Dairy products	-7.3 (-30.5 ; 15.8)	0.54	7.5 (-24.4 ; 39.4)	0.64
Daily intake, other foods (g/day)				
Bread and cereals	-4.1 (-15 ; 6.7)	0.45	-4.2 (-16.4 ; 8)	0.50
Pastries	0.3 (-3.5 ; 4.1)	0.88	0.4 (-4 ; 4.7)	0.86
Pasta	-10.8 (-19.8 ; -1.8)	0.02	-7.8 (-19.3 ; 3.6)	0.18
Added sugar	-0.06 (-1.3 ; 1.2)	0.93	-0.7 (-2 ; 0.5)	0.26
Vegetable oils	0.4 (-0.8 ; 1.5)	0.54	0.1 (-1.4 ; 1.5)	0.92
Fruits	-21.4 (-62.5 ; 19.7)	0.32	50.4 (-2 ; 103)	0.06
Vegetables	9.7 (-10.4 ; 29.7)	0.34	-17 (-47.9 ; 13.8)	0.28
Dietary intake (% of TEI)				
Total proteins	0.3 (-0.2 ; 0.9)	0.23	0.5 (-0.2 ; 1.2)	0.16
Vegetable proteins	-0.05 (-0.2 ; 0.2)	0.66	-0.2 (-0.4 ; 0.01)	0.06
Animal proteins	0.4 (-0.2 ; 1)	0.22	0.7 (-0.1 ; 1.5)	0.07
Total carbohydrate	-0.8 (-2.3 ; 0.7)	0.28	-1.1 (-2.8 ; 0.6)	0.22
Monosaccharides	-0.04 (-1.5 ; 1.4)	0.96	0.9 (-0.7 ; 2.6)	0.28
Polysaccharides	-0.7 (-2 ; 0.6)	0.27	-2 (-3.5 ; -0.5)	0.01
Total fat	-0.2 (-1.4 ; 1)	0.74	0.4 (-1 ; 1.7)	0.58
SFAs	-0.3 (-0.9 ; 0.2)	0.22	0.2 (-0.5 ; 0.8)	0.62
MUFAs	0.1 (-0.5 ; 0.7)	0.75	0.1 (-0.6 ; 0.8)	0.82
PUFAs	0.03 (-0.2 ; 0.3)	0.85	0.1 (-0.2 ; 0.4)	0.60
Alcohol (g/day)	8.8 (-4.2 ; 21.7)	0.18	3.6 (-10.4 ; 17.6)	0.61
Fibre (g)	-0.8 (-2.2 ; 0.7)	0.29	0.6 (-1.2 ; 2.4)	0.52
Cholesterol (mg)	-13.9 (-35.7 ; 7.9)	0.21	19.4 (-9.8 ; 48.6)	0.19
Ca (mg)	-44 (-124 ; 36)	0.28	19.8 (-81.7 ; 121)	0.70
Fe (mg)	-0.2 (-0.8 ; 0.4)	0.45	0.3 (-0.6 ; 1.2)	0.50

Retinol (µg)	-56.6 (-160 ; 46.6)	0.28	75.4 (-78.2 ; 229)	0.34
Carotene (mg)	-0.2 (-0.8 ; 0.3)	0.38	0.2 (-0.4 ; 0.9)	0.47
Vitamin D (µg)	-0.05 (-0.4 ; 0.3)	0.78	0.4 (-0.1 ; 0.9)	0.11

[1]Values are coefficients β (95% CI) for each item comparing postmenopausal to non-menopausal women. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[2]Stratified by level of body mass index (normal <25 kg/m² vs. overweight/obese ≥25 kg/m²).

[3]Obtained from linear model adjusted for age, education level, civil status, cardiovascular/diabetes diseases and antihypertensive and hypolipidemic treatments have been applied.

Supplementary Table 6. Multivariable longitudinal association between menopausal categories (premenopausal as reference group, menopausal transition and postmenopausal) and dietary intake in the first and second follow-up (after 5 years) of the CoLaus study stratified by BMI[1]

	Pre - post menopause				**Post - post menopause**			
	BMI[2] < 25 kg/m²		**BMI [2]≥ 25 kg/m²**		**BMI[2] < 25 kg/m²**		**BMI[2]≥ 25 kg/m²**	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Total energy (kcal/d)	-106 (-221 ; 8.8)	0.07	54.1 (-132 ; 240)	0.57	-52.7 (-160 ; 54.9)	0.34	-12.8 (-207 ; 181)	0.90
Daily intake, animal products (g/day)								
Meat	-1.2 (-10.5 ; 8.2)	0.81	14.2 (-2.5 ; 30.8)	0.10	-5.2 (-13.9 ; 3.6)	0.25	4.7 (-12.7 ; 22.1)	0.60
Fish	0.9 (-5.3 ; 7.1)	0.78	0.5 (-7.2 ; 8.2)	0.90	0.6 (-5.2 ; 6.5)	0.83	-3.7 (-11.8 ; 4.3)	0.37
Milk	-16.9 (-37.1 ; 3.3)	0.10	0.01 (-24.1 ; 24.1)	0.99	-9.2 (-28.1 ; 9.8)	0.34	-4.2 (-29.4 ; 21)	0.75
Dairy products	-12.9 (-38.2 ; 12.3)	0.32	30.7 (-10.2 ; 71.7)	0.14	-16.3 (-39.9 ; 7.3)	0.18	24.2 (-18.6 ; 67)	0.27
Daily intake, other foods (g/day)								
Bread and cereals	-5.7 (-19.2 ; 7.8)	0.41	3.6 (-12.6 ; 19.9)	0.66	-0.6 (-13.3 ; 12.1)	0.93	10.3 (-6.7 ; 27.2)	0.24
Pastries	1.8 (-2.7 ; 6.4)	0.43	-3.1 (-9.2 ; 3.1)	0.33	0.8 (-3.5 ; 5.1)	0.71	-7.4 (-13.8 ; -0.9)	0.02
Pasta	-11.4 (-22.7 ; -0.1)	0.05	-15.3 (-30.8 ; 0.3)	0.06	-2.7 (-13.3 ; 7.8)	0.61	-7.2 (-23.5 ; 9)	0.38
Added sugar	-0.3 (-1.8 ; 1.2)	0.68	-1.2 (-2.7 ; 0.4)	0.15	-0.8 (-2.2 ; 0.7)	0.30	-1 (-2.7 ; 0.6)	0.22
Vegetable oils	0.2 (-1.2 ; 1.6)	0.78	0.9 (-1 ; 2.9)	0.35	0.5 (-0.8 ; 1.8)	0.47	0.2 (-1.8 ; 2.2)	0.86
Fruits	-18.3 (-69.1 ; 32.5)	0.48	69.8 (5.9 ; 134)	0.03	-6.4 (-53.9 ; 41.2)	0.79	24 (-42.7 ; 90.7)	0.48

Vegetables	3.9 (-20.7 ; 28.4)	0.76	-4.9 (-39 ; 29.2)	0.78	-6.4 (-29.4 ; 16.6)	0.59	2.4 (-33.2 ; 38)	0.90
Dietary intake (% of TEI)								
Total proteins	0.2 (-0.5 ; 0.9)	0.54	0.6 (-0.2 ; 1.4)	0.14	-0.5 (-1.2 ; 0.1)	0.10	0.6 (-0.3 ; 1.5)	0.17
Vegetable proteins	-0.02 (-0.3 ; 0.2)	0.89	-0.1 (-0.4 ; 0.1)	0.33	0.1 (-0.2 ; 0.3)	0.48	0.1 (-0.2 ; 0.4)	0.50
Animal proteins	0.2 (-0.5 ; 1)	0.56	0.8 (-0.2 ; 1.7)	0.11	-0.6 (-1.3 ; 0.1)	0.09	0.5 (-0.5 ; 1.5)	0.31
Total carbohydrate	-0.7 (-2.6 ; 1.1)	0.44	-0.9 (-3.1 ; 1.3)	0.41	-0.1 (-1.8 ; 1.6)	0.93	0.3 (-2 ; 2.6)	0.81
Monosaccharides	-0.7 (-2.4 ; 1)	0.44	1.2 (-0.9 ; 3.2)	0.27	-1 (-2.6 ; 0.6)	0.24	0.4 (-1.8 ; 2.5)	0.73
Polysaccharides	-0.1 (-1.7 ; 1.5)	0.92	-2.1 (-3.9 ; -0.2)	0.03	0.8 (-0.6 ; 2.3)	0.27	-0.1 (-2 ; 1.8)	0.93
Total fat	-0.2 (-1.5 ; 1.2)	0.83	0.4 (-1.3 ; 2.1)	0.65	0.4 (-0.9 ; 1.7)	0.54	-0.5 (-2.2 ; 1.3)	0.59
SFAs	-0.3 (-1 ; 0.4)	0.37	-0.2 (-1.1 ; 0.6)	0.56	-0.1 (-0.7 ; 0.6)	0.81	-0.5 (-1.3 ; 0.4)	0.26
MUFAs	0.1 (-0.7 ; 0.9)	0.76	0.4 (-0.5 ; 1.3)	0.37	0.3 (-0.4 ; 1.1)	0.36	0.2 (-0.8 ; 1.1)	0.75
PUFAs	0.1 (-0.2 ; 0.4)	0.61	0.2 (-0.1 ; 0.6)	0.24	0.1 (-0.1 ; 0.4)	0.32	-0.06 (-0.4 ; 0.3)	0.78
Alcohol (g/day)	5.7 (-9.7 ; 21.2)	0.47	-1.2 (-20.2 ; 17.7)	0.90	0.1 (-14.3 ; 14.5)	0.99	-4.2 (-24 ; 15.6)	0.68
Fibre (g)	-1 (-2.8 ; 0.8)	0.29	1.8 (-0.6 ; 4.1)	0.14	-0.2 (-1.8 ; 1.5)	0.85	1.2 (-1.2 ; 3.6)	0.33
Cholesterol (mg)	-12.4 (-38 ; 13.2)	0.34	2.2 (-36.3 ; 40.7)	0.91	-6.9 (-30.8 ; 17.1)	0.57	-8.5 (-48.7 ; 31.8)	0.68
Ca (mg)	-60.7 (-153 ; 31.6)	0.20	56.8 (-72.1 ; 186)	0.39	-92.6 (-179 ; -6.1)	0.04	39 (-95.6 ; 174)	0.57
Fe (mg)	-0.5 (-1.2 ; 0.2)	0.13	0.4 (-0.6 ; 1.5)	0.44	-0.3 (-1 ; 0.3)	0.36	0.2 (-1 ; 1.3)	0.77
Retinol (µg)	-63 (-170 ; 43.5)	0.25	51.3 (-102 ; 204)	0.51	-55.7 (-155 ; 44)	0.27	-0.5 (-160 ; 159)	0.99
Carotene (mg)	-0.4 (-1.1 ; 0.2)	0.22	0.2 (-0.7 ; 1.1)	0.70	-0.3 (-0.9 ; 0.4)	0.42	-0.2 (-1.1 ; 0.8)	0.71
Vitamin D (µg)	-0.1 (-0.5 ; 0.3)	0.59	0.3 (-0.1 ; 0.8)	0.16	-0.2 (-0.5 ; 0.2)	0.33	-0.1 (-0.6 ; 0.4)	0.77

[1]Values are coefficients β (95% CI) for each item comparing postmenopausal to non-menopausal women and women still in post menopause after 5 years. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs,

polyunsaturated fatty acids. [2]Stratified by level of body mass index (normal <25 kg/m² vs. overweight/obese ≥25 kg/ m²). [3]Obtained from linear mixed effect models adjusting for age, body mass index continuous, civil status, cardiovascular/diabetes diseases and hypertensive and hypolipidemic treatments have been applied.

Supplementary Table 7. Multivariable longitudinal association between menopausal categories (premenopausal as reference group, menopausal transition and postmenopausal) and dietary intake in the first and second follow-up (after 5 years) of the CoLaus study using generalized linear mixed models[1]

	Pre - post menopause		**Post - post menopause**	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Sample size	*n* = 229		*n* = 1,168	
Total energy (kcal/d)	-36.6 (-118 ; 44.7)	0.38	-34.8 (-118 ; 48)	0.41
Daily intake, animal products (g/day)				
Meat	-1.4 (-8.9 ; 6)	0.71	5.1 (-2.4 ; 12.7)	0.18
Fish	-0.8 (-4.8 ; 3.3)	0.72	1 (-3.1 ; 5.1)	0.64
Milk	-6.8 (-19.3 ; 5.7)	0.28	-9.6 (-22.2 ; 3.2)	0.14
Dairy products	-1.8 (-20.5 ; 16.8)	0.85	4.9 (-14.1 ; 23.9)	0.61
Daily intake, other foods (g/day)				
Bread and cereals	3.2 (-5.3 ; 11.7)	0.46	-1.4 (-10 ; 7.2)	0.76
Pastries	-1.8 (-4.8 ; 1.3)	0.26	0.1 (-3 ; 3.2)	0.94
Pasta	-3.8 (-11.3 ; 3.7)	0.32	-11.6 (-19.3 ; -4)	0.003
Added sugar	-0.9 (-1.7 ; -0.005)	0.05	-0.7 (-1.6 ; 0.2)	0.11
Vegetable oils	0.4 (-0.5 ; 1.4)	0.36	0.6 (-0.4 ; 1.5)	0.25
Fruits	4.8 (-28 ; 53.6)	0.78	20.3 (-13.1 ; 53.6)	0.23
Vegetables	-2.9 (-19.7 ; 13.8)	0.73	2.5 (-14.6 ; 19.6)	0.77
Dietary intake (% of TEI)				
Total proteins	-0.1 (-0.6 ; 0.3)	0.59	0.4 (-0.1 ; 0.8)	0.10
Vegetable proteins	0.1 (-0.1 ; 0.2)	0.25	-0.04 (-0.2 ; 0.1)	0.57
Animal proteins	-0.2 (-0.7 ; 0.3)	0.40	0.4 (-0.1 ; 0.9)	0.10
Total carbohydrate	0.02 (-1.1 ; 1.2)	0.97	-0.8 (-1.9 ; 0.4)	0.21
Monosaccharides	-0.5 (-1.6 ; 0.5)	0.34	0.03 (-1 ; 1.1)	0.95
Polysaccharides	0.5 (-0.5 ; 1.5)	0.30	-0.8 (-1.8 ; 0.2)	0.13
Total fat	0.1 (-0.8 ; 1)	0.79	0.06 (-0.9 ; 1)	0.91
SFAs	-0.2 (-0.6 ; 0.2)	0.33	-0.3 (-0.7 ; 0.1)	0.18
MUFAs	0.3 (-0.2 ; 0.8)	0.29	0.2 (-0.3 ; 0.8)	0.37
PUFAs	0.1 (-0.1 ; 0.3)	0.44	0.1 (-0.05 ; 0.3)	0.15
Alcohol (g/day)	-1.5 (-10.4 ; 7.4)	0.73	2.1 (-7 ; 11.2)	0.65

Fibre (g)	0.3 (-0.8 ; 1.5)	0.56	0.3 (-0.9 ; 1.5)	0.62
Cholesterol (mg)	-7.6 (-25.6 ; 10.5)	0.41	-7.7 (-26.1 ; 10.7)	0.41
Ca (mg)	-48 (-111 ; 15)	0.62	-16.2 (-80.3 ; 47.9)	0.62
Fe (mg)	-0.1 (-0.6 ; 0.4)	0.62	-0.1 (-0.6 ; 0.4)	0.74
Retinol (µg)	-41 (-119 ; 37.2)	0.30	-9.2 (-88.8 ; 70.4)	0.82
Carotene (mg)	-0.3 (-0.7 ; 0.2)	0.26	-0.2 (-0.7 ; 0.3)	0.39
Vitamin D (µg)	-0.2 (-0.4 ; 0.1)	0.23	0.1 (-0.2 ; 0.3)	0.57

[1]Values are coefficients β (95% CI) for each item comparing postmenopausal to non-menopausal women and women still in post menopause after 5 years. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[2]Obtained from generalized linear mixed model adjusting for age, body mass index continuous, civil status, cardiovascular/diabetes diseases and hypertensive and hypolipidemic treatments have been applied.

Supplementary Table 8. Multivariable cross-sectional association between menopausal status (postmenopausal versus premenopausal women) and dietary intake at the first follow-up of the CoLaus study excluding age as covariate[1]

	β (95% CI)	**P-value**
Sample size	*n* = 2,439	
Total energy (Kcal/d)	-19.5 (-79.6 ; 40.6)	0.52
Daily intake, animal products (g/day)		
Meat	-3.7 (-10.7 ; 3.2)	0.29
Fish	-2.6 (-6.3 ; 1.2)	0.18
Milk	-7.7 (-17.4 ; 2)	0.12
Dairy products	16.8 (2.1 ; 31.6)	0.02
Daily intake, other foods (g/day)		
Bread and cereals	6.2 (0.03 ; 12.4)	0.05
Pastries	0.3 (-1.9 ; 2.5)	0.77
Pasta	-25.9 (-31.4 ; -20.5)	**0.001**
Added sugar	-1.4 (-2.1 ; -0.6)	**0.001**
Vegetable oils	0.2 (-0.5 ; 0.8)	0.65
Fruits	38.3 (14.4 ; 62.1)	0.002
Vegetables	-8.2 (-21.8 ; 5.3)	0.23
Dietary intake (% of TEI)		
Total proteins	-0.2 (-0.5 ; 0.2)	0.35
Vegetable proteins	-0.005 (-0.1 ; 0.1)	0.93
Animal proteins	-0.2 (-0.5 ; 0.2)	0.42
Total carbohydrate	-0.01 (-0.9 ; 0.8)	0.98
Monosaccharides	-0.3 (-0.6 ; 0.1)	0.13
Polysaccharides	-0.1 (-0.2 ; 0.1)	0.37
Total fat	-0.3 (-0.9 ; 0.4)	0.43
SFAs	0.1 (-0.2 ; 0.4)	0.71
MUFAs	0.03 (-0.5 ; 0.5)	0.90
PUFAs	-0.1 (-0.2 ; 0.1)	0.37
Alcohol (g/day)	7.1 (-0.1 ; 14.2)	0.05
Fibre (g)	1 (0.2 ; 1.9)	0.02
Cholesterol (mg)	-10.2 (-23.9 ; 3.6)	0.15
Ca (mg)	51.5 (2.9 ; 100)	0.04

Fe (mg)	0.01 (-0.4 ; 0.4)	0.97
Retinol (µg)	39.3 (-29.1 ; 108)	0.26
Carotene (mg)	-0.2 (-0.5 ; 0.1)	0.27
Vitamin D (µg)	-0.02 (-0.2 ; 0.2)	0.88
Adherence to dietary guidelines	OR	*P* value
Fruits	1.4 (1.1 ; 1.7)	**0.001**
Vegetables	1 (0.7 ; 1.4)	0.91
Meat [a]	1.3 (1.1 ; 1.6)	0.01
Fish [b]	1.1 (0.9 ; 1.4)	0.30
Dairy products	1.9 (0.8 ; 4.6)	0.13
Guidelines adherence score		
At least 3 recommendation	1.3 (1 ; 1.7)	0.03

[1]Values are coefficients β (95% CI) for each item and as OR (95% CI) for dietary guidelines [18] comparing postmenopausal to non-menopausal women. [a] Included poultry; [b] Included fresh and fried/baked fish. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[2]Obtained from linear or logistic regression models adjusted for body mass index continuous, education level, civil status, cardiovascular/diabetes diseases and antihypertensive and hypolipidemic treatments have been applied.

Supplementary Table 9. Multivariable longitudinal association between menopausal categories (premenopausal as reference group, menopausal transition and postmenopausal) and dietary intake in the first and second follow-up (after 5 years) of the CoLaus study excluding age as covariate[1]

	Pre - post menopause		**Post - post menopause**	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Sample size	*n* = 229		*n* = 1168	
Total energy (Kcal/d)	-19.6 (-118 ; 78.5)	0.70	31.7 (-45.9 ; 109)	0.42
Daily intake, animal products (g/day)				
Meat	-4.3 (-12.8 ; 4.2)	0.32	-6.1 (-12.8 ; 0.6)	0.08
Fish	-1.2 (-5.9 ; 3.5)	0.61	-1 (-4.7 ; 2.7)	0.60
Milk	-6.2 (-21 ; 8.6)	0.41	-7.1 (-18.8 ; 4.6)	0.24
Dairy products	4.8 (-16.9 ; 26.4)	0.67	30.5 (13.4 ; 47.7)	**0.001**
Daily intake, other foods (g/day)				
Bread and cereals	6.1 (-3.9 ; 16)	0.23	9.8 (1.9 ; 17.7)	0.02
Pastries	-1.8 (-5.4 ; 1.8)	0.32	-0.04 (-2.9 ; 2.8)	0.98
Pasta	-8.1 (-17 ; 0.8)	0.08	-28.4 (-35.5 ; -21.3)	**0.001**
Added sugar	-1 (-2 ; 0.1)	0.08	-1.1 (-1.9 ; -0.2)	0.01
Vegetable oils	0.4 (-0.7 ; 1.6)	0.44	0.6 (-0.3 ; 1.4)	0.22
Fruits	12.6 (-25.6 ; 50.9)	0.52	50.9 (20.7 ; 81.2)	**0.001**
Vegetables	-3.8 (-23.1 ; 15.5)	0.70	-0.8 (-16 ; 14.5)	0.92
Dietary intake (% of TEI)				
Total proteins	-0.3 (-0.8 ; 0.2)	0.20	-0.4 (-0.8 ; -0.04)	0.03
Vegetable proteins	0.1 (-0.1 ; 0.3)	0.27	-0.005 (-0.1 ; 0.1)	0.94
Animal proteins	-0.4 (-0.1 ; 0.1)	0.13	-0.4 (-0.9 ; 0.01)	0.06
Total carbohydrate	0.3 (-1.1 ; 1.6)	0.68	0.3 (-0.8 ; 1.4)	0.58
Monosaccharides	-0.3 (-1.5 ; 1)	0.68	1 (0.04 ; 2)	0.04
Polysaccharides	0.5 (-0.6 ; 1.7)	0.36	-0.7 (-1.6 ; 0.2)	0.11
Total fat	0.04 (-1 ; 1.1)	0.94	-0.3 (-1.1 ; 0.5)	0.49
SFAs	-0.1 (-0.6 ; 0.4)	0.64	0.06 (-0.3 ; 0.4)	0.78
MUFAs	0.2 (-0.4 ; 0.7)	0.59	-0.3 (-0.7 ; 0.2)	0.25
PUFAs	0.03 (-0.2 ; 0.2)	0.76	-0.03 (-0.2 ; 0.1)	0.71
Alcohol (g/day)	-0.2 (-11.7 ; 11.2)	0.97	7.2 (-1.8 ; 16.2)	0.12
Fibre (g)	0.7 (-0.6 ; 2.1)	0.31	1.8 (0.7 ; 2.8)	0.002

Cholesterol (mg)	-7.1 (-28.2 ; 13.9)	0.51	-7.5 (-24.2 ; 9.1)	0.38
Ca (mg)	-26.6 (-100 ; 46.5)	0.48	67.2 (9.3 ; 125)	0.02
Fe (mg)	-0.04 (-0.6 ; 0.5)	0.88	0.2 (-0.2 ; 0.7)	0.34
Retinol (µg)	-26 (-112 ; 60.5)	0.56	49.3 (-19.1 ; 118)	0.16
Carotene (mg)	-0.3 (-0.8 ; 0.2)	0.31	-0.3 (-0.7 ; 0.1)	0.21
Vitamin D (µg)	-0.2 (-0.5 ; 0.1)	0.22	-0.03 (-0.2 ; 0.2)	0.82
Adherence to dietary guidelines	OR	*P* value	OR	*P* value
Fruits	0.1 (-0.4 ; 0.6)	0.64	0.6 (0.2 ; 1)	**0.001**
Vegetables	0.1 (-0.6 ; 0.7)	0.81	-0.1 (-0.6 ; 0.5)	0.81
Meat [a]	0.5 (0.01 ; 1)	0.05	0.7 (0.3 ; 1.1)	**0.001**
Fish [b]	0.06 (-0.5 ; 0.6)	0.84	0.1 (-0.3 ; 0.5)	0.66
Dairy products	-0.3 (-1 ; 1.4)	0.70	-0.3 (-1.9 ; 1.3)	0.68
Guidelines adherence score				
At least 3 recommendation	0.002 (-0.5 ; 0.5)	0.99	0.6 (0.2 ; 1.1)	0.002

[1]Values are coefficients β (95% CI) for each item and as OR (95% CI) for dietary guidelines [18] comparing postmenopausal to non-menopausal women and women still in post menopause after 5 years. [a] Included poultry; [b] Included fresh and fried/baked fish. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[2]Obtained from linear or logistic mixed effect models adjusting for body mass index continuous, civil status, cardiovascular/diabetes diseases and hypertensive and hypolipidemic treatments have been applied.

Supplementary Table 10. Multivariable longitudinal association between menopausal categories (premenopausal as reference group, menopausal transition and postmenopausal) and dietary intake in the first and second follow-up (after 5 years) of the CoLaus study with adjustment for BMI at two time points, and additionally for baseline physical activity[1]

	Pre - post menopause		**Post - post menopause**	
	β (95% CI)	P-value	β (95% CI)	P-value
Sample size	*n* = 229		*n* = 1168	
Total energy (Kcal/d)	-48.6 (-152 ; 55.6)	0.36	-44.9 (-152 ; 61.9)	0.41
Daily intake, animal products (g/day)				
Meat	-0.6 (-9.6 ; 8.5)	0.90	5.8 (-3.4 ; 15.1)	0.22
Fish	-1.2 (-6 ; 3.5)	0.61	-0.6 (-5.5 ; 4.2)	0.80
Milk	-13.4 (-29 ; 2.3)	0.10	-9.2 (-25.2 ; 6.9)	0.26
Dairy products	-4.8 (-28 ; 18.3)	0.68	0.8 (-22.9 ; 24.6)	0.95
Daily intake, other foods (g/day)				
Bread and cereals	4.1 (-6.6 ; 14.8)	0.45	-1.5 (-12.4 ; 9.4)	0.78
Pastries	-0.6 (-4.4 ; 3.2)	0.76	0.5 (-3.4 ; 4.4)	0.81
Pasta	-5.6 (-14.9 ; 3.7)	0.24	-11 (-20.5 ; -1.4)	0.02
Sugar	-1.1 (-2.2 ; 0.05)	0.06	-0.8 (-2 ; 0.3)	0.16
Vegetable oils	0.2 (-0.9 ; 1.4)	0.67	0.6 (-0.6 ; 1.8)	0.34
Fruits	2.2 (-38 ; 42.6)	0.91	17.3 (-23.9 ; 58.6)	0.41
Vegetables	-0.8 (-21.5 ; 19.8)	0.94	3.7 (-17.5 ; 24.9)	0.73
Dietary intake (% of TEI)				
Total proteins	-0.1 (-0.6 ; 0.5)	0.80	0.4 (-0.2 ; 0.9)	0.20
Vegetable proteins	0.2 (-0.03 ; 0.3)	0.10	0.02 (-0.2 ; 0.2)	0.88
Animal proteins	-0.2 (-0.8 ; 0.4)	0.45	0.3 (-0.3 ; 0.9)	0.27
Total carbohydrate	0.3 (-1.1 ; 1.7)	0.68	-0.4 (-1.9 ; 1)	0.57
Monosaccharides	-0.6 (-1.9 ; 0.7)	0.38	0.2 (-1 ; 1.6)	0.73
Polysaccharides	0.9 (-0.3 ; 2.1)	0.16	-0.6 (-1.9 ; 0.6)	0.30
Total fat	-0.1 (-1.1 ; 1)	0.90	-0.2 (-1.3 ; 0.9)	0.77
SFAs	-0.2 (-0.7 ; 0.3)	0.42	-0.3 (-0.8 ; 0.2)	0.26
MUFAs	0.2 (-0.4 ; 0.8)	0.55	0.1 (-0.5 ; 0.7)	0.75
PUFAs	0.1 (-0.2 ; 0.3)	0.53	0.1 (-0.1 ; 0.4)	0.26

Alcohol (g/day)	-3.8 (-15.7 ; 8.2)	0.54	0.5 (-11.8 ; 12.7)	0.94
Fibre (g)	0.4 (-1 ; 1.9)	0.54	0.4 (-1.1 ; 1.9)	0.57
Cholesterol (mg)	-9.3 (-31.3 ; 12.8)	0.41	-9.9 (-32.5 ; 12.7)	0.39
Ca (mg)	-61.5 (-139 ; 16.3)	0.12	-29.1 (-109 ; 50.6)	0.47
Fe (mg)	-0.1 (-0.7 ; 0.5)	0.79	-0.2 (-0.7 ; 0.6)	0.94
Retinol (µg)	-41 (-129 ; 46.7)	0.36	-9.2 (-98.5 ; 80.1)	0.84
Carotene (mg)	-0.3 (-0.9 ; 0.3)	0.29	-0.2 (-0.8 ; 0.4)	0.51
Vitamin D (µg)	-0.2 (-0.5 ; 0.1)	0.18	-0.1 (-0.4 ; 0.2)	0.70
Adherence to dietary guidelines	OR	*P* value	OR	*P* value
Fruits	-0.1 (-0.6 ; 0.4)	0.66	-0.2 (-0.7 ; 0.3)	0.45
Vegetables	0.1 (-0.6 ; 0.8)	0.70	0.2 (-0.5 ; 0.9)	0.56
Meat [a]	0.3 (-0.2 ; 0.8)	0.24	0.1 (-0.4 ; 0.6)	0.66
Fish [b]	0.2 (-0.4 ; 0.7)	0.60	0.2 (-0.4 ; 0.8)	0.59
Dairy products	-0.3 (-1 ; 1.4)	0.70	-0.3 (-1.9 ; 1.3)	0.68
Guidelines adherence score				
At least 3 recommendation	-0.2 (-0.7 ; 0.4)	0.59	0.1 (-0.5 ; 0.6)	0.82

[1]Values are coefficients β (95% CI) for each item and as OR (95% CI) for dietary guidelines [18] comparing postmenopausal to non-menopausal women and women still in post menopause after 5 years. [a] Included poultry; [b] Included fresh and fried/baked fish. TEI, total energy intake; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[2]Obtained from linear or logistic mixed effect models adjusting for age, body mass index at two time points, physical activity, civil status, cardiovascular/diabetes diseases and hypertensive and hypolipidemic treatments have been applied.

3.2. Article 2. Dietary factors and onset of natural menopause: a systematic review and meta-analysis

Dietary factors and onset of natural menopause: a systematic review and meta-analysis

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Contribution: I participated in the conceptualization of study, did abstract and full-text screening of hits, and extracted the data. I performed the analysis, made the figures, and wrote the first draft of the manuscript. After that, I incorporated co-authors' and reviewers' comments.

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Dietary factors and onset of natural menopause: A systematic review and meta-analysis

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ABSTRACT

Background: Diet has been suggested to play a role in determining the age at natural menopause; however, the evidence is inconsistent.
Objective: We systematically reviewed and evaluated published research about associations between diet and onset of natural menopause (ONM).
Methods: We searched 6 databases (Medline, Embase, Cochrane, PubMed, Web of Science and Google Scholar) through January 21,2021 to identify prospective studies assessing the association between diet and ONM. Two independent reviewers extracted data using a predesigned data-collection form. Pooled hazard risks (HRs) were calculated using random effect models.
Results: Of the 6,137 eligible references we reviewed, we included 15 articles in our final analysis. Those 15 articles included 91,554 women out of 298,413 who experienced natural menopause during follow-up. Overall, there were 89 food groups investigated, 38 macronutrients and micronutrients, and 6 dietary patterns. Among the food groups, higher intake of green and yellow vegetables was associated with earlier age of ONM, while high intakes of some dairy products, such as low-fat, skimmed milk, and low intake of alcohol were associated with a later onset. We observed no consistent association between macronutrient and micronutrient intake and ONM. Our results suggests that a vegetarian diet could be associated with early ONM; we did not observe any other consistent effect from other dietary patterns. Limitations included the number of studies, lack of replication studies and the research being of an observational nature; most studies (11/15) were at medium risk of bias.
Conclusion: Although some food items were associated with ONM, the overall evidence about associations between diet and ONM remains controversial.
Prospero id: CRD42021232087

1. Introduction

Menopause represents the end of reproductive years due to the ultimate decrease in follicular activity [1]. It is an unavoidable event of aging and occurs naturally between the ages of 50 and 52, with 95% of women having final menstrual period between ages 44 and 56; due to

Abbreviations: AMH, anti-Müllerian hormone; CI, confidence interval; HR, hazard ratio; NHSII, Nurses' Health Study II; NOS, Nine-star Newcastle-Ottawa Scale; ONM, onset of natural menopause; OR, odd ratio; SD, standard deviation; UKWCS, UK Women's Cohort Study.

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different ethnic background, geographic area, and genetic factors [2]. The onset of menopause is associated with changes in physiology and hormonal balance and may be seen as an aging and health marker since it impacts future health outcomes [3]. Menopause before the age of 45 is defined as early menopause, and it is associated with increased risk of type 2 diabetes, cardiovascular diseases, bone fractures, mood disorders and decline in cognitive functions [4]. Conversely, late menopause (at age 55 years or older) is associated with an increased risk of ovarian, endometrial and breast cancer [4].

Understanding factors, such as diet, that can influence the timing of natural menopause has emerged as an important and relevant public health topic in reducing adverse outcomes related to early or late natural menopause, or the impact on family planning. For instance, studies show trends of natural menopause occurring at an older age in recent years; in the United States, the onset of natural menopause (ONM) is currently occurring 1.5 years later than in 1959 [5]. Some studies have reported genetic factors have a relatively small influence on the variation of menopausal timing, yet emerging evidence suggests that modifiable lifestyle factors, such as diet (e.g., food groups or dietary patterns), may play an important role in ovarian aging [6–8]. The role that modifiable lifestyle might play in menopause onset fluctuates between 15 and 70% [4]. Several studies have explored the association between age at natural menopause and diet [4,9]. For instance, high consumption of refined pasta and rice was associated with an earlier age at natural menopause, while high intakes of oily fish, fresh legumes and plant-based proteins was associated with a lower risk of early natural menopause [10]. Yet, a modest inverse association of early natural menopause with dairy foods, calcium and vitamin D from dietary sources was found [7], and some studies reported modest alcohol intake to be associated with delayed natural menopause development [11,12]. Several studies have attempted to explore the impact of dietary patterns on ONM, and they have tried to identify a dietary pattern that has the potential to delay ONM, suggesting a vegetarian diet increases the risk of early natural menopause [10,13].

Therefore, we conducted a comprehensive systematic review and meta-analysis of prospective studies to understand how dietary factors can influence the timing of natural menopause.

2. Methods

We conducted our systematic review and meta-analysis according to the recent 24-step guide about designing and conducting systematic reviews [14] and followed the PRISMA guidelines [15]. The protocol for our study is registered in PROSPERO (ID: CRD42021232087).

2.1. Data sources and search strategy

We searched 6 electronic databases (Medline [Ovid], Embase [Ovid], Cochrane CENTRAL, PubMed, Web of Science Core Collection and Google Scholar) from inception until January 21, 2021. The computer-based searches combined terms related to the exposure (e.g., macronutrient and micronutrient, dietary patterns and single food items) and outcomes (e.g., onset of natural menopause, pre menopause, early and late menopause and premature ovarian cessation). We screened relevant studies' references lists to identify additional studies. We also contacted experts in the field. Our complete search strategy is described in the Appendix.

2.2. Study selection and eligibility criteria

Using the inclusion and exclusion criteria, 2 independent reviewers screened article titles and study abstracts that we initially identified from the search. A third reviewer helped resolve disagreements or doubts. We included studies if they (i) were case-cohort studies, prospective cohort studies or randomized controlled trials; (ii) included pre- and/or peri-menopausal women; (iii) reported ONM or early/late natural menopause; (iv) reported food intakes, dietary patterns, macronutrients or micronutrients; (v) examined the association between diet (any type of diet of food assessment intake) with the ONM; and (vi) were conducted in humans. We excluded conference abstracts, cost-effectiveness studies, letters, conference proceedings, systematic reviews or meta-analyses, and cross-sectional and case-control studies. We also excluded studies that included post-menopausal women or women with medical conditions at baseline (e.g., breast cancer, HIV-infected women); reported solely unnatural menopause; and evaluated biomarkers of dietary intake. We retrieved full texts for all studies that satisfied our selection criteria. In this study, we defined ONM as the age of the last menstruation for women experiencing natural menopause and was analyzed as continuous; early natural menopause is defined as menopause occurring before the age of 45 years (dichotomized yes/no). Late menopause was defined as onset of natural menopause at age of 55 years or older. We did not apply language or date of publication restrictions, although our search concluded January 21, 2021.

2.3. Data extraction and quality assessment

We collected authors' names, year of publication, study design, study name, baseline population, location, age at baseline and menopause, duration of the follow-up, methods used to assess dietary intake, level of adjustment, type of outcome, type of exposure and reported risk estimates on a form. We applied the nine-star Newcastle-Ottawa Scale (NOS) to assess the quality of studies. NOS allocates a maximum 9 points based on 3 predefined domains: participant selection (population representativeness); comparability (adjustment for confounders) and ascertainment of outcomes of interest [16]. We classified studies as low risk of bias if they received a score of 9 points; medium risk of bias if the studies scored 7 or 8 points; and the rest were considered at a high risk of bias.

2.4. Statistical analysis

The hazard ratio (HR) was used as the common measure of association across studies. We were unable to convert the odds ratio (OR) to HR for Nagata et al. [17]; so we considered OR as equivalent measure of HR, as suggested [18]. We meta-analysed a specific food intake if it was reported in at least 3 studies; only alcohol intake matched with our inclusion criteria. We used the inverse-variance weighted method to combine HRs to produce a pooled HR using random-effect models to allow for between-study heterogeneity. We classified heterogeneity as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $<75\%$) or high ($I^2 \geq 75\%$) based on the I^2 statistic [19]. Our results from fixed-effect models were also reported in forest plots and were also used to pool HRs from the same study (e.g., the estimate for consumers vs non-consumers was pooled using fixed-effect models when risk estimates were reported for different categories of alcohol intake); for the latter, the generated estimates were then used for the meta-analysis across different studies. A sensitivity analysis was conducted excluding Nagata et al., 2012 as the rest of the studies reported only Caucasian women. All tests were two-tailed. For the description of results in the narrative part of the review, the significance was based on the *p*-value threshold defined by the individual studies, while for the meta-analysis, a *p*-value lower than 0.05 was defined as significant. For statistical analyses, we used Stata version 15.1 for Windows (Stata Corp, College Station, TX, USA).

3. Results

3.1. Identification of relevant studies

Our search strategy identified 5,612 citations, and we located another set of 525 new citations from the reference lists of relevant articles for a total of 6,137 references. Our screening procedure is summarized in Fig. 1. Based on our initial screening of article titles and study

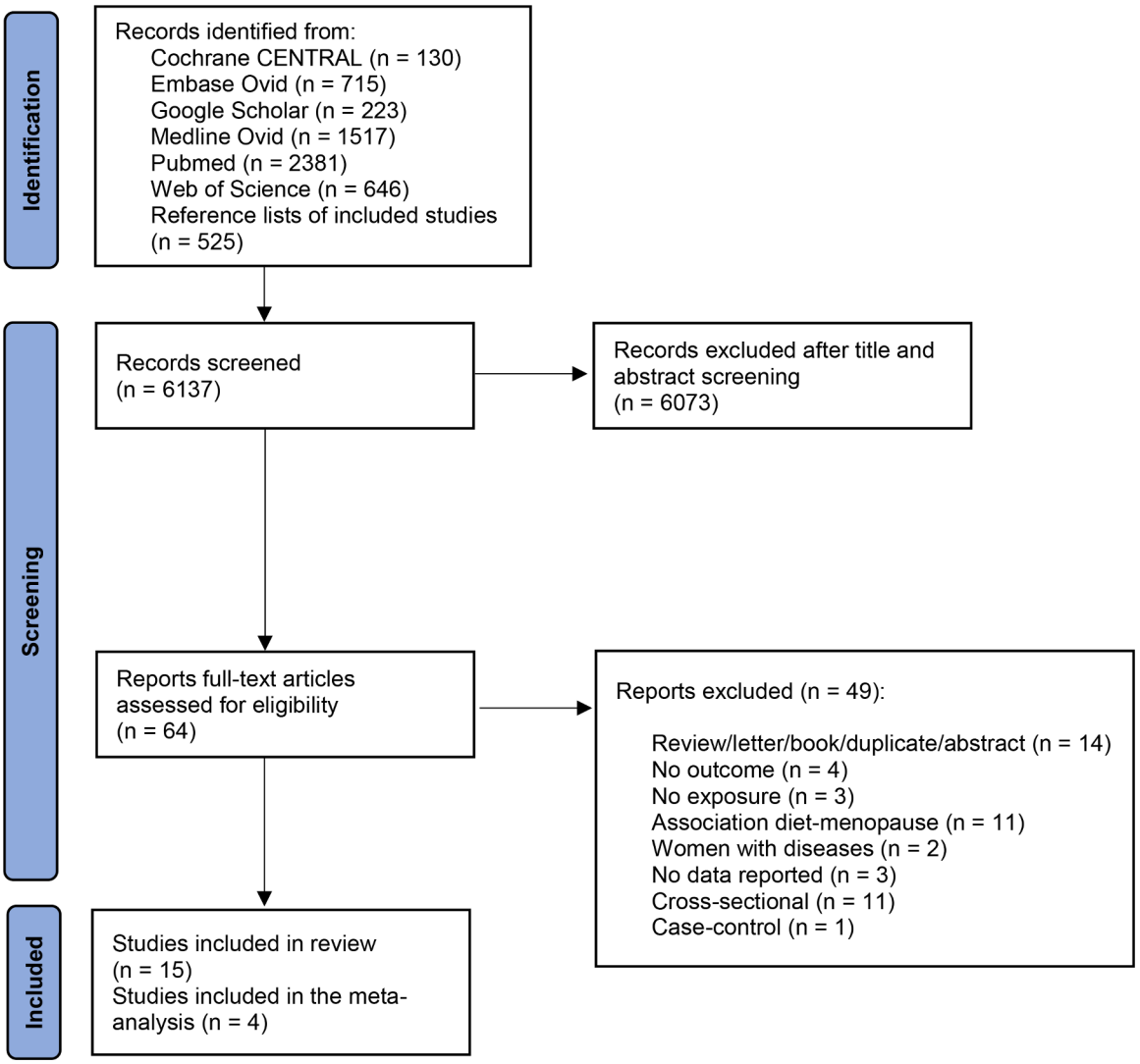

Fig. 1. PRISMA flow diagram of search strategy.

abstracts, we retrieved and further evaluated 64 articles. We excluded 49 of these articles because they did not meet our inclusion criteria. In total, 15 articles based on 11 unique observational studies (non-overlapping study population) met our selection criteria, and we included these 15 articles in our final analysis (Table 1).

3.2. Characteristics of included studies

Overall, we included a total of 298,413 women in this study of whom 91,554 experienced natural menopause during the follow-up period. The follow-up ranged from 3-20 years (Table 1). The mean and standard deviation (SD) of age at baseline among participants was 43.4 (4). Among studies reporting mean age of natural menopause, the mean (SD) was 50.1 (3.4) [13,20–22]. Most studies were from the USA (n=6) [7,8,23,24,28,29], while the remaining were from the UK (n=3) [10,13,27], Japan (n=2) [17,26], Australia (n=1) [25], China (n=1) [22], Germany (n=1) [20], and Spain (n=1) [21]. Three studies examined early natural menopause as outcome defined as menopause occurring before the age of 45 years [7,8,23]. The other studies examined ONM [10,13,17,20,21,22,24–29] as continuous outcome; no study was found to explore the association between diet and late onset of menopause, defined as onset of menopause at 55 years or older. Among the 15 included articles [7,8,10,13,17,20–29], 7 took into account repeated measures of diet [7,8,23–25,28,29], while the rest used only one single time measurement. Also, the studies in general adjusted for several confounders including age, body mass index (BMI), smoking status, age at menarche, caloric intake, parity, physical activity, alcohol, breastfeeding, education level, oral contraceptive use, and hormone replacement therapy. However, only 4 out 15 studies adjusted simultaneously for age, body mass index, smoking status, age at menarche, caloric intake, and parity [7,8,20,23].

In total, there were 89 food groups investigated, 38 macronutrients and micronutrients and 6 dietary patterns (Table 2). As reported in Fig. 2, 11 out of 15 studies could not be pooled due to the different exposure or outcome assessments; we included the remaining 4 studies—that examined alcohol intake—in our meta-analysis [13,17,20,21].

3.3. Food intake and menopause onset

Fourteen studies reported the association between food intake and ONM [8,10,13,17,20–29]; the results are presented in Table 2. Of them, 2 studies (86,240 women) examined the association of food intake with early natural menopause as outcome (n=2,049) and 12 studies (208,871 women) examined the association between food intake and ONM (n=89,505). Among those that examined early natural menopause as outcome, data were used from the Nurses' Health Study II (NHSII) cohort [8]. They reported that some foods such as refined pasta, dark bread and cereal were associated with a lower risk of early natural menopause. Conversely, red meat intake was associated with a higher

Table 1
General characteristics of prospective studies (n= 15) in a systematic review and meta-analysis of the association of food intake and macro/micronutrient intake with onset of natural menopause.

Author, publication year	Study design	Study name	Country	Sample size	Cases	Follow-up time	Age mean (SD)	Covariates adjusted	Outcome	Quality	Exposure
Boutot et al., 2017	Cohort study	Nurses' Health Study II (NHSII)	USA	85,682	2,041	20 years	35.8 (4.6)[1]	Age, total caloric intake (quintiles), pack-years of smoking (never, <20 years or ≥20 years), body mass index (weight (kg)/height (m)2; <18.5, 18.5–24.9, 25–29.9 or ≥30.0), age at menarche (≤11, 12, 13–15 or ≥16 years), total duration of breastfeeding (never, ≤2 years or >2 years), oral contraceptive use (never, former or current), number of pregnancies ≥6 months (0, 1–2 or ≥3), dairy protein (quintiles), and physical activity level (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, 27.0–41.2 or ≥42.0 metabolic equivalent of task hours per week). Vegetable protein adjusted for animal protein (quintiles) and vice versa	Early menopause cases	7	• Total protein: Q1-Q5, per 1% increase in calories per day • Vegetable protein: Q1-Q5, per 1% increase in calories per day • Animal protein: Q1-Q5, per 1% increase in calories per day • All meat • Red meat • Processed meat • Chicken/turkey • Seafood • Eggs • Soy/tofu • Peanuts • Peas/lima beans • Other nuts • Peanut butter • Pasta • Dark bread • Cold cereal
Purdue-Smith et al., 2017	Prospective study	Nurses' Health Study II (NHSII)	USA	86,234	2,041	20 years	35.8 (4.6) [1]	Age, pack-years of smoking (0–10, 11–20 or≥21), BMI (in kg/m2;,18.5, 18.5 to,25, 25 to,30 or ≥30), age at menarche (continuous), parity (nulliparous, 1–2 or ≥3), breastfeeding duration (months; continuous), physical activity (continuous metabolic equivalent task-hours per week), percentage of total calories from vegetable protein (quintiles 1–3 or 4 + 5) and alcohol intake (10 or ≥10 g/d)	Early menopause cases	7	• Total vitamin D: Q1-Q5, RDA (Recommended Daily Allowance) <600IU/d, RDA ≥600IU/d • Dietary vitamin D: Q1-Q5 • Vitamin D from dairy sources: Q1-Q5 • Vitamin D from non-dairy dietary: Q1-Q5 • Supplemental IU/d: 0, 1-599, ≥600 • Total calcium: Q1-Q5, RDA (Recommended Daily Allowance) <1000mg/d, RDA ≥1000mg/d • Dietary calcium: Q1-Q5 • Calcium from dairy sources: Q1-Q5 • Calcium from non-dairy dietary: Q1-Q5 • Calcium supplemental: 0, 1-399, 400-899, ≥900 • Vitamin D or calcium supplement use: nonuser, vitamin D only, calcium only, calcium and Vitamin D
Purdue-Smith et al., 2018	Prospective study	Nurses' Health Study II (NHSII)	USA	86,240	2,049	20 years	35.8 (4.6) [1]	Age, pack-years of smoking (0–10, 11–20 or ≥21), BMI (in kg/m2; <18.5, 18.5 to 24.9, 25 to 29.9 or ≥30), age at menarche (continuous), parity (nulliparous, 1–2 or ≥3), breastfeeding duration (months; continuous), percentage of total	Early menopause cases	7	• Total dairy food: ≤4/weeks, 5-6/week, 1/day, 2-3/day, ≥4/day, per 1-serving/day increment • High-fat dairy food: ≤3/month, 1/week, 2-4/week, 5-6/

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Table 1 (*continued*)

								kilocalories from vegetable protein (quintiles 1–3 or 4 + 5), alcohol intake (<10 or ≥10 g/d), current multivitamin use (y/n), total vitamin D intake (IU/d; continuous) and total calcium intake (mg/d; continuous).			week, 1/day, ≥2/day, per 1-serving/day increment • Low-fat dairy food: ≤3/month, 1/week, 2-4/week, 5-6/week, 1/day, ≥2/day, per 1-serving/day increment • Skim milk: per 1-serving/day increment • Yogurt: per 1-serving/day increment • Frozen yogurt/sherbet: per 1-serving/day increment • Cottage/ricotta cheese: per 1-serving/day increment • Low-fat other cheese: per 1-serving/day increment • Whole milk: per 1-serving/day increment • Cream: per 1-serving/day increment • Ice cream: per 1-serving/day increment • Cream cheese: per 1-serving/day increment • High-fat other cheese: per 1-serving/day increment • Butter: per 1-serving/day increment
Kinney et al., 2006	Longitudinal analysis	N/A	USA	494	159	4 years	48.7 (3.3) [1]	Outcome of the index pregnancy (chromosomally normal livebirth, chromosomally normal spontaneous abortion, trisomy spontaneous abortion) and the other exposures	Onset of natural menopause	8	• Alcohol: none, 1-2, 3-4, 5-7, 1-7 • Caffeine: 0-100, >100-200, >200-400, >400, >100
Pearce et al., 2016	Cohort study	Melbourne Collaborative Cohort Study (MCCS)	Australia	1,146	N/A	12.5 years	46.8 (3.1) [1]	Level of education, parity, age of menarche, BMI, smoking status, total energy intake, amount of alcohol consumer daily and total exercise index	Onset of natural menopause	7	• Energy intake • Protein • Carbohydrates • Fat • Saturated fat • Monounsaturated fat • Polyunsaturated fat • Fibre • β-cryptoxanthin • α-carotene • β-carotene • β-carotene equivalent • Retinol • Retinol equivalent from Vitamin A • Folate • Lutein and zeaxanthin • Lycopene • Cholesterol • Calcium • Iron • Magnesium • Niacin • Niacin equivalent

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Table 1 (*continued*)

											• Phosphorous • Potassium • Riboflavin • Sodium • Thiamine • Vitamin C • Vitamin E • Zinc • Fruit • Vegetables • Cereals • Dairy • Eggs • Total meat • Chicken • Fish • Vegetables oils • Oil blends
Nagata et al., 2000	Prospective study	Population-based cohort Takayama Study	Japan	1,130	296	6 years	42.7 (4.3) [1]	Age, BMI, smoking status and age at which regular menstrual cycle began	Onset of natural menopause	8	• Total energy: low, middle, high • Total protein: low, middle, high • Animal protein: low, middle, high • Vegetable protein: low, middle, high • Carbohydrates: low, middle, high • Total fat: low, middle, high • Animal fat: low, middle, high • Fat from fish: low, middle, high • Vegetable fat: low, middle, high • Cholesterol: low, middle, high • Calcium: low, middle, high • Crude fibre: low, middle, high • Vitamin A: low, middle, high • Retinol: low, middle, high • Carotene: low, middle, high • Vitamin C: low, middle, high • Vitamin E: low, middle, high • Green and yellow vegetables: low, middle, high • Other vegetables: low, middle, high • Soy products: low, middle, high
Nagata et al., 2012	Prospective study	Population-based cohort Takayama Study	Japan	3,115	1,790	10 years	43 (4.5) [1]	Age, BMI, smoking status, parity, years of education, age at menarche, lifelong irregular menstrual cycles and physical activity	Onset of natural menopause	7	• Total energy: Q1-Q4 • Total fat: Q1-Q4 • Saturated fat: Q1-Q4 • Monounsaturated fat: Q1-Q4 • Polyunsaturated fat: Q1-Q4 • Long n-3 fatty acids: Q1-Q4 • Dietary fibre: Q1-Q4

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Table 1 (*continued*)

Nagel et al., 2005	Prospective study	European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Heidelberg	Germany	5,110	1,009	5.8 years	51.3 (4.7)[2]	Age, total energy intake, educational level, BMI, leisure time physical activity, alcohol intake, smoking, number full term pregnancies, age at menarche, time till regular menses occurred after menarche, age at first full term pregnancy and ever HRT-use	Onset of natural menopause	8	• Soy isoflavones: Q1-Q4 • Alcohol: Q1-Q4 • Total fat: Q1-Q4 • Protein: Q1-Q4 • Carbohydrates: Q1-Q4 • Added animal fat: Q1-Q4 • Added vegetable fat: Q1-Q4 • Alcohol: Q1-Q4 • Meat: Q1-Q4 • Dairy products: Q1-Q4 • Fish: Q1-Q4 • Vegetables: Q1-Q4 • Fruit: Q1-Q4 • Cereal products: Q1-Q4 • Fibre: Q1-Q4 • Soy products: Q1-Q4 • Sweets: Q1-Q4
Dunneram et al., 2018	Cohort study	UK Women's Cohort Study (UKWCS)	UK	14,172	914	4 years	49.4 (3.1) [1]	Physical activity level, alcohol consumption, smoking and social class	Onset of natural menopause	6	• Wholegrain • Refined grain • Low-fibre breakfast cereals • High-fibre breakfast cereals • Plain potatoes • Potatoes with added fat • Refined pasta and rice • Wholegrain pasta and rice • Low-fat dairy products • High-fat dairy products • Butter and hard margarine • Margarine • Low-fat spreads • High-fat dressing • Low-fat dressing • Soya bean • Textured vegetable protein • Pulses • Eggs/eggs dishes • Fish and fish dishes • Oily fish • Shell fish • Red meat • Processed meat • Poultry • Offal • Vegetable dishes • Allium • Fresh legumes • Mediterranean vegetables • Salad vegetables • Cruciferous vegetables • Tomatoes • Mushrooms • Roots and tubers • Stone fruit • Deep orange and yellow fruit • Grapes • Citrus family fruit • Rhubarb

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Table 1 (*continued*)

											• Berries • Bananas • Pomes • Dried fruit • Sauces• Pickles/chutneys • Soups• Confectionery and spreads • Nuts and seeds • Savoury snacks • Biscuits • Cakes • Pastries and puddings • Tea • Herbal tea • Coffee • Other hot beverages • Juices • Soft drinks • Low calorie/diet soft drinks • Wines • Beer and cider • Port, sherry, liqueurs • Spirits • Fibre • % energy from fats • % energy from proteins • % energy from carbohydrates • % energy from saturated fats • % energy from polyunsaturated fats • % energy from monounsaturated fats • Vitamin C • Vitamin B1 • Vitamin B2 • Vitamin B6 • Vitamin B12 • Folate • Vitamin D • Vitamin A • Vitamin E • Calcium • Iron • Zinc
Dunneram et al., 2021	Prospective study	UK Women's Cohort Study (UKWCS)	UK	14,765	N/A	4 years	45.3 (5.5) [1]	Smoking status, education level, social class and physical activity.	Onset of natural menopause	6	• Vegetables and legumes • Animal proteins • Fruit • Fats and sweets • Low-calories fats • Sweets, pastries and puddings • Low-fat dairy and meat • Red meat and processed meat
Lujan-Barroso et al., 2018	Cohort study	EPIC-Spain sub-cohort	Spain	12,562	1,166	3 years	49.3 (1.5) [2]	Total energy	Onset of natural menopause	7	• Vegetable • Fruit • Legumes • Cereals • Fish

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Table 1 (*continued*)

										• Dairy products • Meat • Olive oil • Alcohol: never-consumer, ≤ 6, > 6-12, > 12, Missing • Nuts: Non consumers, ≤ 5, ≥ 5 • Isoflavones • Lignans • Vitamin D • Fibre • % of energy from fat • % of energy from carbohydrate • arMED score
Carwile et al., 2013	Prospective study	Nurses' Health Study (NHS)	USA	46,059	30,816	20 years	48.3 (3) [1]	Total energy intake, age at menarche, age at the first birth and parity, moderate to vigorous activity, 1980 height, BMI, oral contraceptive use, smoking, marital status, red meat consumption and egg consumption.	Onset of natural menopause	7	• Low-fat dairy (32.5-50.9y): 0 servings/d, 0.1-1.0 servings/d, 1.1-2.0 servings/d, 2.1-3.0 servings/d, >3 servings/d • Low -fat dairy (51-60.5y): 0 servings/d, 0.1-1.0 servings/d, 1.1-2.0 servings/d, 2.1-3.0 servings/d, >3 servings/d • High-fat dairy (32.5-50.9y): 0 servings/d, 0.1-1.0 servings/d, 1.1-2.0 servings/d, 2.1-3.0 servings/d, >3 servings/d • High-fat dairy (51-60.5y): 0 servings/d, 0.1-1.0 servings/d, 1.1-2.0 servings/d, 2.1-3.0 servings/d, >3 servings/d • Skim milk (32.5-50.9y): 0-1/mo, 1.1/mo-2/wk, 2.1-4/wk, 4.1-6/wk, >6/wk • Skim milk (51-60.5y): 0-1/mo, 1.1/mo-2/wk, 2.1-4/wk, 4.1-6/wk, >6/wk • Whole milk (32.5-50.9y): 0-1/mo, 1.1/mo-2/wk, 2.1-4/wk, 4.1-6/wk, >6/wk • Whole milk (51-60.5y): 0-1/mo, 1.1/mo-2/wk, 2.1-4/wk, 4.1-6/wk, >6/wk • Dairy fat (32.5-50.9y): Q1-Q5 • Dairy fat (51-60.5y): Q1-Q5 • Dairy protein (32.5-50.9y): Q1-Q5 • Dairy protein (51-60.5y): Q1-Q5 • Calcium (32.5-50.9y): Q1-Q5 • Calcium (51-60.5y): Q1-Q5 • Vitamin D (32.5-50.9y): Q1-Q5 • Vitamin D (51-60.5y): Q1-Q5 • Lactose (32.5-50.9y): Q1-Q5 • Lactose (51-60.5y): Q1-Q5
Gold et al., 2013	Longitudinal analysis		USA	3,302	N/A	11 years	46.2 (3.1) [1]	Race/ethnicity, financial strain, baseline smoking, maternal type/age at FMP (years),		9	• Alcohol: baseline, change since baseline

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Table 1 (*continued*)

		Study of Women's Health Across the Nation (SWAN)						marital status, ever diabetes, self-reported health, baseline, educational level, baseline ever-use of oral contraceptives, exogenous hormone therapy, current employment, baseline height, parity, physical activity score, passive smoking, baseline weight and change in weight	Onset of natural menopause		• Log total calories (unadjusted): baseline, change since baseline
Dorjgochoo et al., 2008	Prospective study	Shanghai Women's Health Study	China	74,942	33,054	3 years	49.2 (3.7) [2]	Age (continuous), education, occupation, age at menarche (categorized), number of live births (categorized), past use of oral contraceptives (never/ever), weight gain between age 20 and 50 (categorized), cigarette smoking (ever/ never) except for the same variable, leisure-time physical activity pattern in adolescence and adulthood (categorized) and energy intake (continuous) except for the same variable	Onset of natural menopause	9	• Total vegetables • Total fruit • Red meat • Total soy • Alcohol • Tea use • Total energy • Total fat • Saturated fat • Total protein • Total fibre • Total carbohydrates
Morris et al., 2012	Prospective study	United Kingdom-based Breakthrough Generations Study (BGS)	UK	50,678	21,511	5.8 years	50.7 (3.7) [2]	Age at last follow-up, parity, smoking status and BMI at 40y of age	Onset of natural menopause	8	• Alcohol: 0, 0.1-6.9, 7-13.9, ≥14 • Vegetarians (y/n)

[1] Age at baseline
[2] Age at menopause
BMI: body mass index; HRT: hormone replacement therapy; PA: physical activity; Q: Quantile; SD: standard deviation;

Table 2
Association between food groups, macronutrients and dietary patterns with early or late menopause for each study.

	Early menopause	Late menopause	No association
Food groups		Total calories (Dorjgochoo et al., 2008)	Total calories (Nagata et al., 2000 and 2012; Gold et al., 2013)
		Fruit (Dorjgochoo et al., 2008; Pearce et al., 2016)	Fruit (Lujan-Barroso et al., 2018; Nagel et al., 2005; Dunneram et al., 2018* and 2021*) Orange and yellow fruit (Dunneram et al., 2018*) Grapes (Dunneram et al., 2018*) Citrus family fruit (Dunneram et al., 2018*) Rhubarb (Dunneram et al., 2018*) Berries (Dunneram et al., 2018*) Banana (Dunneram et al., 2018*) Pomes (Dunneram et al., 2018*) Dried fruit (Dunneram et al., 2018*)
	Vegetable [Nagata et al., 2000 (green and yellow)]		Vegetable (Dorjgochoo et al., 2008; Lujan-Barroso et al., 2018; Nagata et al., 2000 (others); Nagel et al., 2005; Dunneram et al., 2018*) Vegetable and legumes (Dunneram et al., 2021*) Mediterranean vegetables (Dunneram et al., 2018*) Allium (Dunneram et al., 2018*) Salad (Dunneram et al., 2018*) Cruciferous (Dunneram et al., 2018*) Tomatoes (Dunneram et al., 2018*) Mushrooms (Dunneram et al., 2018*) Fibre (Dorjgochoo et al., 2008; Lujan-Barroso et al., 2018; Nagata et al., 2000 and 2012; Nagel et al., 2005; Dunneram et al., 2018*) Soy/tofu (Dorjgochoo et al., 2008; Nagata et al., 2000 and 2012; Nagel et al., 2005; Dunneram et al., 2018*; Boutot et al., 2017)
		Legumes (Dunneram et al., 2018*)	Legumes (Lujan-Barroso et al., 2018) Pulses (Dunneram et al., 2018*) Beans/lentils (Boutot et al., 2017) Peanuts (Boutot et al., 2017) Peans/lima beans (Boutot et al., 2017) Other nuts (Lujan-Barroso et al., 2018; Dunneram et al., 2018*; Boutot et al., 2017) Peanut butter (Boutot et al., 2017)
	Cereal products (Nagel et al., 2005)		Cereal products (Lujan-Barroso et al., 2018) Low fibre breakfast cereal (Dunneram et al., 2018*) High fibre breakfast cereal (Dunneram et al., 2018*)
	Refined pasta/rice (Dunneram et al., 2018*)	Refined pasta/rice (Boutot et al., 2017)	
			Wholegrain pasta/rice (Dunneram et al., 2018*)
		Dark bread (Boutot et al., 2017) Cold cereal (Boutot et al., 2017)	
			Whole grain products (Dunneram et al., 2018*) Refined grain products (Dunneram et al., 2018*) Savoury snacks (Dunneram et al., 2018*) Biscuits (Dunneram et al., 2018*) Cakes (Dunneram et al., 2018*) Pastries and puddings (Dunneram et al., 2018*) Sweets (Nagel et al., 2005) Plain potatoes (Dunneram et al., 2018*) Potatoes with added fat (Dunneram et al., 2018*) Roots and tubers (Dunneram et al., 2018*)
		Meat (Nagel et al., 2005)	Meat (Lujan-Barroso et al., 2018; Boutot et al., 2017[1])

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Table 2 (*continued*)

	Early menopause	Late menopause	No association
	Red meat (Boutot et al., 2017)		Red meat (Dorjgochoo et al., 2008; Dunneram et al., 2018*)
			Processed meat (Dunneram et al., 2018*; Boutot et al., 2017[1])
			Chicken/turkey (Dunneram et al., 2018*; Boutot et al., 2017[1])
			Offal (Dunneram et al., 2018*)
			Seafood (Lujan-Barroso et al., 2018; Nagel et al., 2005; Dunneram et al., 2018*; Boutot et al., 2017)
			Shell fish (Dunneram et al., 2018*)
		Oily fish (Dunneram et al., 2018*)	
			Olive oil (Lujan-Barroso et al., 2018)
			Eggs (Dunneram et al., 2018*; Boutot et al., 2017[1])
			Dairy products (Lujan-Barroso et al., 2018; Nagel et al., 2005; Purdue-Smithe et al., 2018[1])
		Low-fat dairy (Carwile et al., 2013 (32.5-50.9y); Purdue-Smithe et al., 2018[1])	Low-fat dairy (Dunneram et al., 2018*; Carwile et al., 2013 (51-60.5y))
			High-fat dairy (Dunneram et al., 2018*; Carwile et al., 2013 (32.5-50.9, 51-60.5y); Purdue-Smithe et al., 2018[1])
		Skim milk (Carwile et al., 2013 (32.5-50.9y); Purdue-Smithe et al., 2018[1])	Skim milk (Carwile et al., 2013 (51-60.5y))
			Whole milk (Carwile et al., 2013 (32.5-50.9, 51-60.5y); Purdue-Smithe et al., 2018[1])
			Cream (Purdue-Smithe et al., 2018[1])
			Ice cream (Purdue-Smithe et al., 2018[1])
			Cream cheese (Purdue-Smithe et al., 2018[1])
			Yogurt (Purdue-Smithe et al., 2018[1])
			Frozen yogurt/ sherbet (Purdue-Smithe et al., 2018[1])
			Cottage/ricotta cheese (Purdue-Smithe et al., 2018[1])
			Low-fat other cheese (Purdue-Smithe et al., 2018[1])
			High-fat other cheese (Purdue-Smithe et al., 2018[1])
			Low-fat spreads (Dunneram et al., 2018*)
			Confectionary and spreads (Dunneram et al., 2018*)
			Butter (Dunneram et al., 2018*; Purdue-Smithe et al., 2018[1])
			Margarine (Dunneram et al., 2018*)
			Sauces (Dunneram et al., 2018*)
			Pickles/chutneys (Dunneram et al., 2018*)
			Soups (Dunneram et al., 2018*)
			Low-fat dressing (Dunneram et al., 2018*)
			High-fat dressing (Dunneram et al., 2018*)
		Alcohol (Kinney et al., 2006; Morris et al., 2012; Gold et al., 2013)	Alcohol (Dorjgochoo et al., 2008; Lujan-Barroso et al., 2018; Nagata et al., 2012; Nagel et al., 2005)
			Spirits (Dunneram et al., 2018*)
			Port/sherry/ liqueurs (Dunneram et al., 2018*)
			Beer and cider (Dunneram et al., 2018*)
			Wines (Dunneram et al., 2018*)
			Low calorie/diet soft drinks (Dunneram et al., 2018*)
			Soft drinks (Dunneram et al., 2018*)
			Juices (Dunneram et al., 2018*)
			Tea (Dorjgochoo et al., 2008; Dunneram et al., 2018*)
			Herbal tea (Dunneram et al., 2018*)
			Caffeine (Kinney et al., 2006; Dunneram et al., 2018*)

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Table 2 (*continued*)

	Early menopause	Late menopause	No association
			Other hot beverages (Dunneram et al., 2018*)
Macronutrients			% energy from fats (Lujan-Barroso et al., 2018; Dunneram et al., 2018*)
			% energy from proteins (Dunneram et al., 2018*)
			% energy from carbohydrates (Lujan-Barroso et al., 2018; Dunneram et al., 2018*)
			% energy from SFA (Dunneram et al., 2018*)
			% energy from PUFA (Dunneram et al., 2018*)
			% energy from MUFA (Dunneram et al., 2018*)
		Total protein (Dorjgochoo et al., 2008)	Total protein (Nagata et al., 2000; Nagel et al., 2005; Boutot et al., 2017[1])
		Vegetable protein (Boutot et al., 2017[1])	Vegetable protein (Nagata et al., 2000; Dunneram et al., 2018*)
		Animal protein (Dunneram et al., 2021*)	Animal protein (Nagata et al., 2000; Boutot et al., 2017[1])
		Dairy protein (Carwile et al., 2013 (32.5-50.9y))	Dairy protein [Carwile et al., 2013 (51-60.5y)]
			Total fat (Dorjgochoo et al., 2008; Nagata et al., 2000 and 2012; Nagel et al., 2005)
			Saturated fat (Dorjgochoo et al., 2008; Nagata et al., 2012)
	Polyunsaturated fat (Nagata et al., 2012)		
			Monounsaturated fat (Nagata et al., 2012)
		Dairy fat (Carwile et al., 2013 (32.5-50.9y))	Dairy fat [Carwile et al., 2013 (51-60.5y)]
			Animal fat (Nagata et al., 2000; Nagel et al., 2005)
			Vegetable fat (Nagata et al., 2000; Nagel et al., 2005)
			Low-calories fats (Dunneram et al., 2021*)
			Long n-3 fatty acids (Nagata et al., 2012)
	Carbohydrates (Nagel et al., 2005)	Carbohydrates (Dorjgochoo et al., 2008)	Carbohydrates (Nagata et al., 2000)
Micronutrients			

Table 2 (*continued*)

	Early menopause	Late menopause	No association
		β-cryptoxanthin (Pearce et al., 2016)	
		Calcium (Purdue-Smithe et al., 2017[1] (dietary, dairy sources, and supplemental); Purdue-Smithe et al., 2018[1])	Calcium (Nagata et al., 2000; Dunneram et al., 2018*; Carwile et al., 2012 (32.5-50.9, 51-60.5y); Purdue-Smithe et al., 2017[1] (total and no dairy sources))
			Retinol (Nagata et al., 2000)
			Carotene (Nagata et al., 2000)
		Lactose (Carwile et al., 2013 (32.5-50.9y))	Lactose (Carwile et al., 2013 (51-60.5y))
			Isoflavones (Lujan-Barroso et al., 2018)
			Lignans (Lujan-Barroso et al., 2018)
			Vitamin B1 (Dunneram et al., 2018*)
			Vitamin B2 (Dunneram et al., 2018*)
		Vitamin B6 (Dunneram et al., 2018*)	
			Vitamin B12 (Dunneram et al., 2018*)
			Vitamin C (Nagata et al., 2000; Dunneram et al., 2018*)
		Vitamin D (Purdue-Smithe et al., 2017[1] (dietary); Purdue-Smithe et al., 2018[1])	Vitamin D [Lujan-Barroso et al., 2018; Dunneram et al., 2018*; Carwile et al., 2013 (32.5-50.9, 51-60.5y); Purdue-Smithe et al., 2017[1] (total, dairy sources, no dairy sources, supplemental)]
			Vitamin A (Nagata et al., 2000; Dunneram et al., 2018*)
			Vitamin E (Nagata et al., 2000; Dunneram et al., 2018*)
			Folate (Dunneram et al., 2018*)
			Iron (Dunneram et al., 2018*)
			Zinc (Dunneram et al., 2018*)
Dietary pattern		'Animal protein' (Dunneram et al., 2021*)	
			'Red meat and processed meat' (Dunneram et al., 2021*)
			'Sweets, pastries and puddings' (Dunneram et al., 2021*)

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Table 2 (*continued*)

	Early menopause	Late menopause	No association
			'Low-fat dairy and meat' (Dunneram et al., 2021*)
	'Vegetarian' (Morris et al., 2012; Dunneram et al., 2018*)		
			'Mediterranean score' [2] (Lujan-Barroso et al., 2018)

SFA: saturated fatty acid; PUFA: polyunsaturated fatty acid; MUFA: monounsaturated fatty acid

[1] studies with early menopause as outcome

[2] it incorporates fruit, vegetables, legumes, fish, olive and cereals. It consists of a 16-point scale

[*] low-quality studies assessed by Newcastle Ottawa Scale (NOS)

risk of developing early natural menopause. No significant association between processed meat, chicken/turkey, seafood, eggs, beans/lentils, peanuts, peas/lima beans and peanut butter with early natural menopause was found [8].

Also derived from the NHSII cohort, low-fat dairy food intake, such as skim milk and yogurt, may reduce the risk of early natural menopause up to 17% [23]. In line with the significant association between dairy products and menopause reported above, data from the Nurses' Health Study (NHS) cohort reported a higher intake of total low-fat dairy and skim milk as a predictor of a modest delay in menopause among women aged under 51 years. For example, women consuming more than 3 servings of low-fat dairy daily reported reaching natural menopause 3.6 months later than those consuming no low-fat dairy products [28].

The remaining 12 studies examined ONM as outcome. A study with 494 women reported that for women who consumed alcohol 5-7 days each week, when compared to women who usually consumed no alcohol, the estimated median age of natural menopause was 2.2 years later [24]. Results were similar when alcohol intake was defined in terms of drinks per week; for any alcohol vs none, the estimated delay in ONM was 1.3 years [24]. Further findings derived from the Breakthrough Generations Study (BGS). They followed 50,678 women over 5 years and reported that, independent of smoking and other confounders, women who regularly consumed alcohol had a higher risk of late natural menopause [13]. In contrast, it was reported that alcohol intake was unrelated to the occurrence of menopause [17,21,22].

With regards to fruits, using the Melbourne Collaborative Cohort Study (MCCS) with 1,146 women, an association between fruit intake (times/day) and late natural menopause was found [25]. A study derived from Shanghai Women's Health Study followed 74,942 women over 3 years. They reported higher fruit intake was associated with slightly later natural menopause, while no impact of vegetable intake on ONM was found [22]. A small study with 1,130 women reported vegetable intake, in particular green and yellow vegetable, to be significantly associated with early natural menopause [26]. However, data derived from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, based on 5,110 participants and 5.8 years follow-up, confirmed that vegetable intake was not associated with early natural menopause [20].

Also, the consumption of fibre, soy and cereal products was associated with an earlier natural menopause, whereas increased red meat consumption was associated with late natural menopause [20]. Regarding soy and fibre intake, a prospective study reported a null impact of these dietary foods on the timing of menopause [22]. A study derived from the UK Women's Cohort Study (UKWCS) followed 14,172 participants over 4 years. They reported that the intake of refined pasta and rice was associated with an earlier natural menopause, whereas each additional increment in fresh legumes and oily fish (portion/day) was associated with a later natural menopause by 0.9 and 3 years, respectively [10].

3.4. Macronutrients/micronutrients and menopause onset

Ten studies [7,8,10,17,20–22,25,26,28] reported the association between macronutrient and micronutrient intake and menopause onset; the results are summarized in Table 2. Of those, 2 studies (86,234 women) examined the association of macronutrient or micronutrient intake with early natural menopause as outcome (n=2,041 women) and 8 studies (145,137 women) examined the association between macronutrient or micronutrient intake and ONM (n=66,669 women). Among those that examined early menopause as outcome, data derived from the NHSII cohort; they reported a higher plant-based protein intake to be associated with a lower likelihood of early natural menopause. In fact, women consuming around 6.5% of their daily calories as plant-based protein had a significant 16% lower risk of early natural menopause than those consuming around 4% of their caloric intake as plant-based protein. High levels of animal-based protein intake were not associated with early natural menopause [8]. Regarding micronutrient intake, women with high intake (highest quintile) of dietary vitamin D had a significant 17% lower risk of early natural menopause than women with low intake (lowest quintile). Dietary calcium intake in the highest quintile compared with the lowest was associated with a borderline significantly lower risk of early natural menopause. Furthermore, the associations were stronger for vitamin D and calcium from dairy than non-dairy products. High supplement use was not associated with lower risk of early natural menopause [7].

The remaining 8 studies examined ONM as outcome. A study derived from the MCCS followed 1,146 women over 12 years. They reported β-cryptoxanthin intake to be associated with later natural menopause [25]. A study derived from the population-based cohort Takayama Study found a borderline significant ($p = 0.07$) association of carotene intake with earlier natural menopause [26]. Also, derived from the same cohort polyunsaturated fat intake was moderately, yet significantly associated with an earlier natural menopause, while the dose-response relationship between monounsaturated fat and age of menopause was borderline significant ($p = 0.05$) [17]. High intake of total fat and protein was associated with a late natural menopause, while high carbohydrate intake was associated with an early natural menopause [20]. In contrast, a prospective study reported a borderline significant ($p < 0.06$)

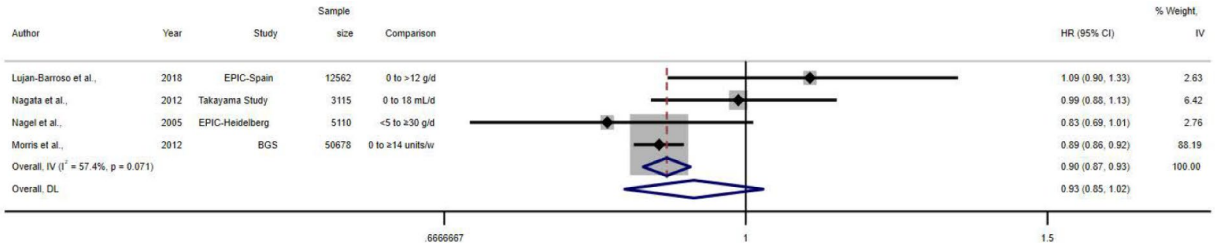

Fig. 2. Pooled relative risks for menopause onset when comparing women who reported lowest intake versus highest intake of alcohol in longitudinal studies. IV: random-effects model; Assessment of heterogeneity, I^2.

association between carbohydrate intake and later natural menopause [22]. In alignment with the findings reported above, the same study also reported an association between total protein intake and late natural menopause [22]. Yet, 2 studies—using the UKWCS and the NHS with over 140,000 and 46,000 women, respectively—reported that vitamin B6, zinc intake, lactose, dairy protein and dairy fat intake to be associated with late natural menopause [10,28].

3.5. Dietary patterns and menopause onset

Dietary patterns and ONM results are summarized in Table 2. Among those that examined ONM as outcome, data were used from the UKWCS cohort. They followed 14,765 women for 4 years and, after adjustment for potential confounders, showed that "animal proteins" and "red meat and processed meat" dietary patterns were positively associated with a late natural menopause, whereas no association was found with the "sweets, pastries and puddings" and "low-fat dairy and meat" patterns [27]. Also, derived from the UKWCS reported that vegetarian women had an earlier age at menopause compared with non-vegetarians [10]. In support of these findings, another study reported that vegetarians reach natural menopause at a mean age of 50.1 years, which was significantly earlier than non-vegetarians with a mean age of 50.7 years [13].

3.6. Meta-analysis of alcohol consumption and onset of natural menopause

A total of 71,465 women were included in the meta-analysis of alcohol intake and ONM with a total of 25,476 women experiencing ONM during the follow-up period. Four prospective studies [13,17,20,21] reported highest alcohol intake in quartile compared to a reference group (lowest intake) in relation to ONM. The pooled HR for experiencing natural menopause between lowest vs highest intake was 0.93 (95% CI: 0.85–1.02) (Fig. 2). The results changed when the analysis was restricted to studies comparing the ONM between alcohol consumers and non-consumers [13,17,21]. Pooled HR was 0.94 (95% CI: 0.90–0.99; heterogeneity (I^2) 50.7%, $p = 0.132$) and showed alcohol consumers to be at lower risk of early natural menopause (Fig. 3). Sensitivity analysis conducted between lowest vs. highest alcohol intake showed a null association as in the main analysis (data not shown), after exclusion of Nagata et al., 2012.

3.7. Assessments of study quality

The overall NOS scores are reported in Supplementary Table 1. Two studies were judged to be at low risk of bias [22,29], 11 studies at medium risk [7,8,13,17,20,21,23–26,28] and 2 studies at high risk of bias [10,27].

4. Discussion

To our knowledge, ours is the first systematic review and meta-analysis about the association between dietary intake and ONM. Overall, we found inconsistent associations between specific foods and macronutrient or micronutrient intake and age at natural menopause. Although several studies suggested some food items, such as green and yellow vegetables, dairy products and alcohol, and a vegetarian diet, could impact ONM the findings in general were not replicated among the studies we included in our systematic review and meta-analysis.

4.1. Alcohol intake and menopause onset

The association between alcohol consumption and late ONM is not fully understood [12]; our analysis reveals the complexity of making associations between alcohol intake and menopause onset, as well as opportunities for further research. In our previous systematic review and meta-analysis about associations between alcohol consumption and ONM, we reported low and moderate alcohol intake might be associated with late ONM [11]. However, the magnitude of the association was low and could be confounded by other factors not considered in the primary studies [11]. For example, alcohol can induce a rise in circulating oestrogen levels, which has been associated with delayed natural menopause [29,30]; still, studies exploring possible associations between alcohol intake and oestrogen metabolism are limited [31]. In addition, our findings should be read within the context of the complex association of alcohol with menopause-related health conditions. Although low to moderate alcohol consumption has been linked to a reduced risk of cardiovascular disease and type 2 diabetes [32,33], a dose-response association has been reported between high alcohol intake and increased risk of breast cancer in premenopausal women [34].

4.2. Food intake and menopause onset

Our analysis revealed inconsistent findings about the impact of fruit intake on menopause onset, which points to openings for replication studies to parse these inconsistencies. For example, 2 studies [22,25] showed high fruit intake was associated with later ONM, yet 4 other studies found no association [10,20,21,27]. β-cryptoxanthin was associated with later ONM in 1 study [25], suggesting that this micronutrient may be a potential active ingredient in fruit responsible for prolonging reproductive life. However, these findings were not replicated in another independent study. Also, 1 study reported that high fruit intake was inversely associated with the annual reduction in anti-Müllerian hormone (AMH); hence, prolonging reproductive life [35].

We obtained consistent findings regarding the lack of impact of total vegetable intake on menopause onset. Still, this association may depend on the type of vegetable being consumed. For instance, green and yellow vegetable intake could be associated with earlier natural menopause; the antioxidative mechanism may explain this association [26]. A study suggests that age-related changes in the central nervous system initiate the transition to menopause [36] and the antioxidant activity of carotenoids may be related to the menopausal transition due to a change in follicle-stimulating hormone secretion [37]. However, another study with over 85,000 women showed an association between vegetable protein intake and risk of early menopause [8]. Conversely, this finding was not supported by a study with a sample size of 1,130 women [10].

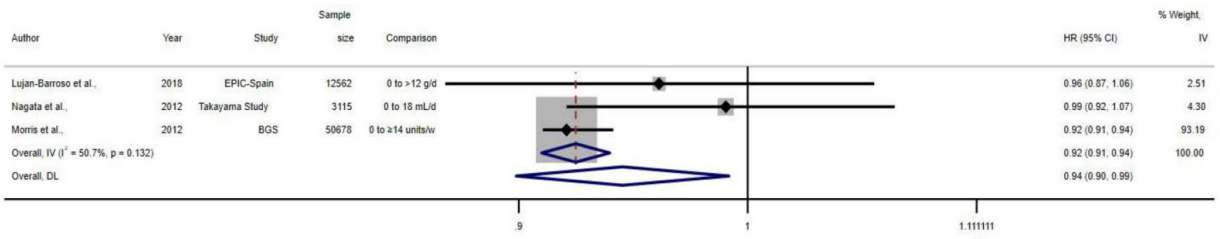

Fig. 3. Pooled relative risks for menopause onset when comparing alcohol consumers versus non-consumers in longitudinal studies. IV: random-effects model; Assessment of heterogeneity, I^2.

Also, 2 studies [10,13] reported that when compared to women who were not vegetarian, women who were vegetarian experienced an earlier natural menopause, suggesting that vegetable intake may be associated with an earlier natural menopause. However, further studies are needed to confirm the strength of this association, and impact of unmeasured confounders on the association between vegetarian diet and ONM. On account of high phytoestrogen content, previously it was suggested that vegetable intake could have beneficial effect delaying natural menopause. However, due to activating/inhibiting oestrogen receptors, these compounds may also induce or inhibit oestrogen action; therefore, they have the potential to disrupt oestrogen signalling [38]. Furthermore, theses studies' findings were inconsistent regarding phytoestrogen-rich foods, including soy/tofu, beans and legumes and any beneficial impact delaying natural menopause.

On the whole, 3 studies included in our review suggested that total dairy products might not impact ONM [20,21,23]. Nevertheless, our review indicates that some dairy products may be associated with ONM. Low-fat dairy-food intake, such as skim milk and yogurt, may reduce the risk of early natural menopause up to 17% [7,23]. Similarly, dairy protein and dairy fat were associated with a late natural menopause [28]. These findings align with a study of 227 women followed for 16 years. In this study, total dairy, milk and fermented dairy products were showed to reduce the rate of AMH decline, prolonging reproductive life [35]. Yet, higher dietary intakes of calcium from dairy sources, free galactose and lactose were also associated with both lower annual reduction in AMH and the odds of its rapid decline [35]. Further, a cross-sectional study reported the highest tertile of calcium—an important component in dairy products—was significantly associated with later natural menopause [39].

4.3. Dietary patterns and menopause onset

As opposed to single nutrient approach, dietary patterns have several advantages, such as limiting potential confounding by other features of diet, assessing the cumulative effects of foods and allowing for interactions. In our review, we found only a dietary pattern characterized by high animal-based protein intake to be associated with late natural menopause, albeit based on a single study [27]. Other studies failed to show any impact from high intake of animal-protein rich foods, such as meat, red and processed meat or chicken and turkey, delaying natural menopause. In contrast, a vegetarian diet was reported in 2 studies [10, 13] to be associated with early natural menopause onset. Due to its anti-atherogenic activity and ability to impact pre- and post-menopausal women's oestrogen levels, a plant-based diet was previously suggested to positively impact ONM. Additionally, better atherogenic profiles have been suggested to increase blood flow to the ovaries; therefore to slow depletion of the follicle pool [40].

4.4. Strengths and limitations

Strengths of our systematic review and meta-analysis include assessments for bias of included studies, adherence to strict inclusion criteria and comprehensive search strategy.

Our study has several limitations. First, age at natural menopause and diet were self-reported, which indicates the possibility of inaccurate reporting; the reproducibility and validity of self-reported menopausal status has been shown to be highly accurate [41]. Still, the biological mechanisms behind the association between food intake and menopause onset are still unclear; possible interpretations and explanations are reported in some study but, in general, they do not provide biological insights limiting the interpretation of the findings. Since our review was based on different populations, time periods, and different methods were used to analyse dietary intake, these differences precluded us from comprehensively comparing findings across these studies. Also, we were only able to run meta-analysis for alcohol intake because of other studies' heterogeneity in exposure assessment (e.g., continuous or categorical variables; different units of assessment), outcomes (e.g., different definitions of natural menopause) and a limited number of available studies that met our inclusion criteria. Most of the included studies reported a length of follow-up more than 5 years and, even though approaching menopause is not associated with important changes in dietary habits, analyzing dietary intake close to menopause could provide more insights of the diet impact on menopause onset; nevertheless, long-term effects of diet should not be excluded. For the last, longitudinal changes of diet over time should be accounted in the analyses by using repeated measure of diet, which was only taken into account in 7 of the 15 included articles in this review. Yet, the impact of dietary factors on timing of menopause is not clear with regard to absolute months/years women would gain in delaying menopause; some published studies report how a specific food intake reduce or increase the risk of early or late menopause by percentage, months/years, while some others do not report this information. There is need for translation of reported estimates into scales that can be helpful for clinicians, nutritionist, other experts, and for public communication. Among the included studies, only 4 studies account for competing risks, such as occurrence of hysterectomy, cancer or use of hormone therapy. Future studies should explore further the impact of competing risks on the association between diet and menopause onset. Still, 4 out 15 studies adjusted simultaneously for important confounders on the association between diet and ONM, including age, BMI, smoking status, age at menarche, caloric intake, parity; the studies also adjusted for one or more additional confounders such as physical activity, alcohol intake, breastfeeding, education level, oral contraceptive use, hormone replacement therapy, protein and animal proteins, multivitamin use, and marital status. Last, our alcohol intake meta-analysis should be interpreted cautiously since there were few studies included in the meta-analysis, which means they could have bias.

4.5. Implications for public health and research

Our systematic review may have several implications. Although it suggests that diet may impact ONM, this is underscored by the absence of replication and comprehensive studies available about this topic. Thus, our review calls for future prospective and randomized studies to investigate whether diet can influence ONM. For instance, explorations of associations between diet and sex hormones and consequent ONM; foods that affect sex hormones the most; or further study of the possible role of soy, tofu and phytoestrogen on menopause timing. Understanding whether and how dietary factors influence ONM could have a positive impact on family planning, and it could also lead to a new approach in reducing adverse outcomes related to early or late natural menopause.

5. Conclusion

Although some food items were associated with ONM, the number of studies is limited and the overall evidence about associations between diet and ONM remains controversial. Further studies are needed to understand associations between diet and menopause onset.

Contributors

Giorgia Grisotto conceptualized the study, analysed data and wrote the manuscript, contributed to the literature review, analysis and interpretation of data, has full access to the data used in this study and takes responsability for the integrity of the data and accuracy of the data analysis..

Julian S. Farago conceptualized the study, analysed data and wrote the manuscript, contributed to the literature review, analysis and interpretation of data, and critically revised the manuscript.

Petek E. Taneri contributed to the literature review, analysis and interpretation of data, and critically revised the manuscript.

Faina Wehrli contributed to the literature review, analysis and interpretation of data, and critically revised the manuscript.

Zayne M. Roa-Díaz contributed to the literature review, and critically revised the manuscript.

Beatrice Minder contributed to the literature review, and critically revised the manuscript.

Marija Glisic contributed to the literature review, and critically revised the manuscript.

Valentina Gonzalez-Jaramillocontributed to the literature review, and critically revised the manuscript.

Trudy Voortman contributed to the literature review, and critically revised the manuscript.

Pedro Marques-Vidal contributed to the literature review, analysis and interpretation of data, and critically revised the manuscript.

Oscar H. Franco contributed to the literature review, and critically revised the manuscript..

Taulant Muka conceptualized the study, analysed data and wrote, contributed to the literature review, analysis and interpretation of data, and critically revised the manuscript.

All authors read and approved the final manuscript.

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Research data (data sharing and collaboration)

Data described in the manuscript, code book and analytic code will be made available upon request to info@ispm.unibe.ch.

Declaration of competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.maturitas.2021.12.008.

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Contents

Supplementary Table 1. The NOS to evaluate the quality of included prospective cohort studies to assess the effect of diet on age at natural menopause.

Author, year	Selection				Comparability	Outcome/ Exposure			Total Score
	1	2	3	4	1	1	2	3	max: 9
Gold et al., 2013	*	*	*	*	**	*	*	*	9
Dorjgochoo et al., 2008	*	*	*	*	**	*	*	*	9
Kinney et al., 2006		*	*	*	**	*	*	*	8
Nagata et al., 2000	*	*		*	**	*	*	*	8
Nagel et al., 2005	*	*		*	**	*	*	*	8
Morris et al., 2012	*	*		*	**	*	*	*	8
Boutot et al., 2017		*		*	**	*	*	*	7
Purdue-Smith et al., 2017		*		*	**	*	*	*	7
Purdue-Smith et al., 2018		*		*	**	*	*	*	7
Pearce et al., 2016	*	*	*	*	**		*		7
Nagata et al., 2012	*	*		*	**	*	*		7
Lujan-Barroso et al., 2018	*	*	*	*	**			*	7
Carwile et al., 2013		*		*	**	*	*	*	7
Dunneram et al., 2018	*	*		*	**	*			6
Dunneram et al., 2021	*	*		*	**	*			6

Supplementary Table 2. Detailed search strategies used in this review.

Embase (Ovid)

exp food/ or exp diet/ or exp dietary intake/ or exp diet therapy/ or exp beverage/ or (diet or dieting* or diets or dietary or nutri* or macro-nutrient* or macronutrient* or micro-nutrient* or micronutrient* or food or dairy or milk or ((sugar or caloric or energy) and intake) or alcohol* or coffee or caffeine or coffea or tea or beer or wine or juic* or eggs or fruit* or meat or nuts or seeds or vegetable* or drinking behavior* or drinking behaviour*).ti,ab,kw.

AND

early menopause/ or exp premature ovarian failure/ or (((menopaus* or climacter*) adj3 (earl* or late* or age or prematur* or onset or timing)) or "cessation of ovulation" or primary ovarian insufficienc* or premature ovarian failur* or premature ovarian insufficienc* or climacterium praecox or climacterium precox).ti,ab,kw.

NOT (exp animal/ not human/) **NOT** (letter or note or editorial or conference).pt.

Medline (Ovid)

exp Food/ or exp Diet/ or exp Plant Proteins, Dietary/ or exp Diet Therapy/ or Dietary Carbohydrates/ or Dietary Fiber/ or Dietary Sugars/ or exp Beverages/ or (diet or dieting* or diets or dietary or nutri* or macro-nutrient* or macronutrient* or micro-nutrient* or micronutrient* or food or dairy or milk or ((sugar or caloric or energy) and intake) or alcohol* or coffee or caffeine or coffea or tea or beer or wine or juic* or eggs or fruit* or meat or nuts or seeds or vegetable* or drinking behavior* or drinking behaviour*).ti,ab,kw.

AND

Menopause, Premature/ or Primary Ovarian Insufficiency/ or (((menopaus* or climacter*) adj3 (earl* or late* or age or prematur* or onset or timing)) or "cessation of ovulation" or primary ovarian insufficienc* or premature ovarian failur* or premature ovarian insufficienc* or climacterium praecox or climacterium precox).ti,ab,kw.

NOT (exp animals/ not humans/) **NOT** (letter or news or comment or editorial or congress).pt.

PubMed

("Food"[Mesh] OR "Diet"[Mesh] OR "Plant Proteins, Dietary"[Mesh] OR "Diet Therapy"[Mesh] OR "Dietary Carbohydrates"[Mesh:NoExp] OR "Dietary Fiber"[Mesh:NoExp] OR "Dietary Sugars"[Mesh:NoExp] OR "Beverages"[Mesh] OR diet[tiab] OR dieting*[tiab] OR diets[tiab] OR dietary[tiab] OR nutri*[tiab] or macro-nutrient*[tiab] or macronutrient*[tiab] or micro-nutrient*[tiab] or micronutrient*[tiab] or food[tiab] or dairy[tiab] or milk[tiab] or ((sugar[tiab] or caloric[tiab] or energy[tiab]) AND (intake[tiab])) or alcohol*[tiab] or coffee[tiab] or caffeine[tiab] or coffea[tiab] or tea[tiab] or beer[tiab] or wine[tiab] or juic*[tiab] or eggs[tiab] or fruit*[tiab] or meat[tiab] or nuts[tiab] or seeds[tiab] or vegetable*[tiab] or drinking behavior*[tiab] or drinking behaviour*[tiab])

AND

("Menopause, Premature"[Mesh] OR "Primary Ovarian Insufficiency"[Mesh] OR ((menopaus*[tiab] OR climacter*[tiab]) AND (earl*[tiab] OR late[tiab] OR age[tiab] OR prematur*[tiab] OR onset[tiab] OR timing[tiab])) OR "cessation of ovulation"[tiab] OR primary ovarian insufficienc*[tiab] OR premature ovarian failur*[tiab] OR premature ovarian insufficienc*[tiab] OR climacterium praecox[tiab] OR climacterium precox[tiab])

NOT ("animals"[mesh] NOT "humans"[mesh]) **NOT** (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congress[pt])

Cochrane CENTRAL

(diet or dieting* or diets or dietary or nutri* or macro-nutrient* or macronutrient* or micro-nutrient* or micronutrient* or food or dairy or milk or ((sugar or caloric or energy) AND intake) or alcohol* or coffee or caffeine or coffea or tea or beer or wine or juic* or eggs or fruit* or meat or nuts or seeds or vegetable* or (drinking NEXT behavior*) or (drinking NEXT behaviour*)):ti,ab,kw

AND

(((menopaus* OR climacter*) NEAR/3 (earl* OR late* OR age OR prematur* OR onset OR timing)) OR "cessation of ovulation" OR "primary ovarian insufficiency" OR "premature ovarian failure" OR "premature ovarian insufficiency" OR "climacterium praecox" OR "climacterium precox"):ti,ab,kw

Web of Science Core Collection

TS=(diet or dieting* or diets or dietary or nutri* or macro-nutrient* or macronutrient* or micro-nutrient* or micronutrient* or food or dairy or milk or ((sugar or caloric or energy) AND intake) or alcohol* or coffee or caffeine or coffea or tea or beer or wine or juic* or eggs or fruit* or meat or nuts or seeds or vegetable* or (drinking NEAR/2 behavior*) or (drinking NEAR/2 behaviour*))

AND

TS=(((menopaus* OR climacter*) NEAR/3 (earl* OR late* OR age OR prematur* OR onset OR timing)) OR "cessation of ovulation" OR "primary ovarian insufficiency" OR "premature ovarian failure" OR "premature ovarian insufficiency" OR "climacterium praecox" OR "climacterium precox")

NOT TS=((animal* OR plant* OR rats OR mice OR pigs) NOT (human* OR patient*))

AND DT=(article)

Google scholar

"early|late|premature menopause|menopausal|climacteric"|"timing|onset * menopause|menopausal|climacterium"
diet|dietary|food|nutrient|coffee|caffeine|coffea|alcohol|wine|beer|dairy|milk|tea|eggs|fruits|meat|vegetables|nuts

3.3. Article 3. Association of plant-based diet and early onset of natural menopause

Association of plant-based diet and early onset of natural menopause

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Contribution: I participated by designing the study and co-supervising the study procedure. I did the analyses, made the figures, and wrote the first draft of the manuscript. After that, I incorporated co-authors' and reviewers' comment.

Association of plant-based diet and early onset of natural menopause Running title:

Plant-based diet and early menopause

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ABSTRACT

Objective: To evaluate the association of plant-based diet index (PDI) with early onset of natural menopause in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII). **Methods:** We conducted a prospective study with a mean follow-up time of 20 years among premenopausal women living across the US. Participants of the NHS (n = 121,701) and NHSII (n = 116,429) were included from 1984 [age mean (standard deviation, SD); 44.9 (4.3)] and 1991 [age mean (SD); 36.4 (4.6)], respectively. Early menopause was self-reported and defined as natural menopause before age 45 years. PDI was derived from semi-quantitative food frequency questionnaires (FFQ) administered every four years. Cox proportional hazards models were used to assess the association between PDI in quintiles and early menopause in NHS and NHSII separately, and fixed-effect models to pool the results from both cohorts.

Results: During follow-up, 715 and 2,185 women experienced early natural menopause in NHS and NHSII, respectively. After adjustment for potential confounders, no association was observed between PDI and incidence of early natural menopause in either cohort, or when pooling the results from both cohorts, with an exception for unhealthy plant-based diet (uPDI) index which was associated with higher risk of early menopause with increasing levels of consumption [*P* trend = 0.04].

Conclusion: Adherence to PDI was not associated with timing of menopause while uPDI might be associated with higher risk of experiencing early menopause.

Keywords: Early natural menopause, menopause onset, prospective study, plant-based diet, healthy plant-based diet, unhealthy plant-based diet.

Introduction

Menopause, the cessation of ovarian function, occurs generally between ages of 45-55 years, and represents the end of a woman's reproductive life. Around 5-10% of women in Western countries experience menopause before age of 45, defined as early menopause.[1] Early menopause is associated with long-term health consequences, including osteoporosis, type 2 diabetes (T2D), cardiovascular disease (CVD), neurological outcomes and overall mortality.[2] Emerging evidence suggests that early menopause may be associated with genetic factors,[3] but other studies suggest that modifiable lifestyle factors such as diet also may play an important role in ovarian aging.[4-6]

Several studies have investigated the association between dietary intake and menopause onset, providing controversial results.[7] High consumption of refined pasta and rice has been previously associated with an earlier age at menopause while high intakes of oily fish, fresh legumes, plant proteins as well as vitamin B6 and zinc have been reported to lower the risk of early menopause.[8] Yet, a modest inverse association of early menopause with dairy foods, calcium, and vitamin D from dietary sources was found,[9] while low or moderate alcohol intake might be associated with later onset of menopause.[6]

In the light of these findings, we hypothesised that overall plant-based diet index (PDI), a dietary pattern characterized by low intake of animal foods and higher intakes of plant foods including fruits, vegetables, whole grains, legumes, nuts and seeds and micronutrients such as vitamin B12, folic acid, and iron, would be associated with menopause onset. PDI includes both healthy plant-based diet index (hPDI) and unhealthy plant-based diet index (uPDI); hPDI emphasizes intake of healthy plant foods such as whole grains, fruits, and vegetables and uPDI emphasizes consumption of less healthy plant foods known to be associated with a higher risk of adverse outcomes.[10]

PDI has been associated with lower risk of several health conditions such as T2D, CVD and overall mortality,[11] and has been linked to levels of estrogen in both pre- and postmenopausal women, implicating PDI in reproductive health.[12] Also, PDI may be anti-atherogenic, and a better atherogenic

profile has been suggested to increase blood flow to the ovaries, and therefore to slow depletion of the follicle pool.[13] To date, no epidemiological studies have investigated the association between PDI and incidence of early menopause. For health promotion and disease prevention related to early menopause, it is important to understand whether PDI can affect timing of the menopausal transition.

We prospectively investigated the association between PDI and incidence of early menopause among women enrolled in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods

Study population

The study was carried out within the NHS and NHSII prospective cohort studies, with participants recruited from across the US. The NHS began in 1976 when 121,701 women, aged 30 - 55 years, responded to a baseline questionnaire on medical, lifestyle and other health information. The NHSII began in 1989 when 116,429 women, aged 25 - 42 years, completed a mailed questionnaire and provided information on past and current health conditions, prescription medication use, and lifestyle factors. In both cohorts, participants have completed a new questionnaire biennially to update information, with a cumulative response rate of > 90%. The protocols were approved by the Institutional Review Boards at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health in Boston, Massachusetts.

Nurses' Health Study

Baseline in NHS was 1984 and follow-up ended in 1992 when all women were older than 45 years and no longer at risk for early menopause (< 45 years). From the 121,701 women at the time of enrolment we excluded women reporting menopause before 1984 (n = 56,492), and those who did not report age at menopause (n = 20,290). We excluded women who did not respond to the 1984 FFQ or had implausible caloric intake (n = 11,778), who died before 1984 (n = 1,918) or women with cancer diagnosis (n = 3,372). A total of 27,851 eligible participants were followed until 1992.

Nurses' Health Study II

Follow-up for the NHSII analysis started in 1991 and ended in 2011 when all women were 45 years or older and no longer at risk for early menopause (< 45 years). From 116,429 cohort members, we excluded women reporting menopause before 1991 (n = 3,942), and those who did not report an age at menopause (n = 5,341). We excluded women who did not respond to the 1991 FFQ or had implausible caloric intake (n = 18,518), who died before 1991 (none) or women with cancer diagnosis (n = 724). A total of 87,904 eligible participants were followed until 2011. *Early menopause*

Menopausal status has been assessed every 2 years in the NHS and NHSII starting in 1980 and 1989, respectively. Nurses were asked if their periods had ceased permanently, and if so, at what age their period ceased (open response), for what reason the period ceased (response options were surgery, radiation or chemotherapy, and natural), their current and past use of menopausal hormone therapy, and if they had had a hysterectomy or oophorectomy (bilateral or unilateral). In this study, we defined cases of early natural menopause as women who reported natural menopause before age 45 years for each period from 1984 in NHS and 1991 in NHSII until 1992 and 2011, respectively.[14]

Self-assessment of menopause has been validated and the reproducibility is very high; over 98% of women in post menopause in 1979 accurately confirmed their menopause status within 1 year and, 82% who experiencing menopause reported the same age of menopause within a year from the previous questionnaire.[15]

Dietary Assessment

We calculated the cumulative average of PDI, including hPDI and uPDI, using a semi- quantitative FFQ collected every 4 years from the baseline; indices were cumulatively averaged over follow-up to better capture long-term diet. Beginning in 1984 forNHS and in 1991 for NHSII, participants reported how often they consumed defined portions of 126 food items. Responses ranged in 9 categories, from "never or less than once/month" to "≥ 6times/day". The reliability and validity of FFQ have been described elsewhere.[16,17]

Plant-Based Diet

An overall PDI, a hPDI, and an uPDI were created.[10] The hPDI represents a high-quality plant- based diet rich in whole grains, fruits, vegetables, and nuts and low in fruit juices, refined grains, and sweets, while uPDI includes less-quality diet rich in fruit juices, refined grains, potatoes, sugar sweetened beverages, sweets, and desserts and low in high-quality plant-based diet. Initially, three large categories were created; healthy plant foods (whole grains, fruits, vegetables, nuts, legumes, vegetable oils, tea/coffee), less healthy plant foods (fruit juice, refined grains, potatoes, sugar-sweetened beverages, sweet/desserts) and animal foods (animal fat, dairy eggs, fish/seafood, meat, miscellaneous animal-based foods). Within these large groups, another 18 food groups were created, and ranked into quintiles of consumption with positive or reverse scores. PDI was created given a positive score for foods in plant food group, and reverse score was given for foods included in animal food group. For creating hPDI, foods in healthy plant food group were given positive scores, and foods in less healthy plant food group and animal food group were given reverse scores. For uPDI, foods in less healthy plant food group were given positive scores, while foods in healthy plant food group and animal food group were given reverse scores. The 18 food groups scores were summed to obtain the indices, with a theoretical range of 18 (lowest possible score) to 90 (highest possible score). Ranges in the study population were 24 - 85 for PDI, 28 - 86 for hPDI and 27 - 90 for uPDI.

Covariates

In this study, age was calculated by subtracting the participant's date of birth from the questionnaire return date, and height that was collected at baseline in 1976 (NHS) and 1989 (NHSII). Updated information on weight was used to calculate body mass index (BMI), defined as weight (kg)/height $(m)^2$ (Kg/m^2; < 21, 21-22.9, 23-24.9, 25-29.9, > 30), age at first birth and parity defined as pregnancies lasting > 6 months, (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use (continuous), breastfeeding (last time 2003 - categorical), smoking status and quantity (former, current 1-14, current 15-24, current 25+) and packs per year was collected biennially throughout follow-up. Physical activity was assessed every four years

and was based on metabolic equivalent of task hours per week (MET-h/wk). Dietary factors, including total caloric intake (Kcal/day), vitamin D with/without supplement, were assessed via FFQ, as described earlier.

Statistical analysis

Statistical analyses were conducted with SAS version 9.3 software (SAS Institute Inc, Cary, NC). We evaluated the association between baseline PDI with incidence of early menopause using Cox proportional hazards models to calculate hazard ratio (HR) and 95% CI in both NHS and NHSII cohorts. The proportional hazard assumption of the Cox model was checked by visual inspection of log minus log plots and by performing a test for heterogeneity of exposure over time. There was no evidence for violation of the proportionality assumption in any of the models (*P* for time-dependent interaction terms > 0.05). The results are reported in Quintile (Quintile 1, Quintile 2, Quintile 3, Quintile 4 and Quintile 5), using Quintile 1 as the reference group.

The included participants contributed follow-up time from the date of return of the questionnaire at baseline until the onset of early menopause (< 45 years), death, loss to follow-up, experienced no natural menopause (e.g., surgery, radiation or chemotherapy), cancer diagnosis, or the end of follow-up, whichever came first. Our initial model (Model 1) was adjusted only for age. The covariate selection for multivariable models (Model 2) was based on factors identified *a priori* (age and caloric intake in quintiles) based on literature. Additionally, we adjusted for smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use (continuous), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, > 30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol and physical activity (MET-h/wk) (Model 3).

Finally, we evaluated the association between PDI, hPDI and uPDI with incidence of early menopause using fixed-effects meta-analysis to combine the summary results from both cohorts, NHS and NHSII. Relative risk (RR), 95% CI, and *P* for trend are reported for each quantile.

Sensitivity analysis

As a sensitivity analysis, we used the Cox proportional hazards model to explore whether PDI was associated with natural early menopause after censoring women who used hormone therapy before menopause occured. Results are reported as HR and 95% CI.

To investigate possible effect modification, we stratified the main analysis (association between PDI and early menopause) by BMI categories (< 25, 25-29.9, ≥ 30 kg/m^2), smoking status (never, former, current 1-14, current 15-24, current 25+) and oral contraceptive use categories (never use, current use, former use < 5 years, former ≥ 5 years) in both NHS and NHSII cohorts.

To explore the interaction of PDI with BMI, smoking status and oral contraceptive use on early menopause, we used Cox proportional hazard models to calculate HR and 95% CI, adjusted for all covariates.

Results

Characteristics of participants by quintile of PDI are shown in **Table 1** for NHS. Women who had the highest intake of PDI were older [mean (SD), Q5 45.1 (4.2) vs. Q1 44.8 (4.3) years], reported less use of oral contraceptives [Q5 28.4 (40.3) vs. Q1 34.1 (45.8), months], smoked less packs per year [Q5 7.4 (11.9) vs. Q1 11 (14.4)], less likely to be overweight and obese, more physically active [Q5 15.6 (24.8) vs. Q1 13.2 (19.6) MET-h/wk], and reported higher total caloric intake [Q5 2108 (516) vs. Q1 1486 (453)] than women with lower intake of PDI.

For NHSII cohort, characteristics of participants by quintile of PDI are shown in **Table 2**. Women who had the highest intake of PDI, were older [mean (SD), Q5 36.9 (4.5) vs. Q1 36 (4.7) years], reported less use of oral contraceptives [Q5 44.2 (43.7) vs. Q1 51.8 (49.4), months], smoked less packs *per* year [Q5 3.5 (6.7) vs. Q1 4.7 (8.3)], less likely to be overweight and obese, more physically active [Q5 25 (31.1) vs. Q1 17.7 (24) MET-h/wk], reported higher total caloric intake [Q5 2137 (527) vs. Q1 1478 (463)] than women with lower intake of PDI.

Results from the association between PDI and early menopause in NHS and NHSII are presented in **Table 3**. In the age-adjusted model (Model 1), PDI was not associated with early menopause in either the NHS [HR (95%CI), Q5 vs. Q1 0.85 (0.66 to 1.08)] or NHSII [Q5 vs. Q1 0.89 (0.78 to 1.01)]. Also, results adjusted for age and caloric intake (Model 2) [NHS, Q5 vs. Q1 0.9 (0.68 to 1.17); NHSII, Q5 vs. Q1 0.95 (0.82 to 1.1)] and for all other potential factors (Model 3) [NHS, Q5vs. Q1 0.94 (0.73 to 1.2); NHSII, Q5 vs. Q1 0.95 (0.83 to 1.08)] showed no association of plant foodsintake with early menopause in both cohorts.

In **Table 4**, we conducted a meta-analysis (of the above described cohorts) to evaluate the possible association between PDI, hPDI and uPDI with early menopause and an association was found between uPDI and early menopause [HR (95%CI), Q4 vs. Q1 1.16 (1.03 to 1.31), *P* trend =0.04].

Sensitivity analyses conducted in both cohorts showed a null association between PDI with natural early menopause after censoring women who took hormone therapy before menopause occurred (see Table, Supplemental Digital Content 1, which illustrates the associations between PDI and early menopause after censoring for hormone therapy use before menopause).

Further, results from analyses stratified by BMI categories (< 25, 25-29.9, > 30 kg/m2) (see Table, Supplemental Digital Content 2, which illustrates the associations between PDI and early menopause stratified by BMI) and smoking status (never, former, current 1-14, current 15-24, current 25+) (see Table, Supplemental Digital Content 3, which illustrates the associations between PDI and early menopause stratified by smoking status) showed no significant interaction with PDI on the association with early menopause. Yet, in the fully-adjusted model stratified by oral contraceptive use categories (never use, current use, former use < 5 years, former ≥ 5 years) (see Table, Supplemental Digital Content 4, which illustrates the associations between PDI and early menopause stratified by oral contraceptive use), a null association between PDI and early menopause was observed.

Same sensitivity analyses applied to PDI were also undertaken for hPDI and uPDI, which showed similar results as the main analysis (data not shown).

Discussion

In this prospective study, no significant association between PDI and early menopause was observed. The results remained consistent across strata of BMI, smoking status and oral contraceptive use. Similar results were found for hPDI and uPDI as they were not associated with early menopause, although the fixed-effect model showed uPDI to be associated with a modest higher risk of early menopause.

Several studies investigated how diet is associated with timing of menopause but, to our knowledge, no other studies have reported the association between PDI, hPDI and uPDI. In line with our findings, two previous studies have shown no positive impact of vegetarian diet in delaying menopause onset, contrary, both studies suggested that vegetarian women were more likely to develop early menopause than non-vegetarian.[8,18] Also, studies exploring the impact of fruits intake, a component of PDI, have shown controversy results; two studies have showed high fruit intake to be associated with delayed menopause,[19,20] while four other studies have found no association.[8,21-23] Similarly, studies on vegetable intake and menopause onset have in general shown null association.[8,19,21,24] A prospective study conducted in Japan with 1,130 women reported that higher green and yellow vegetable intake was significantly associated with later age at natural menopause due to carotenoids. Such dietary antioxidant components could preventthe age-related reduction in the ovulation rate,[24] preserving the number and the quality of ovarian follicles.[25]

A longitudinal study in Germany with participants followed for an average of 5.8 years observed that high intake of carbohydrate, fiber, and cereal products were related to an earlier menopause, whereas women with higher intake of fat, protein and meat experienced a delayed onset of natural menopause.[22] In contrast, a diet intervention study to prevent breast cancer in over 2,600 women, showed how high carbohydrate did not influence the timing of menopause, except a significantly earlier menopause was observed in those women with low BMI.[26]

Further, Shanghai Women's Health Study observed that higher intake of calories and proteins were significantly associated with later age at natural menopause, whereas soy and fiber were not related to age at menopause.[19] Other studies reported that increased meat or alcohol consumption is significantly associated with later age at menopause [27,28] and such findings confirm the hypothesis that meat may modify the interaction of hormones along hypothalamic- pituitary-ovarian axis.

Although studies have been done to identify the role of single food intake on onset of menopause, the role of dietary pattern needs further studies to substantiate it. In light of the findings reported above, our review calls for future prospective studies to investigate whether uPDI, including less- quality diet and low in high-quality plant-based diet, can influence onset of natural menopause. Understanding whether specific dietary factors might be associated with menopause onset could also lead to a new approach in reducing unhealthy dietary habits and adverse outcomes related to early or late natural menopause.

Our study has several limitations. Cumulative PDI, hPDI and uPDI were self-reported by FFQ. This technique is well validated but some misclassification of intake is possible due to under- or over-reporting. However, calculation of cumulative averages can reduce measurement errors.29 We relied on self-reported menopausal status to determine timing of menopause. Misclassification of the outcome was minimized by using only the first reported age at menopause and by collecting data every two years. Yet, a high proportion of NHS participants had already experienced menopause by baseline with potential consequences on results. Finally, NHS and NHSII participants are not a random sample of the general U.S. population although our results should not differ from other women in U.S. or elsewhere.

In conclusion, we observed a null association between PDI and early menopause, but additional prospective studies are needed. A better understanding of how a specific food item or dietary patterns are associated with ovarian aging may be the corner stone to modify the risk of early onset of menopause and associated adverse health conditions.

Conclusion

In conclusion, adherence to a PDI is not associated with onset of early menopause even after stratification by BMI, smoking status and oral contraceptive use, although higher adherence to uPDI might be associated with risk of early menopause.

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Contributions: G.G.: Study execution, Data curation, Formal analysis, Writing original draft. L.C.R: Data curation, Draft review. L.Y.: Data curation, Formal analysis, Draft review. B.J.E.R.: Data curation, Draft review. B.M.: Data curation, Draft review. F.O.H.: Draft review. H.F.B.: Draft review. M.T.: Study execution, Data curation, Draft review. E.A.H.: Study execution, Data curation, Draft review.

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Table 1. Baseline characteristics of women in NHS.

	PDI				
Characteristics [a]	**Quintile 1 (n=5575)**	**Quintile 2 (n=5970)**	**Quintile 3 (n=5079)**	**Quintile 4 (n=5899)**	**Quintile 5 (n=5188)**
Age, years	44.8 (4.3)	44.8 (4.2)	44.9 (4.3)	45 (4.3)	45.1 (4.2)
Height, cm	164.1 (6.2)	164.1 (6.1)	164.2 (6.2)	164 (6.2)	164.3 (6.1)
Oral contraceptive use [b]	34.1 (45.8)	32.8 (43.8)	31 (42.6)	30.8 (42)	28.4 (40.3)
History of high blood cholesterol, %	91	91	92	91	91
History of hypertension, %	92	93	93	93	94
Parity, %					
1 or 2 kids	41	40	39	39	40
3 or 4 kids	43	44	45	45	46
> 5 kids	8	10	10	10	9
Breast feeding [c]	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)	0.5 (0.5)
Smoking status, %					
Former	33	31	32	31	32
Current, 1-14	7	8	7	7	6
Current 15-24	10	9	9	9	8
Current 25+	10	7	7	5	4
Pack years [b]	11 (14.4)	9.5 (13.6)	9.4 (13.3)	8.2 (12.4)	7.4 (11.9)
BMI, kg/m^2, %					
<21	17	18	19	19	22
21-22.9	22	23	22	24	25
23-24.9	19	19	20	20	20
25-29.9	24	23	23	22	21
30+	14	13	12	11	9
Physical activity, MET-h/wk	13.2 (19.6)	13.4 (20.4)	14.1 (22.9)	14.5 (22.5)	15.6 (24.8)
Total caloric intake, kcal/day	1486 (453)	1648 (486)	1770 (485)	1905 (512)	2108 (516)
Vitamin D no supplement, IU	200.6 (107.6)	187 (96.8)	178.3 (91)	168.3 (80)	155.5 (71.2)
Vitamin D with supplement, IU	324.4 (269.8)	297.1 (233.2)	287.6 (222.8)	274.5 (209.6)	263 (192.4)
PDI	45 (2.9)	50.6 (1.1)	54 (0.8)	57.4 (1.1)	62.9 (2.8)
uPDI	55.7 (7.5)	56.2 (8.1)	56.1 (8.2)	55.7 (8)	55 (7.3)
hPDI	51.3 (6.9)	52.4 (7.3)	52.8 (7.4)	53.6 (7.1)	55.4 (6.6)

Abbreviations: MET, metabolic equivalent task; IU, International Unit.

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables are standardized to the age distribution of the study population.

[a] Age-adjusted and time period.

[b] Includes among users only.

[c] Includes parous women only.

Table 2. Baseline characteristics of women in the NHSII.

	PDI				
Characteristics [a]	**Quintile 1 (n=19299)**	**Quintile 2 (n=13457)**	**Quintile 3 (n=20644)**	**Quintile 4 (n=17819)**	**Quintile 5 (n=16876)**
Age, years	36 (4.7)	36.2 (4.7)	36.4 (4.6)	36.6 (4.6)	36.9 (4.5)
Height, cm	164.7 (6.7)	164.8 (6.6)	164.9 (6.6)	164.8 (6.6)	164.9 (6.6)
Oral contraceptive use [b]	51.8 (49.4)	49.6 (47.8)	48.4 (47.2)	46.5 (45.6)	44.2 (43.7)
History of high blood cholesterol, %	15	14	14	14	14
History of hypertension, %	7	7	6	5	5
Parity, %					
1 or 2 kids	51	54	54	54	55
3 or 4 kids	17	18	20	21	21
> 5 kids	1	1	1	1	1
Breast feeding [c]	11.4 (12.5)	12.3 (12.8)	13.3 (13.4)	14.3 (13.7)	15.8 (14.2)
Smoking status, %					
Former	22	22	22	22	23
Current 1-14	6	5	5	5	5
Current 15-24	6	5	5	4	3
Current 25+	3	2	2	1	1
Pack years [b]	4.7 (8.3)	4.2 (7.7)	3.9 (7.4)	3.6 (7)	3.5 (6.7)
BMI, kg/m^2, %					
<21	21	23	24	26	29
21-22.9	21	22	23	23	24
23-24.9	18	17	17	17	17
25-29.9	21	21	20	20	18
30+	16	15	13	11	10
Physical activity, MET-h/wk	17.7 (24)	19.2 (25.1)	20.7 (27)	21.8 (27.3)	25 (31.1)
Total caloric intake, kcal/day	1478 (463)	1642 (486)	1773 (501)	1937 (513)	2137 (527)
Vitamin D no supplement, IU	285.1 (144.6)	264.2 (128.1)	253.4 (118.9)	239.6 (109.5)	219.2 (102)
Vitamin D with supplement, IU	423 (302.3)	404.9 (273.1)	388.5 (256.9)	372.4 (241.9)	349.9 (217.8)
PDI	45.8 (2.9)	51 (0.8)	54.5 (1.1)	58.4 (1.1)	64.1 (3)
uPDI	56 (7.5)	55.6 (8.1)	54.9 (8.1)	54 (7.8)	53.4 (7)
hPDI	52.3 (7)	53.7 (7.3)	54.6 (7.4)	55.6 (7.2)	57.9 (7)

Abbreviations: MET, metabolic equivalent of task; IU, International Unit.

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables are standardized to the age distribution of the study population.

[a] Age-adjusted and time period.

[b] Includes among users only.

[c] Includes parous women only.

Table 3. HRs and 95% CIs for associations between PDI and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c].

		Model 1 [d]		Model 2 [e]		Model 3 [f]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	159/33251	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	144/32485	0.91	0.72 to 1.15	0.92	0.73 to 1.17	0.94	0.75 to 1.2
Quantile 3	137/31463	0.93	0.74 to 1.18	0.95	0.75 to 1.21	0.98	0.77 to 1.24
Quantile 4	157/31818	1.1	0.85 to 1.34	1.1	0.87 to 1.4	1.15	0.91 to 1.44
Quantile 5	118/28471	0.85	0.66 to 1.08	0.9	0.68 to 1.17	0.94	0.73 to 1.2
***P* trend**		0.50		0.87		0.84	
NHSII							
Quantile 1	477/225594	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	384/212761	0.90	0.78 to 1.03	0.92	0.8 to 1.05	0.92	0.8 to 1.06
Quantile 3	489/258222	0.90	0.79 to 1.02	0.94	0.82 to 1.07	0.93	0.82 to 1.06
Quantile 4	421/232647	0.86	0.75 to 0.98	0.91	0.79 to 1.04	0.91	0.79 to 1.04
Quantile 5	414/219820	0.89	0.78 to 1.01	0.95	0.82 to 1.1	0.95	0.83 to 1.08
***P* trend**		0.06		0.48		0.39	

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Table 4. Meta-analysis in longitudinal studies NHS and NHSII between PDI, hPDI, uPDI and women who experienced early natural menopause.

	Q1	*Q2 vs Q1*	*Q3 vs Q1*	*Q4 vs Q1*	*Q5 vs Q1*	*P for trend (read of P in meta output)*
PDI [a]						
NHS	1.0 (ref)	0.94 (0.75 to 1.2)	0.98 (0.77 to 1.24)	1.15 (0.91 to 1.44)	0.94 (0.73 to 1.2)	0.84
NHSII	1.0 (ref)	0.92 (0.8 to 1.06)	0.93 (0.82 to 1.06)	0.91 (0.79 to 1.04)	0.95 (0.83 to 1.08)	0.39
Meta-analysis	1.0 (ref)	0.93 (0.82 to 1.04)	0.94 (0.84 to 1.05)	0.96 (0.86 to 1.08)	0.95 (0.84 to 1.06)	0.52
hPDI [a]						
NHS	1.0 (ref)	1.19 (0.97 to 1.46)	1.02 (0.81 to 1.28)	0.96 (0.74 to 1.24)	1.15 (0.88 to 1.5)	0.70
NHSII	1.0 (ref)	0.99 (0.87 to 1.14)	0.98 (0.86 to 1.12)	0.95 (0.83 to 1.09)	1.07 (0.93 to 1.23)	0.51
Meta-analysis	1.0 (ref)	1.05 (0.94 to 1.17)	0.99 (0.88 to 1.11)	0.95 (0.85 to 1.07)	1.09 (0.96 to 1.23)	0.45
uPDI [a]						
NHS	1.0 (ref)	0.92 (0.69 to 1.22)	0.97 (0.75 to 1.27)	0.98 (0.76 to 1.28)	1.12 (0.88 to 1.44)	0.19
NHSII	1.0 (ref)	1.03 (0.9 to 1.18)	1.1 (0.95 to 1.26)	1.21 (1.06 to 1.39)	1.05 (0.91 to 1.21)	0.11
Meta-analysis	1.0 (ref)	1.01 (0.89 to 1.14)	1.07 (0.95 to 1.21)	1.16 (1.03 to 1.31)	1.07 (0.95 to 1.21)	**0.04**

Quantiles and P for trend (significant < 0.05), read by meta-analysis, are reported. RRs and 95% CIs for PDI, hPDI and uPDI in NHS and NHSII.

[a] Adjusted for smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age <25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplemental Digital Content 1. HRs and 95% CIs for associations between PDI and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] after censoring for hormone therapy use before menopause occurred.

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 to 1.15	0.97	0.81 to 1.16	0.97	0.8 to 1.16
Quantile 3	672/31394	0.88	0.73 to 1.06	0.90	0.74 to 1.08	0.89	0.72 to 1.08
Quantile 4	760/31712	1	0.83 to 1.19	1.03	0.85 to 1.24	1.05	0.87 to 1.26
Quantile 5	637/28396	0.82	0.67 to 0.99	0.86	0.70 to 1.06	0.85	0.7 to 1.05
***P* trend**			0.096		0.338		0.317
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 to 1.06	0.96	0.85 to 1.08	0.94	0.81 to 1.09
Quantile 3	233/255255	0.88	0.79 to 0.99	0.92	0.82 to 1.04	0.9	0.78 to 1.04
Quantile 4	230/229978	0.86	0.77 to 0.97	0.92	0.81 to 1.04	0.9	0.78 to 1.04
Quantile 5	238/217459	0.89	0.79 to 1	0.95	0.84 to 1.09	0.93	0.8 to 1.08
***P* trend**			0.021		0.336		0.262

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplemental Digital Content 2. HRs and 95% CIs for associations between PDI with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by BMI categories (<25, 25-29.9, >30 kg/m2).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS [a]						
BMI < 25						
Event/person-y	799/17012	838/17662	754/17506	773/18638	653/17620	
HR (95% CI)	1.00 (ref)	1.11 (0.87 to 1.43)	1.04 (0.8 to 1.34)	1.12 (0.87 to 1.43)	0.94 (0.72 to 1.22)	0.696
BMI 25-29.9						
Event/person-y	834/8150	674/7718	517/7345	730/7127	565/6016	
HR (95% CI)	1.00 (ref)	0.78 (0.52 to 1.16)	0.65 (0.43 to 0.98)	0.86 (0.58 to 1.26)	0.69 (0.44 to 1.08)	0.143
BMI > 30						
Event/person-y	775/5033	707/4669	637/4081	867/3575	797/2634	
HR (95% CI)	1.00 (ref)	0.91 (0.54 to 1.52)	0.88 (0.51 to 1.49)	1.18 (0.7 to 1.99)	0.92 (0.5 to 1.66)	0.912
NHS II [a]						
BMI < 25						
Event/person-y	258/161024	253/158249	233/199994	235/183488	237/180183	
HR (95% CI)	1.00 (ref)	0.97 (0.82 to 1.14)	0.92 (0.79 to 1.08)	0.93 (0.79 to 1.1)	0.95 (0.81 to 1.12)	0.489
BMI 25-29.9						
Event/person-y	247/42894	224/36601	212/38739	186/32184	217/25321	
HR (95% CI)	1.00 (ref)	0.82 (0.57 to 1.18)	0.76 (0.53 to 1.09)	0.65 (0.43 to 0.98)	0.78 (0.52 to 1.18)	0.089

BMI > 30						
Event/person-y	262/10698	243/7809	293/7499	358/5859	244/4092	
HR (95% CI)	1.00 (ref)	0.95 (0.38 to 2.38)	1.26 (0.49 to 3.23)	1.8 (0.72 to 4.51)	1.37 (0.43 to 4.36)	0.244

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplemental Digital Content 3. HRs and 95% CIs for associations between PDI with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by smoking status (never, former, current 1-14, current 15-24, current 25+).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81 to 1.47)	0.88 (0.65 to 1.2)	1.17 (0.88 to 1.56)	0.84 (0.61 to 1.15)	0.445
Former						
Event/person-y	688/11488	680/11022	682/10844	568/10391	648/9411	
HR (95% CI)	1.00 (ref)	1.01 (0.72 to 1.41)	0.98 (0.7 to 1.37)	0.82 (0.57 to 1.17)	0.99 (0.7 to 1.41)	0.616
Current, 1-14 number of cigarettes per day						
Event/person-y	972/2161	917/2182	845/1894	1481/1891	594/1516	
HR (95% CI)	1.00 (ref)	0.93 (0.44 to 1.99)	1.1 (0.49 to 2.46)	1.74 (0.85 to 3.57)	0.62 (0.24 to 1.62)	0.929
Current, 15-24 number of cigarettes per day						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81 to 1.47)	0.88 (0.65 to 1.2)	1.17 (0.88 to 1.56)	0.84 (0.61 to 1.15)	0.445
Current, 25+ number of cigarettes per day						
Event/person-y	1754/2451	1202/1913	1086/1657	948/1372	842/950	
HR (95% CI)	1.00 (ref)	0.79 (0.42 to 1.49)	0.68 (0.34 to 1.36)	0.66 (0.31 to 1.39)	0.85 (0.36 to 2.03)	0.365
NHS II[a]						
Never						

Event/person-y	221/146121	221/142204	199/174042	216/159498	222/150354	
HR (95% CI)	1.00 (ref)	0.97 (0.81 to 1.18)	0.91 (0.76 to 1.09)	0.96 (0.8 to 1.15)	1.01 (0.84 to 1.22)	0.930
Former						
Event/person-y	232/50760	242/48310	269/58791	211/53125	244/52082	
HR (95% CI)	1.00 (ref)	1.06 (0.78 to 1.44)	1.12 (0.84 to 1.48)	0.93 (0.68 to 1.26)	1.06 (0.78 to 1.44)	0.998
Current, 1-14 number of cigarettes per day						
Event/person-y	418/11952	380/9480	233/11142	315/9216	303/8263	
HR (95% CI)	1.00 (ref)	0.79 (0.42 to 1.47)	0.37 (0.18 to 0.77)	0.68 (0.36 to 1.26)	0.58 (0.3 to 1.13)	0.091
Current, 15-24 number of cigarettes per day						
Event/person-y	797/5020	656/4573	737/4479	771/3244	826/2783	
HR (95% CI)	1.00 (ref)	0.56 (0.3 to 1.06)	0.7 (0.4 to 1.2)	0.68 (0.37 to 1.24)	0.69 (0.36 to 1.34)	0.275
Current, 25+ number of cigarettes per day						
Event/person-y	583/4117	472/2541	740/2701	716/1955	817/1470	
HR (95% CI)	1.00 (ref)	0.83 (0.28 to 2.42)	1.38 (0.52 to 3.68)	0.81 (0.25 to 2.6)	4.42 (1.21 to 16.13)	0.132

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplemental Digital Content 4. HRs and 95% CIs for associations between PDI with rate of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by oral contraceptive use categories (never use, current use, former use <5 years, former ≥5 years).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never use						
Event/person-y	625/9760	672/9975	416/9605	423/10162	426/9618	
HR (95% CI)	1.00 (ref)	1 (0.68 to 1.48)	0.65 (0.42 to 1)	0.7 (0.46 to 1.07)	0.7 (0.45 to 1.08)	0.030
Current use						
Event/person-y	-	-	-	-	-	
HR (95% CI)	-	-	-	-	-	
Former use, <5 years						
Event/person-y	919/19810	825/19511	845/19054	967/18921	770/16622	
HR (95% CI)	1.00 (ref)	0.96 (0.77 to 1.19)	0.98 (0.78 to 1.22)	1.17 (0.94 to 1.45)	0.9 (0.71 to 1.14)	0.987
Former use, ≥5 years						
Event/person-y	340/2356	582/1890	176/1707	478/1672	399/1253	
HR (95% CI)	1.00 (ref)	1.78 (0.57 to 5.57)	0.56 (0.12 to 2.58)	1.21 (0.34 to 4.38)	1.43 (0.37 to 5.5)	0.889
NHS II[a]						
Never use						
Event/person-y	232/30173	187/30001	213/37568	224/35241	214/35107	
HR (95% CI)	1.00 (ref)	1.17 (0.71 to 1.91)	1.13 (0.71 to 1.8)	1.12 (0.7 to 1.8)	1.22 (0.76 to 1.94)	0.519
Current use						

Event/person-y	182/26416	180/23310	147/27197	210/23296	182/19764	
HR (95% CI)	1.00 (ref)	0.88 (0.52 to 1.49)	0.63 (0.36 to 1.1)	1.02 (0.62 to 1.66)	0.7 (0.39 to 1.24)	0.411
Former use, <5 years						
Event/person-y	266/138080	262/132184	246/163276	228/148051	243/142665	
HR (95% CI)	1.00 (ref)	0.93 (0.78 to 1.10)	0.93 (0.79 to 1.10)	0.86 (0.72 to 1.02)	0.96 (0.8 to 1.13)	0.41
Former use, ≥5 years						
Event/person-y	320/24074	313/21105	261/22957	295/19335	329/15806	
HR (95% CI)	1.00 (ref)	0.96 (0.6 to 1.54)	0.92 (0.57 to 1.47)	1.06 (0.65 to 1.73)	1.18 (0.72 to 1.95)	0.482

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Contents

Supplementary Table 1. Associations between PDI and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] after censoring for hormone therapy use before menopause occurred

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 - 1.15	0.97	0.81 - 1.16	0.97	0.8 - 1.16
Quantile 3	672/31394	0.88	0.73 - 1.06	0.90	0.74 - 1.08	0.89	0.72 - 1.08
Quantile 4	760/31712	1	0.83 - 1.19	1.03	0.85 - 1.24	1.05	0.87 - 1.26
Quantile 5	637/28396	0.82	0.67 - 0.99	0.86	0.70 - 1.06	0.85	0.7 - 1.05
***P* trend**		0.096		0.338		0.317	
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 - 1.06	0.96	0.85 - 1.08	0.94	0.81 - 1.09
Quantile 3	233/255255	0.88	0.79 - 0.99	0.92	0.82 - 1.04	0.9	0.78 - 1.04
Quantile 4	230/229978	0.86	0.77 - 0.97	0.92	0.81 - 1.04	0.9	0.78 - 1.04
Quantile 5	238/217459	0.89	0.79 - 1	0.95	0.84 - 1.09	0.93	0.8 - 1.08
***P* trend**		0.021		0.336		0.262	

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 2. Associations between PDI with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by BMI categories (<25, 25-29.9, >30 kg/m2)

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS [a]						
BMI < 25						
Event/person-y	799/17012	838/17662	754/17506	773/18638	653/17620	
HR (95% CI)	1.00 (ref)	1.11 (0.87-1.43)	1.04 (0.8-1.34)	1.12 (0.87-1.43)	0.94 (0.72-1.22)	0.696
BMI 25-29.9						
Event/person-y	834/8150	674/7718	517/7345	730/7127	565/6016	
HR (95% CI)	1.00 (ref)	0.78 (0.52-1.16)	0.65 (0.43-0.98)	0.86 (0.58-1.26)	0.69 (0.44-1.08)	0.143
BMI > 30						
Event/person-y	775/5033	707/4669	637/4081	867/3575	797/2634	
HR (95% CI)	1.00 (ref)	0.91 (0.54-1.52)	0.88 (0.51-1.49)	1.18 (0.7-1.99)	0.92 (0.5-1.66)	0.912
NHS II [a]						
BMI < 25						
Event/person-y	258/161024	253/158249	233/199994	235/183488	237/180183	
HR (95% CI)	1.00 (ref)	0.97 (0.82-1.14)	0.92 (0.79-1.08)	0.93 (0.79-1.1)	0.95 (0.81-1.12)	0.489
BMI 25-29.9						
Event/person-y	247/42894	224/36601	212/38739	186/32184	217/25321	
HR (95% CI)	1.00 (ref)	0.82 (0.57-1.18)	0.76 (0.53-1.09)	0.65 (0.43-0.98)	0.78 (0.52-1.18)	0.089
BMI > 30						
Event/person-y	262/10698	243/7809	293/7499	358/5859	244/4092	
HR (95% CI)	1.00 (ref)	0.95 (0.38-2.38)	1.26 (0.49-3.23)	1.8 (0.72-4.51)	1.37 (0.43-4.36)	0.244

[a] Early menopause defined as women who experience menopause status < 45 years.
[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.
[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.
[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 3. Associations between PDI with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by smoking status (never, former, current 1-14, current 15-24, current 25+)

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Former						
Event/person-y	688/11488	680/11022	682/10844	568/10391	648/9411	
HR (95% CI)	1.00 (ref)	1.01 (0.72-1.41)	0.98 (0.7-1.37)	0.82 (0.57-1.17)	0.99 (0.7-1.41)	0.616
Current, 1-14 number of cigarettes per day						
Event/person-y	972/2161	917/2182	845/1894	1481/1891	594/1516	
HR (95% CI)	1.00 (ref)	0.93 (0.44-1.99)	1.1 (0.49-2.46)	1.74 (0.85-3.57)	0.62 (0.24-1.62)	0.929
Current, 15-24 number of cigarettes per day						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Current, 25+ number of cigarettes per day						
Event/person-y	1754/2451	1202/1913	1086/1657	948/1372	842/950	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.49)	0.68 (0.34-1.36)	0.66 (0.31-1.39)	0.85 (0.36-2.03)	0.365
NHS II[a]						
Never						
Event/person-y	221/146121	221/142204	199/174042	216/159498	222/150354	
HR (95% CI)	1.00 (ref)	0.97 (0.81-1.18)	0.91 (0.76-1.09)	0.96 (0.8-1.15)	1.01 (0.84-1.22)	0.930
Former						
Event/person-y	232/50760	242/48310	269/58791	211/53125	244/52082	
HR (95% CI)	1.00 (ref)	1.06 (0.78-1.44)	1.12 (0.84-1.48)	0.93 (0.68-1.26)	1.06 (0.78-1.44)	0.998
Current, 1-14 number of cigarettes per day						
Event/person-y	418/11952	380/9480	233/11142	315/9216	303/8263	

HR (95% CI)	1.00 (ref)	0.79 (0.42-1.47)	0.37 (.18-0.77)	0.68 (0.36-1.26)	0.58 (0.3-1.13)	0.091
Current, 15-24 number of cigarettes per day						
Event/person-y	797/5020	656/4573	737/4479	771/3244	826/2783	
HR (95% CI)	1.00 (ref)	0.56 (0.3-1.06)	0.7 (0.4-1.2)	0.68 (0.37-1.24)	0.69 (0.36-1.34)	0.275
Current, 25+ number of cigarettes per day						
Event/person-y	583/4117	472/2541	740/2701	716/1955	817/1470	
HR (95% CI)	1.00 (ref)	0.83 (0.28-2.42)	1.38 (0.52-3.68)	0.81 (0.25-2.6)	4.42 (1.21-16.13)	0.132

[a] Early menopause defined as women who experience menopause status < 45 years.
[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.
[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.
[d] Adjusted for age, pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 4. Associations between PDI with rate of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by oral contraceptive use categories (never use, current use, former use <5 years, former ≥5 years)

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never use						
Event/person-y	625/9760	672/9975	416/9605	423/10162	426/9618	
HR (95% CI)	1.00 (ref)	1 (0.68-1.48)	0.65 (0.42-1)	0.7 (0.46-1.07)	0.7 (0.45-1.08)	0.030
Current use						
Event/person-y	-	-	-	-	-	
HR (95% CI)	-	-	-	-	-	
Former use, <5 years						
Event/person-y	919/19810	825/19511	845/19054	967/18921	770/16622	
HR (95% CI)	1.00 (ref)	0.96 (0.77-1.19)	0.98 (0.78-1.22)	1.17 (0.94-1.45)	0.9 (0.71-1.14)	0.987
Former use, ≥5 years						
Event/person-y	340/2356	582/1890	176/1707	478/1672	399/1253	
HR (95% CI)	1.00 (ref)	1.78 (0.57-5.57)	0.56 (0.12-2.58)	1.21 (0.34-4.38)	1.43 (0.37-5.5)	0.889
NHS II[a]						
Never use						
Event/person-y	232/30173	187/30001	213/37568	224/35241	214/35107	
HR (95% CI)	1.00 (ref)	1.17 (0.71-1.91)	1.13 (0.71-1.8)	1.12 (0.7-1.8)	1.22 (0.76-1.94)	0.519
Current use						
Event/person-y	182/26416	180/23310	147/27197	210/23296	182/19764	
HR (95% CI)	1.00 (ref)	0.88 (0.52-1.49)	0.63 (0.36-1.1)	1.02 (0.62-1.66)	0.7 (0.39-1.24)	0.411
Former use, <5 years						
Event/person-y	266/138080	262/132184	246/163276	228/148051	243/142665	
HR (95% CI)	1.00 (ref)	0.93 (0.78-1.10)	0.93 (0.79-1.10)	0.86 (0.72-1.02)	0.96 (0.8-1.13)	0.41
Former use, ≥5 years						

Event/person-y	320/24074	313/21105	261/22957	295/19335	329/15806	
HR (95% CI)	1.00 (ref)	0.96 (0.6-1.54)	0.92 (0.57-1.47)	1.06 (0.65-1.73)	1.18 (0.72-1.95)	0.482

[a] Early menopause defined as women who experience menopause status < 45 years.
[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.
[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.
[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

3.4. Article 4. Association of dietary iron intake and early onset of natural menopause: a prospective study

Association of dietary iron intake and early onset of natural menopause: a prospective study

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Original article.

Contribution: I participated by designing the study and co-supervising the study procedure. I did the analyses, made the figures, and wrote the first draft of the manuscript. After that, I incorporated co-authors' and reviewers' comment.

Association of dietary iron intake and early onset of natural menopause: a prospective study

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Conflict of interest

Authors have no conflicts of interest to declare

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List of abbreviation: NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; SD, standard deviation; FFQ, food-frequency questionnaire; T2D, type 2 diabetes; CVD, cardiovascular disease; HR, hazard ratio; RR, relative risk; CI, confidence interval.

ABSTRACT

Background: Early natural menopause, defined as the permanent natural cessation of menstruation before the age of 45, is associated with an increased risk of adverse health outcomes. Few studies have investigated whether dietary iron intake could potentially impact menopause timing.

Objective: To evaluate the association of dietary iron heme, iron non-heme and iron supplement intake with early natural menopause in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Design: We conducted a prospective study with a mean follow-up time of 20 years among premenopausal women living across the US. Participants of the NHS (n = 121,701) and NHSII (n = 116,429) were included from 1984 [age mean (standard deviation, SD); 44.9 (4.2)] and 1991 [age mean (SD); 36.4 (4.6)], respectively. Early menopause was self-reported and defined as natural menopause before age 45 years. Iron heme, non-heme and supplement were derived from semi-quantitative food frequency questionnaires (FFQ) administered every four years. Cox proportional hazards models were used to assess the association between iron heme, iron non-heme and iron supplement in quintiles and early natural menopause in NHS and NHSII separately, and fixed-effect models to pool the results from both cohorts.

Results: During follow-up, 715 and 2,185 women experienced early natural menopause in NHS and NHSII, respectively. After adjustment for age (M1), age and caloric intake (M2), and all potential confounders (M3), an association was observed between iron heme and incidence of early natural menopause in NHSII cohort. Yet, an association was found between iron non-heme and risk of early natural menopause in NHS, only in fully adjusted model (M3) [Q5; HR (95%CI), 1.3 (1.03;1.64), *P* value 0.02]. When pooling the results, the results have been confirmed for iron heme [Q5 vs. Q1; 1.24 (1.09;1.41), *P* value 0.001].

Conclusion: Intake of iron heme is strongly associated with incidence of early natural menopause although highest intake of iron non-heme may be also associated with risk of early natural menopause. The association between iron heme and early natural menopause seems to be stronger in women with BMI < 25, former or current (+25 cigarettes) smokers.

Keywords: Early natural menopause, menopause onset, Nurses' Health Study, prospective study, iron heme, iron non-heme, iron supplement.

Introduction

Early natural menopause is defined as the permanent cessation of ovarian function before the age of 45 years and affects approximately 10% of Western women[1]. It is associated with increased risk of type 2 diabetes, cardiovascular diseases, bone fractures, mood disorders and decline in cognitive functions[2].

The etiology of early menopause is not fully understood, but dietary factors may be involved[1,3]. Emerging studies suggest high consumption of refined pasta and rice to be associated with early menopause while oily fish, fresh legumes, plant proteins as well as vitamin B6 and zinc have been reported to lower the risk of early menopause[4]. Yet, a modest inverse association of early menopause with dairy foods, calcium, and vitamin D from dietary sources was found associated with later onset of menopause[5].

In light of these findings, we hypothesised that dietary iron intake would be associated with menopause onset. Iron is essential for oxygen transport, electron transfer reactions, gene regulation, and regulation of cell growth and differentiation[6]. Iron from food comes in two forms: heme and non-heme. Heme is found only in animal flesh like meat, poultry, and seafood and is highly bioavailable (25-30% is absorbed). Non-heme iron is found in plant foods like whole grains, nuts, seeds, legumes, and leafy greens and the absorption is more variable (1-10%). Non-heme iron is also found in animal flesh and fortified foods[7,8]. Iron storage increases by two to threefold from before menopause to after menopause[9]. Epidemiological studies have reported an association between high iron stores and increased risk of cardiovascular disease, metabolic syndrome, gestational diabetes, and type 2 diabetes[10], accelerated bone loss[11], menopausal symptoms, and oxidative stress in skin when exposed to UV[9]. Women had the greatest changes in iron over menopause but, to date, no epidemiological studies have investigated whether dietary iron intake is associated with the incidence of early natural

menopause. We prospectively investigated the association between dietary iron intake and incidence of early natural menopause among women enrolled in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods

Study population

The study was carried out within the NHS and NHSII prospective cohort studies, with participants recruited from across the US. The NHS began in 1976 when 121,701 women, aged 30 - 55 years, responded to a baseline questionnaire on medical, lifestyle and other health information. The NHSII began in 1989 when 116,429 women, aged 25 - 42 years, completed a mailed questionnaire and provided information on past and current health conditions, prescription medication use, and lifestyle factors. In both cohorts, participants have completed a new questionnaire biennially to update information, with a cumulative response rate of > 90%. The protocols were approved by the Institutional Review Boards at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health in Boston, Massachusetts.

Nurses' Health Study

Baseline in NHS was 1984 and follow-up ended in 1992 when all women were older than 45 years and no longer at risk for early menopause (< 45 years). From the 121,701 women at the time of enrolment we excluded women reporting menopause before 1984 (n = 56,492), and those who did not report age at menopause (n = 20,290). We excluded women who did not respond to the 1984 FFQ or had implausible caloric intake (n = 11,778), who died before 1984 (n = 1,918) or women with cancer diagnosis (n = 3,372). A total of 27,851 eligible participants were followed until 1992.

Nurses' Health Study II

Follow-up for the NHSII analysis started in 1991 and ended in 2011 when all women were 45 years or older and no longer at risk for early menopause (< 45 years). From 116,429 cohort members, we excluded women reporting menopause before 1991 (n = 3,942), and those who did not report an age at menopause (n = 5,341). We excluded women who did not respond to the 1991 FFQ or had implausible caloric intake (n = 18,518), who died before 1991 (none) or women with cancer diagnosis (n = 724). A total of 87,904 eligible participants were followed until 2011.

Early menopause

Menopausal status has been assessed every 2 years in the NHS and NHSII starting in 1980 and 1989, respectively. Nurses were asked if their periods had ceased permanently, and if so, at what age their period ceased (open response), for what reason the period ceased (response options were surgery, radiation or chemotherapy, and natural), their current and past use of menopausal hormone therapy, and if they had had a hysterectomy or oophorectomy (bilateral or unilateral). In this study, we defined cases of early natural menopause as women who reported natural menopause before age 45 years for each period from 1984 in NHS and 1991 in NHSII until 1992 and 2011, respectively[12].

Self-assessment of menopause has been validated and the reproducibility is very high; over 98% of women in post menopause in 1979 accurately confirmed their menopause status within 1 year and, 82% who experiencing menopause reported the same age of menopause within a year from the previous questionnaire[13].

Iron intake

In Nurses' Health Study we calculated the cumulative average of iron heme, iron non-heme, and iron supplement using a semi-quantitative FFQ collected every 4 years from the baseline; indices were cumulatively averaged over follow-up to better capture long-term diet. Beginning in 1984 for NHS and in 1991 for NHSII, participants reported how often they consumed defined portions

of 126 food items. Responses ranged in 9 categories, from "never or less than once/month" to "≥ 6 times/day". The reliability and validity of FFQ have been described elsewhere[14,15]. An overall iron heme, an iron non-heme, and an iron supplement were created. The iron heme is found only in animal flesh like meat, poultry, and seafood and is highly bioavailable, while iron non-heme is found mainly in plant foods like whole grains, nuts, seeds, legumes, and leafy greens.

Covariates

In Nurses' Health Study, age was calculated by subtracting the participant's date of birth from the questionnaire return date, and height that was collected at baseline in 1976 (NHS) and 1989 (NHSII). Updated information on weight was used to calculate body mass index (BMI), defined as weight (kg)/height $(m)^2$ (Kg/m^2; <21, 21-22.9, 23-24.9, 25-29.9, >30), age at first birth and parity defined as pregnancies lasting > 6 months, (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use (continuous), breastfeeding (last time 2003 - categorical), smoking status and quantity (former, current 1-14, current 15-24, current 25+) and packs per year was collected biennially throughout follow-up. Physical activity was assessed every four years and was based on metabolic equivalent of task hours per week (MET-h/wk). Dietary factors, including total caloric intake (Kcal/day), vitamin D with/without supplement, were assessed via FFQ, as described earlier.

Statistical analysis

Statistical analyses were conducted with SAS version 9.3 software (SAS Institute Inc, Cary, NC).

We evaluated the association between baseline iron heme, iron non-heme and iron supplement with incidence of early natural menopause using Cox proportional hazards models to calculate hazard ratio (HR) and 95% CI in both NHS and NHSII cohorts. The proportional hazard assumption of the Cox model was checked by visual inspection of log minus log plots and by

performing a test for heterogeneity of exposure over time. There was no evidence for violation of the proportionality assumption in any of the models (*P* for time-dependent interaction terms >0.05). The results are reported in Quintile (Quintile 1, Quintile 2, Quintile 3, Quintile 4 and Quintile 5), using Quintile 1 as the reference group.

The included participants contributed follow-up time from the date of return of the questionnaire at baseline until the onset of early menopause (< 45 years), death, loss to follow-up, experienced no natural menopause (e.g., surgery, radiation or chemotherapy), cancer diagnosis, or the end of follow-up, whichever came first. Our initial model (Model 1) was adjusted only for age. The covariate selection for multivariable models (Model 2) was based on factors identified *a priori* (age and caloric intake in quintiles) based on literature. Additionally, we adjusted for smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use (continuous), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, > 30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol and physical activity (MET-h/wk) (Model 3).

Finally, we evaluated the association between iron heme, iron non-heme and iron supplement with incidence of early natural menopause using fixed-effects meta-analysis to combine the summary results from both cohorts, NHS and NHSII. Relative risk (RR), 95% CI, and *P* for trend are reported for each quantile.

Sensitivity analysis

We run sensitivity analyses only in Nurses' Health Study. As a sensitivity analysis, we used the Cox proportional hazards model to explore whether iron heme, iron non-heme and iron supplement were associated with natural early menopause after censoring women who used hormone therapy before menopause occurred. Results are reported as HR and 95% CI.

To investigate possible effect modification, we stratified the main analysis (association between PDI and early menopause) by BMI categories (< 25, 25-29.9, ≥ 30 kg/m^2), smoking status (never, former, current 1-14, current 15-24, current 25+) and oral contraceptive use categories (never use, current use, former use < 5 years, former ≥ 5 years) in both NHS and NHSII cohorts.

To explore the interaction of iron heme, iron non-heme and iron supplement with BMI, smoking status and oral contraceptive use on early menopause, we used Cox proportional hazard models to calculate HR and 95% CI, adjusted for all covariates.

Results

Characteristics of participants by quintile of iron heme are shown in **Table 1** for NHS. Women who had the highest intake of iron heme reported more use of oral contraceptives [Q5 34.2 (44.9) vs. Q1 28.3 (40.7), months], smoked more packs per year [Q5 10.1 (13.9) vs. Q1 8.2 (12.6)], more likely to be overweight and obese, less physically active [Q5 13 (19.1) vs. Q1 15.9 (28.1) MET-h/wk], and reported lower total caloric intake [Q5 1698 (495) vs. Q1 1784 (533)] than women with lower intake of iron heme.

For NHSII cohort, characteristics of participants by quintile of iron heme are shown in **Table 2**. Women who had the highest intake of iron heme, reported more use of oral contraceptives [Q5 50.8 (48.2) vs. Q1 44.5 (46), months], smoked more packs *per* year [Q5 4.4 (8) vs. Q1 3.7 (7.1)], more likely to be overweight and obese, less physically active [Q5 19.3 (25.4) vs. Q1 24.6 (32) MET-h/wk], reported less total caloric intake [Q5 1737 (544) vs. Q1 1787 (570)] than women with lower intake of iron heme.

Results from the association between iron heme, iron non-heme and iron supplement and early natural menopause in NHS and NHSII are presented in **Table 3**. Iron heme was strongly associated with early natural menopause in NHSII in all 3 models [Model 1: HR (95%CI), Q5 vs. Q1 1.28 (1.11;1.47); Model 2: Q5 vs. Q1 1.27 (1.1;1.46); Model 3: Q5 vs. Q1 1.26

(1.09;1.46)]. In NHS, only in the fully adjusted model (Model 3), iron non-heme was associated with early natural menopause [Q5 vs. Q1 1.3 (1.03;1.64)]. Also, iron supplement was found to be not associated with early natural menopause. In **Table 4**, we conducted a meta-analysis (of the above-described cohorts) to evaluate the possible association between iron heme, iron non-heme and iron supplement with early natural menopause and only iron heme was confirmed to be associated with early natural menopause [RR (95%CI), Q5 vs. Q1 1.24 (1.09;1.41), *P* trend = 0.001]. Sensitivity analyses conducted for iron heme, iron non-heme and iron supplement, showed a strong association between iron heme with natural early menopause in NHSII, after censoring women who took hormone therapy before menopause occurred, in all three models (**Supplementary Table 1)**. Further, results from analyses stratified by BMI categories (< 25, 25-29.9, > 30 kg/m^2) showed an association between iron heme and risk of early natural menopause among women with BMI < 25 Kg/m^2, in NHSII (**Supplementary Table 4**). Analyses stratified by smoking status (never, former, current 1-14, current 15-24, current 25+) showed a significant interaction with iron heme on the association with early natural menopause among former and current smokers (+25 number of cigarettes per day), in NHS; in NHSII cohort, never smokers reported an association between iron heme intake and early natural menopause (**Supplementary Table 7**). Yet, iron non-heme was found to be slightly associated with risk of early natural menopause among former smokers, only in NHS (**Supplementary Table 8**). In the fully adjusted model stratified by oral contraceptive use categories (never use, current use, former use < 5 years, former ≥ 5 years) (**Supplementary Table 10**), an association between iron heme and early natural menopause was observed in NHSII; women who never used oral contraceptive nor former users (< 5 years) had higher risk to experience early natural menopause. In NHS cohort, the association between iron non-heme intake and risk of early natural menopause was also reported among never oral contraceptive users (**Supplementary Table 11**).

Discussion

To our knowledge, this is the first large study to comprehensively investigate the associations between iron intake and onset of natural menopause. In the Nurses' Health Study, we investigated the association between iron heme, iron non-heme, and iron supplement with onset of early natural menopause; a strong association between dietary iron heme intake and early natural menopause was observed in NHSII cohort, also confirmed by fixed-effects meta-analysis. The results remained constant after censoring women who used hormone therapy before menopause occurred. After stratification by BMI, we found an association between iron heme and early natural menopause only in women with BMI < 25 in NHSII cohort. The stratification for smoking status showed an association between iron heme and risk to experience early natural menopause for former and current (+25 cigarettes/day) smokers in NHS cohort and with never smokers in NHSII cohort. Yet, iron heme was found to be associated with higher incidence of early natural menopause among never and former use (<5 years) after stratification by oral contraceptive use only in NHSII cohort.

In NHS cohort, iron non-heme was found to be associated with a modest higher risk of early natural menopause (only the highest quintile) after full adjustment, although the fixed-effect model showed iron non-heme to be not associated with early natural menopause. In NHS cohort, after stratification by smoking status and oral contraceptive use, iron non-heme was found to be associated with former smokers and never users, respectively. Null association was found between iron supplements and incidence or early natural menopause.

Several studies investigated how single food item are associated with timing of menopause but, to our knowledge, no other studies have reported the association between iron heme, iron non-heme and iron supplements.

Animal products are rich of iron heme. In line with our findings, a prospective study conducted in U.S. with 2,041 women reported that higher red meat intake is associated with early natural

192 menopause, although, the same study, reported as processed meat, chicken/turkey, seafoods are
193 not associated with early menopause[16]. In contrast, two longitudinal studies conducted in 2,041
194 and 1,009 women reported as meat intake and oily fish are associated with late menopause[1, 17].
195 These results are in contrast with our findings.

196 Vegetable products are rich in iron non-heme. Two studies suggested that vegetarian women
197 were more likely to develop early menopause than non-vegetarian[16, 17], although other studies
198 have shown null association[1, 16, 17, 18]. Also, a longitudinal study in Germany with participants
199 followed for an average of 5.8 years observed that high intake of carbohydrate, fibre, and cereal
200 products were related to an earlier menopause[19]. Our findings do not confirm such association as
201 a null association between iron non-heme and early natural menopause was found.

202 Iron heme and iron non-heme, in both cohorts, were found to be associated with higher risk of
203 early natural menopause among never or former (<5 years) oral contraceptive users; this strong
204 association may denote a possible protective role of oral contraceptive on onset of early
205 menopause, but further studies are needed.

206 In the last year, the role of iron on health status has come under the spotlight and, in particular,
207 the association of iron with adverse outcomes in women undergoing menopause. Understanding
208 whether dietary iron intake might be associated with menopause onset could lead to a new
209 approach in reducing medical complications mostly in post-menopause but, also, in pre-
210 menopause women.

211 *Study limitations*

212 Our study has several limitations. In Nurses' Health Study, cumulative iron was self-reported by
213 FFQ. This technique is well validated, but some misclassification of intake is possible due to
214 under- or over-reporting. However, calculation of cumulative averages can reduce measurement
215 errors[20]. We relied on self-reported menopausal status to determine timing of menopause.

Misclassification of the outcome was minimized by using only the first reported age at menopause and by collecting data every two years. Yet, a high proportion of NHS participants had already experienced menopause by baseline with potential consequences on results. Finally, NHS and NHSII participants are not a random sample of the general U.S. population although our results should not differ from other women in U.S. or elsewhere.

Although studies have been done to identify the role of food intake on onset of menopause, the role of dietary patterns needs further studies. Our review calls for future prospective studies to investigate whether dietary iron intake can influence onset of natural menopause and long-term health consequences on women's life. Understanding the possible association between dietary factors and onset of menopause is important in reducing unhealthy dietary habits and adverse outcomes related to early or late natural menopause.

Conclusion

In conclusion, iron heme is associated with incidence of early natural menopause and this association seems to be stronger in women with BMI < 25, former or current (+25 cigarettes) smokers. Also, highest intake of iron non-heme may be also associated with risk of early natural menopause.

Acknowledgments

Author contributions

Data availability

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Table 1. Baseline characteristics of women in NHS.

	Iron				
Characteristics [a]	Quintile 1 (n=5412)	Quintile 2 (n=4947)	Quintile 3 (n=5212)	Quintile 4 (n=6402)	Quintile 5 (n=5738)
Age, years	45 (4.2)	44.8 (4.2)	44.8 (4.3)	44.9 (4.2)	45 (4.3)
Height, cm	164.3 (6.1)	164.3 (6.1)	164.2 (6.2)	164.1 (6.2)	163.8 (6.1)
Oral contraceptive use [b]	28.3 (40.7)	29.9 (41.5)	31 (42.4)	33.5 (44.6)	34.2 (44.9)
History of high blood cholesterol, %	92	91	91	91	91
History of hypertension, %	93	93	93	93	93
Parity, %					
1 or 2 kids	40	38	40	40	41
3 or 4 kids	44	46	45	45	43
> 5 kids	9	10	9	9	9
Breast feeding [c]	0.2 (0.4)	0.2(0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
Smoking status, %					
Former	32	33	31	32	30
Current, 1-14	7	7	7	7	7
Current 15-24	8	8	9	9	10
Current 25+	5	6	7	7	8
Pack years [b]	8.2 (12.6)	8.6 (12.6)	9.1 (13.4)	9.3 (13.4)	10.1 (13.9)
BMI, kg/m^2, %					
<21	25	20	18	17	15
21-22.9	25	25	24	22	21
23-24.9	20	20	20	20	19
25-29.9	19	21	23	24	25
30+	8	11	12	13	16
Physical activity, MET-h/wk	15.9 (28.1)	15 (23.6)	14.1 (21.5)	13 (17.4)	13 (19.1)
Total caloric intake, kcal/day	1784 (533)	1774 (550)	1823 (561)	1813 (527)	1698 (495)
Vitamin D no supplement, IU	184.2 (101.8)	182.7 (92.5)	182.3 (89.2)	175.3 (85.9)	168.5 (88.4)
Vitamin D with supplement, IU	316.6 (251.1)	301 (233.7)	291.2 (225.1)	275.3 (209.6)	268.5 (220.2)
Iron heme[d]	0.6 (0.1)	0.8 (0.05)	1 (0.05)	1.3 (0.08)	1.8 (0.3)
Iron non-heme[d]	17.4 (18.3)	16.9 (17.8)	16.3 (16.3)	16.1 (17)	15.8 (16.6)
Iron supplement[d]	6.8 (17.6)	6.4 (17.2)	5.9 (15.8)	5.6 (16.6)	5.5 (16.3)

Abbreviations: MET, metabolic equivalent task; IU, International Unit.

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables, and are standardized to the age distribution of the study population.

[a] Age-adjusted and time period.

[b] Includes among users only.

[c] Includes parous women only.

[d] Unit of measure: mg.

Table 2. Baseline characteristics of women in the NHSII.

	Iron				
Characteristics [a]	Quintile 1 (n=14171)	Quintile 2 (n=17246)	Quintile 3 (n=18273)	Quintile 4 (n=20630)	Quintile 5 (n=17775)
Age, years	36.2 (4.7)	36.1 (4.6)	36.3 (4.6)	36.6 (4.6)	36.8 (4.6)
Height, cm	165.2 (6.6)	165 (6.6)	164.9 (6.6)	164.7 (6.6)	164.5 (6.7)
Oral contraceptive use [b]	44.5 (46)	47 (46.3)	48.6 (46.7)	48.7 (46.7)	50.8 (48.2)
History of high blood cholesterol, %	12	13	14	15	16
History of hypertension, %	4	5	6	7	8
Parity, %					
1 or 2 kids	49	54	54	55	54
3 or 4 kids	17	20	20	20	19
> 5 kids	1	1	1	1	1
Breast feeding [c]	11.4 (12.5)	12.3 (12.8)	13.3 (13.4)	14.3 (13.7)	15.8 (14.2)
Smoking status, %					
Former	24	23	22	22	20
Current 1-14	5	5	5	6	6
Current 15-24	4	4	4	5	6
Current 25+	2	2	2	2	3
Pack years [b]	3.7 (7.1)	3.7 (7.1)	3.8 (7.2)	4 (7.5)	4.4 (8)
BMI, kg/m^2, %					
<21	34	28	25	21	17
21-22.9	25	24	23	22	20
23-24.9	15	17	18	18	18
25-29.9	15	18	20	22	24
30+	8	10	12	15	18
Physical activity, MET-h/wk	24.6 (32)	21.2 (27.9)	20.1 (25.2)	19.8 (25.2)	19.3 (25.4)
Total caloric intake, kcal/day	1787 (570)	1827 (537)	1807 (540)	1795 (544)	1737 (544)
Vitamin D no supplement, IU	266.5 (135.8)	264.4 (121.6)	256.5 (118.6)	246.4 (116.5)	233.1 (126)
Vitamin D with supplement, IU	429.1 (286.8)	400.1 (251.3)	391.1 (253.1)	373.7 (254.6)	355 (261.2)
Iron heme[d]	0.5 (0.2)	0.8 (0.05)	1 (0.05)	1.3 (0.08)	1.7 (0.3)
Iron non-heme[d]	26.6 (27.9)	24 (25)	23.3 (24.7)	22.1 (23.3)	20.9 (22.2)
Iron supplement[d]	12.8 (26.8)	11 (24.2)	10.6 (24)	9.5 (22.7)	8.6 (21.7)

Abbreviations: MET, metabolic equivalent of task; IU, International Unit.

Values are means (SD) for continuous variables; percentages or ns or both for categorical variables, and are standardized to the age distribution of the study population.

[a] Age-adjusted and time period.

[b] Includes among users only.

[c] Includes parous women only.

[d] Unit of measure: mg.

Table 3. HRs and 95% CIs for associations between dietary iron heme, iron non-heme and iron supplement intake and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c].

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 - 1.15	0.97	0.81 - 1.16	0.97	0.8 - 1.16
Quantile 3	672/31394	0.88	0.73 - 1.06	0.90	0.74 - 1.08	0.89	0.72 - 1.08
Quantile 4	760/31712	1	0.83 - 1.19	1.03	0.85 - 1.24	1.05	0.87 - 1.26
Quantile 5	637/28396	0.82	0.67 - 0.99	0.86	0.70 - 1.06	0.85	0.7 - 1.05
***P* trend**			0.096		0.338		0.317
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 - 1.06	0.96	0.85 - 1.08	0.94	0.81 - 1.09
Quantile 3	233/255255	0.88	0.79 - 0.99	0.92	0.82 - 1.04	0.9	0.78 - 1.04
Quantile 4	230/229978	0.86	0.77 - 0.97	0.92	0.81 - 1.04	0.9	0.78 - 1.04
Quantile 5	238/217459	0.89	0.79 - 1	0.95	0.84 - 1.09	0.93	0.8 - 1.08
***P* trend**			**0.021**		**0.336**		**0.262**

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Table 4. Meta-analysis in longitudinal studies NHS and NHSII between dietary iron heme, iron non-heme and iron supplement and women who experienced early natural menopause.

	Q1	*Q2 vs Q1*	*Q3 vs Q1*	*Q4 vs Q1*	*Q5 vs Q1*	*P for trend (read of P in meta output)*
PDI[a]						
NHS	1.0 (ref)	0.97 (0.8, 1.16)	0.89 (0.73, 1.08)	1.05 (0.87, 1.26)	0.85 (0.7, 1.05)	0.317
NHSII	1.0 (ref)	0.94 (0.81, 1.09)	0.9 (0.78, 1.04)	0.9 (0.78, 1.04)	0.93 (0.8, 1.08)	**0.262**
Meta-analysis	1.0 (ref)	0.95 (0.85, 1.07)	0.90 (0.80, 1.01)	0.95 (0.85, 1.07)	0.90 (0.80, 1.02)	**0.134**
hPDI[a]						
NHS	1.0 (ref)	1.07 (0.9, 1.26)	1.04 (0.87, 1.25)	0.93 (0.76, 1.15)	1.13 (0.92, 1.4)	**0.588**
NHSII	1.0 (ref)	0.98 (0.85, 1.13)	0.97 (0.84, 1.12)	0.96 (0.83, 1.1)	1.11 (0.96, 1.29)	0.263
Meta-analysis	1.0 (ref)	1.01 (0.92, 1.12)	0.98 (0.89, 1.08)	0.97 (0.88, 1.07)	1.07 (0.96, 1.19)	0.436
uPDI[a]						
NHS	1.0 (ref)	1.01 (0.8, 1.26)	1.02 (0.82, 1.27)	1.09 (0.88, 1.35)	1.14 (0.93, 1.4)	0.12
NHSII	1.0 (ref)	0.99 (0.85, 1.15)	1.05 (0.9, 1.22)	1.09 (0.94, 1.27)	1 (0.86, 1.17)	0.592
Meta-analysis	1.0 (ref)	1 (0.88, 1.13)	1.04 (0.92, 1.18)	1.09 (0.97, 1.23)	1.05 (0.93, 1.19)	**0.178**

Quantiles and P for trend (significant < 0.05), read by meta-analysis, are reported. RRs and 95% CIs for PDI, hPDI and uPDI in NHS and NHSII.

[a] Adjusted for smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 1. HRs and 95% CIs for associations between iron heme and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] after censoring for hormone therapy use before menopause occurred.

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 - 1.15	0.97	0.81 - 1.16	0.97	0.8 - 1.16
Quantile 3	672/31394	0.88	0.73 - 1.06	0.90	0.74 - 1.08	0.89	0.72 - 1.08
Quantile 4	760/31712	1	0.83 - 1.19	1.03	0.85 - 1.24	1.05	0.87 - 1.26
Quantile 5	637/28396	0.82	0.67 - 0.99	0.86	0.70 - 1.06	0.85	0.7 - 1.05
***P* trend**			0.096		0.338		0.317
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 - 1.06	0.96	0.85 - 1.08	0.94	0.81 - 1.09
Quantile 3	233/255255	0.88	0.79 - 0.99	0.92	0.82 - 1.04	0.9	0.78 - 1.04
Quantile 4	230/229978	0.86	0.77 - 0.97	0.92	0.81 - 1.04	0.9	0.78 - 1.04
Quantile 5	238/217459	0.89	0.79 - 1	0.95	0.84 - 1.09	0.93	0.8 - 1.08
***P* trend**			**0.021**		**0.336**		**0.262**

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk)

Supplementary Table 2. HRs and 95% CIs for associations between iron non-heme and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] after censoring for hormone therapy use before menopause occurred.

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 - 1.15	0.97	0.81 - 1.16	0.97	0.8 - 1.16
Quantile 3	672/31394	0.88	0.73 - 1.06	0.90	0.74 - 1.08	0.89	0.72 - 1.08
Quantile 4	760/31712	1	0.83 - 1.19	1.03	0.85 - 1.24	1.05	0.87 - 1.26
Quantile 5	637/28396	0.82	0.67 - 0.99	0.86	0.70 - 1.06	0.85	0.7 - 1.05
***P* trend**			0.096		0.338		0.317
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 - 1.06	0.96	0.85 - 1.08	0.94	0.81 - 1.09
Quantile 3	233/255255	0.88	0.79 - 0.99	0.92	0.82 - 1.04	0.9	0.78 - 1.04
Quantile 4	230/229978	0.86	0.77 - 0.97	0.92	0.81 - 1.04	0.9	0.78 - 1.04
Quantile 5	238/217459	0.89	0.79 - 1	0.95	0.84 - 1.09	0.93	0.8 - 1.08
***P* trend**			0.021		0.336		0.262

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk)

Supplementary Table 3. HRs and 95% CIs for associations between iron supplement and risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] after censoring for hormone therapy use before menopause occurred.

		Model 1[a]		Model 2[b]		Model 3[c]	
PDI	**Event/person-y**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
NHS							
Quantile 1	781/33156	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	753/32385	0.96	0.8 - 1.15	0.97	0.81 - 1.16	0.97	0.8 - 1.16
Quantile 3	672/31394	0.88	0.73 - 1.06	0.90	0.74 - 1.08	0.89	0.72 - 1.08
Quantile 4	760/31712	1	0.83 - 1.19	1.03	0.85 - 1.24	1.05	0.87 - 1.26
Quantile 5	637/28396	0.82	0.67 - 0.99	0.86	0.70 - 1.06	0.85	0.7 - 1.05
P **trend**		0.096		0.338		0.317	
NHSII							
Quantile 1	257/222681	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quantile 2	247/210223	0.94	0.83 - 1.06	0.96	0.85 - 1.08	0.94	0.81 - 1.09
Quantile 3	233/255255	0.88	0.79 - 0.99	0.92	0.82 - 1.04	0.9	0.78 - 1.04
Quantile 4	230/229978	0.86	0.77 - 0.97	0.92	0.81 - 1.04	0.9	0.78 - 1.04
Quantile 5	238/217459	0.89	0.79 - 1	0.95	0.84 - 1.09	0.93	0.8 - 1.08
***P* trend**		**0.021**		0.336		0.262	

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age.

[e] Adjusted for age and caloric intake (quintiles).

[f] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk

Supplementary Table 4. HRs and 95% CIs for associations between iron heme with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by BMI categories (<25, 25-29.9, >30 kg/m2).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS [*]						
BMI < 25						
Event/person-y	799/17012	838/17662	754/17506	773/18638	653/17620	
HR (95% CI)	1.00 (ref)	1.11 (0.87-1.43)	1.04 (0.8-1.34)	1.12 (0.87-1.43)	0.94 (0.72-1.22)	0.696
BMI 25-29.9						
Event/person-y	834/8150	674/7718	517/7345	730/7127	565/6016	
HR (95% CI)	1.00 (ref)	0.78 (0.52-1.16)	0.65 (0.43-0.98)	0.86 (0.58-1.26)	0.69 (0.44-1.08)	0.143
BMI > 30						
Event/person-y	775/5033	707/4669	637/4081	867/3575	797/2634	
HR (95% CI)	1.00 (ref)	0.91 (0.54-1.52)	0.88 (0.51-1.49)	1.18 (0.7-1.99)	0.92 (0.5-1.66)	0.912
NHS [II] [a]						
BMI < 25						
Event/person-y	258/161024	253/158249	233/199994	235/183488	237/180183	
HR (95% CI)	1.00 (ref)	0.97 (0.82-1.14)	0.92 (0.79-1.08)	0.93 (0.79-1.1)	0.95 (0.81-1.12)	**0.489**
BMI 25-29.9						
Event/person-y	247/42894	224/36601	212/38739	186/32184	217/25321	
HR (95% CI)	1.00 (ref)	0.82 (0.57-1.18)	0.76 (0.53-1.09)	0.65 (0.43-0.98)	0.78 (0.52-1.18)	0.089
BMI > 30						
Event/person-y	262/10698	243/7809	293/7499	358/5859	244/4092	
HR (95% CI)	1.00 (ref)	0.95 (0.38-2.38)	1.26 (0.49-3.23)	1.8 (0.72-4.51)	1.37 (0.43-4.36)	0.244

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 5. HRs and 95% CIs for associations between iron non-heme with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by BMI categories (<25, 25-29.9, >30 kg/m2).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS [*]						
BMI < 25						
Event/person-y	799/17012	838/17662	754/17506	773/18638	653/17620	
HR (95% CI)	1.00 (ref)	1.11 (0.87-1.43)	1.04 (0.8-1.34)	1.12 (0.87-1.43)	0.94 (0.72-1.22)	0.696
BMI 25-29.9						
Event/person-y	834/8150	674/7718	517/7345	730/7127	565/6016	
HR (95% CI)	1.00 (ref)	0.78 (0.52-1.16)	0.65 (0.43-0.98)	0.86 (0.58-1.26)	0.69 (0.44-1.08)	0.143
BMI > 30						
Event/person-y	775/5033	707/4669	637/4081	867/3575	797/2634	
HR (95% CI)	1.00 (ref)	0.91 (0.54-1.52)	0.88 (0.51-1.49)	1.18 (0.7-1.99)	0.92 (0.5-1.66)	0.912
NHS [II] [a]						
BMI < 25						
Event/person-y	258/161024	253/158249	233/199994	235/183488	237/180183	
HR (95% CI)	1.00 (ref)	0.97 (0.82-1.14)	0.92 (0.79-1.08)	0.93 (0.79-1.1)	0.95 (0.81-1.12)	0.489
BMI 25-29.9						
Event/person-y	247/42894	224/36601	212/38739	186/32184	217/25321	
HR (95% CI)	1.00 (ref)	0.82 (0.57-1.18)	0.76 (0.53-1.09)	0.65 (0.43-0.98)	0.78 (0.52-1.18)	0.089
BMI > 30						
Event/person-y	262/10698	243/7809	293/7499	358/5859	244/4092	
HR (95% CI)	1.00 (ref)	0.95 (0.38-2.38)	1.26 (0.49-3.23)	1.8 (0.72-4.51)	1.37 (0.43-4.36)	0.244

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 6. HRs and 95% CIs for associations between iron supplement with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by BMI categories (<25, 25-29.9, >30 kg/m2).

PDI	*Quintile 1*	*Quintile2*	*Quintile 3*	*Quintile 4*	*Quintile 5*	*P trend*	
NHS [a]							
BMI < 25							
Event/person-y	799/17012	838/17662	754/17506	773/18638	653/17620		
HR (95% CI)	1.00 (ref)	1.11 (0.87-1.43)	1.04 (0.8-1.34)	1.12 (0.87-1.43)	0.94 (0.72-1.22)	0.696	
BMI 25-29.9							
Event/person-y	834/8150	674/7718	517/7345	730/7127	565/6016		
HR 95% CI)	1.00 (ref)	0.78 (0.52-1.16)	0.65 (0.43-0.98)	0.86 (0.58-1.26)	0.69 (0.44-1.08)	0.143	
BMI > 30							
Event/person-y	775/5033	707/4669	637/4081	867/3575	797/2634		
HR (95% CI)	1.00 (ref)	0.91 (0.54-1.52)	0.88 (0.51-1.49)	1.18 (0.7-1.99)	0.92 (0.5-1.66)	0.912	
NHS II [a]							
BMI < 25							
Event/person-y	258/161024	253/158249	233/199994	235/183488	237/180183		
HR (95% CI)	1.00 (ref)	0.97 (0.82-1.14)	0.92 (0.79-1.08)	0.93 (0.79-1.1)	0.95 (0.81-1.12)	0.489	
BMI 25-29.9							
Event/person-y	247/42894	224/36601	212/38739	186/32184	217/25321		
HR (95% CI)	1.00 (ref)	0.82 (0.57-1.18)	0.76 (0.53-1.09)	0.65 (0.43-0.98)	0.78 (0.52-1.18)	0.089	
BMI > 30							
Event/person-y	262/10698	243/7809	293/7499	358/5859	244/4092		

HR (95% CI)	1.00 (ref)	0.95 (0.38-2.38)	1.26 (0.49-3.23)	1.8 (0.72-4.51)	1.37 (0.43-4.36)	0.244

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk)

Supplementary Table 7. HRs and 95% CIs for associations between iron heme with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by smoking status (never, former, current 1-14, current 15-24, current 25+).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Former						
Event/person-y	688/11488	680/11022	682/10844	568/10391	648/9411	
HR (95% CI)	1.00 (ref)	1.01 (0.72-1.41)	0.98 (0.7-1.37)	0.82 (0.57-1.17)	0.99 (0.7-1.41)	**0.616**
Current, 1-14 number of cigarettes per day						
Event/person-y	972/2161	917/2182	845/1894	1481/1891	594/1516	
HR (95% CI)	1.00 (ref)	0.93 (0.44-1.99)	1.1 (0.49-2.46)	1.74 (0.85-3.57)	0.62 (0.24-1.62)	0.929
Current, 15-24 number of cigarettes per day						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Current, 25+ number of cigarettes per day						
Event/person-y	1754/2451	1202/1913	1086/1657	948/1372	842/950	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.49)	0.68 (0.34-1.36)	0.66 (0.31-1.39)	0.85 (0.36-2.03)	**0.365**
NHS II[a]						
Never						
Event/person-y	221/146121	221/142204	199/174042	216/159498	222/150354	
HR (95% CI)	1.00 (ref)	0.97 (0.81-1.18)	0.91 (0.76-1.09)	0.96 (0.8-1.15)	1.01 (0.84-1.22)	**0.930**
Former						
Event/person-y	232/50760	242/48310	269/58791	211/53125	244/52082	
HR (95% CI)	1.00 (ref)	1.06 (0.78-1.44)	1.12 (0.84-1.48)	0.93 (0.68-1.26)	1.06 (0.78-1.44)	0.998
Current, 1-14 number of cigarettes per day						
Event/person-y	418/11952	380/9480	233/11142	315/9216	303/8263	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.47)	0.37 (.18-0.77)	0.68 (0.36-1.26)	0.58 (0.3-1.13)	0.091
Current, 15-24 number of cigarettes per day						
Event/person-y	797/5020	656/4573	737/4479	771/3244	826/2783	
HR (95% CI)	1.00 (ref)	0.56 (0.3-1.06)	0.7 (0.4-1.2)	0.68 (0.37-1.24)	0.69 (0.36-1.34)	0.275

Current, 25+ number of cigarettes per day						
Event/person-y	583/4117	472/2541	740/2701	716/1955	817/1470	
HR (95% CI)	1.00 (ref)	0.83 (0.28-2.42)	1.38 (0.52-3.68)	0.81 (0.25-2.6)	4.42 (1.21-16.13)	0.132

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 8. HRs and 95% CIs for associations between iron non-heme with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by smoking status (never, former, current 1-14, current 15-24, current 25+).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Former						
Event/person-y	688/11488	680/11022	682/10844	568/10391	648/9411	
HR (95% CI)	1.00 (ref)	1.01 (0.72-1.41)	0.98 (0.7-1.37)	0.82 (0.57-1.17)	0.99 (0.7-1.41)	**0.616**
Current, 1-14 number of cigarettes per day						
Event/person-y	972/2161	917/2182	845/1894	1481/1891	594/1516	
HR (95% CI)	1.00 (ref)	0.93 (0.44-1.99)	1.1 (0.49-2.46)	1.74 (0.85-3.57)	0.62 (0.24-1.62)	0.929
Current, 15-24 number of cigarettes per day						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Current, 25+ number of cigarettes per day						
Event/person-y	1754/2451	1202/1913	1086/1657	948/1372	842/950	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.49)	0.68 (0.34-1.36)	0.66 (0.31-1.39)	0.85 (0.36-2.03)	0.365
NHS II[a]						
Never						
Event/person-y	221/146121	221/142204	199/174042	216/159498	222/150354	
HR (95% CI)	1.00 (ref)	0.97 (0.81-1.18)	0.91 (0.76-1.09)	0.96 (0.8-1.15)	1.01 (0.84-1.22)	0.930
Former						
Event/person-y	232/50760	242/48310	269/58791	211/53125	244/52082	
HR (95% CI)	1.00 (ref)	1.06 (0.78-1.44)	1.12 (0.84-1.48)	0.93 (0.68-1.26)	1.06 (0.78-1.44)	0.998
Current, 1-14 number of cigarettes per day						
Event/person-y	418/11952	380/9480	233/11142	315/9216	303/8263	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.47)	0.37 (.18-0.77)	0.68 (0.36-1.26)	0.58 (0.3-1.13)	0.091
Current, 15-24 number of cigarettes per day						
Event/person-y	797/5020	656/4573	737/4479	771/3244	826/2783	
HR (95% CI)	1.00 (ref)	0.56 (0.3-1.06)	0.7 (0.4-1.2)	0.68 (0.37-1.24)	0.69 (0.36-1.34)	0.275

Current, 25+ number of cigarettes per day						
Event/person-y	583/4117	472/2541	740/2701	716/1955	817/1470	
HR (95% CI)	1.00 (ref)	0.83 (0.28-2.42)	1.38 (0.52-3.68)	0.81 (0.25-2.6)	4.42 (1.21-16.13)	0.132

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 9. HRs and 95% CIs for associations between iron supplement with risk of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by smoking status (never, former, current 1-14, current 15-24, current 25+).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Former						
Event/person-y	688/11488	680/11022	682/10844	568/10391	648/9411	
HR (95% CI)	1.00 (ref)	1.01 (0.72-1.41)	0.98 (0.7-1.37)	0.82 (0.57-1.17)	0.99 (0.7-1.41)	0.616
Current, 1-14 number of cigarettes per day						
Event/person-y	972/2161	917/2182	845/1894	1481/1891	594/1516	
HR (95% CI)	1.00 (ref)	0.93 (0.44-1.99)	1.1 (0.49-2.46)	1.74 (0.85-3.57)	0.62 (0.24-1.62)	0.929
Current, 15-24 number of cigarettes per day						
Event/person-y	655/13733	691/14327	593/14327	765/15417	590/14417	
HR (95% CI)	1.00 (ref)	1.09 (0.81-1.47)	0.88 (0.65-1.2)	1.17 (0.88-1.56)	0.84 (0.61-1.15)	0.445
Current, 25+ number of cigarettes per day						
Event/person-y	1754/2451	1202/1913	1086/1657	948/1372	842/950	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.49)	0.68 (0.34-1.36)	0.66 (0.31-1.39)	0.85 (0.36-2.03)	0.365
NHS II[a]						
Never						
Event/person-y	221/146121	221/142204	199/174042	216/159498	222/150354	
HR (95% CI)	1.00 (ref)	0.97 (0.81-1.18)	0.91 (0.76-1.09)	0.96 (0.8-1.15)	1.01 (0.84-1.22)	0.930
Former						

Event/person-y	232/50760	242/48310	269/58791	211/53125	244/52082	
HR (95% CI)	1.00 (ref)	1.06 (0.78-1.44)	1.12 (0.84-1.48)	0.93 (0.68-1.26)	1.06 (0.78-1.44)	0.998
Current, 1-14 number of cigarettes per day						
Event/person-y	418/11952	380/9480	233/11142	315/9216	303/8263	
HR (95% CI)	1.00 (ref)	0.79 (0.42-1.47)	0.37 (.18-0.77)	0.68 (0.36-1.26)	0.58 (0.3-1.13)	0.091
Current, 15-24 number of cigarettes per day						
Event/person-y	797/5020	656/4573	737/4479	771/3244	826/2783	
HR (95% CI)	1.00 (ref)	0.56 (0.3-1.06)	0.7 (0.4-1.2)	0.68 (0.37-1.24)	0.69 (0.36-1.34)	0.275
Current, 25+ number of cigarettes per day						
Event/person-y	583/4117	472/2541	740/2701	716/1955	817/1470	
HR (95% CI)	1.00 (ref)	0.83 (0.28-2.42)	1.38 (0.52-3.68)	0.81 (0.25-2.6)	4.42 (1.21-16.13)	0.132

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), duration of oral contraceptive use, BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 10. HRs and 95% CIs for associations between iron heme with rate of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by oral contraceptive use categories (never use, current use, former use <5 years, former ≥5 years).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never use						
Event/person-y	625/9760	672/9975	416/9605	423/10162	426/9618	
HR (95% CI)	1.00 (ref)	1 (0.68-1.48)	0.65 (0.42-1)	0.7 (0.46-1.07)	0.7 (0.45-1.08)	0.030
Current use						
Event/person-y	-	-	-	-	-	
HR (95% CI)	-	-	-	-	-	
Former use, <5 years						
Event/person-y	919/19810	825/19511	845/19054	967/18921	770/16622	
HR (95% CI)	1.00 (ref)	0.96 (0.77-1.19)	0.98 (0.78-1.22)	1.17 (0.94-1.45)	0.9 (0.71-1.14)	0.987
Former use, ≥5 years						
Event/person-y	340/2356	582/1890	176/1707	478/1672	399/1253	
HR (95% CI)	1.00 (ref)	1.78 (0.57-5.57)	0.56 (0.12-2.58)	1.21 (0.34-4.38)	1.43 (0.37-5.5)	0.889
NHS ^{II}[a]						
Never use						
Event/person-y	232/30173	187/30001	213/37568	224/35241	214/35107	
HR (95% CI)	1.00 (ref)	1.17 (0.71-1.91)	1.13 (0.71-1.8)	1.12 (0.7-1.8)	1.22 (0.76-1.94)	**0.519**
Current use						
Event/person-y	182/26416	180/23310	147/27197	210/23296	182/19764	
HR (95% CI)	1.00 (ref)	0.88 (0.52-1.49)	0.63 (0.36-1.1)	1.02 (0.62-1.66)	0.7 (0.39-1.24)	0.411
Former use, <5 years						
Event/person-y	266/138080	262/132184	246/163276	228/148051	243/142665	
HR (95% CI)	1.00 (ref)	0.93 (0.78-1.10)	0.93 (0.79-1.10)	0.86 (0.72-1.02)	0.96 (0.8-1.13)	**0.41**
Former use, ≥5 years						
Event/person-y	320/24074	313/21105	261/22957	295/19335	329/15806	
HR (95% CI)	1.00 (ref)	0.96 (0.6-1.54)	0.92 (0.57-1.47)	1.06 (0.65-1.73)	1.18 (0.72-1.95)	0.482

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 11. HRs and 95% CIs for associations between iron non-heme with rate of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by oral contraceptive use categories (never use, current use, former use <5 years, former ≥5 years).

PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5	*P* trend
NHS[a]						
Never use						
Event/person-y	625/9760	672/9975	416/9605	423/10162	426/9618	
HR (95% CI)	1.00 (ref)	1 (0.68-1.48)	0.65 (0.42-1)	0.7 (0.46-1.07)	0.7 (0.45-1.08)	**0.030**
Current use						
Event/person-y	-	-	-	-	-	
HR (95% CI)	-	-	-	-	-	
Former use, <5 years						
Event/person-y	919/19810	825/19511	845/19054	967/18921	770/16622	
HR (95% CI)	1.00 (ref)	0.96 (0.77-1.19)	0.98 (0.78-1.22)	1.17 (0.94-1.45)	0.9 (0.71-1.14)	0.987
Former use, ≥5 years						
Event/person-y	340/2356	582/1890	176/1707	478/1672	399/1253	
HR (95% CI)	1.00 (ref)	1.78 (0.57-5.57)	0.56 (0.12-2.58)	1.21 (0.34-4.38)	1.43 (0.37-5.5)	0.889
NHS II[a]						
Never use						
Event/person-y	232/30173	187/30001	213/37568	224/35241	214/35107	
HR (95% CI)	1.00 (ref)	1.17 (0.71-1.91)	1.13 (0.71-1.8)	1.12 (0.7-1.8)	1.22 (0.76-1.94)	0.519
Current use						
Event/person-y	182/26416	180/23310	147/27197	210/23296	182/19764	
HR (95% CI)	1.00 (ref)	0.88 (0.52-1.49)	0.63 (0.36-1.1)	1.02 (0.62-1.66)	0.7 (0.39-1.24)	0.411
Former use, <5 years						
Event/person-y	266/138080	262/132184	246/163276	228/148051	243/142665	
HR (95% CI)	1.00 (ref)	0.93 (0.78-1.10)	0.93 (0.79-1.10)	0.86 (0.72-1.02)	0.96 (0.8-1.13)	0.41
Former use, ≥5 years						
Event/person-y	320/24074	313/21105	261/22957	295/19335	329/15806	
HR (95% CI)	1.00 (ref)	0.96 (0.6-1.54)	0.92 (0.57-1.47)	1.06 (0.65-1.73)	1.18 (0.72-1.95)	0.482

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25

and parity > 2), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m^2), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).

Supplementary Table 12. HRs and 95% CIs for associations between iron supplement with rate of early menopause[a] among women in the NHS, 1984-1992[b] and NHSII, 1991-2011[c] stratified by oral contraceptive use categories (never use, current use, former use <5 years, former ≥5 years).

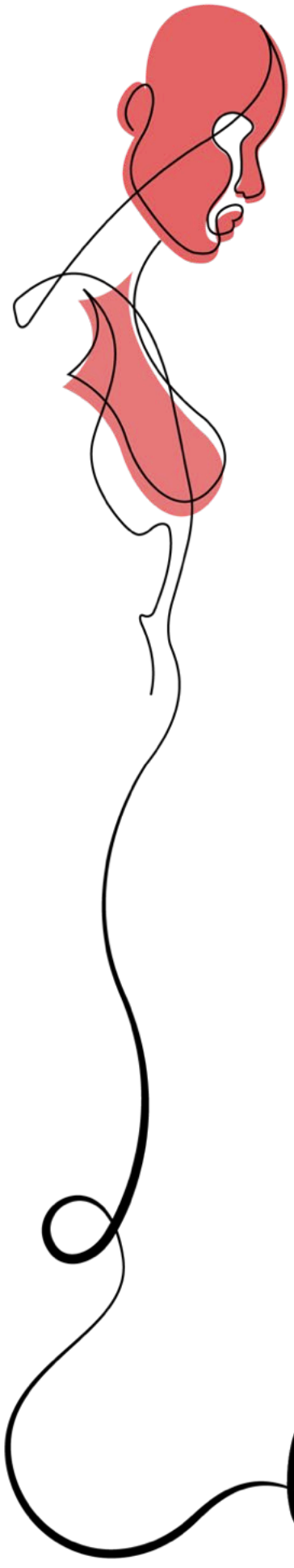
PDI	Quintile 1	Quintile2	Quintile 3	Quintile 4	Quintile 5
NHS[a]					
Never use					
Event/person-y	625/9760	672/9975	416/9605	423/10162	426/9618
HR (95% CI)	1.00 (ref)	1 (0.68-1.48)	0.65 (0.42-1)	0.7 (0.46-1.07)	0.7 (0.45-1.08)
Current use					
Event/person-y	-	-	-	-	-
HR (95% CI)	-	-	-	-	-
Former use, <5 years					
Event/person-y	919/19810	825/19511	845/19054	967/18921	770/16622
HR (95% CI)	1.00 (ref)	0.96 (0.77-1.19)	0.98 (0.78-1.22)	1.17 (0.94-1.45)	0.9 (0.71-1.14)
Former use, ≥5 years					
Event/person-y	340/2356	582/1890	176/1707	478/1672	399/1253
HR (95% CI)	1.00 (ref)	1.78 (0.57-5.57)	0.56 (0.12-2.58)	1.21 (0.34-4.38)	1.43 (0.37-5.5)
NHS II[a]					
Never use					
Event/person-y	232/30173	187/30001	213/37568	224/35241	214/35107
HR (95% CI)	1.00 (ref)	1.17 (0.71-1.91)	1.13 (0.71-1.8)	1.12 (0.7-1.8)	1.22 (0.76-1.94)
Current use					
Event/person-y	182/26416	180/23310	147/27197	210/23296	182/19764
HR (95% CI)	1.00 (ref)	0.88 (0.52-1.49)	0.63 (0.36-1.1)	1.02 (0.62-1.66)	0.7 (0.39-1.24)
Former use, <5 years					
Event/person-y	266/138080	262/132184	246/163276	228/148051	243/142665
HR (95% CI)	1.00 (ref)	0.93 (0.78-1.10)	0.93 (0.79-1.10)	0.86 (0.72-1.02)	0.96 (0.8-1.13)
Former use, ≥5 years					
Event/person-y	320/24074	313/21105	261/22957	295/19335	329/15806
HR (95% CI)	1.00 (ref)	0.96 (0.6-1.54)	0.92 (0.57-1.47)	1.06 (0.65-1.73)	1.18 (0.72-1.95)

[a] Early menopause defined as women who experience menopause status < 45 years.

[b] Diet was assessed in 1984, 1986, 1988, 1990 and 1992.

[c] Diet was assessed in 1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009 and 2011.

[d] Adjusted for age, smoking status (never, former, current 1-14, current 15-24, current 25+), pack years, age at first birth and parity (nulliparous, age < 25 and parity 1 or 2, age < 25 and parity > 2, age ≥ 25 and parity 1 or 2, age ≥ 25 and parity > 2), BMI (< 21, 21-22.9, 23-24.9, 25-29.9, >30 Kg/m²), breast feeding, history of hypertension, history of high blood cholesterol, physical activity (MET-h/wk).



4. Discussion

"I'm a great believer in luck, and I find the harder I work the more I have of it."

Thomas Jefferson

female health

4. DISCUSSION

4.1. Summary of findings

4.1.1. Article 1. Evaluating the association between menopausal status and changes in dietary intake in Swiss adult women: a cross-sectional and longitudinal study (Chapter 3.1)

In the CoLaus population-based study, I evaluated the association between transition to menopause and changes in dietary intake among adult women in Switzerland and compliance with the Swiss Food Pyramid according to menopause stages. At the first follow-up, compared with premenopausal women, postmenopausal women were older, had higher BMI, and had more prevalent CVD and T2D. Compared with premenopausal women, postmenopausal women reported consuming less meat, pasta, added sugar, polysaccharides, monounsaturated fatty acids (MUFAs), and cholesterol and more dairy products, fruits, monosaccharides, and retinol. However, the multivariable linear regression analysis showed no association between menopause status, TEI, and the intake of micro- and macronutrients. In the prospective analysis, compared with women who remained premenopausal during follow-up (n = 244), no differences were found in changes in TEI, dietary intakes, or adherence to the Swiss dietary recommendations among women transitioning from premenopausal to postmenopausal (n = 229) and who remained postmenopausal (n = 1168).

4.1.2. Article 2. Dietary factors and onset of natural menopause: a systematic review and meta-analysis (Chapter 3.2)

The role that modifiable lifestyle might play in menopause onset can vary between 15 and 70%; thus, it is important to understand how dietary factors can influence the timing of natural menopause. In total, 15 articles based on 11 unique observational studies (non-overlapping study population) were included in the final analysis of the systematic review; 91,554 women experienced natural menopause during follow-up. I classified studies as low risk of bias if they received a score of 9 points; medium risk of bias if the studies scored 7 or 8 points; and the rest were considered at a high risk of bias. Two studies were judged as low risk of bias, 11 studies at medium risk, and 2 studies at high risk of bias.

I investigated 89 food groups, 38 macronutrients and micronutrients, and 6 dietary patterns. Among the food groups, higher intakes of green and yellow vegetables were associated with early age of ONM, while high intake of some dairy products, such as low-fat, skim milk, and low intake of alcohol were associated with a later onset. I observed no consistent association between macronutrient and micronutrient intake and ONM, although vegetarian diet could be associated with early ONM.

4.1.3. Article 3. Association of plant-based diet and early onset of natural menopause (Chapter 3.3)

Using data from a large perspective cohort in the United States, I observed that women who had the highest intake of PDI were older, reported less use of oral contraceptives, smoked fewer packs of cigarettes per year, were less overweight and obese, and more physically active than women with lower intake of PDI in both NHS and NHSII cohorts. During mean follow-up with 715 in NHS and 2,185 in NHSII, incidence of early natural menopause events, I observed no significant association between PDI and early natural menopause; the results remained consistent across strata of BMI, smoking status and oral contraceptive use. I found similar results for hPDI and uPDI as they were not associated with early menopause, although the fixed-effect model showed uPDI to be associated with a modest higher risk of early menopause.

4.1.4. Article 4. Association of dietary iron intake and early onset of natural menopause: a prospective study (Chapter 3.4)

Using data from a large prospective cohort in U.S., I observed a strong association between dietary iron heme intake and early natural menopause in the NHSII cohort even after censoring women who used hormone therapy before menopause occurred. After stratification by BMI, I found an association between iron heme and early natural menopause only in women with BMI <25 in the NHSII cohort. The stratification for cigarette smoking status showed an association between iron heme and risk to experience early natural menopause for former and current (+25 cigarettes/day) smokers in the NHS cohort, and with never smokers in the NHSII cohort. Iron heme was found to be associated with higher incidence of early natural menopause among never and former user (<5 years) after stratification by oral contraceptive use only in the NHSII cohort.

In the NHS cohort, iron non-heme was found to be associated with a modest higher risk of early natural menopause after full adjustment, although the fixed-effect model showed iron non-heme to not be associated with early natural menopause. In the NHS cohort, after stratification by smoking status and oral contraceptive use, iron non-heme was found to be associated with former smokers and never users, respectively.

4.2. Strengths and limitations

4.2.1. Strengths

There are several strengths of the articles included in this thesis. First, using a well-defined prospective study design, article 1 provides new insights about women's dietary changes during and after menopause transition that have important public health implications for the prevention of menopause-related diseases. From the CoLaus study, I was able to identify three groups of women and investigate longitudinal changes in diet through different reproductive stages. Second, I provide the first systematic review on the

association between diet and menopause onset, as well as examine the role of PDI and iron on early natural menopause onset in article 2. Furthermore, our systematic review relied on strict inclusion and exclusion criteria, systematically searching different bibliographic databases, and assessing study quality on the topic; we also provide new insights with implications for guiding future research. Third, in the NHS and NHSII cohorts, I used repeated measures of diet; thus, considering diet changes over time. Furthermore, our study is among the largest exploring dietary factors affecting menopause onset; we included 715 and 2,185 incidents of early menopause during a long follow-up of up to 20 years from the NHS and NHSII, respectively.

4.2.2. Limitations

In **Table 6**, I summarize possible limitations and new approaches for future research that address those limitations. For article 1 (**Chapter 3.1**), the food-frequency questionnaire is based on self-reported data with the possibility of inaccurate reporting and recall bias. Although FFQ can be used to estimate TEI, the overall TEI would be a less accurate estimate [126]. The food questionnaire also focused on a limited number (97) of food items, and some food groups were missing. We only had information on total intake of carotene, not type of carotene intake; therefore, we cannot exclude the possibility that women may have changed their consumption of different types of carotenoids. Despite studies demonstrating that FFQ when compared with 24-hour dietary recalls have greater reproducibility in detecting differences in self-reported dietary intake over time, FFQ may not be sensitive enough to detect dietary changes [127]. Furthermore, our study only included Caucasian women in Lausanne, so it might not be generalizable for all people in Switzerland and other populations and ethnicities. Self-reported data and missing information regarding the absence of menstruation in the past 12 months might have led to misclassification of menopause status. Finally, when compared with women included in our cross-sectional analysis, excluded women were less frequently married or single and more frequently divorced or widowed, less educated, and more current smokers with higher prevalence of diabetes.

In our systematic review and meta-analysis (**Chapter 3.2**) in article 2, the included studies were based on different populations, time periods, and methods used to analyse dietary intake; thus, these differences precluded the possibility of meta-analyses on different food items and menopause onset. In addition, high heterogeneity in other exposure assessments (e.g., continuous or categorical variables; different units of assessment), outcomes (e.g., different definitions of natural menopause), and a limited number of available studies that met our inclusion criteria meant we were only able to meta-analyse alcohol intake involving 4 studies. Further, our review highlighted important methodological issues about diet and menopause onset evidence. Longitudinal changes of diet over time should be accounted for in these analyses by using repeated measures of diet, which was only considered in 7 of the 15 included articles in this systematic review.

Most of the studies did not translate estimates into months or years women could delay menopause by consuming certain food items; some published studies reported how specific food intake reduces or increases the risk of early or late menopause by percentage or months and years, while others did not report this information. Among the included studies, only 4 studies account for competing risks, such as occurrence of hysterectomy, cancer, or HRT. Future studies should explore the impact of competing risks on the association between diet and menopause onset. Only 4 out 15 studies adjusted simultaneously for important confounders on the association between diet and ONM, including age, BMI, smoking status, age at menarche, caloric intake, and parity; the studies also adjusted for one or more additional confounders, such as physical activity, alcohol intake, breastfeeding, education level, oral contraceptive use, HRT, protein and animal proteins, multivitamin use, and marital status. Future studies should focus on the role of biomarkers, such as AMH, to explore in-depth the physiological mechanisms behind menopause onset.

In the last 2 original studies (**Chapter 3.3** and **Chapter 3.4**) in articles 3 and 4, although our results should not differ from other women in United States or elsewhere, NHS and NHSII participants are not a random sample of the general U.S. population. Also, cumulative PDI, hPDI, and uPDI were self-reported by FFQ—a well-validated technique with some misclassification of intake possible due to under- or overreporting. Finally, we relied on self-reported menopausal status to determine timing of menopause.

LIMITATIONS	WHAT TO DO?
ORIGINAL RESEARCH	
self-reported food frequency questionnaire	-> more food items; dietary index; dietary patterns
self-reported menopause status	-> 'do you miss your period for at least 12 consecutive months?'; using only the first reported age at menopause
no random population	-> random and replication studies
no biomarkers included	-> Anti-Müllerian hormone, Follicle-stimulating hormone
SYSTEMATIC REVIEW AND META-ANALYSIS	
different populations	-> replication studies in the same ethnic group
different time period	-> for longitudinal anaylses including follow-up > 5y
different methods	-> standardized unit of measure for food intake; months/year women gain in delaying/earlying menopause
few competing risks	-> more competing risks
analyses adjusted for few/different confounders	-> reporting the most important confounders such as age, BMI, smoking status, age at menarche, caloric intake, parity, and alcohol intake

Table 6. Summary of limitations and approaches for future research.

4.3. Implications and interpretation

Article 1 (**Chapter 3.1**) revealed low adherence to nutrition recommendations and a tendency to change dietary habits among women experiencing menopausal transition. Since there are National Swiss Food Pyramid guideline, recommendation, and care inconsistencies, I suggest other prevention measures are necessary, such as healthier eating habits and specific educational campaigns throughout women's lives—the key word is 'prevention.' Other prevention measures could be important for maintaining optimal health and reducing the development of several medical complications during menopausal years. Since there is little research examining effects of dietary changes during menopausal transition on metabolic and cardiovascular health, future studies should examine which dietary components or dietary patterns are associated with better health during menopausal transition and whether the identified dietary components or patterns have beneficial and long-term effects among women.

Our systematic review (**Chapter 3.2**) in article 2 calls for future prospective and randomized studies to investigate whether diet can influence menopause onset; heterogeneity in exposure and outcome assessment, similar longitudinal changes of diet over time, and analyses adjusted simultaneously for the same important confounders may be the cornerstone for improving the quality of future studies. The impact of diet on menopause onset is underscored by the absence of replication and comprehensive studies available about this topic. For instance, explorations of associations between diet and sex hormones and consequent ONM; foods that affect sex hormones the most, or further studies about the possible role of soy, tofu, and phytoestrogen on menopause timing. Understanding whether and how dietary factors influence ONM could have a positive impact on family planning, as well as when applying reproductive techniques, and it could also lead to a new approach in reducing adverse outcomes related to early or late natural menopause.

In article 3 (**Chapter 3.3**), I revealed a non-significant association between PDI and early natural menopause, although uPDI including less-quality diet and low in high-quality PDI can influence ONM. These results suggest that a balanced diet, based on more fruit and vegetable intake and fewer animal products, may have no adverse impact on menopause onset, while broader implications in terms of menopause-related health outcomes remains to be elucidated in the future.

Furthermore, in article 4 we reported a strong association between dietary iron heme intake and higher risk of early natural menopause in our last original article (**Chapter 3.4**); iron heme is found mainly in animal products and this association confirms other findings reporting an association between meat intake and early natural menopause [128]. The association between iron and menopause is still unclear even though oestrogen and iron are mutually influenced and possibly act synergically [129]. Further studies are needed to

confirm our results among another population using biomarkers of iron body status, such as ferritin and hepcidin.

In conclusion, understanding whether specific dietary factors might be associated with menopause onset could also lead to new approaches for reducing unhealthy dietary habits and adverse outcomes related to early or late natural menopause.

4.4. Outlook and perspective

Despite emerging evidence supporting diet as a factor influencing menopause onset and menopause-related issues, training for specialists in clinical practice, such as gynaecologist and health care personnel, on counselling patients about diet is still lacking. This gap in the health care system suggests it is time to develop more patient-centred strategies. In the future, we need to better understand the role of diet on reproductive health, and in parallel improve clinical practice by incorporating dietary counselling. To understand short and long-term effects of diet on menopause onset, research can be improved by prospectively collecting dietary data through FFQs, assessing dietary biomarkers, and including women of different ages. Since the timing of menopause is a long-term process, anticipatory care planning should be explored. For example, in studies on diet and menopause, younger participants should be included along with participants who are close to menopause or who are experiencing the annoying climacteric symptoms. Campaigns in medical schools or active enrolment of gynaecologists in information campaigns may be a good starting point for improving knowledge about the role of lifestyle factors on health. Since 'lifestyle' is not just diet and 'health' is not just related to menopause, the goal is to promote information regarding the impact of a healthy diet, physical activity, mental health on our health (e.g., clinical conditions, mental status) and the long-term consequences of healthy aging and menopause experience. Finally, more focused campaigns can be directed toward biological women to increase their awareness of menopause-related diseases and improve their understanding of how diet can improve adverse outcomes.

Although national guidelines have been developed in countries around the world, it is unlikely that most of the world population can access or understand them. In fact, sometimes interpreting guidelines is hard for specialists too. First, to be easily understood by a wide range of professionals and the public, the guidelines should be written in plain language. Second, they should be freely and easily accessible for everyone through widespread availability among health care providers and public institutions. Third, even though different definitions of menopause are generally well-reported (e.g., peri-menopause, early menopause, late menopause, premature menopause), some of them need standardized definitions. For instance, although 'premenopause' is widely used, it is an ambiguous term referring to either 1–2 years immediately before menopause or the whole reproductive period prior to menopause; users of 'premenopause' should define it specifically or standardize it globally [130]. Additionally, accounting for previous

considerations, patient-centred strategies to increase discussions about lifestyle approaches for menopause management might include organizing informative talks. Ideally, these talks pave the way for discussions with specialists (e.g., gynaecologist, physician) at the patient's convenience. In addition, it is important to have administrative support by allocating staff time for these kinds of discussions. One of the main barriers is the limited evidence about this topic. To overcome this barrier, new or replication studies are needed. For instance, nowadays few articles investigate the role of diet to moderate the adverse effect of climacteric symptoms [125], the perception of menopause and menopause symptoms around the world [39], the influence of genetic factors on menopause timing, and the impact on clinical conditions such as cardiometabolic health or metabolic syndrome [45]. Also, it is important to identify dietary factors that can have a beneficial impact on cancers related to late menopause.

Recently, some progress has been made; however, more progress is needed. The process of learning is complex and the mechanisms involved in doing so are many and varied. Future research could also use prediction models of menopause onset to identify women who might be at risk of early menopause and for whom public health interventions, such as diet, could be tailored. Indeed, personalized diet approaches are the new frontier in medicine, so generalizing dietary findings and making reliable guidelines are difficult tasks. However, if patients continue to receive adequate information and support, the goal for widespread healthy lifestyles through making health-conscious decisions becomes more realistic.

4.5. Conclusion

In my thesis, I contribute knowledge bridging the gaps and addressing the challenges of understanding the association between diet and menopause. I show gaps regarding adherence to the dietary recommendations in Switzerland among women transitioning from premenopausal to postmenopausal. Additionally, I provide knowledge about inconsistent associations between macronutrient and micronutrient intake and the onset of menopause. Since a vegetarian diet could be associated with menopause timing, I suggest that focus on replication studies is needed. I assessed 2 studies to identify the association of macro- and micronutrients with menopause onset: the first reported a non-significant association between PDI and early natural menopause. Yet I found an association between uPDI and early natural menopause, which indicates further studies are needed to confirm such association. The second study reported a strong association between heme-iron—rich in animal products—and early natural menopause; those findings may support other studies reporting associations between meat intake and early menopause. The association of iron and menopause is a new research frontier, and it should be investigated further to better understand this field. Overall, our dietary habits influence our overall physical and psychological health, so our goal should be to promote and enhance wellbeing.

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6. SUPPLEMENTARY MATERIAL

6.1. Supplementary material 1. Swiss Food Pyramid

Swiss Food Pyramid

Sweets, Salty Snacks & Alcohol
In small quantities.

Oils, Fats & Nuts
Oils and nuts in small quantities daily. Butter/margarine sparingly.

Dairy Products, Meat, Fish, Eggs & Tofu
3 portions of dairy products and 1 portion of meat/fish/eggs/tofu ... per day.

Grains, Potatoes & Pulses
3 portions per day. Grains should preferably be wholegrain.

Vegetables & Fruit
5 portions per day of different colours.

Beverages
1–2 litres of unsweetened beverages per day. Preferably water.

At least 30 minutes of physical activity daily and sufficient relaxation.

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Swiss Food Pyramid

Recommendations for a healthy and enjoyable adult diet

Beverages

1–2 litres per day, preferably in the form of sugar-free drinks, e.g. tap/mineral water or fruit/herbal tea. Beverages containing caffeine, such as coffee, black and green tea, can contribute to liquid intake.

Vegetables & Fruit

5 portions per day of different colours, at least 3 portions should be vegetables and 2 fruit. 1 portion = 120 g. One daily portion of fruit or vegetables can be replaced by 2 dl of vegetable or fruit juice (with no added sugar).

Grains, Potatoes & Pulses

3 portions per day. Cereals should preferably be whole grain. 1 portion = ▶ 75–125 g bread/pastry or ▶ 60–100 g pulses (dry weight) or ▶ 180–300 g potatoes or ▶ 45–75 g crisp bread/whole-grain crackers/flakes/flour/pasta/rice/corn/other grains (dry weight).

Dairy Products, Meat, Fish, Eggs & Tofu

3 portions per day of milk or dairy products. 1 portion = ▶ 2 dl milk or ▶ 150–200 g yoghurt/fresh cheese (quark)/cottage cheese/other dairy products or ▶ 30 g semi/hard cheese or ▶ 60 g soft cheese.
In addition, 1 daily portion of another protein-rich food (e.g. meat, poultry, fish, eggs, tofu, quorn, seitan, cheese or fresh cheese [quark]). Alternate between these sources of protein. 1 portion = ▶ 100–120 g meat/poultry/fish/tofu/quorn/seitan (fresh weight) or ▶ 2–3 eggs or ▶ 30 g semi/hard cheese or ▶ 60 g soft cheese or ▶ 150–200 g fresh cheese (quark)/cottage cheese.

Oils, Fats & Nuts

2–3 tablespoons per day (20–30 g) of vegetable oil, of which at least half should be rape-seed oil.
1 portion per day (20–30 g) of unsalted nuts, seeds or kernels. In addition, butter, margarine, cream, etc. can be used, however, **sparingly** (approx. 1 tablespoon = 10 g per day).

Sweets, Salty Snacks & Alcohol

Consume sweets, sweetened drinks, salty snacks and alcoholic beverages **in moderation.**

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Swiss Food Pyramid
Further information about the recommendations

▶ *A well-balanced diet is vital in promoting a healthy lifestyle. It influences our mental and physical well-being and helps in the prevention of illnesses.*

The recommendations of the Swiss food pyramid are for adults. Other recommendations may apply for specific age groups and population categories (e.g. children, pregnant women, athletes), as well as for those suffering from illnesses or requiring weight reduction. The food pyramid depicts a balanced diet and is based on the following core principles:

▶ Food groups

Food is summarised in groups according to its respective compositions. Typical examples of the individual groups are illustrated in the food pyramid.

▶ Quantities

Food in the lower levels of the pyramid should be consumed in larger quantities, whereas those from the upper levels should be consumed in smaller quantities. All foods are allowed, but correct food combinations and proportions are essential for a balanced diet.

▶ Diversity

A balanced diet is a diverse diet that takes different food groups, as well as different foods within the food groups into consideration.

The food pyramid is not a rigid diet; it allows for the individual composition of food, beverages and meals according to personal likes and dislikes and habits. The listed food quantities serve as a guideline. Smaller or larger portions apply according to energy requirements (depending on age, gender, height, physical activity, etc.). The recommendations are meant to be observed on a long-term basis, i.e. in the course of a whole week, and not just on a daily basis. Recommendations regarding liquid intake are an exception, and should be observed daily.

A diet that follows the food pyramid ensures a sufficient supply of nutrients and protective compounds – with a few exceptions. One of these exceptions is vitamin D. As food sources only contain small amounts of vitamin D, it is also important to regularly spend time outdoors so that the body can produce its own vitamin D from sunlight. In winter, when the body's production of vitamin D is reduced, a supplement (e.g. from fortified foods or a dietary supplement) can counteract the deficit.

Careful preparation of food also helps to retain beneficial nutrients. Use salt with added iodine and fluoride but only in limited quantities. Other sea-soning containing salt, such as seasoning sauce, soya sauce, stock, etc. should also be kept to a minimum. Herbs and spices are a creative way to flavour dishes.

Mealtimes are not just about the intake of energy and nutrients; they are also about pleasure, relaxation and social contact. Taking time, switching off and eating and drinking in peace and quiet help to promote the enjoyment of eating.

In addition to a balanced diet, the following also contribute to a healthier way of life: ▶ at least 30 minutes of daily physical exercise ▶ going outdoors every day ▶ taking regular breaks and relaxing ▶ avoiding smoking and excessive alcohol consumption.

What we eat impacts not only our own health but also our environment (humans, animals, nature). Sustainable eating habits comprise: ▶ preference of plant-based foods ▶ foods that are environment- and animal-friendly, seasonal, regional and in compliance with fair trade principles ▶ avoiding food waste.

▶ *Old habits die hard! In order to achieve a healthier and sustainable lifestyle, it helps to set small and realistic goals and implement them step by step. Even small changes can make a difference.*

Swiss Food Pyramid

Additional recommendations for adolescents

▶ *In addition to the principles of well-balanced nutrition for adults, as represented by the food pyramid, the following also needs to be considered for adolescents:*

▶ For growth and development

Adolescents are still in their growth and development phase. Therefore they have a greater need of energy and individual nutrients than adults, depending upon age and sex. This requirement can be well covered by balanced nutrition.

▶ Fast Food? Vegetarian?

Fast food and snacks frequently contain high amounts of energy, fat and/or sugar, but few dietary fibres, vitamins or minerals. Therefore, high-energy fast foods and snacks should only be eaten occasionally and in small portions and be combined with salads or fruit. Water is recommended as opposed to sweet beverages. And last but not least, meals should be enjoyed slowly and in a sitting position.

With a vegetarian diet, the conscious selection of foods is particularly important to ensure an adequate supply of nutrients (e.g. vitamin B_{12}). Meat should be regularly replaced by other sources of protein such as tofu, legumes, cheese or eggs.

▶ Beverages & Co.

Ideal beverages are tap/mineral water, unsweetened fruit or herbal teas and strongly diluted juices. Soft and energy drinks are unsuitable thirst-quenchers as due to their high sugar content, these beverages provide too much energy without giving a genuine feeling of satiety. This can lead to becoming overweight. Additionally, sugar and acids in these beverages attack the teeth. Light beverages also contain acids and, like sugared beverages, can lead to a strong preference for sweet tastes.

Alcoholic beverages (beer, wine, liqueurs and drinks manufactured from a mix of these) should not be drunk at all by people under 16 years of age and only exceptionally, if at all, by adolescents over 16. The risks of alcohol consumption are generally underestimated (e.g. danger of road and sports accidents, increased aggression, risky sexual behaviour, alcohol poisoning).

▶ Eat regularly – with pleasure

Regular meals, such as three main meals a day and, if necessary, two small intermediate meals are recommended. A balanced breakfast or morning tea provide a good start to the day and promote concentration and efficiency at school and during training. Unfortunately, regular meals are ever more frequently replaced by constant and unconscious intermediate snacking which confuses normal feelings of hunger and satiety. In addition, there is the fact that snacks are usually very energy-rich and poorly balanced. Over the long-term, this eating pattern can lead to becoming overweight. Peace and time to concentrate on the meal without any distractions (TV, computer) contribute to conscious, pleasurable meals.

▶ Too fat? Too thin? Or normal?

Many adolescents are dissatisfied with their body. Both extreme crash diets and the uncontrolled consumption of muscle-developing supplements can lastingly disturb the metabolism. Such behaviour can result in eating disorders such as bulimia and anorexia.

▶ *A positive perception of one's body and self-determined, healthy ways of treating the body such as a balanced diet and regular exercise form the basis for the development and well-being of adolescents.*

Swiss Food Pyramid

Additional recommendations for the elderly

▶ *The recommendations for healthy elderly people are basically the same as those contained in the food pyramid for adults. However, in old age, special attention must be paid to the following:*

▶ Protein

Ensuring adequate protein intake is particularly important in order to preserve muscle and bone mass and maintain various body functions (e.g. immune defences). The easiest way to meet protein requirements is through the daily consumption of food rich in protein such as legumes, milk products, tofu, meat, fish or eggs.

▶ Calcium and vitamin D

These nutrients are vital for the maintaining the strength of bones. Milk and milk products are excellent sources of calcium, as are mineral water that is rich in calcium (over 300 mg per litre), dark green vegetables and nuts.
Not many foods contain vitamin D, which is why a supplementary intake of vitamin D is recommended for people over the age of 60.

▶ Fluids

As the sensation of thirst decreases with age, the elderly must take extra care to drink a sufficient amount of liquid each day, i.e. 1–2 litres. Amongst other things, fluids support intellectual capacities.

▶ Energy

Energy requirements depend on physical activity. People who do not exercise much need correspondingly less energy, but their bodies still require at least the same amount of protein, vitamins and minerals as they did when they were younger. Those who continue to exercise in old age have higher energy requirements and live a healthier life. They can eat more and provide their bodies with all the essential nutrients, and their weight is more likely to remain stable.

▶ Underweight and overweight

Being either under- or overweight can impair quality of life and increase the risk of disease (e.g. malnutrition, heart disease or circulatory problems). Elderly people without much appetite may find it helpful to eat several small portions spread throughout the day to prevent becoming underweight. For those who are overweight, a balanced, low-calorie diet and regular exercise can help.

▶ Food supplements

Protein, fibre, vitamin and mineral requirements are not always covered adequately by our diet. Enriched foods (e.g. multivitamin juices) can help to meet the body's requirements. In some situations it may be advisable to take food supplements (e.g. vitamin tablets), but only after consulting a specialist.

▶ Exercise

Daily exercise such as walking, climbing stairs or gymnastics helps to keep fit, reduces the chances of becoming overweight and helps preserve bones and muscle mass.

▶ *A healthy lifestyle consisting of a balanced diet and sufficient exercise is the best way to ensure that you will stay fit into old age.*

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6.2. Supplementary material 2. PDI, hPDi, and uPDI

Examples of food items for scoring each plant-based diet indices (from the 1986 NHS food frequency questionnaire)

Healthy plant foods	
Whole grains	Whole grain breakfast cereal, other cooked breakfast cereal, cooked oatmeal, dark bread, brown rice, other grains, bran, wheat germ, popcorn
Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, avocado, fresh apples, applesauce, pears, oranges, grapefruit, strawberries, blueberries, peaches, apricots, plums
Vegetables	Tomatoes, tomato juice, tomato sauce, red chili sauce, broccoli, cauliflower, cooked cabbage, coleslaw or uncooked cabbage, Brussels sprouts, raw carrots, cooked carrots, mixed vegetables, yams or sweet potatoes, yellow or winter squash, eggplant or zucchini or other summer squash, kale or mustard or chard greens, cooked spinach, raw spinach, iceberg or head lettuce, romaine or leaf lettuce, green pepper, cucumber, celery, mushrooms, alfalfa sprouts, corn
Nuts	Nuts, peanut butter
Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans
Vegetable oil	Vegetable oil, oil-based salad dressing
Tea and coffee	Tea, coffee, decaffeinated coffee or non-caffeinated tea
Less healthy plant foods	
Fruit juices	Apple cider (nonalcoholic) or juice, orange juice, grapefruit juice, other fruit juice
Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta
Potatoes	French fries, baked or boiled or mashed potatoes, potato or corn chips
Sugar-sweetened beverages	Soda with sugar, noncarbonated fruit drinks with sugar
Sweets and desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked and ready-made), brownies, doughnuts, cake (home-made and ready-made), sweet roll or coffee cake or other pastry, pie (home-baked and ready-made), jams or jellies or preserves or syrup or honey
Animal foods	
Animal fat	Butter added to food, butter or lard used for cooking
Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese
Eggs	Eggs
Fish and seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops
Meat	Chicken or turkey with skin, chicken or turkey without skin, bacon, hot dogs, processed meats, hamburger, liver, beef or pork or lamb as a mixed dish, beef or pork or lamb as a main dish
Miscellaneous animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing

Creating the Plant-based Diet Indices

- Create servings consumed/day for each of ~130 food items (in Harvard cohorts)
- Create 18 food groups by adding up the servings of foods that belong to each food group
  - Food groups created based on nutrient and culinary similarities, but within the larger categories of healthy plant foods, less healthy plant foods, and animal foods
- Rank the 18 food groups into quintiles
- Each food group quintile was assigned a score between 1 & 5
- Add up food group scores to obtain the overall diet indices (theoretical range: 18 to 90)

Overall Plant-based Diet Index (PDI)

Positive

Q1=1
Q2=2
Q3=3
Q4=4
Q5=5

Plant Food Groups	
Healthy	
Whole grains	Whole grain breakfast cereal, other cooked breakfast cereal, cooked oatmeal, dark bread, brown rice, other grains, bran, wheat germ, popcorn
Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or apricots or plums
Vegetables	Tomatoes, tomato juice, tomato sauce, broccoli, cabbage, cauliflower, Brussels sprouts, carrots, mixed vegetables, yellow or winter squash, eggplant or zucchini, yams or sweet potatoes, spinach cooked, spinach raw, kale or mustard or chard greens, iceberg or head lettuce, romaine or leaf lettuce, celery, mushrooms, beets, alfalfa sprouts, garlic, corn
Nuts	Nuts, peanut butter
Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans
Vegetable oils	Oil-based salad dressing, vegetable oil used for cooking
Tea & Coffee	Tea, coffee, decaffeinated coffee
Less healthy	
Fruit juices	Apple cider or juice, orange juice, grapefruit juice, other fruit juice
Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta
Potatoes	French fries, baked or mashed potatoes, potato or corn chips
Sugar sweetened beverages	Colas with caffeine & sugar, colas without caffeine but with sugar, other carbonated beverages with sugar, non-carbonated fruit drinks with sugar
Sweets and Desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked & ready-made), brownies, doughnuts, cake (home-baked & ready-made), sweet roll (home-baked & ready-made), pie (home-baked & ready-made), jams or jellies or preserves or syrup or honey

Reverse

Q1=5
Q2=4
Q3=3
Q4=2
Q5=1

Animal Food Groups	
Animal fat	Butter added to food, butter or lard used for cooking
Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese
Egg	Eggs
Fish or Seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops
Meat	Chicken or turkey with skin, chicken or turkey without skin, bacon, hot dogs, processed meats, liver, hamburger, beef or pork or lamb mixed dish, beef or pork or lamb main dish
Misc. animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing

Healthful Plant-based Diet Index (hPDI)

	Plant Food Groups	
Positive	*Healthy*	
	Whole grains	Whole grain breakfast cereal, other cooked breakfast cereal, cooked oatmeal, dark bread, brown rice, other grains, bran, wheat germ, popcorn
	Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or apricots or plums
	Vegetables	Tomatoes, tomato juice, tomato sauce, broccoli, cabbage, cauliflower, Brussels sprouts, carrots, mixed vegetables, yellow or winter squash, eggplant or zucchini, yams or sweet potatoes, spinach cooked, spinach raw, kale or mustard or chard greens, iceberg or head lettuce, romaine or leaf lettuce, celery, mushrooms, beets, alfalfa sprouts, garlic, corn
	Nuts	Nuts, peanut butter
	Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans
	Vegetable oils	Oil-based salad dressing, vegetable oil used for cooking
	Tea & Coffee	Tea, coffee, decaffeinated coffee
Reverse	*Less healthy*	
	Fruit juices	Apple cider or juice, orange juice, grapefruit juice, other fruit juice
	Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta
	Potatoes	French fries, baked or mashed potatoes, potato or corn chips
	Sugar sweetened beverages	Colas with caffeine & sugar, colas without caffeine but with sugar, other carbonated beverages with sugar, non-carbonated fruit drinks with sugar
	Sweets and Desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked & ready-made), brownies, doughnuts, cake (home-baked & ready-made), sweet roll (home-baked & ready-made), pie (home-baked & ready-made), jams or jellies or preserves or syrup or honey
	Animal Food Groups	
	Animal fat	Butter added to food, butter or lard used for cooking
	Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese
	Egg	Eggs
	Fish or Seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops
	Meat	Chicken or turkey with skin, chicken or turkey without skin, bacon, hot dogs, processed meats, liver, hamburger, beef or pork or lamb mixed dish, beef or pork or lamb main dish
	Misc. animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing

Unhealthful Plant-based Diet Index (uPDI)

	Plant Food Groups	
	Healthy	
Reverse	Whole grains	Whole grain breakfast cereal, other cooked breakfast cereal, cooked oatmeal, dark bread, brown rice, other grains, bran, wheat germ, popcorn
	Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or apricots or plums
	Vegetables	Tomatoes, tomato juice, tomato sauce, broccoli, cabbage, cauliflower, Brussels sprouts, carrots, mixed vegetables, yellow or winter squash, eggplant or zucchini, yams or sweet potatoes, spinach cooked, spinach raw, kale or mustard or chard greens, iceberg or head lettuce, romaine or leaf lettuce, celery, mushrooms, beets, alfalfa sprouts, garlic, corn
	Nuts	Nuts, peanut butter
	Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans
	Vegetable oils	Oil-based salad dressing, vegetable oil used for cooking
	Tea & Coffee	Tea, coffee, decaffeinated coffee
Positive	*Less healthy*	
	Fruit juices	Apple cider or juice, orange juice, grapefruit juice, other fruit juice
	Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta
	Potatoes	French fries, baked or mashed potatoes, potato or corn chips
	Sugar sweetened beverages	Colas with caffeine & sugar, colas without caffeine but with sugar, other carbonated beverages with sugar, non-carbonated fruit drinks with sugar
	Sweets and Desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked & ready-made), brownies, doughnuts, cake (home-baked & ready-made), sweet roll (home-baked & ready-made), pie (home-baked & ready-made), jams or jellies or preserves or syrup or honey
Reverse	***Animal Food Groups***	
	Animal fat	Butter added to food, butter or lard used for cooking
	Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese
	Egg	Eggs
	Fish or Seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops
	Meat	Chicken or turkey with skin, chicken or turkey without skin, bacon, hot dogs, processed meats, liver, hamburger, beef or pork or lamb mixed dish, beef or pork or lamb main dish
	Misc. animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing

6.3. Supplementary material 3. Nine-star Newcastle-Ottawa Scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community ✸
b) somewhat representative of the average _____ in the community ✸
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort ✸
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (eg surgical records) ✸
b) structured interview ✸
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes ✸
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) ✸
b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
a) independent blind assessment ✸
b) record linkage ✸
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ✸
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ✸
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

7. RELATED PUBLICATIONS AS CO-AUTHOR

7.1. What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review

IJPH | SSPH+

International Journal of Public Health
REVIEW
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What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review

Lucía Aguirre Sánchez[1,2]*, *Zayne M. Roa-Díaz*[3,4], *Magda Gamba*[3,4], *Giorgia Grisotto*[3,4,5], *Ana María Moreno Londoño*[6], *Blanca Patricia Mantilla-Uribe*[7], *Alba Yaneth Rincón Méndez*[7], *Mónica Ballesteros*[8], *Doris Kopp-Heim*[9], *Beatrice Minder*[9], *L. Suzanne Suggs*[1,2,10] and *Oscar H. Franco*[3,5,10]

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Objectives: Global environmental challenges demand sustainable behaviours and policies to protect human and planetary health. We aimed to summarize the evidence about the factors related to Sustainable Food Consumption (SFC) behaviours of university students, and to propose an operational categorization of SFC behaviours.

Methods: Seven databases were searched for observational studies evaluating Sustainable Food Consumption (SFC) among university students and that reported at least one behavioural outcome measure. Qualitative synthesis was conducted, and PRISMA guidelines for reporting were followed.

Results: Out of 4,479 unique references identified, 40 studies were selected. All studies examined personal factors, while 11 out of 40 also measured social or situational factors. Except for food waste, females had higher levels of SFC behaviours, but situational factors moderated this association. Knowledge and attitudes showed mixed results. Overall, sustainable food consumers reported healthier lifestyles.

Conclusions: Healthy lifestyle of sustainable food consumers suggests possible synergies between human health and sustainability in terms of motivations for food choice. Moderation effects of social and situational factors on personal factors reveal opportunities to design and examine the effects of choice architecture interventions.

Keywords: sustainable food consumption, sustainable diets, pro-environmental behaviour, health behaviour, university students, young adults, young people, systematic review

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INTRODUCTION

Food connects human and planetary health. Diet-related factors are among the top contributors to the global burden of disease [1], and the food sector is the leading cause of environmental change, contributing to 19–29% of the global Greenhouse gas (GHG) emissions [2]. Climate change drives adverse effects back into human health [3], affecting food availability, the nutritional contents of foods, and putting populations at risk of nutritional deficiencies [4].

FAO defines sustainable diets as those with "low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations [. . .]" [5], in line with earlier definitions of sustainable consumption [6]. The EAT-Lancet Commission proposes a healthy diet from sustainable food systems [3], identifying three main spheres for food system transformation: improvements in production, widespread change in dietary patterns, and waste reduction. However, to date, there is no operational and widely accepted definition of sustainable food consumption behaviours, and the factors associated remain unclear.

While health and environmental co-benefits of sustainable diets have been reported in the literature [7–10], from the consumer perspective, sustainable food consumption may pose a tension between individual and collective interests, adding a pro-social aspect to food consumption. Therefore, behavioural approaches are needed to understand what drives the adoption of healthier and more sustainable eating behaviours, especially those with lower environmental impact [3, 11]. However, research about behavioural aspects of sustainable food consumption is considered scarce compared to the extensive body of evidence on the adverse environmental and health impact of eating behaviours [12–14].

University students, in particular, are more willing to adopt changes in their eating behaviours, and are more environmentally conscious than older generations [15]. Universities are the organizations where studies on behaviour and consumption are most frequently conducted, with estimations of up to 80% of the literature in this field is based on student samples [16].

University students engage in unhealthy eating behaviours [17], which has yielded a vast body of literature on the importance of healthy diets among this population. The adherence to food consumption behaviours that are healthy and also sustainable has gained some attention [18–20]. Hence, we aimed to systematically summarize the evidence regarding the underlying factors that can determine or constrain sustainable food consumption among university students and propose an operational categorization of Sustainable Food Consumption (SFC) behaviours.

METHODS

This systematic review was conducted following the guide proposed by Muka and colleagues [21] and the PRISMA guidelines for reporting [22]. The protocol is registered in PROSPERO: CRD42021233347.

Data Source and Search Strategy

The search strategy (See search strategies in **Supplementary Material**) was developed by the authors, including two librarians. The search was limited to human studies and peer-review publications. The search terms included synonyms of sustainable food consumption and specific behaviours based on relevant literature, on diets and food systems with lower environmental impact [3, 23]. Medline, Embase, PsycInfo, Web of Science, Scopus, LILACS databases and Google Scholar were searched to identify relevant articles from inception until 27 January 2021 without language or geographic restrictions [3, 23, 24]. Backward reference search was conducted on each of the studies selected from the database search. Expert input and a manual search in relevant journals were also used (See Search Strategies in **Supplementary Material**).

Selection Criteria

Studies were included if they: were conducted with university students; were observational (e.g., cross-sectional); presented behavioural outcome measures of SFC, and identified factors associated with SFC. Our operational definition of Sustainable Food Consumption includes both dietary patterns and other consumer behaviours related to how food is produced, processed, transported, managed and wasted. Building on Garnett et al 2014 [23], the outcome also includes behaviours such as choosing foods with less energy-intensive transport modes, such as local and seasonal products, meat eaten in moderate quantities, dairy products or alternatives eaten in moderation, and tap water in preference to other beverages.

Studies were excluded if participants reported comorbidities or were post-doctoral researchers, evaluated the efficacy or effectiveness of interventions focused on farming, agriculture, or other food production-related behaviours, or assessed behavioural intentions, attitudes, and willingness but not actual behaviours. Cost-effectiveness studies, case reports, letters to the editor, conference proceedings, systematic reviews, or meta-analyses were also excluded.

Screening and Study Selection

Pairs of screeners independently reviewed titles and abstracts of the retrieved references. Overlapping references were included for full-text screening. Inclusion disagreements were solved initially by the reviewers and persistent disagreements were solved upon consultation with a third reviewer.

Data Analysis and Synthesis of Results

A tailored data extraction form was developed and piloted for this study. The form included identifiers, general characteristics of the study and participants, and results (See **Supplementary Material**). Qualitative analysis of the reviewed articles was conducted following deductive categorization of behavioural outcomes, data reduction, and narrative synthesis of related factors, as associations, correlations and descriptive group comparisons. The proposed behavioural categories were built deductively from relevant literature, while the target behaviours were extracted from the measurement instruments reported in selected articles. Given the diversity of measurement approaches, quantitative meta-analysis was not performed.

Quality Assessment

Two reviewers independently assessed the quality of included studies using the Newcastle–Ottawa Scale [25] (NOS) for cross-sectional studies; disagreements were solved by consensus. NOS was developed for non-randomized and observational studies and

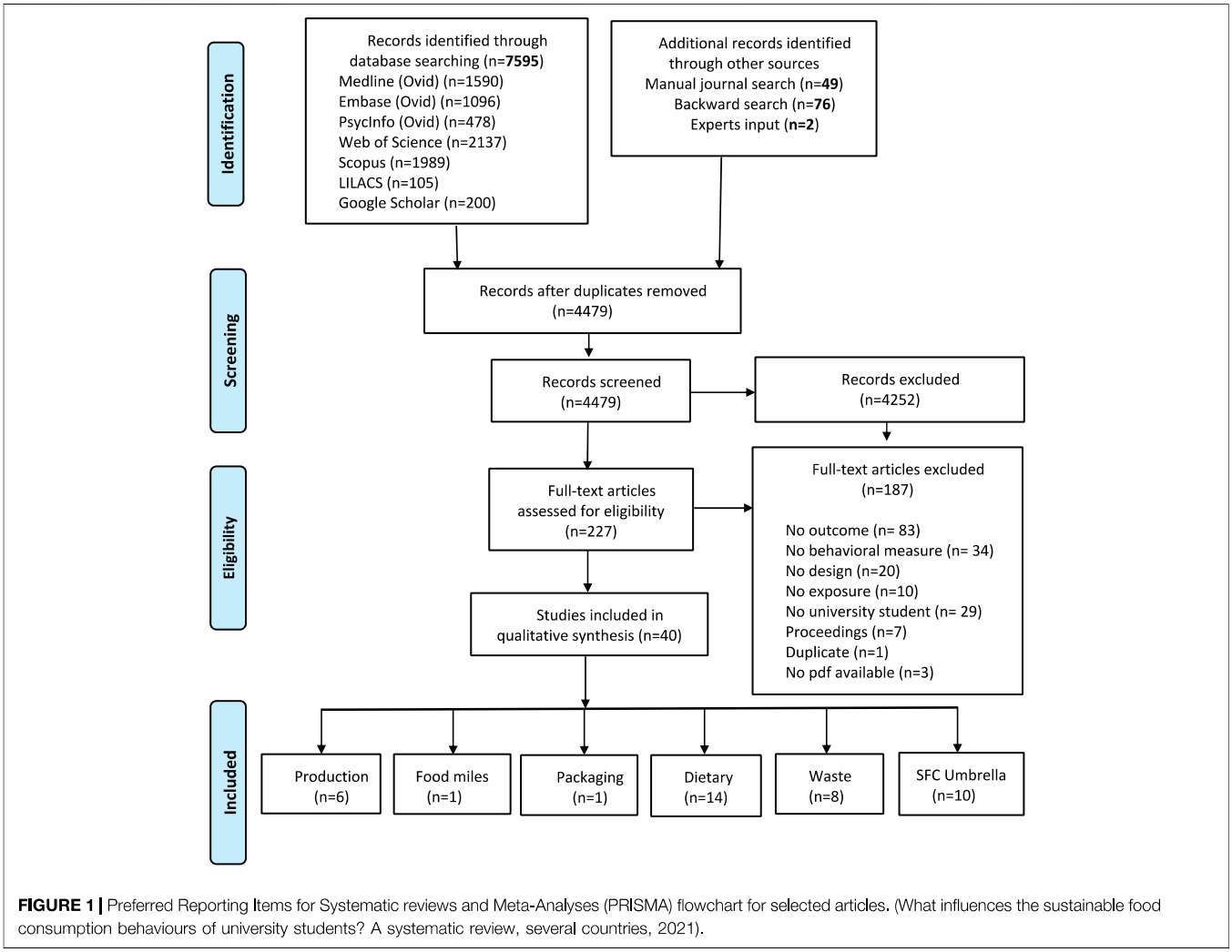

FIGURE 1 | Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart for selected articles. (What influences the sustainable food consumption behaviours of university students? A systematic review, several countries, 2021).

assessed quality in three broad categories: selection of study groups/participants, comparability of the study groups/participants, and the assessment of outcome of interest. Quality was assessed on a 10-point scale and classified as good (10–9 points), moderate (8–6 points), and low quality (≤5 points). All studies were included in the analysis, independently of NOS score.

RESULTS

Study Selection

We identified 4,479 unique references, of which 227 were selected to be screened in full text. Of those, 40 studies comprising 27,946 participants met the selection criteria (See **Figure 1**). A summary of included papers is presented in **Table 1**.

Study Population and Measurement

There were four multi-country studies [26–29] and in total 30 represented countries. The top frequencies of study locations were 10 from the United States (US) [30–39], five from Italy [40–44], and three from Spain [45–47]. All the included papers were cross-sectional and were based on 38 unique samples. Ten articles addressed an umbrella concept (e.g., sustainable, green or climate-friendly food consumption) and measured several target behaviours [31, 37, 43, 48–54], while the rest reported a single outcome relevant for the analysis. Almost a third of the articles adopted a specific theoretical or conceptual framework for hypothesis formation and measurement. The most common was the Theory of Planned Behaviour (TPB) [28, 41, 54–56]. All the 40 studies identified evaluated personal factors while 11 (29%) also included social or situational factors. Being a woman was reported as a factor related to SFC in eight out of the twelve articles that reported significant gender-related differences. Three reported lower levels of food waste in men. The mean age of the study participants ranged from 18 to 29 years. On average, 60.7% were women and two studies were conducted with female students only.

Behavioural Categories of Sustainable Food Consumption (SFC)

This section summarizes the findings about factors related to the observed sustainable, and unsustainable, food consumption

TABLE 1 | Articles included in the review. (What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review, Several countries, 2021).

Author, year, country	n[a], (% of women), age	Behavioural outcome	Examined factors (in addition to demographics[b])	Key results (significant associations or significant group differences)	Quality (NOS)[c]
Akbar et al., 2019, Pakistan	*n* = 221, (33.5), NR	Organic Food Buying Behaviour	Green Perceived Value (GPV) constructs (functional value, social value, emotional value, and conditional value), purchase intention, food neophobia.	Food neophobia moderates the relationship of purchase intention and behaviour.	Moderate
Dahm et al., 2009, United States	*n* = 443, (55.8), *M* = 21.6, SD 5.01	Organic food consumption and purchase	Awareness (knowledge) and attitudes toward organic foods, and attitudes and behaviours regarding other eco-friendly practices.	Attitude predicted purchase and consumption of organic foods on campus.	Low
Giampietri et al., 2020., Italy	*n* = 223, (47.1), *M* = 22.45 SD 2.5	Organic food consumption	Individual risk attitude	More risk averse individuals eat organic food frequently. Trust and social norms were linked to organic food consumption.	Low
Hamilton and Hekmat, 2018, Canada	*n* = 426, (NR), NR	Organic food consumption	Knowledge and attitudes.	Attitudes (safety of organic food, the nutrition value of organic food, the perception that organic food is fresher and better in taste and the perception that organic food is better for animal welfare and the environment) were significantly associated with the frequency of consumption. Perceived safety was highly correlated with organic food consumption.	Low
McReynolds et al., 2017., United States	*n* = 238, (40), *M* = 22.4 SD 6.5	Organic food consumption and purchase	Knowledge and perceptions about organic food, demographic and socioeconomic characteristics	There was a significant correlation between students' knowledge and behaviour. Having experience growing fruits or vegetables had the greatest impact.	Low
Zámková and M. Prokop, 2013, Czech Republic	NR	Organic food consumption	Exposure to organic food advertisement.	Women bought organic food more frequently than men. Main reason of disinterest in buying organic is the price, distrust and not believing that organic food is better than conventional food. Advertising for organic food did not affect purchase.	Low
Fernandez-Ferrin et al., 2017, Spain	*n* = 195, (55.4), *M* = 21.34 SD Not applicable	Locally produced food products	Local identity, brand valuation, and moderating effect of perceived availability.	Perceived availability condition the promoting effect of local identity on purchase of local tomato sauce and local rice. Perceived availability does not moderate purchase of local mineral water and traditional cake.	Low
Diez et al., 2018, Spain	*n* = 632, (61.2), NR	Tap water and bottled water consumption frequency	Perceptions about bottled and tap water.	Students presented the highest proportions of consumption of more than 6 bottles of water per week. Beliefs (e.g., "I trust tap water's quality," "If I drink tap water, I am contributing less plastic to landfills") had statistical differences between low consumption group (0 bottles per week) and high bottled water users (≥6 bottles per week). No associations with gender.	Moderate
Barros et al., 2020, Brazil	*n* = 1841, (54.8), NR	Prevalence of vegetarian diet	Lifestyle characteristics.	Males had less odds of being vegetarians. Those who reported prejudicial alcohol use were almost twice as likely to adopt a vegetarian diet.	Moderate
Forestell et al., 2012, United States	*n* = 240, (100), M = 19.28	Vegetarian, pesco-, semi-vegetarian, and flexitarian compared to omnivores	Food restraint, lifestyle (e.g., drinking alcohol, smoking), personality inventory, variety seeking, food neophobia, general neophobia, food choice, sensory appeal, price,	Vegetarians and pesco-vegetarians were more open to new experiences, variety seeking, and less food neophobic than regular omnivores. Semi-vegetarians and flexitarians were more restrained than omnivores.	Low

(Continued on following page)

TABLE 1 | (*Continued*) Articles included in the review. (What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review, Several countries, 2021).

Author, year, country	n[a], (% of women), age	Behavioural outcome	Examined factors (in addition to demographics[b])	Key results (significant associations or significant group differences)	Quality (NOS)[c]
			familiarity, mood, ethical concern, eating attitudes.		
Forleo et al., 2017, Italy	*n* = 548, (67.1), *M* = 25.05	Adherence to new Italian Mediterranean food pyramid	Living with parents or away, eating at home or away, BMI, pro-environmental behaviours, knowledge on daily caloric needs, physical activity (sports).	Six clusters were identified. Cluster five (26% of the sample), the least compliant to Mediterranean Pyramid, showed an above average consumption of meat and processed meat products, younger students, a higher percentage of females and students living with parents.	Low
Izmirli and Phillips, 2011, Multiple countries	*n* = 3,433, (NR), NR	Consumption of animal products	Attitudes towards animals, and perceived importance of world issues.	Students avoiding some meats cited the environment as the most important reason, and then health, whereas most vegetarian students gave their health as the main reason. Vegans had greater concern for animal welfare.	Low
Kawasaki et al., 2021, Japan	*n* = 215, (100), *M* = 20	Healthful plant-based diet	Mindful eating	Higher scores for healthful plant-based diet were correlated with higher "health of the planet" and "awareness and appreciation for food" sub-scores. "Non-judgmental awareness" was correlated with a low intake of healthful plant-based foods.	Low
Llanaj and Hanley-Cook, 2020., Albania	*n* = 289, (87.19), NR	Adherence to EAT–Lancet diet	Anthropometric measurements, dietary intake, dietary cost and eating out of home	EAT-lancet diet adherence was very low. No associations found.	Moderate
Pocol et al., 2020, Romania, Bulgaria and Moldova.	*n* = 2,378, (NR), NR	Adherence to mixed or vegetarian diets.	Residence, weight.	Mixed diet was slightly higher among men. Semi-vegetarian, ovo-lacto-vegetarian, and lacto-vegetarian diets, was slightly higher among women. Mixed diet decreases with age, while semi-vegetarian and ovo-lacto-vegetarian diets, increases slightly with age.	Low
Menozzi et al 2017, Italy	*n* = 231, (61.9), *M* = 23.6 SD 3.8	Tasting an edible insect food product	Attitudes, subjective norms, perceived behavioural control (PBC), intention, topic of study.	Students enrolled in social sciences-related were less likely to taste the insect-based food product compared to students in food and environmental sciences-related. intention is the main predictor of the behaviour, followed by perceived behavioural control.	Low
Olfert et al., 2020., United States	*n* = 1,078, (66,6), NR	Adherence to vegetarian diet	Perceptions of campus environment, waist, and hip circumference, fruit and vegetable intake, fat intake, stress, eating attitudes, physical activity, sleep quality.	Vegetarians had higher stress, consumed significantly more servings of fruits and/or vegetables per day and obtained a lower percentage of their daily caloric intake from fats than nonvegetarians. Vegetarians had similar mean BMI as nonvegetarians.	Low
Ruby et al. 2016, Argentina, Brazil, France, United States	*n* = 1,695, (65.5), *M* = 22 SD 2.53	Beef consumption	Attitudes toward beef, and toward vegetarians.	Men consumed beef significantly more often than women. Consumption was significantly highest in Brazil, followed by Argentina, then the USA, and finally France. Men ate beef significantly more frequently than did women in Brazil, and the United States, but not in Argentina.	Low
Smith et al., 2000, United States	NR	Adherence to vegetarian, vs. weight loss diet	Reasons for discontinuing diets	Vegetarian group remained on their diet for more than 1 year, whereas the majority of the Weight-Loss participants followed their diet for 1–3 months. Strictness of diets did not differ. Main reasons cited for stopping the vegetarian diet were	Low

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TABLE 1 | (*Continued*) Articles included in the review. (What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review, Several countries, 2021).

Author, year, country	n[a], (% of women), age	Behavioural outcome	Examined factors (in addition to demographics[b])	Key results (significant associations or significant group differences)	Quality (NOS)[c]
				"missed eating (meat)," "inconvenience," and "did not get adequate nutrients."	
Spencer et al., 2007, United States	NR	Self-reported vegetarian diet	Health-related outcomes	Vegetarians were more likely to eat more fruits and vegetables, be women, be Hindu, Buddhist, or Seventh Day Adventist, be politically liberal, have a BMI ≤ 25	Low
Suleiman et al., 2009, Jordan	*n* = 1,500, (65.4), *M* = 20.3 Range 17–28	Prevalence vegetarian diet	Selected demographic and lifestyle characteristics.	The vegetarian group consisted mainly of women, aged between 17 and 20 years, with low income, non-smokers, physically active, using vitamin and mineral supplements and having a normal BMI.	Moderate
Vizcaino et al., 2020, United States	*n* = 99, (70), Median = 18 Interquartile range 18–19	Adherence to a plant-based diet	Self-regulatory system, variety of motivations.	Successful adherents had higher levels of value, self-efficacy, planning/stimulus control and positive affect, were seventeen times more likely to report "To manage or treat a medical condition" and were 94% less likely to report 'To maintain and/or improve my health' as motivation.	Moderate
Al-Domi H, 2011, Jordan	*n* = 600, (37), *M* = 21.5 SD 2.85	Plate waste	Demographic and socioeconomic characteristics.	No differences between the food plate wasted between women and men, except for meat wasted, women waste slightly more than men. Food waste was low in general.	Low
Alattar et al., 2020, United States	*n* = 495, (54), *M* = 21 Range 18–58	Food waste diversion behaviours	Food management skills, food waste attitudes/emotions, perception of cost, food waste knowledge, general sustainability beliefs, perception of personal impact.	The composting index was negatively correlated with food waste diversion intent, but attitudes toward composting were still positively correlated.	Low
Lorenz et al., 2017, Germany	*n* = 238, (48), NR	Leftover behaviour (Food waste)	Personal (Attitudes, PBC, subjective norms, Intention, Personal Norms), social (presence of others), and environmental/situational factors (palatability, portion size, and time pressure)	Perceptions of food (portions size and palatability) was related to food leftovers. For participants under time pressure, gender (being female) becomes a significant determinant for leftover behaviour. Time pressure was not a direct environmental determinant of leftovers.	Low
Lorenz et al., 2018, Germany	*n* = 384, (47), *M* = 24.3	Visually estimated food leftovers	Beliefs (constructs: environment, self-interest, and resources), general attitude (towards the behaviour) and behavioural intention	Larger perceived portion size related to increased leftovers, and more positive taste evaluation related to lower leftovers. Both situational variables are significantly correlated with the self-interest but not with pro-environmental or resource efficiency beliefs.	Moderate
Mondejar-Jimenez et al., 2017, Spain, Italy	*n* = 380, (58), *M* = 20.62 SD 2.62	Positive behaviour towards food waste, and proportion food wasted	Concern about food waste, moral attitude, subjective norms, perceived behavioural control, marketing/sale addiction, intention	Subjective norms and perceived behavioural control promote the positive behaviour. Marketing/sale strategies "addiction" decreased the positive behaviour. The strongest positive significant total effect on behaviour comes from subjective norms.	Low
Morata Verdugo et al., 2020, Spain	*n* = 49, (75,5), *M* = 22.6 SEM ± 6.0	Food waste at home (leftovers)	Eating habits and level of physical activity.	Food waste was slightly higher among women. Lunch generated more wasted food than dinners.	Low
Principato et al, 2015, Italy	*n* = 233, (39), NR Range 19–28	Food waste reduction behaviours	Knowledge, attitudes (level of concern).	Food waste reduction behaviour was negatively associated with higher levels of concern about "the risk of eating unsafe food because is no longer fresh," belief that "only 10% of the food purchased gets thrown away" (compared to those who believe that higher percentages of	Low

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TABLE 1 | (*Continued*) Articles included in the review. (What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review, Several countries, 2021).

Author, year, country	n[a], (% of women), age	Behavioural outcome	Examined factors (in addition to demographics[b])	Key results (significant associations or significant group differences)	Quality (NOS)[c]
				food get thrown away," and believing that "packaging of the food thrown in the trash is a larger environmental problem than food waste."	
Wu, et al., 2019, China	*n* = 551, (46.1), NR	Plate waste	Attitudes, perceived behavioural control, subjective norms, canteens characteristics (e.g., food not tasty, too much food provided), factors related to food waste avoidance (e.g., save money, felling of guilt)	A perception that avoiding food waste is difficult, and higher living expenses were factors promoting food waste. Subjective norms, attitudes, gender, and major had insignificant impacts. Male students wasted significantly less staple foods than female students.	Moderate
Anh et al., 2019, Vietnam	*n* = 791, (NR), NR	Sustainable consumption behaviour in food	Environmental awareness and action, economical and effective options, and sustainable buying options.	The construct of "Environmental awareness and action" (I cook in an energy-efficient way, I avoid eating convenience food because of plastic waste, I use containers instead of plastic wraps/bags, I sort the inorganic or organic waste before throwing into the trash) had the strongest positive impact on the studied outcome.	Low
Anh et al., 2020, Vietnam	*n* = 791, (59), NR	Sustainable consumption behaviour in food and drink	Gender, religion, academic year, love relationship, residence status.	Being in a relationship increased the probability of sustainable consumption behaviour.	Low
Campbell-Arvai, 2015, United States	*n* = 320, (52.5), NR	Food-related environmental behaviours	Demographic and socioeconomic characteristics, value orientation, pro-environmental worldview (NEP – New environmental paradigm scale), and food-related environmental beliefs	Higher BVO (Biospheric value orientation) and environmental belief scores were associated with higher environmental behaviour scores. NEP scores (New environmental paradigm), when controlling for BVO, environmental beliefs and gender, did not make a significant contribution to the model. Males had lower environmental behaviour scores than females.	Low
Dopelt et al., 2019, Israel	*n* = 361, (75), *M* = 29 SD 8.6	Pro-environmental behaviours (food related)	Knowledge, attitudes.	Women had more pro-environmental behaviour than men. Attitudes were the best predictor of pro-environmental food related behaviour. Lack of knowledge on environmental impact of food consumption was negatively correlated to outcome.	Low
Kamenidou et al., 2019., Greece	*n* = 252, (54.8), NR	Sustainable food consumption behaviour	Social norms, ecological purchase behaviour, and clusters based on demographic characteristics.	Two students' segments were identified based on Sustainable food consumption (SFC) behaviour, social norms and ethical behaviour: "The under-consideration students" and "The negatively positioned students". None of them has a high level of SFC, but the first and larger segment is more positively predisposed towards it.	Low
Makiniemi and Vainio, 2013, Finland	*n* = 350, (80), *M* = 24 SD 7.05	Climate-friendly food choices	Perceived moral intensity of climate change	Probable Seriousness of Consequences was by far the most important of the three moral intensity dimensions.	Low
Mäkiniemi and Vainio, 2014, Finland	*n* = 350, (80), *M* = 24 SD 7.05	Climate-friendly food choices	Perceived barriers	Wanting to eat the same as before, Disbelief in climate effects of food choices and lack of time had the greatest negative effect on climate-friendly food choices. Being male decreases the likelihood of choosing climate-friendly foods.	Low
Mohd Suki and Mohd Suki, 2015, Malaysia	*n* = 700, (55), NR Range 18–25	Green food consumption behaviour	Religion: Muslim vs non-Muslim (Hindus and Buddhists), specific needs, convenience, intention,	Muslim consumers have lower scores on the evaluated factors, except for convenience factor correlation.	Low

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TABLE 1 | (*Continued*) Articles included in the review. (What Influences the Sustainable Food Consumption Behaviours of University Students? A Systematic Review, Several countries, 2021).

Author, year, country	n[a], (% of women), age	Behavioural outcome	Examined factors (in addition to demographics[b])	Key results (significant associations or significant group differences)	Quality (NOS)[c]
			promotion/diffusion, governmental efforts	Specific needs were the main contributing factor and the strongest predictor in discriminating between Muslim and non-Muslim consumers' green food consumption.	
Schoolman, 2019, United States	*n* = 2,328, (52,9), NR	Ethical food consumption	Emotional experience of shopping	Purchasing "ethical" or "sustainable" foods is associated with experiencing shopping for food as enjoyable.	Moderate
Vecchio and Annunziata, 2013, Italy	*n* = 500, (58.6), NR	Sustainable food products purchase behaviour	Personality, attitudes, values, lifestyles, demographic and socio-economic characteristics.	Responsible food consumer cluster consisted of: urban citizens, live alone or with other students, medium-high household incomes, higher number of worker-students. Inattentive food consumer cluster consisted of: low degree of knowledge of the main sustainability issues, low-involvement attitude to virtuous lifestyle habits, do not think that their generation is adopting unsustainable consumption patterns, non-urban areas and families with medium household income. Potentially sustainable food consumer consisted of: least satisfied with the available information on sustainable food, majority of students that live in non-urban areas and are part of families with a medium household income.	Moderate

[a]*n, sample size.*
[b]*Examined factors, in addition to demographics such as sex, age.*
[c]*NOS, New-Castle Ottawa Scale.*
[d]*Multiple countries: China, Czech Republic, United Kingdom, Iran, Ireland, South Korea, Macedonia, Norway, Serbia, Spain, and Sweden.*
NR, no reported; M, mean, SD, standard deviation.

behaviours of university students. The results are divided into proposed operational categories of Sustainable Food Consumption (SFC) behaviours. **Figure 2** presents the proposed categories and summarizes the corresponding target behaviours extracted from articles. An exhaustive list of behavioural outcomes was extracted from the selected articles, and data reduction of similar behaviours was performed until reaching saturation.

The articles analysed related to a broad range of sustainable food consumption behaviours of university students, from "farm to dump," reflecting food consumption choices based on a) how food is produced (e.g., organic), b) the environmental impact of food transport or "food miles" (e.g., consumption of local products), c) food packaging, d) specific foods choices or dietary patterns (e.g., plan-based diets, moderate meat consumption), and e) food waste. Most studies in our sample focused on dietary behaviours, followed by food waste. The frequencies of publications per category are presented in the PRISMA flowchart (See **Figure 1**). Outcomes related to air-transported foods avoidance, consumption of seasonal products, or those with low environmental impact (e.g., efficient water, land use, sustainable fisheries) were covered by articles that examined SFC behaviour as an umbrella concept. No studies about cultured meat were eligible for inclusion.

A higher proportion of students already consume organic food, with reports of frequent consumption ranging from 44% [57] to 89%, [58]; seasonal and local food products, reported as the top SFC behaviours by Kamenidou et al. [51] with mean scores of 5.46 and 5.10 out of 7, respectively; avoid some meats (47.4%) [26] or avoided plastic bottled water (34%) [47]. This contrasts with the relatively lower prevalence of self-declared "flexitarians" (15.4%) [33], "pescovegetarians" (11.6%) [33], "semi-vegetarians," 6% [29] to 12.1% [33], vegetarians, ranging from 3.9% [26] to 25% [59], and vegans, ranging from 0.4% [26] to 1.8% [59].

From the Farm: Sustainable Production

Six studies were focused on consumption of organic food (OF) [32, 34, 40, 57, 58, 60]. Three articles reported that knowledge and attitudes about OF had a positive relationship with the purchase and consumption of these foods (Correlation coefficients (r) between 0.24 and 0.28) [32, 34, 58]. Perceived safety, nutritional value and the perception that organic is fresher and has better taste, were also factors correlated with organic food consumption [58]. Positive associations were also found between the knowledge score of students and organic food consumption. McReynolds et al. [34] found that students with

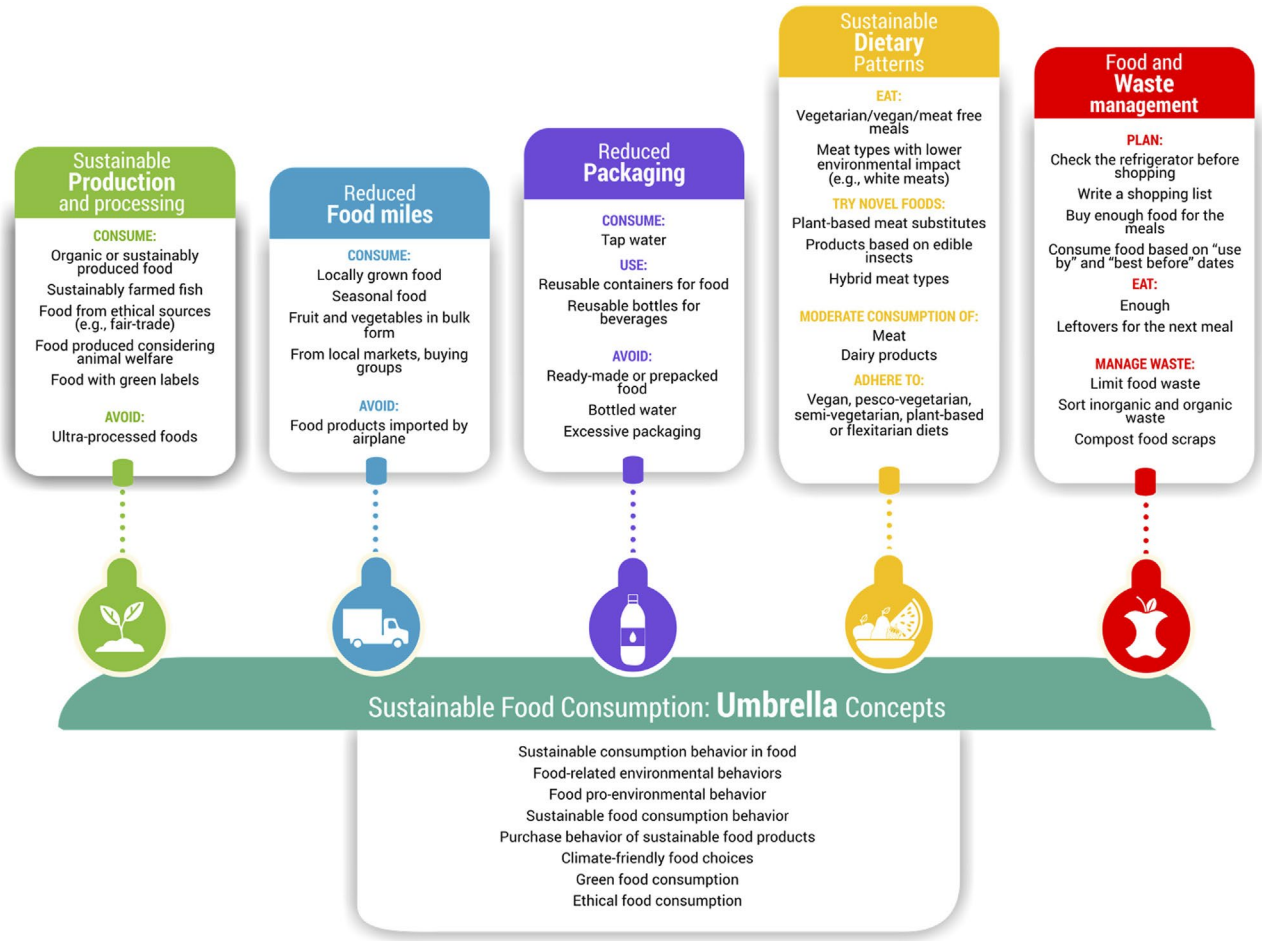

FIGURE 2 | Categorization of Sustainable Food Consumption (SFC) behaviours, and behavioural outcomes extracted from the selected publications after data reduction. (What influences the sustainable food consumption behaviours of university students? A systematic review, several countries, 2021).

experience growing food had a higher frequency of OF purchase consumption ($Chi^2 p = 0.01$) and organic fruit consumption ($Chi^2 p = 0.02$) compared to students without such experience. Females had greater intention to buy organic food but there were no differences in consumption compared to males [34]. A perceived health risk reduction of OF consumption was associated with incremented frequency of OF consumption [40] and Green Perceived Value (GPV) constructs, especially emotional value, had a significant positive effect on purchase intentions, which in turn, had a positive effect on purchase behaviour moderated by food neophobia. In contrast, reported barriers to buying OF were higher price (35.9%), OF perceived as not attractive (20.5%), and distrust in OF being "better" or "non-chemical" (19.8%) [61].

Reduced Food Miles

One study examined the association of local identity, brand valuation and the moderating effect of perceived availability on purchasing four local brands of tomato sauce, rice, mineral water, and a traditional local cake. A direct effect of local identity on effective purchase was only found for the local brand of mineral water, while there was a positive indirect effect of local identity through brand valuation for tomato sauce, rice, and cake brands. This indirect effect was further conditioned to the perceived availability of the tomato sauce and rice brands [45].

Reduced Food Packaging

One article compared the frequency of tap water consumption with the frequency of bottled water consumption. Compared to university faculty and staff, students were the most frequent consumers of bottled water (43.9 and 39.3%, respectively). Agreement (one total disagree to five total agree) with the statement "it is safer to drink bottled water than tap water" varied among bottled water consumers (Kruskal-wallis $p = 0.00$), multiple comparison showed that differences arose from consumers of ≥6 bottles per week having a median of 3 range one to four compared to those consuming one to five bottles per week (Median 2 range 1–2) [47].

The Fork: Sustainable Dietary Patterns

Fourteen articles assessed food-based behaviours. Eleven examined the adherence to full dietary patterns and three

addressed more narrowly the consumption or substitution of meat and animal products.

Studies that examined factors associated with adherence to vegetarian diets [35, 38, 39, 59, 62, 63] found that a vegetarian diet pattern was associated with being female, non-smoker, lower proportion of daily caloric intake from fats, a lower-income, and use of vitamin-mineral supplements. Body mass index (BMI) and physical activity yielded mixed results [35, 38, 59]. Spencer et al. [38], found vegetarians had BMI ≤ 25 [38], Suleiman and colleagues [59] found that vegetarianism was associated with a normal BMI and being physically active among students in Jordan [59], while Olfert et al. [35], did not find significant differences in BMI and physical activity levels between vegetarian and non-vegetarian students in the USA. Surprisingly, Barros et al., in a model adjusted by sex, age, BMI, cohabitants and major, found that students who reported prejudicial alcohol had an 2.6% (95%CI 1.4;4.7) increased odds of adopting vegetarian diet [62], and Olfert et al [35] found higher stress levels among vegetarians.

Forestell and colleagues [64] examined food restraint, demographic, personality and lifestyle characteristics among vegetarian, pesco-vegetarian, semi-vegetarian and flexitarian compared to omnivores. Vegetarians and pesco-vegetarians were more open to new experiences, variety seeking, and had less food neophobia. Vegetarians and pesco-vegetarians did not differ from omnivores in their restraint level, while semi-vegetarians and flexitarians were more restrained than omnivores.

Two studies addressing plant-based diets took a more specific approach to understand factors for successful adherence in the USA, and the role of mindful eating on the adherence to healthful vs. unhealthful plant-based diets in Japan [36, 65]. Successful adherents to a plant-based diet, compared to those who tried without success, had higher levels of value, self-efficacy, planning/stimulus control and positive affect, while self-monitoring and self-criticism were negatively correlated. They were also seventeen times more likely to report "To manage or treat a medical condition," almost seven times more likely to report "To align with my ethical beliefs," and 94% less likely to report "To maintain and/or improve my health."

Students who had higher scores for healthful plant-based diet (hPDI-J) also had higher total "health of the planet" and "awareness and appreciation for food" mindful eating sub-scores. Instead, "non-judgmental awareness" was correlated with a low intake of healthful plant-based foods. Smith et al [39] compared groups of students who had followed vegetarian and/or weight-loss diets and found that the vegetarian group could adhere to their diet for longer. The top reasons to drop the vegetarian diet were missing meat and concerns about nutrient intake [39]. A study in Albania found very low adherence to the EAT-Lancet reference diet and did not find any associations with the factors of interest (BMI, cost and eating out of home) [66]. Lower adherence to the Mediterranean Food Pyramid reference diet and higher meat consumption was found in a cluster of younger students, more females and living with parents [44].

Three articles examined factors concretely related to meat consumption, such as meat avoidance [26], beef consumption [27], and consumption of an insect-based product [41]. A study conducted in 11 countries across Europe and Asia found significant differences regarding the reasons to avoid meat among different groups of meat avoiders. The environment was the main reason for those who avoid some meats; health was the most important reason for most vegetarians, whereas vegans were most concerned about animal welfare-related reasons [26]. Beef consumption frequency was significantly correlated with being male in the USA, France, Brazil, but not in Argentina [27]. Intention and Perceived Behavioural Control (PBC) were the main predictors of tasting an insect-based food product. Students enrolled in social sciences were less likely to taste cricket flour than those in food and environmental sciences [41].

To the Dump: Food and Waste Management

Two main behavioural outcomes were studied. Two studies measured self-reported food waste reduction behaviours (e.g., making a shopping list, using leftovers) [30, 42], while five observed the amount of food waste (plate waste/leftovers) [46, 55, 56, 67, 68], and one assessed both [28].

Three out of the eight articles dealing with food waste reported significant associations with gender. One study in Spain found a significant association between higher food waste and being female [46], while two other studies found that females wasted slightly more meat [67] and staple [56]. Higher-income/living expenses were associated with higher food waste in two studies [42, 56]. Composting [30], "addiction to sales," [28] concerns about food safety, and lack of knowledge about food waste (the belief that only 10% of the food purchased gets thrown away, not knowing that waste is a more serious problem than packaging) [42] were negatively associated with food waste reduction behaviours.

Three papers that examined TPB constructs had mixed results. Alattar and colleagues found that attitudes and intent were the strongest predictors of food waste diversion behaviours among university students in the USA [30]. In contrast, Mondejar-Jimenez et al. [28] found among their student sample in Italy and Spain that the strongest predictor of (correct) behaviour towards food waste were subjective norms followed by PBC. Wu et al. [56] found that more food was wasted in association with low PBC in China, while subjective norms and attitudes had no significant association.

Lorenz et al. [55] explored personal, social and environmental (situational) determinants associated with leftover behaviour, revealing interactions between personal and environmental factors. While time pressure was not a direct environmental determinant of leftovers, being female becomes a significant determinant for this behaviour among students under time pressure. There was a significant relationship between perceptions of food (portions size and palatability) and food leftovers. No significant association was found between the presence of others and food leftovers. In a later study, the

same authors, also in Germany [68], broke down attitudes into more specific subsets of beliefs (self-interest, pro-environmental, resource efficiency), finding interactions between situational variables and self-interested beliefs.

Umbrella Concepts

Ten of the included articles addressed SFC, integrating different behaviours measured by an index, composite measure or score (See **Supplementary Material**). Students "in a relationship" had higher SFC levels than "single" (Mean Difference = −0.16, $p < 0.05$) [49]. High levels of "environmental awareness and action" (engaging in other behaviours such as energy-efficient cooking, avoid plastic waste, and sorting inorganic and organic food) ($\beta = 0.46$, $p < 0.05$) [49], intention ($\beta = 0.74$, $p < 0.001$), perceived seriousness of consequences of climate change ($\beta = 0.10$, $p < 0.05$) [52], biospheric value orientation (BVO) ($\beta = 0.28$, $p < 0.001$), and environmental beliefs ($\beta = 0.24$, $p < 0.001$) [31] were associated with SFC behaviours. Attitudes ($\beta = 0.28$, $p < 0.001$) and knowledge on the environmental impact of food consumption ($\beta = 0.14$, $p < 0.01$) also were associated with SFC [50]. Being male was associated with lower SFC behaviour in two samples of students in the United States ($\beta = -0.11$, $p < 0.05$) [31] and Finland (β = -0.13, $p < 0.01$) [52]. There were no significant differences in green food consumption between Muslim and non-Muslim students in Malaysia, despite significant differences in personal needs, environmental values and perceptions about government efforts related to green food [54]. No other demographic characteristics were significant predictors of SFC.

Two groups of researchers took a factor analysis approach to identify student segments. Kamenidou et al. [51] identified two segments based on SFC behaviour, social norms, and ethical behaviour: "The under-consideration students" and "The negatively positioned students". None of the segments show higher SFC levels, but the first and larger segments were positively predisposed towards it. Frequent SFC behaviours were limited to seasonal and local food consumption. Vecchio and Annunziata [43] identified three clusters: "responsible food consumer" (urban citizens, live alone or with other students, medium-high household incomes, higher amount of worker-students), "inattentive food consumer" (low degree of knowledge of sustainability issues, low-involvement attitude to virtuous lifestyle habits, and medium household income), and "potentially sustainable food consumer" (least satisfied with the available information on sustainable food, majority of students that live in non-urban areas, medium household income). Under the label of "ethical food consumption," Schoolman [37] measured purchase frequency of products that can fall into SFC (locally grown/processed food, organic food, fair trade food, food from humanely treated animals, and fish from sustainable fisheries). This study found that, for each additional point on the ethical food consumption index, students were 51.1% more likely, to declare they enjoyed shopping food daily.

Quality Assessment

Scores for the included papers ranged from 3 to 8, out of 10 possible points, with a median of 5 points; 75% of the articles were classified as low quality and 25% rated moderate. Out of the 17 studies that implemented regression methods, seven adjusted or stratified by sex or age. Thirty-nine studies did not report the response rates, and 26 did not justify the sample size. The quality assessment scores of selected studies are listed in the supplementary material.

DISCUSSION

Based on data from 40 included publications, we found that literature evaluating the related factors associated with SFC behaviours has focused mainly on personal factors, such as intention, knowledge, attitudes, lifestyle, values and beliefs, and there is scarce evidence on social and environmental (situational) factors.

A higher proportion of students already consume organic, seasonal and local food, fewer avoid some meats, and there is a relatively low prevalence of self-declared "flexitarians," "pescovegetarians," "semi-vegetarians," vegetarians, and vegans. This shows a higher reported adoption of SFC behaviours with lower planetary health potential: while the sustainability of organic food can be limited [69] and organic production is only one of many forms of sustainable agriculture, the livestock sector contributes to an estimated 14.5% of the total human-induced GHG emissions [70].

Underlying Factors and Characteristics of Sustainable Food Consumers

Except for food waste [46, 56], being a woman was reported as a factor related to SFC [31, 59], but situational factors moderated this association (e.g., time pressure) [55]. Factors such as knowledge and attitudes yielded mixed results. Concern about food safety was positively associated with organic food consumption [58] but negatively associated with food waste prevention [42]. Composting was associated with higher food waste [30].

Concerning lifestyles, sustainable consumers tended to have healthier lifestyles, better dietary habits [35, 38, 59], and enjoy food shopping more [37] than less sustainable consumers. Similarly, students were able to adhere to vegetarian diets for longer than to weight-loss diets [39]. However, weight control and food restraint associated with SFC require further analyses as they can incur health risks, and the healthfulness and sustainability of eating behaviours are often dose-dependent. Two studies found that vegetarians had higher levels of stress [35] and prejudicial alcohol consumption [62], in samples of university students in the United States, and Brazil. These adverse associations deserve further examination. Similar attention is needed about the consumption of plant-based meat substitutes, included as outcome in one of the selected studies [51] as they have the benefits of vegetable consumption but can be highly processed.

Significant associations were found between knowledge and outcomes for organic food consumption [34] and making a shopping list (food waste prevention) [42]. Conversely, the lack of knowledge on the environmental impact of food was associated with less sustainable food consumption [50]. In

particular, participants underestimated the environmental impact of meat consumption [50] and food waste [42], and overestimated the impact of other behaviours such as food packaging [42]. This low awareness about the environmental impact of food choices is aligned with previous findings [71]. Other studies did not find significant associations between knowledge and organic food consumption [32, 58], suggesting the need for further examination to disentangle the mechanisms involved in knowledge as a predictor of behaviour.

Behavioural outcomes, such as meat reduction and avoidance, were associated with different factors depending on the reported motivations for eating behaviour (health, environment, animal rights). This is compatible with literature on factors linked to different eating motives [72, 73].

Operational Categorization of Sustainable Food Consumption Behaviours

There is still a lack of operational, standardized behavioural definitions of sustainable food consumption from the consumer perspective [12, 74]. Dietary behaviours, such as adherence to vegetarian or flexitarian diets, followed by food waste, were the most studied behavioural categories. While the categories are not meant to be exhaustive, they cover a diverse variety of behaviours.

The lack of behavioural measures was a common reason for exclusion of otherwise eligible studies. Measuring behaviour can be challenging when studying food intake, especially when these behaviours are uncommon (e.g., cultured-meat, edible insects, meat-mushroom blends). Menozzi et al. [41] on cricket flour presents a sound methodological solution to overcome this problem. Behavioural data collected in virtual reality is also a promising alternative as data can be comparable to real-life consumption data [75].

Strengths and Limitations

To the author's knowledge, this is the first literature review integrating a broad range of sustainable food consumption behaviours for a specific population. This comes with the challenge of synthesizing a diversity of outcomes measured in different ways, as studies included were highly heterogeneous, which was a barrier for meta-analysis. However, examining SFC as an umbrella concept, allowed identifying possibly conflicting interactions between different behaviours and factors that would not be possible when reviewing articles for a single target behaviour. We followed a strict definition of behavioural outcomes, excluding studies that did not include self-reported or observed behavioural measures. This was essential to answer the main research question but excluded many otherwise eligible studies that measured acceptance, willingness, attitudes, or behavioural intention, possibly affecting the geographic coverage and variety of target behaviours captured by the review.

The selected studies covered three continents and 30 countries in all income economies levels. Relevant studies that exceeded the scope of this review, e.g. qualitative, case studies, focused on awareness, etc., have been conducted in other countries [18, 76–85]. Since most of the selected studies rely on convenience sampling, generalizations about the country population are not possible. Yet, relative homogeneity of the population supports conclusions about young adults and university students with caution.

The examination of social and situational factors is rather neglected in the selected studies at hand. This may be due to higher interest in personal factors, the fact that some social or environmental/situational factors are classified as personal, but it may also be due to the observational nature of the study designs covered in this review. Other reviews conducted on experimental study designs on meat consumption, for example, yielded more balanced proportions of personal and environmental/situational determinants [86–88].

Conclusion

Our findings support previous evidence about the health and environmental co-benefits of sustainable food consumption [7–10], from the consumer behaviour perspective. Healthy lifestyles of sustainable food consumers suggest possible synergies between environmental and health motivations of food choice and longer-term adherence to healthy diets. Future research areas can examine the effects of communication framings that emphasize the individual health or pro-social environmental benefits of SFC in different populations. There is also a need to further examine the behavioural aspects related to the co-benefits and also the management of risks associated to SFC, at the lifestyle and health outcomes level. Social norms [89, 90], including related variables as eating with others, and situational factors such as time pressure, portion size, palatability [55], availability of sustainable alternatives, food repositioning or labelling [86] deserve further examination. The moderation effects of social and environmental factors on personal factors related to sustainable food consumption reveal opportunities to design choice architecture interventions. Future research could evaluate the interaction between possibly conflicting predictors of different SFC behaviours, the disentangling mechanisms behind attitudes and knowledge as a predictor of behaviour, and the factors to adopt SFC in male consumers.

Practical implications include: for universities, the need for monitoring the effects of their food environments, and situational factors, on the food choices of students; for key actors in the production side of the food chain, the almost absent sustainable produced food consumption alternatives, beyond organic food, show the need for more transparency about other aspects of production sustainability that are increasingly relevant for young consumers; and for food policy actors this work adds to the growing body evidence about diverse SFC behaviours that can be promoted to advance health and sustainability targets. The proposed categorization of behaviours is not meant to be exhaustive but contributes to the behavioural operationalization of sustainable food consumption including but not limited to sustainable diets.

From a planetary health perspective, the sustainability of food consumption becomes a pressing public health issue, as it is recognized that adverse effects on population health result from unsustainable and unhealthy food consumption. This urgency is consistent with an evolving view of sustainable development that acknowledges that healthy economies and societies depend on the life-sustaining capabilities of the ecological system [91].

AUTHOR CONTRIBUTIONS

LAS and ZR-D designed the research and led the review team; BM and DK-H developed and updated the search strategies; LAS, ZR-D, MB, AM, MG, BM-U, GG, and AR conducted screening and data extraction; LAS and ZR-D analysed the data and wrote the manuscript. LSS, OF, LAS, ZR-D, MB, AM, MG, BM-U, GG, and AR were involved in interpreting the results and editing the manuscript. LSS and OF supervised the research. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2021.1604149/full#supplementary-material

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7.2. Gene-diet interactions and cardiovascular diseases: A systematic review of observational and clinical trials

Gene-diet interactions and cardiovascular diseases: A systematic review of observational and clinical trials

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ABSTRACT

Background: Both genetic background and diet are important determinants of cardiovascular diseases (CVD). Understanding gene-diet interactions could help improve CVD prevention and prognosis. We aimed to summarise the evidence on gene-diet interactions and CVD outcomes systematically.

Methods: We searched MEDLINE® via Ovid, Embase, PubMed®, and The Cochrane Library for relevant studies published until May 7th 2021. We considered for inclusion cross-sectional, case-control, prospective cohort, nested case-control, and case-cohort studies as well as randomised controlled trials that evaluated the interaction between genetic variants and/or genetic risk scores and food or diet intake on the risk of related outcomes, including myocardial infarction, coronary heart disease (CHD), stroke and CVD as a composite outcome. The PROSPERO protocol registration code is CRD42019147031.

Results and discussion: We included 54 articles based on data from 29 studies; six articles involved multiple studies, and three did not report details of their source population. The median sample size of the articles was 2562 participants. Of the 54 articles, 19 (35.2%) were qualified as high quality, while the rest were intermediate or poor. Eight (14.8%) articles adjusted for multiple comparisons, four (7.0%) attempted to replicate the findings, 15 (27.7%) were based on Han-Chinese ethnicity, and 28 (52%) did not present Minor Allele Frequency. Forty-nine different dietary exposures and 47 different genetic factors were investigated, with alcohol intake and ADH1C variants being the most examined. Of 249 investigated diet-gene interaction tests, 47 (18.9%) were statistically significant, including CETP-TaqIB and ADH1C variants, which interacted with alcohol intake on CHD risk. However, interactions effects were significant only in some articles and did not agree on the direction of effects. Moreover, most of the studies that reported

significant interactions lacked replication. Overall, the evidence on gene-diet interactions on CVD is limited, and lack correction for multiple testing, replication and sample size consideration.

Keywords: diet; gene-diet interaction; myocardial infarction; stroke; coronary heart disease; cardiovascular diseases

Glossary

Abbreviation	Definition
AA	Arachidonic acid
ABCA1	ATP binding cassette subfamily A member 1
ACE	Angiotensin-converting enzyme
ADH1C/ ADH3	Alcohol dehydrogenase 1C (Also known as: ADH3)
ALA	Alpha-linolenic acid
ALDH2	Aldehyde dehydrogenase 2
APOE	Apolipoprotein E
BCO2	B-carotene 9',10'-oxygenase
CCHS	Copenhagen city heart study
CETP	Cholesteryl ester transfer protein
CGPS	Copenhagen general population study
CHD	Coronary heart disease
CI	Confidence interval
CLOCK	Circadian locomotor output cycles kaput
CRP	C-reactive protein
CVD	Cardiovascular diseases
CYP1A2	Cytochrome P450 family 1 subfamily A member 2
DHA	Docosahexaenoic acid
ECTIM	Etude Cas-Témoin de l'Infarctus du Myocarde
EPA	Eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
FADS1	Fatty acid desaturase 1
FFQ	Food Frequency Questionaire
Fgβ	Fibrinogen beta chain
FISSIC	Fangshan/Family-based Ischemic Stroke Study in China
Fto/FTO	Fat mass and obesity
GESUS	Danish general suburban population study
GRS	Genetic risk score
GSTs	Glutathione-S-transferase
GSTT1	Glutathione S-transferase theta 1
HDI	Healthy diet indicator
HDL	High-density lipoprotein
HPFS	Health Professionals Follow-up Study
HR	Hazard ratio
IL-6	Interleukin 6
IL-8	Interleukin 8
INTERGENE	Interplay between genetic susceptibility and environmental factors on the risk of chronic diseases in West Sweden
KIHD	Kuopio ischemic heart disease risk factor study
LA	Linoleic acid
LCT	Lactase
LDL	Light density lipoprotein
LPL	Lipoprotein lipase

MDC	Malmö Diet and Cancer cohort
MDS	Mediterranean diet score
MI	Myocardial infarction
MMAB	Methylmalonic aciduria (cobalamin deficiency) cblB type
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MTHFD1	Methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1
MTHFR	Methylenetetrahydrofolate reductase
MVK	Mevalonate kinase
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NHS	Nurses' health study
OR	Odds ratio
PDE4D	Phosphodiesterase 4D
PON1	Paraoxonase 1
PUFA	Polyunsaturated fatty acids
RERI	Relative Excess Risk due to interaction
RFS	Recommended food score
RR	Risk ratio
SFA	Saturated fatty acids
SHEEP	Stockholm heart epidemiology program
SNP	Single nucleotide polymorphism/genetic variant
SSB	Sugar-sweetened beverage
TaqIB	Polymorphism in the cholesteryl ester transfer protein (CETP) gene
TFPI-2	Tissue factor pathway inhibitor-2
TRIB1	Tribbles pseudokinase 1
TWB	Taiwan biobank
VLDL	Very low-density lipoprotein
WENBIT	Western Norway B-vitamin intervention randomised trial
WHS	Women's health study
β-actin (ACTB)	ACTB actin beta
5-LO	5-lipoxygenase

INTRODUCTION

Cardiovascular diseases (CVDs), including ischemic heart disease and stroke, are the leading cause of mortality and morbidity and are responsible for more than 18 million deaths globally in 2019 [1]. Several risk factors have been associated with CVD incidence, diet being one of the most studied [2].

Contradictory findings have been reported on the role of micro-and macro-nutrients [3], specific foods [4], and dietary patterns [5] on CVD. These contradictions could be explained by the exclusion of genetic factors [6], which has a causal association with CVD onset [7-9]. Therefore, studying the combined impact of food intake/dietary patterns and genetic risk on CVD may improve CVD prevention and care precision [10]. Several studies have shown dietary components such as carbohydrates, micronutrients, vegetables, fatty acids, and alcohol to be linked with different genetic factors on CVD [11-17]. However, no systematic review summarising the evidence on diet-gene interaction on CVD has been published to date.

Previous systematic reviews published on the topic have primarily focused on evaluating gene-diet interactions on specific genes or have been restricted to particular dietary groups [18,19]. In addition, understanding the association between pathological pathway factors requires distinguishing between statistical and biological interactions. In the context of gene-environment interaction (GxE), statistical interaction is understood as a deviation from the additivity of the effects of two exposures (genetic and environmental) on the outcome. In contrast, biological interactions are defined as the co-participation of two exposures in the same causal mechanism for the development of the outcome, regardless of their statistical ascertainment [20]. This paper focuses on statistical interactions, more frequently tested in the epidemiological literature [21]. Identifying exposure-disease interactions may help recognise groups at increased risk due to

genetic susceptibility and help tailor prognostic tools and intervention strategies [22]. Therefore, we aimed to systematically summarise the evidence on gene-diet interactions and cardiovascular disease risk: CHD, myocardial infarction (MI), stroke, and CVD as a composite outcome.

2. METHODS

The protocol of this systematic review was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/dayisplay_record.php?ID=CRD42019147031). For the conduct and reporting of this systematic review, we followed the steps proposed by Muka et al.[23] and Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline [24].

2.1 Literature search

Studies were primarily identified through structured searches in MEDLINE® via Ovid, Embase, PubMed®, and The Cochrane Library, where we were searched for articles published until May 2021 without language restriction. The search strategy was designed and implemented in collaboration with an experienced medical librarian. This search strategy was designed based on subject headings (e.g. MeSH terms) and free text words related to three search domains: 1) diet, food, nutrition, 2) gene-diet interaction, and 3) cardiovascular diseases. Appendix S1 contains the complete search strategies.

2.2 Study Selection Criteria

Studies conducted in the adult population were eligible for inclusion if (i) they were cross-sectional, case-control, prospective cohort, nested case-control or case-cohort studies, or randomised controlled trials; (ii) evaluated dietary intakes (micro- and macro-nutrients, specific food items, food groups, dietary scores, indexes, or patterns) Table S1 [25]; (iii) evaluated incident or prevalent CVD as a composite outcome or any of the following outcomes: CHD, MI or stroke;

(iv) evaluated the interaction between any genetic variant or genetic risk score (GRS) and food or diet intake; and (v) reported a statistical test for gene-diet interaction. We excluded epigenetic studies and publications that did not report a statistical test and p-values for the interaction between diet and genetics. Abstracts, cost-effectiveness studies, letters to the editor, conference proceedings, systematic reviews and meta-analyses were excluded.

2.3 Screening and study selection

All studies initially identified were screened by pairs of independent authors by applying the selection criteria. After that, the full texts of the studies that met the selection criteria were further evaluated independently by two authors. When there were discrepancies, the two authors reached a consensus or asked for the help of a third senior author.

2.4 Data extraction

Information from the included articles was registered in a pre-designed form. We collected the author's name, year of publication, country of origin of the population, ethnicity, setting, study design, name of the cohort, sample size, number of cases (CVD as a composite outcome, CHD, MI, or stroke), definition of the reported cases, percentage of women included, follow-up time, dietary intake evaluated, dietary intake measurements, genes, genetic variants assessed, minor allele frequency (MAF), and main findings. The estimates and p-values for gene-diet interactions were taken from the most adjusted model.

2.5 Assessing the quality of studies

We applied a quality score designed for gene-diet interaction studies [26]. The score evaluates eight items: interaction as primary study goal, test for interaction, correction for multiple testing, correction for ethnicity, Hardy-Weinberg equilibrium, test for group similarity at baseline,

sample size, and sufficient details of the study procedure. Based on a range scale from -8 to 8, studies were rated as high quality (6 to 8 points), intermediate quality (2 to 5 points), and poor quality (−8 to 1 point). All the included studies were treated equally regardless of their quality.

2.6 Synthesis methods

A meta-analysis could not be carried out given the diversity of dietary exposures, gene-diet interactions, and the methodological heterogeneity of the included studies (different dietary exposures, gene variants and assessed interactions). We summarised the gene-diet interactions finding qualitatively and decided to group the included studies in two stages. First, we grouped the studies according to the assessed outcome into the following categories: CHD, stroke, and CVD as a composite outcome. Second, we presented the gene-diet interaction information according to five dietary intake groups (macronutrients, micronutrients, food and food items categories, other dietary components and dietary scores, indexes, or patterns) Table S1 [25].

The principal characteristics and findings of the included studies are presented in tabular format. Additionally, we represented the interaction between dietary intake groups and genetic variants with CHD, stroke, and CVD through a heat map where p-values of diet-gene interactions are represented by colour intensity where the lowest p values have the most intense colour, and values near 1 have the lightest colour. To standardise the amount/frequency of alcohol intake reported in the interaction with an alcohol dehydrogenase 1C (ADH1C) variant, we transformed grams/day into drinks/week taking as reference the "standard" drink (14 grams of pure alcohol) reported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [27].

3. RESULTS

3.1 Study Identification and Selection.

We identified 7671 articles, of which 4753 were unique citations. After screening titles and abstracts, we screened the full texts of 177 articles, of which 54 met the inclusion criteria and were included in the final analysis (Figure 1). Of the included articles, 13 evaluated MI [16,28-39], 17 evaluated CHD [11-13,40-53], ten evaluated stroke [14,54-62], four examined composite CVD [15,63-65], and ten evaluated at least two of the following outcomes: CHD, MI, CVD or stroke [6,17,66-73]. The definition of all outcomes can be found in Table S2.

3.2 Characteristics of all Included Studies and articles reporting significant gene-diet interactions.

The general characteristics are described in terms of number of articles. Forty-five articles came from 29 unique studies; six articles involved multiple studies, and three did not report details of their source population. Of the 54 articles, 23 (42.6%) were conducted in Europe, 18 (33.3%) in China, six (11.1%) in the USA, five (9.3%) in Costa Rica, one (1.9%) in Taiwan, and one (1.9%) was multicentre. The ethnicity most frequently reported was Chinese-Han in 15 (27.7%) articles, followed by Caucasian in seven (13.0%) articles, Hispanic/Latin American in five (9.2%) articles, and Mediterranean in four (7.4%) articles. The epidemiological designs of the included articles comprised 23 (42.5%) case-control studies, 18 (33.3%) prospective cohort studies, seven (13.0%) nested case-control studies, one (1.9%) case-cohort study, two (3.7%) randomised control trial studies, two (3.7%) family-based studies, and one (1.9%) cross-sectional study. The median sample size in the articles was 2562, ranging from 200 to 347,077 participants. Men and women were analysed in 48 (88.9%) articles; five (9.2%) articles analysed only men, and one (1.9%) article only women. The main interaction results among female study participants were presented in nine (17.0%) articles. The median age of participants among studies was 61 years, ranging from 57 to 72.4 (Table 1).

There were 47 genetic factors (GRS, genes, SNPs) and 49 different dietary exposures studied. A description of the dietary scores, indexes, or patterns reported can be found in Table S2. The most investigated dietary component was alcohol, studied in 26 (48%) articles, and ADH1C studied in 7 (13%) articles. Regarding genetic information, 28 (52%) articles did not present MAF (Table S2). Regarding outcome measurement, 24 (44%) articles included prevalent CVD cases, and 30 (56%) articles included the incidence of CVD cases. Overall, the median CVD events was 759, ranging from 72 to 10,372. Four (7.0%) articles replicated their findings in different samples (Table 1).

Characteristics of included articles reporting significant gene-diet interactions

In total, 29 articles reported significant gene-diet interactions. Among the articles reporting significant interactions, the most frequent place of publication was China with 10 (33%) articles, followed by Europe with nine (30%) and Latin America with five (17%). The case-control design was reported in 18 (62%) articles; the median sample size was 3311, ranging from 200 to 77,004. Four (14%) articles evaluated the interaction between alcohol and the cholesterol ester transfer protein (CETP) rs708272 variant, being this interaction the most frequently evaluated.

3.3 Gene-diet interactions and coronary heart disease.

Thirty articles from 21 unique studies evaluated whether specific nutrients, foods or diets modified the association between genetic factors and CHD (Figures 2 and 3, Table 1) [11-13,16,28-53]. The most frequently evaluated dietary exposure and genetic variants were alcohol (n=17) and *ADH1C* (n=6), respectively. *CETP* TaqIB was the second most evaluated genetic variant; estimations for alcohol-*ADH1C and -CETP* interactions on CHD risk can be found in Table 2. The main findings regarding non-significant interactions in the macronutrients category were that PUFA intake did not interact with PLA2G4C, FADS1 or FTO variants on CHD risk. Micronutrients

such as folate and vitamin B did not interact with the *MTHFR* 677CT variant. Other non-significant interactions were milk-LCT-13910, fried food-*ALDH2*, (dietary) cholesterol-*APOE*, alcohol-*ADH1C*, -*CETP*, -*PON1*, -*PLAG2G7*, -*TFPI-2*. Similarly, dietary scores did not significantly interact with GRS of HDL, LDL, triglycerides, or MI [6,11-13,17,33,37,41-45,49-53,66,70,73]. An overview of the non-significant interactions can be found in figures 2 and 3, and more details are provided in Table S3. In the following paragraphs, we will discuss the findings of the articles that reported significant interactions.

Regarding macronutrients, in a Costa Rican case-control study including approximately 3800 patients, Allayee et al.[28] reported a significant (p=0.015) interaction between arachidonic acid (AA) and 5-lipoxygenase (*5-LO*) promoter variants [28]. Consumers of ≥0.25 g/day of AA who carried one or two copies of the shorter three and four repeats of *5-LO* had a higher MI odds ratio (OR) 1.31 (95% CI 1.07, 1.61) than consumers of <0.25 g/day of AA who are 55 homozygote carriers. In comparison, among consumers of <0.25 g/day of AA who were carriers of one or two copies of the shorter three and four repeats, lower odds was observed [OR 0.77 (95% CI 0.63, 0.94)] [28]. In the same study, Hartiala et al. found a significant (p=0.005) interaction between PUFA and a variant of *PLA2G4C* (rs12746200) [33]. Subjects with high dietary n-6 PUFA intake (≥6.93 g/day) who were carriers of AG/GG genotype had lower odds for MI [OR 0.71 (95% CI 0.59, 0.87)] than AA homozygote subjects [33].

In a case-control study using Wuhan (China) data, Liu F et al.[46] found a significant (p=0.028) interaction between PUFA and a variant of *FADS1* (rs174547). Subjects in the lowest tertile of EPA and DHA intake who are carriers of T alleles had higher odds of developing CHD [OR 3.04 (95% CI 1.94, 4.76)] and [OR 2.56 (95% CI 1.64, 3.98)], respectively, compared to subjects in the

highest tertile of EPA intake and DHA consumption, who are also carriers of rs174547 C/C genotype. No association was observed in the middle tertile of EPA or DHA intake [46].

Regarding micronutrients, the Western Norway B-vitamin intervention randomised trial (WENBIT) prospectively evaluated interactions between folic acid, vitamins B12/B6 and an *MTHFD1* variant (rs1076991) in 2381 participants [16]. In this trial, carriers of the rs1076991 T allele who received folic acid/vitamin B12 and vitamin B6 combined treatment had a hazard ratio (HR) for MI of 2.35 (95% CI 1.55, 3.57) (p=0.047) when compared to the placebo group. On the other hand, no association with MI was observed in the groups who had vitamin B6 or folic acid/B12 separately [16].

In the food and food items categories, a case-control study using data from 52 countries (the INTERHEART study)[17], and a case-control study analysing data from a Hispanic population [30], reported interactions between high vegetable intake and four variants (rs10757274, rs2383206, rs10757278, rs1333049) of the chromosome 9p21 [17] and the Glutathione S-transferase theta 1 (*GSTT1*) gene variants [30]. Subjects whose vegetable intake was classified in the highest tertile who were carriers of the functional GSTT1*1 allele had lower odds for MI [OR 0.70 (95% CI 0.58, 0.84)] compared to those whose intake was classified in the lowest tertile (p=0.006) [30]. In contrast, carriers of risk alleles of 9p21 variants had a lower incidence of MI among participants who consumed vegetables daily (p<0.008) [17]. However, the interaction with 9p21 variants was not significant when restricted to cooked vegetables [17].

In a case-control study using data from the same Hispanic population mentioned above, Cornelis et al. reported a significant (p=0.04) interaction between coffee consumption and *CYP1A2* variants on MI risk [31]. The consumers of ≥4 cups/day of coffee carrying the rs762551 variant had higher odds of MI [OR 1.64 (95% CI 1.1, 2.34)][31] compared to those consumed <1 cup/day.

Conversely, a study from Taiwan Biobank (TWB) found a significant (p=0.03) interaction between coffee consumption and a tribbles pseudokinase 1 (*TRIB1*) variant rs17321515 on CHD. Those who drank coffee and were carriers of the GG genotype had reduced odds of CHD [OR 0.62 (95% CI 0.45, 0.85)] compared with non-coffee drinkers [47].

Concerning other dietary components, in a case-control study from the *Etude Cas-Témoin de l'Infarctus du Myocarde* (ECTIM) (n=724), alcohol consumption significantly (p<0.005) interacted with the *CETP* TaqIB variant (rs708272). Subjects who consumed 50g/day or more alcohol and were TaqIB B2B2 homozygotes had a lower odds of MI [OR 0.39 (95% CI 0.20, 0.75)] compared with those who consumed <50 g/day. Additional analysis comparing different alcohol intake categories through B2B2 heterozygotes with B1B1 and B1B2 genotypes found that the protective effect of B2/B2 genotype was significant (p<0.02) in the category of ≥6 drinks per week, Table 2 [32]. Three more authors reported interaction between alcohol and the same variant [12,42,48]. Jensen et al. [12] reported a significant interaction (p=0.02) among drinkers of 5–14.9 g/day of alcohol who were B2 carriers, who had a lower odds of MI [OR 0.7 (95% CI 0.6, 1.0), compared with non-drinkers, however, no significance was observed when the analysis was stratified by sex [12]. Similarly, Mehlig et al. [48] reported that subjects classified in the second [OR 0.21 (95% CI 0.10, 0.44)] and third tertile [OR 0.48 (95% CI 0.26,0.88)] of alcohol intake who were B2/B2 homozygotes had lower MI odds (p=0.008), compared with those in the first alcohol intake tertile. When the analysis was performed by sex, significance was only reported in men[48]. Conversely, Corella et al. [42], evaluating the effect of alcohol consumption and the TaqIB variant, found that B2/B2 homozygotes had an increased odds of CHD [OR 1.55 (95% CI 1.05, 2.29), p= 0.031], compared with B1B1 genotype [42], Table 2.

Similarly, a nested case-control study from the Physicians' Health Study (n=1166) reported a significant (p=0.01) interaction on MI risk between alcohol consumption and ADH1C. The lowest risk was observed in those who consumed ≥1 drink per day and carried ADH1C ($\gamma 2\ \gamma 2$), compared with those who consumed <1 drinks per week [RR 0.14 (95% CI 0.04, 0.45)] [34]. Other studies evaluated the interaction between alcohol and ADH1C but reported no significant interactions (Table 2 and S3).

Han Chinese population matched case-control studies found increased risks of MI due to the interaction of alcohol consumption with the *CXCL12* rs1746048 and *PCSK9* rs11206510 variants [29,38] ($p<0.001$). Participants with the rs1746048 CC genotype and rs11206510 TT genotype consuming 0-250 g/day of alcohol had an MI OR of 14 (95% CI 3.2, 61.4) and 9.63 (95% CI 3.7, 24.9), respectively [29,38], compared to non-drinkers. By contrast, within the same categories of alcohol intake, carriers of the *Cx37* variant rs1764391 with CC genotype had an OR 0.54 (95% CI 0.31, 0.9) [35]. An increased odds of MI was observed between those consuming ≥250 g/day alcohol who carried the rs1764391 CC genotype, rs1746048 CC genotype, and rs11206510 TT genotype, with ORs of 32.7 (95% CI 4.4, 241.6), 24.0 (95% CI 4.9, 116.3), and 14.0 (95% CI 5.1, 42.1), respectively [29,35,38].

A case-control study by Zheng et al.[39] analysed data from a Hispanic population and reported a significant (p=0.03) interaction between SSB consumption and the GRS of 9p21 variants (rs4977574, rs2383206, rs1333049). The OR of an MI incident (per allele risk of GRS) was 1.00 (95% CI 0.94, 1.07) in participants with SSB intake of <1 serving/day, 1.07 (95% CI 0.99, 1.14) in participants with an intake of 1–2 servings/day, and 1.12 (95% CI 1.05, 1.20) in participants with an intake of >2servings/day [39]. Additionally, a case-control study from the Nanning province (China) showed that participants who consumed alcohol and were carriers of the mevalonate

kinase *(MVK)* variant rs3759387 with AA/AC genotypes had reduced odds of having CHD [OR 0.66 (95% CI 0.38, 1.03, p< 0.001], compared to non-drinkers [72]. On the contrary, a study performed in Wuhan (China) found a significant (p=0.001) interaction between alcohol intake and Interleukin-6 (*IL-6*) variant rs1800795; current drinkers who were carriers of the rs1800795-C allele had an OR of 3.17 (95% CI 2.20, 4.24) [40], compared to never-drinkers.

In terms of dietary scores/indices, in a prospective analysis comprising 77004 participants from the UK Biobank, Livingstone et al. [71] reported a marginal (p=0.049) interaction between Healthy Diet Indicator (HDI) (Table S2) and GRS-CVD. In addition, the study found a significant (p=0.026) interaction with the MDS and GRS-CVD on the risk of MI (Table S2); individuals adhering to the Mediterranean diet (high MDS) with higher genetic CVD risk had a stronger risk reduction [HR 0.91 (95% CI 0.85, 0.97)]. In comparison, there was no evidence of an interaction of MDS on MI in participants with low GRS-CVD [HR 1.03 (95% CI 0.94, 1.12)] [71].

3.5 Gene-diet interactions and stroke.

Eighteen articles from 14 unique studies evaluated whether specific foods or diets modified the association between genetic factors and stroke (Figure 4, Table 1) [6,14,54-62,67-73]. Non-significant interactions were reported for alcohol intake and *APOE, IL-8* variant, *PDE4D*, *CONNEXIN37* genes. Similarly, different dietary scores did not interact with *CLOCK* gene variants or GRS-CVD and GRS-stroke [57,60-62,67,70,72], Table S3.

In the macronutrients category, the MDC cohort study evaluated interactions between fatty acids and the *FADS1* rs174546 variant. This study found that only the interaction between ALA and FADS1 rs174546 TT genotype was significant (p=0.03). Participants in the higher ALA consumption quintile carriers of TT genotype had a decreased risk of stroke [HR 0.50 (95% CI

0.27, 0.94)], compared to carriers of the TT genotype in the lowest quintile of ALA intake. At the same time, no association was observed in CC and CT genotypes in the other quintiles [6].

Within the food and food items categories, the FISSIC found a significant (p=0.006) interaction between the egg intake and ABCA1 variant (rs2066715) [59]. In the same study, a significant interaction between vegetable intake and the *PON1* rs662 variant on the risk of stroke was found. Each standard deviation increment in vegetable intake was associated with a 40% reduction in the risk of stroke among carriers of the *PON1* rs662 AA genotype. On the contrary, each standard deviation increment in vegetable intake was associated with a 51% increased risk of stroke among rs662 GG carriers; after adjustment for fruit intake, the interaction was not significant (p=0.12) [56].

Concerning other dietary components, a case-control study from Beijing in China found a significant (p=0.001) interaction between alcohol and *CRP* variant rs3093059. Drinkers with the rs1800947 GC [OR 11.11 (95% CI 1.22, 100.45)] and GG genotypes [OR 2.99 (95% CI 1.73, 5.19)] had an increased odds of having a stroke compared with non-drinkers and carriers of GG genotype. On the other hand, non-drinkers with the rs1800947 GC genotype had an OR of 2.95 (95% CI 1.05, 8.29) [54]. Similarly, another case-control study in a Chinese Han population found a significant (p=0.003) interaction between drinking status and the *Fgβ* 148CT variant. Drinkers who are also carriers of CT/TT genotype had increased odds of having a stroke (OR 22.7 (95% CI 2.95, 173.76) compared to non-drinker carriers of the CC genotype [55]. Another case-control study from the Community Hypertension Survey in the Chinese city of Yixing found a significant (p=0.048) interaction between drinking status and rs852426 β-actin (ACTB) variant on stroke risk [HR 0.54 (95% CI 0.29, 0.99)][14]. Another Han population case-control study found a significant (p=0.001) interaction between alcohol status and rs4846049. Drinkers with rs4846049 CA/AA

genotype had an OR of having a stroke of 3.12 (95% CI 1.83, 4.45) compared with never drinkers and rs4846049 CC genotype. None of the other *MTHFR* variants evaluated significantly interacted with alcohol [62].

In the category of dietary patterns, the PREDIMED trial found a significant (p=0.04) interaction between the Mediterranean diet and the LPL rs13702 variant. Participants assigned to the intervention group (Mediterranean diet plus supplementation with extra-virgin olive oil and nuts (30 g/day)) who were carriers of the C allele had a reduced stroke risk [HR 0.58 (95% CI 0.37, 0.91)] in comparison to the TT genotype. At the same time, no association was reported for the control group (fat intake reduction) [68]. Finally, Helstrand et al. [70], analysing data from the MDC cohort, reported a significant (p=0.04) interaction between diet quality index and GRS-LDL-cholesterol on stroke risk (Table S2). Participants with low/medium diet quality had an HR of 1.09 (95% CI 1.03, 1.16) per standard deviation of increment of GRS-LDL-cholesterol[70].

3.6 Diet-Gene interactions and cardiovascular diseases as a composite outcome

Eight articles from four unique studies evaluated diet-gene interactions on cardiovascular diseases as composite outcome [6,15,53,63,64,69,70,73] (Figure 5, Table 1). Non-significant interactions were reported for drinking status-ADH1C variant, and diet quality with GRS of HDL, -LDL and -triglycerides [6,63-65,69,70], Table S3.

In the macronutrients category, a borderline (p=0.06) interaction was reported between ALA/LA intake ratio and the *FADS1* variant on CVD incidence. No statistically significant interaction was observed with any of the other fatty acids evaluated [6]. Regarding micronutrients, neither folate nor vitamin B intake interacted with MTHFR variants on CVD risk [73].

Regarding food and food items categories, Hindy et al.[64], analysing data from the MDC cohort, reported a significant (p=0.043) interaction between vegetable intake and chromosome 9p21 variant rs4977574. When the analysis was restricted to medium or high tertile of vegetable intake, carriers of the G allele had an increased risk of CVD with HR 1.27 (95% CI 1.17, 1.38) and 1.19 (95% CI 1.08, 1.30), respectively, compared to AA homozygote genotype. No interaction was reported for fruit intake [64]. Moreover, Sonestedt et al.[15], in another analysis of the same MDC cohort, found no interaction between vegetable intake and GRS of HDL cholesterol, LDL cholesterol or triglycerides on CVD risk [15]. Additionally, in the UK Biobank, there was no interaction between coffee intake and CYP1A2 genotype or with a GRS of caffeine metabolism on CVD risk (p>0.53) [65].

Concerning other dietary components, in the MDC cohort, a significant (p=0.029) interaction was found between wine consumption and chromosome 9p21 variant rs4977574 on CVD risk. However, the effect was limited to the non/low wine intake tertile in the stratified analysis. In that group, carriers of the G allele had an increased risk of CVD [HR 1.23 (95% CI 1.14,1.34)] compared to the AA homozygote genotype. At the same time, no association was observed when total alcohol intake was evaluated [64].

Risk of bias of the included studies

Nineteen (35.2%) articles were classified as high quality, 33 (61.1%) as intermediate quality, and two (3.7%) as poor quality. Small sample size, lack of correction for multiple testing (8 (14.8%) articles adjusted for multiple comparisons), lack of generalisation (e.g., no different ethnicities being represented) often limited the methodological quality (Table S4), a report of the SWiM items can be found in Table S5.

4. DISCUSSION

Of the 54 included articles, 30 reported a statistically significant gene-diet interaction. Dietary and genetic exposure were very heterogeneous, which precluded us from conducting a meta-analysis of the results. *CETP* and alcohol dehydrogenase (*ADH1C*) variants were the most frequently assessed and were shown to interact with alcohol to modify the risk of MI and CHD. Other studies investigating plausible biological interactions such as *FADS* gene and fatty acids interactions, vitamin B6, vitamin B12 and folic acid did not show consistent findings. While several studies investigated the interactions between genes and dietary factors on CVD risk, the current literature is limited and not consistent in showing gene-diet interactions with clinical and public health impacts, mainly because the reported positive findings were derived from case-control studies and lacked replication.

Previous systematic reviews on gene-diet interactions and CVD have primarily focused on specific genes or diets. In contrast, our study provides a comprehensive assessment of all genes and dietary exposures interactions on CVD. Similar to previous findings, we identified a lack of consistency in the results of interaction studies [19,74]. In this review, the lack of reproducibility in the genetic-dietary variables operationalisation and the different levels of validation and reliability of the used dietary questionnaires could have led to an increased risk of exposure misclassification. This risk could be more relevant in case-control studies, in which recall bias could occur differently between cases and controls since the cases are aware of the condition [75]. Additionally, misclassification due to genotype errors can be another source of bias. Genotyping error has been reported to vary between about 1% and 30%, and its extension is related to variations in DNA sequence, quality of the analysed DNA, biochemical artefacts and human factors [76].

Another methodological concern of studies looking at gene-diet interaction and CVD is the sample size of the studies. Low statistical power leads to a reduced capacity to detect interactions. Genotyping errors, allele frequency and the precision of the dietary exposure and outcome measures are some of the criteria that researchers should consider when calculating adequate sample size to evaluate interactions [77]. Nevertheless, most of the studies included in this paper were secondary analyses, and there was no information on whether studies had enough power to detect an interaction. It has been estimated that detecting the interaction between two binary exposures requires a sample size four times larger than that required to detect main associations of the same magnitude [78].

Similarly, studies with 95% of power and a MAF of 20% looking for interactions of 1.5 of magnitude between genetic variants and continuous exposures require a sample size of up to 30,906 subjects [78]. In this paper, 50% of the included studies had a sample size below 2562 individuals. Just four studies exceeded 30,000 participants, and two of them did not clearly state the MAF frequency [69,71]. The lack of information on the main factors involved in calculating power in almost half of the included studies limited the evaluation of their sample robustness for detecting gene-diet interactions. Notably, of the four studies that exceeded 30,000 participants, only one found a significant interaction [71].

Comparing specific foods and gene variants generates multiple comparison scenarios that could increase the Family-wise error rate [79], where the probability of false-positive findings increases with each additional comparison [80]. Therefore, including a correction for multiple testing is a suitable approach in studies with these phenomena, even though in this study, just two studies stated a correction for multiple comparisons in their methodology [17,72].

Alcohol was the most evaluated exposure; its interaction with the CETP polymorphism (rs708272) was not consistent for CHD. The results did not agree with the direction of reported interactions, and most of the interactions lost statistical significance in the sex-stratified analysis. The low prevalence of alcohol intake could explain this difference and hypertriglyceridemia in the populations evaluated. [12,42]. In addition, only two studies included incident cases. However, the protective effect of the CETP-alcohol interaction could be related to the synergy between the B2 allele of CETP, which is associated with lower plasma CETP activity[81], and the inhibitory effect of alcohol on CETP activity [12]. Both may increase HDL concentrations, decrease LDL and VLDL fractions, and, consequently, reduce CVD risk.

Similarly, concerning lipid metabolism, a matched case-control study reported an interaction between the *ADH1C* variant and alcohol intake that decreases the incidence of MI in men who drank daily and were homozygous for the y^2 allele. Carriers of the y^2 allele are slow metabolisers of alcohol, which could enhance the beneficial effect of moderate alcohol consumption on lipid metabolism. In addition, the study stated that up to 50% of the observed decrease in MI risk could be attributed to increased HDL levels [34]. However, findings on *ADH1C* polymorphism and alcohol interactions were not homogeneous, and five studies did not report significant interactions, even though different alcohol intake categories were tested among these studies [11,13,36,44,52]. These findings suggest that the interactions between alcohol consumption and the *ADH1C* variant on CVD might be mediated through mechanisms independent of HDL cholesterol[63].

The increased risk of MI in the WENBIT trial could be explained by the association of vitamin B6 and folate intake with elevated hepatic adenosylmethionine (SAM). SAM is an inhibitor of betaine-homocysteine methyltransferase, an enzyme that regulates hepatic lipids and induces

ApoB expression and VLDL assembly. Furthermore, the *MTHFD1* variant (rs1076991) minor T-allele has been associated with an approximately 62.5% drop-in transcription rate of the MTHFD1 enzyme, which could also be associated with intercellular SAM accumulation, conditions that lead to dyslipidaemia and the consequent increased CVD risk [16]. However, when MI was evaluated as part of CVD composite outcome or individually in WHS, the folate or B-vitamin - MTHFD1 interaction was not found [73]. It is important to note that meta-analyses of the association of MTHFR and CVD have found substantial geographical heterogeneity and null associations for MTHFR and CVD in North American populations, such as women involved in the Women's Health Study [73].

Strengths and limitations

A significant strength of this paper is the comprehensive search strategy implemented to retrieve gene-diet interaction studies. We included all food and dietary exposures and epidemiological designs, providing a comprehensive overview of the literature. Also, we provided a critical evaluation of the quality of the current evidence on the topic. In addition, the included studies point to several biological mechanisms that could underlie the differences in the susceptibility to food/diet exposures and cardiometabolic diseases. However, it is a limitation for this study that, so far, no gene-diet interaction critical appraisal tool has been developed. This tool could standardise the evaluation of the studies' risk of bias and methodological quality, identifying the most significant weaknesses. Other issues were the lack of replication in the evaluation of interactions, few studies evaluated the same dietary and genetic exposures (SNP, GRS). Moreover, authors evaluating the same genetic variants used different genetics models (e.g. recessive model, co-dominant model or dominant model). This heterogeneity limited the synthesis of the findings and are also a great weakness for the progress in the identification of

population at higher risk of cardiometabolic diseases due to their genetic background and food/diet exposures.

Future research and implications

Identifying the mechanisms underlying gene-diet interactions is a priority; therefore, variants identified in GWAS are required to be investigated in functional studies, a challenge that could benefit from computational modelling. In addition, studies assessing interactions should provide more information on the origin of biases in the genetic exposures assessed (genotype misclassification, population stratification). Future studies should analyse samples with a suitable size for evaluating interaction hypotheses, for which data sharing through consortia may play a crucial role. Replication in independent samples is also essential, for which the selection of a single reference group is a critical factor in facilitating the comparability among studies. Besides, studies should provide information on the size of interactions and the effects of gene and dietary exposures separately and in joint effect. Finally, the use of prospective data that allows the evaluation of gene-diet interactions effects on incident outcomes should be prioritised.

5. CONCLUSION

Current evidence for gene-diet interaction in CVD is limited, as most interactions have been evaluated in single studies, without multiple correction testing, and mainly in European ethnicities; furthermore, studies have limited information to assess the robustness of sample size. Therefore, data-sharing platforms that combine large studies are needed to address current methodological problems and facilitate replication. In addition, priority should be given to the inclusion of diverse ethnicities and sample size-focused reporting to provide more conclusive

evidence of gene-diet interaction with CVD that allows the development of nutritional personalized interventions.

6. DECLARATIONS

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

Authors have no conflicts of interest to declare.

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Author contributions

TM contributed to the conception and design, the analysis and interpretation and critically revised the manuscript. ZMRD contributed to the design, analysis and interpretation, drafting and critically revision of the manuscript. BM contributed to the systematic search and critically revision of the manuscript. JT, MG, MB, GG, FW, EG contributed to analysis and interpretation,

drafting and critically revision of the manuscript. LZR, SGO, SV, MFV, contributed to the analysis and critically revision of the manuscript. OHF, AD, RP, PMV contributed, interpretation and critically revision of the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Table 1. Study characteristics

Reference	Country (Ethnicity)	Study Type (Recruitment setting)	Cohort name (FU years)	No. of participants (cases/total)	Sex	Interactor diet (Type of measurement)	(Gene/chromosome region) and (SNP/GRS)	Significant interactions	Replication
Coronary Heart Disease - Myocardial infarction									
Allayee H et al., 2008 [28]	Costa Rica (Hispanic)	Case-Control (Population)	-	1885/3770	Both	Arachidonic acid intake (Questionnaire)	5-LO (33-37; 44-46; 48; 55-59; 66; 67)	Yes	No
Chen Q et al, 2017 [29]	China (Han-Chinese)	Case-Control (Population)	-	300/600	Both	Alcohol (Standardized questionnaires)	PCSK9 (rs11206510)	Yes	No
Cornelis M et al, 2007 [30]	Costa Rica (Hispanic)	Case-Control (Population)	-	2042/4084	Both	Cruciferous vegetables (FFQ)	GSTT1, GSTP1, GSTM1(-)	Yes	No
Cornelis M et al, 2006 [31]	Costa Rica (Hispanic)	Case-Control (Population)	-	2014/4028	Both	Coffee (Questionnaire)	CYP1A2 (rs762551)	Yes	No
Ding Y et al, 2016 [16]	Norway (European)	Cohort (Clinical)	WENBIT (5)	206/2381	Both	Vitamin B12 and vitamin B6 (According to the cohort data)	MTHFD1 (rs1076991)	Yes	No
Fumeron F et al., 1995 [32]	France (White Europeans)	Case-Control (Population)	ECTIM Etude Cas-Témoin de l'Infarctus du Myocarde(NR)	608/1332	Men	Alcohol (Questionnaire)	CETP (rs708272 (CETP/TaqIB))	Yes	No
Hartiala J et al, 2012 [33]	Costa Rica (Latin American)	Case-Control (Clinical)	-	1936/3971	Both	PUFAs (Polyunsaturated fatty acids) (Questionnaire)	PLA2G4A (rs12746200)	Yes	Yes
Hines L et al, 2001 [34]	United States (not described)	nested case-Control (Population)	Physicians' Health Study (NR)	396/1166	Men	Alcohol (Questionnaire)	ADH1C (rs698)	Yes	No

Li J et al, 2020 [35]	China (Han-Chinese)	Case-Control (Population)	-	344/688	Both	Alcohol (Standardised questionnaire)	CONNEXIN 37 (rs1764391)	Yes	No
Tolstrup J et al, 2009 [36]	Denmark (Danish general population)	Cohort (Population)	CCHS (16)	663/9584	Both	Alcohol (Questionnaire)	ADH1C/ ADH1B (rs698, rs1229984)	No	No
Trichopolou A et al, 2008 [37]	Greece (Mediterranean)	Nested Case-Control (Population)	Greek - EPIC(NR)	202/399	Both	Mediterranean diet (Questionnaire)	APOA5, APOC3, APOE, IL1β, IL6, LPL, MTHFR, NOS3, and TNF (GRS-MI (rs429358, rs7412, rs662799, rs5128, rs1801177, rs268, rs328, rs1801133, rs1799983, rs16944, rs1800795, rs1800629))	No	No
Wang F et al., 2019 [38]	China (Han-Chinese)	Case-Control (Population)	-	300/600	Both	Alcohol (Interview on alcohol intake in the last 12 months)	CXCL12 (rs1746048)	Yes	No
Zheng Y et al., 2016 [39]	Costa Rica (Hispanic)	Case-Control (Population)	-	1560/3311	Both	Sugar-sweetened beverages (Questionnaire)	CDKN2B-AS1 (GRS (rs4977574, rs2383206, rs1333049))	Yes	No
Coronary Heart Disease									
Chen H et al., 2018 [40]	China (Han-Chinese)	Case-Control (Clinical)	-	429/751	Both	Alcohol (Self-reported)	Il6 (rs1800795, rs1800796, rs1800797)	Yes	No
Chi Y et al, 2018 [41]	China (Han-Chinese)	Case-Control (Clinical/ Population)	-	631/1269	Both	Alcohol (Questionnaire)	PLA2G7 (rs1805018, rs16874954, rs1805017 and rs1051931)	No	No
Corella D et al, 2010 [42]	Spain (Mediterranean)	Nested Case-Control (Population)	Spanish EPIC (10)	557/1737	Both	Alcohol (Questionnaire)	CETP (rs708272 (CETP/TaqIB))	Yes	No

Ebrahim S et al, 2008 [11]	United Kingdom (not described)	Cohort (Population)	BWHHS and Caerphilly cohorts (NR)	283/4547	Both	Alcohol (Questionnaire)	ADH1C (rs1693482)	No	Yes
Gustavsson J et al, 2016 [43]	Sweden (not described)	Case-Control (Population)	SHEEP and INTERGENE	1381/5671	Both	PUFA, SFA, Carbohydrates, Sucrose, Protein, Fat (semi-quantitative FFQ)	FTO (rs9939609)	No	No
Heidrich J et al, 2007 [44]	Germany (Caucasian)	Cohort (Population)	MONICA-KORA project (7.8)	72/3664	Both	Alcohol (Interview)	ADH1C (rs698)	Yes	No
Huang L et al, 2018 [45]	China (Han)	Nested Case-Control (Population)	Yinzhou District of Ningbo, Zhejiang Province, China (3)	161/656	Both	Dessert and fried food (Questionnaire)	ALDH2 (rs671)	No	No
Jensen M et al, 2008 [12]	United States (not described)	Nested Case-Control (Population)	NHS and HPFS (NR)	505/1504	Both	Alcohol (Questionnaire)	CETP (rs708272 (CETP/TaqIB))	Yes	Yes
Liu F et al, 2015 [46]	China (not described)	Case-Control (Clinical)	-	838/1278	Both	n-3 Polyunsaturated Fatty Acid (n-3 LCPUFA) (Questionnaire)	FADS1 (rs174547)	Yes	No
Liu Y et al, 2020 [47]	Taiwan (not described)	Case-Control (Population)	TWB (NR)	1116/8969	Both	Coffee (Interview on coffee intake in the last 6 months, regular intake defined as 3 or more cups of coffee/week)	TRIB1 (rs17321515)	Yes	No
Mehlig K et al, 2014 [48]	Sweden (not described)	Case-Control (Population)	INTERGENE	618/3539	Both	Alcohol (Interview)	CETP (rs708272 (CETP/TaqIB))	Yes	No
Tolstrup J et al, 2010 [13]	Denmark (Caucasian)	Nested Case-Cohort (Population)	Danish Diet, Cancer and Health Cohort (NR)	770/1645	Men	Alcohol (FFQ)	ADH1B/ ADH1C (rs1229984/rs1693482)	No	No
Virtanen J et al, 2016 [50]	Finland (not described)	Cohort (Population)	KIHD (20.8)	230/1032	Men	Egg/ Cholesterol (Guided 4-d food records)	APOE4 (E2/2, E2/3, E2/4, E3/3, E3/4 and E4/4)	No	No

Yiannakouris N et al, 2014 [51]	Greece (European)	Nested Case-Control (Population)	Greek-EPIC (10)	477/1748	Both	Mediterranean diet (Questionnaire)	PCSK9, CELSR2-PSRC1-SORT1, MIA3, WDR12, PHACTR1, CXCL12, LDLR, SLC5A3-MRPS6-KCNE2, CDKN2A/2B (GRS-CHD (rs11206510, rs646776, rs17465637, rs6725887, rs9349379, rs1746048, rs1122608, rs9982601 and rs1333049))	No	No
Younis J et al., 2005 [52]	United Kingdom (not described)	Cohort (Clinical)	NPHS II(NR)	220/2773	Men	Alcohol (Questionnaire)	ADH1C ($\gamma^1\gamma^1$, $\gamma^1\gamma^2$, $\gamma^2\gamma^2$)	No	No
Zhou H et al., 2019 [53]	China (Han-Chinese)	Case-Control (Clinical)	-	610/1833	Both	Alcohol (Questionnaire filled out in face-to-face interviews)	TFPI-2 (rs59805398, rs34489123, rs4264, rs4271)	No	No
Mukamal K et al, 2009 [49]	United States (American)	Nested Case-Control (Population)	NHS and HPFS (7)	506/1524	Both	Alcohol (Questionnaire)	PON1	No	No
Stroke									
Mukamal K et al., 2005 [58]	United States (not described)	Cohort (Population)	CHS Cardiovascular Health Study (9.2)	434/4410	Both	Alcohol (Questionnaire)	APOE (-)	No	No
Chen Z et al, 2015 [54]	China (Han-Chinese)	Case-Control (Population)	-	159/334	Both	Alcohol (Questionnaire)	CRP (rs1800947, rs3093059)	Yes	No
Gao X et al, 2006 [55]	China (Han-Chinese)	Case-Control (Clinical)	-	100/200	Both	Alcohol (Questionnaire)	FgB (FgBCT/TT)	Yes	No

Juan J et al, 2017 [56]	China (not described)	Family-based case-control-study (Clinical/ Population)	FISSIC (NR)	1007/2158	Both	Vegetable and fruit intake (Semi-quantitative FFQin face-to-face survey)	PON1 (rs662)	No	No
Luo S et al, 2013 [57]	China (Han-Chinese)	Case-Control (Clinical)	-	308/602	Both	Alcohol (Medical history)	Il8 (Il8 +781 C/T)	No	No
Song J et al, 2019 [59]	China (not described)	Family-based-cohort-study (Population)	FISSIC	1213/5869	Both	Eggs (Semi-quantitative FFQ)	ABCA1 (rs2066715)	No	No
Yang S et al, 2020 [14]	China (Han-Chinese)	Case-Control and cohort	-(5)	2012/4222	Both	Alcohol (Interview)	ACTB (rs852426, rs852423 and rs2966449)	Yes	Yes
Zhang L et al, 2019 [60]	China (Han-Chinese)	Case-Control (Clinical)	-	881/1773	Both	Alcohol (Interview)	CONNEXIN 37 and PDE4D (rs1764391, rs1764390, rs918592 and rs966220)	No	No
Zhao T et al, 2019 [61]	China (Han-Chinese)	Case-Control (Population/ Clinical)	-	161/644	Both	Fruits/ Vegetables (Semi-quantitative FFQ)	BCO2(rs10431036) BCO2(rs11214109) TRIB1(rs17321515) TRIB1(rs2954029)	No	No
Zheng X et al, 2020 [62]	China (Han-Chinese)	Case-Control (Population)	-	860/1722	Both	Alcohol (NR)	MTHFR (rs4846049, rs1537514, rs3737967, and rs4846048)	Yes	No
Cardiovascular disease									
Djousse L et al, 2005 [63]	United States (not described)	Cohort (Population)	Framingham Heart Study (NR)	132/1805	Both	Alcohol (Interview)	ADH1C (rs698, rs1693482)	No	No
Hindy G et al, 2014 [64]	Sweden (Caucasian)	Cohort (Population)	MDCS (15)	3164/23949	Both	Vegetable, fruit, wine, alcohol (Diet history)	9p21 locus(rs4977574)	Yes	No

Sonestedt S et al, 2015 [15]	Sweden (not described)	Cohort (Population)	MDCS (14)	2921/26455	Both	Sucrose, fibre, vegetables, fruits and berries, juice, potatoes, whole grains, refined grains, cookies and cakes, sugar and sweets, sugar-sweetened beverages (Questionnaire)	-(GRS-dyslipidaemia (26 SNPs for triglycerides, 41 SNPs for HDL-C and 32 SNPs for LDL-C))	No	No
Zhou A et al., 2019 [65]	United Kingdom (not described)	Cohort (Population)	UK Biobank (NR)	8368/347077	Both	Coffee (Interview)	CYP1A2 (rs762551/ GRS for metabolism of caffeine (rs4410790, rs6968554, rs10275488, rs2892838, rs12909047, rs35107470, rs2470893, and rs2472297))	No	No
Articles evaluating at least two of the outcomes (CHD, MI, CVD or Stroke)									
Livingstone M et al., 2021 [71]	United Kingdom (not described)	Cohort (Population)	UK Biobank (7.8)	1141 MI, 748 IS/77004	Both	Recommended Food Score RFS(Oxford WebQ (24-hour dietary assessment tool))	-(GRS formed from over 300 different SNPs associated with CVD)	Yes	No
Hellstrand S et al., 2016 [70]	Sweden (White)	Cohort (Population)	MDCS (15)	3068/24799	Both	Diet quality index (168-item dietary questionnaire 7-day menu book 1-h diet history interview)	-(Genetic risk score for LDL, HDL and Triglycerides)	Yes	No
Hellstrand S et al, 2014 [6]	Sweden (not described)	Cohort (Population)	MDCS (14)	2648/24032	Both	PUFAs (Questionnaire)	FADS1 (rs174546)	Yes	No
Zee R et al, 2007 [73]	United States (White)	Cohort (Population)	WHS (9.9)	812/24968	Women	Folate intake, VB2, VB6 and VB12 intake (Questionnaire)	MTHFR (677C>T)	No	No
Heianza Y et al, 2020 [69]	United Kingdom (not described)	Cohort (Population)	UK Biobank (5)	1812/156148	Both	Plant-based diet index (Participants completed a web-based 24-h dietary	Genetic risk score GRS for stroke and myocardial infarction ()	No	No

						assessment, the Oxford WebQ, during 2009–2012.)			
Do R et al., 2011 [17]	Multicentre (European, South Asian, Chinese, Latin American, Arab)	Case-control/ cohort (Population)	INTERHEART study and FINRISK study (NR)	3709/27243	Both	Dietary risk score and specifically different types of food (FFQ)	9p21 locus (rs10757274, rs2383206, rs10757278, rs1333049)	Yes	No
Miao L et al, 2017 [72]	China (Han-Chinese)	Case-Control (Clinical)	-	846/2562	Both	Alcohol (Questionnaire)	MVK-MMAB (rs3759387, rs7134594, rs877710, rs9593)	Yes	No
Corella D et al, 2014 [68]	Spain (Mediterranean)	Randomised controlled trial (Clinical)	PREDIMED Trial (4.8)	268/7187	Both	Mediterranean diet, extra-virgin olive oil +nuts(NR)	LPL (rs13702)	Yes	No
Bergholdt H et al, 2015 [66]	Denmark (European descent)	cross-sectional and Mendelian randomization (Population)	CCHS, CGPS and GESUS (5.4)	10372 IHD, 4188 MI /98529	Both	Milk (Questionnaire)	LCT13910 (rs4988235)	No	No
Corella D et al, 2016 [67]	Spain (Mediterranean)	Randomised controlled trial (Clinical)	PREDIMED Trial (4.8)	150/7098	Both	Mediterranean diet supplemented with extra virgin olive oil (Validated FFQ)	CLOCK (rs4580704)	No	No

FU: Follow-up; IS: Ischemic stroke; MI: Myocardial infarction; CHD: coronary heart disease; CVD: cardiovascular diseases
NR (Not reported)
British Women's Heart & Health Study (BWHHS)
Copenhagen City Heart Study (CCHS)

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort
Fangshan / Family-based Ischemic Stroke Study in China (FISSIC)
Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)
Second Northwick Park Heart Study NPHS II
Taiwan Biobank (TWB)
Women's Health Study (WHS)

Table 2. Estimates of the interaction between alcohol intake and ADH1C variants on CHD risk.

Author	Categorisation of Alcohol (Drinks/week)	No. of Events	Association measure	Gene, variant, and genotypes Estimate (CI 95%)			Interaction *P*-value
CHD							
				CETP (rs708272 (CETP/TaqIB))			
				B1B1	B1B2	B2B2	
*Fumeron et al, 1995 [32]	Non-drinkers	92	OR	1	1.04 (0.68-1.59)		<0.02
	<2	234		1	0.97 (0.58-1.61)		
	≥2 to 3	134		1	0.96 (0.51-1.81)		
	≥4 to 5	66		1	0.56 (0.22-1.47)		
	≥6	125		1	0.34 (0.14-0.83)		
Jensen et al, 2008 [12]	Non-drinkers[a]	118	OR	1	1		0.4
	<2.5[a]	77		1.1 (0.5–2.3)	0.8 (0.5–1.4)		
	≥ 2.5 to 6[a]	31		1.4 (0.6–3.7)	0.3 (0.2–0.6)		
	≥ 7 to 14[a]	20		1.3 (0.5–3.8)	0.4 (0.2–0.9)		
	Non-drinkers[b]	63		1	1		0.2
	<2.5 [b]	63		1.7 (0.7–4.1)	0.9 (0.5–1.6)		
	≥ 2.5 to 6[b]	66		1.9 (0.8–4.5)	0.9 (0.5–1.6)		
	≥ 7 to 14[b]	80		1.6 (0.6–4.4)	0.8 (0.4–1.5)		
	Non-drinkers[c]	181		1	No data		
	≥ 2.5 to 6[c]	87		1.6 (1.1–2.3)	0.7 (0.6–1.0)		0.02
Corella et al, 2010 [42]	Non-drinkers	139	OR	1	0.74 (0.42–1.32)	0.57 (0.24–1.34)	0.031
	Drinkers	418		1	1.17 (0.90–1.55)	1.55 (1.05–2.29)	
Mehlig et al, 2014 [48]	Abstainers			1.12 (0.77-1.62)		0.76 (0.36-1.64)	0.008
	Low			1		1	
	Intermediate			0.80 (0.59-1.06)		0.21 (0.10-0.44)	
	High			1.03 (0.77-1.36)		0.48 (0.26-0.88)	
				ADH1C			

				1/1	1/2	2/2	
*Tolstrup et al, 2009 [36]	<1	175	HR	1	1.38 (0.97 – 1.96)	1.60 (1.04 – 2.47)	0.49
	1 to 13	307		0.99 (0.70 – 1.40)	0.98 (0.71 – 1.37)	0.83 (0.55 – 1.25)	
	≥14	146		0.80 (0.53 – 1.23)	0.82 (0.56 – 1.19)	0.88 (0.55 – 1.42)	
*Heidrich et al, 2007 [44]	<1	24	HR	1	0.69 (0.31– 1.55)		0.07
	1 to 6	13		0.56 (0.19 – 1.61)	0.83 (0.34– 2.07)		
	≥7	35		1.06 (0.50 – 2.25)	0.36 (0.16– 0.80)		
*Younis et al, 2005 [52]	<1	44	HR	1	0.82 (0.47 – 1.45)	0.64 (0.24 – 1.68)	0.49
	1 to 6	64		0.70 (0.40 – 1.22)	0.56 (0.32 – 0.99)	0.66 (0.31 – 1.38)	
	≥7	102		0.57 (0.33 – 0.98)	0.77 (0.47 – 1.26)	0.68 (0.36 – 1.27)	
*Hines et al, 2001[34]	<1	117	RR	1	1.01 (0.58 – 1.75)	0.59 (0.28 – 1.23)	0.01
	1 to 6	191		1.11 (0.67 – 1.84)	0.66 (0.40 – 1.08)	1.02 (0.55 – 1.88)	
	≥7	87		0.62 (0.34 – 1.13)	0.68 (0.40 – 1.15)	0.14 (0.04 – 0.45)	
Tolstrup et al, 2010 [13]	<1	68	HR	0.96 (0.47–1.93)	1.86 (0.94–3.65)	1.45 (0.47–4.47)	0.95
	1–6	230		1	1.38 (0.87–2.19)	1.10 (0.59–2.08)	
	7–20	266		0.88 (0.56–1.39)	0.97 (0.62–1.51)	0.91 (0.52–1.58)	
	>21	206		0.97 (0.59–1.59)	0.73 (0.45–1.19)	0.84 (0.46–1.54)	
*Ebrahim S. et al.2008 [11]	No data						0.26
				CVD			
Djoussé et al, 2019 [63]	0	56	OR	1	0.85 (0.43–1.68)	1.10 (0.47–2.54)	0.48
	>0	76		0.90 (0.49–1.67)	0.72 (0.39–1.31)	0.63 (0.28–1.44)	

1= Reference category. *Articles reporting grams/day were transformed into drink/week taking as reference "standard" drink (or one alcoholic drink equivalent) contains roughly 14 grams of pure alcohol [27]

[a] Women estimates (Nursing Health Study data), [b] Men estimates (Health Professional Study HPFS), [c] estimates from a pooled dataset (NHS+HPFS)

HR=Hazar ratio; RR=relative risk; OR odds ratio

Figure 1. Flow chart of study selection.

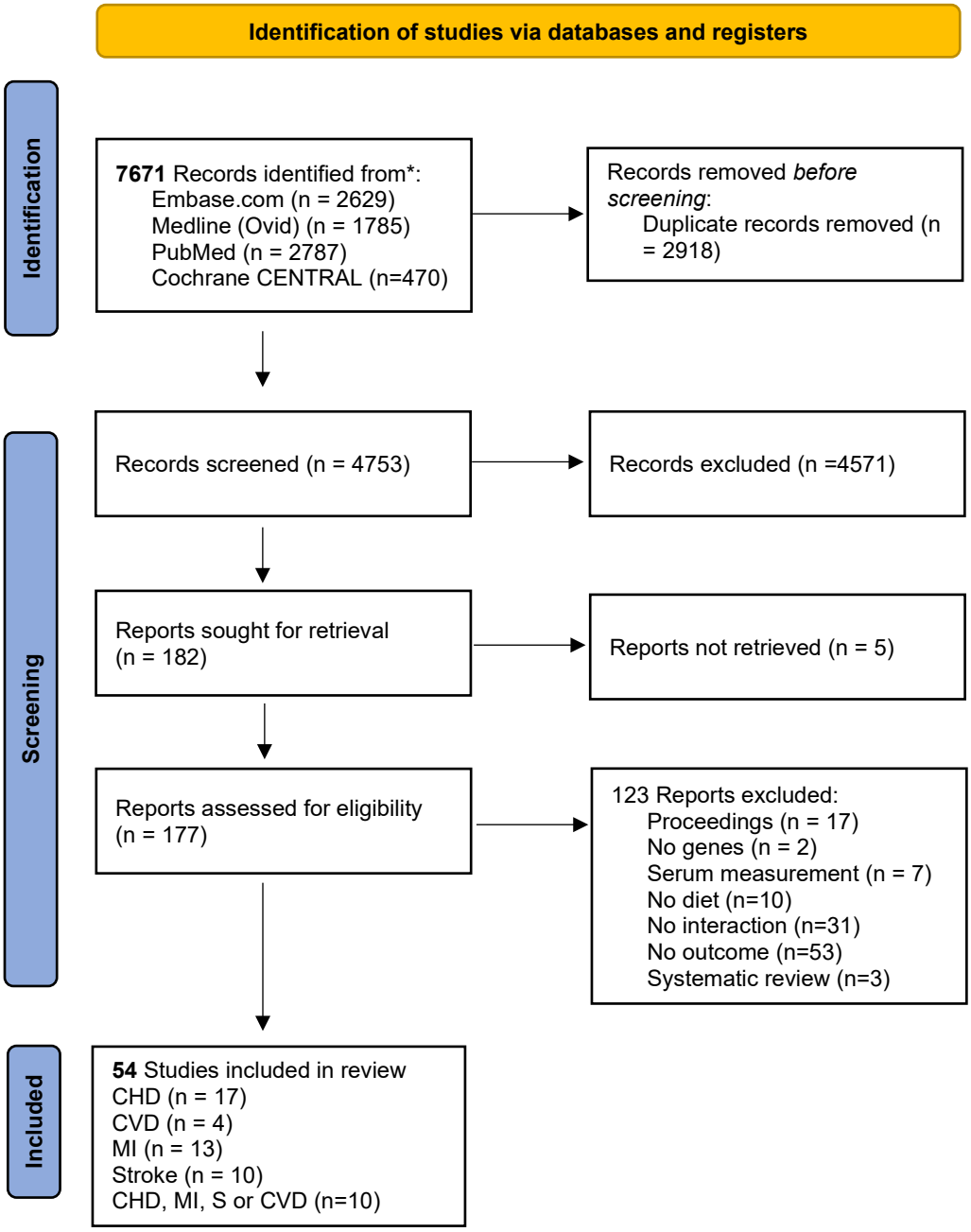
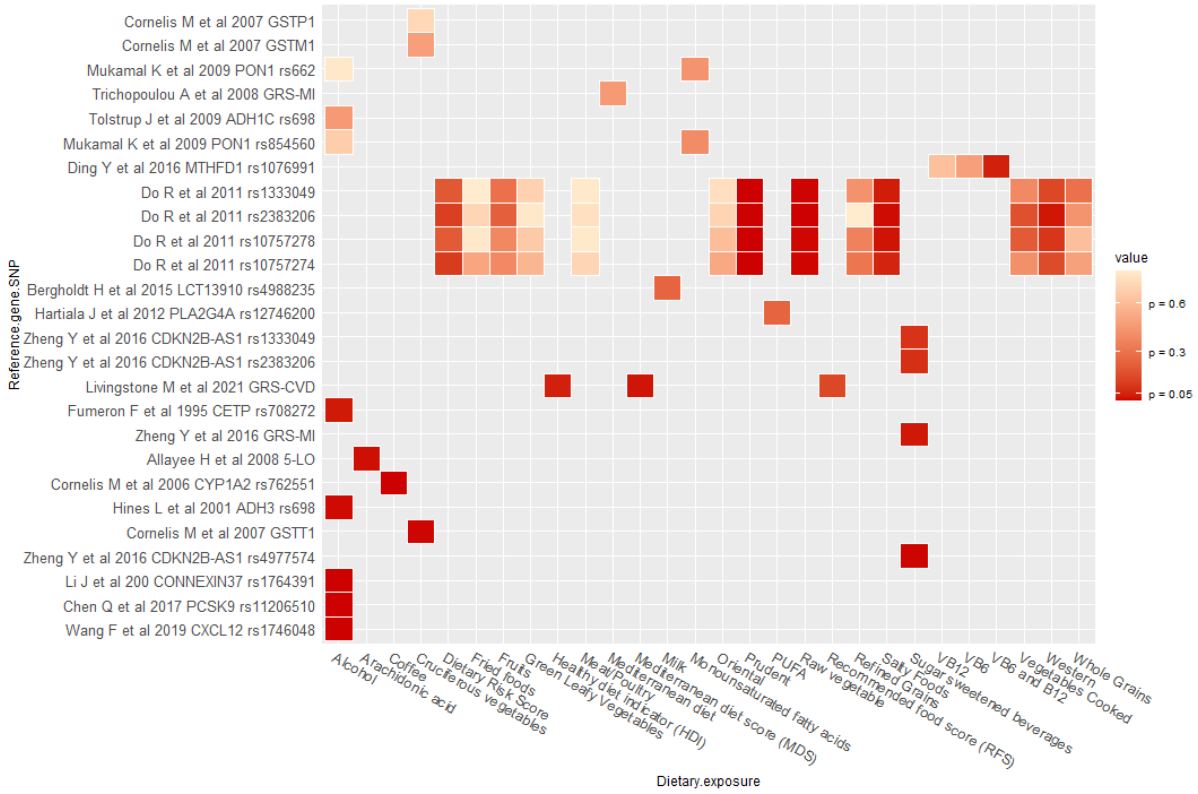
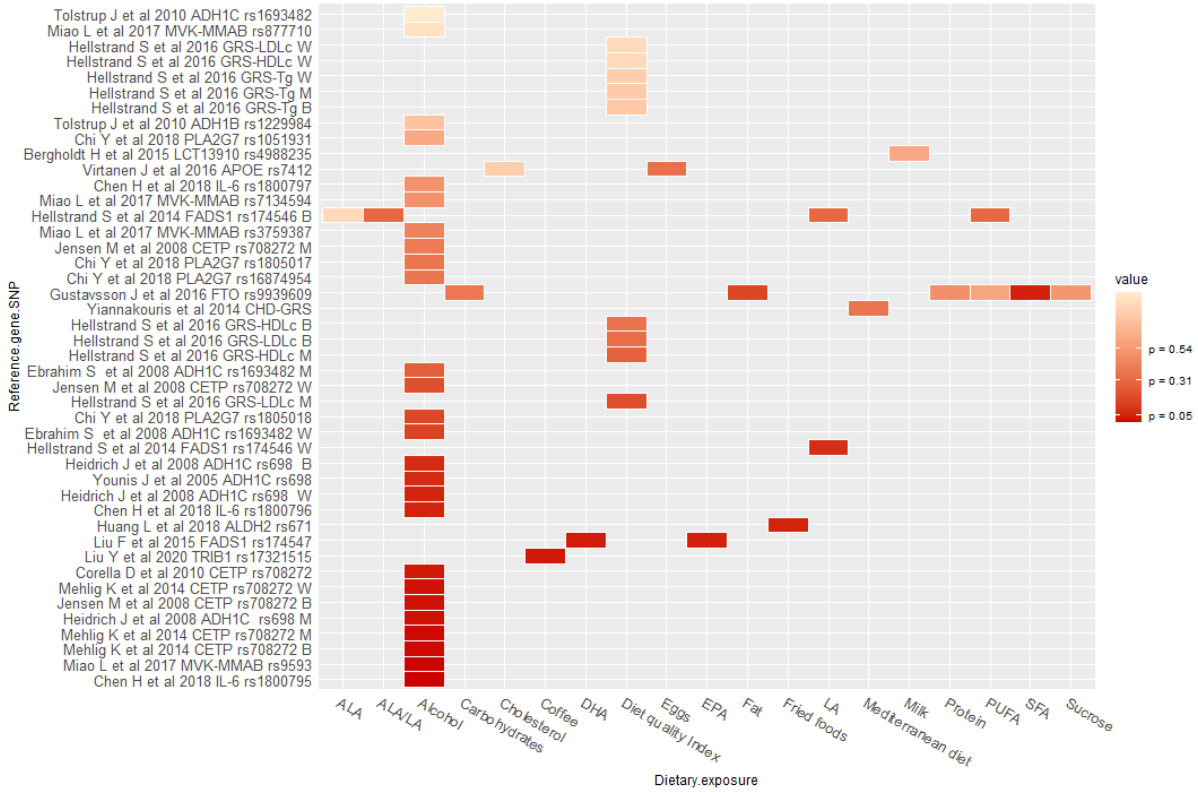


Figure 2. Findings for interaction between genetic variants and diet in relation to myocardial infarction



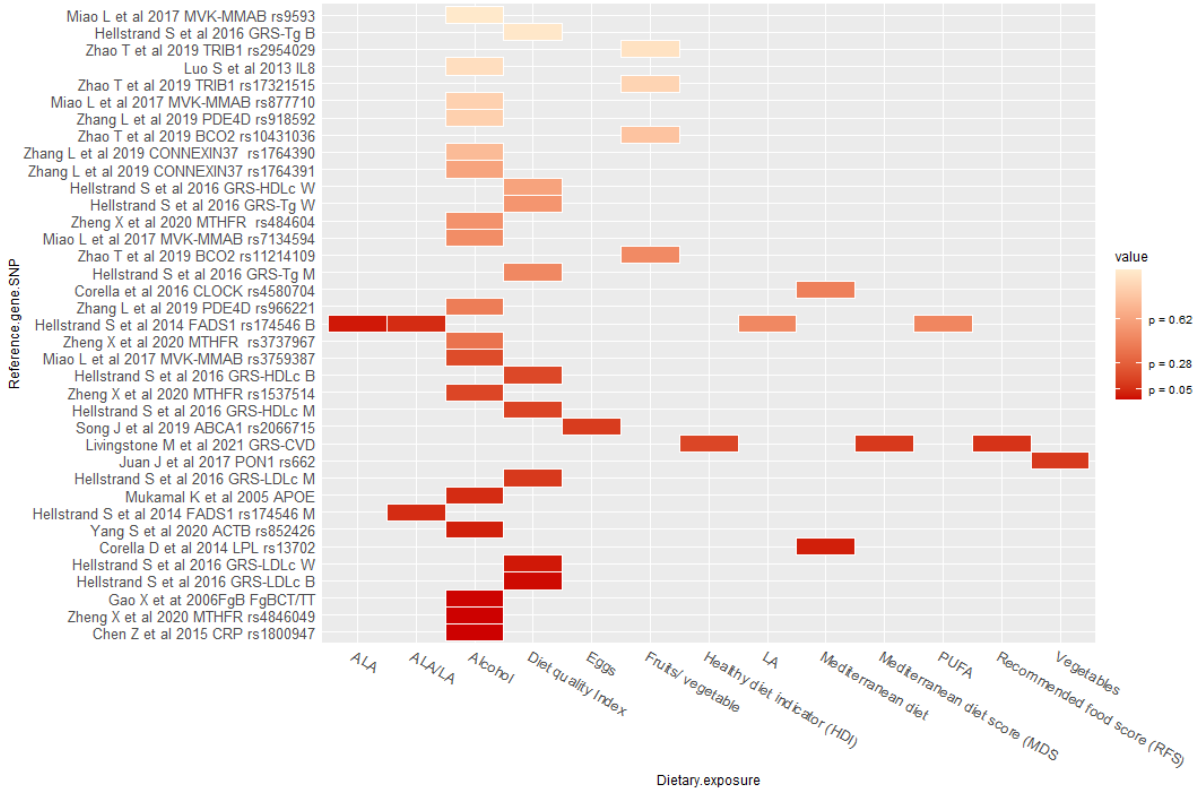
W=women, M=men, B=Both (Men and women)

Figure 3. Findings for interaction between genetic variants and diet in relation to coronary heart diseases.



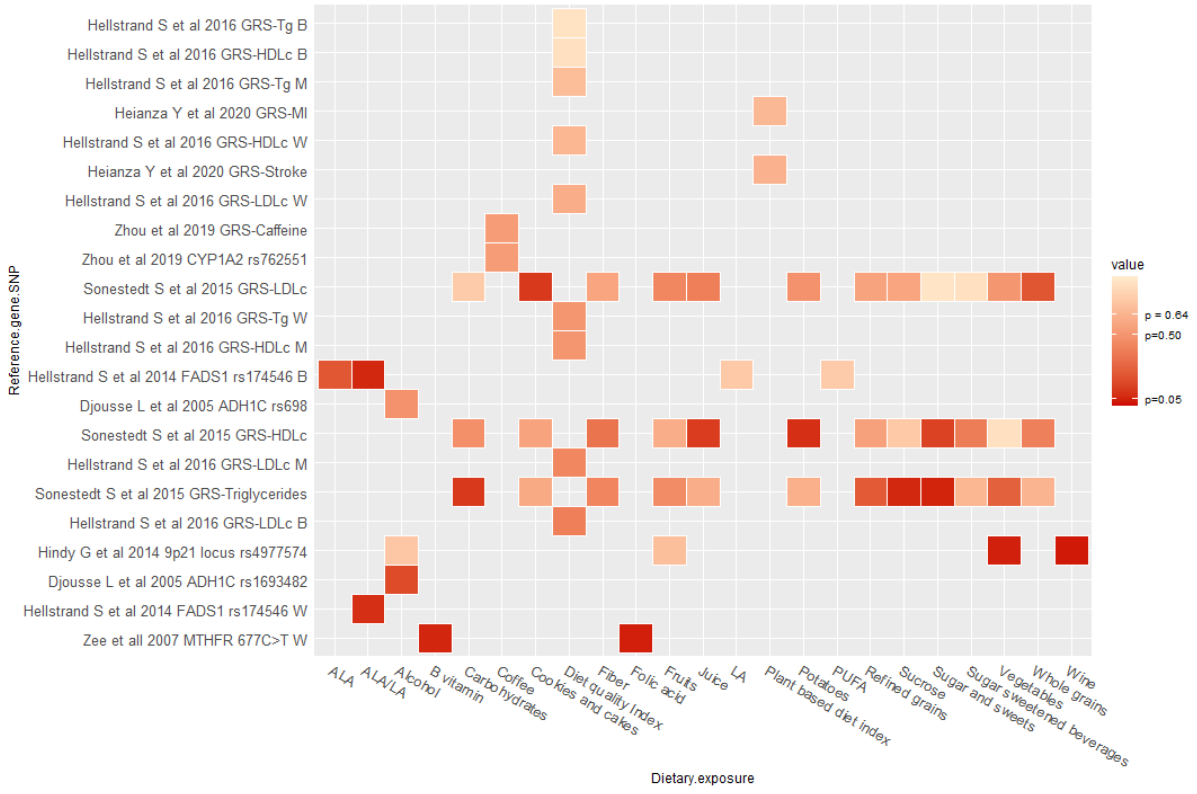
W=women, M=men, B=Both (Men and women)

Figure 4. Findings for interaction between genetic variants and diet in relation to stroke



W=women, M=men, B=Both (Men and women)

Figure 5. Findings for interaction between genetic variants and diet in relation to cardiovascular diseases as composite outcomes



W=women, M=men, B=Both (Men and women)

8. Other Activities

8.1. Internship

Bern, 21/02/2022

GHS COMMITTEE - INTERNSHIP

PhD student: Giorgia Grisotto

Matriculation number: 18-129-320

University: Universität Bern - ISPM (Lifestyle Group)

Thesis advisor and co-promotor: Prof. Oscar H. Franco and Prof. Taulant Muka

PhD project: Diet and menopause (01.02.2019 - 31.07.2022)

Duration Internship: 3 months (14.03.2022 - 14.06.2022)

Location Internship: Clinica Luganese Moncucco - Via Moncucco 10, 6900 Lugano, Ticino (CH)

It is a great opportunity to explore the clinic field, working in a dynamic environment. As nutritionist, I will have the opportunity to work with experts in the nutrition field to assess dietary plans for patients. In parallel, I will be involved in the rehabilitation program for cancer patients, working on the nutritional intervention. Women undergo to chemo/radiotherapy may experience earlier menopause with increased risk of type 2 diabetes, cardiovascular diseases, bone fractures, and overall mortality. With a personalized nutrition intervention, our goal is to lead to a new approach in improving overall quality of life of women cancer patients, reducing burden of early menopause related diseases, and treating hot flushes and other symptoms that accompany menopause.

Aim:

- Collaboration with dietitians to assess personalized dietary plans in the clinic.
- Collaboration with dietitians in hospital departments (surgery, oncology, geriatrics, internal medicine).
- Collaboration with rehabilitation program of cancer patients to improve nutritional status.

Further details: During this non-academic internship in Clinica Luganese Moncucco, I will be supervised by Pala Giacomo and Triaca Simone, dietitians at Clinica Luganese Moncucco, and I will have regular meetings with my co-supervisor and supervisor (Taulant Muka and Oscar H. Franco) to discuss my work. An internship in a non-academic field for at least 3 months is mandatory for the GlobalP3HS | SSPH+ program within my PhD career (defence in July 2022). The Internship is unpaid.

X
Oscar H. Franco
Professor

X
Taulant Muka
Professor

X
Giacomo Pala
Dietitian

X
Simone Triaca
Dietitian

Giorgia Grisotto

8.2. Collaboration CoLaus-Rotterdam study

Project title: A posteriori-derived dietary pattern for healthy ageing in post-menopausal women.

Team members: Mojgan Amiri, Giorgia Grisotto, Taulant Muka, and Trudy Voortman

INTRODUCTION

Menopause is a physiological process in which the menstrual period stops permanently in women (1). Loss of ovarian reproductive function and changes in endogenous sex hormones in women are associated with psychological (2), somatic (3), sexual (4), urogenital (5), and vasomotor (6) symptoms. Additionally, physiological changes in menopause lead to a drastic drop in oestrogen and an increase in iron levels, causing adverse cardio metabolic changes including increase risk of central obesity, inflammation, atherosclerosis, glucose homeostasis imbalance, insulin resistance, raised blood pressure, and endothelial dysfunction (7-11). The severity of the mentioned symptoms can vary among individuals (12), nonetheless, they affect the quality of women's lives (13). Since women live about 33 percent of their lives after the menopausal stage (14), coping with adverse health consequences after menopause should be a core focus of health-care providers' attention.

Diet can have substantial role in modification of menopausal consequences (15, 16). For example, it has been shown that higher intake of dietary lignans is associated with higher insulin sensitivity and lower adiposity indices in post-menopausal women (17). Results of a randomized clinical trial showed the decrease effect of a vegetable oil (safflower oil versus conjugated linoleic acid) on HbA1C and CRP and the increase effect on insulin sensitivity (18). Also, a hypocaloric low-fat diet with physical activity has been shown to improve plasma lipid profile in post-menopausal women (19). A population based study revealed that post-menopausal women with higher adherence to the Mediterranean diet were less likely to have dyslipidemia or to be obese (20). Although the results of The Women's Health Initiative (WHI) study on 48,835 post-menopausal women showed no significant effect of a low-fat diet as compared to a usual-diet on coronary heart disease risk in the intervention duration (over an 8.5-y), subsequent long-term non-intervention follow up of this population showed a considerable lower CHD and diabetes risk without any adverse effect of a low-fat diet (21). Additionally, more consumption of fruits and vegetables and higher intake of processed foods, respectively, may cause less bone resorption and lower bone mineral density in the stated population (22). However in 104 post-menopausal women, none of extracted dietary patterns, including 'dairy, fruit and vegetables', 'fats, potatoes and sugars', 'nuts and cereals' and 'potatoes, fish and alcohol', were statistically effective on cognitive function measurements in post-menopausal women (23).

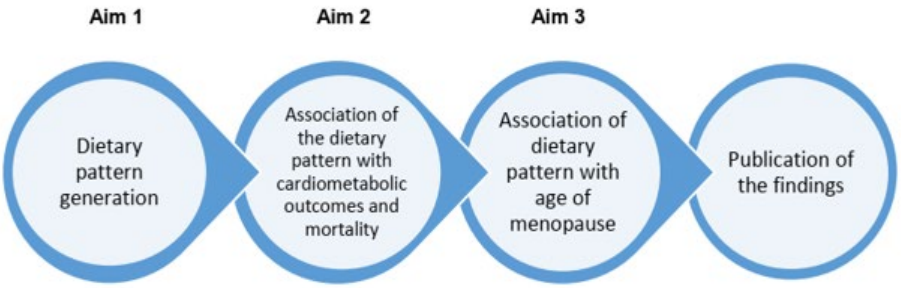
To date, there are no specific dietary approaches/ recommendation/ guidelines for post-menopausal women to improve physiological processes relevant for this population. The current project is designed to extract a dietary pattern, which can predict the lower risk of a group of the most health-related issues in post-menopausal women, containing

cardiovascular health, body composition, bone health, insulin resistance, sleep disturbance, inflammation, cognition, and depression, not just a single domain. So, we aim to identify a dietary pattern optimal for post-menopausal women to decrease risk of the adverse consequences of menopausal transition and diseases relevant for this population.

AIMS

In this project, the main emphasis is on extracting a dietary pattern for healthy aging in women, specified as below:

1. To identify a dietary pattern that is most predictive of a lower risk of most common health issues among postmenopausal women.
2. To validate the extracted dietary pattern in CoLaus study, Lausanne, Switzerland.



METHODS

Study population:

The current study will be conducted based on the Rotterdam Study (RS). The Rotterdam study is a prospective cohort study, consisting of 14,926 participants aged 45 years and older at baseline, ongoing since 1990 in the city of Rotterdam, Netherlands. This study was designed to consider cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, otolaryngological, locomotor, and respiratory diseases as the main targets (24). The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. Additional information about this study is available at **http://www.epib.nl/research/ergo.htm.**

For the current project, the data of post-menopausal women will be used. Cessation of menses for 12 consecutive months was used to define menopause in this population. The spontaneously occurrence of menopause was defined as natural menopause. For non-natural menopause, investigators validated the date of surgery by checking the General Practitioners' patient records and hospital discharge letters.

The extracted dietary patterns will be validated in CoLaus study, a single-centre, cross-sectional study to phenotype and genotype 6188 Caucasian subjects aged 35-75 years old (25). CoLaus study was approved by the Institutional Ethics Committee of the University of Lausanne. The details of this study is reported elsewhere (**www.CoLaus-Psycolaus.ch**). In this study, demographic data, socioeconomic and marital status, mood, and several lifestyle factors, including diet and physical activity were recorded by questionnaires. In

addition, each participant was phenotyped regarding cardiovascular risk factors and blood parameters, anthropometric indices, and bone health status were assessed as well.

Dietary assessments:

At the baseline of all the Rotterdam sub cohorts, a validated, semi-quantitative food frequency questionnaire (FFQ) was used to assess food intakes, which details are described elsewhere (26). In brief, for the baseline measurements of RS-I and II (1989-1993 and 2000-2001), food intakes were assessed by a validated FFQ containing 170 food items (27), and food intakes at baseline in RS-III (and follow up measurements in RS-I and II), performed between 2006 and 2008, was assessed by an updated validated FFQ with 389 food items (28). Both FFQs have been validated against other dietary assessment methods and show adequate ranking for nutrient intakes (29). For all of the sub cohorts, Dutch Food Composition Tables were used to calculate energy and nutrient intake.

Table 1. shows the suggested food groups for this project.

Response variables:

To construct the dietary pattern, we will account for the main health issues women face during the post-menopause stage, containing cardiovascular health, body composition abnormalities, bone health, insulin resistance, sleep disturbance, inflammation, cognitive disorder, and depression. So, on this purpose, we will use the below listed markers as the response variables, including:

1. Cardiovascular risk factors (containing: total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), and systolic blood pressure (SBP))
2. Body composition indices (containing: waist circumference (WC), WC to hip circumference ratio (WHR), body mass index (BMI), fat-free mass, and fat mass)
3. Osteoporosis indices (containing: bone mineral density)
4. Insulin resistance (containing: Fasting blood sugar (FBS), Insulin, HOMA-IR)
5. Sleep disturbance (containing: total sleep time and sleep quality)
6. Inflammation (containing: serum C reactive protein (CRP) level)
7. Cognition (containing: MMSE score, Geriatric Mental Schedule (GMS))
8. Depression (CES-D score)

The above mentioned markers are presented in Table 2.

Assessment of response variables:

Height (cm) and weight (kg) were measured in our research centre using a digital scale and stadiometer, while participants wore light clothes and no shoes. A non-stretchable tape was used to measure waist and hip circumferences. Body composition indices were measured by dual-energy X-ray absorptiometry (DXA) using a Lunar DPX-densitometer, leading to calculation of BMD (g/cm^2), fat-free mass index, and fat mass index.

Fasting blood samples were taken to evaluate serum concentration of TC, HDL, TG, insulin, FBS and CRP. Blood lipids and glucose were measured using automatic enzyme procedures (Roche Diagnostic GmbH, Mannheim, DE). Insulin concentrations were evaluated by an automatic immunoassay (Roche Diagnostic GmbH) and Rate Near Infrared Particle Immunoassay were used to measure CRP. In order to assess insulin resistance,

HOMA-IR was calculated based on FBS (mmol/dL) times fasting insulin (mU/L) divided by 22.5.

Blood pressure (mmHg) was assessed by a random sphygmomanometer on the right arm after 5 minutes rest when participants were in the seated mode.
Pittsburgh Sleep Quality Index (PSQI), a self-rated 19-item questionnaire, was used to assess the sleep quality. The PSQI score (0-21) contains sleep onset latency, sleep efficiency, sleep quality, sleep disturbances, sleep duration, daytime dysfunction, and use of sleeping medication in the past month.
Psychiatric examinations, self-reported histories of depression, and medical records were used to obtain depression data. For the psychiatric examinations, participants were asked to fill a depression scale questionnaire (CES-D) in the centre. Also, a semi-structured clinical interview conducted by a clinician to diagnose depressive disorders. Additionally, individuals were screened for dementia by Mini-Mental State Examination (MMSE) and Geriatric Mental Schedule (GMS) at baseline and follow-up visits to the research centre.

Covariates:

Information about reasons for and age at menopause was collected at the interview in our research centre among women. The individuals' age was recorded at the baseline visit. Data on educational level [primary education with or without a partially completed higher education (primary); lower vocational or lower secondary education (lower); intermediate vocational education and or general secondary (intermediate); or higher vocational or university education (higher)], paid employment (yes/ no) as well as smoking status (never, past, or current smoker) were collected through self-report information and through the interview. Physical activity was assessed using the Zutphen Study Physical Activity Questionnaire and total time of physical activity was calculated as minutes per week for each type of activity. Physical activities were weighted and expressed in METh/week. Use of hormone replacement therapy (as never or ever) and medications were recorded from both the interview and through pharmacy records.

Statistical analysis:

We will apply Reduced rank regression (RRR) to derive dietary patterns. The details of this analytical method has been described by Hoffman et al (30). In brief, RRR determines the linear combination of predictor variables, which explain the most possible variation in the response variables.
In the current study, predictor variables contain food groups and the response variables define the most important health issues among women based on previous evidence, as specified above. Following this method, each participant will receive a factor score for the generated dietary patterns. These scores are the adherence status of participants to the dietary patterns. For the current study, we will select the first / first few dietary patterns that explain most variation for further analyses.

Table 1. Suggested food groups (predictor variables) to extract a dietary pattern using RRR.

Plant products				Animal products		Beverages	Others
Carbohydrate	**Vegetables**	**Fruits**	**Nuts**	**Meats/eggs**	**Dairy (low fat/high fat)**		
Whole grain products	Root vegetables	Canned fruits	All nuts	Processed meat	Milk (skimmed/ low/ high fat)	Sugar sweetened beverages	Plant-based oils and margarines
Non-whole/ refined grain products	Leafy vegetables	Raw fruits	Seeds	Fish (fatty/non fatty)	Fermented products (skimmed/ low/ high fat)	Beer and wine/ alcohol	Fast foods and take away foods
Legumes/ Beans	Cooked vegetables			Unprocessed red meat		Tea and coffee	Sweets
				Unprocessed poultry meat		Juice	
				Eggs			

Table 2. Response variables to extract a dietary pattern using RRR.

Cardiovascular risk factors	Body composition indices	Osteoporosis indices	Insulin resistance	Sleep disturbance	Inflammation	Cognition	Depressive symptoms
TC	WC	BMD	FBS	Total sleep time	CRP	MMSE score	CES-D score
HDL	WHR		Insulin	Sleep quality		GMS	
SBP	BMI		HOMA-IR				
TG	Fat-free mss						
	Fat mass						

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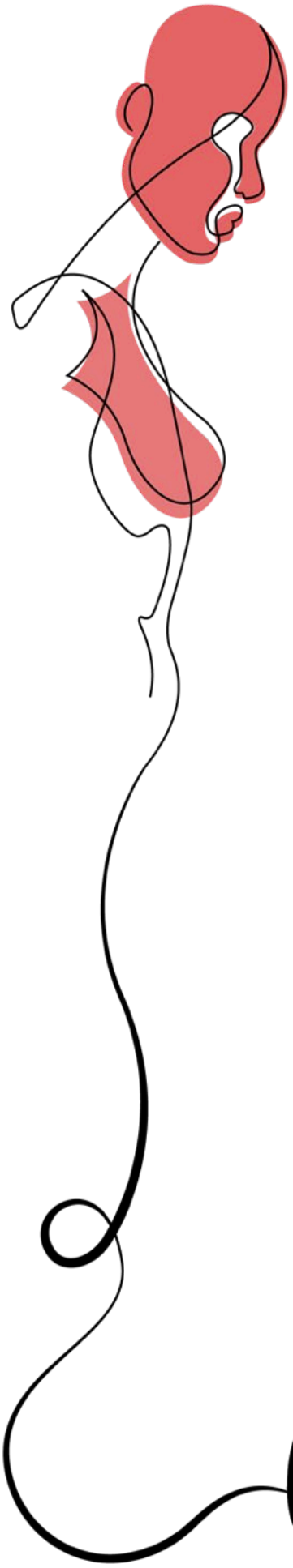

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"Every successful individual knows that his or her achievement depends on a community of persons working together."

Paul Ryan

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	Lucía Aguirre Sánchez, Zayne Milena Roa- Díaz, Magda Gamba, **Giorgia Grisotto**, Ana Maria Moreno Londoño, Blanca Patricia Mantilla-Uribe, Alba Yaneth Rincón Méndez, Mónica Ballesteros, Doris Kopp-Heim,Beatrice Minder, L. Suzanne Suggs,Oscar H. Franco. What influences the sustainable food consumption behaviours of university students? A Systematic Review. International Journal of Public Health (IJPH) 2021. doi:10.3389/ijph.2021.1604149

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Swiss Society of Endocrinology and Diabetology	2020 Online. Poster presentation: "Dietary behaviour changes before and after menopause in Swiss women."
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*Canceled to Covid-19

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11. DECLARATION OF ORIGINALITY

Declaration of Originality

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I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Bern, 9/05/2022

Signature