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Runing title: BMI and Thromboembolism

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Abstract

Background: The relationship between Body Mass Index (BMI) and Risk of Venous thromboembolism (VTE) and Pulmonary Embolism (PE) is a controversial issue. This dose-response meta-analysis was performed to investigate the association between BMI and risk of VTE and PE incidence based on cohort studies.

Method: A comprehensive systematic search was conducted up to August 2019 in MEDLINE/PubMed, SCOPUS, and Cochrane. DerSimonian and Laird random-effects models were run to estimate combined hazard ratios (HRs) with 95% confidence intervals (CIs). Dose-response analysis was also carried out based on BMI values.

Results: Eleven articles with 16 arms and 3,910,747 participants were eligible for inclusion in this systematic review and meta-analysis. Pooled results showed a positive association between BMI and risk of VTE in the obese participants compared to participants classified in the normal BMI category (HR: 1.62, 95% CI: 1.29 -2.04, I^2=95%). Furthermore, results showed a significant association between lower BMI (underweight versus normal BMI category) and reduced risk of PE (HR: 0.80, 95% CI: 0.70 -0.92, I^2=9%) and higher risk of PE in obese versus normal BMI participants (HR: 2.24, 95% CI: 1.93 -2.60, I^2=0%). There was a significant linear relationship between BMI and risk of VTE ($p<0.001$) and PE ($p<0.001$).

Conclusions: This systematic review and dose-response meta-analysis with 3,910,747 participants highlights obesity as a significant risk factor related to the incidence of VTE and PE.

Keywords: Body Mass Index; Venous thromboembolism; Pulmonary Embolism.

1. INTRODUCTION

Venous thromboembolism (VTE) is a composite disease, comprising of both deep venous thrombosis (DVT) and pulmonary embolism (PE). PE is often life threatening, but both diseases represent a major public health challenge in the 21st century [1]. Current estimates of incidence in Europe is between 104-183 per 100,000 person-years, making it comparable to cerebrovascular incidents [2]. With a growing ageing population, incidence rates may be as high as 700 per 100,000 among individuals aged >70 years [3].

In tandem with this rise in VTE incidence, the global prevalence of obesity has increased, reaching pandemic rates, possibly driven by environmental factors associated with Westernization [4]. While close attention has been given to the chronic metabolic sequelae of obesity, the role of phenotype, which puts individuals at elevated risk of other life-altering diseases such as VTE, is poorly understood [5-7]. A number of existing biologically plausible theories, which align with Virchow's triad, include: endothelial dysfunction as a result of the low-grade inflammation associated with obesity [8]; excess truncal adiposity and intra-abdominal pressure resulting in poor venous return and hemostasis [9]; and low-grade inflammation-induced hypercoagulable/hypofibrinolytic state (*i.e.*, elevated circulating plasma fibrinogen and plasminogen activator inhibitor-1) [10]. A trend analysis by Wei and colleagues showed that DVT rates among VTE patients plateaued between 1985 and 2009, but overall VTE rates continue to climb as a result of increased PE incidence [11]. Despite medical advancement in addressing many of the known risk factors of VTE, such as rapid post-operative mobilization, anti-embolism stockings, and prophylactic heparin, the incidence is still rising. This perhaps indicates scope for evaluating other risk factors, known or unknown.

This systematic review and meta-analysis therefore aimed to evaluate and synthesize clinical evidence from cohort studies which examined the relationship between body mass index

(BMI) and risk of VTE and PE. In addition, we explore the relationship between BMI and the two disease states in a dose-response manner.

2. MATERIALS AND METHODS

The MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines were applied to the present meta-analysis [12]. A literature search for prospective cohort studies in PubMed/MEDLINE, Scopus, and Cochrane Library databases was performed by two independent reviewers and without any time or language restrictions up to August 2019. This comprehensive search was designed using Mesh and relative keywords of Body Mass Index and thromboembolism (Supplementary Table 1). An email alert service was activated to avoid the omission of any new articles published after the search period and a reference list of relevant original and review papers was scrutinized to identify additional studies.

2.1. Inclusion criteria

1) Cohort design studies; 2) reporting hazard ratio (HR) or risk ratio and the corresponding 95% confidence interval (CI) of thromboembolism (venous thromboembolism and/or pulmonary embolism) based on BMI categories. VTE in this study is referring to both DVT and PE.

2.2. Exclusion criteria

1) Studies performed on cohorts with concomitant gastrointestinal disorders; 2) reviews, editorials, non-human, in vitro, case reports, ecological, and letters studies; 3) studies performed in children.

2.3. Data extraction and quality assessment

Data extraction was performed using designed and piloted extraction forms by two independent authors and discrepancies were resolved through discussion with the senior author. Extraction forms contained the following variables: first author, publication year, study country of origin, number of participants, mean age, gender, name of cohort, length of study follow-up, type of thromboembolism, BMI category, and hazard ratios with corresponding 95% CIs. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the methodological quality of the studies.

2.4. Statistical analysis

All statistical analyses were performed using STATA 14.0 statistical software (Stata Corporation, College Station, Texas, USA). DerSimonian and Laird random-effects model was run to combine risk estimates in included studies [13]. Cohort studies that reported each gender separately were considered as two arms. When authors did not report mean data for BMI categories, the median or mean in each category was used as the reference category. Underweight and obese categories were compared to normal category of BMI as a reference category. According WHO standards, we considered BMI below 18.5 as underweight, 18.5 to 25 as normal, 25 to 30 as overweight, and above 30 as obese. When two or more category of BMI in each original papers fell into the same category of our cut-points, risk estimates of those categories were combined, furthermore, if one category of BMI of included study covered two or more categories of our cutpoints, risk estimates of that category were assigned with its median. The heterogeneity among included studies was estimated by the Cochran Q test (p heterogeneity) and I^2 statistic. Random-effects meta-regression based on age of participants was conducted to identify the source of heterogeneity. Curve-linear association was examined by modeling concentration level using restricted cubic splines [14]. Linear results are based on exponential with y = mx +c formula and used to check the general trend between BMI and outcome, but nonlinear analysis is based on the coefficient with ax2 +

by2 = c formula, which was used for comparing underweight or obesity versus normal weight. Funnel plot, Begg's rank correlation test, and Egger's regression asymmetry test were conducted to evaluate publication bias among included studies.

3. RESULTS

3.1. Literature search

The flow chart of included studies is presented in Figure 1. The initial database search yielded 5544 records, of these 1418 articles were subsequently removed as duplicates. At title and/or abstract screening, 4059 irrelevant articles were excluded, and 67 articles were included in full text screening. At full text screening, 56 articles were removed using the inclusion and exclusion criteria. Eleven articles with 16 arms and 3,910,747 participants were eligible for inclusion in this systematic review and meta-analysis [15-25].

3.2. Study characteristics and quality assessment

Baseline characteristics of included studies are presented in Table 1. Studies were published between 2009 and 2018. Five studies were conducted in USA [15, 17, 20, 22, 24], two in Denmark [18, 25], one in Israel [16], one in Norway [21], one in Italy [23], and one in New Zealand[19] . The mean age of participants was 44 years, with a range from 17 to 60 years. The mean length of follow-up was 13 years, with a range from 4 to 28 years. Four studies [16, 19, 20, 24] evaluated pulmonary embolism in four arms and venous thromboembolism in 13 arms [15, 17-23, 25]. All studies had good quality and seven of them achieved the maximum score on the Newcastle-Ottawa Quality Assessment Scale (9).

3.3. Main results of the meta-analysis

Three studies with five arms provided a total of 1,395,384 participants reporting risk of VTE in underweight participants versus normal weight as outcome measures [15, 19, 25]. The pooled HR (95% CI) in the underweight versus the normal category of BMI was (HR: 1.01, 95% CI: 0.91-1.23, I^2=89%) for risk of VTE (Fig. 2). Meta-regression identified that participant's age was the source of heterogeneity among included studies (p=0.01).

Nine studies with 12 arms provided a total of 1,529,382 participants for evaluating the risk of VTE in obese participants versus normal weight [15, 17-23, 25]. Combined results of included studies demonstrated a positive association between BMI and risk of VTE in the obese participants versus participants classified in the normal BMI category (HR: 1.62, 95% CI: 1.29 - 2.04, I^2=95%) (Fig. 3). Meta-regression based on participants age was identified as the source of heterogeneity in the study results, with higher BMI among older participants showing a stronger relation with risk of VTE (p=0.01) (Supplementary Fig. 1).

Four studies with 3,572,774 participants provided data for evaluating the relationship between BMI and risk of PE [16, 19, 20, 24]. Combined results using a random effects model showed a significant association between lower BMI (underweight versus normal BMI category) and reduced risk of PE (HR: 0.80, 95% CI: 0.70 -0.92, I^2=9%) (Fig. 4). Furthermore, results showed higher risk of PE in obese versus normal BMI participants (HR: 2.24, 95% CI: 1.93 -2.60, I^2=0%) (Fig. 5).

3.4. Dose-response analysis

The dose-response relationships between BMI and risk of VTE are presented in Figure 6. Although there was a significant linear relationship between BMI and risk of VTE (p<0.001), an insignificant, non-linear relationship was apparent (p=0.69). Figure 7 shows a significant relationship between BMI and risk of PE (p<0.001) and an insignificant, non-linear relationship (p=0.32).

3.5. Publication bias

Funnel plots did not show any asymmetry among included studies (Supplementary Figure 3). No publication bias was found among the studies (the Begg's p=0.99 and 0.27 and Egger tests p=0.80 and 0.35 for risk of VTE in underweight and obese versus normal weight, respectively and the Begg's p=0.99 and 0.05 and Egger tests p=0.48 and 0.17 for risk of pulmonary embolism in underweight and obese versus normal weight, respectively).

4. Discussion

This systematic review critically appraised and summarized the evidence base using large scale cohort studies that evaluated the relationship between body mass index and the risk of VTE and PEThe findings of this systematic review suggest that a higher body mass index increases the risk of venous and pulmonary embolism. We found no evidence of a relationship between being underweight and developing VTE (HR: 1.06 95% CI: 0.91-1.23). However, a protective relationship was found between being underweight and the risk of PE(HR: 0.80 95% CI: 0.70-0.92); but this might be due to the complexity involved with diagnosing PE[26]. The hazard ratio was 1.5 times higher (HR: 1.62 95% CI: 1.29-2.04) for VTE and two-fold (HR: 2.24 95% CI: 1.93-2.60) for PE among obese individuals compared with normal BMI. These results are supported by evidence from a previous review that showed a two-fold increase in risk of VTE[5]. A review by Yi and colleagues (2016) evaluated risk factors for VTE and atherosclerosis. The authors reported higher prevalence of VTE among participants with BMI $\geq 30\,kg/m^2$ than their counterparts with lower BMI. Although the authors did not adjust for sex as a confounding variable and included data from case-controlled studies prone to bias when establishing baseline exposure and outcome [27], the results showed consistent and large estimates similar to evidence generated by this review.

4.1. Clinical significance

obesity may be an independent risk factor for VTE and PE but the mechanism of action for this association is unclear [28]. These vascular disorders are most likely triggered by biological stimuli of pathophysiological responses (characteristic of inflammation, hypercoagulability, and endothelial injury) within blood vessels or adipose tissue. Multiple interacting factors are associated with the risk of VTE and PE; therefore, reducing their impact may require multiple intervention approaches [28]. For example, anticoagulation treatment alone may not alter immune response to inflammation in VTE and PE [29]. Moreover, findings from studies included in this review may be more applicable to clinical settings within developed countries due to differences in environmental factors, prophylaxis and medical interventions such as biomarkers risk stratification [30]. It might be helpful for future studies to explore the relationship between inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-alpha, IL-6, and IL-8, and risk of VTE or PE. This would help to inform clinical decision making, and the design and delivery of preventative treatment strategies [29].

Adequate management of BMI as a risk factor might reverse or reduce risk of VTE and PE by reducing circulating hypercoagulation factors within the blood stream [27]. This mechanism of action is probably partly mediated by the protective effect of improving lipid profiles in arterial thrombosis and the release of antioxidants that reduce inflammation. Our findings suggest that weight loss in addition to other preventive strategies within primary and secondary care settings are integral to reducing the incidence of VTE and PE. However, the precise nature through which the dose-dependent relationship could guide treatment dosage remains unclear. For example, uncovering the mechanism of action could determine guidelines for treatment regimens such as weight-to-prophylaxis ratio or suitable target weight for improving surgical outcomes [31].

4.2. Limitations

A comprehensive search strategy was developed and used to identify relevant articles. In addition, we did not identify any evidence of publication bias, but papers published in the grey literature may have been missed. Even assessments of publication bias, though helpful, can still be misleading with heterogeneous samples and/or small study numbers. Furthermore, although we reported a dose-response relationship between higher BMI and risk of VTE and PE, this does not imply causality. As randomized controlled trials (RCTs) which elucidate causality may be difficult to execute, it might be useful to perform analysis of routine data to illustrate current obesity trends, absolute risks and numbers needed-to-treat. Secondary data analysis of RCTs that account for known and unknown confounders may prove helpful to evaluate the effect of reduced body weight and physiological drivers of coagulation within blood vessels to enhance therapy.

Furthermore, using BMI as a self-reported, surrogate outcome measure for classifying risk profiles is prone to measurement errors due to misclassification bias. Anthropometric measures such as central obesity, and waist and hip circumference have been reported to be more sensitive indicators of risks than BMI. Although we adjust for the effect of age, we did not explore the effect of unknown or residual confounding variables such as genetics, anti-coagulative therapy, levels of physical activity, duration of follow-up, existing comorbidities, lifestyle or demographic factors and their interactions with each other.

For VTE, the associated I-squared statistic showed significant heterogeneity, whilst our meta-regression indicated that age was the source of heterogeniety. Indeed, specific to this finding, it was evident that among older particpants, the relationship between high BMI and risk of VTE was stronger. Clearly, this highlights the agemust be taken into consideration when interpreting the results. Whilst extrapolating this finding into clinical practice would dictate that, in aging patients, a high BMI should be far more acutely considered and managed. Moreover, in the

presence of such extreme I-squared values, Higgins et al suggest that a wider investigation of variability across studies, with respect to the source of heterogeneity, in our case, age, be undertaken to better understand and delineate clinical implications. Whilst we show that age is a significant source of heterogeneity, BMI and VTE was the focus of our investigation, and therefore, it was out of the scope of the present work to further address this heterogeneity. However, we therefore suggest that further work, with specific age groups be conducted to allow better understanding of how and why certain age groups may be more or less at risk of VTE.

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5. Conclusions

This systematic review provides up-to-date evidence on the relationship between body mass index and risk of venous and pulmonary embolism and demonstrated a positive and strong relationship between BMI and venous or pulmonary embolism. Studies that investigate other confounding factors of cardiovascular risk are necessary for clinical recommendations to provide complementary evidence.

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