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Relative to processed red meat, alternative protein sources are associated with a lower risk of hypertension and diabetes in a prospective cohort of French women

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Abstract

Many dietary guidelines recommend restricting the consumption of processed red meat (PRM) in favour of healthier foods such as fish, to reduce the risk of chronic conditions such as hypertension and diabetes. The objective of this study was to estimate the potential effect of replacing PRM for fatty fish, lean fish, red meat, eggs, pulses, or vegetables, on the risk of incident hypertension and diabetes. This was a prospective study of women in the E3N cohort study. Cases of diabetes and hypertension were based on self-report, specific questionnaires, and drug reimbursements. In the main analysis, information on regular dietary intake was assessed with a single food history questionaire, and food substitutions were modelled using cox proportional hazard models. 95 % confidence intervals were generated via bootstrapping. 71 081 women free of diabetes and 45 771 women free of hypertension were followed for an average of 18·7 and 18·3 years, respectively. 2681 incident cases of diabetes and 12 327 incident cases of hypertension were identified. Relative to PRM, fatty fish was associated with a 15 % lower risk of diabetes (HR = 0·85, 95 CI (0·73, 0·97)) and hypertension (HR = 0 85 (0·79, 0·91)). Between 3 and 10 % lower risk of hypertension or diabetes was also observed when comparing PRM with vegetables, unprocessed red meat or pulses. Relative to PRM, alternative protein sources such as fatty fish, unprocessed red meat, vegetables or pulses was associated with a lower risk of hypertension and diabetes.

Key words: **Processed red meat: Fish: Substitutions: Hypertension: Diabetes**

Hypertension and diabetes are two of the main drivers of cardiovascular disease (CVD)[1–3], with both diseases augmenting the risk of stroke and heart attack. A large proportion of hypertension and diabetes cases could be prevented via changes to one's lifestyle[4–7], for example, diet-based changes.

A high consumption of processed red meat (PRM), such as sausages, salami, ham and bacon, has been consistently associated with a higher risk of diabetes and hypertension[8–16]. Many dietary guidelines recommend limiting or reducing the consumption of these foods[17–20].

However, intake of one specific food does not exist in isolation. In the context of making dietary changes, it may be more relevant to assess food substitutions[21] rather than overall intakes of a certain food, as people may choose to replace one 'unhealthy' food, for another 'healthier' food.

Many previous studies investigating associations between PRM and these diseases adjust on total energy intake to account for confounding[22]. However, including total energy in a regression is known to introduce a substitution effect[23] as energy is implied to be fixed in these models. Different food substitutions may have different effects, beneficial, harmful, or neutral. Certain epidemiological studies using methods that attempt to assess specific food substitutions at the population level[24] have suggested that the relative to PRM, 'healthier' foods, such as non-PRM, poultry, fish or vegetables, are associated with a lower risk of diabetes[25] and hypertension[26].

Abbreviations: POP, persistent organic pollutants; PRM, processed red meat; T2D, type 2 diabetes.

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The aim of this study was to determine if relative to PRM, other foods including poultry, fish, eggs, unprocessed red meat or pork, pulses, or vegetables could be associated with a lower risk of hypertension and diabetes in a large prospective cohort of French women.

Methods

Study population

The E3N[27] is a French prospective cohort started in 1990 comprising 98 995 women aged 40–65 years at baseline and insured by the MGEN, a health insurance plan for employees of the French education system and their families. The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés) (ClinicalTrials.gov Identifier: NCT03285230), and all participants in the study signed an informed consent form. Follow-up questionnaires were sent every 2 to 3 years (1993, 1995, 1997, 2000. 2002, 2005, 2008, 2011 and 2014).

Incident cases of diabetes and hypertension were analysed independently, using two disease-free sub-cohorts of the E3N study. Women were included in the study if they completed the first dietary questionnaire and did not report prevalent hypertension/diabetes, respectively, when studying each disease separately, or CVD including stroke or myocardial infarction. We then excluded women with no reported meat or fish intake, and women consuming fewer than 1000 or more than 4000 calories per day. This resulted in a population of 71 081 for the analysis of incident diabetes cases and 45 771 for incident hypertension cases (see online Supplementary Fig. 1).

Estimation of dietary intake

Habitual dietary intake was assessed using two food history questionnaires, sent in 1993 and 2005. From these questionnaires, mean daily intakes of 238 food items, energy (excluding alcohol) and various nutrients were estimated. In the main analyses, only data from the first food history questionnaire were considered, with the second being used in sensitivity analyses.

In this analysis, we considered PRM as the main exposure, and non-processed red meat (non-PRM), poultry, fish, eggs, pulses, and vegetables as potential comparison foods. PRM was defined as the sum of reported sausage, ham, charcuterie and pâté (a sensitivity analysis excluded pâté). Non-PRM included beef, pork, rabbit and veal. Fish was classed as either fatty fish (salmon, sardines, trout and mackerel) or lean fish (cod, sole, bass, ling, ray, whiting and haddock). Vegetables included both leafy and root vegetables (excluding potatoes and pulses). Portions were considered as 150 grams (as per previous studies[28]) for PRM, non-PRM, poultry, fish, eggs, pulses and vegetables. In a sensitivity analysis, we also considered servings in terms of calories and defined 150 kilocalories (kcal) servings based on calorie values from the food composition table.

In a validation study, the correlation coefficients between the first dietary questionnaire and twelve 24-h recalls were 0·39 for fish, 0·50 for vegetables, 0·25 for pulses, 0·40 for eggs, 0·52 for poultry and unprocessed red meat, and 0·39 for PRM[29]. Correlation coefficients between the two diet history questionnaires in 1993 and 2005 were similar at 0·41 for fatty fish, 0·42 for lean fish, 0·41 for vegetables, 0·22 for pulses, 0·40 for eggs, 0·30 for poultry, 0·36 for unprocessed red meat and 0·41 for PRM.

Assessment of incident diabetes and hypertension cases

Type 2 diabetes. Incident type 2 diabetes (T2D) was ascertained through a combination of self-report, validation questionnaires and drug reimbursement files from 1993 until last validation of cases in 2012. Until 2004, all potential cases of T2D were identified through follow-up questionnaires that included questions on the diagnosis of T2D, diabetes-specific diets, diabetes drugs and hospitalisations for T2D. Potential cases were contacted and asked to answer a diabetes-specific questionnaire that included questions on the circumstances of diagnosis (year of diagnosis, symptoms, biological examinations, and fasting or random glucose concentration at diagnosis), T2D therapy (prescription of diet or physical activity, list of all glucose-lowering drugs already used), and the most recent concentrations of fasting glucose and HBA1c. The validation was based on WHO criteria as follows: fasting glucose of 7·0 mmol/l (126 mg/dl) or random glucose of 11·1 mmol/l (200 mg/dl)) and/or women who reported taking diabetic drugs, and/or their last values of fasting glucose or glycated Hb concentrations reported to be 7·0 mmol/l (126 mg/dl) or 7 %, respectively. After 2004, T2D cases were identified through the reimbursement database. All women with at least two reimbursements for any glucose-lowering medication within a 1-year period were considered to have T2D, with the date of diagnosis defined as the date of their first reimbursement.

Hypertension

Participants were asked to report whether they had hypertension at baseline (1993) and in each follow-up questionnaire (1995, 1997, 2000. 2002, 2005, 2008, 2011 and 2014), the date of diagnosis and the use of antihypertensive treatments. The month and year of diagnosis were provided for most cases (69 %). For individuals who were missing the month of diagnosis (14 % of cases), it was imputed to June of the year of diagnosis. The median time between the date of diagnosis and the date of response to the first questionnaire after diagnosis was 12 months. Thus, for the cases with no year of diagnosis (*n* 17 %), we assigned it to be 12 months before they reported hypertension in a questionnaire. In 2004, a drug reimbursement database became available for 97·6 % of participants. We used the self-reported date of diagnosis or the first date of drug reimbursement for antihypertensive medications (Anatomical Therapeutic Chemical Classification System codes C02, C03, C07, C08 and C09) whatever happened first, as the date of diagnosis for cases identified after 2004.

In addition, using the information of the MGEN health insurance plan drug claim database, the validity of self-reported hypertension within the E3N cohort was assessed. Hypertension self-reports were compared with antihypertensive drug reimbursement (any of the above-specified codes). A positive predictive value of 82 % was observed among women alive

in January 2004 and followed up to their response to the questionnaire in 2008[24]. We considered all self-reported hypertension cases since there was high agreement between self-report and medication reimbursement.

Assessment of potential confounding factors

Most covariates were assessed at the third questionnaire, corresponding to the first diet history questionnaire, with the exception that BMI from the previous questionnaire was used, to temporally separate the measurement of BMI, ensuring it did not mediate associations. Height and weight were self-reported and used to calculate BMI (kg/m^2). Smoking was based on self-reports and participants were classified as current smokers, ex-smokers, never smokers or non-responders. Family history of CVD (stroke or myocardial infarction) was based on self-reports. Education level was self-reported and used as a proxy for social class. Total physical activity was self-reported and detailed time spent undergoing various activities (such as walking, housework and sports), considering the seasons of the year (winter or summer). Total metabolic equivalents (MET-hours) were estimated for each individual using the compendium of physical activity and used to represent the total physical activity of study participants[30]. Use of menopausal hormone therapy was self-reported during follow-up. Among postmenopausal women, age at menopause was defined as either (in decreasing order of priority) age at last menstrual period, age at bilateral oophorectomy, self-reported age at menopause, age at start of menopausal hormone therapy or the age at the start of menopausal symptoms. If unavailable, the median age at menopause for the cohort (51 years for natural menopause and 47 years for surgical menopause) was imputed. Intakes of alcohol and sugar-sweetened beverages were assessed from the diet history questionnaire. If a covariate value was missing, the value was imputed from the previous questionnaire where possible; otherwise, a missing value indicator was used for categorical variables, or the median value for continuous variables.

Statistical analysis

Primary analysis. PRM in grams was considered in quintiles of the population distribution to generate descriptive statistics, and as a continuous variable in portions (150 g/week) when considering survival models and food comparisons in the main analysis. Cox proportional hazard models with age as the timescale were used to determine averaged hazard ratios over follow-up for incident hypertension or diabetes. Time at entry was the age at the beginning of follow-up (date of return of 1993 questionnaire), exit time was the age when participants were diagnosed with hypertension or diabetes, died (dates of death were obtained from the participants' medical insurance records), were lost to follow-up, or at the end of the follow-up period (31 December 2011 for diabetes and 2014 for hypertension).

To calculate the hazard ratios for specified food comparisons or "substitutions", we used "food substitution models"[24]. PRM, non-PRM, poultry, fish, eggs and vegetables were included in a cox model as continuous variables (portions), along with total energy intake (kcal, continuous). The difference in risk attributed to a "substitution" of food 1 and food 2 can then be determined by the exponential of the difference of the regression coefficients for food 1 and food 2[24]. The interpretation of this new coefficient has been proposed as the ratio in disease risk, if one portion of food 1 was exchanged for one portion of food 2 in the population. Confidence intervals (95 %) for food substitutions were generated by bootstrapping the analysis with 1000 repetitions. Models were adjusted on smoking status (current/ex/never), alcohol intake (g/week, continuous), sugar-sweetened beverage intake (g/week, continuous), weekly physical activity (METS, continuous), family history of CVD (yes/no), BMI (kg/m^2, continuous), and education level (university/high school/no high school), age at menopause and use of menopausal hormone therapy at baseline.

In a secondary analysis, to determine if there was any effect modification, the food substitution models (using 150 g/week serving) were then assessed stratified over potential modifying factors, including body weight (BMI >= 25, BMI < 25), smoking status (smoker, ex-smoker or never smoker), and prevalent hypertension or diabetes.

Sensitivity analyses. Several sensitivity analyses were performed. Firstly, we excluded cases occurring within 3 years to determine if results were due to recent dietary changes. We also excluded pâte from the definition of PRM due to uncertainty on its inclusion. Recent work has suggested that the energy partition model may give a less biased estimate of effects[23]. In a supplementary sensitivity analysis, we used the energy partition model to assess food substitutions, with serving units of 150 kcal. This model considers the energy from the food of interest (i.e. PRM), adjusted on the remaining energy from all other food sources (i.e. energy from red meat, poultry, fatty fish, lean fish, eggs, vegetables and other food groups). Individually, the regression coefficients obtained in this manner can be considered as the effect for a 1-unit increase of each food, and similarly to the previous analysis, their subtraction gives an estimate of one food compared to another[31]. This model was adjusted as previously described and is presented in the supplementary material.

To determine if these results were confounded by previous dietary intake, we considered a model among disease-free survivors with baseline at the second dietary questionnaire in 2005. We repeated the primary analysis in this subgroup of the cohort using the more recent FFQ responses and then adjusted on previous dietary exposure (i.e. from the 1993 FFQ), with the hypothesis that previous diet is a confounder or effect modifier of the relationship between current diet and disease (see simplified DAG in online Supplementary Fig. 2). In effect, this allows an assessment of the association of a more recent dietary exposure from that of a long-term exposure[32]. Finally, in a similar manner, we considered the mean of reported consumption from both dietary questionnaires as the exposure, with 2005 as baseline. Confounder values were updated to that of the second FFQ for these analyses, except for BMI being assessed at the questionnaire prior to the FFQ, as previously mentioned. Missing data were treated in the same way. If a covariate value was missing, first choice was to use the value from the previous question, if this was not possible the value was imputed using the median value. Food substitutions were assessed in the same manner as previously described for all analyses.

All statistical analyses were performed using R and R studio. Statistical significance was considered if the hazard ratio 95 % CI did not contain 1.

Results

Diabetes

Among the 71 081 women included in the diabetes study, 2681 cases were identified over an average of 18·7 years of follow-up, and a total of 1 327 257 person-years (PY), giving an incidence rate of two cases/1000 PY. Average consumption of PRM was 23 (IQR: 12:37) grams per day or 1·1 servings per week. Comparing women at baseline according to their consumption of PRM, the highest consumers were generally younger, were more likely to be smokers or to have hypertension, were less educated, and had higher BMI and total energy intake (Table 1). They also consumed more red meat, poultry, eggs, alcohol and sugar-sweetened beverages.

Relative to one weekly serving of PRM, one serving of either fatty fish, unprocessed red meat, and eggs, pulses, or vegetables was associated with a lower risk of diabetes (fatty fish HR: 0·85 (0·73, 0·97); red meat: 0·92 (0·87, 0·96); eggs: 0·96 (0·86, 0·99); pulses: 0·92 (0·88, 0·96); vegetables: 0·89 (0·85, 0·92)) (Table 2). Weaker evidence of a lower risk was observed for lean fish, but the estimate was in the same direction (lean fish HR: 0·95 (0·87, 1·01)).

When considering models stratified over potential effect modifiers (Table 3), associations were weaker among smokers and participants with a BMI greater or equal to 25. Among smokers, relative to PRM, lean fish was associated with an higher risk of diabetes (lean fish HR: 1·08 (1·01, 1·15)).

In sensitivity analyses, results were unchanged when excluding participants who developed the disease within 3 years, and when excluding pâté from the PRM definition (not presented). When considering the energy partition model, a lower risk of diabetes was observed relative to 150 kcal of PRM for red meat, pulses and vegetables (red meat HR: 0·98 (0·96, 1·00), pulses: 0·97 (0·93, 1·00); vegetables: 0·95 (0·91, 0·98), online Supplementary Table 1). Relative to PRM, fatty fish was associated with a lower risk of diabetes, but with a larger CI than in the main model (fatty fish HR: 0·93 (0·81:1·03), online Supplementary Table 1).

Finally, we considered PRM and other food intakes at the second FFQ over 7 years of follow-up. Differences in food intakes and characteristics are presented in the supplementary material (supplementary results 1·2). Only 150 g of poultry was associated with a reduced risk of diabetes relative to PRM (poultry HR: 0·74 (0·55, 0·92), Table 4, analysis 1). This was consistent when adjusting on previous dietary intake (poultry HR: 0·72 (0·53, 0·90), Table 4, analysis 2). When considering the average consumption over the two FFQ, 150 g of vegetables was associated with a lower risk of diabetes relative to PRM (vegetables HR: 0·93 (0·86, 1·00), Table 4, analysis 3).

Hypertension

At baseline, 45 771 women free of hypertension were included in the study. During an average 18·3 years of follow-up, 12 327

Table 1. Characteristics of the population under study considering diabetes, stratified on processed red meat intake (Mean values and standard deviation; median values and interquartile range for dietary data)

	Entire cohort (*n* 71 081)		Q1 (*n* 14 011)		Q3 (*n* 14 168)		Q5 (*n* 14 205)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Cases of diabetes (*n*)	2681		405		494		763	
Age (years)								
Mean	52·8		54·0		52·8		51·9	
SD	6·7		6·9		6·6		6·3	
BMI (kg/m^2)								
Mean	22·9		22·4		22·9		23·6	
SD	3·2		3·0		3·1		3·6	
Physical activity (MET-h/week)								
Mean	54·8		54·6		55·2		54·2	
SD	30·2		30·3		29·9		30·2	
Smoker (%)	13·5		12·3		12·9		15·7	
Ex-smoker (%)	32·5		31·3		32·3		33·2	
Never smoker (%)	54·0		56·4		54·8		51·1	
History of hypertension (%)	36·5		35·6		35·6		38·7	
Family history of CVD (%)	5·9		6·1		5·7		5·9	
University education (4 years) (%)	36·4		37·0		35·8		36·4	
Dietary intakes (g/d)								
Processed red meat intake	23	12, 37	4·3	1, 7	23	20, 25	54	47, 67
Total calories	2080	1746, 2460	1823	1528, 2153	2055	1754, 2394	2401	2048, 2805
Intake of red meat	62	41, 87	23	58, 67	62	58, 67	112	101, 131
Intake of poultry	15	9, 21	13	7, 20	15	9, 21	16	10, 23
Intake of fatty fish	6	3, 10	6	2, 10	6	3, 10	6	6, 19
Intake of lean fish	18	10, 28	17	9, 28	17	10, 28	18	10, 28
Intake of eggs	21	12, 33	14	7, 26	21	13, 32	29	16, 43
Intake of vegetables	146	87, 220	161	92, 238	144	86; 216	158	86, 213
Intake of pulses	13	5, 29	13	3, 27	13	6, 29	16	7, 33
Alcohol intake	48	12, 116	27	4, 80	51	13, 112	70	20, 150

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Table 2. Associations between various food 'substitutions' for processed red meat, and the risk of diabetes and hypertension (Hazard ratio and 95 % confidence intervals)

	Diabetes											
	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
150 g serving	0·85	0·73, 0·97	0·95	0·87, 1·01	0·98	0·88, 1·08	0·92	0·87, 0·96	0·96	0·86, 0·99	0·89	0·85, 0·93	0·92	0·88, 0·96
Hypertension														
	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
150 g serving	0·85	0·79, 0·91	1·04	1·00, 1·07	0·99	0·94, 1·03	0·97	0·95, 0·99	0·98	0·95, 1·01	0·96	0·94, 0·98	0·97	0·95, 0·99

Hazard ration and 95 % CI for food 'substitution' estimates (HR (95 CI)). Adjusted for BMI, physical activity, total calories, smoking status, total energy intake, alcohol intake, sugar-sweetened beverage intake, education level, family history of CVD and prevalent hypertension/diabetes in the case of studying the other disease.

incident cases were identified at an incidence rate of 14·7 cases/1000 PY. Average consumption of PRM in this population was 22 (IQR: 12:37) grams per day or 1·0 serving per week. Women who ate the most PRM were slightly younger, more likely to be smokers or have diabetes, were less educated, and had higher BMI and total energy intake (Table 5); they also consumed more eggs, red meat, more alcohol and less fish.

When considering one weekly serving of fatty fish, unprocessed red meat, vegetables or pulses relative to PRM, a lower risk of hypertension was observed (fatty fish HR: 0·85 (0·79, 0·91); red meat: 0·97 (0·95, 0·99); vegetables: 0·96 (0·94, 0·98); pulses 0·97 (0·95, 0·99), Table 2). Relative to PRM, lean fish was associated with a higher risk of hypertension (lean fish HR: 1·04 (1·00, 1·07)). No clear difference in risk was observed for eggs or poultry.

When considering models stratified over potential effect modifiers, associations were generally more pronounced among non-smokers (Table 3). Associations observed for lean fish were observed among women who smoked at baseline (lean fish HR: 1·11 (1·00, 1·20)).

In sensitivity analysis, results were unchanged when excluding participants who developed the disease within 3 years, and when excluding pâté from the PRM definition (not presented). When considering the energy partition model, a lower risk of hypertension was observed for fatty fish and vegetables relative to PRM (fatty fish HR: 0·92 (0·86, 0·96), vegetables: 0·98 (0·96, 0·99), supplementary results 2·1. online Supplementary Table 1), but all associations were in the same direction as in the primary analysis.

Finally, we considered PRM and other food intakes at the second FFQ, among survivors over 9 years of follow-up. Differences in food intakes and demographics are presented in the supplementary material (supplementary results 2·2). Relative to 150 g of PRM, fatty fish, eggs, pulses and vegetables were associated with a lower risk of hypertension (fatty fish HR: 0·91 (0·84, 0·99), eggs: 0·96 (0·92, 1·00); vegetables: 0·96 (0·93, 0·99); pulses: 0·96 (0·93, 0·99), Table 4, secondary analysis 1). These associations were attenuated towards the null when adjusting on previous dietary intake, but of a similar magnitude and direction. When considering the average consumption over the two food questionaires, relative to 150 g of PRM, fatty fish, red meat, pulses andvegetables were associated with a lower risk of hypertension, with weaker evidence for eggs (fatty fish HR: 0·83 (0·71, 0·94), red meat: 0·92 (0·85, 0·98); vegetables: 0·94 (0·90, 0·97); pulses: 0·93 (0·89, 0·97), eggs: 0·95 (0·90, 1·01), Table 4, secondary analysis 3).

Discussion

The results from this large prospective study of French women suggest that relative to PRM, foods such as fish, eggs, vegetables, pulses and non-PRM, are associated with a lower risk of diabetes and hypertension. The strongest difference in risk was observed when considering PRM relatvive tofatty fish, which was associated with a 15 % lower risk of both hypertension and diabetes. In this study, we considered population-level comparisons of 150 g per week of PRM for other foods. The 150 g portion size

Table 3. Associations between various food 'substitutions' in servings/week of 150 g and the risk of hypertension and diabetes, stratified over potential modifying factors (Hazard ratio and 95 % confidence intervals)

Diabetes

	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
BMI < 25, *n* 56 463, cases = 1048	0·82	0·75, 0·88	1·04	1·00, 1·08	0·97	0·91, 1·02	0·88	0·81, 0·95	0·97	0·94, 1·01	0·85	0·80, 0·90	0·85	0·79, 0·91
BMI >= 25, *n* 14 618, cases = 1633	0·94	0·81, 1·08	1·05	0·97, 1·12	1·02	0·91, 1·12	0·91	0·86, 0·96	1·00	0·94, 1·06	0·88	0·84, 0·91	0·91	0·87, 0·95
Smoker, *n* 9629, cases = 410	0·88	0·75, 1·01	1·08	1·01, 1·15	1·06	0·98, 1·14	1·02	0·89, 1·16	0·98	0·93, 1·05	1·02	0·91, 1·12	1·02	0·91, 1·14
Non-smoker, *n* 37 826, cases = 1416	0·92	0·73, 1·09	0·87	0·77, 0·96	0·98	0·85, 1·11	0·87	0·82, 0·93	0·96	0·85, 1·07	0·85	0·81, 0·90	0·88	0·83, 0·92
Ex-smoker, *n* 23 046, cases = 827	0·84	0·60, 1·05	0·92	0·79, 1·04	0·89	0·71, 1·05	0·93	0·85, 1·01	0·96	0·85, 1·07	0·87	0·81, 0·93	0·91	0·83, 0·98
No history of hypertension (*n* 45, 137, cases = 1145)	0·88	0·67, 1·09	1·00	0·85, 1·15	0·92	0·81, 1·01	0·87	0·81, 0·93	0·91	0·82, 1·00	0·90	0·85, 0·95	0·93	0·87, 0·98
History of hypertension (*n* 25 944, cases = 1536)	0·84	0·67, 1·00	0·97	0·87, 1·07	0·97	0·85, 1·09	0·95	0·89, 1·01	0·94	0·86, 1·01	0·87	0·83, 0·93	0·89	0·83, 0·95

Hypertension

	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
BMI < 25, *n* 38 479, cases = 9509	0·82	0·76, 0·88	1·04	1·00, 1·08	0·97	0·90, 1·02	0·96	0·93, 0·99	0·97	0·94, 1·00	0·95	0·93, 0·98	0·96	0·94, 0·99
BMI >= 25, *n* 7292, cases = 2818	0·94	0·81, 1·08	1·05	0·98, 1·11	1·02	0·92, 1·11	0·97	0·92, 1·01	1·01	0·96, 1·06	0·98	0·93, 1·01	0·99	0·95, 1·03
Smoker, *n* 6606, cases = 1726	0·87	0·72, 1·05	1·11	1·00, 1·20	0·98	0·85, 1·10	0·98	0·92, 1·04	0·98	0·91, 1·05	0·99	0·94, 1·04	1·03	0·97, 1·08
Ex-smoker, *n* 15 219, cases = 4055	0·88	0·80, 0·97	1·05	0·99, 1·12	0·94	0·86, 1·02	0·99	0·95, 1·03	0·99	0·94, 1·05	0·97	0·94, 1·00	0·97	0·93, 1·01
Non-smoker, *n* 23 946, cases = 6546	0·83	0·74, 0·91	1·01	0·96, 1·07	1·00	0·94, 1·06	0·95	0·92, 0·98	0·97	0·94, 1·01	0·95	0·92, 0·97	0·96	0·93, 0·98
History of diabetes (*n* 631, cases = 242)	0·52	0·24, 0·81	1·15	0·79, 1·42	0·88	0·63, 1·13	0·98	0·84, 1·11	0·97	0·76, 1·16	0·96	0·84, 1·07	1·02	0·87, 1·17
No history of diabetes (*n* 45 140, cases = 12085)	0·85	0·79, 0·92	1·04	1·00*, 1·07	0·99	0·94, 1·03	0·97	0·95, 0·99	0·98	0·95:1·01	0·96	0·94:0·98	0·97	0·95:0·99

Hazard ration and 95 % CI for food 'substitution' estimates (HR (95 % CI)). Adjusted for BMI, physical activity, total calories, smoking status, total energy intake, alcohol intake, sugar-sweetened beverage intake, education level, family history of CVD and prevalent hypertension/diabetes in the case of studying the other disease.
* Rounded up to 1·00.

Table 4. Secondary analysis considering food substitutions using data from the second food questionnaire (Hazard ratio and 95 % confidence intervals)

Diabetes														
	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Analysis 1 – processed red meat and substitutions at the second FFQ														
150 g serving	0·99	0·83, 1·14	1·01	0·92, 1·11	0·74	0·55, 0·92	1·06	0·98, 1·15	0·99	0·92, 1·07	0·96	0·91, 1·00	0·97	0·92, 1·03
Analysis 2 – additional adjustment on pre-baseline dietary variables														
150 g serving	1·02	0·85, 1·18	1·04	0·94, 1·15	0·72	0·53, 0·90	1·08	0·99, 1·17	1·00	0·94, 1·08	0·97	0·90, 1·02	0·98	0·92, 1·04
Analysis 3 – average intake of both FFQ														
150 g serving	0·94	0·69, 1·17	0·99	0·85, 1·13	0·94	0·71, 1·16	1·00	0·87, 1·15	0·97	0·88, 1·07	0·93	0·86, 1·00	0·96	0·88, 1·04
Hypertension														
	Processed red meat for fatty fish		Processed red meat for lean fish		Processed red meat for poultry		Processed red meat for red meat		Processed red meat for eggs		Processed red meat for vegetables		Processed red meat for pulses	
Analysis 1 – processed red meat and substitutions at the second FFQ														
150 g serving	0·91	0·84, 0·99	1·00	0·94, 1·05	1·06	0·96, 1·15	0·98	0·94, 1·01	0·96	0·92, 1·00	0·96	0·93, 0·99	0·96	0·93, 0·99
Analysis 2 additional adjustment on pre-baseline dietary variables														
150 g serving	0·94	0·86, 1·02	1·01	0·95, 1·06	1·06	0·96, 1·16	0·99	0·95, 1·04	0·96	0·91, 1·00	0·97	0·94, 1·01	0·97	0·94, 1·01
Analysis 3 – average intake of both FFQ														
150 g serving	0·83	0·71, 0·94	1·00	0·93, 1·07	1·10	0·98, 1·21	0·92	0·85, 0·98	0·95	0·90, 1·01	0·94	0·90, 0·97	0·93	0·89, 0·97

Hazard ration and 95 % CI for food 'substitution' estimates (HR (95 CI)). Adjusted for BMI, physical activity, total calories, smoking status, total energy intake, alcohol intake, sugar-sweetened beverage intake, education level, family history of CVD and prevalent hypertension/diabetes in the case of studying the other disease.
Analysis 1 uses the second FFQ as baseline, with updated exposure and covariate values.
Analysis 2 considers additional adjustment for food items and total calorie intake from the first FFQ.
Analysis 3 considers the average intake of both FFQ, with the second FFQ as baseline.

Table 5. Characteristics of the population under study considering hypertension, stratified on processed red meat intake (Mean values and standard deviation; median values and interquartile range for dietary data)

	Entire cohort (*n* 45 771)		Q1 (*n* 9152)		Q3 (*n* 9105)		Q5 (*n* 9141)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Cases of hypertension	12 327		2258		2481		2620	
Age (years)								
Mean	51·8		53·0		51·8		51·1	
SD	6·3		6·6		6·3		5·9	
BMI (kg/m^2)								
Mean	22·5		22·0		22·4		23·0	
SD	2·9		2·7		2·8		3·1	
Physical activity (MET-h/week)								
Mean	54·2		62·1		54·5		53·9	
SD	29·8		37·6		29·4		29·8	
Smoker (%)	14·4		13·4		13·8		16·7	
Ex-smoker (%)	33·3		31·8		33·4		34·0	
Never smoker (%)	52·3		54·8		52·8		49·3	
History of diabetes (%)	1·4		1·3		1·1		1·7	
Family history of CVD (%)	5·3		5·5		5·0		5·4	
University education (4 years) (%)	39·1		39·9		38·3		38·8	
Dietary intakes (g/d)								
Processed red meat intake	22	12, 37	4	1, 7	22	20, 25	54	46, 66
Total calories (kcal)	2078	1747, 2451	1825	1529, 2154	2055	1755, 2394	2395	2040, 2792
Intake of red meat	62	40, 87	22	14, 29	62	57, 67	112	110, 130
Intake of poultry	15	9, 21	13	7, 20	15	9, 21	16	10, 23
Intake of fatty fish	6	3, 10	6	2, 11	6	3, 10	6	3, 10
Intake of lean fish	17	10, 28	28	15, 45	17	10, 28	18	6, 19
Intake of eggs	21	12, 32	14	7, 27	20	13, 31	29	16, 43
Intake of vegetables	146	88; 219	161	93, 239	145	86, 216	143	85, 213
Intake of pulses	13	7, 29	13	3, 27	13	7, 29	17	7, 33
Alcohol intake	49	12, 115	27	3, 79	53	14, 112	70	21, 150

per week was chosen as an interpretable figure, making the results easier to comprehend in terms of food servings. Similarly, reasonable food comparisons were selected, that is, PRM for other animal products or pulses. One-hundred and fifty grams of chicken, for example, may come from 1·5 average-sized breasts per week and could replace one packet of store-bought salami or fifteen 10 g slices.

Diabetes

PRM intake has been associated with the risk of diabetes in previous studies[13–16], including in the E3N cohort[33], but few studies have compared specific foods. Those studies that did have suggested that relative to PRM, other foods were associated with a lower risk of these diseases. Ibsen *et al.* in a prospective study of 53 163 Danish participants[28] found that relative toPRM, poultry and fish were associated with a lower risk of diabetes. A lower risk of diabetes was also observed in a European case–control setting[34] which compared red meat and PRM with cheese, yogurt, nuts and cereals, but this study found no evidence for lower risk when PRM was compared to fish. In a pooled analysis of American prospective observational cohort studies[25], including 8763 incident diabetes cases, relative to PRM, poultry, seafood, dairy products, vegetables, nuts and eggs were all associated with a lower risk of diabetes. Interestingly, in our study, relative to PRM, poultry was associated with a lower risk of diabetes only in the sensitivity analysis that considered follow-up from the second FFQ. This may be due to changes in the consumption of poultry over time, to lifestyle changes that could be related to poultry consumption, or to unmeasured confounding. That these associations are not consistently seen in both primary and sensitivity analyses is hard to explain.

In this study, inverse associations were observed between diabetes risk, and fatty fish relative to PRM, and null or positive associations for lean fish relative to PRM. Differing results have been seen in a pooled analysis of American cohort studies[35], and in the Women's Health Study[36]. Results from Kaushik *et al.*[35] among 195 204 health professionals in a prospective setting found an association between higher consumption of fish and a higher risk of incident diabetes. Similarly, Djoussé *et al.*[36] found an increased risk of incident diabetes among women who consumed more fish in a prospective study of 36 328 women free of diabetes at baseline. Neither of these studies separated fatty and lean fish in analysis, and neither considered specific food comparisons in their models; thus, the inherent substitution in their models cannot be interpreted in the same manner as our results.

Positive associations between lean fish and diabetes were observed among smokers in our stratified analysis. It is possible that this could be explained by pollutants present in certain fish[37] such as persistent organic pollutants (POPs), including polychlorinated biphenyls. One meta-analysis of cross-sectional has shown that POPs measured in serum are associated with the odds of diabetes in a wide variety of populations, and one study

conducted using data from Swedish men and woman[38] identified a significant interaction between smoking status and POPs serum concentration on all-cause mortality. However, since POPs are more present in fatty fish rather than lean fish, it is perhaps more likely that this result is explained by some unmeasured confounding.

Previous studies that have found PRM to be positively associated with diabetes have suggested that nitrites present in PRM could be causing the disease[39], perhaps by increasing nitric oxide-related oxidative stress[40]. Our results help clarify these associations, by specifying the alternative foods and thus the possible mechanism that may be responsible. For example, consumption of PRM has been shown to increase markers of oxidative stress in a randomised crossover study of people with diabetes[41]; thus, replacing PRM with vegetables high in antioxidants may act to lessen the oxidative stress burden, reducing the risk of diabetes.

Hypertension

PRM intake has previously been associated with the risk of hypertension, including in the E3N cohort[10], but few studies have assessed the possible association with hypertension when considering comparisons between PRM and other foods. A recent prospective observational study of 5394 Chinese adults[26] found that relative to 50 g of red PRM, eggs, dairy or other animal-source foods were associated with a lower risk of hypertension. Similarly, Becerra-Tomas *et al.*[42] identified a lower risk of metabolic syndrome among 1868 participants when comparing PRM to vegetables, poultry, rabbit, fish and eggs. Regarding other forms of CVD, two Danish observational studies found that relative to PRM, fatty fish was associated with a 22 % lower risk of stroke[43] and a 12 % lower risk of peripheral artery disease[44].

In most subgroup analyses, most associations were consistent, except weaker associations among smokers, perhaps due to the smaller size of this subgroup. Among smokers, a borderline positive association with hypertension when comparing one portion of PRM to lean fish was observed. This may be explained by specific unmeasured confounding among smokers, such as some socio-economic factors related to smoking, diet and disease, as these results were not observed among other subgroups, or, as previously discussed for diabetes, could be explained by contamination by POP[45].

Associations between different foods and hypertension are perhaps explained by differences in overall saturated fat, salt and cholesterol intake, which are particularly high in PRM, and healthy micronutrients such as *n*-3 fatty acids, antioxidants or dietary fibres in other foods, which can lower the risk of hypertension. For example, replacing PRM with vegetables could reduce the risk of hypertension due to the antioxidant effects of certain molecules such as polyphenols and vitamins, since oxidative stress is involved in the development of hypertension[46]. The inverse associations observed regarding fatty fish types are possibly explained by their high content of *n*-3 fatty acids. These fatty acids have been shown to have vasodilatory effects and can reduce blood pressure, especially in hypertensive adults[47].

Study design and limitations

A major issue in many nutritional epidemiological studies is the use of only a single measurement of diet, as previous diet may confound or modify associations between current diet and disease[32], and that diet may change during follow-up. In this study, we explored the confounding hypothesis in a secondary analysis, which considered a second food questionnaire as baseline, with adjustment on dietary data obtained from the first food questionnaire (i.e. adjustment on pre-baseline exposure). Adjustment on previous diet did not significantly affect effect estimates, suggesting that such confounding may be relatively minor in this cohort. However, it is possible that the gap between the two FFQ (12 years) is too large to adequately control for confounding. Interestingly, associations were slightly different in the analysis for diabetes, whether controlling on previous diet or not (although not hypertension, where observations were similar). For diabetes, replacement of PRM for poultry was associated with a reduced risk of disease over 9 years of follow-up, which was not observed in the primary analysis. These differences could be explained by changes in the amount or type of poultry consumed, changes in the preparation method, or could possibly be linked to other concurrent lifestyle changes such as giving up smoking or increasing physical activity. These sensitivity analyses may not be comparable to the principal analysis, due to the different cohort characteristics, smaller number of cases and a shorter follow-up (7 *v.* 18 years). Associations were similar to the main analysis when considering the average intake over the two FFQ. This may be explained by the two exposures considering different exposure windows, with the average intake considering a longer-term exposure to diet, but with a less clear interpretation. Despite this, the secondary analysis was designed to assess if previous diet was a strong confounder for the associations between current diet and disease, which did not seem to be the case.

Despite finding similar associations to previous studies, these results are perhaps non-generalisable to other populations due to differences in background diet and should be interpreted as specific to this cohort of healthy middle-aged French women with a relatively low consumption of PRM. Specifying food comparisons can aid in reproducibility in nutritional epidemiology, since single food exposure studies are essentially comparing the intake of one food to the populations background diet (when isocaloric models are used[23]), which is likely to differ in different populations. The pairs of foods studied can also be influenced by other dietary factors, which were not controlled for (i.e. foods commonly eaten alongside). It is possible to include other foods in the model which may reduce this possible residual confounding. However, if the two foods that are compared are different in energy, this could cause residual energy substitutions to come from unrealistic sources. This is not a problem when using the energy partition model, but in this situation the difference in weight implied by calories may represent an unrealistic comparison.

Statistically, there are other methods for assessing food substitutions at the population level. One alternative method is to include the sum variable of all considered food substitutions and then leave out the food of interest to be replaced. This

method has been shown to be mathematically equivalent to the method used in this work[24,48]. One recent study used compositional transformation substitution analysis that can consider the differing proportion of foods consumed[26]. We assessed multiple different methods of modelling the food pairs, including different units, and different statistical models. When comparing the standard model, which includes foods and total energy intake, results were comparable to that of the energy partition model. The energy partition model has recently been argued to provide less biased effect estimates in simulations[23], but it is unclear if this extends to the setting of using a FFQ to assess food intake.

This study does have several limitations. Primarily, diet was based on self-reported data, which may be subject to error. The main analysis considered only a single measure of diet, with the assumption that dietary intake rests stable over time and is adequately captured in the food questionnaire. It is likely that diet would change over time, and to properly assess time-varying associations between diet and disease it is necessary to use more complex methods (i.e. g-methods) to control for time-varying confounders. This can be facilitated by using target trial framework, as has recently been demonstrated[32,49]. A major limitation of FFQ-based baseline data is that we cannot accurately emulate the assignment of different dietary strategies, as would be done in a trial. This means that strong assumptions must be made to define the time point when a person in the study started eating in a specific way.

Hypertension and diabetes were in part based on self-report; it is therefore possible that some misclassification of disease status is present in this study. Confounder data were largely based on self-report, which can be prone to classification error. Similarly, unmeasured confounders may introduce bias to these results. All these factors, as well as the observational nature of the study means that this evidence alone cannot be considered causal. There are also several strengths. The study was able to include a large sample of women who were free of disease at baseline, and a relatively high number of incident cases of hypertension and diabetes were identified. Despite unmeasured confounding being a concern, we were able to adjust on many factors known to be related to diet and to the risk of hypertension and diabetes such as physical activity, BMI, alcohol intake and smoking. We were able to incorporate two measures of diet in the sensitivity analysis, and we considered adjustments on previous diet to study shorter-term associations and used an average measurement of the two FFQ to study longer-term associations. We clearly defined the exposures by considering relative estimates, reducing the severity of errors in our interpretation of the results.

In conclusion, relative to PRM, fatty fish, unprocessed red meat, eggs, vegetables or pulses were associated with a lower risk of hypertension and diabetes. Fatty fish showed the most consistent association, with the risk of both diabetes and hypertension being 15 % lower compared to PRM.

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The authors have no conflicts of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522002689

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