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Dietary patterns and age of natural menopause: evidence from the UK Women's Cohort Study

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ABSTRACT

Objectives

To investigate prospective associations between dietary patterns and age of natural menopause.

Study design and main outcome measures

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

Results

Five patterns were identified from the PCA, labelled as: 'vegetables and legumes', 'animal proteins', 'fruits', 'fats and sweets' and 'low-fat products'. Three patterns were derived from RRR: 'sweets, pastries and puddings', 'low-fat dairy and meat', and 'red meat and processed meat'. Women who scored 1 standard deviation higher on the 'animal proteins' pattern were 6% more likely to experience a later natural menopause over the study (HR= 0.94, 95% CI: 0.90 to 0.97) compared to those who scored lower. The 'red meat and processed meat' pattern similary predicted a 7% higher risk for a later menopause during the study (HR= 0.93, 95% CI: 0.87 to 1.00) per 1 standard deviation.

Conclusions

Diets which are highly loaded with animal proteins, as well as, red and processed meats are more likely to have a later natural menopause.

Keywords: dietary patterns, natural menopause, UK Women's Cohort Study, principal component analysis, reduced ranked regression

1. Introduction

The current life expectancy of females in the United Kingdom is estimated to be 82.9 years [1], and the average age of menopause is 51 years [2]. Women in the UK therefore spend around one-third of their life in the menopausal state. The timing of menopause influences future health outcomes, such that an early age at menopause increases risk of bone fractures and cardiovascular diseases while an increased risk of breast, ovarian and endometrial cancer have been associated with a late onset of menopause [3]. The onset of menopause is influenced by several factors, potentially including diet.

Recently, emphasis has been placed on exploring dietary patterns rather than individual food or food groups in examining diet and disease relationships. The complex mechanisms, by which the diet may influence a disease or a health outcome makes the study of dietary patterns important [4, 5]. Several different methods have been used to define dietary patterns including theoretical, empirical and hybrid methods [6]. Principal component analysis (PCA), one of the empirical methods, uses the correlation matrix of food intake variables to identify common patterns of food consumption within the data by accounting for the largest amount of variation in the diet [6, 7]. Reduced rank regression (RRR), is a hybrid method recently used to generate dietary patterns [8]. This technique identifies dietary patterns based on several nutrients or biomarkers which are linked to the disease of interest [7]. The strength of PCA can be the limitation of RRR and vice versa. Both methods use data reduction techniques to generate dietary patterns. PCA derived dietary patterns tend to reflect the actual dietary behaviours of the population while RRR dietary patterns could be behaviourally irrelevant as the food components forming part of the patterns may not be consumed together [9]. Dietary patterns derived from RRR are based on biologically relevant factors. Therefore, comparing findings using both methods could provide useful insights for this study.

To date, mostly individual foods and food groups have been studied in relation to age at menopause [10, 11]. Therefore, this study aims to compare dietary patterns derived by PCA and RRR and to investigate their associations prospectively with age at natural menopause. For RRR, selected response variables represent important risk factors of the timing of natural menopause. Factors such as age at menarche, body mass index (BMI) and total energy intake [3, 10-12] have all been associated with the timing of menopause. However, the conflicting findings make a definitive conclusion on risk factors difficult. Therefore, the RRR derived dietary patterns should be considered as an initial hypothesis, rather than patterns with a confirmed association.

2. Methods

2.1. Study design and participants

14,172 women from the UKWCS [13] who participated at both baseline and follow-up were considered for this study. Informed consent was obtained from all participants at baseline. Women aged 35 years or more responded to self-administered questionnaires which asked about demographic details, weight history, physical activity, reproductive history, anthropometric, and other health-related factors. Age at natural menopause was defined as the age at the last menstrual period prior to permanent cessation of menstruation for 12 consecutive months [14]. To be considered naturally postmenopausal at follow-up, women at baseline had to be pre or peri-menopausal, that is, having one or more menstrual periods in the previous 12 months, not pregnant and never used hormone therapy as well as not using hormone therapy at follow-up since these endogenous hormones may influence the bleeding pattern.

2.2. Dietary assessment

Diet was assessed using a validated 217-item food frequency questionnaire (FFQ) which was developed from the FFQ used in the European Prospective Investigation into Cancer (EPIC) study. Participants were asked to report their consumption frequency based on 10 pre-coded classifications of frequency of consumption ranging from ‘never’ to ‘6 or more times per day’ over the last 12 months. The reported frequency for each food item was then converted to daily intake.

2.3. Statistical analyses

PCA and RRR were used to derive dietary patterns. While the rank of the covariance matrix used for PCA corresponds to the number of foods/food groups; in the RRR method, the rank corresponds to the number of selected response variables. To compare the results from PCA and RRR, we followed previous recommendations to base this on the minimum number of foods/food groups and response variables for each method [7]. Therefore, to simplify our data, the 217 individual food items (in grams/day) were classified into 64 food groups according to the similarity of nutrient profiles and culinary usage of the foods [15]. All 64 food groups were subsequently used to identify dietary patterns. The number of factors retained was according to the combination of food group components with an eigenvalue >1.0 and examination of the breakpoint in the scree plot (Supplementary figure 1), resulting in five factors retained from PCA for further analyses. The factors were rotated by an orthogonal transformation (Varimax option) to achieve a simpler structure with greater interpretability. Food groups with a factor loading ≥0.2 on a component were considered informative for interpretation of the dietary patterns.

RRR was applied to derive dietary patterns predictive of age at natural menopause using Stata (StataCorp, version 14.0) in combination with the PLS procedure in SAS (version 9.3; SAS Institute). The aim of the RRR method is to determine the linear combinations of predictor variables (e.g., food group intake) that explain as much as of the variation in the response variables (e.g., nutrients, biomarkers or risk factors) as possible, which can potentially affect disease risk, in this case, menopausal status [7, 16]. A directed acyclic graph was used as the conceptual framework for the RRR (Supplementary figure 2). The 64 food groups were entered as the predictor variables and the variables BMI, total energy intake and age at menarche were treated as response variables. Factor scores were calculated for each of the derived patterns by summing the products of the observed consumption frequency and the factor loading for each of the significant food groups. The groups that had a negative factor loading were also retained to maintain the complexity of eating habits.

Cox's proportional hazard models were fitted for each dietary pattern (using the dietary pattern scores as exposure) separately to identify the predictors of age at natural menopause using Stata (StataCorp, version 14.0). At follow-up, if the event was not a natural menopause, this was considered as censored. Age at phase 2 was considered as the time-scale variable for women who were still menstruating at follow-up while for those who were naturally postmenopausal at phase 2, their age of last natural period was used as the time variable [17]. Therefore, women who were postmenopausal, using hormone therapy, had a hysterectomy or oophorectomy at baseline; using hormone therapy at follow-up when still menstruating and those for whom age at natural menopause was either before the age of 40y (as this could be chemically induced) or after 65y were all excluded from the analyses (**Error! Reference source not found.**). Moreover, in this time-to-event model, women who were already postmenopausal at baseline were excluded as no information were available to infer whether they had a natural menopause. The proportional hazards assumption was tested graphically for all exposures and covariates in the model as well as using Schoenfeld residuals. The regression models were adjusted for potential confounding factors: physical activity (MET-hours/week), smoking status (current vs. not current smoker), alcohol consumption (g/day) and social class (routine/manual, intermediate, professional/ managerial) as suggested by a directed acyclic graph (DAG) (Supplementary material). Results of the regression models are expressed as hazard ratios (HR) and 95% CIs. A HR >1.00 represented a positive association with the incidence of a natural menopause, that is risk of an earlier menopause, per standard deviation (SD) of the continuous dietary pattern score.

3. Results

3.1. Dietary patterns

Using PCA, five dietary patterns were identified that together explained 16% of the variance in dietary intake as measured by the FFQ (**Error! Reference source not found.**). Factor 1 was labelled 'vegetables and legumes', Factor 2 as 'animal proteins', Factor 3 as 'fruits', Factor 4 as 'fats and sweets' and Factor 5 as 'low-calorie fats' (Supplementary material). Whilst these labels are subjective, they describe the over-riding characteristics of the components, which formed distinct components after rotation.

For the RRR method, three dietary patterns were identified and allocated a subjective label. The three dietary patterns explained about 29% of the total variance in dietary intake. Factor 1: 'sweets, pastries and puddings', Factor 2: 'low-fat dairy and meat', Factor 3: 'red meat and processed meat' (**Error! Reference source not found.**).

3.2. Participants' characteristics

General characteristics and nutrient intake of included and excluded participants are shown in Table 2. Excluded participants, mostly as a result of not completing the phase 2 questionnaire, were older at baseline compared to particpants included in the final analysis (mean±standard deviation: 45.3y±5.5 vs 56.7y±8.1). Fewer excluded participants had achieved a degree level and were from the professional and managerial class. The excluded women also had a higher BMI and lower physical activity level and alcohol consumption as compared to included women. Participants' characteristics also differed according to the lowest versus the highet quintiles of the dietary patterns' score as described in Supplementary tables 1 and 2.

3.3. Correlation between dietary patterns derived using principal component analysis and reduced rank regression

The ‘vegetables and legumes’ dietary pattern was strongly and positively correlated to the ‘sweets, pastries and puddings’ dietary pattern while it was negatively correlated with the ‘red meat and processed meat’ dietary pattern (Table 3). The ‘animal proteins’ dietary pattern had a positive correlation with the ‘low-fat dairy and meat’ and ‘red meat and processed meat dietary patterns. ‘Low-calorie fats’ had a strong positive correlation with the ‘low-fat dairy and meat’ dietary pattern. It conversely had a weak negative correlation with the ‘red meat and processed meat’.

3.4. Association between dietary patterns and age at natural menopause

For dietary patterns derived by PCA, the unadjusted model demonstrated 5% higher risk for a later natural menopause among women who scored 1 SD higher on the ‘animal proteins’ (HR=0.95, 95% CI: 0.91 to 0.98) compared to women who had a lower score. On the other hand, the ‘fruits’ pattern was associated with a lower risk for a later natural menopause (HR=1.05, 95% CI: 1.01 to 1.09) per 1 SD. No evidence of an association was found between the ‘vegetables and legumes’, ‘fats and sweets’, and ‘low-calorie fats’ and age at natural menopause (Table 4). After adjusting for potential confounders, the ‘animal proteins’ dietary pattern was still associated with a risk for a later age at natural menopause (HR=0.94, 95% CI: 0.90 to 0.97) per 1 SD.

In the unadjusted model, no evidence of an association was found between the dietary patterns derived from the RRR. After adjusting for potential confounders: smoking status, education level, social class, physical activity level, women who scored 1 SD higher on the ‘red meat and processed meat’ pattern were more likely to have a later menopause (HR=0.93, 95% CI: 0.87 to 1.00), while no evidence of an association was found with the ‘sweets, pastries and puddings’ (HR=0.96, 95% CI: 0.88 to 1.04) per 1 SD and ‘low-fat dairy and meat’ patterns (HR=0.97, 95% CI: 0.90 to 1.04) per 1 SD.

4. Discussion

Our objective was to determine whether certain dietary patterns are associated with the likelihood of becoming menopausal during the ~4 year follow-up period of the UKWCS. We identified five dietary patterns using PCA while three patterns were derived using RRR.

Dietary patterns generated from this study are in line with other studies that looked at dietary patterns and health outcomes among postmenopausal women [18, 19]. To our knowledge, this is the first study demonstrating a link between dietary patterns and age at natural menopause.

Given that the aims of the two statistical methods differ, such that PCA derived patterns usually reflect the dietary behaviours in the population; while RRR derived patterns are based on the risk factors for the health outcome, different dietary patterns can be expected in the same study sample. Nevertheless, in this study dietary patterns generated by the two methods indicated similar concepts which were correlated. We found that the 'animal proteins' pattern was moderately correlated with the RRR-patterns 'low-fat dairy and meat' and the 'red meat and processed meat'. The PCA-pattern 'fats and sweets' was moderately correlated with the 'sweets, pastries and puddings' pattern derived from RRR. Sauvageot et al. [20] also reported dietary patterns derived using PCA and RRR to be similar.

Comparing the relationship between dietary patterns and the chance of experiencing menopause, we found that the 'animal proteins' pattern derived from PCA and the 'red meat and processed meat' pattern derived from RRR were found to be associated with a higher chance of experiencing a later menopause. As no previous study has specifically investigated dietary patterns in relation to the timing of natural menopause direct comparison with other studies is impossible. However, in line with the few studies that have evaluated the association between food groups or individual food items and age at natural menopause, a later onset of menopause has been demonstrated with the consumption of meat [11, 21]. On the other hand, according to a recent study including women from the Nurses' Health Study II, a higher risk of an earlier menopause was reported with each serving per day of red meat and no evidence of an association was demonstrated between animal protein intake and an early menopause [22]. This disparity in findings may be due to meat consumption being explored individually in those studies rather than as part of a dietary pattern. Additionally, the Nurses' Health Study II consisted of much younger women at study entry (25-42 years) to investigate the risk of an early menopause, while women in the UKWCS were older at baseline and we explored the association between overall risk of menopause and diet.

Some components in red meat such as heme iron, heterocyclic amines in cooked meat and exogenous hormone residues are potentially estrogenic [23]. Therefore, the consumption of red and processed meats could lead to a higher circulating estrogen level and contribute to the feedback mechanisms of the menstrual cycle. Supporting this hypothesis, a randomized controlled trial among 272 premenopausal women demonstrated that serum levels of estrone and estradiol were higher among non-vegetarians as compared to with minimal meat intake (vegetarians and pescatarians) [24]. Moreover, according to a cross-sectional study among women in the Nurses' Health Study, a 'Western' dietary pattern which was highly loaded with intakes of red and processed meats, refined grains, sweets, and desserts was associated with a higher level of estradiol [25]. On the other hand, a traditional Mediterranean diet, that is lower in animal fats and proteins and higher in vegetables and fruits was associated with a reduced endogenous level of estrogen [26]. Similarly, in our study, the 'animal proteins' pattern was positively correlated with the RRR-derived 'sweets, pastries and puddings' and 'red meat and processed meat' patterns. The 'red meat and processed meat' pattern was also negatively correlated with the 'vegetables and legumes' pattern generated from PCA.

According to a systematic review, premature ovarian failure is characterised by amenorrhea, hypergonadotropinemia as well as estrogen deficiency [27]. Furthermore, an increased level of follicle stimulating hormones (FSH) at the start of the menstrual cycle could mean an earlier reproductive ageing [28]. Estrogen and FSH levels are related; higher estrogen levels have been associated with a reduced level of FSH which possibly lead to delayed or skipped ovulations. Consequently, it is plausible that by sustaining the hormonal feedback loop and by preventing or delaying the ovum from undergoing ovulation, a higher estrogen level could delay the onset of menopause. However, the exact mechanism for the association between estrogen level and the timing of menopause still needs to be elucidated.

Our study has some potential limitations. These include the use of an FFQ to estimate dietary intake, and self-reported age at natural menopause which are both prone to measurement error. However, the FFQ used in this study has been previously validated against biomarkers [13]. The participants were also unaware of the study hypothesis at the time of completing the questionnaire, so they are unlikely to have recalled the outcome or diet selectively. Additionally, losses to follow-up are inevitable in cohort studies. However, there was no evidence that these losses were not related to diet. The RRR method is also limited due to the data-driven approaches, including that the identified dietary patterns are specific to the population under study. This issue can be partly addressed by validating the method in other populations [29]. Another concern is that RRR is unlikely to generate dietary patterns that are linked to most or all potential pathways through which diet can influence the age at onset of natural menopause. In addition, it is important that the response variables have been investigated in relation to the health outcome in the same population [30]. Therefore, caution should be applied when extrapolating these findings in different study populations. Furthermore, both RRR and PCA have several weaknesses owing to the subjective choices for determining the variable scale, the number of variables and factors as well as interpretation of the dietary patterns [31].

An important strength of our study is the prospective investigation of dietary patterns with regard to age at natural menopause in a large cohort. Previous studies have mainly investigated the relationship between individual food items and the age at natural menopause instead. The advantage of using dietary pattern is that it can be a proxy measure for other variables which can be associated with age at natural menopause as they may be a constituent of a larger pattern of healthy or unhealthy habits. This study also benefits from including two different methods, PCA and RRR, to study dietary patterns in relation to incidence of being naturally menopausal. Moreover, after controlling for potential confounders, dietary patterns derived from PCA and RRR were still significantly associated with the onset of natural menopause. Thiébaut and Bénichou [17] demonstrated that the use of age as the time-scale for Cox's regression in cohort studies results in less bias than time-on-study, especially where the exposure is strongly associated with age. Therefore, age at follow-up was considered as the time-scale variable for women who were still menstruating at follow-up instead of time-on-study. Using age as the time-scale allows for flexible control of the effects of age and avoids the need to include age as a confounder. Moreover, this method provides a more meaningful basis to explore the fact that the risk of becoming menopausal changes over time [32].

5. Conclusion

Our study showed that a diet rich in animal proteins as well as red and processed meats was associated with a delayed onset of menopause. Both PCA and RRR are useful in deriving dietary patterns that are associated with the onset of natural menopause. These findings will contribute to an improved understanding of the timing of natural menopause in relation to diet, which may also have implications associated with longer-term health outcomes in post-menopausal women.

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Table 1 Factor loadings for food groups with a value ≥0.2 in varimax rotated principal components and for reduced rank regression*

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

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

Table 2 General characteristics and nutrient intake for included and excluded participants

General characteristics	**Included participants (n=5,312)**	**Excluded participants (n=8,860)**
Age at baseline, y[a]	45.3 ± 5.5	56.7 ± 8.1
Body mass index, kg/m²	23.5 ± 4.2	24.5 ± 4.3
Obese, ≥30 kg/m² [*n* (%)]	309 (6.0)	809 (9.5)
Physical activity, min/day	0.3 ± 0.5	0.2 ± 0.5
Alcohol consumption, g/day	9.2 ± 10.5	7.9 ± 10.5
Smoking, [*n* (%)]	449 (8.6)	734 (8.6)
Parous, [*n* (%)]	3,741 (74.0)	6,739 (81.5)
Ever married, [*n* (%)]	4,135 (78.8)	6,518 (74.8)
Degree level, [*n* (%)]	2,001 (39.1)	1,988 (25.1)
Professional and managerial class, [*n* (%)]	3,685 (70.3)	5,507 (63.6)
Nutrient intake		
Fibre (g)	26.1 ± 10.9	26.3 ± 10.8
% energy from fats	32.6 ± 5.7	31.9 ± 5.7
% energy from proteins	14.7 ± 2.5	15.5 ± 2.6
% energy from carbohydrates	50.0 ± 6.2	50.3 ± 6.4
Vitamin C (mg)	169.2 ± 94.8	177.1 ± 89.4
Vitamin B_1 (mg)	3.3 ± 2.8	3.0 ± 2.5
Vitamin B_2 (mg)	2.5 ± 0.9	2.6 ± 0.9
Vitamin B_6 (mg)	2.7 ± 1.0	2.8 ± 1.0
Vitamin B_{12} (µg)	170.2 ± 380.5	214.1 ± 450.0
Folate (µg)	403.0 ± 144.2	413.6 ± 146.5
Vitamin D (µg)	3.0 ± 1.7	3.3 ± 1.9
Vitamin A (µg)	1198.6 ± 567.4	1293.5 ± 625.2
Vitamin E (mg)	10.3 ± 4.7	9.8 ± 4.5
Calcium (mg)	1151.6 ± 408.3	1167.8 ± 400.0
Iron (mg)	18.4 ± 7.4	18.8 ± 8.0
Zinc (mg)	11.1 ± 4.4	11.6 ± 4.0

[a]mean ± SD (all such values)

Table 3 Correlation between dietary patterns derived from principal component analysis and reduced rank regression (n=13,916)

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

Table 4 Adjusted and unadjusted hazard ratios (HR) for age at natural menopause and corresponding 95% confidence intervals (CI)

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

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

Figure 1 Flow diagram for participant selection