Health outcomes associated with vegetarian diets: An umbrella review of systematic reviews and meta-analyses

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ABSTRACT

BACKGROUND: Several meta-analyses evaluated the association between vegetarian diets and health outcomes. To integrate the large amount of the available evidence, we performed an umbrella review of published meta-analyses that investigated the association between vegetarian diets and health outcomes.

METHODS: We performed an umbrella review of the evidence across meta-analyses of observational and interventional studies. PubMed, Embase, Cochrane Database of Systematic Reviews, and ISI Web of Knowledge. Additional articles were retrieved from primary search references. Meta-analyses of observational or interventional studies that assessed at least one health outcome in association with vegetarian diets. We estimated pooled effect sizes (ESs) using four different random-effect models: DerSimonian and Laird, maximum likelihood, empirical Bayes, and restricted maximum likelihood. We assessed heterogeneity using I^2 statistics and publication bias using funnel plots, radial plots, normal Q-Q plots, and the Rosenthal's fail-safe N test.

RESULTS: The umbrella review identified 20 meta-analyses of observational and interventional research with 34 health outcomes. The majority of the meta-analyses (80%) were classified as moderate or high-quality reviews, based on the AMSTAR2 criteria. By comparison with omnivorous diets, vegetarian diets were associated with a significantly lower concentration of blood total cholesterol (pooled ES = -0.549 mmol/L; 95% CI: -0.773 to -0.325; P < 0.001), LDL-cholesterol (pooled ES = -0.467 mmol/L; 95% CI: -0.600 to -0.335); P < 0.001), and HDL-cholesterol (pooled ES = -0.082 mmol/L; 95% CI: -0.095 to -0.069; P < 0.001). In comparison to omnivorous diets, vegetarian diets were associated with a reduced risk of negative health outcomes with a pooled ES of 0.886 (95% CI: 0.848 to 0.926; P < 0.001). In comparison to omnivores, Seventh-day Adventists (SDA) vegetarians had a significantly reduced risk of negative health outcomes with a pooled ES of 0.721 (95% CI: 0.625 to 0.832; P < 0.001). Non-SDA vegetarians had no significant reduction of negative health outcomes when compared to omnivores (pooled ES = 0.973; 95% CI: 0.873 to 1.083; P = 0.51). Vegetarian diets were associated with harmful outcomes on one-carbon metabolism markers (lower concentrations of vitamin B12 and higher concentrations of homocysteine), in comparison to omnivorous diets.

CONCLUSIONS: Vegetarian diets are associated with beneficial effects on the blood lipid profile and a reduced risk of negative health outcomes, including diabetes, ischemic heart disease, and cancer risk. Among vegetarians, SDA vegetarians could represent a subgroup with a further reduced risk of negative health outcomes. Vegetarian diets have adverse outcomes on one-carbon metabolism. The effect of vegetarian diets among pregnant and lactating women requires specific attention. Well-designed prospective studies are warranted to evaluate the consequences of the increased prevalence of vitamin B12 deficiency during pregnancy and infancy on later life and of trace element deficits on cancer risks.

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INTRODUCTION

For several centuries, the vegetarian diet has been practiced by several ethnic or religious groups [1]. In recent years, the vegetarian diet has been proposed as a therapeutic approach that can potentially reduce the risk of chronic non-communicable diseases, while maintaining an adequate nutritional intake [1]. Vegetarian dietary patterns can be quite diverse because of the variety of food choices available and the factors that motivate people to adopt such patterns [2]. Typically, a vegetarian diet excludes the consumption of all types of meat (e.g., pork, beef, mutton, lamb, and poultry), fish, and seafood [3]. According to different dietary pattern combinations, several subgroups could be identified in the literature, notably: 1) vegan diets which include only fruits, vegetables, legumes, whole grains, and nuts, and which may exclude honey, roots or tubers such as in Jain vegetarianism; 2) lacto-, ovo-, or lacto-ovo-vegetarian diets which are vegan diets that incorporate dairy products, eggs, or both of them, respectively. Other vegetarian diets are less stringent in terms of meat, fish, or chicken intake and are called flexitarian diets [4]. Flexitarians are individuals who follow a primarily but not strictly vegetarian diet, occasionally eating meat, fish, or chicken [4]. Flexitarian diets encounter two main categories: 1) semi-vegetarian diets which are vegetarian diets that incorporate a low consumption of meat between once per month to less than once per week; and 2) pesco- or pollo-vegetarian diets which are characterized by typical lacto-ovo-vegetarian diets that incorporate the consumption of fish or chicken, respectively (**Figure 1**).

Numerous studies evaluated the association between vegetarian diets and a wide range of nutritional, metabolic, or health outcomes including lipid metabolism, one-carbon metabolism, trace elements, bone mineral density, body weight, obesity-related metaflammatory profile, diabetes risk, cardiovascular risk, cancer risk, and all-cause mortality. In this context, several meta-analyses evaluated the association between vegetarian diets and health outcomes. To integrate the large amount of the available evidence, we performed an umbrella review of published meta-analyses that investigated the association between vegetarian diets and health outcomes.

METHODS

Umbrella Review Concept

According to Poole *et al.,* umbrella reviews "systematically search, organize, and evaluate existing evidence from multiple systematic reviews and/or meta-analyses on all health outcomes associated with a particular exposure" [5]. Umbrella reviews include the highest level of evidence, namely other systematic reviews and meta-analyses, which thus represent the analytical units of the review [6].

Literature search

We searched PubMed, Embase, Cochrane Database of Systematic Reviews, and ISI Web of Knowledge Reviews from inception to March 2018 for meta-analyses of observational or interventional studies that examined the association between vegetarian diets and any health outcome. The detailed electronic strategy is available in the **Supplementary Methods**. Additional articles were retrieved from primary search references. EndNote X7.8 was used for reference management [7]. Three investigators (AO, JL, J-LG) independently reviewed the titles and abstracts of all citations identified by the literature search. The systematic review protocol was prospectively registered on PROSPERO (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018092470). The present systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

Eligibility Criteria

Three investigators (AO, JL, CB) reviewed full-text articles for eligibility. We retained a systematic review in the umbrella review if it reported at least one pooled effect size (ES) or a frequency range concerning a health outcome in association with vegetarian diets. The different groups of vegetarian diets considered in the present umbrella review were: vegans, lacto-vegetarians, ovo-vegetarians, lacto-ovo-vegetarians, and Seventh-day Adventists (SDA). The exclusion criteria were as follows: non-English language publication; meeting abstract; editorial; narrative review; no data on health outcome; systematic review protocol; systematic review focusing only on patients with diabetes; systematic review considering the effect of fasting; and duplicate results. The PICO strategy used in the present umbrella review was: **1) Problem:** Are vegetarian diets associated with a modification of health outcomes in comparison to non-vegetarian diets? **2) Intervention:** vegetarian diets; **3) Compare to:** non-vegetarian diets; **4) Outcome:** Lipid metabolism; One-carbon metabolism; Trace elements; Obesity, metaflammation, and diabetes; Cardiovascular risk; Cancer risk; and All-cause mortality.

Data Extraction

Three investigators independently extracted data from eligible articles (AO, CB, JL). Disagreement in data extraction was resolved by consensus. The following data were extracted based on a predefined protocol, using Microsoft Excel®: First author; year of publication; primary aim; study type and setting; number of studies included in the meta-analysis; number of patients included in the meta-analysis; the summary measures related to the primary aim; and the main conclusion of the meta-analysis in relation to the primary aim. We did not evaluate the articles included in each reported meta-analysis.

Assessment of the Methodological Quality of Included Studies

Three authors (AO, JL, CB) assessed the methodological quality of meta-analyses using the AMSTAR 2 Checklist [9]. The AMSTAR tool was developed to evaluate systematic reviews of randomized trials [10]. The initial AMSTAR tool had a good agreement, reliability, construct validity, and feasibility [10]. The newest version (AMSTAR 2) enables a more detailed assessment of systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both [9]. By comparison with the original tool, AMSTAR 2 retains 10 of the original domains which include 16 items in total, has simpler response categories, and has an overall rating based on weaknesses in critical domains (i.e., protocol registered before commencement of the review, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included in the review, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting the results of the review, and assessment of presence and likely impact of publication bias) [9]. AMSTAR 2 would identify systematic reviews with a high level of evidence for better use by decision-makers [9, 10].

Data Synthesis and Analysis

Using the umbrella meta-analysis approach, we estimated the pooled effect size for the association between vegetarian diets and blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides). We also estimated the overall ES of the negative binary health outcomes (e.g., cancer, cardiovascular disease, all-cause mortality) associated with exposure to vegetarian diets. We calculated the pooled ES using the generic inverse variance method based on estimates and their standard errors. ESs and their standard errors were entered as natural logarithms since they represented ratio measures of the intervention effect. In the inverse variance method, the weight given to each study is the inverse of the variance of the effect estimate. Thus, larger studies are given more weight than smaller studies, which have larger standard errors [11]. This choice of weight minimizes the imprecision (uncertainty) of the pooled effect estimate. The overall summary from the meta-analysis was calculated by combining all studies, and the meta-analysis was performed using four different random-effect model estimators: DerSimonian and Laird, maximum likelihood, empirical Bayes, and restricted maximum likelihood. The calculated summary effect was denoted by the solid diamond at the bottom of the forest plots, the width of which represents the 95% CI. The statistical significance for heterogeneity was assessed by the use of the $\chi2$-based Q statistic and the I^2 statistic for the extent of heterogeneity. Heterogeneity was considered significant if $P < 0.1$ and $I^2 > 50\%$ [12]. We used several methods for assessing publication bias: funnel plots with rank (Kendall's τ) and regression (Egger's) tests for funnel plot asymmetry, radial plots, normal Q-Q plots, Log-likelihood profile plot for the between-studies variance (tau-squared, τ^2), trim and fill analysis, and the

Rosenthal's fail-safe N test which computes the number of missing studies that would need to be added to the analysis to yield a statistically non-significant overall effect. We also calculated the pooled ESs for the reported binary health outcomes among SDA and non-SDA vegetarians. All reported *P*-values were two-sided, with alpha set at 0.05. The meta-analysis was performed using the following statistical software packages: Comprehensive Meta-Analysis (version 2.2.050, BioStat Software, Englewood, USA); JASP Team (2018), JASP (Version 0.9.1, Amsterdam, The Netherlands); and MedCalc (v18.10.2, MedCalc Software, Belgium).

Credibility Assessment

We applied credibility assessment criteria to classify evidence from meta-analyses of observational studies, as previously reported [13-15]. The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13-15]. The algorithm defining the class of evidence is reported in **Supplemental Table 1**. By analogy, the results from meta-analyses of randomized controlled trials were assessed using the five following criteria: summary effect *P*-value ($P < 0.01$, $0.01 \leq P < 0.05$, and $P \geq 0.05$); summary effect 95% CI (excluding the null or not); heterogeneity ($I^2 > 50\%$ or not); small study effects ($P > 0.10$); and evidence of bias ($P > 0.10$) [13-15].

RESULTS

Literature Review

The systematic search generated 155 citations, of which 105 were excluded based on title and/or abstract. Of the 49 remaining references, 29 were excluded based on the selection criteria (**Supplemental Table 2**), leaving 20 systematic reviews with a meta-analysis eligible for the umbrella review (**Figure 2**) [16-35]. Eleven systematic reviews assessed blood lipids (n = 5) [16-20], one-carbon metabolism markers (n = 3) [21-23], trace elements (n = 3) [24-26], and bone mineral density (n = 1) [27]. Five meta-analyses investigated body weight [20, 28, 29], obesity-related inflammatory profiles[30], and the risk of diabetes [31]. Four meta-analyses concerned cardiovascular morbidity and mortality [20, 32-34] and three others addressed cancer risk in vegetarians [20, 32, 35]. Among the 20 meta-analyses reported in the present umbrella review, 10 (50%) were scored as "high-quality reviews" [18-20, 25, 27-31, 34], six (30%) as "moderate quality reviews" [16, 17, 26, 32, 33, 35], three (15%) as "low-quality reviews" [21, 23, 24], and one (5%) as a "critically low-quality review" [22], according to the AMSTAR2 criteria (Supplemental **Table 3**). Of the 20 meta-analyses included in the umbrella review, 15 (75%) formally reported an assessment for potential confounders for the studies that were included in the pooled analysis or performed meta-regression analysis on potential confounders [16-21, 25, 28-35] (**Supplemental Table 4**). Among the 15 studies, 11 reported in detail the potential confounders for each study [18-20, 25, 28, 30-35].

Across all meta-analyses included in the umbrella review, we retrieved 34 health outcomes that we classified in seven groups (***Group #1, Lipid metabolism***: total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides; ***Group #2, One-carbon metabolism***: vitamin B12 deficiency, vitamin B12 status, homocysteine; ***Group #3, Trace elements***: zinc intake, zinc concentration, ferritin, bone mineral density; ***Group #4, Obesity, metaflammation, and diabetes***: body mass index, weight reduction, hs-CRP, diabetes risk (binary outcome), glucose (continuous variable outcome); ***Group #5, Cardiovascular risk***: ischemic heart disease, circulatory disease, cerebrovascular disease, cardiovascular disease, cardiac events, systolic blood pressure, diastolic blood pressure; ***Group #6, Cancer***: cancer incidence, colorectal cancer risk, prostate cancer risk, breast cancer risk, all cancer-related mortality, breast cancer-related mortality, colorectal cancer-related mortality, prostate cancer-related mortality, lung cancer-related mortality, breast cancer incidence; and ***Group #7,* All-cause mortality**).

Blood Lipids (Table 1)

Description of meta-analyses included in the umbrella review

The comparison of blood lipids between subjects who adhered to a vegetarian diet and omnivores have been subject to several cross-sectional studies. The first meta-analysis that reported the association between vegetarian diets and blood triglyceride concentration was published in 2012 and included 12 studies (11 cross-sectional and one cohort study) on 1,300 subjects [16]. In comparison to omnivorous diets, vegetarian diets were significantly associated with a lower plasma triglycerides concentration with a standardized mean difference (SMD) of -1.28 mmol/L (95% CI: -2.14 to -0.42) [16]. A subsequent meta-analysis of cross-sectional and cohort studies (n = 12; 4,177 subjects) assessed the magnitude of the association in regards to the plasmatic concentration of high-density lipoprotein (HDL) cholesterol [17]. In the whole analysis, vegetarian diets were not associated with significantly lower HDL cholesterol concentration (SMD = 0.02 mmol/l; 95% CI: -0.19 to 0.22) [17]. The lack of a significant difference between vegetarians and omnivores was maintained regardless of the location of the study or cultural circumstances of the participants [17]. An updated meta-analysis published in 2017 screened data from 86 cross-sectional studies that compared 56,461 vegetarians and 8,421 vegans with 184,167 omnivores [20]. In overall analysis, vegetarians had a significantly lower serum total cholesterol (weighted mean difference [WMD] = -28.16 mg/dL; 95%CI -31.22 to -25.10; 64 studies), LDL cholesterol (WMD = -21.27 mg/dL; 95% CI: -24.27 to -18.27; 46 studies), HDL cholesterol (WMD = -2.72 mg/dL; 95% CI: -3.40 to -2.04; 51 studies), and triglycerides (WMD = -11.39 mg/dL; 95% CI: -17.42 to -5.37; 55 studies) in comparison to omnivores [20].

Several interventional studies assessed the effect of vegetarian diets on blood lipids. A meta-analysis of eleven randomized controlled trials assessed the efficacy of vegetarian diets on blood lipids reduction (total cholesterol, low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglycerides) [18]. Vegetarian diets significantly lowered blood concentrations of total cholesterol (WMD = -0.36 mmol/L; 95% CI: -0.55 to -0.17), LDL cholesterol (WMD = -0.34 mmol/L; 95% CI: -0.57 to -0.11), and HDL cholesterol (WMD = -

0.10 mmol/L; 95% CI: -0.14 to -0.06) [18]. Conversely, vegetarian diets were not significantly associated with a lowering of blood triglyceride concentrations (WMD = 0.04 mmol/L; 95% CI: -0.05 to 0.13) [18].

A meta-analysis included controlled trials and observational studies performed during at least four weeks [19]. Thirty observational studies and 19 clinical trials met the inclusion criteria and included 1,484 patients with a mean age of 49 years [19]. Among the 30 observational studies, 23 included participants who had been on a vegetarian diet for more than one year [19]. Concerning clinical trials, the mean duration was 25.5 weeks [19]. In comparison to omnivorous diets, vegetarian diets were associated with a significantly lower mean concentrations of total cholesterol (-29.2 mg/dL; 95 CI: -34.6 to -23.8 and -12.5 mg/dL; 95% CI: -17.8 to -7.2), LDL cholesterol (-22.9 mg/dL; 95% CI: -27.9 to -17.9 and -12.2 mg/dL; 95% CI: -17.7 to -6.7), and HDL cholesterol (-3.6 mg/dL; 95% CI: -4.7 to -2.5; and -3.4 mg/dL; 95% CI: -4.3 to -2.5) in observational studies and clinical trials, respectively [19]. There was no significant influence of vegetarian diets on triglyceride levels, both in observational studies and clinical trials [19].

Pooled effect sizes for the association between vegetarian diets and blood lipids

In the umbrella meta-analysis, vegetarian diets were associated with a significantly reduced concentration of blood total cholesterol with a pooled ES of -0.549 mmol/L (95% CI: -0.773 to -0.325; $P < 0.001$; Rosenthal's fail-safe N = 502) and a significant heterogeneity (I^2 = 91.67%; 95% CI: 74.24 to 99.43; $P < 0.001$). Assessment by funnel plot revealed a moderate risk of bias. The QQ-plot did not reveal a significant departure from normality (rank correlation test for funnel plot asymmetry, $P = 0.75$). Consistently, vegetarian diets were associated with a significantly reduced concentration of LDL-cholesterol with a pooled ES of -0.467 mmol/L (95% CI: -0.600 to -0.335; $P < 0.001$; Rosenthal's fail-safe N = 332) and a significant heterogeneity (I^2 = 74.70%; 95% CI: 22.41 to 98.43; $P = 0.008$). The funnel plot revealed a low risk of bias. The QQ-plot did not reveal a significant departure from normality (rank correlation test for funnel plot asymmetry, $P = 0.33$). Vegetarian diets were associated with a significantly reduced concentration of HDL-cholesterol with a pooled ES of -0.082 mmol/L (95% CI: -0.095 to -0.069; P < 0.001; Rosenthal's fail-safe N = 252) without significant heterogeneity (I^2 = 5.50; 95% CI: 0 to 98.19; P = 0.38) or study bias. The QQ-plot did not reveal a significant departure from normality (rank correlation test for funnel plot asymmetry, P = 0.48). Vegetarian diets were not associated with a significant reduction of triglyceride concentration in comparison to non-vegetarian diets (pooled ES = -0.126 mmol/L; 95% CI: -0.339 to 0.086; P = 0.24) (**Figure 3 and Supplemental Results**).

Vitamin B12 Deficiency and Related One-Carbon Metabolism Markers (Table 2)

It is well known that vegetarians are at increased risk of vitamin B12 (cobalamin) deficiency [36]. Vitamin B12 deficiency is associated with increased homocysteine levels, which represents a debated surrogate marker of cardiovascular disease [36]. A meta-analysis reported the rate of cobalamin deficiency from 18 studies that included participants adhering to different types of vegetarian diets [22]. Cobalamin deficiency was ascertained using methylmalonic acid (MMA), holo-transcobalamin II (holo-TC), or both according to the following thresholds: holo-TC < 35 pmol/L; urinary MMA (> 4.0 µg/mg creatinine); serum MMA > 260 µmol/L to > 0.75 µmol/L [22]. Cobalamin deficiency rates were: 62% among pregnant women, 25 to 86% among children, 21 to 41% among adolescents, and 11 to 90% among older adults [22]. Vegans and individuals who adhered to a vegetarian diet since birth had higher rates of cobalamin deficiency in comparison to vegetarians and subjects who adopted such a diet later in life [22]. Furthermore, vegetarians developed cobalamin deficiency regardless of the type of vegetarian diet [22]. These results were consistent with a systematic review of 40 studies that assessed the rate of low vitamin B12 status among individuals adhering to vegetarian diets [23]. Serum vitamin B12 was assessed using various specific methods (radioimmunoassay, immunochemiluminometric methods, microparticle assay, chemiluminescence immunoassays, and microbiological assays) [23]. The reported prevalence of low cobalamin status among subjects adhering to vegetarian diets was 45% among infants, 17 to 39% among pregnant women, and 0 to 86.5% among adults and older adults [23]. Higher prevalence rates of low cobalamin status were reported among vegans in comparison to other vegetarian categories, namely: semi-vegetarians, lacto-vegetarians, lacto-ovo-vegetarians, ovo-vegetarians, macrobiotic diet, raw food diets [23]. A major drawback in this meta-analysis is the lack of assessment of functional markers such as MMA and homocysteine to estimate the true picture of cobalamin deficiency [23]. Furthermore, several serum vitamin B12 thresholds were used for defining low cobalamin status and ranged from 95 to 250 pmol/L even if most studies used a serum concentration < 130 to 150 pmol/L [23].

A pooled analysis appraised the magnitude of the association between one-carbon metabolism markers and vegetarian diets [21]. The meta-analysis included six cohorts and eleven cross-sectional studies (3,230 participants) and compared the concentrations of plasma homocysteine and serum vitamin B12 in omnivores, lacto-vegetarians or lacto-ovo-vegetarians, and vegans [21]. The mean serum vitamin B12 was significantly lower in lacto-vegetarians or lacto-ovo-vegetarians (209 pmol/L, standard deviation [SD] = 47; $P < 0.005$) and vegans (172 pmol/L, SD = 59; $P < 0.005$) in comparison to that of omnivores (303 pmol/L, SD = 72) [21]. Consistently, the mean plasma homocysteine concentration was significantly higher among lacto-vegetarians or lacto-ovo-vegetarians (13.91 µmol/L, SD = 2.89; $P < 0.025$) and vegans (16.41 µmol/L, SD = 4.8; $P < 0.005$) in comparison to that of omnivores (11.03 µmol/L, SD = 2.89) [21].

Trace Elements (Table 3)

A meta-analysis of 18 case-control studies demonstrated that dietary zinc intake was significantly reduced among vegetarians in comparison to omnivores (mean difference = -0.88 mg/day; standard error [SE] = 0.15; $P < 0.001$) [24]. The same meta-analysis on 13 case-control studies demonstrated a significantly lower serum zinc concentration among vegetarians in comparison to omnivores (mean difference = -0.93 µmol/L; SE = 0.27; $P = 0.001$) [24]. However, actual zinc concentrations were not reported, so it is unclear whether zinc concentrations fell below the level consistent with clinical deficiency. A meta-analysis of six observational studies confirmed that vegetarian pregnant women had lower zinc intake in comparison to non-vegetarian pregnant women (-1.38 mg/day; SE = 0.35; $P < 0.001$) [25]. A meta-analysis of 24 cross-sectional studies assessed the impact of vegetarian diets on iron status [26]. Adult subjects who adhered to a vegetarian diet had a significantly lower serum ferritin concentration in comparison to non-vegetarians (-29.71 µg/L; 95% CI: -39.69 to -19.73; $P < 0.01$) [26].

Only one meta-analysis assessed the association between vegetarian diets and bone mineral density [27]. A pooled analysis of nine studies on 2,749 subjects (1,880 women and 869 men) reported a 4% reduction of bone mineral density among vegetarians when compared to omnivores at both the femoral neck (95% CI: 2 to 7; $P = 0.0008$) and the lumbar spine (95% CI: 2 to 7; $P = 0.0005$) [27]. The authors concluded to a modest effect of vegetarian diets on bone mineral density and that the ES was unlikely to result in a clinically important increase in fracture risk [27].

Body Weight, Metaflammation, and Diabetes Risk (Table 4)

Several case-control and interventional studies assessed the influence of vegetarian diets on body weight. A meta-analysis of 71 case-control studies reported a significantly lower body mass index (BMI) among vegetarians (n = 57,724) in comparison to omnivores (n = 199,230) with a WMD of -1.49 kg/m^2 (95% CI: -1.72 to -1.25) [20]. A meta-analysis of 15 interventional trials estimated the effect of vegetarian diets of ≥4 weeks' duration without energy intake limitation on the variation in body weight [28]. The mean weight variation in patients who were prescribed vegetarian diets were -3.4 kg (95% CI: -4.4 to -2.4; $P < 0.001$) and -4.6 kg (95% CI: -5.4 to -3.8; $P < 0.001$) in intention-to-treat and per-protocol analyses, respectively [28]. Interestingly, positive predictors of a greater weight loss after vegetarian diet prescription were: high baseline body weight, male gender, older age, longer duration of the trial, and studies in which weight loss was the primary endpoint [28]. These results were confirmed by a meta-analysis of randomized controlled trials that evaluated the net change in body weight after the initiation of a vegetarian diet [29]. The pooled analysis was performed on twelve randomized controlled trials, with a total of 1,151 subjects who received the intervention over a median duration of 18 weeks [29]. Subjects randomized in the vegetarian group lost significantly more weight than those assigned to the non-vegetarian group (WMD: -2.02 kg; 95 % CI: -2.80 to -1.23) [29].

It has been suggested that obesity and metabolic syndrome are associated with chronic low-grade inflammation, recently referred to as metaflammation [37]. In this setting, several cross-sectional studies compared the concentration of inflammatory blood biomarkers among vegetarians and omnivores. A meta-analysis of 18 cross-sectional studies on 2,398 patients investigated the association between vegetarian diets and inflammatory biomarkers [30]. In the overall analysis, there was no significant difference in high-sensitivity C-reactive protein (hs-CRP) level between vegetarians and omnivores (SMD = -0.15; 95 % CI: -0.35 to 0.05) [30].

In a meta-analysis of 14 observational studies, vegetarians had a significantly lower risk of diabetes in comparison to non-vegetarians (odds ratio [OR] = 0.726; 95% CI: 0.608 to 0.867) [31]. These results were consistent with those of a meta-analysis of 27 cross-sectional studies which reported a significantly lower blood glucose level among vegetarians in comparison to omnivores (WMD = -5.08 mg/dL; 95% CI: -5.98 to -4.19) [20].

Cardiovascular Risk (Table 5)

A meta-analysis of seven prospective cohort studies (124,706 participants) investigated the cardiovascular disease mortality among vegetarians and non-vegetarians [32]. Vegetarians had a reduced risk of ischemic heart disease (-29%; relative risk [RR] = 0.71; 95% CI: 0.56 to 0.87) and a non-significant trend towards a reduced risk of circulatory diseases (-16%; RR = 0.84; 95% CI: 0.54 to 1.14) and cerebrovascular disease (-12%; RR = 0.88; 95% CI: 0.70 to 1.06), when compared to omnivores [32]. These results were confirmed in a meta-analysis of cross-sectional and cohort studies that assessed the association with the risk of ischemic heart disease (RR = 0.75; 95% CI: 0.68 to 0.82), cardiovascular disease (RR = 0.93; 95% CI: 0.86 to 1.00), and cerebrovascular disease (RR = 0.93; 95% CI: 0.78 to 1.10) [20]. An updated meta-analysis of eight cohort studies (183,321 participants) compared the risk of cardiovascular disease between vegetarians and omnivores taking into account the subgroup of subjects who adhered to an SDA diet [33]. SDA vegetarians do not consume tobacco, alcohol, or pork, and many adhere to a lacto-ovo-vegetarian diet [38]. Vegetarians had a significantly lower risk of ischemic heart disease or cardiac event, with a greater ES noted among SDA vegetarians in comparison to non-SDA vegetarians (-40%, RR = 0.60; 95% CI: 0.43 to 0.80 vs. -16%, RR = 0.84; 95% CI: 0.74 to 0.96, respectively) [33].

To explain the relationship between cardiovascular risk and vegetarian diets, a meta-analysis of 39 studies (seven clinical trials and 32 observational studies) examined the association between vegetarian diets and blood pressure [34]. In the seven controlled trials that included 311 participants with a mean age of 44.5 years, the consumption of vegetarian diets was associated with a significant reduction in both systolic and diastolic blood pressure (-4.8 mm Hg; 95% CI: -6.6 to -3.1 and -2.2 mm Hg; 95% CI: -3.5 to -1.0, respectively) when compared to omnivorous diets [34]. In the 32 observational studies that included 21,604 participants with a mean age of 46.6 years, vegetarian diets were also associated with a significant reduction in both mean systolic and diastolic blood pressure (-6.9 mm Hg; 95% CI: -9.1 to -4.7 and -4.7 mm Hg; 95% CI: -6.3 to -3.1, respectively) when compared to omnivorous diets [34].

Cancer Risk (Table 6)

Several studies assessed the association between cancer risk and vegetarian diets, but the results have been inconclusive. A pooled meta-analysis of seven prospective cohort studies (124,706 participants) reported a significantly reduced cancer incidence by 18% among vegetarians in comparison to omnivores (RR = 0.82; 95% CI: 0.67 to 0.97) [32]. More specifically, a recently published meta-analysis investigated the association between vegetarian diets and the risk of breast, colorectal, and prostate cancer [35]. Among the 686,629 individuals included in the meta-analysis, 3,441, 4,062, and 1,935 cases of breast, colorectal, and prostate cancer were recorded respectively [35]. In the full analysis, vegetarian diets were not associated with a significant reduction of the risk of either breast, colorectal, or prostate cancer by comparison with non-vegetarian diets [35].

A pooled analysis of multiple prospective vegetarian cohorts assessed the association with global cancer incidence, cancer mortality, breast cancer incidence, breast cancer mortality, colorectal cancer mortality, prostate cancer mortality, and lung cancer mortality [20]. In comparison to omnivores, vegetarians had a significantly reduced risk of cancer incidence (RR = 0.92; 95% CI: 0.87 to 0.98) and a non-significant trend toward a reduced risk of breast cancer incidence (RR = 0.94; 95% CI: 0.84 to 1.06) and colorectal cancer mortality (RR = 0.90; 95% CI: 0.76 to 1.05) [20]. The meta-analysis did not show a significant difference between vegetarians and omnivores regarding all cancer-related mortality, breast cancer mortality, prostate cancer mortality, and lung cancer mortality [20].

All-cause Mortality (Table 7)

Several meta-analyses addressed the relationship between vegetarian diets and all-cause mortality. A meta-analysis of seven cohort studies showed no significant reduction of all-cause mortality among vegetarians when compared to omnivores (RR = 0.91; 95% CI: 0.66 to 1.16) [32]. A meta-analysis of five prospective cohort studies confirmed the lack of a significant association between vegetarian diets and a reduced risk of all-cause mortality (RR = 0.94; 95% CI: 0.86 to 1.04) [20]. Kwok *et al*. reported an updated meta-analysis on seven cohort studies (183,321 participants after the exclusion of the Japanese Zen Priest study [39] and adding the Adventist Health Study 2 [40]) and performed a subgroup analysis on cohorts that included SDA subjects [33]. The relative risk for all-cause mortality was significantly reduced in SDA cohorts (RR = 0.68; 95% CI: 0.45 to 1.02) when compared to non-SDA cohorts (RR = 1.04; 95% CI: 0.98 to 1.10) [33].

Effect of Vegetarian Diets on Negative Health Outcomes

Four meta-analyses reported ESs regarding 16 negative health outcomes in association with vegetarian diets [20, 31, 32, 35]. These negative health outcomes included ischemic heart disease, cardiovascular disease, cerebrovascular disease, diabetes, cancer, cancer-related mortality, and all-cause mortality and are detailed in **Figure 4**. In the full analysis, the vegetarian diets were associated with a significantly reduced risk of negative health outcomes with a pooled ES of 0.886 (95% CI: 0.848 to 0.926; $P < 0.001$) without significant heterogeneity ($I^2 = 43.16\%$; 95% CI: 3.55 to 66.51; $P = 0.02$) (**Figure 4**). The assessment of study bias through the funnel plot, the radial version of the funnel plot, and the QQ-plot did not reveal a significant departure from normality (rank correlation test for funnel plot asymmetry, $P = 0.07$). The number of missing studies that would need to be added to the analysis to yield a statistically non-significant overall effect (Rosenthal's fail-safe N) was 372. The results of the pooled ESs, heterogeneity testing, and study bias were similar using the four meta-analysis methods (**Supplemental Results**). Two meta-analyses reported ESs regarding five negative health outcomes among SDA and non-SDA vegetarians [20, 33]. In comparison to omnivores, SDA vegetarians had a significantly reduced risk of negative health outcomes with a pooled ES of 0.721 (95% CI: 0.625 to 0.832; $P < 0.001$) without significant heterogeneity ($I^2 = 52.54\%$; 95% CI: 0.00 to 81.06; $P = 0.06$) or study bias (rank correlation test for Funnel plot asymmetry, $P = 0.99$; Rosenthal's fail-safe N = 113) (**Figure 5** and **Supplemental Results**). Non-SDA vegetarians had no significant reduction of negative health outcomes when compared to omnivores (pooled ES = 0.973; 95% CI: 0.873 to 1.083; $P = 0.51$) with a high risk of heterogeneity ($I^2 = 84.99\%$; 95% CI: 69.15 to 92.69; $P < 0.0001$) (**Figure 5** and **Supplemental Results**).

DISCUSSION

Main Findings of the Umbrella Review (Table 8)

In comparison to omnivorous diets, vegetarian diets are associated with clinically relevant positive outcomes on both total and LDL cholesterol and body weight. Subjects adhering to vegetarian diets have a significantly lower risk of diabetes, ischemic heart disease, and cancer, in comparison to omnivores. Among vegetarians, SDA vegetarians could represent a subgroup with a further reduced risk of negative health outcomes. Vegetarian diets were associated with a higher rate of vitamin B12 deficiency (lower concentrations of vitamin B12 and higher concentrations of homocysteine), in comparison to omnivorous diets.

Positive Outcomes of Vegetarian Diets on Blood Lipids, Body Weight and the Risk of Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease

The umbrella review highlighted the beneficial effects of vegetarian diets on the blood lipid profile. Interestingly, total cholesterol, LDL-cholesterol, and HDL-cholesterol all were significantly lowered in association with vegetarian diets. However, the magnitude of the reduction in terms of effect sizes was 7 and 6 times greater for total cholesterol and LDL-cholesterol, respectively, when compared to that observed for HDL-cholesterol. In a multicenter randomized controlled trial, patients who received a vegetarian diet intervention had a significant reduction of total cholesterol (-0.22 mmol/L; 5% CI: -0.34 to -0.10; $P < 0.001$), LDL-cholesterol (-0.19 mmol/L; 95% CI: -0.30 to -0.08; $P < 0.001$), and HDL-cholesterol (-0.08 mmol/L; 95% CI: -0.12 to -0.04; $P < 0.001$) [41]. In this randomized trial, the magnitudes of effect sizes were similar to those reported in the present umbrella review. The reduction in HDL-cholesterol in association with vegetarian diets could be attributed to a reduction in apolipoprotein A-I production rate [42]. In the umbrella review, the variation observed for HDL-cholesterol, although statistically significant, seems of less clinical relevance in comparison to that of total and LDL-cholesterol. The relationship between HDL-cholesterol and cardiovascular risk is unclear and is subject to debate. In an observational cohort study (CANHEART: Cardiovascular Health in Ambulatory Care Research Team) on 631,762 individuals with a mean follow-up of 4.9 years, HDL-cholesterol level was unlikely to represent a cardiovascular specific risk factor given similarities in its associations with non-cardiovascular outcomes [43]. Alcohol intake increases total HDL-cholesterol [44]. Results from the prospective KIHD cohort study (Kuopio ischemic heart disease risk factor study) with a mean follow-up of 12.4 years confirmed that raised concentration of HDL-cholesterol was associated with a risk reduction for coronary events among men whose gamma-glutamyltransferase activity was within the normal range, suggesting low alcohol intake [44].

The implication of HDL-cholesterol in the risk of cardiovascular disease, notably in the setting of vegetarian diets, deserves further investigation [45].

There is clear evidence that vegetarian diets are associated with positive health outcomes regarding body weight and disease burden related to obesity (**Figure 6**). The global epidemic of obesity has disrupted the epidemiological landscape of non-communicable diseases. Vegetarian diets influence the endogenous metabolism and gut microbiota [46]. A metabolomic study compared the plasma of healthy human vegans to that of healthy omnivores in an urban US environment [47]. Despite similar intestinal metagenomic profiles, as shown by 16S rRNA-tagged sequencing, the plasma metabolome differed significantly between vegans and omnivores [47]. On the 361 metabolites tested, 30 metabolites, roughly categorized into six areas (amino acids, carbohydrates, cofactors and vitamins, lipids, nucleotides, and xenobiotics), were highly discriminant for distinguishing vegans from omnivores [47]. The effects of diet on gut microbiota should also be considered since changes in gut microbiota and related metabolites may influence health outcomes. Vegans exhibit higher concentrations of plant-derived metabolites produced by the gut microbiota, while omnivores exhibit increased levels of lipids and amino acids linked to the consumption of animal products [47]. Animal-based diets decrease the abundance of Firmicutes, while plant-based diets increase the *Prevotella* genus and some fiber-degrading Firmicutes [48, 49]. Low adherence to a Mediterranean diet —characterized by a high-level consumption of cereals, fruit, vegetables, and legumes— increases urinary trimethylamine-N-oxide (TMAO) levels [49]. The metabolism by the gut microbiome of dietary L-carnitine, a compound that is abundant in red meat, produces TMAO and accelerates atherosclerosis in mice [50]. Among human subjects, omnivores produced significantly higher levels of TMAO than vegetarians following the ingestion of L-carnitine through a microbiota-dependent mechanism [50]. In a cohort of 2,595 patients undergoing a cardiac evaluation and who presented with high TMAO levels, the concentration of plasma L-carnitine was a significant predictor of prevalent cardiovascular disease and incident major adverse cardiac events (myocardial infarction, stroke or death) [50]. Taken together, these data suggest evaluating the influence of microbiome-related metabolomic profiles on the potential benefit of vegetarian diets, in particular for cardiovascular outcomes.

Vegetarian diets have a potentially positive impact on the obesity-related metaflammatory profile (**Figure 7**). An alteration in the cross-talk between gut microbiota and the host could trigger and contribute to the development and maintenance of chronic non-communicable diseases [37, 51]. A cross-sectional study on 268 non-diabetic individuals compared strict vegetarians, lacto-ovo-vegetarians, and omnivores regarding their clinical, biochemical, circulating inflammatory markers, and the composition of gut microbiota [52]. Inflammatory markers exhibited a gradual and significant increase from the vegetarians and lacto-ovo-vegetarians to the omnivorous group [52]. *Succinivibrio* and *Halomonas* from the Proteobacteria phylum were overrepresented in omnivores, which exhibited higher values of anthropometric data, insulin level, insulin resistance index (HOMA-IR), and a worse lipid profile. Taken together, these data suggest that animal-based diets may be associated with an intestinal environment which could trigger low-grade endotoxemia through bacterial translocations, low-grade systemic inflammation and metabolic dysfunction, the whole, representing the immunometabolic disease cluster (**Figure 7**) [37]. Even if the diet is a contributor to cardiovascular risk, other modifiable (physical inactivity, tobacco, hypertension, and obesity) or non-modifiable (genetics, diabetes, age, gender, ethnicity, socioeconomic status) risk factors could influence the association between diet and cardiovascular risk.

A high-quality systematic review has shown that vegetarians had a significantly reduced risk (-27%) to develop diabetes in comparison to non-vegetarians [31]. Consistently, non-diabetic vegetarians had a significantly reduced blood glucose level (WMD = -0.28 mmol/L; 95% CI: -0.33 to -0.23) when compared to omnivores [20]. Among patients with type 2 diabetes, a meta-analysis of nine randomized-controlled trials (n = 664 patients) showed that the vegetarian diet was associated with a significant reduction of glycated hemoglobin (HbA1c) (mean difference = -0.29%; 95% CI: -0.45 to -0.12%) and fasting glucose level (mean difference = -0.56 mmol/L; 95% CI: -0.99 to -0.13 mmol/L) [53]. The Canadian Diabetes Association has included vegetarian diets among the recommended dietary patterns to be used in medical nutrition therapy for persons with type 2 diabetes [54, 55]. The position statement from the Canadian Diabetes Association concluded that "*plant-based diets were just as effective, if not more effective, than other diabetes diets in improving body weight, cardiovascular risk factors, insulin sensitivity, glycated hemoglobin levels, oxidative stress markers, and renovascular markers*" and urged for the development of user-friendly plant-based diet practice guidelines for the management of type 2 diabetes [55].

Association of Vegetarian Diets with a Higher Rate of Vitamin B12 Deficiency during Pregnancy, Early Life and Adulthood

Vegetarian diets are associated with a higher rate of vitamin B12 deficiency, in particular, among infants and pregnant women with adverse outcomes on cobalamin status and one-carbon metabolism (**Figure 6**). The highest prevalence rate of low cobalamin status was reported among vegans, in comparison to other vegetarian categories. However, it paradoxical that vitamin B12 deficiency has deserved less interest than other outcomes addressed by the meta-analyses, in particular in infants and pregnant women (**Table 2**). Vitamin B12 plays critical roles both in cellular and mitochondrial metabolisms, through its methylcobalamin and adenosylcobalamin forms, respectively. At the cellular level, methylcobalamin is required for the methionine synthase reaction which recycles homocysteine into methionine through the addition of a methyl group provided by methyltetrahydrofolate, a process called remethylation [36, 56]. The methionine allows the generation of the S-adenosylmethionine, which is a methyl-donor required for epigenetic reactions, including methylation of DNA, histones, and other regulators of gene expression [36, 56, 57]. Cobalamin deficiency results in the accumulation of homocysteine and methylmalonic acid along with the reduced synthesis of methionine and S-adenosylmethionine [36].

Two meta-analyses reported a high rate of vitamin B12 deficiency among vegetarian adults [22, 23]. Hyperhomocysteinemia has been established through several epidemiological studies as a marker of chronic diseases such as cardiovascular disease, cerebrovascular disease, and dementia-type disorders [58]. Furthermore, a meta-analysis of 83 case-control studies involving 35,758 individuals has shown that hyperhomocysteinemia may be a potential risk factor for cancer and that vitamin B12 level was inversely associated with urinary-system and gastrointestinal cancers [59]. Vitamin B12 is not a component of plant foods [2]. Vegetarians should carefully design their diet, explicitly focusing on increasing their intake of vitamin B12 to reduce their risk of non-communicable diseases further. Milk and eggs in the usual amounts are not a reliable source of vitamin B12 and should not represent the unique source of cobalamin [2]. Vegetarians and vegans must regularly consume reliable sources of cobalamin, namely, cobalamin-fortified foods and cobalamin-containing supplements [2]. Even if vitamin B12 deficiency is recognized as a determinant of hyperhomocysteinemia, it is possible that other factors, such as riboflavin deficiency, could also induce hyperhomocysteinemia [60, 61].

Vitamin B12 deficiency has deserved less interest than other outcomes in infants and pregnant women under vegetarian diets (**Table 2**). This is critical in regard to the crucial role of vitamin B12 during pregnancy and early life. Barker and Osmond suggested the paradigm of the influence of dietary exposure in early life on long-term health outcomes [62]. A great deal of experimental data and epidemiologic evidence supports that maternal B12 status influences fetal growth and development and later outcomes related to morbid obesity and brain aging [63, 64]. Maternal vitamin B12 deficiency is associated with an increased risk of neural tube defect, an excess of adiposity, increased insulin resistance, and altered risk of cancer in the offspring [63]. The results of the Pune Maternal Nutrition Study (PMNS) conducted in India —one of the world's regions most at-risk of vitamin B12 deficiency, intrauterine growth restriction, and low birth weight— perfectly illustrate the significant influence of a vitamin B12 deficiency on fetal programming [65]. A striking feature highlighted by the PMNS study was that Indian babies were thin but exhibited higher amounts of visceral adipose tissue by comparison with European babies, leading to the concept of “thin-fat” babies [65]. Importantly, the PMNS established micronutrient-rich foods as strong determinants of fetal size [65]. Moreover, children born to mothers who were vitamin B12 deficient and who had a high folate level were at high risk of insulin resistance [65]. Interestingly, low serum vitamin B12/high folate is also associated with insulin resistance and metabolic syndrome in a cohort of adults with morbid obesity [66]. Taken together, these data suggest that a strict vegetarian diet exposes pregnant females to a high risk of vitamin B12 deficiency, thereby driving epigenetic alterations with a subsequent long-term risk of non-communicable diseases. This would be particularly critical in Canada and the USA, two countries in which folate fortification in cereals has been introduced 20 years ago and could aggravate the consequences of B12 deficiency [67]. Well-designed longitudinal studies integrating a multi-omics approach with in-depth clinical and biological phenotyping of cohorts of vegetarian mothers and their children will better address this knowledge gap that is highlighted in our umbrella review. This is particularly critical in regard to the association of vitamin B12 deficiency during pregnancy with both lower birth weight and preterm birth that was reported in two recent meta-analyses [68, 69]. The specific influence of vegetarian diets on these health outcomes could not be addressed in these meta-analyses.

Trace Elements and Their Mitigating Effects on the Risk of Cardiovascular Disease and Cancer

Vegetarian diets expose to a potential risk of zinc deficiency. Zinc is second to iron as the most abundant trace element in the body with total body stores of 1.5 g and 2.5 g in women and men, respectively. There is a growing body of evidence supporting that zinc, which is a key constituent or cofactor of over 300 mammalian proteins, may play a major role in host defense against cancer initiation and progression [70]. More specifically, zinc is essential for DNA-binding proteins with zinc fingers, copper/zinc superoxide dismutase, and several proteins involved in DNA repair [70]. It has been demonstrated that low intracellular zinc status causes oxidative DNA damage along with a dysfunctional p53 protein, which severely compromises DNA repair [71]. A meta-analysis of 114 case-control, cohort and cross-sectional studies that have included 22,737 participants reported a significantly decreased serum zinc concentration in patients with liver (ES = -2.29), stomach (ES = -1.59), prostate

(ES = -1.36), head and neck (ES = -1.43), lung (ES = -1.04), and breast (ES = -0.93) cancers [72]. Furthermore, a recently published meta-analysis on two prospective cohorts and five case-control studies (1,659 subjects) concluded that the highest category of dietary zinc intake was significantly associated with a reduced risk of pancreatic cancer, especially among American populations [73]. Foods rich in zinc include red meat and seafood. Zinc sources for vegetarians include soy products, legumes, whole grains, cheese, seeds, and nuts [2]. Organic acids, such as citric acid can enhance zinc absorption [2]. It is noteworthy that the two meta-analyses reported by Foster *et al.* did not report zinc levels but the variation of zinc levels from baseline without providing evidence of a serum zinc concentration below the reference values. Furthermore, making a firm diagnosis of zinc deficiency should not be based solely on zinc levels. For instance, serum zinc levels are influenced by the acute-phase response [74]. Moreover, the recognizable clinical syndrome of zinc deficiency is usually associated with quite low levels of serum zinc, and there are no biomarkers to identify functional tissue deficiency [74]. Thus, currently available meta-analyses do not allow firm conclusion regarding the association between vegetarian diets and the risk of zinc deficiency. However, the working group of the Italian Society of Human Nutrition recommends that vegetarians consume more dietary zinc than the population reference intake suggested for omnivores [3].

By comparison with omnivores, vegetarians typically have lower iron stores. Lower iron stores have been associated with a lower risk for the development of metabolic syndrome [75]. In a 5-years follow-up study on 18,022 healthy Korean men, subjects with the highest quintile of serum ferritin had a significantly increased risk for developing metabolic syndrome when compared with those from the lowest quantile of serum ferritin concentration (hazard ratio = 1.66; 95% CI: 1.38 to 2.01) [75]. The role of iron in colorectal cancer risk is ambivalent. A meta-analysis of ten observational studies involving 3,318 subjects with colorectal adenoma has demonstrated that heme iron intake was significantly associated with an increased risk of colorectal adenoma (RR = 1.23; 95% CI: 1.03 to 1.48), whereas non-heme iron intake was inversely associated with the risk of colorectal adenoma (RR =

0.73; 95% CI: 0.54 to 0.97) [76]. These results were consistent with those reported in a meta-analysis of 59 epidemiologic studies, investigating total iron, dietary iron, and heme iron intakes along with biomarkers of iron status in relation to cancer risk [77]. For each increase of 1 mg/day of heme iron intake, there was a significant increase of colorectal (RR = 1.08; 95% CI: 1.00 to 1.17], colon (RR = 1.12; 95% CI: 1.03 to 1.22), breast (RR = 1.03; 95% CI: 0.97 to 1.09), and lung cancer (RR = 1.12; 95% CI: 0.98 to 1.29) [77]. Thus, a higher intake of heme iron could be considered as a cancer risk. More studies are warranted to decipher the complex role of iron in cancer development. Well-designed and well-powered prospective studies are warranted to understand the observed associations between vegetarian diets and health outcomes, notably cancer risk, in association with vitamin B12 and zinc status.

Strengths and Weaknesses of the Umbrella Review

This umbrella review reports the most comprehensive review of the literature on the published associations between vegetarian diets and health outcomes. We have assessed the evidence using the recently reported AMSTAR2 criteria for estimating the quality of assessed meta-analyses. Among the nine meta-analyses that assessed the association between vegetarian diets and “body weight, obesity-related metaflammatory markers, and diabetes risk”, “cardiovascular risk”, and “cancer risk”, seven (78%) were scored as high-quality reviews and two as moderate quality reviews (22%) (**Supplemental Table 2**). Three-quarters of the meta-analyses included in the present umbrella review reported a formal assessment for potential confounding factors in their analysis. We used four random effect model estimators for calculating the pooled ES and eight methods for evaluating bias. All these methods yielded concordant results both on the ES estimation and the absence of significant bias regarding the association of vegetarian diets with a reduced risk of adverse health outcomes. The present umbrella review allowed assessment of the role of the SDA lifestyle as a potential modifier of the association between vegetarian diets and adverse health outcomes. We acknowledge several potential limitations of the present umbrella review that should be considered in the interpretation of our findings. We were able to report only on those health outcomes that were included in the meta-analyses. Several nutrients considered to be at risk due to low intake in vegetarian diets (e.g., calcium, n-3 fatty acids, vitamin D) were not included in the present umbrella review. Several adverse health outcomes have not been addressed in the present umbrella-review, due to the lack of meta-analyses. Because of their potential risk among vegetarians, the following health outcomes deserve more consideration: iron deficiency anemia, particularly in women during their reproductive years, osteoporosis, and sarcopenia among older adults. Furthermore, neurodegenerative diseases are a growing public health issue, and there is some concern that lack of vitamin B12 and low blood levels of docosahexaenoic acid may be associated with an increased risk of Alzheimer's disease.

Future Research Directions

A worldwide survey conducted in 2018 on 20,313 adults across 28 countries reported that omnivores represented 73% of the population, followed by flexitarians (14%), vegetarians (8%; including 3% of vegans), and pesco-vegetarians (3%) [78]. According to this survey, 25% of the respondents report following a vegetarian diet regimen in the broad sense of the definition [78]. Vegetarian diets could represent the key to healthy aging, provided that these diets deliver an adequate intake of micronutrients. However, there are still many areas of unmet need regarding the relationship between the consumption of vegetarian diets and their influence on human health. Future research programs should integrate multiple omics approaches in the setting of well-designed and well-powered prospective studies. In particular, these approaches should allow deciphering the interplay between the diet, the microbiota, and the epigenome. Several nutritional outcomes in association with vegetarian diets have not been subject to extensive studies. These include the consequences of B12 deficiency in vegetarians from countries applying food-fortification program with folic acid, and the influence of vegetarian diets on n-3 fatty acids, iodine, calcium, and vitamin D. The effect of vegetarian diets on age-stratified populations requires specific attention, notably in subgroups such as pregnant and lactating women, infants, children, adolescents, and the elderly. Besides well-designed prospective observational studies combined with omics approaches that may provide epidemiological and mechanistic arguments, the fact remains that randomized controlled interventional trials will be able to address specific outcomes and promote the implementation of evidence-based intervention procedures and public health policy strategies.

Diets are considered as a significant driver of environmental sustainability and human health [79]. Indeed, the gradual transition to a western lifestyle is dramatically altering the epidemiological landscape of non-communicable diseases worldwide with a lowering of global life expectancies [79]. It is, thus, evident that the tryptic "diet-environment-health" represents one of the most significant challenges faced by *Homo sapiens* during the 21st century.

In conclusion, vegetarian diets are associated with positive health outcomes on the metabolic disease cluster, including blood lipid profile and body weight, but also with a significantly reduced risk of adverse health outcomes. Among vegetarians, SDA vegetarians could represent a subgroup with a further reduced risk of adverse health outcomes. Well-designed and well-powered prospective studies are warranted to understand the observed associations between vegetarian diets and health outcomes, notably on the consequences of the increased prevalence of vitamin B12 deficiency in pregnancy and infancy in later life and on the consequences of trace element deficits on cancer risk.

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Conflict of Interest (COI) Statement

The authors declare no conflict of interest.

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Authors' Contributions

AO: literature review and data extraction; data synthesis and statistical analysis; drafting/revision of the manuscript; analysis and interpretation of data; approved the final draft; **JL:** literature review and data extraction; drafting/revision of the manuscript; analysis and interpretation of data; approved the final draft; **CB:** literature review and data extraction; drafting/revision of the manuscript; analysis and interpretation of data; approved the final draft; **DHA:** drafting/revision of the manuscript; analysis and interpretation of data; approved the final draft; **J-LG:** study concept, literature review; drafting/revision of the manuscript; analysis and interpretation of data; approved the final draft.

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TABLES

Table 1. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Blood Lipids

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Zhang, 2013 Nutrition	Moderate quality review	Vegetarian vs. omnivorous diets	Triglycerides	– Cross-sectional – Cohort	12 studies (1,300)	• In comparison to omnivorous diets, vegetarian diets were significantly associated with a lower plasma triglycerides concentration with an SMD of -1.28 mmol/L (95% CI: -2.14 to -0.42); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[16]
Zhang, 2014 PLoS One	Moderate quality review	Vegetarian vs. omnivorous diets	HDL cholesterol	– Cross-sectional – Cohort	12 studies (4,177)	• In the whole analysis, vegetarian diets were not associated with a significantly lower HDL cholesterol concentration (SMD = 0.02 mmol/l; 95% CI: -0.19 to 0.22); • The lack of a significant difference between vegetarians and omnivores was maintained regardless of the studied continent or cultural circumstances; • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[17]
Wang, 2015 Journal of American Heart Association	High-quality review	Vegetarian vs. omnivorous diets	– Total cholesterol – LDL cholesterol – HDL cholesterol – Triglycerides	Trial (modality of intervention not reported)	11 clinical trials (832)	• Vegetarian diets significantly lowered blood concentrations of total cholesterol (WMD = -0.36 mmol/L; 95% CI: -0.55 to -0.17), LDL cholesterol (WMD = -0.34 mmol/L; 95% CI: -0.57 to -0.11), and HDL cholesterol (WMD = -0.10 mmol/L; 95% CI: -0.14 to -0.06); • Vegetarian diets were not significantly associated with a lowering of blood triglycerides concentrations (WMD = 0.04 mmol/L; 95% CI: -0.05 to 0.13); • Subgroup analysis, according to the vegetarian diet: no effect in meta-regression analysis (lactovegetarian, lacto-ovo-vegetarian, vegan).	Class IV	[18]
Yokoyama, 2017 Nutrition	High-quality review	Vegetarian vs. omnivorous	– Total cholesterol – LDL cholesterol – HDL cholesterol	– Cross-sectional – Trial	30 observational (10,143)	• In comparison to omnivorous diets, vegetarian diets were associated with a significantly lower mean	Class IV	[19]

Review		diets	– Triglycerides	(modality of intervention not reported)	19 trials (1,484)	concentrations of total cholesterol (-29.2 mg/dL; 95 CI: -34.6 to -23.8 and -12.5 mg/dL; 95% CI: -17.8 to -7.2), LDL cholesterol (-22.9; 95% CI: -27.9 to -17.9 and -12.2 mg/dL; 95% CI: -17.7 to -6.7), and HDL cholesterol (-3.6 mg/dL; 95% CI: -4.7 to -2.5; and -3.4 mg/dL; 95% CI: -4.3 to -2.5) in observational studies and clinical trials, respectively; • There was no significant influence of vegetarian diets on triglyceride level, both in observational studies and clinical trials.		
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	– Total cholesterol – LDL cholesterol – HDL cholesterol – Triglycerides	– Cross-sectional – Cohort	86 studies (249,049) 10 cohorts (72,298)	• Vegetarians had a significantly lower serum total cholesterol (WMD = -28.16 mg/dL; 95%CI -31.22 to -25.10; 64 studies), LDL cholesterol (WMD = -21.27 mg/dL; 95% CI: -24.27 to -18.27; 46 studies), HDL cholesterol (WMD = -2.72 mg/dL; 95% CI: -3.40 to -2.04; 51 studies), and triglycerides (WMD = -11.39 mg/dL; 95% CI, -17.42 to -5.37; 55 studies) in comparison to omnivores; • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class II to I	[20]

HDL: high-density lipoprotein; **LDL**: low-density lipoprotein; **MD**: mean difference; **SMD**: standardized mean difference; **WMD**: weighted mean difference.
The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 5**.

Table 2. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Vitamin B12 deficiency and Related One-Carbon Metabolism Markers

First author, Year Journal	AMSTAR 2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Obersby, 2013 British Journal of Nutrition	Low-quality review	Vegetarian vs. omnivorous diets	– Serum vitamin B12 – Plasma homocysteine	– Cross-sectional – Cohort	11 cross-sectional 6 cohorts (whole: 3,230)	• The mean serum vitamin B12 was significantly lower in lacto-vegetarians or lacto-ovo-vegetarians (209 pmol/L, SD = 47; $P < 0.005$) and vegans (172 pmol/L, SD = 59; $P < 0.005$) in comparison to that of omnivores (303 pmol/L, SD = 72); • Consistently, the mean plasma homocysteine concentration was significantly higher among lacto-vegetarians or lacto-ovo-vegetarians (13.91 µmol/L, SD = 2.89; $P < 0.025$) and vegans (16.41 µmol/L, SD = 4.8; $P < 0.005$) in comparison to that of omnivores (11.03 µmol/L, SD = 2.89); • Subgroup analysis, according to the vegetarian diet: available in summary measures; lacto-vegetarians or lacto-ovo-vegetarians, vegans).	Class IV to III	[21]
Pawlak, 2013 Nutrition Reviews	Critically low-quality	Vegetarian diets	Cobalamin deficiency	Cross-sectional	18 studies NA	• Cobalamin deficiency rates were: 62% among pregnant women, 25 to 86% among children, 21 to 41% among adolescents, and 11 to 90% among older adults; • Vegans and individuals who had adhered to a vegetarian diet since birth had higher rates of cobalamin deficiency in comparison to vegetarians and subjects who adopted such a diet later in life; • Furthermore, vegetarians developed cobalamin deficiency regardless of the type of vegetarian diet; • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[22]
Pawlak, 2014 European Journal of Clinical Nutrition	Low-quality review	Vegetarian diets	Low cobalamin status	Cross-sectional	40 studies NA	• The reported prevalence of low cobalamin status among subjects adhering to vegetarian diets was 45% among infants, 17 to 39% among pregnant women, and 0 to 86.5% among adults and older adults; • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[23]

NA: not available; **SD**: standard deviation.

The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 6**.

Table 3. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Trace Elements

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Foster, 2013 Journal of the Science of Food and Agriculture	Low-quality review	Vegetarian vs. omnivorous diets	– Dietary zinc intake – Zinc status	Cross-sectional	34 studies NA	• In comparison to non-vegetarians, vegetarians had significantly lower dietary zinc intakes (MD = -0.88 mg/day; SE = 0.15; *P* < 0.001) and significantly lower zinc concentrations in blood (MD = -0.93 µmol/L; SE = 0.27; *P* = 0.001); • Among vegetarians, vegans had the strongest negative impact of their diet on zinc intake and status; • Subgroup analysis, according to the vegetarian diet: – Dietary zinc intake (mg/day): vegan (MD = -1.65, SE = 0.19; *P* < 0.0001); lacto-vegetarians (MD = -2.65, SE = 1.02; *P* = 0.009); lacto-ovo-vegetarians (MD = -0.28, SE = 0.25; *P* = 0.27); flexitarians (MD = -1.24, SE = 0.36; *P* = 0.001); – Serum zinc concentration (µmol/L): vegan (MD = -1.17, SE = 0.45, *P* = 0.009); lacto-vegetarians (MD = -1.23, SE = 0.94, *P* = 0.19); lacto-ovo-vegetarians (MD = -0.75, SE = 0.42; *P* = 0.08); flexitarians (MD = 0.11, SE = 0.81; *P* = 0.89).	Class IV to III	[24]
Foster, 2015 Nutrients	Moderate quality review	Vegetarian vs. omnivorous diets during pregnancy	– Dietary zinc intake – Zinc status	Cross-sectional	6 studies NA	• Vegetarian pregnant women had lower zinc intake in comparison to non-vegetarian pregnant women (-1.38 mg/day; SE = 0.35; *P* < 0.001); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV to III	[25]
Haider, 2016 Critical Reviews in Food Science and Nutrition	Moderate quality review	Vegetarian vs. omnivorous diets	Serum ferritin	– Cross-sectional – Trial (planned or self-selected vegetarian diet)	24 studies (1,085)	• Adult subjects who adhered to a vegetarian diet had a significantly lower serum ferritin concentration in comparison to non-vegetarians (-29.71 µg/L; 95% CI: -39.69 to -19.73); • In subgroup analyses, the vegetarian diet had a stronger impact on ferritin status in men (-61.88 µg/L; 95% CI: -85.59 to -38.17) in comparison to women (-13.50 µg/L; 95% CI: -22.96 to -4.04); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV to III	[26]

Ho-Pham, 2009 American Journal of Clinical Nutrition	High-quality review	Vegetarian vs. omnivorous diets	Bone mineral density	Cross-sectional	9 studies (2,749)	• The meta-analysis reported a 4% reduction of bone mineral density among vegetarians when compared to omnivores at both the femoral neck (95% CI: 2% to 7%) and the lumbar spine (95% CI: 2% to 7%); • Subgroup analysis, according to the vegetarian diet: – Vegan: Femoral neck BMD -6% (-9% to -2%); Lumbar spine BMD -6% (-11% to -2%); – Lacto-ovo-vegetarian: Femoral neck BMD -2% (-4% to -1%); Lumbar spine BMD -2% (-4% to -1%).	Class IV to III	[27]

MD: mean difference; **NA**: not available; **SE**: standard error.
The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 7**.

Table 4. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Body Weight, Obesity-Related Metaflammatory Markers, and Diabetes Risk

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Barnard, 2015 Journal of the Academy of Nutrition and Dietetics	High-quality review	Vegetarian vs. omnivorous diets	Weight loss	Trial (planned or self-selected vegetarian diet)	15 clinical trials (755)	• The mean weight variation in patients who were prescribed vegetarian diets were -3.4 kg (95% CI: -4.4 to -2.4) and -4.6 kg (95% CI: -5.4 to -3.8) in intention-to-treat and per-protocol analyses, respectively; • Subgroup analysis, according to the vegetarian diet: – Vegan: -3.2 kg (95% CI: -4.0 to -2.4; *P* < 0.0001); – Lacto-ovo-vegetarian: -2.9 kg (-4.1 to -1.6; *P* < 0.0001).	Class IV	[28]
Huang, 2016 Journal of General Internal Medicine	High-quality review	Vegetarian vs. omnivorous diets	Weight loss	Trial (modality of intervention not reported)	12 clinical trials (1,151)	• Subjects that were randomized in the vegetarian group lost significantly more weight than those assigned to the non-vegetarian diet groups (WMD: -2.02 kg; 95 % CI: -2.80 to -1.23); • Subgroup analysis, according to the vegetarian diet: – Vegan: -2.52 kg (95 % CI: -3.02 to -1.98); – LOV : -1.48 kg (95 % CI: -3.43 to 0.47).	Class IV	[29]
Haghighatdoost, 2017 Public Health Nutrition	Moderate quality review	Vegetarian vs. omnivorous diets	Inflammatory biomarker	Cross-sectional	17 studies (2,398)	• In the overall analysis, there was no significant difference in high-sensitivity C-reactive protein (hs-CRP) concentration between vegetarians and omnivores (SMD = -0.15; 95 % CI: -0.35 to 0.05); • Subgroup analysis, according to the vegetarian diet: no evidence indicating that it might be the source of heterogeneity (*P* = 0.363; vegan, lactovegetarian, ovo-vegetarian, and lacto-ovo-vegetarian).	Class IV	[30]
Lee, 2017	High-quality review	Vegetarian vs.	Risk of diabetes	– Cross-sectional	11 studies (428,825)	• Vegetarians had a significantly lower risk of diabetes in comparison to non-vegetarians	Class II	[31]

Nutrients		omnivorous diets		– Cohort	2 cohorts (49,788)	(OR = 0.726; 95% CI: 0.608 to 0.867); • In subgroup analyses, the strongest effect sizes were observed in Western Pacific (OR = 0.514; 95% CI: 0.304 to 0.871) and Europe/North America (OR = 0.756; 95% CI: 0.589 to 0.971) regions; • Subgroup analysis, according to the vegetarian diet: – Vegan: OR = 0.593 (95% CI: 0.386 to 0.911; *P* = 0.017); – Lacto-vegetarian: OR = 0.762 (95% CI: 0.613 to 0.949; *P* = 0.016); – Lacto-ovo-vegetarian: OR = 0.564 (95% CI: 0.517 to 0.616; *P* = 0.30); – Pesco-vegetarian: OR = 0.867 (95% CI: 0.636 to 1.180; *P* = 0.008); – Semi-vegetarian: OR = 0.799 (95% CI: 0.667 to 0.956; *P* = 0.002).		
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	– Body mass index – Blood glucose level	– Cross-sectional – Cohort	86 studies (249,049) 10 cohorts (72,298)	• Significantly lower body mass index among vegetarians (n = 57,724) in comparison to omnivores (n = 199,230) with a WMD of -1.49 kg/m2 (95% CI: -1.72 to -1.25); • Significantly lower blood glucose level among vegetarians in comparison to omnivores (WMD = -5.08 mg/dL; 95% CI: -5.98 to -4.19); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class II to I	[20]

OR: odds ratio; **SMD**: standardized mean difference; **WMD**: weighted mean difference.

The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 8**.

Table 5. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Cardiovascular Risk

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Huang, 2012 Annals of Nutrition and Metabolism	Moderate quality review	Vegetarian vs. omnivorous diets	– Ischemic heart disease – Circulatory diseases – Cerebrovascular disease	Cohort	7 cohorts (124,706)	• In comparison to non-vegetarians, vegetarians had a reduced risk of ischemic heart disease (-29%; RR = 0.71; 95% CI: 0.56 to 0.87) and a non-significant trend towards a reduced risk of circulatory diseases (-16%; RR = 0.84; 95% CI: 0.54 to 1.14) and cerebrovascular disease (-12%; RR = 0.88; 95% CI: 0.70 to 1.06); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class II to I (Ischemic heart disease) Class IV (Circulatory diseases and Cerebrovascular disease)	[32]
Kwok, 2014 International Journal of Cardiology	Moderate quality review	Vegetarian vs. omnivorous diets	– Ischemic heart disease or cardiac event – Cerebrovascular disease	Cohort	8 cohorts (183,321)	• Vegetarians had a significantly lower risk of ischemic heart disease or cardiac event, with a greater effect size noted among SDA studies in comparison to non-SDA studies (-40%, RR = 0.60; 95% CI: 0.43 to 0.80 vs. -16%, RR = 0.84; 95% CI: 0.74 to 0.96, respectively); • The risk of cerebrovascular disease was not significantly reduced in both SDA (RR = 0.71; 95% CI: 0.41 to 1.20) and non-SDA (RR = 1.05; 95% CI: 0.89 to 1.24) cohorts; • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class III to II (Ischemic heart disease or cardiac event) Class IV (Cerebrovascular disease)	[33]
Yokoyama, 2014 JAMA Internal Medicine	High-quality review	Vegetarian vs. omnivorous diets	– Systolic blood pressure – Diastolic blood pressure	– Trial (planned or self-selected vegetarian diet) – Cross-sectional	7 clinical trials (311) 32 observational studies (21,604)	• In the seven controlled trials that included 311 participants with a mean age of 44.5 years, the consumption of vegetarian diets was associated with a significant reduction in both systolic and diastolic blood pressure (-4.8 mm Hg; 95% CI: -6.6 to -3.1 and -2.2 mm Hg; 95% CI: -3.5 to -1.0, respectively) when compared to	Class IV to III (Systolic blood pressure, Trials) Class II (Systolic blood pressure, Cross-sectional)	[34]

						omnivorous diets; • In the 32 observational studies that included 21,604 participants with a mean age of 46.6 years, the consumption of vegetarian diets was also associated with a significant reduction in both mean systolic and diastolic blood pressure (-6.9 mm Hg; 95% CI: -9.1 to -4.7 and -4.7 mm Hg; 95% CI: -6.3 to -3.1, respectively) when compared to omnivorous diets; • Subgroup analysis, according to the vegetarian diet: *Clinical trials:* – Systolic blood pressure: vegan: -4.3 mm Hg (95% CI: -10.2 to 1.5; *P* = 0.15); lacto-vegetarian: -3.3 mm Hg (95% CI: -9.1 2.6; *P* = 0.28); lacto-ovo-vegetarian: -4.8 mm Hg (95% CI: -7.5 to -2.0; *P* = 0.001); – Diastolic blood pressure: Vegan: -4.8 mm Hg (95% CI: -8.2 to -1.3; *P* = 0.007); lacto-vegetarian: -2.5 mm Hg (95% CI: -9.2 to 4.2; *P* = 0.46); lacto-ovo-vegetarian: -1.8 mm Hg (95% CI: -3.2 to -0.5; *P* = 0.007). *Observational Studies:* – Systolic blood pressure: vegan: -9.5 mm Hg (95% CI: -15.5 to -3.6; *P* = 0.002); lacto-vegetarian: mm Hg (95% CI: -5.6 to -13.6; *P* = 2.3 0.163); lacto-ovo-vegetarian: -8.7 mm Hg (95% CI: -12.3 to -5.1; *P* < 0.001); – Diastolic blood pressure: vegan: -3.7 mm Hg (95% CI: -8.1 to 0.7; *P* = 0.10); lacto-vegetarian: -5.0 mm Hg (95% CI: -11.3 to 1.3; *P* = 0.12); lacto-ovo-vegetarian: -5.4 mm Hg (95% CI: -8.2 to -2.6; *P* < 0.001).	Class IV to III (Diastolic blood pressure, Trials) Class II (Diastolic blood pressure, Cross-sectional)	
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	– Ischemic heart disease – Cardiovascular disease – Cerebrovascular disease	– Cross-sectional – Cohort	86 studies (249,049) 10 cohorts (72,298)	• By comparison with omnivores, vegetarians had a significantly reduced risk of ischemic heart disease (RR = 0.75; 95% CI: 0.68 to 0.82), a borderline significance for a reduced risk of cardiovascular disease (RR = 0.93; 95% CI: 0.86 to 1.00) and no significantly	I (Ischemic heart disease) Class IV (Cardiovascular disease)	[20]

	reduced risk of cerebrovascular disease (RR = 0.93; 95% CI: 0.78 to 1.10); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV (Cerebrovascular disease)

RR: relative risk; **SDA**: Seventh-day Adventists.
The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 9**.

Table 6. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets and Cancer Risk

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Huang, 2012 Annals of Nutrition and Metabolism	Moderate quality review	Vegetarian vs. omnivorous diets	Cancer incidence	Cohort	7 studies (124,706)	• Vegetarians had a significantly reduced cancer incidence by 18% in comparison to omnivores (RR = 0.82; 95% CI: 0.67 to 0.97); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class I	[32]
Godos, 2017 Journal of Human Nutrition and Dietetics	Moderate quality review	Vegetarian vs. omnivorous diets	– Breast cancer risk – Colorectal cancer risk – Prostate cancer risk	Cohort	9 studies (686,629)	• In the full analysis, vegetarian diets were not associated with a significant reduction of the risk of either breast, colorectal, or prostate cancer by comparison with non-vegetarian diets; • Subgroup analysis, according to the vegetarian diet: – Semi-vegetarian: RR = 0.86; 95% CI: 0.79 to 0.94 (for colorectal cancer risk); – Pesco-vegetarian: RR = 0.67; 95% CI: 0.53 to 0.83 (for colorectal cancer risk).	Class IV	[35]
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	– Cancer incidence – Breast cancer incidence – All cancer-related mortality – Colorectal cancer mortality – Breast cancer mortality – Prostate cancer mortality – Lung cancer mortality	– Cross-sectional – Cohort	86 studies (249,049) 10 cohorts (72,298)	• In comparison to omnivores, vegetarians had a significantly reduced risk of cancer incidence (RR = 0.92; 95% CI: 0.87 to 0.98) and a trend toward a reduced risk of breast cancer incidence (RR = 0.94; 95% CI: 0.84 to 1.06) and colorectal cancer mortality (RR = 0.90; 95% CI: 0.76 to 1.05); • The meta-analysis did not show a significant difference between vegetarians and omnivores regarding all cancer-related mortality, breast cancer mortality, prostate cancer mortality, and lung cancer mortality; • Subgroup analysis, according to the vegetarian diet: no reported summary	Class I (Cancer incidence) Class IV (all other outcomes)	[20]

measure.

RR: relative risk.
The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 10**.

Table 7. Meta-Analyses That Have Assessed the Association Between Vegetarian Diets Diets and All-Cause Mortality

First author, Year Journal	AMSTAR2 score	Exposure	Outcome	Study type	Number of studies (number of subjects)	Summary measures	Credibility Assessment	Ref.
Huang, 2012 Annals of Nutrition and Metabolism	Moderate quality review	Vegetarian vs. omnivorous diets	All-cause mortality	Cohort	7 cohorts (124,706)	• No significant reduction of all-cause mortality among vegetarians when compared to omnivores (RR = 0.91; 95% CI: 0.66 to 1.16); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[32]
Kwok, 2014 International Journal of Cardiology	Moderate quality review	– SDA vegetarians vs. omnivores – Non-SDA vegetarians vs. omnivores	All-cause mortality	Cohort	8 cohorts (183,321)	• The relative risk for all-cause mortality was significantly reduced in SDA cohorts (RR = 0.68; 95% CI: 0.45 to 1.02) when compared to non-SDA cohorts (RR = 1.04; 95% CI: 0.98 to 1.10); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[33]
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	All-cause mortality	– Cross-sectional – Cohort	86 studies (249,049) 10 cohorts (72,298)	• No significant reduction of all-cause mortality among vegetarians when compared to omnivores (RR = 0.94; 95% CI: 0.86 to 1.04); • Subgroup analysis, according to the vegetarian diet: no reported summary measure.	Class IV	[20]

RR: relative risk; **SDA**: Seventh-day Adventists.
The results from meta-analyses of observational studies were classified into four categories (Class I: convincing; Class II: Highly suggestive; Class III: Suggestive; and Class IV: Weak) [13] [14] [15]. Details related to the credibility assessment of the studied meta-analyses are available in **Supplemental Table 11**.

Table 8. Health Outcomes Associated with Vegetarian Diets: Synoptic View of the Meta-Analyses Included in the Umbrella Review with Their Main Conclusions

References	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]	[35]
Cardiac events																				
Systolic blood pressure																				
Diastolic blood pressure																				
Cancer risk																				
Cancer incidence																				
Colorectal cancer risk																				
Prostate cancer risk																				
Breast cancer risk																				
All cancer-related mortality																				
Breast cancer-related mortality																				
Colorectal cancer-related mortality																				
Prostate cancer-related mortality																				
Lung cancer-related mortality																				
Breast cancer incidence																				
All-cause mortality																		*		

NOTE. **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **hs-CRP**: high sensitive C-reactive protein.

Green: positive outcome; **light green**: trends toward a positive outcome; **marron**: adverse outcome; **light blue**: no significant effect; **light gray**: not assessed.

* A significant effect was observed among Seventh-day Adventists cohorts [33].

FIGURES LEGENDS

Figure 1. The spectrum of dietary patterns from vegan to omnivorous diets. A vegetarian diet excludes the consumption of all types of meat (e.g., pork, beef, mutton, lamb, and poultry), fish, and seafood. Vegan diets include only fruits, vegetables, legumes, whole grains, and nuts, and may exclude honey, roots or tubers, such as in Jain vegetarianism; 2) Lacto-, ovo-, or lacto-ovo-vegetarian diets are vegan diets that incorporate dairy products, eggs, or both of them, respectively. Flexitarian diets encounter two categories: 1) semi-vegetarian diets which are vegetarian diets that include low consumption of meat between once per month to less than once per week; 2) pesco- or pollo-vegetarian diets, characterized by typical lacto-ovo-vegetarian diets that incorporate the consumption of fish or chicken, respectively. Seventh-day Adventist (SDA) vegetarians do not consume tobacco and alcohol, and many adhere to a lacto-ovo-vegetarian diet. Vegetarian diets other than the SDA regimen do not formally advise against consuming alcoholic beverages and tobacco.

Figure 2. PRISMA flow diagram of the umbrella review concerning the association between vegetarian diets and health outcomes. A total of 36 unique health outcomes were retrieved from the umbrella review and were classified in seven groups (**Group #1**: lipid metabolism; **Group #2**: one-carbon metabolism; **Group #3**: trace elements; **Group #4**: obesity, metaflammation, and diabetes; **Group #5**: Cardiovascular risk; **Group #6**: cancer, and **Group #7**: all-cause mortality).

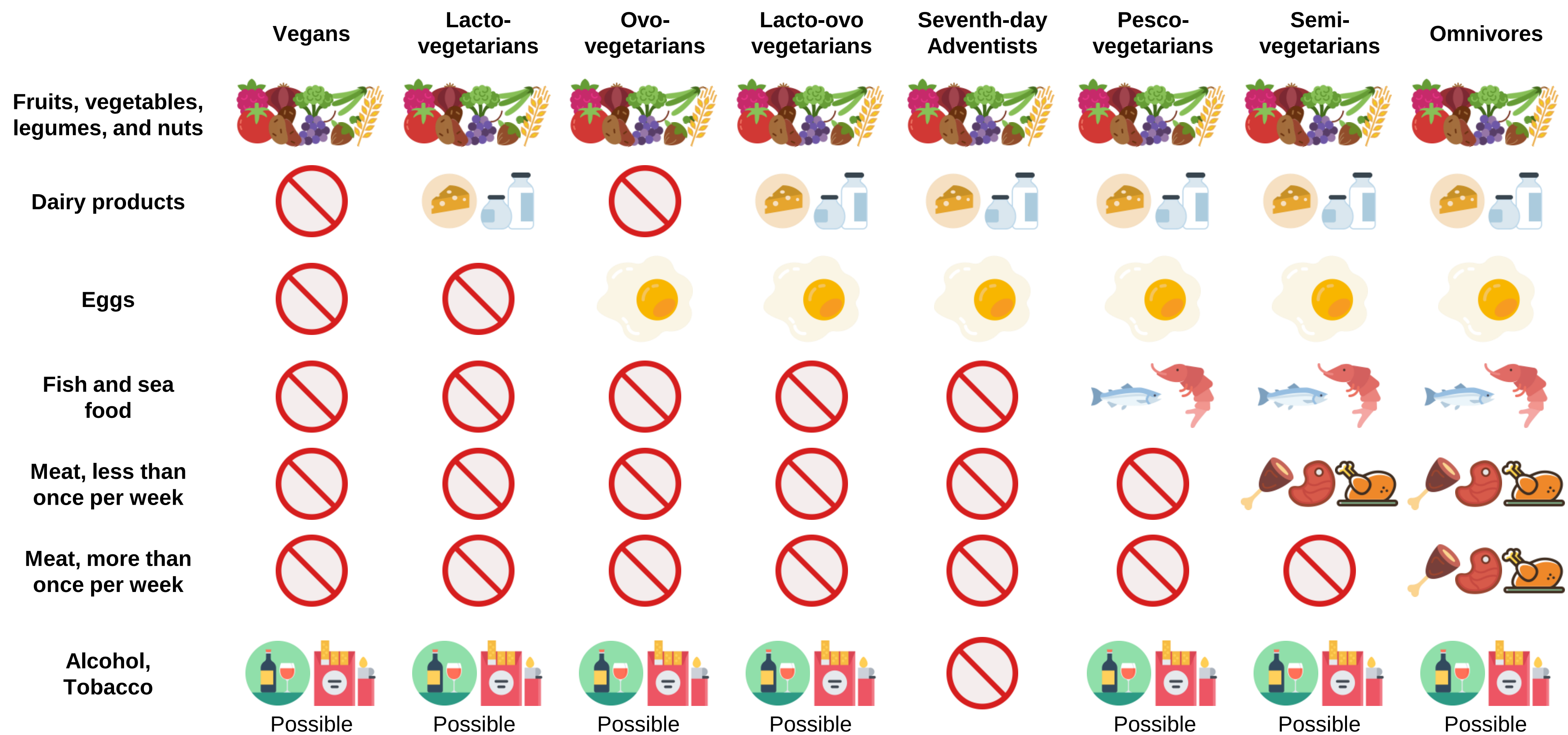
Figure 3. Forest plot reporting the magnitude of the association between vegetarian diets and blood lipids (total cholesterol [A], LDL-cholesterol [B], HDL-cholesterol [C], triglycerides [D]), in comparison to omnivorous diets. The calculated summary effect is denoted by the solid diamond at the bottom of the forest plots, the width of which represents the 95% confidence interval.

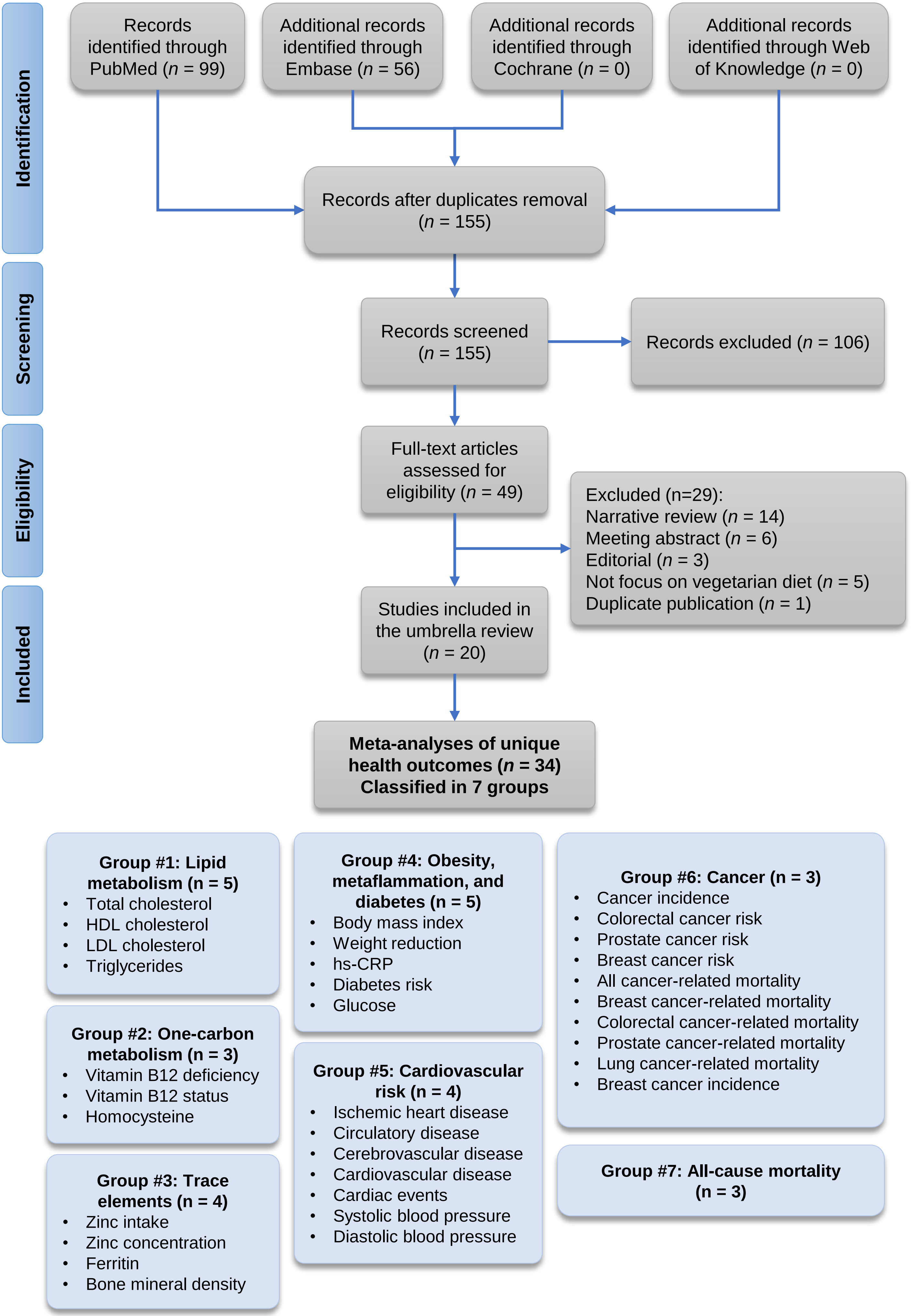
Figure 4. Forest plot reporting the magnitude of the association between vegetarian diets and adverse health outcomes in comparison to omnivores. The calculated summary effect is denoted by the solid diamond at the bottom of the forest plots, the width of which represents the 95% confidence interval.

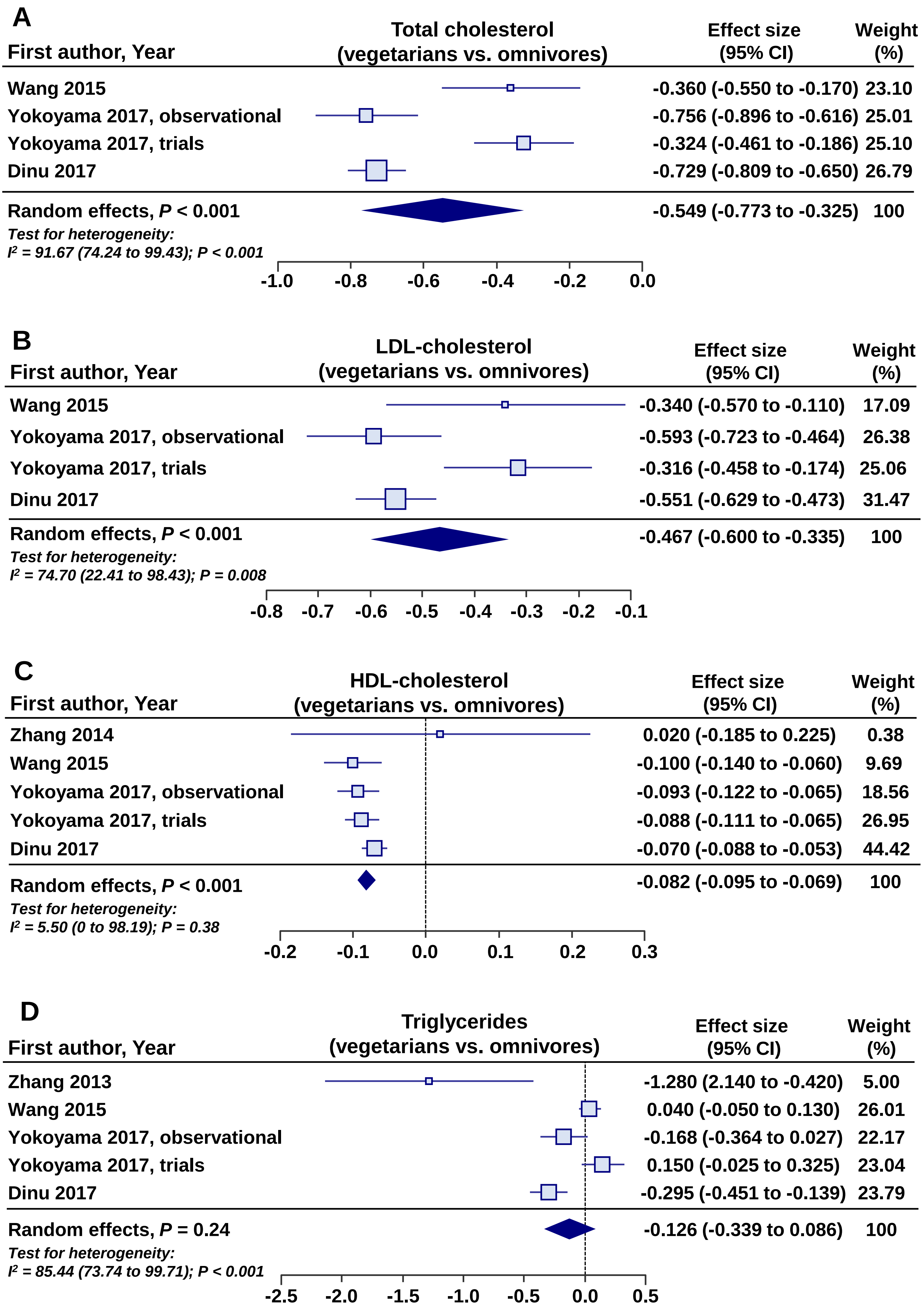
Figure 5. Forest plot reporting the magnitude of the association between vegetarian diets and adverse health outcomes among Seventh-day Adventists (panel A) and non-Seventh day Adventists (panel B) in comparison to omnivores. The calculated summary effect is denoted by the solid diamond at the bottom of the forest plots, the width of which represents the 95% confidence interval.

Figure 6. Infographic representation of the health outcomes associated with vegetarian diets. Vegetarian diets are associated with beneficial effects on the metabolic disease cluster, including blood lipid profile and body weight. Vegetarian diets are associated with a reduced risk of adverse health outcomes, including diabetes, ischemic heart disease, and cancer risk. Vegetarian diets, notably vegan diets, are potentially associated with adverse outcomes on one-carbon metabolism and trace elements (Icons made by flaticon, flaticon.com; CC-BY-3.0).

Figure 7. Overview of the major known and postulated pathophysiological pathways linking animal-based diets with immunometabolic disease clusters and cardiovascular risk. Vegetarian diets may prevent the modulation of the gut microbiome to a pro-inflammatory phenotype, which might be a driver of systematic low-grade inflammation and metabolic dysfunction. Animal-based diets contribute to atherosclerosis in part via the metabolism of dietary carnitine and choline, forming trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) (Icons made by flaticon, flaticon.com; CC-BY-3.0).

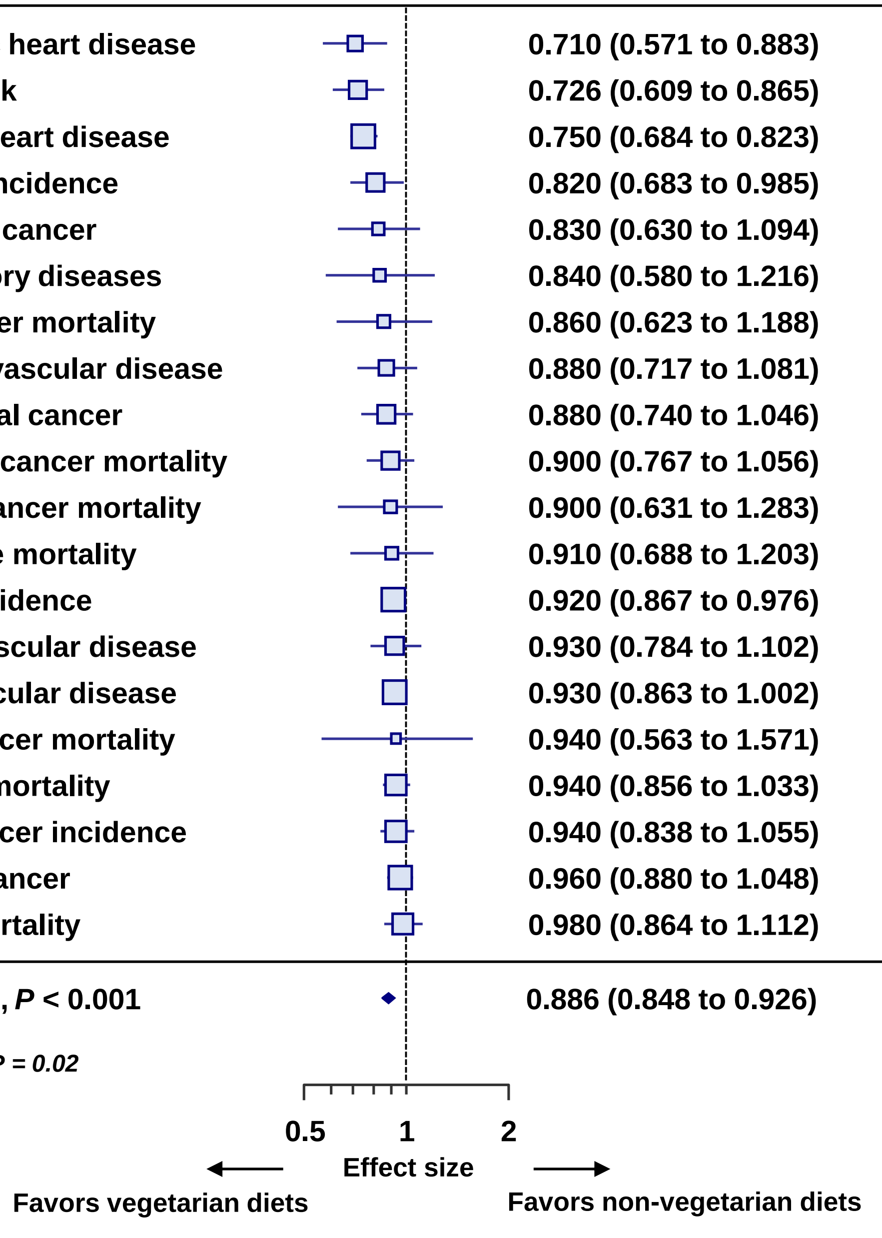

Vegans
Lacto-vegetarians
Ovo-vegetarians
Lacto-ovo vegetarians
Seventh-day Adventists
Pesco-vegetarians
Semi-vegetarians
Omnivores
Fruits, vegetables, legumes, and nuts
Dairy products
Eggs
Fish and sea food
Meat, less than once per week
Meat, more than once per week
Alcohol, Tobacco
Possible
Possible
Possible
Possible
Possible
Possible
Possible

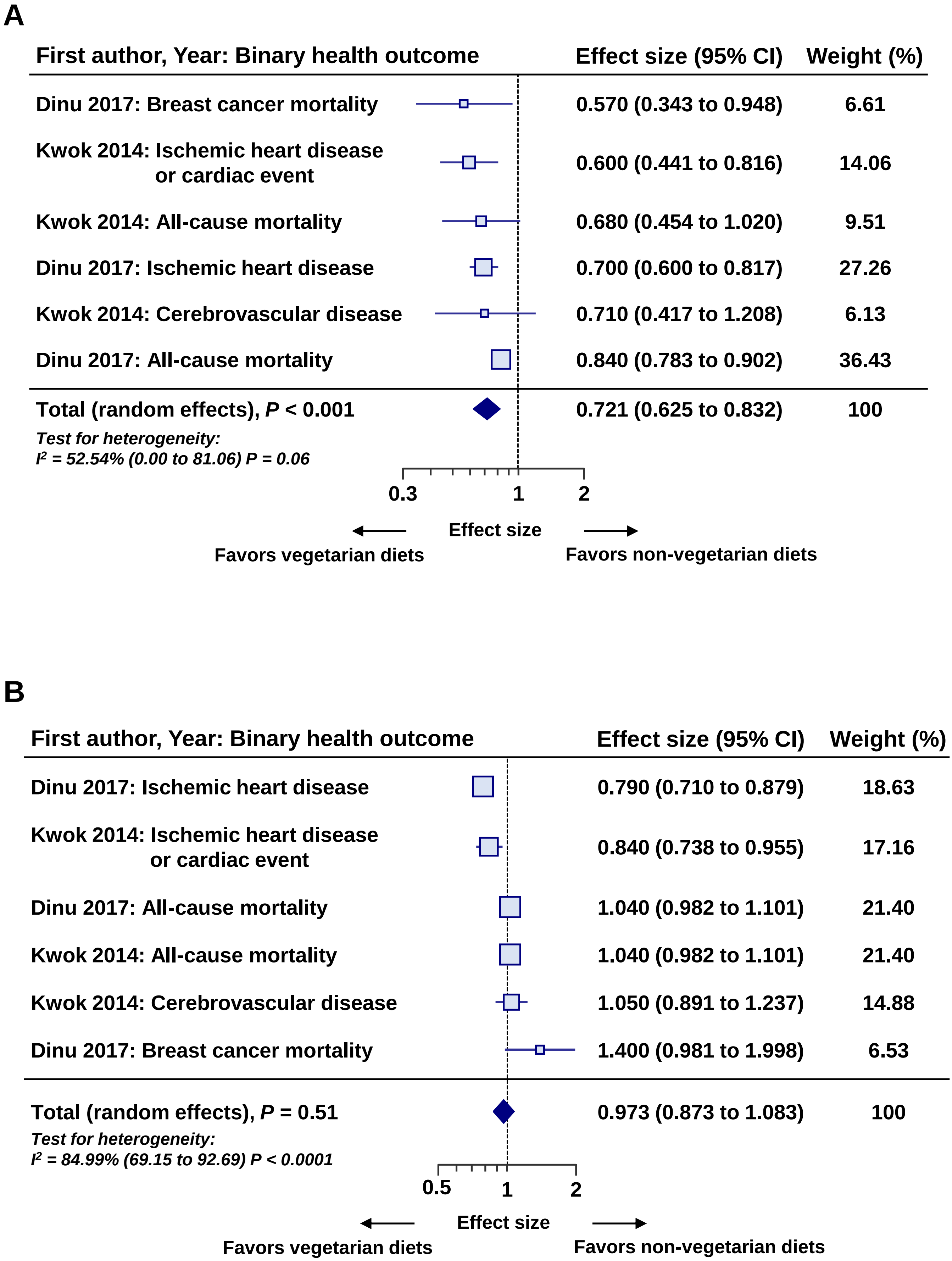

Identification
Screening
Eligibility
Included
Records identified through PubMed (n = 99)
Additional records identified through Embase (n = 56)
Additional records identified through Cochrane (n = 0)
Additional records identified through Web of Knowledge (n = 0)
Records after duplicates removal (n = 155)
Records screened (n = 155)
Records excluded (n = 106)
Full-text articles assessed for eligibility (n = 49)
Excluded (n=29):
Narrative review (n = 14)
Meeting abstract (n = 6)
Editorial (n = 3)
Not focus on vegetarian diet (n = 5)
Duplicate publication (n = 1)
Studies included in the umbrella review (n = 20)
Meta-analyses of unique health outcomes (n = 34) Classified in 7 groups
Group #1: Lipid metabolism (n = 5)
• Total cholesterol
• HDL cholesterol
• LDL cholesterol
• Triglycerides
Group #2: One-carbon metabolism (n = 3)
• Vitamin B12 deficiency
• Vitamin B12 status
• Homocysteine
Group #3: Trace elements (n = 4)
• Zinc intake
• Zinc concentration
• Ferritin
• Bone mineral density
Group #4: Obesity, metaflammation, and diabetes (n = 5)
• Body mass index
• Weight reduction
• hs-CRP
• Diabetes risk
• Glucose
Group #5: Cardiovascular risk (n = 4)
• Ischemic heart disease
• Circulatory disease
• Cerebrovascular disease
• Cardiovascular disease
• Cardiac events
• Systolic blood pressure
• Diastolic blood pressure
Group #6: Cancer (n = 3)
• Cancer incidence
• Colorectal cancer risk
• Prostate cancer risk
• Breast cancer risk
• All cancer-related mortality
• Breast cancer-related mortality
• Colorectal cancer-related mortality
• Prostate cancer-related mortality
• Lung cancer-related mortality
• Breast cancer incidence
Group #7: All-cause mortality (n = 3)

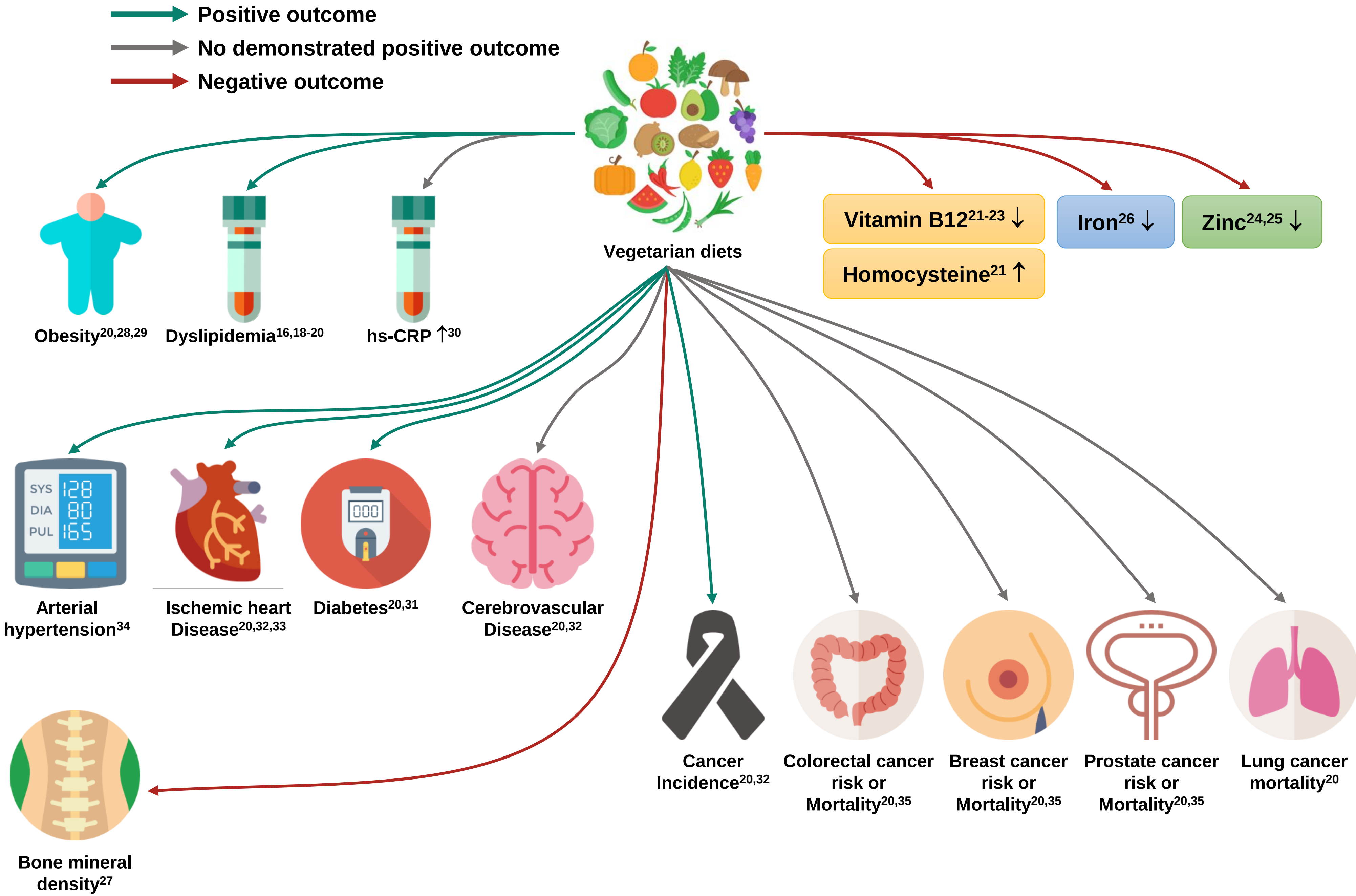

A
First author, Year
Total cholesterol (vegetarians vs. omnivores)
Effect size (95% CI)
Weight (%)
Wang 2015
-0.360 (-0.550 to -0.170)
23.10
Yokoyama 2017, observational
-0.756 (-0.896 to -0.616)
25.01
Yokoyama 2017, trials
-0.324 (-0.461 to -0.186)
25.10
Dinu 2017
-0.729 (-0.809 to -0.650)
26.79
Random effects, P < 0.001
-0.549 (-0.773 to -0.325)
100
Test for heterogeneity:
I2 = 91.67 (74.24 to 99.43); P < 0.001
-1.0 -0.8 -0.6 -0.4 -0.2 0.0
B
First author, Year
LDL-cholesterol (vegetarians vs. omnivores)
Effect size (95% CI)
Weight (%)
Wang 2015
-0.340 (-0.570 to -0.110)
17.09
Yokoyama 2017, observational
-0.593 (-0.723 to -0.464)
26.38
Yokoyama 2017, trials
-0.316 (-0.458 to -0.174)
25.06
Dinu 2017
-0.551 (-0.629 to -0.473)
31.47
Random effects, P < 0.001
-0.467 (-0.600 to -0.335)
100
Test for heterogeneity:
I2 = 74.70 (22.41 to 98.43); P = 0.008
-0.8 -0.7 -0.6 -0.5 -0.4 -0.3 -0.2 -0.1
C
First author, Year
HDL-cholesterol (vegetarians vs. omnivores)
Effect size (95% CI)
Weight (%)
Zhang 2014
0.020 (-0.185 to 0.225)
0.38
Wang 2015
-0.100 (-0.140 to -0.060)
9.69
Yokoyama 2017, observational
-0.093 (-0.122 to -0.065)
18.56
Yokoyama 2017, trials
-0.088 (-0.111 to -0.065)
26.95
Dinu 2017
-0.070 (-0.088 to -0.053)
44.42
Random effects, P < 0.001
-0.082 (-0.095 to -0.069)
100
Test for heterogeneity:
I2 = 5.50 (0 to 98.19); P = 0.38
-0.2 -0.1 0.0 0.1 0.2 0.3
D
First author, Year
Triglycerides (vegetarians vs. omnivores)
Effect size (95% CI)
Weight (%)
Zhang 2013
-1.280 (2.140 to -0.420)
5.00
Wang 2015
0.040 (-0.050 to 0.130)
26.01
Yokoyama 2017, observational
-0.168 (-0.364 to 0.027)
22.17
Yokoyama 2017, trials
0.150 (-0.025 to 0.325)
23.04
Dinu 2017
-0.295 (-0.451 to -0.139)
23.79
Random effects, P = 0.24
-0.126 (-0.339 to 0.086)
100
Test for heterogeneity:
I2 = 85.44 (73.74 to 99.71); P < 0.001
-2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5

First author, Year: Binary health outcome	Effect size (95% CI)	Weight (%)
Huang 2012: Ischemic heart disease	0.710 (0.571 to 0.883)	3.14
Lee 2017: Diabetes risk	0.726 (0.609 to 0.865)	4.33
Dinu 2017: Ischemic heart disease	0.750 (0.684 to 0.823)	8.76
Huang 2012: Cancer incidence	0.820 (0.683 to 0.985)	4.08
Godos 2017: Prostate cancer	0.830 (0.630 to 1.094)	2.14
Huang 2012: Circulatory diseases	0.840 (0.580 to 1.216)	1.27
Dinu 2017: Lung cancer mortality	0.860 (0.623 to 1.188)	1.63
Huang 2012: Cerebrovascular disease	0.880 (0.717 to 1.081)	3.45
Godos 2017: Colorectal cancer	0.880 (0.740 to 1.046)	4.42
Dinu 2017: Colorectal cancer mortality	0.900 (0.767 to 1.056)	4.92
Dinu 2017: Prostate cancer mortality	0.900 (0.631 to 1.283)	1.37
Huang 2012: All-cause mortality	0.910 (0.688 to 1.203)	2.10
Dinu 2017: Cancer incidence	0.920 (0.867 to 0.976)	11.44
Dinu 2017: Cerebrovascular disease	0.930 (0.784 to 1.102)	4.53
Dinu 2017: Cardiovascular disease	0.930 (0.863 to 1.002)	10.16
Dinu 2017: Breast cancer mortality	0.940 (0.563 to 1.571)	0.69
Dinu 2017: All-cause mortality	0.940 (0.856 to 1.033)	8.65
Dinu 2017: Breast cancer incidence	0.940 (0.838 to 1.055)	7.21
Godos 2017: Breast cancer	0.960 (0.880 to 1.048)	9.15
Dinu 2017: Cancer mortality	0.980 (0.864 to 1.112)	6.55
Total (random effects), *P* < 0.001	0.886 (0.848 to 0.926)	100

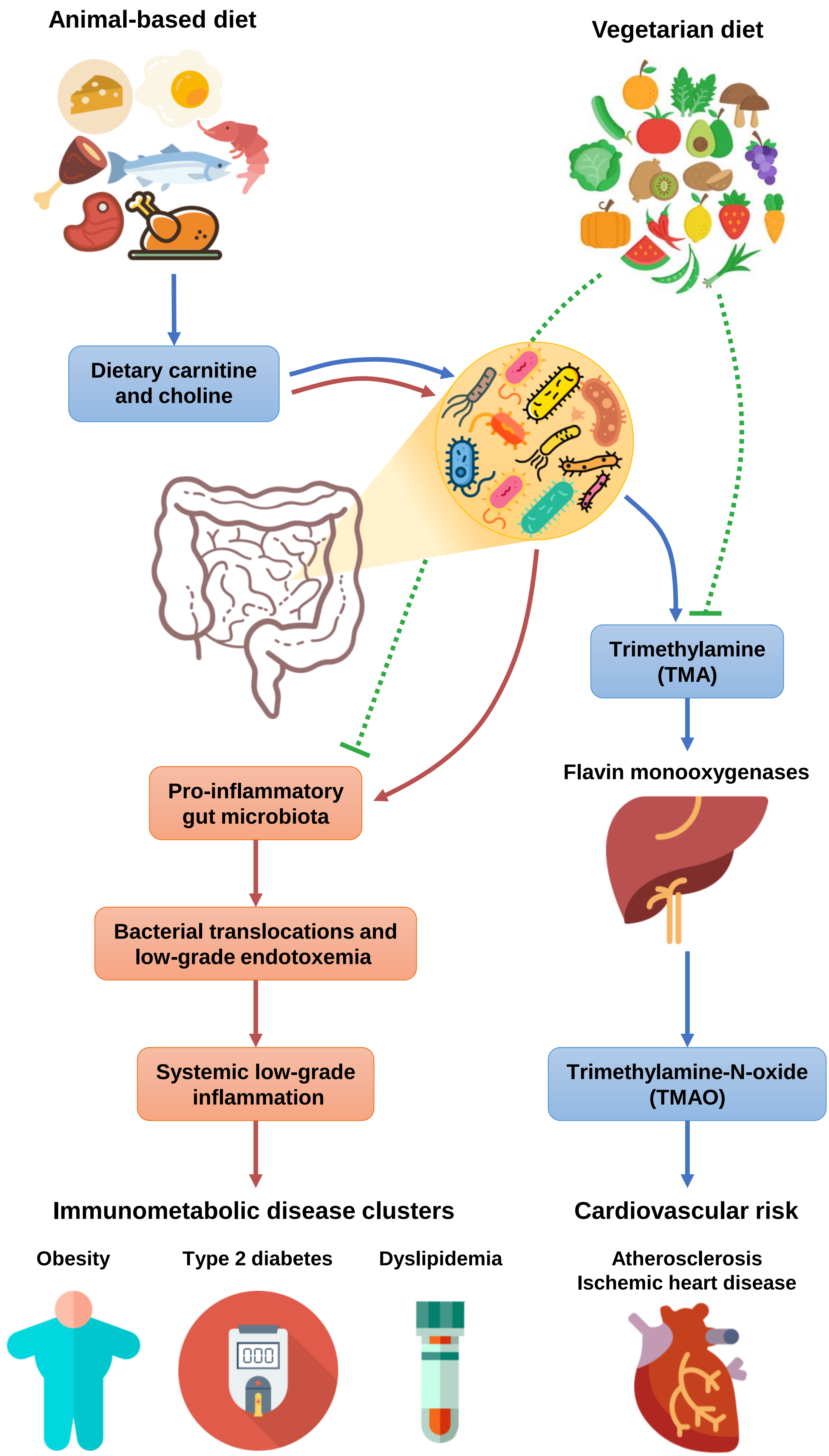
Test for heterogeneity:
I^2 = 43.16% (3.55 to 66.51) P = 0.02




A
First author, Year: Binary health outcome
Effect size (95% CI)
Weight (%)
Dinu 2017: Breast cancer mortality
0.570 (0.343 to 0.948)
6.61
Kwok 2014: Ischemic heart disease or cardiac event
0.600 (0.441 to 0.816)
14.06
Kwok 2014: All-cause mortality
0.680 (0.454 to 1.020)
9.51
Dinu 2017: Ischemic heart disease
0.700 (0.600 to 0.817)
27.26
Kwok 2014: Cerebrovascular disease
0.710 (0.417 to 1.208)
6.13
Dinu 2017: All-cause mortality
0.840 (0.783 to 0.902)
36.43
Total (random effects), P < 0.001
0.721 (0.625 to 0.832)
100
Test for heterogeneity:
I2 = 52.54% (0.00 to 81.06) P = 0.06
0.3
1
2
Effect size
Favors vegetarian diets
Favors non-vegetarian diets
B
First author, Year: Binary health outcome
Effect size (95% CI)
Weight (%)
Dinu 2017: Ischemic heart disease
0.790 (0.710 to 0.879)
18.63
Kwok 2014: Ischemic heart disease or cardiac event
0.840 (0.738 to 0.955)
17.16
Dinu 2017: All-cause mortality
1.040 (0.982 to 1.101)
21.40
Kwok 2014: All-cause mortality
1.040 (0.982 to 1.101)
21.40
Kwok 2014: Cerebrovascular disease
1.050 (0.891 to 1.237)
14.88
Dinu 2017: Breast cancer mortality
1.400 (0.981 to 1.998)
6.53
Total (random effects), P = 0.51
0.973 (0.873 to 1.083)
100
Test for heterogeneity:
I2 = 84.99% (69.15 to 92.69) P < 0.0001
0.5
1
2
Effect size
Favors vegetarian diets
Favors non-vegetarian diets



Positive outcome
No demonstrated positive outcome
Negative outcome
Vegetarian diets
Obesity20,28,29
Dyslipidemia16,18-20
hs-CRP ↑30
Vitamin B1221-23 ↓
Iron26 ↓
Zinc24,25 ↓
Homocysteine21 ↑
SYS 128
DIA 80
PUL 165
000
Arterial hypertension34
Ischemic heart Disease20,32,33
Diabetes20,31
Cerebrovascular Disease20,32
Cancer Incidence20,32
Colorectal cancer risk or Mortality20,35
Breast cancer risk or Mortality20,35
Prostate cancer risk or Mortality20,35
Lung cancer mortality20
Bone mineral density27


Animal-based diet
Vegetarian diet
Dietary carnitine and choline
Trimethylamine (TMA)
Flavin monooxygenases
Pro-inflammatory gut microbiota
Bacterial translocations and low-grade endotoxemia
Systemic low-grade inflammation
Trimethylamine-N-oxide (TMAO)
Immunometabolic disease clusters
Cardiovascular risk
Obesity
Type 2 diabetes
Dyslipidemia
Atherosclerosis
Ischemic heart disease