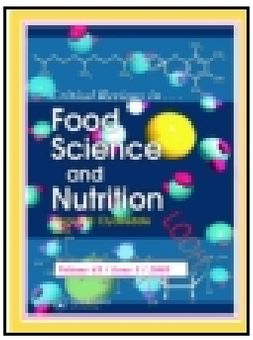

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

# Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies

**Monica Dinu MSc, Rosanna Abbate MD, Gian Franco Gensini MD, Alessandro Casini MD & Francesco Sofi MD, PhD**

**To cite this article:** Monica Dinu MSc, Rosanna Abbate MD, Gian Franco Gensini MD, Alessandro Casini MD & Francesco Sofi MD, PhD (2016): Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2016.1138447

**To link to this article:** http://dx.doi.org/10.1080/10408398.2016.1138447

# Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies

Monica DINU, MSc [1,2], Rosanna ABBATE, MD [1], Gian Franco GENSINI, MD [1,3], Alessandro CASINI, MD [1,2], Francesco SOFI, MD, PhD [1-3]

[1] Department of Experimental and Clinical Medicine, University of Florence, Italy; [2] Unit of Clinical Nutrition, University Hospital of Careggi, Florence, Italy; [3] Don Carlo Gnocchi Foundation Italy, Onlus IRCCS, Florence, Italy

**Corresponding author:** Monica Rodica DINU, MSc, Department of Experimental and Clinical Medicine, University of Florence, Italy, Largo Brambilla 3, 50134 Florence, Italy, e-mail: monicarodica.dinu@unifi.it



**Authors' contributions:** Conception and design: F. Sofi, M. Dinu, Analysis and interpretation of the data: F. Sofi, M. Dinu, Drafting of the article: M. Dinu, R. Abbate, A. Casini, F. Sofi, Critical revision of the article for important intellectual content: R. Abbate, G.F. Gensini, A. Casini, Final approval of the article: R. Abbate, G.F. Gensini, A. Casini, F. Sofi, Statistical expertise: F. Sofi, M. Dinu

**Financial disclosure**: Nothing to declare

**Disclosure of interest**: All authors declare that there are no conflicts of interest

**Guarantor of the paper:** F. Sofi

**Abstract**

**Background:** Beneficial effects of vegetarian and vegan diets on health outcomes have been supposed in previous studies.

**Objectives:** Aim of this study was to clarify the association between vegetarian, vegan diets, risk factors for chronic diseases, risk of all-cause mortality, incidence and mortality from cardio-cerebrovascular diseases, total cancer and specific type of cancer (colorectal, breast, prostate and lung), through meta-analysis.

**Methods:** A comprehensive search of Medline, EMBASE, Scopus, The Cochrane Library and Google Scholar was conducted.

**Results:** Eighty-six cross-sectional and 10 cohort prospective studies were included. The overall analysis among cross-sectional studies reported significant reduced levels of body mass index, total cholesterol, LDL-cholesterol, and glucose levels in vegetarians and vegans versus omnivores. With regard to prospective cohort studies, the analysis showed a significant reduced risk of incidence and/or mortality from ischemic heart disease (RR 0.75; 95% CI, 0.68 to 0.82) and incidence of total cancer (RR 0.92; 95% CI 0.87 to 0.98) but not of total cardiovascular and cerebrovascular diseases, all-cause mortality and mortality from cancer. No significant association was evidenced when specific types of cancer were analyzed. The analysis conducted among vegans reported significant association with the risk of incidence from total cancer (RR 0.85; 95% CI, 0.75 to 0.95), despite obtained only in a limited number of studies.

**Conclusions:** This comprehensive meta-analysis reports a significant protective effect of a vegetarian diet versus the incidence and/or mortality from ischemic heart disease (-25%) and incidence from total cancer (-8%). Vegan diet conferred a significant reduced risk (-15%) of incidence from total cancer.

**Key words**

Vegetarian; Vegan; Diet; Meta-Analysis

## Introduction

Vegetarian diet, defined as a dietary profile characterized by abstention from consuming meat and meat products, poultry, seafood and flesh from any other animal, is experiencing a considerable popularity in the general population.[1] The reasons for adoption of this dietary profile are different, ranging from ethical motivations, religious beliefs, environmental and cultural issues, to health-related aspects.[1-2] Health benefits of vegetarian diet have been widely reported by cross-sectional and prospective cohort studies during the last 50 years, but uncertainties due to the limited sample sizes of some of these studies and to the fact that some large prospective cohort studies included particular cohort of subjects still remain.[3-4] Indeed, generally speaking, vegetarians tend to be more conscious for the health aspects, slimmer, and in better health when compared with omnivores, and specific cohorts have been demonstrated to be not generalizable to the general population for the low prevalence of risk factors.[5] These findings might indicate the presence of flaws in the analysis of possible health benefits of vegetarian diet. To date, vegan diet, i.e. the total exclusion of any animal-derived substance is a pattern that is attracting a relevant interest among the general population. Few studies reported that vegan diet appears to be healthful, but no conclusive data have been obtained.[6-7] The aim of this study was to conduct a comprehensive systematic review with meta-analysis of all cross-sectional and cohort studies hitherto published in order to obtain an estimate of the association between vegetarian, vegan diets, and multiple health outcomes, including risk factors for chronic diseases, risk of all-cause mortality, incidence and mortality from cardio-cerebrovascular diseases, total cancer and specific types of cancer.

## METHODS

### Search strategy, inclusion criteria and data extraction

The review question was structured using the following elements -- Population of interest (P); Intervention (I); Comparisons (C); Outcome (O); and Time frame (T) -- namely, the PICOT format.[8] For this study, Setting (S) was also included. The operationalisation of these elements is displayed in Table 1.

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [9] we systematically identified all potentially relevant articles through a computerized search of main electronic databases: Medline (1950 through April 2015), Embase (1980 through April 2015), Scopus (through April 2015), The Cochrane Library, and Google Scholar. Additional searches were conducted by scanning references of the identified articles, reviews and meta-analyses. Search terms included the following key words, used in combination as MeSH terms and text words: "vegetarian", "vegetarians", "vegetarianism", "vegetarian diet", "vegetarian diets", "vegan", "vegans", "veganism", "vegan diet", "vegan diets" and their variants, which were used in combination with words relating to health status "plasma lipids", "cholesterol", "triglycerides", "glycemia", "hematic parameters", "cancer", "circulatory diseases", "cardiovascular disease", "ischemic heart disease", "cerebrovascular disease", "mortality", "health effects", "health status", and their variants. The search was limited to human studies. When multiple articles for a single study were present, we used the latest publication and supplemented it, if necessary, with data from the most complete or updated publication.

Eligible studies included any observational study conducted in humans (i.e. cross-sectional studies, case-control, nested case-control, or case-cohort design) that reported a measure of association (such as hazard ratios or incident rate ratios for prospective studies) between vegetarian or vegan diet, assessed by questionnaires, and risk factors for chronic degenerative diseases [body mass index (BMI), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood

glucose], risk of all-cause mortality, incidence and mortality from cardio-cerebrovascular diseases, total cancer and specific types of cancer, confirmed by medical records or registry linkage.

The decision to include studies was hierarchical and initially made on the basis of the study title, then of the study abstract, and finally of the complete study manuscript. Eligible studies were included if they met the inclusion criteria for study design, study population (clinically healthy subjects ≥ 18 years old), exposure (vegetarian diet, defined as a diet excluding meat and meat products, poultry, seafood and flesh from any animal; vegan diet, defined as a diet that omit all the animal-derived products), reference group (omnivore diet, defined as a diet consuming all types of foods including meat and meat-products, poultry, seafood and flesh from any animal), outcome and statistics (sufficient data to allow calculation of differences between individuals consuming a vegetarian or a vegan diet and those consuming an omnivore diet).



Two reviewers (M.D., F.S.) independently extracted data from all the studies fulfilling the inclusion criteria and any disagreement was resolved by consensus. The following data were extracted from the original articles by using a standardized data extraction form: lead author, year of publication, country of the study population, study design characteristics, characteristics of different groups, follow-up duration, outcomes, effect size measurements (i.e., hazard ratio/relative risk, mean difference) and variables that entered into the multivariable model as potential confounders.

**Assessment of methodological quality**

Two reviewers (M.D., F.S.) assessed the methodological quality independently, and any incongruity was discussed and resolved. The methodological quality of the trials included was assessed using elements of the Newcastle-Ottawa Scale (NOS) for assessing risk of bias in observational studies. A total of 9 points coming from 3 domains were reported for each study: selection, comparability, and ascertainment of exposure(s) or outcome(s).[10]

**Statistical analysis**

We used Review Manager (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Copenhagen, Denmark) to pool data for each risk factor and outcome of interest. We conducted pooled analyses using the generic inverse variance method with random-effects weighting. As for cross-sectional studies, we calculated the weighted mean differences (WMD) between the subjects following vegetarian or vegan diet and those following an omnivore diet with 95% confidence intervals (CIs). With regard to prospective studies, pooled results were reported as relative risks (RRs) and presented with 95% CIs. $P < 0.05$ was considered statistically significant. When available, we used the results of the original studies from multivariate models with the most complete adjustment for potential confounders.

Statistical heterogeneity was evaluated by using the $I^2$ statistic, which assessed the appropriateness of pooling the individual study results. The $I^2$ value provided an estimate of the amount of variance across studies because of heterogeneity rather than chance. Where $I^2$ was > 50%, the heterogeneity was considered substantial. Moreover, to further investigate the heterogeneity across the studies we performed sensitivity analyses by dividing studies into groups according to their main characteristics. Subgroup analyses were then performed according to cohorts (Adventists; Non-Adventists), mean sample size of the study populations (<9,500; ≥9,500), country (U.S.; non-U.S.), mean duration of follow-up (<14 years; ≥14 years), and quality of the studies (Moderate = studies with scores ranging from 4-6 on the NOS, High = studies with scores ≥7 on the NOS). We removed each single study from the meta-analyses and recalculated the summary association (the "leave one out" approach). [11] A study whose removal either pushed the significance level of the overall association from <0.05 to ≥0.05 (or vice versa), or altered the nominal effect size

by 10% or more, was considered an influential outlier. If ≥5 studies were available, we explored the possibility of publication bias by visual inspection of funnel plot of effect size against standard error.

## RESULTS

### Literature search

Our search yielded a total of 10,516 unique citations. After review and excluding duplicate reports we identified 433 citations as potentially relevant for the analysis. Of these, 325 were excluded after full-text reviews for the reasons described in Figure 1. Overall, a total of 108 articles were finally included in the meta-analysis (Figure 1).



Selected cross-sectional studies examined the effect of vegetarian diet (n = 86) and vegan diet (n = 24) on the following risk factors for chronic degenerative diseases: BMI (71 studies for vegetarian diet; 19 studies for vegan diet), total cholesterol (64 studies for vegetarians, 19 for vegans), LDL-cholesterol (46 for vegetarians, 13 for vegans), HDL-cholesterol (51 for vegetarians, 15 for vegans), triglycerides (55 for vegetarians, 13 for vegans), and blood glucose (27 for vegetarians, 4 for vegans). Selected cohort prospective studies examined the association between vegetarian diet (n = 10), vegan diet (n = 2) and different clinical outcomes: all-cause mortality (5 studies for vegetarians, 2 studies for vegans), incidence and mortality from cardiovascular diseases (4 studies, all for vegetarians), ischemic heart disease (5 studies, all for vegetarians), cerebrovascular disease (3 studies, all for vegetarians), incidence of total cancer (2 studies for vegetarians; 2 studies for vegans) and mortality from total cancer (3 studies for vegetarians). In addition, some of these prospective studies reported the association with a specific localization of cancer and the vegetarian diet, such as incidence of breast cancer (2 studies), mortality from breast cancer (2 studies), prostate cancer (2 studies), colorectal cancer (3 studies), and lung cancer (2 studies).

### Cross-sectional studies

Characteristics of the included cross-sectional studies reporting the effect of vegetarian and vegan diets on different risk parameters, including the risk-of-bias assessment, are reported in Supplementary tables 1-12. The overall analysis comprised a total number of 56,461 vegetarians and 8,421 vegans compared with 184,167 omnivorous and the mean age varied widely, ranging from 18 to 81 years old. The risk-of-bias assessment for each cross-sectional study included in the meta-analysis reported a low risk of bias only in 2 studies, whereas in the others a moderate-to-high risk was present.

Table 2 and 3 show the pooled estimates of effect size and 95% CIs expressed as WMD for the effects of vegetarian and vegan diets vs. omnivore diet on risk factors for chronic degenerative diseases. At the overall analysis, vegetarian diet was significantly associated with lower BMI (-1.49), serum total cholesterol (-28.16 mg/dL), LDL-cholesterol (-21.27 mg/dL), HDL-cholesterol (-2.72 mg/dL), serum triglycerides (-11.39 mg/dL), and blood glucose levels (-5.08 mg/dL) with respect to omnivores. Similarly, vegan diet reported significantly lower BMI (-1.72), serum total cholesterol (-31.02 mg/dL), LDL-cholesterol (-22.87 mg/dL), and blood glucose levels (-6.38 mg/dL), but non-significant lower HDL-cholesterol and triglycerides with respect to omnivores. Significant heterogeneity ($p < 0.001$) was present among the studies.



**Prospective cohort studies**

The characteristics of the included prospective cohort studies, including risk-of-bias assessment, are presented in tables 4,5. The overall analysis for all the different clinical outcomes comprised a total number of 72,298 vegetarians followed for a period ranging from 4.1 to 21 years. One study included only women and 8 studies included men and women. The risk-of-bias assessment for the included study reported a low risk of bias in 4 studies [15,16,18,20] and a moderate risk for the remaining.

The results of the pooled analysis for the all included studies are depicted in figure 2. The relation between vegetarian diet and all-cause mortality was evaluated in five studies [12,13,14,15,19] including 66,018 vegetarians and 8,216 deaths by obtaining a non-significant (p = 0.24) association with an RR of 0.94 (95% CI 0.86 to 1.04) and a significant heterogeneity ($I^2$ = 83%; p<0.001). After exclusion of studies by Key et al. (2009)[12], which included the cohorts of the Adventist Mortality and Health-1 studies the heterogeneity disappeared ($I^2$ = 21%; p = 0.28) and the result did not change (RR 1.01, 95% CI 0.95 to 1.07). For vegans and all-cause mortality the risk ratio was 0.88 (RR 0.88, 95% CI 0.75 to 1.02; p = 0.42). Similarly, no significant association (p = 0.07) was also found among vegetarians when incidence and/or mortality from cardiovascular diseases were taken as a unique outcome (RR 0.93, 95% CI 0.86 to 1.00). However, as incidence and/or mortality from ischemic heart disease were analyzed separately, vegetarian diet was found to be significantly (p<0.001) associated with the outcome, with a reduced risk of -25% (RR 0.75, 95% CI 0.68 to 0.82), and non-significant heterogeneity ($I^2$ = 35%; p = 0.16), while non-significant (p = 0.39) association for incidence and/or mortality from cerebrovascular disease (RR 0.93, 95% CI 0.78 to 1.10) was observed.

With regard to incidence of total cancer, meta-analytic pooling under a random-effects model showed significant (p = 0.002) lower risk of cancer among vegetarians (RR 0.92, 95% CI 0.87 to 0.98) and vegans (RR 0.85 95% CI 0.75 to 0.95) with a non-significant heterogeneity among the studies ($I^2$ = 0%; p = 0.35, p = 0.71 for vegetarians and vegans, respectively). Finally, by analyzing different localizations of cancer, non-significant reduced risk of incidence of breast cancer (RR 0.94, 95% CI 0.84 to 1.06), as well as mortality from colorectal (RR 0.90, 95% CI 0.76 to 1.05), breast (RR 0.94, 95% CI 0.56 to 1.58), prostate (RR 0.90, 95% CI 0.63 to 1.29) and lung (RR 0.86, 95% CI 0.62 to 1.19) cancer was reported when vegetarians were compared to omnivores.

**Sensitivity analysis and publication bias**

In order to investigate the possible differences across the studies we performed some sensitivity analyses by grouping studies according to some characteristics such as cohorts (Adventists/Non-Adventists), size of the studies (mean size of the study samples: 9,500), country (U.S./Non-U.S.), length of follow-up (mean duration: 14 years), and study quality (Moderate = studies with scores ranging from 4-6 on the NOS, High = studies with scores ≥7 on the NOS). As for all-cause mortality and breast cancer mortality, vegetarian diet demonstrated a significant association only among studies conducted in the U.S. Adventist cohorts, with a shorter duration of follow-up whereas studies conducted among non-Adventists cohorts living in European countries did not report any significant association with the outcome. With regard to ischemic heart disease, sensitivity subgroups did not change the significant association reported in the overall analysis (Table 6). Publication bias was assessed by both funnel plot and Egger's linear regression test. Both methods demonstrated no evidence of publication bias. In figure 3, funnel plot for the outcome of ischemic heart disease is reported.

**Discussion**

The present is the first systematic review with meta-analysis that encompasses all the available observational studies estimating the association between vegetarian and vegan diets and multiple health outcomes including risk factors for chronic diseases, as well as incidence and mortality from cardio-cerebrovascular and neoplastic diseases. The overall analysis comprised a large amount of studies (98 cross-sectional studies and 10 cohort prospective studies) for a total population of over than 130,000 vegetarians and 15,000 vegans.

The results of the present meta-analysis report that vegetarians and vegans show significantly lower levels of the most relevant risk factor for chronic disease such as BMI, lipid variables and

fasting glucose, when compared to non-vegetarians and non-vegans. These findings, however, are significantly affected by the nature of the cross-sectional studies, which are highly susceptible to biases, as otherwise observed by the moderate-to-high risk of bias assessment in each included study. Nevertheless, as cohort prospective studies are taken into account, significant results in terms of reduction for risk of incidence of ischemic heart disease (-25%) and incidence of total cancer (-8%) were observed for vegetarians. Similarly, although in a very limited number of studies, vegan diet showed a significant association with a reduced risk of total cancer incidence (-15%).



In the last years, the number of subjects who began to adopt a vegetarian and/or vegan dietary pattern has increased with respect to the past, when the population of vegetarians was limited only to few and selected cohorts. [1-2] Accordingly, the healthy aspect of these dietary profiles has gained interest in both medical and lay communities, but some uncertainties in the literature still remain. [20] Historically, the hypothesis that vegetarian diet is able to determine a reduced risk of occurrence of disease and mortality was linked to data whose strength of evidence was limited, suffering from some drawbacks. In fact, cross-sectional studies suffer from a high risk of bias and scarce quality and were, in most of the cases, old and conducted in a limited number of subjects; moreover, the low prevalence of some relevant cardiovascular risk factors (e.g. smoking habit, hypertension, high body mass index, among all) in certain cohorts raise some concerns about the generalizability of these results in general population.[5]

We aimed to conduct the present systematic review with meta-analysis in order to give an insight into the intricate literature on this issue. Other systematic reviews with meta-analysis that analyzed the possible association between vegetarian pattern and clinical outcomes have been published so far. [5,22] The present paper, however, is the first that conducted a comprehensive

analysis of the literature in different types of analytical studies (cross-sectional and cohort prospective), in different outcomes, and the first that included also vegan diet.

With regard to the analysis of cross-sectional studies we found, in a total population of more than 56,000 subjects consuming a plant-based dietary pattern, significantly lower levels of body mass index, total cholesterol, LDL-cholesterol, triglycerides, and blood glucose when vegetarians were compared with non-vegetarians, and body mass index, total cholesterol and LDL-cholesterol when vegans were compared to non-vegans. Actually, the reasons for the beneficial effects of vegetarianism and veganism on total and LDL-cholesterol are different and lie mainly on the lower intake of total and saturated fats, but reasons can also reside on the large consumption of foods known to decrease these parameters, such as soybean, legumes, nuts and vegetable oils. Similarly, the lower body mass index found in the vegetarian/vegan people was not surprising as this is in total agreement with the literature, being linked to the lower intake of energy usually reported by these populations. However, data obtained from cross-sectional studies need to be interpreted with caution because of the moderate-to-high risk of bias reported in the vast majority of these studies, and also because of the high degree of heterogeneity evidenced in our overall analysis.

The overall analysis among prospective cohort studies documented a 25%-reduction of incidence and/or mortality from ischemic heart disease [22] but not of incidence and/or mortality from total cardiovascular and cerebrovascular diseases, and an 8%-reduction of incidence of total cancer but not of mortality from cancer when vegetarians were compared to non-vegetarians. These results, although partly surprising, could be explained by the fact that incidence and mortality are two very different outcomes, with cardiovascular and cancer mortality being greatly influenced by the treatment approaches. Moreover, the overall analysis in the cohort studies reported no significant association with specific localizations of cancer disease, such as incidence and mortality

from breast cancer, as well as incidence of lung, colon-rectum and stomach cancer. This fact can be explained by the low statistical power, due to a low number of studies evaluating this aspect and a low sample size.

The present study has some strengths and limitations. This is the first systematic review and meta-analysis that analyzed all the available data evaluating both vegetarian and vegan diets from different types of studies (cross-sectional, cohort) in relation to different health parameters and outcomes. Such a large number of studies included allowed us to perform sensitivity analyses by grouping studies with similar characteristics. By analyzing studies according to some specific characteristics, we have noted a difference of association for vegetarians and all-cause mortality according to cohort (Adventists; Non-Adventists), duration of follow-up (<14 years; >14 years) and country of origin of the cohort (U.S.; Non-U.S.). U.S. Adventists reported to have a greater significant estimate of association versus all-causes mortality as compared to European non-Adventists. Such difference has been already partly reported by the other recent meta-analysis on cardiovascular mortality but not on all-cause mortality, [5] thus reinforcing the hypothesis that the studies coming from Adventist cohorts present a low degree of generalizability when compared to other cohorts.

However, our study suffers from some limitations, which are intrinsic of the studies included in the overall analysis. For instance, we could not analyze an important datum such as the duration of adherence to the vegetarian or to the vegan pattern in the different cohorts. Indeed, only one study explicated this finding that is extremely relevant for understanding the relationship with mortality and incidence of disease. In addition, the definition of the control group i.e. those following an omnivorous diet was not really well-defined, including in some cases subjects

consuming a high intake of meat and meat products and in other cases subjects with a reduced consumption of meat and derivatives. A final potential weakness is the accuracy of the assessment of vegetarian and vegan status. There are several slight differences in the population of vegetarians throughout the world, and the possibility that some studies could have included vegetarians and vegan altogether cannot be ruled out.

In conclusion, through using a systematic review and meta-analytical approach we attempted to give some answers to common questions such as: are the vegetarian and vegan diets associated with a protection versus cardiovascular and cancer disease? From the analysis of the studies available in the literature we were able to determine that a significant protection versus ischemic heart disease and cancer is present in vegetarian subjects, but that this protection is not significant for overall mortality, cardio and cerebrovascular diseases. In addition, vegan diet seems to be associated with a lower rate of cancer incidence, but this result must be interpreted with caution, because of the very small sample size and the low number of studies evaluating this aspect. These findings are extremely interesting for helping to give correct information to subjects who want to adopt such dietary patterns.

**References**


1. Leitzmann C. Vegetarian nutrition: past, present, future. Am J Clin Nutr 2014; 100: 496S-502S.
2. Craig WJ, Mangels AR; American Dietetic Association. Position of the American Dietetic Association: vegetarian diets. J Am Diet Assoc 2009; 109: 1266-1282.
3. Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh day Adventists. Am J Clin Nutr 1999; 70: 532S-538S.
4. Fraser GE. Vegetarian diets: what do we know of their effects on common chronic diseases? Am J Clin Nutr 2009; 89: 1607S-1612S.
5. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: A systematic review and meta-analysis. Int J Cardiol 2014; 176: 680-686.
6. Le LT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. Nutrients 2014; 6: 2131-2147.
7. Craig WJ. Health effects of vegan diets. Am J Clin Nutr 2009; 89: 1627S-1633S.
8. Whittemore R, Knafl K. The integrative review: Updated methodology. Journal of Advanced Nursing 2005; 52: 546-553.
9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
10. Higgins JPT, Green S (eds). Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Available at: http://www.cochrane-handbook.org

11. Greenhouse JB, Iyengar S. Sensitivity analysis and diagnostics. In: Cooper HM, Hedges LV, Valentine JC, eds. The handbook of research synthesis and meta-analysis. 2nd ed. Russell Sage Foundation, 2009:423-24.

12. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, Burr ML, Chang-Claude J, Frentzel-Beyme R, Kuzma JW, Mann J, McPherson K. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr 1999; 70: 516S-524S.

13. Appleby PN, Key TJ, Thorogood M, Burr ML, Mann J. Mortality in British vegetarians. Public Health Nutr 2002; 5: 29-36.

14. Chang-Claude J, Hermann S, Eilber U, Steindorf K. Lifestyle determinants and mortality in German vegetarians and health-conscious persons: results of a 21-year follow-up. Cancer Epidemiol Biomarkers Prev 2005; 14: 963-968.

15. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Am J Clin Nutr 2009; 89: 1613S-1619S.

16. Cade JE, Taylor EF, Burley VJ, Greenwood DC. Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. Nutr Cancer 2010; 62: 300-306.

17. Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. Cancer Epidemiol Biomarkers Prev 2013; 22: 286-294

18. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. Am J Clin Nutr 2013; 97: 597-603.

19. Orlich MJ, Singh PN, Sabaté J, Jaceldo-Siegl K, Fan J, Knutsen S, Beeson WL, Fraser GE. Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA Intern Med 2013; 173: 1230-1238.

20. Key TJ, Appleby PN, Crowe FL, Bradbury KE, Schmidt JA, Travis RC. Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. Am J Clin Nutr 2014; 100: 378S-385S.

21. Orlich MJ, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, Knutsen SF, Beeson WL, Jaceldo-Siegl K, Butler TL, Herring RP, Fraser GE. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med 2015; 175: 767-776.

22. Ashen DM. Vegetarian diets in cardiovascular prevention. Curr Treat Options Cardiovasc Med 2013; 15: 735-745.

23. Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review. Ann Nutr Metab 2012; 60: 233-240.



 

Table 1. Use of the PICOTS format, as applied to this study

| PICOTS format | Description |
|---|---|
| **P**opulation | Presumably healthy subjects ≥ 18 years old |
| **I**ntervention | Vegetarian diet, defined as a diet excluding meat and meat products, poultry, seafood and flesh from any animal Vegan diet, defined as a diet that omit all the animal-derived products |
| **C**omparisons | Omnivore diet, defined as a diet consuming all types of foods including meat and meat-products, poultry, seafood and flesh from any animal |
| **O**utcome | Risk factors for chronic degenerative diseases (body mass index, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood glucose); all-cause mortality; incidence and mortality from cardio-cerebrovascular diseases, total cancer and specific type of cancer (colorectal, breast, prostate, lung) |
| **T**ime | Not applicable |
| **S**etting | Institutional and community setting |



 

Table 2. Effects of vegetarian diet on risk factors for chronic degenerative diseases in case-control studies, expressed as weighted mean difference (WMD)

| Outcome | N studies | Vegetarians (n) | Omnivores (n) | WMD | 95% CI | P value |
|---|---|---|---|---|---|---|
| BMI ($kg/m^2$) | 71 | 57 724 | 199 230 | -1.49 | -1.72 to -1.25 | < 0.0001 |
| Total cholesterol (mg/dL) | 64 | 5 561 | 23 573 | -28.16 | -31.22 to -25.10 | < 0.0001 |
| LDL-cholesterol (mg/dL) | 46 | 5 583 | 22 934 | -21.27 | -24.27 to -18.27 | < 0.0001 |
| HDL-cholesterol (mg/dL) | 51 | 6 194 | 23 660 | -2.72 | -3.40 to -2.04 | < 0.0001 |
| Triglycerides (mg/dL) | 55 | 4 008 | 22 083 | -11.39 | -17.42 to -5.37 | 0.02 |
| Blood glucose (mg/dL) | 27 | 2 256 | 2 192 | -5.08 | -5.98 to -4.19 | < 0.0001 |

BMI = Body Mass Index; To convert mmol/L cholesterol to mg/dL, we multiplied mmol/L by 38.67. To convert mmol/L triglyceride to mg/dL, we multiplied mmol/L by 88.57. To convert mmol/L blood glucose to mg/dL, we multiplied mmol/L by 18.

Table 3. Effects of vegan diet on risk factors for chronic degenerative diseases in case-control studies, expressed as weighted mean difference (WMD)

| Outcome | N studies | Vegans (n) | Omnivores (n) | WMD | 95% CI | P value |
|---|---|---|---|---|---|---|
| BMI (kg/m$^2$) | 19 | 8 376 | 123 292 | -1.72 | -2.21 to -1.22 | < 0.0001 |
| Total cholesterol (mg/dL) | 19 | 1 272 | 12 213 | -31.02 | -34.82 to -27.21 | < 0.0001 |
| LDL-cholesterol (mg/dL) | 13 | 728 | 11 670 | -22.87 | -29.92 to -15.82 | < 0.0001 |
| HDL-cholesterol (mg/dL) | 15 | 1 175 | 12 114 | -1.54 | -2.96 to -0.12 | 0.61 |
| Triglycerides (mg/dL) | 13 | 483 | 10 110 | -9.35 | -20.28 to 1.57 | 0.09 |
| Blood glucose (mg/dL) | 4 | 83 | 125 | -6.38 | -12.35 to -0.41 | 0.04 |

BMI = Body Mass Index; To convert mmol/L cholesterol to mg/dL, we multiplied mmol/L by 38.67. To convert mmol/L triglyceride to mg/dL, we multiplied mmol/L by 88.57. To convert mmol/L blood glucose to mg/dL, we multiplied mmol/L by 18.

**Table 4. Characteristics of prospective cohort studies evaluating vegetarian diet and different clinical outcomes**

| Author, y | Country | Cohort | Sex | Age, y | F-up, y | n/N | Outcome | RR (95% IC) | Adjustment | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Key et al., (1999) [12] | U.S. | Adventist mortality study | M/F | 52.5 | 5.6 | 1635/10258 | All-cause mortality | 0.83 (0.76 to 0.92) | Age, sex, smoking status | moderate |
| | | | | | | 598/10258 | IHD | 0.74 (0.63 to 0.88) | | |
| | | | | | | 182/10258 | Cerebrovascular | 0.65 | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | disease | (0.48 to 0.87) | | |
| | | | | | | 41/10258 | Colorectal cancer mortality | 1.37 (0.73 to 2.56) | | |
| | | | | | | 6/10258 | Lung cancer mortality | 0.59 (0.10 to 3.28) | | |
| | | | | | | 26/10258 | Breast cancer mortality | 0.65 (0.2 | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 8 to 1.52) | | |
| | | | | | | 15/10258 | Prostate cancer mortality | 1.41 (0.49 to 4.04) | | |
| Key et al., (1999)[12] | U.S. | Adventist Health Study-1 | M/F | 52.5 | 11.1 | 3564/80 03 | All-cause mortality | 0.80 (0.74 to 0.87) | Age, sex, smoking status | moderate |
| | | | | | | 921/8003 | IHD | 0.62 (0.53 | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | to 0.73) | | |
| | | | | | | 317/8003 | Cerebrovascular disease | 0.93 (0.73 to 1.19) | | |
| | | | | | | 104/8003 | Colorectal cancer mortality | 1.01 (0.66 to 1.56) | | |
| | | | | | | 96/8003 | Lung cancer mortality | 0.69 (0.37 to | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1.27) | | |
| | | | | | | 64/8003 | Breast cancer mortality | 0.52 (0.27 to 0.97) | | |
| | | | | | | 66/8003 | Prostate cancer mortality | 0.79 (0.44 to 1.41) | | |
| Key et al., (1999) [12] | Germany | Heidelberg Study | M/F | 46.5 | 9.9 | 31/1083 | Cerebrovascular disease | 1.69 (0.69 to 4.1 | Age, sex, smoking status | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 5) | | |
| | | | | | | 5/1083 | Colorectal cancer mortality | 0.35 (0.06 to 2.11) | | |
| | | | | | | 5/1083 | Breast cancer mortality | 1.09 (0.18 to 6.67) | | |
| | | | | | | 3/1083 | Prostate cancer mortality | 1.67 (0.14 to 19.6) | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Appleby et al., (2002) [13] | U.K. | Oxford Vegetarian Study | M/F | 42.3 | 17.6 | 532/4674 | All-cause mortality | 1.01 (0.89 to 1.14) | Age, sex, smoking status | moderate |
| | | | | | | 214/4674 | Cardiovascular diseases | 0.93 (0.77 to 1.12) | | |
| | | | | | | 109/4674 | IHD | 0.86 (0.67 to 1.12) | | |
| | | | | | | 63/4674 | Cerebrovas | 1.0 | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | cular disease | 8 (0.75 to 1.54) | | |
| | | | | | | 156/4674 | Cancer mortality | 0.89 (0.72 to 1.10) | | |
| | | | | | | 25/4674 | Colorectal cancer mortality | 1.20 (0.68 to 2.13) | | |
| | | | | | | 16/4674 | Lung cancer | 0.82 | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | mortality | (0.44 to 1.56) | | |
| | | | | | | 22/4674 | Breast cancer mortality | 1.02 (0.57 to 1.84) | | |
| | | | | | | 8/4674 | Prostate cancer mortality | 0.50 (0.22 to 1.17) | | |
| Appleby et al., (2002) [13] | U.K. | Health Food Shoppe | M/F | 42.8 | 18.7 | 963/4600 | All-cause mortality | 1.03 (0.9 | Age, sex, smoking status | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | rs Study | | | | | | 5 to 1.13) | | |
| | | | | | | 445/4600 | Cardiovascular diseases | 0.95 (0.84 to 1.07) | | |
| | | | | | | 256/4600 | IHD | 0.85 (0.71 to 1.01) | | |
| | | | | | | 141/4600 | Cerebrovascular disease | 0.99 (0.79 | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | to 1.24) | | |
| | | | | | | 203/4600 | Cancer mortality | 1.12 (0.95 to 1.32) | | |
| | | | | | | 33/4600 | Colorectal cancer mortality | 0.79 (0.51 to 1.22) | | |
| | | | | | | 24/4600 | Lung cancer mortality | 1.05 (0.64 to | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1.72) | | |
| | | | | | | 41/4600 | Breast cancer mortality | 1.73 (1.11 to 2.69) | | |
| | | | | | | 16/4600 | Prostate cancer mortality | 1.24 (0.64 to 2.41) | | |
| C-Claude et al., (2005) [14] | Germany | Heidelberg Study | M/F | 50 | 21 | 322/1225 | All-cause mortality | 1.10 (0.89 to 1.3 | Age, gender, smoking, level of activity, alcohol | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 6) | consumption, education level, BMI. | |
| | | | | | | 145/1225 | Cardiovascular diseases | 0.83 (0.62 to 1.12) | | |
| | | | | | | 41/1225 | IHD | 0.70 (0.41 to 1.18) | | |
| | | | | | | 76/1225 | Cancer mortality | 1.04 (0.86 to 1.34) | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Key et al., (2009) [15] | U.K. | EPIC Oxford Study | M/F | 37 | 17 | 385/16081 | All-cause mortality | 1.05 (0.93 to 1.19) | Age, sex, smoking status, alcohol consumption | low |
| | | | | | | 118/16081 | Cardiovascular diseases | 0.97 (0.78 to 1.21) | | |
| | | | | | | 46/16081 | Cerebrovascular disease | 1.10 (0.77 to 1.58) | | |
| Cade et | U.K. | United | F | 49 | 9 | 130/649 | Breast | 0.8 | Age, | low |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| al., (2010) [16] | | Kingdom Women's Cohort Study | | | | 1 | cancer incidence | 8 (0.69 to 1.11) | energy intake, menopausal status, calorie adjusted fat, BMI, physical activity, OCP use, HRT use, smoking status, parity, age at menarche, ethanol, educational level, total days breast feeding, | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | socioeconomic class | |
| Tantamango-Bartley et al., (2012) [17] | U.S. | Adventist Health Study - 2 | M/F | 57.5 | 4.1 | 878/19735 | Cancer incidence | 0.95 (0.86 to 1.04) | Race, family history of cancer, BMI, education, smoking, alcohol, age at menarche, pregnancies, OCP use, breastfeeding, menopause status, HRT. | moderate |
| Crowe et al., | U.S. | EPIC Oxford | M/F | 40.1 | 11.6 | NS/15120 | IHD | 0.72 | Age, smoking | low |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (2013) [18] | | study | | | | | | (0.61 to 0.85) | status, alcohol, physical activity, educational level, Townsend Deprivation Index, OCP use or HRT use for menopause in woman, BMI | |
| Orlich et al., (2013) [19] | U.S. | Adventist Health Study - 2 | M/F | 57.5 | 5.9 | 815/21177 | All-cause mortality | 0.91 (0.82 to 1.0 | Age, race, smoking status, exercise, personal income, | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0) | educationa l level, marital status, alcohol, region, sleep | |
| | | | | | | NS/21177 | Cardiovascular diseases | 0.90 (0.76 to 1.06) | | |
| | | | | | | NS/21177 | IHD | 0.82 (0.62 to 1.06) | | |
| | | | | | | NS /21177 | Cancer mortality | 0.90 (0.75 to 1.09) | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Key et al., (2014) [20] | U.K. | Oxford Vegetarian Study + EPIC Oxford Study | M/F | 40 | 14.9 | 1098/18298 | Cancer incidence | 0.90 (0.84 to 0.97) | BMI, smoking status, alcohol consumption, physical activity level, for the women only-cancers, parity, OCP | low |
| | | | | | | 325/18298 | Breast cancer incidence | 0.96 (0.84 to 1.10) | | |
| Orlich et al., (2015) [21] | U.S. | Adventist Health Study - 2 | M/F | 58.3 | 7.3 | 147/22424 | Colorectal cancer mortality | 0.83 (0.66 to 1.05) | Age, race, sex, BMI, educational level, alcohol use, moderate | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | or vigorous exercise, HRT, history of peptic ulcer, family history of colorectal cancer, dietary energy, history of inflammatory bowel disease, treatment for diabetes mellitus within the | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | past year, used aspirin at least weekly at least 2 of the past 5 years, used statins at least 2 of the past 5 years, supplemental calcium use, supplemental vitamin D, fiber intake, prior colonoscopy or | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | flexible sigmoidoscopy | |

IHD = Ischemic heart disease; BMI = Body Mass Index; OCP = oral contraceptive pills; HRT = hormone replacement therapy; NS = not specified.



 

**Table 5. Characteristics of prospective cohort studies evaluating vegan diet and different clinical outcomes**

| Author, y | Country | Cohort | Sex | Age, y | F-up, y | n/N | Outcomes | RR (95% IC) | Adjustment | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Key et al., (1999) [12] | U.S. | AMS + AHS-1 + HEIDELB + OXF + HFSS | M/F | 52.5 | 10.6 | 68/753 | All-cause mortality | 1.00 (0.70 to 1.44) | Age, sex, smoking status | moderate |
| Tantamango-Bartley et al., (2012) [17] | U.S. | Adventist Health Study - 2 | M/F | 57.5 | 4.1 | 190/4922 | Cancer incidence | 0.86 (0.73 to 1.00) | Race, family history of cancer, BMI, education, smoking, alcohol, age at | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | menarche, pregnancies, breastfeeding, OCP use, menopause status, HRT. | |
| Orlich et al., (2013) [19] | U.S. | Adventist Health Study - 2 | M/F | 57.5 | 5.9 | 197/5548 | All-cause mortality | 0.85 (0.73 to 1.01) | Age, sex, race, smoking, exercise, personal income, educational level, marital status, alcohol, region, sleep, | moderate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | menopause, hormone therapy. | |
| Key et al., (2014) [20] | U.K. | Oxford Vegetarian Study + EPIC Oxford Study | M/F | 37.8 | 14.9 | 105/22046 | Cancer incidence | 0.82 (0.68 to 1.00) | BMI, smoking status, OCP, alcohol consumption, parity, physical activity level, for the women only-cancers. | low |

BMI = Body Mass Index; OCP = oral contraceptive pills; NS = not specified.

AHS-1 = Adventist Health Study-1; AMS = Adventist Mortality Study; OXF = Oxford Vegetarian Study; HFSS = Health Food Shoppers Study; EPIC = EPIC Oxford Study.

Table 6. Subgroup analyses

| | n | All-cause mortality | n | Ischemic heart disease | n | Breast cancer mortality |
|---|---|---|---|---|---|---|
| Cohort | | | | | | |
| Adventists | 3 | 0.84 (0.78 to 0.90) | 3 | 0.70 (0.60 to 0.82) | 2 | 0.57 (0.34 to 0.95) |
| Non-Adventists | 4 | 1.04 (0.98 to 1.10) | 4 | 0.79 (0.71 to 0.88) | 3 | 1.40 (0.98 to 2.01) |
| Duration of follow-up | | | | | | |
| < 14 years | 3 | 0.84 (0.78 to 0.90) | 4 | 0.84 (0.73 to 0.96) | 3 | 0.59 (0.36 to 0.98) |
| ≥ 14 years | 4 | 1.04 (0.98 to 1.10) | 3 | 0.70 (0.63 to 0.78) | 2 | 1.38 (0.82 to 2.30) |
| Country | | | | | | |
| U.S. | 3 | 0.84 (0.78 to 0.90) | 4 | 0.84 (0.73 to 0.96) | 2 | 0.57 (0.34 to 0.95) |
| Non-U.S. | 4 | 1.04 (0.98 to 1.10) | 3 | 0.70 (0.63 to 0.78) | 3 | 1.40 (0.98 to 2.01) |
| Sample size | | | | | | |
| < 9,500 subjects | 4 | 0.97 (0.83 to 1.13) | 4 | 0.75 (0.62 to 0.92) | 4 | 1.02 (0.56 to 1.86) |
| ≥ 9,500 subjects | 3 | 0.92 (0.81 to | 3 | 0.74 (0.67 to 0.83) | 1 | 0.65 (0.28 to |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 1.05) | | | | 1.51) |
| Study quality | | | | | | |
| Medium (4-6 points, NOS) | 6 | 0.93 (0.84 to 1.03) | 6 | 0.74 (0.68 to 0.81) | 5 | 0.94 (0.56 to 1.58) |
| High (7-9 points, NOS) | 1 | 1.05 (0.93 to 1.19) | 1 | 0.72 (0.61 to 0.85) | 0 | - |

NOS = Newcastle-Ottawa Scale



 

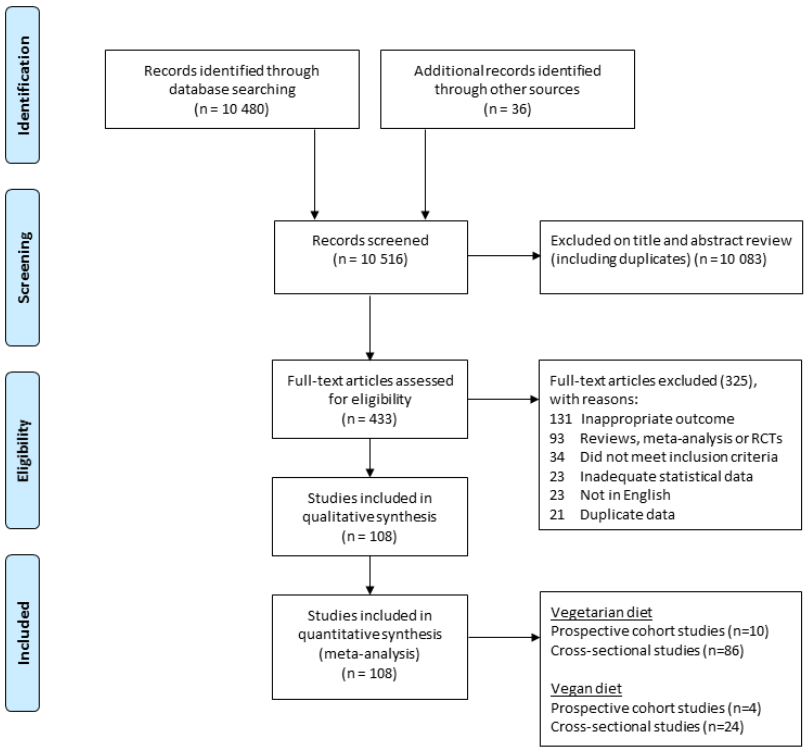


**Figure 1.** PRISMA flow diagram for search strategy

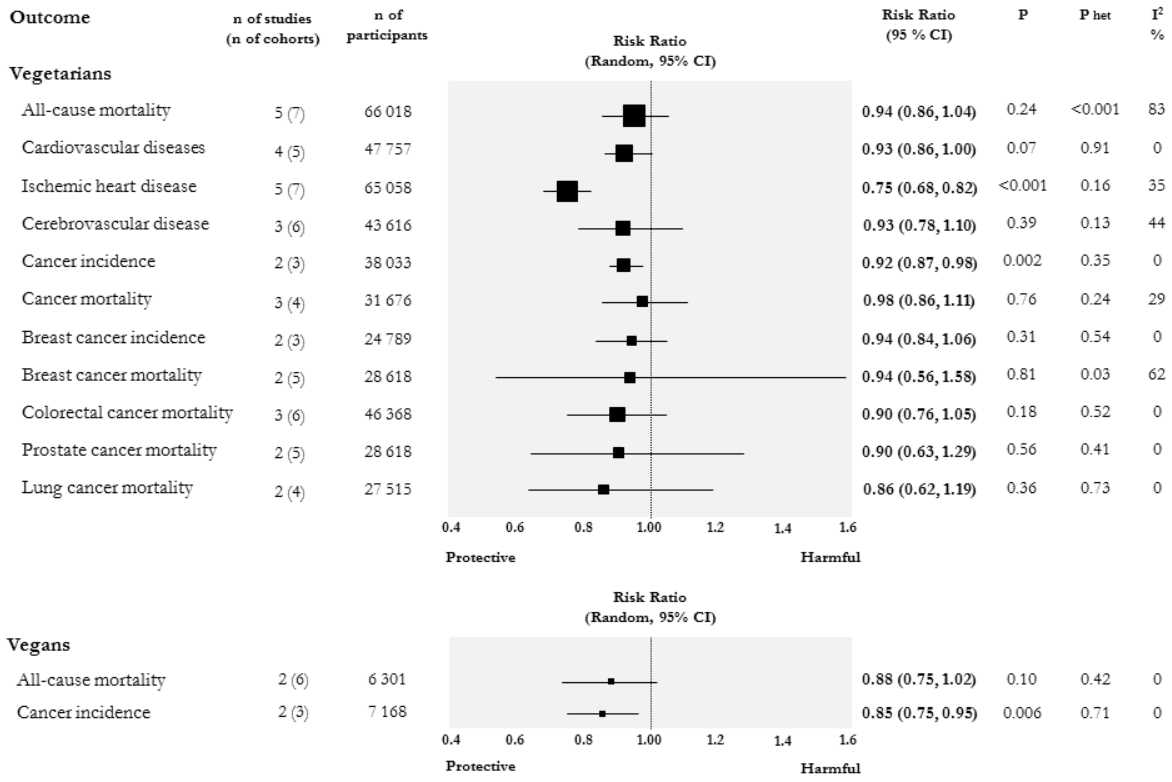


**Figure 2.** Forest plot summary of all-cause mortality, incidence and mortality from cardio-cerebrovascular diseases, total cancer and specific type of cancer. P value is for Z test of no overall association between exposure and outcome; P het is for test of no differences in association measure among studies; $I^2$ estimates from heterogeneity rather than sampling error.

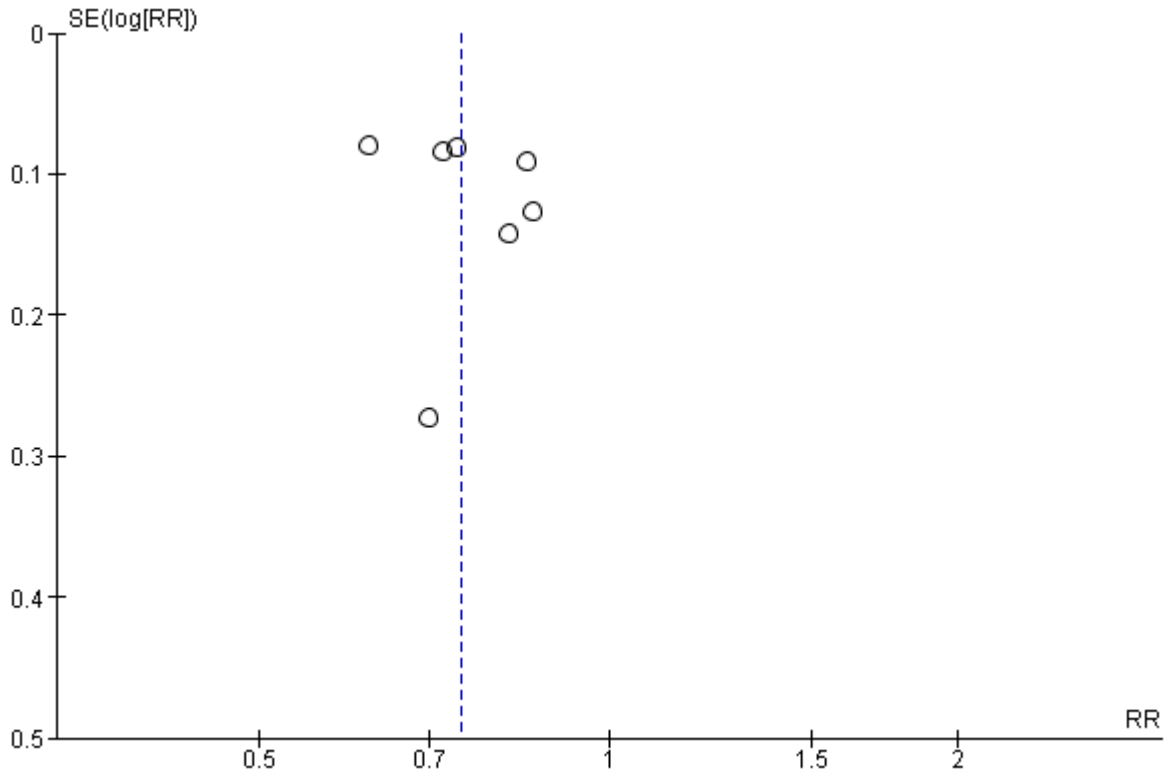


**Figure 3**. Funnel plot for studies investigating the incidence and/or mortality of ischemic heart disease in vegetarians.