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1 **Health Outcomes Associated with Vegetarian Diets: An Umbrella Review of**
2 **Systematic Reviews and Meta-Analyses**

3
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25

1 **ABSTRACT**

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

6
7 **METHODS:** We performed an umbrella review of the evidence across meta-analyses of
8 observational and interventional studies. PubMed, Embase, Cochrane Database of
9 Systematic Reviews, and ISI Web of Knowledge. Additional articles were retrieved from
10 primary search references. Meta-analyses of observational or interventional studies that
11 assessed at least one health outcome in association with vegetarian diets. We estimated
12 pooled effect sizes (ESs) using four different random-effect models: DerSimonian and Laird,
13 maximum likelihood, empirical Bayes, and restricted maximum likelihood. We assessed
14 heterogeneity using I^2 statistics and publication bias using funnel plots, radial plots, normal
15 Q-Q plots, and the Rosenthal's fail-safe N test.

16
17 **RESULTS:** The umbrella review identified 20 meta-analyses of observational and
18 interventional research with 34 health outcomes. The majority of the meta-analyses (80%)
19 were classified as moderate or high-quality reviews, based on the AMSTAR2 criteria. By
20 comparison with omnivorous diets, vegetarian diets were associated with a significantly lower
21 concentration of blood total cholesterol (pooled ES = -0.549 mmol/L; 95% CI: -0.773 to -
22 0.325; $P < 0.001$), LDL-cholesterol (pooled ES = -0.467 mmol/L; 95% CI: -0.600 to -0.335);
23 $P < 0.001$), and HDL-cholesterol (pooled ES = -0.082 mmol/L; 95% CI: -0.095 to -0.069; $P <$
24 0.001). In comparison to omnivorous diets, vegetarian diets were associated with a reduced
25 risk of negative health outcomes with a pooled ES of 0.886 (95% CI: 0.848 to 0.926; $P <$
26 0.001). In comparison to omnivores, Seventh-day Adventists (SDA) vegetarians had a
27 significantly reduced risk of negative health outcomes with a pooled ES of 0.721 (95% CI:
28 0.625 to 0.832; $P < 0.001$). Non-SDA vegetarians had no significant reduction of negative

1 health outcomes when compared to omnivores (pooled ES = 0.973; 95% CI: 0.873 to 1.083;
2 $P = 0.51$). Vegetarian diets were associated with harmful outcomes on one-carbon
3 metabolism markers (lower concentrations of vitamin B12 and higher concentrations of
4 homocysteine), in comparison to omnivorous diets.

5

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

14

15 **PROSPERO REGISTRATION NUMBER:** CRD42018092470.

1 INTRODUCTION

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

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

1 **METHODS**

2 **Umbrella Review Concept**

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

8

9 **Literature search**

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

21

22 **Eligibility Criteria**

23 Three investigators (AO, JL, CB) reviewed full-text articles for eligibility. We retained a
24 systematic review in the umbrella review if it reported at least one pooled effect size (ES) or
25 a frequency range concerning a health outcome in association with vegetarian diets. The
26 different groups of vegetarian diets considered in the present umbrella review were: vegans,
27 lacto-vegetarians, ovo-vegetarians, lacto-ovo-vegetarians, and Seventh-day Adventists
28 (SDA). The exclusion criteria were as follows: non-English language publication; meeting

1 abstract; editorial; narrative review; no data on health outcome; systematic review protocol;
2 systematic review focusing only on patients with diabetes; systematic review considering the
3 effect of fasting; and duplicate results. The PICO strategy used in the present umbrella
4 review was: **1) Problem:** Are vegetarian diets associated with a modification of health
5 outcomes in comparison to non-vegetarian diets? **2) Intervention:** vegetarian diets; **3)**
6 **Compare to:** non-vegetarian diets; **4) Outcome:** Lipid metabolism; One-carbon metabolism;
7 Trace elements; Obesity, metaflammation, and diabetes; Cardiovascular risk; Cancer risk;
8 and All-cause mortality.

9

10 **Data Extraction**

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

18

19 **Assessment of the Methodological Quality of Included Studies**

20 Three authors (AO, JL, CB) assessed the methodological quality of meta-analyses using the
21 AMSTAR 2 Checklist [9]. The AMSTAR tool was developed to evaluate systematic reviews
22 of randomized trials [10]. The initial AMSTAR tool had a good agreement, reliability,
23 construct validity, and feasibility [10]. The newest version (AMSTAR 2) enables a more
24 detailed assessment of systematic reviews that include randomized or non-randomized
25 studies of healthcare interventions, or both [9]. By comparison with the original tool,
26 AMSTAR 2 retains 10 of the original domains which include 16 items in total, has simpler
27 response categories, and has an overall rating based on weaknesses in critical domains (i.e.,
28 protocol registered before commencement of the review, adequacy of the literature search,

1 justification for excluding individual studies, risk of bias from individual studies being included
2 in the review, appropriateness of meta-analytical methods, consideration of risk of bias when
3 interpreting the results of the review, and assessment of presence and likely impact of
4 publication bias) [9]. AMSTAR 2 would identify systematic reviews with a high level of
5 evidence for better use by decision-makers [9, 10].

6

7 **Data Synthesis and Analysis**

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

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

9

10 **Credibility Assessment**

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

20

21 **RESULTS**

22 **Literature Review**

23 The systematic search generated 155 citations, of which 105 were excluded based on title
24 and/or abstract. Of the 49 remaining references, 29 were excluded based on the selection
25 criteria (**Supplemental Table 2**), leaving 20 systematic reviews with a meta-analysis eligible
26 for the umbrella review (**Figure 2**) [16-35]. Eleven systematic reviews assessed blood lipids
27 ($n = 5$) [16-20], one-carbon metabolism markers ($n = 3$) [21-23], trace elements ($n = 3$) [24-
28 26], and bone mineral density ($n = 1$) [27]. Five meta-analyses investigated body weight [20,

1 28, 29], obesity-related inflammatory profiles[30], and the risk of diabetes [31]. Four meta-
2 analyses concerned cardiovascular morbidity and mortality [20, 32-34] and three others
3 addressed cancer risk in vegetarians [20, 32, 35]. Among the 20 meta-analyses reported in
4 the present umbrella review, 10 (50%) were scored as “high-quality reviews” [18-20, 25, 27-
5 31, 34], six (30%) as “moderate quality reviews” [16, 17, 26, 32, 33, 35], three (15%) as “low-
6 quality reviews” [21, 23, 24], and one (5%) as a “critically low-quality review” [22], according
7 to the AMSTAR2 criteria (Supplemental **Table 3**). Of the 20 meta-analyses included in the
8 umbrella review, 15 (75%) formally reported an assessment for potential confounders for the
9 studies that were included in the pooled analysis or performed meta-regression analysis on
10 potential confounders [16-21, 25, 28-35] (**Supplemental Table 4**). Among the 15 studies, 11
11 reported in detail the potential confounders for each study [18-20, 25, 28, 30-35].

12

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

26

27

28

1 **Blood Lipids (Table 1)**

2 ***Description of meta-analyses included in the umbrella review***

3 The comparison of blood lipids between subjects who adhered to a vegetarian diet and
4 omnivores have been subject to several cross-sectional studies. The first meta-analysis that
5 reported the association between vegetarian diets and blood triglyceride concentration was
6 published in 2012 and included 12 studies (11 cross-sectional and one cohort study) on
7 1,300 subjects [16]. In comparison to omnivorous diets, vegetarian diets were significantly
8 associated with a lower plasma triglycerides concentration with a standardized mean
9 difference (SMD) of -1.28 mmol/L (95% CI: -2.14 to -0.42) [16]. A subsequent meta-analysis
10 of cross-sectional and cohort studies (n = 12; 4,177 subjects) assessed the magnitude of the
11 association in regards to the plasmatic concentration of high-density lipoprotein (HDL)
12 cholesterol [17]. In the whole analysis, vegetarian diets were not associated with significantly
13 lower HDL cholesterol concentration (SMD = 0.02 mmol/l; 95% CI: -0.19 to 0.22) [17]. The
14 lack of a significant difference between vegetarians and omnivores was maintained
15 regardless of the location of the study or cultural circumstances of the participants [17]. An
16 updated meta-analysis published in 2017 screened data from 86 cross-sectional studies that
17 compared 56,461 vegetarians and 8,421 vegans with 184,167 omnivores [20]. In overall
18 analysis, vegetarians had a significantly lower serum total cholesterol (weighted mean
19 difference [WMD] = -28.16 mg/dL; 95%CI -31.22 to -25.10; 64 studies), LDL cholesterol
20 (WMD = -21.27 mg/dL; 95% CI: -24.27 to -18.27; 46 studies), HDL cholesterol (WMD = -2.72
21 mg/dL; 95% CI: -3.40 to -2.04; 51 studies), and triglycerides (WMD = -11.39 mg/dL; 95% CI:
22 -17.42 to -5.37; 55 studies) in comparison to omnivores [20].

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

1 0.10 mmol/L; 95% CI: -0.14 to -0.06) [18]. Conversely, vegetarian diets were not significantly
2 associated with a lowering of blood triglyceride concentrations (WMD = 0.04 mmol/L; 95%
3 CI: -0.05 to 0.13) [18].

4 A meta-analysis included controlled trials and observational studies performed during at least
5 four weeks [19]. Thirty observational studies and 19 clinical trials met the inclusion criteria
6 and included 1,484 patients with a mean age of 49 years [19]. Among the 30 observational
7 studies, 23 included participants who had been on a vegetarian diet for more than one year
8 [19]. Concerning clinical trials, the mean duration was 25.5 weeks [19]. In comparison to
9 omnivorous diets, vegetarian diets were associated with a significantly lower mean
10 concentrations of total cholesterol (-29.2 mg/dL; 95 CI: -34.6 to -23.8 and -12.5 mg/dL; 95%
11 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%
12 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;
13 95% CI: -4.3 to -2.5) in observational studies and clinical trials, respectively [19]. There was
14 no significant influence of vegetarian diets on triglyceride levels, both in observational studies
15 and clinical trials [19].

16

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

18 In the umbrella meta-analysis, vegetarian diets were associated with a significantly reduced
19 concentration of blood total cholesterol with a pooled ES of -0.549 mmol/L (95% CI: -0.773 to
20 -0.325; $P < 0.001$; Rosenthal's fail-safe $N = 502$) and a significant heterogeneity ($I^2 =$
21 91.67%; 95% CI: 74.24 to 99.43; $P < 0.001$). Assessment by funnel plot revealed a moderate
22 risk of bias. The QQ-plot did not reveal a significant departure from normality (rank
23 correlation test for funnel plot asymmetry, $P = 0.75$). Consistently, vegetarian diets were
24 associated with a significantly reduced concentration of LDL-cholesterol with a pooled ES of -
25 0.467 mmol/L (95% CI: -0.600 to -0.335; $P < 0.001$; Rosenthal's fail-safe $N = 332$) and a
26 significant heterogeneity ($I^2 = 74.70\%$; 95% CI: 22.41 to 98.43; $P = 0.008$). The funnel plot
27 revealed a low risk of bias. The QQ-plot did not reveal a significant departure from normality
28 (rank correlation test for funnel plot asymmetry, $P = 0.33$). Vegetarian diets were associated

1 with a significantly reduced concentration of HDL-cholesterol with a pooled ES of -0.082
2 mmol/L (95% CI: -0.095 to -0.069; $P < 0.001$; Rosenthal's fail-safe $N = 252$) without
3 significant heterogeneity ($I^2 = 5.50$; 95% CI: 0 to 98.19; $P = 0.38$) or study bias. The QQ-plot
4 did not reveal a significant departure from normality (rank correlation test for funnel plot
5 asymmetry, $P = 0.48$). Vegetarian diets were not associated with a significant reduction of
6 triglyceride concentration in comparison to non-vegetarian diets (pooled ES = -0.126 mmol/L;
7 95% CI: -0.339 to 0.086; $P = 0.24$) (**Figure 3 and Supplemental Results**).

8

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

10 It is well known that vegetarians are at increased risk of vitamin B12 (cobalamin) deficiency
11 [36]. Vitamin B12 deficiency is associated with increased homocysteine levels, which
12 represents a debated surrogate marker of cardiovascular disease [36]. A meta-analysis
13 reported the rate of cobalamin deficiency from 18 studies that included participants adhering
14 to different types of vegetarian diets [22]. Cobalamin deficiency was ascertained using
15 methylmalonic acid (MMA), holo-transcobalamin II (holo-TC), or both according to the
16 following thresholds: holo-TC < 35 pmol/L; urinary MMA (> 4.0 $\mu\text{g}/\text{mg}$ creatinine); serum
17 MMA > 260 $\mu\text{mol}/\text{L}$ to > 0.75 $\mu\text{mol}/\text{L}$ [22]. Cobalamin deficiency rates were: 62% among
18 pregnant women, 25 to 86% among children, 21 to 41% among adolescents, and 11 to 90%
19 among older adults [22]. Vegans and individuals who adhered to a vegetarian diet since birth
20 had higher rates of cobalamin deficiency in comparison to vegetarians and subjects who
21 adopted such a diet later in life [22]. Furthermore, vegetarians developed cobalamin
22 deficiency regardless of the type of vegetarian diet [22]. These results were consistent with a
23 systematic review of 40 studies that assessed the rate of low vitamin B12 status among
24 individuals adhering to vegetarian diets [23]. Serum vitamin B12 was assessed using various
25 specific methods (radioimmunoassay, immunochemiluminometric methods, microparticle
26 assay, chemiluminescence immunoassays, and microbiological assays) [23]. The reported
27 prevalence of low cobalamin status among subjects adhering to vegetarian diets was 45%
28 among infants, 17 to 39% among pregnant women, and 0 to 86.5% among adults and older

1 adults [23]. Higher prevalence rates of low cobalamin status were reported among vegans in
2 comparison to other vegetarian categories, namely: semi-vegetarians, lacto-vegetarians,
3 lacto-ovo-vegetarians, ovo-vegetarians, macrobiotic diet, raw food diets [23]. A major
4 drawback in this meta-analysis is the lack of assessment of functional markers such as MMA
5 and homocysteine to estimate the true picture of cobalamin deficiency [23]. Furthermore,
6 several serum vitamin B12 thresholds were used for defining low cobalamin status and
7 ranged from 95 to 250 pmol/L even if most studies used a serum concentration < 130 to 150
8 pmol/L [23].

9 A pooled analysis appraised the magnitude of the association between one-carbon
10 metabolism markers and vegetarian diets [21]. The meta-analysis included six cohorts and
11 eleven cross-sectional studies (3,230 participants) and compared the concentrations of
12 plasma homocysteine and serum vitamin B12 in omnivores, lacto-vegetarians or lacto-ovo-
13 vegetarians, and vegans [21]. The mean serum vitamin B12 was significantly lower in lacto-
14 vegetarians or lacto-ovo-vegetarians (209 pmol/L, standard deviation [SD] = 47; $P < 0.005$)
15 and vegans (172 pmol/L, SD = 59; $P < 0.005$) in comparison to that of omnivores (303
16 pmol/L, SD = 72) [21]. Consistently, the mean plasma homocysteine concentration was
17 significantly higher among lacto-vegetarians or lacto-ovo-vegetarians (13.91 $\mu\text{mol/L}$, SD =
18 2.89; $P < 0.025$) and vegans (16.41 $\mu\text{mol/L}$, SD = 4.8; $P < 0.005$) in comparison to that of
19 omnivores (11.03 $\mu\text{mol/L}$, SD = 2.89) [21].

20

21 **Trace Elements (Table 3)**

22 A meta-analysis of 18 case-control studies demonstrated that dietary zinc intake was
23 significantly reduced among vegetarians in comparison to omnivores (mean difference = -
24 0.88 mg/day; standard error [SE] = 0.15; $P < 0.001$) [24]. The same meta-analysis on 13
25 case-control studies demonstrated a significantly lower serum zinc concentration among
26 vegetarians in comparison to omnivores (mean difference = -0.93 $\mu\text{mol/L}$; SE = 0.27; $P =$
27 0.001) [24]. However, actual zinc concentrations were not reported, so it is unclear whether
28 zinc concentrations fell below the level consistent with clinical deficiency. A meta-analysis of

1 six observational studies confirmed that vegetarian pregnant women had lower zinc intake in
2 comparison to non-vegetarian pregnant women (-1.38 mg/day; SE = 0.35; $P < 0.001$) [25]. A
3 meta-analysis of 24 cross-sectional studies assessed the impact of vegetarian diets on iron
4 status [26]. Adult subjects who adhered to a vegetarian diet had a significantly lower serum
5 ferritin concentration in comparison to non-vegetarians (-29.71 $\mu\text{g/L}$; 95% CI: -39.69 to -
6 19.73; $P < 0.01$) [26].

7 Only one meta-analysis assessed the association between vegetarian diets and bone
8 mineral density [27]. A pooled analysis of nine studies on 2,749 subjects (1,880 women and
9 869 men) reported a 4% reduction of bone mineral density among vegetarians when
10 compared to omnivores at both the femoral neck (95% CI: 2 to 7; $P = 0.0008$) and the lumbar
11 spine (95% CI: 2 to 7; $P = 0.0005$) [27]. The authors concluded to a modest effect of
12 vegetarian diets on bone mineral density and that the ES was unlikely to result in a clinically
13 important increase in fracture risk [27].

14

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

16 Several case-control and interventional studies assessed the influence of vegetarian diets on
17 body weight. A meta-analysis of 71 case-control studies reported a significantly lower body
18 mass index (BMI) among vegetarians ($n = 57,724$) in comparison to omnivores ($n = 199,230$)
19 with a WMD of -1.49 kg/m^2 (95% CI: -1.72 to -1.25) [20]. A meta-analysis of 15 interventional
20 trials estimated the effect of vegetarian diets of ≥ 4 weeks' duration without energy intake
21 limitation on the variation in body weight [28]. The mean weight variation in patients who
22 were prescribed vegetarian diets were -3.4 kg (95% CI: -4.4 to -2.4; $P < 0.001$) and -4.6 kg
23 (95% CI: -5.4 to -3.8; $P < 0.001$) in intention-to-treat and per-protocol analyses, respectively
24 [28]. Interestingly, positive predictors of a greater weight loss after vegetarian diet
25 prescription were: high baseline body weight, male gender, older age, longer duration of the
26 trial, and studies in which weight loss was the primary endpoint [28]. These results were
27 confirmed by a meta-analysis of randomized controlled trials that evaluated the net change in
28 body weight after the initiation of a vegetarian diet [29]. The pooled analysis was performed

1 on twelve randomized controlled trials, with a total of 1,151 subjects who received the
2 intervention over a median duration of 18 weeks [29]. Subjects randomized in the vegetarian
3 group lost significantly more weight than those assigned to the non-vegetarian group (WMD:
4 -2.02 kg; 95 % CI: -2.80 to -1.23) [29].

5 It has been suggested that obesity and metabolic syndrome are associated with chronic low-
6 grade inflammation, recently referred to as metaflammation [37]. In this setting, several
7 cross-sectional studies compared the concentration of inflammatory blood biomarkers among
8 vegetarians and omnivores. A meta-analysis of 18 cross-sectional studies on 2,398 patients
9 investigated the association between vegetarian diets and inflammatory biomarkers [30]. In
10 the overall analysis, there was no significant difference in high-sensitivity C-reactive protein
11 (hs-CRP) level between vegetarians and omnivores (SMD = -0.15; 95 % CI: -0.35 to 0.05)
12 [30].

13 In a meta-analysis of 14 observational studies, vegetarians had a significantly lower risk of
14 diabetes in comparison to non-vegetarians (odds ratio [OR] = 0.726; 95% CI: 0.608 to 0.867)
15 [31]. These results were consistent with those of a meta-analysis of 27 cross-sectional
16 studies which reported a significantly lower blood glucose level among vegetarians in
17 comparison to omnivores (WMD = -5.08 mg/dL; 95% CI: -5.98 to -4.19) [20].

18

19 **Cardiovascular Risk (Table 5)**

20 A meta-analysis of seven prospective cohort studies (124,706 participants) investigated the
21 cardiovascular disease mortality among vegetarians and non-vegetarians [32]. Vegetarians
22 had a reduced risk of ischemic heart disease (-29%; relative risk [RR] = 0.71; 95% CI: 0.56 to
23 0.87) and a non-significant trend towards a reduced risk of circulatory diseases (-16%; RR =
24 0.84; 95% CI: 0.54 to 1.14) and cerebrovascular disease (-12%; RR = 0.88; 95% CI: 0.70 to
25 1.06), when compared to omnivores [32]. These results were confirmed in a meta-analysis of
26 cross-sectional and cohort studies that assessed the association with the risk of ischemic
27 heart disease (RR = 0.75; 95% CI: 0.68 to 0.82), cardiovascular disease (RR = 0.93; 95% CI:
28 0.86 to 1.00), and cerebrovascular disease (RR = 0.93; 95% CI: 0.78 to 1.10) [20]. An

1 updated meta-analysis of eight cohort studies (183,321 participants) compared the risk of
2 cardiovascular disease between vegetarians and omnivores taking into account the
3 subgroup of subjects who adhered to an SDA diet [33]. SDA vegetarians do not consume
4 tobacco, alcohol, or pork, and many adhere to a lacto-ovo-vegetarian diet [38]. Vegetarians
5 had a significantly lower risk of ischemic heart disease or cardiac event, with a greater ES
6 noted among SDA vegetarians in comparison to non-SDA vegetarians (-40%, RR = 0.60;
7 95% CI: 0.43 to 0.80 vs. -16%, RR = 0.84; 95% CI: 0.74 to 0.96, respectively) [33].

8 To explain the relationship between cardiovascular risk and vegetarian diets, a meta-analysis
9 of 39 studies (seven clinical trials and 32 observational studies) examined the association
10 between vegetarian diets and blood pressure [34]. In the seven controlled trials that included
11 311 participants with a mean age of 44.5 years, the consumption of vegetarian diets was
12 associated with a significant reduction in both systolic and diastolic blood pressure (-4.8 mm
13 Hg; 95% CI: -6.6 to -3.1 and -2.2 mm Hg; 95% CI: -3.5 to -1.0, respectively) when compared
14 to omnivorous diets [34]. In the 32 observational studies that included 21,604 participants
15 with a mean age of 46.6 years, vegetarian diets were also associated with a significant
16 reduction in both mean systolic and diastolic blood pressure (-6.9 mm Hg; 95% CI: -9.1 to -
17 4.7 and -4.7 mm Hg; 95% CI: -6.3 to -3.1, respectively) when compared to omnivorous diets
18 [34].

19

20 **Cancer Risk (Table 6)**

21 Several studies assessed the association between cancer risk and vegetarian diets, but the
22 results have been inconclusive. A pooled meta-analysis of seven prospective cohort studies
23 (124,706 participants) reported a significantly reduced cancer incidence by 18% among
24 vegetarians in comparison to omnivores (RR = 0.82; 95% CI: 0.67 to 0.97) [32]. More
25 specifically, a recently published meta-analysis investigated the association between
26 vegetarian diets and the risk of breast, colorectal, and prostate cancer [35]. Among the
27 686,629 individuals included in the meta-analysis, 3,441, 4,062, and 1,935 cases of breast,
28 colorectal, and prostate cancer were recorded respectively [35]. In the full analysis,

1 vegetarian diets were not associated with a significant reduction of the risk of either breast,
2 colorectal, or prostate cancer by comparison with non-vegetarian diets [35].

3 A pooled analysis of multiple prospective vegetarian cohorts assessed the association with
4 global cancer incidence, cancer mortality, breast cancer incidence, breast cancer mortality,
5 colorectal cancer mortality, prostate cancer mortality, and lung cancer mortality [20]. In
6 comparison to omnivores, vegetarians had a significantly reduced risk of cancer incidence
7 (RR = 0.92; 95% CI: 0.87 to 0.98) and a non-significant trend toward a reduced risk of breast
8 cancer incidence (RR = 0.94; 95% CI: 0.84 to 1.06) and colorectal cancer mortality (RR =
9 0.90; 95% CI: 0.76 to 1.05) [20]. The meta-analysis did not show a significant difference
10 between vegetarians and omnivores regarding all cancer-related mortality, breast cancer
11 mortality, prostate cancer mortality, and lung cancer mortality [20].

12

13 **All-cause Mortality (Table 7)**

14 Several meta-analyses addressed the relationship between vegetarian diets and all-cause
15 mortality. A meta-analysis of seven cohort studies showed no significant reduction of all-
16 cause mortality among vegetarians when compared to omnivores (RR = 0.91; 95% CI: 0.66
17 to 1.16) [32]. A meta-analysis of five prospective cohort studies confirmed the lack of a
18 significant association between vegetarian diets and a reduced risk of all-cause mortality (RR
19 = 0.94; 95% CI: 0.86 to 1.04) [20]. Kwok *et al.* reported an updated meta-analysis on seven
20 cohort studies (183,321 participants after the exclusion of the Japanese Zen Priest study [39]
21 and adding the Adventist Health Study 2 [40]) and performed a subgroup analysis on cohorts
22 that included SDA subjects [33]. The relative risk for all-cause mortality was significantly
23 reduced in SDA cohorts (RR = 0.68; 95% CI: 0.45 to 1.02) when compared to non-SDA
24 cohorts (RR = 1.04; 95% CI: 0.98 to 1.10) [33].

25

26 **Effect of Vegetarian Diets on Negative Health Outcomes**

27 Four meta-analyses reported ESs regarding 16 negative health outcomes in association with
28 vegetarian diets [20, 31, 32, 35]. These negative health outcomes included ischemic heart

1 disease, cardiovascular disease, cerebrovascular disease, diabetes, cancer, cancer-related
2 mortality, and all-cause mortality and are detailed in **Figure 4**. In the full analysis, the
3 vegetarian diets were associated with a significantly reduced risk of negative health
4 outcomes with a pooled ES of 0.886 (95% CI: 0.848 to 0.926; $P < 0.001$) without significant
5 heterogeneity ($I^2 = 43.16\%$; 95% CI: 3.55 to 66.51; $P = 0.02$) (**Figure 4**). The assessment of
6 study bias through the funnel plot, the radial version of the funnel plot, and the QQ-plot did
7 not reveal a significant departure from normality (rank correlation test for funnel plot
8 asymmetry, $P = 0.07$). The number of missing studies that would need to be added to the
9 analysis to yield a statistically non-significant overall effect (Rosenthal's fail-safe N) was 372.
10 The results of the pooled ESs, heterogeneity testing, and study bias were similar using the
11 four meta-analysis methods (**Supplemental Results**). Two meta-analyses reported ESs
12 regarding five negative health outcomes among SDA and non-SDA vegetarians [20, 33]. In
13 comparison to omnivores, SDA vegetarians had a significantly reduced risk of negative
14 health outcomes with a pooled ES of 0.721 (95% CI: 0.625 to 0.832; $P < 0.001$) without
15 significant heterogeneity ($I^2 = 52.54\%$; 95% CI: 0.00 to 81.06; $P = 0.06$) or study bias (rank
16 correlation test for Funnel plot asymmetry, $P = 0.99$; Rosenthal's fail-safe N = 113) (**Figure 5**
17 and **Supplemental Results**). Non-SDA vegetarians had no significant reduction of negative
18 health outcomes when compared to omnivores (pooled ES = 0.973; 95% CI: 0.873 to 1.083;
19 $P = 0.51$) with a high risk of heterogeneity ($I^2 = 84.99\%$; 95% CI: 69.15 to 92.69; $P < 0.0001$)
20 (**Figure 5** and **Supplemental Results**).

21

22 **DISCUSSION**

23 **Main Findings of the Umbrella Review (Table 8)**

24 In comparison to omnivorous diets, vegetarian diets are associated with clinically relevant
25 positive outcomes on both total and LDL cholesterol and body weight. Subjects adhering to
26 vegetarian diets have a significantly lower risk of diabetes, ischemic heart disease, and
27 cancer, in comparison to omnivores. Among vegetarians, SDA vegetarians could represent a
28 subgroup with a further reduced risk of negative health outcomes. Vegetarian diets were

1 associated with a higher rate of vitamin B12 deficiency (lower concentrations of vitamin B12
2 and higher concentrations of homocysteine), in comparison to omnivorous diets.

3

4 **Positive Outcomes of Vegetarian Diets on Blood Lipids, Body Weight and the Risk of** 5 **Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease**

6 The umbrella review highlighted the beneficial effects of vegetarian diets on the blood lipid
7 profile. Interestingly, total cholesterol, LDL-cholesterol, and HDL-cholesterol all were
8 significantly lowered in association with vegetarian diets. However, the magnitude of the
9 reduction in terms of effect sizes was 7 and 6 times greater for total cholesterol and LDL-
10 cholesterol, respectively, when compared to that observed for HDL-cholesterol. In a
11 multicenter randomized controlled trial, patients who received a vegetarian diet intervention
12 had a significant reduction of total cholesterol (-0.22 mmol/L; 5% CI: -0.34 to -0.10; $P <$
13 0.001), LDL-cholesterol (-0.19 mmol/L; 95% CI: -0.30 to -0.08; $P <$ 0.001), and HDL-
14 cholesterol (-0.08 mmol/L; 95% CI: -0.12 to -0.04; $P <$ 0.001) [41]. In this randomized trial,
15 the magnitudes of effect sizes were similar to those reported in the present umbrella review.
16 The reduction in HDL-cholesterol in association with vegetarian diets could be attributed to a
17 reduction in apolipoprotein A-I production rate [42]. In the umbrella review, the variation
18 observed for HDL-cholesterol, although statistically significant, seems of less clinical
19 relevance in comparison to that of total and LDL-cholesterol. The relationship between HDL-
20 cholesterol and cardiovascular risk is unclear and is subject to debate. In an observational
21 cohort study (CANHEART: Cardiovascular Health in Ambulatory Care Research Team) on
22 631,762 individuals with a mean follow-up of 4.9 years, HDL-cholesterol level was unlikely to
23 represent a cardiovascular specific risk factor given similarities in its associations with non-
24 cardiovascular outcomes [43]. Alcohol intake increases total HDL-cholesterol [44]. Results
25 from the prospective KIID cohort study (Kuopio ischemic heart disease risk factor study)
26 with a mean follow-up of 12.4 years confirmed that raised concentration of HDL-cholesterol
27 was associated with a risk reduction for coronary events among men whose gamma-
28 glutamyltransferase activity was within the normal range, suggesting low alcohol intake [44].

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

3 There is clear evidence that vegetarian diets are associated with positive health outcomes
4 regarding body weight and disease burden related to obesity (**Figure 6**). The global epidemic
5 of obesity has disrupted the epidemiological landscape of non-communicable diseases.
6 Vegetarian diets influence the endogenous metabolism and gut microbiota [46]. A
7 metabolomic study compared the plasma of healthy human vegans to that of healthy
8 omnivores in an urban US environment [47]. Despite similar intestinal metagenomic profiles,
9 as shown by 16S rRNA-tagged sequencing, the plasma metabolome differed significantly
10 between vegans and omnivores [47]. On the 361 metabolites tested, 30 metabolites, roughly
11 categorized into six areas (amino acids, carbohydrates, cofactors and vitamins, lipids,
12 nucleotides, and xenobiotics), were highly discriminant for distinguishing vegans from
13 omnivores [47]. The effects of diet on gut microbiota should also be considered since
14 changes in gut microbiota and related metabolites may influence health outcomes. Vegans
15 exhibit higher concentrations of plant-derived metabolites produced by the gut microbiota,
16 while omnivores exhibit increased levels of lipids and amino acids linked to the consumption
17 of animal products [47]. Animal-based diets decrease the abundance of Firmicutes, while
18 plant-based diets increase the *Prevotella* genus and some fiber-degrading Firmicutes [48,
19 49]. Low adherence to a Mediterranean diet —characterized by a high-level consumption of
20 cereals, fruit, vegetables, and legumes— increases urinary trimethylamine-N-oxide (TMAO)
21 levels [49]. The metabolism by the gut microbiome of dietary L-carnitine, a compound that is
22 abundant in red meat, produces TMAO and accelerates atherosclerosis in mice [50]. Among
23 human subjects, omnivores produced significantly higher levels of TMAO than vegetarians
24 following the ingestion of L-carnitine through a microbiota-dependent mechanism [50]. In a
25 cohort of 2,595 patients undergoing a cardiac evaluation and who presented with high TMAO
26 levels, the concentration of plasma L-carnitine was a significant predictor of prevalent
27 cardiovascular disease and incident major adverse cardiac events (myocardial infarction,
28 stroke or death) [50]. Taken together, these data suggest evaluating the influence of

1 microbiome-related metabolomic profiles on the potential benefit of vegetarian diets, in
2 particular for cardiovascular outcomes.

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

20 A high-quality systematic review has shown that vegetarians had a significantly reduced risk
21 (-27%) to develop diabetes in comparison to non-vegetarians [31]. Consistently, non-diabetic
22 vegetarians had a significantly reduced blood glucose level (WMD = -0.28 mmol/L; 95% CI: -
23 0.33 to -0.23) when compared to omnivores [20]. Among patients with type 2 diabetes, a
24 meta-analysis of nine randomized-controlled trials (n = 664 patients) showed that the
25 vegetarian diet was associated with a significant reduction of glycated hemoglobin (HbA1c)
26 (mean difference = -0.29%; 95% CI: -0.45 to -0.12%) and fasting glucose level (mean
27 difference = -0.56 mmol/L; 95% CI: -0.99 to -0.13 mmol/L) [53]. The Canadian Diabetes
28 Association has included vegetarian diets among the recommended dietary patterns to be

1 used in medical nutrition therapy for persons with type 2 diabetes [54, 55]. The position
2 statement from the Canadian Diabetes Association concluded that “*plant-based diets were*
3 *just as effective, if not more effective, than other diabetes diets in improving body weight,*
4 *cardiovascular risk factors, insulin sensitivity, glycated hemoglobin levels, oxidative stress*
5 *markers, and renovascular markers*” and urged for the development of user-friendly plant-
6 based diet practice guidelines for the management of type 2 diabetes [55].

7

8 **Association of Vegetarian Diets with a Higher Rate of Vitamin B12 Deficiency during** 9 **Pregnancy, Early Life and Adulthood**

10 Vegetarian diets are associated with a higher rate of vitamin B12 deficiency, in particular,
11 among infants and pregnant women with adverse outcomes on cobalamin status and one-
12 carbon metabolism (**Figure 6**). The highest prevalence rate of low cobalamin status was
13 reported among vegans, in comparison to other vegetarian categories. However, it
14 paradoxical that vitamin B12 deficiency has deserved less interest than other outcomes
15 addressed by the meta-analyses, in particular in infants and pregnant women (**Table 2**).
16 Vitamin B12 plays critical roles both in cellular and mitochondrial metabolisms, through its
17 methylcobalamin and adenosylcobalamin forms, respectively. At the cellular level,
18 methylcobalamin is required for the methionine synthase reaction which recycles
19 homocysteine into methionine through the addition of a methyl group provided by
20 methyltetrahydrofolate, a process called remethylation [36, 56]. The methionine allows the
21 generation of the S-adenosylmethionine, which is a methyl-donor required for epigenetic
22 reactions, including methylation of DNA, histones, and other regulators of gene expression
23 [36, 56, 57]. Cobalamin deficiency results in the accumulation of homocysteine and
24 methylmalonic acid along with the reduced synthesis of methionine and
25 S-adenosylmethionine [36].

26 Two meta-analyses reported a high rate of vitamin B12 deficiency among vegetarian adults
27 [22, 23]. Hyperhomocysteinemia has been established through several epidemiological
28 studies as a marker of chronic diseases such as cardiovascular disease, cerebrovascular

1 disease, and dementia-type disorders [58]. Furthermore, a meta-analysis of 83 case-control
2 studies involving 35,758 individuals has shown that hyperhomocysteinemia may be a
3 potential risk factor for cancer and that vitamin B12 level was inversely associated with
4 urinary-system and gastrointestinal cancers [59]. Vitamin B12 is not a component of plant
5 foods [2]. Vegetarians should carefully design their diet, explicitly focusing on increasing their
6 intake of vitamin B12 to reduce their risk of non-communicable diseases further. Milk and
7 eggs in the usual amounts are not a reliable source of vitamin B12 and should not represent
8 the unique source of cobalamin [2]. Vegetarians and vegans must regularly consume reliable
9 sources of cobalamin, namely, cobalamin-fortified foods and cobalamin-containing
10 supplements [2]. Even if vitamin B12 deficiency is recognized as a determinant of
11 hyperhomocysteinemia, it is possible that other factors, such as riboflavin deficiency, could
12 also induce hyperhomocysteinemia [60, 61].

13 Vitamin B12 deficiency has deserved less interest than other outcomes in infants and
14 pregnant women under vegetarian diets (**Table 2**). This is critical in regard to the crucial role
15 of vitamin B12 during pregnancy and early life. Barker and Osmond suggested the paradigm
16 of the influence of dietary exposure in early life on long-term health outcomes [62]. A great
17 deal of experimental data and epidemiologic evidence supports that maternal B12 status
18 influences fetal growth and development and later outcomes related to morbid obesity and
19 brain aging [63, 64]. Maternal vitamin B12 deficiency is associated with an increased risk of
20 neural tube defect, an excess of adiposity, increased insulin resistance, and altered risk of
21 cancer in the offspring [63]. The results of the Pune Maternal Nutrition Study (PMNS)
22 conducted in India—one of the world's regions most at-risk of vitamin B12 deficiency,
23 intrauterine growth restriction, and low birth weight— perfectly illustrate the significant
24 influence of a vitamin B12 deficiency on fetal programming [65]. A striking feature highlighted
25 by the PMNS study was that Indian babies were thin but exhibited higher amounts of visceral
26 adipose tissue by comparison with European babies, leading to the concept of “thin-fat”
27 babies [65]. Importantly, the PMNS established micronutrient-rich foods as strong
28 determinants of fetal size [65]. Moreover, children born to mothers who were vitamin B12

1 deficient and who had a high folate level were at high risk of insulin resistance [65].
2 Interestingly, low serum vitamin B12/high folate is also associated with insulin resistance and
3 metabolic syndrome in a cohort of adults with morbid obesity [66]. Taken together, these
4 data suggest that a strict vegetarian diet exposes pregnant females to a high risk of vitamin
5 B12 deficiency, thereby driving epigenetic alterations with a subsequent long-term risk of
6 non-communicable diseases. This would be particularly critical in Canada and the USA, two
7 countries in which folate fortification in cereals has been introduced 20 years ago and could
8 aggravate the consequences of B12 deficiency [67]. Well-designed longitudinal studies
9 integrating a multi-omics approach with in-depth clinical and biological phenotyping of
10 cohorts of vegetarian mothers and their children will better address this knowledge gap that
11 is highlighted in our umbrella review. This is particularly critical in regard to the association of
12 vitamin B12 deficiency during pregnancy with both lower birth weight and preterm birth that
13 was reported in two recent meta-analyses [68, 69]. The specific influence of vegetarian diets
14 on these health outcomes could not be addressed in these meta-analyses.

15

16 **Trace Elements and Their Mitigating Effects on the Risk of Cardiovascular Disease** 17 **and Cancer**

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

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

19 By comparison with omnivores, vegetarians typically have lower iron stores. Lower iron
20 stores have been associated with a lower risk for the development of metabolic syndrome
21 [75]. In a 5-years follow-up study on 18,022 healthy Korean men, subjects with the highest
22 quintile of serum ferritin had a significantly increased risk for developing metabolic syndrome
23 when compared with those from the lowest quantile of serum ferritin concentration (hazard
24 ratio = 1.66; 95% CI: 1.38 to 2.01) [75]. The role of iron in colorectal cancer risk is
25 ambivalent. A meta-analysis of ten observational studies involving 3,318 subjects with
26 colorectal adenoma has demonstrated that heme iron intake was significantly associated
27 with an increased risk of colorectal adenoma (RR = 1.23; 95% CI: 1.03 to 1.48), whereas
28 non-heme iron intake was inversely associated with the risk of colorectal adenoma (RR =

1 0.73; 95% CI: 0.54 to 0.97) [76]. These results were consistent with those reported in a meta-
2 analysis of 59 epidemiologic studies, investigating total iron, dietary iron, and heme iron
3 intakes along with biomarkers of iron status in relation to cancer risk [77]. For each increase
4 of 1 mg/day of heme iron intake, there was a significant increase of colorectal (RR = 1.08;
5 95% CI: 1.00 to 1.17], colon (RR = 1.12; 95% CI: 1.03 to 1.22), breast (RR = 1.03; 95% CI:
6 0.97 to 1.09), and lung cancer (RR = 1.12; 95% CI: 0.98 to 1.29) [77]. Thus, a higher intake
7 of heme iron could be considered as a cancer risk. More studies are warranted to decipher
8 the complex role of iron in cancer development. Well-designed and well-powered prospective
9 studies are warranted to understand the observed associations between vegetarian diets and
10 health outcomes, notably cancer risk, in association with vitamin B12 and zinc status.

11

12 **Strengths and Weaknesses of the Umbrella Review**

13 This umbrella review reports the most comprehensive review of the literature on the
14 published associations between vegetarian diets and health outcomes. We have assessed
15 the evidence using the recently reported AMSTAR2 criteria for estimating the quality of
16 assessed meta-analyses. Among the nine meta-analyses that assessed the association
17 between vegetarian diets and “body weight, obesity-related metaflammatory markers, and
18 diabetes risk”, “cardiovascular risk”, and “cancer risk”, seven (78%) were scored as high-
19 quality reviews and two as moderate quality reviews (22%) (**Supplemental Table 2**). Three-
20 quarters of the meta-analyses included in the present umbrella review reported a formal
21 assessment for potential confounding factors in their analysis. We used four random effect
22 model estimators for calculating the pooled ES and eight methods for evaluating bias. All
23 these methods yielded concordant results both on the ES estimation and the absence of
24 significant bias regarding the association of vegetarian diets with a reduced risk of adverse
25 health outcomes. The present umbrella review allowed assessment of the role of the SDA
26 lifestyle as a potential modifier of the association between vegetarian diets and adverse
27 health outcomes. We acknowledge several potential limitations of the present umbrella
28 review that should be considered in the interpretation of our findings. We were able to report

1 only on those health outcomes that were included in the meta-analyses. Several nutrients
2 considered to be at risk due to low intake in vegetarian diets (e.g., calcium, n-3 fatty acids,
3 vitamin D) were not included in the present umbrella review. Several adverse health
4 outcomes have not been addressed in the present umbrella-review, due to the lack of meta-
5 analyses. Because of their potential risk among vegetarians, the following health outcomes
6 deserve more consideration: iron deficiency anemia, particularly in women during their
7 reproductive years, osteoporosis, and sarcopenia among older adults. Furthermore,
8 neurodegenerative diseases are a growing public health issue, and there is some concern
9 that lack of vitamin B12 and low blood levels of docosahexaenoic acid may be associated
10 with an increased risk of Alzheimer's disease.

11

12 **Future Research Directions**

13 A worldwide survey conducted in 2018 on 20,313 adults across 28 countries reported that
14 omnivores represented 73% of the population, followed by flexitarians (14%), vegetarians
15 (8%; including 3% of vegans), and pesco-vegetarians (3%) [78]. According to this survey,
16 25% of the respondents report following a vegetarian diet regimen in the broad sense of the
17 definition [78]. Vegetarian diets could represent the key to healthy aging, provided that these
18 diets deliver an adequate intake of micronutrients. However, there are still many areas of
19 unmet need regarding the relationship between the consumption of vegetarian diets and their
20 influence on human health. Future research programs should integrate multiple omics
21 approaches in the setting of well-designed and well-powered prospective studies. In
22 particular, these approaches should allow deciphering the interplay between the diet, the
23 microbiota, and the epigenome. Several nutritional outcomes in association with vegetarian
24 diets have not been subject to extensive studies. These include the consequences of B12
25 deficiency in vegetarians from countries applying food-fortification program with folic acid,
26 and the influence of vegetarian diets on n-3 fatty acids, iodine, calcium, and vitamin D. The
27 effect of vegetarian diets on age-stratified populations requires specific attention, notably in
28 subgroups such as pregnant and lactating women, infants, children, adolescents, and the

1 elderly. Besides well-designed prospective observational studies combined with omics
2 approaches that may provide epidemiological and mechanistic arguments, the fact remains
3 that randomized controlled interventional trials will be able to address specific outcomes and
4 promote the implementation of evidence-based intervention procedures and public health
5 policy strategies.

6 Diets are considered as a significant driver of environmental sustainability and human health
7 [79]. Indeed, the gradual transition to a western lifestyle is dramatically altering the
8 epidemiological landscape of non-communicable diseases worldwide with a lowering of
9 global life expectancies [79]. It is, thus, evident that the tryptic “diet-environment-health”
10 represents one of the most significant challenges faced by *Homo sapiens* during the 21st
11 century.

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

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1 REFERENCES

- 2 [1] Mann J. Vegetarian diets. *BMJ*. 2009;339:b2507.
- 3 [2] Melina V, Craig W, Levin S. Position of the Academy of Nutrition and Dietetics:
4 Vegetarian Diets. *J Acad Nutr Diet*. 2016;116:1970-80.
- 5 [3] Agnoli C, Baroni L, Bertini I, Ciappellano S, Fabbri A, Papa M, et al. Position paper on
6 vegetarian diets from the working group of the Italian Society of Human Nutrition. *Nutr Metab*
7 *Cardiovasc Dis*. 2017;27:1037-52.
- 8 [4] Derbyshire EJ. Flexitarian Diets and Health: A Review of the Evidence-Based Literature.
9 *Front Nutr*. 2016;3:55.
- 10 [5] Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee
11 consumption and health: umbrella review of meta-analyses of multiple health outcomes.
12 *BMJ*. 2017;359:j5024.
- 13 [6] Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing
14 systematic reviews: methodological development, conduct and reporting of an umbrella
15 review approach. *Int J Evid Based Healthc*. 2015;13:132-40.
- 16 [7] Reuters T. EndNote X7. Thomson Reuters: Philadelphia, PA, USA. 2013.
- 17 [8] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The
18 PRISMA statement for reporting systematic reviews and meta-analyses of studies that
19 evaluate health care interventions: explanation and elaboration. *Ann Intern Med*.
20 2009;151:W65-94.
- 21 [9] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical
22 appraisal tool for systematic reviews that include randomised or non-randomised studies of
23 healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- 24 [10] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is
25 a reliable and valid measurement tool to assess the methodological quality of systematic
26 reviews. *J Clin Epidemiol*. 2009;62:1013-20.
- 27 [11] Oussalah A, Levy J, Filhine-Tresarrieu P, Namour F, Gueant JL. Association of TCN2
28 rs1801198 c.776G>C polymorphism with markers of one-carbon metabolism and related

- 1 diseases: a systematic review and meta-analysis of genetic association studies. *The*
2 *American journal of clinical nutrition*. 2017;106:1142-56.
- 3 [12] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-
4 analyses. *BMJ*. 2003;327:557-60.
- 5 [13] Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, Ioannidis JP, et al. Serum uric acid
6 levels and multiple health outcomes: umbrella review of evidence from observational studies,
7 randomised controlled trials, and Mendelian randomisation studies. *BMJ*. 2017;357:j2376.
- 8 [14] Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E, et al. Dietary
9 fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses.
10 *The American journal of clinical nutrition*. 2018;107:436-44.
- 11 [15] Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to
12 health and disease in later life: an umbrella review of systematic reviews and meta-analyses.
13 *BMC Med*. 2016;14:147.
- 14 [16] Zhang Z, Ma G, Chen S, Li Z, Xia E, Sun Y, et al. Comparison of plasma triacylglycerol
15 levels in vegetarians and omnivores: a meta-analysis. *Nutrition (Burbank, Los Angeles*
16 *County, Calif)*. 2013;29:426-30.
- 17 [17] Zhang Z, Wang J, Chen S, Wei Z, Li Z, Zhao S, et al. Comparison of vegetarian diets
18 and omnivorous diets on plasma level of HDL-c: a meta-analysis. *PloS one*. 2014;9:e92609.
- 19 [18] Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of Vegetarian Diets on Blood
20 Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of*
21 *the American Heart Association*. 2015;4:e002408.
- 22 [19] Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and
23 plasma lipids: a systematic review and meta-analysis. *Nutrition reviews*. 2017;75:683-98.
- 24 [20] Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple
25 health outcomes: A systematic review with meta-analysis of observational studies. *Critical*
26 *reviews in food science and nutrition*. 2017;57:3640-9.

- 1 [21] Obersby D, Chappell DC, Dunnett A, Tsiami AA. Plasma total homocysteine status of
2 vegetarians compared with omnivores: a systematic review and meta-analysis. *The British*
3 *journal of nutrition*. 2013;109:785-94.
- 4 [22] Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucas D. How prevalent is vitamin B12
5 deficiency among vegetarians? *Nutrition reviews*. 2013;71:110-7.
- 6 [23] Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among
7 vegetarians assessed by serum vitamin B12: A review of literature. *European Journal of*
8 *Clinical Nutrition*. 2014;68:541-8.
- 9 [24] Foster M, Chu A, Petocz P, Samman S. Effect of vegetarian diets on zinc status: a
10 systematic review and meta-analysis of studies in humans. *Journal of the science of food*
11 *and agriculture*. 2013;93:2362-71.
- 12 [25] Foster M, Herulah UN, Prasad A, Petocz P, Samman S. Zinc Status of Vegetarians
13 during Pregnancy: A Systematic Review of Observational Studies and Meta-Analysis of Zinc
14 Intake. *Nutrients*. 2015;7:4512-25.
- 15 [26] Haider LM, Schwingshackl L, Hoffmann G, Ekmekcioglu C. The effect of vegetarian diets
16 on iron status in adults: A systematic review and meta-analysis. *Critical reviews in food*
17 *science and nutrition*. 2016:1-16.
- 18 [27] Ho-Pham LT, Nguyen ND, Nguyen TV. Effect of vegetarian diets on bone mineral
19 density: a Bayesian meta-analysis. *The American journal of clinical nutrition*. 2009;90:943-
20 50.
- 21 [28] Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes
22 in body weight in clinical trials of vegetarian diets. *Journal of the Academy of Nutrition and*
23 *Dietetics*. 2015;115:954-69.
- 24 [29] Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian Diets and Weight Reduction: a
25 Meta-Analysis of Randomized Controlled Trials. *Journal of general internal medicine*.
26 2016;31:109-16.

- 1 [30] Haghighatdoost F, Bellissimo N, Totosy de Zepetnek JO, Rouhani MH. Association of
2 vegetarian diet with inflammatory biomarkers: a systematic review and meta-analysis of
3 observational studies. *Public health nutrition*. 2017;20:2713-21.
- 4 [31] Lee Y, Park K. Adherence to a Vegetarian Diet and Diabetes Risk: A Systematic Review
5 and Meta-Analysis of Observational Studies. *Nutrients*. 2017;9.
- 6 [32] Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality
7 and cancer incidence in vegetarians: a meta-analysis and systematic review. *Annals of*
8 *nutrition & metabolism*. 2012;60:233-40.
- 9 [33] Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day
10 Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis.
11 *International journal of cardiology*. 2014;176:680-6.
- 12 [34] Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, et al.
13 Vegetarian diets and blood pressure: a meta-analysis. *JAMA internal medicine*.
14 2014;174:577-87.
- 15 [35] Godos J, Bella F, Sciacca S, Galvano F, Grosso G. Vegetarianism and breast, colorectal
16 and prostate cancer risk: an overview and meta-analysis of cohort studies. *Journal of human*
17 *nutrition and dietetics : the official journal of the British Dietetic Association*. 2017;30:349-59.
- 18 [36] Green R, Allen LH, Bjorke-Monsen AL, Brito A, Gueant JL, Miller JW, et al. Vitamin B12
19 deficiency. *Nat Rev Dis Primers*. 2017;3:17040.
- 20 [37] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature*.
21 2017;542:177-85.
- 22 [38] Thygesen LC, Gimsing LN, Bautz A, Hvidt NC, Johansen C. Chronic Neurodegenerative
23 Illnesses and Epilepsy in Danish Adventists and Baptists: A Nationwide Cohort Study. *J*
24 *Alzheimers Dis*. 2017;56:1429-35.
- 25 [39] Ogata M, Ikeda M, Kuratsune M. Mortality among Japanese Zen priests. *J Epidemiol*
26 *Community Health*. 1984;38:161-6.

- 1 [40] Orlich MJ, Singh PN, Sabate J, Jaceldo-Siegl K, Fan J, Knutsen S, et al. Vegetarian
2 dietary patterns and mortality in Adventist Health Study 2. *JAMA internal medicine*.
3 2013;173:1230-8.
- 4 [41] Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND. A multicenter randomized
5 controlled trial of a plant-based nutrition program to reduce body weight and cardiovascular
6 risk in the corporate setting: the GEICO study. *Eur J Clin Nutr*. 2013;67:718-24.
- 7 [42] Desroches S, Paradis ME, Perusse M, Archer WR, Bergeron J, Couture P, et al.
8 Apolipoprotein A-I, A-II, and VLDL-B-100 metabolism in men: comparison of a low-fat diet
9 and a high-monounsaturated fatty acid diet. *J Lipid Res*. 2004;45:2331-8.
- 10 [43] Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, et al. High-Density Lipoprotein
11 Cholesterol and Cause-Specific Mortality in Individuals Without Previous Cardiovascular
12 Conditions: The CANHEART Study. *J Am Coll Cardiol*. 2016;68:2073-83.
- 13 [44] Salonen JT. Liver damage and protective effect of high density lipoprotein cholesterol.
14 *BMJ*. 2003;327:1082-3.
- 15 [45] Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet*. 2014;384:618-25.
- 16 [46] Tilg H, Kaser A. Gut microbiome, obesity, and metabolic dysfunction. *The Journal of*
17 *clinical investigation*. 2011;121:2126-32.
- 18 [47] Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, et al. Comparative
19 metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota
20 metabolite production. *Gut*. 2016;65:63-72.
- 21 [48] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet
22 rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559-63.
- 23 [49] De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Stora A, Laghi L, et al. High-level
24 adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated
25 metabolome. *Gut*. 2016;65:1812-21.
- 26 [50] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota
27 metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*.
28 2013;19:576-85.

- 1 [51] Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature*.
2 2016;535:65-74.
- 3 [52] Franco-de-Moraes AC, de Almeida-Pititto B, da Rocha Fernandes G, Gomes EP, da
4 Costa Pereira A, Ferreira SRG. Worse inflammatory profile in omnivores than in vegetarians
5 associates with the gut microbiota composition. *Diabetol Metab Syndr*. 2017;9:62.
- 6 [53] Vigiouk E, Kendall CW, Kahleova H, Rahelic D, Salas-Salvado J, Choo VL, et al.
7 Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic
8 review and meta-analysis of randomized controlled trials. *Clin Nutr*. 2019;38:1133-45.
- 9 [54] Sievenpiper JL, Dworatzek PD. Food and dietary pattern-based recommendations: an
10 emerging approach to clinical practice guidelines for nutrition therapy in diabetes. *Can J*
11 *Diabetes*. 2013;37:51-7.
- 12 [55] Rinaldi S, Campbell EE, Fournier J, O'Connor C, Madill J. A Comprehensive Review of
13 the Literature Supporting Recommendations From the Canadian Diabetes Association for the
14 Use of a Plant-Based Diet for Management of Type 2 Diabetes. *Can J Diabetes*.
15 2016;40:471-7.
- 16 [56] Gueant JL, Namour F, Gueant-Rodriguez RM, Daval JL. Folate and fetal programming:
17 a play in epigenomics? *Trends Endocrinol Metab*. 2013;24:279-89.
- 18 [57] Gueant JL, Caillerez-Fofou M, Battaglia-Hsu S, Alberto JM, Freund JN, Dulluc I, et al.
19 Molecular and cellular effects of vitamin B12 in brain, myocardium and liver through its role
20 as co-factor of methionine synthase. *Biochimie*. 2013;95:1033-40.
- 21 [58] Maron BA, Loscalzo J. The treatment of hyperhomocysteinemia. *Annu Rev Med*.
22 2009;60:39-54.
- 23 [59] Zhang D, Wen X, Wu W, Guo Y, Cui W. Elevated homocysteine level and folate
24 deficiency associated with increased overall risk of carcinogenesis: meta-analysis of 83
25 case-control studies involving 35,758 individuals. *PloS one*. 2015;10:e0123423.
- 26 [60] Jacques PF, Kalmbach R, Bagley PJ, Russo GT, Rogers G, Wilson PW, et al. The
27 relationship between riboflavin and plasma total homocysteine in the Framingham Offspring

- 1 cohort is influenced by folate status and the C677T transition in the
2 methylenetetrahydrofolate reductase gene. *J Nutr.* 2002;132:283-8.
- 3 [61] Hustad S, Ueland PM, Vollset SE, Zhang Y, Bjorke-Monsen AL, Schneede J. Riboflavin
4 as a determinant of plasma total homocysteine: effect modification by the
5 methylenetetrahydrofolate reductase C677T polymorphism. *Clin Chem.* 2000;46:1065-71.
- 6 [62] Barker DJ, Osmond C. Diet and coronary heart disease in England and Wales during
7 and after the second world war. *J Epidemiol Community Health.* 1986;40:37-44.
- 8 [63] Rush EC, Katre P, Yajnik CS. Vitamin B12: One carbon metabolism, fetal growth and
9 programming for chronic disease. *European Journal of Clinical Nutrition.* 2014;68:2-7.
- 10 [64] Gueant JL, Elakoum R, Ziegler O, Coelho D, Feigerlova E, Daval JL, et al. Nutritional
11 models of foetal programming and nutrigenomic and epigenomic dysregulations of fatty acid
12 metabolism in the liver and heart. *Pflugers Archiv : European journal of physiology.*
13 2014;466:833-50.
- 14 [65] Yajnik CS, Deshmukh US. Fetal programming: maternal nutrition and role of one-carbon
15 metabolism. *Rev Endocr Metab Disord.* 2012;13:121-7.
- 16 [66] Li Z, Gueant-Rodriguez RM, Quilliot D, Sirveaux MA, Meyre D, Gueant JL, et al. Folate
17 and vitamin B12 status is associated with insulin resistance and metabolic syndrome in
18 morbid obesity. *Clin Nutr.* 2017.
- 19 [67] Dodds L, Fell DB, Dooley KC, Armson BA, Allen AC, Nassar BA, et al. Effect of
20 homocysteine concentration in early pregnancy on gestational hypertensive disorders and
21 other pregnancy outcomes. *Clin Chem.* 2008;54:326-34.
- 22 [68] Sukumar N, Rafnsson SB, Kandala NB, Bhopal R, Yajnik CS, Saravanan P. Prevalence
23 of vitamin B-12 insufficiency during pregnancy and its effect on offspring birth weight: a
24 systematic review and meta-analysis. *The American journal of clinical nutrition.*
25 2016;103:1232-51.
- 26 [69] Rogne T, Tielemans MJ, Chong MF, Yajnik CS, Krishnaveni GV, Poston L, et al.
27 Associations of Maternal Vitamin B12 Concentration in Pregnancy With the Risks of Preterm

- 1 Birth and Low Birth Weight: A Systematic Review and Meta-Analysis of Individual Participant
2 Data. *Am J Epidemiol.* 2017;185:212-23.
- 3 [70] Ho E. Zinc deficiency, DNA damage and cancer risk. *J Nutr Biochem.* 2004;15:572-8.
- 4 [71] Ho E, Ames BN. Low intracellular zinc induces oxidative DNA damage, disrupts p53,
5 NFkappa B, and AP1 DNA binding, and affects DNA repair in a rat glioma cell line. *Proc Natl*
6 *Acad Sci U S A.* 2002;99:16770-5.
- 7 [72] Gumulec J, Masarik M, Adam V, Eckschlager T, Provaznik I, Kizek R. Serum and tissue
8 zinc in epithelial malignancies: a meta-analysis. *PloS one.* 2014;9:e99790.
- 9 [73] Li L, Gai X. The association between dietary zinc intake and risk of pancreatic cancer: a
10 meta-analysis. *Biosci Rep.* 2017;37.
- 11 [74] Alpers DH. Subclinical micronutrient deficiency: a problem in recognition. *Curr Opin*
12 *Gastroenterol.* 2012;28:135-8.
- 13 [75] Park SK, Ryoo JH, Kim MG, Shin JY. Association of serum ferritin and the development
14 of metabolic syndrome in middle-aged Korean men: a 5-year follow-up study. *Diabetes Care.*
15 2012;35:2521-6.
- 16 [76] Cao H, Wang C, Chai R, Dong Q, Tu S. Iron intake, serum iron indices and risk of
17 colorectal adenomas: a meta-analysis of observational studies. *European journal of cancer*
18 *care.* 2017;26.
- 19 [77] Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and
20 meta-analysis of the epidemiological evidence. *Cancer epidemiology, biomarkers &*
21 *prevention : a publication of the American Association for Cancer Research, cosponsored by*
22 *the American Society of Preventive Oncology.* 2014;23:12-31.
- 23 [78] An Exploration Into Diets Around the World -August 2018. Ipsos.
- 24 [79] Tilman D, Clark M. Global diets link environmental sustainability and human health.
25 *Nature.* 2014;515:518-22.

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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Total cholesterol LDL cholesterol HDL cholesterol Triglycerides 	Trial (modality of intervention not reported)	11 clinical trials (832)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Total cholesterol LDL cholesterol HDL cholesterol 	– Cross-sectional – Trial	30 observational (10,143)	<ul style="list-style-type: none"> 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;			
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)	<ul style="list-style-type: none"> • There was no significant influence of vegetarian diets on triglyceride level, both in observational studies and clinical trials. • 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	<ul style="list-style-type: none"> – Serum vitamin B12 – Plasma homocysteine 	<ul style="list-style-type: none"> – Cross-sectional – Cohort 	11 cross-sectional 6 cohorts (whole: 3,230)	<ul style="list-style-type: none"> • 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 $\mu\text{mol/L}$, SD = 2.89; $P < 0.025$) and vegans (16.41 $\mu\text{mol/L}$, SD = 4.8; $P < 0.005$) in comparison to that of omnivores (11.03 $\mu\text{mol/L}$, 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> 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 $\mu\text{mol/L}$; 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: <ul style="list-style-type: none"> 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 ($\mu\text{mol/L}$): 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	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Adult subjects who adhered to a vegetarian diet had a significantly lower serum ferritin concentration in comparison to non-vegetarians (-29.71 $\mu\text{g/L}$; 95% CI: -39.69 to -19.73); In subgroup analyses, the vegetarian diet had a stronger impact on ferritin status in men (-61.88 $\mu\text{g/L}$; 95% CI: -85.59 to -38.17) in comparison to women (-13.50 $\mu\text{g/L}$; 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)	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> – 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]
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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)	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Vegetarians had a significantly lower risk of diabetes in comparison to non-vegetarians 	Class II	[31]

Nutrients	omnivorous diets	– Cohort	2 cohorts (49,788)	<p>(OR = 0.726; 95% CI: 0.608 to 0.867);</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> – Vegan: OR = 0.593 (95% CI: 0.386 to 0.911; <i>P</i> = 0.017); – Lacto-vegetarian: OR = 0.762 (95% CI: 0.613 to 0.949; <i>P</i> = 0.016); – Lacto-ovo-vegetarian: OR = 0.564 (95% CI: 0.517 to 0.616; <i>P</i> = 0.30); – Pesco-vegetarian: OR = 0.867 (95% CI: 0.636 to 1.180; <i>P</i> = 0.008); – Semi-vegetarian: OR = 0.799 (95% CI: 0.667 to 0.956; <i>P</i> = 0.002). 		
Dinu, 2017 Critical Reviews in Food and Nutrition	High-quality review	Vegetarian vs. omnivorous diets	<ul style="list-style-type: none"> – Body mass index – Blood glucose level <p>– Cross-sectional – Cohort</p>	<p>86 studies (249,049)</p> <p>10 cohorts (72,298)</p>	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> - Ischemic heart disease - Circulatory diseases - Cerebrovascular disease 	Cohort	7 cohorts (124,706)	<ul style="list-style-type: none"> • 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. 	<p>Class II to I (Ischemic heart disease)</p> <p>Class IV (Circulatory diseases and Cerebrovascular disease)</p>	[32]
Kwok, 2014 International Journal of Cardiology	Moderate quality review	Vegetarian vs. omnivorous diets	<ul style="list-style-type: none"> - Ischemic heart disease or cardiac event - Cerebrovascular disease 	Cohort	8 cohorts (183,321)	<ul style="list-style-type: none"> • 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. 	<p>Class III to II (Ischemic heart disease or cardiac event)</p> <p>Class IV (Cerebrovascular disease)</p>	[33]
Yokoyama, 2014 JAMA Internal Medicine	High-quality review	Vegetarian vs. omnivorous diets	<ul style="list-style-type: none"> - Systolic blood pressure - Diastolic blood pressure 	<ul style="list-style-type: none"> - Trial (planned or self-selected vegetarian diet) - Cross-sectional 	7 clinical trials (311) 32 observational studies (21,604)	<ul style="list-style-type: none"> • 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 	<p>Class IV to III (Systolic blood pressure, Trials)</p> <p>Class II (Systolic blood pressure, Cross-sectional)</p>	[34]

			<ul style="list-style-type: none"> - Ischemic heart disease - Cardiovascular disease - Cerebrovascular disease 	<ul style="list-style-type: none"> - Cross-sectional - Cohort 	<p>86 studies (249,049)</p> <p>10 cohorts (72,298)</p>	<ul style="list-style-type: none"> 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: <p><i>Clinical trials:</i></p> <ul style="list-style-type: none"> - 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; $P = 0.007$). <p><i>Observational Studies:</i></p> <ul style="list-style-type: none"> - 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; $P < 0.001$). 	<p>Class IV to III (Diastolic blood pressure, Trials)</p> <p>Class II (Diastolic blood pressure, Cross-sectional)</p>	
<p>Dinu, 2017 Critical Reviews in Food and Nutrition</p>	<p>High-quality review</p>	<p>Vegetarian vs. omnivorous diets</p>				<ul style="list-style-type: none"> • 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 	<p>I (Ischemic heart disease)</p> <p>Class IV (Cardiovascular disease)</p>	<p>[20]</p>

reduced risk of cerebrovascular disease (RR = 0.93; 95% CI: 0.78 to 1.10);	Class IV (Cerebrovascular disease)
<ul style="list-style-type: none"> Subgroup analysis, according to the vegetarian diet: no reported summary measure. 	

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)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Breast cancer risk Colorectal cancer risk Prostate cancer risk 	Cohort	9 studies (686,629)	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Cancer incidence Breast cancer incidence All cancer-related mortality Colorectal cancer mortality Breast cancer mortality Prostate cancer mortality Lung cancer mortality 	<ul style="list-style-type: none"> Cross-sectional Cohort 	<ul style="list-style-type: none"> 86 studies (249,049) 10 cohorts (72,298) 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 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)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> – SDA vegetarians vs. omnivores – Non-SDA vegetarians vs. omnivores 	All-cause mortality	Cohort	8 cohorts (183,321)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> – Cross-sectional – Cohort 	<ul style="list-style-type: none"> 86 studies (249,049) 10 cohorts (72,298) 	<ul style="list-style-type: none"> 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**.

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.

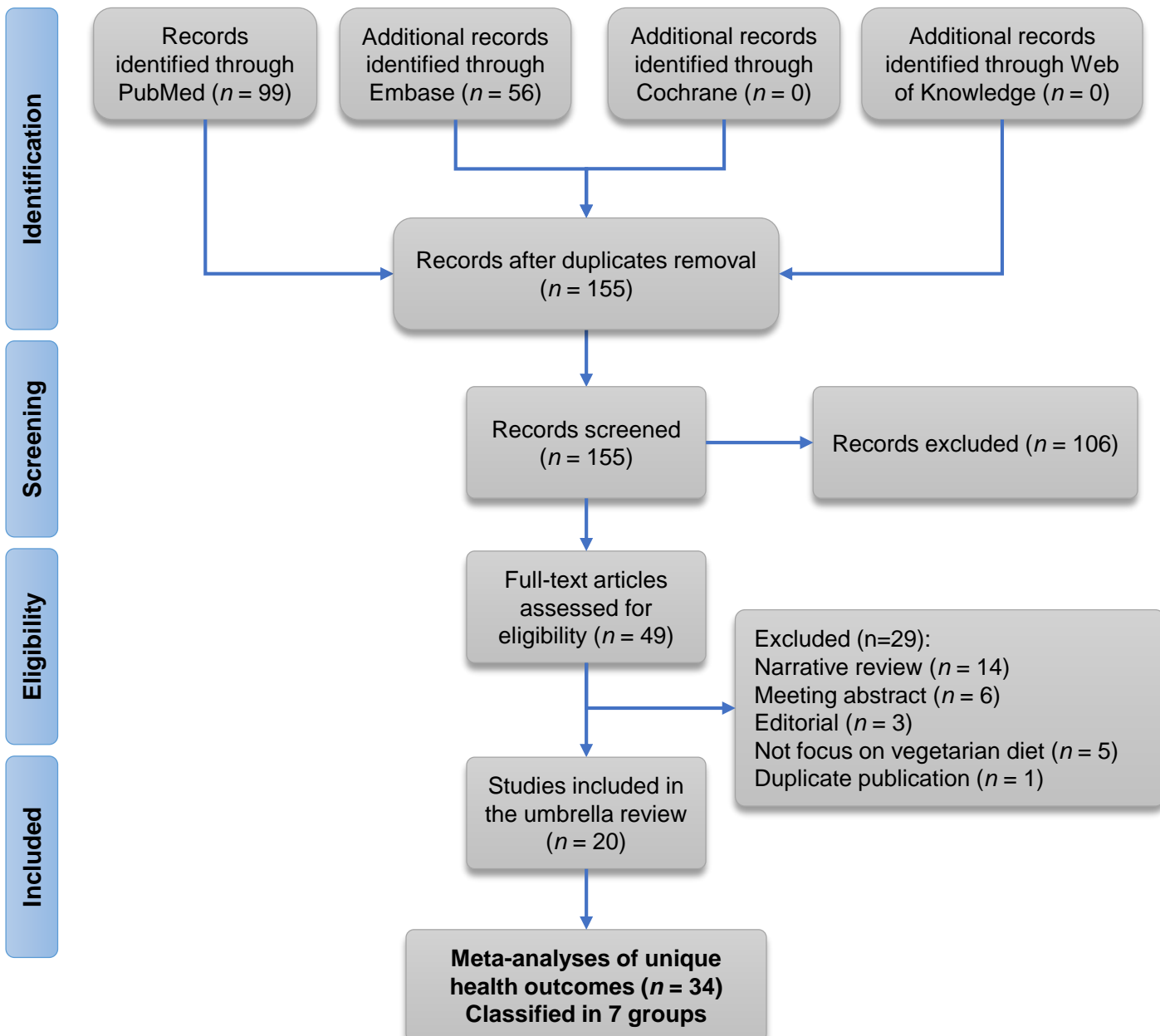
Figure 4. Forest plot reporting the magnitude of the association between vegetarian diets and adverse health outcomes in comparison to omnivores. The calculated summary effect is denoted by the solid diamond at the bottom of the forest plots, the width of which represents the 95% confidence interval.

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



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

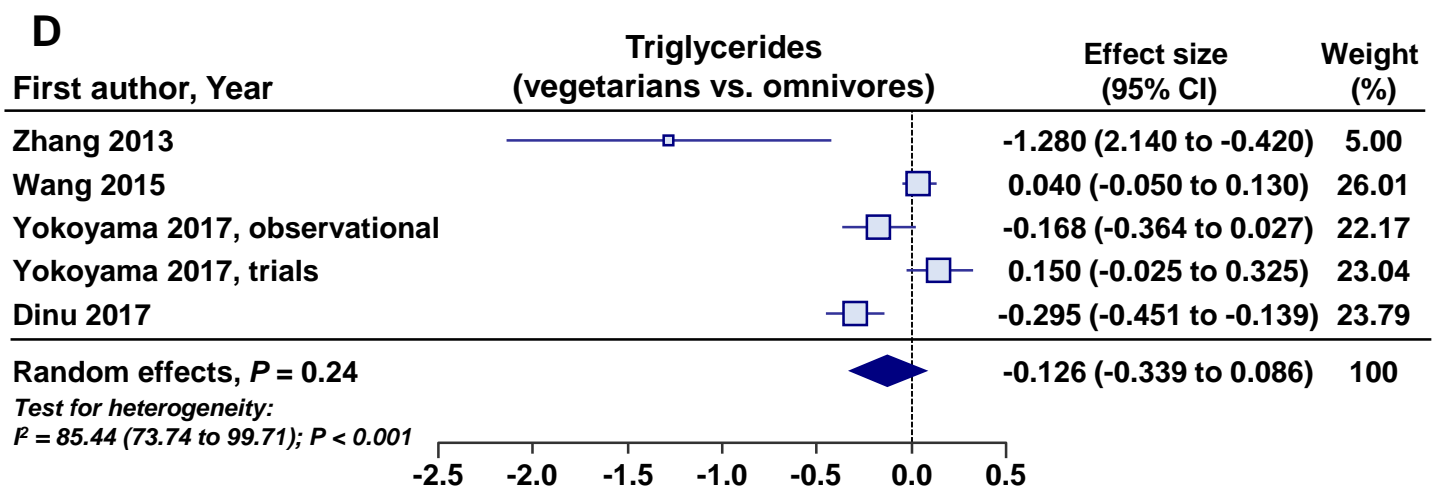
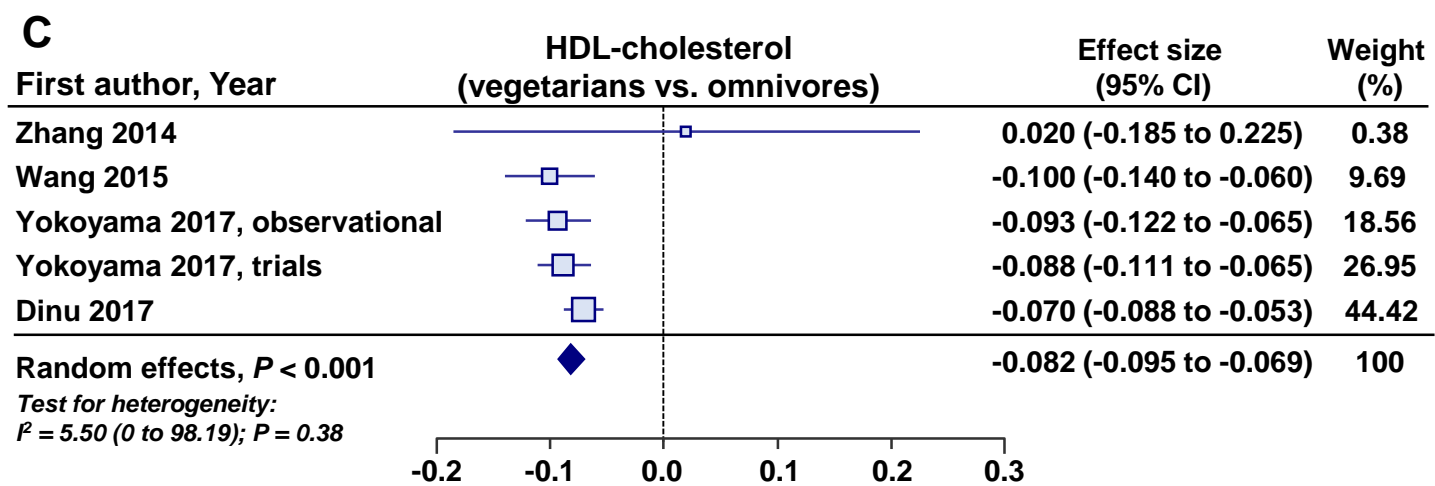
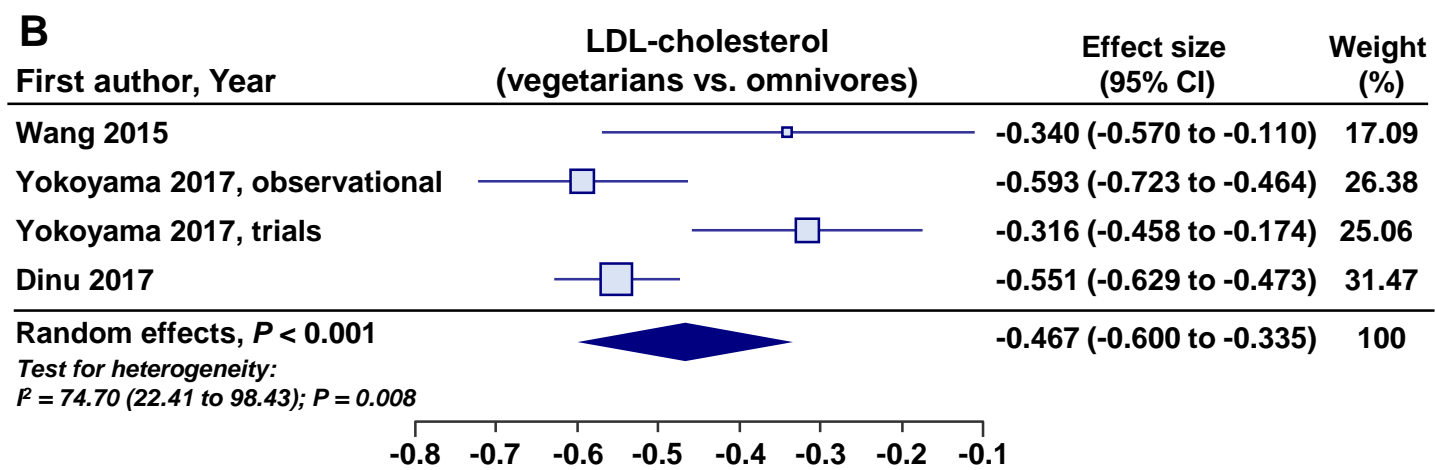
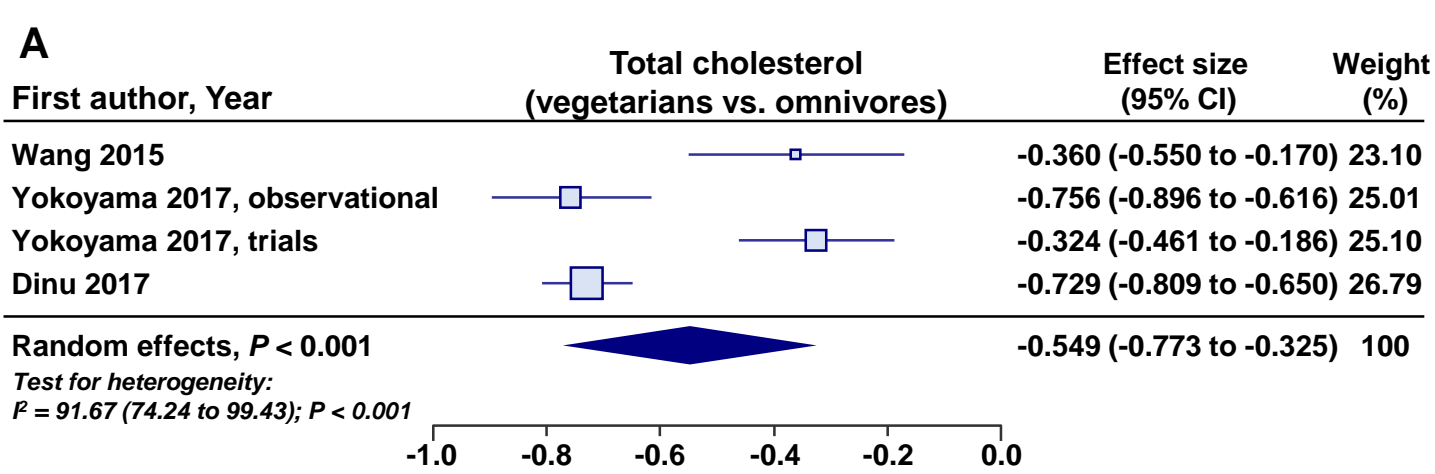
Group #5: Cardiovascular risk ($n = 4$)

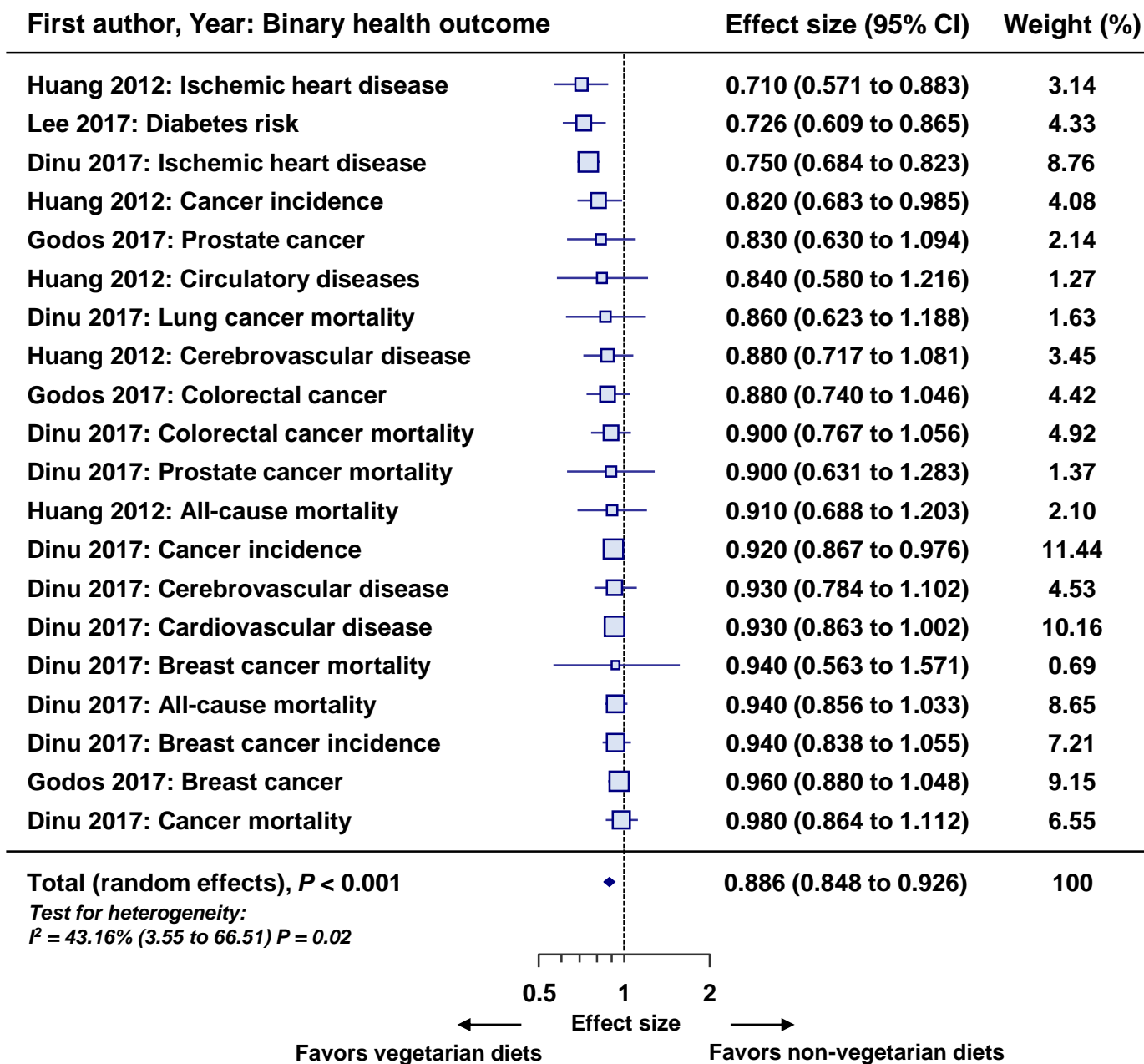
- Ischemic heart disease
- Circulatory disease
- Cerebrovascular disease
- Cardiovascular disease
- Cardiac events
- Systolic blood pressure
- Diastolic blood pressure

Group #6: Cancer ($n = 3$)

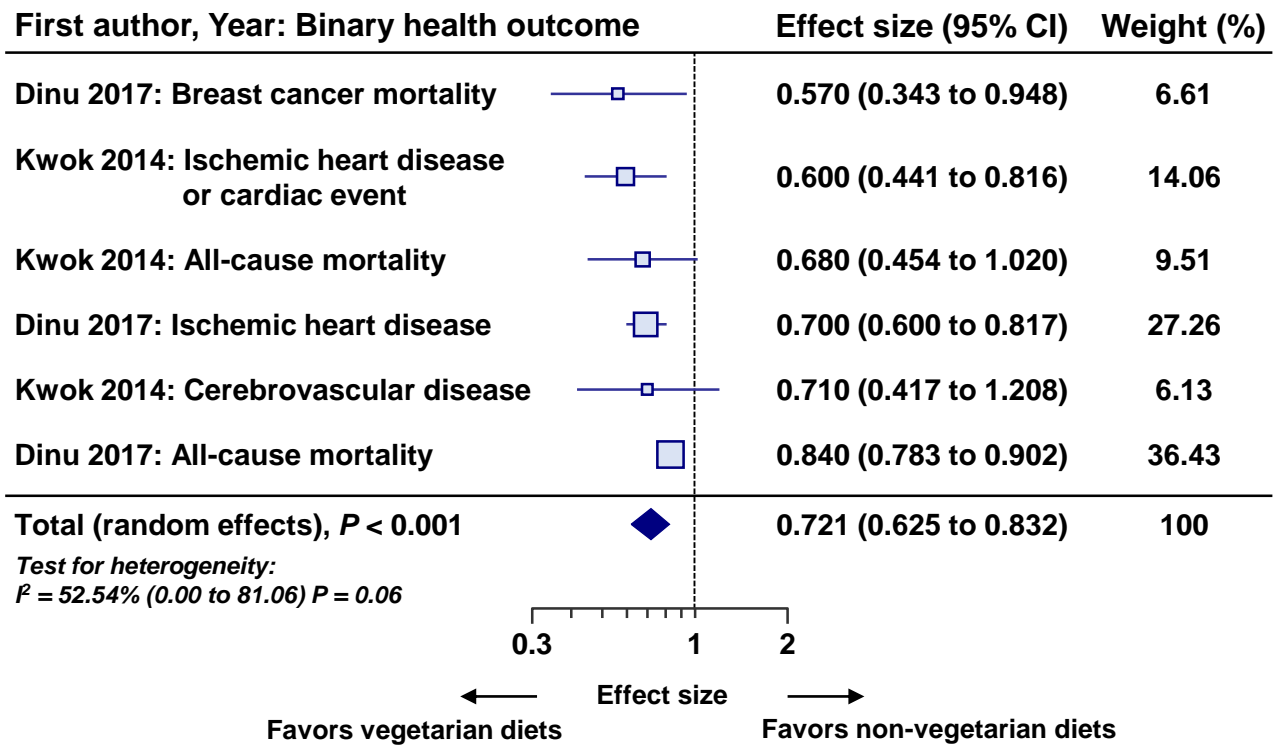
- Cancer incidence
- Colorectal cancer risk
- Prostate cancer risk
- Breast cancer risk
- All cancer-related mortality
- Breast cancer-related mortality
- Colorectal cancer-related mortality
- Prostate cancer-related mortality
- Lung cancer-related mortality
- Breast cancer incidence

Group #7: All-cause mortality ($n = 3$)

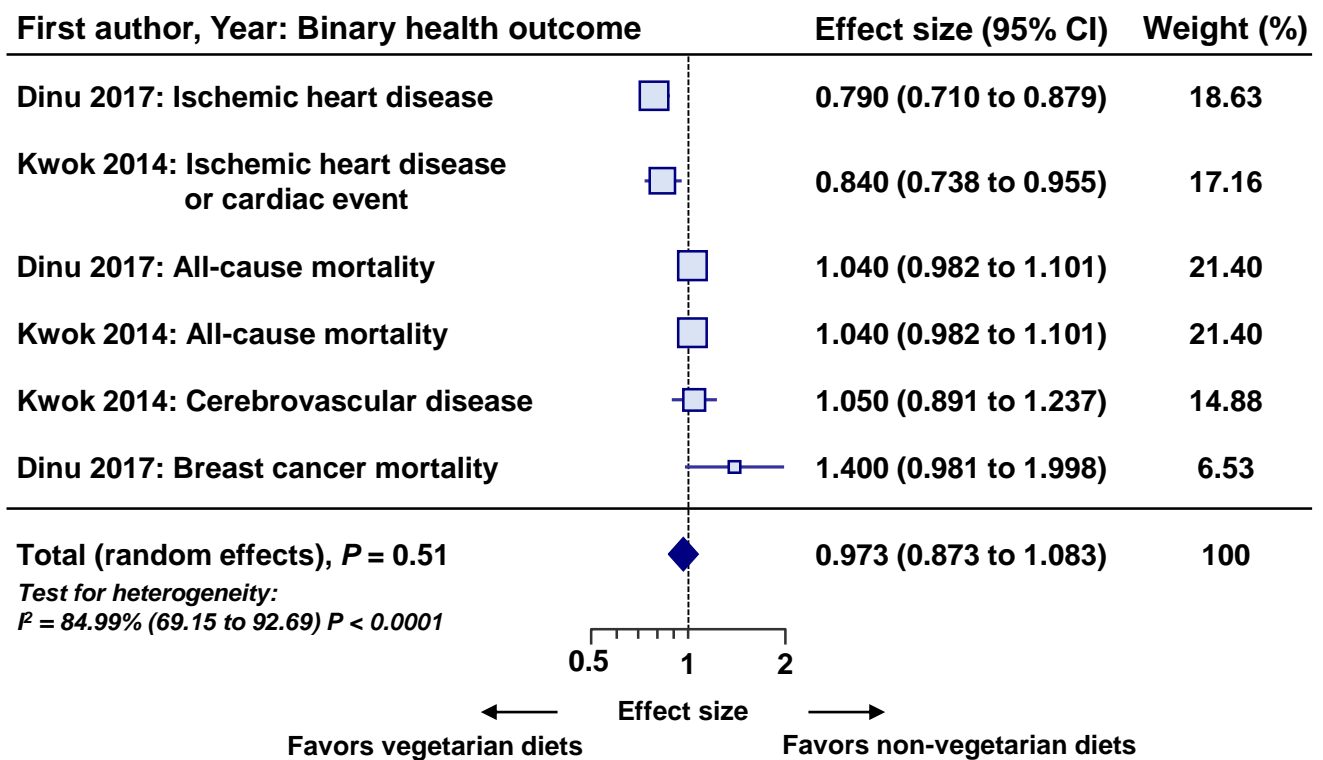




A



B



➔ Positive outcome
➔ No demonstrated positive outcome
➔ Negative outcome



Vegetarian diets

Obesity^{20,28,29} Dyslipidemia^{16,18-20} hs-CRP ↑³⁰

Vitamin B12²¹⁻²³ ↓ Iron²⁶ ↓ Zinc^{24,25} ↓
Homocysteine²¹ ↑

Arterial hypertension³⁴

Ischemic heart Disease^{20,32,33}

Diabetes^{20,31}

Cerebrovascular Disease^{20,32}

Cancer Incidence^{20,32}

Colorectal cancer risk or Mortality^{20,35}

Breast cancer risk or Mortality^{20,35}

Prostate cancer risk or Mortality^{20,35}

Lung cancer mortality²⁰

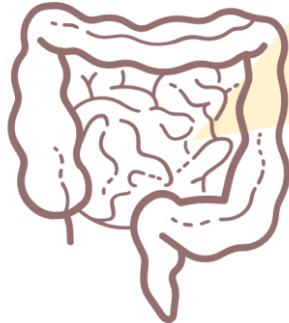
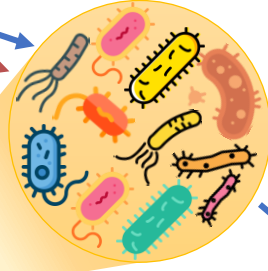
Bone mineral density²⁷

Animal-based diet



Dietary carnitine and choline

Vegetarian diet



Pro-inflammatory gut microbiota

Bacterial translocations and low-grade endotoxemia

Systemic low-grade inflammation

Immunometabolic disease clusters

Obesity



Type 2 diabetes

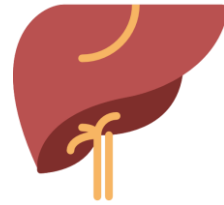


Dyslipidemia



Trimethylamine (TMA)

Flavin monooxygenases



Trimethylamine-N-oxide (TMAO)

Cardiovascular risk

**Atherosclerosis
Ischemic heart disease**

