# Venous thrombosis in the elderly: risk factors and consequences

Wang, H.

# CHAPTER 4

## Association between cardiovascular risk factors and venous thromboembolism in the elderly

**Huijie Wang, Frits R. Rosendaal, Mary Cushman, Astrid van Hylckama Vlieg**

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## ABSTRACT

### Background

The preponderance of the evidence supports no association between traditional cardiovascular risk factors and venous thromboembolism (VTE), other than obesity. There is limited data in older people.

### Objectives

To investigate whether cardiovascular risk factors (body mass index, smoking, alcohol intake, hypertension and diabetes) are associated with the risk of VTE in elderly and to assess the combined effect between cardiovascular risk factors and genetic risk factors for VTE (factor V Leiden (FVL)/prothrombin 20210A (PT20210), positive family history of VTE, and non-O blood group).

### Methods

The AT-AGE study is a multi-center case-control study performed in Vermont, USA and Leiden, NL, comprising of 401 cases with first VTE and 431 control subjects, all aged ≥70 years. To assess the risk of VTE, odds ratios (OR) with 95% confidence intervals(CI) were calculated, adjusting for potential confounders.

### Results

Both height and weight were positively associated with VTE risk: the ORs were 2.2 (95%CI: 1.2-3.9) and 1.5 (95%CI: 1.0-2.4) in top quartile in for height and weight separately. This risk was more pronounced for unprovoked VTE. Smoking, alcohol intake and diabetes were not associated with VTE. Higher systolic and diastolic blood pressure, and hypertension, were associated with a decreased risk of VTE. In the presence of a genetic predisposition, height and weight further increased the risk of VTE.

### Conclusions

In the elderly, height and weight are positively associated with the risk of VTE. With genetic predisposition, higher levels of height and weight further increase the risk of VTE.

## INTRODUCTION

Venous thromboembolism (VTE) is a frequent and severe disorder associated with acquired and genetic risk factors. The incidence of VTE rises dramatically with age (up to 1 per 100 annually in the old) [1], indicating that increasing age is the most important risk factor for VTE. Acquired risk factors include immobilization, surgery, trauma, and malignant disease. Genetic risk factors include deficiencies of anticoagulants protein S, C, and antithrombin and numerous genetic variants of which the most common are the factor V Leiden and prothrombin 20210A mutations [2, 3]. Non-O blood group and family history of VTE are also important determinants of VTE [4-7]. Furthermore, several cardiovascular risk factors have been associated with the risk of VTE in young and middle aged populations, albeit results were often inconsistent [8-38].

Some studies reported a positive association between obesity [8-25], smoking [8, 9, 12, 15, 24-28], hypertension [15], and diabetes [29, 30], and the risk of VTE. However, the conclusions of other studies varied from no association for smoking [19, 21, 31, 32], alcohol intake [9, 19, 21], hypertension [26], systolic or diastolic blood pressure [21, 33] and diabetes [26, 34] to an inverse association for alcohol intake [35], systolic and diastolic blood pressure [12, 26] and the risk of VTE. Most studies included a broad age range including individuals of older age but did not perform a stratified analysis on age. Thus, we have limited information on the role of cardiovascular risk factors in VTE development in the elderly. Among elderly people, obesity is a risk factor for VTE [18, 37, 39] and low to moderate alcohol consumption was associated with a decreased risk of VTE [38].

Several studies evaluated the combined effects between lifestyle risk factors (body mass index [BMI] body height and smoking) and genetic risk factors (FVL, PT20210A or a genetic risk score) on the risk of VTE [6, 16, 36, 40-43]. In individuals carrying a prothrombotic genetic variant, the risk of VTE may be mitigated by a healthy lifestyle, in particular a normal weight [41, 42].

The aim of this study was to investigate whether cardiovascular risk factors are associated with the risk of VTE in people aged 70 years and older, and to assess the combined effect between common genetic risk factors for VTE (factor V Leiden (FVL) / prothrombin 20210A (PT20210), positive family history of VTE, non-O blood group) and cardiovascular risk factors.

## METHODS

### Study design

The Age and Thrombosis, Acquired and Genetic risk factors in the elderly (AT-AGE) study is a two-center, population-based case-control study designed to study risk factors for VTE in older people. The design of the AT-AGE study was described in detail previously [44]. In brief, from June 2008 to August 2011 in Leiden, the Netherlands and December 2008 to July 2011 in Vermont, US, all consecutive patients 70 years and older with a first imaging- confirmed deep vein thrombosis of the leg (DVT) or pulmonary embolism (PE with or without DVT) were identified. Patients were identified from the anticoagulation clinics in Haarlem and Leiden and from the Vascular Laboratory and the Radiology department of the University of Vermont Medical Center (Burlington, Vermont, United States). Control subjects were randomly selected from five primary care practices in Leiden and four in Vermont. Individuals with active malignancy or severe psychiatric or cognitive disorders were excluded. Active malignancy was defined as diagnosis of cancer within six months before the thrombotic event (or date of telephone call for the control subjects) or chemotherapy or radiation therapy for cancer in the last six months. All participants provided written informed consent. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre and by the Committee on Human Research of the University of Vermont.

### Data collection

For all participants, at a home visit, a structured interview was completed by trained personnel and a blood sample or buccal swab was collected. In total, 401 patients and 431 controls completed the interview. It was calculated that, with a 10% exposure to the risk factor of interest in the controls, recruitment of 283 patients and 283 controls were needed to detect an odds ratio as low as 2.0 with 80% power and alpha 0.05. The questionnaires included items on body height, body weight, smoking, alcohol intake, diabetes mellitus, family history of VTE (first degree relatives), and medication use (including statins use). All diagnoses obtained from the questionnaires (including diabetes mellitus) were self-reported and were not validated with the medical records. Body height, body weight, and blood pressure were measured during the visit.

Participants were categorized as non-smokers, former smokers, and current smokers. Alcohol intake was dichotomized into current use yes / no. Hypertension was defined as a systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg or the use of antihypertensive medication. Family history of VTE was considered positive when at least

one first-degree relative was reported to have experienced VTE. Individuals (304 patients and 377 controls) who did not know whether a first-degree relative had VTE were classified as having a negative family history. Provoked VTE was defined as thrombosis after hospitalization (including recent surgery), fracture, plaster cast, splint, minor injuries of lower extremities (such as a sprained ankle or contusion of the lower leg), or transient immobility at home ≥ 4 successive days in the three months before the index date. The index date was defined as the date of diagnosis of thrombosis for the patients and the date of the home visit for the control subjects.

**Laboratory Assays**

During the home visit, blood samples were drawn into vacuum tubes containing 0.1-volume 0.106-mol/L trisodium citrate or when no blood sample could be drawn, a buccal swab was collected (N=30) for patients and controls. DNA analysis for the factor V Leiden mutation (rs6025) and the prothrombin G20210A mutation (rs1799963) was performed using a combined polymerase chain reaction with the TaqMan assay (Applied Biosystems, Foster City, CA, USA). The 20146G/-(rs8176719), 21463C/G(rs7853989), 21867A/G(rs8176749) and 21996C/-(rs8176750) blood group polymorphisms were determined by a 5' nuclease assay (Taqman; Applied Biosystems, Foster City, CA, USA) using a PCR reaction mix (Taqman Genotyping Master Mix, Applied Biosystems) and an allele-specific fluorescent probe equipped with a minor groove binding moiety.



Genetic predisposition was defined as having any of genetic factors (factor V Leiden, prothrombin G20210A mutation, family history of VTE and non-O blood group).

**Statistical analysis**

To estimate relative risks, we calculated odds ratios (ORs) and 95% confidence intervals (95%CI) of VTE for all risk factors. Body mass index (BMI) was calculated by dividing body weight (kg) by squared height ($m^2$). BMI was further categorized according to the criteria of the World Health Organization, with BMI <18.5 $kg/m^2$ as underweight, BMI between 18.5 and 25 $kg/m^2$ as normal weight, BMI 25 to 30 $kg/m^2$ as overweight, and BMI equal to or greater than 30 $kg/m^2$ as obesity. BMI was analysed continuously and in World Health Organization (WHO) categories. The separate elements of BMI (body height and body weight) were also assessed, again continuously and after stratification into quartiles based on the distribution of the controls.

Blood pressure, i.e., systolic and diastolic blood pressure, were analysed continuously and in quartiles based on the distribution of the controls.

Using multivariable logistic regression models, we calculated the risk of VTE associated with cardiovascular risk factors, adjusted for potential confounders. Confounding factors considered were age, sex, study center, cardiovascular risk factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction). Considering patients after 70 years are often on statins for cardiovascular risk prevention (particularly in those with diabetes) and the use of statins may reduce the risk of VTE [45, 46], we therefore assessed the risk of VTE associated with cardiovascular risk factors after additional adjustment for statin use. We further assessed the risk of VTE associated with cardiovascular risk factors, a genetic predisposition (carrying factor V Leiden or prothrombin 20210A or positive family history of VTE or non-O blood group) or the combination of both risk factors.

Analyses were also performed separately for DVT and PE and for provoked and unprovoked VTE. IBM SPSS 25.0 for Windows (SPSS Inc, Chicago, Ill) was used for all data analysis.

## RESULTS

Table 1 shows characteristics of the patients and control subjects. The mean age of patients was 78.7 years (range: 70.0-100.9), similar to controls (mean age: 77.5, range: 70.3-96.3). The majority of participants were Caucasian (95.8% of the patients and 94.7% of the controls). There were slightly more women than men. 166 (41.4%) of the patients had DVT only, while 235 (58.6%) had PE (with or without DVT). The VTE events were provoked in 48.9% (n=196) and unprovoked in 48.6% (n=195) of the patients. A positive family history of VTE was more common in patients than in controls (24.2% versus 12.5%), as were non-O blood group and prothrombotic gene variants. There were more controls using statins than patients (25.3% versus 18.2%). The distribution of comorbidities was similar in patients and controls.

**Table 1.** Baseline characteristics of patients and controls.

| | **Patients N=401** | **Controls N=431** |
|---|---|---|
| Men, n (%) | 166 (41.4) | 209 (48.5) |
| Age, mean (range) | 78.7 (70.0-100.9) | 77.5 (70.3-96.3) |
| Ethnicity(Caucasian), n (%)* | 384 (95.8) | 408 (94.7) |
| Type of VTE | | |
| Deep vein thrombosis (DVT), n (%) | 166 (41.4) | - |
| Pulmonary embolism (PE±DVT), n (%) | 235 (58.6) | - |
| Provoked VTE, n (%)* | 196 (48.9) | - |
| Unprovoked VTE, n (%)* | 195 (48.6) | - |
| Factor V Leiden, n (%)* | 34 (8.6) | 18 (4.2) |
| Prothrombin G20210A mutation, n (%)* | 9 (2.3) | 7 (1.6) |
| Non-O blood group, n (%)* | 231 (61.4) | 232 (53.8) |
| Positive family history of VTE, n (%)* | 97 (24.2) | 54 (12.5) |
| Statins use | 73 (18.2) | 109 (25.3) |
| Comorbidities | | |
| Heart failure, n (%) | 20 (5.0) | 19 (4.4) |
| Angina, n (%)* | 42 (10.6) | 33 (7.7) |
| Myocardial infarction, n (%) | 53 (13.2) | 51 (11.8) |
| Cerebral bleeding, n (%)* | 7 (2.0) | 7 (1.6) |
| Transient ischemic attack, n (%)* | 44 (11.0) | 42 (10.0) |
| Cerebral infarction, n (%)* | 23 (5.8) | 23 (5.3) |

N=number, VTE=venous thromboembolism ,
* 4 missing in ethnicity of patients and 5 missing in ethnicity of controls. 10 missing in provoked and unprovoked VTE. 7 missing in factor V Leiden of patients and 5 missing in factor V Leiden of controls. 16 missing in prothrombin G20210A mutation of patients and 4 missing in prothrombin G20210A mutation of controls. 25 missing in non-O blood group of patients and 15 missing in non-O blood group of controls. 1 missing in positive family history of VTE of controls. 3 missing in angina of patients. 59 missing in myocardial infarction of patients. 3 missing in transient ischemic attack of patients. 1 missing in cerebral infarction of patients and 10 missing in cerebral infarction of controls.

As shown in Table 2, the overall distribution of cardiovascular risk factors was not notably different between patients and controls. Assessing the association between continuous cardiovascular risk factors (BMI, body height, body weight, systolic blood pressure, and diastolic blood pressure) and the risk of VTE, the odds ratios of VTE associated with each standard deviation increment were 1.1 (95% CI: 0.9-1.3) for BMI, 1.4 (95% CI: 1.1-1.7) for body height, 1.2 (95% CI: 1.0-1.4) for body weight, 0.7 (95% CI: 0.6-0.8) for systolic blood pressure, 0.7 (95% CI: 0.6-0.8) for diastolic blood pressure.

**Table 2.** The distribution of cardiovascular risk factors among patients and controls.

| | **Patients N=401** | **Controls N=431** |
|---|---|---|
| Body weight in kg, mean (range) | 77.8 (38.0-132.3) | 76.3 (42.8-140.4) |
| Body height in cm, mean (range) | 169.0 (147.0-195.0) | 167.9 (145.0-196.0) |
| Body mass index(BMI), mean($kg.m^{-2}$) (range) * | 27.2 (14.5-45.4) | 27.0 (17.0-49.7) |
| underweight, n (%) | 5 (1.2) | 3 (0.7) |
| normal, n (%) | 119 (29.7) | 144 (33.4) |
| overweight, n (%) | 166 (41.4) | 175 (40.6) |
| obese, n (%) | 88 (21.9) | 94 (21.8) |
| Smoking status* | | |
| never, n (%) | 123 (30.7) | 120 (27.8) |
| former, n (%) | 234 (58.4) | 255 (59.2) |
| current, n (%) | 43 (10.7) | 55 (12.8) |
| Alcohol intake* | | |
| none, n (%) | 161 (40.1) | 160 (37.1) |
| current, n (%) | 238 (59.3) | 270 (62.6) |
| Hypertension, n (%) | 333 (83.0) | 374 (86.8) |
| Diabetes, n (%) | 69 (17.2) | 67 (15.5) |
| Systolic blood pressure, mm Hg (SD) | 143 (22) | 152 (23) |
| Diastolic blood pressure, mm Hg (SD) | 83 (13) | 86 (13) |

N=number, SD=standard deviation.
*BMI had 23 missing in patients and 15 missing in controls. Smoking status had 1 missing in patients and 1 missing in controls; Alcohol intake had 2 missing in patients and 1 missing in controls.

The risk of VTE associated with categorical cardiovascular risk factors is shown in Table 3. Individuals who were underweight had an OR of 1.6, 95%CI: 0.4-7.3 compared with individuals with normal weight. Being overweight was associated with an OR of 1.2 compared with normal weight, as was obesity: OR 1.2, 95%CI: 0.7-1.9. The risk of VTE associated with being overweight or obese compared with normal weight was most pronounced for unprovoked VTE (ORs overweight or obese compared with normal weight: 1.5 (95%CI: 0.9-2.3) and 1.6 (95%CI: 0.9-2.8), respectively), albeit for all estimates for BMI, confidence intervals were wide. The odds ratios of VTE increased from 1.2 (95%CI: 0.8-1.9) to 2.2 (95%CI: 1.2-3.9) across the top three quartiles of body height compared with the first quartile, and from 1.0 (95%CI: 0.6-1.5) to 1.5 (95%CI: 1.0-2.4) across top three quartiles of body weight when compared to the first quartile. Similar to BMI, risks were most pronounced for unprovoked VTE.

**Table 3.** The risk of venous thromboembolism associated with cardiovascular risk factors.

| Risk factor | OR crude (95%CI) | OR all VTE * (95%CI) | OR DVT* (95% CI) | OR PE±DVT* (95% CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Patients (N=401) | Patients (N=401) | Patients (N=166) | Patients (N=235) | Patients (N=196) | Patients (N=195) |
| BMI(kg/m$^2$) | | | | | | |
| underweight | 2.0(0.5-8.6) | 1.6(0.4-7.3) | 1.1(0.1-11.0) | 2.2(0.4-11.2) | 1.8(0.3-9.9) | 1.7(0.3-11.1) |
| normal | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| overweight | 1.1(0.8-1.6) | 1.2(0.8-1.7) | 1.3(0.8-2.2) | 1.1(0.8-1.8) | 0.9(0.6-1.5) | 1.5(0.9-2.3) |
| obese | 1.1(0.8-1.7) | 1.2(0.7-1.9) | 1.7(0.9-3.1) | 1.0(0.5-1.6) | 0.9(0.5-1.6) | 1.6(0.9-2.8) |
| Height # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 1.1(0.7-1.7) | 1.2(0.8-1.9) | 1.0(0.6-1.8) | 1.4(0.8-2.4) | 0.9(0.5-1.5) | 1.9(1.1-3.3) |
| P50-P75 | 1.3(0.9-1.9) | 1.8(1.1-2.8) | 1.0(0.5-2.0) | 2.5(1.4-4.3) | 1.4(0.8-2.6) | 2.3(1.2-4.2) |
| ≥P75 | 1.3(0.9-1.9) | 2.2(1.2-3.9) | 1.6(0.8-3.4) | 2.7(1.4-5.2) | 1.5(0.7-3.0) | 3.4(1.7-6.9) |
| Weight # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 0.9(0.6-1.4) | 1.0(0.6-1.5) | 0.9(0.5-1.5) | 1.1(0.7-1.8) | 0.9(0.5-1.4) | 1.2(0.7-2.1) |
| P50-P75 | 1.1(0.8-1.7) | 1.3(0.8-2.0) | 1.2(0.7-2.2) | 1.3(0.8-2.1) | 1.0(0.6-1.7) | 1.5(0.9-2.7) |
| ≥P75 | 1.3(0.9-1.9) | 1.5(1.0-2.4) | 1.6(0.9-2.9) | 1.4(0.8-2.5) | 1.2(0.7-2.1) | 2.0(1.1-3.6) |
| Smoking | | | | | | |
| never | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| former | 0.9(0.7-1.2) | 1.2(0.8-1.8) | 1.0(0.6-1.7) | 1.3(0.8-2.0) | 1.3(0.8-2.1) | 1.0(0.6-1.7) |
| current | 0.8(0.5-1.2) | 0.8(0.5-1.5) | 1.0(0.5-2.0) | 0.7(0.4-1.3) | 0.6(0.3-1.2) | 1.1(0.6-2.0) |
| Alcohol intake | | | | | | |
| no | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| yes | 0.9(0.7-1.2) | 1.1(0.8-1.5) | 1.4(0.9-2.3) | 1.0(0.7-1.4) | 0.8(0.5-1.2) | 1.5(1.0-2.3) |
| Systolic blood pressure(mmHg) # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 0.8(0.6-1.2) | 0.9(0.6-1.4) | 0.8(0.4-1.4) | 0.9(0.6-1.5) | 0.6(0.4-1.1) | 1.1(0.6-1.8) |
| P25-P50 | 0.5(0.3-0.8) | 0.5(0.3-0.8) | 0.4(0.2-0.8) | 0.6(0.4-1.0) | 0.6(0.3-1.0) | 0.5(0.3-1.0) |
| ≥P75 | 0.4(0.3-0.6) | 0.4(0.3-0.7) | 0.6(0.3-1.1) | 0.3(0.2-0.6) | 0.3(0.2-0.6) | 0.6(0.3-1.1) |
| Diastolic blood pressure(mmHg) # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 0.7(0.4-1.0) | 0.5(0.3-0.8) | 0.4(0.2-0.8) | 0.6(0.3-1.0) | 0.4(0.2-0.8) | 0.6(0.3-1.0) |
| P50-P75 | 0.8(0.5-1.1) | 0.5(0.3-0.9) | 0.6(0.3-1.0) | 0.5(0.3-0.9) | 0.4(0.2-0.8) | 0.7(0.4-1.2) |
| ≥P75 | 0.6(0.4-0.9) | 0.4(0.2-0.6) | 0.4(0.2-0.7) | 0.4(0.2-0.7) | 0.3(0.2-0.5) | 0.5(0.2-0.8) |
| Blood pressure | | | | | | |

Table 3. The risk of venous thromboembolism associated with cardiovascular risk factors. (continued)

| Risk factor | OR crude (95%CI) | OR all VTE * (95%CI) | OR DVT* (95% CI) | OR PE±DVT* (95% CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Patients (N=401) | Patients (N=401) | Patients (N=166) | Patients (N=235) | Patients (N=196) | Patients (N=195) |
| normal | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| hypertensive | 0.7(0.5-1.1) | 0.6(0.4-1.0) | 0.7(0.4-1.4) | 0.6(0.3-1.0) | 0.7(0.4-1.2) | 0.7(0.4-1.2) |
| Diabetes | | | | | | |
| no | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| yes | 0.9(0.6-1.3) | 1.1(0.7-1.7) | 1.1(0.6-2.0) | 1.1(0.6-1.8) | 1.1(0.6-2.0) | 1.0(0.6-1.7) |

OR=odds ratio, CI=confidence interval, VTE=venous thromboembolism, DVT=deep vein thrombosis, PE±DVT=pulmonary embolism, ref=reference.
# Cut-off values for quartiles:
Height: P25: 162 cm P50: 168 cm P75: 174 cm
Weight: P25: 65.1 kg P50: 74.9 kg P75: 84 kg
Systolic blood pressure: P25: 135 mm Hg P50: 152 mm Hg P75: 168 mm Hg
Diastolic blood pressure: P25: 78 mm Hg P50: 86 mm Hg P75: 94 mm Hg
* Height and weight adjusted for each other and for age, sex, and study center, all other ORs adjusted for age, sex, study center, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction).

There was no association between current smoking or former smoking (compared with never smoking) and the risk of VTE (OR current smoking 0.8, 95%CI: 0.5-1.5; OR former smoking: 1.2, 95%CI: 0.8-1.8). Current alcohol intake compared with no alcohol intake was also not associated with the risk of VTE (OR 1.1, 95% CI: 0.8-1.5). A dose-response relationship was observed between systolic blood pressure and the risk of VTE, i.e., after stratification into quartiles, the risk of VTE decreased gradually across increasing quartiles of systolic blood pressure to odds ratio of 0.4 (95%CI: 0.3-0.7) for systolic blood pressure in the highest quartile compared with the lowest quartile. The relationship between diastolic blood pressure and VTE risk was similar. Hypertension was also associated with a decreased risk of VTE (OR 0.6, 95%CI: 0.4-1.0). The results were similar when hypertension was defined using blood pressure only, i.e., not considering blood pressure lowering medication use (OR 0.5, 95%CI: 0.3-0.7). There was no association between diabetes and VTE risk (OR 1.1, 95%CI: 0.7-1.7). The risks of VTE associated with cardiovascular risk factors were similar for DVT and PE±DVT.

We assessed the risk of VTE associated with a genetic predisposition, a cardiovascular risk factor, or the combination of both (Table 4). When focusing on unprovoked VTE events where risk estimates are most pronounced, a genetic predisposition in the absence of a cardiovascular risk factor increased the risk of VTE 1.9 to 4.7 fold compared with

**Table 4.** Combined effect of cardiovascular risk factors and genetic predisposition on the risk of venous thromboembolism .

| Genetic predisposition (combined) | Cardiovascular risk factors | Patients N | Controls N | OR overall* (95%CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Obesity | | | | | |
| no | no | 67 | 127 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 23 | 24 | 1.6(0.7-3.5) | 1.5(0.6-3.9) | 2.0(0.7-5.5) |
| yes | no | 214 | 192 | 2.1(1.4-3.1) | 1.5(0.9-2.5) | 2.9(1.7-5.0) |
| yes | yes | 58 | 66 | 1.6(0.9-2.8) | 1.0(0.5-2.0) | 2.7(1.4-5.3) |
| | Height [a] | | | | | |
| no | <P50 | 47 | 61 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 49 | 91 | 1.0(0.5-1.8) | 0.8(0.4-1.6) | 1.5(0.7-3.3) |
| yes | <P50 | 111 | 134 | 1.2(0.7-2.0) | 0.8(0.5-1.5) | 1.9(1.0-3.7) |
| yes | ≥P50 | 167 | 127 | 2.4(1.4-4.2) | 1.8(0.9-3.4) | 3.8(1.9-8.0) |
| | Weight [b] | | | | | |
| no | <P50 | 41 | 78 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 50 | 73 | 1.3(0.8-2.4) | 0.9(0.5-1.8) | 2.2(1.0-5.0) |
| yes | <P50 | 119 | 129 | 1.7(1.1-2.8) | 1.2(0.7-2.1) | 3.2(1.6-6.4) |
| yes | ≥P50 | 156 | 130 | 2.5(1.5-4.0) | 1.6(0.9-2.8) | 4.3(2.1-8.8) |
| | Smoking[#] | | | | | |
| no | no | 85 | 125 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 13 | 28 | 0.6(0.3-1.3) | 0.5(0.2-1.3) | 0.8(0.3-2.2) |
| yes | no | 255 | 237 | 1.7(1.1-2.5) | 1.3(0.8-2.0) | 2.3(1.4-3.9) |
| yes | yes | 28 | 26 | 1.5(0.8-2.8) | 0.8(0.3-1.9) | 2.5(1.2-5.6) |
| | Alcohol intake | | | | | |
| no | no | 48 | 51 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 50 | 102 | 0.7(0.4-1.3) | 0.6(0.3-1.2) | 1.0(0.4-2.2) |
| yes | no | 102 | 103 | 1.3(0.7-2.2) | 0.9(0.5-1.8) | 1.9(0.9-3.9) |
| yes | yes | 180 | 159 | 1.6(1.0-2.8) | 1.0(0.5-1.8) | 2.9(1.4-5.8) |
| | Hypertension | | | | | |
| no | no | 17 | 24 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 81 | 129 | 0.8(0.4-1.8) | 0.8(0.3-1.9) | 1.2(0.4-3.9) |
| yes | no | 48 | 31 | 2.5(1.0-6.0) | 1.5(0.5-4.2) | 4.7(1.3-16.2) |
| yes | yes | 235 | 232 | 1.4(0.7-3.0) | 1.0(0.4-2.3) | 2.6(0.9-8.2) |
| | Diabetes | | | | | |
| no | no | 75 | 130 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 23 | 23 | 1.3(0.6-2.8) | 1.1(0.4-2.8) | 1.8(0.7-4.9) |
| yes | no | 239 | 220 | 2.0(1.3-2.9) | 1.4(0.9-2.2) | 2.9(1.7-5.0) |
| yes | yes | 44 | 43 | 1.5(0.8-2.8) | 1.1(0.5-2.4) | 2.3(1.1-5.1) |

N=number, CI=confidence interval, ref=reference.

[a] Cut-off value: P50: 168 cm

[b] Cut-off value: P50: 74.9 kg

[#] former and never smoking combined equals "no smoking", current smoking equals "yes smoking".

* Height and weight adjusted for each other and for age, sex, and study center, all other ORs adjusted for age, sex, study center, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction).

individuals without a genetic predisposition and no cardiovascular risk factor. For both weight and height, being above the median as measured in controls, point estimates indicated a further increase in the risk of VTE in individuals with a genetic predisposition to VTE. In contrast, for hypertension point estimates indicated a decreased risk of VTE in individuals with a genetic predisposition to VTE, i.e., compared with individuals without hypertension and without a genetic predisposition, individuals with a genetic predisposition and no hypertension had a 4.7-fold increased risk of VTE (95%CI: 1.3-16.2) while individuals with a genetic predisposition with hypertension had a 2.6-fold increased risk of VTE (95%CI: 0.9- 8.2). Diabetes, alcohol intake, smoking, and obesity did not further increased the risk of VTE in individuals with a genetic predisposition when compared with individuals without a genetic predisposition and not having these risk factors The combined effects between cardiovascular risk factors and the separate elements of the genetic predisposition (FVL/PT20210A, blood group non-O, and a positive family history of VTE) are shown in supplemental tables 1-3.

After the adjustment for statin use, risk estimates for cardiovascular risk factors only marginally changed compared with those in Table 3 (see supplemental table 4).

## DISCUSSION

In this case-control study of people aged 70 and older, greater height and body weight were associated with an increased risk of VTE, while no association was observed for smoking, alcohol intake, and diabetes. Higher systolic and diastolic blood pressure were associated with a decreased risk of VTE. A reduced VTE risk was also observed in people with hypertension. In the presence of a genetic predisposition, being in the top 50% of the distribution as measured in the controls for height and weight further increased the risk of VTE while hypertension attenuated the risk of VTE associated with a genetic predisposition of VTE.

Several studies have evaluated body weight or body height as risk factors for VTE in young and middle-aged populations [13, 16, 19, 20, 39, 47-49]. The MEGA study and the LITE study reported that body weight and body height both increased the risk of VTE in both young and older individuals (age range 18 to 70 years old) [16, 39]. The Physician's Health Study, the Tromsø study and the lowa Women's Health study reported on the association between height and the risk of VTE and also showed that height was a risk factor for VTE [13, 19, 47]. Height was also associated with fatal PE in a meta-analysis of cohort studies [48]. Body weight was positively associated with risk of VTE in a Danish cohort study [49].

Numerous studies have focused on the association between BMI and VTE risk in young and middle aged individuals, most of which reported a positive association between BMI and VTE risk [8-17, 20-25]. This is consistent with the current results in the elderly albeit that the relative risk in the elderly was increased for unprovoked VTE only. In previous analyses of elderly individuals, both Stein et al. and White et al. reported that a higher BMI was associated with a higher risk of VTE [18, 37], in accordance with our results for unprovoked events, but the risk estimates were more pronounced than ours. We do not have a clear explanation as to why body weight appeared to be more strongly associated with VTE risk than BMI. We could speculate that fat distribution plays a role which is not clearly reflected by BMI in this age group. A positive association between weight (and BMI) and risk of VTE may be explained by an increase in levels of prothrombotic factors (fibrinogen, von Willebrand factor, factor VII and viscosity) [50], hypofibrinolysis characterized by high PAI- 1 levels [51], lack of exercise, or venous stasis [21], although at least one study reported no attenuation of this association after adjusting for procoagulant factors [39].



Current and former smoking were not associated with risk of VTE, which is in line with the results of several studies in young and middle aged populations [19, 21, 31, 32]. Previous results were inconsistent as one case-control study and three prospective cohort studies reported that smoking was an independent risk factor for VTE [11, 24, 25, 28]. Also two meta-analyses and a recent review reported a modestly increased risk of VTE associated with smoking [15, 26, 52]. The discrepancy between these studies may be explained by participant characteristics, adjustment for different sets of confounders, and exclusion of people with cancer. In addition, in the current study, we studied the association between smoking status in general and the risk of VTE. As no association was observed, we did not further study the association between different types of tobacco use (cigarettes, cigars, pipe etc) or duration of smoking.

No association was observed for alcohol intake and the risk of VTE, which agrees with the results of the ARIC Study and the Physician's Health Study [19, 21]. However, the MEGA study and a cohort study among elderly [35, 38] indicated that moderate alcohol consumption was associated with a decreased risk of VTE. While potentially alcohol use is associated with a protective effect on VTE risk, these results indicate that this effect is small. Potential explanations for discrepancy between the current study and specifically the cohort study among the elderly [38] are the study design (case-control study design versus prospective cohort design) and adjustments for a different set of potential confounders (e.g., in the cohort study risk estimates were also adjusted for race, education, income, and cognitive function).

We found a decreased risk of VTE associated with hypertension. Several studies reported no association between hypertension and the risk of VTE [19, 21, 26], while the definition of hypertension in these studies was similar to ours. In contrast, the Nurses' Health Study and a meta-analysis also reported an increased risk of VTE associated with hypertension[15, 25]. For the latter two, various definitions of hypertension were provided (e.g., higher cut-off values of blood pressure (>160/90 mmHg) and self-reported hypertension). In this study, higher systolic or diastolic blood pressure were inversely associated with the risk of VTE, in accordance with the results of HUNT2 study [12] but different from other observational studies which found either no association [21, 33] or an inverse association only for systolic blood pressure [26]. In a Mendelian randomization study, no association was found between systolic blood pressure and risk of VTE [53], which suggests that association between blood pressure and VTE may be explained by unmeasured confounding.

Studies have reported conflicting results on diabetes. Two meta-analyses and a more recently published case-control study found no association between diabetes and the risk of VTE [26, 34, 54], which is consistent with our finding. However, three other meta-analyses concluded that diabetes was associated with a small increased risk of VTE [15, 29, 30], albeit in one study, the association disappeared after further adjustment for traditional cardiovascular risk factors (obesity, hypertension, dyslipidemia, sedentarity or smoking) [29]. The differences among studies may be due to different in- and exclusion criteria and the number of included confounders. In our study, we adjusted most important confounders (age, sex, study center, cardiovascular risk factors and comorbidities), increasing the validity of our results.

Notably, statin use may influence the risk of VTE in older individuals. Previous studies investigated the association between statin use and the risk of recurrent VTE in older patients [45, 46, 55]. Two of them showed that statin use was associated with a decreased risk of recurrent VTE [45, 46], while Nguyen et al. found that statin use among patients over 80 years of age was not significantly associated with a lower risk of recurrent VTE [55]. In our study, we considered the influence of statin use on the risk estimates of cardiovascular risk factors and we further adjusted for statin use in our model, but the results only marginally changed.

With regard to the combined effect of a genetic predisposition and the presence of a cardiovascular risk factor, we observed that, in the presence of a genetic predisposition, being in the top 50% of the distribution of height and weight could further increase the risk of VTE albeit confidence intervals overlapped. Several studies investigated the combined effect of genetic markers and cardiovascular risk factors in young and middle-

aged population [6, 16, 28, 36, 40, 41, 43, 56] and they showed that smoking and obesity could further increase the risk of VTE caused by the factor V Leiden or prothrombin mutations [16, 28, 36, 40, 41, 56] and that obesity further increased the risk of VTE in individuals with non-O blood type [6, 36]. Horvei et al. found that prothrombotic genotypes did not yield excess risk of VTE in taller people [43], in contrast with our results. The discrepancy between our results and the previous ones may be largely due to the restriction to the elderly.

Our study has several limitations that need to be acknowledged. As we restricted to the elderly, index event bias may, partly explain the absence of an association between the cardiovascular risk factors and VTE or even a reversed association when comparing the results with findings in young and middle aged populations. The problem of index-event bias can be minimized by adjusting for as many other risk factors for VTE as possible. We observed that the risk estimates for the cardiovascular risk factors, when adjusting for other risk factors, i.e. age, sex, BMI, study center, other cardiovascular risk factors, comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction), only marginally changed. This may indicate that index-event bias did not play a major role in explaining our findings. Furthermore, for most cardiovascular risk factors (body height, body weight, smoking, alcohol intake, hypertension and diabetes), we found similar results as young and middle-aged population. Overall, while the ORs trended towards an increased risk of VT with obesity, which is well known in other research, we could not confirm this because confidence intervals were wide. Potentially, this was due to the limited sample size in our subgroup analyses. Quist-Paulsen et al. also found a decreased VTE risk with elevated blood pressure with no clear biological explanation [12]. Smoking, alcohol use and diabetes were self-reported, so results may have been affected by recall bias. In our study, we visited the participants soon after the first VTE event which renders misclassification unlikely. In addition, a previous study demonstrated that self-reported smoking was a good measure of true smoking status [57]. Another limitation is the restriction of the population to mostly Caucasian people, which means results may not be generalizable to other race or ethnicity. Absolute risk estimates cannot obtained from our case-control data. Larger studies are required to study the potential effect of cardiovascular risk factors on VTE risk due to individual genetic risk factors for VTE.

Strengths of our study are the large sample size of elderly people and the measurement of several genetic markers and multiple cardiovascular risk factors, enabling us to perform detailed analysis on the risk of VTE for individual risk factors and their combinations.

In conclusion, this study demonstrated that, in patients aged 70 years and older, body weight and body height are positively associated with the risk of VTE. Systolic blood pressure, diastolic blood pressure and hypertension showed an inverse association with VTE. No association was observed between smoking, alcohol intake, diabetes and the risk of VTE. In the presence of a genetic predisposition, higher levels of height and weight further increased the risk of VTE.

## REFERENCES


1. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692-699.
2. Bertina RM, Koeleman BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369(6475):64-67.
3. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88(10):3698-3703.
4. Dentali F, Sironi A, Ageno W, et al. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. Semin Thromb Hemost. 2012;38(5):535-548.
5. Jick H, Westerholm B, Vessey MartinP, et al. Venous thromboembolic disease and abo blood type. Lancet. 1969;293(7594):539-542.
6. Ohira T, Cushman M, Tsai MY, et al. ABO blood group, other risk factors and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost. 2007;5(7):1455-1461.
7. Zöller B, Li X, Ohlsson H, Ji J, Sundquist J, Sundquist K. Family history of venous thromboembolism as a risk factor and genetic research tool. Thromb Haemost. 2015;114(5):890-900.
8. Gregson J, Kaptoge S, Bolton T, et al. Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol. 2019;4(2):163-173.
9. Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. Thromb Haemost. 2012;108(3):508-515.
10. Christiansen SC, Lijfering WM, Naess IA, et al. The relationship between body mass index, activated protein C resistance and risk of venous thrombosis. J Thromb Haemost. 2012;10(9):1761-1767.
11. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121(17):1896-1903.
12. Quist-Paulsen P, Naess IA, Cannegieter SC, et al. Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2). Haematologica. 2010;95(1):119-125.
13. Lutsey PL, Virnig BA, Durham SB, et al. Correlates and consequences of venous thromboembolism: the Iowa Women's Health Study. Am J Public Health. 2010;100(8):1506-1513.
14. Kabrhel C, Varraso R, Goldhaber SZ, Rimm EB, Camargo CA. Prospective study of BMI and the risk of pulmonary embolism in women. Obesity (Silver Spring, Md.). 2009;17(11):2040-2046.
15. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117(1):93-102.
16. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJM. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139(2):289-296.
17. Oren E, Smith NL, Doggen CJM, Heckbert SR, Lemaitre RN. Body mass index and the risk of venous thrombosis among postmenopausal women. J Thromb Haemost. 2006;4(10):2273-2275.
18. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-980.

**19.** Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005;162(10):975-982.

**20.** Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost. 2003;89(3):493-498.

**21.** Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002;162(10):1182-1189.

**22.** Vayá A, Mira Y, Ferrando F, et al. Hyperlipidaemia and venous thromboembolism in patients lacking thrombophilic risk factors. Br J Haematol. 2002;118(1):255-259.

**23.** Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000;160(22):3415-3420.

**24.** Hansson P-O, Eriksson H, Welin L, Svärdsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med. 1999;159(16):1886-1890.

**25.** Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA. 1997;277(8):642-645.

**26.** Mahmoodi BK, Cushman M, Anne Næss I, et al. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of prospective studies. Circulation. 2017;135(1):7-16.

**27.** Cheng Y-J, Liu Z-H, Yao F-J, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med. 2013;10(9):e1001515.

**28.** Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008;83(2):97-102.

**29.** Gariani K, Mavrakanas T, Combescure C, Perrier A, Marti C. Isdiabetes mellitus a risk factor for venous thromboembolism? A systematic review and meta-analysis of case-control and cohort studies. Eur J Intern Med. 2016;28:52-58.

**30.** Bai J, Ding X, Du X, Zhao X, Wang Z, Ma Z. Diabetes is associated with increased risk of venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2015;135(1):90-95.

**31.** Blondon M, Wiggins KL, McKnight B, et al. The association of smoking with venous thrombosis in women. A population-based,case-control study. Thromb Haemost. 2013;109(5):891-896.

**32.** Brækkan SK, et al. Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso study. Arterioscler Thromb Vasc Biol. 2012;32(2):487-491.

**33.** Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromsø study. J Thromb Haemost. 2008;6(11):1851-1857.

**34.** Bell EJ, Folsom AR, Lutsey PL, et al. Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2016;111:10-18.

**35.** Pomp ER, Rosendaal FR, Doggen CJ. Alcohol consumption is associated with a decreased risk of venous thrombosis. Thromb Haemost. 2008;99(1):59-63.

**36.** Ribeiro DD, Lijfering WM, Rosendaal FR, Cannegieter SC. Risk of venous thrombosis in persons with increased body mass index and interactions with other genetic and acquired risk factors. J Thromb Haemost. 2016;14(8):1572-1578.

**37.** White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med. 2000;343(24):1758-1764.

**38.** Pahor M, Guralnik JM, Havlik RJ, et al. Alcohol consumption and risk of deep venous thrombosis and pulmonary embolism in older persons. J Am Geriatr Soc. 1996;44(9):1030-1037.

**39.** Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: the Longitudinal Investigation of Thromboembolism Etiology. Thromb Res. 2016;144:127-132.

**40.** Juul K, Tybjærg-Hansen A, Schnohr P, Nordestgaard BG. Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. Ann Intern Med. 2004;140(5):330-337.

**41.** Severinsen MT, Overvad K, Johnsen SP, et al. Genetic susceptibility, smoking, obesity and risk of venous thromboembolism. Br J Haematol. 2010;149(2):273-279.

**42.** Evans CR, Hong C-P, Folsom AR, et al. Lifestyle moderates genetic risk of venous thromboembolism: The ARIC study. Arterioscler Thromb Vasc Biol. 2020;40(11):2756-2763.

**43.** Horvei LD, Braekkan SK, Smith EN, et al. Joint effects of prothrombotic genotypes and body height on the risk of venous thromboembolism: the Tromsø study. J Thromb Haemost. 2018;16(1):83-89.

**44.** Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. J Thromb Haemost. 2014;12(3):290-296.

**45.** Tagalakis V, Eberg M, Kahn S, Azoulay L. Use of statins and reduced risk of recurrence of VTE in an older population. A population-based cohort study. Thromb Haemost. 2016;115(6):1220-1228.

**46.** Kronenberg RM, Beglinger S, Stalder O, et al. Statin therapy and recurrent venous thromboembolism in the elderly: a prospective cohort study. Sci Rep. 2019;9(1):14804.

**47.** Braekkan SK, Borch KH, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: the Tromsø study. Am J Epidemiol. 2010;171(10):1109-1115.

**48.** Emerging Risk Factors Collaboration. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol. 2012;41(5):1419-1433.

**49.** Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjønneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. Circulation. 2009;120(19):1850-1857.

**50.** Rosito G, D'Agostino R, Massaro J, et al. Association between obesity and a prothrombotic state: the Framingham offspring study. Thromb Haemost. 2004;91(4):683-689.

**51.** Smalberg JH, Kruip MJHA, Janssen HLA, Rijken DC, Leebeek FWG, de Maat MPM. Hypercoagulability and hypofibrinolysis and risk of deep vein thrombosis and splanchnic vein thrombosis: similarities and differences. Arterioscler Thromb Vasc Biol. 2011;31(3): 485-493.

**52.** Folsom AR, Cushman M. Exploring opportunities for primary prevention of unprovoked venous thromboembolism: ready for prime time? J Am Heart Assoc. 2020;9(23):e019395.

**53.** Nazarzadeh M, Pinho-Gomes AC, Mohseni H, et al. Blood pressure and risk of venous thromboembolism: a large-scale prospective cohort analysis and a Mendelian randomisation study. J Hypertens. 2019;37:e95.

**54.** Li-Gao R, Morelli VM, Lijfering WM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. Glucose levels and diabetes are not associated with the risk of venous thrombosis: results from the MEGA case-control study. Br J Haematol. 2019;184(3):431-435.

**55.** Nguyen CD, Andersson C, Jensen TB, et al. Statin treatment and risk of recurrent venous thromboembolism: a nationwide cohort study. BMJ Open. 2013;3(11):e003135.

**56.** Yang G, De Staercke C, Hooper WC. The effects of obesity on venous thromboembolism: a review. Open J Prev Med. 2012;2(4):499-509.

**57.** Caraballo RS, Giovino GA, Pechacek TF, Mowery PD. Factors associated with discrepancies between self-reports on cigarette smoking and measured serum cotinine levels among persons aged 17 years or older: third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol. 2001;153(8):807-814.

## SUPPLEMENTARY TABLES

**Supplemental table 1.** Combined effect of cardiovascular risk factors and genetic risk factors (factor V Leiden and prothrombin mutation) on the risk of venous thromboembolism

| FVL or prothrombin 20210A | Cardiovascular risk factors | Patients N | Controls N | OR overall* (95%CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Obesity | | | | | |
| no | no | 255 | 307 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 81 | 87 | 1.1(0.7-1.7) | 0.9(0.5-1.6) | 1.3(0.8-2.2) |
| yes | no | 34 | 19 | 1.7(0.9-3.4) | 1.4(0.6-3.2) | 1.9(0.9-4.2) |
| yes | yes | 5 | 6 | 1.0(0.3-3.8) | 0.9(0.1-5.4) | 1.4(0.3-6.2) |
| | Height [a] | | | | | |
| no | <P50 | 150 | 189 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 197 | 209 | 1.6(1.0-2.4) | 1.6(1.0-2.7) | 1.6(1.0-2.6) |
| yes | <P50 | 15 | 12 | 1.6(0.7-3.6) | 2.0(0.8-5.0) | 1.1(0.3-3.3) |
| yes | ≥P50 | 25 | 13 | 3.1(1.4-6.8) | 2.3(0.9-6.0) | 3.9(1.6-9.4) |
| | Weight [b] | | | | | |
| no | <P50 | 150 | 196 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 189 | 199 | 1.4(1.0-1.9) | 1.2(0.8-1.8) | 1.5(1.0-2.2) |
| yes | <P50 | 17 | 14 | 1.4(0.7-3.1) | 1.8(0.7-4.2) | 0.9(0.3-2.8) |
| yes | ≥P50 | 23 | 11 | 3.1(1.4-6.8) | 1.9(0.7-5.3) | 4.2(1.7-10.1) |
| | Smoking | | | | | |
| no | no | 313 | 350 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 39 | 51 | 0.7(0.5-1.2) | 0.5(0.3-1.0) | 1.0(0.6-1.9) |
| yes | no | 37 | 22 | 1.4(0.8-2.7) | 1.3(0.6-2.7) | 1.7(0.8-3.5) |
| yes | yes | 4 | 3 | 1.8(0.3-11.1) | 1.6(0.1-19.8) | 1.7(0.2-12.9) |
| | Alcohol intake | | | | | |
| no | no | 140 | 146 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 213 | 254 | 1.1(0.8-1.6) | 0.8(0.5-1.3) | 1.5(0.9-2.3) |
| yes | no | 15 | 12 | 1.4(0.5-3.6) | 1.3(0.4-4.1) | 1.7(0.5-5.5) |
| yes | yes | 25 | 13 | 1.8(0.8-3.8) | 1.1(0.4-3.0) | 2.5(1.0-6.2) |
| | Hypertension | | | | | |
| no | no | 62 | 54 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 291 | 347 | 0.7(0.4-1.1) | 0.7(0.4-1.3) | 0.7(0.4-1.3) |
| yes | no | 5 | 1 | 20.0(0.4-1075.0) | 13122854(0-) | 36.7(0.6-2332.1) |
| yes | yes | 36 | 24 | 1.0(0.5-2.0) | 0.9(0.4-2.3) | 1.0(0.4-2.5) |
| | Diabetes | | | | | |
| no | no | 296 | 339 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 57 | 62 | 0.9(0.5-1.4) | 0.8(0.4-1.5) | 1.0(0.5-1.8) |
| yes | no | 31 | 21 | 0.9(0.3-2.4) | 0.6(0.2-2.1) | 1.5(0.5-4.7) |
| yes | yes | 10 | 4 | 2.6(0.4-16.4) | 2.3(0.3-18.0) | 5.3(0.5-52.3) |

N=number, CI=confidence interval, ref=reference.
[a] Cut-off value: P50: 168 cm [b] Cut-off value: P50: 74.9 kg
* Height and weight adjusted for each other and for age, sex, and study center, all other ORs adjusted for age, sex, study center, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction).

**Supplemental table 2.** Combined effect of cardiovascular risk factors and non-O blood group on the risk of venous thromboembolism .

| non-O blood group | Cardiovascular risk factors | Patients N | Controls N | OR overall* (95%CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Obesity | | | | | |
| no | no | 106 | 149 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 30 | 33 | 1.0(0.5-2.0) | 0.9(0.4-2.1) | 1.3(0.6-3.1) |
| yes | no | 171 | 170 | 1.4(0.9-2.0) | 1.0(0.7-1.6) | 1.8(1.1-2.9) |
| yes | yes | 50 | 57 | 1.2(0.7-2.0) | 0.8(0.4-1.7) | 1.7(0.9-3.3) |
| | Height [a] | | | | | |
| no | <P50 | 67 | 77 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 75 | 106 | 1.2(0.7-2.0) | 1.0(0.5-2.0) | 1.5(0.8-3.0) |
| yes | <P50 | 90 | 119 | 1.0(0.7-1.6) | 0.8(0.5-1.4) | 1.4(0.8-2.5) |
| yes | ≥P50 | 137 | 111 | 2.1(1.3-3.6) | 1.7(0.9-3.2) | 3.0(1.6-5.7) |
| | Weight [b] | | | | | |
| no | <P50 | 58 | 92 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 79 | 90 | 1.4(0.9-2.4) | 1.1(0.6-2.0) | 2.1(1.1-4.1) |
| yes | <P50 | 101 | 116 | 1.4(0.9-2.2) | 1.0(0.6-1.7) | 2.3(1.2-4.2) |
| yes | ≥P50 | 123 | 112 | 2.0(1.3-3.2) | 1.4(0.8-2.5) | 3.0(1.6-5.6) |
| | Smoking | | | | | |
| no | no | 125 | 152 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 20 | 32 | 0.7(0.4-1.4) | 0.6(0.3-1.4) | 0.9(0.4-2.2) |
| yes | no | 211 | 209 | 1.3(0.9-1.9) | 1.1(0.7-1.6) | 1.7(1.1-2.7) |
| yes | yes | 20 | 23 | 0.9(0.4-1.8) | 0.4(0.2-1.3) | 1.5(0.6-3.3) |
| | Alcohol intake | | | | | |
| no | no | 71 | 65 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 74 | 119 | 0.8(0.5-1.3) | 0.7(0.4-1.2) | 0.9(0.5-1.9) |
| yes | no | 76 | 90 | 0.9(0.5-1.5) | 0.8(0.4-1.4) | 1.1(0.6-2.2) |
| yes | yes | 154 | 141 | 1.3(0.8-2.1) | 0.8(0.5-1.5) | 2.1(1.1-3.8) |
| | Hypertension | | | | | |
| no | no | 20 | 28 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 125 | 156 | 1.0(0.5-2.2) | 1.0(0.4-2.4) | 1.5(0.5-4.3) |
| yes | no | 44 | 28 | 2.4(1.0-5.6) | 1.8(0.6-4.9) | 4.2(1.3-13.5) |
| yes | yes | 187 | 204 | 1.2(0.6-2.5) | 0.9(0.4-2.2) | 2.2(0.8-6.1) |
| | Diabetes | | | | | |
| no | no | 111 | 151 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 34 | 33 | 1.1(0.6-2.2) | 0.9(0.4-2.1) | 1.6(0.7-3.7) |
| yes | no | 199 | 200 | 1.4(1.0-2.1) | 1.1(0.7-1.8) | 1.9(1.1-3.0) |
| yes | yes | 32 | 32 | 1.3(0.6-2.5) | 1.0(0.4-2.4) | 1.7(0.7-4.0) |

N=number, CI=confidence interval, ref=reference.

[a] Cut-off value: P50: 168 cm [b] Cut-off value: P50: 74.9 kg

* Height and weight adjusted for each other and for age, sex, and study center, all other ORs adjusted for age, sex, study center, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction).

**Supplemental table 3.** Combined effect of cardiovascular risk factors and positive family history of venous thromboembolism on the risk of venous thromboembolism

| Family history of venous thromboembolism | Cardiovascular risk factors | Patients N | Controls N | OR overall* (95%CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| | Obesity | | | | | |
| no | no | 222 | 291 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 64 | 78 | 1.2(0.8-2.0) | 0.9(0.5-1.7) | 1.5(0.9-2.7) |
| yes | no | 71 | 37 | 2.7(1.7-4.4) | 2.5(1.4-4.5) | 2.7(1.5-4.8) |
| yes | yes | 24 | 16 | 1.6(0.8-3.3) | 1.7(0.7-4.1) | 1.7(0.7-3.9) |
| | Height [a] | | | | | |
| no | <P50 | 132 | 171 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 167 | 202 | 1.5(1.0-2.3) | 1.4(0.8-2.4) | 1.6(0.9-2.6) |
| yes | <P50 | 37 | 32 | 1.6(0.9-2.7) | 1.6(0.8-3.0) | 1.5(0.7-2.9) |
| yes | ≥P50 | 58 | 22 | 4.3(2.3-8.1) | 4.3(2.1-9.1) | 4.3(2.1-8.9) |
| | Weight [b] | | | | | |
| no | <P50 | 134 | 184 | 1(ref) | 1(ref) | 1(ref) |
| no | ≥P50 | 155 | 186 | 1.2(0.9-1.8) | 0.9(0.6-1.5) | 1.5(1.0-2.3) |
| yes | <P50 | 36 | 27 | 1.6(0.9-2.9) | 1.3(0.7-2.7) | 1.9(0.9-3.7) |
| yes | ≥P50 | 60 | 26 | 3.3(1.9-5.6) | 3.0(1.6-5.6) | 3.5(1.8-6.7) |
| | Smoking | | | | | |
| no | no | 273 | 326 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 31 | 50 | 0.7(0.4-1.2) | 0.5(0.2-1.1) | 0.9(0.5-1.8) |
| yes | no | 85 | 49 | 2.1(1.4-3.3) | 2.2(1.3-3.8) | 1.9(1.1-3.2) |
| yes | yes | 12 | 5 | 2.3(0.8-6.8) | 1.7(0.4-7.4) | 3.0(0.9-9.8) |
| | Alcohol intake | | | | | |
| no | no | 125 | 140 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 178 | 235 | 1.1(0.7-1.6) | 0.8(0.5-1.3) | 1.4(0.9-2.3) |
| yes | no | 36 | 19 | 2.5(1.2-5.1) | 2.4(1.1-5.6) | 2.3(1.0-5.6) |
| yes | yes | 61 | 35 | 2.3(1.3-3.9) | 1.8(0.9-3.4) | 2.9(1.5-5.4) |
| | Hypertension | | | | | |
| no | no | 58 | 53 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 246 | 323 | 0.6(0.4-0.9) | 0.6(0.3-1.1) | 0.6(0.3-1.1) |
| yes | no | 10 | 4 | 1.6(0.4-5.8) | 1.5(0.3-7.4) | 1.5(0.3-6.9) |
| yes | yes | 87 | 50 | 1.4(0.8-2.5) | 1.5(0.8-3.1) | 1.4(0.7-2.8) |
| | Diabetes | | | | | |
| no | no | 248 | 321 | 1(ref) | 1(ref) | 1(ref) |
| no | yes | 56 | 55 | 1.1(0.6-1.9) | 0.9(0.5-1.9) | 1.4(0.7-2.6) |
| yes | no | 84 | 42 | 2.9(1.8-4.6) | 2.7(1.5-4.8) | 2.8(1.6-4.9) |
| yes | yes | 13 | 12 | 1.4(0.6-3.6) | 1.9(0.6-5.7) | 1.1(0.4-3.6) |

N=number, CI=confidence interval, ref=reference.

[a] Cut-off value: P50: 168 cm

[b] Cut-off value: P50: 74.9 kg

* Height and weight adjusted for each other and for age, sex, and study center, all other ORs adjusted for age, sex, study center, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction)

**Supplemental table 4.** The risk of venous thromboembolism associated with cardiovascular risk factors after adjustment of statin use.

| Risk factor | OR crude (95%CI) | OR all VTE* (95%CI) | OR DVT* (95% CI) | OR PE±DVT* (95% CI) | OR provoked* (95%CI) | OR unprovoked* (95%CI) |
|---|---|---|---|---|---|---|
| BMI(kg/m$^2$) | | | | | | |
| underweight | 2.0(0.5-8.6) | 1.6(0.4-7.0) | 1.0(0.1-10.4) | 2.1(0.4-10.7) | 1.6(0.3-9.1) | 1.7(0.2-11.0) |
| normal | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| overweight | 1.1(0.8-1.6) | 1.2(0.9-1.8) | 1.3(0.8-2.2) | 1.2(0.8-1.8) | 1.0(0.6-1.6) | 1.5(0.9-2.4) |
| obese | 1.1(0.8-1.7) | 1.2(0.8-2.0) | 1.7(0.9-3.2) | 1.0(0.6-1.7) | 0.9(0.5-1.6) | 1.6(0.9-2.9) |
| Smoking | | | | | | |
| never | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| former | 0.9(0.7-1.2) | 1.2(0.8-1.8) | 1.0(0.6-1.7) | 1.3(0.8-2.1) | 1.3(0.8-2.2) | 1.0(0.6-1.7) |
| current | 0.8(0.5-1.2) | 0.9(0.5-1.5) | 1.0(0.5-2.1) | 0.7(0.4-1.4) | 0.7(0.3-1.4) | 1.1(0.6-2.1) |
| Alcohol intake | | | | | | |
| no | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| yes | 0.9(0.7-1.2) | 1.1(0.8-1.5) | 1.4(0.9-2.2) | 1.0(0.6-1.4) | 0.8(0.5-1.2) | 1.5(1.0-2.3) |
| Systolic blood pressure(mmHg) # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 0.8(0.6-1.2) | 0.9(0.6-1.3) | 0.8(0.4-1.3) | 0.9(0.6-1.5) | 0.6(0.4-1.0) | 1.1(0.6-1.8) |
| P25-P50 | 0.5(0.3-0.8) | 0.5(0.3-0.8) | 0.4(0.2-0.8) | 0.6(0.4-1.0) | 0.5(0.3-0.9) | 0.5(0.3-1.0) |
| ≥P75 | 0.4(0.3-0.6) | 0.4(0.3-0.7) | 0.6(0.3-1.0) | 0.3(0.2-0.6) | 0.3(0.2-0.6) | 0.6(0.3-1.1) |
| Diastolic blood pressure(mmHg) # | | | | | | |
| ≤P25 | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| P25-P50 | 0.7(0.4-1.0) | 0.5(0.3-0.8) | 0.4(0.2-0.8) | 0.5(0.3-0.9) | 0.4(0.2-0.8) | 0.6(0.3-1.0) |
| P50-P75 | 0.8(0.5-1.1) | 0.5(0.3-0.9) | 0.6(0.3-1.0) | 0.5(0.3-0.9) | 0.4(0.2-0.8) | 0.7(0.4-1.2) |
| ≥P75 | 0.6(0.4-0.9) | 0.4(0.2-0.6) | 0.4(0.2-0.7) | 0.4(0.2-0.6) | 0.3(0.1-0.5) | 0.4(0.2-0.8) |
| Blood pressure | | | | | | |
| normal | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| hypertensive | 0.7(0.5-1.1) | 0.6(0.4-1.0) | 0.7(0.4-1.4) | 0.6(0.4-1.0) | 0.7(0.4-1.3) | 0.7(0.4-1.2) |
| Diabetes | | | | | | |
| no | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| yes | 0.7(0.6-1.3) | 1.0(0.6-1.6) | 1.0(0.5-1.9) | 1.0(0.6-1.7) | 1.0(0.5-1.8) | 1.0(0.5-1.7) |

OR=odds ratio, CI=confidence interval, VTE=venous thromboembolism, DVT=deep vein thrombosis, PE±DVT=pulmonary embolism, ref=reference.

# Cut-off values for quartiles:

Systolic blood pressure: P25: 137mm Hg P50: 154mm Hg P75: 168mm Hg

Diastolic blood pressure: P25: 78mm Hg P50: 86mm Hg P75: 96mm Hg

* All ORs adjusted for age, sex, study center, statin use, cardiovascular factors (BMI, smoking, alcohol intake, hypertension, diabetes; depending on the exposure) and comorbidities (heart failure, angina, myocardial infarction, cerebral bleeding, transient ischemic attack and cerebral infarction).