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Unprocessed Red and Processed Meats and Risk of Coronary Artery Disease and Type 2 Diabetes – An Updated Review of the Evidence

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Abstract Growing evidence suggests that effects of red meat consumption on coronary heart disease (CHD) and type 2 diabetes could vary depending on processing. We reviewed the evidence for effects of unprocessed (fresh/frozen) red and processed (using sodium/other preservatives) meat consumption on CHD and diabetes. In meta-analyses of prospective cohorts, higher risk of CHD is seen with processed meat consumption (RR per 50 g: 1.42, 95 %CI=1.07–1.89), but much lower or no risk is seen with unprocessed meat consumption. Differences in sodium content (~400 % higher in processed meat) appear to account for about two-thirds of this risk difference. In similar analyses, both unprocessed red and processed meat consumption are associated with incident diabetes, with much higher risk per g of processed (RR per 50 g: 1.51, 95 %CI=1.25–1.83) versus unprocessed (RR per 100 g: 1.19, 95 % CI=1.04–1.37) meats. Contents of heme iron and dietary cholesterol may partly account for these associations. The overall findings suggest that neither unprocessed red nor processed meat consumption is beneficial for cardiometabolic health, and that clinical and public health guidance should especially prioritize reducing processed meat consumption.

Keywords Review · Meat · Red meat · Processed meat · Cardiovascular disease · Diabetes

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Introduction

Red meat consumption is considered a major dietary risk factor for cardiometabolic diseases, including coronary heart disease (CHD) and type 2 diabetes mellitus (DM). In a 2010 meta-analysis, we provided evidence that relationships of meat consumption with development of these conditions might vary depending on the extent of processing [1••], i.e., whether or not the meat is unprocessed (e.g., fresh or frozen) or has been processed and preserved for long-term storage, e.g., by adding high amounts of salt and/or other preservatives such as nitrates. Since the publication of our findings, several additional studies have evaluated how eating unprocessed red meats or processed meats relates to development of CHD and DM. Understanding potential differences in the associations of these different types of meats with disease outcomes, as well as the magnitude and dose-response of such effects, is relevant for elucidating the potentially relevant harmful constituents and for informing priorities for clinical and public health dietary guidance.

In this report, we review the current evidence for effects of unprocessed red and processed meat consumption on CHD and DM. Relevant issues considered herein include: (1) the characterizations and definitions of the type of meat consumed,

(2) the evidence for effects on clinical endpoints, including the magnitudes and dose-responses of effect, (3) the potential mechanisms for similar or differing associations of different meat types with various cardiometabolic diseases, (4) the potential for bias in the evidence, and (5) the implications of the evidence for clinical and public health priorities.

Categorizations of Meat Consumption

For understanding relations with disease endpoints, foods are often investigated in broad groupings, such as total meats, vegetables, fruits, fish, nuts, and so on. Such categories are helpful to group together similar foods when they have similar potential health effects, but can provide incomplete or misleading information when foods with differing health effects are combined into a single group. For example, whereas fish consumption is typically considered as a single category, we and others have shown that consumption of fatty or oily fish, which are highest in omega 3 s, is most strongly associated with lower CHD mortality, whereas consumption of fried fish or fish sandwiches, which are typically low in omega-3 s and can be commercially fried in unhealthy oils, are not [2]. Similarly, there are potentially important nutritional differences in different types of meat, including the contents of calories, specific fats, iron, or preservatives such as sodium or nitrites. Different cooking methods (e.g., broiling, baking, grilling, frying) could also likely alter health effects—for example, charring and blackening of meats introduces products such as heterocyclic amines and polycyclic aromatic hydrocarbons that likely increase cancer risk [3]—but the effects of cooking methods on cardiometabolic risk have thus far been studied much less and will not be considered further in the present review.

Based on fat, cholesterol, and iron contents, meats are often broadly categorized into red (e.g., beef, pork, lamb) or white (e.g., chicken, turkey, rabbit) meats. Each of these types of meat can also be either preserved, typically by the addition of high levels of salt and/or chemical preservatives (referred to hereafter as "processed meat"), or consumed without such preservatives (referred to hereafter as "unprocessed meat"). Additional potential categories could include offal meat (i.e., organ meat) or non-domesticated meat (i.e., game).

Considering these different major groupings and possible sub-groupings, it becomes evident that many differing definitions and categorizations of meats could be considered. As discussed below, no randomized controlled trials (RCTs) focusing on meat consumption and any chronic disease outcome have been performed. Furthermore, interpretation of any such RCT would be limited by the lack of blinding, by noncompliance, and by cross-over over time. Consequently, prospective observational studies provide the most robust available evidence for understanding the effects of meat consumption on the development of chronic diseases. Because such studies must be very large and follow participants for many years, the dietary assessment methods in such studies generally do not permit reliable quantification of every possible subtype of meat. Rather, the most reliable groupings of types of meat that have been considered in such studies, which we will review herein, are of total unprocessed red meat consumption, including beef, pork, and lamb; and total processed meat consumption, including bacon, hot dogs, sausage, salami, and processed deli or luncheon meats.

Evaluating Effects of Meat Consumption on Cardiometabolic Health

Dietary habits can affect a wide range of intermediate biologic pathways, including blood cholesterol concentrations, lipoprotein levels, blood pressure, insulin resistance, endothelial function, inflammation, adiposity, arrhythmic risk, and myocardial function and efficiency [4]. Consequently, effects of dietary habits on any one or even several of these surrogate outcomes are often insufficient for making strong inference about effects on clinical endpoints. An Institute of Medicine report on the use of biomarkers and similar surrogate markers concluded that the evidence does not support using such markers, including LDL cholesterol levels, as a surrogate endpoint for the effects of dietary habits on clinical events [5].

Several authors and organizations have proposed comprehensive methods for evaluating effects of dietary habits on chronic disease endpoints [6–9]. These methods each highlight the primacy of evidence derived from studies of clinical endpoints rather than surrogate markers. Dietary habits and chronic disease endpoints can be studied in well-conducted RCTs or well-conducted, large prospective cohort studies, with further careful pooling of such findings in systematic reviews and meta-analyses to derive the best available evidence from all studies worldwide. Similar to most other lifestyle risk factors (e.g., smoking, physical activity, obesity, consumption of salt, dietary cholesterol, fruits, vegetables, nuts, whole grains), the effects of meat consumption on cardiometabolic endpoints have not, to our knowledge, been investigated in any RCTs. This is unsurprising given practical, ethical, and cost considerations, as well as inherent methodological limitations, such as the inability to perform blinding and inevitable noncompliance and cross-over during the long periods of time required to detect effects on chronic disease. Thus, prospective cohort studies provide the best available evidence to estimate causal effects of meat consumption on cardiometabolic events, with consideration of evidence for temporality, consistency, magnitude, and dose-response, as well as support from studies of biomarkers and surrogate markers to provide plausible biologic mechanisms [6–9]. We review this evidence below.

Coronary Heart Disease

In a 2010 systematic review and meta-analysis [1••], we separately evaluated the associations of unprocessed red and processed meats with the development of cardiometabolic events. For comparability across studies, all reported RR's were standardized to 100 g serving sizes for unprocessed red meats and 50 g serving sizes for processed meats. To minimize potential bias, particular efforts were made to extract or directly obtain from the authors the risk estimates with the greatest control for potential confounders, and crude risk estimates were excluded a priori. Whenever possible, the multivariable model was selected that did not include variables that could be potential intermediates in the causal pathway (e.g., blood cholesterol concentrations).

We identified a total of three prospective cohort studies and one case-control study that evaluated the relationship between unprocessed red meat consumption and incident CHD [10–13]. The pooled dose-response, including 56,311 participants and 769 events, found no significant association between unprocessed red meat consumption and CHD risk (RR=1.00 per 100 g serving/day, 95 % CI=0.81–1.23) (Fig. 1). Pooled findings restricted to prospective cohorts [10–12] were similar to the overall pooled estimate (RR=0.92, 95 % CI=0.74–1.15).

We identified six observational studies including 614,062 participants and 21,308 events [1••] that evaluated processed meat consumption and incident CHD [10, 12–15]. In pooled analyses, each 50 g serving/day of processed meats was associated with 42 % higher risk (RR=1.42, 95 % CI=1.07–1.89) (Fig. 1). This stonger association was seen despite the smaller serving size (50 g) compared with unprocessed red meats (100 g). Matching the serving sizes, each 100 g serving/day of processed meats was associated with 2-fold higher risk of CHD (RR=2.02, 95 % CI=1.14–3.57). When the analysis was restricted to prospective cohorts [10, 12, 14, 15], similar findings were observed, with 44 % higher CHD risk per 50 g serving/day (RR=1.44, 95 % CI=1.07–1.95). Of note, in many of these studies, processed hot dogs and deli meats, which would include processed poultry meats (chicken, turkey), were included in total processed meats but were not separately assessed.

Following publication of these findings, two large studies have evaluated the associations between eating unprocessed red meat and risk of incident CHD [16•] and CVD mortality [17•]. In the prospective Nurse's Health Study (NHS), Bernstein and colleagues evaluated the association between unprocessed red and processed meat consumption and CHD risk [16•]. The analysis included 84,136 women with 3,162 CHD events. After adjusting for various lifestyle and dietary factors, each 100 g serving/day of unprocessed red meats was associated with 19 % higher risk of CHD (RR=1.19, 95 % CI=1.07–1.32), and each 50 g serving/day of

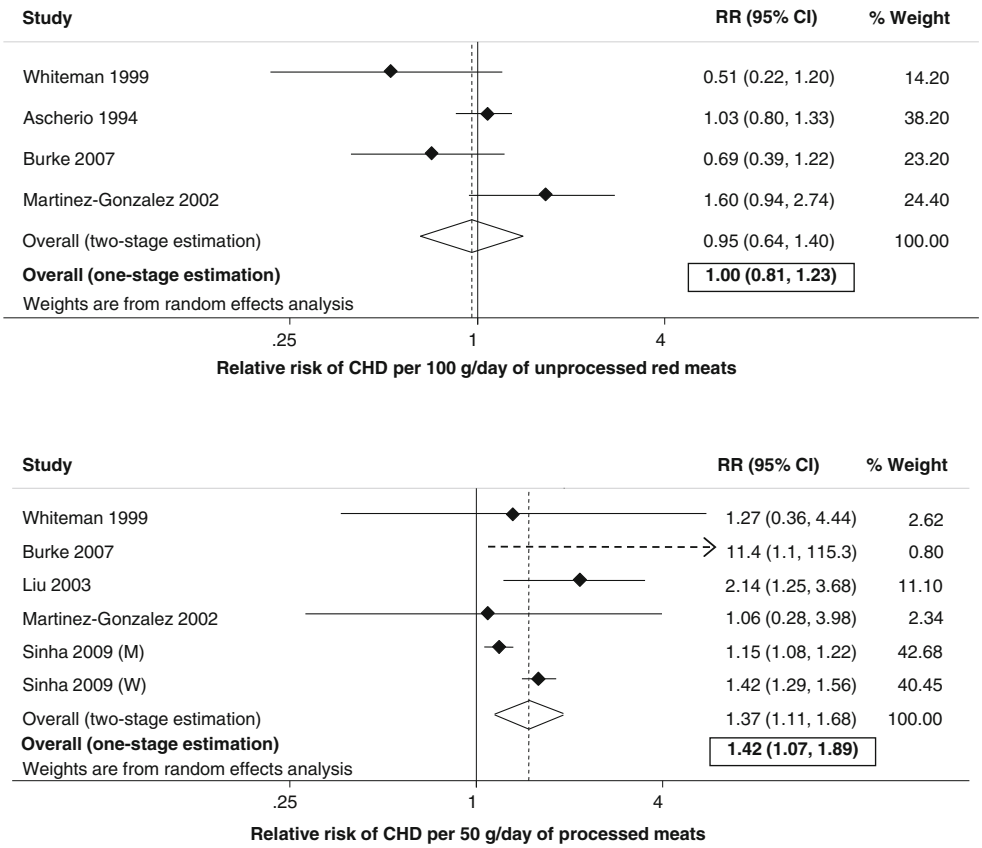

Fig. 1 Risk of incident coronary heart disease (CHD) associated with each 100 g serving per day of unprocessed red meats (top; three cohort studies and one case-control study, 56,311 participants, and 769 events); and each 50 g serving per day of processed meats (bottom; four cohort studies and one case-control study, 614 ,062 participants, and 21,308 events). The study by Sinha et al. (2009) assessed total cardiovascular (CHD plus stroke) mortality only. Solid diamonds and lines represent the study-specific relative risk (RR) and 95 % CI, respectively, derived from generalized least squares models for trend (GLST). The dashed line and open diamond represent the overall pooled RR and 95 % CI, respectively, as derived from both two-stage and one-stage GLST least squares for trend estimation. Reproduced with permission from Micha et al. (2010) [1••]

processed meats was associated with 20 % higher risk (RR=1.20, 95 % CI=1.03–1.40). Matching the serving sizes, each daily 100 g serving of processed meats was associated with 44 % higher risk (RR=1.44, 95 % CI=1.06–1.96), or about 2-fold higher than the risk for 100 g of unprocessed meats. Pan and colleagues [17•] re-evaluated the NHS and added the Health Professionals Follow-up Study (HPFS) cohort to assess the relationships between unprocessed red and processed meat consumption and risk of CVD death [17•]. Pooling the results of the two cohorts, each serving/day of unprocessed red meats was associated with 18 % higher risk of CVD mortality (RR=1.18, 95 % CI=1.13–1.23), and each serving/day of processed meats was associated with 21 % higher risk of CVD mortality (RR=1.21, 95 % CI=1.13–1.31). Matching for serving sizes, each daily 100 g serving of processed meats was associated with 46 % higher risk (RR=1.46, 95 % CI=1.28–1.72), about 2-fold higher compared to unprocessed red meats.

The findings from both our 2010 meta-analysis [1••] and these two updated publications suggest that for every 100 g serving/day, processed meat consumption has substantial associations with cardiovascular events (RR's of 2.02, 1.44, and 1.46 in our meta-analysis, the updated NHS analysis, and the updated NHS/HPFS analysis, respectively). In comparison, unprocessed red meat consumption has lesser or no associations with cardiovascular events (corresponding RR's of 1.00, 1.19, and 1.18, respectively). Notably, these RR's correspond to daily consumption of 100 g of these meats, i.e., one serving/day or 7 servings/week. The corresponding RR's for weekly consumption of 100 g (i.e., one serving/week) are 1.11, 1.05, and 1.06 for processed meat consumption, and 1.00, 1.03, and 1.02 for unprocessed red meat consumption.

The magnitudes of these RR's for daily vs. weekly consumption are informative for considering risk across populations. For example, based on our analysis of 2003-2006 NHANES dietary recall data, the median energy-adjusted intakes of unprocessed red meats and processed meats among American adults are 1.9 and 1.6 100 g servings/week (0.3 and 0.2 servings/day), respectively, and the 90th percentile intakes are 9.2 and 6.6 servings/week (1.3 and 0.9 servings/day), respectively. Thus, the risk observed per weekly serving is relevant to much of the US population, and the risk seen per daily serving is relevant to the highest consumers of meats.

What about subcategories of unprocessed red or processed meats, e.g., hamburger, hot dogs, or deli meats alone? Unfortunately, relatively few studies have reported on such subcategories, raising concern for both publication bias and less generalizability. In our meta-analysis [1••], we identified only two prospective cohorts that reported associations of subtypes of unprocessed red meats with CHD [11], and no prospective studies that reported associations of subtypes of processed meats with CHD. The two newer reports described above [16•, 17•] updated the findings from two earlier reports on subtypes of unprocessed red and processed meats and CVD. Overall, associations appeared relatively similar for subtypes of unprocessed red meats, as well as for most subtypes of processed meats including deli meats that would often be processed chicken or turkey except that bacon and hot dogs appeared associated with relatively higher CHD risk compared with other processed meat subtypes.

Type 2 Diabetes Mellitus

Using the methods reported in our meta-analysis [1••], an updated meta-analysis by Pan and colleagues [18•] evaluated the relationship between unprocessed red and processed meat consumption and incident DM, including our previously identified studies plus updated findings from three Harvard cohorts [19–21]. Consistent with our meta-analysis, serving sizes were standardized to 100 g for unprocessed red and 50 g for processed meats. Nine prospective cohort studies, including 447,333 individuals and 28,206 events, assessed the relationship between unprocessed red meat consumption and incident DM (Fig. 2). Six of nine studies observed a significant independent positive relationship. In a pooled analysis, each daily 100 g serving of unprocessed red meats was associated with 19 % higher risk (RR=1.19, 95 % CI=1.04–1.37). Per weekly 100 g serving, the corresponding RR was 1.03 (95 % CI=1.01–1.05).

Eight prospective cohort studies, including 372,391 individuals and 26,234 events, assessed the relationship between processed meat consumption and incident DM (Fig. 2). Eight of nine studies observed a significant independent positive relationship. In a pooled analysis, each 50 g daily serving of processed meats was associated with 51 % higher risk (RR=1.51, 95 % CI=1.25–1.83). Matching the serving sizes for comparability, each daily 100 g serving of processed meats was associated with a more than 2-fold higher risk of diabetes (RR=2.28, 95 % CI=1.56–3.35). Per weekly 100 g serving, the corresponding RR was 1.06 (95 % CI=1.03–1.09).

Similar to our meta-analysis [1••], in these updated reports processed meats were predominantly red meats but also included some processed poultry meats (e.g., chicken or turkey deli meats and hot dogs) that were not separately evaluated. Much less is known about these or other subtypes of processed meats. In our systematic review and meta-analysis [1••], we identified five prospective cohort studies [19–23] that reported RR's for subtypes of processed meat consumption and incident DM. The pooled dose-response demonstrated that each daily serving of bacon (2 slices) was

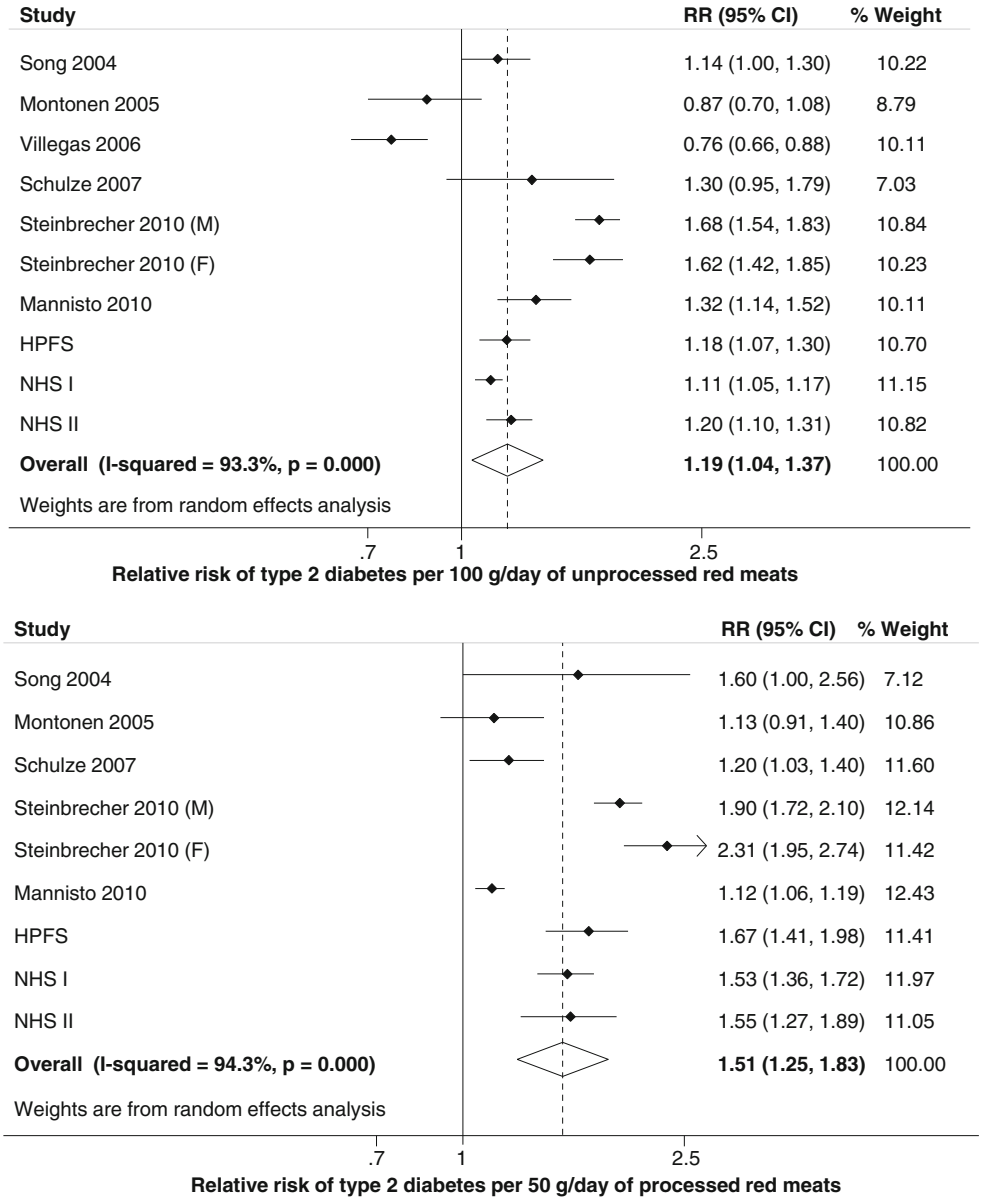

Fig. 2 Risk of incident type 2 diabetes associated with each 100 g serving per day of unprocessed red meats (top; nine cohort studies, 447,333 participants, and 28,206 events) and 50 g serving per day of processed meats (bottom; eight cohorts, 372,391 participants, and 26,234 events). Reproduced with permission from Pan et al. (2010) [18•]. Squares and lines are study-specific RRs and 95 % CI, respectively. Dashed line and open diamond are pooled estimate and 95 % CI, respectively

associated with 2-fold higher risk of incident DM (RR= 2.07, 95 % CI=1.40–3.04); of hot dogs, with similarly 2-fold higher risk (RR=1.92, 95 % CI=1.33–2.78); and of other processed meats, with relatively similar 66 % higher risk (RR=1.66, 95 % CI=1.13–2.42). Thus, although overall data are still somewhat limited, the available evidence suggests that different types of processed meats, including deli meats that would be often be processed white meats, have relatively similar associations with DM.

Following the publication of these findings, Fretts and colleagues evaluated relationships between unprocessed red and processed meat consumption and incident diabetes in the Strong Heart Family Study [24•], a population of American Indians with high rates of obesity and diabetes. In multivariable adjusted analysis including 2,001 participants and 243 incident DM cases, high vs. low processed meat consumption was associated with 35 % higher risk (RR= 1.35, 95 % CI=0.81–2.25), while high vs. low unprocessed red meat consumption was not associated with risk (RR= 0.88, 95 % CI=0.57, 1.35). In this [24•] and other prospective cohorts [20–22], relatively similar relationships were observed for various subtypes of unprocessed red meats.

Potential Underlying Mechanisms

Similarities and differences in constituents of unprocessed red and processed meats can inform potential mechanisms for their varying relationships with CHD and DM. For instance, the average saturated fat content of unprocessed red and processed meats is similar (Table 1), making it unlikely that saturated fat content accounts for the different observed

Table 1 Average nutritional and preservative contents in unprocessed red and processed meats per 50 g servings, as consumed in the US

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)

Reproduced with permission from Micha et al. (2010) [1••]. Based on data from the 2005-06 US National Health and Nutrition Survey (NHANES) [60] and a report of published nitrate, nitrite, and nitrosamine contents of foods [61], each analyzed according to actual US consumption levels and accounting for the NHANES sampling and weighting strategies. All mean differences were significant at $p<0.05$

relationships with disease risk. This is supported by evidence for no overall association of saturated fat consumption with incident CHD or DM [4, 25–30], perhaps because such effects vary depending on both the food source of saturated fat [31] and the macronutrient replacing saturated fat [27]. Average total fat content is higher in processed meats, but largely due to higher contents of monounsaturated and polyunsaturated fats, which are not linked to higher CHD or DM risk. Together these findings suggest that other components of meats may be relevant to cardiometabolic effects.

Average contents of dietary cholesterol are similar in unprocessed red and processed meats, or even a bit lower in the latter, likely due to low-cholesterol white deli meats (Table 1). Whereas few prospective studies have evaluated dietary cholesterol and incident CHD or DM, the available evidence suggests little association with incident CHD in the general population, but a positive association with incident DM [26, 32–35]. Thus, dietary cholesterol content could partly account for the associations of unprocessed red and processed meat consumption with DM, although the similar contents of dietary cholesterol would not explain the substantially higher DM risk seen with processed meats.

Dietary heme iron may increase oxidative stress and insulin resistance, and has been associated with higher risk of DM [36–38]. Thus, heme iron in both unprocessed red and processed meats could partly explain their relations with incident DM. However, average heme iron content is lower in processed meats (consistent with higher fat and lower protein; Table 1), so this also would not explain the stronger association of processed meats with DM risk.

Among major constituents, the largest difference between processed and unprocessed meats is in the content of preservatives, especially sodium (Table 1). On average, processed meats contain about 400 % more sodium and 50 % more nitrates per gram. Dietary sodium increases blood pressure (BP), and may also increase peripheral vascular resistance and impair arterial compliance [39]. Based on the established effects of sodium on BP [40] and the relationship between BP and clinical CHD events [41], the average sodium consumed from one daily 50 g serving of processed meats would predict about 27 % higher risk of CHD, or more than two-third (on the log RR scale) of the observed 42 % higher risk seen in cohort studies. Thus, sodium content alone is likely to account for a substantial portion of the observed CHD risk with processed meat consumption. In addition, the much lower average sodium content in unprocessed meats likely explains its smaller association with CHD. Other preservatives used in processed meats, such as nitrates and their byproducts (e.g., peroxynitrite), experimentally promote endothelial dysfunction, atherosclerosis, and insulin resistance [42–44]; and streptozotocin, a nitrosamine-related compound, is a known diabetogenic compound [45]. Nitrites and nitrous compounds have also been associated with type 1 diabetes in children [46, 47]; while in adults, nitrate concentrations have been used as a biomarker of endothelial dysfunction [48] and impaired insulin response [49]. Thus, higher nitrates/nitrates in processed meats could further explain their stronger relationships with both CHD and DM.

Different meat preparation methods could also influence health effects. High temperature commercial cooking or frying, commonly used in preparing processed meats, can introduce heterocyclic amines and polycyclic aromatic hydrocarbons, which could increase risk of both CHD and DM [50–52]. Relatively little human research has been done on meat preparation methods and these disease outcomes, and further study is urgently needed.

Meat Consumption and Cardiometabolic Diseases—Potential for Bias

Considering the major criteria for evaluating causality [6–9], there appears to be consistency, temporality, dose-response, and plausible mechanisms for each of the associations

described above. In observational studies, residual confounding due to imprecisely measured or unmeasured confounders can never be fully excluded. Thus, a key additional criterion is the magnitude of the association, which (if large) can provide reassurance that residual confounding is less likely to fully explain the relationship; or (if small) can raise concern that much or all of the observed associations may be due to bias or residual confounding. For processed meats and risk of CHD and DM, the magnitudes of the associations suggest that residual confounding is unlikely to fully account for the observed higher risk. For unprocessed meats and risk of CHD and DM, however, the more modest associations do raise concern for potential bias.

It is relevant to consider the plausible directions of effects of such bias. In each of the cohorts that have evaluated meat consumption and chronic diseases, greater meat consumption is associated with less favorable lifestyle and dietary behaviors, including for example less physical activity, increased smoking, increased total energy (consistent with higher BMI), and lower fruit, vegetable, dietary fiber, whole grains and fish intake, and higher alcohol and trans fat intake [15, 16•, 17•, 18•, 22, 23]. Residual confounding by these factors, or their correlates, would cause overestimation of harmful effects of meat consumption. Consequently, the magnitude of the observed harmful associations between unprocessed red or processed meat consumption and CHD and DM could be overestimated, particularly in studies that do not comprehensively adjust for a range of lifestyle and dietary habits.

The possible magnitude of such overestimation can be challenging to quantify. In such circumstances, use of a "negative control" is informative: i.e., the evaluation of a separate health outcome for which the exposure of interest has little plausible biologic mechanism or expectation for a meaningful causal effect. One recent report provides useful data in this regard [15]. This large prospective cohort study reported positive associations for both total (processed and unprocessed) red meat and processed meat consumption and risk of cancer and CVD mortality (separate associations for unprocessed red meats were not published and could not be obtained by direct contact with the authors). Notably, this report also evaluated other causes of mortality, including a category of "all other deaths" that would predominantly be from chronic pulmonary diseases, pneumonia, diabetes, and chronic liver disease [53, 54]. Except for diabetes, there is little plausible biologic mechanism for a large effect of meat intake on these other types of deaths, and certainly none expected to be as great as effects on cancer or cardiovascular death. However, in this analysis, the observed associations of total red meat and processed meat consumption with these "other deaths" was actually considerably stronger than for cancer or cardiovascular deaths. One could hypothesize that meat consumption did have some very powerful, heretofore unrecognized causal effects on deaths from chronic pulmonary disease, pneumonia, and chronic liver disease. More plausibly, participants consuming more meats had other important lifestyle behaviors affecting mortality that were not fully accounted for in the analysis. Plausible confounders included major risk factors that were assessed but measured with imprecision, such as education, physical activity, smoking, alcohol use, adiposity, and fruit and vegetable consumption; and other potential confounders not included in the model at all, such as income, second-hand smoke, air pollution, alcohol patterns (e.g., binge drinking), and consumption of starches, refined carbohydrates, sugars, trans fat, dietary fiber, whole grains, nuts, seeds, and legumes [54].

Bias can also reduce observed associations. In large observational studies, random errors in measurement of self-reported diet can cause bias toward the null, causing underestimation of true associations. Similarly, adjustment for factors which could be potential intermediates in the causal pathway between meat consumption and CHD or DM would also cause inappropriate bias toward the null. Several of the studies in our meta-analysis did adjust for factors that could be either confounders or intermediates, mainly blood lipids and/or blood pressure concentrations [12, 13, 19, 21, 55–57]. Thus, the net effects of residual confounding (which here would overestimate effects) versus random errors in dietary assessment and overadjustment for intermediates (which here would underestimate effects) should always be considered. Large observed effects in the setting of comprehensive covariate adjustment are reassuring; small observed effects in the setting of incomplete adjustment are concerning, particularly when relations with "negative control" outcomes are similar or even more robust.

Conclusions

The available evidence indicates strong associations of processed meat consumption with incident CHD and DM, more modest associations of unprocessed red meat consumption with incident DM, and small or no associations of unprocessed red meat consumption with incident CHD. Our review of this evidence also highlights the importance of appropriate categorization of meat types and careful consideration of magnitudes and directions of bias (e.g., due to confounding, overadjustment, or misclassification) when evaluating associations of meat intake with clinical endpoints. The most relevant constituents for cardiometabolic effects may include dietary cholesterol, heme iron, and nitrates/nitrites for risk of DM; and sodium and nitrates/nitrites for risk of CHD. These findings suggest that

clinical and public health guidance should prioritize reduction of processed meat consumption to reduce CHD and DM risk, as well as reduction of sodium and other preservative contents of processed meats. The 2010 US Dietary Guidelines for Americans recommend selecting lean meats, increasing the amount of seafood consumed in place of some meat and poultry, and specifically limiting processed meats [58]. The recommendation to select lean meats was partly based on saturated fat and dietary cholesterol content and consequent effects on blood LDL-cholesterol. Interestingly, our analysis suggests that other constituents may be more relevant.

Our findings have additional implications. First, it may be misguided to promote consumption of processed deli meats, such as processed chicken, turkey, or bologna, as "healthy" alternatives on the basis of their lower total fat or saturated fat contents. The current evidence suggests that processed meats are particularly harmful for CHD and DM, and that the content of sodium and other preservatives, rather than total fat or saturated fat, may be most relevant. While further investigation is needed to determine if different subcategories of processed meats have different effects on cardiometabolic risk, based on the current evidence it would be prudent to minimize consumption of all processed meats. Second, because sodium and possibly other preservatives appear particularly relevant, especially for CHD risk, new industry focus on reducing these additives would be particularly important for reducing the harms of processed meat consumption.

Whereas the evidence indicates that reducing processed meat consumption should be a priority for clinical and public health guidance, and that unprocessed red meat consumption has smaller effects on DM and little or no effect on CHD, no evidence from these studies suggested any cardiometabolic benefits of unprocessed red meat consumption. Additionally, cattle farming has tremendous adverse environmental impacts, including on deforestation, water use, and carbon and methane emissions [59]. Thus, healthier alternatives with strong evidence for cardiometabolic benefits, such as fish, nuts, fruits, whole grains, and vegetables, are vastly preferable dietary choices to consuming unprocessed red meats. Still, for individual and public health focus, prioritizing reduction in processed meats as well as other harmful dietary factors, such as partially hydrogenated vegetable oils, high-sodium foods, and refined grains, starches, and sugars, is likely to produce the largest net benefits for both individual and population health.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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