

# BMJ Open Correlation between masked hypertension and endothelial dysfunction measured by flow-mediated dilation: a protocol of systematic review and meta-analysis

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## ABSTRACT

**Introduction** A surrogate marker to evaluate artery endothelial response when stimulated by reactive hyperaemia, known as brachial flow-mediated dilation (FMD), has prognostic value in predicting hypertensive organ damage and cardiovascular disease events. However, the degree of correlation between brachial FMD and masked hypertension (MH) outcomes is still unclear. Therefore, the purpose of this study is to pool data regarding FMD with respect to MH.

**Methods and analysis** Electronic databases MEDLINE, EMBASE, China National Knowledge Infrastructure and Cochrane Library will be searched for the following keywords: endothelial dysfunction, flow-mediated dilation, and masked hypertension, masked uncontrolled hypertension (MUCH) and prehypertension. The following are the eligibility criteria: population—adults (18 years old or older) without hypertension at baseline, with suspected endothelial dysfunction, or from MH/MUCH populations (office blood pressure <140/90 mm Hg and home blood pressure ≥135 mm Hg and/or 85 mm Hg) and from controlled clinical trials, cohort studies, or randomised and controlled trials; exposures—any metrics for FMD; comparisons—participants without MH or MUCH; and outcome—change in FMD between the case group and the control group. Two authors will be engaged in screening and collecting data independently; disagreements will be resolved through discussion. Data extraction will include primary data designated as HR, OR, correlations and regression coefficients. Comprehensive Meta-Analysis V.2.0 will be used to conduct related subgroup and sensitivity analyses and publication bias.

**Ethics and dissemination** This study does not require ethics approval. It will be submitted to a peer-reviewed journal.

**PROSPERO registration number** CRD42020208362.

## BACKGROUND

It was discovered that those taking antihypertensive medication, defined by masked uncontrolled hypertension (MUCH), showed increased prevalence of MH compared with those not receiving antihypertensive

## Strengths and limitations of this study

- This is the first meta-analysis we are aware of to report the correlation between masked hypertension and endothelial dysfunction measured by flow-mediated dilation.
- The study will evaluate a new method of diagnosing masked hypertension or masked uncontrolled hypertension.
- Since we include different types of studies and studies in various regions worldwide, relevant bias cannot be avoided.

treatment. Masked hypertension (MH) is defined as possessing a normal blood pressure in the office and an elevated measurement outside of it.<sup>1</sup> Diagnosing MH still has inherent challenges. Both missed and excess diagnoses have undesirable consequences. Undiagnosed MH could frequently develop into damage at targeted organs prior to transitioning to sustained hypertension.<sup>2</sup> Masked control of hypertension is more common in patients with hypertension, with a prevalence rate of 30%–50%.<sup>3</sup> MH, described as normal office blood pressure and a 24-hour mean increase in ambulatory blood pressure monitoring (ABPM), has been associated with cardiovascular disease (CVD). Moreover, it was discovered that taking antihypertensive medication, defined by masked uncontrolled hypertension (MUCH), has an increased prevalence rate for MH compared with those not receiving antihypertensive treatment.<sup>4</sup> A definitive and accurate diagnosis is therefore required for all patients with suspected MH. Although studies have shown that hypertension is associated with an increased risk of CVD, the actual concern surrounding this health risk is not the mild elevation in blood

pressure that may be measured in the clinic, but with MH being underestimated.

The diagnostic strategy starts with clinical probability assessment and measurement of blood pressure in the clinic. In patients with high/likely clinical probability, ABPM and home blood pressure monitoring (HBPM) are required. ABPM is currently the predominant test for MH. The test has been universally verified in terms of diagnostic accuracy and outcome studies.<sup>5–7</sup> However, ABPM has some limitations. It is inconvenient compared with HBPM,<sup>8</sup> difficult to operate, and has constant concerns about possible overdiagnosis and overtreatment of hypertension.

In recent years, the technology around quantifying endothelial function has rapidly evolved, which allowed for the introduction of flow-mediated dilation (FMD), a non-invasive method of assessing endothelial dysfunction.<sup>9</sup> FMD has been reported to be a predictor of hypertensive organ damage and CVD events,<sup>10 11</sup> largely replacing the invasive method administered during cardiac catheterisation. Many studies aimed at assessing the correlation between FMD and CVD risk. More recently, a few systematic reviews and meta-analyses have been published and concluded that FMD is positively associated with risk of future cardiovascular events.<sup>12 13</sup> However, the clinical community remains uncertain about the relationship between MH or MUCH diagnosed through ABPM and flow-mediated vasodilation responses. Indeed, the concrete relationship that exists between FMD and MH or MUCH remains uncertain. For example, there is a bias inherent in FMD results in some studies, thus influencing the conclusion on ultimate diagnosis. Therefore, although previously published meta-analyses focusing on brachial FMD have been reported for CVD outcomes, summarised results related to MH or MUCH are still lacking.

## METHODS

### Aims

The study aims to synthesise present reports regarding FMD and MH. The reporting of this study protocol will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (online supplemental appendix 1) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database.<sup>14</sup> Any changes to this study will be updated on PROSPERO.

### Search strategy

We will search for relevant articles in English and Chinese in the following databases: MEDLINE, EMBASE, China National Knowledge Infrastructure and Cochrane Library. The search period will be from the date when each database was established to November 2020. In addition, we will perform a manual search of related references except from the electronic search. We will contact the authors to obtain more information if necessary. Grey literature and

## Box 1 Search string

### MEDLINE

- ▶ “flow-mediated vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) dependent vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) function (or dysfunction), or FMD or vascular reactivity, and brachial artery” AND “cardiovascular diseases (or coronary disease) or masked hypertension (or hypertension or white coat hypertension or prehypertension or masked uncontrolled hypertension)”.

unpublished research will be excluded. The MEDLINE search strategy is presented in [box 1](#).

### Eligibility criteria

- ▶ Population: adults (18 years old or older) without hypertension at baseline, with suspected endothelial dysfunction, and from MH/MUCH populations (office blood pressure <140/90 mm Hg and home blood pressure ≥135 mm Hg and/or 85 mm Hg).<sup>15</sup>
- ▶ Exposure: any measurement of FMD using any general metric.
- ▶ Comparator/control: participants without MH or MUCH, including participants with normotension, white-coat hypertension, prehypertension, sustained hypertension, etc.
- ▶ Outcomes: change in FMD between the case group and the control group, including FMD magnitude expressed as percentage change from baseline, integrated FMD response calculated as the area under the dilation curve, etc.

### Study design

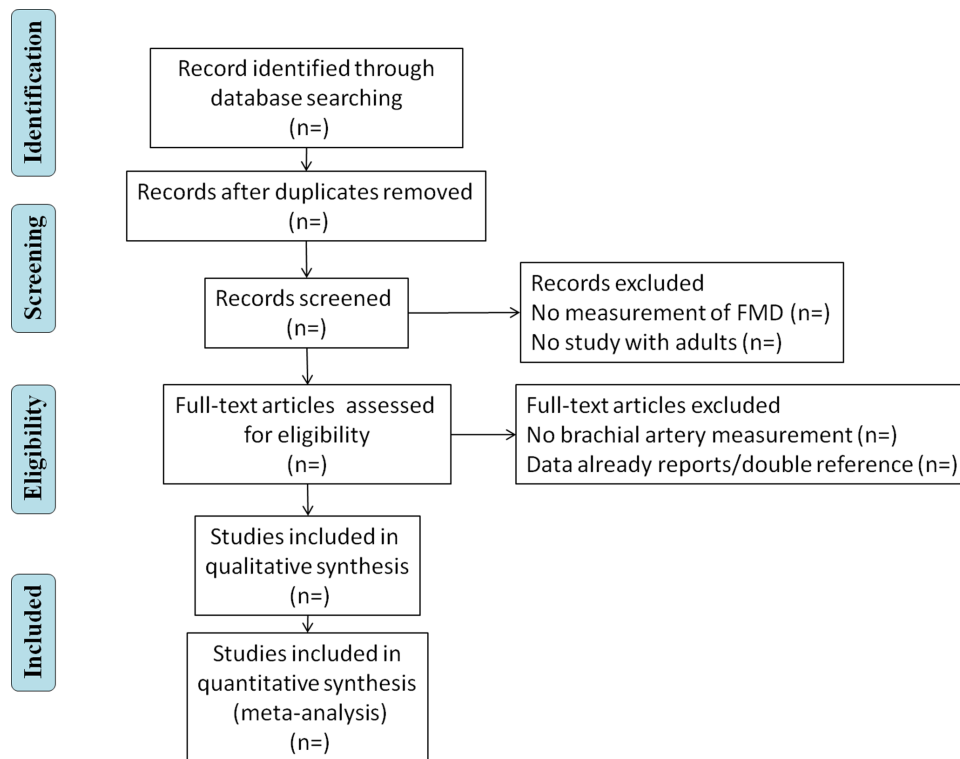
Experimental studies designed as randomised controlled trials and non-randomised trials, observational studies designed as case–control studies, and longitudinal cohort will be eligible. Prospective and retrospective studies will also be included. We will exclude any cross-sectional studies, case reports and series.

### Exclusion

Studies adopting patient self-reporting to determine MH, including self-reporting in a physician’s diagnosis, which is not further verified consistently with the diagnostic criteria defined by the study outcomes are excluded.

### Study selection process

All citations identified through our search strategy will be imported into an EndNote library; any duplicates will be eliminated. First, two review authors will select the titles and abstracts from studies by searching and identifying potentially eligible studies independently. Then they will check against the inclusion criteria. Any disagreements at all stages during the selection process will be resolved through consultation or consensus with the corresponding author. Finally, a PRISMA flow chart will provide the selection process and the reasons for any exclusions (as shown in [figure 1](#)).



**Figure 1** Flow chart of the study selection procedure. FMD, flow-mediated dilation.

### Data extraction

After selecting initial studies, eligibility information will be extracted from each study relating to study identification (authors, years of publication, countries where the study took place and other information), study design and study characteristics (eg, sample size, adverse events and duration of follow-up), characteristics of the population being studied (age, sex, body mass index, dyslipidaemia, smoking and stroke history, diabetes, kidney disease, liver disease and coronary heart disease) and methods of measuring blood pressure. Any collected primary outcome data will include office blood pressure (systolic and diastolic blood pressure), 24-hour ABPM (systolic and diastolic blood pressure), hypertension phenotypes and brachial artery FMD outcomes, reported as categorical numbers. One author for all studies will extract these data, which will be checked by another author to reduce human error. All disagreements will be resolved by the two authors.

### Risk of bias

We will use the RTI item bank to evaluate methodological bias in all included studies (online supplemental appendix 2).<sup>16</sup>

### Patient and public involvement

No patients and members of the public will be directly involved. Only data that already exist in the literature and the sources mentioned above will be used in this study.

### Data synthesis

We will present a detailed description of the results of all included studies in both text and table lists. We will describe these studies with the information of study identification (authors, year of publication, countries where the study took place and other information), study design and study characteristics (experimental or observational, sample size, adverse events, and duration of follow-up), patients (age, sex and body mass index), methods used to measure different blood pressures and the values of FMD.

### Meta-analysis

Comprehensive Meta-Analysis V.2.0 will be used to conduct the meta-analysis. Summary effect measures may include HR, OR, correlations, regression coefficients, etc. When data are pooled together, we will use a fixed-effects model. In case a significant heterogeneity appears, we will use a random-effects model to make an estimate of the effect size. If the characteristics of the included studies are extremely heterogeneous, we will not pool the results. Instead, we will make a narrative table listing the related findings by context description.

We will utilize the  $\chi^2$  test to evaluate statistical heterogeneity and the I<sup>2</sup> statistics to estimate heterogeneity. We will consider a value of  $p < 0.05$  as to indicate heterogeneity in the  $\chi^2$  test, whereas, according to the Cochrane Handbook for Systematic Reviews,<sup>17 18</sup> studies will be categorized low, moderate, high heterogeneity if I<sup>2</sup> <50%, 51%-80%, >80%, respectively.<sup>19</sup> We will test the reasons for heterogeneity through a subgroup analysis.

### Subgroup and sensitivity analyses

Considering the possibility of using different covariates in the study, we will conduct a subgroup analysis to assess the impact of each study feature on the study's primary outcome. We will conduct a subgroup analysis of patients with MH and MUCH. Subgroup analyses will also be conducted for combined MH outcomes stratified by sex and age if possible. Study setting (rural vs urban or developed vs developing country) will also be considered. Sensitivity analyses will be implemented with the effects of age <50 and >50 years old, or as mean or median age in meta-regression alternatively, due to varied incidence rates of hypertension in different ages.<sup>20</sup>

### Assessment of publication bias

Egger's regression asymmetry method will be used to evaluate publication bias.<sup>21</sup>

### GRADE framework for quality of evidence

The included study will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines<sup>22</sup> to evaluate the quality of evidence and strength of recommendations.

### DISCUSSION

The purpose of this study is to provide the latest evidence on the risk of MH and endothelial dysfunction measured by FMD. Our study will contribute to this field by clarifying whether FMD, derived from ultrasound imaging, is associated with these blood pressure outcomes. It is of the actual, consistent evidence that there is an increased risk of CVD related to MH.<sup>23</sup> The findings might also inform clinical physicians and policymakers with respect to hypertension management, especially when diagnosing MH.

There are a few limitations that will weaken the findings and applications of the study due to endothelial dysfunction being the result of multiple interactions between cardiovascular regulatory function and environmental and behavioural factors.<sup>24</sup> As such, we are incapable of discovering antecedent risk factors for higher FMD or ways to modulate and lessen the risk of MH. Similarly, FMD is interdependent with blood pressure in some forms; thus, it may be challenging to illustrate the effects of FMD independent of blood pressure. The included studies will also probably measure blood pressure by different methods, which could cause methodological heterogeneity. Limitations will also be associated with the outcomes of MH based on varying levels of effectiveness and heterogeneity. The ability to correctly judge the prognosis of MH outcomes will be related to participants' age, follow-up duration and diseases. Furthermore, original studies may also include study heterogeneity and a high risk of bias, thus limiting the final conclusion drawn in this field. Moreover, as the included studies will only involve English and Chinese languages, the generalisability of the study results published in other languages and other settings is finite in measurement.

In conclusion, given there are no studies available that assess endothelial functionality measured by FMD within the scope of MH, there is a pressing need to perform a meta-analysis on how FMD performs in diagnosing MH. The study will help summarise the available research evidence, and the findings may have guiding significance in clinical practice and in diagnosing hypertension.

**Contributors** WZ proposed the conception and acquired funding. YL and CZ were involved in the study design and project administration. XZ, LG and CZ drafted the manuscript.

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