Clinical Nutrition 61 (2026) 106654

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Isocaloric substitution of animal protein with plant protein and its impact on all-cause, cardiovascular, and cancer mortality: A systematic review and meta-analysis

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A R T I C L E I N F O

Article history:
Received 17 October 2025
Received in revised form
19 February 2026
Accepted 28 March 2026

Keywords:
Isocaloric substitution
Cohort studies
Animal protein
Plant protein
Mortality

S U M M A R Y

Background and Aims: Epidemiological evidence indicates that isocaloric substitution of animal-protein sources with plant-protein sources may reduce all-cause mortality (ACM), cardiovascular mortality (CVM), and cancer mortality (CM). However, the impact of substituting different proportions of animal-protein with plant-protein remains unclear. This systematic review and meta-analysis aimed to evaluate the effects of isocaloric substitution of animal-protein with plant-protein at two levels—3% and 5% of total caloric value (TCV)—on ACM, CVM and CM, and to assess whether these effects differ between substitution levels.

Methods: Three databases—PubMed, Embase and Web of Science—were systematically searched up to December 2025. Prospective observational studies with multivariable adjustment evaluating isocaloric substitution of 3% and 5% of animal-protein with plant-protein on ACM, CVM and CM were included. Risk of bias was assessed using ROBINS-E. Hazard ratios (HR) for mortality outcomes were pooled using a random-effects model, with heterogeneity assessed with Tau^2, Chi^2 and I^2., Statistical analysis was performed using Review Manager 5.4.

Results: Nine cohort studies including 1,036,799 participants and 19, 904,866 person-years of follow-up were analyzed. Pooled results from studies examining 3% and 5% substitution of TCV from animal-protein with plant-protein significantly reduced ACM (HR 0.91; 95% CI 0.87–0.94; $p < 0.00001$; $I^2 = 77\%$) with no significant difference between substitution levels (p = 0.96). CVM was significantly reduced with both 3% (HR 0.88; 95% CI 0.83–0.93; $p < 0.00001$; $I^2 = 60\%$) and 5% substitution (HR 0.77; 95% CI 0.70–0.86; $p < 0.00001$; $I^2 = 0\%$), with a significant subgroup difference ($p = 0.03$). CM was significantly reduced with 3% substitution (HR 0.95; 95% CI 0.92–0.98; $p = 0.003$; $I^2 = 8\%$), with a significant subgroup difference ($p = 0.008$).

Conclusions: Isocaloric substitution of animal-protein with plant-protein is associated with lower ACM, CVM and CM, with stronger cardiovascular benefits observed at the 5% substitution level. These findings support the potential role of increased plant-protein intake in dietary strategies aimed at reducing mortality risk.

Registration: PROSPERO, CRD42024614889.

1. Introduction

Dietary protein is fundamental to human health, contributing to important physiological functions such as muscle maintenance, immune response, and metabolic regulation [1]. A growing body of evidence suggests that protein sources, whether animal-based or plant-based, may differentially impact long-term health outcomes, including all-cause mortality [2,3]. Although animal-protein has

Abbreviations: ACM, All-cause mortality; CVM, Cardiovascular mortality; CM, Cancer mortality; TCV, Total Caloric Value.

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https://doi.org/10.1016/j.clnu.2026.106654

traditionally been a staple in many diets worldwide, excessive consumption has been associated with an increased risk of chronic diseases such as cardiovascular disease and cancer [4–6]. Conversely, plant-protein sources, including legumes, nuts, and whole grains, are rich in fiber and antioxidants, which may provide protective health effects and potentially lower mortality risk [7,8]. In addition to health implications, the environmental impact of dietary protein choices has garnered considerable attention. Shifting dietary patterns toward plant-protein offers a dual opportunity to improve population health while reducing environmental impact [9,10].

In nutrition research, the reported health effects of a specific food or nutrient are often influenced by the dietary component it replaces. This concept, known as the isocaloric principle, highlights the importance of maintaining energy intake constant when assessing dietary shifts [11]. Because diet is compositional in nature, reducing one food component typically results in a compensatory increase in another. Therefore, understanding the effects of dietary substitutions requires a nuanced approach that specifies both what is being reduced and what replaces it [12]. When the replacement component is not specified, the estimated effect represents an average over multiple implicit substitutions across the remainder of the diet—each with potentially different health implications—thereby complicating interpretation [13–15].

In this context, substituting animal-protein with plant-protein not only reduces specific components such as saturated fats and cholesterol, but also increases the intake of fiber, phytonutrients, and other potentially beneficial compounds [16]. This dietary shift aligns with evidence-based recommendations for chronic disease prevention and further reinforces the need for analytic models that incorporate well-defined dietary contrasts [13]. Previous meta-analyses have examined the health effects of substituting animal-protein with plant-protein [3,17,18]. Some studies in these analyses assessed the impact of replacing animal-protein with an amount equivalent to one daily serving of different dietary protein sources (e.g. fish, poultry, or legumes). However, fewer than 5% of participants actually achieved an intake equal to or greater than one daily serving of these food groups, limiting the generalizability of the findings to the broader population [19–21]. Other meta-analyses have examined the substitution of 3% of energy from animal-protein with plant-protein, but they did not assessed the potential additional effects of larger substitutions [18]. Against this backdrop, evaluating the effects of isocaloric replacement of animal-protein with plant-protein on mortality provides valuable insights for developing sustainable dietary strategies that promote both human and planetary health.

This systematic review and meta-analysis aimed to evaluate the effect of isocaloric substitution of animal-protein with plant-based protein at two levels (3% and 5% of total energy intake (TCV)) on all-cause mortality (ACM), cardiovascular mortality (CVM), and cancer mortality (CM), and to assess whether these effects differ between the two substitution levels. We hypothesized that replacing 3% and 5% of energy from animal-protein with plant-protein would be associated with a significant reduction in the risk of ACM, CVM, and CM.

2. Methods

This systematic review and meta-analysis was conducted following the Cochrane Collaboration Handbook for Systematic Review of Interventions [22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines [23]. The prospective meta-analysis protocol was registered on PROSPERO on November 26, 2024, under registration number CRD42024614889. After registration, the study was updated in December 2025.

2.1. Isocaloric substitution modeling

In nutritional epidemiology, substitution analyses are designed to estimate the health effects of replacing one dietary component with another while holding total energy intake constant, thereby respecting the compositional nature of diet. Statistically, this approach is typically implemented using multivariable Cox regression models in which total energy intake is included as a covariate and the exposure of interest is modeled as the simultaneous decrease in energy from one source and increase in energy from another. This approach follows the energy partition framework commonly used in nutritional epidemiology. Under this framework, the estimated hazard ratio represents the expected difference in risk associated with reallocating energy between two specified dietary components, rather than the effect of increasing or decreasing a single exposure in isolation [24].

Two main modeling strategies are commonly described: non-specified substitution models, which estimate the effect of increasing one dietary component while implicitly averaging over decreases in the remainder of the diet, and specified (partition-based) substitution models, which explicitly define both the food or nutrient being reduced and the one replacing it [25]. In this framework, interpretation is clearer when the substitution is explicitly specified, as the estimated effect corresponds to a well-defined dietary contrast rather than a mixture of implicit replacements with potentially heterogeneous health implications.

In the present meta-analysis, we focused exclusively on studies that implemented specified isocaloric substitutions of energy from animal-protein with energy from plant-protein. This restriction reduces ambiguity in interpretation and aligns the estimated effects with realistic dietary decisions, in which increasing intake of one protein source necessarily displaces another under conditions of relatively stable total energy intake. Importantly, the substitution effect should be interpreted as a joint contrast, lower animal-protein intake together with higher plant-protein intake, rather than the independent effect of either component alone.

The substitution magnitudes evaluated in this study (3% and 5% of total energy intake) correspond to modest but realistic dietary changes within habitual intake ranges observed in large prospective cohorts. For example, a 3% energy substitution from animal-protein to plant-protein approximates the replacement of a small daily portion of animal-based protein with legumes, nuts, or whole grains, whereas a 5% substitution reflects a more pronounced yet still attainable dietary shift. Modeling multiple substitution levels within the same analytical framework allows assessment of whether the magnitude of dietary reallocation influences the estimated association with mortality outcomes.

3. Search strategy

A systematic literature search was conducted using PubMed, Embase, and Web of Science in December 2025. The search strategy followed the PECOTT (Population, Exposure, Comparator, Outcome, Timing, and Type of Study) framework. A generalized search strategy was applied uniformly across all three databases, without customizing search terms for individual platforms. Three independent reviewers (G.B., P.A., and A.R.) systematically searched for studies using the following terms combined with Boolean operators: (animal-protein OR meat protein OR animal-based protein) AND (plant-protein OR vegetable protein OR legume protein OR plant-based protein) AND (substitution OR replacement OR swap OR isocaloric replacement OR isocaloric substitution) AND (cohort study OR prospective study OR longitudinal study) AND (mortality OR all-cause mortality OR cardiovascular mortality OR cardiovascular disease OR cancer mortality).

4. Eligibility criteria

The PECOTT framework used for study selection was as follows: [1] Participants: adults aged ≥18 years; [2] Exposure: isocaloric substitution of animal-protein with plant-protein, quantified as a 3% or 5% replacement of TCV; [3] Comparator: habitual intake of animal-protein or no substitution [4] Outcomes: ACM, CVM and CM; [5] Timing: minimum follow-up period of 5 years; [6] Type of study: observational prospective cohort studies.

5. Data collection

Two reviewers (G.B. and P.A.) independently extracted the following information from each article: [1] first author name and year of publication; [2] study design and location; [3] name of the cohort; [4] cohort recruitment and longitudinal follow-up; [5] mean follow-up period (person-years); [6] number of participants; [7] mean age of the population (including range); [8] sex distribution (male/female); [9] primary outcomes assessed (ACM, CVM, and CM); [10] dietary substitution model; [11] covariables; [12] dietary assessment method; [13] frequency of diet assessment and relationship with substitution; and [14] protein source categorized as animal-based or plant-based.

A third reviewer (E.J.) independently verified the accuracy of the extracted data. Any discrepancies were resolved through consensus discussion among the reviewers.

6. Risk of bias and quality assessment

The risk of bias in prospective studies was assessed using the Risk of Bias in Non-randomized Studies - of Exposures tool (ROBINS-E). Two authors (P.A. and E.J.) conducted the risk of bias assessment. Disagreements were resolved through a consensus after discussing the reasons for the discrepancy. Publication bias was assessed using funnel plot analysis of point estimated for ACM, CVM and CM.

The quality of evidence was further assessed using the Nutrigrade scoring system, a validated tool designed for grading the certainty of evidence in meta-analyses of observational studies and randomized controlled trials. The Nutrigrade assessment was performed independently by two reviewers (P.A. and G.B.), and any discrepancies were resolved by consensus. Each domain was scored according to Nutrigrade's criteria, and the overall score was used to classify the certainty of the evidence into high, moderate, low, or very low confidence levels.

7. Statistical analyses

A meta-analysis was conducted when at least three studies addressed the same outcome. Given the anticipated between-study heterogeneity, a random-effects model was used to pool the hazard ratios (HR) for mortality outcomes associated with the isocaloric substitution of energy from animal-protein with plant-protein. The calculation of HR and their corresponding 95% confidence intervals (CI) was performed using Review Manager (RevMan) version 5.4. For each analyzed outcome (ACM, CVM, and CM), we input the HR values and their 95% CI (upper and lower bounds) as directly reported by each study into the software. Heterogeneity was assessed using Tau^2, Chi^2, and I^2 statistics, and was classified as low (<25%), moderate (25–75%), or high (>75%), according to the Cochrane Handbook for Systematic Reviews of Interventions [22]. A sensitivity analysis was conducted by adjusting the weights assigned to each study in the meta-analysis to assess the robustness of the pooled estimates. The recalculated hazard ratios and confidence intervals were compared with the original estimates to assess stability. A p-value <0.10 was considered indicative of significant heterogeneity, in accordance with the recommendations provided by the Cochrane Handbook when assessing heterogeneity in meta-analyses of observational studies.

Additionally, in three studies that stratified their HRs by specific animal-protein sources [2,26,27], we applied a standardized procedure to obtain a single summary HR per outcome [53]. Each HR and its 95% CI were first converted to logHR and corresponding standard error (SE). A weighted average of the logHRs was then calculated, with weights equal to the inverse of the variances. The combined logHR was subsequently exponentiated to obtain the overall HR per study and outcome. The variance of the combined logHR was derived as the reciprocal of the sum of the weights, and the corresponding 95% CI was calculated accordingly. This approach preserved the internal validity of individual studies and provided an unbiased estimate of the overall substitution effect, while avoiding unit-of-analysis errors that could arise from including stratified HRs multiple times in forest plots [22].

8. Results

A total of 111 studies were identified through the systematic search process (Fig. 1). Prior to screening the studies, 35 duplicate records were removed. Of the remaining 76 studies, 6 were excluded based on title and/or abstract as they were not related to the topic of systematic review and meta-analysis. The remaining 70 studies were assessed for eligibility. The following studies were excluded: 11 lacked an isocaloric substitution range, 16 did not meet the required study design, 18 investigated different exposures, 11 evaluated outcomes outside the scope, and 5 involved specific populations not contemplated in the inclusion criteria. Finally, 9 studies were included in both systematic review and meta-analysis.

9. Study characteristics

Table 1 summarizes the main characteristics of the included studies. These studies were conducted in prospective cohorts from various regions, specifically: United States of America (N = 5), Europe (N = 3) and Japan (N = 1). The total follow-up measured in person-years was 19, 904, 866, comprising a sample of 1,036,799 participants aged between 20 and 83 years. Regarding the evaluated outcomes, the studies reported on all-cause mortality (ACM), cardiovascular mortality (CVM), and cancer mortality (CM). Among the included studies, the majority evaluated the isocaloric substitution of 3% of total energy intake [5,8,26–28,31,32], while two studies [29,30] assessed substitutions of 5%. The main adjustment variables include demographic factors, lifestyle, energy and nutrient intake, health history, alcohol and tobacco consumption, hormone replacement therapy, and body mass index.

In terms of dietary assessment tools, all of the studies utilized validated Food Frequency Questionnaires (FFQs) [5,8,26–32]. Crucially, for the majority of these cohorts, diet was assessed only once at baseline, with no follow-up dietary assessments to capture changes in habits over time [5,8,27–30,32]. In contrast, two studies [26,31] conducted repeated assessments every four years, allowing for the calculation of a cumulative average of dietary intake. Regarding protein sources, animal proteins typically included red and processed meats, poultry, eggs, and dairy, while plant proteins were mainly derived from legumes, nuts, soy, and whole grains.

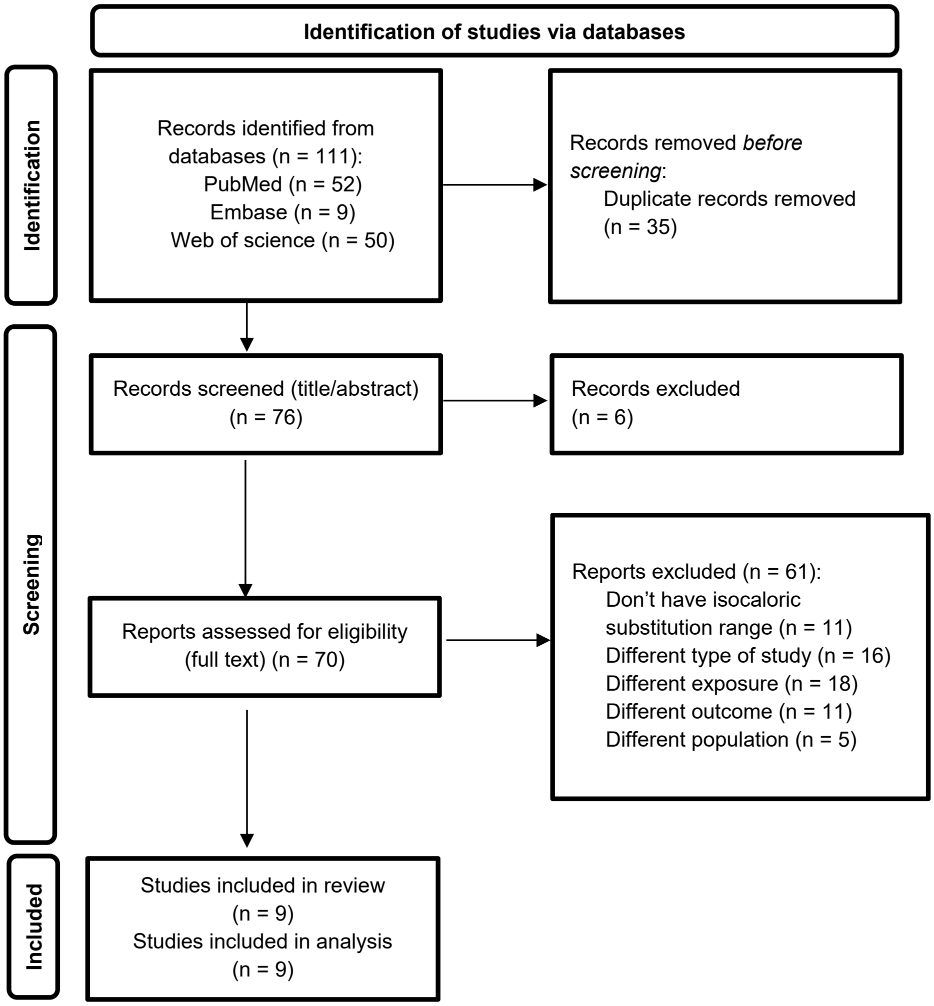

Fig. 1. Flowchart of Study Selection for the Meta-Analysis on Isocaloric Substitution of Animal Proteins with Plant Proteins. PRISMA flow diagram illustrating the study selection process. A total of 111 records were identified through databases (PubMed, Embase, and Web of Science) and additional sources. After removing 35 duplicates, 76 titles/abstracts were screened and 6 were excluded during the initial screening phase. Out of 70 studies assessed for eligibility, 61 were excluded for not meeting the inclusion criteria. Ultimately, 9 studies were included in both the review and the analysis.

10. Meta-analyses

The pooled analysis across both isocaloric substitution scenarios of 3% and 5% of TCV from animal-protein to plant-protein sources were significantly associated with a reduction in ACM (pooled HR 0.91; 95% CI: 0.87–0.94; $p < 0.00001$; $I^2 = 0\%$), with no significant differences observed between substitution percentages in the subgroup analysis ($p = 0.96$) (Fig. 2). For CVM, a significant risk reduction was observed with both the 3% TCV substitution (HR 0.88; 95% CI: 0.83–0.93; $p < 0.00001$; $I^2 = 60\%$) and the 5% TCV substitution from animal-protein to plant-protein sources (HR 0.77; 95% CI: 0.70–0.86; $p < 0.00001$; $I^2 = 0\%$), with a statistically significant difference between the substitution levels ($p = 0.03$) (Fig. 3). Regarding CM, a modest but significant reduction was reported with isocaloric substitution of 3% of TCV from animal-protein to plant-protein (HR 0.95; 95% CI: 0.92–0.98; $p = 0.0003$; $I^2 = 8\%$), with significant differences between substitution percentages in the subgroup analysis ($p = 0.008$) (Fig. 4).

Funnel plot analysis did not reveal marked asymmetry for ACM, CVM or CM, suggesting a low likelihood of small-study effects or publication bias across outcomes. The distribution of studies appeared relatively symmetrical around the pooled hazard ratio in each plot (Figs. 5–7).

11. Sensitivity analysis

Sensitivity analyses confirmed the overall stability and robustness of the meta-analysis results across all outcomes. The direction of effect toward reduced mortality risk remained consistent for ACM, CVM, and CM, with pooled HR varying modestly ($\leq$0.02) from the primary estimates (Table S2–4).

12. Quality assessment

The Nutrigrade scoring system was used to assess the quality of evidence. The meta-analysis scored 7.3/10, corresponding to moderate certainty of the effect estimates. In brief, we obtained high scores for precision and directness, with small deductions for inconsistency/heterogeneity and for the absence of dose–response or trial design items.

13. Risk of bias assessment

Risk of bias was evaluated with the ROBINS-E tool (Table S1). All analyzed cohorts presented an overall moderate risk [5,8,26–32]. In the bias due to confounding domain, all studies were classified as moderate (0/9 low; 9/9 moderate), which is explained by the

Table 1
Characteristics of studies included in the meta-analysis on isocaloric substitution of animal proteins with plant proteins.

Study	Type of Study and Location	Name of the cohort	Cohort recruitment and longitudinal follow-up	Mean Follow-up (Person-years)	Number of Participants	Mean Age (Range)	Population (Male/Female)	Main Outcomes	Substitutional Model	Variables for Adjustment	Dietary Assessment Instrument	Frequency of diet assessment and relationship with substitution	Source of Protein (Animal/Plant)
Bajracharya et al., 2023 [5]	Prospective cohort, Germany	European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg)	It recruited its participants and collected baseline data between 1994 and 1998. Follow-up ran from June 1994 to May 2019.	22.9 years, 524.234[a] Person-years	24.106	51.4, 43.5–57.5	11.323 (46.9%) 12.783 (53.1%)	All-cause mortality, cardio vascular mortality andc ancer mortality.	Isocaloric substitution of 3% of the energy from animal-proteinw ith otherm acronutrients and plant-protein.	Age, sex, total energy, smoking, BMI, alcohol intake at recruitment and fiber intake.	Self-administered FFQ validated in prior studies.	Participants' diet was assessed only once at baseline (1994–1998), with no follow-up assessments. Nutrient substitution used isocalorics tatistical modeling rather than observed changes (specifically, "leave-one-out method"). Researchers modeled exchanging 3% of energy from animal-protein for equivalent macronutrients.	–
Budhathoki et al., 2019 [27]	Prospective cohort, Japan	Japan Public Health Center-Based Prospective Study (JPHC)	It recruited its participants and collected baseline data between 1995 and 1999. Follow-up ran from January 1, 1995, to December 31, 2016.	18 years, 1.272.528[a] Person-years	70.696	55.6, 40–74	32.201 (45.5%) 38.495 (54.5%)	All-cause mortality, cardio vascular mortality and c ancer mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein.	Age, sex, BMI,t otal energy, % of energy from fats, carbohydrates, smoking, alcohol intake, physicala ctivity, occupation status, intakes of green tea and coffee.	Self-administered FFQ validated in prior studies.	Participants' diet was assessed only once at baseline (1995–1999), with no follow-up assessments. Nutrient substitution used isocalorics tatistical modeling rather than observedc hanges. Researchers modeled exchanging 3% of energy from animal-protein for plant-protein.	Fish and shellfish, meat and processed meat, eggs, milk, and dairy products/cereal, soy protein, vegetable, fruit, nut and sweets.
Fontana et al., 2022 [28]	Prospective cohort, Italy	European Prospective Investigation into Cancer and Nutrition (EPIC-Italy)	It recruited its participants and collected baseline data between 1993 and 1998. Follow-up ran from recruitment until December 2009 for the Varese center, and until December 2010 for the centers of	15.2 years, 644.254 Person-years	45.009	50.7, 35–65	14,300 (31.77%) 30,709 (68.23%)	All-cause mortality, cardio vascular mortality and cancer mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein or carbohydrates.	Age, sex, energy, BMI, smoking, education, physical activity, fiber, alcohol and total fat intake.	Adapted and validated in previous studies.	Participants' diet was assessed only once at baseline (1993–1998), with no follow-up assessments. Nutrient substitution used isocalorics tatistical modeling rather than observedc hanges.	Processed and unprocessed red meat, poultry, fish, egg and dairy products/bread, cereals, pasta, nuts, and legumes.

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Table 1 (*continued*)

Study	Type of Study and Location	Name of the cohort	Cohort recruitment and longitudinal follow-up	Mean Follow-up (Person-years)	Number of Participants	Mean Age (Range)	Population (Male/Female)	Main Outcomes	Substitutional Model	Variables for Adjustment	Dietary Assessment Instrument	Frequency of diet assessment and relationship with substitution	Source of Protein (Animal/Plant)
			Florence, Turin, Ragusa, and Naples.									Researchers modeled exchanging 3% of energy from animal-protein for equivalent amounts of plant-protein or carbohydrates to estimate mortalityr isk.	
Glenn et al., 2024 [31]	Prospective cohort, United States of America	(a) Nurses' Health Study(NHS),(b) Nurses' Health Study II (NHSII) and (c) Health Professionals Follow-up Study (HPFS)	(a) Nurses' Health Study (NHS): Recruited in 1976, baseline data collected in 1984. Follow-up ran from 1984 to June 2016.(b) Nurses' Health Study II (NHSII): Recruited in 1989, baseline data collected in 1991. Follow-up ran from 1991 to June 2017.(c) Health Professionals Follow-up Study (HPFS): Recruited in 1986, baseline data collected in 1986. Follow-up ran from 1986 to January 2016.	88 years, 5.415.998[b] Person-years	202.863	62.7, 50–79	160,123 (79%) 42.740 (21%)	Cardio vascular mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein.	Sex, age, study center, energy intake, education,p hysical activity,s moking, alcohol intake, dietary fiber, glycemic index, BMI, self-reported history of diabetes, hypertension and dyslipidemia.	Self-administereds emi-quantitative FFQ once every 4 years and validatedw ith other dietary records.	Participants' diet was assessedr epeatedly every 4 years using validated food frequency questionnaires (starting in 1984, 1986, or 1991 depending on thec ohort), which allowed researchers to calculate ac umulative average of dietary intake to represent long-term habits. Nutrient substitution used isocalorics tatistical modeling rather than observedc hanges (specifically, “leave-one-out method”). Researchers modeled exchanging 3% of energy from animal-protein for plant-protein.	Poultry, red meat and dairy/refined grains, whole grains, potatoes, nuts and legumes.
Huang et al., 2020 [8]	Prospective cohort, United States of America	National Institutes of Health (NIH)-AARP Diet and Health Study	It recruited its participants and collected baseline data between 1995 and 1996. Follow-up ran from the time of study entry (1995–1996) to December 31, 2011.	16 years, 6.009.748 Person-years	416.104	62.1, 50–71	237.036 (57%) 179.068 (43%)	All-cause mortality, cardiovas cular mortality and cancer mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein.	Age at entry, BMI,a lcohol intake, smoking status,p hysical activity,e thnic group,e ducational level,m arital status,d iabetes, health status, vitamins upplement use,d aily dietary total energy, animal-protein, saturated fat, polyunsaturated	Self-administered FFQ once in baseline validated in prior studies.	Participants' diet was assessed only once at baseline (1995-1996), with no follow-up assessments. Nutrient substitution used isocalorics tatistical modeling rather than observedc hanges (specifically,	Red meat, white meat and dairy products/bread, cereal, pasta, nuts, beans and legumes.

										fat, monounsaturated fat, trans fat, fiber, vegetables and fruit intake,h istory of cancer in a first-degreer elative and postmenopausal hormone replacement therapy.		"leave-one-out method"). Researchers modeled exchanging 3% of energy from animal-protein for plant-protein.	
Kelemen et al., 2005 [29]	Prospective cohort, United States of America	Iowa Women's Health Study	It recruited its participants and collected baseline data in January 1986. Follow-up ran from January 1986 to December 31, 2000.	15 years, 475.755 Person-years	29.017	75.8, 75.4–76.2	29.017	All-cause mortality, cardio vascular mortality and cancer mortality.	Isocaloric substitution of 5% of energy from dietary protein with carbohydrate, and from animal-protein with plant-protein.	Age, energy intake,c arbohydrate, saturated fat,p olyunsaturated fat, monounsaturated fat, trans-fat, total fiber, dietaryc holesterol, dietarym ethionine, alcohol intake, activity level, BMI, history of hypertension, postmenopausal hormone use,m ultivitamin use,v itamin E supplement use,e ducation and family history of cancer.	Self-administered FFQ once in baseline validated in prior studies.	Participants' diet was assessed only once at baseline (1986),w ith no follow-up dietary assessments. Nutrient substitution used isocalorics tatistical modeling (specifically, nutrient density models) rather than observedc hanges. Researchers modeled exchanging the difference in median energy intake between the highest and lowest quintiles,s pecifically 3.7%–6.1% of energy from animal-protein with plant-protein.	Processed and red meat, chicken and poultry, fish and seafood, eggs,s weets and desserts/nuts, tofu, legumes, whole grains, refined grains, white bread, rice or pasta, potatoes, fruit and vegetables.
Song et al., 2016 [26]	Prospective cohort, United States of America	(a) Nurses' Health Study (NHS) and (b) Health Professionals Follow-up Study (HPFS)	(a) Nurses' Health Study (NHS): It recruited its participants in 1976 and collected baseline dietary data in 1980. Follow-up ran from 1980 to June 1, 2012.(b) Health Professionals Follow-up Study (HPFS): It recruited itsp articipants and collected baseline data in 1986. Follow-up ran from 1986 to January 31, 2012.	58 years, 3.540.79[c] Person-years	131.342	49, 22–76	46.329 (35.3%) 85.013 (64.7%)	All-cause mortality and cancer mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein.	Age, sex, BMI,p hysical activity level, alcohol intake, history of hypertension,c urrentm ultivitamin use, and smoking habits (includingp ack-years of smoking) and current hormoneu se.	FFQ once every 4 years, statistically validated.	Participants' diet was assessed repeatedly every four years using validated FFQ from baseline (1980 for NHS and 1986 for HPFS) until the end of follow-up in 2012. Researchers calculated the cumulative average of protein intake to better represent long-term dietary habits and reducer andom within-person variation. Nutrient substitution used isocalorics tatistical modeling (specifically, a	Red meat, processed redm eat, poultry, fish, eggs, dairy /grains, nuts, legumes and vegetables.

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Table 1 (*continued*)

Study	Type of Study and Location	Name of the cohort	Cohort recruitment and longitudinal follow-up	Mean Follow-up (Person-years)	Number of Participants	Mean Age (Range)	Population (Male/Female)	Main Outcomes	Substitutional Model	Variables for Adjustment	Dietary Assessment Instrument	Frequency of diet assessment and relationship with substitution	Source of Protein (Animal/Plant)
												nutrient densitym odel) rather than observed changes. Researchers modeled exchanging 3% of energy from animal-protein for plant-protein.	
Sun et al., 2021 [30]	Prospective cohort, United States of America	Women's Health Initiative (WHI)	It recruited its participants and collected baseline data between 1993 and 1998. Follow-up ran from the date of study entry until February 28, 2017.	18 years, 1.876.205 Person-years	102.521	62.7, 41.4–83	102.521 (100%)	All-cause mortality, cardio vascular mortality and cancer mortality.	Isocaloric substitution of 5% energy from animal-protein with plant-protein.	Age, race/ethnicity, socioeconomic status, dietary, lifestyle, baseline health status, and family history of diseases.	Self-administered FFQ once in baseline validated in prior studies.	Participants' diet was assessed only once at baseline (1993-1998), with no follow-up assessments. Nutrients ubstitution used isocalorics tatistical modeling rather than observedc hanges.	Red meat, poultry, fish, seafood, eggs, dairy/nuts, legumes, whole grains, tofu and soy derivatives
Zheng et al., 2024 [32]	Prospective cohort, Europe (Spain, Italy, United Kingdom, Netherlands, Germany, Denmark, Sweden)	European Prospective Investigation into Cancer and Nutrition (EPIC)	It recruited its participants and collected baseline data between 1992 and 2000. Follow-up ran from the date of recruitment (1992–2000) until the end of the follow-up period, which varied by center between 2003 and 2010.	9.6 years, 145.353[a] Person-years	15.141	52.5, 25.5–79.5	5,938 (39,22%) 9,203 (60,78%)	Cardio vascular mortality.	Isocaloric substitution of 3% energy from animal-protein with plant-protein.	Age, sex, center, energy intake, education,p hysical activity,s moking, alcohol intake, dietary fiber, glycemic index, BMI, reported history of diabetes, hypertension, and hyperlipidemia.	Self-administered and interviewer administered FFQ once in baseline validated in prior studies.	Participants' diet was assessed only once at baseline (1992–2000), with no follow-up assessments. Nutrients ubstitution used isocalorics tatistical modeling rather than observed changes.	Red meat, poultry, processed meat, dairy products, fish, and egg intake/cereal,c ereal products, legumes and nuts.

Summary of the studies included in the meta-analysis evaluating the effect of isocaloric substitution of animal proteins with plant proteins on all-cause mortality, cardiovascular mortality, and cancer mortality. The table presents the type of study, name of the cohort, cohort recruitment and longitudinal follow-up, follow-up period, number of participants, mean age, population distribution by sex, main outcomes, substitution model, variables for adjustment, dietary assessment instruments, frequency of diet assessment and relationship with substitution, and the primary sources of animal and plant proteins in each study. Studies span across different countries and employ diverse methodologies, including food frequency questionnaires (FFQs) and diet records, with comprehensive adjustments for potential confounders, like (TCV, PP, AP, body mass index, age, sex, alcohol intake, physical activity, fiber intake, total fat intake, chronic diseases, ethnic group, smoking status, educational level).
BMI: Body Mass Index; FFQ: Food Frequency Questionnaires.

[a] Calculated.

[b] The persoyears calculated for Glenn are based solely on the outcome of interest that meets our inclusion criteria, CVD mortality.

[c] Person-years include the follow-up of CVD cases, since they do not report the disaggregation of person-years by outcome.

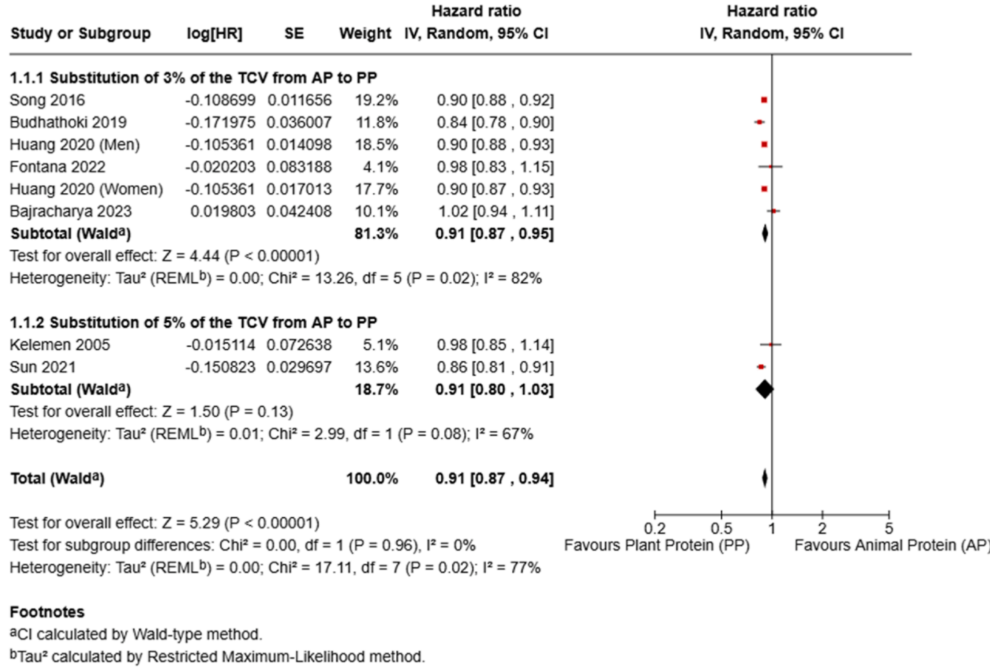

Fig. 2. Effect of isocaloric substitution of animal protein (AP) with plant protein (PP) at different percentages of total caloric value (TCV) on all-cause mortality (ACM): Multivariable-adjusted analysis.

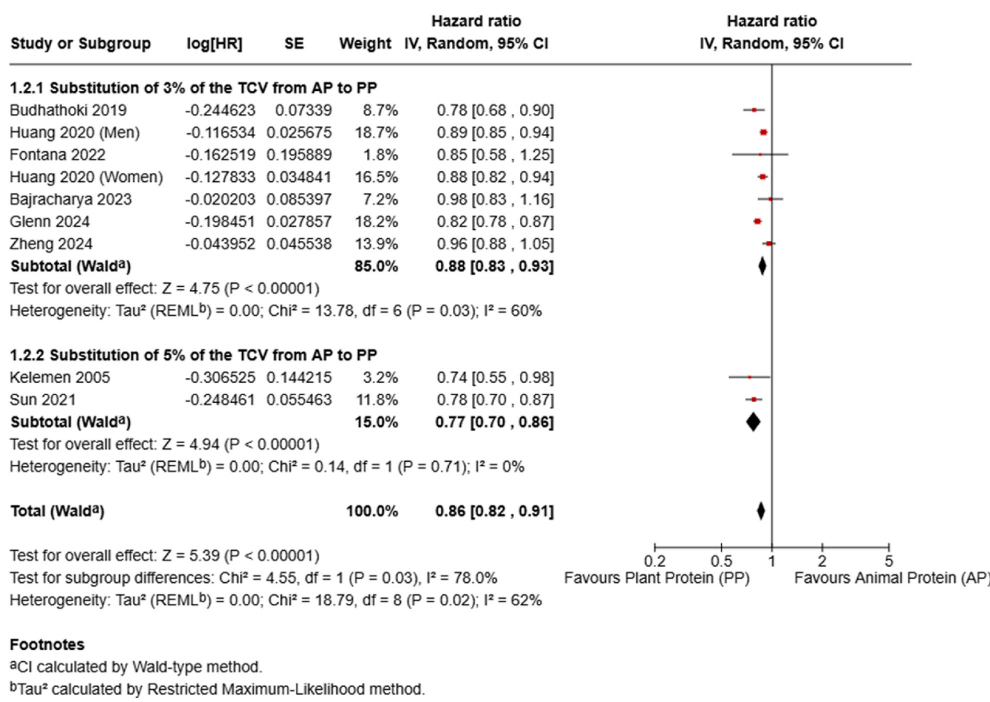

Fig. 3. Effect of isocaloric substitution of animal protein (AP) with plant protein (PP) at different percentages of total caloric value (TCV) on cardiovascular mortality (CVM): Multivariable-adjusted analysis.

intrinsic difficulty of isolating the specific effect of protein from a generalized healthy lifestyle, leaving a latent risk of residual confounding from unmeasured factors. The bias in selection of participants into the study was mostly low (7/9 low; 2/9 moderate), with moderate ratings appearing only for two studies [29,30] due to their exclusive focus on postmenopausal women, which limits the representativeness of their findings. Similarly, bias in classification of interventions was moderate in all cases (0/9 low; 9/9 moderate) because of the reliance on self-administered Food Frequency Questionnaires (FFQs) prone to recall error and the fact that most research assessed diet only once at baseline. Regarding bias due to deviations from intended interventions, there was more variation (2/9 low; 7/9 moderate), as only two studies [26,31] achieved a low risk by employing repeated dietary assessments

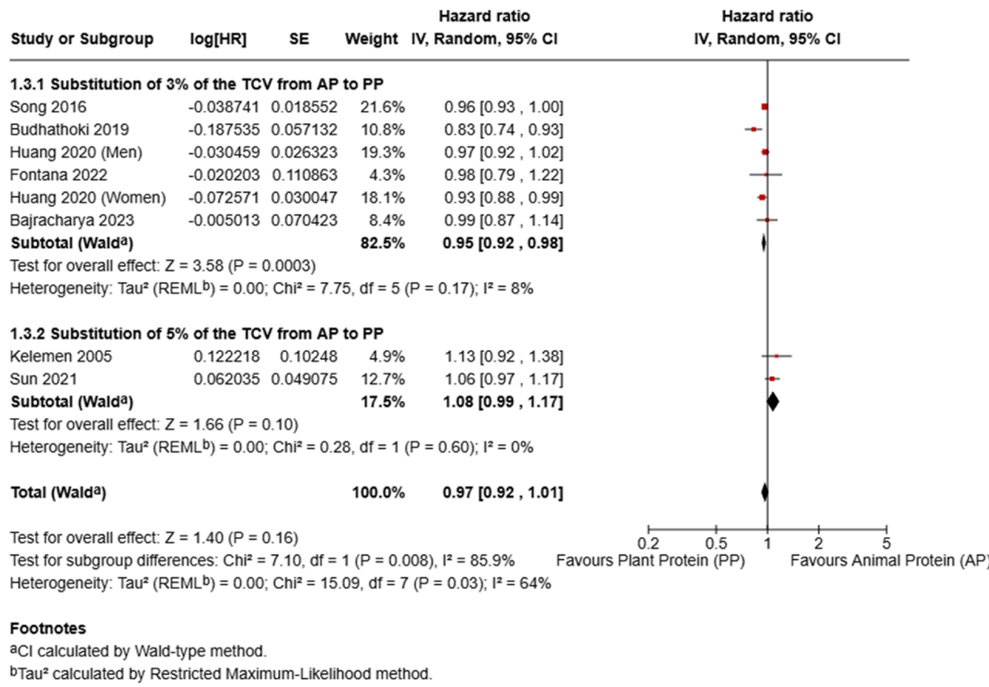

Fig. 4. Effect of isocaloric substitution of animal protein (AP) with plant protein (PP) at different percentages of total caloric value (TCV) on cancer mortality (CM): Multivariable-adjusted analysis.

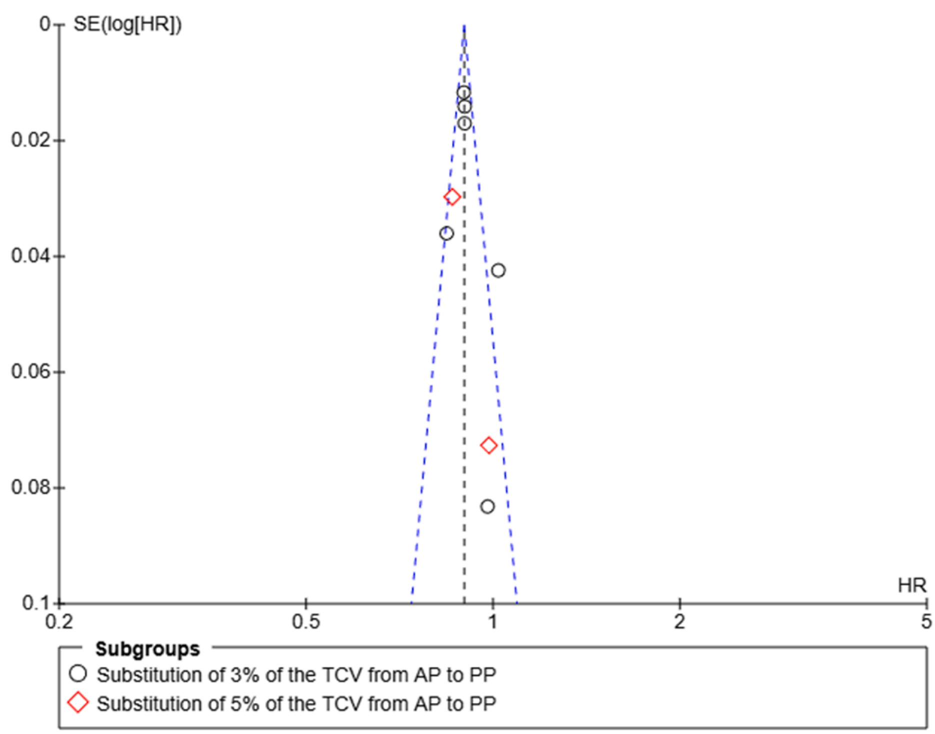

Fig. 5. Funnel plot for All-Cause Mortality (ACM) showing the standard error (SE) of the log Hazard Ratio (HR) versus HR values. Circles represent 3% and red diamonds 5% substitution of Animal Protein (AP) with Plant Protein (PP). Dashed lines indicate confidence limits and overall effect.

every four years to capture shifts in participants habits. Bias due to missing data was predominantly low (7/9 low; 2/9 moderate), while bias in measurement of outcomes was the only domain with optimal performance across the entire sample (9/9 low; 0/9 moderate) thanks to the use of objective official records. Finally, bias in selection of the reported result was unanimously moderate (0/9 low; 9/9 moderate) because the findings do not stem from observed real-time behavioral changes but from theoretical isocaloric substitution simulations that do not capture the full metabolic complexity of a real dietary intervention.

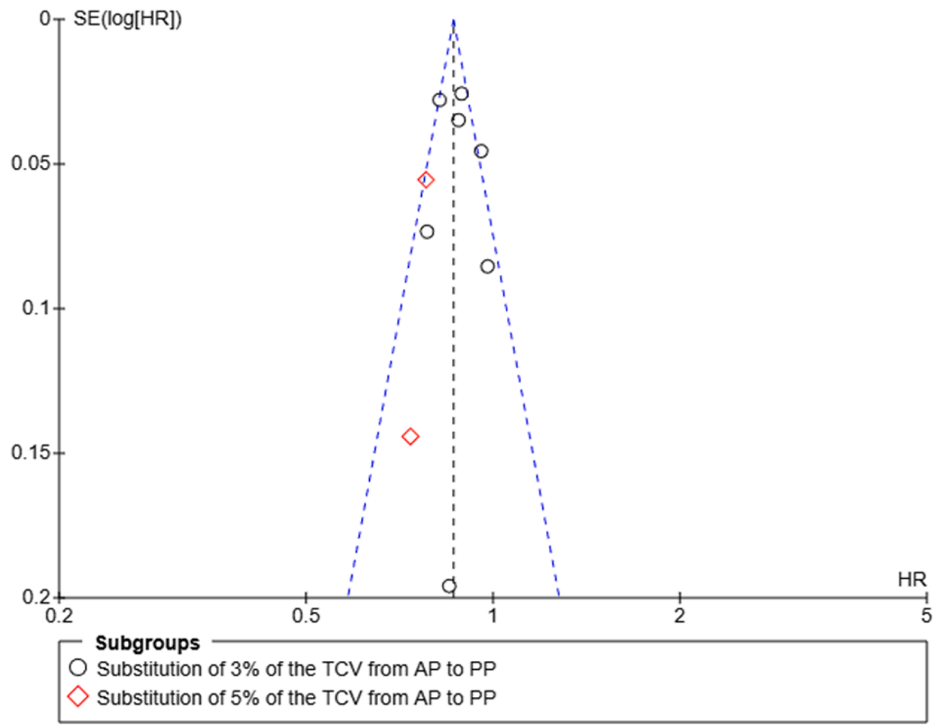

Fig. 6. Funnel plot for Cardiovascular Mortality (CVM) showing the standard error (SE) of the log Hazard Ratio (HR) versus HR values. Circles represent 3% and red diamonds 5% substitution of Animal Protein (AP) with Plant Protein (PP). Dashed lines indicate confidence limits and overall effect.

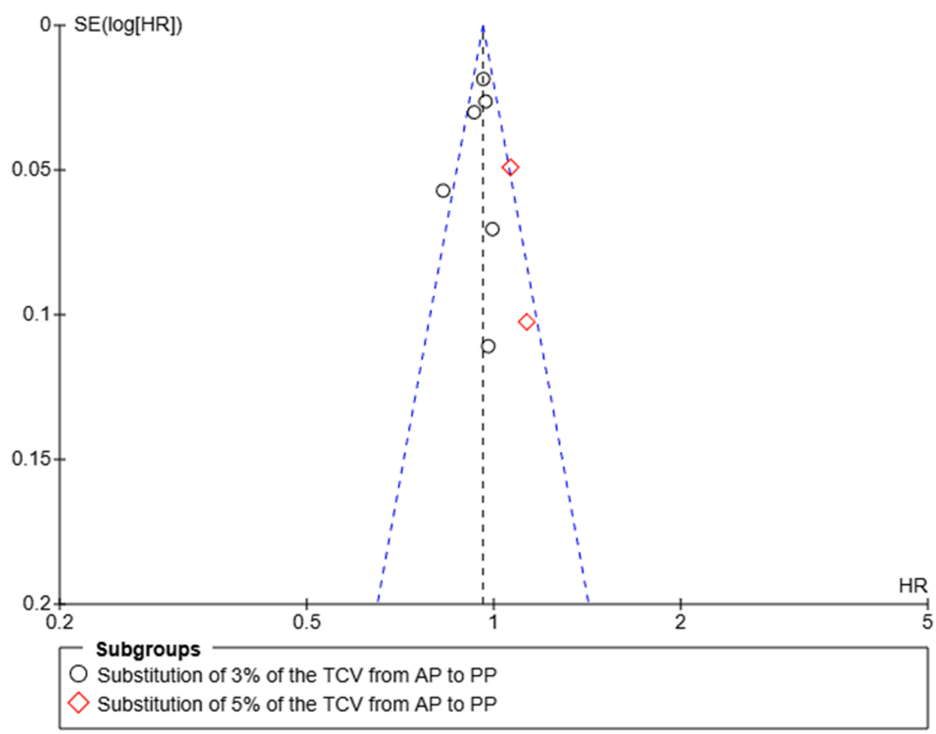

Fig. 7. Funnel plot for Cancer Mortality (CM) showing the standard error (SE) of the log Hazard Ratio (HR) versus HR values. Circles represent 3% and red diamonds 5% substitution of Animal Protein (AP) with Plant Protein (PP). Dashed lines indicate confidence limits and overall effect.

14. Discussion

This is the first meta-analysis evaluating the differences between various magnitudes of isocaloric substitutions of animal-protein with plant-protein on mortality outcomes. We found that substituting animal-protein with plant-protein was associated with a reduced risk of ACM and CVM. Notably, a statistically significant reduction in CVM and risk was observed with both 3% and 5% isocaloric substitution, with the 5% substitution yielding a more pronounced effect.

Our findings are consistent with previous systematic reviews showing a significant reduction in ACM with isocaloric substitution of animal-protein by plant-protein [2]. Our results also complement the evidence from Wallerer et al. [36], who reported benefits of replacing animal-based macronutrients with plant-based alternatives (HR 0.87; 95% CI: 0.84–0.91). Whereas those reviews considered broader substitution sets, including carbohydrates and fats, here we focus specifically on replacing animal-protein for plant-protein and explicitly comparing two pre-specified substitution magnitudes (3% and 5% of TCV). In this context, Song et al. [26] who reported HRs by the animal-protein source displaced observed up to a 34% reduction in ACM when processed meat was isocalorically replaced with plant-protein, with smaller effects for unprocessed red meat; however, their models did not adjust for several dietary mediators like fiber, which may partly explain the larger magnitude, whereas Huang et al. [8], with more extensive adjustment, reported 10% lower risk. Multivariable adjustments can attenuate apparent benefits by accounting for favorable co-occurring dietary components of plant-protein, thereby isolating the net effect of protein source. Across included cohorts, plant-protein was defined as a composite of foods from different sources, primarily legumes, nuts, and whole grains, rather than specific food categories. In our meta-analysis, ACM risk was reduced with animal-protein for plant-protein substitution, but the difference between 3% and 5% was not statistically significant ($p = 0.96$). This lack of significance is most plausibly due to limited information in the 5% subgroup (fewer contributing studies and wider CIs), exposure measurement error from FFQs that attenuates dose–response contrasts, and variability in the animal-protein sources displaced across cohorts, rather than the absence of a true gradient [35,36].

Regarding mortality from specific causes, the overall pooled estimate for CVM showed a significant reduction with isocaloric substitution of animal-protein by plant-protein (HR 0.86; 95% CI 0.82–0.91). This direction is consistent with Zheng et al. [32], who use a large prospective cohort and report lower CVM when animal-protein was replaced by plant-protein, although the magnitude varied by the animal-protein source displaced and some confidence intervals crossed the null. Importantly, Zheng et al. [32] did not compare different substitution magnitudes (3% vs 5% of total energy). In our meta-analysis we evaluated both levels separately and found a clearer benefit at 5% than at 3% (3%: HR 0.88, 95% CI 0.83–0.93; 5%:HR 0.77, 95% CI 0.70–0.86; test for subgroup differences $p = 0.03$). These findings complemented those reported in RCTs, further supporting a causal link between the substitution of animal-protein with plant-protein sources and mortality reduction [54]. In this way, meta-analyses of RCTs have shown that replacing animal-protein for plant-protein sources leads to improvements in cardiovascular risk factors, such as low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol [37]. In that sense, a biologically plausible mechanism underlying the observed reduction in cardiovascular mortality is the lipid profile. However, most included studies adjusted for dietary factors closely related to this pathway, including dietary cholesterol, saturated fat, fiber, and total energy intake. These findings underscore the importance of substitution percentage as a key factor in the magnitude of the observed effect and contribute to a better understanding of the isocaloric replacement of animal-protein with plant-protein sources and its impact on cardiovascular risk.

Our meta-analysis of CM revealed a statistically significant reduction in risk associated with the isocaloric substitution of 3% of TCV from animal-protein with plant-protein and between 3% and 5% substitution percentages. These findings align with previous scientific literature suggesting that these animal-protein sources increase cancer risk, particularly colorectal cancer, regardless of the comparator [38]. However, the results of our meta-analysis indicate a less pronounced effect for CM; the overall effect was not statistically significant. This may be explained by the fact that the magnitude of the dietary impact on cancer risk depends on tumor location, with a greater effect observed for colorectal cancer compared to lung cancer, importantly, the included studies did not permit a consistent analysis by cancer site; and the majority of them, were located in places with less potential change with dietary interventions. Among the studies reporting larger effect sizes, we observe an amplified heterogeneity, which most likely reflects imprecision (arising from limited exposure contrast, few events, heterogeneous follow-up, population differences, dietary measurement error inherent to FFQs, and variation in covariate adjustment sets) rather than absence of association. In contrast, two studies [8,27] specifically evaluated substitutions involving red and processed meats and yielded more protective estimates, plausibly because these animal-protein sources carry a higher baseline risk and thus create a larger contrast when replaced with plant-protein. Taken together, these considerations account for the attenuated pooled effect and indicate that methodological and exposure heterogeneity, rather than a true null association, primarily shapes the precision and magnitude of the CM estimates.

Considering that the studies included in this meta-analysis performed multivariable adjustments for potential confounders, including: total energy intake, saturated fatty acids (SFA), fiber, cholesterol, total fat, and other dietary components (Table 1), It can be suggested that the observed health outcomes are influenced by the replacement of animal-protein with plant-protein itself, rather than by the food matrices alone. However, this inference must be balanced against the inherent limitations of residual confounding and the use of statistical isocaloric simulations, which do not fully replicate real-world dietary interventions. Despite these observational constraints, the consistency of the findings across more than 19 million person-years suggests that the differential impact of these proteins on health is likely rooted in their intrinsic amino acid profiles and their subsequent metabolic effects. Animal-protein sources, which are rich in branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine, have been associated with adverse metabolic health outcomes when consumed beyond the Dietary Reference Intake [39,40,49]. Diets low in BCAAs have been shown to improve cardiometabolic health by activating beneficial metabolic pathways, including reduced mTOR signaling, which lowers insulin resistance and chronic inflammation; enhanced AMPK activation, promoting glucose uptake and mitochondrial function; and suppressed PPARγ activity, leading to improved lipid metabolism and reduced ectopic fat accumulation. Additionally, lower BCAA levels have been linked to reduced activation of mTORC1 in the liver, mitigating hepatic steatosis and improving overall metabolic homeostasis [39]. Additionally, high consumption of animal-protein sources has been linked to increased levels Insulin-like Growth Factor 1, a hormone associated with higher risks of type 2 diabetes, cardiovascular disease, and certain types of cancer [41,42]. This association is further supported by evidence suggesting that individuals with genetic predisposition to elevated IGF-1 levels may have an increased risk of these pathologies [41]. Furthermore, animal-protein from processed sources, may contain harmful contaminants such as dioxins and polychlorinated biphenyls [43], which bioaccumulate in the food chain and contribute to an increased risk of chronic disease [42,44].

15. Future implications

A key area for future research is to elucidate the broader implications of these findings for dietary policies and recommendations. Different dietary guidelines, including the Peruvian dietary guidelines, often emphasize the daily consumption of red meat and animal products as part of a healthy diet [45–50]. Our results challenge this approach, suggesting that promoting plant-protein instead could yield significant global health benefits. Investigating how these changes could be implemented at the population level, while addressing cultural and economic barriers, represents an essential next step toward transitioning to healthier and more sustainable eating patterns.

Notably, although the substitution levels evaluated may appear modest, replacing 3%–5% of total energy intake in a 2,000 kcal diet corresponds to approximately 100 kcal per day, which may involve replacing a serving of red or processed meat with plant-protein sources such as soy, tofu, or legumes. From both clinical and population perspectives, this magnitude of dietary change is relevant, particularly given the higher risk burden associated with certain types of animal-protein. Understanding how such shifts could be implemented at the population level, while addressing cultural and economic barriers, represents an essential next step toward transitioning to healthier and more sustainable dietary patterns.

Future research should prioritize isocaloric substitutions models to address the inherent limitations of observational studies that often lack a clearly defined comparator, thereby strengthening the evidence base for effective public health recommendation [13]. Expanding studies to include cohorts with higher baseline plant-protein intake would also enhance understanding in this field. While this meta-analysis provides valuable insights, RCTs are needed to further establish a causal relationship between plant-protein substitution and mortality reduction. This study provides direction for future research, establishing a foundation for accessible, evidence-based public health strategies aimed at promoting longer and healthier lives [51].

16. Strengths and limitations

The inclusion of studies with multivariable adjustments was a key strength of our meta-analysis, as it enabled us to reduce confounding variables and more accurately assess the specific effect of protein sources. Additionally, this systematic review includes the largest sample size to date in the context of isocaloric substitution of animal-protein with plant-protein. The total sample in person-years was 19, 904, 866 including a total sample of 1,036,799 participants, providing statistical power to detect associations between protein substitution and mortality outcomes. Furthermore, we conducted sensitivity analyses and funnel plots to assess publication bias, which were not included in previous meta-analyses [18,32,36,52]. Another important strength of our meta-analysis is the separate analysis of 3% and 5% isocaloric substitutions of animal-protein with plant-protein. Unlike prior studies that typically analyzed a single substitution level or aggregated multiple levels together, this approach enables a more nuanced understanding of dose–response effects, highlighting potential threshold differences in the impact on ACM, CVM, and CM. Furthermore, we performed formal statistical tests comparing the 3% and 5% substitution models to determine whether increasing the percentage of substitution resulted in significantly greater reductions in mortality.

However, our study has some limitations. Given the observational design of the included studies, the results reflect associations rather than causal effects and may be influenced by residual confounding, measurement error, and other inherent limitations of observational research. It is important to acknowledge that the generalizability of our findings to the broader population may be limited by the inherent complexity of food matrices and the influence of potential mediating factors that modulate the health effects of different protein sources. A major limitation of this meta-analysis lies in the limited availability of isocaloric substitution data stratified by specific types of animal-protein. This constraint precluded the estimation of robust risk estimates for individual animal-protein sources, thereby limiting our ability to discern source-specific associations with health outcomes [30]. Additionally, to avoid cohort overlap between the Glenn and Song studies, only Glenn's study [31] was included due to its larger sample size for the CVM outcome, while Song's study [26] was excluded. It is also relevant to mention that a specific limitation was observed in Kelemen ‘s study [29], where the baseline quintile (Q1) used to define the null hypothesis corresponded to a substantial level of isocaloric substitution 3.7% of animal-protein by plant-protein. This relatively high baseline reduces the contrast in exposure between the first and last quintiles (Q5 at 6.1%), potentially attenuating the observed effect size. It is plausible that a greater separation between Q1 and Q5 in terms of substitution percentage could have yielded a stronger effect estimate, as a larger contrast in exposure that typically enhances the ability to detect true associations. Additionally, an important methodological limitation in prospective cohort substitution analyses is that dietary intake is generally assessed only at baseline [5,8,27–30,32]) except for two studies [26,31]. This single time-point measurement assumes relative stability of dietary patterns during follow-up, which may introduce misclassification errors if substantial changes in diet occur. Additionally, dietary intake was predominantly assessed using self-administered Food Frequency Questionnaire [5,8,27,29–32] apart from two studies [26,28], which have inherent inaccuracies due to recall errors and possible underreporting of foods considered unhealthy. Nevertheless, it is important to contextualize these limitations. Baseline dietary assessment remains the most feasible and widely accepted approach in large-scale cohort studies, providing reasonably valid estimates of long-term habitual intake when properly modeled and adjusted.

17. Conclusion

Replacing animal with plant protein under isocaloric conditions is consistently associated with lower mortality. From a public-health perspective, emphasizing plant-protein as a replacement for animal-protein—rather than simply reducing animal foods— provides a precise and actionable strategy to lower mortality risk while supporting sustainability goals. More broadly, the isocaloric substitution framework offers a rigorous basis for causal interpretation and should become a central paradigm in nutrition research, where clearly defined counterfactual comparisons are essential. Future research should prioritize clearly specified isocaloric substitution models, larger contrasts in exposure, and randomized trials to elucidate biological mechanisms and refine dietary recommendations.

Credit authorship contribution statement

Specifically, GB designed the research, provided essential materials, and was responsible for all aspects of the manuscript. GB, PA, AR, and EJ conducted the research. GB and PA analyzed the data. GB, PA, AR, EJ, and ML drafted the manuscript. ML-M and GB had primary responsibility for the final content. All authors read and approved of the final manuscript. No author received funding or financial support.

Authorship

No one eligible for authorship has been excluded from the list of authors.

Data availability

This systematic review does not include original data. Data are extracted from literature and is publicly available. The data generated for the present analyses is available upon request to the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI or AI-assisted technologies were used in the preparation of this manuscript. The authors take full responsibility for the content of this publication.

Funding

The authors declare that the study received no specific funding from any public, commercial, or non-profit funding agency.

Conflict of interest

ML-M reported receiving consulting fees from Danone outside the submitted work. All other authors declare that they have no relevant financial or non-financial interests to disclose.

Acknowledgements

We sincerely thank all the authors for their valuable contributions, dedication, and the excellent teamwork demonstrated throughout this study. We would also like to express our special gratitude to Randerson Cardoso for his invaluable guidance and training at Meta-Analysis Academy, whose support and knowledge were essential to the completion of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106654.

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