Associations of unprocessed and processed meat intake with mortality and cardiovascular disease in 21 countries [Prospective Urban Rural Epidemiology (PURE) Study]: a prospective cohort study

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ABSTRACT

Background: Dietary guidelines recommend limiting red meat intake because it is a major source of medium- and long-chain SFAs and is presumed to increase the risk of cardiovascular disease (CVD). Evidence of an association between unprocessed red meat intake and CVD is inconsistent.

Objective: The study aimed to assess the association of unprocessed red meat, poultry, and processed meat intake with mortality and major CVD.

Methods: The Prospective Urban Rural Epidemiology (PURE) Study is a cohort of 134,297 individuals enrolled from 21 low-, middle-, and high-income countries. Food intake was recorded using country-specific validated FFQs. The primary outcomes were total mortality and major CVD. HRs were estimated using multivariable Cox frailty models with random intercepts.

Results: In the PURE study, during 9.5 y of follow-up, we recorded 7789 deaths and 6976 CVD events. Higher unprocessed red meat intake (≥250 g/wk vs. <50 g/wk) was not significantly associated with total mortality (HR: 0.93; 95% CI: 0.85, 1.02; *P*-trend = 0.14) or major CVD (HR: 1.01; 95% CI: 0.92, 1.11; *P*-trend = 0.72). Similarly, no association was observed between poultry intake and health outcomes. Higher intake of processed meat (≥150 g/wk vs. 0 g/wk) was associated with higher risk of total mortality (HR: 1.51; 95% CI: 1.08, 2.10; *P*-trend = 0.009) and major CVD (HR: 1.46; 95% CI: 1.08, 1.98; *P*-trend = 0.004).

Conclusions: In a large multinational prospective study, we did not find significant associations between unprocessed red meat and poultry intake and mortality or major CVD. Conversely, a higher intake of processed meat was associated with a higher risk of mortality and major CVD. *Am J Clin Nutr* 2021;114:1049–1058.

Keywords: unprocessed red meat, poultry, processed meat intake, mortality, cardiovascular disease, cohort study

Introduction

Dietary guidelines recommend limiting the consumption of unprocessed red meat because it is a source of medium- and long-chain SFAs and is presumed to increase the risk of cardiovascular disease (CVD) (1). However, there is mounting evidence that has challenged conventional restrictions on SFA intake for CVD prevention. Several meta-analyses of cohort studies have shown that higher intakes of SFAs were not associated with a higher risk of CVD (1–3) but may be associated with a lower risk of mortality and stroke (4, 5). The uncertainty about SFA intake and its association with CVD is partly due to the variation in its major food sources, heterogeneity in its biological effects, and gene–diet interaction—all of which modulate associations between SFA intake and health outcomes (6).

Cohort studies have consistently found that processed meat, which is modified to improve its taste or to extend its shelf life, has an adverse association with CVD. However, there is uncertainty about the association between unprocessed red meat and CVD. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, including 448,568 participants across 10 European countries with >26,000 deaths, found no significant association between unprocessed red meat intake and total or cause-specific mortality (7). In contrast, a pooled analysis of 29,682 individuals from 6 US prospective cohort studies found that each additional 2 servings of unprocessed red meat and poultry per week were associated with a 3% and 4% higher risk of mortality, respectively (8). The Nutritional Recommendations (NutriRECS) Consortium has recently recommended that adults do not need to change their meat consumption due to the uncertainty of increased risk associated with higher consumption (9). Most of the evidence on meat intake and health outcomes is from studies conducted in North America, Europe, and Japan, where the amount and type of meat consumed differ from other regions of the world (e.g., South Asia and Africa). Therefore, data from all world regions are essential for making global dietary recommendations.

We aimed to examine the association between different types of processed and unprocessed meat with mortality and CVD using data from the Prospective Urban Rural Epidemiology (PURE) Study.

Methods

Study design and participants

The design of the PURE study has been described previously (10). Briefly, the study is a large-scale prospective cohort study of 164,007 individuals aged 35–70 y from 21 low-, middle-, and high-income countries. The low-income countries included Bangladesh, India, Pakistan, Tanzania, and Zimbabwe. Middle-income countries included Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestine territory, Philippines, Poland, South Africa, and Turkey; and high-income countries were Canada, Saudi Arabia, Sweden, and the United Arab Emirates. Recruitment began on 1 January 2003 and follow-up visits were conducted every 3 y. During recruitment, the initial response rate was 78% of those eligible, and the first wave had a >96% follow-up rate at 10 y. Details of the follow-up visits overall and by country are provided in **Supplemental Tables 1** and **2**. This analysis is based on the data collected in the first 2 phases of the PURE study. Individuals were enrolled from 21 countries and had completed at least 1 cycle of follow-up visits. Information on vital status was available for 98% of participants, and CVD information was available for 95% of participants. We included all outcome events known to us until 30 June 2019. Details of the sampling and recruitment strategy are described in **Supplemental Figure 1**. For present analysis, we excluded participants with a history of CVD (n = 11,462), history of cancer (n = 1,707), missing information on age and sex, and those with an implausible value of energy intake (<500 or >5000 kcal/d; n = 16,541). All participants provided written informed consent. The ethics committees approved the study protocol at each participating institution (**Supplemental Material**).

The study was coordinated by the Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada.

Procedures

Standardized questionnaires were used for collecting information about demographic factors, lifestyle, health history, and medication use at baseline and CVD events and mortality information (classified by cause) during follow-up. The disease and mortality information was adjudicated in each country by trained physicians using common definitions. Participants were followed up at 3, 6, and 9 y.

Dietary information

Country-specific (or region-specific in India) validated FFQs were used for collecting information on usual dietary intake from all of the participants at baseline. Where validated FFQs were not available, we developed and validated the FFQs using standard methods (**Supplemental Tables 3** and **4**). The FFQs contained a list of food items commonly consumed over the previous year, and the number of food items in the FFQs varied from 95 to 250. All FFQs contained predefined frequencies of consumption that varied from never to >6 times/d along with local portion sizes. To estimate total energy and nutrient intakes, the USDA food-composition database was used as the base with modifications and adaptations from local databases and collected recipes of some of the food items (11). However, for Canada, China, India, Malaysia, South Africa, Sweden, and Turkey, we used the food-composition database available in that country.

Unprocessed red meat was defined as the consumption of beef, mutton, veal, and pork. Poultry included the flesh of all birds. Processed meat included any types of meat that had been salted, cured, or treated with preservatives and/or food additives. The amount of meat intake was computed by multiplying the daily frequency of consumption by local portion size and then converting to grams per week for further analysis.

The external funders of the study had no role in the design of the study, its implementation at different sites globally for data collection, data analysis, interpretation of the data, or writing of the manuscript. The corresponding author (MD) and co-authors (RI, AM, SR, SY) had access to all the data.

Supplemental Figures 1–5, Supplemental Tables 1–8, and Supplemental Material are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CV, cardiovascular; CVD, cardiovascular disease; MET, metabolic equivalent; MI, myocardial infarction; PURE, Prospective Urban Rural Epidemiology.

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Outcomes

The primary outcomes were total mortality and major cardiovascular events (fatal CVD, nonfatal myocardial infarction, stroke, and heart failure). Secondary outcomes were myocardial infarction (MI), stroke, heart failure, cardiovascular mortality, and noncardiovascular mortality (including cancer mortality). The definitions for these events have been published previously (10).

Statistical analysis

Age, wealth index, and unprocessed red meat, poultry, processed meat, and total energy intakes were reported as continuous variables. The location was categorized as urban or rural. Smoking status was categorized as never, former, or current. Categories of education were none or primary school (first 6 y), secondary school (7–11 y), and college, trade school, or university (>11 y). Physical activity was categorized based on the metabolic equivalent of task (MET) per minute per week into low (<600 MET-min/wk), moderate (600–3000 MET-min/wk), and high (>3000 MET-min/wk) activity. In the PURE study, most participants were from low- and middle-income countries, and meat consumption (an expensive food item) might be more affordable for high-socioeconomic-status individuals than those of low socioeconomic status. To account for socioeconomic factors, we adjusted for both education and wealth index in the multivariable models. Wealth index was developed using information collected on household possessions such as electricity, car, computer, television, phone, etc., and then conducting principal components analysis as a data-reduction technique to create a wealth index.

Due to cultural similarities in the dietary intake, participants were grouped into 7 regions that included North America and Europe, South America, Africa, the Middle East, South Asia, South East Asia, and China.

Daily unprocessed red meat, poultry, and processed meat intakes were adjusted for 1000 kcal/d. For unprocessed red meat and poultry, we grouped participants into those consuming <50 g/wk, 50 to <150 g/wk, 150 to <250 g/wk, and ≥250 g/wk.

For processed meat analysis, since 45% of participants reported "never" consuming processed meat, we restricted our analysis to those countries where median consumption was ≥10 g/d ($n = 31{,}640$). The countries included were Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden. Participants were grouped into 0 g/wk, >0 to <50 g/wk, 50 to <150 g/wk, and ≥150 g/wk. Also, we assessed associations between unprocessed red meat, poultry, and processed red meat per 100-g increase per week.

To calculate HRs, we used the Cox frailty models with random intercepts to account for center-level clustering, which took into account region- and country-level clustering effects. Estimates of HRs and 95% CIs are presented for consumption categories using the lowest intakes as the reference group. All models were adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medication, study center, total energy intake, and intakes of fruit, vegetables, dairy, fish, processed foods, refined grains, legumes, and total dietary fiber. We adjusted the analysis of unprocessed red meat intake for poultry intake and vice versa.

In the subgroup analyses, we excluded participants who reported any CVD in the first 2 y after recruitment. We assessed the association in 7 geographic regions separately since the amount of unprocessed red meat and poultry consumption varied across regions. Also, the association between unprocessed red meat and poultry intake was assessed using vegetarians as a reference group. Additionally, we conducted competing risk analyses using the Fine and Gray (12) approach for CVD mortality and major CVD for unprocessed red meat, poultry, and processed meat. In these competing risk regressions, we considered risk of cardiovascular (CV) mortality and major CVD in the absence of non-CV mortality as the competing risk. We also conducted the stratified analysis defining smoking status as never or ever smoker. Further, we examined the association between processed meat and death due to injury as a negative control and computed E-values using the VanderWeele method (13). The potential nonlinear nature of the association of all exposures with outcomes was examined using cubic splines with 3 knots for the exposures. Data were analyzed with the Stata software package, version 15 (StataCorp).

Results

Table 1 shows the characteristics of participants by categories of unprocessed red meat, poultry, and processed meat intake. Participants with higher unprocessed red meat intake consumed more poultry, fruit, vegetables, and dairy, but less starchy foods. A similar pattern was found among poultry consumers. For processed meat intake, compared with nonconsumers, those with higher processed meat intake consumed more unprocessed red meat, poultry, fruit, and vegetables.

During the median follow-up of 9.5 y, we recorded 7789 deaths and 6976 major cardiovascular events (2968 MI, 3335 stroke, and 659 heart failure). **Table 2** shows the association between the consumption of unprocessed red meat and health outcomes. No association was observed between higher consumption of unprocessed red meat (≥250 g/wk vs. <50 g/wk) with total mortality (HR: 0.93; 95% CI: 0.85, 1.02; *P*-trend = 0.14) or major CVD (HR: 1.01; 95% CI: 0.92, 1.11; *P*-trend = 0.72). Similarly, we did not observe any significant association between unprocessed red meat intake and risk of CV mortality, non-CV mortality, cancer mortality, MI, stroke, or heart failure.

Higher consumption of poultry was also not significantly associated with total mortality (HR: 0.96; 95% CI: 0.86, 1.06; *P*-trend = 0.21) or major CVD (HR: 1.02; 95% CI: 0.90, 1.16; *P*-trend = 0.95) and other health outcomes (**Table 3**).

Higher intake of processed meat (≥150 g/wk vs. 0 g/wk) was associated with higher total mortality (HR: 1.51; 95% CI: 1.08, 2.10; *P*-trend = 0.009), major CVD (HR: 1.46; 95% CI: 1.08, 1.98; *P*-trend = 0.004), non-CV mortality (HR: 1.50; 95% CI: 1.03, 2.19; *P*-trend = 0.02), cancer mortality (HR: 1.84; 95% CI: 1.14, 2.97; *P*-trend = 0.02), MI (HR: 1.62; 95% CI: 0.98, 2.69; *P*-trend = 0.03), and stroke (HR: 1.56; 95% CI: 0.94, 2.58; *P*-trend = 0.04). Further, we found a higher risk of events with each 100-g/wk increase in processed meat intake (**Table 4**).

When individuals with events occurring within 24 mo were excluded in sensitivity analyses, the results were unchanged for both unprocessed red meat and poultry (Tables 2 and 3). Additionally,

TABLE 1 Characteristics of participants by categories of unprocessed red meat and poultry ($n = 134{,}297$) and processed meat intake ($n = 31{,}640$)[1]

	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*
Unprocessed red meat intake					
n	38,878	33,644	23,198	38,577	
Age, mean ± SD, y	49.6 ± 10.1	50.4 ± 9.8	50.4 ± 9.6	50.0 ± 9.6	<0.001
Men, *n* (%)	15,611 (40.1)	14,132 (42.0)	9838 (42.4)	16,452 (43.0)	<0.001
Urban, *n* (%)	15,392 (39.6)	18,188 (54.1)	14,106 (60.8)	22,173 (57.5)	<0.001
Current smoker, *n* (%)	7891 (20.4)	7275 (21.8)	4647 (20.2)	8164 (21.3)	<0.001
Trade, college, or university, *n* (%)	4979 (12.9)	6363 (19.0)	5789 (25.0)	8329 (21.6)	<0.001
Highly active, *n* (%)	15,485 (44.7)	13,852 (44.0)	9685 (44.0)	17,015 (46.0)	<0.001
History of diabetes, *n* (%)	3176 (8.2)	2329 (7.0)	1492 (6.4)	2484 (6.5)	<0.001
Taking blood pressure medication, *n* (%)	2970 (7.6)	3992 (12.0)	3267 (14.1)	5647 (14.6)	<0.001
Food intake, mean ± SD, g/d					
Unprocessed red meat	5 ± 6	30 ± 15	62 ± 25	137 ± 76	<0.001
Poultry	16 ± 33	31 ± 40	32 ± 39	33 ± 36	<0.001
Processed meat	3 ± 11	9 ± 18	10 ± 17	9 ± 14	<0.001
Fish	44 ± 99	31 ± 55	30 ± 48	25 ± 40	<0.001
Refined grains	150 ± 211	199 ± 204	179 ± 170	186 ± 169	<0.001
Legumes	83 ± 95	55 ± 68	52 ± 56	47 ± 53	<0.001
Fruit	127 ± 203	214 ± 262	236 ± 255	205 ± 199	<0.001
Vegetables	193 ± 190	258 ± 216	292 ± 207	282 ± 194	<0.001
Dairy	125 ± 191	164 ± 228	214 ± 240	205 ± 216	<0.001
Fiber	16 ± 13	24 ± 16	26 ± 15	24 ± 13	<0.001
Energy intake, mean ± SD, kcal/d	2062 ± 833	2134 ± 818	2209 ± 814	2210 ± 788	<0.001
Poultry intake					
n	69,349	36,793	17,069	11,086	
Age, mean ± SD, y	49.9 ± 10	50.2 ± 10	50.2 ± 10	50.3 ± 9.7	<0.001
Men, *n* (%)	29,182 (42)	15,405 (42)	7012 (41)	4434 (40)	<0.001
Urban, *n* (%)	30,681 (44)	22,180 (60)	10,656 (62)	6342 (57)	<0.001
Current smoker, *n* (%)	15,656 (22)	7190 (20)	3163 (19)	1968 (18)	<0.001
Trade, college, or university, *n* (%)	10,322 (15)	9063 (25)	3835 (23)	2240 (20)	<0.001
Highly active, *n* (%)	29,118 (45)	15,567 (46)	6927 (43)	4425 (42)	<0.001
History of diabetes, *n* (%)	3826 (6)	2822 (8)	1605 (9)	1228 (11)	<0.001
Taking blood pressure medication, *n* (%)	6139 (9)	5010 (14)	2775 (16)	1952 (18)	<0.001
Food intake, mean ± SD, g/d					
Unprocessed red meat	46 ± 60	72 ± 72	79 ± 78	64 ± 66	<0.001
Poultry	5 ± 5	30 ± 16	63 ± 24	107 ± 62	<0.001
Processed meat	5 ± 13	12 ± 19	11 ± 17	8 ± 14	<0.001
Fish	30 ± 73	35 ± 62	38 ± 59	34 ± 54	<0.001
Refined grains	202 ± 234	159 ± 141	154 ± 117	124 ± 91	<0.001
Legumes	64 ± 79	57 ± 66	57 ± 64	53 ± 66	<0.001
Fruit	146 ± 210	233 ± 244	244 ± 230	240 ± 261	<0.001
Vegetables	216 ± 162	286 ± 232	298 ± 234	292 ± 253	<0.001
Dairy	145 ± 200	212 ± 242	204 ± 238	171 ± 202	<0.001
Fiber	21± 15	23 ± 15	23 ± 15	22 ± 15	<0.001
Energy intake, mean ± SD, kcal/d	2076 ± 779	2255 ± 859	2279 ± 807	2043 ± 842	<0.001
Processed meat intake, g/wk	0	<50	50 to <150	≥150	
n	3009	14,597	10,923	3111	
Age, mean ± SD, y	52.2 ± 10.0	52.0 ± 9.5	50.1 ± 9.3	52.0 ± 9.5	<0.001
Men, *n* (%)	936 (31.0)	5516 (38.0)	5224 (48.0)	1267 (41.0)	<0.001
Urban, *n* (%)	1578 (52.4)	9495 (65.0)	6976 (64.0)	1922 (62.0)	<0.001
Current smoker, *n* (%)	786 (26.4)	2806 (19.3)	2436 (22.4)	755 (24.4)	<0.001
Trade, college, or university, *n* (%)	558 (19.0)	5302 (36.5)	3899 (35.8)	1144 (37.0)	<0.001
Highly active, *n* (%)	1156 (52.3)	7418 (56.0)	5552 (57.0)	1590 (57.7)	<0.001
History of diabetes, *n* (%)	180 (6.0)	864 (5.9)	624 (5.7)	179 (5.8)	0.88
Taking blood pressure medication, *n* (%)	654 (10.4)	2960 (46.8)	2095 (33.1)	612 (9.6)	0.01
Food intake, mean ± SD, g/d					
Unprocessed red meat	47 ± 66	92 ± 89	81 ± 73	57 ± 52	<0.001
Poultry	36 ± 39	45 ± 38	40 ± 33	32 ± 30	<0.001
Processed red meat	0	8 ± 5	27 ± 13	67 ± 34	<0.001
Fish	14 ± 24	20 ± 26	22 ± 24	24 ± 23	<0.001
Refined grains	125 ± 102	157 ± 117	137 ± 93	121 ± 74	<0.001
Legumes	33 ± 56	42 ± 56	54 ± 68	36 ± 44	<0.001

(*Continued*)

TABLE 1 (*Continued*)

	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*
Fruit	204 ± 253	256 ± 214	244 ± 214	226 ± 186	<0.001
Vegetables	232 ± 248	351 ± 264	345 ± 231	288 ± 203	<0.001
Dairy	205 ± 260	318 ± 290	308 ± 284	240 ± 231	<0.001
Fiber	23 ± 13	28 ± 15	26 ± 12	24 ± 11	<0.001
Energy intake, mean ± SD, kcal/d	1714 ± 727	2272 ± 822	2194 ± 783	1992 ± 739	<0.001

[1] To test for differences across categories of unprocessed red meat, poultry, and processed meat intake, we used ANOVA test of means and chi-square test for categorical variables. The analysis for processed meat was conducted only among participants from countries with a median consumption of ≥10 g/d (Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden).

we observed a similar association between unprocessed red meat, poultry, and outcomes using vegetarians as the reference group (**Supplemental Table 5**). In the competing risk analyses, the HRs for both CV mortality and major CVD were similar to the conventional estimates from the Cox models (**Supplemental Table 6**).

We further stratified our analysis using smoking status as ever or never smoker. No significant associations were found with smoking status, and the associations between unprocessed red meat and poultry intake with mortality or major CVD were not significant among ever and never smokers (**Supplemental Figure 2**). Higher processed meat intake was associated with higher mortality and the risk of major CVD in both ever and never smokers (**Supplemental Figure 3**). Also, when death due to injury was considered as a negative control, higher consumption of processed meat was not significantly associated with death due to injury (**Supplemental Table 7** and **Supplemental Figure 4**). The E-value suggests that substantial unmeasured confounding would be needed to explain away the observed association between processed meat and events.

Additionally, when we stratified our analyses by geographic regions, for all regions, except for South Asia, no significant differences were found in the associations between unprocessed red meat for total mortality (*P*-interaction for regions and unprocessed red meat = 0.4). Similarly, there was a nonsignificant association between poultry and total mortality in almost all regions. However, a significant positive association was observed for China (*P*-interaction for regions and poultry = 0.6, respectively) (Supplemental Figure 5A, B).

Multivariable cubic splines for unprocessed red meat and poultry showed no significant associations with total mortality. A significant positive linear association was found for processed meat intake and total mortality (**Figure 1**).

Discussion

In a large multinational cohort study of 134,297 participants, including 7789 deaths and 6976 CVD events from 21 countries, we did not find significant associations between unprocessed red meat and poultry intake with mortality or major CVD. In contrast, higher processed meat intake was associated with higher risks of total mortality and major CVD.

Our finding of a nonsignificant association between unprocessed red meat intake and health outcomes is supported by the results of some (but not all) previous studies (14). Unprocessed red meat consumption has generally been associated with increased risks of total mortality and CVD (15). In contrast, a meta-analysis of 6 observational studies involving 1,330,352 individuals, with 137,376 deaths, indicated that unprocessed red meat was not associated with an increased risk of mortality (16). Similarly, in a meta-analysis of 17 prospective cohort studies conducted globally, higher unprocessed red meat consumption was not associated with total mortality (HR: 1.05; 95% CI: 0.93, 1.19; $P = 0.43$) (17). However, recent analyses of US prospective cohort studies reported that higher unprocessed red meat intake was associated with higher risks of mortality and CVD (8, 18). Possible reasons for these differences include differences in the amount of unprocessed red meat intake in different regions of the world [e.g., 100 g/d for the Nurses' Health Study and the Health Professionals Follow-Up Study (18) and ∼57 g/d for the other 6 US cohort studies (8)] compared with the substantially lower intake amounts (37 g/d) among the PURE participants. However, in 1 study where an adverse association was reported between red meat consumption and all-cause and CVD mortality, the reference group was nonconsumers of red meat who may be different in many other behavioral factors that might not have been captured by the study, leading to residual confounding (19). Other factors include differences in cooking methods (e.g., stewed vs. grilled meat preferences) and the background replacement foods (e.g., refined grains vs. animal foods). In addition, most of the studies that have reported adverse associations were from the Western countries, whereas no significant association was observed among studies conducted in Asia (20).

We found an adverse association between processed meat intake and health outcomes, consistent with meta-analyses of observational studies (17, 21, 22). A meta-analysis of 9 observational studies, including 1,330,352 individuals and 137,376 deaths, showed 23% higher mortality among higher processed meat consumers (16). The potential adverse impact of processed meat on health may not be entirely due to its saturated fat or cholesterol content as the amounts of these nutrients are similar in processed and unprocessed meats (23). The amounts of preservative and food additives in processed and unprocessed meats differ markedly, which may partly explain their different effects on health (24). In a large cohort study conducted in 6 states and 2 metropolitan areas of the United States, processed meat's nitrate content explained a large proportion of the increased risk of CVD mortality (25). Similarly, in a European study, adverse associations with CV mortality and respiratory mortality were observed only for processed meat consumption due to high nitrite content (26).

TABLE 2 Association of unprocessed red meat intake and outcome events[1]

	Intake					
	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*-trend[2]	Per 100-g/wk increase
N	38,878	33,644	23,198	38,577		
Total mortality						
No. of events	3433	1938	930	1488		0.98 (0.97, 1.00)
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.90, 1.03)	0.88 (0.81, 0.96)	0.84 (0.78, 0.92)	0.001	
Multivariable	1.00 (ref)	1.01 (0.94, 1.09)	0.99 (0.90, 1.08)	0.93 (0.85, 1.02)	0.14	
Excluding those with event in first 24 mo	1.00 (ref)	1.03 (0.96, 1.11)	0.99 (0.89, 1.10)	0.96 (0.87, 1.07)	0.43	
CV mortality						
No. of events	1287	642	305	561		0.99 (0.96, 1.02)
Age, sex, and center adjusted	1.0 (ref)	0.92 (0.83, 1.03)	0.83 (0.71, 0.96)	0.88 (0.77, 1.02)	0.04	
Multivariable	1.0 (ref)	0.91 (0.83, 1.06)	0.90 (0.76, 1.05)	0.97 (0.84, 1.14)	0.68	
Excluding those with event in first 24 mo	1.0 (ref)	0.99 (0.86, 1.13)	0.88 (0.74, 1.05)	1.02 (0.86, 1.21)	0.95	
Non-CV mortality						
No. of events	2326	1388	664	980		
Age, sex, and center adjusted	1.0 (ref)	0.96 (0.89, 1.04)	0.89 (0.80, 0.99)	0.81 (0.73, 0.89)	0.001	0.98 (0.96, 1.00)
Multivariable	1.0 (ref)	1.02 (0.94, 1.11)	1.02 (0.91, 1.14)	0.89 (0.79, 1.00)	0.10	
Excluding those with event in first 24 mo	1.0 (ref)	1.03 (0.94, 1.12)	1.03 (0.91, 1.15)	0.91 (0.81, 1.03)	0.21	
Cancer mortality						
No. of events	578	518	311	486		0.98 (0.95, 1.01)
Age, sex, and center adjusted	1.0 (ref)	0.98 (0.86, 1.12)	0.87 (0.74, 1.01)	0.81 (0.69, 0.94)	0.002	
Multivariable	1.0 (ref)	1,04 (0.90, 1.20)	0.98 (0.83, 1.16)	0.90 (0.76, 1.05)	0.10	
Excluding those with event in first 24 mo	1.0 (ref)	1.03 (0.90, 1.20)	0.98 (0.82, 1.17)	0.92 (0.78, 1.09)	0.25	
Major CVD						
No. of events	2449	1673	1027	1827		
Age, sex, and center adjusted	1.0 (ref)	0.95 (0.88, 1.02)	0.91 (0.84, 1.00)	0.95 (0.87, 1.03)	0.22	1.00 (0.98, 1.01)
Multivariable	1.0 (ref)	0.98 (0.91, 1.06)	1.00 (0.91, 1.10)	1.01 (0.92, 1.11)	0.72	
Excluding those with event in first 24 mo	1.0 (ref)	0.98 (0.90, 1.07)	0.98 (0.90, 1.09)	1.04 (0.94, 1.15)	0.35	
Myocardial infarction						
No. of events	1255	621	374	718		
Age, sex, and center adjusted	1.0 (ref)	0.92 (0.82, 1.03)	0.87 (0.76, 1.01)	0.99 (0.86, 1.13)	0.87	
Multivariable	1.0 (ref)	0.91 (0.81, 1.03)	0.90 (0.77, 1.05)	0.98 (0.85, 1.13)	0.89	1.00 (0.97, 1.03)
Excluding those with event in first 24 mo	1.0 (ref)	0.91 (0.80, 1.04)	0.85 (0.72, 1.00)	0.99 (0.84, 1.15)	0.89	
Stroke						
No. of events	971	870	556	938		
Age, sex, and center adjusted	1.0 (ref)	1.02 (0.92, 1.13)	1.00 (0.88, 1.12)	0.96 (0.85, 1.07)	0.34	
Multivariable	1.0 (ref)	1.09 (0.98, 1.22)	1.15 (1.01, 1.31)	1.10 (0.97, 1.25)	0.18	1.00 (0.97, 1.02)
Excluding those with event in first 24 mo	1.0 (ref)	1.10 (0.97, 1.23)	1.17 (1.02, 1.35)	1.15 (1.00, 1.32)	0.04	
Heart failure						
No. of events	208	166	115	167		
Age, sex, and center adjusted	1.0 (ref)	0.77 (0.61, 0.97)	0.87 (0.67, 1.13)	0.78 (0.60, 1.01)	0.15	
Multivariable	1.0 (ref)	0.82 (0.63, 1.06)	0.98 (0.73, 1.31)	0.80 (0.59, 1.07)	0.28	0.97 (0.92, 1.03)
Excluding those with event in first 24 mo	1.0 (ref)	0.81 (0.62, 1.07)	0.85 (0.62, 1.18)	0.79 (0.58, 1.09)	0.23	

[1] $n = 134{,}297$. Values are HRs (95% CIs) unless otherwise indicated. Multivariable models adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medications, fruits, vegetable, dairy, poultry, fish, refined grains, processed foods, legumes, total dietary fiber, total energy intake, and center as a random effect. CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

Our study has several strengths. First, the PURE study is one of the largest multinational studies that has examined the association between different types of meat and health outcomes in different regions of the world and the only cohort study to cover 5 continents. Second, a large number of fatal and nonfatal events were recorded in this study, making our findings robust. Third, country-specific validated FFQs were used for the collection of the dietary data by well-trained staff. The PURE study covers substantially more diverse populations and broad patterns of diet. The sampling strategy used in PURE ensures representation from urban and rural communities from different geographic areas (27).

Furthermore, our results were robust in different populations with varying meat intake levels, which suggests that the findings are widely applicable. In the current study, the sample comprised 134,297 participants with a completed FFQ and without a history of CVD or cancer at baseline. Baseline characteristics were generally similar between people who were included or excluded from the current analysis. The follow-up rates in the PURE study were high (96% at 9 y), so loss to follow-up was unlikely to significantly impact our findings.

Nonetheless, our study also has some potential limitations. First, dietary intake was self-reported and variations in reporting might lead to random errors that could distort the associations.

TABLE 3 Association of poultry intake and outcome events[1]

	Intake					
	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*-trend[2]	Per 100-g/wk increase
n	69,349	36,793	17,069	11,086		
Total mortality						
No. of events	4570	1805	868	546		
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.89, 1.02)	0.80 (0.74, 0.87)	0.80 (0.73, 0.87)	<0.001	
Multivariable	1.00 (ref)	0.93 (0.87, 1.00)	0.88 (0.81, 0.97)	0.96 (0.86, 1.06)	0.21	1.00 (0.97, 1.03)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.91, 1.06)	1.07 (0.96, 1.19)	1.03 (0.91, 1.16)	0.64	
CV mortality						
No. of events	1670	634	300	191		
Age, sex, and center adjusted	1.00 (ref)	0.90 (0.81, 1.01)	0.88 (0.76, 1.02)	0.85 (0.71, 1.01)	0.03	
Multivariable	1.00 (ref)	0.93 (0.82, 1.06)	1.03 (0.87, 1.22)	0.91 (0.75, 1.11)	0.56	1.00 (0.95, 1.05)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.86, 1.12)	1.07 (0.89, 1.29)	1.00 (0.80, 1.24)	0.81	
Non-CV mortality						
No. of events	3068	1281	622	387		
Age, sex, and center adjusted	1.00 (ref)	0.87 (0.80, 0.94)	0.89 (0.80, 0.99)	0.88 (0.77, 0.99)	0.01	
Multivariable	1.00 (ref)	0.96 (0.88, 1.05)	1.08 (0.96, 1.21)	1.01 (0.88, 1.16)	0.56	1.00 (0.97, 1.04)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.89, 1.07)	1.06 (0.94, 1.20)	1.02 (0.89, 1.19)	0.54	
Cancer mortality						
No. of events	1,075	458	217	143		
Age, sex, and center adjusted	1.00 (ref)	0.82 (0.73, 0.93)	0.90 (0.76, 1.06)	0.93 (0.76, 1.14)	0.17	
Multivariable	1.00 (ref)	0.91 (0.80, 1.04)	1.00 (0.83, 1.21)	1.05 (0.85, 1.30)	0.79	1.00 (0.95, 1.06)
Excluding those with event in first 24 mo	1.00 (ref)	0.92 (0.80, 1.06)	0.94 (0.77, 1.15)	1.05 (0.84, 1.31)	0.98	
Major CVD						
No. of events	4248	1642	656	430		
Age, sex, and center adjusted	1.00 (ref)	0.93 (0.87, 1.00)	0.91 (0.83, 1.01)	0.98 (0.87, 1.10)	0.19	
Multivariable	1.00 (ref)	0.98 (0.91, 1.05)	0.98 (0.88, 1.09)	1.02 (0.90, 1.16)	0.95	1.00 (0.97, 1.04)
Excluding those with event in first 24 mo	1.00 (ref)	1.01 (0.93, 1.09)	0.98 (0.87, 1.10)	1.03 (0.90, 1.19)	0.86	
Myocardial infarction						
No. of events	1725	699	321	223		
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.87, 1.07)	1.01 (0.87, 1.17)	1.13 (0.95, 1.34)	0.33	
Multivariable	1.00 (ref)	1.00 (0.89, 1.11)	1.07 (0.92, 1.25)	1.15 (0.95, 1.39)	0.16	1.04 (0.98, 1.08)
Excluding those with event in first 24 mo	1.00 (ref)	1.06 (0.94, 1.19)	1.09 (0.92, 1.30)	1.23 (1.00, 1.50)	0.05	
Stroke						
No. of events	2222	734	248	131		
Age, sex, and center adjusted	1.00 (ref)	0.92 (0.84, 1.02)	0.87 (0.75, 1.02)	0.79 (0.65, 0.97)	0.01	
Multivariable	1.00 (ref)	0.98 (0.88, 1.09)	0.90 (0.76, 1.07)	0.84 (0.67, 1.04)	0.10	0.96 (0.91, 1.02)
Excluding those with event in first 24 mo	1.00 (ref)	1.01 (0.91, 1.13)	0.88 (0.74, 1.06)	0.77 (0.60, 0.98)	0.06	
Heart failure						
No. of events	306	198	77	75		
Age, sex, and center adjusted	1.00 (ref)	0.91 (0.74, 1.12)	0.73 (0.54, 0.97)	1.10 (0.81, 1.49)	0.77	
Multivariable	1.00 (ref)	0.93 (0.74, 1.18)	0.80 (0.58, 1.10)	1.16 (0.83, 1.61)	0.83	1.02 (0.94, 1.11)
Excluding those with event in first 24 mo	1.00 (ref)	0.95 (0.74, 1.22)	0.77 (0.54, 1.09)	1.25 (0.88, 1.78)	0.62	

[1] $n = 134{,}297$. Values are HRs (95% CIs) unless otherwise indicated. Multivariable models adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medications, fruits, vegetable, dairy, unprocessed red meat, fish, refined grains, processed foods, legumes, total dietary fiber, total energy intake, and center as a random effect. CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

However, given the large sample size of the study it is less likely that the findings of the study would be affected by random error. We did not measure diet after the baseline assessment, and some individuals might have changed their diet over time. However, in large observational studies with 4 different approaches for assessing the association of dietary fats with risk of CHD using repeated dietary measurements (baseline diet only, the most recent diet, and 2 different algorithms for calculating cumulative average diets) similar results were reported (28). Therefore, we are confident that, with a relatively short follow-up (<10 y), our estimates would not differ with repeated measures. A further limitation was that we were unable to include method of cooking for each country. We acknowledge that this limitation might attenuate the association between unprocessed red meat and poultry and health outcomes. Moreover, dietary data obtained from FFQs are generally not considered a measure of absolute intake, and are usually used to rank individuals into categories of intake. As with any observational study, there is a chance of residual confounding in our analysis. However, extensive established and potential risk factors were considered during

TABLE 4 Association of processed meat intake and outcome events[1]

	Intake					
	0 g/wk	<50 g/wk	50 to <150 g/wk	≥150 g/wk	*P*-trend[2]	Per 100-g/wk increase
n	3009	14,597	10,923	3111		
Total mortality						
No. of events	222	688	506	159		
Age, sex, and center adjusted	1.00 (ref)	1.08 (0.92, 1.27)	1.16 (0.98, 1.37)	1.30 (1.03, 1.62)	0.01	
Multivariable	1.00 (ref)	1.21 (0.96, 1.52)	1.34 (1.05, 1.71)	1.51 (1.08, 2.10)	0.009	1.16 (1.04, 1.28)
Excluding those with event in first 24 mo	1.00 (ref)	1.23 (0.97, 1.57)	1.40 (1.08, 1.82)	1.64 (1.16, 2.33)	0.003	
CV mortality						
No. of events	80	178	145	50		
Age, sex, and center adjusted	1.00 (ref)	0.90 (0.68, 1.20)	1.05 (0.79, 1.41)	1.43 (0.97, 2.10)	0.07	
Multivariable	1.00 (ref)	0.90 (0.60, 1.35)	0.98 (0.63, 1.53)	1.39 (0.73, 2.63)	0.42	1.06 (0.84, 1.33)
Excluding those with event in first 24 mo	1.00 (ref)	0.93 (0.59, 1.48)	1.15 (0.69, 1.89)	1.83 (0.90, 3.70)	0.10	
Non-CV mortality						
No. of events	178	543	383	125		
Age, sex, and center adjusted	1.00 (ref)	1.06 (0.89, 1.28)	1.08 (0.89, 1.31)	1.16 (0.90, 1.49)	0.29	
Multivariable	1.00 (ref)	1.29 (1.00, 1.68)	1.42 (1.06, 1.88)	1.50 (1.03, 2.19)	0.02	1.18 (1.05, 1.32)
Excluding those with event in first 24 mo	1.00 (ref)	1.27 (0.96, 1.67)	1.41 (1.04, 1.89)	1.53 (1.04, 2.27)	0.02	
Fatal cancer						
No. of events	38	260	187	58		
Age, sex, and center adjusted	1.00 (ref)	1.46 (1.03, 2.07)	1.52 (1.06, 2.19)	1.58 (1.02, 2.44)	0.06	1.18 (1.03, 1.34)
Multivariable	1.00 (ref)	1.44 (0.98, 2.11)	1.55 (1.03, 2.31)	1.84 (1.14, 2.97)	0.02	
Excluding those with event in first 24 mo[3]						
Major CVD						
No. of events	104	489	447	166		
Age, sex, and center adjusted	1.00 (ref)	1.12 (0.90, 1.40)	1.37 (1.09, 1.71)	1.77 (1.35, 2.32)	<0.001	
Multivariable	1.00 (ref)	0.98 (0.77, 1.26)	1.15 (0.89, 1.48)	1.46 (1.08, 1.98)	0.004	1.16 (1.05, 1.29)
Excluding those with event in first 24 mo	1.00 (ref)	0.95 (0.73, 1.25)	1.14 (0.87, 1.51)	1.46 (1.04, 2.03)	0.003	
Myocardial infarction						
No. of events	39	217	202	73		
Age, sex, and center adjusted	1.00 (ref)	1.01 (0.71, 1.44)	1.20 (0.84, 1.72)	1.65 (1.08, 2.51)	0.003	
Multivariable	1.00 (ref)	1.05 (0.70, 1.57)	1.21 (0.80, 1.84)	1.62 (0.98, 2.69)	0.03	1.14 (0.98, 1.32)
Excluding those with event in first 24 mo	1.00 (ref)	0.97 (0.64, 1.49)	1.16 (0.75, 1.81)	1.70 (0.99, 2.91)	0.02	
Stroke						
No. of events	41	195	177	62		
Age, sex, and center adjusted	1.00 (ref)	1.14 (0.81, 1.62)	1.42 (1.00, 2.03)	1.70 (1.11, 2.61)	0.002	
Multivariable	1.00 (ref)	0.95 (0.64, 1.40)	1.13 (0.74, 1.71)	1.56 (0.94, 2.58)	0.04	1.23 (1.07, 1.43)
Excluding those with event in first 24 mo	1.00 (ref)	0.97 (0.62, 1.50)	1.28 (0.81, 2.03)	1.68 (0.96, 2.92)	0.01	
Heart failure						
No. of events	17	62	70	28		
Age, sex, and center adjusted	1.00 (ref)	1.10 (0.63, 1.93)	1.65 (0.94, 2.87)	1.84 (0.96, 3.55)	0.009	
Multivariable	1.00 (ref)	1.13 (0.53, 2.44)	1.55 (0.71, 3.42)	1.55 (0.60, 4.00)	0.14	1.19 (0.93, 1.52)
Excluding those with event in first 24 mo	1.00 (ref)	1.21 (0.53, 2.76)	1.50 (0.64, 3.50)	1.54 (0.55, 4.30)	0.27	

[1] $n = 31,640$. Values are HRs (95% CIs) unless otherwise indicated. Multivariable model adjusted for age; sex; location; education; wealth index; smoking status; physical activity; diabetes status; blood pressure–lowering medication; fruit; vegetables; legumes; unprocessed meats; starchy foods; % of energy from SFAs, MUFAs, and PUFAs; total energy intake; and center as a random effect. The analysis for processed meat was conducted only among participants from countries with a median consumption of ≥10 g/d (Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden). CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

[3] Due to the limited number of events, the model did not converge.

analysis of mortality and CVD and other dietary variables. We measured risk factors (e.g., education, smoking, etc.) using standardized questionnaires adopted from 2 large international case-control studies of INTERHEART and INTERSTROKE (29, 30), and there is less chance that residual confounders diverted the associations. Furthermore, the consistency of results across different regions with markedly different lifestyles and unprocessed red meat and poultry intakes makes it less likely that confounders, which might have varied in different regions, explained our observations.

In conclusion, we observed no significant association between the consumption of unprocessed red meat and poultry intake and health outcomes, and higher intake of processed meat was associated with higher risks of mortality and CVD. These findings may indicate that limiting the intake of processed meat should be encouraged.

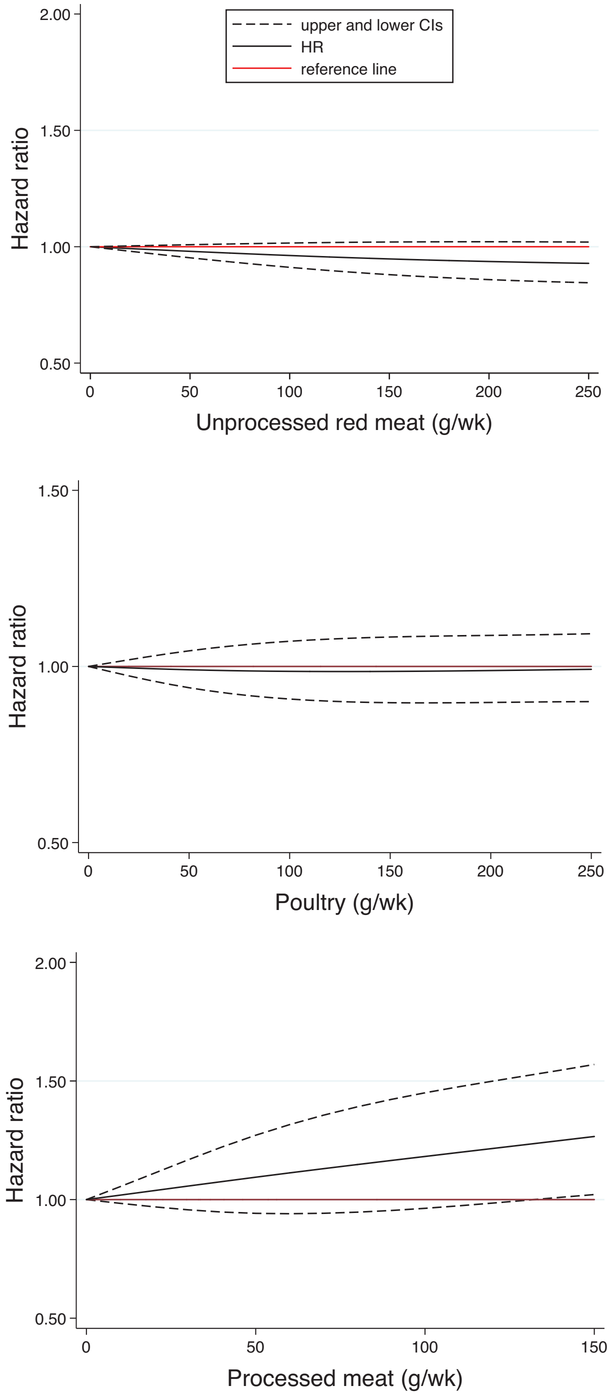

FIGURE 1 Association between unprocessed red meat, poultry, and processed meat intake and total mortality: cubic spline analysis. The multivariable model adjusted for age; sex; education; wealth index; smoking; location; physical activity; history of diabetes; blood pressure–lowering medication; daily intakes of fruits, vegetables, dairy, refined grains, processed foods, legumes, total dietary fiber, total daily energy; and center as a random effect. Models for unprocessed red meat are adjusted for poultry and vice versa.

The authors' responsibilities were as follows—SY: conceived and initiated the PURE study, supervised its conduct, and reviewed and commented on the draft; RI, MD, AM, and SY: had primary responsibility for writing of the manuscript; SR: coordinated the worldwide study and reviewed and commented on drafts; MD: coordinated the entire nutrition component of the PURE study and performed all data analyses; all other authors: coordinated the study in their respective countries and provided comments on drafts of the manuscript; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, codebook, and analytic code will not be made available for the PURE study because the PURE study is an ongoing study and during the conduct only the investigators who have participated/contributed to the study can have access to the data. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals 3 y after the study has been completed (i.e., complete recruitment and a minimum of 10 y follow-up in all) and the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will be contributing to the conduct of the study and requested analyses.

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