

Article

# Dietary Protein Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies

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**Abstract:** Recently, some studies have focused on the relationship between dietary protein intake and the risk of type 2 diabetes mellitus (T2DM), but the conclusions have been inconsistent. Therefore, in this paper, a systematic review and meta-analysis of cohort studies regarding protein consumption and T2DM risk are conducted in order to present the association between them. We searched the PubMed and Embase databases for cohort studies on dietary protein, high-protein food consumption and risk of T2DM, up to July 2017. A summary of relative risks was compiled by the fixed-effect model or random-effect model. Eleven cohort studies regarded protein intake and T2DM (52,637 cases among 483,174 participants). The summary RR and 95% CI (Confidence Interval) of T2DM was 1.12 (1.08–1.17) in all subjects, 1.13 (1.04–1.24) in men, and 1.09 (1.04–1.15) in women for total protein; 1.14 (1.09–1.19) in all subjects, 1.23 (1.09–1.38) in men, and 1.11 (1.03–1.19) in women for animal protein; 0.96 (0.88–1.06) in all subjects, 0.98 (0.72–1.34) in men, and 0.92 (0.86–0.98) in women for plant protein. We also compared the association between different food sources of protein and the risk of T2DM. The summary RR (Relative Risk) and 95% CI of T2DM was 1.22 (1.09–1.36) for red meat, 1.39 (1.29–1.49) for processed meat, 1.03 (0.89–1.17) for fish, 1.03 (0.64–1.67) for egg, 0.89 (0.84–0.94) for total dairy products, 0.87 (0.78–0.96) for whole milk, 0.83 (0.70–0.98) for yogurt, 0.74 (0.59–0.93) in women for soy. This meta-analysis shows that total protein and animal protein could increase the risk of T2DM in both males and females, and plant protein decreases the risk of T2DM in females. The association between high-protein food types and T2DM are also different. Red meat and processed meat are risk factors of T2DM, and soy, dairy and dairy products are the protective factors of T2DM. Egg and fish intake are not associated with a decreased risk of T2DM. This research indicates the type of dietary protein and food sources of protein that should be considered for the prevention of diabetes.

**Keywords:** protein; diabetes; systematic review; meta-analysis

## 1. Introduction

Type 2 diabetes is rapidly increasing in the world. Ninety percent of patients with diabetes have type 2 diabetes [1]. Type 2 diabetes patients are at increased risk of cardiovascular disease, neuropathies, nephropathies, gangrene, and leg ulcers [2]. From the date of diagnosis, patients with T2DM have to face at least eight years of economic burden [3].

Evidence suggests that dietary factors may influence the risk of T2DM [4]. Many previous studies have focused on dietary macronutrient intake associated with diabetes risk [5,6], but the main content of those studies was carbohydrates and fats. Recently, some studies focused on the relationship

between dietary protein intake and the risk of T2DM. High-protein diets have shown beneficial effects on glucose homeostasis in some short-term trials [7,8]. Subsequent longitudinal studies have evaluated the associations between dietary protein intake and risk of T2DM as well as the type of dietary protein and risk of T2DM. A study focusing on the Mediterranean islands showed that animal protein consumption was associated with a higher prevalence of diabetes among the elderly, and a recommended range of protein from plant sources appears to be considerably protective [9]. Some other publications have also reported an increased risk of T2DM with a high intake of total protein [10–14] and animal protein [10,13–15], and a decreased risk of T2DM with a high intake of plant protein [14,15]. However, there have been no reports that show an association between T2DM and total protein [15–18], animal protein [16–18] and plant protein intake or a high risk of T2DM with a high intake of plant protein [10,13]. The association between dietary protein and T2DM is still debated.

In the present study, we conducted a systematic review and meta-analysis of cohort studies to clarify the association of protein consumption with risk of T2DM. In order to provide a better dietary instruction for the lay public, we also conducted a systematic review and meta-analysis of cohort studies to study the association between different kinds of high-protein food and the risk of T2DM.

## 2. Materials and Methods

### 2.1. Search Strategy

We searched relevant studies from the Embase and PubMed electronic databases from their starting dates to July 2017.

Protein: search items included: ‘dietary protein’ or ‘protein intake’ or ‘plant protein’ or ‘animal protein’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Meat: search items included: ‘red meat’ or ‘processed meat’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Fish: search items included: ‘fish’ or ‘seafood’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Egg: search items included: ‘egg’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Dairy: search items included: ‘dairy’ or ‘milk’ or ‘dairy product’ or ‘yogurt’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Soy: search items included: ‘soy’ or ‘legume’ or ‘soy product’ or ‘food’ and ‘diabetes’ or ‘diabetes mellitus’ or ‘T2DM’ and ‘population’ or ‘human’.

Eligible studies are selected by further manual scanning of all included studies and relevant reference lists.

### 2.2. Study Selection

All included studies should match the following criteria: (1) the study must have a cohort design; (2) the endpoint of the study was the incidence or mortality of the T2DM; (3) the study had to report risk ratios and the results had to be within a 95% CI in the paper (if this not clear, we requested this information from the authors); and (4) the study had to show the participants’ intake of dietary protein or other high-protein foods such as meat, fish, egg, dairy, soy.

### 2.3. Data Extraction

We extracted the following information from each publication we selected: first the author of the publication, publication year, the country where the study was conducted, the number of the samples and cases, T2DM diagnosis and criteria, the year the study began and finished, the years of follow-up, the methods of diet exposure assessment, the RRs and 95% CI, and the adjustment factors (Tables S1–S12).

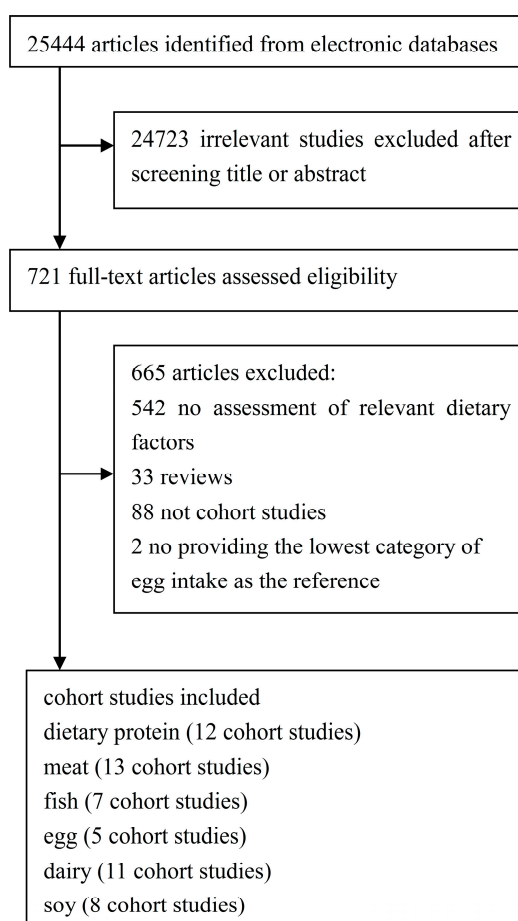
## 2.4. Statistical Methods

We used effect models to calculate the summary RRs and 95% confidence to compare the highest dietary protein consumption with the lowest dietary protein consumption [19]. Two-sided  $p < 0.05$  was considered statistically significant. The black square in the forest plots represents the weight contribution of every study. In order to evaluate the extent of variability, the  $I^2$ -test statistic was adapted to estimate the heterogeneity [20]. When  $I^2 < 50\%$  and  $p > 0.05$ , there was no heterogeneity; we used the fixed-effect model. The random-effect model was selected when  $I^2 > 50\%$  or  $p < 0.05$ . We used the Egger linear regression test and Begg rank correlation test to search for publication bias. When  $p > 0.05$ , there was no publication bias. Comprehensive Meta-Analysis V2 was employed for data analysis.

## 3. Results

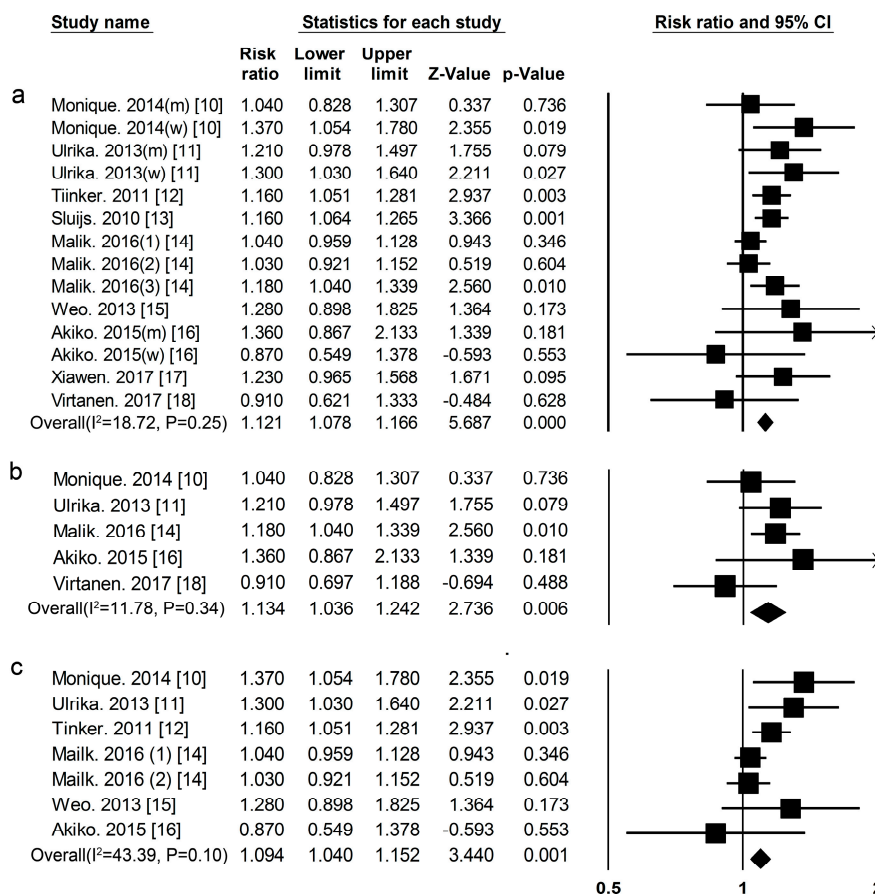
### 3.1. Dietary Protein Intake and Risk of T2DM

We included 11 cohort studies in the analysis (Figure 1, Tables S1 and S2). Six of the studies were from the United States, three from Europe, one from Asia, one from Melbourne, one from Finland.



**Figure 1.** Flow chart for study selection.

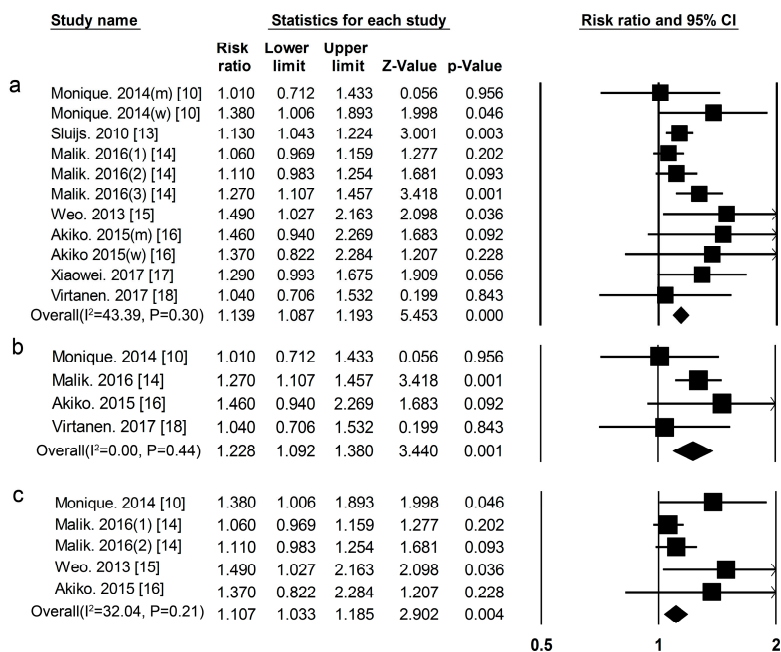
**Total Protein** Eleven cohort studies [10–18] researched the association between total protein intake and the risk of T2DM, included 52,637 cases among 483,174 participants. The summary RR and 95% CI for high vs. low values of all studies was 1.12 (1.08–1.17) (Figure 2a), ( $I^2 = 18.72$ ,  $p = 0.25$ ) in all subjects, 1.13 (1.04–1.24) (Figure 2b) ( $I^2 = 11.78$ ,  $p = 0.34$ ) in men, and 1.09 (1.04–1.15) (Figure 2c) ( $I^2 = 43.39$ ,  $p = 0.10$ ) in women.



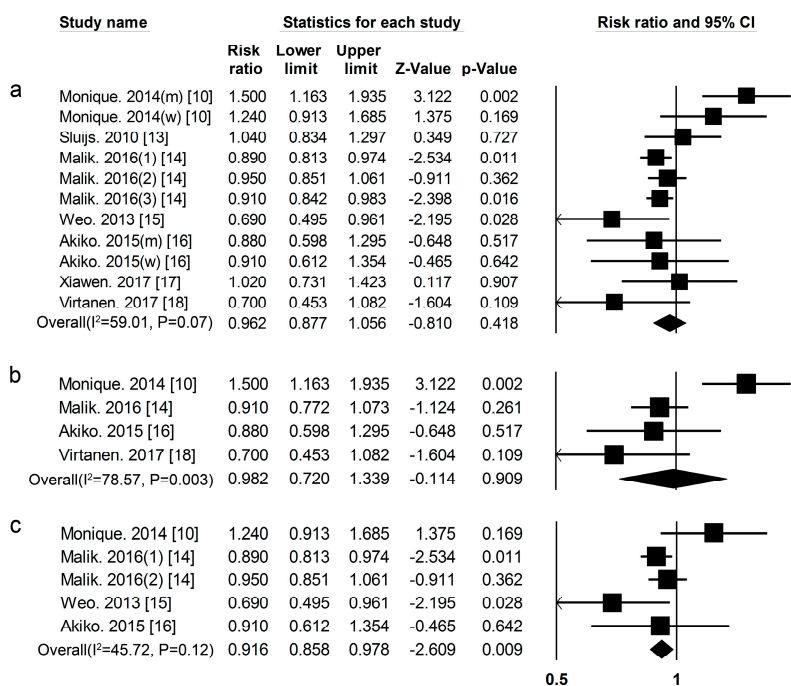
**Figure 2.** Total protein and type 2 diabetes relative risks(RRs) for (a) the highest vs. the lowest intake in all subjects and (b) the highest vs. the lowest intake in men (c) the highest vs. the lowest intake in women. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

**Animal Protein** Nine cohort studies [10,13–18] researched the association between animal protein intake and the risk of T2DM. This included 31,557 cases among 380,689 participants. The summary RR and 95% CI for high vs. low values of all studies was 1.14 (1.09–1.19) (Figure 3a), ( $I^2 = 43.39$ ,  $p = 0.30$ ) in all subjects, 1.23 (1.09–1.38) (Figure 3b), ( $I^2 = 0.00$ ,  $p = 0.44$ ) in men, and 1.11 (1.03–1.19) (Figure 3c), ( $I^2 = 32.04$ ,  $p = 0.21$ ) in women.

**Plant Protein** Nine cohort studies [10,13–18] researched the association between plant protein and the risk of T2DM, included 31,817 cases among 381,879 participants. The summary RR and 95% CI for high vs. low values of all studies was 0.96 (0.88–1.06) (Figure 4a), ( $I^2 = 59.01$ ,  $p = 0.07$ ) in all subjects. We used a sensitivity analysis to exclude the most influential studies: the summary RR and 95% CI ranged from 0.92 (0.87–0.98) when the European men’s study [10] was excluded to 0.98 (0.87–1.10) when the USA men’s study [14] was excluded. The heterogeneity was partly because of the European men’s study [10] and when we excluded this study, there was moderate heterogeneity ( $I^2 = 14.85$ ,  $p = 0.31$ ). The summary RR and 95% CI was 0.98 (0.72–1.34) (Figure 4b) ( $I^2 = 78.57$ ,  $p = 0.003$ ) in men. A sensitivity analysis was used to exclude the most influential studies: the summary RR and 95% CI ranged from 0.88 (0.76–1.02) when the European study [10] was excluded to 1.07 (0.75–1.52) when the Finnish men’s study [18] was excluded. The heterogeneity in men still existed after sensitivity analysis, partly because there were only four cohort studies about the association between plant protein intake and the risk of T2DM in men. The summary RR and 95% CI was 0.92 (0.86–0.97) (Figure 4c) ( $I^2 = 45.72$ ,  $p = 0.12$ ) in women.



**Figure 3.** Animal protein and type 2 diabetes RRs for (a) the highest vs. the lowest intake in all subjects and (b) the highest vs. the lowest intake in men (c) the highest vs. the lowest intake in women. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

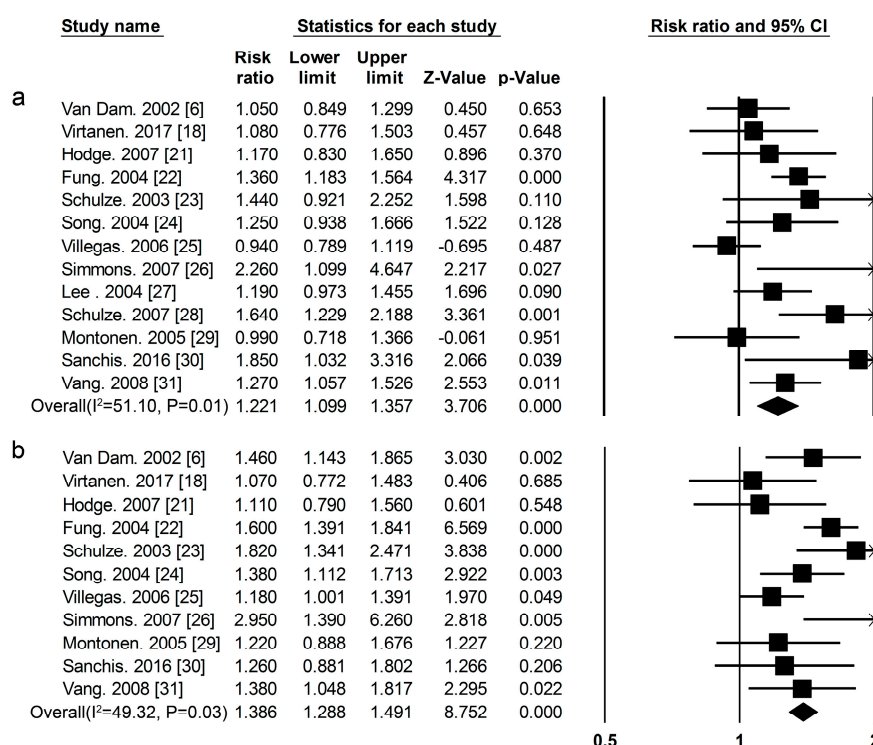


**Figure 4.** Plant protein and type 2 diabetes RRs for (a) the highest vs. the lowest intake in all subjects and (b) the highest vs. the lowest intake in men (c) the highest vs. the lowest intake in women. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

### 3.2. High-Protein Food and Risk of T2DM

We also conducted a systematic review and meta-analysis of cohort studies to clarify the association with high dietary protein food consumption and the risk of T2DM.

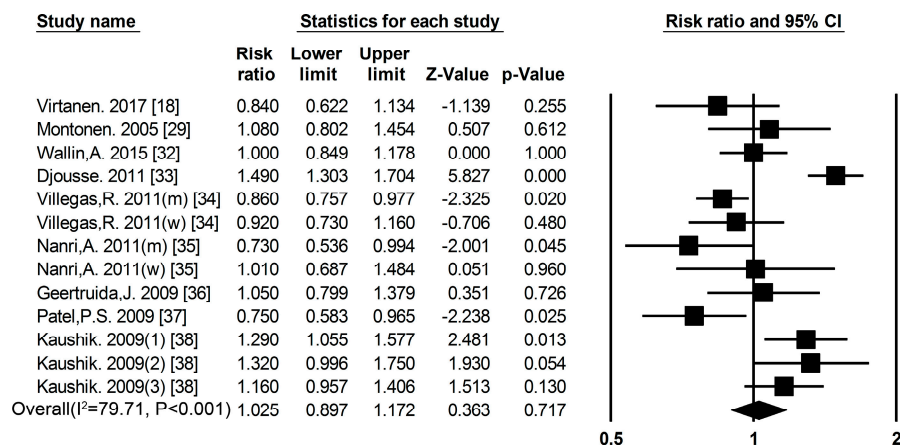
**Red Meat** Thirteen cohort studies [6,18,21–31] researched the association between red meat consumption and the risk of T2DM (Figure 1, Tables S3 and S4). The summary RR and 95% CI for high vs. low red meat consumption was 1.22 (1.09–1.36) (Figure 5a) ( $I^2 = 51.11, p = 0.01$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR and 95% CI ranged from 1.20 (1.07–1.35) when the U.S. Study [24] was excluded to 1.26 (1.15–1.38) when the Chinese study [25] was excluded. The heterogeneity was partly because of the Chinese study [25], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 27.68, p = 0.17$ ).



**Figure 5.** (a) Red meat (b) processed meat and type 2 diabetes RRs for the highest vs. the lowest intake in all subjects. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

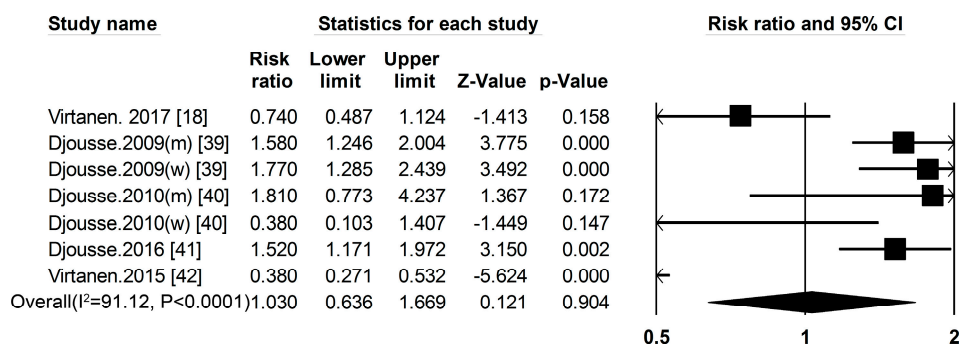
**Processed Meat** Eleven cohort studies [6,18,21–26,29–31] researched the association between processed meat consumption and the risk of T2DM (Figure 1, Tables S3 and S4), the summary RR and 95% CI for high vs. low of processed meat consumption was 1.39 (1.29–1.49) (Figure 5b) ( $I^2 = 49.32, p = 0.03$ ).

**Fish** Nine cohort studies [18,29,32–38] researched the association between fish consumption and the risk of T2DM (Figure 1, Tables S5 and S6), the summary RR and 95% CI for high vs. low values of fish consumption was 1.03 (0.89–1.17) (Figure 6) ( $I^2 = 79.71, p < 0.001$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.99 (0.89–1.10) when the American study [33] was excluded to 1.50 (0.92–1.20) when the Japanese study [35] was excluded. The heterogeneity was partly because of the Japanese study [35], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 79.41, p < 0.001$ ).



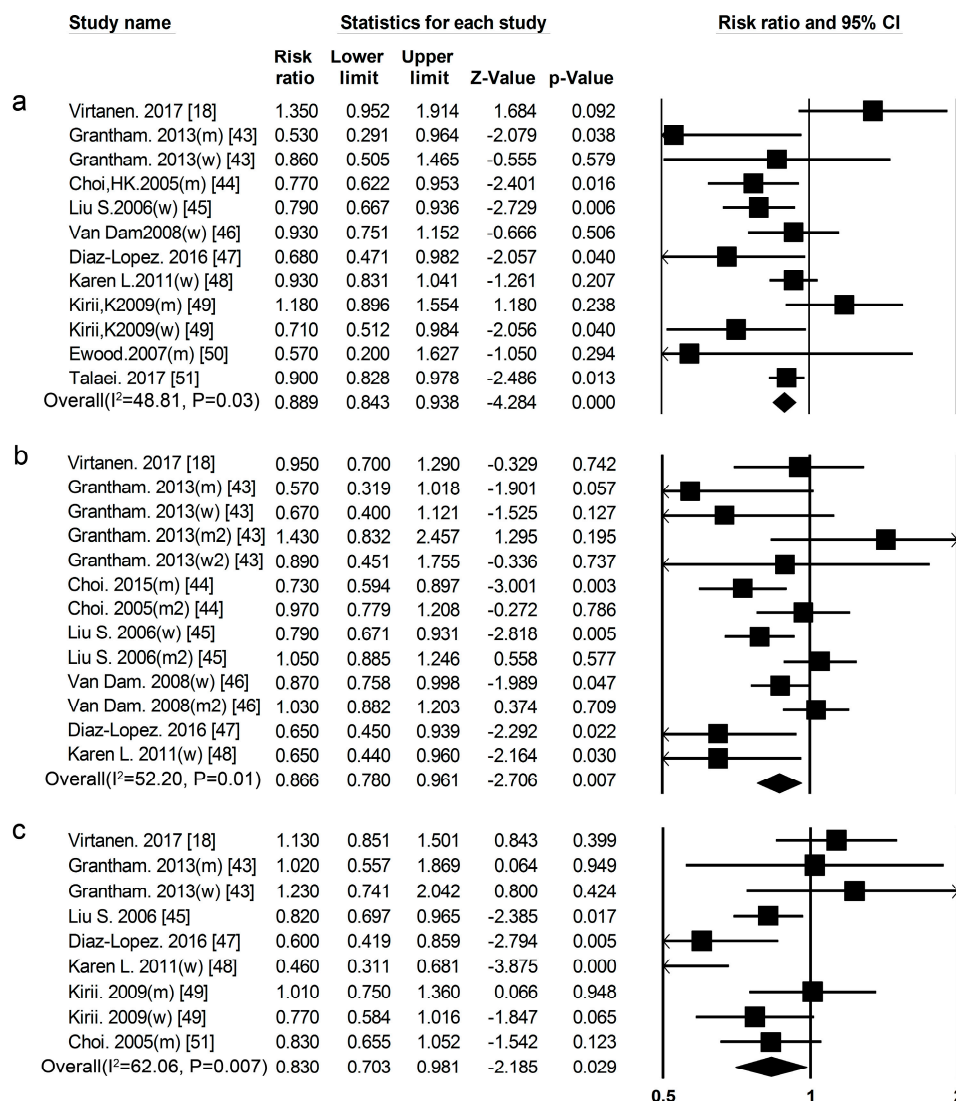
**Figure 6.** Fish and type 2 diabetes RRs for the highest vs. the lowest intake in all subjects. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

**Egg** Five cohort studies [18,39–42] researched the association between egg consumption and the risk of T2DM (Figure 1, Tables S7 and S8), the summary RR and 95% CI for high vs. low of egg consumption was 1.03 (0.64–1.67) (Figure 7) ( $I^2 = 91.12$ ,  $p < 0.001$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.97 (0.49–1.88) when the Lithuanian study [39] was excluded to 1.57 (1.30–1.89) when the Finnish study [42] was excluded. The heterogeneity was partly because of the Finnish study [42], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 69.43$ ,  $p = 0.06$ ).



**Figure 7.** Egg and type 2 diabetes RRs for the highest vs. the lowest intake in all subjects. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

**TotalDairyProduct Consumption** Eleven cohort studies [18,43–52] researched the association between total dairy product consumption and the risk of T2DM (Figure 1, Tables S9 and S10), the summary RR and 95% CI for high vs. low total dairy product consumption was 0.89 (0.84–0.94) (Figure 8a) ( $I^2 = 48.81$ ,  $p = 0.03$ ).



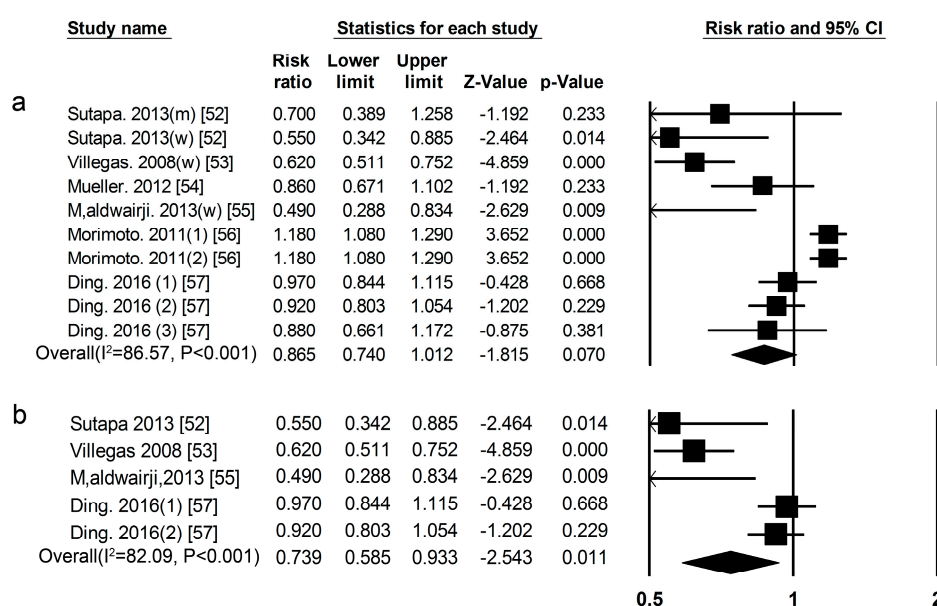
**Figure 8.** (a) Total dairy products (b) whole milk (c) yogurt and type 2 diabetes RRs for the highest vs. the lowest intake in all subjects. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

**Whole Milk** Seven cohort studies [18,43–48] researched the association between whole milk consumption and risk of T2DM (Figure 1, Tables S9 and S10), the summary RR and 95% CI for high vs. low of fat dairy consumption was 0.87 (0.78–0.96) (Figure 8b) ( $I^2 = 52.20$ ,  $p = 0.01$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.85 (0.76–0.94) when the American study [46] was excluded to 0.89 (0.80–0.99) when the Japanese study [44] was excluded. The heterogeneity was partly because of the American study [46], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 46.87$ ,  $p = 0.04$ ).

**Yogurt** Seven cohort studies [18,43,44,47–49] researched the association between yogurt consumption and the risk of T2DM (Figure 1, Tables S9 and S10). The summary RR for high vs. low yogurt consumption was 0.83 (0.70–0.98) (Figure 8c) ( $I^2 = 62.06$ ,  $p = 0.01$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.81 (0.67–0.97) when the Japanese study [49] was excluded to 0.88 (0.76–1.00) when USA study [48] was excluded. The heterogeneity was partly because of the Japanese study [49], and when we excluded this study there was moderate heterogeneity ( $I^2 = 40.61$ ,  $p = 0.11$ ).



**Soy** Eight cohort studies [52–57] researched the association between legume consumption and the risk of T2DM (Figure 1, Tables S11 and S12), the summary RR for high vs. low soy consumption was 0.87 (0.74–1.01) (Figure 9a) ( $I^2 = 86.57, p < 0.01$ ). We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.82 (0.68–0.98) when the American study [56] was excluded to 0.93 (0.81–1.06) when the Chinese study [53] was excluded. The heterogeneity was partly because of the American study [56], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 69.34, p < 0.01$ ). However, the summary RR for high vs. low soy was 0.74 (0.59–0.93) (Figure 9b), ( $I^2 = 82.09, p < 0.001$ ) in women. We used a sensitivity analysis to exclude the most influential studies: the summary RR ranged from 0.66 (0.49–0.90) when the American study [57] was excluded to 0.81 (0.65–1.00) when the Chinese study [54] was excluded. The heterogeneity was partly because of the American study [57], and when we excluded this study, there was moderate heterogeneity ( $I^2 = 0.00, p = 0.67$ ).



**Figure 9.** Soy and type 2 diabetes RRs for (a) the highest vs. the lowest intake in all subjects and (b) the highest vs. the lowest intake in women. The RR of each study is represented by a square, 95% CI are represented by the horizontal lines, and the diamond represents the estimate and its 95% CI.

### 3.3. Publication Bias

No significant publication bias was detected in the Begg-Mazumdar’s test and Egger’s test of our meta-analyses, provided in Table 1.

**Table 1.** Public bias and meta-analysis.

Proteins and Foods Sources	Begg-Mazumdar’s Test	Egger’s Test
Total protein (all)	0.74	0.38
Total protein (men)	0.46	0.74
Total protein (women)	0.55	0.33
Animal protein (all)	0.64	0.07
Animal protein (men)	0.73	0.57
Animal protein (women)	0.22	0.10
Plant protein (all)	0.76	0.50
Plant protein (men)	0.73	0.90
Plant protein (women)	0.81	0.91

Table 1. Cont.

Proteins and Foods Sources	Begg-Mazumdar's Test	Egger's Test
Red meat	0.30	0.33
Processed meat	0.88	0.99
Fish	0.58	0.43
Total dairy product	0.45	0.43
Whole milk	0.67	0.35
Yogurt	0.92	0.99
Egg	0.23	0.50
Soy	0.46	0.13

#### 4. Discussion

According to the results of this meta-analysis, the intake of total protein and animal protein was associated with a high risk of T2DM both in males and females. The intake of plant protein was associated with low risk of T2DM in females, but not in males. In high animal protein food, red meat, and processed meat were associated with a high risk of T2DM in all subjects, while total dairy products, low-fat dairy, and yogurt were associated with a low risk of T2DM in all subjects, and egg and fish were not associated with a decreased risk of T2DM. In high plant protein food, soy was associated with a low risk of T2DM in females.

Higher intake of dietary protein is often associated with lifestyles, including physical activity, body weight, smoking, drinking. For example, we already know that overweight and obesity are risk factors for T2DM, and a meta-analysis showed that each unit increase of BMI would increase the risk for T2DM by approximately 20% [58]. In our meta-analysis, most studies were adjusted for known influencing factors, including age, BMI (Body Mass Index), smoking, physical activity, alcohol consumption, energy intake, family history of T2DM and menopausal status (among women).

The statistical power of the results could be significantly increased as the number of studies and the sample size increase, but it could also lead to heterogeneity. Some heterogeneity was due to different participants' characteristics and regions, and different dietary assessment methods. Thus, heterogeneity is usually used to explain the study characteristics and is difficult to interpret. In our study, the heterogeneities of total protein and animal protein were in the acceptable range, but the heterogeneity of plant protein was outside of the range. We found that the European study [10] contributed to the heterogeneity. When this study was excluded, the heterogeneities of both the overall and subgroup analyses were much lower. The reason that the European study [10] had inconsistent results compared with other studies was not clear, but it could partly be due to the participants in this study having a lower plant protein intake than other studies [13–18]. For red meat and processed meat, we found that the Chinese study [25] contributed to the heterogeneity. When this study is excluded, the heterogeneities were much lower. The reason that the Chinese study [25] had inconsistent results may be due to the participants in this study having a lower meat intake than other participants [6,18,21–24,26–31]. For fish, we found that the Japanese study [35] contributed to the heterogeneity, but the heterogeneity was not moderate when it was excluded, which means the association between fish and T2DM needs further refinement. For egg, we found that the Finnish study [42] contributed to the heterogeneity. When this study is excluded, the heterogeneity was much lower. The reason why the Finnish study [42] had inconsistent results compared with other studies was not clear, but it could partly be due to the participants in this study being older than the other studies [18,39–41]. For whole milk, we found that the American study [46] contributed to the heterogeneity, and the heterogeneity was moderate when it was excluded. The reason why the American study [46] had heterogeneity may be due to the milk intake of black women in America being different from the participants of other studies' [18,43–45,47,48]. For yogurt, the Japanese study [49] contributed to the heterogeneity. The reason why the Japanese study [49] had inconsistent results was

not clear, but it could partly be due to the female participants in this study being older than other studies [18,43,44,47,48].

As meta-analysis is based on published studies, the publication bias affect is inevitable. It is particularly important to evaluate publication bias. In our meta-analysis, we used the Egger linear regression test and Begg rank correlation test to determine publication bias, and we found that there was no publication bias in our study.

Dietary protein and amino acids are involved in the modulations of insulin sensitivity and glucose metabolism. However, the results from human studies were still inconsistent. Some studies showed that high intake of dietary protein had negative effects on glucose homeostasis by facilitating insulin resistance and increasing gluconeogenesis [7,59,60]. Amino acid signaling may facilitate insulin resistance, by activation of the mammalian target of rapamycin (mTOR), a nutrient sensor that operates a detrimental feedback loop toward insulin receptor substrate 1 signaling [61–64]. Moreover, amino acids may also inhibit glucose uptake through phosphorylation of downstream factors of the insulin signaling cascade by the translation initiation factor serine-kinase-6-1 [63,65]. On the other hand, *in vivo* and *in vitro* studies also demonstrated that amino acids play a beneficial role in glucose homeostasis by modulating insulin action on hepatic glucose production and muscle glucose transport, secretion of glucagon and insulin, as well as various tissues gene and protein expression [64,66]. One of the possible mechanisms that might explain this was that higher protein reduced the amount of carbohydrate intake under isoenergy conditions and thus a smaller amount of glucose was absorbed after ingestion of the meals, with the consequence of a reduced store of glycogen and, thus, a decrease in glycogenolysis rate [67,68]. The other possible causal mechanism was amino acids stimulating the insulin secretion to intervene in the glucose metabolism and serve as substrates for gluconeogenesis; thus, increased gluconeogenesis could stimulate insulin secretion, which might prevent hyperglycemia [69]. Additionally, some scientists think that different qualities rather than quantities of proteins play a more important role in insulin resistance [69]. Our study supported the hypothesis that animal proteins caused a high risk of T2DM in males and females, and plant proteins were protection factors of T2DM in females. We can find some support for this from the literature. The abundance in certain amino acids are different between animal proteins and plant proteins. This may contribute to the different effects between them on the risk of T2DM. Typically, plant protein contains lower levels of the branched chain amino acids leucine, isoleucine and valine and of the sulfur amino acid methionine as compared with animal proteins [70]. Branched chain amino acids and higher methionine intake have been associated with insulin resistance and type 2 diabetes [71,72]. In addition, dietary glycine is also mainly consumed from animal-based foods and some cohort studies have shown that glycine was positively associated with T2DM, and hypertension [72,73]. On the other hand, dietary glutamic acid, an amino acid that is mainly consumed from plant protein was found to be inversely associated with risks of hypertension and arterial stiffness [73,74]. So far, three intervention studies have compared the effects of animal protein with plant protein meals on glycaemic variables in people with T2DM, but they were obtained from three different results [75–77]. This should be further investigated in future studies.

From the current literature available, the inconsistency in association between plant protein and T2DM was probably due to gender difference. The negative association between plant protein or soy and T2DM was observed mainly in women, while most of the studies in men found null results. Therefore, results from all subjects without considering gender difference were different and the proportion of women in the study may influence the results. However, the exact mechanism is unclear.

In order to further refine and compare the association between different food sources of protein and T2DM, and facilitate dietary guidance, we have analyzed the relationship between different high-protein food and the risk of type 2 diabetes. We found that different high-protein foods play different roles in T2DM, even if they are all animal-based foods. Our results indicated that the intake of red meat and processed meat are risk factors for T2DM. They are also positively associated with weight gain [78], stroke [79], coronary heart disease [80] and mortality [81]. First, the increased meat protein

may increase iron load, which was associated with the increased risk of T2DM [82]. Moreover, the other nutrients in red and processed meat, including nitrites and advanced glycation end products, were also thought to mediate the association between meat intake and the risk of T2DM [83]. The relationship between egg consumption and T2DM was not clear. Some studies have shown that egg intake was associated with a lower risk of T2DM [42]. Some research showed that egg consumption was positively associated with the risk of T2DM in our study [39,84,85], and this result was supported by the AHA dietary guidelines which advise restricted egg consumption in adults for preventing cardiometabolic diseases [86–88]. We found that total dairy products, whole milk, and yogurt intake were protective factors for T2DM. Some studies showed that milk proteins, like whey protein, may enhance satiety and reduce risk factors for T2DM [89]. The calcium and vitamin D in milk and its products may also contribute to its beneficial effects on T2DM [90]. In our study, fish consumption was not associated with decreased risk of T2DM. This result may partly relate on the increase in plasma selenium level with the increment of fish intake, which may increase the risk of diabetes [91,92]. The relationship between fish intake and the risk of T2DM needs further refinement. For high plant protein-based foods, there was a negative association between soy consumption and the risk of T2DM in this study. Soy protein may inhibit insulin secretion from pancreatic  $\beta$  cells or inhibit lipogenesis and enhance lipolysis in the adipose and liver to reduce adiposity [93]. This protective effect may also be associated with biologically active ingredients such as phytoestrogen in soybeans [94].

Our meta-analysis also had limitations. First, publications into our research were adjusted for BMI, but some studies had measurement errors because of self-reporting of height and weight, resulting in the BMI relying on self-reporting, which could lead to confounding results. Second, some important factors that influence T2DM such as fiber, lipids, and carbohydrates, were only adjusted in some of these studies, which may also lead to confounding results. Additionally, limitations might be due to temporal bias. Studies with longer follow-up might be less influenced by temporal bias. In our studies, the follow-up period of each research study was different, so the temporal bias might impact the association between dietary protein intake and the risk of T2DM.

## 5. Conclusions

In summary, we found that total protein and animal protein consumption were the risk factors for T2DM, and plant protein was the protective factor for T2DM in women, but not in men. We also found that different high-protein foods have a different effect on T2DM risk, even if they all belong to animal proteins. These results underline the significance of taking into account what kind of dietary protein and food sources of protein are recommended for the prevention of diabetes.

**Supplementary Materials:** The following are available online at [www.mdpi.com/2072-6643/9/9/982/s1](http://www.mdpi.com/2072-6643/9/9/982/s1), Table S1: Characteristics of participants and follow-up in included studies of protein consumption in relation to the risk of T2DM, Table S2: Prospective cohort studies of protein consumption and type 2 diabetes, Table S3: Characteristics of participants and follow-up in included studies of meat consumption in relation to the risk of T2DM, Table S4: Prospective cohort studies of meat consumption and type 2 diabetes, Table S5: Characteristics of participants and follow-up in included studies of fish consumption in relation to the risk of T2DM, Table S6: Prospective cohort studies of fish consumption and type 2 diabetes, Table S7: Characteristics of participants and follow-up in included studies of egg consumption in relation to risk of T2DM, Table S8: Prospective cohort studies of egg consumption and type 2 diabetes, Table S9: Characteristics of participants and follow-up in included studies of dairy consumption in relation to the risk of T2DM, Table S10: Prospective cohort studies of dairy consumption and type 2 diabetes, Table S11: Characteristics of participants and follow-up in included studies of soy consumption in relation to the risk of T2DM, Table S12: Prospective cohort studies of soy consumption and type 2 diabetes.

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**Author Contributions:** Shuang Tian analyzed the data, and wrote the manuscript. Qian Xu, Ruyue Jiang and Tianshu Han supervised the analysis, reviewed the manuscript, and contributed to the discussion. Lixin Na and Changhao Sun developed the study design, acquired funding and administrated the project.

**Conflicts of Interest:** The authors declare no conflicts interest.

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