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Review

Legume Consumption and Risk of All-Cause and Cause-Specific Mortality: A Systematic Review and Dose–Response Meta-Analysis of Prospective Studies

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A B S T R A C T

There is an equivocal and inconsistent association between legume consumption and health outcomes and longevity. The purpose of this study was to examine and quantify the potential dose–response relationship between legume consumption and all-cause and cause-specific mortality in the general population. We conducted a systematic literature search on PubMed/Medline, Scopus, ISI Web of Science, and Embase from inception to September 2022, as well as reference lists of relevant original papers and key journals. A random-effects model was used to calculate summary HRs and their 95% CIs for the highest and lowest categories, as well as for a 50 g/d increment. We also modeled curvilinear associations using a 1-stage linear mixed-effects meta-analysis. Thirty-two cohorts (31 publications) involving 1,141,793 participants and 93,373 deaths from all causes were included. Higher intakes of legumes, compared with lower intakes, were associated with a reduced risk of mortality from all causes (HR: 0.94; 95% CI: 0.91, 0.98; $n = 27$) and stroke (HR: 0.91; 95% CI: 0.84, 0.99; $n = 5$). There was no significant association for CVD mortality (HR: 0.99; 95% CI: 0.91, 1.09; $n = 11$), CHD mortality (HR: 0.93; 95% CI: 0.78, 1.09; $n = 5$), or cancer mortality (HR: 0.85; 95% CI: 0.72, 1.01; $n = 5$). In the linear dose–response analysis, a 50 g/d increase in legume intake was associated with a 6% reduction in the risk of all-cause mortality (HR: 0.94; 95% CI: 0.89, 0.99; $n = 19$), but no significant association was observed for the remaining outcomes. The certainty of evidence was judged from low to moderate. A higher legume intake was associated with lower mortality from all causes and stroke, but no association was observed for CVD, CHD, and cancer mortality. These results support dietary recommendations to increase the consumption of legumes.

Keywords: legume, mortality, cardiovascular disease, stroke, cancer, all-cause mortality

Statement of Significance

Higher legume consumption was associated with a lower incidence of all causes and stroke, but there was no association with CVD, CHD, or cancer mortality. In the linear dose–response analysis, each additional 50 g/d increase in legume consumption was associated with a 6% decrease in the risk of all-cause mortality.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluations; ROBINS-I, Risk Of Bias In Non-Randomized Studies - of Interventions.

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death and are a major contributor to morbidity worldwide [1]. In 2019, there were an estimated 523 million prevalent CVD cases and >18 million deaths worldwide [2]. After CVDs, cancer is the second most common cause of mortality and a major cause of morbidity globally, with 10 million deaths and 20 million incident cases observed in 2020 [3]. In 2016, dietary risk factors accounted for ~2 million CVD deaths in the WHO European Region, ~22% of all-cause deaths and 49% of CVD deaths [4]. Dietary risk factors for cancer have also emerged as part of public health strategies and prevention activities in an attempt to reduce the global burden of cancer [5, 6].

In addition to the well-known benefits of consumption of fruits, vegetables, nuts, and whole grains [7–9], the potential health impact of legume consumption needs clarification. Legumes or pulses are classified as beans, peas, and soybeans in general [10]. Legumes are renowned for their unique nutrient profile, which is high in protein, dietary fiber, B vitamins, magnesium, potassium, a variety of beneficial phytonutrients, and a low GI [11]. Because of their nutritional properties and a range of potential health benefits, legumes are considered a beneficial part of healthy diets worldwide and are recommended by several health organizations [12]. However, some concerns have been raised with regard to the phytate content of legumes, which can impair nutrient absorption [13]. Studies have shown varying results regarding the association between legume consumption and health-related outcomes. Previous meta-analyses indicated that legume consumption was associated with a decreased risk of CVD [14], several cancers [15–17], and obesity [18]; however, no association was observed with type 2 diabetes [19], stroke [20], or metabolic syndrome [21]. There are discrepancies in the findings of prospective studies that studied the association between legume consumption and chronic disease mortality or all-cause mortality. Several studies have found an inverse association between legume consumption and the risk of all-cause mortality [22–25], whereas others have shown a null association [26–29] or even positive associations [30, 31].

Although there have been meta-analyses on the association between legumes and mortality [18, 32, 33], these studies have missed several cohort studies [30, 34–37] and did not consider cause-specific deaths. In addition, 14 prospective cohort studies examining the association between legume consumption and mortality have been published recently [25–29, 31, 38–45], which include over half a million participants; thus, an updated meta-analysis is warranted. Consequently, our objectives were to conduct an updated systematic review and meta-analysis of prospective observational studies in the general population to determine the association between legume consumption and the risk of mortality from all causes, as well as CVD, CHD, stroke, and cancer, and to evaluate the strength and shape of the dose–response relationships and certainty of the evidence for these associations.

Methods

This systematic review and meta-analysis was reported in compliance with the standards of the PRISMA guidelines [46]. The protocol of this survey was registered previously and is available at International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, ID = CRD42022296260).

Search strategy

A systematic literature search was carried out in PubMed/Medline, ISI Web of Science, Embase, and Scopus from inception to December 2021, and was then updated to September 2022. We combined relative keywords for the study exposure (legumes) AND outcomes (all-cause mortality and cause-specific mortality) AND study design (prospective studies). There were no date or language restrictions imposed by the search. The complete history of our search strategy for each electronic database is available in Supplemental Table 1. The reference lists of relevant original papers, meta-analyses, and reviews were reviewed as potential sources of additional eligible studies. Additionally, key journals were searched manually.

Eligibility and study selection

Two independent authors (NZ and SMM) performed full-text, title, and abstract screenings. The eligible studies were included based on the following eligibility criteria.: (1) prospective cohort studies consisting of adults (aged ≥18 y); (2) studies that reported total or subtypes of legume consumption, excluding soy foods, as the exposure or one of the exposure variables; (3) studies in which the risk of mortality from all causes and/or other causes (including CVDs, coronary heart disease, stroke, and cancer) was examined; (4) studies that reported adjusted effect estimates with corresponding 95% CIs as HRs or RRs. Any disagreements were resolved through discussion with a third reviewer (AE). For the dose–response analysis, studies had to provide the following information: a numerical quantity of legume consumption (i.e., servings per day or week, grams per day or week) for ≥2 categories with corresponding adjusted HRs and 95% CIs, total or category-specific number of cases and noncases or person-years, or risk estimates on a continuous scale. When duplicate publications from the same cohorts were published, we selected the publication with the largest number of deaths or the longest follow-up. Nevertheless, when the same study published results as categorical and continuous, the categorical model was chosen for the high and low analyses, and continuous estimates were used for linear analysis. The excluded studies and the relevant reasons for exclusion are provided in Supplemental Table 2.

Data extraction

Two researchers extracted the following data independently (NZ and SMM): first author's name, cohort name, year of publication, study location, duration of follow-up, mean or range age at entry, total sample size, sex and the number of deaths, dietary and outcome assessment method, legume intake frequency as an amount or unit of legume consumption, the fully-adjusted risk assessments with corresponding 95% CIs, confounding variables in multivariable analysis. If a study reported age or sex-specific risk estimates, the estimates were pooled using a fixed effects model, and the pooled estimate was used in the overall analysis to include each cohort only once.

Risk of bias assessment and certainty of the evidence

The Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias [47]. It includes the risk of bias due to confounding variables, selection of participants, assessment of exposure, exposure misclassification, missing data, outcome measurement, and selective reporting of results. Two investigators (NZ and SMM) independently evaluated each study, with any disagreements being resolved by discussion with a third reviewer (AE) or mutual conversation. We also used the updated Grading of Recommendations Assessment, Development, and Evaluations (GRADE) system to assess the strength of evidence for each association, integrated with the ROBINS-I tool [48]. Unlike the previous edition [49], observational studies also commence with a high level of evidence certainty.

Data synthesis and statistical analysis

The random-effects model by DerSimonian and Laird [50], which considers both between-study and within-study variations (heterogeneity), was used to calculate the summary HRs (95% CIs) of all-cause and cause-specific mortality for the highest and lowest categories of legume consumption and for a 50 g/d increment. For studies that only reported reported risk estimates on a continuous scale, we converted the HRs per-unit increment to the highest and lowest level of intake using the average difference between the midpoints of the upper and lower categories of the remaining studies included in the analysis [51].

The linear dose–response analysis was performed using the method described by Greenland and Longnecker [52] and Orsini et al. [53]. For each study, we calculated the HRs and 95% CIs for a 50 g/d increase in legume consumption. For this purpose, studies that reported the distribution of cases, person-years, and the median or range of legume consumption with corresponding risk estimates across categories were included. We used the median of legume consumption in each category when reported directly, and we estimated the midpoint of each category by taking the mean of the lower and upper bounds when intake was reported as a range. If the highest and lowest categories were open-ended, we assumed their lengths to be the same as the adjacent intervals. Legume intake was converted from servings to grams by assuming a portion size of 100 g of legumes as 1 serving for studies that reported legume intake as servings.

We used restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution to model the potential nonlinear association [54]. The correlation within each category of HR was considered, and the study-specific estimates were combined using a 1-stage linear mixed-effects meta--analysis [55]. Compared with the traditional 2-stage method, this approach estimates the study-specific slope lines and combines them to obtain an overall average slope in a single stage, and it is more precise, flexible, and efficient [52, 56].

We assessed the heterogeneity between studies using the Cochran's Q test [57] and the I^2 statistic [58]. Substantial heterogeneity was considered when I^2 was $\geq$50% and *P*-heterogeneity was $<$0.10. Subgroup analyses were conducted to identify potential sources of heterogeneity and were stratified by geographical location (Europe, Asia/Australia, United States, international), gender (male, female, both), duration of follow-up ($<$10 y/$\geq$10 y), dietary assessment method (FFQ/food recall), number of participants ($<$10,000/$\geq$10,000), and adjustment for main covariates such as energy intake, BMI, smoking, physical activity, alcohol consumption, hypertension, diabetes, blood pressure, and serum cholesterol. To investigate the robustness of the pooled effect sizes, influence analysis was performed using the leave-one-out method [59]. When $\geq$10 studies were included in the analysis, we assessed publication bias by visually inspecting the funnel plot and using Egger's regression test. [60]. All statistical analyses were conducted using Stata software version 15.0 (StataCorp). *P* values of $<$0.05 were considered statistically significant.

Results

The initial database search identified 8810 papers. After the exclusion of 2851 duplicate records and 5716 irrelevant documents based on title and abstract screening, 216 potentially relevant full-text articles were considered for further review. After further exclusions were made, 32 prospective cohorts (31 publications) were included in the analyses [22–31, 34–36, 38–45, 61–70]. Of the 31 articles, 1 included data from 2 cohort studies [24]. Twenty-seven cohorts were included in the analysis of all-cause mortality, 11 studies were included in the analysis of CVD mortality, and 5 studies were included in the analysis of CHD, stroke, and cancer mortality. Figure 1 displays the results of our literature search, screening, and selection process.

All of the studies included were original papers that were published between 1995 and 2022. All were population-based cohort studies that were conducted in the general adult population, and studies in patients with a history of disease were excluded. Five studies were conducted in the United States [29, 40, 43, 44, 61], 14 in Europe [26, 30, 31, 34, 35, 39, 41, 64–70], 10 in Asia [23, 24, 27, 28, 36, 38, 42, 45, 63], 1 in Australia [62], and 2 internationally [22, 25]. These studies enrolled 1,141,793 participants, ranging from 161 to 258,911. Over 3–26 y of follow-up, 93,373 deaths from all causes, 18,056 CVD deaths, 2037 CHD deaths, 2317 stroke deaths, and 12,890 cancer deaths were recorded. Of the 31 studies (32 cohorts) included, 3 were conducted exclusively among men [24, 68, 70] and 2 among women [24, 29], 2 reported separate risk estimates for men and women [63, 65], and others included both men and women. Twenty-seven cohorts used FFQs [22–27, 29–31, 34–36, 38, 39, 42, 44, 45, 61–69] to examine dietary legume intake, whereas the remaining 5 used 24-h recalls or food records [28, 40, 41, 43, 70]. The main characteristics of the included studies are summarized in Supplemental Table 3–7, separately for each outcome. According to the ROBINS-I tool, 27 studies (85%) were judged as having a moderate risk of bias, whereas 5 studies (15%) had a serious risk of bias (Supplemental Table 8). Because there is a potential risk of bias due to residual confounding in observational studies and measurement error in dietary assessments, the risk of bias from confounding and exposure assessment will never be low.

Legumes and all-cause mortality

Twenty-seven prospective cohort studies (26 publications) [22–31, 34–36, 38–41, 43–45, 61, 62, 66, 68–70] investigated the association between legume consumption and risk of all-cause mortality, including 989,209 participants and 93,373 deaths. Comparing the highest with the lowest categories of legume consumption, the summary HR indicated a significant inverse

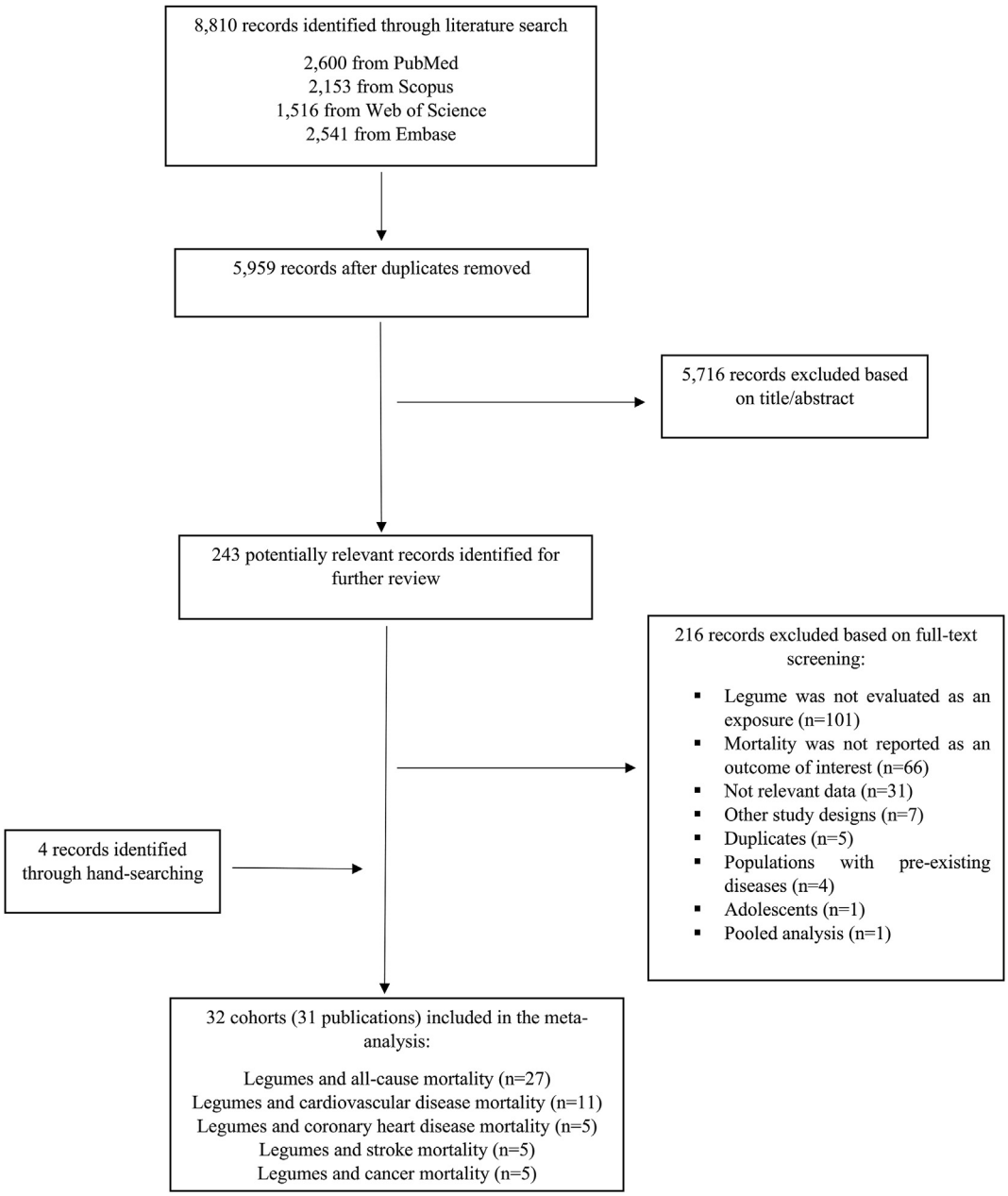

FIGURE 1. Flow diagram of screening and selection process of the included studies.

association between legume consumption and risk of all-cause mortality (HR: 0.94; 95% CI: 0.91, 0.98), with substantial heterogeneity between studies (I^2 = 64.6%; *P*-heterogeneity < 0.001) (Figure 2). In the sensitivity analysis, we found that the association between legume consumption and risk of all-cause mortality did not depend on any individual study (Supplemental Figure 1). There was a significant association across subgroups in the subgroup analyses, except that the association was not significant in studies conducted in the United States (HR: 1.00; 95% CI: 0.96, 1.05; $n = 5$), and Europe (HR: 1.01; 95% CI: 0.95, 1.07; $n = 11$), those that included only women (HR: 0.95; 95% CI: 0.83, 1.10; $n = 2$), those with <10 y follow-up duration (HR: 0.94; 95% CI: 0.88, 1.00; $n = 13$), and those that used food recall or record for dietary assessment (HR: 1.01; 95% CI: 0.96, 1.07; $n = 4$) (Table 1). The association between legume consumption and risk of all-cause mortality was significant in studies that controlled for energy intake, smoking status, BMI, alcohol consumption, hypertension, and diabetes. Geographical location, participant number, gender, dietary assessment method, adjustment for physical activity, and diabetes were all potential sources of heterogeneity. No evidence of publication bias was found with Egger's test ($P = 0.15$) or by visual inspection of the funnel plot (Supplemental Figure 2).

Nineteen cohorts provided sufficient data for inclusion in the linear dose–response analysis [22–26, 29–31, 34–36, 38, 39, 41, 44, 61, 62, 66]. The summary estimate showed that each 50 g/d increase in legume consumption was associated with a 6% reduction in the risk of all-cause mortality (HR: 0.94; 95% CI: 0.89, 0.99; Supplemental Figure 3). Ten studies were included in the nonlinear analysis [23, 25, 26, 29, 31, 38, 41, 61, 64, 66]. However, no evidence of a nonlinear association was found (*P*-nonlinearity = 0.31; Figure 3 and Supplemental Table 9).

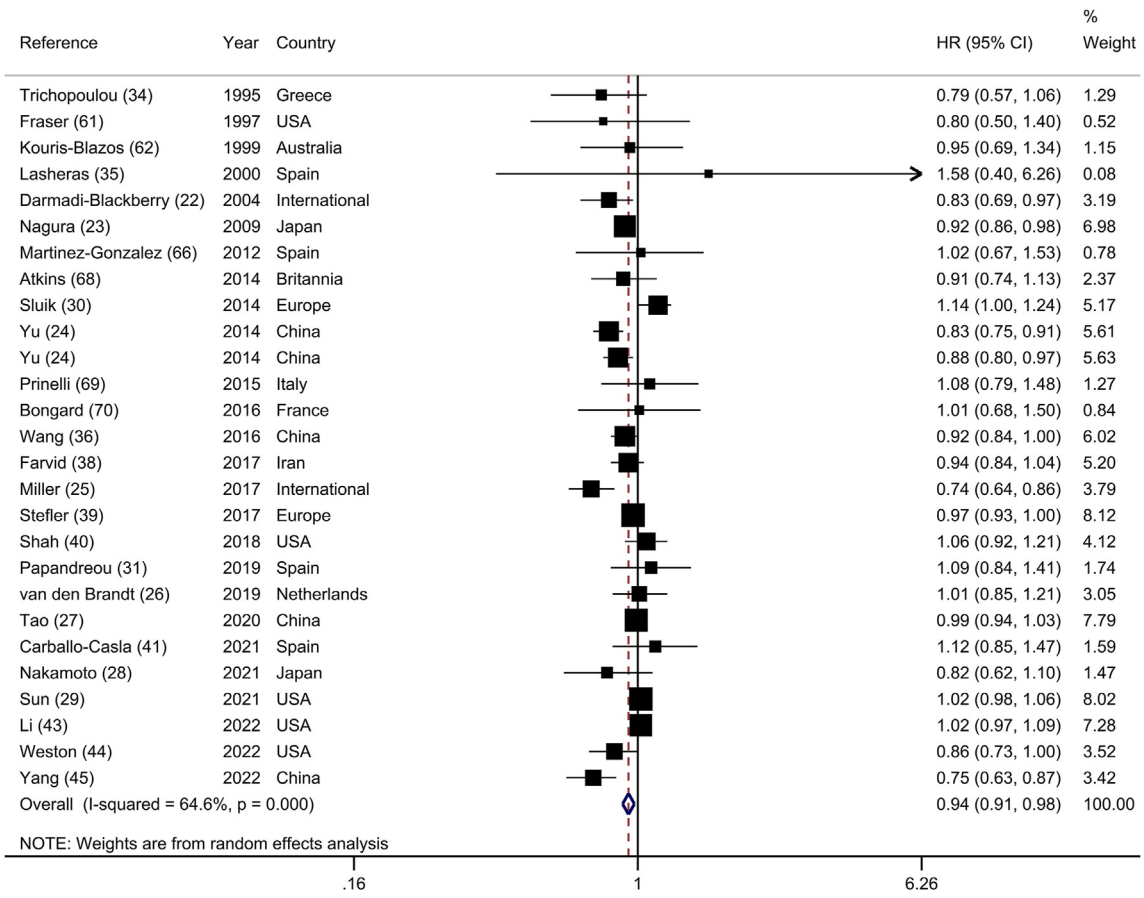

FIGURE 2. Forest plot of the association between dietary intakes of legumes and risk of all-cause mortality, comparing the highest and lowest categories.

Legumes and CVD mortality

Eleven prospective cohorts [23, 25, 26, 29, 31, 38–40, 45, 63, 68], composed of 546,306 participants and 18,056 CVD deaths, were included in the analysis of the highest and lowest categories of legume intake and CVD mortality. The summary HR was 0.99 (95% CI: 0.91, 1.09), with moderate heterogeneity ($I^2 = 56.6\%$; P-heterogeneity = 0.02) (Figure 4). A sensitivity analysis excluding 1 study at a time did not materially change the summary estimate (Supplemental Figure 4). Subgroup analyses revealed that geographical location, number of participants, and adjustments for energy intake, BMI, hypertension, serum cholesterol, and diabetes were all potential sources of heterogeneity (Supplemental Table 10). Egger's regression test (P = 0.98) and visual inspection of the funnel plot did not show any evidence of publication bias (Supplemental Figure 5).

Eight studies contained sufficient data to be included in the linear dose–response analysis [23, 25, 26, 29, 31, 38, 39, 63]. The summary HR for CVD mortality per 50 g/d increment in legume intake was 1.01 (95% CI: 0.94, 1.08; $I^2 = 41.0\%$; Supplemental Figure 6). There was no indication of a nonlinear association (P-nonlinearity = 0.58; Figure 3 and Supplemental Table 9).

Legumes and CHD mortality

Five cohort studies [23, 36, 38, 39, 65] evaluated the relation between legume intake and CHD mortality, including 147,595 participants and 2,037 events. The summary HR showed no association between legume consumption and risk of CHD mortality (HR: 0.93; 95% CI: 0.78, 1.09), with substantial heterogeneity across studies ($I^2 = 65.9\%$; P-heterogeneity = 0.02) (Figure 5). This finding was not altered when each primary study was removed one at a time (Supplemental Figure 7). The potential sources of heterogeneity could be explained by geographical location, number of participants, and adjustments for energy intake, physical activity, and blood pressure (Supplemental Table 11).

All studies were included in the linear dose–response analysis. The summary HR for CHD mortality per 50 g/d increase in legume consumption was 0.90 (95% CI: 0.71, 1.13; $I^2 = 54.7\%$; Supplemental Figure 8). There was no indication of a nonlinear association between legume consumption and CHD mortality based on 2 studies [23, 38] (P-nonlinearity = 0.58; Figure 3).

Legumes and stroke mortality

The association between the highest and lowest categories of legume consumption and stroke mortality was studied in 5 cohort studies [23, 36, 38, 39, 67], including 147,595 subjects and 2,317 stroke deaths. Stroke mortality risk was reduced by 9% when these studies were combined (HR: 0.91; 95% CI: 0.84, 0.99), and there was no evidence of heterogeneity across studies ($I^2 = 0.0\%$; P-heterogeneity = 0.46) (Figure 6). However, after the stepwise exclusion of each study in the sensitivity analysis, this association was not robust, and the results were influenced by the "Linxian Nutrition Intervention Trials" [36] and "Health Alcohol and Psychosocial Factors in Eastern Europe" [39]. When

TABLE 1
Subgroup analyses of legume consumption and risk of all-cause mortality

		Highest vs. lowest category				Dose–response (per 50 g/d)			
		n	HR (95% CI)	I^2 (%)	P_h[1]	*n*	HR (95% CI)	I^2 (%)	P_h[1]
All studies		27	0.94 (0.91, 0.98)	64.6	<0.001	19	0.94 (0.89, 0.99)	67.1	<0.001
Geographic location									
United States		5	1.00 (0.96, 1.05)	28.0	0.23	3	0.93 (0.78, 1.11)	61.4	0.07
Europe		11	1.01 (0.95, 1.07)	20.5	0.25	8	1.05 (0.93, 1.18)	33.4	0.16
Asia and Australia		9	0.90 (0.85, 0.95)	62.9	0.01	6	0.89 (0.84, 0.94)	25.4	0.24
International		2	0.78 (0.69, 0.87)	0.0	0.32	2	0.90 (0.78, 1.02)	54.3	0.14
Sex									
Male		3	0.85 (0.78, 0.93)	0.0	0.51	1	0.81 (0.72, 0.89)	—	—
Female		2	0.95 (0.83, 1.10)	87.1	0.01	2	0.94 (0.81, 1.10)	87.9	0.01
Male and female		22	0.95 (0.91, 0.99)	60.2	0.01	16	0.95 (0.90, 0.99)	30.2	0.12
Duration of follow-up, y									
<10		13	0.94 (0.88, 1.00)	71.4	<0.001	11	0.93 (0.85, 1.01)	58.5	0.01
≥10		14	0.94 (0.89, 0.99)	58.5	0.01	8	0.94 (0.88, 1.00)	67.5	0.01
No. of participants									
<10,000		14	0.89 (0.84, 0.95)	10.3	0.34	9	0.88 (0.81, 0.96)	0.0	0.68
≥10,000		13	0.96 (0.92, 1.00)	75.7	<0.001	10	0.95 0.89, 1.00)	78.8	<0.001
Dietary assessment tools									
FFQ		23	0.93 (0.89, 0.97)	67.5	<0.001	18	0.93 (0.88, 0.98)	68.4	<0.001
Food recall and record		4	1.01 (0.96, 1.07)	0.0	0.45	1	1.14 (0.83, 1.56)	—	—
Adjustment for confounders									
Energy intake	Yes	17	0.92 (0.88, 0.97)	71.1	<0.001	11	0.98 (0.87, 0.99)	73.5	<0.001
	No	10	0.97 (0.91, 1.03)	50.0	0.03	8	0.95 (0.86, 1.06)	55.2	0.03
Smoking	Yes	26	0.94 (0.90,0.98)	65.7	<0.001	18	0.94 (0.89, 0.99)	68.6	<0.001
	No	1	1.58 (0.39, 6.25)	—	—	1	1.64 (0.35, 7.67)	—	—
BMI	Yes	19	0.94 (0.91, 0.98)	61.2	0.01	11	0.93 (0.87, 0.99)	70.1	<0.001
	No	8	0.91 (0.81, 1.02)	73.9	<0.001	7	0.95 (0.85, 1.06)	59.8	0.02
Physical activity	Yes	22	0.95 (0.91, 0.99)	68.0	<0.001	15	0.95 (0.90, 1.00)	70.7	<0.001
	No	5	0.89 (0.83, 0.95)	0.0	0.69	4	0.87 (0.78, 0.96)	0.0	0.79
Alcohol consumption	Yes	16	0.94 (0.90, 0.99)	70.8	<0.001	10	0.94 (0.88, 1.01)	78.7	<0.001
	No	11	0.93 (0.84, 1.03)	53.2	0.02	9	0.93 (0.89, 0.97)	0.0	0.73
Hypertension	Yes	11	0.92 (0.86, 0.97)	68.9	0.02	7	0.89 (0.83, 0.96)	41.3	0.09
	No	16	0.96 (0.91, 1.01)	60.5	0.01	12	0.96 (0.91, 1.02)	61.1	0.01
Blood pressure	Yes	2	0.91 (0.76, 1.08)	80.7	<0.001	1	0.92 (0.74, 1.15)	—	—
	No	25	0.94 (0.91, 0.98)	62.8	<0.001	18	0.94 (0.89, 0.99)	68.8	<0.001
Serum cholesterol	Yes	7	0.94 (0.84, 1.04)	69.5	0.01	4	0.96 (0.84, 1.10)	36.2	0.19
	No	20	0.94 (0.90, 0.98)	60.1	<0.001	15	0.93 (0.88, 0.97)	51.6	0.01
Diabetes	Yes	12	0.91 (0.85, 0.97)	79.3	<0.001	9	0.93 (0.87, 0.99)	78.7	<0.001
	No	15	0.97 (0.94, 1.01)	27.7	0.15	10	0.94 (0.85, 1.04)	44.9	0.06

[1] *P* for heterogeneity within each subgroup.

these studies were excluded from the main analysis, a nonsignificant association between legume consumption and risk of stroke mortality was observed (HR: 0.92; 95% CI: 0.82, 1.03, and HR: 0.92; 95% CI: 0.81, 1.03, respectively) (Supplemental Figure 9). The results of the subgroup analyses of legume consumption and risk of stroke mortality are presented in Supplemental Table 12.

The linear dose–response analysis included all 5 studies [23, 36, 38, 39, 67] and showed a summary hazard ratio of 0.90 (95% CI: 0.76, 1.06; Supplemental Figure 10) per 50 g/d increase in legume intake. Furthermore, 2 studies provided sufficient data for nonlinear dose–response analysis and showed no significant association or evidence of nonlinearity (*P*-nonlinearity = 0.08; Figure 3).

Legumes and cancer mortality

The analysis of the highest and lowest categories of legume consumption and total cancer mortality included 5 prospective cohorts [26, 29, 31, 38, 42], with 314,235 participants and 12,890 cancer deaths. High legume consumption was not significantly associated with a lower risk of cancer mortality (HR: 0.85; 95% CI: 0.72, 1.01), along with substantial heterogeneity across studies (I^2 = 70.8%; *P*-heterogeneity = 0.01) (Figure 7). Excluding the Netherlands Cohort Study [26] in the influence analysis made the summary estimate significant, implying a 21% reduction in cancer mortality (HR: 0.79; 95% CI: 0.63, 0.99) (Supplemental Figure 11). Based on subgroup analyses, geographical location may explain the between-study heterogeneity. Stratified analysis also indicated an inverse significant association in studies that were conducted in Asia (HR: 0.76; 95% CI: 0.64, 0.90; *n* = 2) (Supplemental Table 13).

The dose–response analysis was conducted on all 5 studies [26, 29, 31, 38, 42]. There was no association between every 50 g/d increment in legume consumption and cancer mortality (HR: 0.82; 95% CI: 0.61, 1.10; I^2 = 72.2%; Supplemental Figure 12). We also observed no indication of a nonlinear relationship (*P*-nonlinearity = 0.19; Figure 3 and Supplemental Table 9).

Certainty of evidence

The GRADE system was used to assess the degree of certainty in the evidence. None of the associations had a high level of

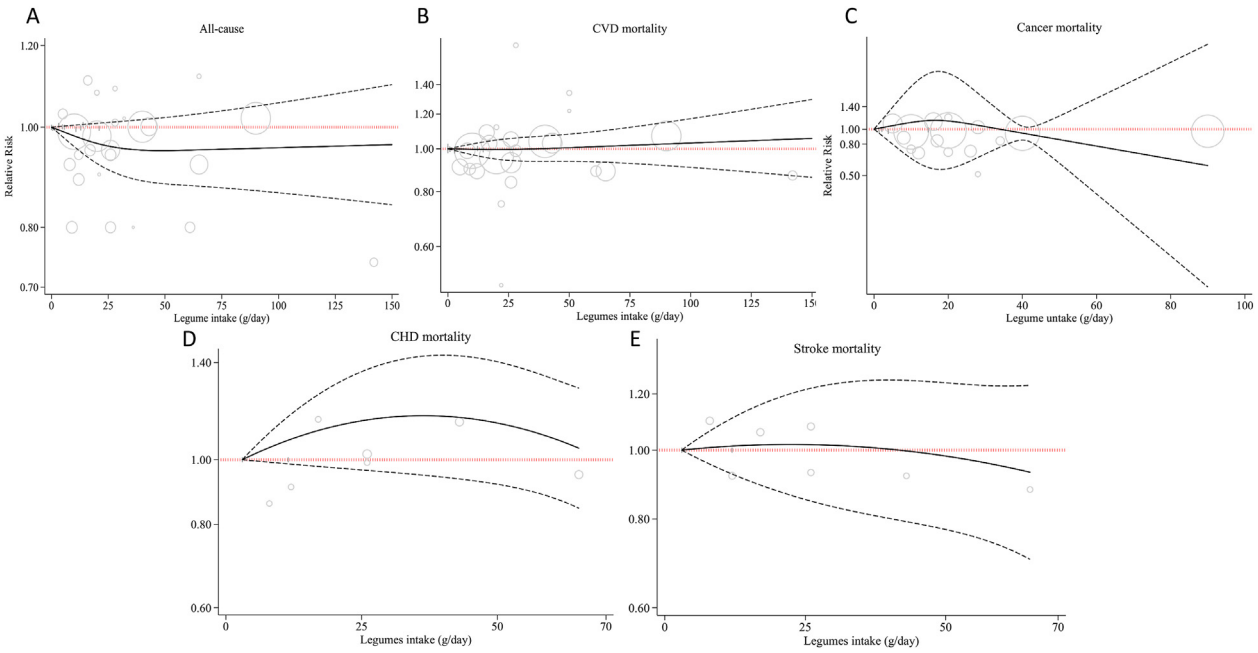

FIGURE 3. Nonlinear dose–response association between legume consumption with risk of mortality from (A) all causes, (B) CVD, (C) cancer, (D) coronary heart disease (CHD), and (E) stroke. The solid line represents nonlinear dose–response, and dotted lines represent 95% CIs. Circles represent hazard ratio point estimates for legume consumption categories from each study, with circle size proportional to the inverse of SE. Each study's baseline legume intake categories are indicated by small vertical black lines.

evidence certainty. However, the level of evidence for mortality from all causes, and stroke was rated "moderate," whereas it was rated "low" for CVD, CHD, and cancer mortality (Supplemental Table 14). This judgment was chiefly influenced by concerns due to the risk of bias due to residual confounding and inconsistency.

Discussion

Principal findings

In this systematic review and dose–response meta-analysis of data from 32 prospective cohort studies, higher legume intake was associated with 6% and 9% reductions in the risk

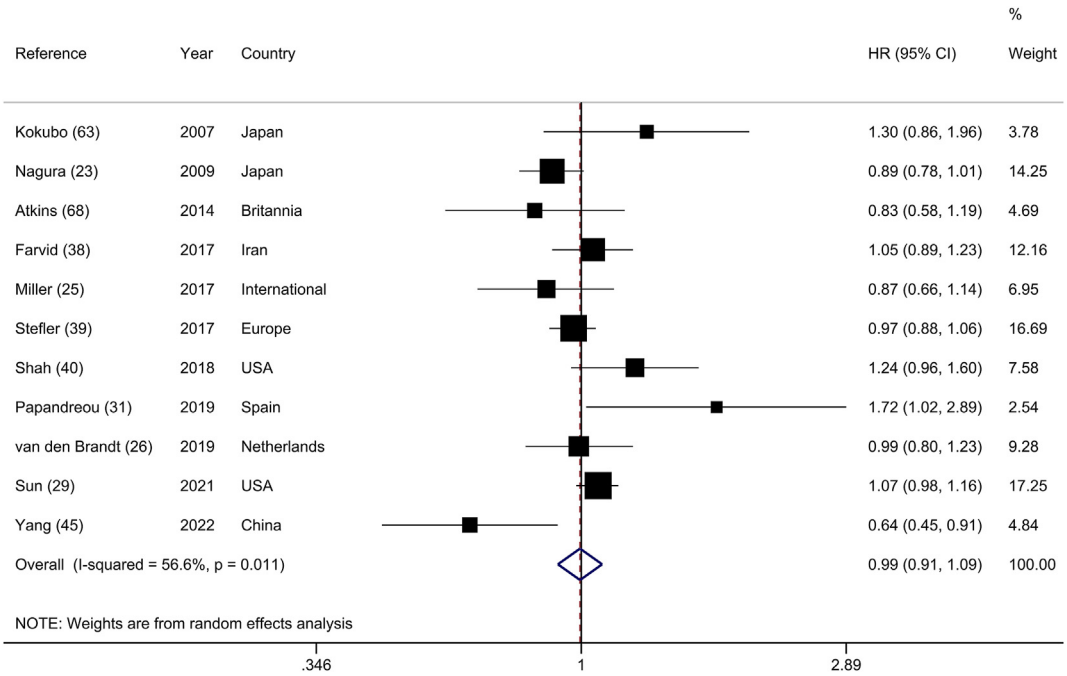

FIGURE 4. Forest plot of the association between dietary intakes of legumes and risk of CVD mortality, comparing the highest and lowest categories.

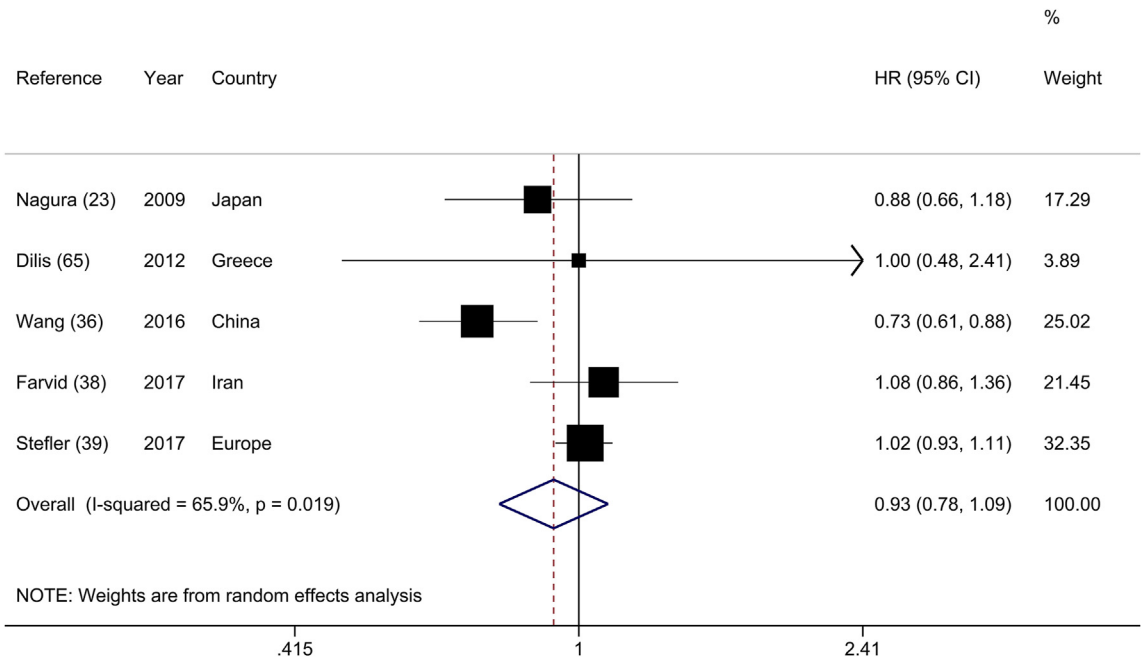

FIGURE 5. Forest plot of the association between dietary intakes of legumes and the risk of coronary heart disease mortality, comparing the highest and lowest categories.

of all-cause, and stroke mortality, respectively. However, there was no significant association between legume intake and CVD, CHD, and cancer mortality. Each 50 g/d increase in legume consumption was associated with a 6% reduction in the risk of all-cause mortality. There was also no evidence of a nonlinear association between legume consumption and risk of mortality from all-cause, CVD, CHD, strokes, or cancer mortality.

Comparison with other studies

Recognized healthy eating patterns (Dietary Approaches to Stop Hypertension diet and Mediterranean diet) recommend a certain amount of legumes in addition to other foods (seeds, olive oil, dairy, fruits, etc.) that protect against overall, CVD and cancer mortality [71, 72]. A series of systematic reviews and meta-analyses involving data from 185 prospective studies and 58 clinical trials reported a 15%–30% reduction in all-cause

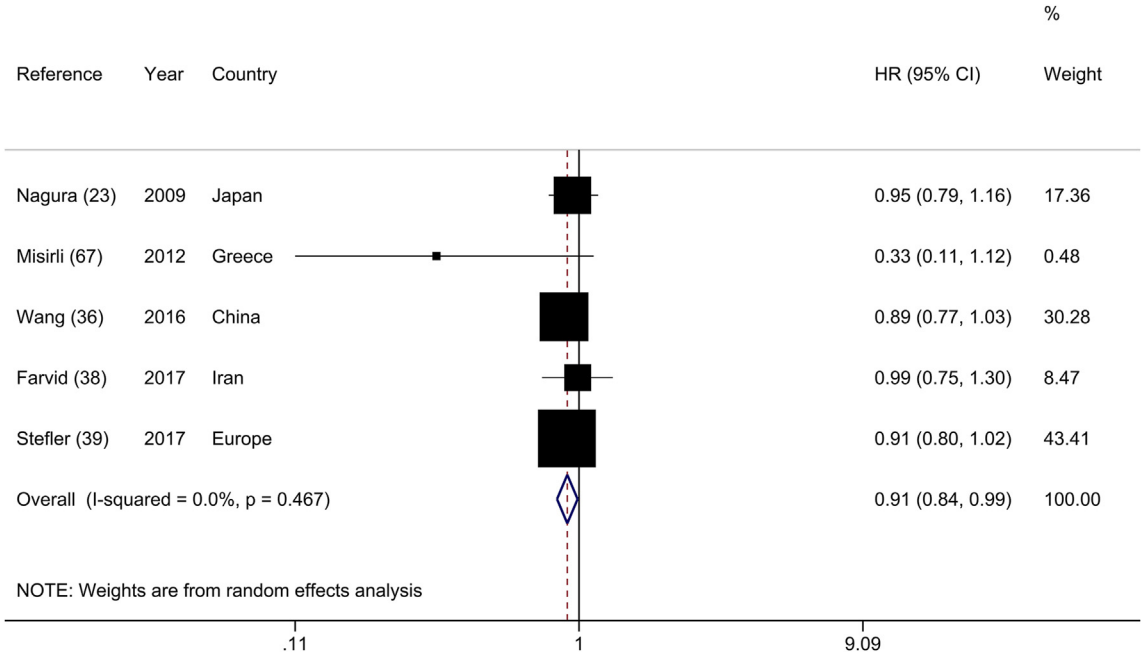

FIGURE 6. Forest plot of the association between dietary intakes of legumes and risk of stroke mortality, comparing the highest and lowest categories.

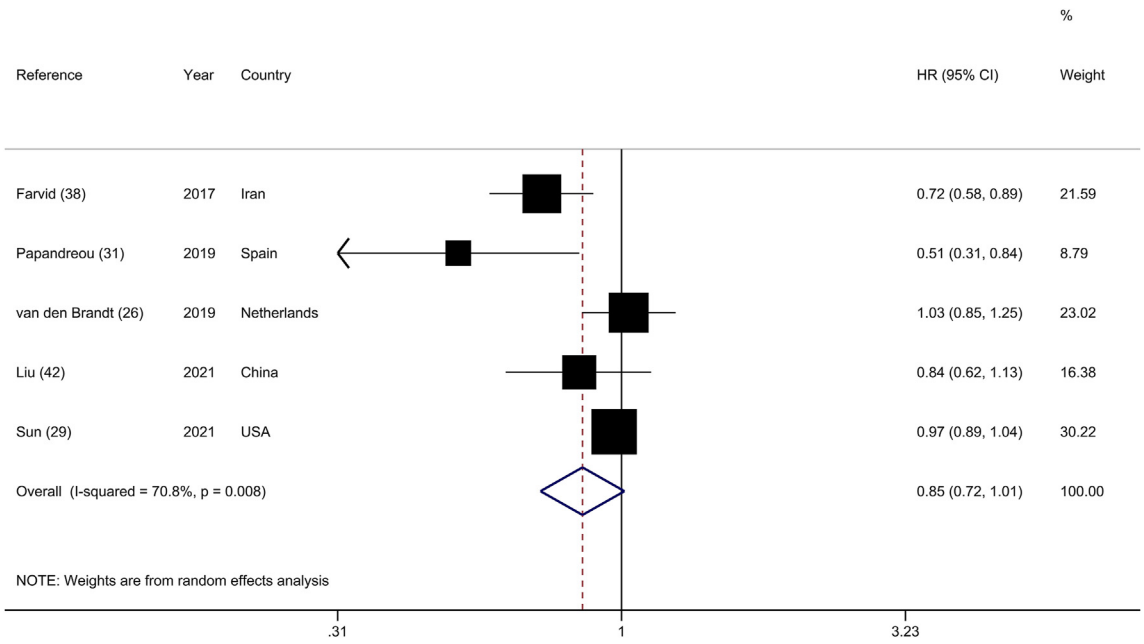

FIGURE 7. Forest plot of the association between dietary intakes of legumes and risk of cancer mortality, comparing the highest and lowest categories.

and CVD-related mortality, as well as the incidence of CHD, stroke, and colorectal cancer when high-fiber consumers were compared with low-fiber consumers [73]. These associations were particularly noticeable for dietary fiber intakes ranging from 25 to 29 g/d, implying that increasing legume intake may be a reasonable approach to achieving this goal. In a prospective cohort study using data from the US NHANES from 1999 to 2014 (37,233 adults aged ≥20 y), the risk of total mortality was reduced by 9% (HR: 0.91; 95% CI: 0.87, 0.95) and 11% (HR: 0.89; 95% CI: 0.85, 0.93) for healthy low-carbohydrate and healthy low-fat diet scores, respectively, which were defined as a dietary pattern not only restricted in carbohydrates and fats but also rich in vegetable proteins and whereby legumes were a prevalent food item [74]. Even as carbohydrate sources, legumes can be included in low-carbohydrate diets because these eating patterns involve <45% of energy intake from carbohydrates, which differs from very-low-carbohydrate diets or ketogenic diets, which are consistent with less than 40–50 g of carbohydrates per day [75].

In the present meta-analysis, an inverse association was found between legume consumption and all-cause mortality and stroke mortality but not with other specific causes of mortality. The results for stroke mortality, however, were strongly influenced by the findings of 2 studies in the sensitivity analysis. The reported discrepancies between the risk of incidence of all-cause mortality and death from CVD, CHD, and cancer are not totally evident. The protective association is most likely because of a greater number of studies in this area and, as a result, a greater number of participants and deaths. More precise estimates are required to properly assess the association between legume consumption and CVD, CHD, and cancer mortality. Our meta-analysis provides the most up-to-date estimates of the association between legume consumption and all-cause and cause-specific mortality, and it is in line with the previous reviews and meta-analyses on the topic [18, 32, 33]. Despite this, the current meta-analysis includes 1.5–4 times the number of studies as the previously published meta-analyses, as well as roughly twice the number of participants and deaths. For instance, we included 27 cohorts (93,373 deaths) in the highest and lowest analysis of legume consumption and all-cause mortality, compared with 17 studies (53,085 deaths) [33] and 4 studies (18,408 deaths) [32] in previous meta-analyses. In the linear dose–response analysis for all-cause mortality, we included 19 cohorts as opposed to 6 studies in 1 meta-analysis [33]. In addition, we examined the certainty of evidence and dose–response relationships for cause-specific mortality that had not previously been studied.

Mechanisms

Several potential mechanisms could contribute to the beneficial associations observed with legume consumption in this meta-analysis. Because of a variety of constituent parts, legumes are thought to have cholesterol-lowering properties. Soluble fiber, in particular, has been shown to bind to bile acids in the digestive tract, preventing bile acids from being reabsorbed into the body [76]. As a result, increased bile acid synthesis decreases the liver's cholesterol pool and increases serum cholesterol absorption, lowering blood cholesterol levels [77]. Phytosterols, a component of plant cell membranes that have been shown to lower blood cholesterol levels, are found in low to moderate concentrations in a variety of legumes, including chickpeas [78, 79]. Legumes are also high in saponins, which may help reduce cholesterol absorption from the gut [80]. Nonsoy legumes and whole soy foods have been shown to improve glycemic control indicators in various ways. Carbohydrates with a slow rate of digestion can be found in nonsoy legumes [81]. Resistant starch, which contains a higher proportion of amylose to amylopectin than other starchy carbohydrates, may be responsible for this characteristic. When combined with the high fiber content of nonsoy legumes, this characteristic lowers the GI, which may

explain the beneficial effects on glucose control indicators [82]. Furthermore, because of their high fiber and protein content, as well as their low GI, nonsoy legumes may help people lose weight by increasing satiety [83] through various mechanisms [84]. Increased intraluminal viscosity reduces gastric emptying and macronutrient absorption by slowing digestion and increasing gastric distention caused by chewing effort; by influencing gut hormone secretion; and producing SCFAs (propionate, butyrate, and acetate) derived from the fermentation of fiber by colonic bacteria, which slows digestion and increases gastric distention. Foods with a low GI stimulate the digestive tract receptors for a longer time, resulting in fullness signals [85]. Because patients with CVD who are also inflamed have a poor prognosis and are more likely to relapse, the antioxidant and anti-inflammatory properties of legumes may play a role in reducing stroke mortality. The potential mechanisms underlying the inverse association between legume consumption and stroke mortality may include the following. A high concentration of phytosterols is found in legumes, and meta-analyses of randomized controlled trials have shown that they significantly reduce total cholesterol, LDL cholesterol, atherogenic apolipoprotein levels, and free fatty acids [86, 87]. These compounds might also reduce the risk of atherosclerosis [88]. Alternatively, the high fiber content of legumes, as a plant-derived food, has been associated with a reduced risk of stroke in prospective studies [89]. Fiber is believed to reduce chronic inflammation and to improve body metabolism by regulating body weight, serum cholesterol levels, blood pressure, and insulin resistance, as well as fibrinolysis and coagulation, which may be relevant in the context of existing atherosclerotic plaques [90]. Because patients with CVD who are also inflamed have a poor prognosis and are more likely to relapse [28], the antioxidant and anti-inflammatory properties of legumes may play a role in reducing stroke mortality [91].

Strengths and limitations

The primary strength of our study is that it includes prospective cohort studies and a large number of participants and deaths, providing greater statistical power to quantitatively evaluate the association between legume consumption and mortality. We also conducted linear and nonlinear dose–response analyses to elucidate the strength and shape of the observed associations. Other strengths include the use of comprehensive search strategy, extensive subgroup, sensitivity, and influence analyses, assessing the risk of bias and the certainty of evidence for each association.

Our findings should be interpreted in light of several limitations. First, because of the observational nature of the included studies, the observed associations may be influenced by residual or unmeasured confounding factors. Furthermore, causality cannot be established based only on observational data. Second, there was substantial heterogeneity between studies in the analyses of legumes and all-cause, CVD, CHD, and cancer mortality. Although we accounted for potential sources of heterogeneity, such as geographical location, participant numbers, gender, duration of follow-up, and confounding variables, studies may have also differed in the types of legumes consumed, the precision with which legume intake was measured, the cooking method, and the definition of legumes. Third, most included studies assessed legumes only once at the study's baseline and did not account for changes in legume consumption over time, suggesting that measurement errors in legume intake may have influenced findings. Fourth, most studies lacked information on the preparation and cooking of legumes. Legumes' nutritional value and nutrient loss vary according to their cooking method [92]. Differences in the types of legumes, as well as mixed dishes or settings in which legumes are consumed, could have influenced the observed associations. For example, beans are often eaten with bacon, sausages, and eggs in Europe and United States, which could have a different impact on health than a dish with mung dahl, vegetables, and brown rice. Whether this could explain the geographical differences in results requires further study. Fifth, the association of dietary legume consumption with stroke and cancer mortality was not stable in the influence analysis, and relatively few studies were included in the analyses of CHD and stroke mortality. Therefore, more research is required before these associations can be conclusive. Sixth, regional differences in legume intake may have influenced the highest and lowest legume intake categories, as well as the results of these comparisons. To deal with these differences and the overlap of legume intake ranges between the studies, we conducted the dose–response analysis. Finally, one of the major limitations of meta-analyses today is their inability to address the critical issue of substitution in practice. Legumes, for example, may be more beneficial than a very common starch and refined sugar breakfast, but they may not be as beneficial as a breakfast of whole grains and nuts.

Conclusions, policy implications, and future research

Altogether, higher legume intake was associated with a reduced risk of all-cause and stroke mortality; however, no association was found for CVD, CHD, and cancer mortality. Each 50-g increase in legume intake was associated with a 6% lower risk of all-cause mortality in the linear dose–response analysis. Our findings, therefore, strongly support current dietary recommendations to consume more legumes in the general population. This meta-analysis is of importance for public health globally, as increased consumption of legumes is likely to be cost-effective and bring health benefits over time. Although this meta-analysis focused on total legume intake, which is an important item to base overall conclusions on, further epidemiological research is warranted to elucidate the effects of particular types of legumes on the risk of specific chronic diseases and causes of death.

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Author disclosures

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the articles, data extraction, data analysis, and wrote the manuscript; SMM: contributed to the literature search, data extraction, data analysis, and manuscript drafting; HOS, SHR, BL: contributed to manuscript drafting and approving the final manuscript; DA: contributed to the data analysis and approving the final manuscript; and all authors: acknowledge full responsibility for the analyses and interpretation of the report and have read and approved the final manuscript. The corresponding author certifies that all of the listed authors meet the authorship criteria and that no other authors who meet the criteria have been overlooked.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2022.10.009.

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