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# Metabolically healthy obesity and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: a protocol for a systematic review and meta-analysis of prospective studies



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| Complete List of Authors: | tian, simiao; Affiliated Zhongshan Hospital of Dalian University, Department of Scientific Research Project<br>Liu, Yazhuo; Affiliated Zhongshan Hospital of Dalian University, Department of Clinical Nutrition and Metabolism<br>Feng, Ao; Affiliated Zhongshan Hospital of Dalian University, Department of Clinical Nutrition and Metabolism<br>Lou, Keli; Affiliated Zhongshan Hospital of Dalian University, Department of Clinical Nutrition and Metabolism<br>Dong, Huimin; Affiliated Zhongshan Hospital of Dalian University, Department of Clinical Nutrition and Metabolism |
| Keywords: | obesity, metabolic health, cardiovascular disease, mortality |
| | |

**Title:** Metabolically healthy obesity and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: a protocol for a systematic review and meta-analysis of prospective studies

**Author**: Simiao Tian[1,*], Yazhuo Liu[2], Ao Feng[2], Keli Lou[2] and Huimin Dong[2]

[1]Department of Scientific Research Project, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001; simiao_tian@sina.com (S.T.)

[2]Department of Clinical Nutrition and Metabolism, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001; yazhuo_liu@126.com(Y.L.); fengaoydwin@126.com(A.F.); loukeli@126.com (K.L.); dhm0622@icloud.com (H.D.)

***Corresponding author**: Dr. SimiaoTian, Department of Scientific Research Project, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001. Telephone: +86 (0)411 62887084. Fax: +86 (0)411 62893555. E-mail: Simiao_Tian@sina.com

## Abstract

**Introduction** Metabolically healthy obese phenotype (MHO) refers to obese individuals with an adequate metabolic profile and absence of metabolic syndrome. Many prospective studies have reported the benign condition relating the MHO phenotype and its potential role in reducing risk of cardiovascular disease, total cancer, and all cause and cause specific mortality. However, inconsistent results were found and the question remains controversial. We aim to conduct a systematic review and meta-analysis to clarify the associations these associations from relevant prospective studies.

**Methods and analysis** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 statement was used to prepare this protocol. MEDLINE, Web of Science databases, EMBASE and Cochrane Database will be used for literature search from their inception up to December 2019 with restriction of published studies in English. Published prospective studies reporting adjusted relative risk estimates for the association between MHO phenotype and cardiovascular disease, total cancer, all cause or cause specific mortality will be included. The process of study screening, selection and data extraction will be performed independently by two reviewers, and the risk of bias for the studies included will be assessed using the Newcastle-Ottawa Quality Assessment Scale. Hazard ratios (HRs) or relative risks (RRs) for disease events and mortality with 95% confidence intervals will be considered as primary outcomes, and summary HRs/RRs will be pooled using random-effects models. The Cochrane's Q and the $I^2$ statistics will be used to assess

and quantify heterogeneity, respectively. Subgroup analysis will also be carried out according to study characteristics to investigate potential sources of heterogeneity.

**Ethics and dissemination** As this meta-analysis is performed based on the published studies, no ethical approval and patient safety considerations are required. The findings of the study will be reported and submitted to a peer-reviewed journals for publication.

**PROSPERO registration number** CRD42019121766.

## Strength and limitations of this study

- This review is anticipated to be the first comprehensive meta-analysis of prospective studies to address the metabolically healthy obesity (MHO) to the risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and all cause mortality as well as less common causes of death.
- This systematic review and meta-analysis will provide a more up-to-date and comprehensive assessment of the MHO and several health outcomes
- This meta-analysis has a comprehensive literature search strategy involving restriction of studies to prospective studies, and will ensure that both the risk of bias and the quality of evidence of the included studies is properly assessed by Cochrane risk of bias assessment tool and Newcastle-Ottawa Quality Scale, respectively.
- Only included studies written in English may lead to publication bias.

## Introduction

Obesity is now one of the major public health problems and becomes a worldwide epidemic in the past four decades. Its prevalence has risen globally from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women in the same period.[1] The excess body weight was estimated to affect nearly 2 billion people, and accounted for approximately 4 million deaths and 120 million disability-adjusted life-years.[2,3] Obesity is a well-established risk factor for a great number of cardiovascular diseases (CVDs) and metabolic disorders,[4-6] and also has been shown as the main cause of CVD, cancer mortality and all-cause mortality.[7-10] However, obese people may vary in their body fat distribution and cardiometabolic profiles, thereby their association with morbidity and mortality could be heterogeneous in the obese people.[11,12] In this context, recent search focused on a novel subgroup of obese individuals who seem to have an adequate metabolic profile and do not have metabolic syndrome whilst being categorized as obese, referred as metabolically healthy obese (MHO).[13,14] Multiple studies showed that MHO phenotype accounted for as much as 10-50 % of the obese adults, depending on the population and the criteria used to ascertain metabolic health.[12,15] A very recent meta-analysis of 40 population-based studies reported an overall prevalence of 35% among obese adults.[16]

The extent to which the MHO phenotype is the benign condition and is associated with a lower risk of adverse health outcomes and all-cause mortality remains controversial. Some studies have confirmed a protective effect and no increased risk of CVD and mortality among MHO individuals, particularly compared with at-risk

obese;[17-19] whereas several other studies have shown a higher risk of CVD, cancer incidence and mortality in this group compared with metabolically healthy normal weight (MH-NW) individuals.[20-22] For instance, a 10-years follow-up study of 25,626 women aged 45 years and more found no increased CVD risk for MHO individuals,[23] a finding replicated in 15-year follow up Italian study of obesity and insulin sensitivity.[24] In contrast, another study showed that overweight and obese individuals without the metabolic syndrome had an increased risk of CVD compared with MHNW individuals after a 17 year follow-up, a finding justified by using 5 different metabolic health definitions.[25] It is important to note that inconsistent results depend on study design, population, follow-up time and MHO definition used. Several meta-analysis studies have investigated this ongoing controversy;[26-28] however the reliability of summarized evidences was questionable due to methodological constraints. Some roughly merged the incidents of CV events and all-cause mortality together instead of differentiating these two outcomes, some calculated the pooled risk estimate based on unadjusted risk estimates, and some only considered metabolic syndrome as MHO definitions, resulting in a limited number of analyzed studies.[26,27] The meta-analysis conducted by Zhang *et al.*, including a large sample size, enabled the determination of a robust and reliable risk estimates of CV events and mortality for MHO individuals by using both raw data and fully adjusted effect sizes from original studies,[28] but their meta-analysis study was not up-to-date, and more importantly, the association with cancer events and various cause specific mortality is still scarce.

**Objectives:**

The protocol study is designed to establish an explicit methodology for systematically and comprehensively conducting a review evidence and meta-analysis, and the aim is to (1) clarify whether is there an increase in risk of developing cardiovascular disease, total cancer, and all cause and cause specific mortality in adults with MHO, compared with their MH-NW peers; (2) and to define more accurate estimates of risk.

## Methods and analysis

### Registration and Review design

The study protocol has been registered with the international prospective register of systematic reviews (PROSPERO), and the registration number is CRD42019121766. The procedure for this study will be conducted in accordance with the guidelines provided by the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P).[29]

### Search strategy

A literature search will be undertaken using the following electronic databases: MEDLINE (via PubMed), ISI Web of Knowledge databases, EMBASE and the Cochrane Database to identify published studies. The databases will be searched from their inception to December 2019. In addition, the literature search will be later

updated and supplemented through the manual review of reference list of obtained articles. The following search terms will be used as keywords or (and) MeSH terms in the electronic search: BMI, obesity, metabolic, metabolically, healthy, metabolic syndrome, cardiovascular disease, risk, mortality, cause of death. Details of search terms and strategy for MEDILINE is provided in Table 1, and this strategy will be adapted to suit other databases.

**Inclusion criteria**

All prospective studies of MHO and incidence or mortality from coronary heart disease, stroke, cardiovascular disease, total cancer, and all cause and cause specific mortality will be considered eligible and included if they meet the following criteria:

1. The study design is a prospective cohort study;
2. Metabolically healthy obesity and other obesity phenotypes (e.g. metabolically healthy normal-weight and metabolically unhealthy obese) are defined according to the cross-classification of obesity criteria and metabolic health status. Obesity is defined using body mass index (BMI), waist circumference (WC) or body fat%; metabolic health status is defined using any of the following published metabolic syndrome (MetS) criteria: the Adult Treatment Panel-III (ATP-III)-based criterion (including any extended or modified ATP III criteria), the International Diabetes Federation (IDF) criteria, Joint Interim Statement (JIS) criteria, Harmonized MetS criteria, the Wildman criteria, the Karelis criteria, insulin

resistance (IR)- or risk score-based criteria (e.g. the Homeostasis model assessment of IR (HOMA-IR) index of having HOMA-IR in the upper quartile of the HOMA index and the TyG index of having TyG >8.82/8.73 for men/women), or other cardiometabolic clusterings.

3. The main outcomes of interest are coronary heart disease (total coronary heart disease or major coronary event, non fatal myocardial infarction (MI), any MI, fatal MI, incident ischaemic heart disease, fatal ischaemic heart disease, acute coronary syndrome), stroke (total stroke, ischaemic, haemorrhagic, intracerebral and subarachnoidal haemorrhage), total cardiovascular disease (coronary heart disease and stroke combined), and total cancer and all-cause mortality; the secondary outcomes will be cause-specific mortality from any cause of death.

4. Outcomes are measured by multivariate Cox proportional hazards models, and the relative ratio (RR) or hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) are reported.

5. Population of adults or participants are aged 18 years and older.

6. Studies are published in English.

**Study selection**

All investigators will be properly trained prior to data screening task. Two review author (KL and HD) will first screen the title and abstract of the searched studies independently and in duplicate to assess the eligibility of the searched studies.

Then, all potentially eligible studies will be retrieved and the same review authors will review full-text articles for inclusion, according to prespecified inclusion criteria. When disagreements occur, it will be resolved by group discussion or, if required, a third author (AF) will be consulted to evaluate the full text and the discrepancy. In addition, excluded studies and the rationale for exclusion will be documented. Figure 1 depicts the study selection processes in a PRISMA flow diagram.

**Data extraction**

We will extract results and study characteristics into tables using a standardized data collection form from eligible studies. Information that needed to be extracted will be as follow: first author's name, year of publication, country or region, duration of follow up, study location, sample size and number of events or deaths, gender proportion and age at baseline year, baseline MHO sample size, MHO definition, adjustments or covariates in the models, outcomes, the size of the association (HRs, RRs or ORs with 95% CI). If one article contained several MHO definitions, we will treat each definition as an independent one. The data extraction will be independently conducted by KL and HD, and be checked for accuracy by AF. All disagreements will be settled by discussion until a consensus is reached. In case of lacking key information, authors of primary studies will be contacted and consulted for obtaining missing data.

## Study quality assessment

Study quality of included studies will be assessed by the Newcastle-Ottawa Quality Scale (NOS) adopted for cohort studies,[30] and this scale awards 0-9 score points based on the selection, comparability, and outcome assessment. Specifically, the NOS includes the following criteria with associated points: (1) representativeness (*); (2) selection of non-exposed cohort (*); (3) exposure-ascertainment (*); (4) demonstration of outcome not present at start (*); (5) Adjustment for age/Adjustment for any other factor (**); (6) assessment of outcome (*); (7) long enough follow-up (*) and (8) adequacy of follow-up (*). We will consider studies with 0-3, 4-6, and 7-9 points to represent low, medium, and high quality studies, respectively. The study quality will be independently assessed by two reviewers (XX and XX), and if any discrepancies, we will resolved by group discussion or consultation from with a third reviewer.

## Data synthesis and statistical analysis

Once the data extraction has been completed, we will conduct the statistical analysis. All statistical analyses will be done with R version 3.2 software (R Foundation for Statistical Computing, Vienna, Austria)[31] and "*metafor*" package of R.[32] In the present meta-analysis, the HR with its 95% CI will be as a common measure of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, and total cancer, and of all-cause mortality for the MHO group

compared with the MHNW group (the reference group). For studies that reported several multivariable-adjusted HR, we will use the most fully adjusted for potential confounders in the meta-analysis. Heterogeneity between studies will be evaluated using the Cochrane's Q and Higgins $I^2$ statistics, respectively.[33] For the Q statistic a P $< 0.1$ is considered to be significant, and $I^2$ values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively. Either fixed- or random-effects models, depending on heterogeneity magnitude, will be applied to calculate the summary risk estimates and 95% CI for outcomes in the MHO group. In the fixed-effect model, the pooled HR is obtained by averaging the lnHR (HR value in log scale) weighted by the inverses of their variances.[34] In the random-effect model, the DerSimonian-Laird method is used to further incorporate between-study heterogeneity.[35]

In case of substantial heterogeneity, subgroup analyses will be further performed to investigate the potential source of between-study heterogeneity using following variables: gender (men and women), follow-up duration (<5 years, 5-10 years and >10 years), participant's age at baseline (<50 year old and $\geq$ 50 year old), model adjusted for physical activity (No vs Yes), criterion used to define metabolic health (ATP-III, JIF or IDF, HOMA vs others), geographic location (Asia, Europe, North America, others), sample size (<5000, 5000-10000, >10000) and study quality (0-3 stars, 4-6 stars, 7-9 stars).

Furthermore, a sensitivity analysis will be conducted by removing one study in each turn, the rest of the studies are analyzed to investigate the robustness of the

findings.[36] Potential publication bias will be assessed with the aid of the Egger's rank and regression test,[37,38] and the visual assessment of funnel plots will also be used if there are sufficient studies (10 or more) in the meta-analysis.[39]

## Patient and public involvement

Patients and/or the public were not directly involved in this study.

## Potential protocol amendments

The current protocol as written will not be modified in the course of the study. However, any modification will be concisely described in the final review.

## Ethics and dissemination

This study will not conduct a primary data collection, but will only include previous published studies. Therefore, no ethical approval will be required.

The findings of the study will be reported according to the PRISMA-compliant guidelines and submitted to a peer-reviewed journals for publication and also presented at conferences.

**Acknowledgments** The authors would like to thank the experts from Native EE for invaluable assistance in English language editing.

**Contributions** ST designed the study protocol and registered the protocol on the PROSPERO database. YL and AF drafted the manuscript. KL and HD tested the feasibility of the study. AF will perform the data collection and analyses. ST revised and finalized the study protocol. All authors reviewed and approved the final manuscript for submission.

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**Competing interests** None declared.

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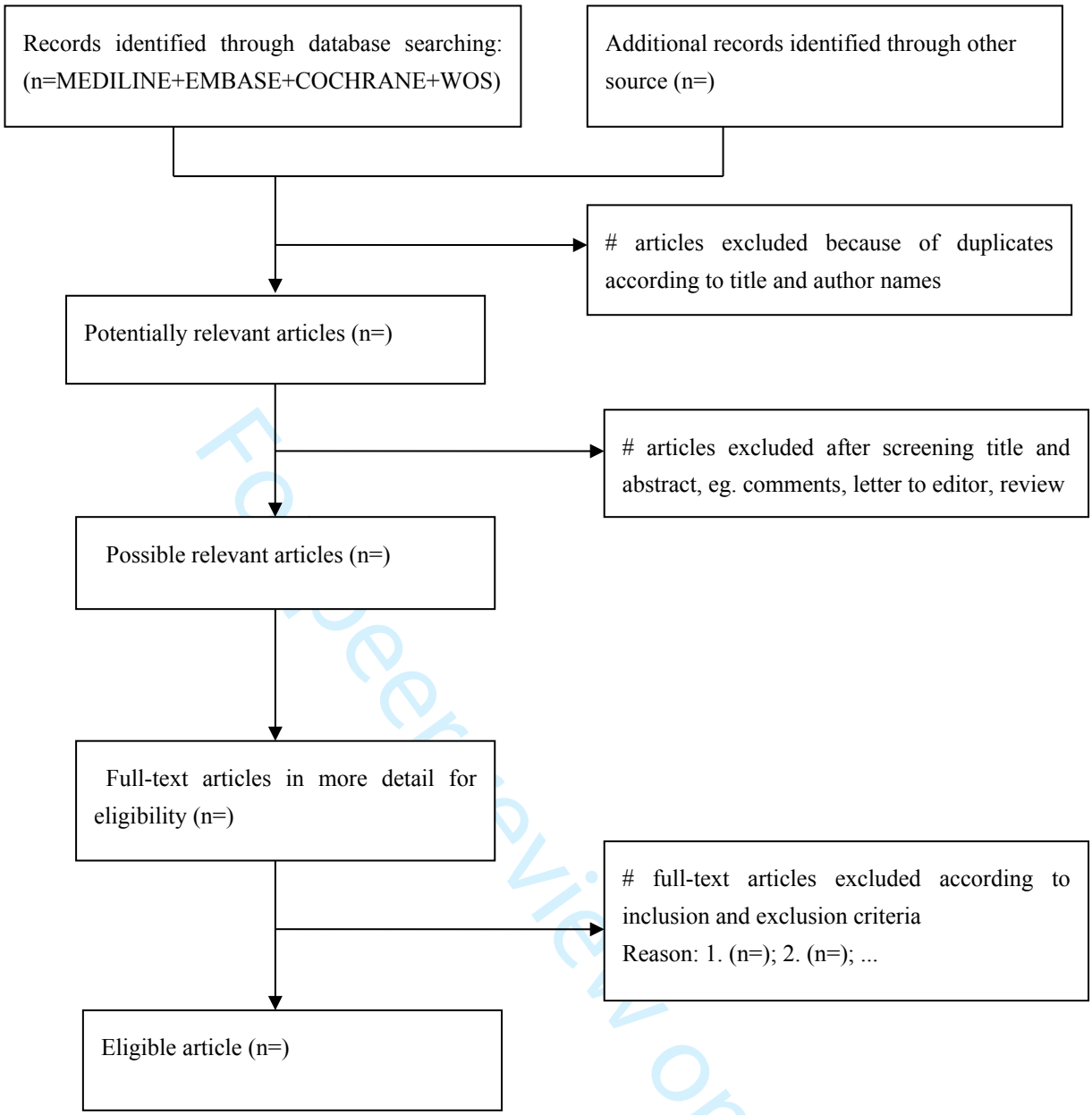
## Figure legends

**Figure 1.** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study selection.

Table 1. Proposed search terms

| | Search items |
|---|---|
| 1. | "Body mass index" OR "Obesity.mp. or OBESITY/" OR "Adiposity.mp. or ADIPOSITY/" OR "Waist Circumference.mp. or Waist Circumference/" OR "body fat or adipose tissue" |
| 2. | "Metabolic Syndrome.mp. or Metabolic Syndrome/" OR "Insulin Resistance.mp. or Insulin Resistance/" OR "Insulin sensitive.mp." OR "Metabolic Health.mp." OR "Metabolically Healthy.mp." OR "Obesity/ or Metabolically Benign.mp. or Overweight/" OR "Metabolically Healthy Obesity.mp. or Obesity, Metabolically Benign/" OR "Metabolically Benign Obesity.mp. or Obesity, Metabolically Benign/" |
| 3. | #1 AND #2 |
| 4. | "coronary heart disease" or "heart disease" or "ischemic heart disease" or "ischaemic heart disease" or "CHD" or "coronary artery disease" or "myocardial infarction" or "stroke" or "ischemic stroke" or "haemorrhagic stroke" or "cardiovascular disease" or CVD or cancer or "total cancer" or mortality or "all-cause mortality" or "total mortality" or "survival" |
| 5. | "case-control" or "cohort" or "cohorts" or "prospective" or "longitudinal" or "retrospective" or "follow-up" or "cross-sectional" or "population-based" or "relative risk" or "relative risk" or "odds ratio" or "hazard ratio" or "incidence rate ratio" |
| 6. | #3 AND #4 AND #5 |



# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7-8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6-7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 8-9 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 9-10 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6-7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 10-11 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 10-11 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 11-12 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 12 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 13 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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**Title:** Metabolically healthy obesity and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: a protocol for a systematic review and meta-analysis of prospective studies

**Author**: Simiao Tian[1,*], Yazhuo Liu[2], Ao Feng[2], Keli Lou[2] and Huimin Dong[2]

[1]Department of Scientific Research Project, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001; simiao_tian@sina.com (S.T.)

[2]Department of Clinical Nutrition and Metabolism, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001; yazhuo_liu@126.com(Y.L.); fengaoydwin@126.com(A.F.); loukeli@126.com (K.L.); dhm0622@icloud.com (H.D.)

***Corresponding author**: Dr. SimiaoTian, Department of Scientific Research Project, Affiliated Zhongshan Hospital of Dalian University, NO. 6 Jiefang Street Zhongshan District, Dalian, Liaoning Province, People's Republic of China, 116001. Telephone: +86 (0)411 62887084. Fax: +86 (0)411 62893555. E-mail: Simiao_Tian@sina.com

## Abstract

**Introduction** Metabolically healthy obese phenotype (MHO) refers to obese individuals with an adequate metabolic profile and absence of metabolic syndrome. Many prospective studies have reported the benign condition relating the MHO phenotype and its potential role in reducing risk of cardiovascular disease, total cancer, and all cause and cause specific mortality. However, inconsistent results were found and the question remains controversial. We aim to conduct a systematic review and meta-analysis to clarify the associations these associations from relevant prospective studies.

**Methods and analysis** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 statement was used to prepare this protocol. MEDLINE, Web of Science databases, EMBASE and Cochrane Database will be used for literature search from their inception up to December 2019 with restriction of published studies in English. Published prospective studies reporting adjusted relative risk estimates for the association between MHO phenotype and cardiovascular disease, total cancer, all cause or cause specific mortality will be included. The process of study screening, selection and data extraction will be performed independently by two reviewers, and the risk of bias for the studies included will be assessed using the Newcastle-Ottawa Quality Assessment Scale. Hazard ratios (HRs) or relative risks (RRs) for disease events and mortality with 95% confidence intervals will be considered as primary outcomes, and summary HRs/RRs will be pooled using random-effects models. The Cochrane's Q and the $I^2$ statistics will be used to assess

and quantify heterogeneity, respectively. Subgroup analysis will also be carried out according to study characteristics to investigate potential sources of heterogeneity.

**Ethics and dissemination** As this meta-analysis is performed based on the published studies, no ethical approval and patient safety considerations are required. The findings of the study will be reported and submitted to a peer-reviewed journals for publication.

**PROSPERO registration number** CRD42019121766.

## Strength and limitations of this study

- This review is anticipated to be the first comprehensive meta-analysis of prospective studies to address the metabolically healthy obesity (MHO) to the risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and all cause mortality as well as less common causes of death.
- This systematic review and meta-analysis will provide a more up-to-date and comprehensive assessment of the MHO and several health outcomes
- This meta-analysis has a comprehensive literature search strategy involving restriction of studies to prospective studies, and will ensure that both the risk of bias and the quality of evidence of the included studies is properly assessed by Cochrane risk of bias assessment tool and Newcastle-Ottawa Quality Scale, respectively.
- Only included studies written in English may lead to publication bias.

## Introduction

Obesity is now one of the major public health problems and becomes a worldwide epidemic in the past four decades. Its prevalence has risen globally from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women in the same period.[1] The excess body weight was estimated to affect nearly 2 billion people, and accounted for approximately 4 million deaths and 120 million disability-adjusted life-years.[2,3] Obesity is a well-established risk factor for a great number of cardiovascular diseases (CVDs) and metabolic disorders,[4-6] and also has been shown as the main cause of CVD, cancer mortality and all-cause mortality.[7-10] However, obese people may vary in their body fat distribution and cardiometabolic profiles, thereby their association with morbidity and mortality could be heterogeneous in the obese people.[11,12] In this context, recent search focused on a novel subgroup of obese individuals who seem to have an adequate metabolic profile and do not have metabolic syndrome whilst being categorized as obese, referred as metabolically healthy obese (MHO).[13,14] Multiple studies showed that MHO phenotype accounted for as much as 10-50 % of the obese adults, depending on the population and the criteria used to ascertain metabolic health.[12,15] A very recent meta-analysis of 40 population-based studies reported an overall prevalence of 35% among obese adults.[16]

The extent to which the MHO phenotype is the benign condition and is associated with a lower risk of adverse health outcomes and all-cause mortality remains controversial. Some studies have confirmed a protective effect and no increased risk of CVD and mortality among MHO individuals, particularly compared with at-risk

obese;[17-19] whereas several other studies have shown a higher risk of CVD, cancer incidence and mortality in this group compared with metabolically healthy normal weight (MH-NW) individuals.[20-22] For instance, a 10-years follow-up study of 25,626 women aged 45 years and more found no increased CVD risk for MHO individuals,[23] a finding replicated in 15-year follow up Italian study of obesity and insulin sensitivity.[24] In contrast, another study showed that overweight and obese individuals without the metabolic syndrome had an increased risk of CVD compared with MHNW individuals after a 17 year follow-up, a finding justified by using 5 different metabolic health definitions.[25] It is important to note that inconsistent results depend on study design, population, follow-up time and MHO definition used. Several meta-analysis studies have investigated this ongoing controversy;[26-28] however the reliability of summarized evidences was questionable due to methodological constraints. Some roughly merged the incidents of CV events and all-cause mortality together instead of differentiating these two outcomes, some calculated the pooled risk estimate based on unadjusted risk estimates, and some only considered metabolic syndrome as MHO definitions, resulting in a limited number of analyzed studies.[26,27]

Another two recent meta-analyses reported that, compared with participants with MHNW, those with MHO were at higher risk of cardiovascular events but not all-cause mortality.[28,29] The systematic review and meta-analysis by Eckel *et al.* is particularly important because it was the first to carefully consider the full range of possible definitions of metabolic health,[28] and this aspect is crucial when addressing the role of this complex condition for the prediction and prevention of

cardiometabolic diseases and possibly of certain types of cancer.[30] Besides, the meta-analysis conducted by Eckel *et al.* extended literature search to include only prospective studies with strict standard of reference groups considered, and perform a comprehensive subgroup analyses.[28] The meta-analysis conducted by Zheng *et al.*,[29] including a large sample size, enabled the determination of a robust and reliable risk estimates of CV events and mortality for MHO individuals by using both raw data and fully adjusted effect sizes from original studies, but these two aforementioned meta-analysis study were not up-to-date, with their literature search until April 2014 and September 2015, respectively, and since then, according to our general search, there are more than 17 new publications investigating MHO and health outcomes between 2016-2019. More importantly, the association with cancer events and various cause specific mortality is still scarce.

**Objectives:**

The protocol study is designed to establish an explicit methodology for systematically and comprehensively conducting a review evidence and meta-analysis, and the aim is to (1) clarify whether is there an increase in risk of developing cardiovascular disease, total cancer, and all cause and cause specific mortality in adults with MHO, compared with their MH-NW peers; (2) and to define more accurate estimates of risk.

## Methods and analysis

### Registration and Review design

The study protocol has been registered with the international prospective register of systematic reviews (PROSPERO), and the registration number is CRD42019121766. The procedure for this study will be conducted in accordance with the guidelines provided by the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P).[31]

### Search strategy

A literature search will be undertaken using the following electronic databases: MEDLINE (via PubMed), ISI Web of Knowledge databases, EMBASE and the Cochrane Database to identify published studies. The databases will be searched from their inception to December 2019. In addition, the literature search will be later updated and supplemented through the manual review of reference list of obtained articles. The following search terms will be used as keywords or (and) MeSH terms in the electronic search: BMI, obesity, metabolic, metabolically, healthy, metabolic syndrome, cardiovascular disease, risk, mortality, cause of death. Details of search terms and strategy for MEDILINE is provided in Table 1, and this strategy will be adapted to suit other databases.

### Inclusion criteria

All prospective studies of MHO and incidence or mortality from coronary heart disease, stroke, cardiovascular disease, total cancer, and all cause and cause specific mortality will be considered eligible and included if they meet the following criteria:

1. The study design is a prospective cohort study;
2. Metabolically healthy obesity and other obesity phenotypes (e.g. metabolically healthy normal-weight and metabolically unhealthy obese) are defined according to the cross-classification of obesity criteria and metabolic health status. Obesity is defined using body mass index (BMI), waist circumference (WC) or body fat%; metabolic health status is defined using any of the following published metabolic syndrome (MetS) criteria: the Adult Treatment Panel-III (ATP-III)-based criterion (including any extended or modified ATP III criteria), the International Diabetes Federation (IDF) criteria, Joint Interim Statement (JIS) criteria, Harmonized MetS criteria, the Wildman criteria, the Karelis criteria, insulin resistance (IR)- or risk score-based criteria (e.g. the Homeostasis model assessment of IR (HOMA-IR) index of having HOMA-IR in the upper quartile of the HOMA index and the TyG index of having TyG >8.82/8.73 for men/women), or other cardiometabolic clusterings.
3. The main outcomes of interest are coronary heart disease (CHD) (total coronary heart disease or major coronary event, non fatal myocardial infarction (MI), any MI, fatal MI, incident ischaemic heart disease, fatal ischaemic heart disease, acute coronary syndrome), stroke (total stroke, ischaemic, haemorrhagic, intracerebral

and subarachnoidal haemorrhage), total cardiovascular disease (coronary heart disease and stroke combined), and total cancer and all-cause mortality; the secondary outcomes will be cause-specific mortality from any cause of death.

4. Outcomes are measured by multivariate Cox proportional hazards models, and the relative ratio (RR) or hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) are reported.

5. Population of adults or participants are aged 18 years and older.

6. Studies are published in English.

**Study selection**

All investigators will be properly trained prior to data screening task. Two review author (KL and HD) will first screen the title and abstract of the searched studies independently and in duplicate to assess the eligibility of the searched studies. Then, all potentially eligible studies will be retrieved and the same review authors will review full-text articles for inclusion, according to prespecified inclusion criteria. When disagreements occur, it will be resolved by group discussion or, if required, a third author (AF) will be consulted to evaluate the full text and the discrepancy. In addition, excluded studies and the rationale for exclusion will be documented. Figure 1 depicts the study selection processes in a PRISMA flow diagram.

**Data extraction**

We will extract results and study characteristics into tables using a standardized data collection form from eligible studies. Information that needed to be extracted will be as follow: first author's name, year of publication, country or region, duration of follow up, study location, sample size and number of events or deaths, gender proportion and age at baseline year, baseline MHO sample size, MHO definition, adjustments or covariates in the models, outcomes, the size of the association (HRs, RRs or ORs with 95% CI). We compared the risk of having various health outcomes, such as mortality and CVD events, and calculate the pooled risk estimates for the MHO, metabolically unhealthy normal weight (MUNW) and metabolically unhealthy obesity (MUO) phenotypes using metabolically healthy normal-weight (MHNW) participants as the reference. If one article contained several obesity and metabolic health definitions, we will treat each definition as an independent one. It is noteworthy mentioning that several studies revealed that MUNW individuals, even though with a normal BMI range, was unexpected associated with higher risk of all-cause mortality and/or cardiovascular events.[26] In this regard, Stefan *et al.* provided a comprehensive review and data addressing to what extent major risk phenotypes determine metabolic health in lean compared to overweight and obese people and provide support for the existence of a lipodystrophylike phenotype in the general population.[32] Therefore, for the sake of integrity of the study, the risk of MUNW and other obesity phenotypes with health outcomes will also be summarized in the present study.

The data extraction will be independently conducted by KL and HD, and be

checked for accuracy by AF. All disagreements will be settled by discussion until a consensus is reached. In case of lacking key information, authors of primary studies will be contacted and consulted for obtaining missing data.

**Study quality assessment**

Study quality of included studies will be assessed by the Newcastle-Ottawa Quality Scale (NOS) adopted for cohort studies,[33] and this scale awards 0-9 score points based on the selection, comparability, and outcome assessment. Specifically, the NOS includes the following criteria with associated points: (1) representativeness (*); (2) selection of non-exposed cohort (*); (3) exposure-ascertainment (*); (4) demonstration of outcome not present at start (*); (5) Adjustment for age/Adjustment for any other factor (**); (6) assessment of outcome (*); (7) long enough follow-up (*) and (8) adequacy of follow-up (*). We will consider studies with 0-3, 4-6, and 7-9 points to represent low, medium, and high quality studies, respectively. The study quality will be independently assessed by two reviewers (XX and XX), and if any discrepancies, we will resolved by group discussion or consultation from with a third reviewer.

**Data synthesis and statistical analysis**

Once the data extraction has been completed, we will conduct the statistical analysis. All statistical analyses will be done with R version 3.2 software (R

Foundation for Statistical Computing, Vienna, Austria)[34] and "*metafor*" package of R.[35] In the present meta-analysis, the HR with its 95% CI will be as a common measure of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, and total cancer, and of all-cause mortality for the MHO group compared with the MHNW group (the reference group). For studies that reported several multivariable-adjusted HR, we will use the most fully adjusted for potential confounders in the meta-analysis. Heterogeneity between studies will be evaluated using the Cochrane's Q and Higgins $I^2$ statistics, respectively.[36] For the Q statistic a P $< 0.1$ is considered to be significant, and $I^2$ values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively. Either fixed- or random-effects models, depending on heterogeneity magnitude, will be applied to calculate the summary risk estimates and 95% CI for outcomes in the MHO group. In the fixed-effect model, the pooled HR is obtained by averaging the lnHR (HR value in log scale) weighted by the inverses of their variances.[37] In the random-effect model, the DerSimonian-Laird method is used to further incorporate between-study heterogeneity.[38]

The sensitivity analyses will also performed when metabolic syndrome was used for metabolic health criteria. In literature, several studies defined metabolic health by the absence of all metabolic factors, and this stricter definition may lead a different conclusion.[28] This findings were consistent with a very recent evidence based on the large European Prospective Investigation into Cancer and Nutrition study ('EPIC-CVD').[39] In this case-cohort analysis including 520000 Europeans after a

median follow-up of 12.2 years, Lassale *et al.* found that the MHO phenotype, defined as none of MetS component, was not associated with increased risk of CHD (HR, 1.21, 95% CI 0.76-1.92) whereas MHO individuals were at higher risk of CHD with loose definition of MetS (HR, 1.28, 95% CI 1.03-1.58).[39] For the sake of the integrity of the study and comparability with other meta-analysis, we will also perform additional sensitivity analyses with different definitions of metabolic health when MetS criteria was used: excluding the WC criterion from the definition of MetS, modifying the definition of metabolically healthy to be <2 abnormalities; (vii) defining metabolically healthy participants as having none of four possible abnormalities (elevated blood pressure, triglyceridaemia, hyperglycaemia, low HDL-cholesterol).

**Subgroup analyses**

In case of substantial heterogeneity, subgroup analyses will be further performed to investigate the potential source of between-study heterogeneity using following variables: gender (men and women), model adjusted for physical activity (PA) (No vs Yes), follow-up duration (<5 years, 5-10 years and >10 years), participant's age at baseline (<50 year old and ≥ 50 year old), criterion used to define metabolic health (ATP-III, JIF or IDF, HOMA vs others), geographic location (Asia, Europe, North America, others), sample size (<5000, 5000-10000, >10000) and study quality (0-3 stars, 4-6 stars, 7-9 stars).

It is noteworthy mentioning that among various factors, PA and/or cardiorespiratory fitness (CRF) has been recognized as a novel characteristic of the MHO, as well as play an important role in MHO prognosis.[40] Specially, based on Aerobics Center Longitudinal Study,[40] MHO individuals have a significantly higher CRF level than the individuals with MUO, and this findings have been confirmed by recent meta-analysis of Ortega *et al.* that MHO, compared with MUO, have higher levels of PA, lower levels of sedentary behavior, and higher levels of CRF.[41] Recently, Lavie *et al.* provided a state-of-the-art review on the causes of obesity and effective modalities for this prevention, and the importance of fitness and lifestyle consideration to protect MHO from cardiovascular diseases.[40] Therefore, the impact of PA/CRF will be taken into account in the subgroup analysis for the prognosis of future all-cause mortality and other health outcomes in MHO individuals compared with MHNW.

It is also important to recognize that follow-up duration is a critical element in evaluating low-risk populations for future events. Several studies observed that an increased risk of adverse clinical outcomes occurred only after 8-10 years of follow-up,[42,43] which suggests a transient nature of the MHO phenotype. Indeed, based on a large-scale Nurses' Health Study including 90257 women, Eckel *et al.* found that after 30 year follow-up, the majority of MHO converted to unhealthy phenotypes, and among those who maintained MHO status during follow-up were still at a higher CVD compared with their MHNW peers (HR 1.57, 95% CI 1.03-2.38).[44] In this regard, whether or not MHO is a benign obesity phenotype may be impacted

on the length of follow-up; thus the duration of follow-up is another important factor to take into account in the subgroup analysis.

Furthermore, a sensitivity analysis will be conducted by removing one study in each turn, the rest of the studies are analyzed to investigate the robustness of the findings.[45] Potential publication bias will be assessed with the aid of the Egger's rank and regression test,[46,47] and the visual assessment of funnel plots will also be used if there are sufficient studies (10 or more) in the meta-analysis.[48]

## Patient and public involvement

Patients and/or the public were not directly involved in the design or planning of the study.

## Potential protocol amendments

The current protocol as written will not be modified in the course of the study. However, any modification will be concisely described in the final review.

## Ethics and dissemination

This study will not conduct a primary data collection, but will only include previous published studies. Therefore, no ethical approval will be required.

The findings of the study will be reported according to the PRISMA-compliant guidelines and submitted to a peer-reviewed journals for publication and also presented at conferences.

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**Contributions** ST designed the study protocol and registered the protocol on the PROSPERO database. YL and AF drafted the manuscript. KL and HD tested the feasibility of the study. AF will perform the data collection and analyses. ST revised and finalized the study protocol. All authors reviewed and approved the final manuscript for submission.

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**Competing interests** None declared.

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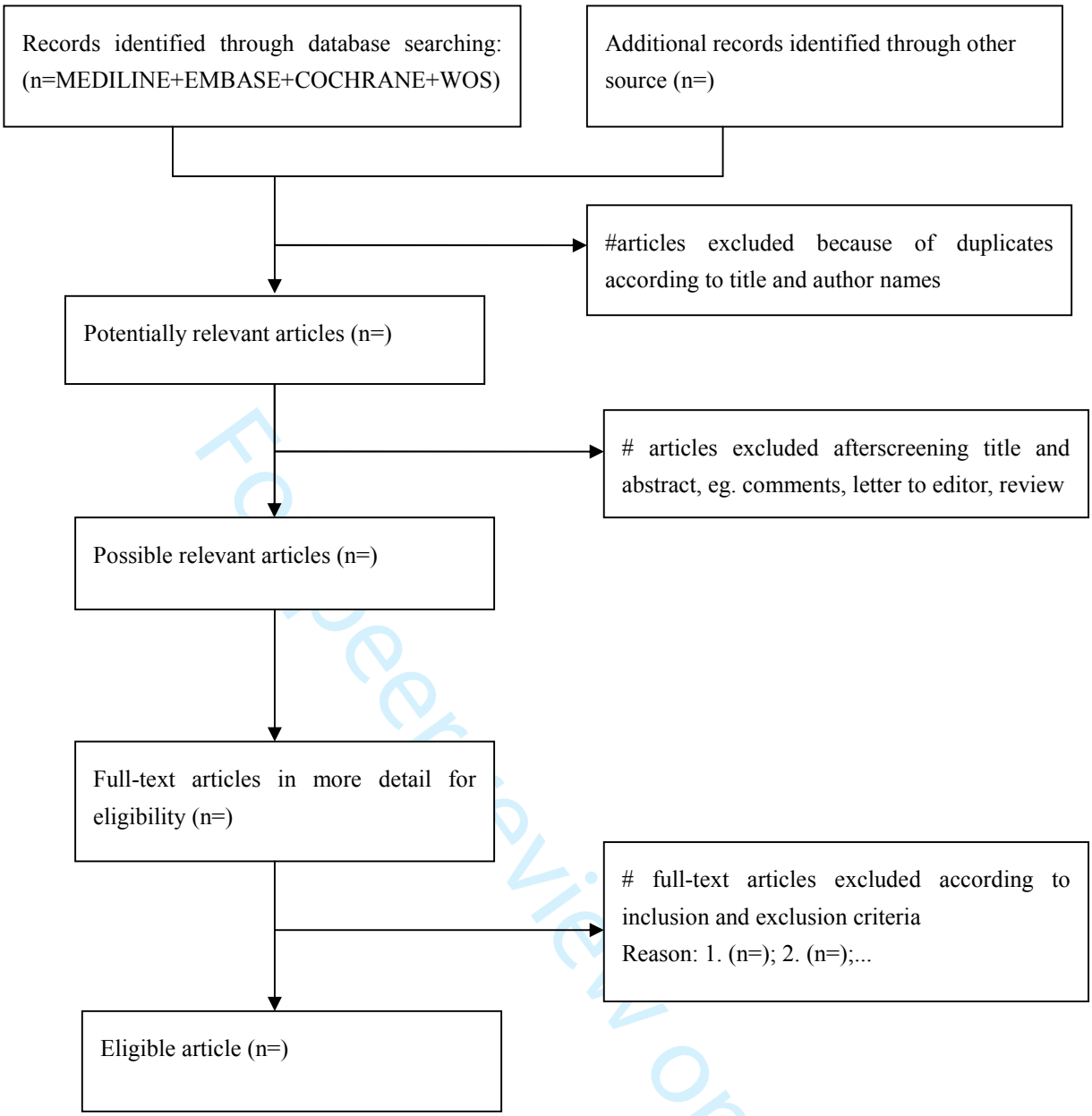
## Figure legends

**Figure 1.** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study selection.

Table 1. Proposed search terms

| | Search items |
|---|---|
| 1. | "Body mass index" OR "Obesity.mp. or OBESITY/" OR "Adiposity.mp. or ADIPOSITY/" OR "Waist Circumference.mp. or Waist Circumference/" OR "body fat or adipose tissue" |
| 2. | "Metabolic Syndrome.mp. or Metabolic Syndrome/" OR "Insulin Resistance.mp. or Insulin Resistance/" OR "Insulin sensitive.mp." OR "Metabolic Health.mp." OR "Metabolically Healthy.mp." OR "Obesity/ or Metabolically Benign.mp. or Overweight/" OR "Metabolically Healthy Obesity.mp. or Obesity, Metabolically Benign/" OR "Metabolically Benign Obesity.mp. or Obesity, Metabolically Benign/" |
| 3. | #1 AND #2 |
| 4. | "coronary heart disease" or "heart disease" or "ischemic heart disease" or "ischaemic heart disease" or "CHD" or "coronary artery disease" or "myocardial infarction" or "stroke" or "ischemic stroke" or "haemorrhagic stroke" or "cardiovascular disease" or CVD or cancer or "total cancer" or mortality or "all-cause mortality" or "total mortality" or "survival" |
| 5. | "case-control" or "cohort" or "cohorts" or "prospective" or "longitudinal" or "retrospective" or "follow-up" or "cross-sectional" or "population-based" or "relative risk" or "relative risk" or "odds ratio" or "hazard ratio" or "incidence rate ratio" |
| 6. | #3 AND #4 AND #5 |



**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 |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification | 1a | Identify the report as a protocol of a systematic review **(Page 1)** |
| 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 **(Page 3)** |
| Authors: | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **(Page 1)** |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review **(Page 16)** |
| 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 (**Page 15**) |
| Support: | | |
| Sources | 5a | Indicate sources of financial or other support for the review **(Page 16)** |
| Sponsor | 5b | Provide name for the review funder and/or sponsor **(Page 16)** |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (**Page 16**) |
| **INTRODUCTION** | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known **(Page 4-6)** |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **(Page 6)** |
| **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 **(Page 7-9)** |
| 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 **(Page 7)** |
| 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 **(Page 7)** |
| Study records: | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review **(Page 9-10)** |

| | | |
|---|---|---|
| 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) **(Page 9-11)** |
| 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 **(Page 9, 10-11)** |
| 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 **(Page 11)** |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **(Page 11-12)** |
| 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 **(Page 12)** |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised |
| | 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 $\tau$) **(Page 12)** |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **(Page 12-14)** |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **(Page 15, lines 300-304)** |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) **(Page 11, lines 219-230)** |

*** 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.**

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