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Body size measures and risk of venous thromboembolism: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Obesity is significant risk factor for venous thromboembolism (VTE); however, the related mechanisms remain unclear. Previous studies have suggested that this might be related to physical factors including anthropometric measures. We intend to conduct a systematic review and meta-analysis of prospective studies to summarise the extant literature on the associations between a set of seven measures of body size and the risk of VTE.

Methods and analysis The current systematic review will include prospective cohort studies assessing the association between seven measures of body size (height, weight, body mass index, waist and hip circumferences, waist-to-hip ratio, waist-to-height ratio) and the risk of VTE. We will conduct comprehensive searches of MEDLINE and Excerpta Medica Database (EMBASE) for articles published from inception through 31 August 2017, without any language restriction. Two investigators will independently screen, select studies and perform data extraction and risk of bias assessment, with discrepancies resolved by a third investigator. For each body size measure, study-specific relative risks will be pooled using random effects meta-analysis models. Statistical heterogeneity will be assessed using Cochran's Q statistic, H and the I^2 statistics. Sources of heterogeneity will be investigated using subgroup and meta-regression analyses as deemed appropriate. Publication bias will be assessed with funnel plots supplemented by Egger's test.

Ethics and dissemination This systematic review will use data from published literature; therefore, ethical approval is not required. We expect our findings to supplement previous epidemiological studies by providing an updated and comprehensive synthesis of the available evidence on the association between body size measures and risk of VTE in the general population. Findings will be published in peer-reviewed journal and presented at scientific meetings.

PROSPERO registration number CD CRD42017071996.

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis to comprehensively assess the association between several anthropometric measures and the risk of venous thromboembolism.
- We will use robust statistical techniques and will methodically assess risk of bias in included studies.
- It is anticipated that some studies might have used different categorisations of the exposure variables.
- Likewise, we anticipate some evidence of statistical heterogeneity across included studies.

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), represents a common multifactorial disease, with short-term and long-term complications and a potentially fatal outcome.[1] With an average annual incidence of about 1 to 3 per 1000 adults,[1 2] it constitutes the third most common cardiovascular disease (CVD) in the USA.[3] Although factors such as a prior episode, surgery, trauma, prolonged immobilisation, malignancy, use of hormonal replacement therapy, ageing and prothrombotic mutations have been shown to be associated with VTE events, a vast majority (30% to 50%) of the VTE events still occur in the absence of any obvious predisposing factors.[4–6]

Several studies have shown that obesity is a strong and independent predictor of VTE.[3 7 8] However, the mechanism through which obesity increases the risk of VTE is uncertain, and whether this higher risk is due to central or peripheral obesity is not clearly established.[9] The vast majority of studies that have assessed the association between obesity and VTE used body mass index (BMI) as the primary exposure of interest. Although BMI is a relatively good marker of total body fat in adults, it fails to consider the distribution of adipose tissue in the body. The distribution of body fat may have a differential impact on the risk of CVD.[10] Numerous investigations have shown that abdominal obesity measured as waist-to-hip ratio or waist circumference is a better predictor of arterial thromboembolic events such as coronary heart disease and stroke than general obesity measured as

BMI.[10–12] It is well known that arterial and venous thromboses share several pathways, as they commonly occur together, and both are strongly related to older age and obesity.[3 5]

Although several studies have reported on the association between various measures of body size and the risk of VTE, the findings have been inconsistent across studies and genders.[3 9 11 12] In 2005, Glynn *et al* in the Physicians Health Study found that a higher height was associated with an increased risk of VTE in men.[3] This gender-specific increase in the risk of VTE was recently found in taller men, but not in women.[8 12 13] A large cohort of Danish adults found a statistically significant positive association between VTE and waist circumference in men but not in women. Conversely, hip circumference was positively associated with VTE in women but not in men.[11]

We aim to conduct a systematic review and meta-analysis of prospective studies in order to summarise the available evidence on the associations between a set of seven anthropometric measures (height, weight, BMI, waist and hip circumferences, waist-to-hip ratio, waist-to-height ratio) and incident VTE.

Review question

What is the association between a set of seven anthropometric measures (height, weight, body mass index, waist and hip circumferences, waist-to-hip ratio, waist-to-height ratio) and the risk of venous thromboembolism in population-based studies?

METHODS AND ANALYSIS

This review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[14] This protocol is presented according to the PRISMA Protocols (PRISMA-P) 2015 checklist,[15] and registered with PROSPERO (CD CRD42017071996).[16]

Inclusion criteria

We will include studies that meet the following criteria: (1) the study design is a prospective cohort study conducted in subjects aged 18 and above; (2) each body size was measured at baseline; (3) the outcome of interest was the occurrence of any VTE; (4) VTE was confirmed by diagnostic procedures, including compression ultrasound, venography, spiral CT, ventilation/perfusion scan (moderate or high probability for PE), pulmonary angiography or autopsy; (5) the diagnosis of VTE was made by a physician as indicated by the medical record; and (6) the relative risk (RR) and its corresponding 95% CI (or data to calculate them) were reported.

Exclusion criteria

We will exclude studies conducted in participants selected on the basis of VTE, cross-sectional or retrospective studies, and studies limited to specific populations known to be at increased risk for VTE (eg, pregnant women, people with malignancies, postoperative patients).

Search strategy and selection of studies

We will conduct a comprehensive search of MEDLINE and Excerpta Medica Database (EMBASE) from inception through 31 August 2017 using search terms related to height, weight, hip circumference, waist circumference, BMI, waist-to-hip ratio, DVT and PE, without language restriction. The PubMed search strategy is illustrated in table 1 and will be adapted for EMBASE. Two investigators (AK and JJB) will independently screen articles for inclusion, beginning with titles and abstracts, followed by full-text review. Additionally, we will manually scan reference lists of identified articles, and citing references will be screened via the ISI Web of Knowledge database, for potential additional eligible articles. Agreement between reviewers will be assessed using Cohen's kappa (κ) coefficient. Disagreement will be resolved through arbitration by a third investigator Jobert Richie Nansseu (JRNN).

Data extraction

Two investigators (AK and JJB) will independently abstract data from eligible studies and conduct quality assessment. Data on the following items will be extracted: the first author's name, publication year, study period, country of study origin, number of participants, mean age, age range, sex distribution of the participants, study duration, body size measure(s) assessed by each study, method used to assess the body size, study end point(s) (DVT, PE or composite), outcome definition, maximally adjusted HR

Table 1 PubMed search strategy

Search	Search terms
1	"Body Size" [Mesh] OR "body size" [tiab] OR "Body Height" [Mesh] OR "body height" [tiab] OR "height" [tiab] OR "Body Weight" [Mesh] OR "body weight" [tiab] OR "weight" [tiab] OR "Body Mass Index" [Mesh] OR "bmi" [tiab] OR "body mass index" [tiab] OR "Obesity" [Mesh OR "Waist-Hip Ratio" [Mesh] OR "waist to hip ratio" [tiab] OR "waist to hip" [tiab] OR "waist-to-hip" [tiab] OR "Waist-Height Ratio" [Mesh] OR "waist to height ratio" [tiab] OR OR "waist to height" [tiab] OR "Waist Circumference" [Mesh] OR "Waist Circumference" [tiab] OR "Waist" [tiab] OR "hip circumference" [Mesh] OR "hip Circumference" [tiab] OR "hip" [tiab]
2	("Venous Thromboembolism" [Mesh] OR "Venous Thromboembolism" [tiab] "venous thrombosis" [Mesh] OR "venous thrombosis" [tiab] OR "Pulmonary Embolism" [Mesh] OR "Pulmonary Embolism" [tiab] OR "thromboembolism" OR "thrombosis"
3	Numbers 1 AND 2

or RR and its associated 95% confidence limits, and variables included in the maximally adjusted model, when available.

Assessment of study quality

The risk of bias in the included studies will be assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.[17] The NOS for cohort studies allocates a maximum of nine stars to studies of the highest quality based on three parameters: selection of study groups, comparability of groups and ascertainment of the outcome of interest.[17] Studies will be considered as high quality (7–9 stars), moderate quality (4–6 stars) or low quality (0–3 stars).

Statistical analysis

For each anthropometric measure, we will use the maximally adjusted RR from each study. For studies reporting RRs per a unit change in a body size measure, we will calculate the corresponding risk estimate for 1 SD change to undertake comparisons across studies, assuming a log-linear association. For studies assessing body size measures as categorical variables, the lower category will be used for reference. We will perform DerSimonian-Laird random effects meta-analysis models to estimate the pooled RR and associated 95% CI. The random effects model is the most conservative approach as it allows for within-study and between-study heterogeneity. The z statistic will be used to test the null hypothesis (that each measure is not associated with the endpoint). We plan to perform stratified analyses by gender. Heterogeneity between studies will be evaluated using Cochran's Q statistic, H and the I^2 statistics.[18 19] I^2 statistics ≤25%, 50% and ≥75% correspond to low, moderate and high heterogeneity, respectively. Whenever significant heterogeneity will be found, we plan to conduct subgroup and meta-regression analyses examining the following prespecified variables, sample size, mean age, follow-up period, publication year and adjustment levels. The robustness of our findings will be assessed by conducting influence analyses, omitting one study at a time and assessing the effect on the pooled estimate. Publication bias will be evaluated by contour-enhanced funnel plots, which will be supplemented by formal statistical testing with Egger'test.[20] All tests will be two-sided and a P value <0.05 shall be deemed as statistically significant. All analyses will be done using Stata software (Stata Corp, V.14). In case of high clinical heterogeneity, we plan to conduct a narrative synthesis.

Ethics and dissemination

The present study is based on published data; hence, ethical consideration is not a requirement. Findings from this systematic review and meta-analysis are expected to have significant clinical and public health impacts. First, it will inform on the association between various body size measures and the risk of VTE. Second, knowing the factors that drive the risk of VTE will inform strategies that could be used to curb the risk of VTE. The final report of this systematic review and meta-analysis will be presented at scientific meetings and published in a peer-reviewed journal. The study selection process will be summarised using a flow diagram. Reasons for exclusion of studies will be specified following the PRISMA guidelines. Quality scores and risk of bias for each eligible study will be reported. Quantitative data will be presented in tables summarising individual studies as well as summary tables and forest plots as appropriate. We anticipate that the main limitations of this study might include the heterogeneity across the studies, which would be in part explained by between-study differences in population structures or by regional disparities. Another potential limitation might be differences in terms of the categorisations of the various body size measures. However, we aim to address these limitations magnitude using the methods described above.

Contributors AK conceived, designed the protocol and drafted the manuscript. JJB, JRNN and JJNN revised the first draft of manuscript. All authors approved the final version of the manuscript prior to its submission.

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