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Host-related factors for venous thromboembolism following total joint replacement: A meta-analysis of 89 observational studies involving over 14 million hip and knee replacements

Matthew C. Barrett Bsc[a], Michael R. Whitehouse PhD[b,c], Ashley W. Blom PhD[b,c], Setor K. Kunutsor PhD[b,c,*]

[a]*Barts and The London School of Medicine and Dentistry, 4 Newark St, Whitechapel, London E1 2AT*

[b]*National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK*

[c]*Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK*

***Corresponding author at:**

Setor K. Kunutsor, Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK; Phone: +44-7539589186; Fax: +44-1174147924; Email address: setor.kunutsor@bristol.ac.uk

Abstract

Background: Venous thromboembolism, a potential complication of total joint replacement, is associated with preventable mortality and morbidity and is likely to be influenced by host-related factors such as sociodemographic characteristics, body mass index, medical and surgical histories, as well as circulating biomarkers. We conducted a systematic review and meta-analysis to assess the associations between host-related factors and venous thromboembolism risk following total hip and knee replacements.

Methods: We searched MEDLINE, Embase, Web of Science, and Cochrane Library to March 2018 for longitudinal studies reporting these associations. Summary measures of association were relative risks (95% confidence intervals).

Results: We identified 89 studies with data on 14,763,963 joint replacements and 150,086 venous thromboembolism events. Comparing males to females, age ≥70 to <70 years, and blacks to whites, relative risks for venous thromboembolism were 0.83 (0.75-0.91), 1.24 (1.03-1.50), and 1.26 (1.20-1.31) respectively. Comparing body mass indices ≥25 vs. <25; ≥30 vs. <30; and ≥50 vs. <50 kg/m^2, relative risks were 1.40 (1.24-1.57); 1.65 (1.23-2.22); and 1.72 (1.10-2.67) respectively. Histories of venous thromboembolism; cardiovascular disease; congestive heart failure; cardiac arrhythmia; chronic pulmonary disease; coagulopathy; neurological disease; fluid & electrolyte imbalance; bariatric surgery; and comorbidity indices were associated with increased venous thromboembolism risk. Comparing a total knee with a hip replacement, relative risk for venous thromboembolism was 1.69 (1.32-2.15).

Conclusions: Enhanced venous thromboembolism prophylaxis should be considered in those with nonmodifiable risk factors such as older black female knee replacement patients. Modifiable risk factors such as high body mass index and fluid & electrolyte imbalance should be addressed prior to elective surgery.

Systematic review registration: PROSPERO 2018: CRD42018089625

1. Introduction

Total joint replacement (TJR) remains one of the most successful and common orthopedic interventions. In the United Kingdom alone, approximately 96,000 hips and 104,000 knees were replaced during 2016.(1) Despite the marked benefits of arthroplasty, which include reduced pain, improved function and quality of life, joint replacement carries a high risk of complications including wound infection, implant failure, and importantly venous thromboembolism (VTE). Without sufficient thrombophylaxis, VTE (comprising of deep vein thrombosis [DVT] and pulmonary embolism [PE]) can occur in up to 60% of patients within 7-14 days after undergoing major orthopedic surgery.(2) About one-third of patients with DVT will develop a PE, which can cause sudden death in up to 34% of patients.(3)

The risk of VTE has been reduced by thromboprophylactic protocols which typically involve physical or mechanical measures, such as graduated or pneumatic compression stockings, and/or pharmacological thromboprophylaxis, commonly in the form of anticoagulants.(4, 5) Despite the implementation of these protocols, VTE still remains a significant complication following TJR. VTE increases resource expenditure in healthcare and is a preventable cause of death and morbidity, with long-term sequalae including pulmonary hypertension, recurrent VTE and post-thrombotic syndrome.(6) As such, there is a need to identify those at a greater risk of developing VTE following TJR, to aid in the implementation of more efficacious preventative strategies.

The literature is a minefield of studies of different designs that have reported on the associations of several established and emerging risk factors with VTE development following joint replacement. Host-related factors such as sociodemographic characteristics, anthropometric measures, past medical or surgical history and circulating levels of VTE-related blood biomarkers, may play a crucial role in influencing the risk of developing VTE following TJR, but the nature and magnitude of their associations are uncertain. Studies to date poorly quantify the magnitude of the associations because of their small sample sizes and inadequate adjustment for confounders. A number of published reviews have also attempted to aggregate the existing data, but with several drawbacks. Zhang et al.(7) evaluated the associations of a number of risk markers with VTE in patients who underwent total hip and knee replacement in 14 studies; however, this review evaluated only 10 factors and inadequate attempts at subgroup analysis were made. Similarly, Yi et al.(8) conducted a meta-analysis involving 16 studies reporting the associations of preoperative comorbidities (past medical

history) with VTE risk. In addition to limitations such as (i) the few number of pooled studies which did not provide adequate power to evaluate the associations; (ii) focus on a limited number of potential host factors, especially past medical history; and (iii) failure to adequately explore potential sources of heterogeneity among the contributing studies using formal tests; none of the reviews assessed for preferential publication bias or small study effects. Furthermore, no reviews have reported on the associations of circulating baseline preoperative circulating blood biomarkers such as glucose, albumin, and C-reactive protein with risk of VTE. Finally, several relevant individual reports have been published since the publication of these previous reviews.

Given these limitations and the uncertainty in the evidence, there is a need to improve our understanding of host-related factors that contribute to VTE, which could aid in stratifying those at high risk following TJR and help tailor preventive strategies. In this context, we aimed to assess in greater detail than ever before, the nature, magnitude, and specificity of the associations of several host-related factors (sociodemographic characteristics, anthropometric measures, medical and surgical histories, and circulating blood markers) with the risk of VTE following TJR, using a systematic meta-analytic approach.

2. Methods

2.1. Data sources and search strategy

This review was conducted in accordance with PRISMA and MOOSE guidelines (**Appendices A-B**) using a pre-defined protocol which was registered with the prospective register of systematic reviews, PROSPERO (CRD42018089625). We systematically searched MEDLINE, Embase, Web of Science and Cochrane databases for studies reporting host-related factors with the incidence of VTE following TJR. The search was restricted to human studies conducted in the English language and included those published from the date of inception of each database to 28 March 2018. Full details of the search strategy are reported in **Appendix C.** The titles and abstracts of all potentially relevant studies were screened and the full-text articles were accessed for the relevant studies to determine whether they fulfilled our eligibility criteria. Furthermore, the reference lists of the full-text articles were manually assessed to identify any studies that were not identified by our original search. Any disagreements in whether a study should be included were discussed by two reviewers and an agreement reached with consensus of a third reviewer.

2.2. Eligibility criteria

Studies were included in our analyses if they were longitudinal studies (prospective or retrospective case-control/cohort, case-cohort, nested-case control, or clinical trials) that reported the association of any host-related factor, such as: (i) sociodemographic characteristics; (ii) anthropometric measures [weight, height, or body mass index (BMI)]; (iii) past medical and/or surgical history; or (iv) circulating blood biomarkers, with VTE following TJR (including primary or revision total replacement of the hips and knees). Since VTE cases may begin intraoperatively, with about 90% of cases occurring within the first post-operative week(9) and other cases developing long after surgery,(10) studies were eligible if they reported follow-up of any duration. Outcome was defined as any VTE, including either DVT or PE. Given that our aim was to evaluate patient- or host-related factors that could potentially be used to predict the risk of VTE, the administration of thromboprophylaxis for VTE prevention was not evaluated as we consider it a surgery-related factor and hence it is outside the scope of this exercise. Moreover, given that there exist several prophylactic regimens for VTE prevention, it is a huge research topic and should be considered on its own.

2.3. Data extraction and quality assessment

Two independent authors performed data extraction using a pre-designed, standardized, data collection spreadsheet. We attempted to contact the authors of any study where further information was required. In the scenario where the same cohort had been described in multiple publications, the study with the most up-to-date or comprehensive information was included. The quality of each study was assessed using the nine-star Newcastle-Ottawa Scale (NOS), a validated tool for assessing the quality of non-randomised studies included in systematic or meta-analytic reviews. NOS measures the quality of evidence from a score of zero to nine, based on three pre-defined domains including: (i) selection of participants; (ii) comparability; and (iii) ascertainment of outcomes of interest.

2.4. Statistical analyses

Relative risk (RRs) with 95% confidence intervals (CIs) was used as the common and summary measure of association across studies (risk estimates). Hazard ratios (HRs) and odds ratios (ORs) were assumed to approximate the same measure of RR following Cornfield's rare disease outcome assumption.(11) Fully-

adjusted risk estimates were used if available, otherwise crude RRs were estimated from studies that provided raw counts. To ensure consistency in the pooling approach and enhance comparability and interpretation of the findings, reported study-specific RRs (e.g. per 10 unit change) were transformed to a common scale (per unit change) before pooling where possible, using standard statistical methods reported previously.(12) The inverse variance-weighted method was used to combine summary measures using pre-specified random-effects models to minimize the effect of heterogeneity. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. Several pre-defined study-level characteristics which may explain heterogeneity were evaluated using stratified analysis and random effects meta-regression. Funnel plots and Egger's regression symmetry tests were used to assess publication bias or small study effects. All statistical analyses were two-sided and performed with STATA release 15 (Stata Corp, College Station, Texas, USA), where statistical significance was regarded as a p-value<0.05.

3. Results

3.1. Study identification and selection

The literature search strategy identified 4,100 potentially relevant articles. After the initial screening of titles and abstracts, 185 articles remained for full text evaluation. Following detailed evaluation, 96 articles were excluded. The remaining 89 articles corresponding to 89 observational studies met the inclusion criteria and were included in the review (**Figure 1; Table 1; Appendix D**).

3.2. Study characteristics and study quality

Table 1 provides a summary of key characteristics of studies included in the review. **Appendix E** summarizes the key characteristics and quality assessment scores of the 97 individual studies. Overall, the studies involved approximately 14,763,963 patients or hip and knee replacements and 150,086 VTE cases. The average baseline age of participants in the included studies ranged from 50.9 to 76.3 years. All studies were observational studies. The mean follow-up for VTE outcomes ranged from 2 days to 3.2 years. Methodological quality of included studies ranged from 6-9.

3.3. Associations of sociodemographic characteristics with VTE risk

The associations of several sociodemographic characteristics with risk of VTE are reported in **Figure 2**. Older age was associated with an increased risk of VTE when evaluated as the following risk comparisons: per one-year increase (8 studies) as well as when comparing patients ≥70 years with those <70 years (8 studies); RRs (95% CIs) of 1.03 (1.02-1.05) and 1.24 (1.03-1.50) respectively. Comparing males to females in 48 studies, the pooled variably adjusted RR (95% CI) for VTE was 0.83 (0.75-0.91) (**Figure 2; Appendix F**). There was evidence of substantial between-study heterogeneity in the gender analysis (I^2 =87%; 95% CI 83, 89%; p<0.001), which was partly explained by location (p for meta-regression = 0.02); study design (p for meta-regression = 0.02); and size of study (p for meta-regression = 0.01) (**Appendix G**). In pooled analysis of three studies, black race was associated with an increased VTE risk compared to white race, RR (95% CI) 1.26 (1.20-1.31). Comparing smokers with non-smokers (5 studies), there was a decreased risk of VTE RR (95% CI) 0.62 (0.47-0.82) with no evidence of heterogeneity between contributing studies (I^2 =0%; 95% CI 0, 79%; p=0.69). There was no evidence of any statistically significant associations of VTE with alcohol abuse (1 study)(13) and pre-operative air travel (1 study).(14) Drug abuse was associated with an increased VTE risk in one study.(13)

3.4. Associations of anthropometric measures with VTE risk

The associations of BMI categories with VTE risk were reported in 26 unique studies (**Figure 3**). In pooled analysis of seven studies, the RR (95% CIs) for VTE comparing BMI ≥25 vs. <25 kg/m^2 was 1.40 (1.24-1.57). The pooled variably adjusted RR (95% CI) for VTE for individuals with a BMI ≥30 vs. <30 kg/m^2 was 1.65 (1.23-2.22) in 16 studies (**Figure 3; Appendix H**). There was evidence of substantial between-study heterogeneity in the contributing studies (I^2 =96%; 95% CI 95, 97%; p<0.001), which was partly explained by type of VTE event (p for meta-regression = 0.01) (**Appendix I**). The pooled RR (95% CIs) for VTE in three studies comparing BMI ≥50 vs. <50 kg/m^2 was 1.72 (1.10-2.26). Comparing BMIs ≥40 vs. <40 and ≥35 vs. <35 kg/m^2, there were no significant associations with VTE risk. One study comparing underweight vs. morbidly obese patients (BMI <18.5 vs. 40-49 kg/m^2) reported a RR (95% CI) of 3.10 (1.12-8.57) for VTE. In another study comparing underweight vs. patients with normal BMI (<18.5 vs. 18.5-25 kg/m^2), there was no evidence of a significant association with VTE. In pooled analysis of two studies, a unit increase in BMI was

not associated with risk of VTE. Only one study assessed the association between weight and VTE risk. Comparing weight >65 vs. ≤65 kg, the RR (95% CI) for VTE was 0.85 (0.64-1.14).

3.5. Medical and surgical history and VTE risk

Fifty-six studies reported on the associations between several medical and surgical history characteristics with risk of VTE (**Figure 4**). Comparing patients with a history of diabetes vs. no diabetes, pooled analysis of 19 studies showed no evidence of an association with VTE risk RR (95% CI) 0.98 (0.86, 1.11) (**Figure 4; Appendix J**). There was evidence of substantial between-study heterogeneity (I^2 =72%; 95% CI 56, 82%; p<0.001) and which was partly explained by study location (p for meta-regression = 0.01) (**Appendix K**). In pooled analysis of 15 studies comparing a history of VTE vs. none, there was an increased risk of VTE, RR (95% CI) 2.58 (1.47, 4.53) (**Figure 4; Appendix L**) with substantial heterogeneity between contributing studies (I^2 =95%; 95% CI 94, 97%; p<0.001). Average baseline age (p for meta-regression<0.001); type of VTE outcome (p for meta-regression<0.001); and degree of adjustment (p for meta-regression=0.03) partly explained the heterogeneity (**Appendix M**).

In pooled analyses of available studies, histories of CVD; congestive heart failure (CHF); cardiac arrhythmia; chronic pulmonary disease (CPD); renal disease and neurological disease were each associated with an increased risk of VTE. There were marginally significant associations of histories of cancer and chronic kidney disease (CKD) with increased risk of VTE. In pooled analysis of 14 studies, patients who had a total knee replacement (TKR) had an increased risk of VTE compared to those who had total hip replacement (THR), RR (95% CI) 1.69 (1.32-2.15) (**Figure 4; Appendix N**). There was evidence of substantial between-study heterogeneity between the contributing studies (I^2 =97%; 95% CI 95, 97%; p<0.001). In results of single reports, there was evidence of statistically significant associations of VTE with histories of having coronary artery bypass graft (CABG), angioplasty, or stenting; haemophilia; urinary tract infection (UTI); epilepsy; coagulopathy; peripheral vascular disease (PVD); stroke; lymphoma; and fluid & electrolyte imbalance.

In evaluation of other medical and surgical characteristics, Charlson Comorbidity Index (CCI) (≥3 vs. 0) and previous bariatric surgery (compared with BMI >40 or <25) were each associated with an increased risk of VTE (**Figure 5**). Except for a single reported which demonstrated an increased risk of VTE with rheumatoid

arthritis, none of the evaluated surgical indications for joint replacement (osteoarthritis and osteonecrosis) was significantly associated with VTE risk.

3.6. Circulating blood biomarkers and VTE risk

Seven relevant studies reported on the associations between a number of circulating blood biomarkers measured before joint replacement and the risk of VTE following TJR. RRs (95% CIs) for these associations are reported in **Appendix O**. One study reported increased circulating homocysteine to be associated with an increased risk of VTE and another study reported pre-operative glucose levels of ≥ 11.1 vs. <6.1 mmol/l to be associated with an increased risk of VTE. One study reported increased haemoglobin (Hb) to be associated with decreased risk of VTE.

3.7. Publication bias

Funnel plots for all analyses that involved ten or more studies were all symmetrical under visual examination, with the exception of studies that evaluated associations of history of diabetes, history of VTE, and history of hypertension with risk of VTE (**Appendix P**). The results were consistent with Egger's regression tests showing little evidence of publication bias for all analyses except for the associations of histories of diabetes, VTE, and hypertension with risk of VTE.

4. Discussion

4.1. Key findings

This systematic review and meta-analysis of the published literature has identified and summarized the associations of a comprehensive list of host-related factors (sociodemographic and anthropometric factors, past medical and surgical history, and pre-operative circulating blood biomarker levels) with the incidence of VTE following TJR. With respect to sociodemographic factors, there was a significantly higher risk of VTE following TJR with increasing age; in females compared with males, and in black compared with white patients. No associations were observed for smoking status, alcohol consumption, drug abuse or pre-operative air travel. On evaluation of anthropometric measures, except for these BMI comparisons ≥40 vs. <40 and ≥35 vs. <35 kg/m^2, comparisons that involved cut-offs of >25 kg/m^2 or higher were significantly associated with

an increased risk of VTE. One study compared underweight with morbidly obese patients and reported an increased risk of VTE. On the role of medical and surgical history, a significantly higher incidence of VTE was reported for the following: previous history of VTE; CVD; CHF; cardiac arrhythmia; CPD; coagulopathy; neurological disease; fluid & electrolyte imbalance; raised CCI (≥3 vs. <3 and per unit increase); ASA score (≥2 vs. <2); previous bariatric surgery; and TKR compared with THR. Results from single reports highlighted increased VTE risk with a history of UTI, haemophilia, or epilepsy; whereas VTE risk was decreased in those with a history of CABG, angioplasty, or stenting. We found no associations between VTE risk and any of the evaluated surgical indications for joint replacement. Findings on the associations between circulating blood biomarkers and VTE risk were based on single reports. Elevated homocysteine and glucose were each associated with VTE risk; haematocrit with a reduced risk of VTE; and haemoglobin with both an increase and decrease in VTE risk.

4.2. Comparison with previous work

A number of meta-analyses have attempted to evaluate the associations of a variety of host factors with VTE risk following TJR. Zhang et al.(7) in their pooled analysis of 14 studies comprising of 1,723,350 joint replacements, evaluated only 10 factors. Consistent with our results, they reported significant associations with age, black race, gender, previous history of VTE and no association with diabetes mellitus. They also reported associations with varicose veins, hypertension, and active cancer, findings not observed in our study which was based on a larger number of studies and participants. Finally, though they reported obesity to be associated with VTE risk, our assessment was based on several BMI categories. Yi et al. al.(8) in pooled analysis of 16 studies including 7,395,847 patients, reported some associations which were consistent with our findings: significant associations for CVD, previous history of VTE, neurological disease, ASA ≥3 vs. <2 and null associations for malignant disease, respiratory disease, urinary & kidney disease, coronary artery disease (CAD), endocrine disease, and haematological disease. Their study identified significant heterogeneity for the pooled results, but these were not explored. Finally, Saleh et al.(15) in their narrative review of 14 articles relating to shoulder replacement, reported a previous history of VTE, thrombophilia, major surgery, advanced age (>60 years), active cancer, immobility and bed confinement to be associated with an increased risk of VTE. Overall, though some of our findings concur generally with previous reports on the topic, our

assessment includes a wide-ranging array of host factors previously not evaluated. We also conducted subgroup analyses by relevant study level characteristics to investigate for sources of heterogeneity.

4.3. Possible explanations for findings

A number of mechanisms may account for some of the associations demonstrated. Older age, which is an established risk factor for VTE, is associated with several prothrombotic factors, including multiple comorbidities, reduced post-operative mobility, venous valve dysfunction, increased blood viscosity and vascular sclerosis.(16) It has been reported that VTE risk approximately doubles every 10 years.(17) The role of gender in venous thromboembolism is a controversial one. However, it has been reported that the increased risk seen in women may be related to the use of hormonal therapy and pregnancy, although pregnancy is highly unlikely in cohorts undergoing elective joint replacement, who have a median age of approximately 68 years.(1) The increased risk of VTE associated with black race may be linked to the higher prevalence of VTE risk factors such as obesity, hypertension and diabetes in these populations. None of the studies compared VTE risk in the Asian race; however, evidence suggests VTE risk is lowest in people of Asian descent compared with whites and African-Americans.(18) The risk is highest in African-Americans(19) and this has been attributed to the presence of genetic and acquired thrombophilia, principally Factor V Leiden mutation in African-Americans.(20) Though there exists a relationship between BMI and VTE risk, the contributions of the various cut-offs have not been consistent, with disparities in the literature thought to result from variations in the definition of obesity.(21) It has been postulated that those with a higher BMI are at increased risk of VTE following TJR due to a combination of prothrombotic factors including slow mobilisation following surgery, an underlying inflammatory state, suboptimal thromboprophylatic dosing and physical restriction to venous return.(22) Despite lowering pre-operative BMI, previous bariatric surgery was associated with increased VTE risk. Bariatric surgery is associated with gastrointestinal malabsorption, which may lead to a longer in-hospital recovery period and delayed wound healing,(23) subsequently leading to an increased risk of VTE. Our results showed a strong association of a previous history of VTE with the risk of post-operative VTE, and this has been postulated to be due to previous endothelial damage and/or the presence of genetic or acquired thrombophilia in these patients.(22) A history of cardiovascular pathology including CVD, arrhythmia, and CHF was associated with an increased VTE risk, which is not a surprising finding given that

VTE is closely linked with CVD(24) and both conditions share common antecedent risk factors.(25) Neurological conditions such as cerebrovascular disease and dementia are regarded as strong risk markers for VTE(26) and postulated mechanisms underlying the associations include poor mobilisation and systemic inflammation following cerebral injury.(27) Though Zhang and colleagues(7) previously found an association between active malignancy and VTE risk, we did not find this in our study despite the inclusion of several other studies in the pooled analysis. The heterogeneity of different cancer types including the stage, grade and treatment history in these patients may account for the differential findings. We report a higher incidence of VTE following TKR compared to THR. TKR tends to be associated with an increased DVT risk in comparison to THR, possibly due to the use of tourniquet in TKR, but not in THR. However, THR has a stronger association with proximal DVTs and have greater clinical significance as these thrombi are more likely to progress to PE and are more often fatal, whereas distal DVTs are more likely to resolve spontaneously and may be clinically silent.(28) In our evaluation of pre-operative circulating blood biomarkers, we identified an increased risk of VTE with increased homocysteine levels in one study. Circulating homocysteine is emerging as a novel risk factor for vascular pathology. As the intermediary metabolic product of methionine, homocysteine may be involved in thrombogenesis through altered platelet function and enhanced blood coagulability.(29) The associations of haematological markers (haemoglobin and haematocrit) with VTE risk were conflicting. It has been reported that some haematological conditions such as polycythaemia rubra vera and other myeloproliferative neoplasms are associated with higher VTE risk,(30) but more studies are needed to investigate these associations in patients who undergo TJR.

4.4. Implications of our findings

With an aging population and a growing burden due to osteoarthritis, it is projected that there will be a large increase in the numbers of TJRs being performed worldwide over the coming decades.(31) As a serious consequence of TJR surgery, VTE incidence is expected to rise proportionately. The current findings highlight potentially host modifiable VTE risk factors as well as factors that can be easily assessed prior to joint replacement surgery. It has recently been shown that very few VTE risk prediction scores that aid in VTE risk stratification in lower limb joint replacement patients exist for use in clinical practice and these have not been well validated.(32) In addition to established VTE risk factors, some of the factors we have identified have the

potential to be used to identify patients who are at high risk of VTE and can also be combined within risk prediction scores or prognostic models to predict VTE outcome risk for individuals.

4.5. Study strengths and limitations

This systematic review and meta-analysis has several strengths compared to other relevant reviews on the topic. To our knowledge, the current study is the most comprehensive analysis of host-related factors for VTE following TJR. Compared to previous reviews, we had enhanced power to assess the associations in greater detail. We were also able to standardize and harmonize the reported associations (to a common scale) from some contributing studies before pooling, which ensured consistency and enhanced interpretation. In analyses that involved 10 or more studies, formal tests including subgroup analysis by study size, were unable to detect publication bias for the majority of the analyses. Some notable limitations to our current study deserve mention. There was significant heterogeneity among contributing studies in some of the analyses; however, these were investigated systematically by employing detailed sub-group analysis of pre-defined study-level characteristics and random effects meta-regression. We were unable to characterize the shape of any dose-response relationships between some host factors (e.g., BMI) and VTE, given our use of published data and lack of consistent reporting by included studies. Some of our findings were based on single or few reports, hence they need interpretation with caution and also need replication in further studies. In addition, due to inadequate data, we were unable to explore the associations by whether DVT was asymptomatic or symptomatic. Inherent limitations that could have influenced our findings include errors in coding past medical or surgical history by the individual studies and that all 97 included studies were observational studies.

5. Conclusions

This aggregate published data comprising the largest number of patients on the topic to date, highlights the potential role of several host-related factors in the development of VTE following TJR. Our analyses identified VTE to be associated with sociodemographic characteristics and anthropometric measures including older age, female sex, increasing BMI and black race. Histories of VTE, CVD, CHF, cardiac arrhythmia, CPD, coagulopathy, neurological disease, fluid & electrolyte imbalance, bariatric surgery, and other indices of

comorbidity were each associated with increased VTE risk; as was total knee vs. total hip replacement surgery. Enhanced VTE prophylaxis should be considered in those with nonmodifiable risk factors such as older black female knee replacement patients. Modifiable risk factors such as high BMI and fluid and electrolyte imbalance should be addressed prior to elective surgery. The clinical utility of these factors as potential risk assessment tools and causal therapeutic targets for VTE also warrant investigation.

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Figure captions and legends

Figure 1. PRISMA flow diagram

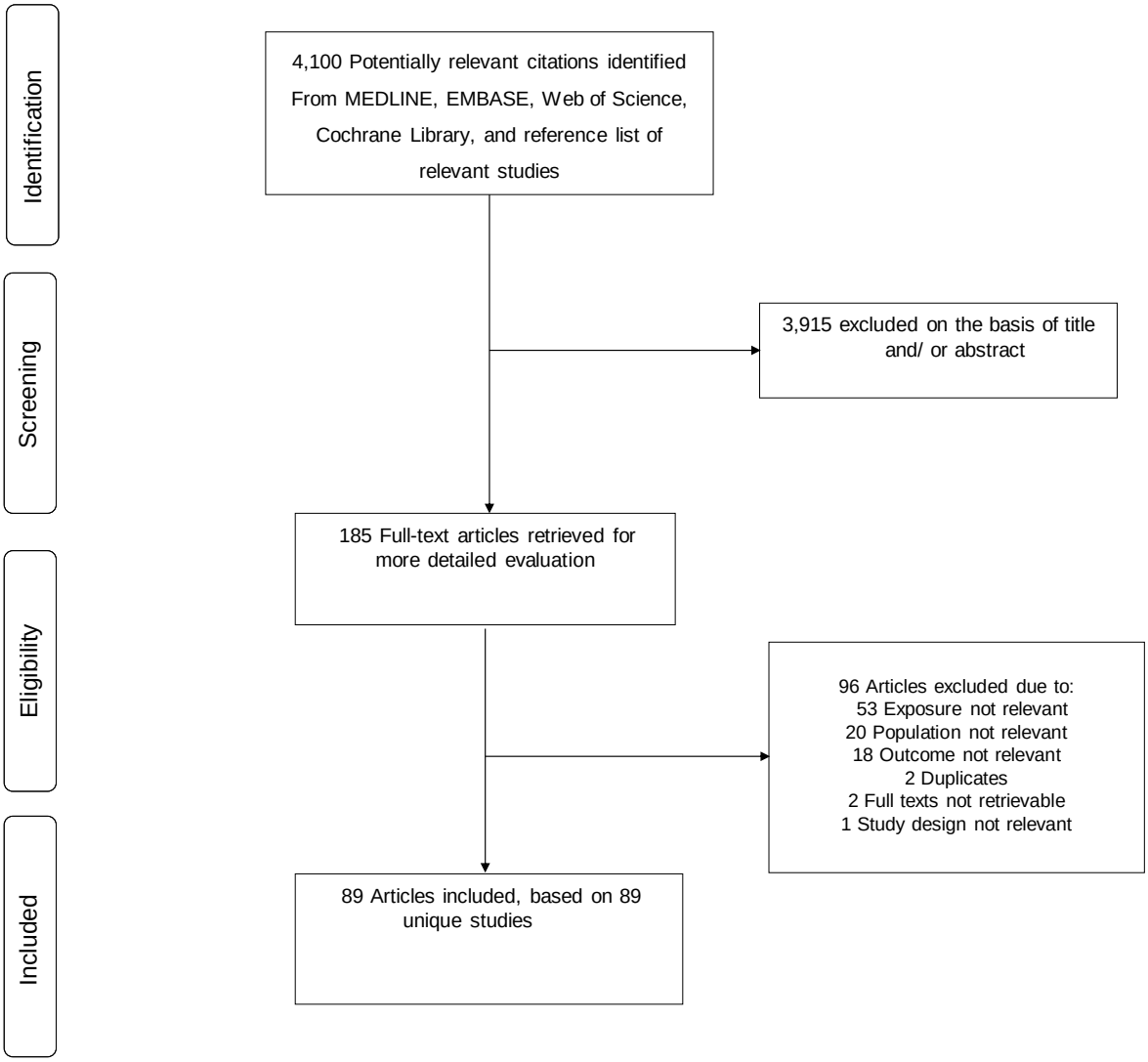
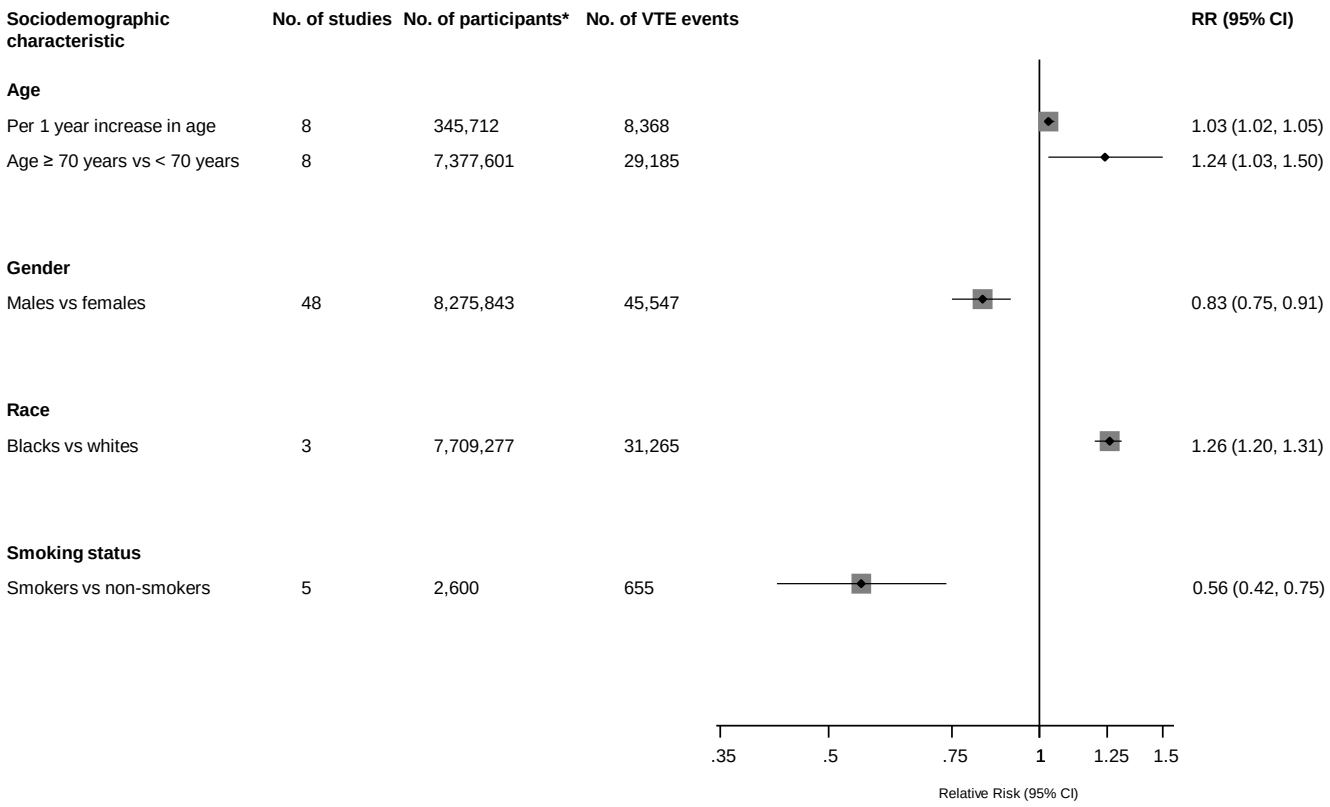
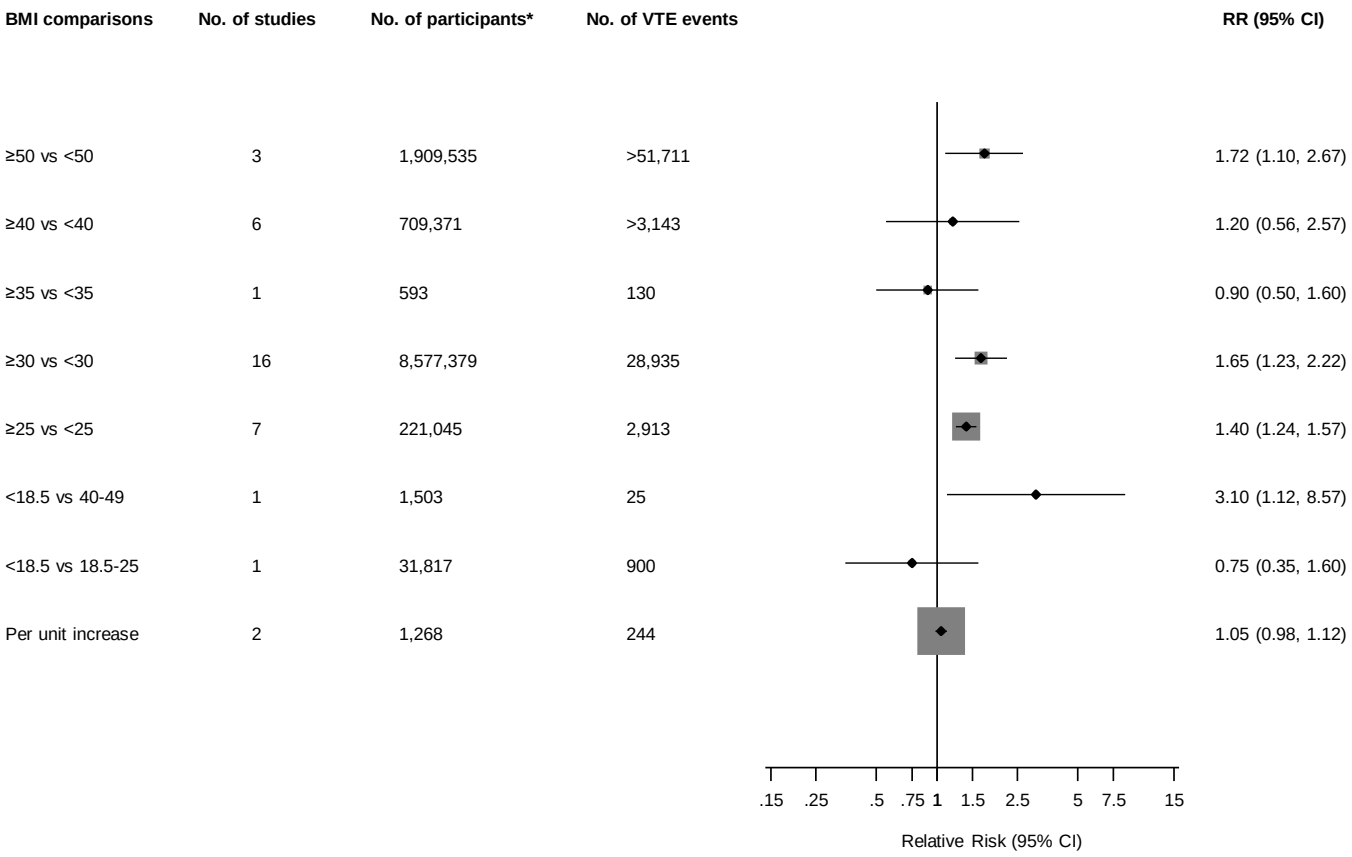


Figure 2. Sociodemographic characteristics comparisons and risk of venous thromboembolism



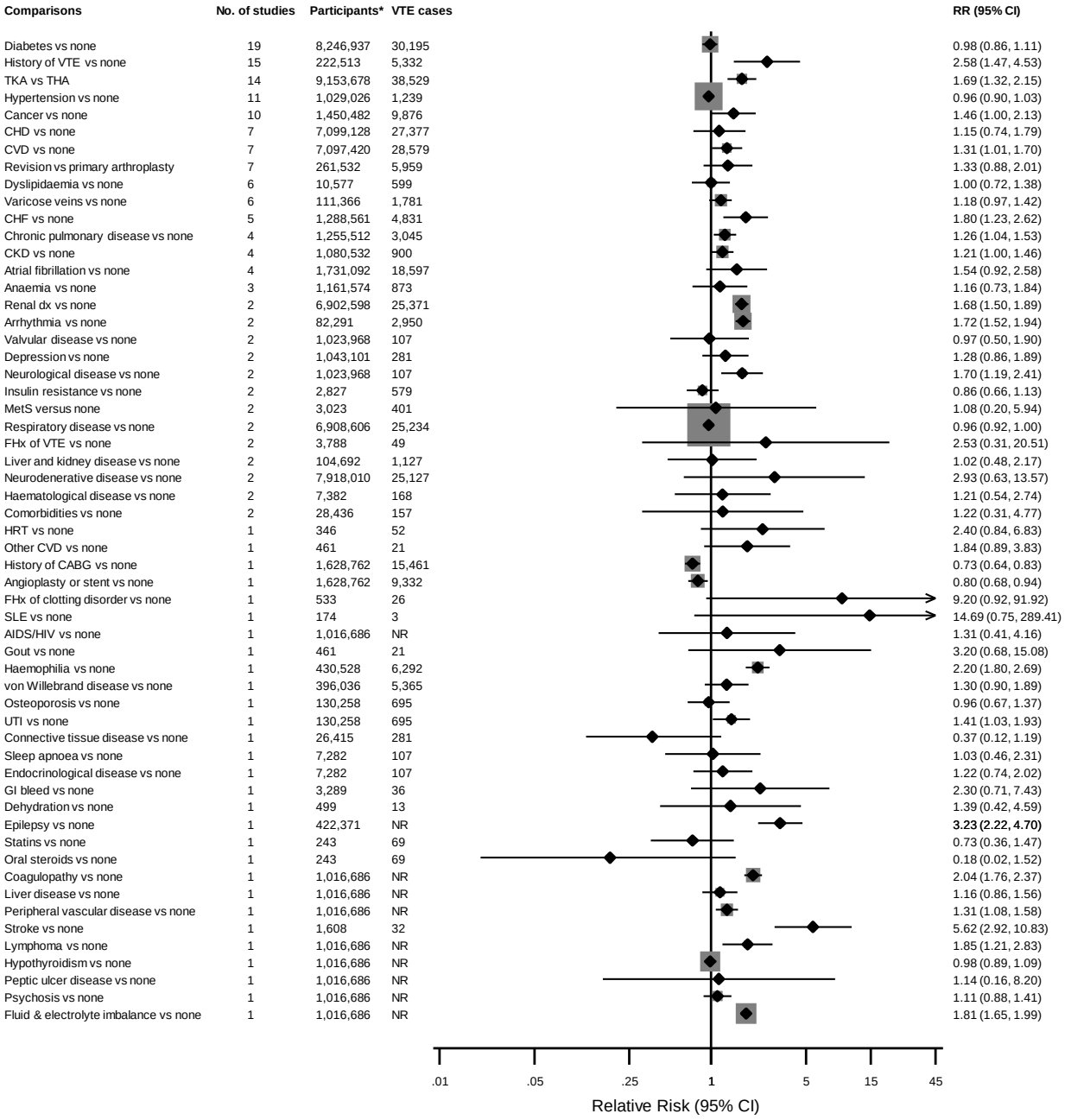
CI, confidence interval (bars); RR, relative risk; *, are number of participants or joint replacements

Figure 3. Body mass index comparisons and risk of venous thromboembolism



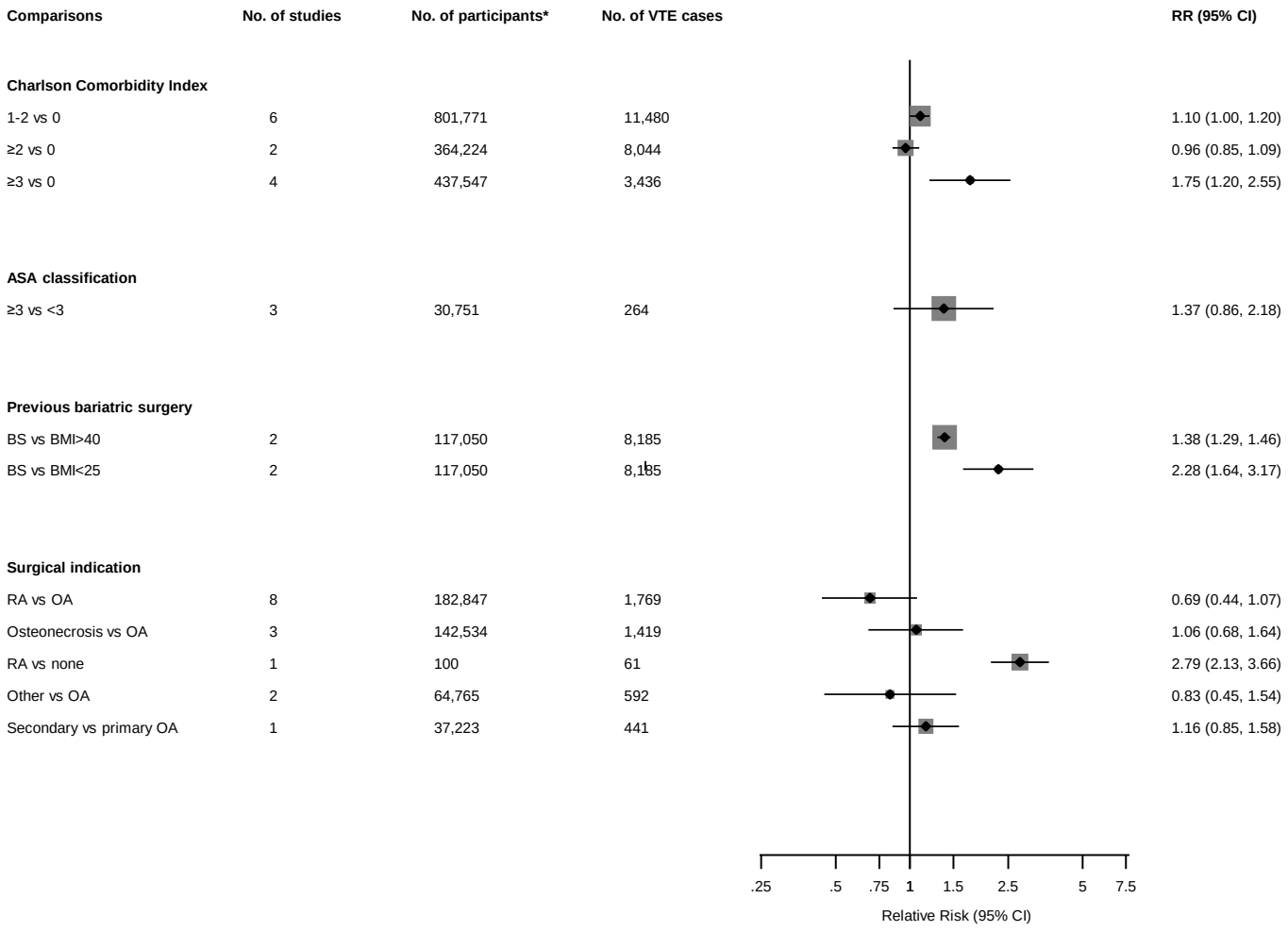
BMI, body mass index; CI, confidence interval (bars); RR, relative risk; VTE, venous thromboembolism; *, are number of participants or joint replacements

Figure 4. Medical and surgical history comparisons and risk of venous thromboembolism



CI, confidence interval (bars); RR, relative risk; VTE, venous thromboembolism; *, are number of participants or joint replacements; NR, number of events not provided in reports

Figure 5. Other medical and surgical history comparisons and risk of venous thromboembolism



BMI, body mass index; BS, bariatric surgery; CI, confidence interval (bars); OA, osteoarthritis; RA, rheumatoid arthritis; RR, relative risk; VTE, venous thromboembolism; *, are number of participants or joint replacements

Table 1. Summary characteristics of the 89 included studies

Characteristics	
Participants	**N**
Total number of participants or joint replacements	14,763,963
Total number of VTE cases	150,086
Study characteristics	
Location	N studies (N participants or joint replacements)
North America	39 (14,006,329)
Asia	33 (477,404)
Europe	14 (383,749)
Oceania	3 (1173)
Study design	N studies (N participants or joint replacements)
Retrospective cohorts	73 (14,471,062)
Prospective cohorts	8 (50,318)
Case-control studies	8 (347,275)
Median (IQR) study quality score	8 (7-8)
Study level participant characteristics	
Median (IQR) age, years	67.2 (65.2-69.0)
Median (IQR) % males	35.9 (23.0-41.2)
Joint type	N studies (N participants or joint replacements)
Hip and knee	37 (11,575,429)
Knee	34 (1,783,042)
Hip	18 (1,510,184)

IQR=interquartile range; N, number; VTE, venous thromboembolism