

Are Abdominal Obese Metabolically Healthy Phenotype a Benign Condition? Protocol for a Systematic Review

Abstract

Background: The prevalence of obesity is increasing worldwide. Obesity is associated with severe health effects. Abdominal obesity has a strong association with metabolic dysfunction. A subgroup of people with central obesity has been identified without typical metabolic disorders associated with obesity that has been known metabolically healthy abdominal obese (MHAO). The purpose of this review is to evaluate the MHAO phenotype in the context of type 2 DM incidence, risk of cardiovascular diseases, and all-cause of mortality. **Methods:** This is a protocol of systematic review. We will search PubMed/MEDLINE, EMBASE, Web of Science, Cochrane Library, and ProQuest. Additional studies will be identified through manual searching of reference lists. Quantitative studies evaluating abdominal obesity phenotype outcomes in adults will be included. Primary results will be assaying abdominal obesity phenotype results, including DM2 incidence, cardiovascular disease risk, and all-cause mortality. Two reviewers will independently screen full-text articles and abstract data. **Statistical Analysis Used:** Potential conflicts will be resolved through discussion. **Results:** The study methodological quality (or bias) will be appraised using appropriate tools. If feasible, we will conduct a random-effects meta-analysis. The researchers will also assess the quality of the articles independently based on Newcastle-Ottawa scale. **Conclusions:** The results of this review will provide a useful reference for the effect of abdominal obesity on metabolic dysfunction and cardiovascular or all-cause mortality

Keywords: “All-cause mortality”, abdominal obesity, cardiovascular disease, metabolically healthy

Introduction

The prevalence of obesity is rising across the world. In the United States, the rate of obesity in adults was about 35.7% in 2010.^[1] Obesity is associated with obesity induced inflammations such as high level C-reactive protein or insulin and severe health effects such as hypertension, dyslipidemia, insulin resistance, type 2 diabetes (DM2), and cardiovascular disease (CVD).^[2-4]

Abdominal obesity has a stronger association with metabolic dysfunction than generalized obesity.^[3] Some studies have shown that abdominal obesity is an independent risk factor for DM2, dyslipidemia, hypertension, and coronary artery events.^[4] The risk of cardiovascular and all-cause mortality increases in abdominal obese populations in parallel with waist circumference (WC).^[5-7]

It appears that a certain percentage of obese individuals have a normal metabolic profile despite having high BMI so called

“metabolically healthy” obese (MHO). Whether or not “MHO” Individuals by their favorable metabolic profile, may have lower mortality rates or CVD than their “metabolically unhealthy” obese counterparts, remains unclear.^[8,9] Although some reports suggest that MHO phenotype might be at lower risk of diabetes, CVD, and all-cause mortality compared with their unhealthy counterparts, this phenotype might still have increased risks when compared to metabolically healthy non-obese individuals and controversies about the concept of “benign obesity” persist.^[8] Causes of these controversies can be due to different definition of metabolically healthy, duration of follow up or difference in abdominal fat. Visceral obesity is an important factor for progression to metabolic derangements.^[10] MHO individuals may have lower visceral fat (despite high BMI) that protect them from metabolic dysfunction. Abdominal fat may be a factor explaining differences in CVD or mortality risk in previous

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studies between metabolically healthy and unhealthy obese individuals (based on BMI).^[11-13]

This led to categorization of obesity phenotypes based on WC and metabolic syndrome. People were classified into 4 groups based on abdominal obesity and metabolic dysfunction.^[13,14] A subgroup of people with central obesity has been identified without typical metabolic disorders associated with obesity. Metabolically healthy abdominal obesity (MHAO) phenotype has been previously defined as a subgroup of abdominal obese individuals who do not have insulin resistance, dyslipidemia, or hypertension.^[15] Some studies indicate that 23.5% of abdominal obese cases can be categorized as MHAO.^[13,14]

The purpose of this review is to evaluate the MHAO phenotype in the context of type 2 DM incidence, cardiovascular disease risk, and all-cause mortality. We are going to answer that “are people with abdominal obesity and metabolically healthy at higher risk for DM2, CVD and mortality or metabolically healthy abdominal obesity is considered as a benign phenotype”?

Methods

This is a protocol of systematic review. The protocol of the systematic review was drafted and uploaded to the PROSPERO website. The protocol code was issued by PROSPERO (CRD42019111056) and will be reported based on the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA P) statement.^[16] The methods and results will also be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[17]

Eligibility criteria

Types of studies

Human quantitative studies (e.g., cohort studies) evaluating the association between abdominal obesity phenotype outcomes in adults will be included [Table 1].

Types of participants

We will assess all studies targeting adults (>20 years old) of abdominal obese phenotypes and evaluating the association of different abdominal obesity phenotypes (in compared with healthy non-abdominal obese phenotype individuals as the reference group) with DM2 incidence, risk of cardiovascular disease, and all-cause mortality.

We will consider at least four groups as exposure:

- (i) Metabolically healthy abdominal obese (abdominal obese without metabolic syndrome),
- (ii) Metabolically healthy non-abdominal obese (non-abdominal obese without metabolic syndrome),
- (iii) Metabolically unhealthy abdominal obese (abdominal obese with metabolic syndrome),

Table 1: PICO (population, intervention, comparator, outcome)

Topic	Abdominal obesity phenotypes
	A systematic review and meta-analysis
Population	Human Adults (≥20 years)
Intervention/ exposure	4 groups as exposure : (i) Metabolically healthy abdominal obese (abdominal obese without metabolic syndrome) (ii) Metabolically healthy non abdominal obese (non abdominal obese without metabolic syndrome) (iii) Metabolically unhealthy abdominal obese (abdominal obese with metabolic syndrome) (iv) Metabolically unhealthy non abdominal obese (non abdominal obese with metabolic syndrome)
Comparison	Metabolically healthy non abdominal obese participants will be considered as comparator group and all participants compare them
Outcome	all-cause mortality, cardiovascular disease (fetal & non fetal) and/or risk of type 2 DM

- (iv) Metabolically unhealthy non-abdominal obese (non-abdominal obese with metabolic syndrome).

Types of result

We will assess all studies with their primary outcomes on DM2 incidence, risk of cardiovascular disease (fetal or non-fetal), or all-cause mortality.

Electronic database search

To access studies conducted on abdominal obesity phenotypes and their outcomes (risk of type 2 DM, cardiovascular disease, and all-cause mortality, we will search PubMed/MEDLINE, EMBASE, Web of Science, Cochrane Library, and ProQuest (from inception onwards). Additional studies will be identified through manual searching of reference lists. The search will include a broad range of terms and keywords, including “central adiposity”, “abdominal obesity”, “obesity, abdominal”, “abdominal fat”, “diabetes mellitus type 2”, “cardiovascular diseases”, mortality, and “metabolically healthy”. To access all relevant articles, the reference list of review articles and meta-analyses (backward searching), cited articles (forward-searching), and papers introduced as “related articles” will be checked. Searches resulting in peer-reviewed articles, letters, abstracts, or editorials will be excluded.

The time of the actual start search was 27 September 2018 and time of updating the search was 7 June 2020.

Selection of studies

All studies obtained from different sources will be transferred to Endnote, and duplicates will be systematically removed so that a merged library can be created. Two reviewers will independently screen titles and abstracts according to predefined inclusion and

exclusion criteria checklist to identify potential studies for reviewing and exclude unrelated articles. In case of disagreement between the two reviewers, the final decision and judgment for including the study will be made based on the inclusion criteria with the opinion of a third person.

Full texts will be read by the two individuals separately, and final decisions will be made based on the inclusion criteria checklist.

As criteria to define metabolically healthy or abdominal obesity may vary in different studies, we will accept the definitions of them provided by authors in each study. If necessary and possible, we will contact the authors of studies to resolve any ambiguities. A third reviewer will decide any discrepancies in the selection of studies for inclusion in the review. All three reviewers will verify the final list of included studies in the review, and a PRISMA diagram will be used to show steps for inclusion of selected articles. [Figure 1].

In this study, the search strategy and the screening and selection of the data will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

An extraction form will be designed to collect information from each study that will include the following:

Study characteristics: title, study design, year of publication, journal, author, and period of follow up.

Methods: eligibility of study based on inclusion criteria, purpose of study, method of data collection, and sampling methods.

Participant characteristics: sample size, age (e.g., mean with standard deviation, range, etc.), gender, and definition of abdominal obesity and metabolic syndrome.

Results: primary results including DM2 incidence, risk of cardiovascular disease, and all-cause mortality.

Data synthesis

The information for each study (i.e., study characteristics, participants, outcomes, and findings) will be used to build evidence tables of an overall description of the included studies.

If necessary and possible, we will contact the authors of original studies to obtain missing or unpublished data and resolve any ambiguities.

Additional analyses

We will report risks as an incidence rate, relative risk (RR), or odds ratio (OR) and their respective 95% confidence intervals (CIs). We will determine statistical heterogeneity using I^2 . In all statistical analyses, P value of <0.05 will consider statistically significant. We will meta-analyze data from comparable studies if at least two studies are available. If studies are sufficient, and all data are available, sources of heterogeneity of studies will be further investigated by subgroup or meta-regression analysis. We will use the Cochran Q test to evaluate heterogeneity between studies, and consider a threshold P value less than 0.05 as statistically significant.

Heterogeneity assessment

We will also plan to evaluate the heterogeneity magnitude between studies using the I^2 testing. We will consider an I^2 index $\geq 50\%$ as an indication for serious heterogeneity. In the presence of heterogeneity, if possible, subgroup analyses based on age, sex, quality of article (low, moderate, or high risk of bias), length of follow up, and clinical outcome will be performed. We will explore any indications of significant inconsistency using meta-regression analyses.

Appraisal of study quality

The two researchers will also assess the quality of articles independently based on Newcastle-Ottawa scale (NOS) the Quality Assessment Form for cohort study.^[18] Studies will be classified based on cohort selection, comparability of groups and assessment of outcomes (good, fair, and poor quality):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure

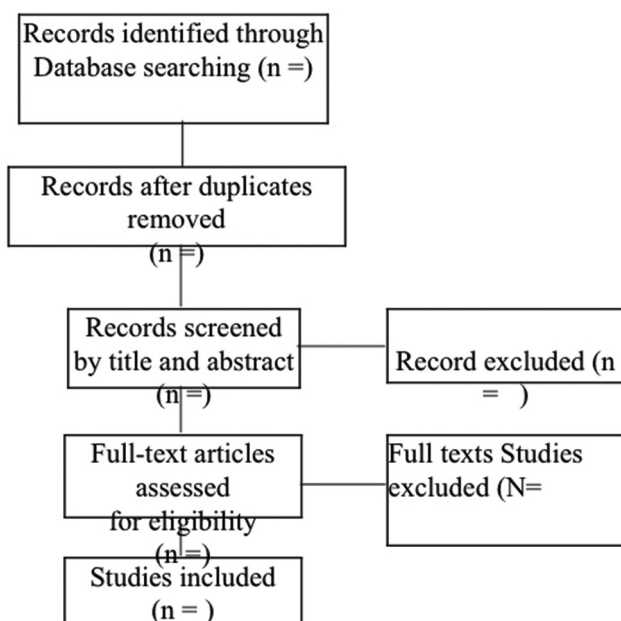


Figure 1: PRISMA diagram

domain. In this analysis, studies with at least 6 points will be considered of good quality. The results of the assessment will be shown in a table format. All three reviewers will resolve any differences in the quality assessment of articles by discussion.

If quantitative synthesis is not appropriate, we will use a summary table to describe definitions of metabolically healthy and abdominal obesity, sample size, outcome of interest, and duration of follow up. The findings of articles will be discussed, and the conclusion will depend on the power and strength of each study.

Discussion

This systematic review and meta-analysis will be the first of its kind in explaining the relationship between abdominal obesity phenotypes, mortality, and morbidity.

It appears that a certain proportion of abdominal obese individuals have a normal metabolic profile. It is unclear whether this group (MHAO) express a lower risk of all-cause mortality, CVD, or DM2 compared to “metabolically unhealthy” abdominal obese. Although individuals with MHO phenotype appear to be less at risk for cardiovascular events or mortality than those with metabolically healthy normal weight (MHNW) phenotype,^[19-21] abdominal obesity can be associated with increased cardiac and overall mortality, independent of generalized obesity, based on BMI.^[11,22] Lower WC in MHO phenotype, despite higher BMI, may justify a reduction in mortality or CVD in this group.^[23] Therefore, abdominal obesity may be a more important factor than BMI for CVD or mortality.

It seems that MHAO, cannot be defined as a truly healthy phenotype, since this group still has a higher all-cause mortality or CVD risk than “metabolically healthy” but non abdominal obese group in some studies.^[14,24] but in another study, MHAO was not at higher risk of all-cause mortality.^[13] In addition to the differences in definition of metabolically healthy or abdominal obesity in different studies, an important reason for the inconsistent findings might be the length of follow-up; studies with shorter follow-up have shown that “metabolically healthy” abdominal obese are not at increased risk while studies with longer follow-up have shown higher risk, especially when primary outcome is mortality.^[24] The findings suggest that it may take at least a decade for obesity-induced metabolic changes.^[25,26]

This systematic review will summarize evidence regarding the association between abdominal obesity phenotypes with DM2, cardiovascular disease and all-cause mortality.

Strengths and limitations of this study

This study is the first protocol of systematic review to examine the outcomes of abdominal obesity phenotypes.

This systematic review and meta-analysis will assess only the risk of DM2, CVD, and all-cause mortality, design does not allow the evaluation of other outcomes of abdominal obesity phenotype such as risk of cancer or renal failure or fatty liver.

Conclusions

The results of this review will provide a useful reference for the effect of abdominal obesity on metabolic dysfunction and cardiovascular or all-cause mortality.

Ethics and dissemination

The findings of the proposed review will be disseminated in peer-reviewed journals and presented at conferences.

Abbreviations

MHAO = Metabolically healthy abdominal obese, MNAO = Metabolically healthy non-abdominal obese, MUAO = Metabolically unhealthy abdominal obese, MUNAO = Metabolically unhealthy non-abdominal obese, MHO = Metabolically healthy obese, MONW = Metabolically Obese Normal Weight, PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Statement-Protocol Extension, WC = waist circumference, BMI = body mass index, CVD = cardiovascular disease, DM2: diabetes mellitus type 2, NOS = Newcastle-Ottawa scale.

Financial support and sponsorship

This protocol of review do not have any sponsor.

Conflicts of interest

There are no conflicts of interest.

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Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative (**one star**)
 - b) Somewhat representative (**one star**)
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort (**one star**)
 - b) Drawn from a different source
 - c) No description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) (**one star**)
 - b) Structured interview (**one star**)
 - c) Written self report
 - d) No description
 - e) Other

- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes (*one star*)
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a) The study controls for age, sex and marital status (*one star*)
 - b) Study controls for other factors (list) _____ (*one star*)
 - c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment (*one star*)
 - b) Record linkage (*one star*)
 - c) Self report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (*one star*)
 - b) NoIndicate the median duration of follow-up and a brief rationale for the assessment above: _____
- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for (*one star*)
 - b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (*one star*)
 - c) Follow up rate less than 80% and no description of those lost
 - d) No statement

E-18.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.