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SYSTEMATIC REVIEWS AND META-ANALYSES

Associations of dietary protein intake with all-cause, cardiovascular disease, and cancer mortality: A systematic review and meta-analysis of cohort studies

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Abstract *Background and aims:* The relationships between dietary protein intake and risk of all-cause, cardiovascular disease (CVD), and cancer mortality are still unclear. We conducted a systematic review with meta-analysis of cohort studies to summarize the evidence.
Methods and results: We searched PubMed and Web of Science for relevant studies through February 2020. The associations of total, animal, and plant proteins with all-cause, CVD, and cancer mortality were evaluated. Study-specific relative risks (RR) were pooled using the fixed effect model when no significant heterogeneity was detected; otherwise the random effect model was employed. Twelve cohort studies were eligible for the study. Increased total protein showed no clear association with risk of all-cause, CVD, and cancer mortality. In the stratified analysis by protein sources, higher plant protein intake was associated with a reduced risk of all-cause mortality (highest vs lowest intake: RR = 0.92; 95% CI: 0.88, 0.96; each 3% increment of intake: RR = 0.97; 95% CI: 0.94, 0.99), and may be associated with a reduced risk of CVD mortality (highest vs lowest intake: RR = 0.90; 95% CI: 0.80, 1.01; each 3% increment of intake: RR = 0.95; 95% CI: 0.91, 0.99). Moreover, higher intake of animal protein may be associated with an increased risk of CVD mortality (highest vs lowest intake: RR = 1.11; 95% CI: 1.01, 1.22; each 3% increment of intake: RR = 1.02; 95% CI: 0.98, 1.06).
Conclusion: This study demonstrates that higher plant protein intake is associated with a reduced risk of all-cause and CVD-related mortality. Persons should be encouraged to increase their plant protein intake to potentially decrease their risk of death.

Introduction

Cardiovascular disease (CVD) and cancer are the most frequently diagnosed non-communicable diseases and the leading cause of death worldwide [1]. Primary prevention of CVD and cancer death is therefore a critical public health challenge worldwide. Diet is one of the most

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important modifiable risk factors for CVD and other noncommunicable diseases.

Dietary protein is one of the most widely consumed macronutrition in the world [2,3]. Given its popularity worldwide, even small effects of dietary protein on individuals may exert a large effect on public health [2,4]. The US National Academy of Medicine sets a wide range for acceptable protein intake from 10% to 35% of calories each day [5]. Beyond that, there is relatively little solid information on the ideal amount of protein in the diet or the healthiest target for calories contributed by protein. In a US cohort of more than 130,000 men and women who were followed for up to 32 years, the percentage of calories from total protein intake was not related to overall mortality or to specific causes of death [6]. Two large prospective cohort studies suggested that higher intake of total protein was associated with a lower risk of all-cause mortality [7,8].

Of note, the source of protein was important. Animal-based foods such as meat, poultry, fish, eggs, and dairy foods tend to be main sources of animal protein, while plant-based foods such as fruits, vegetables, grains, nuts, and seeds tend to be main sources of plant protein. Available evidence indicates that it is the source of protein, rather than the amount of protein, that likely makes a difference for a person's health [9–11]. Previous studies of the association between animal and plant protein intakes and risk of all-cause, CVD, and cancer mortality have produced inconsistent results [6–8,10–15]. A secondary analysis of the PREDIMED trial suggested that a higher consumption of animal protein was associated with an increased risk of CVD and all-cause mortality when protein substituted carbohydrates or fat [14]. Moreover, two prospective cohort studies in US and Japanese population found that higher plant protein intake was associated with a lower risk of CVD and all-cause mortality [6,11]. However, such significant associations were not observed in other previous cohort studies [10,12,14,16].

Since the relationships between total, animal, and plant protein intakes and risk of all-cause, CVD, and cancer mortality were still unclear, we conducted a systematic review with a meta-analysis of cohort studies to assess these associations in general population.

Methods

Ethical review

Because this was a study-level meta-analysis, and did not involve collection and analysis of any individual-level data, ethical approval was not sought for this study.

Study selection strategy

This systematic review of cohort studies was reported using MOOSE guidelines [17]. A comprehensive, computerized literature search through February 2020 was performed using PubMed and Web of Science with the following MeSH words and key words (dietary protein OR total protein OR animal protein OR plant protein) AND (mortality OR death) AND (cohort OR prospective OR longitudinal OR follow-up). The identified publications were reviewed independently for their relevance to the research topic by two authors. We also manually searched the reference lists of relevant publications to identify additional studies. When only abstracts were published, we contact with the author for the additional information.

A set of pre-specified inclusion criteria was applied during the review and discrepancies were resolved by consensus. To be included in the meta-analysis, studies had to: (a) conduct in a general healthy population, (b) present information on protein intake as the exposure of interest, (c) report all-cause, CVD, or cancer-specific mortality as the outcome of interest, (d) provide relative risk (RR), hazard ratio estimates with confidence intervals (CIs) or standard errors, and (e) use an observational, prospective cohort design. When these information were not available in the publication, we try to contact with the authors.

We used the reported RR as the measure of the association between protein intake and the risk of all-cause, CVD, and cancer mortality. If multiple estimates were provided, priority was given to the multivariable adjusted risk estimates which adjusted for the most potential confounding factors. If more than one study was conducted in the same population, we selected the most recent report.

Data extraction and study quality assessment

We used a standardized reporting form to abstract the following data from each publication: the first author's name, the year of publication, the country in which the study was performed, the duration of follow-up, the size of the cohort, the number of deaths, the assessment of protein intake, the primary study outcome, the categories of protein intake, the RRs, and 95% CIs for all outcomes associated with protein intake and the covariates included for adjustment in multivariable models.

To assess study quality, a 9-point system on the basis of the Newcastle-Ottawa Scale [18] was used in which a study was judged on three broad categories for cohort studies as follows: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest.

Statistical analysis

To examine associations between dietary protein intake and risk of all-cause, CVD, and cancer mortality, we pooled the RR estimates for the highest versus the lowest intake category from each study. We used a fixed effect model to pool the study specific estimates unless significant heterogeneity was observed, then the random effect model proposed by DerSimonian and Laird was used [19]. When a significant association was identified, the potential dose–response relationship would be further examined. The pooled RR for per 3% increment of energy from protein intake would be estimated using a procedure described by

Orsini and Greenland [20]. When median intakes per category were not presented in the publications, we estimated the mean protein intake in each category by calculating the midpoint of the upper and lower boundaries. When the upper boundary of the highest intake category was not reported, we assumed that it had the same magnitude of intake as the preceding category.

Heterogeneity among studies was assessed with the Q and the I^2 statistic, and results were defined as heterogeneous for an I^2 >50% [21]. Small study effects such as publication bias were evaluated by Egger's tests [22]. Statistical analyses were conducted using Stata version 14.0 (StataCorp LP, College Station, Texas).

Results

Characteristics of included studies

Our systematic literature search yielded 898 records from the two databases. After removed the 150 duplicate records, 748 records were screened for the titles and abstracts based on the pre-specified inclusion criteria. After excluding 727 records non-relevant to the study topic, 21 studies were further assessed for eligibility. After the full-text review, five studies were excluded because the study population were patients with chronic kidney disease, hypertension, or breast cancer [23–27], one study was excluded as no useful estimates were reported [28], three studies excluded because the exposure of interest was not reported [9,29,30]. Thus, we included 12 studies in the final analysis [6–8,10–16,31,32] (Fig. 1).

The included studies were conducted in North America (n = 4), Europe (n = 4), Asia (n = 3), and multi-countries (n = 1). There were a total of 483,615 men and women with 68,876 deaths in the 12 studies. There were eight, seven and eight studies reporting the total, animal, and plant protein analyses, respectively. To measure the dietary protein intake, seven studies used validated food-frequency questionnaires (FFQ), one study used 24-h dietary recall, one study used a mailed questionnaire, and three studies used a 3- or 4-day dietary record, which is a prospective, open-ended survey method collecting data about the foods and beverages consumed over a previously specified period of time. Most studies included adjustment for the potential

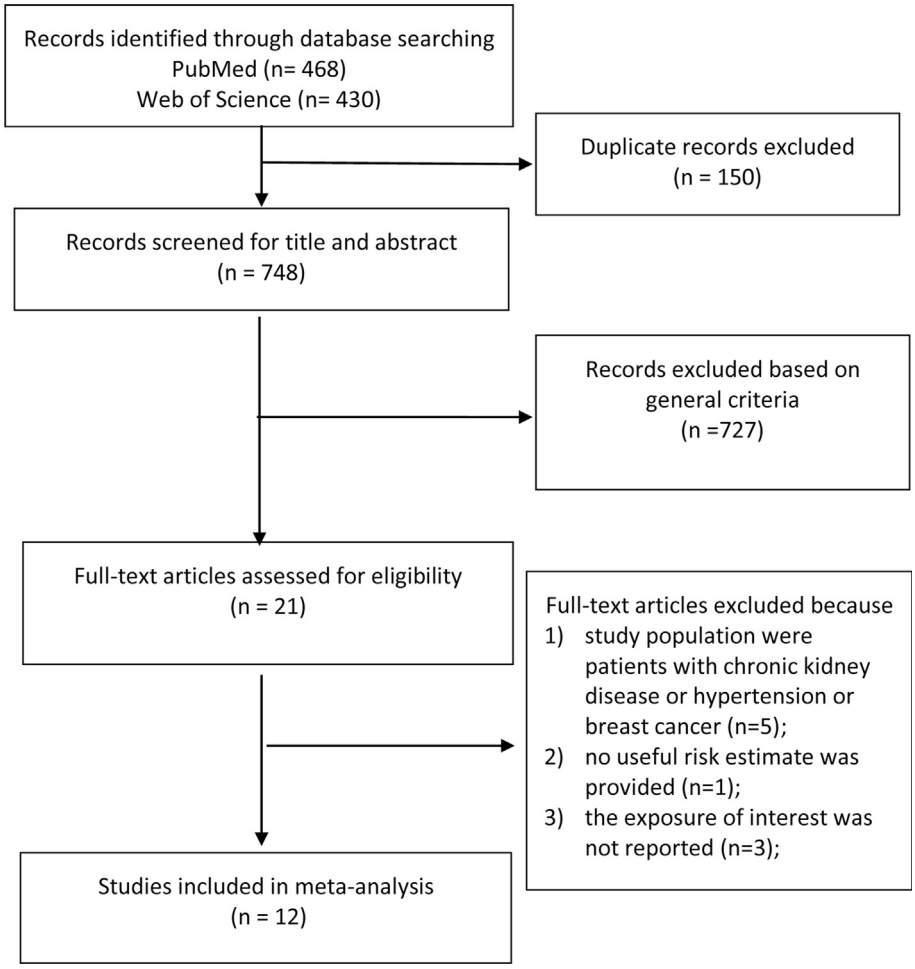

Figure 1 Flow diagram of study selection.

Table 1 Characteristics of included studies in the systematic review and meta-analysis.

Study	Publication Year	Country	Age	Gender	Size of cohorts	Deaths	Exposure	Outcome	Follow-up	Adjustments of confounders
Kelemen	2005	US	55 and 69 years	Women	29,017	3978 total deaths; 1676 cancer deaths	Total protein, animal protein and vegetable protein; Mailed questionnaires	All-cause, cancer mortality; linkage with the National Death Index	Total follow-up of 15 years	Age, total energy, saturated fat, polyunsaturated fat, monounsaturated fat, and trans-fat, total fiber, dietary cholesterol, dietary methionine, alcohol, smoking, activity level, BMI, history of hypertension, postmenopausal hormone use, multivitamin use, vitamin E supplement use, education, and family history of cancer. In addition to all of the above variables, the animal protein model is also adjusted for vegetable protein and vice versa.
Bates	2010	UK	>65 years	Men and women	1100	741 total deaths	total protein; 4 day weighed dietary record	all-cause, CVD and cancer mortality; linkage to the National Register of Births and Deaths	From 1994 to 2008	Age and sex, BMI, physical activity, alcohol consumption, receipt of welfare benefit and cigarette smoking
Levine	2014	US	50–65 years	Men and women	6381	2552 total deaths	total protein; 24 h dietary recall	all-cause, CVD and cancer mortality; linkage with the National Death Index	Total follow up of 18 years	Age, sex, race/ethnicity, education, waist circumference, smoking, chronic conditions (diabetes, cancer, myocardial infarction), trying to lose weight in the last year, diet changed in the last year, reported intake representative of typical diet, and total calories. % kcals from total fat, % kcals from total carbohydrates, % kcals from animal protein. Protein intake were expressed as percentage of energy.
Song	2016	US	mean age of 49 years	Men and women	131,342	36,115 total deaths	animal protein, plant protein; validated food frequency questionnaires	all-cause, CVD and cancer mortality; identified deaths from state statistics records, the NationalDeath Index, next of kin, and the postal system	Total follow up of 27 years	Age as the time scale was stratified by sex and calendar time and adjusted for total caloric intake and percentage of energy from saturated fat, polyunsaturated fat, monounsaturated fat, and trans-fat, multivitamin use, smoking status, pack-years of smoking, BMI, physical activity, alcohol consumption, history of hypertension diagnosis, glycemic index, and intake of whole grains, total fiber, fruits, and vegetables. Mutual adjustment was conducted for animal protein and plant protein analysis. Protein intake were expressed as percentage of energy.

(*continued on next page*)

Table 1 (*continued*)

Study	Publication Year	Country	Age	Gender	Size of cohorts	Deaths	Exposure	Outcome	Follow-up	Adjustments of confounders
Hernandez-Alonso	2016	Spanish	men (55−80 years) and women (60−80 years)	Men and women	7216	323 total deaths	total protein, animal protein, plant protein; FFQ	all-cause, CVD and cancer mortality; Repeated contact with participants, contact with family physicians, and annual review of medical records and consultation of the National Death Index.	Median follow-up of 4.8 years	Intervention group, node, sex, age, BMI, smoking status, leisure time physical activity, cumulative average alcohol intake, prevalence of diabetes, hypertension, hypercholesterolemia, family history of coronary heart disease, use of aspirin, antihypertensive medication, oral anti-diabetic medication, insulin medication and hypocholesterolemic medication; and nutritional variables as follows: quintiles of cumulative average percentage of total energy intake, energy from fats, energy from carbohydrates, energy-adjusted omega-3 fatty acids and fiber, and glycemic index. Protein intake were expressed as percentage of energy.
Dehghan	2017	18 countries	35−70 years	Men and women	135,335	5796 total deaths	total protein; validated food frequency questionnaires	all-cause, CVD and cancer mortality; follow by telephone or by a face-to face interview	Median duration of follow-up was 7·4 years	Age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake. Centre was also included as a random effect and frailty models were used. Protein intake were calculated as percentage of energy
Tharrey	2018	US and Canada	Mean age about 53−60 years	Men and women	81,337	2276 CVD deaths	animal protein, plant protein; validated food frequency questionnaire	CVD mortality; biennial follow-up and linkage with the National Death Index	Mean follow-up time of 9.4 years	Age, sex, race, energy intake, BMI, physical activity, smoking status, alcohol consumption, income, education, marital status the type of diet in the vegetarian spectrum polyunsaturated fatty acids, saturated fatty acids, sodium and vitamins A, C, E, B6, B9 and B12. Animal and plant protein intake were energy-adjusted using the residual method
Kurihara	2018	Japan	>30 years	Men and women	7744	1213 deaths; 352 CVD deaths	Plant protein; 3-day semi-weighed dietary record	CVD mortality	Mean follow-up of 13.9 years	Age, sex, BMI, animal protein intake, animal fat intake, vegetable fat intake, sodium, potassium, total dietary fiber, smoking, alcohol intake.

Budhathoki	2019	Japan	45−74 years	Men and women	70,696	12,381 total deaths	total protein, animal protein, plant protein; validated food frequency questionnaire	all-cause, CVD and cancer mortality; annually linkage to the residential registry	Mean follow-up of 18 years	Age, sex, and percentage of energy from saturated fat, monounsaturated fat, polyunsaturated fat, and other fat, body mass index, smoking, alcohol use, physical activity, occupation status, intake of green tea and coffee, and total energy. Mutual adjustment was performed for animal protein and plant protein in the respective analysis. Protein intake was expressed as a percentage of total energy
Virtanen	2019	Finland	42−60 years	Men	2641	1225 total deaths	total protein, animal protein, plant protein; 4-d dietary records at baseline	all-cause, CVD and cancer mortality; linkage to national Causes of Death Register	Average follow-up of 22.3 y	Age, examination year, and energy intake, income, education years, marital status, leisure-time physical activity pack-years of smoking, alcohol intake, BMI and diagnosis of type 2 diabetes, CVD disease, cancer, or hypertension or use of cardiac, hypercholesterolemia, hypertension, or diabetes medications and intakes of fiber and saturated, monounsaturated, polyunsaturated, and trans fatty acids). For animal and plant proteins, mutual adjustment was conducted. Intakes of protein sources and energy-adjusted proteins were expressed as g/d.
Chan	2019	China	≥65 years	Men and women	3020	963 total deaths, 205 CVD deaths and 336 cancer deaths	Total protein, animal protein and plant protein; food frequency questionnaire	All-cause, CVD and cancer mortality; linkage to the Hong Kong Government Death Registry.	Median of 13.8 follow-up years	Age, BMI, smoking, alcohol, education, PASE, marital status, daily energy intake, and self-reported history of hypertension and diabetes, energy adjusted fiber intake, sex-specific quintiles of daily total grains intake, daily fruit intake, and daily vegetable intake.
Chen	2020	Netherlands	Mean age at baseline was 63.7 ± 8.7 years,	Men and women	7786	3589 total deaths, 877 CVD deaths, 896 cancer deaths.	total protein, animal protein, plant protein; validated food frequency questionnaire	All-cause, CVD and cancer mortality; Vital status was obtained from clinical follow-up data collection and from municipal records.	Median follow-up of 13.0 years	Age, sex, RS-cohort (RS-I, −II, and −III), intake of total energy, saturated fat acids, monounsaturated fat acids, polyunsaturated fat acids, trans fat acids, alcohol, fiber, overall diet quality score, physical activity, education level, smoking status, and BMI

BMI, body mass index; CVD, cardiovascular disease.

confounders, such as age, sex, smoking, alcohol consumption, total energy intake, body mass index (BMI), physical activity, etc. (Table 1) All the included studies were assessed as high-quality studies, with relatively low risk of bias within studies (Supplementary File 1).

Dietary protein and all-cause mortality

Total protein was not associated with risk of all-cause mortality. The pooled RR for the highest intake compared with the lowest intake was 0.97 (95% CI: 0.89, 1.07), with moderate heterogeneity (I^2 = 68.9%, P = 0.001). The pooled RR was 0.99 (95% CI: 0.96, 1.01) per 3% increment of energy from total protein intake. When we stratified by protein sources, higher intake of plant protein was associated with a lower risk of all-cause mortality (highest vs lowest intake: RR = 0.92; 95% CI: 0.88, 0.96; I^2 = 35.6%, P = 0.156). Animal protein was not associated with risk of all-cause mortality (highest vs lowest intake: RR = 1.04; 95% CI: 0.95, 1.14; I^2 = 68.9%, P = 0.004) (Fig. 2). The pooled RRs were 0.97 (95% CI: 0.94, 0.99) and 1.00 (95% CI: 0.98, 1.04) per 3% increment of energy from plant and animal protein intakes, respectively. No indication of publication bias was detected from the results of Egger's test (total protein: coefficient = 0.13; 95% CI: −3.58, 3.84; P = 0.937; plant protein: coefficient = 1.55; 95% CI: −0.55, 3.65; P = 0.117; animal protein: coefficient = 0.13; 95% CI: −3.12, 3.39; P = 0.920). The funnel plots are shown in Supplementary File 2.

Dietary protein and CVD mortality

Total protein was not associated with risk of CVD mortality. The pooled RR for the highest intake compared with

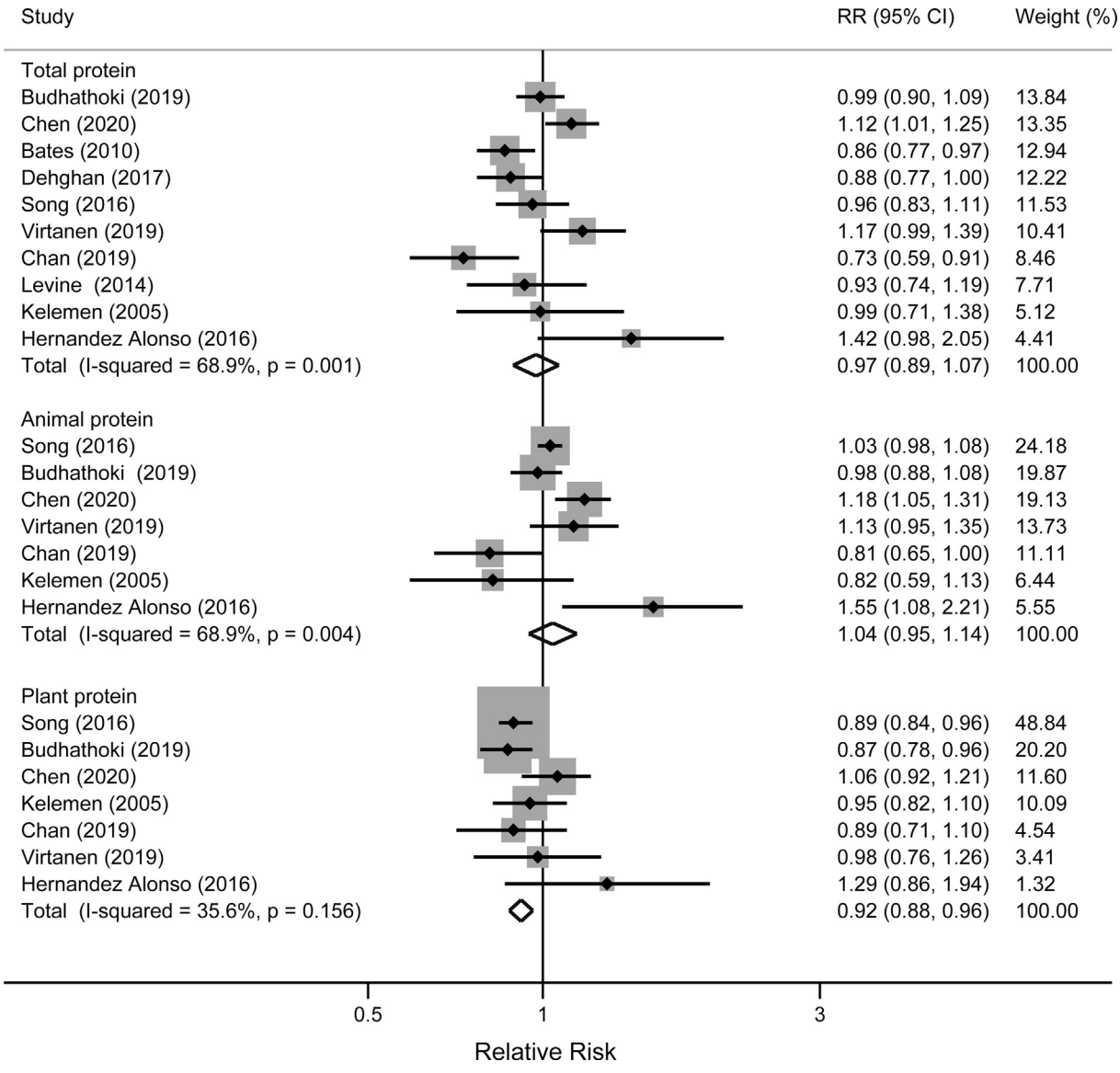

Figure 2 Forest plot for the associations of dietary protein intake with risk of all-cause mortality.

the lowest intake was 1.01 (95% CI: 0.93, 1.10). Low statistical heterogeneity was detected (I^2 = 25.1%, P = 0.228). The pooled RR was 0.99 (95% CI: 0.96, 1.02) per 3% increment of energy from total protein intake. When we stratified by protein sources, higher intake of plant protein may be associated with a lower risk of CVD mortality (highest vs lowest intake: RR = 0.90; 95% CI: 0.80, 1.01; I^2 = 51.7%, P = 0.053), while higher intake of animal protein was associated with an increased risk of CVD mortality (highest vs lowest intake: RR = 1.11; 95% CI: 1.01, 1.22; I^2 = 51.0%, P = 0.069) (Fig. 3). The pooled RRs were 0.95 (95% CI: 0.91, 0.99) and 1.02 (95% CI: 0.98, 1.06) per 3% increment of energy from plant and animal protein intake, respectively. No indication of publication bias was detected from the results of Egger's test (total protein: coefficient = 0.15; 95% CI: −2.77, 3.08; P = 0.903; plant protein: coefficient = −0.15; 95% CI: −2.53, 2.23; P = 0.877; animal protein: coefficient = 0.36; 95% CI: −2.54, 3.25; P = 0.748). The funnel plots are shown in Supplementary File 2.

Dietary protein and cancer mortality

Total, animal, and plant proteins were not associated with risk of cancer mortality. The pooled RRs for the highest intake compared with the lowest intake were 0.96 (95% CI: 0.89, 1.04; I^2 = 41.1%, P = 0.117), 1.00 (95% CI: 0.93, 1.07; I^2 = 38.1%, P = 0.152) and 0.96 (95% CI: 0.88, 1.04; I^2 = 0%, P = 0.752) for total, animal, and plant proteins, respectively (Fig. 4). The pooled RRs were 0.98 (95% CI: 0.95, 1.00), 0.98 (95% CI: 0.92, 1.03) and 1.00 (95% CI: 0.97, 1.02) for per 3% increment of energy from total, plant and animal protein intakes, respectively. No indication of publication bias was detected from the results of Egger's test (total protein: coefficient = −0.08; 95% CI: −2.56, 2.40; P = 0.936; plant protein: coefficient = −0.19; 95% CI:

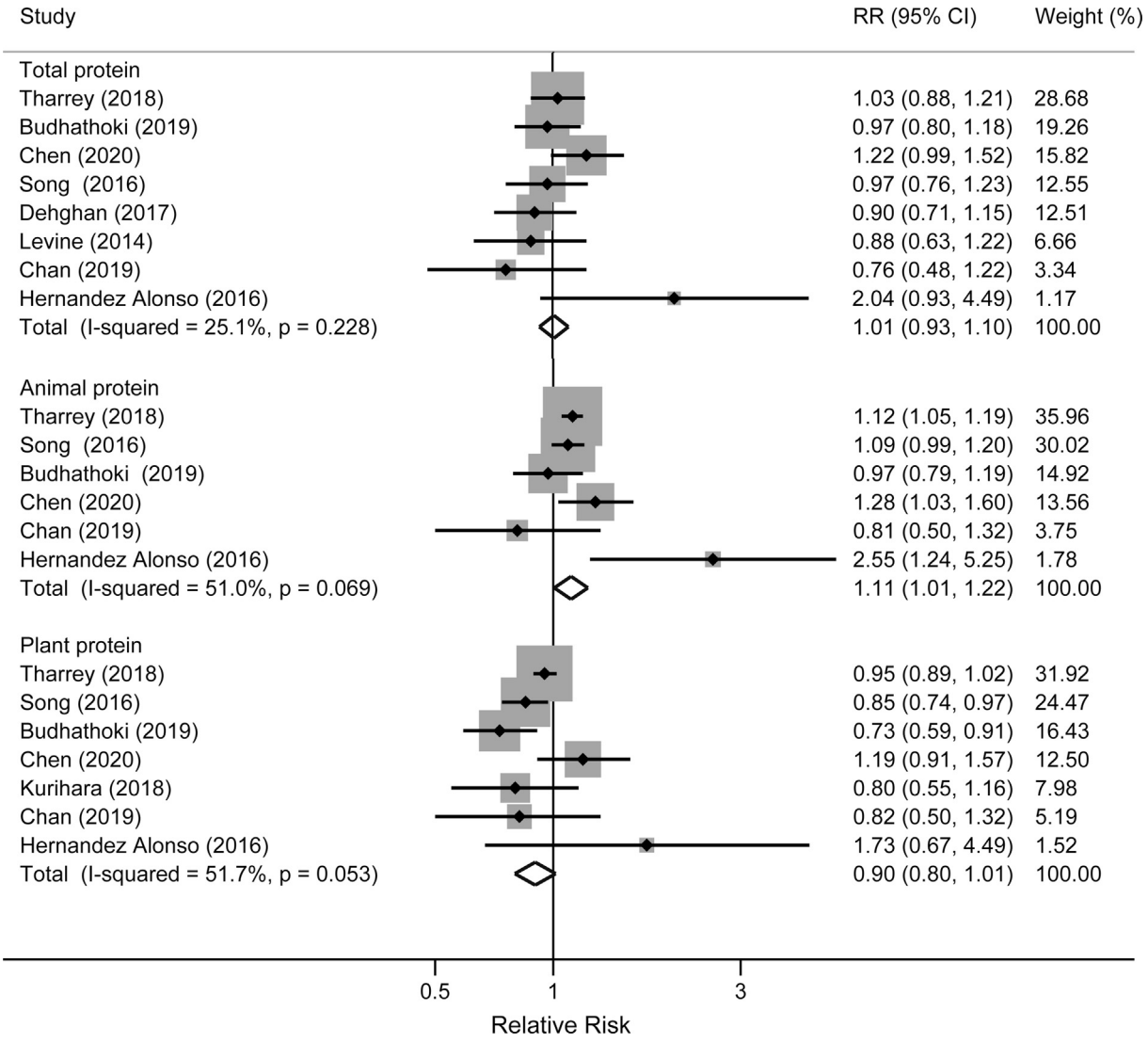

Figure 3 Forest plot for the associations of dietary protein intake with risk of cardiovascular disease mortality.

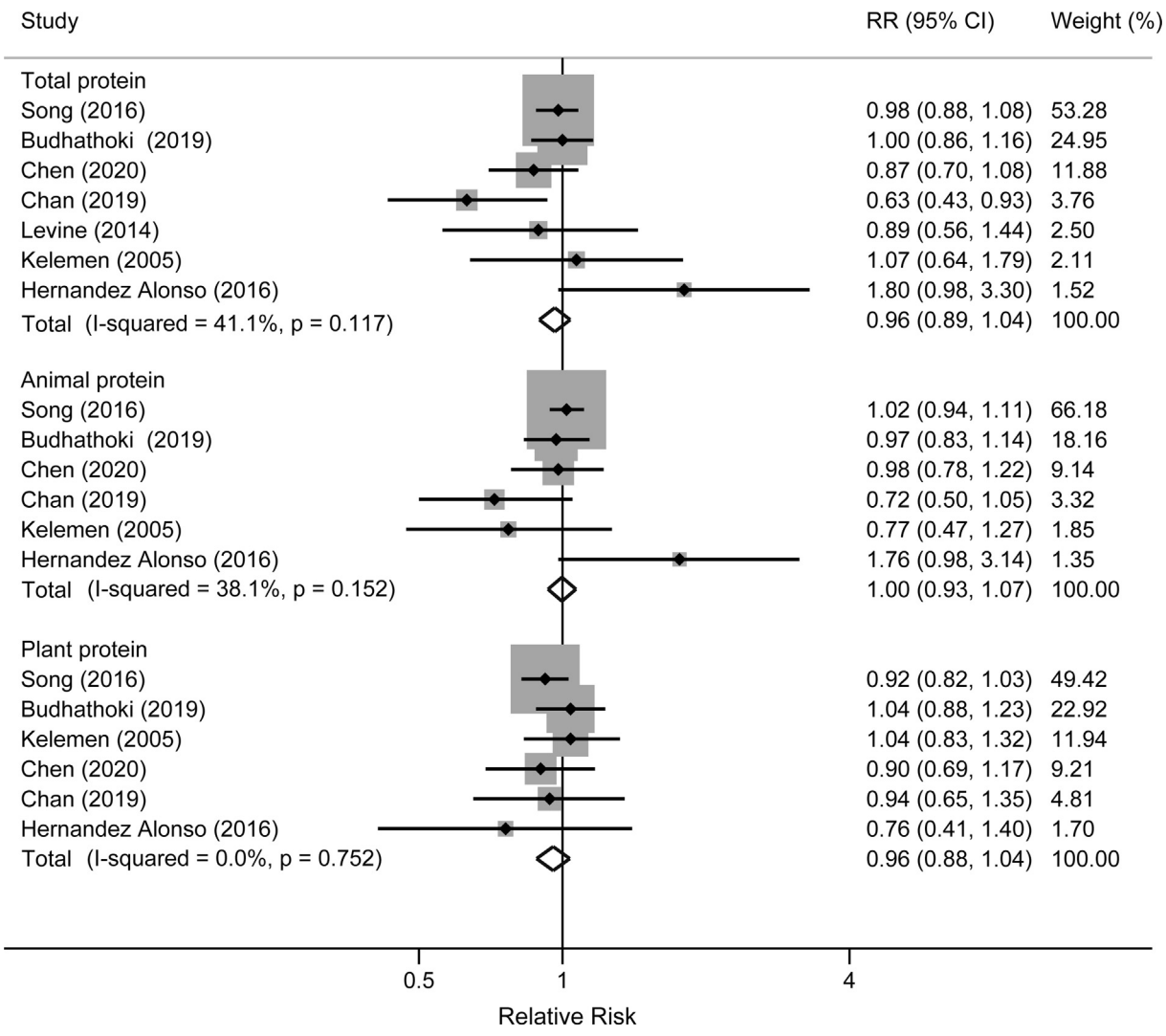

Figure 4 Forest plot for the associations of dietary protein intake with risk of cancer mortality.

−2.20, 1.82; P = 0.804; animal protein: coefficient = −0.39; 95% CI: −3.06, 2.29; P = 0.708). The funnel plots are shown in Supplementary File 2.

Discussion

To our knowledge, this is the first meta-analysis to evaluate the relationships of dietary protein and different proteins sources with risk of all-cause and cause-specific mortality. We found that total protein was not associated with risk of all-cause, CVD, and cancer mortality. Of note, in the stratified analysis, higher plant protein intake was associated with reduced risk of all-cause and CVD-related mortality. The dose–response analysis showed that per 3% increment of energy from plant protein intake was associated with 3% and 5% lower risk of all-cause and CVD-related mortality, respectively. Moreover, higher intake of animal protein may be associated with an increased risk of CVD mortality.

This meta-analysis was consistent with previous large-scale cohort studies from US and Japan, which suggested that plant protein was associated with a reduced risk of all-cause and CVD-related mortality [6,11]. We found a potential increased risk of CVD mortality associated with animal protein intake, which was also reported in three previous US cohorts [6,13]. It was suggested that substitution of plant protein for animal protein from a variety of food sources, particularly processed red meat, was associated with a lower risk of mortality, suggesting that the protein source was important for long-term health [6]. Cereals, legumes, vegetables, and fruits were the major sources of plant protein intake. Intake of nuts and grains or legumes, a rich source of plant protein, was associated with lower all-cause and CVD-related mortality [33,34], whereas higher intake of red or processed meat, major sources of animal protein, was associated with higher all-cause and CVD-related mortality [35,36]. Indeed, unlike animal protein, plant protein has not been associated with increased insulin-like growth factor 1 levels [15,37,38] and

has been linked to lower blood pressure [39], reduced low-density lipoprotein levels [40], and improved insulin sensitivity [41]. Numerous studies suggested that substitution of plant protein for animal protein has been associated with a lower incidence of major chronic disease, such as CVD and type 2 diabetes [42–47]. Reduction in the incidence of these major chronic diseases may lead to improvement of the population health and reduced risk of total mortality. These data together with our current finding support the importance of protein sources for the long-term health outcome and suggest that plants constitute a preferred protein source compared with animal foods.

A strength of this study was the prospective cohort design of the included studies. Compared with the case–control design, cohort studies may less likely expose to the selection and recall bias. Moreover, the large sample size with a total of 483,615 participants with 68,876 deaths provided sufficient statistical power to detect small effect size. In addition, we were able to conduct the dose–response analysis to further support the hypothesis of an inverse linear association between plant protein intake and all-cause and CVD-related mortality. Moreover, the included studies were all assessed as high-quality studies, which may further lend confidence to the summary results.

Our study also has some limitations. We did not search non-English databases for publications in other language, which may lead to publication bias. However, no publication bias was detected by Egger's test for the meta-analysis. Because of the observational design, residual confounding may distort the observed associations, and we were not able to address problems with confounding inherent in the original studies. However, most studies included in this meta-analysis adjusted for the major potential confounders, such as age, sex, smoking, alcohol consumption, total energy intake, BMI, and physical activity. As such, the present pooled estimates may less likely be biased. Another limitation is misclassification of protein intake, due to the self-reported nature of the exposure. However, most of the FFQ were validated in the original studies, and results from validation studies indicated that protein intake was assessed with relatively high validity. For example, the Spearman correlation coefficient of intake assessed by the FFQs and 7-day dietary record was 0.56 for animal protein and 0.66 for plant protein in the Nurses' Health Study and the Health Professionals Follow-up Study [6]. In cohort studies, even if misclassification occurred, it would most likely be non-differential and would bias results toward the null. Therefore, the association between plant protein intake and risk of all-cause and CVD-related mortality may be even stronger. Finally, there was significant heterogeneity among study results. There are several potential explanations for the observed between-study heterogeneity. First, the range of protein intake between the high and low categories varied between studies. The risk estimates would be assumed to be higher in studies with broader ranges of protein intake. Second, the size of cohort and the length of follow-up varied from study to study. Because the strength of the association differed between studies, which resulted in statistical heterogeneity, the summary risk estimates should be interpreted with caution.

This systematic review and meta-analysis demonstrates that an increased plant protein intake is associated with reduced risk of all-cause and CVD-related mortality. These findings add to and extend the evidence that increased plant protein intake may have protective effects on death risk; thus, persons should be encouraged to increase their plant protein intake to potentially decrease their risk of death. Moreover, the underlying mechanisms and active compounds in plant protein that are responsible for this association remain to be further elucidated.

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Authorship

Peng Shen had the idea for the article, Xiang-Xiu Qi and Peng Shen performed the literature search and data analysis, and Xiang-Xiu Qi and Peng Shen drafted and/or critically revised the work.

Declaration of Competing Interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.03.008.

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