Red and Processed Meat Consumption and Risk of Incident Coronary Heart Disease, Stroke, and Diabetes Mellitus

A Systematic Review and Meta-Analysis

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Background—Meat consumption is inconsistently associated with development of coronary heart disease (CHD), stroke, and diabetes mellitus, limiting quantitative recommendations for consumption levels. Effects of meat intake on these different outcomes, as well as of red versus processed meat, may also vary.

Methods and Results—We performed a systematic review and meta-analysis of evidence for relationships of red (unprocessed), processed, and total meat consumption with incident CHD, stroke, and diabetes mellitus. We searched for any cohort study, case-control study, or randomized trial that assessed these exposures and outcomes in generally healthy adults. Of 1598 identified abstracts, 20 studies met inclusion criteria, including 17 prospective cohorts and 3 case-control studies. All data were abstracted independently in duplicate. Random-effects generalized least squares models for trend estimation were used to derive pooled dose-response estimates. The 20 studies included 1 218 380 individuals and 23 889 CHD, 2280 stroke, and 10 797 diabetes mellitus cases. Red meat intake was not associated with CHD (n=4 studies; relative risk per 100-g serving per day=1.00; 95% confidence interval, 0.81 to 1.23; P for heterogeneity=0.36) or diabetes mellitus (n=5; relative risk=1.16; 95% confidence interval, 0.92 to 1.46; P=0.25). Conversely, processed meat intake was associated with 42% higher risk of CHD (n=5; relative risk per 50-g serving per day=1.42; 95% confidence interval, 1.07 to 1.89; P=0.04) and 19% higher risk of diabetes mellitus (n=7; relative risk=1.19; 95% confidence interval, 1.11 to 1.27; P<0.001). Associations were intermediate for total meat intake. Consumption of red and processed meat were not associated with stroke, but only 3 studies evaluated these relationships.

Conclusions—Consumption of processed meats, but not red meats, is associated with higher incidence of CHD and diabetes mellitus. These results highlight the need for better understanding of potential mechanisms of effects and for particular focus on processed meats for dietary and policy recommendations. **(*Circulation*. 2010;121:2271-2283.)**

Key Words: cardiovascular diseases ■ diabetes mellitus ■ diet ■ meat ■ meta-analysis

The 2005 US Dietary Guidelines for Americans recommend that consumption of red and processed meat should be moderated.[1] Such recommendations are in large part derived from expected effects of saturated fat in meat on low-density lipoprotein and total cholesterol levels. However, relationships of meat consumption with disease end points such as coronary heart disease (CHD), stroke, and type 2 diabetes mellitus are not well established, with considerably conflicting results in prior studies.[2–19] Thus, sufficient evidence for direct relationships with chronic cardiometabolic diseases has been lacking to support more quantitative recommendations about specific consumption levels of meats or potential differences between unprocessed red meat (referred to hereafter as simply "red meat") versus processed meats.

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Red versus processed meats may have some important nutritional differences, such as in contents of calories, specific fats, sodium, iron, or additives (eg, nitrites), or differences in their preparation methods (eg, high-temperature commercial cooking) that could produce differing effects on cardiometabolic risk. However, potential differences in effects of red meat versus processed meat consumption on risk of CHD, stroke, or diabetes mellitus have not been systematically evaluated. In the United States alone, 1 700 000 new cases of diabetes mellitus,[20] 600 000 myocardial infarctions, and 780 000 new or recurrent strokes occur each year.[21] Documenting and quantifying the effects of meat consumption on these outcomes, as well as potential differences in effects of red versus processed meat, are of great scientific and public health importance. To address these important questions and elucidate the conflicting results of prior studies, we performed a systematic review and meta-analysis of the evidence for relationships of red meat, processed meat, and red and processed meat combined (referred to hereafter as "total meat") consumption with risk of CHD, stroke, and diabetes mellitus.

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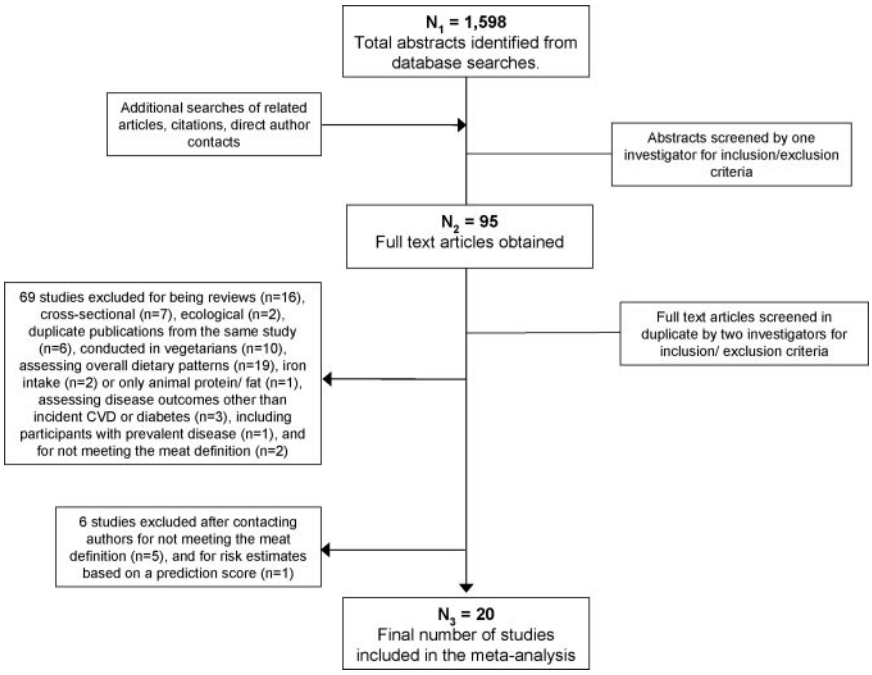

Figure 1. Screening and selection process of studies of meat consumption and CHD, stroke, and diabetes mellitus risk.

Methods

Search Strategy

We followed Meta-Analysis of Observational Studies in Epidemiology[22] protocols throughout the design, implementation, analysis, and reporting. We searched for all prospective or case-control studies or randomized controlled trials that provided effect estimates for potential associations of red, processed, or total meat consumption and incidence of CHD, stroke, total cardiovascular disease (CVD), or diabetes mellitus in adults. Searches were performed with the use of MEDLINE (see Methods in the online-only Data Supplement), EMBASE, AGRIS, AMED, HMIC, PsycINFO, Cochrane Library, Web of Knowledge, CABI, CINAHL, conference abstracts (ZETOC), Faculty of 1000, gray literature sources (SIGLE), related articles, hand-searching of reference lists, and direct author contact. Key words were *meat*, *meat products*, *beef*, *ham*, other specific unprocessed red and processed meat subtypes, *cardiovascular diseases*, and *diabetes mellitus*, including the earliest available online indexing year through March 2009 without language restrictions. "Red meat" was defined as unprocessed meat from beef, hamburgers, lamb, pork, or game and excluding poultry, fish, or eggs[23]; "processed meat" was defined as any meat preserved by smoking, curing, or salting or addition of chemical preservatives, such as bacon, salami, sausages, hot dogs, or processed deli or luncheon meats, and excluding fish or eggs[24]; and "total meat" was defined as the total of these 2 categories. Processed meat was primarily processed red meat, although in some studies deli meats, a subcategory of processed meats, may also have included some processed poultry meats that could not be separately excluded. We excluded a priori studies focused on comparing only vegetarians versus nonvegetarians because such comparisons could likely be strongly modified or biased by other differences in diet and lifestyle behaviors in vegetarians. We also recognized that the lowest intake category in each of the included studies would include a subset of individuals (including likely at least some vegetarians) consuming no red or processed meat. Thus, such individuals were captured in the included studies but without the higher potential for bias when analyses were restricted only to special vegetarian populations. We also excluded a priori cross-sectional or ecological studies; commentaries, general reviews, or case reports; and studies reporting only crude risk estimates.

Selection of Articles

Of 1598 identified articles, 1505 were excluded on the basis of review of the title and abstract (Figure 1). Full texts of the 95 remaining manuscripts were independently assessed in duplicate by 2 investigators to determine inclusion/exclusion, with differences resolved by consensus or, if necessary, group consultation among all investigators. Seventy-five studies were excluded because they were reviews (n=16), cross-sectional (n=7), ecological (n=2), conducted in vegetarians (n=10), or repeated publications from the same study (n=6); assessed only overall dietary patterns (n=19), only iron intake (n=2), or only animal protein/fat (n=1); included poultry in the meat definition (n=7); did not assess incident CHD, stroke, or diabetes mellitus (n=3); reported only crude risk estimates (n=1); or included participants with prevalent disease (n=1) (see Methods in the online-only Data Supplement). Initial inclusion/exclusion adjudications were 97% concordant. For 29 studies, authors were contacted to request missing data or clarify meat definitions used; sufficient responses were received for 23 of 29 studies to characterize the exposure or missing data. For example, several articles initially appeared to report findings separately for red meat versus processed meat but on detailed review or direct contact were found to have included processed meat in the red meat category, requiring direct contact to obtain risk estimates for unprocessed red meat alone.

Data Extraction

For each of the 20 final identified studies, data were extracted independently and in duplicate by 2 investigators, including years the study was performed and reported, study design, sample size, definition(s) of meat intake and disease outcomes, study location, inclusion and exclusion criteria, duration of follow-up, covariates adjusted for, and adjusted risk estimates and confidence intervals (CIs). When >1 multivariable model was reported, risk estimates with the greatest control for potential confounders were extracted. If multivariable models were reported with and without additional adjustment for variables that could be either confounders or intermediates (eg, high cholesterol), the multivariable model without such variables was selected. If the only multivariable model included such variables, this was selected in preference to crude or minimally adjusted models. Accepted standardized quality scores for observational studies are not available. Therefore, quality assessment was performed by evaluating and scoring 5 design criteria on an integer scale (0 or 1, with 1 being better), including appropriateness and reporting of inclusion and exclusion criteria, assessment of exposure, assessment of outcome, control of confounding, and evidence of bias. These scores were summed; quality scores from 0 to 3 were considered lower quality, and scores of 4 to 5 were considered higher quality. Differences in data extracted or quality assessment scores between investigators were unusual and were resolved by consensus. Missing

Table 1. Identified Studies Evaluating the Consumption of Red, Processed, or Total Meat and Incidence of CHD, Stroke, or Diabetes Mellitus

First Author (Year)	Country	Type of Meat*	Consumption in Lowest Category, Median Servings/wk	Consumption in Highest Category, Median Servings/wk	Disease Outcome	Disease Ascertainment	Study Name
Cohort studies							
Burke (2007)[5]	Australia	Red	3.00	8.00	CHD (total)	Regional hospital records and death registry	AAC
		Processed	0.53	2.13	CHD (total)		
Villegas (2006)[18]	China	Red	1.19	6.00	T2DM	Supplementary questionnaire	SWHS
		Processed (and subtypes)	0.00	3.89	T2DM		
Salonen (1992)[10]	Finland	Total meat	6.07	16.49	CHD (total MI)	Regional MI registry	KIHD
Kröger (unpublished data, 2009)‖	Germany	Red	0.67	4.16	T2DM	*ICD-10* criteria, validated by physician	EPIC-Potsdam
		Processed	3.18	17.61	T2DM		
Sauvaget (2003)[11]	Japan	Red	0.00	5.50	Stroke (fatal)	National death registry	HNLSS
		Processed	0.00	5.50	Stroke (fatal)		
Whiteman (1999)[2]	UK	Red	0.50	5.50	CHD (fatal)	National death registry	OXCHECK
		Processed	0.50	5.50	CHD (fatal)		
Ascherio (1994)[4]	US	Red (and subtypes)	1.11	10.16	CHD (total)	Physician review of medical records, autopsy reports, or death certificate	HPFS
Meyer (2001)[19]	US	Processed	0.00	3.50	T2DM	Self-report	IWHS
		Total meat	2.00	13.50	T2DM		
van Dam (2002)[15]	US	Red (and subtypes)	0.98	9.03	T2DM	WHO diabetes criteria, using validated supplementary questionnaire	HPFS
		Processed (and subtypes)	0.00	7.00	T2DM		
He (2003)[13]	US	Total meat	0.50	8.00	Stroke (hemorrhagic)	Physician review of medical records, autopsy reports, or death certificate	HPFS
		Total meat	0.50	8.00	Stroke (ischemic)		
Liu (2003)[7]	US	Processed	0.08	2.41	CHD (total)	Physician review of medical records, autopsy reports, or death certificate	NHS1
		Total meat	2.21	12.31	CHD (total)		
Schulze (2003)[17]	US	Red (and subtypes)	0.00	7.49	T2DM	National Diabetes Data Group criteria, using validated supplementary questionnaire	NHS2
		Processed (and subtypes)	0.25	7.00	T2DM		
Fung (2004)[14]	US	Red	1.47	6.72	T2DM	National Diabetes Data Group criteria, using validated supplementary questionnaire	NHS1
		Processed (and subtypes)	0.28	3.85	T2DM		
		Total meat	2.24	9.87	T2DM		

(*Continued*)

Table 1. Continued

Population	Age, y	Sample Size	Follow-Up, y	No. of Events	Person-Years	Prespecified Analysis	Adjustments†	Quality Score‡	Additional Information§
Australian Aborigines	15–88	514	13	118	4381	Yes (primary)	+++	3	Yes
Australian Aborigines	15–88	514	13	118	4381	Yes (primary)			
Women in Shanghai	40–70	70 609	4.6	1969	326 625	Yes (primary)	+++	3	Yes
Women in Shanghai	40–70	70 609	4.6	1969	326 625	Yes (primary)			
Eastern Finnish men	42–60	1931	3	51	5586	No	++	3	Yes
People in Potsdam, Germany	19–70	25 069	7	844	716 277	Yes (primary)	+++	5	Yes
People in Potsdam, Germany	19–70	25 069	7	844	716 277	Yes (primary)			
Atomic bomb survivors	34–103	37 130	16	1224	498 651	Yes (primary)	++	3	Yes
Atomic bomb survivors	34–103	37 130	16	958	473 404	Yes (primary)			
Patients in Bedfordshire, UK	35–64	10 522	9	94	93 464	Yes (primary)	+++	3	No
Patients in Bedfordshire, UK	35–64	10 522	9	91	93 429	Yes (primary)			
Male health professionals	40–75	44 933	4	386	157 010	No	+++	4	Yes
Women in Iowa	55–69	35 988	11	1890	336 204	Yes (secondary)	++	3	Yes
Women in Iowa	55–69	35 988	11	1890	336 204	Yes (secondary)			
Male health professionals	39–78	42 504	12	1320	466 508	Yes (primary)	+++	5	Yes
Male health professionals	39–78	42 504	12	1320	466 508	Yes (primary)			
Male health professionals	40–75	43 732	14	125	602 693	Yes (secondary)	+++	5	No
Male health professionals	40–75	43 732	14	455	609 623	Yes (secondary)			
Female nurses	30–55	57 031	18	1351	752 353	Yes (primary)	+++	5	Yes
Female nurses	30–55	57 031	18	1351	752 353	Yes (primary)			
Female nurses	26–46	91 246	8	741	716 276	Yes (primary)	+++	5	Yes
Female nurses	26–46	91 246	8	741	716 276	Yes (primary)			
Female nurses	38–63	69 554	14	2475	856 539	Yes (secondary)	+++	4	Yes
Female nurses	38–63	69 554	14	2475	856 539	Yes (secondary)			
Female nurses	38–63	69 554	14	2475	856 539	Yes (secondary)			

(*Continued*)

Table 1. Continued

First Author (Year)	Country	Type of Meat*	Consumption in Lowest Category, Median Servings/wk	Consumption in Highest Category, Median Servings/wk	Disease Outcome	Disease Ascertainment	Study Name
Fung (2004)[12]	US	Red	0.07	11.90	Stroke (ischemic)	Physician review of medical records, autopsy reports, or death certificate	NHS1
		Processed (and subtypes)	0.07	11.90	Stroke (ischemic)		
		Total meat	0.07	11.90	Stroke (ischemic)		
Song (2004)[16]	US	Red (only subtypes)			T2DM	Self-report	WHS
		Processed (and subtypes)	0.00	3.92	T2DM		
		Total meat	0.91	9.94	T2DM		
Kelemen (2005)[8]	US	Total meat	3.92	16.80	CHD (fatal)	National death registry	IWHS
Sinha (2009)[3]	US	Total meat	1.37	8.75	CVD (fatal)	National death registry	NIH-AARP
		Processed	0.45	6.33	CVD (fatal)		
		Total meat	1.37	8.75	CVD (fatal)		
		Processed	0.45	6.33	CVD (fatal)		
Case-control studies							
Kontogianni (2008)[9]	Greece	Total meat	0.28	1.25	CHD (nonfatal)	Physician diagnosis	CARDIO-2000
Tavani (2004)[29]	Italy	Processed (only subtypes)			CHD (nonfatal MI)	Physician diagnosis	3ITALCC
Martinez-Gonzalez (2002)[6]	Spain	Red	3.50	13.30	CHD (nonfatal MI)	Physician diagnosis	SPAINCC
		Processed	0.88	5.25	CHD (nonfatal MI)		

T2DM indicates type 2 diabetes mellitus; *ICD-10, International Statistical Classification of Diseases, 10th Revision*; WHO, World Health Organization; 3ITALCC, 3 Italian case-control studies; AAC, Australian Aboriginal cohort; CARDIO-2000, Greek case-control study; EPIC-Potsdam, European Prospective Investigation Into Cancer and Nutrition–Potsdam Study; HNLSS, Hiroshima/Nagasaki Life Span Study; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; NHS1, Nurses' Health Study 1; NHS2, Nurses' Health Study 2; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OXCHECK, OXford and Collaborators HEalth ChecK; SPAINCC, Spanish case-control study; SWHS, Shanghai Women's Health Study; and WHS, Women's Health Study.

*Including red meat (unprocessed red meat), processed meat (total processed meat), and total meat (red and processed combined), as well as subtypes (eg, beef, pork, hamburger, ham) within each meat category when available.

data or definitions were resolved by direct contact with authors as described above. To provide some perspective in regard to why cardiometabolic effects of red versus processed meats might differ, we evaluated nationally representative average nutrient and preservative contents of red and processed meats consumed in the United States. To estimate average nutrient qualities, we analyzed data from the 2005–2006 US National Health and Nutrition Examination Survey (NHANES), accounting for NHANES sampling and weighting strategies to provide nationally representative estimates[25,26] (see Methods in the online-only Data Supplement). Foods consumed in this US survey were grouped to match the definitions of our meta-analysis for red and processed meat. Preservative contents were obtained from a recent report of published nitrate, nitrite, and nitrosamine contents of foods commonly consumed in the United States[26] and applied directly to meats in the NHANES database with the use of methods similar to those used for nutrients. We recognized that such nutrient data may not be fully generalizable outside the United States, but comparable data were not available from Europe, Asia, or Australia.

Statistical Analysis

All included studies were observational and reported either relative risks (RRs; prospective cohorts) or odds ratios (case-control studies) across several different categories of meat intake. Odds ratios were assumed to approximate RRs[24]; we also performed analyses limited to prospective cohorts only. The midpoint in each category was used to define median intake in that category, with standardization across studies to a serving size of 100 g (3.5 oz) for red and total meat and 50 g (1.8 oz) for processed meat. For studies with an open-ended highest category that did not report median intake, we assumed that the difference from the lowest range to the median was equivalent to the same difference in the

Table 1. Continued

Population	Age, y	Sample Size	Follow-Up, y	No. of Events	Person-Years	Prespecified Analysis	Adjustments†	Quality Score‡	Additional Information§
Female nurses	38–63	71 768	14	476	957 988	No	++	4	Yes
Female nurses	38–63	71 768	14	476	957 988	No			
Female nurses	38–63	71 768	14	476	478 994	No			
Female health professionals	≥45	37 309	8.8	1539–1555	326 876	Yes (primary)	+++	4	No
Female health professionals	≥45	37 309	8.8	1543	326 876	Yes (primary)			
Female health professionals	≥45	37 309	8.8	1558	326 876	Yes (primary)			
Women in Iowa	55–69	29 017	15	739	475 755	Yes (secondary)	+++	4	Yes
Male members of AARP	50–71	322 263	10	14 221	236 937	Yes (primary)	+++	3	No
Male members of AARP	50–71	322 263	10	14 221	236 937	Yes (primary)			
Female members of AARP	50–71	223 390	10	5356	191 254	Yes (primary)			
Female members of AARP	50–71	223 390	10	5356	191 254	Yes (primary)			
Hospitalized patients, matched controls	26–86	848 cases; 1078 controls	. . .	844	. . .	Yes (primary)	++	3	Yes
Hospitalized patients, matched controls	17–79	558 cases; 1044 controls	. . .	558	. . .	Yes (primary)	++	2	Yes
Hospitalized patients, matched controls	<80	171 cases; 171 controls	. . .	171	. . .	Yes (secondary)	+++	4	Yes
Hospitalized patients, matched controls	<80	171 cases; 171 controls	. . .	171	. . .	Yes (secondary)			

†Degree of adjustment for confounders: +, sociodemographics; ++, sociodemographics plus either other risk factors or dietary variables; +++, sociodemographics plus other risk factors and dietary variables.

‡Quality assessment was performed by review of study design, including inclusion and exclusion criteria, assessment of exposure, assessment of outcome, control of confounding, and evidence of bias. Each of the 5 quality criteria was evaluated and scored on an integer scale (0 or 1, with 1 being better) and summed; quality scores from 0 to 3 were considered lower quality and 4 to 5 higher quality.

§Authors provided additional information to characterize the exposure or missing data.

‖Includes most recent results from the EPIC-Potsdam Study; Kröger J, Schulze MB, Heidemann C, Schienkiewitz A, Boeing H. Dietary fatty acids and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Submitted.

closest adjacent category. To maximize use of the data to calculate pooled dose response, summary estimates of log-linear dose-response regressions were made with the use of random-effects generalized least squares models for trend estimation[27] (GLST in STATA [StataCorp, College Station, Tex]). This method is ideal for meta-analyses of studies having multiple risk estimates per study because it accounts for appropriate variance-covariance relationships between and within studies. Covariance was fit with the use of total numbers of cases and of subjects (controls plus cases) for case-control data or person-years for cohort data, at each level of exposure. Evidence for statistical heterogeneity between studies was tested with goodness of fit (χ^2). Generalized least squares models for trend take advantage of the multiple data points in all studies simultaneously to provide the best overall pooled estimate of dose response in a single (1-stage) estimation. To construct funnel plots and evaluate the Begg adjusted-rank correlation test for publication bias,[28] explore potential sources of heterogeneity, and visually display the individual study results in Forest plots, we also performed 2-stage estimation: Separate generalized least squares models for trend were evaluated for each study to derive study-specific log-linear dose responses (log RR), and then each study-specific log RR was pooled in a second generalized least squares model for trend. Our prespecified primary outcome was based on the 1-stage estimation that better estimates the variance-covariance matrix by using all available β coefficients in each study rather than the 2-stage estimation that first derives a single β coefficient per study and then estimates the variance-covariance matrix. We performed sensitivity analyses, when data were available, for subgroups of specific processed meats. Prespecified potential sources of heterogeneity explored were study location (United States, Asia/Australia, Europe), degree of covariate adjustment (minimal, sociodemographics; adequate, sociodemographics plus either other

risk factors or dietary variables; optimal, all 3), overall quality score (0 to 3, 4 to 5), single versus repeated dietary assessment methods, and (to address potential publication bias of "positive" findings) whether the reported analysis was prespecified or post hoc in each article. Analyses were performed with the use of STATA 10.0 (StataCorp, College Station, Tex), with 2-tailed $\alpha < 0.05$.

Results

The 20 identified investigations included 17 prospective cohorts studies and 3 case-control studies conducted in the United States (n=11), Europe (n=6), Asia (n=2), and Australia (n=1) and included 1 218 380 unique individuals in whom 23 889 cases of CHD, 2280 cases of stroke, and 10 797 cases of diabetes mellitus were identified (Table 1). No randomized controlled trials of red, processed, or total meat consumption and incidence of CHD, stroke, or diabetes mellitus were identified. Reported categories of meat consumption typically ranged from never or less than once a month (lowest category of intake) to variable highest categories of intake. Averaged across studies, consumption (mean±SD) levels in the lowest versus highest category of intake were 1.1±1.1 versus 8.3±2.7 servings per week for red, 0.4±0.8 versus 5.7±3.9 servings per week for processed, and 1.8±1.7 versus 10.5±4.2 servings per week for total meat intake, respectively. Most studies used validated multiitem food frequency questionnaires to quantify meat consumption; some used interview-based[5,10,29] or fewer-item food frequency[2] questionnaires. Total numbers of participants (n=342 to 322 263) and events (n=51 to 14 221) varied widely between studies. Extent of covariate adjustment also varied, especially for dietary variables that were often not controlled for[3,4,6,8,13,17] (and J. Kröger, MSc, unpublished data, 2009). Approximately half of the studies included variables that could be confounders or intermediates (eg, lipid levels) in addition to sociodemographic and/or dietary variables.[5,7,9,10,13,15,17,29] Four studies reported how red versus processed meat intake was associated with other dietary and lifestyle factors at baseline.[7,16,18] Relationships with these other risk factors were similar for red versus processed meat. For example, higher consumption of both red and processed meat tended to be similarly associated with current smoking, higher body mass index, family history of diabetes mellitus, hypertension, higher education and income level, and higher intake of total energy, total fat, saturated, monounsaturated, and polyunsaturated fats, dietary cholesterol, and protein. In addition, red and processed meat consumption levels were similarly associated with less physical activity, multivitamin use, prevalence of high cholesterol, glycemic load, and intake of carbohydrate, fiber, and magnesium. For all but 3 of the studies,[4,10,12] the reported exposure-outcome assessment was a prespecified primary or secondary aim.

Meat Intake and CHD

Nine studies provided 16 separate estimates for relationships of consumption of red, processed, or total meat and incident CHD (Figure 2).

Red Meat

Consumption of red meat was not associated with CHD (RR=1.00 per serving per day; 95% CI, 0.81 to 1.23), with no statistically significant between-study heterogeneity (P=0.36) (Figure 2, top panel). Findings were similar in analyses restricted to cohort studies[2,4,5] (RR=0.92; 95% CI, 0.74 to 1.15) or studies for which this exposure-outcome assessment was prespecified[2,5,6] (RR=0.95; 95% CI, 0.66 to 1.35).

Processed Meat

Each serving per day of processed meat was associated with 42% higher risk of CHD (RR=1.42; 95% CI, 1.07 to 1.89) (Figure 2, middle panel). Statistical between-study heterogeneity was present (P=0.04), not accounted for by any of our prespecified sources of heterogeneity. For all included studies, this exposure-outcome assessment was prespecified. Restricting the analysis to cohort studies[2,3,5,7] resulted in similar findings, with 44% higher CHD risk per serving per day (RR=1.44; 95% CI, 1.07 to 1.95). Restricting the analysis to US studies[3,7] resulted in similar findings (RR=1.40; 95% CI, 1.03 to 1.91). With the exclusion of 1 large US study that evaluated only total CVD mortality[3] (not CHD alone), each serving per day of processed meat consumption was associated with nearly 2-fold higher risk of CHD (RR=1.90; 95% CI, 1.00 to 3.62), with no evidence for between-study heterogeneity (P=0.29).

Total Meat

Total meat consumption was associated with a trend toward higher CHD risk (RR=1.27; 95% CI, 0.94 to 1.72) (Figure 2, bottom panel). Between-study heterogeneity was present (P=0.002), observed to be due to extreme findings in the smallest study,[9] which was also the only case-control study. With the exclusion of this study, total meat consumption was associated with 25% higher CHD risk (RR=1.25; 95% CI, 1.21 to 1.29). These findings were largely driven by 1 study that assessed only total CVD mortality[3] (not CHD alone); with the exclusion of this study, a significant association was not confirmed between total meat intake and CHD risk (RR=1.96; 95% CI, 0.67 to 5.70), but CIs were broad. Findings restricted to studies[3,7,9] with prespecified aims to assess this exposure-outcome relationship were similar to the overall pooled estimate (RR=1.31; 95% CI, 0.92 to 1.85).

Meat Intake and Diabetes Mellitus

Seven studies provided 15 separate estimates for relationship of red, processed, or total meat consumption and incidence of diabetes mellitus (Figure 3).

Red Meat

Consumption of red meat was not significantly associated with incident diabetes mellitus (pooled RR=1.16 per serving per day; 95% CI, 0.92 to 1.46) (Figure 3, top panel). Statistical heterogeneity between studies was not evident (P=0.25). All included studies were cohorts, for which the exposure-outcome assessments were prespecified.

Processed Meat

Seven studies evaluated the relationship of processed meat consumption and incident diabetes mellitus (Figure 3, middle panel). All studies were cohorts for which this exposure-outcome assessment was prespecified. In the overall pooled estimate, each serving per day was associated with 19% higher risk (RR=1.19; 95% CI, 1.11 to 1.27). Significant between-study heterogeneity was present (P<0.001), identified in metaregression as related to study location (P=0.03). With the exclusion of 1 study in Asia/Australia,[18] each

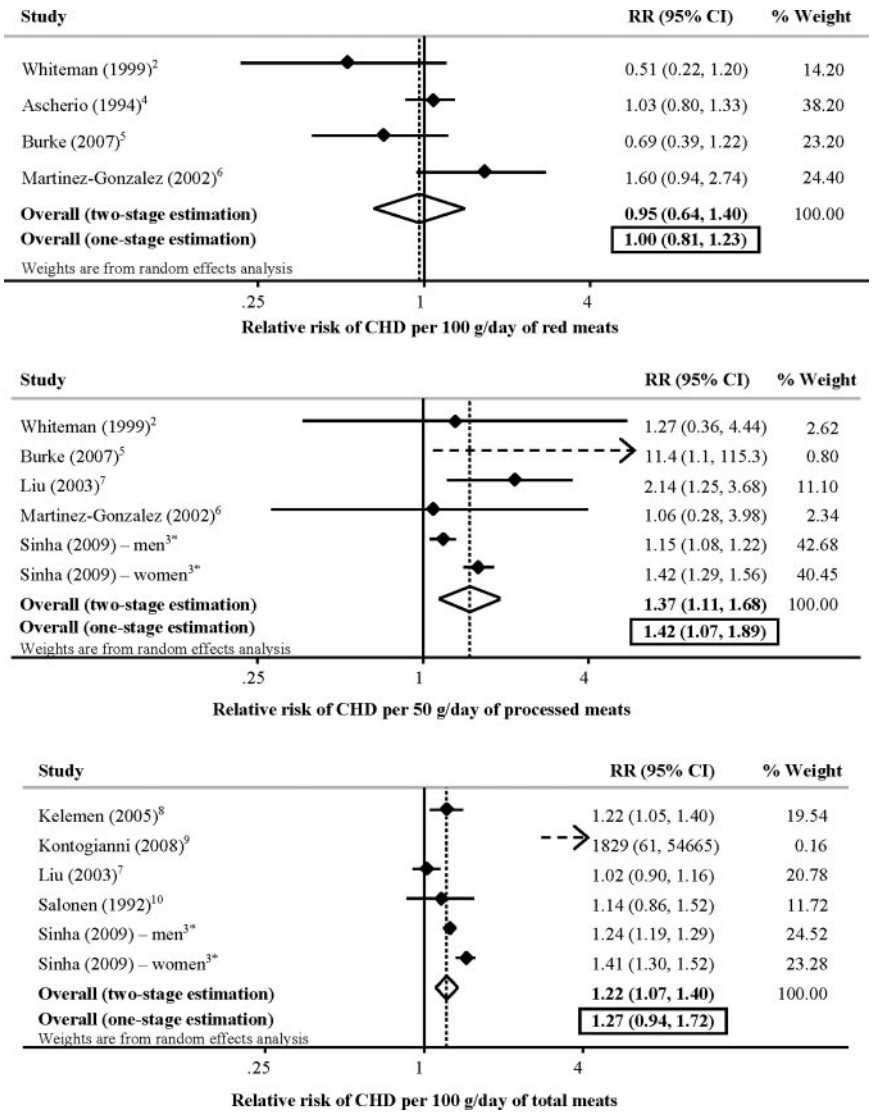

Figure 2. Risk of incident CHD associated with servings per day of red meat (top; 3 cohort studies and 1 case-control study, 56 311 participants, and 769 events), processed meat (middle; 4 cohort studies and 1 case-control study, 614 062 participants, and 21 308 events), and total meat (bottom; 4 cohort studies and 1 case-control study, 635 558 participants, and 22 562 events). *Assessed total cardiovascular (CHD+stroke) mortality only. Solid diamonds and lines are study-specific dose-response and 95% CI, respectively. Dashed line and open diamond are pooled dose-response and 95% CI, respectively, combining each study-specific dose-response (two-stage). The overall dose-response and 95% CI from generalized least squares for trend estimation (one-stage) is also shown.

serving per day was associated with 27% higher risk of diabetes mellitus (RR=1.27; 95% CI, 1.18 to 1.37). When restricted to US studies,[14,17,19] each serving per day was associated with 53% higher risk of diabetes mellitus (RR=1.53; 95% CI, 1.37 to 1.71).

Five studies provided estimates for 3 subtypes of processed meat, including (1) bacon (5 estimates, 5 studies)[14–18]; (2) hot dogs (4 estimates, 4 studies)[14–17]; and (3) other processed meats (4 estimates, 4 studies).[14–17] Each serving (2 slices) per day of bacon was associated with a 2-fold higher incidence of diabetes mellitus (RR=2.07; 95% CI, 1.40 to 3.04); of hot dogs (each 1 per day), with nearly a 2-fold higher incidence (RR=1.92; 95% CI, 1.33 to 2.78); and of other processed meats (each 1 piece per day), with a 66% higher incidence (RR=1.66; 95% CI, 1.13 to 2.42). All of these latter analyses were cohort studies and were reported as prespecified primary or secondary aims.

Total Meat

Each serving per day of total meat was associated with 12% (RR=1.12; 95% CI, 1.05 to 1.19) higher risk of diabetes mellitus (Figure 3, bottom panel). Statistical heterogeneity between studies was not evident (P=0.29). All of these studies were cohorts for which this exposure-outcome assessment was prespecified.

Meat Intake and Stroke

Only 3 identified studies,[11–13] all cohorts, evaluated relationships of red, processed, or total meat consumption and incidence of total stroke or stroke subtypes, including 152 630 individuals and 2280 stroke events (Figure 4). Generally, no 2 studies evaluated the same meat and stroke subtype, limiting ability to pool results. Two studies[11,12] evaluated red meat intake and either total ischemic stroke (1 study) or total stroke mortality (1 study); when these studies were pooled, the risk estimate was not significant (RR=1.17; 95% CI, 0.40 to 3.43) (Figure 4, top panel). Two studies[11,12] evaluated processed meat intake and either total ischemic stroke (1 study) or total stroke mortality (1 study); when these studies were pooled, the risk estimate was not significant (RR=1.14; 95% CI, 0.94 to 1.39) (Figure 4, middle panel). Two studies[12,13] evaluated total meat consumption and total ischemic stroke; the pooled risk estimate demonstrated 24%

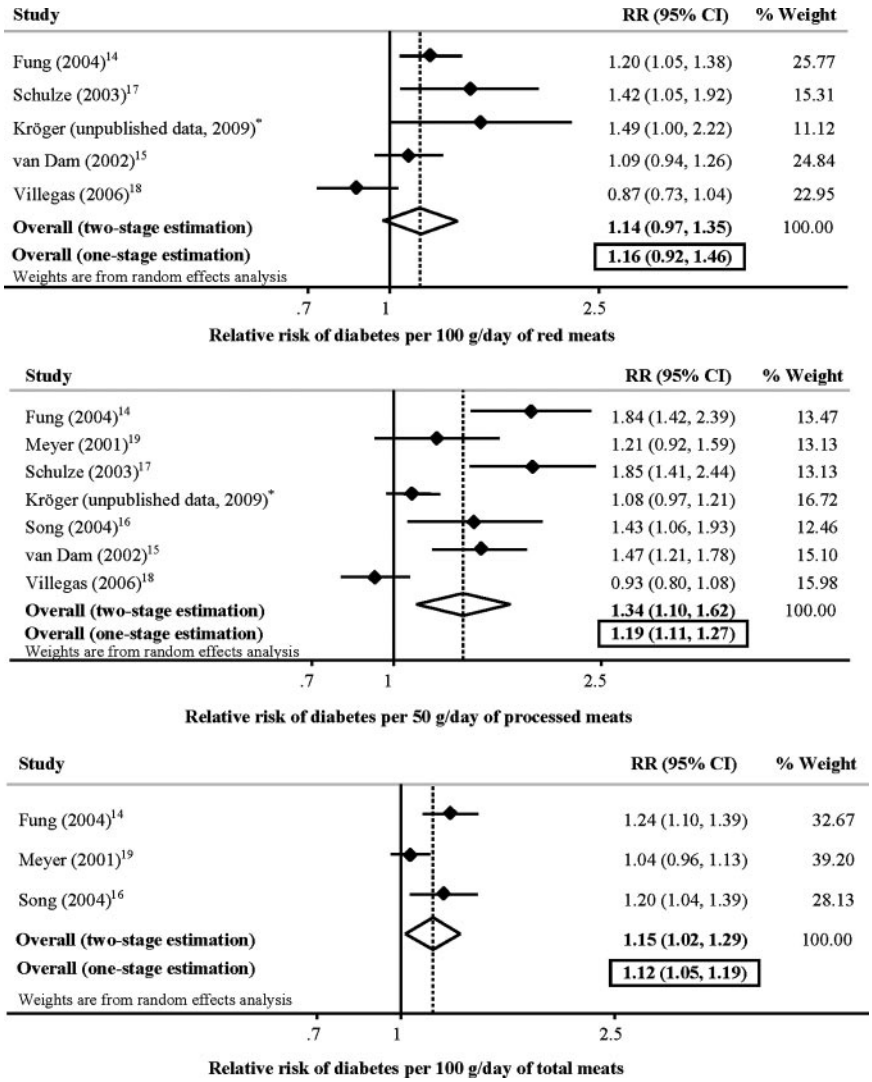

Figure 3. Risk of incident diabetes mellitus associated with servings per day of red meat (top; 5 cohort studies, 298 982 participants, and 7349 events), processed meat (middle; 7 cohort studies, 372 279 participants, and 10 782 events), and total meat (bottom; 3 cohort studies, 142 851 participants, and 5923 events). *European Prospective Investigation Into Cancer and Nutrition–Potsdam Study, includes most recent results. Solid diamonds and lines are study-specific dose-response and 95% CI, respectively. Dashed line and open diamond are pooled dose-response and 95% CI, respectively, combining each study-specific dose-response (two-stage). The overall dose-response and 95% CI from generalized least squares for trend estimation (one-stage) is also shown.

higher risk per daily serving (RR=1.24; 95% CI, 1.08 to 1.43) (Figure 4, bottom panel). Only 1 study[13] reported an association for total meat consumption and hemorrhagic stroke (RR per daily serving=1.64; 95% CI, 0.75 to 3.60). Evaluation for between-study heterogeneity was limited by the few studies and estimates.

Publication Bias

Evidence for publication bias was not apparent for most of these exposure-outcome relationships on the basis of either visual inspection of the funnel plot or by the Begg test, a statistical analog of the visual funnel plot (Figure I in the online-only Data Supplement), although such tests have limited statistical power in the setting of relatively few studies. The funnel plot suggested possible publication bias in reporting of studies for processed meat intake and risk of CHD; the Begg test did not achieve statistical significance (P=0.57), and excluding the smallest study with the most unbalanced results on the funnel plot[5] had little effect on results (RR=1.37; 95% CI, 1.05 to 1.79). The funnel plot also suggested possible publication bias in reporting of studies for red meat intake and diabetes mellitus risk, but the Begg test did not achieve statistical significance (P=0.62); red meat consumption was not significantly associated with diabetes mellitus risk in the overall pooled result (Figure 3, top panel); and excluding the 2 smallest studies with the most unbalanced results on the funnel plot[14] (and J. Kröger, MSc, unpublished data, 2009) did not appreciably alter these results (RR=1.05; 95% CI, 0.73 to 1.49).

Nutritional Qualities of Red and Processed Meats

On the basis of nationally representative data on the types and quantities of meats consumed in the United States, both similarities and differences were identified in average nutrient and/or preservative contents of red versus processed meats (Table 2). Per 50-g serving, processed meats contained modestly higher calories and percent energy from fat and lower percent energy from protein compared with 50 g of red meats. Consistent with lower protein content, processed meats also contained less iron. Processed meats contained relatively similar saturated fat and slightly lower cholesterol, the latter perhaps related to some processed meats being derived from pork and/or lower-cholesterol deli meats. Relatively small differences were present in contents of monounsaturated fat, polyunsaturated fat, or potassium. Largest differences were seen in levels of sodium, with processed meats containing

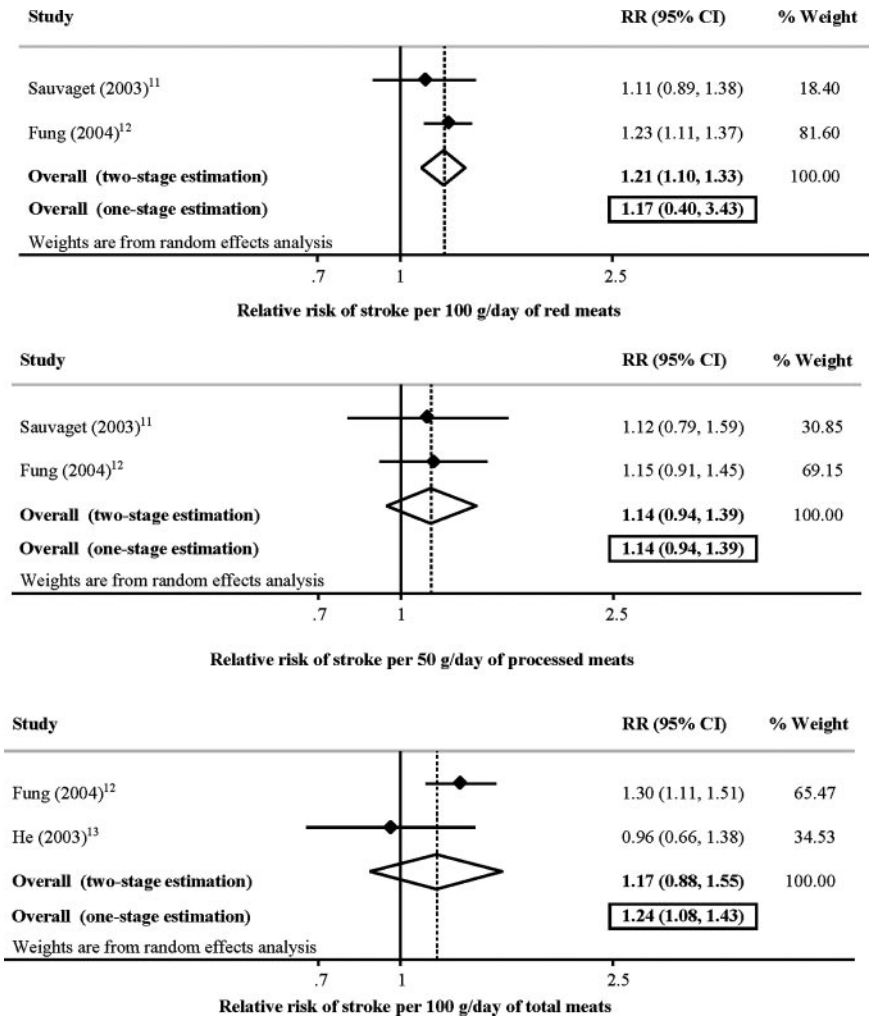

Figure 4. Risk of incident stroke associated with servings per day of red meat (top; 2 cohort studies, 108 898 participants, and 1700 events), processed meat (middle; 2 cohort studies, 108 898 participants, and 1434 events), and total meat (bottom; 2 cohort studies, 115 500 participants, and 931 events). Solid diamonds and lines are study-specific dose-response and 95% CI, respectively. Dashed line and open diamond are pooled dose-response and 95% CI, respectively, combining each study-specific dose-response (two-stage). The overall dose-response and 95% CI from generalized least squares for trend estimation (one-stage) is also shown.

4-fold higher levels (622 versus 155 mg per serving), as well as ≈50% higher nonsalt preservatives including nitrates, nitrites, and nitrosamines.

Discussion

Whereas meat consumption is commonly considered a risk factor for cardiovascular and metabolic diseases, our findings indicate that the effects and magnitudes may vary depending on both the type of meat consumed and the outcome considered. This first systematic review and meta-analysis of these relationships, including 1 218 380 individuals from 10 countries on 4 continents with 23 889 cases of CHD, 2280 cases of stroke, and 10 797 cases of diabetes mellitus, provides the most robust and reliable evidence to date of how unprocessed red and processed meat consumption may influence risk of cardiometabolic diseases. Consumption of processed meats was associated with significantly higher incidence of both CHD and diabetes mellitus, with 42% and 19% higher risk, respectively, per 50-g serving per day. In contrast, consumption of unprocessed red meats was not associated with CHD and was associated with a nonsigificant trend toward higher risk of diabetes mellitus. Associations were intermediate for total meat intake.

Our extensive search of multiple databases and direct contact with authors resulted in the identification of 17 prospective cohorts and 3 case-control studies; no randomized controlled trials were identified that evaluated effects of red, processed, or total meat consumption on CVD or diabetes mellitus events. This is not surprising when it is considered that trials of such effects can be challenging and costly to conduct, with limitations of nonblinding and noncompliance over the long periods of time required to detect clinical end points. In this setting, the best available evidence is derived from long-term prospective cohorts of disease end points such as those identified here, although such studies can be limited by misclassification and residual confounding. Retrospective case-control studies may have additional potential limitations (eg, recall and selection bias).

Thus, each of these individual studies has potential limitations, and our findings should be interpreted in that context. On the other hand, this represents the most complete worldwide evidence to date of the potential effects of red and processed meat consumption on incidence of CHD, stroke, and diabetes mellitus. We also performed multiple sensitivity analyses to evaluate the extent to which our findings might vary depending on underlying study design (cohort versus case-control), presence or absence of prespecified analyses, geographic region (eg, United States versus other), overrepresentation of 1 large study, or other identified sources of heterogeneity. Generally, findings were consistent in each of these sensitivity analyses and similar

Table 2. Differences in Average Nutritional and Preservative Contents Between Red Meats and Processed Meats per 50-g Servings, as Consumed in the United States

Per 50 g of Meat	Red Meats, Mean±SE (Median)	Processed Meats, Mean±SE (Median)
Energy, kcal	123.3±0.7 (124.1)	138.1±2.0 (150.6)
Total fat, % energy	49.6±0.3 (54.1)	57.5±0.6 (69.4)
Total fat, g	7.1±0.1 (7.7)	10.2±0.2 (12.3)
Saturated fat, % energy	18.7±0.1 (20.4)	19.4±0.3 (22.8)
Saturated fat, g	2.7±0.0 (2.9)	3.5±0.1 (4.4)
Monounsaturated fat, % energy	21.4±0.1 (23.9)	25.3±0.3 (30.7)
Monounsaturated fat, g	3.1±0.0 (3.3)	4.5±0.1 (5.3)
Polyunsaturated fat, % energy	2.7±0.0 (1.7)	6.4±0.1 (6.1)
Polyunsaturated fat, g	0.4±0.0 (0.2)	1.1±0.0 (0.6)
Protein, % energy	46.2±0.3 (41.5)	35.4±0.5 (27.4)
Protein, g	13.6±0.0 (13.5)	9.8±0.1 (8.8)
Sodium, mg	154.8±3.4 (127.1)	621.7±7.6 (575.8)
Potassium, mg	161.0±0.8 (152.8)	170.2±1.9 (153.6)
Cholesterol, mg	41.9±0.2 (43.8)	34.1±0.3 (28.3)
Iron, mg	1.1±0.0 (1.2)	0.6±0.0 (0.6)
Nitrates, mg	3.3±0.0 (2.9)	4.6±0.1 (3.0)
Nitrites, mg	0.5±0.0 (0.7)	0.8±0.0 (0.6)
Nitrosamines, μg	0.1±0.0 (0.2)	0.3±0.0 (0.2)

Based on data from the 2005–2006 US NHANES and a report of published nitrate, nitrite, and nitrosamine contents of foods,[26] each analyzed according to actual US consumption levels and accounting for the NHANES sampling and weighting strategies. All mean differences were significant at the 0.05 level.

to the overall pooled results. Thus, although limitations of the individual studies should not be ignored, our results provide the best current evidence for how red, processed, and total meat consumption relate to CHD, stroke, and diabetes mellitus and highlight specific gaps in knowledge that are essential for policy decisions relating to these important diet-disease relationships.

For example, our findings of different relationships of red versus processed meat consumption with incident CHD and diabetes mellitus events support the need to better characterize which particular components of meats may increase cardiometabolic risk. At least in the United States, where most of the studies were performed, processed meats contain, on average, similar saturated fat and lower cholesterol and iron compared with red meats, suggesting that differences in these constituents may not account for different associations with disease risk. Other constituents may be relevant in determining health effects. In particular, the observed substantially higher sodium and nitrate preservative levels in processed meats could plausibly contribute to increased CVD and diabetes mellitus risk and account, at least in part, for the present findings. Dietary sodium significantly increases blood pressure,[30–32] and habitual consumption may also worsen arterial compliance and promote vascular stiffness.[33] Nitrates and their byproducts (eg, peroxynitrite) experimentally promote atherosclerosis and vascular dysfunction,[34] reduce insulin secretion,[35,36] and impair glucose tolerance,[36] and streptozotocin, a nitrosamine-related compound, is a known diabetogenic compound.[37] In observational studies in children, nitrites and nitrous compounds are associated with type 1 diabetes mellitus,[38,39] and nitrite concentrations in adults have been used as a biomarker of endothelial dysfunction[40] and impaired insulin response.[41] Differences in types of foods commonly replaced when individuals consume red versus processed meats could also partly account for their different associations with risk.

Our study had several strengths. We reviewed multiple databases broadly and systematically for all investigations of meat consumption and incidence of CHD, stroke, or diabetes mellitus, making it likely that we identified all major published reports. Multiple authors were contacted directly and clarified findings or provided additional data, minimizing both misclassification and effects of publication bias. Study inclusion/exclusion and data extraction were performed independently and in duplicate by 2 investigators, increasing the validity of results. Studies were identified from the United States, Europe, Asia, and Australia, increasing generalizability. Large numbers of disease end points were identified, providing substantial statistical power to detect clinically meaningful associations. We used generalized least squares models for trend estimation, which explicitly assesses dose response rather than simply categorical comparisons. We carefully identified and separately evaluated red, processed, and total meat consumption; in particular, relatively few prior reports have separately considered unprocessed red meats. Indeed, several key prior reports on red meat consumption included processed meats in this category,[3,7,8,19,24] limiting inference on effects of unprocessed red meats alone. For example, a systematic review by the World Cancer Research Fund and American Institute for Cancer Research concluded that both red and processed meat consumption increased colorectal cancer[24]; however, red meats in several of the included studies were the sum of unprocessed and processed meats. Interestingly, their identified relationship of red (commonly total, ie, unprocessed red plus processed) meat intake with colorectal cancer (22% higher risk per 100 g/d) was approximately half that for processed meat alone (46% higher risk per 100 g/d), consistent with our results that much of the association between total meat intake and CHD and diabetes mellitus may result from effects of processed meats.

Potential limitations should also be considered. As with all meta-analyses, analyses were restricted to available published and unpublished data. Most of these studies did not separately assess extensive details about specific subcategories of deli meats consumed. Processed meats may have included small amounts of processed poultry, which could theoretically have smaller effects and cause underestimation of effects of processed red meats. We did not have data on cooking methods that could alter health effects of red or processed meats.[42–44] Both red and processed meats represent somewhat heterogeneous categories, and thus our findings should be interpreted as the average overall association rather than the particular effect of 1 specific subtype of such meats. This interpretation would be similar, for example, to analyses or meta-analyses of effects of other classes of dietary factors, such as fruits, vegetables, fish, whole grains, and alcohol. A recent meta-analysis of relationships between meat consumption and diabetes mellitus has been reported[45]; this study also found higher risk with processed meat intake but included crude (unadjusted) risk estimates and also did not separately evaluate unprocessed red meats.

All studies were observational, and residual confounding by imprecisely or unmeasured factors cannot be excluded. In particular, several studies did not adjust for other dietary habits or socioeconomic status. Thus, associations of processed meat consumption with diabetes mellitus or CHD could relate to generally less healthy diet or lifestyle rather than causal effects of processed meats. Conversely, most studies adjusted for at least several major demographic and other risk factors; the reported potential confounding factors related to red versus processed meat consumption were similar, yet only the latter was related to risk; and specific ingredients in processed meats (eg, salt, other preservatives) provide biological plausibility for the observed relationships. Several studies adjusted for factors that could be either confounders or intermediates in the causal pathway, which could potentially attenuate the observed risk estimates between meat consumption and disease risk. We standardized all servings to 100 g for red and total meat and 50 g for processed meat, and risks could vary when serving sizes are lower or higher. Representative nutrient and preservative data were available only for the United States, and such values should be considered illustrative rather than definitive for other countries. Too few studies were present to formally exclude publication bias with sufficient statistical power. On the other hand, our extensive direct contact with multiple authors and inclusion of unpublished findings minimizes the potential impact of publication bias. Notably, if publication bias were present, it might cause overestimation of harmful associations between processed meats and diabetes mellitus or CHD (ie, identified harmful associations might more likely be published) but would unlikely contribute to null associations between red meats and CHD or diabetes mellitus or between meats and stroke (ie, publication bias is unlikely to favor reporting of null associations).

Our findings demonstrate that consumption of processed meat in particular is associated with incidence of CHD and diabetes mellitus, highlighting the importance of separate consideration of health effects, underlying mechanisms, and policy implications of different types of processed versus unprocessed meats. Our findings also identify critical gaps in our understanding of how meat consumption influences cardiometabolic risk, including potential effects of red meat consumption on diabetes mellitus or CHD; of any meat consumption on stroke risk; and of specific ingredients that could be underlying these relationships. On the basis of our evaluation of average nutrient and preservative contents of red and processed meats, constituents in meats other than fats may be especially relevant to health effects. On the basis of this systematic review and meta-analysis of all available data, future research should carefully distinguish between different types of meats, and policy measures for improving cardiometabolic health should focus particularly on reducing processed meat consumption, including consideration of recommendations for specific quantitative limits. These findings are particularly timely for current efforts to update the US Dietary Guidelines for Americans, which are also often a reference for other countries around the world.

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Disclosures

None.

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CLINICAL PERSPECTIVE

US dietary-guidelines recommend "eating less" red and processed meat. For cardiovascular disease, these recommendations are based largely on expected effects on blood cholesterol of saturated fat and dietary cholesterol in meats. However, relationships of meat intake with cardiometabolic disease outcomes, including coronary heart disease, stroke, and diabetes mellitus, are not well established. Additionally, few studies have separately evaluated unprocessed red versus processed meats, for which nutritional differences could produce different health effects. We systematically reviewed and pooled all available worldwide data on relationships between meat consumption and risk of coronary heart disease, stroke, or diabetes mellitus. Twenty studies were identified including 1 218 380 individuals from the United States, Europe, Australia, and Asia. When all data were pooled, consumption of unprocessed red meat (eg, unprocessed meat from beef, pork, lamb) was not associated with risk of coronary heart disease or diabetes mellitus. In contrast, each daily serving of processed meat (eg, bacon, hot dog, salami) was associated with 42% higher coronary heart disease and 19% higher diabetes mellitus risk. No associations were seen with stroke, but only 3 studies evaluated these relationships. When nationally representative US data on average types of meats consumed were analyzed, unprocessed red and processed meats contained relatively similar saturated fat and dietary cholesterol; processed meats contained much higher salt and nitrate preservatives. Our findings suggest that unprocessed red and processed meats have differing relationships with cardiometabolic outcomes and also suggest that differences in preservative contents, rather than fats, could at least partly account for these findings. Future research should separately consider potential health effects and underlying mechanisms of unprocessed versus processed meats, and current clinical and policy efforts should especially focus on reducing processed meat consumption.

Red and Processed Meat Consumption and Risk of Incident Coronary Heart Disease, Stroke, and Diabetes Mellitus: A Systematic Review and Meta-Analysis

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SUPPLEMENTAL MATERIAL

Supplemental Methods

MEDLINE Search Query.

(meat[tw] OR meats[tiab] OR "meat products"[tw] OR "meat products"[tiab] **OR** beef[tiab] OR veal[tiab] OR goat[tiab] OR lamb[tiab] OR pork[tiab] OR sausage[tiab] OR sausages[tiab] OR ham[tiab] OR hams[tiab] OR pastrami[tiab] OR bacon[tiab] OR bacons[tiab] OR salami[tiab] OR salamis[tiab] OR "meat protein"[tiab] OR "meat proteins"[tiab] OR "luncheon meat"[tiab] OR "luncheon meats"[tiab] OR "deli meat"[tiab] OR "deli meats"[tiab] OR "animal food"[tiab] OR "animal foods"[tiab]) **AND** (("Diabetes Mellitus"[Mesh] OR diabetes[tiab]) **OR** ("cardiovascular diseases"[Mesh] OR "cardiovascular disease"[tiab] OR "cardiovascular diseases"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "sudden death"[tiab] OR "sudden deaths"[tiab] OR stroke[tiab] OR strokes[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab]))

List of the 75 Excluded Full-Text Manuscripts and Reasons for Exclusion.

Reference	Reason for Exclusion
1. KeyTJ *et al.* 1999(36)	Review
2. Murakami K *et al.* 2005(48)	Review
3. Key TJ *et al.* 1998(35)	Review
4. Fraser GE 1988(14)	Review
5. Harper AE 1983(23)	Review
6. Wahrburg U *et al.* 2002(74)	Review
7. Willett W 2003(75)	Review
8. Stoeckli R, Keller U 2004(67)	Review
9. Biesalski HK 2005(2)	Review
10. Li D 2005(39)	Review
11. Adams SM, Standridge JB 2006(1)	Review
12. Muntoni S, Muntoni S 2006(47)	Review
13. Hodgson JM *et al.* 2007(28)	Review
14. Tappel A 2007(69)	Review
15. Truswell AS 2007(71)	Review
16. Dobbins MJ *et al.* 2007(10)	Review
17. Bilenko N *et al.* 2005(3)	Cross-sectional study
18. Shimakawa T *et al.* 1993(61)	Cross-sectional study
19. Jafar TH 2006(32)	Cross-sectional study
20. Panagiotakos DB *et al.* 2007(52)	Cross-sectional study
21. Qidwai W *et al.* 2005(55)	Cross-sectional study
22. Yan S 1989(76)	Cross-sectional study
23. Pfister R *et al.* 2004(53)	Cross-sectional study
24. Menotti A *et al.* 1999(44)	Ecological study
25. Takeya Y *et al.* 1984(68)	Ecological study
26. Fraser AG *et al.* 1992(13)	Duplicate publication
27. Schulze MB *et al.* 2007(59)	Duplicate publication
28. Hu FB *et al.* 1999(30)	Duplicate publication
29. van Dam RM *et al.* 2002(72)	Duplicate publication
30. Gramenzi A *et al.* 1990(21)	Duplicate publication
31. Lee DH *et al.* 2004(38)	Duplicate publication
32. Chang-Claude J *et al.* 2005(8)	Vegetarians vs. non vegetarians
33. Thorogood M *et al.* 1994(70)	Vegetarians vs. non vegetarians
34. Mann JI *et al.* 1997(41)	Vegetarians vs. non vegetarians
35. Vang A *et al.* 2008(73)	Vegetarians vs. non vegetarians (Adventist Health Study)
36. Fraser GE 1999(15)	Vegetarians vs. non vegetarians (Adventist Health Study)
37. Fraser GE *et al.* 1992(16)	Vegetarians vs. non vegetarians (Adventist Health Study)
38. Fraser GE *et al.* 1997(17)	Vegetarians vs. non vegetarians (Adventist Health Study)
39. Fraser GE *et al.* 1997(18)	Vegetarians vs. non vegetarians (Adventist Health Study)
40. Snowdon DA 1988(63)	Vegetarians vs. non vegetarians (Adventist Health Study)

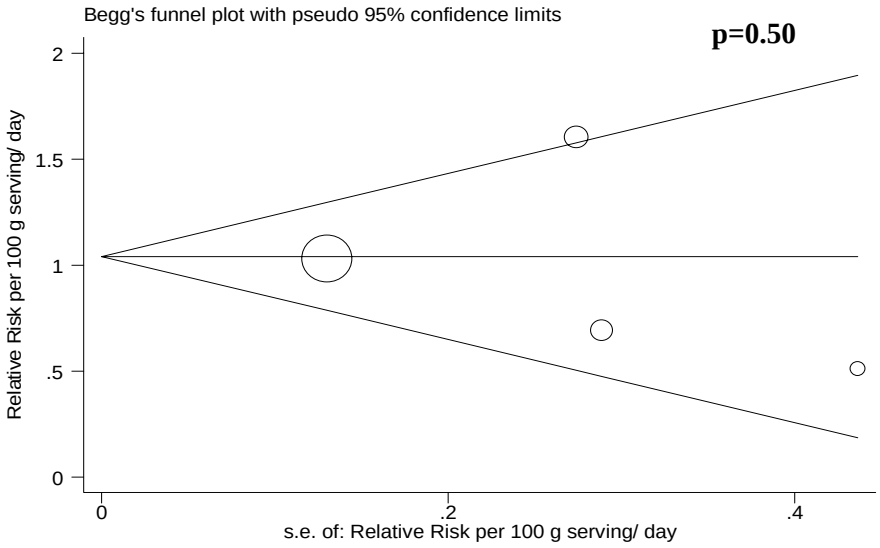
41. Snowdon DA 1984(64)	Vegetarians vs. non vegetarians (Adventist Health Study)
42. Brunner EJ *et al.* 2008(4)	Dietary patterns
43. Drogan D *et al.* 2007(11)	Dietary patterns
44. Fung TT *et al.* 2001(20)	Dietary patterns
45. Harriss LR *et al.* 2007(24)	Dietary patterns
46. Heidemann C *et al.* 2008(26)	Dietary patterns
47. Hu FB *et al.* 2000(29)	Dietary patterns
48. Hu G *et al.* 2006(31)	Dietary patterns
49. Kant AK *et al.* 1995(34)	Dietary patterns
50. Martinez-Ortiz JA *et al.* 2006(42)	Dietary patterns
51. Fung TT *et al.* 2008(19)	Dietary patterns
52. Mitrou PN *et al.* 2007(45)	Dietary patterns
53. McNaughton SA *et al.* 2008(43)	Dietary patterns
54. Hodge AM *et al.* 2007(27)	Dietary patterns
55. Heidemann C *et al.* 2005(25)	Dietary patterns
56. Osler M *et al.* 2001(50)	Dietary patterns
57. Schulze MB *et al.* 2005(60)	Dietary patterns
58. Osler M *et al.* 2002(49)	Dietary patterns
59. Panagiotakos D *et al.* 2007(51)	Dietary patterns
60. Montonen J *et al.* 2005(46)	Dietary patterns
61. Jiang R *et al.* 2004(33)	Iron intake
62. Malaviarachchi D *et al.* 2002(40)	Iron intake
63. Sauvaget C *et al.* 2002(58)	Animal protein/fat
64. Steffen LM *et al.* 2007(66)	Disease outcome other than incident CVD or diabetes
65. Damiao R *et al.* 2006(9)	Disease outcome other than incident CVD or diabetes
66. Burke V *et al.* 2007(5)	Disease outcome other than incident CVD or diabetes
67. Qi L *et al.* 2007(54)	Participants with prevalent disease
68. Qiu D *et al.* 2003(56)	Not meeting meat definition
69. Cai H *et al.* 2007(6)	Not meeting meat definition
70. Kinjo Y *et al.* 1999(37)	Not meeting meat definition
71. Zyriax BC *et al.* 2005(77)	Not meeting meat definition
72. Spencer CA *et al.* 1999(65)	Not meeting meat definition
73. Duc Son le NT *et al.* 2005(12)	Not meeting meat definition
74. Reunanen A *et al.* 1995(57)	Not meeting meat definition
75. Simmons RK *et al.* 2007(62)	Prediction score, not adjusted

Nutritional Qualities of Red and Processed Meats

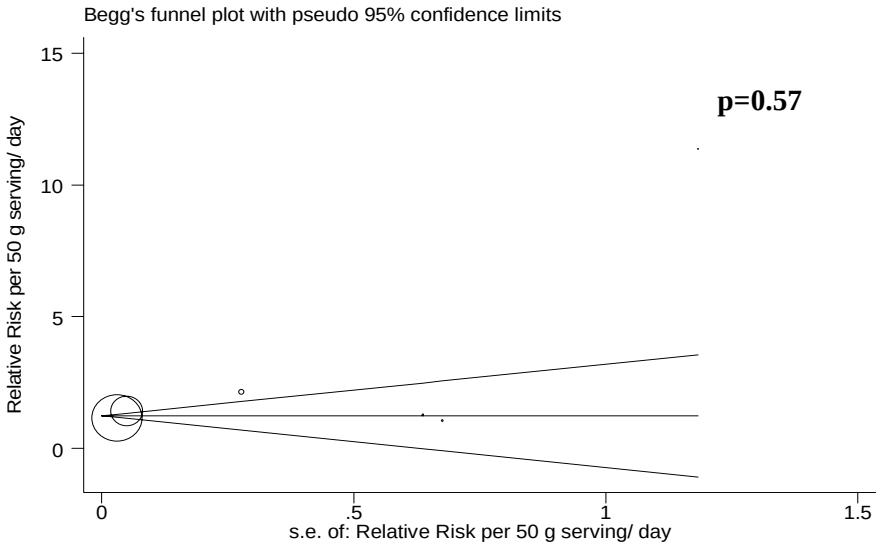
To estimate average nutritional qualities of red and processed meats, we analyzed data from two 24-hr hour diet recalls in the 2005-06 US National Health and Nutrition Examination Survey (NHANES), accounting for NHANES sampling and weighting strategies(7). Foods consumed in this US survey were grouped to match our meta-analysis' definitions for red and processed meat. For red meats the specific codes used in the NHANES were: 210-215 for beef; 220- 222, 224 and 227 for pork; and 230-234 for lamb, veal, and game. For processed meats the specific codes used in the NHANES were: 216 for processed beef; 223 for ham; 225-226 for bacon; and 252 for frankfurters, sausages, lunchmeats, and meat spreads. Preservative contents were obtained from a recent report of published nitrate, nitrite, and nitrosamine contents of foods commonly consumed in the US(22). Preservative contents of subtypes of red and processed meats from this report were applied directly to the subtypes of red and processed meats in the NHANES database, after standardization to the same serving size. The individual subtypes of red and processed meats were first summed, and then averaged across the two days and across all individuals applying the NHANES sampling weights(7) (the survey design was declared in STATA as: svyset [pw=wtdr2d], strata(sdmvstra) psu(sdmvpsu)) to derive the overall average national weighted red and processed meat consumption. Subsequently, average nutrient and preservative contents were estimated for a 50 g serving of red meat and a 50 g serving of processed meat. Analyses were performed using STATA 10.0 (College Station, TX), with two-tailed alpha<0.05.

Supplemental Figure

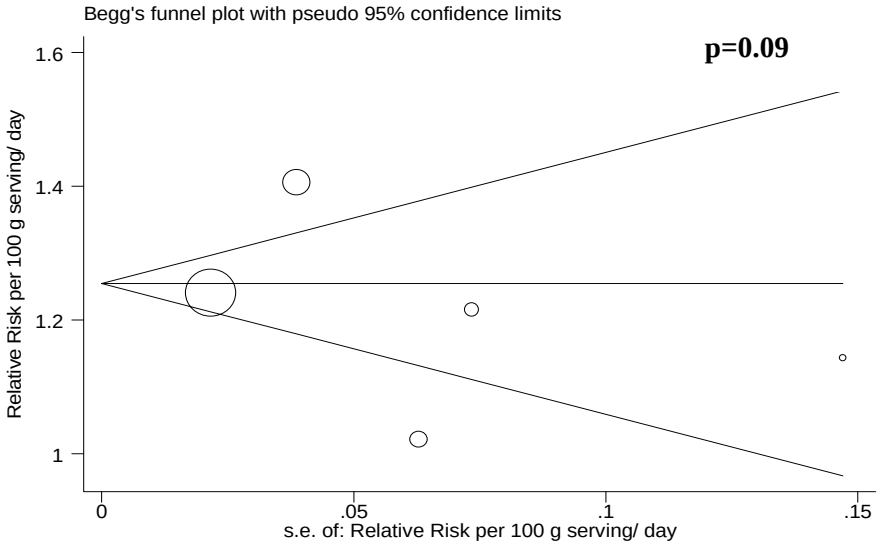
Funnel plots for graphical evaluation of potential publication bias. P values based on the Begg adjusted rank-correlation test for presence of publication bias.



Red meat consumption and risk of CHD

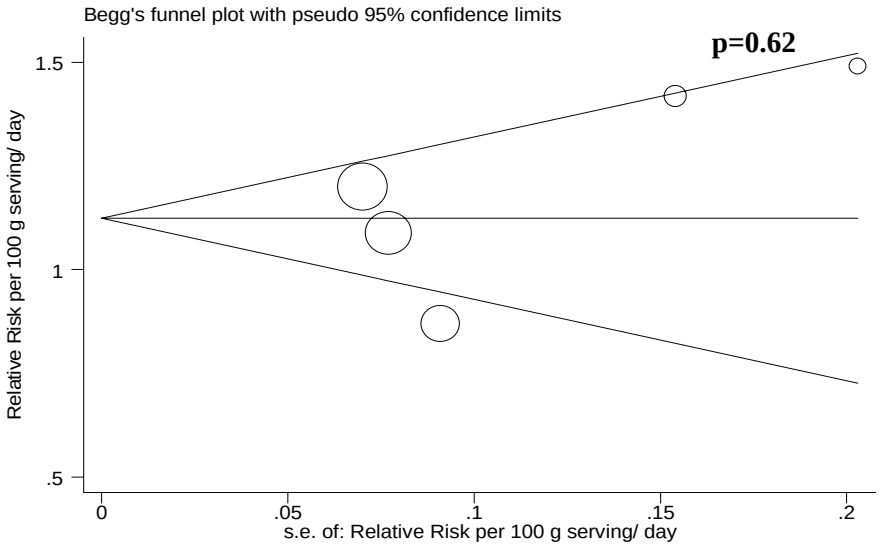


Processed meat consumption and risk of CHD

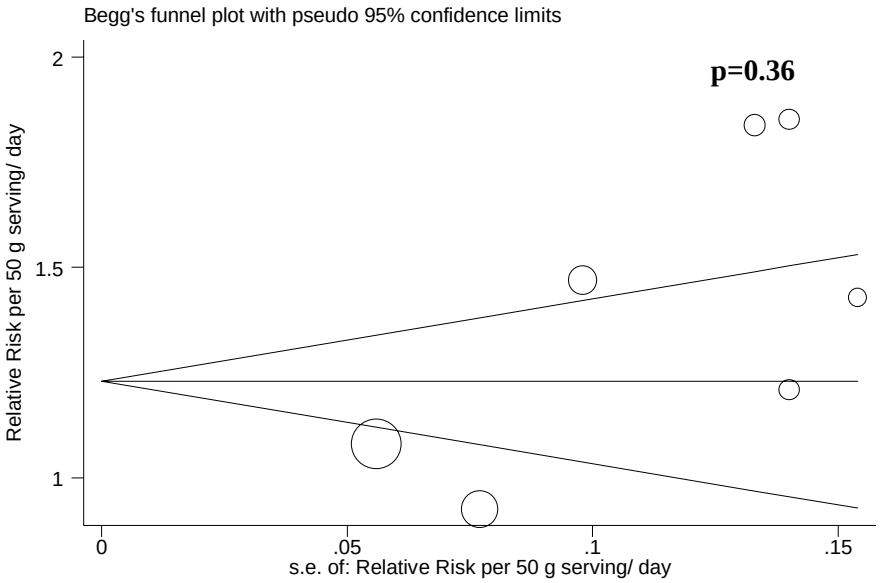


Total meat consumption and risk of CHD

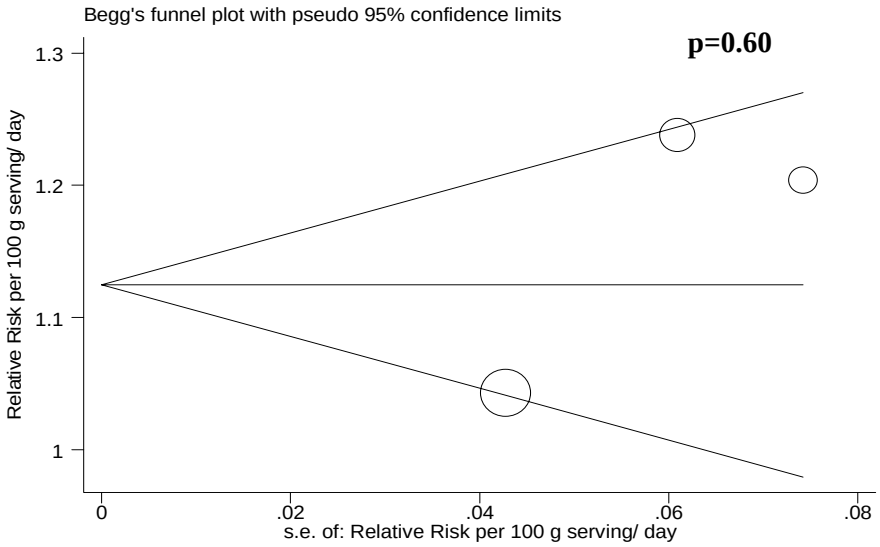
The smallest study with the extreme findings was omitted from the funnel plot, for presentation purposes. The p-value corresponds to the Begg's test when all studies are included.



Red meat consumption and risk of diabetes



Processed meat consumption and risk of diabetes



Total meat consumption and risk of diabetes

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