Protocol for a systematic review and meta-analysis: to investigate the association of adherence to plant-based diets with cardiovascular disease risk [version 2; peer review: 2 approved with reservations]

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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. This protocol is for a review that will: 1) evaluate how a PBD has been defined in studies published globally; and 2) assess the methods used to construct dietary indices that measure adherence to a PBD; with a focus on studies that have assessed the association between adherence to a PBD and CVD risk.

Methods: This protocol was developed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols guidelines. PubMed–Medline, Scopus and biomedical databases within EBSCOhost will be searched up to August 2021. 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. 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. Moreover, 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

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**Author roles:** Lopes T: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; Zemlin AE: Supervision, Writing – Review & Editing; Faber M: Methodology, Writing – Review & Editing; Durao S: Methodology, Writing – Review & Editing; Erasmus RT: Supervision, Writing – Review & Editing; Kengne AP: Conceptualization, Methodology, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

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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 emphasising 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.1 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.2 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.2

A dietary pattern is the amount, variety, combination of foods and beverages in a diet and the frequency with which they are usually consumed.3,4 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.5–7 Different scoring systems can be used to construct a priori indices, which can subsequently measure adherence to a dietary pattern.5

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.1 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 values10 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 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?

- CVD risk outcomes including hypertension, overweight/obesity, diabetes mellitus, metabolic syndrome and CVD risk score
- Cardiovascular outcomes such as myocardial infarction/coronary heart disease, stroke/cerebrovascular disease and cardiac death
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 will be included without language restriction. We will include studies that assessed adherence to a PBD, using any definition including, vegan and/or vegetarian diets 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 measurements 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 and/or DASH diet/dietary patterns which are predominantly plant-based will be excluded from the primary analysis. However, such studies will be included in our secondary analysis; if the authors did not state that they were assessing a PBD as their exposure variable. 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 hyperglycaemia 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 identified records will be exported to the Rayyan application for systematic reviews (RRID:SCR_017584), which will be used to manage and screen the identified records.

Selection process
The Rayyan application will be utilised during the selection process. Two reviewers will independently screen the identified titles and abstracts. The inclusion and exclusion criteria will serve as guide for the reviewers to select eligible records and studies. After completing the titles and abstracts screening, the two reviewers will discuss any discrepancies and reach a consensus to include or exclude the record. Subsequently, the full text of all eligible records will be retrieved. Full text 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, sample size and study design. The PEO strategy will also be utilised to extract study-specific data. For example, data related to the baseline characteristics of cohort study participants, and the duration of follow-up will be extracted. Study-specific data will include the demographics of study participants such as age, sex and ethnicity, the dietary exposure and how it was defined, how adherence was measured including the dietary assessment method and reference period that was used, how the food intake was quantified such as the level of intake (e.g., tertiles of consumption), which dietary pattern analysis approach was applied to construct the dietary index, also which health outcome was assessed and how the outcomes were ascertained. Moreover, we will extract data on which covariates were adjusted for in the regression models of the included studies, and report on the measurement of potential confounders.

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 NHLBI tools will be utilised to assess the risk of bias for all observational study types namely cross-sectional, cohort and case-control studies. The quality scores of the included studies will be calculated based on 14 criteria for cross-sectional and cohort studies and 12 criteria for case-control studies. This risk of bias assessment tool was selected because it was developed by a working group assessing cardiovascular risk which is the outcome of interest for our systematic review. Moreover, the NHLBI tools were developed using a rigorous approach and are accompanied by a user-friendly guide that assists the reviewer(s) to answer/interpret the criteria that are included in each tool. All the included studies will be categorised as having a methodological quality that is good (score > 11), fair (score 6-9), or poor (score < 6).

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. The leave-one-out sensitivity analyses will also be conducted to assess the likely influence of studies on the pooled estimates in meta-analyses. Subgroup analyses will be performed by geographical regions and country, sample size, sex, participant status, the type of dietary pattern analysis approach and scoring system, and study quality. 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 using $I^2$, which indicates the proportion of variation in the observed effects as a result of sampling error and variation in the true effects. 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 will be provided for studies with significant differences to allow pooling of the estimates via meta-analysis.

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 2020 PRISMA-P guidelines.

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

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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Vanessa Bullón-Vela
Department of Medicine and Public Health, University of Navarra, Pamplona, Spain

This presented research is quite interesting. Suggestions are below:

1. Abstract: It has to include the objective.

2. In the secondary outcome, specify the cardiovascular disease risk factors.

3. In the selection process, there is a new version (2020) of the flow diagram and checklist. Also, investigators have to clarify this section.

4. In data extraction, you can also include the level of intake category (tertile, quantile, others), follow-up duration, baseline participant status, outcome ascertainment, covariates that were adjusted in the final models. Moreover, it would be interesting to include other variables (vegan, vegetarian diets).

5. Risk of bias assessment, clarify the threshold for the bias classification, and include relevant information about that. Also, why did you use this tool?

6. Data: In the statistical analyses, authors can also include: Subgroup analysis for study quality, by sex (men, women, or both), participant status. Also, a leave-one-out sensitivity analysis.

Is the rationale for, and objectives of, the study clearly described? 
Yes

Is the study design appropriate for the research question? 
Yes

Are sufficient details of the methods provided to allow replication by others? 
Yes
Are the datasets clearly presented in a useable and accessible format?

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Nutrition Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Author Response 20 Jun 2022**

**Tatum Lopes,** South African Medical Research Council, Cape Town, South Africa

Thank you for reviewing this protocol paper. Your comments and suggestions have been discussed and addressed to improve the manuscript. Herewith is the response to each of the comments/suggestions.

**In response to comment 1:** Please see the amendment below and on page 2 of the revised manuscript.

“This protocol is for a review that will: 1) evaluate how a PBD has been defined in studies published globally; and 2) assess the methods used to construct dietary indices that measure adherence to a PBD; with a focus on studies that have assessed the association between adherence to a PBD and CVD risk.”

**In response to comment 2:** Thank you for your comment. Please see below and stated in the inclusion criteria section on page 5 of the revised manuscript.

CVD risk outcomes
- hypertension
- overweight/obesity
- diabetes mellitus
- metabolic syndrome
- CVD risk score

CV outcomes
- myocardial infarction/coronary heart disease
- stroke/cerebrovascular disease
- cardiac death

**In response to comment 3:** Thank you for your comment regarding the new flow diagram and checklist. We have consulted the updated guideline by Page and colleagues.

In response to comment 4: Thank you for this recommendation. We have amended the data extraction section and added the suggested data items.

“The PEO strategy will also be utilised to extract study-specific data. For example, data related to the baseline characteristics of cohort study participants, and the duration of follow-up will be extracted. Study-specific data will include the demographics of study participants such as age, sex and ethnicity, the dietary exposure and how it was defined, how adherence was measured including the dietary assessment method and reference period that was used, how the food intake was quantified such as the level of intake (e.g., tertiles of consumption), which dietary pattern analysis approach was applied to construct the dietary index, also which health outcome was assessed and how the outcomes were ascertained. Moreover, we will extract data on which covariates were adjusted for in the regression models of the included studies, and report on the measurement of potential confounders.”

We have also specified that vegan and vegetarian diets will be included as exposure variables for our analysis on plant-based diet adherence.

“We will include studies that assessed adherence to a PBD, using any definition including, vegan and/or vegetarian diets to investigate its association with CVD risk.”

In response to comment 5: Thank you for your comment. Please see clarification below and on page 8 of the revised manuscript.

“The NHLBI tools will be utilised to assess the risk of bias for all observational study types namely cross-sectional, cohort and case-control studies. The quality scores of the included studies will be calculated based on 14 criteria for cross-sectional and cohort studies and 12 criteria for case-control studies. This risk of bias assessment tool was selected because it was developed by a working group assessing cardiovascular risk which is the outcome of interest for our systematic review. Moreover, the NHLBI tools were developed using a rigorous approach and are accompanied by a user-friendly guide that assists the reviewer(s) to answer/interpret the questions/criteria that are included in each tool. All the included studies will be categorised as having a methodological quality that is good (score > 11), fair (score 6-9), or poor (score < 6).”

In response to comment 6: Thank you for this suggestion. Please see the amendment below and in the revised manuscript.

“The leave-one-out sensitivity analyses will also be conducted to assess the likely influence of studies on the pooled estimates in meta-analyses. Subgroup analyses will be performed by geographical regions and country, sample size, sex, participant status, the type of dietary pattern analysis approach, scoring system, and study quality.”

**Competing Interests:** No competing interests were disclosed.
This paper is a thorough protocol for a systematic review and potential meta-analysis. The rationale for the study is clear and compelling. I have some specific comments to help clarify parts of the text:

- It seems a shame to limit the review to articles in English and French only when free translators for non-English non-French articles would be readily available. For example, associates known to the research team that speak other languages besides English or French could translate the small proportion of articles that are not in one of these two languages. Then there are free internet translators.

- Under the heading of exclusion criteria, the second sentence in the paragraph is not clear. This could benefit from expansion for clarification.

- The first two sentences under the heading of the selection process are not very clear to me and could benefit from clarification.

- More information about the risk of bias assessment tool to be used could be of benefit. Will this proposed risk of bias assessment tool be applicable to all types of studies that are eligible for inclusion in the current review? What other risk of bias assessment tools have been considered, and why was this tool selected as the most appropriate?

- The last sentence before the heading of ethical approval and dissemination is not clear to me, can you say it another way?

- In the paragraph on heterogeneity, it is mistakenly written that $I^2$ provides an indication of the heterogeneity of the studies in the meta-analysis. It does not. It is the proportion of the observed variation in effect sizes between studies that is due to variability in the true effect size $^1$.

- Reference number 27$^2$ seems old, given that revised Prisma guidelines were released in 2020. It would be better to report and undertake the study in accordance with Prisma 2020 guidelines.

References


**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Yes

**Are the datasets clearly presented in a useable and accessible format?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Obesity and methodology used to assess treatments (e.g., fundamental studies in animals; clinical trials; epidemiological studies; systematic reviews and meta-analyses).

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Author Response 20 Jun 2022**

**Tatum Lopes,** South African Medical Research Council, Cape Town, South Africa

Thank you for reviewing this protocol paper. Your comments and suggestions have been discussed and addressed to improve the manuscript. Herewith the response to each of the comments/suggestions.

**In response to comment 1:** Thank you for this suggestion. We acknowledge that language bias is a study limitation. Please see amendment below and in the revised manuscript.

“Studies published will be included without language restriction.”

**In response to comment 2:** Thank you for your comment. Please see the amendment below and in the revised manuscript.

“Studies that have reported on the Mediterranean and/or DASH diet/dietary patterns, which are predominantly plant-based will be excluded from the primary analysis. However, such studies will be included in our secondary analysis; if the authors did not state that they were assessing a PBD as their exposure variable.”
**In response to comment 3:** Please see the amendment below and on page 7 of the revised manuscript.

“The Rayyan application will be utilised during the selection process. Two reviewers will independently screen the identified titles and abstracts of identified records will be screened independently by two reviewers. The inclusion and exclusion criteria will serve as guide for the reviewers to select eligible records and studies. After completing the titles and abstracts screening, the two reviewers will discuss any discrepancies and reach a consensus to include or exclude the record. Subsequently, the full text of all eligible records will be retrieved. Full text will be reviewed independently by the two reviewers and checked by a third reviewer for consensus.”

**In response to comment 4:** Thank you for your comment. Yes, the NHLBI risk of bias assessment tools will be used to assess the quality of all study types. Please see the amendment below.

“The NHLBI tools will be utilised to assess the risk of bias for all observational study types namely cross-sectional, cohort and case-control studies. The quality scores of the included studies will be calculated based on 14 criteria for cross-sectional and cohort studies and 12 criteria for case-control studies. This risk of bias assessment tool was selected because it was developed by a working group assessing cardiovascular risk which is the outcome of interest for our systematic review. Moreover, the NHLBI tools are accompanied by a user-friendly guide that assists the reviewer(s) to answer/interpret the questions/criteria that are included in each tool.”

**In response to comment 5:** Please see the amendment below and on page 8 of the revised manuscript.

“A narrative summary will be provided for studies with significant differences to allow pooling of the estimates via meta-analysis.”

**In response to comment 6:** Thank you for this comment. We have consulted the reference by Borenstein et al., 2017 and amended the sentence regarding the use of I2. Please see the correction below.

“The degree of heterogeneity will be determined using the I2, which indicates the proportion of variation in the observed effects as a result of sampling error and variation in the true effects.”

**In response to comment 7:** Thank you for the recommendation. Please see the amendment below and on page 11, the reference has been updated.

“Amendments to the study protocol, if any, will be published in accordance with the 2020 PRISMA-P guidelines.”

for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71

*Competing Interests:* No competing interests were disclosed.

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