Citation

Matthew Lee, Luke A McGuinness. A systematic review of Mendelian randomization studies using adiposity as an exposure. PROSPERO 2018 CRD42018096684 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018096684

Review question

What has the application of Mendelian randomization informed us about the causal relevance of adiposity?

Searches

We will search the MEDLINE and EMBASE databases for all published Mendelian randomization studies using measures of adiposity as an exposure. As Mendelian randomization is still a relatively novel method, we assume that many relevant studies may be complete but have not yet been published. Given this, we will also search bioRxiv (a pre-publication repository) from inception to identify potentially relevant articles.

The search strategy used in each database will be developed in an iterative manner, incorporating feedback from experts in the field of Mendelian randomization and adiposity measures to ensure sufficient sensitivity. Searches will use a combination of free text and controlled vocabulary terms. The MEDLINE and Embase search will be re-run prior to final analyses, with new studies being added if they meet the inclusion criteria and all included studies from bioRxiv will be checked to identify whether they have subsequently been published or updated and these versions will be included instead.

Inclusion:

To be included, a study must: be written in English; be available in full text (or in the case of conference abstracts, the authors must be contactable to obtain the relevant data); be published in a peer-reviewed journal or bioRxiv; use Mendelian randomization methodology to investigate the causal association of adiposity on any outcome. Our primary focus will be studies that ascertain the independent direct causal relationship between measure(s) of adiposity and outcome(s). If a study has focused on adiposity alongside other exposures, we will report the effect of each adiposity measure separately, if available, and report the joint effect with these other exposures, if not available.

Studies in which a Mendelian randomization approach is used but not explicitly called ‘Mendelian randomization’ will be included. More specifically, any study in which genetic variants are used as instrumental variables or the direct association between a genetic variant and outcome is employed will be eligible, provided it meets the other inclusion criteria.

Exclusion:

In the case where articles are identified in bioRxiv and a subsequent peer-reviewed text is published, the bioRxiv version will be excluded in favour of the peer-reviewed version. Where a paper has been corrected the corrected version will be included. Methodological papers will be included if a proof of principle is included and meets the inclusion criteria. Reviews and commentaries will be excluded.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/96684_STRATEGY_20180515.pdf

Types of study to be included

All Mendelian randomization studies that have the aim of determining a causal association between measure(s) of adiposity and any outcome will be included.

Condition or domain being studied

All outcomes indicated as being causally associated with measures of adiposity in an MR context.

Participants/population
Participants from observational studies involving genotyping, whose data have been used in a Mendelian randomization framework to investigate causal associations between a adiposity and any outcome(s).

Intervention(s), exposure(s)
Our exposure of interest is any specified measure of adiposity that we deem to be covered by the following terms, each of which will be used in our search strategy (both verbatim and variations of these terms): BMI, Quetelet index, weight, waist circumference, hip circumference, waist hip ratio, waist height ratio, sagittal abdominal diameter, fat mass, android fat, gynoid fat, intra-abdominal fat, fat distribution, lean mass, bioelectrical impedance, subcutaneous to visceral adipose tissue ratio, fat mass index, body composition, body surface, organ size, skinfold thickness, somatotype, body size, lipid accumulation product, absorptiometry, CT/PET scan. We are interested in how these measures, when used as an exposure, associate with outcomes in a Mendelian randomization framework.

Comparator(s)/control
We are interested in the association found in Mendelian randomization studies between measures of adiposity and any outcome. There are no controls or comparators for this assessment. That being said within an MR framework, controls are those that have no copies of the adiposity increasing genotype however this is blurred when looking at genetic risk scores and so will not be considered for this review.

Main outcome(s)
In this narrative synthesis, we will consider any outcome for which a measure of adiposity was examined as a risk factor using Mendelian randomisation methodology.

Additional outcome(s)
None.

Data extraction (selection and coding)
Following deduplication, two reviewers (ML, LAM) will independently select potentially eligible studies in which Mendelian randomization is used to assess the association of measure(s) of adiposity and any outcome, firstly based on titles and abstracts, and then on full text readings. Disagreements between the two main reviewers will be resolved through discussion with a third reviewer (one of our collaborators, mostly likely NT or JH). A PRISMA flowchart will be used to document the different stages of the screening process.

Listed below are the data that will be extracted from the full text of included studies. This list may be modified as the review progresses, and we begin to abstract data from eligible studies. Any changes made will be justified, and we expect the most common reason for an item being dropped will be the absence of relevant data for that item in most/all included studies.

1. Article and author information

a. Title

b. Publication year

c. Full journal name

d. Corresponding author full name, institution, and country of institution (if different from first author)

2. Introduction

a. Hypothesis

b. Rationale

3. Methods section

a. Measure of adiposity used

b. MR study design

c. Selection of genetic variants

i. Description of age, sex, population size, and health status of population used to identify genetic variants

ii. Description of covariates included in model to adjust genetic variant-exposure estimates and standard errors

iii. Data set used for genotyping

iv. Determination of independence

v. Evaluation of potential pleiotropy

vi. P-value threshold for selecting genetic variants for Mendelian randomization study

vii. Identification of palindromic SNPs

viii. Use of proxy SNPs

ix. Testing for Hardy-Weinberg equilibrium to ascertain random assignment of genetic variants

d. Instrumental variables

i. Single genetic variant

ii. Multiple genetic variants

iii. Genetic risk score

e. A priori power calculation (including how calculated, how r^2 determined, etc.)

f. Methods used for estimating causal effect

g. Methods used for testing for pleiotropy

h. Assessment of instrument strength

i. Program used for analysis

j. Quality control

i. Was the analysis checked (or replicated) by an independent researcher?

ii. Was the analysis replicated in the same paper e.g. did they subset the data for discovery and replication analysis?

4. Results section

a. MR/instrumental variable analysis results

5. Discussion section

a. Limitations

i. Horizontal pleiotropy

ii. Population stratification

iii. Statistical power (if non-significant results)

Two review authors will extract the above data items independently. Any discrepancies identified will be resolved through discussion (with a third author, where necessary). Missing data will be requested from study authors, if necessary.

Risk of bias (quality) assessment
We will not formally assess the risk bias of included studies, as there is currently no recognised quality assessment tool for Mendelian randomization studies. As part of our narrative synthesis we will comment on the choice of methods and genetic variants used in included studies.

Strategy for data synthesis
A narrative synthesis will be used to summarise results and design of existing studies, using basic descriptive statistics as appropriate.

Analysis of subgroups or subsets
We will stratify our analysis on:

1. the measure of adiposity used in the MR analysis.

2. MR method/analysis used

3. Platform used for analysis

4. Population used in analysis (European etc.)

5. Instruments used.

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Type and method of review
Epidemiologic, Systematic review

Anticipated or actual start date
28 May 2018

Anticipated completion date
28 May 2019

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ML is the recipient of an MRC GW4 PhD studentship

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Conflicts of interest

Language
English

Country
England

Stage of review
Review Completed not published

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adiposity; Humans; Mendelian Randomization Analysis; Obesity; Random Allocation

Date of registration in PROSPERO
16 May 2018

Date of first submission
15 May 2018

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

16 May 2018
15 February 2021