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ORIGINAL STUDY

Association of plant-based diet and early onset of natural 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]; 44.9 [4.3]) and 1991 (age mean [standard deviation]; 36.4 [4.6]), respectively. Early menopause was self-reported and defined as natural menopause before age 45 years. PDI was derived from semiquantitative food frequency questionnaires administered every 4 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 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 unhealthy plant-based diet might be associated with higher risk of experiencing early menopause.

Key Words: Early natural menopause – Healthy plant-based diet – Menopause onset – Plant-based diet – Prospective study – Unhealthy plant-based diet.

Menopause, the cessation of ovarian function, occurs generally between the ages of 45 and 55 years, and represents the end of a woman's reproductive life. Around 5% to 10% of women in Western countries experience menopause before age 45, defined as early menopause.[1] Early menopause is associated with long-term health consequences, including osteoporosis, type 2 diabetes, cardiovascular disease, 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

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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 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 type 2 diabetes, cardiovascular disease, 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 to 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 to 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, MA.

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 y). From the 121,701 women at the time of enrollment 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 food frequency questionnaires (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 y). 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 postmenopause 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 semiquantitative 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 nine categories, from "never or less than once/month" to "≥ 6 times/d." 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 the plant food group, and reverse score was given for foods included in the animal food group. For creating hPDI, foods in the healthy plant food group were given positive scores, and foods in the less healthy plant food group and animal food group were given reverse scores. For uPDI, foods in the less healthy plant food group were given positive scores, while foods in the 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 to 85 for PDI, 28 to 86 for hPDI and 27 to 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 4 years and was based on metabolic equivalent of task hours per week (MET-h/wk). Dietary factors, including total caloric intake (Kcal/d), 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 y), death, loss to follow-up, experienced no natural menopause (eg, 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, 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 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 y, former ≥ 5 y) 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) y], reported less use of oral contraceptives [Q5 28.4 (40.3) vs. Q1 34.1 (45.8), mo], 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) y], reported less use of oral contraceptives [Q5 44.2 (43.7) vs. Q1 51.8 (49.4), mo], 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 2,137 (527) vs. Q1 1,478 (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

TABLE 1. *Baseline characteristics of women in the Nurses Health Study*

Characteristics[a]	Plant-based diet index (PDI)				
	Quintile 1 (*n* = 5,575)	Quintile 2 (*n* = 5,970)	Quintile 3 (*n* = 5,079)	Quintile 4 (*n* = 5,899)	Quintile 5 (*n* = 5,188)
Age, y	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/d	1,486 (453)	1,648 (486)	1,770 (485)	1,905 (512)	2,108 (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)

Values are means (SD) for continuous variables; percentages for categorical variables are standardized to the age distribution of the study population.
IU, international unit; MET, metabolic equivalent task.
[a]Age-adjusted and time period.
[b]Includes among users only.
[c]Includes parous women only.

age-adjusted model (Model 1), PDI was not associated with early menopause in either the NHS [HR (95% CI), Q5 vs. Q1 0.85 (0.66-1.08)] or NHSII [Q5 vs. Q1 0.89 (0.78-1.01)]. Also, results adjusted for age and caloric intake (Model 2) (NHS, Q5 vs Q1 0.9 [0.68-1.17]; NHSII, Q5 vs Q1 0.95 [0.82-1.1]) and for all other potential factors (Model 3) (NHS, Q5 vs Q1 0.94 [0.73-1.2]; NHSII, Q5 vs Q1 0.95 [0.83-1.08]) showed no association of plant foods intake 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 [1.03-1.31], 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 Supplemental Digital Content 1, http://links.lww.com/MENO/A957, 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 Supplemental Digital Content 2, http://links.lww.com/MENO/A958, 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 Supplemental Digital Content 3, http://links.lww.com/MENO/A959, 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 y, former ≥ 5 y) (see Supplemental Digital Content 4, http://links.lww.com/MENO/A960, 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.

TABLE 2. *Baseline characteristics of women in the Nurses Health Study II*

Characteristics[a]	Plant-based diet index (PDI)				
	Quintile 1 (*n* = 19,299)	Quintile 2 (*n* = 13,457)	Quintile 3 (*n* = 20,644)	Quintile 4 (*n* = 17,819)	Quintile 5 (*n* = 16,876)
Age, y	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/d	1,478 (463)	1,642 (486)	1,773 (501)	1,937 (513)	2,137 (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)

Values are means (SD) for continuous variables; percentages for categorical variables are standardized to the age distribution of the study population.
IU, international unit; MET, metabolic equivalent of task.
[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 NHS II, 1991-2011[c]*

PDI	Event/person-y	Model 1[d]		Model 2[e]		Model 3[f]	
		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	0.72-1.15	0.92	0.73-1.17	0.94	0.75-1.2
Quantile 3	137/31463	0.93	0.74-1.18	0.95	0.75-1.21	0.98	0.77-1.24
Quantile 4	157/31818	1.1	0.85-1.34	1.1	0.87-1.4	1.15	0.91-1.44
Quantile 5	118/28471	0.85	0.66-1.08	0.9	0.68-1.17	0.94	0.73-1.2
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	0.78-1.03	0.92	0.8-1.05	0.92	0.8-1.06
Quantile 3	489/258222	0.90	0.79-1.02	0.94	0.82-1.07	0.93	0.82-1.06
Quantile 4	421/232647	0.86	0.75-0.98	0.91	0.79-1.04	0.91	0.79-1.04
Quantile 5	414/219820	0.89	0.78-1.01	0.95	0.82-1.1	0.95	0.83-1.08
P trend		0.06		0.48		0.39	

BMI, body mass index; HR, hazard ratio; NHS, Nurses Health Study; PDI, plant-based dietary index.
[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 (0.75-1.2)	0.98 (0.77-1.24)	1.15 (0.91-1.44)	0.94 (0.73-1.2)	0.84
NHSII	1.0 (ref)	0.92 (0.8-1.06)	0.93 (0.82-1.06)	0.91 (0.79-1.04)	0.95 (0.83-1.08)	0.39
Meta-analysis	1.0 (ref)	0.93 (0.82-1.04)	0.94 (0.84-1.05)	0.96 (0.86-1.08)	0.95 (0.84-1.06)	0.52
hPDI[a]						
NHS	1.0 (ref)	1.19 (0.97-1.46)	1.02 (0.81-1.28)	0.96 (0.74-1.24)	1.15 (0.88-1.5)	0.70
NHSII	1.0 (ref)	0.99 (0.87-1.14)	0.98 (0.86-1.12)	0.95 (0.83-1.09)	1.07 (0.93-1.23)	0.51
Meta-analysis	1.0 (ref)	1.05 (0.94-1.17)	0.99 (0.88-1.11)	0.95 (0.85-1.07)	1.09 (0.96-1.23)	0.45
uPDI[a]						
NHS	1.0 (ref)	0.92 (0.69-1.22)	0.97 (0.75-1.27)	0.98 (0.76-1.28)	1.12 (0.88-1.44)	0.19
NHSII	1.0 (ref)	1.03 (0.9-1.18)	1.1 (0.95-1.26)	1.21 (1.06-1.39)	1.05 (0.91-1.21)	0.11
Meta-analysis	1.0 (ref)	1.01 (0.89-1.14)	1.07 (0.95-1.21)	1.16 (1.03-1.31)	1.07 (0.95-1.21)	**0.04**

Quantiles and *P* for trend (bold significant <0.05), read by meta-analysis, are reported. RRs and 95% CIs for PDI, hPDI, and uPDI in NHS and NHSII.
BMI, body mass index; NHS, Nurses Health Study; PDI, plant-based dietary index.
[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).

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 nonvegetarian.[8,18] Also, studies exploring the impact of fruit intake, a component of PDI, have shown controversial results, two studies have shown 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 prevent the 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 the 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 2 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 US population although our results should not differ from other women in US 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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