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Consumption of Meat, Fish, Dairy Products, Eggs and Risk of Ischemic Heart Disease: A Prospective Study of 7198 Incident Cases Among 409,885 Participants in the Pan-European EPIC Cohort

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Abstract

Background: There is uncertainty about the relevance of animal foods to the etiology of ischemic heart disease (IHD). We examined meat, fish, dairy products and eggs and risk for IHD in the pan-European EPIC cohort.

Methods: A prospective study of 409,885 men and women in nine European countries. Diet was assessed using validated questionnaires, calibrated using 24-hour recalls. Lipids and blood pressure were measured in a subsample. During 12.6 years mean follow up, 7198 participants had a myocardial infarction or died from IHD. The relationships of animal foods with risk were examined using Cox regression with adjustment for other animal foods and relevant covariates.

Results: The hazard ratio (HR) for IHD was 1.19 (95% CI 1.06-1.33) for a 100 g/d increment in intake of red and processed meat, and this remained significant after excluding the first 4 years of follow-up (HR 1.25 [1.09-1.42]). Risk was inversely associated with intakes of yogurt (HR 0.93 [0.89-0.98] per 100 g/d increment), cheese (HR 0.92 [0.86-0.98] per 30 g/d increment) and eggs (HR 0.93 [0.88-0.99] per 20 g/d increment); the associations with yogurt and eggs were attenuated and non-significant after excluding the first 4 years of follow-up. Risk was not significantly associated with intakes of poultry, fish or milk. In analyses modelling dietary substitutions, replacement of 100 kcal/d from red and processed meat with 100 kcal/d from fatty fish, yogurt, cheese or eggs was associated with approximately 20% lower risk of IHD. Consumption of red and processed meat was positively associated with serum non-HDL cholesterol concentration and systolic blood pressure, and consumption of cheese was inversely associated with serum non-HDL cholesterol.

Conclusions: Risk for IHD was positively associated with consumption of red and processed meat, and inversely associated with consumption of yogurt, cheese and eggs, although the associations with yogurt and eggs may be influenced by reverse causation bias. It is not clear whether the associations with red and processed meat and cheese reflect causality, but they were consistent with the associations of these foods with plasma non-HDL cholesterol, and for red and processed meat with systolic blood pressure, which could mediate such effects.

Key Words: meat; fish; dairy products; eggs; ischemic heart disease

Clinical Perspective

What is new?

- We followed the health of 400,000 men and women in nine European countries for 12 years to examine the relevance of intake of animal foods to the etiology of ischemic heart disease.
- Higher consumption of red and processed meat was positively associated with the risk for ischemic heart disease.
- None of the other animal foods examined were positively associated with risk; intakes of fatty fish, yogurt, cheese and eggs were modestly inversely associated with risk.

What are the clinical implications?

- Higher intake of red and processed meat may increase risk of ischemic heart disease.
- Substituting other foods for red and processed meat may reduce risk of ischemic heart disease

Introduction

Ischemic heart disease (IHD) is the commonest disease and cause of death in Europe.[1] The risk of IHD is affected by diet, but there is uncertainty about the relevance of intake of animal foods such as red and processed meat, poultry, fish, dairy products and eggs. Meat and dairy products are major dietary sources of saturated fatty acids; in the UK, for example, meat and meat products contribute 24% of saturated fat intake in adults, and milk and milk products contribute 22%.[2] Controlled feeding trials have shown that high intakes of saturated fatty acids raise circulating low density lipoprotein (LDL) cholesterol, an established risk factor for IHD, suggesting that higher intakes of foods rich in saturated fatty acids may increase the risk of IHD.[3 4] Meta-analyses of previous prospective studies of meat and incidence of fatal IHD have suggested that intake of processed meat may be associated with higher risk, whereas unprocessed red meat might not.[5 6] For dairy products and eggs, systematic reviews of prospective studies have reported no consistent evidence that higher intakes are associated with a higher risk of IHD.[7 8] Fatty fish consumption might reduce the risk of IHD because it is a rich source of long-chain n-3 fatty acids, and a meta-analysis has suggested an inverse association between overall fish consumption and mortality from IHD.[9]

Here we report the relationships of these foods with risk of IHD in the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort of half a million men and women.[10 11] To assess whether associations might be due to reverse causation, we examined the results after excluding the first four years of follow-up. To assess whether associations might be explained by known metabolic risk factors for IHD, we examined the cross-sectional associations of food intake with cholesterol fractions and blood pressure in a sub-sample of participants, interpreting the relationships of foods with risk with respect to their associations with non-high density lipoprotein (HDL) cholesterol and systolic blood pressure.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the International Agency for Research on cancer at http://epic.iarc.fr/access/index.php.

Study population

EPIC is a prospective study of approximately 520,000 men and women recruited through 23 centres in 10 European countries, mostly between 1992 and 2000.[10, 11] Participants in EPIC completed dietary and lifestyle questionnaires, and the majority also provided blood samples and had their blood pressure measured. The baseline data were centralized at the World Health Organization's International Agency for Research on Cancer (IARC) in Lyon, France. All participants gave written informed consent and the study protocol was approved by the ethical review boards of IARC and the institutions where participants were recruited.[10]

Dietary intake during the year before enrolment was measured by country-specific diet assessment methods, in most centres food frequency questionnaires; these were validated using a standardized, co-ordinated approach.[10] Dietary intakes estimated using a standardized and computerized 24-hour recall method were also collected from an 8% random sample across all centres, approximately 1.4 years after recruitment; the sample was stratified by age and sex, with weighting according to predicted disease rates in these strata, and distributed equally by season and day of the week.[12] Details of the categorization of foods are in the Supplementary material.

Assessments of the non-dietary variables were based on responses in the baseline questionnaires and categorized into the following groups: smoking (never, former, current <10 or unknown number of cigarettes per day, current 10-19 cigarettes per day, current ≥20 cigarettes per day, or unknown (2.4% of the cohort)), alcohol intake (not current drinker, sex-specific fifths of current intake: cut-points in men were 3.5, 9.7, 18.8 and 36.2 g/d, cut-points in women were 0.9, 2.8, 6.9 and 13.9 g/d), physical activity (Cambridge physical activity index, based on occupational physical activity and cycling/other physical exercise, and categorised in approximate quartiles termed inactive, moderately inactive, moderately active, active, and unknown (2.2%))[13], highest education level obtained (none or primary school only, secondary school, vocational qualification or university degree, unknown (4.3%)), employment status (currently employed or student, neither, unknown (11.4%)), histories of diabetes mellitus, hypertension and hyperlipidaemia (each self-reported: yes, no, unknown (4.2%, 5.5% and 23.7% respectively)). Body mass index (BMI: <22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, ≥30.0 kg/m^2 and unknown (0.9%)) was calculated from measured height and weight (except for participants in Norway, and some participants in France and the UK, where height and weight were self-reported). Baseline systolic and diastolic blood pressures were measured in millimetres of mercury by trained personnel (further details in Supplementary material online).[14]

Lipids were measured in stored plasma samples as part of the EPIC-CVD case-cohort study, which is nested within EPIC.[11] The sub-cohort was randomly selected from participants with a stored blood sample, with selection stratified by the 23 EPIC recruitment centres. Details of methods are in the Supplementary material.

Ascertainment and verification of cases of ischemic heart disease

The outcome was IHD, defined as the composite of first non-fatal myocardial infarction (MI: ICD-10 I21) or death from IHD (ICD-10 I20-25). Incident non-fatal MIs were ascertained in each EPIC centre using a combination of record linkage to morbidity or hospital registries, and self-reports followed by confirmation with medical records.[11] Information on vital status was collected from mortality registries at the regional or national level in most centres except in Greece where vital status was ascertained by active follow-up of study participants and next of kin. Centres in Denmark, Greece, Italy, Norway and Spain validated all suspected cases of MI, whereas centres in France, the Netherlands, Sweden and the UK validated a subset of the suspected cases to assess the accuracy of the overall ascertainment process. A range of methods was used to confirm the diagnosis of IHD and included retrieving and assessing medical records or hospital discharge notes, contact with medical professionals, retrieval and assessment of death certificates, or verbal autopsy with the next of kin. The last year of follow-up varied across centres between 2003 and 2010, but was mainly 2008 or 2009.

Statistical analysis

Of the 518,502 participants for whom data were available, those with no dietary data, no non-dietary (lifestyle) data, or those in the top or bottom 1% of the ratio of energy intake to energy requirement, were excluded (n=16,837), as were those who had a self-reported or unknown history of MI or stroke at baseline (n=11,308), 23 cases whose date of diagnosis was after the end of follow-up for each centre, and 23 participants with no follow-up data. These exclusions left a total of 490,311 participants, and further restricting the dataset to EPIC centres with known values for all of the animal foods (which meant excluding Heidelberg, Potsdam, Naples and

Umeå) left a total of 409,885 participants, including 7198 incident cases of non-fatal MI (n=5392) or fatal IHD (n=1806).

Follow-up was measured from recruitment until the date of first non-fatal MI or fatal IHD event, or censoring at the date of death from other causes, non-fatal non-MI IHD, the date at which follow-up for IHD events was considered complete, or emigration or other loss to follow-up (1.3%). Relative risks as hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were estimated using Cox regression models. All analyses were stratified by sex and EPIC centre and adjusted for exact age at recruitment (continuous), smoking, self-reported histories of diabetes, hypertension, and hyperlipidemia, physical activity, employment status, level of education, BMI (these latter eight covariates were all categorical variables, with 'unknown' categories added), current alcohol consumption (categorical), and intakes of energy, fruit and vegetables, dietary fibre from cereals, and percent energy from sugars (each continuous). In the main analyses of calibrated food intakes, the results for each animal source food were also adjusted simultaneously for the other animal source foods.

Participants were divided into fifths of self-reported intake for each animal food based on the recruitment questionnaire (for any foods with more than 20% zero values the categories were approximate fifths), with the quintiles calculated for all included participants, and a trend test performed by scoring the categorical fifths of intake 1 to 5 and treating this as a continuous variable. To test for whether the data were compatible with a linear trend, we also fitted models with the fifths of intake treated as a categorical variable; there were no significant improvements in fit when comparing the categorical intake model with the continuous (trend test) intake model, suggesting that any associations between food intake and risk were approximately linear. Then, to improve the comparability of dietary data across participating centres and to correct for measurement error in relative risk estimates, the dietary data from the subset of participants with 24-hour recalls were used to provide statistically calibrated estimates of dietary intakes for all included participants. HRs were calculated for increments in observed and calibrated intake of each food. Observed food intakes were calibrated using a fixed-effect linear model in which centre and sex specific 24-hour recall data from an 8% random sample of the cohort were regressed on the observed intakes, generating a calibrated intake corresponding to each observed intake.[12 15] The sizes of the increments were chosen to approximate the difference in mean 24 hour recall intake between participants in the lowest and highest fifths of observed intake, and with reference to the increments used in previous publications such the World Health Organization's review of the carcinogenicity of red and processed meat.[16]

Using the results from the mutually-adjusted risks model, the effects of substituting 100 kcal/d of each other animal food for 100 kcal/day of red and processed meat were estimated from the ratios of the risk (as measured by the hazard ratio) for each food in turn and the risk for red and processed meat.[17] For example, if P and R represent the hazard ratios per 100 kcal/day yogurt and per 100 kcal/day red and processed meat in the mutually-adjusted risks model, the effect of substituting 100 kcal/day yogurt for 100 kcal/day red and processed meat is estimated by the ratio P/R; the difference in covariance was used to estimate the 95% confidence interval.

To examine whether the overall results might be influenced by reverse causality, we repeated the analyses after excluding the first 4 years of follow-up (i.e. with follow-up for all participants commencing 4 years after the date of recruitment). To examine whether associations between the animal foods and IHD risk were consistent across sub-groups of other risk factors, we also conducted separate analyses for subsets of sex, smoking status (never, former and current), prior disease status (participants with or without a history of diabetes, hypertension or hyperlipidemia), age at recruitment (<55, 55-64, ≥65 years), BMI (<25.0, 25.0-29.9, ≥30.0 kg/m^2), European region (Northern Europe: Denmark, Norway, Sweden; Central Europe: France excepting Provence and SW France, Netherlands, UK; Southern Europe: Greece, Italy, Spain, Provence, SW France), and countries with partial (France, Netherlands, Sweden, UK) or complete (Denmark, Greece, Italy, Norway, Spain) validation of cases. Tests for heterogeneity of trend between sub-groups were obtained by comparing the risk coefficients for each sub-group using inverse variance weighting, testing for statistical significance using a chi-square test on k-1 degrees of freedom where k is the number of sub-groups.

To examine whether dietary risk factors might act through major established physiological IHD risk factors, we examined the associations of food intakes with non-HDL cholesterol and systolic blood pressure, calculating mean levels of these biomarkers in each category of animal food intake (using linear regression to estimate least-squares means), with adjustment for age, sex and EPIC centre.

All analyses were performed using Stata version 15.1 (Stata Corporation, College Station, TX, USA), and a P-value less than 0.05 was considered statistically significant.

Results

After a mean follow-up of 12.6 years there were 7198 incident cases of MI or death from IHD. Table 1 shows participant characteristics by sex for all cohort participants and also for incident cases. On average, cases were 6-10 years older than average for the cohort, with higher mean BMI and lower mean alcohol intake. Cases were more likely to smoke, be inactive, unemployed, diabetic, have elevated blood pressure or proatherogenic lipids, lower mean observed intakes of fruit and vegetables, and moderate differences in intakes of animal foods.

Table 2 shows the HRs and 95% CIs for IHD in each fifth of observed intake of animal foods, relative to the bottom fifth of intake, and P values for tests of trend based on the observed intakes. HRs in the top fifth of intake compared with the bottom fifth of intake were 1.13 (1.02-1.26) for red and processed meat combined, 1.10 (0.99-1.21) for red meat and 1.10 (0.99-1.22) for processed meat. Intakes of poultry, white fish, fatty fish, milk and eggs were not associated with IHD, whereas intakes of yogurt and cheese were inversely associated with risk, with HRs (95% CIs) in the top fifths of 0.90 (0.84-0.97) and 0.88 (0.80-0.96)

Figure 1 shows the associations of IHD risk with statistically calibrated increments in intake of eight mutually-exclusive animal foods (including red and processed meat combined, but not red meat and processed meat separately), with mutual adjustment of risks for the animal foods (see online Supplemental Table 1 for HRs for uncalibrated and calibrated increments, without mutual adjustment). For red and processed meat combined, the HR (95% CI) was 1.19 (1.06-1.33) for a 100 g/day increment in calibrated intake. The HRs for calibrated intakes of yogurt (100 g/d), cheese (30 g/d) and eggs (20 g/d) were 0.93 (0.89-0.98), 0.92 (0.86-0.98) and 0.93 (0.88-0.99), respectively.

In analyses excluding the first 4 years of follow-up the association of risk with intake of red and processed meat was marginally stronger (HR per 100 g/day increment 1.25 (1.09-1.42), P=0.001), whereas the associations with calibrated intakes of yogurt and eggs were attenuated and neither these associations, nor the association with cheese, were statistically significant (Table 3).

Substitution analyses

Table 4 shows the HRs for modelled substitution of 100 kcal/day of calibrated intake of red and processed meat by 100 kcal/d of each of the other animal foods. Fatty fish, yogurt, cheese and eggs were associated with significantly lower risks for IHD than red and processed meat (15% to 24% reductions in risk per 100 kcal substituted per day).

Sub-group analyses

In analyses subdivided by history of diabetes, previous hypertension or hyperlipidemia, there was no appreciable heterogeneity in the associations of animal foods with IHD risk except for white fish, but this was not significantly associated with risk in either sub-group (see Supplementary material online, Supplemental Table 2). In analyses subdivided by smoking status, there was no appreciable heterogeneity in the associations of animal foods with IHD risk except for yogurt, which was inversely associated with risk in current smokers but not in never smokers or former smokers (Supplemental Table 3). In analyses subdivided by age, there was no appreciable heterogeneity in the associations of animal foods with IHD risk except for red and processed meat, which was strongly positively associated with risk in participants recruited before age 55, but not in older people (Supplemental Table 4). In analyses subdivided by sex, there was no appreciable heterogeneity in the associations of animal foods with IHD risk except for eggs, which were inversely associated with risk in men but not in women (Supplemental Table 5). There was no appreciable heterogeneity in the associations of animal foods with IHD risk subdivided by BMI or by European region (Supplemental Tables 6 and 7). There was evidence of heterogeneity by the extent of validation of cases in the associations of dietary intake with IHD risk for red and processed meat, and for milk (Supplemental Table 8); for red and processed meat, there was a large and highly significant association with risk in the countries with complete case verification, but not in the other countries. For milk there was a small positive association with risk in the countries with complete verification, but not in the other countries.

Associations of foods with plasma lipids and blood pressure

Comparing participants in the highest fifth of intake of red and processed meat with those in the lowest fifth of such intake, non-HDL cholesterol was higher by 0.19 mmol/l (4.3%), and systolic blood pressure was higher by 3.3 mm Hg (2.5%); for processed meat, the difference in systolic blood pressure between these groups of participants was 3.7 mm Hg (2.8%). Comparing participants in the highest fifth of intake of cheese with those in the lowest fifth of such intake, non-HDL cholesterol was lower by 0.10 mmol/l, whereas the intake of cheese was unrelated to systolic blood pressure (see Supplemental Tables 9 and 10).

Discussion

In this large European cohort we observed a positive association between red and processed meat intake and risk of IHD, with a 19% (95% CI 6%-33%) higher risk per 100 g/day increment in calibrated intake. Red and processed meat showed separate (albeit borderline significant) associations with risk, which were each of similar magnitude. The association of risk with red and processed meat was observed after excluding the first 4 years of follow up and in participants without diabetes, or elevated blood pressure or proatherogenic lipids. These additional results, therefore, reduce the likelihood of reverse causation or residual confounding. By comparison, a previous meta-analysis of meat and risk of IHD reported that unprocessed red meat consumption was not associated with risk of IHD, whereas processed meat was, with a 42% higher risk per 50 g/d increment in intake.[5] However, that previous review included only 769 events from four studies for unprocessed red meat, including one case-control study; for processed meat it included 21,308 events from five studies, but most cases derived from one study for which the endpoint was total cardiovascular mortality rather than incident MI and fatal

IHD. A subsequent meta-analysis also concluded that processed meat but not unprocessed red meat was associated with IHD mortality, based on up to 1370 deaths from IHD.[6] Hence, further work is needed to understand potential reasons for the differences with the current study's results, which were based on over 7000 IHD events.

We observed no clear association of IHD risk with consumption of either white fish or fatty fish (although there was a borderline significant inverse association for fatty fish, and a significant inverse association for fatty fish in the substitution analyses; see below). The possible protective role of fish in IHD has been investigated for more than 30 years. A previous analysis of fish consumption and mortality in EPIC found no evidence that higher intakes of total, white or fatty fish were associated with mortality from IHD.[18] By contrast, a meta-analysis of 4472 deaths in 17 cohort studies suggested that there was an overall significant inverse association between fish intake and IHD mortality, but the association was not linear and the relative risk in the highest category of fish intake was not significantly lower than that in the lowest intake.[9]

Dairy products are a major source of dietary saturated fatty acids, but prospective observational studies have generally not shown a higher risk of IHD with a higher intake of foods such as milk, yogurt and cheese.[19 20] We observed no association of milk with risk of IHD, which is consistent with a meta-analysis of 4391 incident IHD cases in six prospective studies.[21] We observed that yogurt consumption was inversely associated with risk of IHD. However, this association did not persist after exclusion of the initial 4 years of follow-up, and it showed heterogeneity by smoking status, with no association in never smokers (suggesting, therefore, that the observed association may partly be explained by changes in diet due to preclinical disease and/or residual confounding by smoking). Yogurt consumption is associated with healthy dietary patterns, behaviors and lifestyle factors[22], yet a meta-analysis of 5 prospective studies (number of cases unclear) reported no association between yogurt consumption and risk of IHD.[23] We also observed that cheese consumption was inversely associated with risk of IHD; again, this inverse association was not significant after excluding the first four years of follow-up, although the estimate was only slightly attenuated. A meta-analysis of 8 prospective studies with 7425 incident cases showed a lower risk for IHD in participants with a relatively high intake of cheese.[24] It has been suggested that cheese has constituents which might act to reduce the risk of IHD, for example that the calcium in cheese forms insoluble soaps with fatty acids thus reducing absorption of saturated fatty acids, and that the calcium also binds to bile acids, reducing their enterohepatic circulation and possibly leading to a cholesterol lowering effect.[19 25]

Egg consumption was inversely associated with IHD risk overall, but this association was no longer evident after excluding the first 4 years of follow up, perhaps due to limited power, or because people with preclinical disease may have reduced their egg consumption. A recent meta-analysis of six prospective studies including 5847 incident cases reported no association of egg consumption with risk of coronary heart disease.[8] , whereas a recent large prospective study in China including 31,169 incident cases of IHD reported that egg intake was inversely associated with risk;[26] it is possible that the risk associations found in the observational studies due to the a dietary pattern often accompanying high egg intake and/or the cluster of other risk factors in people with high egg consumption.[27]

The positive association we observed between red and processed meat and risk of IHD might be related to the saturated fat content of these foods. However, although dairy products are also relatively rich in saturated fats, intake of dairy products was not positively related to IHD risk in this study; in fact there was a suggestion of an inverse association between cheese intake and future risk of IHD. This finding might suggest that different food sources of saturated fat, and/or different proportions of individual saturated fatty acids contained within meat and dairy foods, may differ in their impact on risk of IHD, which would affect the interpretation of previous studies of total dietary saturated fatty acids and risk.[28] It is also possible that plant sources of protein may be associated with a lower risk of IHD than animal foods,[29] and this should be considered in future analyses.

Substitution of other animal foods for red and processed meat

Our analyses showed that red and processed meat were positively associated with risk for IHD, whereas the other animal foods were not associated or inversely associated with risk. We therefore conducted analyses modelling isocaloric dietary substitutions, which showed that fatty fish, yogurt, cheese and eggs were associated with significantly lower risks for IHD when substituting for red and processed meat (15% to 24% lower risk per 100 kcal substituted per day). Plant foods might also be associated with a lower risk of cardiovascular disease than animal foods[27] and may be considered in future analyses.

Possible roles of plasma lipids and blood pressure

The positive associations of red and processed meat and the inverse association of cheese consumption with the risk of IHD might be explained through the associations of these foods with well-established risk factors for IHD, such as cholesterol fractions and systolic blood pressure. Compared to participants in the lowest fifth of intake of red and processed meat, those in the top fifth had a higher non-HDL cholesterol by 0.19 mmol/l and a higher systolic blood pressure by 3.3 mm Hg; the difference in systolic blood pressure was larger for processed meat than for red meat (3.7 and 2.2 mm Hg, respectively), consistent with previous observations and possibly due to the high salt content of most processed meats.[30]

Based on results from the Emerging Risk Factors Collaboration and the Prospective Studies Collaboration[31 32], these differences would be expected to be associated with higher IHD risks of 8% and 12%, respectively. Such modelling suggests that the observed (uncalibrated) 13% higher risk in the top fifth of intake of red and processed meat could be readily explained by the differences in blood lipids and blood pressure. Other mechanisms might also be involved, for example, higher intakes of red and processed meat might increase the risk of IHD through the conversion of carnitine in meat into trimethylamine oxide.[33] Compared to participants in the lowest fifth of intake of cheese, those in the top fifth had lower non-HDL cholesterol by 0.10 mmol/l, but no significant difference in systolic blood pressure. Again on the basis of results from the Prospective Studies Collaboration, this difference in lipids would be expected to be associated with a 4% lower IHD risk, indicating that the observed 12% lower IHD risk in the top fifth of intake of cheese might be only partly explained by standard lipid fractions.

Strengths and limitations

Strengths of this study are the large number of cases, the prospective design, the wide range of diets across Europe, the calibration of the dietary data using 24-hour recalls, and the ability to adjust for major risk factors for IHD and to estimate the impacts of associations with circulating lipids and blood pressure.

As with all observational studies, a potential limitation is that the associations may be influenced by confounding by other risk factors. We have adjusted our results for major risk factors for IHD, including smoking and BMI as well as socio-economic factors. However, as the magnitudes of the associations we observed were relatively modest, we cannot discount that the results have been influenced by residual confounding by adiposity, socio-economic factors or other unmeasured factors. Another potential limitation is that, due to the multi-centre design of

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the cohort, there were some variations in the ascertainment and validation of the endpoint; the positive association of red and processed meat with risk for IHD was strong in the countries with complete validation of cases. It is also possible that associations of specific foods with risk may vary between populations due to differences in associations with other aspects of diet.

Conclusion

This large prospective study in Europe shows a moderate positive association between consumption of red and processed meat and risk of IHD, and it suggests a modest inverse association between consumption of cheese and IHD risk. It is not clear whether these associations reflect causality, but they were consistent with the associations of these foods with plasma non-HDL cholesterol, and for red and processed meat with systolic blood pressure, which could mediate such effects.

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The study was conceived and designed by TJK, PNA, KEB, AB, ER, and JD. The data were analysed by PNA. The first draft of the manuscript was prepared by TJK, PNA and KEB, and edited with input from the writing team (IJ, TK, MS, EW, MW and AMLW). All other authors provided the data and revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published and have contributed to the manuscript. TJK is the guarantor.

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Table 1. Participant characteristics at recruitment in 409,885 participants by gender and incident case status for first non-fatal MI or fatal IHD – EPIC Study

Characteristic	Men		Women	
	All men	Male cases	All women	Female cases
Number of participants	106751	4608	303134	2590
Age, y (SD)	52.7 (10.3)	58.7 (8.3)	51.3 (9.8)	61.0 (8.5)
BMI, kg/m^2 (SD)*	26.6 (3.7)	27.3 (3.8)	25.0 (4.4)	27.0 (4.7)
Alcohol in current drinkers, g/day (SD)	22.4 (23.2)	20.6 (22.4)	9.2 (12.0)	7.9 (11.4)
Not current alcohol drinker, n (%)	5409 (5.1)	304 (6.6)	38716 (12.8)	395 (15.3)
Smoking status and cigarettes/day, n (%)*				
Never smoker	32986 (31.4)	926 (20.3)	168240 (57.0)	1071 (41.7)
Former smoker	38347 (36.5)	1661 (36.5)	68785 (23.3)	563 (21.9)
Current smoker, <10 or number unknown	12198 (11.6)	621 (13.6)	16637 (5.6)	195 (7.6)
Current smoker, 10-19	8216 (7.8)	513 (11.3)	23900 (8.1)	436 (17.0)
Current smoker, ≥20	13281 (12.6)	835 (18.3)	17522 (5.9)	306 (11.9)
Highest level of education completed, n (%)*				
None or primary	37929 (36.8)	2129 (47.9)	85431 (29.5)	1242 (51.8)
Secondary	13854 (13.4)	444 (10.0)	75699 (26.2)	225 (9.4)
Vocational or university	51281 (49.8)	1868 (42.1)	128157 (44.3)	930 (38.8)
Cambridge physical activity index, n (%)*				
Inactive	20078 (19.4)	1188 (26.4)	65052 (21.9)	866 (34.1)
Moderately inactive	31545 (30.4)	1365 (30.4)	103286 (34.8)	855 (33.6)
Moderately active	25068 (24.2)	958 (21.3)	83872 (28.2)	458 (18.0)
Active	27034 (26.1)	985 (21.9)	44910 (15.1)	362 (14.2)
Employed or student, n (%)*				
Yes	68176 (75.0)	2338 (58.2)	176825 (64.9)	886 (37.1)
No	22727 (25.0)	1677 (41.8)	95471 (35.1)	1503 (62.9)
History of diabetes, n (%)*				
No	100468 (96.7)	4095 (93.0)	282565 (97.8)	2233 (91.6)
Yes	3379 (3.3)	308 (7.0)	6220 (2.2)	205 (8.4)
Previous hypertension, n (%)*				
No	83183 (82.5)	3160 (73.0)	238272 (83.2)	1591 (64.4)
Yes	17697 (17.5)	1171 (27.0)	48209 (16.8)	879 (35.6)
Prior hyperlipidemia, n (%)*				
No	67978 (81.3)	2082 (73.7)	200039 (87.2)	1230 (78.6)
Yes	15586 (18.7)	742 (26.3)	29309 (12.8)	335 (21.4)
Region, n (%)[&]				
Northern Europe	34924 (32.7)	2510 (54.5)	80922 (26.7)	1253 (48.4)
Central Europe	32300 (30.3)	1059 (23.0)	135150 (44.6)	936 (36.1)
Southern Europe	39527 (37.0)	1039 (22.5)	87062 (28.7)	401 (15.5)
Energy intake, kcal/day (SD)	2460 (650)	2436 (636)	1949 (536)	1878 (505)
Percent energy from sugars (SD)	17.3 (6.0)	17.7 (6.1)	19.4 (5.8)	20.5 (6.0)
Cereal fibre, g/day (SD)	10.3 (5.7)	10.4 (6.0)	7.8 (4.4)	7.9 (4.6)
Fruit and vegetables, g/day (SD)	455 (292)	387 (255)	484 (267)	423 (243)
Foods, g/day, medians (lower and upper quartiles)				

Red and processed meat	92 (54, 132)	101 (66, 142)	61 (35, 91)	66 (42, 95)
Red meat (g/day)	58 (30, 87)	60 (33, 89)	34 (16, 59)	40 (21, 62)
Processed meat	27 (11, 49)	35 (18, 58)	20 (8, 36)	21 (10, 37)
Poultry meat	16 (8, 33)	16 (6, 31)	14 (5, 23)	13 (4, 24)
White fish	12 (3, 23)	14 (2, 25)	11 (2, 23)	10 (1, 20)
Fatty fish	8 (2, 16)	8 (1, 17)	8 (2, 16)	7 (1, 16)
Milk	171 (38, 321)	216 (55, 432)	148 (19, 294)	218 (70, 387)
Yogurt	13 (0, 55)	8 (0, 61)	36 (3, 97)	27 (2, 94)
Cheese	29 (15, 55)	25 (13, 51)	30 (16, 55)	23 (12, 42)
Eggs	16 (7, 27)	17 (8, 29)	15 (7, 24)	14 (7, 23)

* Value or category unknown for some participants.

[&] Northern Europe: Denmark, Norway, Sweden (Malmö); Central Europe: France excepting Provence and SW France, Netherlands, UK; Southern Europe: Greece, Italy, Spain, Provence, SW France.

Table 2. Hazard ratios* (95% confidence intervals) for first non-fatal MI or fatal IHD in 409,885 participants by overall fifths of observed (self-reported) intake of selected animal foods, relative to the bottom fifth of intake – EPIC Study

Food	No. of cases	Fifth of intake[&]				P for trend[#]
		2	3	4	5	
Red and processed meat	7198	1.03 (0.93-1.13)	1.05 (0.95-1.15)	1.06 (0.96-1.17)	1.13 (1.02-1.26)	0.014
Red meat	7198	0.98 (0.89-1.08)	1.05 (0.96-1.15)	1.06 (0.97-1.17)	1.10 (0.99-1.21)	0.016
Processed meat	7198	0.98 (0.89-1.09)	1.03 (0.93-1.14)	1.07 (0.97-1.18)	1.10 (0.99-1.22)	0.007
Poultry meat	7198	1.00 (0.92-1.09)	0.99 (0.92-1.08)	1.00 (0.92-1.09)	1.01 (0.94-1.10)	0.77
White fish	7198	0.98 (0.90-1.07)	1.00 (0.92-1.08)	0.96 (0.89-1.04)	1.02 (0.94-1.11)	0.93
Fatty fish	7198	0.96 (0.88-1.03)	0.94 (0.88-1.02)	0.95 (0.88-1.03)	0.92 (0.86-0.99)	0.054
Milk	7198	0.91 (0.83-1.00)	0.97 (0.89-1.06)	0.97 (0.89-1.06)	0.97 (0.88-1.06)	0.66
Yogurt	7198	1.05 (0.97-1.14)	0.99 (0.92-1.07)	0.94 (0.87-1.02)	0.90 (0.84-0.97)	0.0004
Cheese	7198	0.95 (0.88-1.01)	0.90 (0.83-0.97)	0.91 (0.84-0.98)	0.88 (0.80-0.96)	0.003
Eggs	7198	0.96 (0.89-1.04)	0.97 (0.90-1.05)	1.02 (0.94-1.09)	0.93 (0.86-1.01)	0.37

* Hazard ratios are adjusted for age (continuous), smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidemia, Cambridge physical activity index, employment status, level of education completed, BMI (all categorical, with 'unknown' categories added), current alcohol consumption (non-drinkers and sex-specific fifths of intake among drinkers), and observed intakes of energy, fruit and vegetables combined, sugars (as % energy) and fibre from cereals (each continuous), and stratified by sex and EPIC centre.

[&] The median observed intakes (g/day) within each fifth of intake were as follows: red and processed meat – 12, 45, 67, 93, 138; red meat – 3, 22, 39, 60, 94; processed meat – 1, 11, 22, 35, 61; poultry meat – 0, 7, 15, 22, 46; white fish – 0, 4, 11, 20, 44; fatty fish – 0, 3, 8, 14, 29; milk – 0, 49, 150, 288, 470; yogurt – 0, 7, 27, 71, 150; cheese – 5, 18, 30, 50, 86; eggs – 4, 9, 15, 22, 40; for any foods with more than 20% zero values the categories were approximate fifths. The mean 24-hour recall intakes (g/day) within each fifth of intake were as follows: red and processed meat – 37, 61, 75, 93, 126; red meat – 24, 33, 44, 54, 69; processed meat – 10, 25, 34, 43, 60; poultry meat – 11, 13, 17, 22, 27; white fish – 11, 7, 13, 17, 31; fatty fish – 8, 10, 12, 14, 21; milk – 33, 79, 176, 240, 384; yogurt – 15, 14, 34, 67, 122; cheese – 15, 25, 33, 40, 54; eggs – 8, 12, 14, 18, 26.

[#] Tests of trend were performed scoring the fifths of intake 1-5.

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Table 3. Mutually-adjusted hazard ratios* (95% confidence intervals) for first non-fatal MI or fatal IHD in 406,908 participants per increment in calibrated intake of selected animal foods after excluding the first 4 years of follow-up – EPIC Study

Food	Increment (g/day)	No. of cases	HR (95% CI), mutually adjusted	P for trend[#]
Red and processed meat	100	5506	1.25 (1.09-1.42)	0.001
Poultry meat	20	5506	0.99 (0.94-1.05)	0.84
White fish	15	5506	1.02 (0.98-1.06)	0.39
Fatty fish	15	5506	0.96 (0.91-1.00)	0.072
Milk	200	5506	1.03 (0.99-1.07)	0.11
Yogurt	100	5506	0.97 (0.92-1.03)	0.28
Cheese	30	5506	0.93 (0.86-1.00)	0.055
Eggs	20	5506	0.96 (0.90-1.03)	0.28

* Hazard ratios are adjusted for age (continuous), smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidemia, Cambridge physical activity index, employment status, level of education completed, BMI (all categorical, with 'unknown' categories added), current alcohol consumption (non-drinkers and sex-specific fifths of intake among drinkers), and calibrated intakes of energy, fruit and vegetables combined, sugars (as % energy), fibre from cereals, and each other food (each continuous), and stratified by sex and EPIC centre.

[#] Tests of trend were performed using the calibrated intake (continuous).

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Table 4. Hazard ratios* (95% confidence intervals) for first non-fatal MI or fatal IHD for substitution of 100 kcal/day increment in calibrated energy intake from each food for 100 kcal/day increment in calibrated energy intake from red and processed meat

Food	HR (95% CI), substituting 100 kcal/day of this food for 100 kcal/day red and processed meat
Poultry meat	0.89 (0.76-1.04)
White fish	1.00 (0.78-1.26)
Fatty fish	0.81 (0.69-0.95)
Milk	0.95 (0.90-1.00)
Yogurt	0.84 (0.76-0.92)
Cheese	0.85 (0.79-0.92)
Eggs	0.76 (0.62-0.92)

* Hazard ratios are adjusted for age (continuous), smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, Cambridge physical activity index, employment status, level of education completed, BMI (all categorical, with 'unknown' categories added), current alcohol consumption (non-drinkers and sex-specific fifths of intake among drinkers), and calibrated intakes of energy, fruit and vegetables combined, sugars (as % energy) and fibre from cereals (each continuous), and each other food, as appropriate (each continuous), and stratified by sex and EPIC centre. Results are based on 7198 cases among 409,885 participants with known values for all of the animal foods.

Figure Legend

Figure 1. Mutually-adjusted hazard ratios (95% confidence intervals) for first non-fatal MI or fatal IHD per increment in statistically calibrated intake of animal foods

Hazard ratios (HR) are adjusted for age (continuous), smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidemia, Cambridge physical activity index, employment status, level of education completed, BMI (all categorical, with 'unknown' categories added), current alcohol consumption (non-drinkers and sex-specific fifths of intake among drinkers), and calibrated intakes of energy, fruit and vegetables combined, sugars (as % energy), fibre from cereals, and each other food (each continuous), and stratified in the analysis by sex and EPIC centre.

Mutually-adjusted hazard ratios (95% CI) for first non-fatal MI or fatal IHD per increment in statistically calibrated intake of selected animal foods

Food	Increment (g/day)	No. of cases	HR (95% CI)	P for trend
Red and processed meat	100	7198	1.19 (1.06-1.33)	0.003
Poultry meat	20	7198	0.99 (0.94-1.04)	0.68
White fish	15	7198	1.01 (0.97-1.04)	0.72
Fatty fish	15	7198	0.96 (0.92-1.01)	0.091
Milk	200	7198	1.02 (0.99-1.06)	0.18
Yogurt	100	7198	0.93 (0.89-0.98)	0.007
Cheese	30	7198	0.92 (0.86-0.98)	0.010
Eggs	20	7198	0.93 (0.88-0.99)	0.023

HR & 95% CI