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

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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.

KEYWORDS

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 (Leitzmann, 2014). The reasons for adoption of this dietary profile are different, ranging from ethical motivations, religious beliefs, environmental and cultural issues, to health-related aspects (Craig and Mangels, 2009; Leitzmann, 2014). 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 (Fraser, 1999, 2009). 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 (Kwok et al., 2014). 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 (Craig, 2009; Le and Sabaté, 2014). 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 (Whittemore and Knafelz, 2005). For this study,

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

PICOTS format	Description
Population	Presumably healthy subjects ≥ 18 years old
Intervention	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
Comparisons	Omnivore diet, defined as a diet consuming all types of foods including meat and meat-products, poultry, seafood and flesh from any animal
Outcome	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)
Time	Not applicable
Setting	Institutional and community setting

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 (Moher et al., 2009) 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) (Higgins and Green, xxxx).

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 ($< 9,500$; $\geq 9,500$), 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 to 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) (Greenhouse and Iyengar, 2009). 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.

Tables 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 nonsignificant 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 (Key et al., 2009, Cade et al., 2010, Crowe et al., 2013, Key et al., 2014) 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 5 studies (Key et al., 1999, 2009; Appleby et al., 2002; Chang-Claude et al., 2005; Orlich et al., 2013) including 66,018 vegetarians and 8,216 deaths by obtaining a nonsignificant ($P = 0.24$) 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), 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

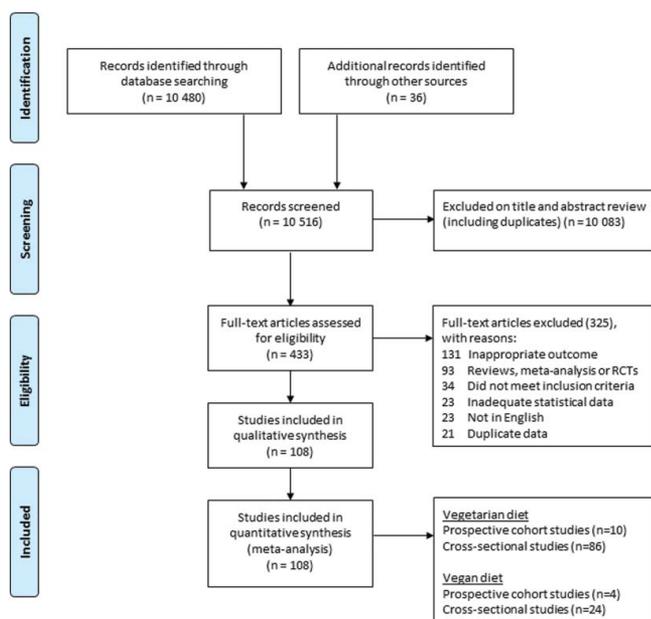


Figure 1. PRISMA flow diagram for search strategy.

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.

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 nonsignificant heterogeneity ($I^2 = 35\%$; $P = 0.16$), while nonsignificant ($P = 0.39$) 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 nonsignificant 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, nonsignificant 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 to 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 nonvegetarians and nonvegans. 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

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 (year)	Country	Cohort	Sex	Age (year)	F-up, y	n/N	Outcome	RR (95% IC)	Adjustment	Risk of bias
Key et al. (1999)	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
							IHD	0.74 (0.63 to 0.88)		
							Cerebrovascular disease	0.65 (0.48 to 0.87)		
							Colorectal cancer mortality	1.37 (0.73 to 2.56)		
							Lung cancer mortality	0.59 (0.10 to 3.28)		
							Breast cancer mortality	0.65 (0.28 to 1.52)		
Key et al. (1999)	U.S.	Adventist Health Study-1	M/F	52.5	11.1	3564/8003	Prostate cancer mortality	1.41 (0.49 to 4.04)	Age, sex, smoking status	Moderate
							All-cause mortality	0.80 (0.74 to 0.87)		
							IHD	0.62 (0.53 to 0.73)		
							Cerebrovascular disease	0.93 (0.73 to 1.19)		
							Colorectal cancer mortality	1.01 (0.66 to 1.56)		
							Lung cancer mortality	0.69 (0.37 to 1.27)		
Key et al. (1999)	Germany	Heidelberg Study	M/F	46.5	9.9	66/8003	Breast cancer mortality	0.52 (0.27 to 0.97)	Age, sex, smoking status	Moderate
							Prostate cancer mortality	0.79 (0.44 to 1.41)		
							Cerebrovascular disease	1.69 (0.69 to 4.15)		
							Colorectal cancer mortality	0.35 (0.06 to 2.11)		
							Breast cancer mortality	1.09 (0.18 to 6.67)		
							Prostate cancer mortality	1.67 (0.14 to 19.6)		
Appleby et al. (2002)	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
							Cardiovascular diseases	0.93 (0.77 to 1.12)		
							IHD	0.86 (0.67 to 1.12)		
							Cerebrovascular disease	1.08 (0.75 to 1.54)		
							Cancer mortality	0.89 (0.72 to 1.10)		
							Colorectal cancer mortality	1.20 (0.68 to 2.13)		
Appleby et al. (2002)	U.K.	Health Food Shoppers Study	M/F	42.8	18.7	963/4600	Lung cancer mortality	0.82 (0.44 to 1.56)	Age, sex, smoking status	Moderate
							Breast cancer mortality	1.02 (0.57 to 1.84)		
							Prostate cancer mortality	0.50 (0.22 to 1.17)		
							All-cause mortality	1.03 (0.95 to 1.13)		
							Cardiovascular diseases	0.95 (0.84 to 1.07)		
							IHD	0.85 (0.71 to 1.01)		
Chang-Claude et al. (2005)	Germany	Heidelberg Study	M/F	50	21	322/1225	Cerebrovascular disease	0.99 (0.79 to 1.24)	Age, gender, smoking, level of activity, alcohol consumption, education level, BMI.	Moderate
							Cancer mortality	1.12 (0.95 to 1.32)		
							Colorectal cancer mortality	0.79 (0.51 to 1.22)		
							Lung cancer mortality	1.05 (0.64 to 1.72)		
							Breast cancer mortality	1.73 (1.11 to 2.69)		
							Prostate cancer mortality	1.24 (0.64 to 2.41)		
Key et al. (2009)	U.K.	EPIC Oxford Study	M/F	37	17	385/16081	All-cause mortality	1.10 (0.89 to 1.36)	Age, gender, smoking, level of activity, alcohol consumption, education level, BMI.	Moderate
							Cardiovascular diseases	0.83 (0.62 to 1.12)		
							IHD	0.70 (0.41 to 1.18)		
							Cancer mortality	1.04 (0.86 to 1.34)		
							All-cause mortality	1.05 (0.93 to 1.19)	Age, sex, smoking status, alcohol consumption	Low
							Cardiovascular diseases	0.97 (0.78 to 1.21)		

Cade et al. (2010)	U.K.	United Kingdom Women's Cohort Study	F	49	9	130/6491	Breast cancer incidence	0.88 (0.69 to 1.11)	Age, 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	Low
Tantamango-Bartley et al. (2012)	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. (2013)	U.S.	EPIC Oxford study	M/F	40.1	11.6	NS/15120	IHD	0.72 (0.61 to 0.85)	Age, smoking status, alcohol physical activity, educational level, Townsend Deprivation Index, OCP use or HRT use for menopause in woman, BMI	Low
Orlich et al. (2013)	U.S.	Adventist Health Study - 2	M/F	57.5	5.9	815/21177	All-cause mortality	0.91 (0.82 to 1.00)	Age, race, smoking status, exercise, personal income, educational level, marital status, alcohol, region, sleep	Moderate
Key et al. (2014)	U.K.	Oxford Vegetarian Study + EPIC Oxford Study	M/F	40	14.9	1098/18298	Cardiovascular diseases	0.90 (0.76 to 1.06)	BMI, smoking status, alcohol consumption, physical activity level, for the women only-cancers, parity, OCP	Low
							IHD	0.82 (0.62 to 1.06)		
							Cancer mortality	0.90 (0.75 to 1.09)		
Orlich et al. (2015)	U.S.	Adventist Health Study - 2	M/F	58.3	7.3	325/18298 147/22424	Breast cancer incidence	0.96 (0.84 to 1.10)	Age, race, sex, BMI, educational level, alcohol use, 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	Moderate
							Colorectal cancer mortality	0.83 (0.66 to 1.05)		

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% CI)	Adjustment	Risk of bias
Key et al., (1999)	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)	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 menarche, pregnancies, breastfeeding, OCP use, menopause status, HRT.	Moderate
Orlich et al., (2013)	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, menopause, hormone therapy.	Moderate
Key et al., (2014)	U.K.	Oxford Vegetarian Study + EPIC Oxford Study	M/F	37.8	14.9	105/2246	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.

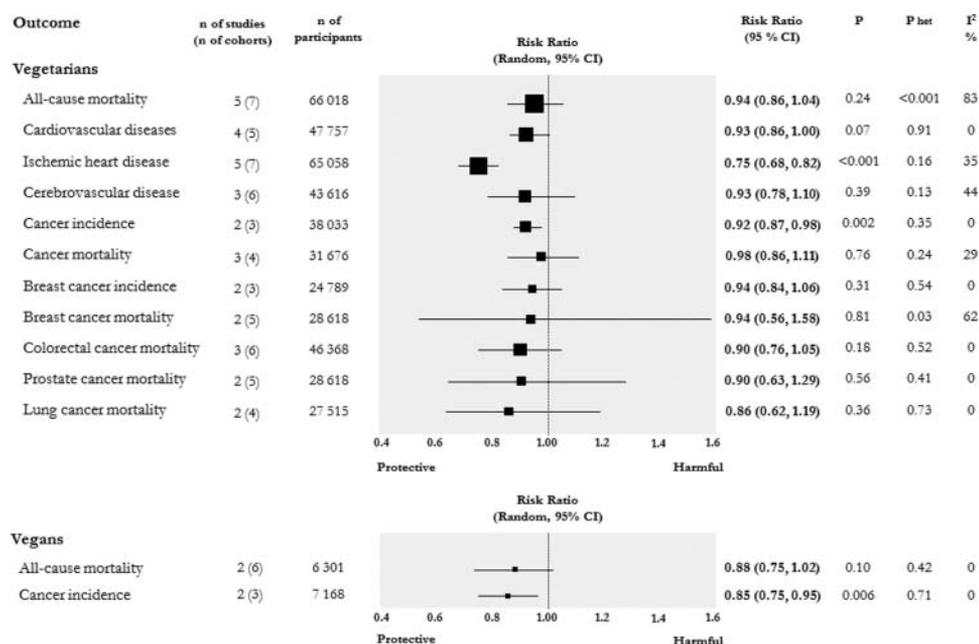


Figure 2. Forest plot summary of all-cause mortality, incidence and mortality from cardio-cerebrovascular diseases, total cancer, and specific type of cancer. *P* value is for Z test of no overall association between exposure and outcome; *P*_{het} is for test of no differences in association measure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

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 (Craig and Mangels, 2009; Leitzmann, 2014). 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 (Key et al., 2014). 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 (Kwok et al., 2014).

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 (Ashen, 2013; Kwok et al., 2014). This 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 nonvegetarians, and body mass index, total cholesterol

Table 6. Subgroup analyses.

	<i>n</i>	All-cause mortality	<i>n</i>	Ischemic heart disease	<i>n</i>	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 1.05)	3	0.74 (0.67 to 0.83)	1	0.65 (0.28 to 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.

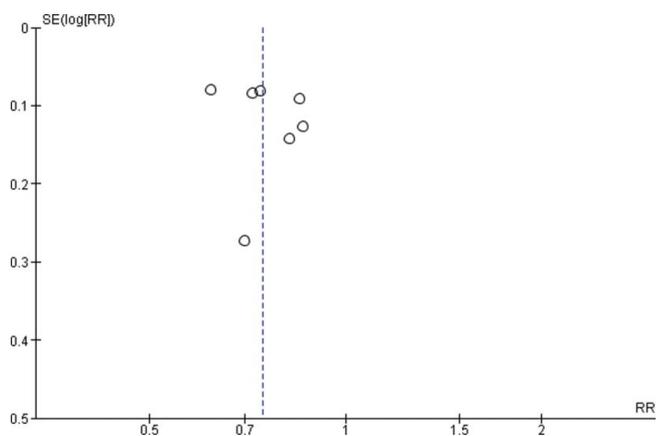


Figure 3. Funnel plot for studies investigating the incidence and/or mortality of ischemic heart disease in vegetarians.

and LDL-cholesterol when vegans were compared to nonvegans. 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 (Ashen, 2013) 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 nonvegetarians. These results, although partly surprising, could be explained by the fact that incidence and mortality are 2 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, (Kwok et al., 2014) 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.

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; and Statistical expertise: F. Sofi, M. Dinu.

Financial disclosure

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Disclosure of interest

All authors declare that there are no conflicts of interest.

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