STUDY PROTOCOL

Protocol for a systematic review and meta-analysis: to investigate the association of adherence to plant-based diets with cardiovascular disease risk [version 1; peer review: awaiting peer review]

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Abstract

Background: Plant-based diets (PBDs) are characterised as healthy dietary patterns that emphasise the intake of plant foods and limit the intake of animal foods. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets are common examples of healthy dietary patterns that are mainly plant based. There are different dietary pattern analysis approaches and scoring systems available to construct indices that measure adherence to a dietary pattern. Nutritional epidemiology studies necessitate the use of appropriate dietary indices when investigating diet-disease associations.

Methods: This systematic review protocol was developed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) guidelines. PubMed–Medline, Scopus and relevant biomedical databases within EBSCOhost will be searched up to August 2021 using relevant key words. Two reviewers will independently screen the identified records and review the eligible full texts for inclusion. Discrepancies will be resolved by consensus or through discussion with a third reviewer. Appropriate meta-analysis will be performed where possible and consistency of the findings checked through subgroup analysis. Heterogeneity across studies will be assessed and quantified, and publication bias investigated. Relevant sensitivity analyses will be performed to substantiate the robustness of the study findings.
Conclusion: Currently, there is some inconsistency in defining and measuring adherence to a PBD across study populations. In addition to this, a lack of global data on the association between adherence to a PBD and CVD risk. This systematic review could aid in promoting the worldwide uptake of these findings for policy and practice purposes. This research will use previously published studies; and therefore, will not require ethical approval.

Keywords
Plant-based diet, dietary methods, diet-disease associations, cardiovascular disease risk

This article is included in the Agriculture, Food and Nutrition gateway.
List of abbreviations
CVD: Cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
HR: Hazard ratio
ISI: Institute for Scientific Information
NHLBI: National Heart, Lung, and Blood Institute
OR: Odds ratio
PBD(s): Plant-based diet(s)
PEO: Population, Exposure, and Outcome
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols
RCTs: Randomized controlled trials
RR: Relative risk
WHO: World Health Organization
95% CIs: 95% Confidence intervals

Introduction
In the literature, there are widespread inconsistencies with regards to how plant-based diets (PBDs) have been described. This is due to the scarcity of data on how to define a PBD. PBDs are known for emphasizing the consumption of foods derived from plants, such as fruits, vegetables, whole grains, legumes, nuts, and seeds. Ostfeld defined a PBD as a diet solely made up of naturally derived plant foods, which does not include any animal foods (e.g. resembling a vegan diet), not exempting eggs or dairy products. Other well-known healthy dietary patterns that predominantly contain plant foods are the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets. The Mediterranean diet encourages the consumption of healthy plant foods namely vegetables, fruits, whole grains, and nuts, with olive oil as primary source of added fat. Moreover, the Mediterranean diet limits the intake of red and processed meat, poultry, and dairy products and is low in sugar. The DASH diet also promotes the consumption of plant foods that are primarily characteristic of a PBD, such as fruits, vegetables, whole grains, nuts, and seeds. Additionally, animal foods are also included in the DASH diet in minimal amounts of red meat, fish, poultry and low-fat dairy products.

A dietary pattern is the amount, variety, combination of foods and beverages in a diet and the frequency with which they are usually consumed. Dietary pattern analysis can be predefined (a priori) or data driven (a posteriori); these are two different approaches used to assess dietary patterns. An a posteriori analysis identifies similarities and assesses the variance (i.e. variables or the foods consumed) within a group (i.e. the observations in a data set or rather the study population). Principal component analysis, cluster analysis and factor analysis are among the multivariable statistical techniques utilised to obtain a posteriori scores. In comparison, a priori analysis assigns a score to each nutrient or food, based on existing nutrition knowledge that has a strong health-related focus, and the recommendations relative to a specific population’s dietary guidelines. Different scoring systems can be used to construct a priori indices, which can subsequently measure adherence to a dietary pattern.

Dietary indices are based on an individual’s reported intake of either nutrients, foods or the combination of them. Certain foods and nutrients are beneficial for health and consumption thereof should be encouraged to achieve nutritional adequacy, while others are detrimental for health and should be limited and consumed in moderation. Dietary indices may include only certain nutrients, foods or food groups in their construction and therefore often do not reflect total dietary intake. Nutrient intake data should preferably be based on country-specific food composition tables, if available. Often energy-adjusted intakes of nutrients or foods are used when constructing dietary indices. Each of the dietary components (e.g. nutrients or foods) included in the dietary index are scored either as absolute using predefined cut-off values or relative based on the distribution of intake (e.g. quintiles).

Predefined cut-off values are based on dietary recommendations and are indicative of healthy intakes. Relative scoring depends on the distribution of intake within a specific population; whereby higher intakes are scored higher for the adequacy components and lower for the moderation components. However, relative scoring may not necessarily reflect optimum intakes. The scores of the individual components are summed to obtain the final dietary index score, which can be used as either a continuous variable or to group individuals in absolute or relative categories. The total score of a dietary index may range depending on the number of food items, grouping of dietary components, and type of scoring system that is used. An example of relative scoring is illustrated in the approach by Satjia et al. In their study they created different versions of a PBD index. Food groups were classified as healthy plant foods, less healthy plant foods, and animal foods. These food groups were ranked by quintiles of consumption and graded with positive or reverse scores, depending on which PBD index was calculated.
Different dietary indices might rank an individual’s PBD adherence differently and create inconsistencies, which may consequently influence the diet–disease associations across published studies. Evidence-based literature has shown that there are diverse associations reported between PBDs and cardiovascular disease (CVD) and CVD risk. A PBD has been encouraged as a lifestyle intervention in two case reports on CVD. These patients with angina refused surgery, but opted to join a Cardiac Wellness Program that recommended adopting a PBD for the reversal of CVD and/or the prevention of CVD risk. Another study by Lara and colleagues reported on the association between a plant-based dietary pattern amongst other dietary patterns and the incidence of CVD hospitalisation due to heart failure. A high adherence to the plant-based dietary pattern was statistically significantly associated with a decreased likelihood of incident heart failure. However, several studies have focussed on the association of PBDs with CVD risk, specifically the reduced risk of developing hypertension and type 2 diabetes.

**Rationale**
Nutrition-based epidemiological studies are crucial to generate findings on the association between a PBD and health outcomes. Evidence of these associations may be inconsistent amongst studies that are conducted across different regions and countries. The latter may be due to studies utilising different dietary pattern analysis and scoring systems to construct plant-based diet indices for measuring adherence to a PBD. Furthermore, the extent of such discrepancies between the definitions of a PBD and measures of adherence as they apply globally; to the study of the associations between adherence to a PBD and CVD risk, warrants further investigation. Thus, considering these variations, it could prove valuable to investigate to what extent different methods may influence study findings. This is important prior to conducting studies in under-researched populations such as Africa, where there is a scarcity of resources and paucity of data on the association of PBDs with CVD risk. Therefore, this review aims to address this gap in the literature on PBD studies.

**Objectives**
This protocol is for a systematic review of studies on the association of PBD with CVD risk in order to:

- Assess how PBDs have been defined across those studies;
- Examine which methods are used to measure adherence to a PBD; and
- Examine the effect of differences in the definition and measures of adherence on the association of PBD with CVD risk

**Review questions**
Across studies of the association of PBD with CVD risk, the review will seek to address the following questions:

**Primary outcomes**
1. How has a PBD been defined across published studies globally?
2. Which methods have been used to measure adherence to a PBD?

**Secondary outcome**
3. Does the association of PBD with CVD risk differ by definition of PBD and methods for measuring adherence to a PBD?

**Protocol**

**Eligibility criteria**

**Inclusion criteria**
Observational (i.e. cohort, cross-sectional and case–control) studies reporting on the association between PBDs and CVD risk will be included in the review. The population, exposure, and outcome (PEO) strategy will be applied to identify relevant studies. Study populations will consist of men and/or women (aged 18 years and above), irrespective of their ethnicity. Studies published in English and French will be eligible. We will include studies that assessed adherence to a PBD, using any definition to investigate its association with CVD risk. However, only studies with a clear description of a PBD as a dietary exposure will be included. These studies should also report which dietary methods they used to measure adherence to a PBD. We will focus on assessing the association between adherence to a PBD and CVD risk as a health outcome. Studies will be eligible if: measurements for hypertension and/or overweight/obesity, and/or biomarkers for assessing dysglycaemia and/or diabetes mellitus and/or dyslipidaemia were reported. Studies will also...
be included if they assessed CVD risk factors in combination as metabolic syndrome and/or reported an absolute CVD risk score. In addition to this, studies reporting on major cardiovascular outcomes, such as myocardial infarction and/or coronary heart disease, stroke and/or cerebrovascular disease and/or sudden cardiac death will be included in the review.

Exclusion criteria

The exclusion criteria will pertain to studies that were conducted in children, female participants that are pregnant or breastfeeding or animals. Studies that have reported on the Mediterranean or DASH diets, which are predominantly plant-based will be included in the secondary analysis; if the authors did not state that they were using it to define a PBD. Published studies without primary data such as reviews, letters to the editor, commentaries and/or editorials will not be eligible. After full-text assessment, studies that have investigated the associations of PBD with CVD risk, but have not reported the risk estimates, measures of correlation and regression analyses will be excluded. Studies will also be excluded if they do not have the necessary supplementary materials or have insufficient information for estimating adherence to a PBD, and such information cannot be obtained from the authors of the study.

Information sources

The literature search will be performed in PubMed–Medline and Scopus databases amongst other biomedical databases within the EBSCOhost platform, i.e. Global Health. The databases will be searched for population and/or hospital-based observational studies that were published up to August 2021. Manual searches will be conducted by screening the reference lists of the eligible studies to identify other articles of interest. The ISI Web of Science will be utilised to trace the citations.

Grey literature

The World Health Organization (WHO) website will be browsed according to themes, i.e. nutrition and non-communicable diseases for any pertinent information or reports available from the Global Health Observatory data repository. The Institute for Scientific Information (ISI) Web of Science will be searched for conference proceedings that are relevant to the review questions. Conference abstracts will be retrieved from the conference websites. If necessary, authors or experts in the field will be contacted for any unpublished studies with relevant data.

Search strategy

A comprehensive literature search will be conducted to identify eligible studies without any restriction to country. A search strategy will be applied in all electronic databases and adapted accordingly. The search terms will utilise the following key words as free texts and/or medical subject headings to find relevant studies: plant-based diet OR plant-based OR adherence to a plant-based diet OR healthy dietary pattern AND dietary pattern analysis OR a priori OR a posteriori OR dietary indices AND cardiovascular disease OR heart disease OR ischaemic/ischemic chest pain OR myocardial infarction OR heart attack OR coronary artery disease OR congestive heart failure OR cardiac arrest OR stroke OR cerebrovascular disease OR sudden death OR sudden cardiac death OR hypertension OR high blood pressure OR diabetes OR dysglycaemia OR dysglycemia OR dyslipidaemia OR dyslipidemia OR hyperglycaemia OR hyperglycemia OR prediabetes OR impaired glucose tolerance OR impaired fasting glycaemia/glycemia OR obesity OR overweight OR metabolic syndrome OR cardiovascular risk score OR cardiovascular risk model.

Study records

Data management

EndNote X8 citation management software (RRID:SCR_014001) will be used to identify any duplicates; Zotero (RRID:SCR_013784) is an open-access alternative. Duplicate records will be removed prior to screening. If multiple publications from the same study are found the most comprehensive publication will be included. The Rayyan application for systematic reviews (RRID:SCR_017584) will be used to manage and screen the identified records.

Selection process

The titles and abstracts of identified records will be screened independently by two reviewers. The full text of all eligible studies will be reviewed independently by the two reviewers and checked by a third reviewer for consensus. The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram will be utilised to summarise the study selection process. Exclusion reasons will be provided and documented for all the full-text reviewed studies, which do not meet the criteria of the review.

Data extraction

Two reviewers will independently extract data from all eligible studies, using the data collection form for RCTs and non-RCTs from the Cochrane Collaboration that will be adapted if necessary. Disagreements will be discussed with a third
reviewer and resolved by consensus. Data items will be captured in Microsoft Excel (RRID:SCR_016137) spreadsheets; Google Sheets (RRID:SCR_017679) is an open-access alternative. The following general data items will be extracted from each study: the first author’s name, year of publication, geographical region, country, and study design and sample size. The PEO strategy will also be utilised to extract study-specific data. It will include the demographics of study participants such as age, sex and ethnicity, the dietary exposure and how it was defined and how adherence was measured including the dietary assessment method and reference period that was used, how the food intake was quantified, which dietary pattern analysis approach was applied to construct the dietary index, also which health outcome was assessed.

Risk of bias assessment
The risk of bias will be assessed independently by two reviewers. Each study will be appraised using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational studies to rate the methodological quality. The quality scores of the included studies will be calculated based on 14 criteria and classified as good, fair or poor.

Data
Synthesis, analysis, and assessment of heterogeneity

Descriptive data will be presented by the major study characteristics of the eligible studies such as the mean or median age with the estimates of variance, sex proportions and ethnicity of the study participants. A list of all the PBD definitions identified across the eligible studies will be compiled and presented in a table depicting the differences and similarities.

We will quantitatively synthesise prevalence data to evaluate the level of adherence to a PBD across studies. The prevalence of adherence to a PBD will be summarised by geographical region and countries, and which method was used to construct the dietary index. Association data of adherence to a PBD with CVD risk and/or CVD will be analysed according to study design, showing the reported measures of association by major CVD risk such as the odds ratio (OR), CVD risk score and/or CVD such as hazard ratio (HR) or risk ratio (RR).

Meta-analytic techniques will be applied to combine the data from studies investigating the association between adherence to a PBD and CVD risk: with sufficient data depending on the study design, assessing the same dietary exposure and health outcome, and with comparable measures of association. Separate forest plots will be generated to present the summary statistics for cross-sectional and/or case–control studies (e.g. ORs) and cohort studies (e.g. RRs) with their 95% confidence intervals (95% CIs). A random-effects model will be used to calculate the pooled estimated measure of association of study populations with adherence to a PBD and at risk of developing or having CVD. Subgroup analyses will be performed by geographical regions and country, sample size, the type of dietary pattern analysis approach and scoring system. Meta-analyses will be stratified according to study population, the type of PBD definition, if the same criteria were used to assess dietary exposure, and by CVD risk for studies that have assessed the same health outcome. Thus, grouping all the studies that investigated association in study participants with similar demographics, using an identical dietary exposure and assessing the same CVD risk and/or CVD.

Heterogeneity across studies included in the meta-analysis will be assessed using the Cochrane Q statistic. The degree of heterogeneity will be determined will be assessed using the inconsistency index (I²): 25%, 50% and 75%, suggesting low, medium, and high heterogeneity, respectively. Publication bias will be evaluated graphically with the funnel plot asymmetry test and statistically using Egger’s test. Sensitivity analysis will be applied to evaluate and confirm the robustness of the findings. The Tweedie and Duval trim and fill methods will be used to impute missing studies and examine the plausibility of the imputed studies. The data analysis will be conducted using the ‘meta’ package of the statistical software R (RRID:SCR_019055; The R Foundation for statistical computing, Vienna, Austria). A narrative summary of the findings will be provided for studies with significant differences in their study designs and methodologies.

Ethical approval and dissemination
This study has a systematic review and meta-analysis design, which will assess published data and does not require ethical approval. This review will form part of a PhD thesis by publication that will be submitted at Stellenbosch University for degree purposes. The PhD study proposal has obtained ethics approval from Stellenbosch University Health Research Ethics Committee (SU HREC number: S19/03/056). The results will be published in peer-reviewed journals. Study findings will be presented at relevant research meetings and conferences.

Strengths and limitations
This systematic review and meta-analysis will investigate the association of PBD adherence with CVD risk profile from a global perspective. Published studies have applied various dietary methods to assess adherence to a PBD, therefore, this
study aims to evaluate which PBD definitions are utilised and assess the accuracy of PBD indices across high and low-to-middle income countries. A considerable degree of heterogeneity may be present due to the different dietary methods and including studies with small sample sizes may be a limitation when performing the meta-analysis. Statistical techniques will be applied to collate and report robust findings in this systematic review.

Potential amendments
Amendments to the study protocol, if any, will be published in accordance with the 2015 PRISMA-P guidelines.\textsuperscript{27}

Conclusion
This systematic review will aim to highlight the inconsistencies in defining a PBD and the need for a universal definition. It will summarise which methods are commonly used to construct dietary indices that measure adherence to a PBD. Furthermore, it will investigate the association of adherence to a PBD with CVD risk from a global perspective. This may be important to improve the global acceptance of these study findings to inform policymakers and practitioners.

Data availability

Reporting guidelines
Figshare: PRISMA-P checklist for “Protocol for a systematic review and meta-analysis: to investigate the association of adherence to plant-based diets with cardiovascular disease risk” https://doi.org/10.6084/m9.figshare.14988249.v1.\textsuperscript{28}

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Author contributions
TL and APK conceived and designed the protocol. TL drafted the manuscript. APK, AEZ, MF, SD and RTE critically revised the manuscript for methodological and clinical content. All authors approved the final version of the manuscript.

References


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