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META-ANALYSIS

Meat consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies

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Abstract
Aims/hypothesis Diet is thought to play an important role in the aetiology of type 2 diabetes. Previous studies have found positive associations between meat consumption and the risk of type 2 diabetes, but the results have been inconsistent. We conducted a systematic review and meta-analysis of cohort studies of meat consumption and type 2 diabetes risk.
Methods We searched several databases for cohort studies on meat consumption and type 2 diabetes risk, up to December 2008. Summary relative risks were estimated by use of a random-effects model.
Results We identified 12 cohort studies. The estimated summary RR and 95% confidence interval of type 2 diabetes comparing high vs low intake was 1.17 (95% CI 0.92–1.48) for total meat, 1.21 (95% CI 1.07–1.38) for red meat and 1.41 (95% CI 1.25–1.60) for processed meat. There was heterogeneity amongst the studies of total, red and processed meat which, to some degree, was explained by the study characteristics.
Conclusions/interpretation These results suggest that meat consumption increases the risk of type 2 diabetes. However, the possibility that residual confounding could explain this association cannot be excluded.

Keywords Diabetes · Diet · Food · Meat · Meta-analysis · Systematic review · Type 2 diabetes

Abbreviation
FFQ Food frequency questionnaire

Introduction

The prevalence of diabetes mellitus is rapidly increasing worldwide. In 2000 an estimated 171 million people had diabetes mellitus worldwide and the number is expected to increase to 366 million by 2030 [1]. Ninety per cent of patients with diabetes have type 2 diabetes mellitus, thus type 2 diabetes accounts for most of the increase in diabetes prevalence. Patients with type 2 diabetes are at increased risk for several complications, including cardiovascular disease, retinopathies, nephropathies, neuropathies, leg ulcers and gangrene [2]. The total costs of diabetes were estimated at US$174 billion in 2007 in the USA [3].

Although overweight, obesity and physical inactivity are established risk factors for type 2 diabetes [4] and may account for much of the increase in rates of type 2 diabetes, evidence suggests that dietary factors may also influence the risk of type 2 diabetes [5]. An ecological study from 1935 [6] and subsequent migration studies [7, 8] suggest that a Western-type diet may be a risk factor for type 2 diabetes. Consistent with this, secular trends in Japan show a positive correlation between the intake of animal fat and protein and the rate of type 2 diabetes among Japanese school children [9]; similar trends have been reported in other Asian

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populations [10–12]. A Western dietary pattern has been associated with an increased risk of type 2 diabetes in cohort studies [13–15], but it is not clear which component(s) of this dietary pattern may increase the risk of type 2 diabetes.

Snowdon and Phillips [16] first reported an association between meat intake and diabetes in a study of Seventh Day Adventists, a population with a high proportion of vegetarians. Meat intake was associated with: an increased prevalence of diabetes in men and women; and an increased diabetes-associated mortality in men, but not in women. Several subsequent publications have reported an increased risk of diabetes or type 2 diabetes with a high intake of processed meat [17–23], red meat [17–19, 22, 24, 25] and total meat [15, 17, 23], but the results have not been consistent [20, 21, 26, 27]. To clarify this association we conducted a systematic review and meta-analysis of cohort studies of meat intake and type 2 diabetes.

Methods

Search strategy We searched the PubMed, Medline (OVID), CINAHL and ISI Web of Science (Science Citation Index Expanded and Conference Proceedings Citation Index-Science) from their starting dates to December 2008 for the following search terms: meat, red meat, processed meat, total meat, food or nutrition combined with diabetes, diabetes mellitus or type 2 diabetes, with the searches limited to humans and adults in PubMed. We had no language restrictions in the searches. The reference lists of all the studies that were included in the analysis and of relevant systematic reviews were examined for further studies. We contacted the authors of five studies [15, 17, 20–22] to obtain sufficient detail in order to conduct a dose–response analysis and we received detailed information from all these studies.

Study selection To be included, the study had to have a cohort design and investigate the relationship between the intake of total meat, red meat and/or processed meat and incidence or mortality of type 2 diabetes. Risk ratios, incidence rate ratios or odds ratios (hereafter referred to as relative risks) had to be available with 95% confidence intervals either in the publication or on request from the authors. For the dose–response analysis, a quantitative measure of intake had to be presented in the publication or be obtainable from the authors. When several publications from the same study were available, only the most recent or most detailed publication was used.

Data extraction We extracted the following information from each publication into a table: the country where the study was conducted, the sample size and number of cases or deaths, the method for identification of cases and whether the method for assessing diabetes status was validated, the year the study started and ended, the duration of follow-up, the method of dietary assessment (food frequency questionnaire [FFQ], or diet history, only baseline or updated dietary assessment and whether the method had been validated), the type of meat and frequency or quantity of intake, the RRs and 95% CIs, and the factors for which adjustment was made (Table 1).

Statistical methods We used random effects models, which take into account within- and between-study variation, to calculate summary RRs and 95% CIs for the highest vs the lowest level of consumption [28]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $p<0.05$ was considered statistically significant. The statistical analyses were conducted using Stata, version 9.2 software (StataCorp, College Station, TX, USA).

We used the method described by Greenland and Longnecker [29] for the dose–response analysis and computed study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of meat intake. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. For studies that did not provide the distribution of cases and person-years/non-cases, we estimated the slopes using variance-weighted least squares regression [30]. The median or mean level of meat consumption in each category of intake was assigned to the corresponding relative risk for each study. For studies that reported meat consumption by ranges of intake we estimated the mean intake in each category by calculating the average of the natural logarithm of the upper and lower boundaries, back transformed to non-log scale and rescaled to g/day [31]. When the highest category was open-ended we assumed the open-ended interval length to be the same as the adjacent interval. When the lowest category was open-ended we set the lower boundary to zero. The average serving size was set to 120 g for total meat and red meat and 50 g for processed meat [31], equivalent to a typical quarterpounder hamburger for total and red meat and one hot dog or a small sausage for processed meat.

Heterogeneity between studies was assessed by the Q test and I^2 [32]. I^2 is the amount of total variation that is explained by between study variation. I^2 values of approximately 25%, 50% and 75% are considered to indicate low, moderate and high heterogeneity, respectively. We conducted subgroup analyses by duration of follow-up (<10 years, ≥10 years), number of cases (<500, ≥500, <1,000, ≥1,000), use of updated or baseline and validated or non-validated dietary assessment methods and adjustment for confounding factors such as body mass index,

physical activity, energy intake, intake of fibre/cereal fibre or whole grains, magnesium, smoking and alcohol intake. We assessed publication bias with the Egger's test [33] and the Begg–Mazumdar's test [34]; the results were considered to indicate publication bias when $p<0.10$. To ensure that the results were not simply due to one large study or a study with an extreme result, we did a sensitivity analysis excluding one study at a time to see whether the results were robust. To assess whether the method of assessment of diabetes status influenced the results, we conducted sensitivity analyses according to whether simple self-report or additional measures were used to identify diabetes cases and whether a validation study of the diabetes-assessment method had been conducted. To address the question of temporality (i.e. whether meat intake was a risk factor for diabetes or a result of dietary changes following diabetes diagnosis) we investigated whether the studies excluded prevalent diabetes cases at baseline, and whether the results changed if cases diagnosed during early follow-up were excluded.

Results

We identified 12 cohort studies in the search that could be included in the analysis (Fig. 1, Table 1). Six of the studies were from the USA, three from Europe, two from Asia and one from Australia.

Total meat Five cohort studies [15, 17, 21, 23, 26] investigated the association between total meat intake and type 2 diabetes risk and included 6,525 cases among 445,323 participants. The summary RR for all studies was 1.17 (95% CI 0.92–1.48) (Fig. 2a), but there was substantial heterogeneity (I^2=86.9%, $p<0.0001$). In a sensitivity analysis we excluded the most influential studies: the summary RR ranged from 1.08 (95% CI 0.86–1.35) when an American study [17] was excluded to 1.31 (95% CI 1.12–1.52) when the Chinese study [21] was excluded (results not shown). The heterogeneity was partly explained by the Chinese study [21], and when this study was excluded there was moderate heterogeneity, (I^2=57.3% and p=0.07). There was no indication of publication bias with the Begg–Mazumdar's test, p=0.23, or with Egger's test, p=0.64, although these tests were based on only a few studies.

Dose–response One study with only two categories of total meat intake was excluded [26], thus four studies [15, 17, 21, 23] were included in the dose–response analysis. The summary RR per 120 g/day increase in total meat intake was 1.26 (95% CI 0.84–1.88, Fig. 2b), but there was substantial heterogeneity (I^2=90.6%, $p<0.0001$). The heterogeneity was partly explained by the Chinese cohort study [21] and when excluded the three remaining studies yielded a summary RR of 1.46 (95% CI 1.02–2.08) with lower, but still high, heterogeneity (I^2=68.1%, p=0.04).

Red meat Ten cohort studies [15, 17–22, 24, 25, 27] investigated the association between red meat intake and type 2 diabetes risk; these included 12,226 cases among 433,070 participants. The summary RR for high vs low intake of red meat was 1.21 (95% CI 1.07–1.38) (Fig. 3a). In the sensitivity analysis the summary RR ranged from 1.19 (1.03–1.36) when an American study [17] was excluded to 1.26 (95% CI 1.12–1.41) when the Chinese study [21] was excluded (results not shown). There was moderate heterogeneity (I^2=58.5%, p=0.01, Table 2), but the Chinese study [21] explained most of the heterogeneity and when it was excluded the heterogeneity was reduced (I^2=36.7%, p=0.12; result not shown). There was significant heterogeneity in several, but not all, subgroups (Table 2). However, the heterogeneity in the subgroup analyses was mainly explained by the Chinese study and was reduced when this study was excluded (results not shown). There was no indication of publication bias with Begg–Mazumdar's test (p=0.38), or with Egger's test (p=0.46).

Dose–response One study that did not quantify red meat intake was excluded [24], thus nine studies [15, 17–22, 25, 27] were included in the dose–response analysis. The summary RR per 120 g/day increase in red meat intake was 1.20 (95% CI 1.04–1.38, Fig. 3b), but there was high heterogeneity (I^2=68.3%, p=0.001).

Processed meat Nine cohort studies [15, 17–23, 27] investigated the association between processed meat intake and type 2 diabetes risk and included 9,999 cases among 380,606 participants. The summary RR for high vs low intake was 1.41 (95% CI 1.25–1.60) (Fig. 4a). In the sensitivity analysis the summary RR ranged from 1.37 (95% CI 1.20–1.56) when an American study [17] was excluded to 1.47 (95% CI 1.30–1.65) when the Chinese study [21] was excluded (results not shown). There was moderate heterogeneity (I^2=53.2%, p=0.03, Table 2), but the latter study [21] explained most of the heterogeneity and when excluded we found the heterogeneity was reduced (I^2=36.6%, p=0.14). Heterogeneity was present in several, but not all, subgroups of studies (Table 2), but when the Chinese cohort study was excluded the heterogeneity in the subgroup analyses was reduced (results not shown). There was no indication of publication bias with Begg–Mazumdar's test (p=0.92), or with Egger's test (p=0.69).

Table 1 Prospective cohort studies of meat consumption and type 2 diabetes

Authors, publication year, country, name of the study (reference no.)	Follow-up period	No. in cohort, sex and age: no. of cases/deaths	Diet assessment method	DM diagnosis and criteria	Exposure	Quantity (highest vs lowest intake)	RR (95% CI)	Adjustment variables
Hirayama , 1990, Japan, The Six Prefectures Cohort Study [26]	1965–1982, 17 years follow-up	265,118 m and w, age ≥40 years: 946 deaths	Baseline FFQ	Linkage to death registry	Meat	Daily vs less	1.17 (0.97–1.41)	NA
					Meat, men	Daily vs none	2.53 (1.00–6.40)	
Van Dam et al., 2002, USA, Health Professionals' Follow-up Study [20]	1986–1998, 12 years, 466,192 person-years	42,504 m, age 40–75 years: 1,321 cases	Updated FFQ (validated), 131 food items	Self-report plus supplemental questionnaires WHO 1985, validated DM2 status	Total processed meat	≥5 vs <1/month	1.46 (1.14–1.86)	Age, total energy, time period, physical activity, cigarette smoking, alcohol, hypercholesterolaemia, cereal hypertension, FH-DM2, fibre, Mg, BMI
					Unprocessed red meat	1.29 vs 0.14 servings/day	1.05 (0.85–1.30)	
					Bacon	2–≥5/week vs <1/month	1.33 (1.11–1.58)	
					Hot dogs	2–≥5/week vs <1/month	1.26 (1.00–1.60)	
					Other processed meat	2–≥5/week vs <1/month	1.18 (0.99–1.41)	
					Hamburgers	≥2/week vs <1/month	1.27 (0.99–1.62)	
Schulze et al., 2003, USA, Nurses' Health Study 2 [18]	1991–1999, 8 years, 716,276 person-years	91,246 w, age 26–46 years: 741 cases	Updated FFQ (similar to a validated FFQ used in Nurses' Health Study 1), 133 food items	Self-report + supplemental questionnaires, validated method for assessment of DM2, NDDG	Total processed meat	≥5 vs <1/week	1.82 (1.34–2.46)	Age, BMI, FH-DM, alcohol, hypercholesterolaemia, smoking, menopausal status, dietary energy, hypertension, physical activity, HRT, OC use. Total red meat and total processed meat were additionally adjusted for cereal fibre, Mg, caffeine, GI
					Total red meat	≥5 vs <1/week	1.44 (0.92–2.24)	
					Bacon	≥2/week vs <1/week	1.83 (1.34–2.50)	
					Hot dogs	≥2/week vs <1/week	1.56 (1.10–2.22)	
					Other processed meats	≥2/week vs <1/week	1.41 (1.14–1.74)	
					Beef or lamb, main dish	≥2/week vs <1/week	1.33 (1.06–1.65)	
					Pork, main dish	≥2/week vs <1/week	1.20 (0.82–1.74)	
					Hamburgers	≥2/week vs <1/week	1.48 (1.18–1.85)	
					Beef, pork, lamb, mixed dish	≥2/week vs <1/week	1.03 (0.83–1.27)	
Lee et al., 2004, USA, Iowa Women's Health Study [24]	1986–1997, 11 years, 332,854 person-years	35,698 w, age 55–69 years: 1,921 cases	Baseline FFQ (similar to a validated FFQ used in Nurses' Health Study 1), 127 food items	Self-report	Red meat	Quintile 5 vs 1	1.19 (0.97–1.45)	Age, total energy, WHR, BMI, physical activity, HRT, cigarette smoking, alcohol, education, marital status, residential area, animal fat, vegetable fat, cereal fibre, Mg
Fung et al., 2004, USA, Nurses' Health Study [17]	1984–1998, 14 years, 892,383 person-years	69,554 w, age 38–63 years: 2,699 cases	Updated FFQ (validated), 61 food items (1980) and 116 food items (1984–)	Self-report + supplemental questionnaires NDDG, validated DM2 status	Red meat	0.96 vs 0.21 servings/day	1.36 (1.18–1.56)	Age, FH-DM2, hypercholesterolaemia, smoking, menopausal status, dietary, hypertension, physical activity, alcohol, BMI, missing FFQ
					Total processed meat	0.55 vs 0.04 servings/day	1.60 (1.39–1.83)	
					Total processed and red meats	1.41 vs 0.32 servings/day	1.55 (1.34–1.80)	
					Bacon	0.19 vs 0 servings/day	1.42 (1.26–1.49)	
					Hot dogs	0.14 vs 0 servings/day	1.33 (1.17–1.51)	
					Other processed meats	0.28 vs 0 servings/day	1.40 (1.23–1.59)	
Song et al., 2004, USA, Women's	1993–2003, 8.8 years,	37,309 w, age ≥45	Baseline FFQ (validated), 131	Self-report + supplemental questionnaires	Red meat	1.06 vs 0.03 servings/day	1.25 (0.94–1.67)	Age, BMI, total energy, smoking, exercise,

Health Study [19]	326,876 person-years	years: 1,558 cases	food items	Blood samples in subgroup using ADA, validated DM2 status	Processed meat	0.92 vs 0 servings/day	1.38 (1.11–1.71)	alcohol, FH–DM, fibre intake, GL, Mg, total fat
					Beef/lamb, main dish	≥2/week vs <1/week	1.12 (0.94–1.33)	
					Pork, main dish	≥2/week vs <1/week	1.06 (0.92–1.23)	
					Beef, pork, lamb, mixed dish	≥2/week vs <1/week	1.12 (0.93–1.34)	
					Hamburgers	≥2/week vs <1/week	1.15 (0.95–1.38)	
					Bacon	≥2/week vs <1/week	1.17 (1.02–1.35)	
					Hot dogs	≥2/week vs <1/week	1.24 (1.05–1.45)	
					Other processed meat	≥2/week vs <1/week	1.07 (0.93–1.23)	
Montonen et al., 2005, Finland, Finnish Mobile Clinic Health Examination Survey [27]	1967–1990, 23 years	4,304 m and w, age 40–69 years: 383 cases	Dietary history interview, >100 food items	Identified from register of persons receiving drug imbursement	Processed meat	≥69 vs <18 g/day	1.22 (0.89–1.69)	Age, sex, BMI, energy intake, smoking, FH–DM, geographic area
					Red meat	≥101 vs <41 g/day	0.99 (0.72–1.38)	
Villegas et al., 2006, China, Shanghai Women's Health Study [21]	1997–2000–2004, 4.6 years, 326,581 person-years	70,609 w, age 40–70 years: 1,972 cases	Updated FFQ (validated), 77 food items	Self-report Analysis of 1,094 cases confirmed by ADA criteria yielded similar results to all cases	Total meat, excluding processed meat	≥89.23 vs <33.65 g/day	0.82 (0.69–0.98)	Age, energy, BMI, WHR, smoking, alcohol, physical activity, vegetable intake, income level, education level, occupation status, hypertension
					Red meat (fresh)	≥67.6 vs <24.5 g/day	0.94 (0.79–1.12)	
					Total processed meat	≥1/month vs never	1.18 (0.99–1.37)	
					Smoked meat/bacon	≥1/month vs never	0.95 (0.79–1.16)	
					Chinese sausage	≥1/month vs never	0.93 (0.79–1.10)	
Hodge et al., 2007, Australia, Melbourne Collaborative Cohort Study [15]	1990–1994, 4 years	31,641 m and w, age 27–75 years: 365 cases	Baseline FFQ, 121 food items	Self-report + physician confirmation for 76% of cases	Total meat	12.5 vs 3.5 servings/week	1.12 (0.80–1.57)	Age, energy intake, FH–DM, country of birth, BMI, WHR
					Fresh red meat	8 vs 2 servings/week	1.17 (0.83–1.66)	
					Processed meat	8 vs 2 servings/week	1.11 (0.79–1.56)	
Schulze et al., 2007, Germany, EPIC-Potsdam Cohort Study [25]	1994–98–2005, 7.0 years	25,167 m and w, age 35–65 years: 849 cases	Baseline FFQ (validated)	Self-report + physician verification	Red meat	Per 150 g/day	1.64 (1.23–2.19)	Age, height, alcohol, waist circumference, hypertension, coffee, whole grains, sports, biking, gardening, smoking
Simmons R et al., 2007, UK, EPIC-Norfolk Cohort Study [22]	1993–98, 4.6 years, 115,137 person-years	25,038 m and w, age 40–79 years: 417 cases	Baseline FFQ (validated)	Self-report, health checks, hospital and general practice registers, HbA_{1C} >7%, medications, validated DM2 status	Meat products (sausages, ham, hamburger)	5–6/week–≥1/day vs never	2.95 (1.39–6.25)	Crude
					Red meat (chops, roasts, stews)	5–6/week–≥1/day vs never	2.26 (1.10–4.66)	
Vang et al., 2008, USA, Adventist Mortality Study, Adventist Health Study [23]	1960–1976, 17 years	8,401 m and w, age 45–88 years: 543 cases	Baseline FFQ (validated)	Self-report	Total meats	≥1/week vs never	1.29 (1.08–1.55)	Age, sex. Exclusion of smokers, alcohol users and those with pre-existing disease did not alter the results
					Red meat, poultry	≥1/week vs never	1.27 (1.06–1.53)	
					Processed meat	Weekly vs never	1.38 (1.05–1.82)	
					Frankfurters	Weekly vs never	1.29 (0.94–1.76)	

ADA, American Diabetes Association criteria; FH-DM, family history of diabetes mellitus; FH-DM2, family history of type 2 diabetes mellitus; GI, glycaemic index; GL, glycaemic load; HRT, hormone replacement therapy; m, men; Mg, magnesium; NA, not available; NDDG, National Diabetes Data Group criteria; OC use, oral contraceptive use; Ref. no., reference number; WHO 1985, WHO criteria for type 2 diabetes, 1985; w, women

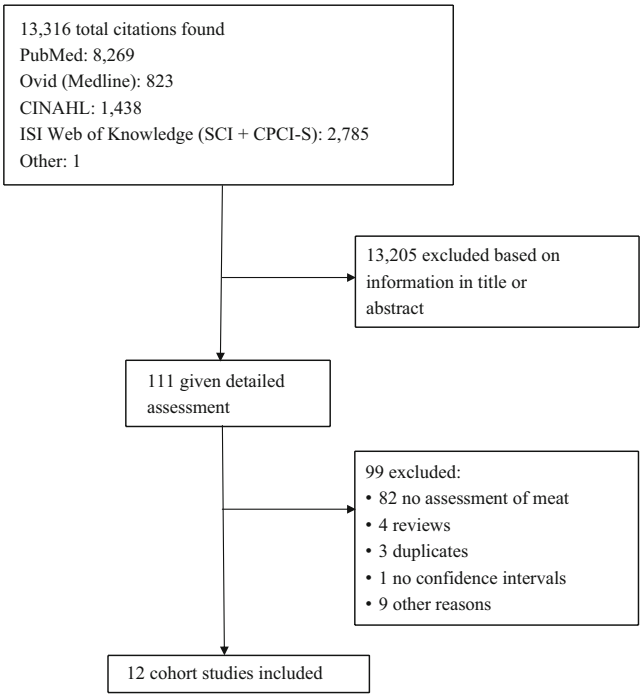

Fig. 1 Flow chart for meta-analysis

Dose–response One study with only two categories of intake was excluded [23], thus eight studies [15, 17–22, 27] were included in the dose–response analysis. The summary RR per 50 g/day was 1.57 (95% CI 1.28–1.93) (Fig. 4b). All studies found a positive association, but there was high heterogeneity (I^2=74.0%, p<0.0001).

Subtypes of red and processed meat Hamburgers, bacon, hot dogs and other processed meats were also associated with an increased risk of type 2 diabetes (Table 2), although these results were based on few studies.

Sensitivity analyses: assessment of type 2 diabetes status, diet instrument and temporality We excluded two studies from the analyses of total meat and processed meat that did not clearly state that the diabetes cases ascertained were of type 2, but where this could be assumed with a degree of certainty because of the age range of the participants [23, 26]. This did not change the results (summary RRs for high vs low intake were 1.13 [95% CI 0.72–1.77] for total meat and 1.42 [95% CI 1.24–1.63] for processed meat). Furthermore, because the studies varied with respect to how they ascertained type 2 diabetes cases, we assessed whether the results varied according to the method of type 2 diabetes ascertainment (i.e. whether simple self-report was used—defined as answering yes or no to a question of type 2 diabetes diagnosis—or whether additional measures were used, including supplementary questionnaires that assessed symptoms, diagnostic tests and treatment or use of medical records, blood tests and health checks or whether type 2 diabetes status had been validated or not). Restricting the analysis to the seven studies of red meat intake that used additional measures to assess type 2 diabetes status [15, 17–20, 22, 25] or the five studies [17–20, 22] that used a validated method to ascertain type 2 diabetes status, gave slightly higher summary risk estimates (Table 2). The same was found for processed meat where six studies [15, 17–20, 22] used additional measures to assess type 2 diabetes status and five studies used a validated method to ascertain type 2 diabetes status [17–20, 22] (Table 2).

All studies but one used the FFQ to collect dietary intake data. Excluding the study that used a dietary history method [27] from the analyses of red and processed meat did not change the conclusions (the summary RRs were 1.24 [95% CI 1.08–1.42] and 1.43 [95% CI 1.26–1.64], respectively).

To address the question of temporality we investigated whether the cohort studies excluded prevalent diabetes cases at baseline and diabetes cases diagnosed during early follow-up. All cohort studies except one [26] stated that

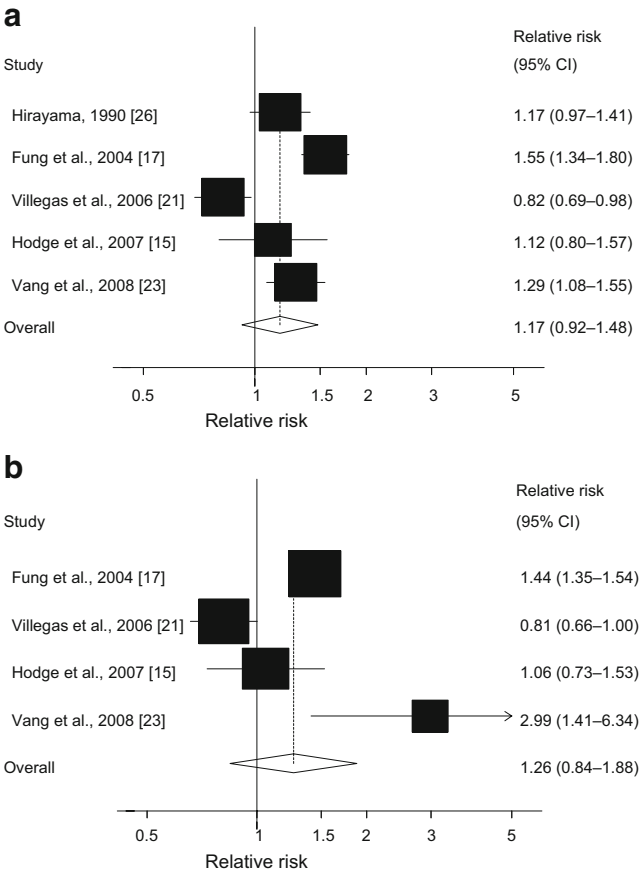

Fig. 2 Total meat and type 2 diabetes. RRs for (**a**) the highest vs the lowest intake and (**b**) per 120 g/day of total meat. The RR of each study is represented by a square and the size of the square represents the weight of each study to the overall estimate. 95% CIs are represented by the horizontal lines and the diamond represents the overall estimate and its 95% CI

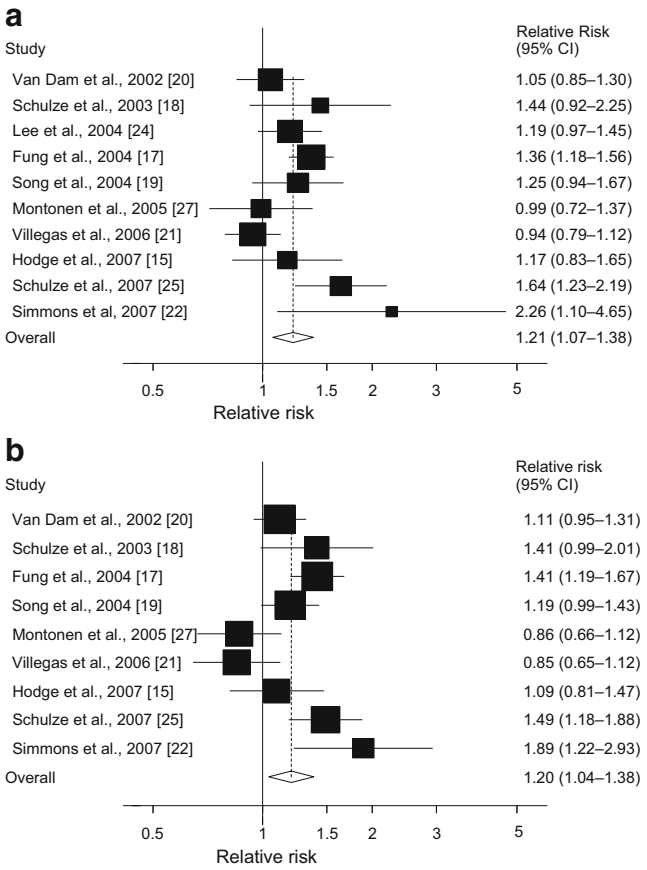

Fig. 3 Red meat and type 2 diabetes. RRs for (**a**) the highest vs the lowest intake and (**b**) per 120 g/day of red meat. The RR of each study is represented by a square and the size of the square represents the weight of each study to the overall estimate. 95% CIs are represented by the horizontal lines and the diamond represents the overall estimate and its 95% CI

they excluded prevalent diabetes cases reported at baseline. This study was only included in the analysis of total meat and when excluded the summary RR remained unchanged. None of the cohort studies stated that they excluded diabetes cases diagnosed during early follow-up, but the subgroups of studies with longer follow-up (≥10 years)—where early follow-up would have less of an impact on the results—found significant positive associations for all the three main meat groups (Table 2, result not shown for total meat).

Discussion

In this meta-analysis, intake of red meat, processed meat and subgroups of meats (hamburger, bacon, hot dogs and other processed meats) was associated with an increased risk of type 2 diabetes.

The possible limitations of our meta-analysis must be taken into consideration. It is possible that the observed positive association between meat intake and type 2 diabetes could be due to unmeasured or residual confounding or temporal bias. Higher meat intake is often associated with other unhealthy lifestyles including physical inactivity, overweight, smoking and unhealthy dietary patterns. However, most of the studies adjusted for known confounding factors such as age, BMI, family history of type 2 diabetes, smoking, physical activity, total energy intake, alcohol, menopausal status and use of hormone replacement therapy (among women) and for other dietary factors. Studies adjusting for a 'Western dietary pattern' also found positive associations, suggesting that confounding from other risk-enhancing foods consumed in this dietary pattern does not explain the adverse effect of meat on the risk of developing type 2 diabetes [17, 18]. Overweight and obesity are major risk factors for type 2 diabetes and a meta-analysis suggested an approximate 20% increase in type 2 diabetes risk for each unit increase in BMI [35]. Even though most of the studies adjusted for BMI, measurement errors due to self-report of BMI could lead to residual confounding that potentially could explain the association between meat intake and type 2 diabetes. However, the studies that relied on self-report of BMI and validated the anthropometric measures found that the correlations between self-reported and measured weight and height were high [23, 36, 37].

Another possible limitation is that these findings could be due to a temporal bias. High-protein diets have been promoted for weight loss by certain groups and in the media, and it is possible that overweight type 2 diabetes patients could increase their meat intake to lose weight. If studies included prevalent type 2 diabetes cases, then these findings could be due to a temporal bias. All the studies except one [26] stated that they excluded prevalent cases at baseline, but none of them excluded cases diagnosed during early follow-up. A temporal bias would be likely to have less impact in studies with longer follow-up than in studies with shorter follow-up, because the number of cases diagnosed during early follow-up constitutes a small fraction of the total number of cases. Restricting the analysis to studies with longer follow-up (≥10 years) gave results similar to those obtained in the overall analysis.

The combination of results from several studies increases the statistical power to detect significant associations due to increased sample size, but it also results in heterogeneity. Some heterogeneity is expected as the studies used different dietary assessment methods, took place in different geographic locations and included participants who differed by age, sex and other characteristics. Heterogeneity was sometimes explained by study characteristics. In general there was significant heterogeneity in many subgroups, but because of the limited number of studies in the subgroup analyses, the results are difficult to interpret. For red and processed meat, and to some degree total meat, we found

Table 2 Subgroup analyses of red meat and processed meat and type 2 diabetes[a]

Study characteristics	Adjustment	Red meat				Processed meat			
		n	RR (95% CI)	I^2 (%)	p_h	*n*	RR (95% CI)	I^2 (%)	p_h
All studies		10	1.21 (1.07–1.38)	58.5	0.01	9	1.41 (1.25–1.60)	53.2	0.03
<10 years' follow-up		6	1.30 (1.03–1.64)	67.8	0.008	5	1.41 (1.13–1.76)	65.8	0.02
≥10 years' follow-up		4	1.18 (1.02–1.36)	49.0	0.12	4	1.50 (1.35–1.66)	0	0.42
Cases <1,000		5	1.35 (1.06–1.73)	49.4	0.09	5	1.45 (1.14–1.84)	56.1	0.06
Cases ≥1,000		5	1.15 (0.99–1.33)	65.9	0.02	4	1.40 (1.20–1.62)	62.4	0.05
Cases <500		3	1.22 (0.86–1.74)	52.3	0.12	3	1.39 (0.93–2.09)	63.6	0.06
Cases ≥500		7	1.22 (1.05–1.41)	65.4	0.008	6	1.44 (1.27–1.63)	52.6	0.06
Dietary assessment									
Baseline only		5	1.19 (1.03–1.37)	8.8	0.36	5	1.34 (1.13–1.60)	31.7	0.21
Updated		5	1.23 (1.00–1.51)	76.8	0.002	4	1.47 (1.22–1.77)	70.9	0.02
Not validated		2	1.07 (0.84–1.36)	NC	0.49	2	1.17 (0.92–1.47)	NC	0.69
Validated		8	1.25 (1.08–1.45)	65.4	0.005	7	1.47 (1.28–1.68)	57.3	0.03
Assessment of type 2 diabetes status									
Self-report only[b]		2	1.05 (0.84–1.32)	NC	0.08	2	1.23 (1.07–1.41)	NC	0.34
Comprehensive		7	1.31 (1.15–1.51)	37.8	0.14	6	1.51 (1.31–1.75)	44.6	0.11
Not validated		5	1.16 (0.96–1.40)	66.8	0.02	4	1.21 (1.08–1.37)	25.8	0.25
Validated		5	1.28 (1.09–1.51)	40.7	0.15	5	1.57 (1.39–1.78)	0	0.75
Adjustment									
Fibre, cereal fibre, whole grains	Yes	5	1.26 (1.08–1.46)	38.9	0.16	3	1.50 (1.29–1.74)	8.0	0.34
	No	5	1.17 (0.93–1.47)	72.8	0.005	6	1.36 (1.14–1.62)	64.5	0.02
Magnesium	Yes	4	1.17 (1.03–1.32)	0	0.56	3	1.50 (1.29–1.74)	8.0	0.34
	No	6	1.24 (1.01–1.54)	74.2	0.002	6	1.36 (1.14–1.62)	64.5	0.02
Energy intake	Yes	8	1.15 (1.02–1.29)	48.3	0.06	7	1.39 (1.22–1.58)	55.1	0.04
	No	2	1.71 (1.31–2.24)	NC	0.42	2	1.86 (0.90–3.84)	NC	0.06
BMI, WHR, waist circumference or weight	Yes	9	1.19 (1.05–1.35)	57.1	0.02	7	1.39 (1.22–1.58)	55.1	0.04
	No	1	2.26 (1.10–4.66)			2	1.86 (0.90–3.84)	NC	0.06
Physical activity	Yes	7	1.22 (1.05–1.41)	65.4	0.008	5	1.45 (1.25–1.68)	61.8	0.03
	No	3	1.22 (0.86–1.74)	52.3	0.12	4	1.35 (1.04–1.74)	47.5	0.13
Smoking	Yes	7	1.22 (1.05–1.41)	65.4	0.008	6	1.42 (1.24–1.62)	56.2	0.04
	No	3	1.22 (0.86–1.74)	52.3	0.12	3	1.45 (0.99–2.13)	63.3	0.07
Alcohol	Yes	7	1.22 (1.05–1.41)	65.4	0.008	5	1.45 (1.25–1.68)	61.8	0.03
	No	3	1.22 (0.86–1.74)	52.3	0.12	4	1.35 (1.04–1.74)	47.5	0.13
Meat subtypes									
Hamburger		3	1.25 (1.10–1.42)	1.5	0.42				
Hamburger[c]		3	1.09 (1.02–1.16)	55.6	0.11				
Bacon						4	1.37 (1.19–1.57)	64.3	0.04
Bacon[c]						4	1.14 (1.06–1.23)	80.8	0.001
Hot dogs						5	1.30 (1.20–1.42)	0	0.81
Hot dogs[c]						4	1.09 (1.05–1.14)	0	0.40
Other processed meats						4	1.25 (1.09–1.44)	63.9	0.04
Other processed meats[c]						4	1.09 (1.04–1.14)	33.1	0.21

[a] Analysis of highest vs lowest intake

[b] The study by Montonen et al., 2005 [27], was excluded from this subgroup analysis

[c] Dose–response, per 1 serving/week

NC, Not calculable

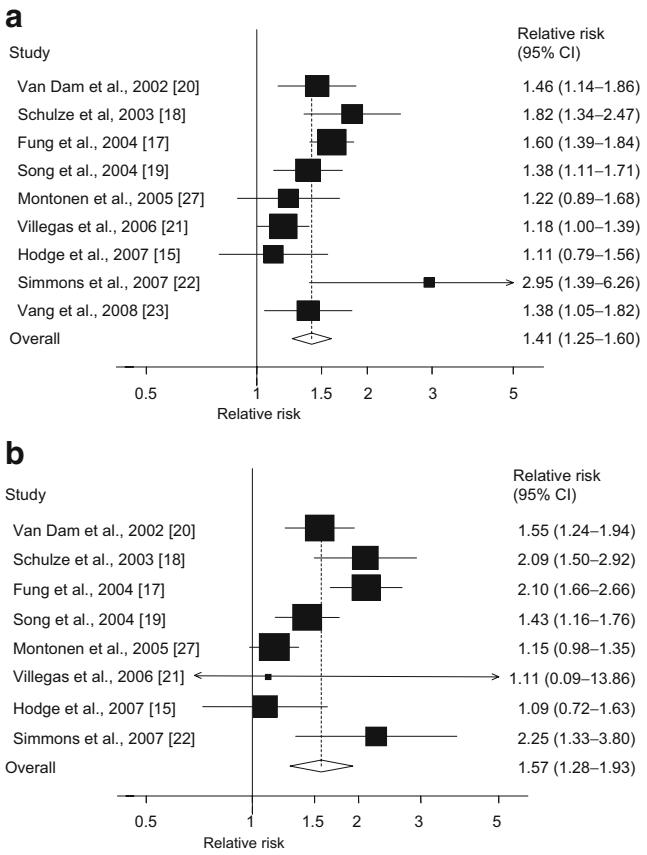

Fig. 4 Processed meat and type 2 diabetes. RRs for (**a**) the highest vs the lowest intake and (**b**) per 50 g/day of processed meat. The RR of each study is represented by a square and the size of the square represents the weight of each study to the overall estimate. 95% CIs are represented by the horizontal lines and the diamond represents the overall estimate and its 95% CI

that one study conducted among Chinese women [21] contributed to the heterogeneity; when this study was excluded, both the subgroup and the overall analyses showed much less heterogeneity. The reason for the inconsistent results in this study compared with those of other studies is not clear, but it could be due to a lower absolute meat intake among the participants than in other populations [17, 19, 25].

As with any meta-analysis based on published studies, publication bias is a potential concern. The statistical tests for publication bias did not suggest the presence of publication bias in this meta-analysis, although we may have had limited statistical power in these tests because of the moderate number of studies. The overall results for red and processed meat were robust to the influence of single studies, though the Chinese study most strongly influenced the estimate for total meat, which was based on fewer studies.

Measurement errors in the exposure variable are known to bias effect estimates [38], but none of the studies in this meta-analysis corrected their results for measurement errors. Repeated exposure assessments are important in cohort studies to reduce misclassification due to dietary changes during follow-up. In a cohort study the RR of type 2 diabetes was 1.28 for high vs low haem-iron intake (as a proxy for meat intake) when using cumulative updated averages of intake, but with only the baseline questionnaire the RR was weaker and not significant (RR 1.08) [39]. Four of the twelve included studies used repeated exposure assessments. In the case of type 2 diabetes, measurement errors may not only affect the exposure variable, but also the outcome due to underreporting of diagnosis in asymptomatic individuals. The summary RRs for the association between red and processed meat and type 2 diabetes risk were slightly higher when we restricted the analyses to studies with validated methods for assessing diabetes status. Because we only included prospective cohort studies in this meta-analysis, the measurement errors in both the assessment of exposure and outcome would most likely be non-differential, and thus give attenuated risk estimates [40].

Several mechanisms may both directly and indirectly explain an adverse effect of meat intake on type 2 diabetes risk. Meat is an important source of total and saturated fat and could increase the risk of type 2 diabetes through overweight/obesity [41–44], the metabolic syndrome [45–47] and hyperinsulinaemia and hyperglycaemia [20, 48–50], although some studies found no association [51, 52]. Another possible mechanism may be through the effects of haem-iron derived from meat [19, 24, 39, 53]. Iron can promote oxidative stress by increasing the formation of hydroxyl radicals [54] which can cause damage to tissues, in particular the pancreatic beta cells [54]. Elevated iron status may interfere with glucose metabolism and may reduce pancreatic insulin synthesis and secretion [55] and one study suggested a detrimental effect of red meat intake on glucose metabolism [56]. A number of processed meats contain nitrites and nitrates which can be converted to nitrosamines by interaction with amino compounds either in the stomach or within the food product. Nitrosamines have been found to be toxic to pancreatic beta cells and to increase the risk of type 1 and type 2 diabetes in animal studies [57–59], and of type 1 diabetes in some [60, 61], but not all [62], epidemiological studies. Other possible mechanisms may involve advanced glycation end-products [63], increased levels of inflammatory mediators [13, 47, 64] and γ-glutamyltransferase [65], and lower levels of adiponectin [66] with high meat intake. Our finding of a positive association between meat intake and type 2 diabetes risk is consistent with the 35–50% lower risk [23] or prevalence [16, 67, 68] of type 2 diabetes among vegetarians compared with omnivores.

In conclusion we found that high intakes of red meat and processed meat are risk factors for type 2 diabetes. We cannot completely rule out the possibility of residual

confounding or a temporal bias, but if the association is real, meat could be added to the list of behavioural factors which can be modified to decrease type 2 diabetes risk.

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