



BMJ Open Ethnic differences between South Asians and white Caucasians in cardiovascular disease-related mortality in developed countries: a systematic literature review protocol

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ABSTRACT

Introduction Cardiovascular disease (CVD) is the leading cause of death worldwide, with significantly worse CVD outcomes in ethnic minorities in developed countries, especially South Asians, compared with the prevailing white ethnic group. This protocol outlines the process for conducting a systematic literature review to investigate the CVD outcome inequalities between South Asian and white Caucasian ethnic groups.

Methods Studies that compared the South Asian ethnic minority with the predominant white ethnicity in developed countries with CVD will be included from inception to 22 April 2021. We will search MEDLINE, Embase, Web of Science and grey literature to find all relevant peer-reviewed articles, reports and online theses. Articles will be screened using inclusion/exclusion criteria applied first at the title and abstract level, and then full texts, both by two independent reviewers. Articles kept in the review will undergo a risk of bias assessment using the Quality In Prognosis Studies tool and data will be extracted. Random-effects meta-analysis and heterogeneity tests will be undertaken, and tests for publication bias, outlying highly-influential observations. If insufficient data is founded or studies are highly heterogeneous, a narrative synthesis will be conducted.

Ethics Formal ethical approval is not required for this review.

Dissemination The results and findings of this systematic literature review will be disseminated through peer-reviewed publications and reports.

PROSPERO registration number CRD42021240865.

INTRODUCTION

Cardiovascular diseases (CVD; a full list of abbreviations are provided in online supplemental appendix 1) are a group of disorders of the heart and blood vessels. They include coronary heart diseases such as angina, myocardial infarction and heart failure, strokes, transient ischaemic attacks, peripheral arterial disease and aortic disease. The WHO estimated that 17.9 million people died from CVD in 2016,¹ representing 31% of all

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review protocol aims to assess how cardiovascular disease-related mortality differs in growing ethnic minorities in developed countries.
- ⇒ This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines.
- ⇒ Comprehensive investigation of bias, quality and meta-analysis assumptions.
- ⇒ Potential for confounding variables when comparing results from different countries, introducing bias.

global deaths. Additionally, over 75% of these deaths occur in low-income and middle-income countries. However, they still pose a substantial mortality risk in developed countries. In the UK alone, heart and circulatory diseases cause a quarter of all deaths each year.²

In the 2011 census, Asian British people amounted to 7.5% of the UK population. This was split into around 2.5% Indian, 2.0% Pakistani, 0.8% Bangladeshi, 0.7% Chinese and 1.5% Other Asian. In particular, the UK's South Asian population was the largest minority ethnic group.³ This was an increase for all the Asian ethnicities from the 2001 census of England and Wales ([figure 1](#)). In the USA, Asian Americans (5.9%) made up the third largest ethnic minority group, after Hispanic and Latino, and Black or African American⁴ and, of these, 1.9% are South Asian. In Canada, South Asian Canadians make up about 5.6% of the total Canadian population as of 2016,⁵ and in Australia, Asian Australians make up about 16.3% of the population, amounting to about 4% from the South Asian countries.⁶

Current understanding of CVD is derived largely from studies of Caucasians of

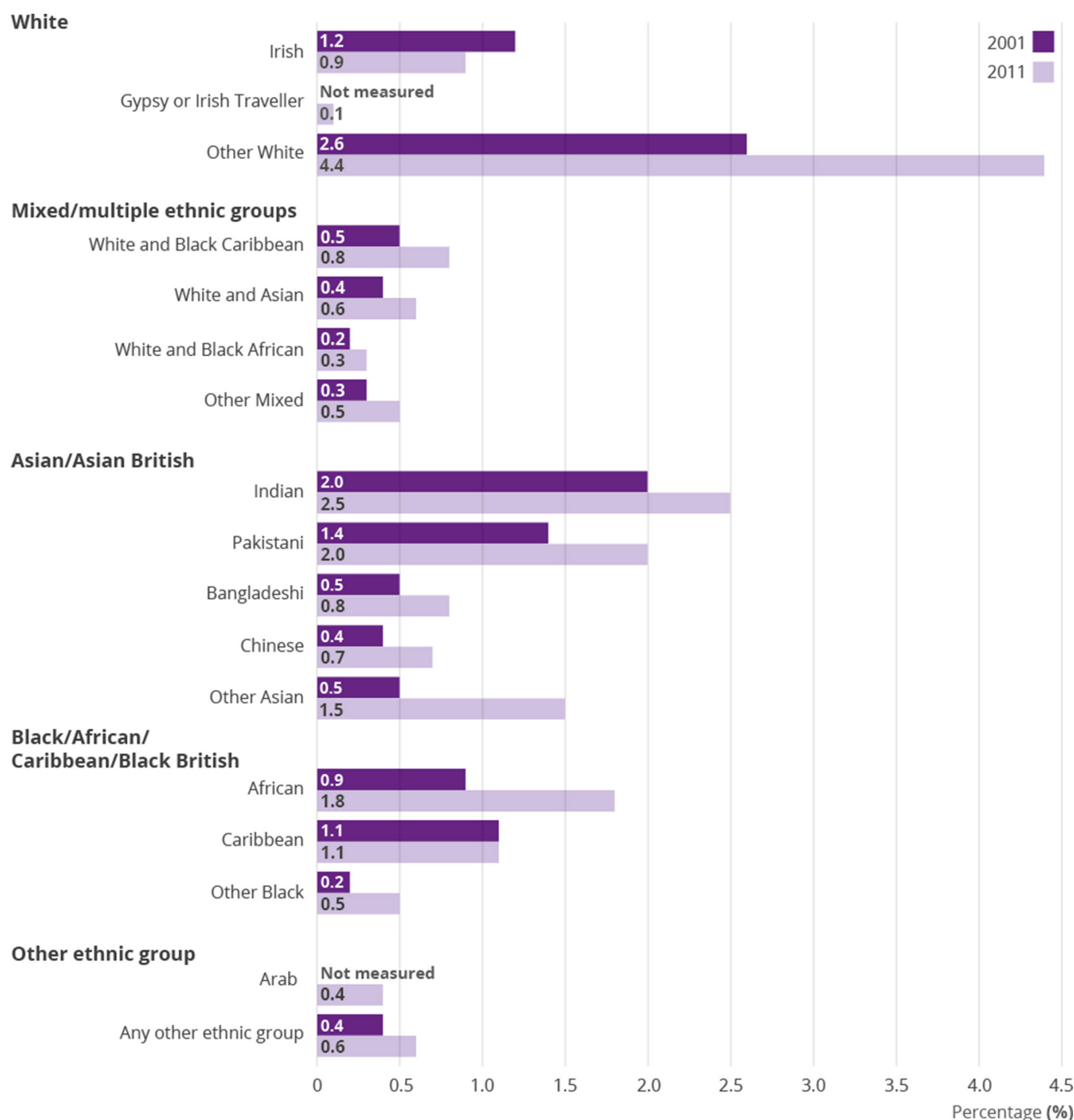


Figure 1 Changes in the percentage of ethnic minority populations in the UK Census between 2001 and 2011, split by ethnic category.

European origin.⁷ However, certain ethnic groups are susceptible to different types of CVD due to the high prevalence of these diseases in certain populations.

In the UK, CVD is more common in people of South Asian, African or Caribbean background,⁸ as people of these ethnicities are more likely to have other risk factors for CVD, such as hypertension or type 2 diabetes mellitus.^{9–11} In most cases, the risk of first heart attack is thought to be related to modifiable risk factors, for example, smoking, high cholesterol, inactivity and excess alcohol consumption.¹²

A 2017 study¹³ investigating the ethnic differences in the initial lifetime presentation of clinical CVD in over one million people from the CALIBER platform found

that age of CVD onset was the lowest in South Asians, and significantly lower in South Asian women compared with South Asian men. However, an older study¹⁴ found CVD death rates were significantly lower in all Asian ethnic groups compared with the other groups from the REACH registry.

A systematic literature review (SLR) will help to quantify and provide clarity on CVD-related mortality inequalities between a major migrant group in some developed countries and the prevailing white ethnicity, and provide guidance for policies promoting health equality. To the best of the authors' knowledge, there have been no SLR which compares the South Asian ethnic population against the prevailing white ethnic population in the UK

and other Western, developed countries in patients with any type of CVD.

Research question

What is the magnitude of difference in CVD-related mortality between South Asian ethnic group and white population in developed countries?

METHODS AND ANALYSIS

Protocol design and registration

This systematic literature review protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement and checklist (online supplemental appendix 2). The review has been registered in the PROSPERO (International prospective register of systematic reviews; <https://www.crd.york.ac.uk/prospero>). Any changes will be updated on PROSPERO accordingly.

Patient and public involvement

No members of the public have been involved in the design process of this SLR.

Eligibility criteria

Population

The population will be restricted to that of the UK and other western, more economically developed countries where the prevailing ethnicity is Caucasian or other white ethnicities, and a comparator group includes South Asians. Studies will be limited to population-based samples and include populations with CVD of any form. Although age is an independent risk factor for CVD,¹⁵ especially in older patients, we will consider all patients aged 18 or older.

An initial comparison of Asian immigration to the European Union and North America between 2000 and 2010¹⁶ suggests that, from European countries, the UK was the main country of destination for immigrants from India and Pakistan, and found a 296.5% net migration for Indian immigrants to the UK in the 10-year period to 2010, and both Indian and Pakistani immigrants migrated to the USA and Canada.

Therefore, we anticipate relevant countries for this review to be the UK, the USA, Canada and Australia only, and will be searched accordingly.

Ethnicity

Ethnicity can be self-reported or defined by proxy, such as country of birth, country of birth of parents or ancestry. **Box 1** shows how ethnic groups were categorised in the 2011 Census of England and Wales. The 2021 census asked about ethnicity in a similar way: asking respondents 'What is your ethnic group?', where the response tick-boxes are grouped under the headings shown in **box 1**. The 2021 census also included the option for the 'Roma' ethnicity under the White category,¹⁷ whose numbers are estimated to exceed 100 000 in the UK alone.¹⁸

Box 1 Ethnic groups categories included in the 2011 Census of England and Wales

White

- ⇒ English, Welsh, Scottish, Northern Irish or British.
- ⇒ Irish.
- ⇒ Gypsy or Irish Traveller.
- ⇒ Roma.*

Any other white background

- ⇒ Mixed or multiple ethnic groups.
- ⇒ White and black Caribbean.
- ⇒ White and black African.
- ⇒ White and Asian.

Any other mixed of multiple ethnic background

- ⇒ Asian or Asian British.
- ⇒ Indian.
- ⇒ Pakistani.
- ⇒ Bangladeshi.
- ⇒ Chinese.
- ⇒ Any other Asian background.

Black, African or Caribbean background

- ⇒ African.
- ⇒ Caribbean.
- ⇒ Any other black, African or Caribbean background.

Other ethnic group

- ⇒ Arab.
- ⇒ Any other ethnic group.

*Roma was included as an option under the White ethnicity group as part of the 2021 census.

Where ethnicity is reported as Indian, Pakistani or Bangladeshi, they will be combined to create the South Asian ethnicity. Moreover, South Asia generally also constitutes Afghanistan, Bhutan, Maldives, Nepal and Sri Lanka. Where this is reported by specific country, this will also be included as South Asian ethnicity.

The UK census groups the East Asian ethnicity, consisting of countries such as China, Japan and South Korea, together with the South Asian countries. However, due to observed differences in mortality between the two,^{7 19–21} data from studies that combine these two ethnicities will be excluded. We will attempt to contact the authors of such studies to request data for South Asians and East Asians separately if possible.

The UK census also reports the Caribbean and African ethnicities under one larger group, as seen in **box 1** under the Black, African or Caribbean background group. Again, due to differences between the two ethnicities in terms of mortality, all-cause²² and cause-specific,²³ these ethnicities will be reported separately in any subgroup analyses, if data is available.

The corresponding census documentation will be consulted for ethnicity categorisation when considering studies not from the UK, such as the 2020 US census for any relevant studies in the USA.

Comparators

The comparator group is the ethnic majority population which includes:

- ▶ White British for the UK only comparison.
- ▶ White Caucasian ethnicity from any country.
- ▶ All other ethnic groups apart from white and South Asian.

Outcomes

The outcome will be CVD-related mortality between the South Asian ethnicity and the prevailing white ethnicity. This can be reported as HR, relative risk or mortality ratio. Where absolute risk of mortality is reported, studies will be included if the estimation of relative risk is possible or by contacting the author for the pertinent information. Outcomes stratified by the confounders will be included when adjusted for age and sex, and all other confounders. For completeness, we will also extract the mortality estimate between other ethnicities. All-cause mortality will be included as a secondary outcome.

We will present a summary of findings table reporting the outcome and key characteristic variables listed in the following section.

Confounders relevant to all or most of the studies

Both age and gender are important risk factors in CVD.²⁴ The prevalence of CVD has been shown to increase with age, and the American Heart Association reports that the incidence of CVD in US men and women is around 38% from 40 to 59 years, increasing to 79% for men and 86% for women aged 80 years or over.²⁵

Results from the PURE (Prospective Urban Rural Epidemiology) study²⁶ found that the incidence of CVD in women (4.1/1000 person-years) was statistically significantly less than in men (6.4/1000 person-years), as well as better outcomes being consistently observed in women than in men.

Other important risk factors as identified by NHS England include hypertension, smoking, hypercholesterolaemia, diabetes, inactivity, overweight or obesity, a family history of CVD, ethnic background and excessive alcohol consumption.

These will be tabulated for each eligible study.

Study types

All observational studies that meet the PICO (population, intervention, comparison, outcome) criteria will be considered for inclusion, such as:

- ▶ Case-control studies.
- ▶ Cross-sectional studies.
- ▶ Longitudinal studies.
- ▶ Cohort studies.

A systematic review²⁷ of cardiovascular cohort studies in the US and Europe found a shortage of information on racial or ethnic minority populations. Moreover, only a few studies gave details on the ethnic composition of the study setting, therefore inclusion will be considered for any cohort studies which included a small amount of data on ethnic minority populations only as a narrative assessment.

Search strategy

Searches will be conducted according to PRISMA guidelines in MEDLINE, Embase and Web of Science. Additionally, searches will be conducted through the Cochrane Library and PROSPERO databases to find pertinent systematic reviews. We will conduct searches of grey literature through OpenGrey and EThOS (e-theses online service). Finally, searches will be conducted in Google Scholar and using the Google search engine to find any unpublished works, such as reports. If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes. We will place no restrictions on the language of publication when searching the electronic databases or reviewing reference lists in identified studies. Searches will be carried out from inception. The search strategy will be repeated prior to publication to find any new articles that have been published since the original search. The Ovid MEDLINE search strategy is provided in online supplemental appendix 3.

Data management

All search results will be exported to EndNote X9.3.3 for screening. A Microsoft Excel file will be used to document the full selection process, including the number of studies identified by each database, the number of studies removed plus reasons for exclusion, additional studies included via pre-prints or grey literature, number of abstracts and full-texts screened and the number of studies included in the final analyses. These numbers will be entered into a PRISMA flow diagram.

Selection process

Two authors (MP and SA) will screen titles and abstracts identified by the search independently for selection into the next step of the review. The next stage involves independent review of the full-text articles, by MP and SA, to confirm their inclusion into the study. Disagreements will be resolved by consensus or, where necessary, by a third reviewer OAU. If multiple studies are identified that analysed the same data set, the study with the longer-term data will be used. If this is the same, then the most recent study will be used.

Data extraction

Data will be entered into data collection forms independently by two authors (MP and SA), who will test the data extraction form prior to data extraction for this review. This form will be based on the Cochrane data extraction forms and past data extraction forms so that all relevant information is extracted for each study included in this SLR.

These data extraction forms will include the following information: study details (study ID, design, duration, funding, conflicts of interest and type), study eligibility (study arms, groups), participant characteristics, study

flow, baseline characteristics, outcomes, adverse events, risk of bias assessment and author's conclusions.

The authors will review both sets of data extraction forms to check for disagreements, which will be resolved either by consensus or with the help of an additional author, if required. Once agreement is reached, data will be collated into a Microsoft Excel spreadsheet. Where important data is missing, we will contact the lead authors requesting this data, or the raw data if possible. Where SD is missing, we will impute these values by assuming the SD of the missing outcome to be the average of the SD from those studies where this information was reported.

Risk of bias assessment

Two authors (MP and SA) will assess the risk of bias of each included study independently. Disagreements will be resolved by consensus, or by consultation with a third author (OAU) if required.

In observational studies, as with other study types, the threats to validity are confounding bias, selection bias, performance bias, detection bias and reporting bias, and the threats to precision are inadequate study size and lack of study efficiency.^{28 29}

Risk of bias will be assessed using the Quality In Prognosis Studies (QUIPS) tool.³⁰ This tool assesses study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Each domain will be rated as having either 'low', 'moderate' or 'high' risk of bias. A study with 'low' risk in all six domains will be rated as having a low risk of bias. A study that has a 'high' risk of bias for any domain will be rated as having a high risk of bias. All other studies will be rated as having a moderate risk of bias. The QUIPS tool is provided in online supplemental appendix 4.

A subgroup analysis is planned based on a study's risk of bias rating. Furthermore, to measure the extent to which highly biased studies influence the overall results, a sensitivity analysis is planned where the high risk of bias studies will be removed.

Data synthesis

Quantitative syntheses will be conducted provided that at least two studies for the comparison between the South Asian and white ethnicities for CVD-related mortality are found; this will also include other ethnicities where data is provided, and if there is sufficient homogeneity. This will be tested alongside the main evidence synthesis, and the details of which are written in subsequent sections.

The main meta-analyses will be conducted using a Bayesian random-effects model with a 100 000 burn-in sample and 100 000 subsequent iterations, and non-informative priors for the true pooled effect size and between-study heterogeneity. We will check for model convergence by checking R in the output; $R=1$ signifies model convergence.

We will favour measures that stratify for the important confounders, like age or gender, over measures that are adjusted for them.

We anticipate that studies will report mortality differently, for example as event rates or estimates of effect size. For all estimates. We will extract SEs or, where only CIs are reported, we will use these to calculate SEs. The definitions of each CVD diagnosis and outcomes will be extracted to facilitate subgroup analyses, both by CVD type and by cause-specific outcomes.

As age remains a fundamental predictor of CVD risk and, according to NHS England, CVD is most common in people over 50 years of age, the majority of people included in this SLR are likely to be over 50 years old, therefore we will conduct subgroup analyses by age (over 50 years vs 50 years or younger). Further planned subgroup analyses will consist of assessing mortality based on the type of CVD, as there are various types, and cause-specific mortality.

The following tests will be performed to test the assumptions of the meta-analysis: (a) heterogeneity, see next section; (b) 95% prediction interval to see if, in some studies, the true outcome may favour one group over the overall estimate; (c) an examination of studentised residuals for outliers; (d) an examination of Cook's distance to check for influential studies; (e) funnel plot (SE vs log estimate) to check for publication bias. If any highly influential or outlying studies are identified, they will be removed for sensitivity analyses. Results and plots from these tests will be provided in the appendices.

All analyses will be conducted by MP using RStudio.³¹

Statistical heterogeneity

Statistical heterogeneity will be tested using the I^2 and Cochran's Q (χ^2) statistics. A high I^2 signifies high heterogeneity. However, the low I^2 does not signify no heterogeneity. As the χ^2 test for heterogeneity is not very powerful in detecting significant results, and that a non-statistically significant result does not indicate the absence of heterogeneity, the significance level will be set at 10%.

If one or both tests concludes the possibility of heterogeneity, $p>0.10$ for the Cochran's Q test or $I^2 > 60\%$, representing substantial to considerable heterogeneity, the feasibility of a random effects meta-regression model will be explored to try to explain statistical heterogeneity, provided a large enough sample size. This model will include the aforementioned confounders. Furthermore, subgroup analyses, detailed in the subgroup analysis section, will be explored to explain heterogeneity.

Subgroup analyses

- ▶ Cause-specific mortality (other than CVD-related).
- ▶ Type of CVD.
- ▶ Age groups (below 50 vs 50+ years).
- ▶ Geo-political regions (Americas vs European studies).
- ▶ Risk of bias rating.

The following subgroup analyses will be undertaken to explore heterogeneity if it is sufficiently high:

- ▶ Subgroups of ethnicities included as part of a larger ethnic-minority group (where sample size is adequate). For example, in the case of South Asians, a subgroup analysis of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka individually.
- ▶ Method of reporting used to determine ethnicity.

Sensitivity analyses

The following sensitivity analyses are planned:

- ▶ Removal of studies identified with a high risk of bias.
- ▶ Removal of non-peer reviewed articles (such as reports or conference articles).
- ▶ By study design.
- ▶ Method of imputation, if applicable.
- ▶ By effect measure.
- ▶ Removal of outlier studies or studies with high influence.

Multiple testing

Due to the high number of hypotheses being tested, the Bonferroni-Holm method³² will be used to correct for multiple testing.

Ethics and dissemination

As this review will not collect any individual patient data and will only include published data, no ethical approval is required. Findings will be published in an open-access peer-reviewed journal and plain language summaries will be created to disseminate to members of the public. To the best of the authors' knowledge, this will be the first SLR to investigate differences in CVD-related mortality between South Asians and white ethnicities in developed countries, and will be of interest to those involved in public health.

Contributors MP conceived the original idea for the study and planned and designed the protocol with respect to the PICO criteria, search strategy, quality assessment and methods of data synthesis, with the assistance of SA and OAU. All authors have contributed and approved the final version of this protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: List of abbreviations

CVD	Cardiovascular disease
SLR	Systematic literature review
AHA	American Heart Association
CALIBER	Randomized Controlled Trial of LINX Versus Double-Dose Proton Pump Inhibitor Therapy for Reflux Disease
IPD	Individual patient data
MEDC	More economically developed countries
NHS England	National Health Service England
PICO	Population, intervention, control, and outcomes criteria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
PURE	Prospective Urban Rural Epidemiology
QUIPS	Quality in prognosis studies
REACH	Resilience, Ethnicity and AdolesCent mental Health
RoB	Risk of bias
UK	United Kingdom
USA	United States of America

Appendix 2: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported? (Y/N)	Location in text
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Y	Page 1; title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y	Page 1; abstract > PROSPERO registration number
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y	Page 13; Author's contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Y	Page 13; Funding statement
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA	
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Y	Page 3;

				Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y	Page 3; Research question
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y	Page 4-5; Eligibility criteria
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y	Page 6; Search strategy
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y	Page 6; Search strategy + appendix 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y	Page 6; Data management
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y	Page 6; Selection process
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y	Page 6-7; Data extraction
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y	Page 5; Confounders relevant to all or most of the studies
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y	Page 5; Outcomes
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y	Page 7; Risk of bias assessment
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y	Page 7; Data

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	Y	synthesis Page 8; Statistical heterogeneity
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y	Page 8; Subgroup analyses + Sensitivity analyses
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y	Page 6; Study types
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y	Page 8; Data synthesis
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y	Page 7; Risk of bias assessment

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 3: Ovid MEDLINE search strategy on 04/03/2021

#	Search terms	Results
1	exp United Kingdom/	371150
2	Britain.mp.	15543
3	exp Europe/ or Europe.mo.	1491709
4	exp United States/	1373045
5	america.mp. Or Americas	102731
6	exp Australia/	149103
7	exp Australasia/	186990
8	1 or 2 or 3 or 4 or 5 or 6 or 7	3039455
9	exp Ethnic Groups/	157848
10	ethnic*.mp	166038
11	exp Minority Groups/ or minorit*.mp.	70673
12	south asian.mp.	4409
13	asian.mp.	129791
14	india*.mp.	184935
15	pakistan*.mp.	23237
16	bangladesh*.mp.	14738
17	black.mp.	106782
18	exp African Continental Ancestry Group/	88885
19	caribbean.mp.	13716
20	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	685371
21	exp Cardiovascular Diseases/	2456551
22	cvd.mp.	29738
23	cardio*.mp.	900551
24	heart*.mp. or exp Heart Diseases/	1699628
25	21 or 22 or 23 or 24	3149038
26	exp Death/	151245
27	mortality.mp. or exp Mortality/	1201498
28	prediction.mp.	212071

29	morbidity.mp. or exp Morbidity/	865304
30	26 or 27 or 28 or 29	2093259
31	8 and 20 and 25 and 30	9303
32	exp Cohort Studies	2095359
33	exp Observational Study/ or observational.mp.	199315
34	32 or 33	2187814
35	31 and 34	3756

Author and year of publication				
Study identifier				
Reviewer				
Biases	Issues to consider for judging overall rating of "Risk of bias"	Study Methods & Comments	Rating of reporting	Rating of "Risk of bias"
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	Goal: To judge the risk of selection bias (likelihood that relationship between <i>PF</i> and <i>outcome</i> is different for participants and eligible non-participants).			
Source of target population	The source population or population of interest is adequately described for key characteristics (LIST) .			
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)			
Recruitment period	Period of recruitment is adequately described			
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described			
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).			
Adequate study participation	There is adequate participation in the study by eligible individuals			
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics (LIST) .			
Summary Study participation	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.			
2. Study Attrition	Goal: To judge the risk of attrition bias (likelihood that relationship between <i>PF</i> and <i>outcome</i> are different for completing and non-completing participants).			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.			
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.			
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.			
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST) . There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.			
Study Attrition Summary	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.			

3. Prognostic Factor Measurement	Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).			
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.			
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.			
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.			
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.			
PF Measurement Summary	PF is adequately measured in study participants to sufficiently limit potential bias.			
4. Outcome Measurement	Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.			
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).			
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.			
Outcome Measurement Summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.			
5. Study Confounding	Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.			
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).			
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.			
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.			
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).			
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).			
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome.			
6. Statistical Analysis and Reporting	Goal: To judge the risk of bias related to the statistical analysis and presentation of results.			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.			
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.			
	The selected statistical model is adequate for the design of the study.			
Reporting of results	There is no selective reporting of results.			
Statistical Analysis and Presentation Summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.			