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

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A R T I C L E I N F O

Keywords:
Natural menopause
Menopause onset
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Late menopause
Diet
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Micronutrient
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A B S T R A C T

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

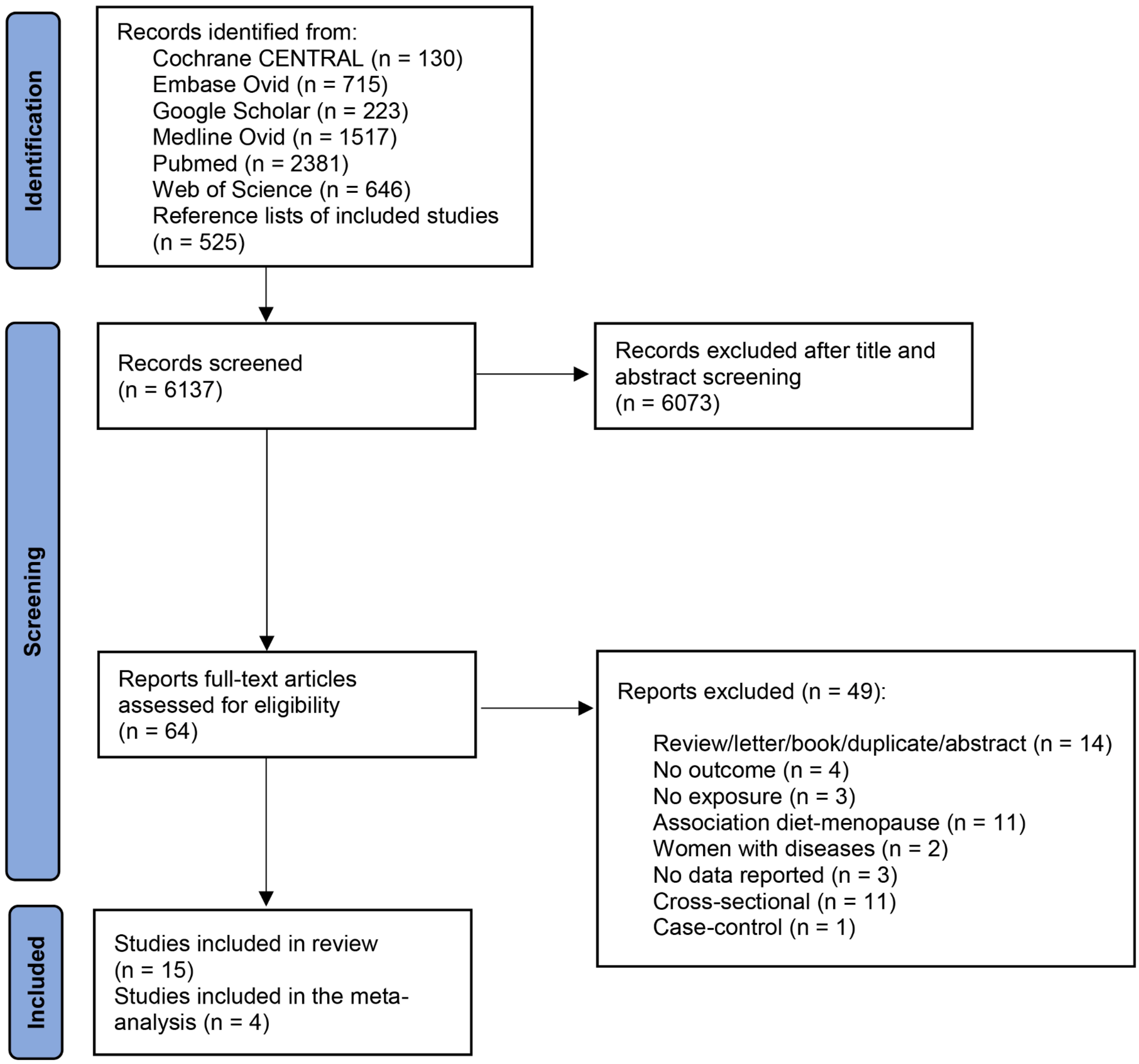

Fig. 1. PRISMA flow diagram of search strategy.

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*)

											• Soy isoflavones: Q1-Q4 • Alcohol: Q1-Q4
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	• 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])

Table 2 (*continued*)

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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			
		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 ($p < 0.06$)

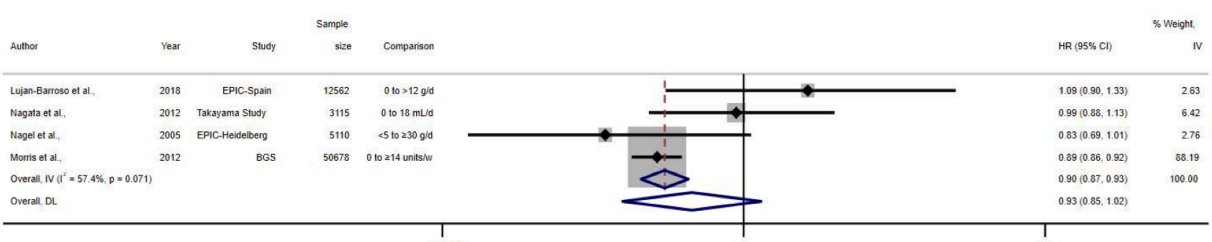

Fig. 2. Pooled relative risks for menopause onset when comparing women who reported lowest intake versus highest intake of alcohol in longitudinal studies. IV: random-effects model; Assessment of heterogeneity, I^2.

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].

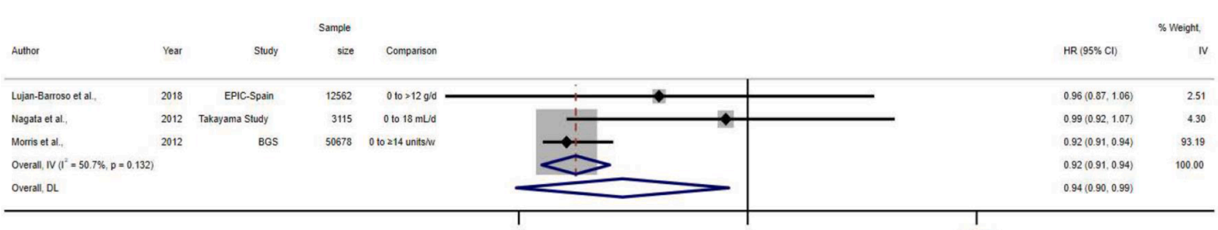

Fig. 3. Pooled relative risks for menopause onset when comparing alcohol consumers versus non-consumers in longitudinal studies. IV: random-effects model; Assessment of heterogeneity, I^2.

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.

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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.

References

[1] D.A. Schoenaker, C.A. Jackson, J.V. Rowlands, G.D. Mishra, Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents, Int. J. Epidemiol. 43 (43) (2014) 1542–1562, https://doi.org/10.1093/ije/dyu094.

[2] S.D. Harlow, M. Gass, J.E. Hall, R. Lobo, P. Maki, R.W. Rebar, S. Sherman, P. M. Sluss, T.J. de Villiers, Executive summary of the stages of reproductive aging workshop+10: addressing the unfinished agenda of staging reproductive aging, J. Clin. Endocrinol. Metab. 97 (2012) 1159–1168, https://doi.org/10.1210/jc.2011-3362.

[3] H.G. Burger, G.E. Hale, D.M. Robertson, L. Dennerstein, A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project, Hum. Reprod. 13 (6) (2007) 559–565, https://doi.org/10.1093/humupd/dmm020.

[4] E.B. Gold, The timing of the age at which natural menopause occurs, Obstet. Gynecol. Clin. North. Am. 38 (2011) 425–440, https://doi.org/10.1016/j.ogc.2011.05.002.

[5] J.H. Beard, S.F. Jacoby, Z. Maher, B. Dong, E.J. Kaufman, J.A. Goldberg, C. N. Morrison, Trends in age at natural menopause and reproductive life span among US women, 1959-2018, JAMA 325 (2021) 13, https://doi.org/10.1001/jama.2021.0278.

[6] J. Simpson, Genetics of premature ovarian failure [abstract], in: International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and the 69th Annual Meeting of the American Society for Reproductive Medicine, 2013, pp. 12–17.

[7] A.C. Purdue-Smithe, B.W. Whitcomb, K.L. Szegda, M.E. Boutot, J.E. Manson, S. E. Hankinson, B.A. Rosner, L.M. Troy, K.B. Michels, E.R. Bertone-Johnson, Vitamin D and calcium intake and risk of early menopause, Am. J. Clin. Nutr. 105 (6) (2017) 1493–1501, https://doi.org/10.3945/ajcn.116.145607.

[8] M.E. Boutot, A. Purdue-Smithe, B.W. Whitcomb, K.L. Szegda, J.E. Manson, S. E. Hankinson, B.A. Rosner, E.R. Bertone-Johnson, Dietary protein intake and early menopause in the Nurses' Health Study II, Am. J. Clin. Nutr. 187 (2) (2017) 270–277, https://doi.org/10.1093/aje/kwx256.

[9] S. Sapre, R. Thakur, Lifestyle and dietary factors determine age at natural menopause, J. Midlife Health 5 (1) (2014) 3–5, https://doi.org/10.4103/0976-7800.127779.

[10] Y. Dunneram, D.C. Greenwood, V.J. Burley, J.E. Cade, Dietary intake and age at natural menopause: results from the UK Women's Cohort Study, J. Epidemiol. Community Health 72 (2018) 733–740, https://doi.org/10.1136/jech-2017-209887.

[11] P.E. Taneri, J.C. Kiefte-de Jong, W.M. Bramer, N.M.P. Daan, O.H. Franco, T. Muka, Association of alcohol consumption with the onset of natural menopause: a systematic review and meta-analysis, Hum. Reprod. 22 (4) (2016) 516–528, https://doi.org/10.1093/humupd/dmw013.

[12] D.J. Torgerson, R.E. Thomas, M.K. Campbell, D.M. Reid, Alcohol consumption and age of maternal menopause are associated with menopause onset, Maturitas 26 (1997) 21–25, https://doi.org/10.1016/S0378-5122(96)01075-4.

[13] D.H. Morris, M.E. Jones, M.J. Schoemaker, E. McFadden, A. Ashworth, A. J. Swerdlow, Body mass index, exercise, and other lifestyle factors in relation to age at natural menopause: analyses from the breakthrough generations study, Am. J. Epidemiol. 175 (19) (2012) 998–1005, https://doi.org/10.1093/aje/kwr447.

[14] T. Muka, M. Glisic, J. Milic, S. Verhoog, J. Bohlius, W. Bramer, R. Chowdhury, O. H. Franco, A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research, Eur. J. Epidemiol. 35 (2020) 49–60, https://doi.org/10.1007/s10654-019-00576-5.

[15] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic review and meta-analyses: the PRISMA statement, PLoS Med. 339 (2009) b2535, https://doi.org/10.1136/bmj.b2535.

[16] G. Wells, B. Shea, D. O'Connell, J. Robertson, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses, 2000. Oxford.

[17] C. Nagata, K. Wada, K. Nakamura, Y. Tamai, M. Tsuji, H. Shimizu, Associations of physical activity and diet with the onset of menopause in Japanese women, Menopause 19 (2012) 75–81, https://doi.org/10.1097/gme.0b013e3182243737.

[18] B.H. Chang, D.C. Hoaglin, Meta-analysis of odds ratios: current good practices, Med. Care 55 (4) (2017) 328–335, https://doi.org/10.1097/MLR.0000000000000696.

[19] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, Br. Med. J. 327 (7414) (2003) 557–560, https://doi.org/10.1136/bmj.327.7414.557.

[20] G. Nagel, H.P. Altenburg, A. Nieters, P. Boffetta, J. Linseisen, Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg, Maturitas 52 (2005) 337–347, https://doi.org/10.1016/j.maturitas.2005.05.013.

[21] L. Lujan-Barroso, K. Gibert, M. Obón-Santacana, M.D. Chirlaque, M.J. Sánchez, N. Larrañaga, A. Barricarte, J.R. Quirós, E. Salamanca-Fernández, S. Colorado-Yohar, B. Gómez-Pozo, A. Agudo, E.J. Duell, The influence of lifestyle, diet, and reproductive history on age at natural menopause in Spain: analysis from the EPIC-Spain sub-cohort, Am. J. Hum. Biol. 30 (2018) e23181, https://doi.org/10.1002/ajhb.23181.

[22] T. Dorjgochoo, A. Kallianpur, Y.T. Gao, H. Cai, G. Yang, H. Li, W. Zheng, X.O. Shu, Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study, Menopause 15 (5) (2008) 924–933, https://doi.org/10.1097/gme.0b013e3181786adc.

[23] A.C. Purdue-Smithe, B.W. Whitcomb, J.E. Manson, S.E. Hankinson, B.A. Rosner, L. M. Troy, E.R. Bertone-Johnson, A prospective study of dairy-food intake and early menopause, Am. J. Epidemiol. 188 (1) (2018) 188–196, https://doi.org/10.1093/aje/kwy212.

[24] A. Kinney, J. Kline, B. Levin, Alcohol, caffeine and smoking in relation to age at menopause, Maturitas 54 (2006) 27–38, https://doi.org/10.1016/j.maturitas.2005.10.001.

[25] K. Pearce, K. Tremellen, Influence of nutrition on the decline of ovarian reserve and subsequent onset of natural menopause, Hum. Fertil. 19 (3) (2016) 173–179, https://doi.org/10.1080/14647273.2016.1205759.

[26] C. Nagata, N. Takatsuka, N. Kawakami, H. Shimizu, Association of diet with the onset of menopause in Japanese women, Am. J. Epidemiol. 152 (9) (2000), https://doi.org/10.1093/aje/152.9.863.

[27] Y. Dunneram, D.C. Greenwood, J.E. Cade, Dietary patterns and age at natural menopause: evidence from the UK Women's Cohort Study, Maturitas 143 (2021) 165–170, https://doi.org/10.1016/j.maturitas.2020.10.004.

[28] J.L. Carwile, W.C. Willett, K.B. Michels, Consumption of low-fat dairy products may delay natural menopause, J. Nutr. 143 (10) (2013) 1642–1650, https://doi.org/10.3945/jn.113.179739.

[29] E.B. Gold, S.L. Crawford, N.E. Avis, C.J. Crandall, K.A. Matthews, L.E. Waetjen, J. S. Lee, R. Thurston, M. Vuga, S.D. Harlow, Factors related to age at natural menopause: longitudinal analyses from SWAN, Am. J. Epidemiol. 178 (1) (2013) 70–83, https://doi.org/10.1093/aje/kws421.

[30] P. Muti, M. Trevisan, A. Micheli, V. Krogh, G. Bolelli, R. Sciajno, H.J. Schunemann, F. Berrino, Alcohol consumption and total estradiol in premenopausal women, Cancer Epidemiol. Biomarkers Prev. 7 (1998) 189–193.

[31] M.C. Playdon, S.B. Coburn, S.C. Moore, L.A. Brinton, N. Wentzensen, G. Anderson, R. Wallace, R.T. Falk, R. Pfeiffer, X. Xu, B. Trabert, Alcohol and oestrogen metabolites in postmenopausal women in the Women's Health Initiative Observational Study, Br. J. Cancer 118 (2018) 448–457, https://doi.org/10.1038/bjc.2017.419.

[32] K.J. Mukamal, C.M. Chen, S.R. Rao, R.A. Breslow, Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002, J. Am. Coll. Cardiology 55 (2010) 13, https://doi.org/10.1016/j.jacc.2009.10.056.

[33] X.H. Li, F.F. Yu, Y.H. Zhou, J. He, Association between alcohol consumption and the risk of incident type 2 diabetes: a systematic review and dose-response meta-analysis, Am. J. Clin. Nutr. 103 (3) (2016) 818–829, https://doi.org/10.3945/ajcn.115.114389.

[34] M. Iwase, K. Matsuo, Y.N.Y. Koyanagi, H. Ito, A. Tamakoshi, C. Wang, M. Utada, K. Ozasa, Y. Sugawara, I. Tsuji, N. Sawada, S. Tanaka, et al., Alcohol consumption and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies, Int. J. Cancer Res. 148 (2021) 2736–2747, https://doi.org/10.1002/ijc.33478.

[35] N. Moslehi, P. Mirmiran, F. Azizi, F.R. Tehrani, Do dietary intakes influence the rate of decline in anti-Mullerian hormone among eumenorrheic women? A population-based prospective investigation, J. Nutr. 18 (2019) 83, https://doi.org/10.1186/s12937-019-0508-5.

[36] B. Perlman, D. Kulak, L.T. Goldsmith, G. Weiss, The etiology of menopause: not just ovarian dysfunction but also a role for the central nervous system, Glob. Reprod. Health 3 (2018) e08, https://doi.org/10.1097/GRH.0000000000000008.

[37] G. Pugliese, L. Barrea, D. Laudisio, S. Aprano, B. Castellucci, L. Framondi, R. Di Matteo, S. Savastano, A. Colao, G. Muscogiuri, Mediterranean diet as tool to manage obesity in menopause: a narrative review, Nutrition (2020) 79–80, https://doi.org/10.1016/j.nut.2020.110991.

[38] S.O. Mueller, S. Simon, K. Chae, M. Metzler, K.S. Korach, Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor a (ERa) and ERb in human cells, Toxicol. Sci. 80 (2004) 14–25, https://doi.org/10.1093/toxsci/kfh259.

[39] C. Nagata, N. Takatsuka, S. Inaba, N. Kawakami, H. Shimizu, Association of diet and other lifestyle with onset of menopause in Japanese women, Maturitas 29 (1998) 105–113, https://doi.org/10.1016/S0378-5122(98)00012-7.

[40] S. Khanduker, R. Ahmed, M. Nazneen, A. Alam, F. Khondokar, A comparative study of lipid profile and Atherogenic Index of Plasma among the pre and post-menopausal women, answer, Khan. Mod. Med. Coll. J. 9 (2018) 1, https://doi.org/10.3329/akmmcj.v9i1.35824.

[41] G.A. Colditz, M.J. Stampfer, W.C. Willett, W.B. Stason, B. Rosner, C.H. Hennekens, F.E. Speizer, Reproducibility and validity of self-reported menopausal status in a prospective cohort study, Am. J. Epidemiol. 126 (2) (1987) 319–325, https://doi.org/10.1093/aje/126.2.319.