**Associations of cardiovascular risk factors with venous thromboembolism**

The Emerging Risk Factors Collaboration†

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1 Supplementary Appendix

**KEY POINTS**

**Question** To what extent are established cardiovascular risk factors associated with risk of venous thromboembolism (VTE)?

**Findings** Among a panel of several established cardiovascular risk factors, older age, smoking, greater adiposity, and lower alcohol consumption were consistently associated with higher VTE risk in an analysis of individual-participant data involving 1.1 million participants.

**Meaning** There is overlap in at least some of major population determinants of important venous and arterial thrombotic diseases.

**ABSTRACT**

**Importance** It is uncertain to what extent established cardiovascular risk factors are associated with venous thromboembolism (VTE).

**Objective** To estimate associations between major cardiovascular risk factors and VTE, i.e., deep-vein thrombosis (DVT) and pulmonary embolism (PE).

**Design** Analysis of individual-participant data from the Emerging Risk Factors Collaboration (ERFC; 731,728 participants; 75 cohorts; latest date of follow-up 2015), and UK Biobank (UKBB; 421,537 participants; latest date of follow-up 2016).

**Setting** Approximately population-based prospective cohort studies.

**Participants** Individuals without cardiovascular disease at baseline.

**Exposures** A panel of several established cardiovascular risk factors.

**Main Outcomes and Measures** Hazard ratios (HRs) per 1-SD higher risk factor levels (or presence/absence). Incident fatal outcomes in ERFC (n=1041 VTE, n=25,131 CHD) and incident fatal/non-fatal outcomes in UKBB (n=2321 VTE, n=3385 CHD). HRs were adjusted for age, sex, smoking status, diabetes mellitus, and body-mass index.

**Results** Adjusted HRs for VTE were: 2.67 (2.45-2.91) in ERFC and 1.81 (1.71-1.92) in UKBB per decade older age; 1.38 (1.20-1.58) in ERFC and 1.23 (1.08-1.40) in UKBB with smoking; 1.43 (1.35-1.50) in ERFC and 1.37 (1.32-1.41) in UKBB per 1-SD higher body-mass index; and 0.75 (0.61-0.93) in ERFC and 0.82 (0.71-0.94) in UKBB with current alcohol consumption. For the preceding factors, there were similar HRs for pulmonary embolism versus deep vein thrombosis in UKBB (except adiposity was more strongly associated with PE; P<0.01), and similar HRs for unprovoked versus provoked VTE. Apart from adiposity, these risk factors were less strongly associated with VTE than coronary heart disease. We noted inconsistent associations with diabetes and blood pressure for VTEs across ERFC and UKBB, and had limited ability to study lipid and inflammation markers.

**Conclusions and Relevance** Older age, smoking, adiposity, and lower alcohol consumption were consistently associated with higher VTE risk.

**INTRODUCTION**

Venous thromboembolism (VTE), consisting of deep-vein thrombosis (DVT) or pulmonary embolism (PE), is a major clinical burden. Globally, there are about 10 million cases every year, the third leading vascular disease after myocardial infarction and stroke.1 PE is a manifestation of VTE, responsible for the large majority of VTE deaths.2 In recent years, efforts to prevent VTE have broadened from focusing mainly on hospital-based risk factors (eg, recent prior surgery, cancer, congestive heart failure) toward adoption of “heart healthy lifestyles”.3 This perspective has challenged traditional views of venous and arterial thrombosis as distinct pathologies, encouraging prevention strategies that concomitantly address VTE and arterial thrombosis.2,4 However, there is uncertainty about extent to which venous and arterial thrombosis share cardiovascular risk factors.5-15 Studies have reported conflicting findings.5-15 Interpretation has been complicated by the use of retrospective case-control designs, limited statistical power, and/or inability to compare VTE and arterial disease outcomes within the same cohorts.16-26

Analysing data from over 1.1 million participants in 76 prospective studies, we investigated associations of several established cardiovascular risk factors with the incidence of VTE outcomes. We aimed to address two principal questions: What are the associations of major cardiovascular risk factors with VTE outcomes (including subtypes)? How do these associations compare with those for coronary heart disease (CHD), a manifestation of arterial thrombotic disease?

**METHODS**

## Data sources and participant inclusion

We analysed data from the Emerging Risk Factors Collaboration (ERFC), a consortium of prospective cohort studies with information on a variety of risk factors, and UK Biobank (UKBB), a single large prospective study. Both the ERFC and UKBB have been described previously.27,28 Both data sources involve a prospective cohort study design and accessible individual-participant data, enabling standardised and detailed analyses using a common protocol, including definitions for VTE and CHD outcomes. However, we conducted parallel (rather than pooled) analyses of the two sources because of potentially important differences in their approaches to VTE ascertainment, i.e., the ERFC recorded only fatal VTE outcomes while UKBB recorded both fatal and non-fatal VTE outcomes, most of which were non-fatal. Information about each of the 76 studies contributing to this analysis is provided in **Table S1** in the **Supplementary Appendix**.

Participants in the contributing studies were eligible for inclusion in the current analysis if they met all of the following criteria: 1) had recorded information on several established cardiovascular risk factors (as a minimum, information on age, sex, smoking status, history of diabetes, and body-mass index [BMI]), 2) did not have a known baseline history of cardiovascular disease ([CVD], defined as coronary heart disease, other heart disease, stroke, transient ischemic attack, peripheral vascular disease or cardiovascular surgery) or VTE (defined as DVT or PE), and 3) had at least 1 year of follow-up after baseline.

As noted above, in the ERFC only fatal VTE events were recorded. Ascertainment was based on death certificates supplemented in 56 studies by medical records, findings on autopsy, and other sources. In UKBB, fatal and non-fatal VTEs were ascertained through linkage with routinely collected medical records. We attempted to sub-categorize VTEs as “provoked” and “unprovoked” using a pragmatic approach that required inference from routine records (**Supplementary Appendix**). Briefly, following the example of previous work,13 we defined a VTE as provoked if, in the 90-day period preceding the VTE, the participant was recorded as: having a malignant neoplasm (as per cancer registry data); starting/ending a hospital episode with a main diagnosis code relating to malignant neoplasm, heart failure, infectious disease or trauma; or having a hospital episode that included certain types of surgical procedures. The specific International Statistical Classification of Diseases and Related Health Problems (ICD) codes and Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures that are included in our definition have been summarised in the **Supplementary Appendix**. All studies used definitions of CHD based on World Health Organization (or similar) criteria. In registering fatal outcomes, the contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause), on the basis of coding from the International Classification of Diseases, Eighth-Tenth Revisions, to at least 3 digits, or according to study-specific classification systems. The date of the latest follow-up was January 2015 in ERFC and February 2016 in UKBB.

**Statistical analysis**

For continuous risk factors, we calculated HRs per 1-SD higher values. For binary risk factors, we compared presence versus absence of the factor. Cox proportional hazards regression models were adjusted for age, smoking status, history of diabetes, and BMI, and stratified by study, sex, and (when appropriate) trial arm. To avoid “over-adjustment”, we did not routinely adjust for systolic blood pressure and lipid measurements (which, for example, can mediate the effects of adiposity). Similarly, we did not adjust for BMI when analysing other measures of adiposity (eg, waist circumference). Participants in the UKBB were censored at first non-fatal CVD event, death, or study exit, whichever occurred first. Participants in ERFC were censored at death or study exit. Because non-fatal CVD may result in hospitalisation (which may, in turn, lead to VTE outcomes), sensitivity analyses additionally censored at the first non-fatal CVD event in the ERFC.

To characterise shapes of associations, HRs calculated within overall fifths of baseline exposure values were plotted against mean usual values of the relevant risk factor within each fifth. We used Plummer’s method to estimate 95% confidence intervals from the variances that correspond to the amount of information underlying each group (including the reference category).29

To correct for regression dilution caused by variability in levels of continuous risk factors, we regressed serial measurements of risk factors obtained from up to 146,749 participants in ERFC (mean interval 8.4 years) and 24,235 participants in UKBB (mean interval 5.2 years) on baseline levels of the relevant characteristics. Correction for within-person variation in risk factors was achieved by use of conditional expectations of long-term average levels (“usual levels”) of the risk factors, which were predicted from regression calibration models and used in estimation of HRs, as described previously.30

As a further aim of the study was to compare associations of risk factors with VTE versus CHD outcomes within the same cohorts, we defined a competing risk model using a record duplication approach, allowing for simultaneous cause-specific hazard regression to estimate cause-specific HRs (referred to throughout as HRs for brevity) for each type of event. In ERFC, we stratified the cause-specific regression model by cohort to allow for a different baseline hazard function in each study. We tested for differences in associations with VTE versus CHD based on the interaction between each exposure variable and the event type indicator variable.31 Interaction terms from these cause-specific hazards models are robust to different weightings across studies and were therefore pooled across ERFC and UKBB using fixed-effects meta-analysis to assess overall evidence for differences.

Analyses were carried out using Stata software (release 13), 2-sided P values, and 95% confidence intervals (CIs). Because of the number of statistical tests done, we have considered the results providing strong evidence if P<0.001.

The study was designed and conducted by this collaboration’s academic coordinating centre, and it was approved by the Cambridgeshire Ethics Review Committee. The funders had no scientific role in the study.

# Results

Data were available on 731,728 participants from 75 ERFC cohorts and 421,537 participants from UKBB (**Table 1** and **Table S1** in the **Supplementary Appendix**). The mean age at baseline was 52 (SD 9) years in ERFC and 56 (SD 8) years in UKBB; 54% and 55%, respectively, were female. The majority of participants in ERFC were enrolled in either Europe (51%) or North America (43%). During a median follow-up of 15.4 years, 1041 fatal VTE events and 25,131 fatal CHD events were recorded in the ERFC. In UKBB, 2321 fatal or non-fatal VTE events and 3385 fatal or non-fatal CHD events were recorded during a median follow-up of 6.1 years.

Associations of several risk factors with VTE were approximately log-linear (**Figure 1**). Older age was associated with higher risk of VTE, with an approximately 2.8-fold higher hazard per decade in ERFC and 1.8-fold higher risk per decade in UKBB (**Figure 2**). Compared to females, males had a higher risk of VTE both in ERFC and UKBB (HRs of 1.17 and 1.44, respectively). Current smoking was associated with VTE risk in both ERFC and UKBB (HRs of 1.38 and 1.23, respectively). Markers of adiposity (BMI, waist-to-hip ratio and waist circumference), were all positively associated with higher VTE risk in both ERFC and UKBB. For example, HRs per 1-SD higher BMI were 1.43 (95% CI 1.35-1.50) in ERFC and 1.37 (1.32-1.41) in UKBB. Current alcohol consumption was inversely associated with VTE risk in both ERFC and UKBB (HRs of 0.75 and 0.82, respectively). In exploratory analyses restricted to current drinkers in UKBB (which should limit the effects of certain residual biases, such as reverse causality related to “sick quitters”32), we found that the inverse association between amount of alcohol consumed and VTE risk persisted (Figure S1).

By contrast, for some other risk factors we studied, we noted potentially directionally discordant associations across ERFC and UKBB. For example, 1-SD higher systolic blood pressure was not clearly associated with risk of VTE in ERFC (HR 1.07, 0.95-1.17), but it was inversely associated with risk of VTE in UKBB (0.83, 0.77-0.90). Conversely, 1-SD diastolic blood pressure was associated with higher risk of VTE in ERFC (1.26, 1.11-1.42), but it was not associated with risk of VTE in UKBB (0.94, 0.87-1.02). In ERFC, history of diabetes was associated with higher risk of VTE (1.67, 1.27-2.19) as was 1-SD higher fasting baseline glucose concentration (1.27, 1.08-1.48), while in UKBB history of diabetes was inversely associated with risk of VTE (0.83, 0.69-0.99). To investigate whether these discordant associations chiefly reflected the different VTE outcomes recorded across ERFC and UKBB, we restricted analysis to the UKBB (which had recorded both fatal and nonfatal VTE outcomes). In UKBB-specific analyses, we found a similar pattern of difference of HRs for fatal versus nonfatal VTEs with blood pressure and diabetes to that observed in our comparison across ERFC and UKBB (**Figure S2**). This result suggests that blood pressure and diabetes may have differing associations with fatal versus nonfatal VTEs.

At the time of our analysis, data on plasma biomarkers were available in the ERFC but not in UKBB (**Figure 2**). In the ERFC, apolipoprotein-B, apolipoproien-A, and lipoprotein(a) each showed inverse associations with risk of VTE, whereas triglycerides, non-high-density-lipoprotein cholesterol, and high-density-lipoprotein-cholesterol each showed no clear associations. Fasting glucose, C-reactive protein, and fibrinogen were each associated with higher risk of VTE.

In analyses comparing PE vs DVT higher body-mass index and higher waist circumference had stronger associations with PE than DVT (**Figure 3**). Further analyses that sub-categorised VTE outcomes as provoked versus unprovoked in UKBB did not reveal major differences in the associations of the majority of CVD risk factors, with the exceptions of older age and male sex (**Figure 4**).

In analyses comparing VTE versus CHD outcomes, associations were stronger for CHD in both ERFC and UKBB for the majority of risk factors, including age, male sex, current smoking status, history of diabetes, and higher systolic and diastolic blood pressure, and pro-atherogenic lipids. In contrast, higher body-mass index, and higher waist circumference had somewhat stronger associations with VTE compared to CHD, whereas circulating inflammatory markers were associated with both conditions to a broadly similar extent (**Figure S3** and **Figure S4**).

Findings were broadly similar in sensitivity analyses that did not adjusted for BMI (**Table S2**), excluded participants with history of cancer diagnosis at baseline (**Figure S5**), censored for first CVD events in ERFC (**Figure S6**), used baseline levels of risk factors, except for the expected decrease in the magnitudes of association when not correcting for within-person variability in the continuous variables (**Figure S7** to **Figure S9**).

**DISCUSSION**

This analysis of individual-level data on several established cardiovascular risk factors among 1.1 million participants in 76 cohorts found that older age, smoking, higher levels of adiposity, and lower alcohol consumption were associated with higher risk of VTE. These findings suggest that there is overlap in at least some of major population determinants of important venous and arterial thrombotic diseases.

Our study characterised dose-response relationships between several clinical measures of excess adiposity (eg, waist circumference, BMI) and VTE risk, showing no evidence of a threshold below which leaner body habitus stopped being associated with lower VTE risk. A cause-and-effect relationship between obesity and VTE is supported by previous Mendelian randomisation studies of genetic variants associated with increased adiposity, which are also associated with increased risk of VTE.33,34 Furthermore, our study found that associations of BMI and waist circumference were somewhat stronger for PE compared to DVT, and about twice as strong for VTE than CHD. These data suggest that efforts to combat the entire spectrum of obesity and overweight should yield important benefits for VTE prevention.

As regards risk behaviours, our study confirmed the known association between current smoking and risk of VTE.9,13 This association was similar in magnitude for PE and DVT outcomes, but weaker than that observed for CHD. Previous studies had suggested that much of the excess risk of VTE in smokers was due to increased hospitalisation for smoking-related diseases, including cancer.35,36 However, in our analysis smoking was similarly associated with both provoked and unprovoked VTE; HRs did not change appreciably after exclusion of participants with history of cancer diagnosis at baseline. We also noted that lower alcohol consumption was associated with higher VTE risk,37,38 a pattern of association previously reported for alcohol consumption with non-fatal myocardial infarction (by contrast, alcohol consumption has previously been positively associated with risks of fatal coronary disease, stroke, and heart failure).32 Although previous studies have reported that moderate alcohol consumption is associated lower levels of haemostatic factors (e.g., fibrinogen, factor VII, von Willebrand factor39,40), further studies are needed to determine whether moderate alcohol consumption has a causal role in VTE.

Our study identified inverse associations of proatherogenic lipids with VTE. For example, apolipoprotein-B and lipoprotein(a) levels were each associated with *lower* risk of VTE, a surprising finding that awaits further elucidation.41 Pro-inflammatory soluble biomarkers (e.g., C-reactive protein) were positively associated with VTE, a finding consistent with the associations we observed for CHD outcomes. Although previous Mendelian randomisation studies suggest that CRP and fibrinogen are unlikely to be direct causal factors in CHD,42,43 such genetic epidemiological data are sparser in relation to VTE.

It is not clear why our study found inconsistent associations of blood pressure and history of diabetes with VTE outcomes across UKBB and the ERFC. One potential explanation is that these data sources recorded mostly differing types of VTE outcomes, i.e., UKBB involved mostly nonfatal outcomes, whereas ERFC involved only fatal outcomes. An exploratory analysis of UKBB data was consistent with this explanation, as it found differing results with blood pressure and diabetes for fatal VTE versus nonfatal VTE similar to those observed in comparisons across UKBB and the ERFC. However, future studies with more detailed clinical information will be needed to understand these possible differences with greater confidence.44

Our study had major strengths. It avoided the limitations of retrospective case-control study designs by analysing prospective cohort data on over 1.1 million participants without CVD at baseline. Access to individual-participant data avoided the limitations of literature-based meta-analyses. It also enabled a common approach to adjustment for potential confounding factors, time-to-event analyses, correction for regression dilution bias, and head-to-head comparisons of VTE and CHD. We explored idiopathic VTE versus VTE provoked by established risk factors (such as cancer or prolonged immobility), albeit using pragmatic record-based definitions.45 The generalizability of our results was enhanced by inclusion of data from 76 prospective studies recruited during 1960 through 2008 in 18 different countries. To enhance power and evaluate the relevance of findings to the contemporary situation, we included data from UK Biobank, which recruited participants during 2006 to 2010.

Our study also had limitations. We did not routinely have information in the ERFC on non-CVD risk factors for VTE (e.g., oral contraception use), or medication use (e.g., anti-coagulants). Mis-classification of disease outcomes could have arisen from inaccuracies in hospital discharge records and death certificates, diluting the strength of the observed associations.46-48 However, two observations argue against major disease mis-classification in our study. First, we observed associations of measures of adiposity with VTE risk similar in size to those previously reported in much smaller studies based on detailed validation of VTE events.6 Second, we observed directionally opposite associations of proatherogenic lipids with VTE and CHD outcomes, despite the two conditions having similar clinical presentations.

**Conclusions**

Among a panel of several established cardiovascular risk factors, older age, smoking, adiposity, and lower alcohol consumption were consistently associated with higher VTE risk. There is overlap in at least some of the major population determinants of important venous and arterial thrombotic diseases.

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Table 1. Summary of baseline characteristics and outcomes recorded.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ERFC** | | | **UK Biobank** | |
| Characteristic, summary | Cohorts | N | Mean (SD) or n (%) or Median (5th, 95th) centiles | N | Mean (SD) or n (%) or Median (5th, 95th) centiles |
| **Demographic and lifestyle factors** |  |  |  |  |  |
| Age at survey (yrs) | 75 | 731728 | 51.9 (9.0) | 421537 | 56.4 (8.1) |
| Male, n(%) | 70 | 731728 | 328332 (44.9%) | 421537 | 187838 (44.6%) |
| Current smoker, n(%) | 75 | 731728 | 222016 (30.3%) | 421537 | 43847 (10.4%) |
| History of diabetes, n (%) | 74 | 731728 | 25982 (3.6%) | 421537 | 17622 (4.2%) |
| Current alcohol drinker, n(%) | 58 | 386831 | 271499 (70.2%) | 421197 | 389507 (92.5%) |
| **Anthropometric and physical markers** |  |  |  |  |  |
| Systolic blood pressure (mmHg) | 73 | 566724 | 131 (19) | 421179 | 137 (19) |
| Diastolic blood pressure (mmHg) | 72 | 565895 | 80.0 (10.9) | 421181 | 82.2 (10.1) |
| Body mass index (kg/m2) | 75 | 731728 | 25.4 (4.2) | 421537 | 27.2 (4.7) |
| Waist:Hip ratio | 34 | 264787 | 0.85 (0.08) | 421440 | 0.87 (0.09) |
| Waist circumference (cm) | 36 | 265465 | 87.6 (12.5) | 421464 | 89.6 (13.2) |
| **Lipid related markers** |  |  |  |  |  |
| Total cholesterol (mmol/l) | 68 | 455177 | 5.75 (1.13) | - | - |
| Non-HDL cholesterol (mmol/l) | 57 | 311888 | 4.43 (1.16) | - | - |
| HDL-C (mmol/l) | 57 | 312207 | 1.37 (0.38) | - | - |
| Log Triglycerides (mmol/l) | 56 | 322096 | 0.30 (0.53) | - | - |
| Apolipoprotein B (g/l) | 20 | 80712 | 1.03 (0.29) | - | - |
| Apolipoprotein A1 (g/l) | 20 | 84483 | 1.37 (0.33) | - | - |
| Log Lp(a) (mg/dl) | 18 | 66382 | 2.20 (1.20) | - | - |
| **Metabolic and inflammatory markers** |  |  |  |  |  |
| Fasting glucose (mmol/l) | 33 | 130322 | 4.91 (1.35) | - | - |
| Log CRP (mg/l) | 28 | 70855 | 0.46 (1.07) | - | - |
| Fibrinogen (µmol/l) | 29 | 115002 | 7.09 (2.02) | - | - |
| Albumin (g/l) | 25 | 115309 | 42.9 (3.9) | - | - |
| **Study period\*** |  |  |  |  |  |
| Baseline survey year | 75 | 731728 | 1986 (1971, 2000) | 421537 | 2009 (2007, 2010) |
| Latest follow up year | 75 | 731728 | 2004 (1989, 2011) | 421537 | 2016 (2016, 2016) |
| **Outcomes** |  |  |  |  |  |
| Time to event or censoring (yrs) | 75 | 731728 | 15.4 (5.5, 32.0) | 421537 | 6.1 (4.8, 7.5) |
| Person-years of follow up (millions) | 75 | 731728 | 12.807 | 421537 | 2.566 |
| Non-fatal MI and Fatal CHD, n | 75 | 731728 | 25131 | 421537 | 3385 |
| Non-fatal MI, n | -† | - | - | 421537 | 2808 |
| Fatal CHD, n | 75 | 731728 | 25131 | 421537 | 577 |
| Venous thromboembolism (VTE), n | 75 | 731728 | 1041 | 421537 | 2321 |
| Non-fatal VTE, n | -† | - | - | 421537 | 2234 |
| Fatal VTE, n | 75 | 731728 | 1041 | 421537 | 87 |
| Pulmonary embolism (PE), n | 75 | 731728 | 855 | 421537 | 1273 |
| Deep venous thromboembolism (DVT), n | 75 | 731728 | 186 | 421537 | 1048 |
| Unprovoked VTE, n | - | - | - | 421537 | 1465 |
| Provoked VTE, n | - | - | - | 421537 | 856 |

ERFC, Emerging Risk Factors Collaboration; HDL-C, high density lipoprotein cholesterol; CRP, C-reactive protein; Lp(a), lipoprotein(a); PE, pulmonary embolism; CHD, coronary heart disease.

\* Follow up and outcome summaries among participants with complete data on age, sex, smoking status, history of diabetes, and BMI.

† Majority of the studies in ERFC did not ascertain non-fatal VTE outcomes; hence analyses in ERFC were restricted to comparison of fatal outcomes only.