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ORIGINAL CONTRIBUTION

# Substitution of red meat with poultry or fish and risk of type 2 diabetes: a Danish cohort study

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## Abstract

**Purpose** We examined associations between substitution of red meat (total, processed and unprocessed, low fat and high fat) with poultry or fish and substitution of processed red meat with unprocessed red meat and the risk of type 2 diabetes.

**Methods** A cohort of 53,163 participants from the Danish Diet, Cancer and Health study were followed for incident type 2 diabetes (6879 cases; median follow-up time 15.4 years). Diet was assessed by a validated 192-item food frequency questionnaire at baseline. Adjusted Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for type 2 diabetes associated with specified food substitutions of 150 g/week.

**Results** Replacing total red meat with fish was associated with a lower risk of type 2 diabetes [HR 0.96 (95% CI 0.94, 0.99)] as was replacement of processed red meat with poultry or fish [HR poultry 0.96 (95% CI 0.93, 0.99)]; HR fish 0.94 [(95% CI 0.91, 0.97)]. Replacing low fat red meat or high fat red meat with fish was associated with a lower risk of type 2 diabetes whereas similar substitutions, with poultry, were not. Replacing processed red meat with unprocessed red meat was also associated with a lower risk of type 2 diabetes [HR 0.96 (95% CI 0.93, 0.99)].

**Conclusions** Replacing processed red meat with poultry, replacing total or processed red meat with fish, and replacing processed red meat with unprocessed red meat were all associated with a lower risk of type 2 diabetes.

**Keywords** Prospective studies · Red meat · Poultry · Fish · Substitution models · Type 2 diabetes mellitus

## Introduction

Diet and lifestyle are considered important modifiable risk factors in the development of type 2 diabetes [1], and meat is a common source of protein in Western diets [2]. Several cohort studies have found an association between intake or increasing intake of processed and/or unprocessed red meat and the risk of type 2 diabetes [3–5]. Especially intake of processed red meat was consistently associated with a higher risk of developing type 2 diabetes in these studies.

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Current dietary guidelines recommend lowering intake of red meat and processed red meat [6]. As most adult individuals maintain a rather constant energy intake over time [7], consuming less red meat and processed red meat must entail a higher intake of other energy-providing foods. Nevertheless, only few studies have investigated which other foods could replace red and processed meats. In three US cohorts, it was found that substitution of one daily serving of red meat with poultry or fish was associated with a lower risk of type 2 diabetes [4]. Implementing dietary changes is a recognized problem in management of diabetes risk [8, 9] and it may be that replacement of low fat or high fat red meat with other meat products or processed red meat with unprocessed red meat is more feasible.

As part of the European Prospective Investigation into Cancer and Nutrition (EPIC) collaboration, associations between individual meat products have been reported previously [10], however, food substitutions were not evaluated. Thus, the aim of this study was to investigate whether substitution of red meat with poultry or fish was associated with a lower risk of type 2 diabetes and whether substitutions of red meat with different contents of fat (low and high) with poultry or fish were associated with type 2 diabetes in a European population. To investigate whether substitution between different types of red meat could be associated with developing type 2 diabetes, we also aimed to examine substitutions of processed red meat with unprocessed red meat.

# Methods

## Study population

The study included participants from the Danish cohort Diet, Cancer and Health. The primary aim of the Diet, Cancer and Health study was to investigate the association between specific dietary components, lifestyle and the risk of cancer and other chronic diseases. Between December 1993 and May 1997, 160,725 citizens living in the two metropolitan areas of Denmark (Aarhus and Copenhagen municipalities) were invited to participate in the cohort. To be eligible for invitation the participants had to be between 50 and 64 years old, born in Denmark and with no entry in the Danish Cancer Register at baseline. Of the invited, 57,053 participants accepted participation. All participants included in the study were invited to a clinic, where they completed a lifestyle questionnaire. Trained laboratory technicians obtained anthropometric measures. Prior to the visit the participants had completed a validated food frequency questionnaire (FFQ), which was checked for reading errors and missing information at the visit to the clinic. Further details about the Diet, Cancer and Health study have been described previously [11]. Participants with cancer, type 2 diabetes, cardiovascular disease or any missing covariates at baseline were excluded from the present study.

## Dietary assessment

The participants reported their average intake of different food and beverage items over the past 12 months on a validated 192-item FFQ [12] with 12 possible intake categories ranging from “never” to “8 or more times per day.” The FFQ was validated against two 7-day weighted diet records taken 2–3 weeks apart with energy-adjusted correlation coefficients ranging from 0.21 to 0.71 for nutrients [11]. Questions concerning consumption of red meat, poultry and fish included both a question about overall intake and questions about more specific dishes. The different meat variables in this study were defined as unprocessed red meat including beef, veal, lamb, pork and offal (liver and heart), processed red meat including bacon, sausages, liver paste and cold cuts, fish including tuna, cod, flounder, garfish, shrimp, shellfish, salmon, mackerel, herring, trout and caviar, and poultry including turkey and chicken (meat and skin). Red meat with > 10 g fat per 100 g was defined as high fat meat, while red meat with ≤ 10 g fat per 100 g was defined as low fat meat. The participants’ average food and nutrient intakes were calculated using FoodCalc [13], which uses sex-specific portion sizes and the reported frequency of portions consumed to calculate intake in grams/week [12].

## Case ascertainment

Incident diabetes cases were determined through linkage to the National Danish Diabetes Register [14]. Information on death or emigration was obtained from the Danish Civil Registration System. The National Danish Diabetes Register links nationwide registers that contain information about aspects of diabetes diagnosis and care. Participants were classified as having diabetes if one of the following criteria was met: diagnosis of diabetes in the National Patient Registry; chiropody for diabetic patients; five blood glucose measurements within 1 year; two blood glucose measurements per year for 5 consecutive years; second purchase of oral glucose-lowering drugs within 6 months; second purchase of prescribed insulin. In a pilot study, the algorithm used for identification of diabetes cases was validated with a positive predictive value of 89% [13]. The National Danish Diabetes Register did not differentiate between diabetes types 1 and 2. While it is possible that some of the diabetes cases in this study were incident or recently deteriorated type 1 diabetes, the most common form of late onset diabetes is type 2 diabetes [15]. As the participants in this study were between 50 and 64 years old at baseline, most, if not all, incident cases were likely to be type 2 diabetes.

## Covariate assessment

Self-administered lifestyle questionnaires were used to collect baseline information about the participants’ socioeconomic status, demographic characteristics, physical activity habits and other health related information. At the research centre, laboratory technicians measured the participants’ anthropometric dimensions, including height, weight and waist circumference according to a standardized protocol [16]. Height and waist circumference were recorded to the nearest 0.5 cm. Height was measured standing without shoes and waist circumference was measured at the narrowest part between the lower ribs and the iliac crest. Weight was recorded to the nearest 100 g using a digital scale [16]. Covariates were selected based on prior knowledge regarding risk factors for type 2 diabetes.

## Statistical analysis

Baseline characteristics are presented as numbers ($n$) and percentages (%) and medians and percentiles (10–90%). Cox proportional hazards regression models using participant age as the underlying timescale were used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Follow-up time was calculated from age at inclusion of the participants into the Diet, Cancer and Health study to age at the registration of type 2 diabetes, end of study (31 December 2011), emigration or death, whichever came first. Intakes of 150 g/week, reflecting a usual serving size of meat or fish, were investigated for each food item, as in previous reports [17]. To construct substitution models, a sum-variable including the participants' total intake of processed and unprocessed red meat, poultry and fish was entered into the Cox regression model in addition to each of these food groups separately, except for the food group to be replaced. For example, to investigate substitution of processed red meat with poultry, fish or unprocessed red meat, we held the total intake of processed and unprocessed red meat, poultry and fish constant using the sum-variable and added the specific variables for poultry, fish and unprocessed red meat into the Cox regression model leaving out the variable for processed red meat. The calculated HR for each of the three food groups is interpreted as the HR for substitution with the omitted variable; in this case the HR for substituting 150 g/week processed red meat with 150 g/week of poultry, fish or unprocessed red meat, respectively, as described previously [18].

Model 1a was stratified by sex and tertiles of both date of enrolment and of baseline age to allow for differences in baseline hazards, and adjusted for total energy intake (kcal/week). Model 1b was further adjusted for smoking status (never, current, former), alcohol intake (continuous, g/day), physical activity (≤ or > 3.5 h/week) and level of education (≤ 7 years, 8–10 years, > 10 years). We have previously observed differences in the underlying food pattern among those with the highest intake of red meat compared to those with the lowest intake of red meat in the Danish Diet, Cancer and Health Cohort [18]. Thus, Model 2 further adjusted for intake of whole grains, fruits, vegetables, dairy products, potatoes, fatty potatoes and soft drinks (all in g/day). Body Mass Index (BMI) (continuous, kg/m$^2$) and waist circumference adjusted for BMI (continuous, cm) may be potential mediators rather than confounders, hence these were further adjusted for in Model 3.

Because the biological mechanisms that link intake of red meat with type 2 diabetes, such as its content of nitrites and nitrates (in processed red meat) [19], may act independent of total energy intake, we removed total energy intake from Model 2 in a secondary analysis. The proportional hazards assumption was investigated using log–log plots. No deviation from proportionality was detected given covariates. Analyses were preformed using STATA 15, StataCorp, College Station, Texas. The figure was created in R 3.5.0, R Core Team, Vienna, Austria, using the ggepi package.

## Results

After exclusion of participants with cancer ($n = 569$), type 2 diabetes ($n = 1385$), cardiovascular disease ($n = 1306$) or missing covariates ($n = 630$) at entry into the study, we included 53,163 persons, of which 6879 developed type 2 diabetes during a median follow-up time of 15.4 years. Table 1 presents the participants' baseline characteristics. Participants who developed type 2 diabetes had a slightly higher intake of red meat (total, processed and unprocessed), were more likely to be men, smokers, have a higher BMI and waist circumference and less likely to have a longer education and be physically active than the cohort as a whole. Table 2 shows the distribution of baseline characteristics across quintiles of total red meat intake. Participants with the highest intake of total red meat tended to have a higher intake of processed red meat, unprocessed red meat, fish and total energy, were more likely to be current smokers, to have more than 10 years of education and to be more physically active compared to those with lower intakes. Baseline characteristics across quintiles of poultry and fish are shown in Supplemental Table 1 and Supplemental Table 2, respectively.

In age, sex and energy-adjusted models, substitution of 150 g red meat/week with 150 g/week poultry or 150 g fish/week was associated with a lower risk of type 2 diabetes (Model 1a; Fig. 1). After adjusting for potential confounders, the associations were slightly attenuated, but the association between substitution of total red meat with poultry and fish were still present (Model 1b; Fig. 1). When total red meat was divided into processed and unprocessed red meat, we observed a lower risk of type 2 diabetes for substitution of processed red meat with poultry or fish and for substitution of unprocessed red meat with fish but not poultry. When investigating low fat and high fat red meat, replacing both high fat and low fat red meat with poultry or fish was associated with a lower risk. Substitution of processed red meat with unprocessed red meat was associated with a lower risk of type 2 diabetes. After adjusting for the underlying food pattern, replacing total red meat, low fat red meat or high fat red meat with fish remained associated with a lower risk of type 2 diabetes, whereas similar substitutions with poultry, was not associated with type 2 diabetes (Model 2; Fig. 1). Replacing processed red meat with poultry, fish or replacing processed red meat with unprocessed red meat was associated with a lower risk of type 2 diabetes (Model 2, Fig. 1). These associations were still present after adjusting for BMI and waist circumference adjusted for BMI (Model 3, Fig. 1). Supplemental Table 3 shows the point estimates and 95% CIs for all the substitutions. Finally, the associations observed in Model 2 were also present when total energy intake was not included in the same model (results not shown).

**Table 1** Baseline characteristics of the total diet, cancer and health cohort and those who developed type 2 diabetes

| Characteristic[a] | Total cohort | Individuals who developed type 2 diabetes |
|---|---|---|
| No. of participants (*n*) | 53,163 | 6879 |
| Total red meat g/day, median (10–90 p) | 105.6 (54.2-–90.2) | 116.4 (60.9–202.3) |
| Processed red meat g/day, median (10–90 p) | 24.5 (7.9–59.0) | 28.5 (9.4–64.9) |
| Unprocessed red meat g/day, median (10–90 p) | 78.0 (40.5–140.3) | 84.3 (44.5–149.0) |
| Poultry g/day, median (10–90 p) | 17.9 (5.3–41.9) | 17.8 (5.3–42.1) |
| Fish g/day, median (10–90p) | 38.0 (16.1–75.3) | 38.3 (15.6–76.7) |
| Energy intake kJ/day, median (10–90p) | 8894.9 (6122.7–12,558.9) | 8963.2 (6172.0–12,707.0) |
| Sex | | |
| Women | 53.2 | 45.3 |
| Age at baseline in years, median (10–90 p) | 56 (51–63) | 56 (51–63) |
| BMI in kg/m$^2$, median (10–90 p) | 25.5 (21.4–31.0) | 28.2 (23.3–34.6) |
| Waist circumference in cm, median (10–90 p)[b] | | |
| Women | 79 (69–95) | 89 (74–108) |
| Men | 94 (84–106) | 101 (89–116) |
| Smoking status | | |
| Never | 35.7 | 30.9 |
| Former | 28.5 | 29.8 |
| Current | 35.8 | 39.3 |
| Alcohol in g/day, median (10–90 p) | 13.0 (1.63–47.2) | 12.6 (1.3–55.7) |
| Level of education | | |
| ≤ 7 years | 14.6 | 18.6 |
| 8–10 years | 23.1 | 22.3 |
| > 10 years | 62.3 | 59.1 |
| Physical activity | | |
| < 3.5 h/week | 60.2 | 66.1 |

*BMI* body mass index

[a]All values are specified in per cent unless otherwise stated

[b]28,262 women in the total cohort, 3114 women developed type 2 diabetes; 24,901 men in the total cohort, 3765 men developed type 2 diabetes

## Discussion

We found that substituting processed red meat with poultry and substituting total red meat, processed red meat, high fat or low fat red meat with fish was associated with a lower risk of developing type 2 diabetes in a European population. In addition, replacing processed red meat with unprocessed red meat was also associated with a lower risk of type 2 diabetes.

To investigate the risk of type 2 diabetes associated with substitutions between different types of meat products, we used a large cohort of middle-aged Danish men and women with a long follow-up. Selection bias is unlikely to have affected our results, as linkage to the Danish registries for participants' diabetes and vital status reduced loss to follow-up in this study. At baseline, the participants filled in a comprehensive validated FFQ that allowed a detailed classification of red meat subgroups. Nevertheless, FFQs are prone to measurement error. With prospectively recorded type 2 diabetes diagnoses, misclassification of the dietary intake is unlikely to be related to the development of type 2 diabetes. Thus, this misclassification would tend to lead to an underestimation of the true association. Incident type 2 diabetes cases were identified using complete data registries, not self-report, thus misclassification of type 2 diabetes is unlikely. Although residual confounding cannot be ruled out, we adjusted our analyses extensively for potential confounders and also investigated the potential mediating effects of BMI and waist circumference.

A previous study also based on the Diet, Cancer and Health cohort investigated patterns of food consumptions and found that intakes of red meat, poultry and fish are accompanied by slightly different underlying food patterns that might be differentially associated with type 2 diabetes. The food patterns showed that women who were in the lowest quintile of red meat intake consumed more whole-grain cereals, fruits, vegetables and dairy products and consumed less poultry, potatoes, fatty potatoes and soft drinks than women in the highest quintile of red meat intake. A similar

**Table 2** Baseline characteristics across quintiles of total red meat intake in the Diet, Cancer and Health cohort ($n = 53,163$)

| Characteristic[a] | Quintiles of total red meat intake | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Total red meat g/day, median (10–90 p) | 54.2 (27.9–66.7) | 81.7 (72.1–91.1) | 105.6 (95.9–116.4) | 135.7 (122.5–151.8) | 190.2 (161.8–266.1) |
| Processed red meat g/day, median (10–90 p) | 9.7 (2.9–20.3) | 18.1 (8.8–31.0) | 25.1 (12.5–42.4) | 34.5 (17.9–57.2) | 52.44 (26.4–94.6) |
| Unprocessed red meat g/day, median (10–90 p) | 41.5 (20.9–54.8) | 62.6 (49.6–75.1) | 80.14 (63.0–94.9) | 100.9 (77.7–121.3) | 140.0 (103.9–198.3) |
| Poultry g/day, median (10–90 p) | 13.6 (3.5–43.3) | 15.6 (5.3–37.7) | 17.6 (6.3–39.5) | 19.3 (6.6–41.1) | 22.5 (7.5–47.8) |
| Fish g/day, median (10–90 p) | 31.0 (12.3–65.0) | 35.0 (15.9–65.8) | 38.0 (17.4–70.6) | 41.1 (18.4–77.4) | 47.5 (19.5–91.6) |
| Energy intake MJ/d, median (10–90 p) | 0.7 (0.5–1.0) | 0.8 (0.6–1.0) | 0.9 (0.6–1.1) | 1.0 (0.7–1.2) | 1.1 (0.8–1.5) |
| Sex | | | | | |
| Women | 86.7 | 75.9 | 56.8 | 33.3 | 13.1 |
| Age at baseline in years, median (10–90 p) | 56 (51–63) | 56 (51–63) | 56 (51–63) | 55 (51–63) | 55 (51–62) |
| BMI in kg/m$^2$, median (10–90 p) | 24.5 (20.7–30.2) | 25.1 (21.3–30.7) | 25.5 (21.5–31.1) | 25.9 (21.9–31.3) | 26.3 (22.3–31.5) |
| Waist circumference in cm, median (10–90 p)[b] | | | | | |
| Women | 79 (69–94) | 80 (70–96) | 81 (70–98) | 82 (70–100) | 83 (71–103) |
| Men | 93 (82–105) | 94 (84–107) | 95 (84–108) | 95 (84–108) | 96 (84–109) |
| Smoking status | | | | | |
| Never | 43.0 | 40.7 | 37.2 | 31.4 | 26.4 |
| Former | 27.5 | 27.9 | 27.9 | 29.9 | 29.1 |
| Current | 29.5 | 31.4 | 34.9 | 38.7 | 44.5 |
| Alcohol in g/day, median (10-90p) | 9.0 (0.9–35.6) | 11.3 (1.5–40.0) | 13.0 (1.8–45.3) | 15.4 (2.3–55.2) | 19.0 (2.8–63.1) |
| Level of education | | | | | |
| ≤ 7 years | 14.5 | 16.2 | 14.9 | 14.0 | 13.4 |
| 8–10 years | 29.3 | 27.7 | 23.3 | 18.8 | 16.7 |
| > 10 years | 56.2 | 56.1 | 61.8 | 67.2 | 69.9 |
| Physical activity | | | | | |
| < 3.5 h/week | 55.0 | 59.2 | 62.7 | 62.5 | 61.5 |

*BMI* body mass index

[a] All values are specified in per cent unless otherwise stated

[b] 28,262 women; 24,901 men

pattern was found for men [18]. Differences between these patterns could be considered confounders or as part of a potential package of beneficial dietary factors that would be changed when substituting red and processed red meat with poultry or fish. After adjusting for this underlying food pattern, substitution of processed red meat with poultry, fish or unprocessed red meat was still associated with a lower risk whereas the association with type 2 diabetes for substitution of high fat or low fat red meat for poultry or fish disappeared. This may indicate that consuming more high fat or low fat red meat was related to an unhealthy pattern of food consumption. Thus, from a purely etiologic perspective, the main results were those of Model 2 (Fig. 1). However, when adjusting for other foods, the interpretation of the substitution models changes as we restrict the difference in the underlying dietary patterns that may be due to differences in intake of different types of meat products. Hence, from a public health perspective, the main results would be those of Model 1b (Fig. 1).

Several studies have found a high intake of red meat, especially processed red meat, to be associated with a greater risk of type 2 diabetes [3–5]. These results are in accordance with the results in our study, although they compare different levels of intake of red meat or changes in intake of red meat irrespective of the dietary components that replace red meat intake in iso-caloric models. Most previous cohort studies on red meat intake and risk of type 2 diabetes adjusted for total energy in the statistical models. This creates an unspecified substitution model in which the food item of interest is replaced by other energy-providing foods [20]. As these food items may be harmful, neutral or beneficial in relation to type 2 diabetes, the interpretation of the obtained risk

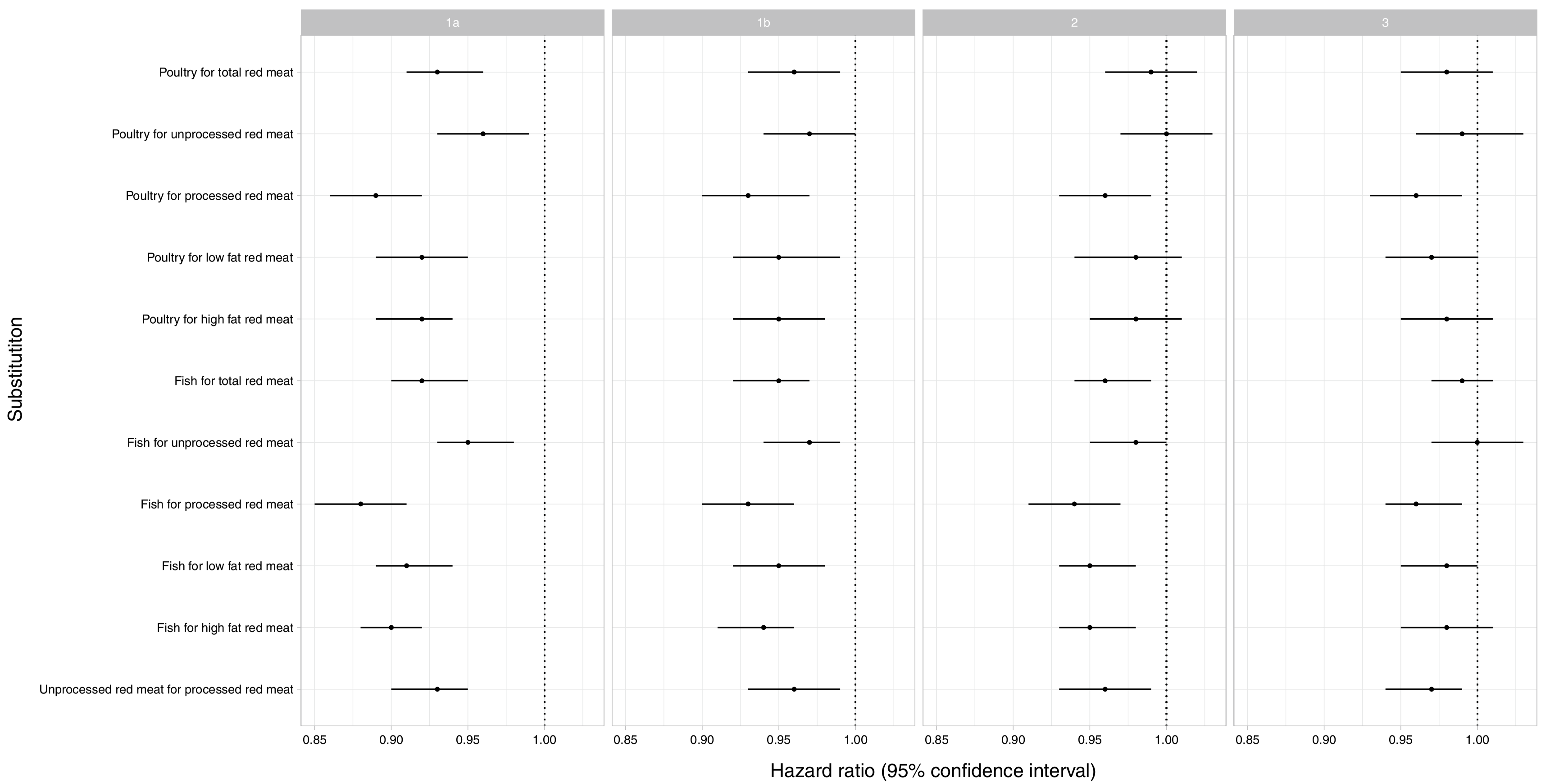


**Fig. 1** Forest plot of hazard ratios (95% confidence intervals) for type 2 diabetes associated with substitutions of 150 g/week of red meat (total, processed and unprocessed, high and low fat) with poultry or fish and processed red meat with unprocessed red meat in the Danish Diet, Cancer and Health cohort ($n=53,163$). Model 1a: Stratified by sex and tertiles of both date of enrolment and baseline age and adjusted for total energy intake. Model 1b: Further adjusted for smoking status, alcohol intake, physical activity and level of education. Model 2: Further adjusted for whole grains, fruits, vegetables, dairy products, potatoes, fatty potatoes and soft drinks. Model 3: Further adjusted for body mass index and waist circumference adjusted for body mass index

estimates is difficult. For instance, while some cohort studies have found an association between a high intake of red meat and risk of type 2 diabetes [21–24], others have only found an association for processed red meat [25, 26]. These differences may be due to the different methodological approaches taken, and to the studies deriving from different parts of the world with different background food cultures resulting in different substitutions. Results from unspecified substitution models for total meat, red meat, processed red meat and poultry have been published elsewhere [10]. We used substitution models wherein specified food substitutions are statistically modelled with regards to the risk of developing type 2 diabetes. Our results indicate that substituting processed red meat, high fat or low fat red meat, but not unprocessed red meat, with poultry or fish is associated with a lower risk of type 2 diabetes. This is in accordance with two cohort studies that also specified food substitutions, which found that replacing processed red meat with poultry or fish was associated with a lower risk of type 2 diabetes [4] and the metabolic syndrome [27]. In contrast to our results, Pan et al. [4] also found that replacing unprocessed red meat with poultry or fish was associated with a lower risk of type 2 diabetes. This may be due to differences in the underlying food pattern, as this was not adjusted for in their substitution analysis or differences in categorization of meat products. A recent randomized controlled trial found no difference in changes in blood glucose or insulin after intake of lean unprocessed red meat as part of a Mediterranean eating pattern compared to a similar diet but with poultry and other protein-rich foods [28]. This, together with our findings adjusted for the underlying dietary pattern, indicate that unprocessed red meat may not increase risk of type 2 diabetes, as part of a healthy eating pattern.

One plausible biological mechanism, whereby processed red meat could cause type 2 diabetes is through its content of nitrites and nitrates. Nitrites and nitrates are used in the processing of red meat. These convert into nitrosamines in the intestinal tract and are toxic to pancreatic beta cells, thereby increasing risk of developing type 2 diabetes [19]. Nitrates and their derivatives have been reported to cause metabolic disturbances in the main organs and tissues, resulting in amongst other cardiometabolic diseases a higher risk of developing type 2 diabetes [29]. As total energy intake is a function of body size, physical activity and metabolic efficiency [20], a higher intake of nitrites and nitrates, may be harmful, independent of differences in total energy intake. Thus, we also investigated the association not adjusted for total energy intake to explore the absolute exposure to nitrites and nitrates. These analyses showed the same pattern of association as the main analysis.

In conclusion, replacing processed red meat with poultry or replacing total red meat, processed red meat, low fat or high fat red meat with fish was associated with a lower risk of type 2 diabetes. Similarly, replacing processed red meat with unprocessed red meat was associated with a lower risk of type 2 diabetes. Adopting a diet that replaces red meat, particularly processed red meat, with poultry or fish may prevent development of type 2 diabetes.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** Relevant scientific and ethical committees and the Danish Data Protection Agency gave approval to the study.

**Informed consent** All study participants provided informed consent and approval to obtain relevant information from medical registers.

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