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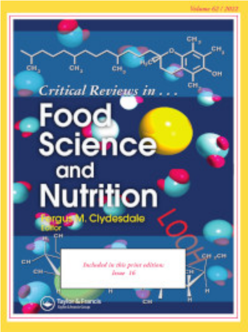

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REVIEW

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Evidence of a vegan diet for health benefits and risks – an umbrella review of meta-analyses of observational and clinical studies

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ABSTRACT
To summarize and evaluate the evidence on the health impact of a vegan diet, we conducted an umbrella review of systematic reviews and meta-analyses. PubMed, Cochrane Library, Web of Science and Epistemonikos were searched up to September 2021. Meta-analyses were recalculated by using a random effects model. The certainty of evidence (CoE) was evaluated by the GRADE approach. For the general healthy population, a vegan diet was effective for reducing body weight [MD (95% CI): −2.52 kg (−3.06, −1.98), n = 8 RCTs; moderate CoE] and was associated with further health benefits (with low CoE), including a lower risk of cancer incidence [SRR (95% CI): 0.84 (0.75, 0.95), n = 2] and a trend for lower risk of all-cause mortality [SRR (95% CI): 0.87 (0.75, 1.01), n = 2], as well as lower ApoB levels [MD (95% CI): −0.19 µmol/L (−0.23, −0.15), n = 7 RCTs). The findings suggested adverse associations for a vegan diet with risk of fractures [SRR (95% CI): 1.46 (1.03, 2.07), n = 3; low CoE]. For persons with diabetes or at high CVD risk, a vegan diet reduced measures of adiposity, total cholesterol, LDL and improved glycemic control (CoE moderate to low). A vegan diet may have the potential for the prevention of cardiometabolic health, but it may also impair bone health. More well-conducted primary studies are warranted.

KEYWORDS
Health; meta-analysis; plant-based; systematic review; umbrella review; vegan diet

Introduction

A transition toward healthy and environmentally sustainable food is among major global challenges. Replacing animal sources, namely red meat and milk, with plant-based sources has the potential to impact on cutting greenhouse gas emissions (Springmann et al. 2018). That is a reason for the growing popularity of diets eliminating or reducing meat, milk, dairy, and eggs, especially in wealthy developed countries. A vegan diet, strictly excluding all kinds of animal-derived foods, has gained popularity and is of immense public health interest (Medawar et al. 2019). Surveys and online polls indicate that the prevalence of veganism has risen worldwide in the last few years (The Vegan Society 2021). According to these sources, 6% of the US population follows a strict plant-based. i.e. vegan diet, compared to up to 4% in Europe and 13% in Asia (The Vegan Society 2021). And though the motivations for following a vegan diet are diverse, including animal welfare, religious aspects, and environmental sustainability, one important reason is health benefits (Norman and Klaus 2020).

With an increasing number of persons reducing or eliminating animal-based sources of food, there is an unmet need for evidence-based guidance on the health effects as well as safety issues and its management at the population level that could be translated into public health as well as primary health care sectors. Emerging scientific interest has yielded several systematic reviews and meta-analyses on this topic in the past decades. Observational studies suggest that a vegan diet might be associated with decreased risk of death, cancer, and other health conditions, such as diabetes (Dinu et al. 2017). In addition, evidence from meta-analyses

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of randomized controlled trials (RCT) pointed to beneficial effects of a vegan diet regarding cardiometabolic parameters, including reduced total cholesterol and LDL-cholesterol, glycemic control, and reductions in body weight and other anthropometric measures among generally healthy individuals or persons with underlying chronic diseases (e.g. diabetes) or at high cardiovascular diseases (CVD) risk (Lopez et al. 2019; Yokoyama, Levin, and Barnard 2017; Huang et al. 2016; Rees et al., 2021). On the other hand, several safety issues have emerged from epidemiological evidence, such as the association of veganism with lower bone density and increased risk of fractures (Rees et al., 2021). Finally, cross-sectional studies on the quality of nutrient intake in vegans and non-vegans showed both beneficial and critical aspects of the nutritional quality in vegans. For example, persons following a vegan diet were observed to have a lower intake of total fat but a higher intake of polyunsaturated fatty acids, dietary fiber, and several micronutrients, including vitamin C and magnesium, compared to omnivores (Clarys et al. 2014; Sobiecki et al. 2016). At the same time, a vegan diet was associated with nutritional deficiencies, especially deficits of vitamin B12, vitamin D, zinc, iron, and iodine as well as a lower protein quality (Clarys et al. 2014; Sobiecki et al. 2016; Elorinne et al. 2016).

To support evidence-based dietary recommendations and guidelines, a systematic and comprehensive overview to summarize and evaluate the existing evidence on a vegan diet and health outcomes is warranted. A recently published umbrella review summarized evidence from systematic reviews and meta-analyses on vegetarian diets (defined as lacto-vegetarians, ovo-vegetarians, lacto-ovo-vegetarians, vegans and Seventh-day Adventists) regarding different health outcomes. This overview indicated that vegetarian diets were associated with beneficial blood lipid values and reduced risk of diabetes, ischemic heart disease, and cancer risk (Oussalah et al. 2020). However, this umbrella review is limited by exploring a combination of vegetarian and vegan diets. Given additional restrictions of a vegan diet compared to vegetarianism, and considering the increased popularity of a strict vegan diet, the evidence needs to be evaluated separately. Moreover, the study did not rate the certainty of evidence (CoE) by using the recommended GRADE approach, that provides a systematic framework for making clinical practice recommendations (Zhang, Akl, and Schunemann 2018).

Therefore, the aim of the current study was to conduct an umbrella review i) to summarize the existing evidence derived from systematic reviews with meta-analyses on a vegan diet regarding health outcomes, nutritional status, and nutrient intakes, ii) to evaluate the CoE of the identified findings, and iii) to identify gaps in knowledge and future research perspectives.

Materials and methods

All analytical steps were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) statement (Page et al. 2021). The umbrella review was a priori registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020173424).

Literature search

The systematic literature search was conducted in PubMed, Web of Science, the Cochrane Library, and Epistemonikos up to September 20th, 2021 without using any filters. The full search strategy can be found in the supplemental material (Table S1). Two researchers independently conducted all steps of the systematic review process. First, titles and abstracts of the retrieved articles were screened for eligibility. Full-texts of relevant studies were checked for inclusion and any disagreements between the two researchers were discussed and resolved by consensus. No restrictions regarding language were applied. The reference lists from the eligible systematic reviews and meta-analyses were checked to identify further relevant studies. To identify studies that were published after the last update, we conducted hand-searches and used the PubMed e-mail alert service.

Eligibility criteria

The detailed selection criteria are shown in Table 1. Briefly, the inclusion criteria for the studies were: (i) investigation of the association between a vegan diet and any health outcome, nutritional status, or nutrient intakes; (ii) systematic reviews including a meta-analysis of observational (e.g. cohort, case-control, cross-sectional) and intervention studies (randomized and non-randomized controlled trials); and (iii) reported effect estimates for the associations [including hazard ratios (HR), relative risks (RR), odds ratios (OR), or mean differences (MD) and mean values] with the 95% confidence interval (95% CIs) or standard deviation (SD). We included meta-analyses based on adults from the general healthy population, children, adolescents, pregnant women, as well as persons with underlying chronic diseases or at high risk (e.g. persons with diabetes, hyperlipidemia, hypertension, or persons at high risk of CVD as previously defined (Rees et al., 2021)). Studies were excluded if: (i) they were primary studies, (ii) no summary estimate was reported (e.g. systematic reviews without meta-analysis or meta-analysis included only one study finding/risk estimate), (iii) they were not systematic, e.g. pooled analyses of cohorts

Table 1. PICOS statement summarizing study rationale and study selection criteria.

Population	Adults from the general population, children, adolescents, pregnant women and patient groups (e.g. with diabetes, hypertension or hyperlipidemia)
Intervention	Vegan diet defined as a plant-based diet avoiding all animal foods such as meat, fish, shellfish, insects, dairy, and eggs
Comparison	Any other diet, mostly omnivore (e.g. diet allowing consumption of all foods of plant or animal origin)
Outcome	Any health outcomes, nutritional status and dietary intake
Study design	Systematic reviews with meta-analysis of observational (prospective, cross-sectional and retrospective) or interventional studies (randomized and non-randomized trials)

with individual data, (iv) or the exposure was not clearly defined as vegan diet (e.g. a mixture of vegetarian and vegan diets). If more than one meta-analysis for one outcome and the same study design was available, the most updated meta-analysis, including the largest number of primary studies and/or number of cases was included.

Data extraction

One researcher extracted the data and a second researcher checked the data for accuracy. The following data were extracted from the meta-analyses and/or if necessary from the primary studies included in these meta-analyses: first author's last name of the meta-analysis with publication year, first author's last name of the included primary studies with publication year, study design, population characteristics, study duration, the definition of a vegan diet, type of comparison, outcome(s), number of studies included, and the number of cases (if applicable), the total sample size of all studies included in the meta-analysis, study effect measures (mean differences with SD or rate ratio with 95% CI), the I^2 statistic as a measure of heterogeneity, the included confounders in the primary studies, and the CoE rated by the GRADE approach if available (Zhang, Akl, and Schunemann 2018).

Risk of bias assessment

The risk of bias was evaluated using the risk of bias in systematic reviews (ROBIS) tool (ROBIS group, 2016). The tool consists of four domains and an overall evaluation. A detailed description of the tool and judgment of the potential risk of bias for each domain can be found in Supplemental Table S2. Two researchers independently assessed the risk of bias of each meta-analysis. Any discrepancies were discussed and resolved by discussion.

Statistical analysis

All meta-analyses were recalculated. The summary risk ratios (SRR) or the mean differences (MDs) with their 95% CIs for a vegan diet compared to a non-vegan diet/control with regard to any identified health outcomes were recalculated using the random effects model by DerSimonian and Laird (DerSimonian and Laird 1986). If an original meta-analysis included other plant-based diets (e.g. lacto-vegetarian diets) together with a vegan diet, we excluded the primary studies on the non-vegan exposure/interventions and calculated a pooled estimate for vegan diets only. In addition, if a published meta-analysis included a study with a definition of a vegan diet that was not per our definition, we excluded this primary study in our recalculations. Heterogeneity was evaluated by calculating I^2. If ≥10 studies were available for one meta-analysis, we investigated publication bias by exploring the funnel plots and by applying the Egger's test (Higgins and Green 2011). A p-value of <0.10 indicated the presence of publication bias. All statistical analyses were performed using Stata (version 15, Stata-Corp, College Station, TX, USA).

Certainty of evidence (CoE)

The CoE was evaluated using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach (Zhang, Akl, and Schunemann 2018). Two reviewers independently rated the CoE. According to the GRADE approach, the process of rating the CoE begins by classifying the design of the included studies. If the included studies are RCTs, the CoE begins as high certainty and if the relevant studies are observational studies, the CoE begins as low certainty. This is followed by the evaluation of eight domains: risk of bias, imprecision, inconsistency, indirectness, publication bias, the magnitude of effects, dose-response relations, and the impact of residual confounding. After evaluating each domain, the overall rating can be categorized into high, moderate, low, or very low. A high CoE means that it is very likely that the true effect lies close to the estimated findings, whereas a very low CoE means that there is very little confidence in the estimated effect/association. Overall using GRADE will strengthen the credibility of potential dietary recommendations (Schwingshackl, Schunemann, and Meerpohl 2021).

Results

After removing duplicates, we identified 398 studies. 121 full texts were checked for eligibility. Finally, 17 published systematic reviews with meta-analyses (Dinu et al. 2017; Lopez et al. 2019; Yokoyama, Levin, and Barnard 2017; Huang et al. 2016; Rees et al., 2021; Iguacel et al. 2019; Lee and Park 2017; Li et al. 2020; Benatar and Stewart 2018; Picasso et al. 2019; Chiavaroli et al. 2018; Craddock et al. 2019; Obersby et al. 2013; Iguacel et al. 2020; Brain et al. 2019; Foster et al. 2013; Viguiliouk et al. 2019), including 79 estimates for a vegan diet and 38 different outcomes were included in the present umbrella review (Figure S1). A list of excluded studies with the reasons for exclusion is shown in Table S3.

Characteristics of the Meta-analyses

Detailed information on the included meta-analyses is provided in Table S4. The identified meta-analyses were conducted among generally healthy individuals and persons with diabetes, hyperlipidemia, or at high CVD risk. No meta-analysis included pregnant, lactating, or pediatric populations. Some primary studies focused on specific religious populations, like Seventh-day Adventists or Buddhist nuns. The published meta-analyses included studies that were conducted in the US, Europe, and Asia. We identified systematic reviews and meta-analyses of observational studies (prospective or cross-sectional studies) and RCTs and non-RCTs. The comparison/control diets were defined as the usual omnivorous diet or other dietary interventions. The confounders adjusted for in the primary studies are shown in Table S5. It became evident that important confounders, such as age, sex, BMI, smoking status, physical activity, and total energy intake were not considered in many of the analyses. The risk of bias was high in 16 reports and low in one (Table S6). Methodological limitations were particularly identified regarding the domains of identification and selection of studies as well as the synthesis of findings. More specifically, the majority of reports were characterized by unclear search terms, inappropriate use of filters, study selection, and data extraction by only one investigator, unclear criteria for study exclusion, or missing risk of bias assessment, and lack of discussion on the risk of bias.

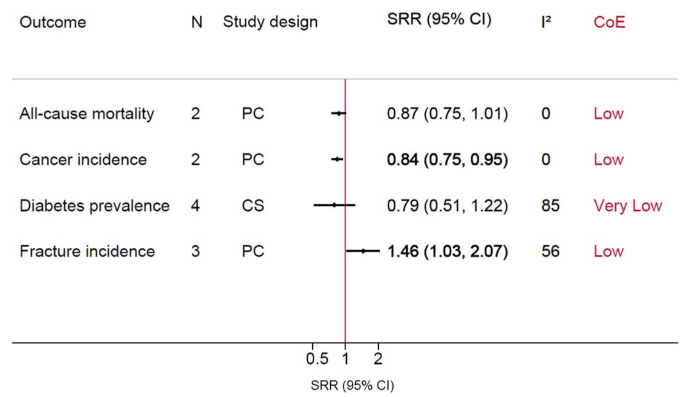

Figure 1. Summary relative risk (SRR) with 95% confidence interval (CI) for a vegan diet compared to an omnivore diet regarding health outcomes.CoE, certainty of evidence; CS, cross-sectional study; N, number; PC, prospective cohort study; SRR, summary risk ratio.

Health outcomes and dietary intake among the general healthy population

We identified systematic reviews and meta-analyses on a vegan diet and risk of all-cause mortality (Dinu et al. 2017), cancer incidence (Dinu et al. 2017), diabetes prevalence (Lee and Park 2017), fractures incidence (Iguacel et al. 2019), weight (Huang et al. 2016; Li et al. 2020), height (Li et al. 2020), BMI (Benatar and Stewart 2018), waist circumference (Benatar and Stewart 2018), systolic and diastolic blood pressure (Lopez et al. 2019), triglycerides (Yokoyama, Levin, and Barnard 2017), total cholesterol (Yokoyama, Levin, and Barnard 2017), LDL-cholesterol (Yokoyama, Levin, and Barnard 2017; Benatar and Stewart 2018), HDL-cholesterol (Yokoyama, Levin, and Barnard 2017; Picasso et al. 2019), Apo B (Chiavaroli et al. 2018), fasting glucose (Yokoyama, Levin, and Barnard 2017), HOMA-IR (Yokoyama, Levin, and Barnard 2017), 10-years CHD risk score (Chiavaroli et al. 2018), CRP (Craddock et al. 2019), bone mass density (lumbar spine, femoral neck, whole-body) (Iguacel et al. 2019), mental disorders (Iguacel et al. 2020), and pain (Brain et al. 2019). The outcome-specified certainty of evidence was mainly very low (Table S7).

Evidence from cohort studies showed an inverse association between a vegan diet and the incidence of cancer (SRR: 0.84; 95% CI: 0.75, 0.95; I^2: 0%; n = 2 studies) and a trend for all-cause mortality (SRR: 0.87; 95% CI: 0.75, 1.01; I^2: 0%; n = 2 studies), both with low CoE (Figure 1). Based on the data from RCTs, a vegan diet was effective in reducing body weight [MD (95% CI): −2.52 kg (−3.06, −1.98); I^2: 3%; n = 8 RCTs; moderate CoE]. There was no clear effect of a vegan diet on SBP and DBP compared to a non-vegan diet. The MD (95% CI) was −1.33 mmHg (−3.50, 0.84) for SBD, and −1.20 mmHg (−3.06, 0.65) for DBP, both rated as low CoE. HDL- and ApoB-levels were reduced by −0.10 mmol/L (95% CI: −0.20, −0.00; I^2:31%; n = 9 RCTs; low CoE) and −0.19 µmol/L (95% CI: −0.23, −0.15; I^2:61%; n = 7 RCTs; low CoE), respectively (Figure 2). There was low CoE for a higher risk of fractures for a vegan diet compared to an omnivore diet (SRR: 1.46; 95% CI: 1.03, 2.07; I^2: 56%; n = 3 studies) (Figure 1).

We identified meta-analyses on dietary intake, including total energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, carbohydrates, protein, zinc intake, zinc serum (Benatar and Stewart 2018; Foster et al. 2013). The CoE was very low for all associations (Figure 3 and Table S7). In addition, we identified one meta-analysis (with very low CoE) that pooled mean values (not mean differences) of vitamin B12 for vegans (172 ± 59 pmol/L) and omnivores (303 ± 72 pmol/L), as well as plasma total homocysteine [vegans: 16.41 ± 4.8 umol/L and omnivores: 11.03 ± 2,89 umol/L) (Obersby et al. 2013).

Health outcomes among persons with underlying diseases or at high CVD risk

We identified meta-analyses on RCTs for the effect of a vegan diet on anthropometric and cardiometabolic markers, including weight (Rees et al., 2021; Viguiliouk et al. 2019), BMI (Rees et al., 2021; Viguiliouk et al. 2019), waist circumference (Picasso et al. 2019), systolic and diastolic blood pressure (Lopez et al. 2019; Rees et al., 2021), triglycerides (Rees et al., 2021; Viguiliouk et al. 2019), total cholesterol (Rees et al., 2021), LDL-cholesterol (Rees et al., 2021; Viguiliouk et al. 2019), HDL-cholesterol (Rees et al., 2021; Viguiliouk et al. 2019), non-HDL-cholesterol (Viguiliouk et al. 2019), fasting glucose (Rees et al., 2021; Viguiliouk et al. 2019), and HbA1c (Rees et al., 2021; Viguiliouk et al. 2019) for persons with diabetes, hyperlipidemia, or at high CVD risk, respectively (Figure 4). The CoE of the findings was mostly moderate or low (Table S7).

For patients with diabetes, a vegan diet was effective in reducing body weight [MD (95% CI): −2.51 kg (−3.37, −1.65); I^2: 0%; n = 4 RCTs; moderate CoE], BMI [MD (95% CI): −0.67 kg/m^2 (- 1.07, −0.28); I^2: 64%; n = 4 RCTs; moderate CoE] and waist circumference [MD (95% CI): −2.32 cm (−3.52, −1.12); I^2: 0%; n = 2 RCTs; low CoE]. For persons with diabetes or at high CVD risk, triglyceride levels were higher for a vegan intervention compared to the control group [MD (95% CI) for person with diabetes: 0.21 mmol/L (0.02, 0.40); I^2: 38%; n = 5 RCTs; moderate CoE, and MD

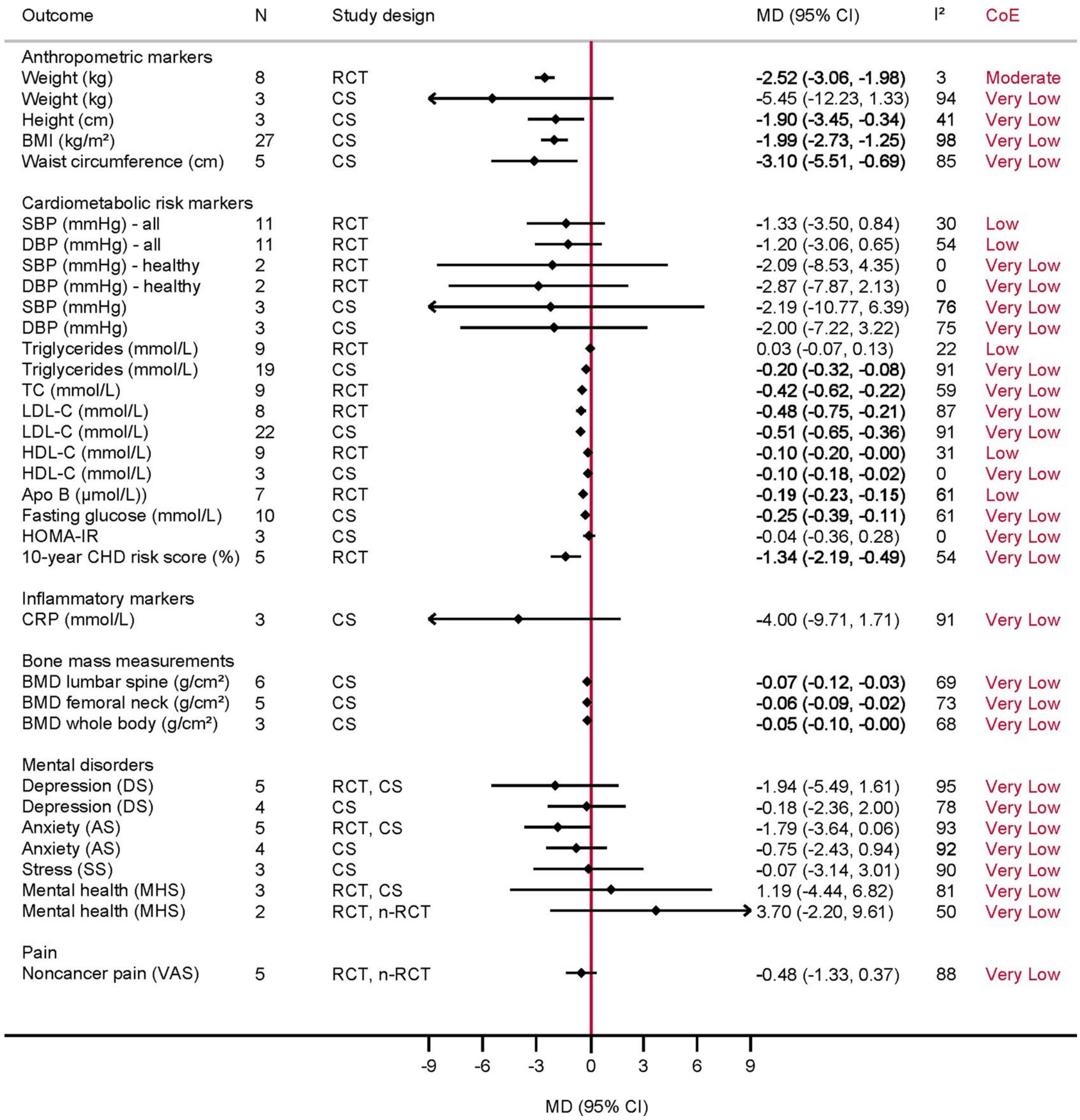

Figure 2. Mean differences with 95% CIs for a vegan diet compared to an omnivore diet regarding health outcomes among the general healthy population.AS, anxiety score; BMD, bone mineral density; BMI, body mass index; CHD, coronary heart disease; CoE, certainty of evidence; CRP, C-reactive protein; CS, cross-sectional study; DBP, diastolic blood pressure; DS, depression subscale; HDL-C, high-density-lipoprotein-cholesterin; LDL-C, low-density-lipoprotein-cholesterin; MHS, mental health scale; RCT, randomized controlled trial; SBP, systolic blood pressure; SS, stress scale; TC, total cholesterol.

(95% CI) for persons at high CVD risk: 0.11 mmol/L (0.01, 0.21); I^2: 0%; n = 4 RCTs; moderate CoE]. Regarding the cholesterol levels, there was moderate CoE that persons at high CVD risk had lower total cholesterol [MD (95% CI): −0.24 mmol/L (−0.36, −0.12); I^2: 0%; n = 4 RCTs], LDL-cholesterol [MD (95% CI): −0.22 mmol/L (−0.32, −0.12); I^2: 0%; n = 4 RCTs] and HDL-cholesterol levels [MD (95% CI): −0.08 mmol/L (−0.11, −0.04); I^2: 0%; n = 4 RCTs] after an intervention with a vegan diet. In patients with diabetes, the intervention was effective in improving glycemic control [MD for HbA1c (95% CI): −0.27% (−0.50, −0.04); I^2: 44%; n = 5 RCTs; moderate CoE].

Publication bias

Meta-analyses based on ≥10 studies, did not indicate publication bias or small study effects (Figure S2).

Discussion

We summarized findings from 17 systematic reviews and meta-analyses of observational and interventional studies, including 79 associations on a vegan diet and 38 different outcomes, including all-cause mortality, cancer incidence, diabetes prevalence, fracture incidence, anthropometric measures (weight, height, BMI, waist circumference), cardiometabolic biomarkers (blood pressure, blood lipids, glycemia) inflammatory biomarkers (CRP), bone health, mental health, pain, and dietary intake. More than half of these findings were rated as very low CoE. For the general healthy population, there was moderate CoE that a vegan diet was associated with weight loss. In addition, there was indication for some further health benefits (low CoE), including a lower relative risk of cancer incidence and a trend to a lower relative risk of all-cause mortality, as well as a reduction in Apo B. On the other hand, the present findings

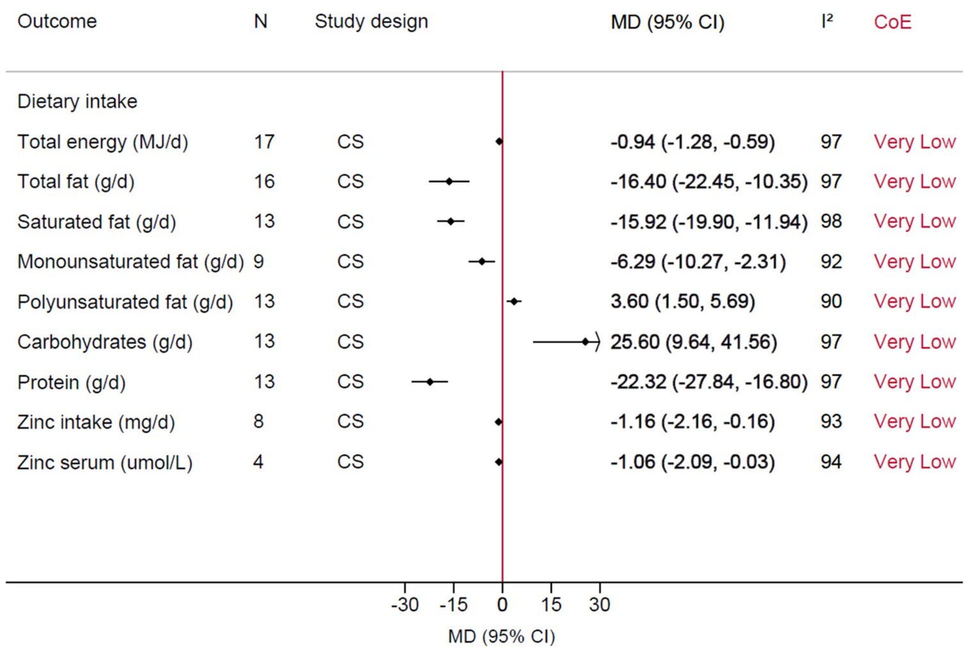

Figure 3. Mean differences with 95% CIs for a vegan diet compared to an omnivore diet regarding nutrient intake among the general healthy population.

suggest adverse health effects of a vegan diet, including an increased risk of fractures and decreased HDL-cholesterol level, with low CoE. There was moderate CoE that a vegan diet might improve some (reduction of body weight, BMI, waist circumference, LDL-cholesterol and HbA1c) but not all (TG, HDL-cholesterol) cardiometabolic health indices, especially in persons with diabetes or at high CVD risk.

Health outcomes and dietary intake among the general healthy population

A vegan diet was related to a lower risk of cancer incidence and tends to be associated with lower all-cause mortality. However, the findings have to be interpreted with caution. The meta-analyses were based on only few studies (2 = primary studies) and the CoE was low. The meta-analysis on diabetes prevalence was rated as very low CoE, included only cross-sectional studies rather than prospective studies and the findings were imprecisely estimated. Interestingly, we did not identify any meta-analysis on risk of CVD, specific cancer types or neurodegenerative diseases (e.g. dementia). The only systematic review (without a meta-analysis) recently published summarized findings on a vegan diet and CVD. The authors identified three studies investigating a vegan compared to an omnivore diet on the risk of future cardiovascular events (total CVD, coronary heart disease, acute myocardial infarction, total stroke, hemorrhagic stroke, and ischemic stroke), and concluded that none of the studies showed clear differences on risks of any outcome among vegans (Kaiser et al. 2021). However, more research, specifically on a vegan diet and the incidence of chronic diseases is needed.

The major risk factor for both cancer and CVD is obesity. As it reaches nowadays pandemic incidence, preventive measures and treatment strategies are urgently needed (Dai et al. 2020). We found that persons on a vegan diet have lower BMI and that a vegan diet was effective in the reduction of body weight in interventional studies when compared to a control diet. This was true for both healthy, diabetes and at-risk populations.

One of the most critically discussed safety concern of a vegan diet is bone health. Indeed, we found that vegans had a higher risk of fractures when compared to omnivores. The findings on a vegan diet regarding bone mineral density were very uncertain. A possible explanation for an adverse effect could be a lower intake of protein, vitamin D, B12, and calcium, which are potentially limited in vegan dietary patterns (Bradbury, Tong, and Key 2017; Tong et al. 2021; Bakaloudi et al. 2021). These nutrients are important for osteoblast proliferation and thus, for the prevention of osteoporosis or osteomalacia (Cashman 2007). However, potential adverse effects need to be clarified in future investigations by considering the influence of potential confounders (e.g. sex, age, BMI), that were mostly not accounted for in the existing meta-analyses, or the primary studies, respectively. In this context, the recent findings from the prospective EPIC-Oxford study showed that vegans had higher risks of total, hip, leg, and other main sites (vertebral, rib and clavicle combined) fractures compared to omnivores and the differences were only partly due to lower BMI (Tong et al. 2020). Of note, the fractures found were not the ones traditionally associated with osteoporosis. There were only a few cases of vertebral fractures, the major osteoporotic fractures, that limit the interpretation of this outcome. Nevertheless, given the increasing number of people following vegan dietary patterns, including families with children who are raised to be vegan since infancy, questions regarding bone health among vegans should become a research priority. Importantly, in the last years, the market for vegan products has grown and many products for vegans are enriched or fortified with potentially critical nutrients such as calcium (Alcorta et al.

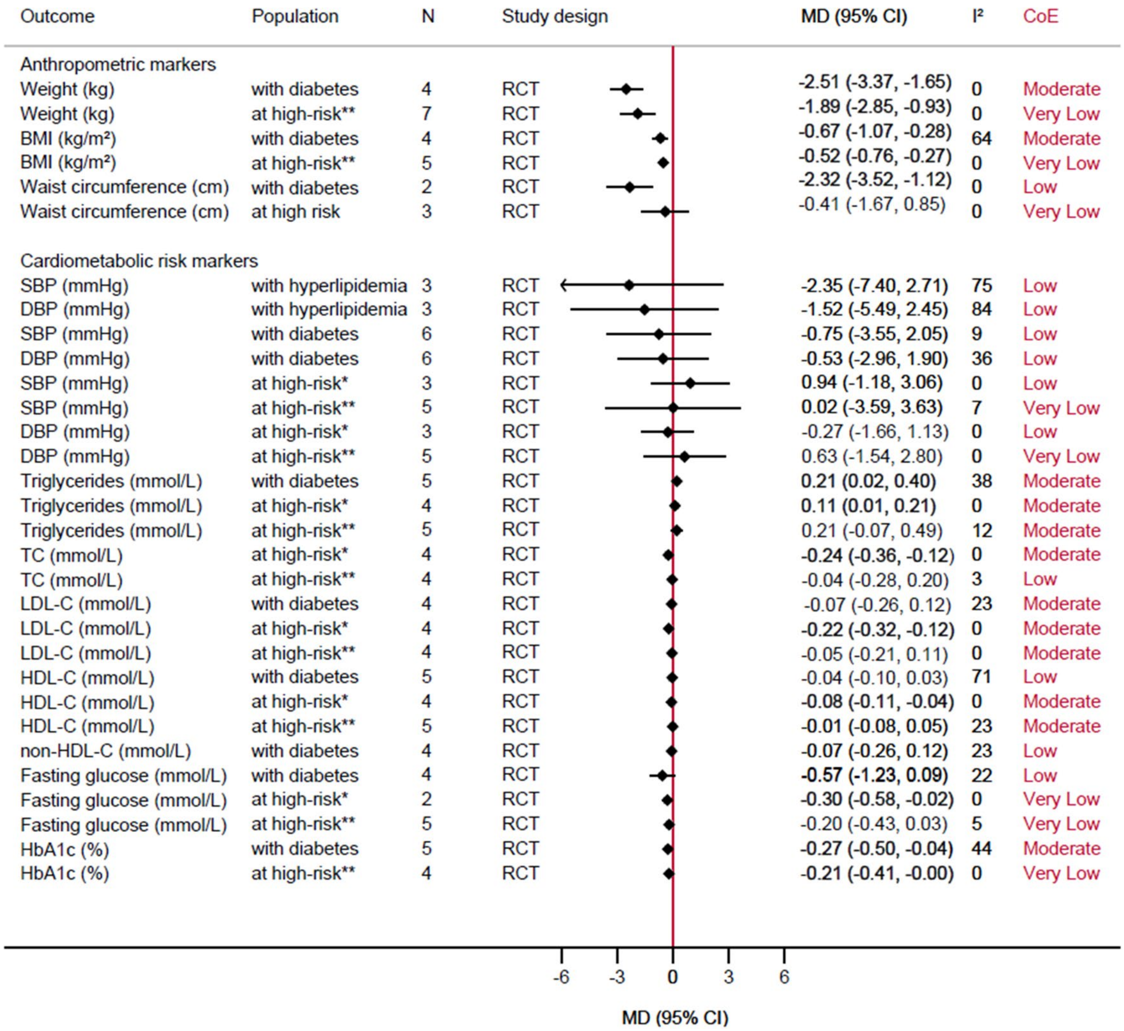

Figure 4. Mean differences with 95% CIs for a vegan diet compared to no/minimal intervention or any other dietary intervention regarding health outcomes among persons with underlying diseases or high-risk populations.* compared to control (no intervention/minimal intervention)** compared to any other dietary interventionBMI, body mass index; CoV, certainty of evidence; DBP, diastolic blood pressure; HDL-C, high-density-lipoprotein-cholesterin; LDL-C, low-density-lipoprotein-cholesterin; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol.

2021). It remains to be verified whether differences in the bone health will be detected also in studies among younger generation of vegans that may have improved nutrient intakes compared to the populations included in the meta-analyses used for the present review.

Health outcomes among persons with underlying diseases or at high CVD risk

For persons with diabetes or at high CVD risk, we exclusively identified meta-analyses of RCTs investigating cardiometabolic risk markers. In general, the confidence in the findings was stronger compared to the observational findings of the general healthy population. Especially for patients with diabetes, a vegan diet was effective in reducing body weight, waist circumference, LDL-cholesterol, fasting glucose, and HbA1c, but also decreased HDL-cholesterol. Some of the findings pointed to the direction, that a vegan diet has the stronger influence on the cardiometabolic markers when compared to a control diet, but the effectiveness was reduced when a vegan diet was compared to any other "healthy" dietary intervention (e.g. a low-fat diet or a diet, suggested by the American Diabetes Association (ADA)). Thus, to elucidate the effectiveness of a vegan diet, future RCTs comparing vegan diets to other recommended "healthy" diets would be of particular interest, especially if conducted under isocaloric conditions. One interesting finding was an increase in triglycerides after receiving a vegan diet. A vegan diet, that is restricted in the intake of fat and increased in carbohydrates, might influence the blood lipid metabolism and thus, the secretion of triglycerides to the blood (Schwingshackl and Hoffmann 2013). Beyond our findings, a few but very heterogeneous studies, investigated the potential of a vegan diet regarding renal markers in patients with diabetes but did not show a clear effect (Pollakova et al. 2021). In addition, one single RCT, reported improvements in measures of neuropathy and related pain in patients with diabetes (Bunner et al. 2015). More studies on the effect of a vegan diet on patient-relevant outcomes are needed.

Mechanisms

There have been many hypotheses explaining the cardiometabolic effects of vegan diets both biologically plausible and confounding. A possible explanation for the beneficial health effects could be a generally more health conscious lifestyle of persons following a vegan diet, including higher levels of physical activity and a diet with lower intake of total energy and energy-dense products. We can provide only limited and very uncertain explanations based on our results. We observed that vegans had a lower intake of energy, total fat and a higher intake of polyunsaturated fatty acids. A lower intake of proteins was also found. It has been previously shown that high intake of plant-based products, including whole-grain products, vegetables, and legumes, containing fiber, vitamins, minerals, and antioxidants, might lead to improvement of LDL-cholesterol, inflammatory markers, insulin sensitivity and improved glycemic outcomes (Marshall et al. 2020; Schwingshackl et al. 2018). On the other hand, exclusion of meat and meat products from the diet, might also result in beneficial health effects. Previous umbrella reviews and meta-analyses have shown that a higher meat intake was associated with an increased risk of premature death, some types of cancer (e.g. colorectal cancer), CVD, and type 2 diabetes (Papadimitriou et al. 2021; Wang et al. 2016; Neuenschwander et al. 2019). Red and processed meat is high in SFAs, especially stearic and palmitic acids that have the potential to increase cardiovascular risk (Vissers et al. 2019). In addition, red and processed meat contains naturally occurring and added chemicals such as heme iron, sodium, nitrates, nitrites and its metabolic compounds (e.g. nitric oxide and N-nitroso compounds), as well as components, derived by processing and storage (e.g. advanced glycation end products). These compounds are related to oxidative stress and chronic low-grade inflammation, and thus, might be linked to chronic disease onset (Misra et al. 2018; Etemadi et al. 2017; Huang, Huang, and Dong 2021).

Strengths and limitations

This is the first umbrella review summarizing and evaluating the certainty of evidence on a vegan diet and multiple health outcomes, nutritional status, and nutrient intake. We followed state-of-art procedures (pre-registered protocol, reporting guidelines) and applied validated tools (ROBIS and GRADE). In addition, we recalculated the meta-analyses because in several cases, the data were only provided for a vegetarian diet and vegan diet combined, and no separate findings were reported for a vegan diet alone.

However, our umbrella review also has limitations, mostly related to the included meta-analyses of primary studies. First, some of the meta-analyses, especially those on clinical endpoints, are based on only a few primary studies due to the lack of long-term cohort studies with a sufficient number of vegan participants. Second, in the meta-analyses of observational studies, some primary studies included specific populations, like Buddhist nuns or Seventh-day Adventists, and the generalizability of these studies is questionable. Third, the definitions of a vegan diet used in the studies were inconsistent. While some studies relied on very strict definitions, excluding all food of animal origin, other studies tolerated some level of animal food intake (e.g., milk or eggs less than once per week). In addition, dietary behavior was only assessed once and no information on changes was available. Fourth, some meta-analyses were based on cross-sectional studies (e.g., height, CRP, bone mass measurements), and thus, the findings are only descriptive and do not provide information about the direction of the association. Fifth, for the meta-analyses of the RCTs, the control groups were heterogeneous (e.g., no intervention, other dietary intervention), which was not always considered in the meta-analyses. Sixth, the risk of bias regarding methodological aspects of the systematic reviews and meta-analyses was high for the majority of the reports. A limitation of the ROBIS tool is the categorization only into high or low risk of bias. Nevertheless, we identified important shortcomings, including incomplete or unclear search terms, the applications of (not-recommended) filters, selection of studies and extraction of data by only one investigator, or missing risk of bias assessment and lacking discussion of the risk of bias. There are also limitations directly related to our umbrella review: first, we only included systematic reviews and meta-analysis and thus, more recent primary studies (not included in the published meta-analyses) were not considered in our evidence synthesis. Second, we did not explore differences in subgroups in detail. For example, we did not explore differences by sex, geographic location, or adjustment factors, in part because of limited data availability. However, we recalculated the meta-analyses and differentiated them by study design. Third, in some cases, multiple reports were available for a similar topic. We chose the meta-analysis including the largest number of primary studies, independently of the methodological quality of this report.

Implications

With the rapid increase in the number of people adopting a vegan diet, there is a need for evidence-based guidance on the health effects of this dietary approach. Our umbrella review reports on the currently existing evidence on the potential beneficial and adverse influence on different health outcomes. Following a vegan diet might have potential regarding weight reduction, improved cardiometabolic intermediates, and possibly chronic disease prevention. However, there may be adverse effects regarding bone health. None of the associations/effects identified by us was rated as high certainty of evidence and only a few as moderate and the majority as low or very low certainty of evidence. Thus, it is conceivable that future studies might change these findings. To strengthen the evidence, more well-conducted primary prospective studies on this topic are needed. Particular consideration should be given to clear definitions of a vegan diet (exclusion of any animal-based products), the comparison group (in observational studies: comparison with omnivores and/or vegetarians; and in RCTs: no intervention or intervention with another dietary approach) and the population. For the latter aspect, it is important to differentiate between the general population, patient groups, and groups in a specific period of the life course i.e. children, adolescents, or pregnant or breastfeeding women. These long-term studies should not only focus on intermediate factors and nutritional status, but also the risk and progression of chronic diseases, including diabetes, CVD, neurodegenerative diseases, and specific cancer types. Finally, given that a vegan diet is often associated with specific socio-economic and lifestyle characteristics, confounders must be accounted for in more detail in observational studies.

The implications of a vegan diet for the environment were beyond the scope of this review. However, a vegan diet has a favorable footprint regarding many ecological indicators, and it is compatible with the 'Planetary Health Diet' recommended by the EAT-Lancet commission to tackle the environmental crisis (Willett et al. 2019). Thus, dietary guidelines for vegans addressing potential adverse health effects by optimized food choices and targeted supplementation of critical nutrients while taking advantage of environmental and individual benefits of a vegan diet are needed.

Conclusions

The existing evidence indicates that a vegan diet might be beneficial for weight reduction among the general healthy population. There is weak evidence that a vegan diet might be associated with a lower risk of mortality and cancer incidence, but a higher risk of fractures. A vegan diet was also effective in body weight reduction and improvement of some cardiometabolic markers (LDL-cholesterol, fasting glucose, HbA1c) in persons with diabetes or at high CVD risk. At the same time, a vegan diet may have adverse effects on HDL-cholesterol and triglyceride levels. More well-conducted prospective studies are warranted to strengthen the evidence on the health effects of a vegan diet and to expand it on further health outcomes.

Author Contributors

JG, TK and SS designed the research. AK, JB and SS conducted the literature search and literature screening. ES, AK, MN, JB, SS extracted the data. JB and MN analyzed the data. AK, ES, JB, MN, SS assessed the risk of bias, LS, MN, SS evaluated the certainty of evidence and ES, MN and SS wrote the first draft of the paper. All authors interpreted the data, read the manuscript, and approved the final version. MN and SS are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria were omitted.

Disclosure statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and no potential conflict of interest was reported by the authors.

Transparency statement

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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