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SYSTEMATIC REVIEWS AND META-ANALYSES

Intake of legumes and cardiovascular disease: A systematic review and dose–response meta-analysis

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Abstract *Aims:* To summarize the evidence on the association between the intake of legumes and the risk of cardiovascular disease (CVD) overall, coronary heart disease (CHD) and stroke, and to identify optimal intake levels for reduced disease risk through a systematic review and dose–response meta-analysis.

Data synthesis: We have systematically searched PubMed, Scopus and Web of Science up to March, 2022 for the retrieval of intervention and observational studies (PROSPERO Reg. number: CRD42021247565). Pooled relative risks (RRs) comparing extreme categories of intake were computed using random-effects models. One-stage dose–response meta-analyses were also performed using random-effects models. 22 831 articles were screened resulting in 26 eligible observational studies (21 prospective cohort and 5 case–control studies). When comparing extreme categories of intake, the consumption of legumes was inversely associated with CVD (n = 25: RR = 0.94; 95%CI:0.89,0.99) and CHD (n = 16: RR = 0.90; 95%CI:0.85,0.96), but not with stroke (n = 9: RR = 1.00; 95%CI:0.93,1.08). We further found evidence for an inverse dose–response association with CHD, increasing in magnitude up to an intake of 400 g/week, after which the benefit seems to level-off.

Conclusions: The intake of legumes was associated with a reduced risk of CVD and CHD, but not with stroke, among individuals with the highest consumption levels. An intake level of 400 g/week seemed to provide the optimal cardiovascular benefit. Further research is needed to better understand the role of legumes in stroke subtypes.

Acronyms: BMI, Body Mass Index; CI, Confidence interval; CVD, Cardiovascular disease; CHD, Coronary heart disease; FFQ, Food frequency questionnaire; HR, Hazard Ratio; LDL, Low-density lipoprotein; MRI, Magnetic resonance imaging; OR, Odds ratio; PRISMA, Preferred reporting items for systematic reviews and meta-Analyses; PROSPERO, International prospective register of systematic reviews; ROBINS-I, Risk of bias in non-randomised studies of interventions; RCT, Randomized controlled trial; RR, Relative risk; T2D, Type 2 diabetes.

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1. Introduction

Legumes are defined as the succulent seeds and pods of the botanical family *Leguminosae* or *Fabaceae*, including a wide variety of species such as beans, peas, chickpeas, lentils, broad beans, soya beans and lupins [1], that can be consumed as whole pods, their fresh shelled products or in the form of dried mature seeds (also commonly known as pulses). There has been an increasing recognition on the potential of legumes as environmentally sustainable plant protein sources, with several benefits for human health [2]. In addition to their high protein content, legumes are sources of fibre, essential minerals such as magnesium, potassium, iron and zinc, B vitamins and other bioactive compounds. Moreover, legumes are naturally low in saturated fat and provide low glycaemic-index carbohydrates [3]. Previous research has consistently linked legumes' consumption with important health benefits, such as reduced incidence of cardiovascular disease (CVD), diabetes, overweight/obesity [4,5] and some types of cancer [6]. Accordingly, there is a growing body of evidence addressing the potential beneficial impact of legumes in cardiovascular health and cardiometabolic factors, highlighting the advantage of integrating legumes in the habitual diet [4,5]. For these reasons, legumes feature in several healthy eating indices [7–9] and dietary guidelines of Scientific Bodies and Medical Societies [10–12]. Globally, CVD is the leading cause of mortality and a major contributor to the loss of years of healthy life due to disability [13]. There is consistent evidence that diet can favourably modify major CVD risk factors, such as dyslipidaemia, diabetes mellitus, hypertension and obesity and further decrease CVD incidence [13,14]. Legumes, as part of a balanced healthy diet, have the potential to protect against the development of CVD through several etiological pathways [4,5].

Previous studies have attempted to summarize the evidence addressing the association between the consumption of legumes and cardiovascular outcomes, indicating a potential beneficial pattern for higher intake levels [15–19]. However, previous meta-analyses have not differentiated between non-soy and soy legumes [15–17], which differ in their nutritional composition [20]; have provided results for combined incidence and mortality data [16,17]; have not assessed dose–response associations or have used methods that cannot be applied in studies with only two categories of exposure [15–19].

We therefore performed a systematic review and dose–response meta-analysis to summarize the evidence on the association between the intake of legumes and the risk of CVD overall, coronary heart disease (CHD) and stroke, and to identify optimal intake levels for a reduced disease risk.

2. Methods

This systematic review and meta-analysis was prepared in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [21]. The study protocol was registered in PROSPERO – International prospective register of systematic reviews (Reg. number CRD42021247565) [22].

2.1. Search strategy

We have conducted a systematic literature search in PubMed, Scopus and Web of Science for original studies published up to March 22, 2022 (Supplemental Table 1), that reported the association between the intake of legumes and CVD (comprising any cardiovascular disease), as well as CHD and stroke in particular. The exposure of interest was defined as the intake of beans, peas, lentils or other species belonging to the *leguminosae* family [1], in their dried or fresh form, reported individually or in combination. Since the association between the intake of soy and CVD has already been extensively reviewed [23], soy or soy products were not considered under the exposure definition, unless combined with other legume subtypes.

2.2. Study selection

A study was considered eligible if 1) it was an intervention or a prospective or retrospective observational study that 2) evaluated the association between the intake of legumes and CVD, CHD or stroke in 3) the general adult population. Additionally, studies were suitable for inclusion if 4) they reported risk estimates as rate ratios (RRs), hazard ratios (HRs), or odds ratios (ORs), with the corresponding 95% confidence intervals (CIs), or data to calculate the respective variance, for all categories of intake. Studies were excluded if 1) not involving human subjects, 2) not presenting original data (e.g., review articles, editorials, reports, comments or guidelines), 3) performed among children (<18 y) and/or pregnant women, 4) having a cross-sectional design, ecological studies, case series, case reports and qualitative studies, 5) addressing exposures other than the intake of legumes as defined above, 6) addressing outcomes other than CVD, CHD or stroke. In addition, studies in which legume intake was expressed as a continuous variable could not be used in the dose–response meta-analysis. Lastly, no restrictions were imposed regarding the study's language, geographical location or publication date.

The titles/abstracts and full-texts of studies identified in the original search were reviewed independently by two authors (VM and ANi) in accordance with the exclusion criteria. Any disagreements were resolved by consensus or after discussion involving a third author (AN). The literature search was complemented by back and forward citation tracking of eligible papers and other relevant systematic reviews and meta-analyses.

2.3. Data extraction

Two authors (VM and ANi) have independently extracted the information using a standardized data collection form. Since no intervention studies were identified at the study selection stage, the following data were extracted: 1) study characteristics (study design, publication year, duration of follow-up when relevant), 2) sample characteristics (country, study cohort, sex, age, sample size), 3) exposure characteristics (definition, data collection methods and categories of intake), 4) outcome characteristics (definition, outcome assessment methods, number of cases) and 5) association measures with CIs for fully-adjusted models and covariates. Estimates were extracted for the whole sample or for different strata, as available. Authors of eligible studies with missing information that was relevant for the calculation of the pooled estimates were contacted and reply was provided by investigators of the Finnish Mobile Clinic Health Examination Survey on legume intake for males and females combined [24].

For each intake category we extracted the mean or median intake value, depending on the available data. If these were missing, the midpoint of each intake category was computed. When the highest and lowest exposure categories were "open", a value that was 20% higher or lower than the closest cut-off point was calculated. For studies where the legume intake was only reported as number of servings/portions, intake was converted into grams using a predefined weight of 100 g per portion, in order to be consistent with the serving size used in previous meta-analyses [15–19,25].

2.4. Risk of bias assessment

The internal validity of eligible studies was assessed independently by two authors (VM and ANi) using the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) tool [26]. In case of disagreement, consensus was achieved involving a third author (AN). The following risk of bias domains were considered: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported results. For each domain, studies were judged to be at low, moderate, serious or critical risk of bias. The tool was tailored to address our specific research question and to accommodate the nature and methodology of studies selected for the analysis, in accordance with the ROBINS-I guidance document [26].

2.5. Statistical analysis

We performed traditional meta-analyses to investigate the association between the intake of legumes and CVD, CHD and stroke by comparing the study-specific highest versus the lowest intake category. Summary RRs and respective 95% CIs were calculated by applying random-effects models [27], as they are generally considered preferable to meta-analyse data presented in peer-reviewed publications [28] and to allow the generalization of results beyond the studies considered [29]. Moreover, in the overall analysis ORs were assumed to approximate RRs in accordance with the "rare disease assumption", a practice commonly followed in this field [30,31]. Heterogeneity was assessed using the I^2 statistic [32]. In order to investigate possible sources of heterogeneity, we conducted subgroup analyses for each outcome of interest according to the a) study design (case–control vs. prospective cohort studies), b) study location (Asian vs non-Asian studies), c) follow-up time ($<$10 years vs. $\geq$10 years) d) validity of the dietary assessment method (validated vs. not validated), e) number of cases ($<$500 vs. $\geq$500 cases) and f) sex (females vs. males vs. both). Sensitivity analyses were performed for each outcome by excluding studies that specifically include soy in their exposure definition and studies that were classified as having a serious/critical risk of bias. Additional sensitivity analyses included the application of alternative standard values (i.e., $\pm$15% and $\pm$25% instead of $\pm$20%) to estimate the highest and lowest exposure categories when these were open [33]. Furthermore, all meta-analyses were repeated by removing each single study (leave-one-out method) in order to evaluate its influence on the pooled effect estimates. We assessed the possibility of publication bias through visual inspection of funnel plots and the Egger's regression test.

Using the methodology established by Greenland and Longnecker (1992) [34], and advanced by Orsini et al. (2012) [35] and Crippa et al. (2019) [36], we have performed a dose–response meta-analysis to identify the association between the intake of legumes and the risk of CVD, CHD and stroke. We applied the 'one-stage' approach [35,36], that allows to include studies assessing only two levels of exposure, using a restricted cubic spline model with 3 knots at fixed percentiles (10, 50, and 90%) of the intake distribution. The restricted cubic spline model was fitted with a generalized least-squares regression taking into account the correlation within each set of the effect estimates and combining the effect estimates using the restricted maximum likelihood method in a random-effects meta-analysis [35,37,38]. All analyses were performed with the Stata statistical software, version 14 (StatCorp, College Station, TX, USA) and RStudio (Version 1.1.456).

3. Results

The complete study selection process is described in Fig. 1. A total of 26 eligible articles from 24 unique prospective cohort and case–control studies assessing the association between the intake of legumes and CVD overall, CHD and/or stroke in particular were identified [24,39–63]. Study characteristics are summarized in Table 1 and a detailed description is available in Supplemental Tables 2–4.

3.1. Legumes and cardiovascular disease

Out of the total of 26 studies identified in the systematic review, Martínez-González MA et al., 2011 [53] was excluded from the analyses addressing the association between the intake of legumes and CVD overall for being performed using the same sample as Mata-Fernández A et al., 2021 [54]. Twenty-five studies were thus included,

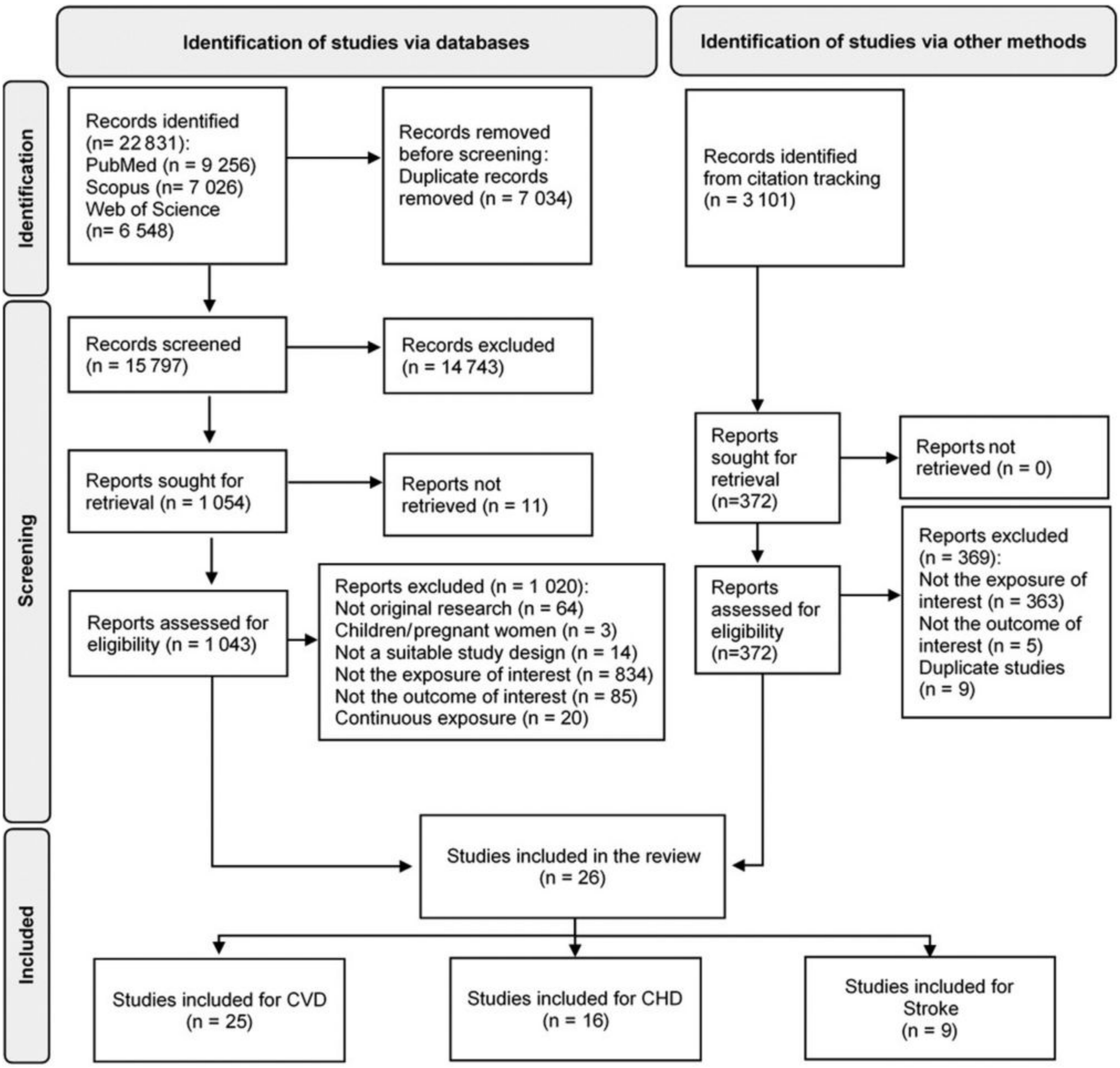


Figure 1 Flow-chart describing the systematic literature search and study selection for the association between the intake of legumes and CVD, CHD and Stroke.

comprising as outcomes CVD as a composite measure, CHD or stroke (Supplemental Table 2). Of these, twenty were prospective cohorts [24,39–43,45–48,50,54–61,63] (mean follow-up: 14.6 y) and five were case–control studies [44,49,51,52,62]. One study was performed in Africa [51], six in Asia [40,44,50,55,56,63], nine in Europe [24,39,52,54,57,59–62] and nine in North America [41–43,45–49,58]. The pooled sample included a total of 1 703 121 participants and 44 181 cases and age ranged between 19 and 83 years. All studies used Food Frequency Questionnaires (FFQs) for the dietary assessment, with the exception of Mizrahi, A et al. (2009) [24] who relied on interviewer-administered diet history. Three studies have explicitly included soy-legumes in their definition along with non-soy ones [42,46,63], while eleven have explicitly excluded them [39,41,43–45,49,50,54–56,61]. For the remaining eleven studies, no details on the exposure definition were provided. CVD cases were ascertained using medical records and vital statistics, with the exception of: Baik, I et al. (2013) [40] (based on self-reporting and vital statistics); Scarmeas N et al. (2011) [58] (using magnetic resonance imaging (MRI)); and Durga AV & Manorenj S (2019) [44] (using MRI or computed tomography scans). Maher MA & Gutbi SS (2017) [51] did not report on the method used to identify new cases.

A summary of the risk of bias assessment is presented in Supplemental Table 5. Four studies were judged to be at

Table 1 Summary description of studies included in the systematic review and meta-analysis (N = 26).

Study reference	Country	Cohort (follow-up duration, y)	Sex	Sample size	Age(y) Mean/Range	Type of legumes included	Outcomes	Exposure contrast
Prospective cohort studies								
Atkins JL et al., 2014 [39]	UK	BRHS (11.3)	M	3328	60–79	Baked or butter beans, lentils, peas, chickpeas, sweetcorn	CVD, CHD incidence	Highest vs. lowest
Baik I et al., 2013 [40]	South Korea	KGES (8)	FM	9026	40–69	Not specified	CVD incidence	Above or below the median
Bazzano LA et al., 2001 [41]	USA	NHEFS (19)	FM	9632	25–74	Beans, lentils and chickpeas	CVD, CHD incidence	Quintiles
Bernstein AM et al., 2010 [43]	USA	NHS (26)	F	84 136	30–55	Beans or lentils, baked or dry	CHD incidence	Quintiles
Bernstein AM et al., 2012 [42]	USA	NHS (26)	F	84 010	30–55	Dry beans, peas, soy, and tofu	Stroke incidence	Quintiles
	USA	HPFS (22)	M	43 150	40–75	Dry beans, peas, soy, and tofu	Stroke incidence	Quintiles
Fraser GE et al., 1992 [45]	USA	AHS (6)	FM	26 473	52	Beans and peas	CHD incidence	Tertiles
Fung TT et al., 2018 [46]	USA	NHS II (20)	F	93 131	27–44	Dry beans, peas, soy, and tofu	CHD incidence	Quintiles
	USA	HPFS (24)	M	43 966	40–75	Dry beans, peas, soy, and tofu	CHD incidence	Quintiles
Haring B et al., 2014 [47]	USA	ARIC (22)	FM	12 066	45–64	Not specified	CHD incidence	Quintiles
Haring B et al., 2015 [48]	USA	ARIC (22.7)	FM	11 601	45–64	Not specified	Stroke incidence	Quintiles
Kokubo Y et al., 2007 [50]	Japan	JPHC (12.5)	FM	40 450	40–59	Beans	CVD, CHD, Stroke incidence	Tertiles
Mata-Fernández A et al., 2021 [54]	Spain	SUN (11.5)	FM	18 631	38.1	Lentils, peas, chickpeas and beans	CVD incidence	Above or below the median
Miller V et al., 2017 [55]	Multinational	PURE (7.4)	FM	135 335	35–70	Beans, black beans, lentils, peas, chickpeas and black-eyed peas	CVD, CHD, Stroke incidence	Quintiles
Martínez-González MA et al., 2011 [53]	Spain	SUN (4.9)	FM	13 609	38	Lentils, peas, chickpeas and beans	CHD incidence	Median
Mizrahi A et al., 2009 [24]	Finland	FMCHES (24)	FM	3932	40–74	Not specified	Stroke incidence	Quartiles
Nouri F et al., 2021 [56]	Iran	ICS (13)	FM	5432	≥35	Beans, chickpeas, lentils	CVD incidence	Tertiles
Perez-Cornago A et al., 2021 [57]	Multinational/Europe	EPIC (12.6)	FM	490 311	35–70	Not specified	CHD incidence	Quintiles
Scarmeas N et al., 2011 [58]	USA	WHICAP (5.8)	FM	707	≥65	Not specified	Stroke incidence	Above or below the median
Schröder H et al., 2014 [59]	Spain	PREDIMED (4.8)	FM	7447	67	Not specified	CVD incidence	Highest vs. lowest
Tektonidis TG et al., 2015 [60]	Sweden	SMC (10.4)	F	32 921	48–83	Not specified	CHD incidence, Ischaemic and haemorrhagic stroke incidence	Above or below the median
Tong TYN et al., 2020 [61]	Multinational/Europe	EPIC (12.7)	FM	418 329	51.2	Beans, chickpeas, split peas, lentils	Stroke incidence	Quintiles
Yu D et al., 2014 [63]	China	SWHS (9.8)	F	67 211	40–70	Fresh & snow peas, soya beans, broad, long and green beans	CHD incidence	Quartiles
	China	SMHS (5.4)	M	55 474	40–74	Fresh & snow peas, soya beans, broad, long and green beans	CHD incidence	Quartiles
Case-control Studies								
Durga AV & Manorenj S 2019 [44]	India	–	FM	300	19–80	Pulses (Red, green, black and bengal gram dhal & whole pulses)	Stroke	Highest vs. lowest

Kabagambe, EK et al., 2005 [49]	Costa Rica	–	FM	4238	<75	Dried mature beans	CHD	Quartiles
Maher, MA & Gutbi SS 2017 [51]	Sudan	–	FM	100	~53	Not specified	CHD	Highest vs. lowest
Martínez-González MA et al., 2002 [52],	Spain	–	FM	342	<80	Not specified	CHD	Quintiles
Turati F et al., 2015 [62]	Italy	–	FM	1442	19–79	Not specified	CHD	Above or below the median

AHS: Adventist Health Study; ARIC: Atherosclerosis Risk in Communities; BRHS: British Regional Heart Study; CHD: Coronary Heart Disease; CI: Confidence Interval; CVD: Cardiovascular Disease; EPIC: European Prospective Investigation into Cancer and Nutrition; FMCHES: Finnish Mobile Clinic Health Examination Survey; HPFS: Health Professionals' Follow-up Study; ICS: Isfahan Cohort Study; JPHC: Japan Public Health Center–Based Study; KGES: Korean Genome Epidemiology Study; NHEFS: National Health and Nutrition Examination Survey Epidemiologic Follow-up Study; NHS: Nurses' Health Study; PREDIMED: Prevention with Mediterranean Diet; PURE: Prospective Urban Rural Epidemiology; RoB: Risk of bias; SMC: Swedish Mammography Cohort; SMHS: Shangai Men's Health Study; SUN: Seguimiento University of Navarra; SWHS: Shangai Women's Health Study; WHICAP: Washington Heights/Hamilton Heights Columbia Aging Project.

serious risk of bias due to either limited control of confounding (i.e. failure to adjust for important confounders, including age, sex, body mass index (BMI) and energy intake; in the absence of BMI, controlling for energy intake and physical activity levels was sufficient; in the absence of energy intake, adjusting for overall food intake was acceptable) [44,59] or concerns regarding exposure classification [44,45,62], while one study was judged to be at critical risk of bias [51] due to possible bias in exposure classification (not using a validated dietary assessment method and not quantifying intake levels).

The meta-analysis comparing the highest versus the lowest category of intake (31 comparisons) showed a protective association between the consumption of legumes and CVD risk (RR = 0.94; 95%CI:0.89, 0.99), with a moderate level of heterogeneity across included estimates (I^2 = 43.1%) (Fig. 2). The Egger's regression asymmetry test showed no publication bias (Supplemental Figs. 1–B), supported by the substantially symmetric distribution of the corresponding funnel plot (Supplemental Figs. 1–A). The pooled estimate was largely determined by prospective cohort studies (20 out of the 25 studies considered) and as expected, the RR remained materially unchanged when the analysis relied only on this study design (n = 20, RR = 0.96, 95%CI: 0.91; 1.00; I^2 = 39.5) (Fig. 2 and Supplemental Table 8). Conversely, the association was stronger when only case–control studies were considered (n = 5, RR = 0.72, 95% CI: 0.60, 0.85; I^2 = 0.0%). An inverse association was also observed among studies conducted in Asia (n = 6, RR = 0.82, 95%CI: 0.74, 0.90; I^2 = 9.9%) and the pooled estimate for non-Asian studies was similar to that observed for the main analysis (n = 19, RR = 0.97, 95%CI: 0.92, 1.02; I^2 = 34.0%) (Supplemental Table 8). The association was stronger considering studies that did not rely on a validated dietary assessment method [10,24,41,44,45,51,62] (n = 6, RR = 0.85, 95%CI: 0.74; 0.96; I^2 = 30.0%), when compared with those using validated methods [39–43,46–50,52,54–61,63] (n = 19, RR = 0.96, 95%CI: 0.91, 1.01; I^2 = 42.2%) (Supplemental Table 8). Subgroup analyses based on follow-up duration, number of included cases and participants' sex did not reveal significant changes (Supplemental Table 8). The inverse association between the intake of legumes and CVD risk also remained after the exclusion of studies specifically assessing soy intake [42,46,63] (RR = 0.93; 95%CI: 0.88; 0.98; I^2 = 47.7%) and judged to be at serious/critical risk of bias [44,45,51,59,62] (RR = 0.94; 95%CI: 0.90; 0.99; I^2 = 37.5%). Furthermore, after selectively removing each individual study (Supplemental Fig. 2), the pooled estimates have consistently remained within the 95% CI of the main analysis. In addition, pooled estimates remained the same after the application of ±15% or ±25% (instead of ±20%) to the closest available boundary (lower or upper) in open categories of intake, indicating that results are robust to the choice of a standard value for these estimations.

Of the twenty-five studies included in the analysis comparing extreme categories of intake, seventeen provided data that were considered in the dose–response

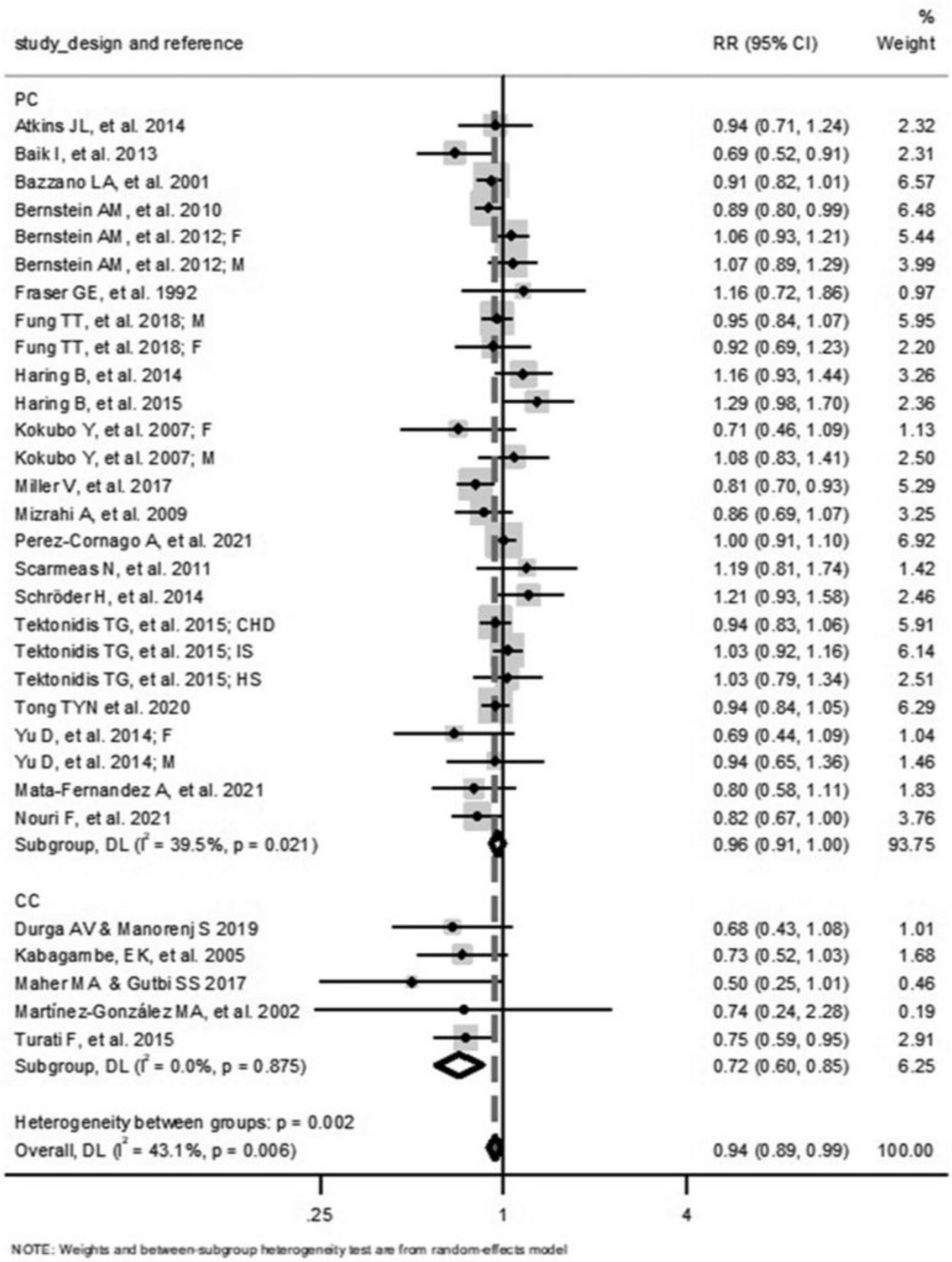
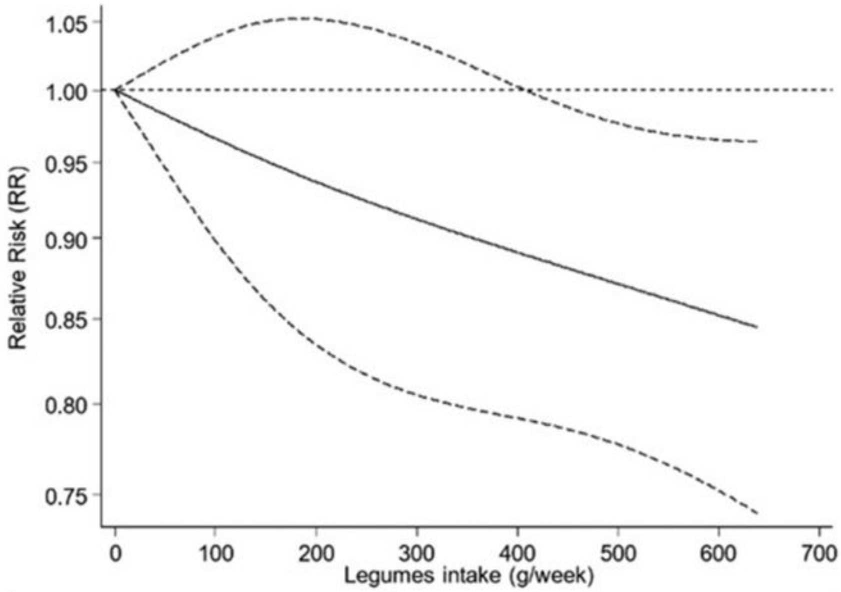


Figure 2 Meta-analysis for the association between the intake of legumes (highest vs. lowest, as specified in the individual studies) and CVD overall in prospective cohort (PC) and case–control studies (CC). Weights and between-subgroup heterogeneity are from random-effects model.

analysis [24,40–43,47–49,52,54,55,57,59–63], comprising a total of 1 489 243 participants and 37 166 CVD cases. Considering an intake level of 0 g/week as reference, one portion of cooked legumes (100 g) per week was associated with a reduced CVD risk (RR = 0.97; 95%CI: 0.90, 1.04), which was further attenuated per each increasing portion (Fig. 3). The subgroup analysis based on study design is presented in supplemental figures 3-A and 3-B. Based on evidence from 14 prospective cohort studies, the inverse association between legume intake and CVD risk remains but is attenuated (Supplemental Figs. 3–A). Conversely, the dose–response analysis performed using data from case–control studies only has indicated a U-shaped association between the intake of legumes and CVD (Supplemental Figs. 3–B). However, the number of included studies was small (n = 3) and the interpretation of this result should be made with caution. Dose–response associations between legume intake and CVD risk by study location are presented in Supplemental Fig. 4. The gradually increasing benefit for every additional weekly portion was observed in non-Asian populations (14 studies, Supplemental Figs. 4–B) and it was more pronounced in Asians (3 studies, Supplemental Figs. 4–A), who have also reported higher intake levels.



	0g/week	100g/week	200g/week	300g/week	400g/week
RR (95% CI)	Ref.	0.97 (0.90, 1.04)	0.94 (0.83, 1.05)	0.91 (0.80, 1.03)	0.89 (0.79, 1.00)

Figure 3 Summary dose−response association (solid line) and respective confidence interval (dashed lines) between the intake of legumes (g/week) and the risk of CVD (17 studies). Estimates were obtained through weighted mixed-effects models with restricted cubic splines with 3 knots at fixed percentiles of legume intake. The value of 0 g/week served as reference.

3.2. Legumes and coronary heart disease

Sixteen eligible studies assessed the association between the intake of legumes and CHD [39,41,43,45−47,49−53,55,57,60,62,63], including a total of 1 114 165 participants and 28 258 cases (Supplemental Table 3). Twelve studies were prospective cohorts [39,41,43,45−47,50,53,55,57,60,62] (mean follow-up: 13.6 y) and four studies followed a case−control design [49,51,52,62]. One study was performed in Africa [51], three were performed in Asia [50,55,63], six in Europe [39,52,53,57,60,62] and six in North America [41,43,45−47,49]. Participants' age ranged from 19 to 83 years old. All studies used FFQs for the dietary assessment. Two studies have included soy and non-soy legumes in their exposure definition [46,63], eight included only non-soy legumes [39,41,43,45,49,50,53,55] and six did not specify the type of legumes included [47,51,52,57,60,62]. CHD cases were assessed using medical records and vital statistics; Maher MA & Gutbi SS (2017) [51] did not report the method used.

The risk of bias assessment is presented in Supplemental Table 6. Two studies were judged to be at serious risk of bias due to concerns in exposure classification [45,62], while one [51] was judged to be at critical risk of bias (not using a validated dietary assessment method and not quantifying intake levels).

The meta-analysis comparing extreme categories of intake (19 comparisons) showed an inverse association between the intake of legumes and CHD, with a 10% decrease in disease risk (RR = 0.90; 95%CI: 0.85, 0.96) and a low level of heterogeneity (I^2 = 27.9%) (Fig. 4). Visual inspection of the funnel plot (Supplemental Figs. 5−A) suggested an underrepresentation of small studies with positive associations, whereas the Egger's regression asymmetry test showed no publication bias (Supplemental Figs. 5−B). The analysis considering only prospective cohort studies (n = 12) resulted in a pooled RR similar to that observed in the main analysis (Fig. 4 and Supplemental Table 8), whereas a stronger association was observed among case−control studies (n = 4, RR = 0.72, 95%CI: 0.60, 0.87; I^2 = 0.0%). A stronger association was also observed in studies conducted in Asia (n = 3, RR = 0.84, 95%CI: 0.71, 1.00; I^2 = 0.0%) comparing with non-Asians (n = 13, RR = 0.91, 95%CI: 0.84, 0.97; I^2 = 42.2%), and among studies that did not use validated dietary assessment methods [41,45,51,62] (n = 4, RR = 0.79, 95%CI: 0.67; 0.94; I^2 = 31.3%), in comparison with those using validated methods [39,43,46,47,49,50,52,53,55,57,60,63] (n = 19, RR = 0.94, 95%CI: 0.89; 0.99; I^2 = 0.0%) (Supplemental Table 8). Subgroup analyses based on follow-up duration, number of included cases and sex of the participants did not reveal substantial changes (Supplemental Table 8). The sensitivity analyses performed excluding studies comprising soy legumes (RR = 0.89; 95%CI: 0.89; 0.96; I^2 = 39.3%) and studies judged to be at a serious/critical risk of bias (RR = 0.91; 95%CI: 0.86; 0.97; I^2 = 18.5%) have not altered substantially the magnitude and the precision of the association. The selective exclusion of each individual study did not influence the pooled estimate observed in the main analysis (Supplemental Fig. 6). The pooled RRs also remained the same after the application of ±15% or ±25% (instead of

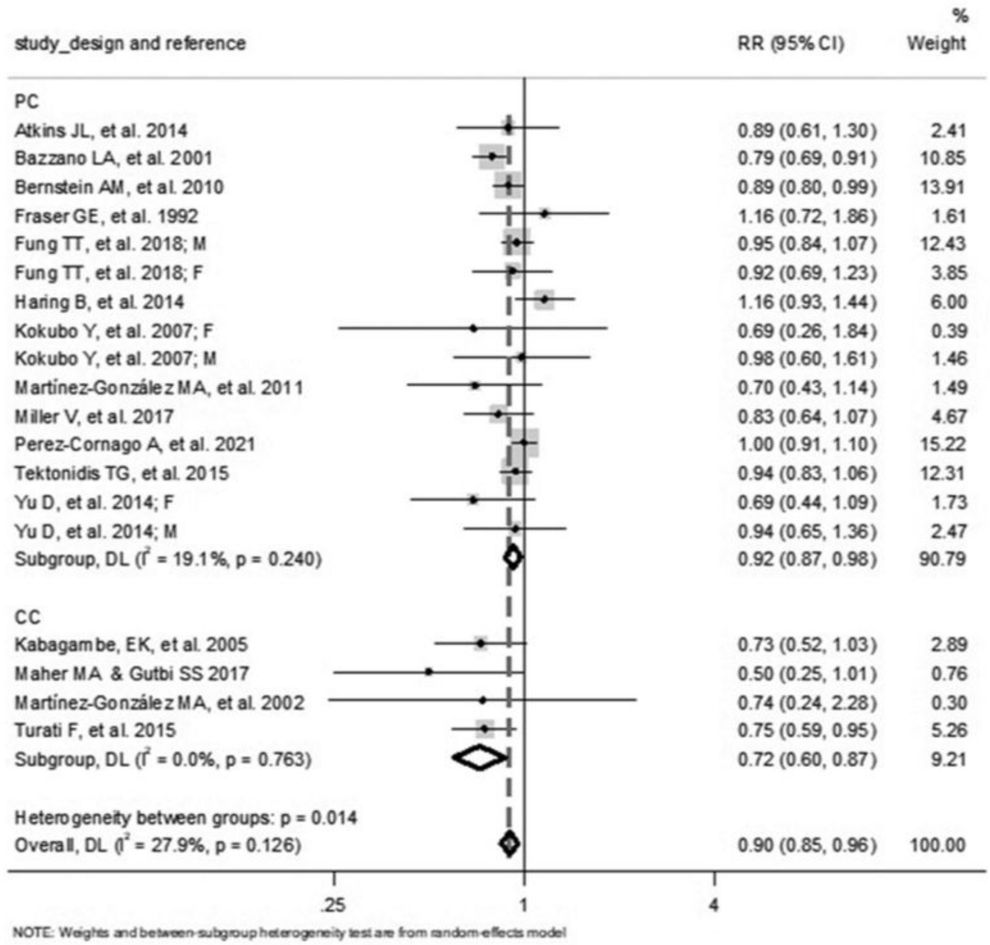


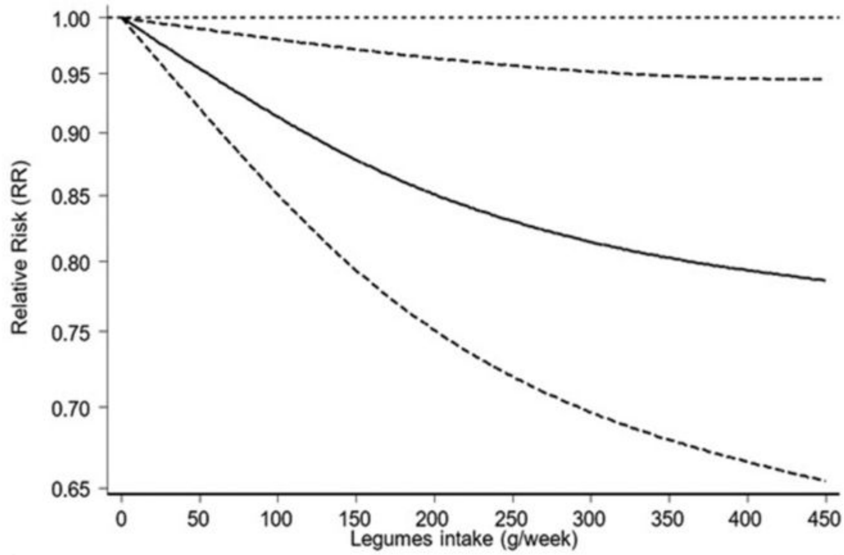
Figure 4 Meta-analysis for the association between the intake of legumes (highest vs. lowest, as specified in the individual studies) and CHD in prospective cohort (PC) and case–control studies (CC). Weights and between-subgroup heterogeneity are from random-effects model.

±20%) to the closest available boundary (lower or upper) in open categories of legume intake, indicating that results are robust to the choice of a standard value for these estimations.

Of the total of eligible studies, eleven were included in the dose–response analysis [41,43,47,49,50,52,53,55,57,60,62,63] (927 701 participants and 23 294 cases). Considering no consumption (0 g/week) as the reference category, an intake of 100 g (about one portion) of legumes per week was associated with a reduction of 9% in CHD risk (RR = 0.91; 95%CI: 0.85, 0.98), with an increased benefit for each additional 100 g/week increment up to an intake of 400 g/week, upon which the association seems to reach a plateau (Fig. 5). Again, as expected, the pattern of association based on prospective cohort studies only was similar to that observed for the main dose–response analysis (Supplemental Figs. 7–B). When considering case–control studies only, we observed a U-shaped association between the intake of legumes and CHD, with the highest benefit level being noted for an intake of 200 g/week, when compared with a consumption of 0 g/week (RR = 0.53, 95%CI: 0.30, 0.95) (Supplemental Figs. 7–A). Considering two Asian studies and no consumption as the reference category, an inverse association was observed for an intake of 100 g/week (RR = 0.93, 95%CI: 0.86, 1.01), which increased further with an additional 100 g (200 g/week: RR = 0.88, 95%CI: 0.76, 1.02) and subsequently reached a plateau as an additional increase in intake did not relate to a further reduction in disease risk (300 g/week: RR = 0.87, 95%CI: 0.75,1.01) (Supplemental Figs. 8–A). For non-Asian studies (n = 9), the relationship pattern observed was, as expected, similar to that of the main dose–response analysis (Supplemental Figs. 8–B).

3.3. Legumes and stroke

Nine studies on the association between the intake of legumes and stroke were identified [24,42,44,48,50,55,58,60,61], including a total of 770 735 participants and 13 590 cases (age range: 19-83 y) (Supplemental Table 4). Eight studies were prospective cohorts (mean follow-up: 15.6 y) while one study [44] had a case–control design. Three studies were performed in Asia [44,50,55], three in Europe [24,60,61] and three in North America [42,48,58]. Almost all studies used FFQs for the dietary assessment; Mizrahi, A et al. assessed intake through a diet history



	0g/week	100g/week	200g/week	300g/week	400g/week
RR (95% CI)	Ref.	0.91 (0.85, 0.98)	0.85 (0.75, 0.96)	0.81 (0.70, 0.95)	0.79 (0.67, 0.95)

Figure 5 Summary dose−response association (solid line) and respective confidence interval (dashed lines) between the intake of legumes (g/week) and the risk of CHD (11 studies). Estimates were obtained through weighted mixed-effects models with restricted cubic splines with 3 knots at fixed percentiles of legume intake. The value of 0 g/week served as reference.

(2009) [24]. Only one study included soy under the definition of legumes [42]; four have included only non-soy legumes [44,50,55,61]; and four did not specify any subtypes [24,48,58,60]. Cases of stroke were ascertained using medical records and vital statistics, with the exception of Scarmeas N et al. (2011) [58] (assessed using MRI) and Durga AV & Manorenj S (2019) [44], (MRI or computed tomography scans).

The risk of bias assessment is shown in Supplemental Table 7. One study was judged to be at serious risk due to bias in the confounding (i.e. failure to adjust for important confounders, including age, sex, body mass index (BMI) and measures of dietary intake/patterns, in the absence of energy intake; or energy intake, and physical activity and clinical CVD risk factors, in the absence of BMI) and exposure classification domains (not using a validated dietary assessment method and not quantifying intake levels) [44].

The pooled RR comparing the highest with the lowest category of intake (12 comparisons) revealed no association between the consumption of legumes and stroke (RR = 1.00; 95%CI: 0.93, 1.08; I^2 = 36.6%) (Fig. 6). No publication bias was detected (supplemental figure 9-A and 9-B). The subgroup analysis based on the geographic origin of the study suggested a possible inverse association in Asian populations (n = 3) (RR = 0.87, 95%CI: 0.66, 1.15; I^2 = 57.8%), while among non-Asians (n = 6) the association was again close to the null (RR = 1.02, 95%CI: 0.95, 1.09; I^2 = 16.4%) (Supplemental Table 8). The remaining stratifications did not materially change the results (Supplemental Table 8). The sensitivity analyses excluding studies comprising soy legumes in their definition [42] (RR = 0.98, 95%CI: 0.89, 1.08; I^2 = 42.9%) or studies judged to be at a serious/critical risk of bias [44] (RR = 1.01, 95%CI: 0.94, 1.09; I^2 = 31.5%) did not substantially influenced the main results. The pooled estimates obtained by selectively removing each single study remained within the initial 95% CI and were consistent with the main analysis (Supplemental Fig. 10). Pooled overall estimates remained the same after the application of ±15% or ±25% (instead of ±20%) to the closest lower or upper boundary available in open categories of legume intake, indicating that results are robust to the choice of a standard value for these estimations.

The dose−response analysis included a total of six studies [24,42,48,55,60,61] (729 278 participants and 12 631 cases), all with a prospective design. We found no evidence of a dose−response association between the intake of legumes and stroke (Fig. 7). The exclusion of the single Asian study [55] resulted in a similar pattern (Supplemental Fig. 11).

4. Discussion

In a meta-analysis of studies reporting on relationships between legume intake and risk of CVD overall and CHD or stroke in particular, we observed an inverse association between the intake of legumes (including soy and non-soy products) and CHD risk, when study-specific highest categories of intake were compared to their corresponding lowest ones. Specifically, there was a 10% decrease (95%CI: 4%, 15%) in the risk of CHD among individuals with the

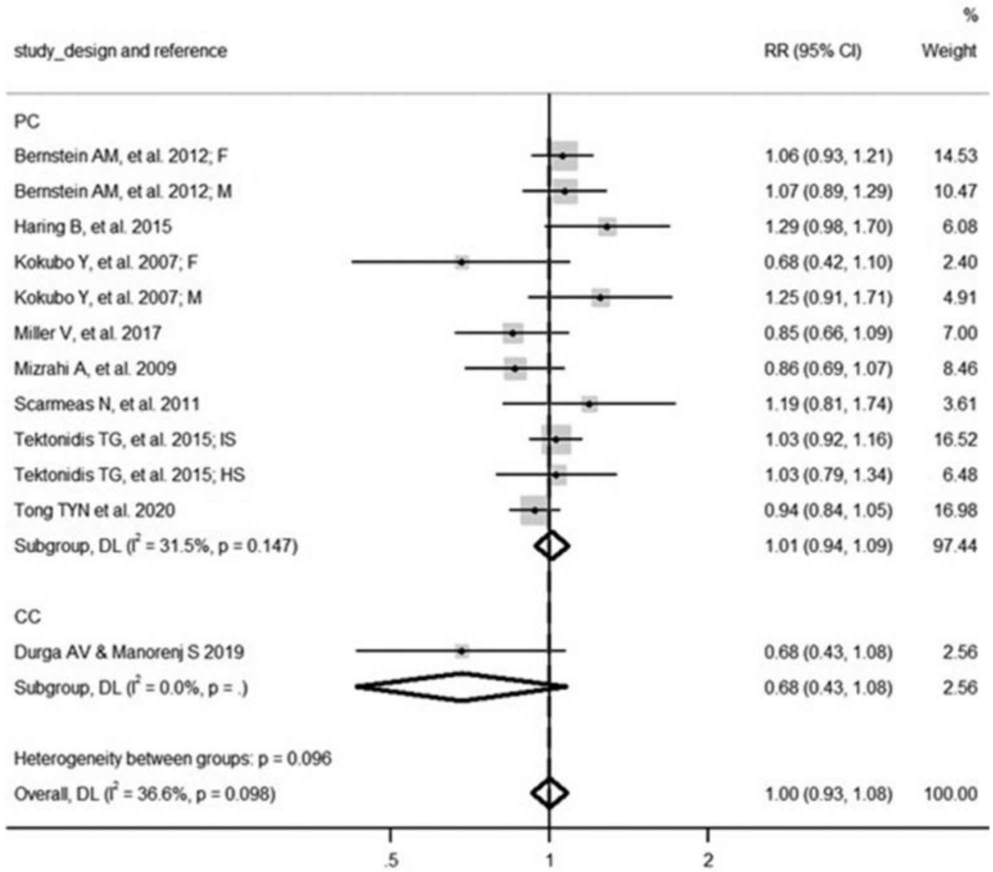
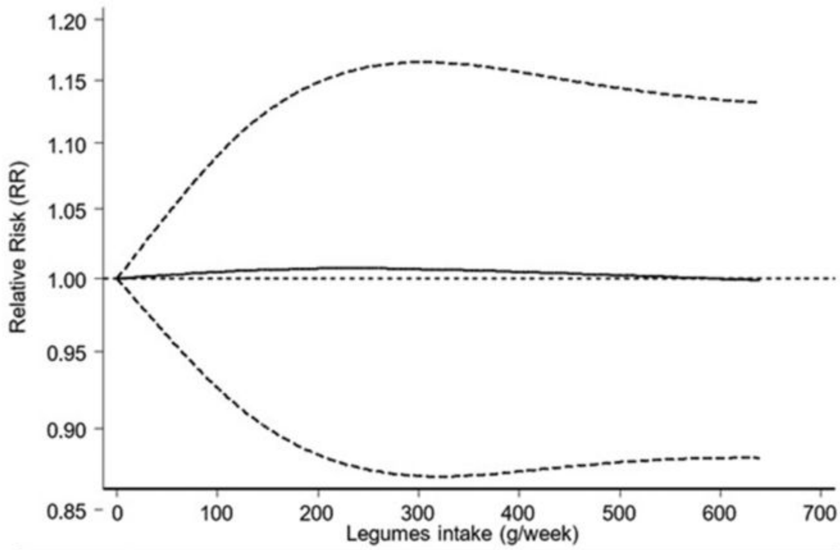


Figure 6 Meta-analysis for the association between the intake of legumes (highest vs. lowest, as specified in the individual studies) and Stroke in prospective cohort (PC) and case–control studies (CC). Weights and between-subgroup heterogeneity are from random-effects model.

highest consumption levels, when compared to those with the lowest. The inverse association between legume intake and CHD risk was confirmed when the analysis solely relied on prospective cohort studies, but the estimate was slightly attenuated (8% decrease in overall CHD risk; 95% CI: 2%, 13%). This association was further evidenced by the dose–response analysis, where a non-linear protective association was observed, with an intake of 100 g/week (about 1 portion of cooked legumes per week) being associated with a reduction of 9% (95%CI: 2%, 15%) in disease risk. The association became stronger as the intake increased and seemed to level off at about 400 g/week. These results remained after the exclusion of studies comprising soy and soy products in their definition of legumes, suggesting that the protective effect observed was independent of this single legume subtype. For CVD, a risk reduction of 6% (95%CI: 1%, 11%) was observed among individuals with the highest legume intake, all studies included, and was reduced to 4% (95%CI: 0%, 9%) when prospective cohort studies were only considered. The dose–response analysis also revealed the inverse association, with each 100 g/week additional increase in legume intake resulting in a stronger inverse association. Taking into account the relationship observed for CHD and CVD, a legume intake of 400 g (4 portions of cooked legumes) per week seemed to be associated with the highest level of cardiovascular benefit. Interestingly, we found no association between legume intake and stroke for the analyses comparing the study-specific extreme categories of intake.

Overall, our results are in line with those reported in previous meta-analyses addressing the association between legume intake and incidence of CVD, CHD and stroke [15–19]. Several lines of evidence seem to support the beneficial role of legumes in cardiovascular health. Legumes are a source of various nutrients and bioactive compounds [3] that has been consistently associated with improved cardiometabolic outcomes, including major CVD-related risk factors [64,65]. A meta-analysis of ten randomised controlled trials (RCTs) including a total of 268 participants and comparing non-soy legume diets with matched macronutrient and energy content control diets reported significantly lower levels of total cholesterol and low-density lipoprotein (LDL-) cholesterol within the intervention group, while high-density lipoprotein cholesterol levels did not significantly change [66]. Ha V et al. (2014) [67] summarized the estimates from 26 RCTs including 1037 subjects and found that a median intake of 130 g/day of pulses also significantly lowered LDL-cholesterol when compared with isocaloric controls. Previous research has also showed beneficial effects from the consumption of legumes in apoliprotein B levels [68–70], a causal factor of atherosclerosis [71] and an important



	0g/week	100g/week	200g/week	300g/week	400g/week
RR (95% CI)	Ref.	1.00 (0.93, 1.09)	1.01 (0.88, 1.15)	1.01 (0.87, 1.16)	1.00 (0.87, 1.16)

Figure 7 Summary dose−response association (solid line) and respective confidence interval (dashed lines) between the intake of legumes (g/week) and the risk of Stroke (6 studies). Estimates were obtained through weighted mixed-effects models with restricted cubic splines with 3 knots at fixed percentiles of legume intake. The value of 0 g/week served as reference.

biomarker of cardiovascular risk [72]. The lipid lowering effects of legumes have been mainly attributed to their content in soluble fibre, which has the capacity to bind bile acids or cholesterol during the intraluminal formation of micelles and to prevent their re-absorption, consequently reducing the cholesterol content in the liver and increasing the uptake and clearance of LDL-cholesterol [73]. Legumes are also great sources of low glycaemic-index carbohydrates, which have been demonstrated to decrease post-prandial glycaemic responses and are important in the prevention and management of type 2 diabetes (T2D) [74]. Their content in phytochemicals such as catechins and procyanidins has been linked with reduced enzymatic activity of α-amylase and α-glucosidase, also improving post-prandial glycaemic control [65,75]. Accordingly, a recent meta-analysis including 27 RCTs showed that the consumption of pulses decreased post-prandial glucose concentration in T2D patients and in normoglycaemic adults, and was inversely associated with fasting glucose, glycated hemoglobin A1c and insulin resistance [76]. Meta-analyses of prospective cohort studies on the association between the intake of legumes and T2D have generally estimated a protective effect [18,19,77]. However, the authors have noted a high degree of heterogeneity across studies. In addition to the effects seen in the lipid profile and glycaemic control, previous research has demonstrated that increased consumption of legumes may reduce arterial blood pressure [19,78], due to their high content in fibre, potassium and magnesium, through well-established physiological pathways [18,79]. Furthermore, in a meta-analysis of 21 RCTs [80], legumes have also been reported of being effective in promoting weight loss by inducing satiety and reducing the bioavailability of calories [80], thus further contributing to an improved overall cardiometabolic profile. Data available for the association between legumes and inflammation biomarkers are more limited, but some studies have demonstrated a favourable impact of higher legume consumption in C-reactive protein levels, interleukine-6 and 8 [81,82]. Lastly, and given their high content in vegetable protein and low glycaemic-index carbohydrates [83], legumes may provide an alternative to foods with high levels of saturated fats, high glycaemic grains and starches, which are in turn associated with adverse CVD-related outcomes [84–86].

Given the body of evidence on the biological pathways for the protective effect of legumes on overall cardiometabolic health, we would expect to observe an inverse association with stroke, as for CVD and CHD risk. However, in our pooled analysis, we found no association between the intake of legumes and stroke. Even though CHD and ischemic stroke share a similar risk factor profile, there is evidence of differences in the predictive ability of some risk factors for each of these cardiovascular outcomes. In particular, serum cholesterol, lipoprotein levels, including apoliprotein A and B, and diabetes, as well as other non-clinical factors, performed better in predicting CHD events when compared to stroke, possibly revealing a strong association with the former but not with the latter [87–91]. Considering the possible mediating role of these risk factors on the association between legumes and CVD outcomes, these differences may partially explain the lack of association observed between legume intake and the risk of stroke. In addition, stroke represents a heterogeneous group of diseases with a wide variety of aetiologies, whereas the pathological pathways for CHD are in general more homogeneous, which may have also contributed to the differences we observed between both outcomes [91]. Haemorrhagic stroke and ischemic stroke have markedly different risk pathways [92], and even within ischemic stroke, there is a high heterogeneity in aetiology and pathophysiology across different ischemic subtypes [93], which is probably also reflected in different risk factor profiles [94]. Unfortunately, we have identified only a very limited number of studies assessing stroke subtypes separately, which did not allow further stratification of our analysis. Despite these hypotheses, the reasons for the differences we have encountered for CHD and stroke are not yet clear and more evidence is necessary to better understand the differential effect of legumes on CVD subtypes, and on stroke in particular.

Another important aspect to consider is the impact that the differences observed for CHD and stroke may have when exploring associations for CVD as a combined measure. Considering that CHD and stroke together are responsible for the majority of the reported CVD cases, it is possible that the protective effect observed for CVD is, at least partially, a continuum of the inverse association found for CHD, attenuated by the lack of association we have observed for stroke. Accordingly, previous research has suggested that CVD risk may be more accurately described when broken down into its different subtypes or, alternatively, restricted to ischemic outcomes [89,90]. In addition, we found evidence of a stronger dose−response association among Asian populations, when compared with non-Asians, particularly for CVD overall. These differences can be partially explained by different dietary patterns across different regions. According to a study by the Global Burden of Disease evaluating 195 countries and including data for the period between 1990 and 2017, the majority of Asian subregions were considered to be within the range of 50−70 g/day of legume intake, while Western regions, and in particular Europe and North America, reported considerably lower levels [14]. Additionally, it is possible that some differences in the characteristics of these populations, including metabolic, may also play a role in these results [95].

The present review has several strengths. Firstly, we have included a high number of comparable studies for CVD, CHD and stroke, with large sample sizes and number of cases, which enhances the quality of our estimates and increases the statistical power necessary to detect clinically significant associations. The majority of the studies included in our analyses had a long duration of follow-up ($\geq$10 years) and comprised population-based samples from several geographic regions. With the exception of three studies [44,51,59], all the included estimates were adjusted for known potential confounders for the association between legumes and cardiovascular outcomes, and had, in general, a low to moderate risk of bias. The exclusion of studies at high risk of bias did not alter our results. Regarding exposure classification, a significant majority of studies have used validated dietary assessment methods to measure intake, excluded participants with implausible energy intakes and/or provided energy-adjusted measures. In addition, our pooled analysis did not rely on substantially heterogeneous studies nor was there statistical evidence of potential publication bias. We have performed a number of sensitivity and subgroup analyses that allowed us to test the robustness of our findings with relative confidence and to detect potential sources of between-study heterogeneity. Additionally, and to the best of our knowledge, this is the first study estimating pooled dose−response associations between the intake of legumes and CVD outcomes using the one-stage method [35,36], which allows to also consider data from studies including only two comparison groups. By using this approach, we were able to synthesize all the evidence available for the investigation of non-linear dose−response relationships between the intake of legumes, CVD, CHD and stroke. However, some limitations should also be recognised. We have not identified RCTs evaluating the association between the intake of legumes and CVD, CHD or stroke and our estimates were based exclusively in observational research, including prospective and retrospective designs. However, and notwithstanding the fact that case−control studies are more prone to selection and information bias, the number of case−control studies included in our estimates was small and our results were largely determined by data collected through prospective cohorts. Given the observational nature of the evidence included in our analyses, and even though the majority has provided estimates adjusted for several potential confounders, the possibility of residual confounding cannot be ruled out.

In conclusion, our findings provide support for a dose−response association between the intake of legumes and risk of CHD and CVD. Any consumption of legumes per week seems to be associated with a reduced risk, but an intake of 400 g/week appears to provide the optimal cardiovascular benefits. In an era of efforts to enhance the consumption of alternate sources of plant proteins, the benefit gained through the consumption of our traditional legumes should not be overlooked.

Disclaimer

EV is employed with the European Food Safety Authority (EFSA) in the Nutrition and Food Innovation Unit that provides scientific and administrative support to the Panel on Nutrition, Novel Foods and Food Allergens, in the area of Novel Foods. However, the present article is published under the sole responsibility of the authors and may not be considered as an EFSA scientific output. The positions and opinions presented in this article are those of the authors alone and do not necessarily represent the views or scientific work of EFSA. To learn about the views or scientific outputs of EFSA, please consult its website under http://www.efsa.europa.eu.

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Declaration of competing interest

No potential conflicts of interest 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.2022.10.006.

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