ORIGINAL ARTICLE

Hand grip strength and risk of incident venous thromboembolism: The Tromsø study

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Abstract

Background: Hand grip strength (HGS), a common proxy of whole-body muscular strength, is associated with a wide range of adverse health outcomes and mortality. However, there are limited data on the association between HGS and risk of venous thromboembolism (VTE).

Objectives: We aimed to investigate the association between HGS and risk of incident VTE in a population-based cohort.

Methods: Participants ($n = 13,704$) from the fourth to seventh surveys of the Tromsø study (Tromsø4–Tromsø7, enrollment: 1994–2016) were followed throughout 2020, and all incident VTEs were recorded. HGS of the nondominant hand was measured using a Martin Vigorimeter (Tromsø4–Tromsø6) and a Jamar Digital Dynamometer (Tromsø7). Hazard ratios (HRs) for VTE with 95% confidence intervals (CIs) according to weak HGS (less than 25th percentile) versus normal HGS (25th percentile or greater) were estimated using Cox regression models and adjusted for age, sex, body height, body mass index, physical activity, cardiovascular disease, and cancer.

Results: During a median of 6.5 years of follow-up, 545 incident VTEs occurred. Participants with weak HGS had a 27% higher risk of VTE (HR, 1.27; 95% CI, 1.03–1.57) compared to those with normal HGS. Subgroup analyses revealed that the point estimates were higher for unprovoked VTE (HR, 1.35; 95% CI, 0.96–1.91) and deep vein thrombosis (DVT; HR, 1.52; 95% CI, 1.14–2.01). Similar results were found in analyses restricted to men, women, and elderly (aged greater than 75 years).

Conclusion: A weak HGS was associated with increased risk of VTE, and particularly unprovoked VTE and isolated DVT. Our findings suggest that weak muscle strength may be a risk factor for VTE.

KEYWORDS
deep vein thrombosis, hand grip strength, muscle strength, risk factor, venous thromboembolism

Essentials

- Hand grip strength (HGS) is associated with a wide range of adverse outcomes and mortality.
- We investigated the association between HGS and risk of venous thromboembolism (VTE).
- Participants with low HGS had a higher risk of VTE compared to those with normal HGS.
- Our findings suggest that weak muscle strength is a risk factor for VTE.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a major cause of human suffering and premature mortality.[1,2] The incidence of VTE rises exponentially with age, from around 1 per 10,000 per year in the young to 1 per 100 per year in the elderly.[3] The reason why aging leads to increased thrombosis risk is not fully understood.[4,5] Physiological function and muscular strength are known to decline with age, and a loss of overall muscle mass, particularly calf muscle strength, may reduce the efficacy of the muscle-vein pump, causing disturbed blood flow and stasis.[6,7] Recently, Houghton et al.[8] reported that reduced calf pump function, assessed by plethysmograph in a cohort of 1532 participants, was associated with increased risk of VTE, and deep vein thrombosis (DVT) in particular.

Hand grip strength (HGS) is a performance-based measure commonly used as a proxy of whole-body muscular strength.[9] HGS is correlated with lower-extremity strength and physical capability in adults and is a main component of intrinsic capacity.[10–13] Studies have shown that a weaker hand grip is associated with a wide range of adverse health outcomes, including cardiovascular and respiratory diseases, cancer, and mortality.[14–20] In the AT-AGE study, which included 401 VTE cases and 431 controls aged greater than 70 years, a weak HGS was associated with a 2.1 times greater risk of VTE. Weak HGS was more strongly associated with DVT than with pulmonary embolism (PE).[21] In contrast, no association between grip strength and VTE was found among 864 participants aged greater than 70 years from the Kupio Ischemic Heart Diseases cohort.[22]

Reduced muscular strength may be associated with increased risk of VTE, particularly in the elderly. However, studies on the association between HGS and VTE are scarce and have provided inconsistent results. Therefore, the aim of this study was to investigate the association between HGS and risk of future VTE in a large population-based cohort. We hypothesized that a weak grip strength measure is associated with an increased risk of VTE.

2 | METHODS

2.1 | Study population

The Tromsø study, initiated in 1974, is a single-center population-based study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway. So far, seven surveys have been conducted, and the present study is based on data from surveys 4–7 (conducted in 1994–1995, 2001–2002, 2007–2008, and 2015–2016, respectively). In the fourth survey of the Tromsø study (Tromsø4), which is the largest completed survey to date, all inhabitants aged 25 years or older were invited, and 27,158 subjects (77% of the eligible population) participated. The fifth survey (Tromsø5) included 8130 subjects aged 30–89 years (79% of those invited), and the sixth survey (Tromsø6) included 12,984 subjects aged 30–87 years (66% of those invited). In Tromsø7, a total of 21,083 subjects aged greater than 40 years participated (65% of those invited). Altogether, 36,627 unique individuals participated in one or more of the Tromsø4–7 surveys.

Hand grip strength was measured in subgroups of the participants at each survey. In Tromsø4, all inhabitants aged 55–74 and 5%–10% of random samples from the other age groups were invited to a more extensive examination that included grip strength measurements. The same participants were reinvited to a second visit in Tromsø5 and Tromsø6, in addition to random samples from the other age groups. In Tromsø7, a random predefined sample was invited to the second, more extensive examination, as well as additionally including former Tromsø study participants not already selected in the random selection process. Grip strength was measured in Tromsø4 (n = 7871), Tromsø5 (n = 1106), Tromsø6 (n = 3630), and Tromsø7 (n = 7864). A total of 13,826 unique individuals aged 25–89 participated in at least one survey, and 4613 of these participated in two or more surveys, as described in Figure 1.

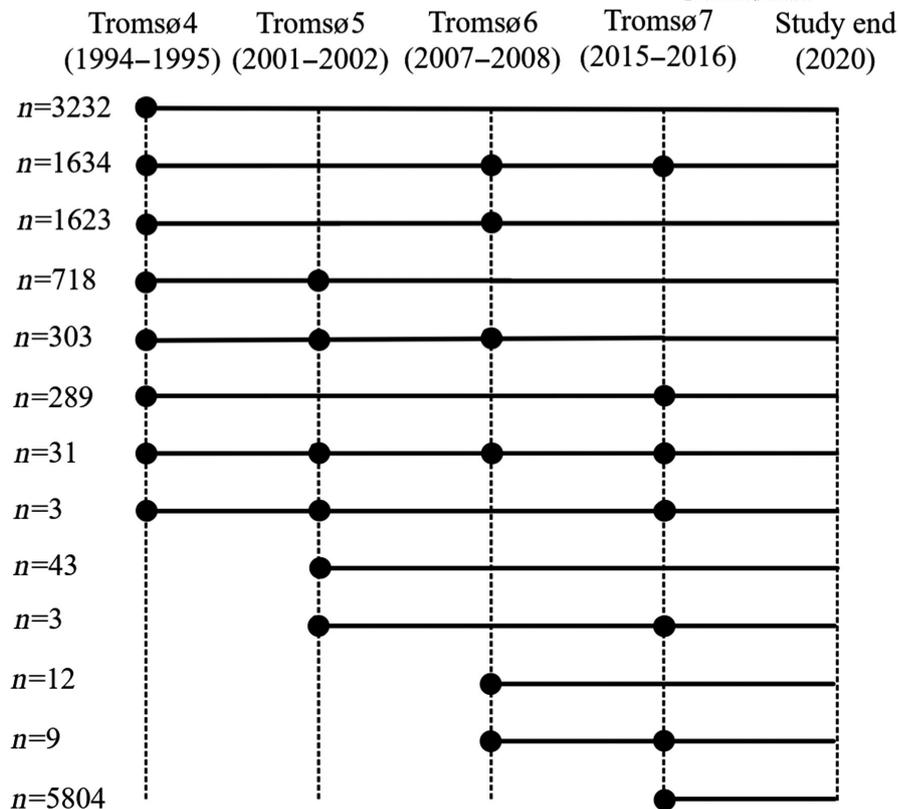Subjects with a known prebaseline history of VTE (n = 114) were excluded from the study. Furthermore, 8 participants were excluded due to insufficient grip strength measures, leaving 13,704 unique participants for final analyses.

2.2 | Hand grip strength

Trained health care professionals assessed grip strength using the same standardized protocol. In Tromsø4–6, the Martin Vigorimeter was used, and this device was replaced in Tromsø7 with the Jamar Digital Dynamometer.

For the Martin Vigorimeter, the largest and medium-sized balloons were used, for men and women, respectively. Each participant was allowed two attempts with the nondominant hand, and the highest score registered was recorded and used in analyses. In the Tromsø7 (2015–2016) study wave, the participants had their grip strength measured with a Jamar Digital Dynamometer, and each participant was allowed three attempts for each hand. To ensure similarity between the Tromsø4–6 and Tromsø7 measurements, we used the highest score of the two first attempts of the nondominant hand in the analyses.

FIGURE 1 Overview of included participants. Dots represent participation at the survey, and lines between dots represent observation periods. A total of 13,704 unique individuals were included in the study.

2.3 | Other measurements

Previously known confounders between HGS and VTE were identified, and baseline information was collected through physical examinations and self-administered questionnaires. Height and weight were measured with standardized procedures, and body mass index (BMI) was calculated from these measures using the weight in kilograms, divided by the square of height in meters (kg/m^2). All information on physical activity, history of cancer and cardiovascular diseases (CVDs) and concurrent diseases was obtained through standard, validated questionnaires. CVD was defined as a history of myocardial infarction, angina pectoris, or cerebral stroke. Information on physical activity was obtained through questions on weekly frequency (never, less than once, once, two to three times, or approximately every day), duration per session (<15 min, 15–29 min, 30–60 min, or more than 1 h) and the sessions intensity (not short-winded or sweaty, becoming short-winded or sweaty, or becoming exhausted). A physical activity index was calculated by multiplying weighted values from the questionnaire responses. A more detailed description of the physical activity index has been published previously.[23,24] Data on previous cancer were obtained from the Cancer Registry of Norway.

2.4 | Assessment of VTE during follow-up

Participants were followed from the date of enrollment to the end of 2020. All first lifetime events of VTE during follow-up were identified by searching the hospital discharge registry, the radiology procedure registry, and the autopsy registry at the University Hospital of North Norway (UNN) and adjudicated by review of medical records. UNN is the only hospital in the region, and all hospital care and relevant diagnostics for VTE are provided by this hospital.

Trained health care personnel who were blinded to the baseline variables reviewed the medical records for each potential VTE case. For subjects derived from the hospital discharge diagnosis register and the radiology procedure register, an episode of VTE was adjudicated and recorded when all four of the following criteria were met: (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography, perfusion–ventilation scan, pulmonary angiography, or autopsy); (ii) the medical record indicated that a physician had made a diagnosis of DVT or PE; (iii) signs and symptoms consistent with DVT or PE were present; and (iv) therapy with anticoagulants, thrombolytics, or vascular surgery was initiated unless contraindications were specified. For subjects derived from the autopsy register, a VTE event was recorded as an outcome when the autopsy record indicated VTE as a cause of death or as a significant condition associated with death. A more detailed description of the VTE register has been published previously.[25,26]

All VTEs were classified as DVT or PE. Cases in which both clinical presentations were present were classified as a PE. VTEs were also classified as either provoked or unprovoked depending on the presence of provoking factors. In this study, provoking factors included surgery or trauma within 8 weeks prior to the event; acute medical conditions (acute myocardial infarction, ischemic stroke,

major infectious disease); active cancer; immobilization (bed rest more than 3 days, wheelchair use, long-distance travel exceeding 4 h within the 14 days prior to the event); and other factors described by physicians in the medical records, for example, intravascular catheters.

2.5 | Statistical analysis

For each participant, person-time of follow-up was accrued from inclusion in first survey with hand grip measurement until an incident VTE, migration from Tromsø, death, or end of follow-up (December 31, 2020), whichever came first. We used a time-varying analysis in which subjects who participated in more than one survey contributed with one observation period per attended survey. This approach allowed for update of the grip strength measure and confounder information for those who were remeasured during follow-up. This resulted in 20,109 observational periods derived from the 13,704 participants (Figure 1). Statistical analyses were performed with STATA 16.0 (Stata Corporation).

Measures of HGS were divided into dynamometer-specific quartiles (as different dynamometers were used in Tromsø4–6 and Tromsø7). Crude incidence rates (IRs) were calculated by dividing the number of events by the total accrued person-time in each quartile and expressed as number of events per 1000 person-years.

Cox proportional hazard regression models, with and without adjustment for potentially relevant confounders, were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE across quartiles of HGS. Age was used as the time scale in the Cox models. An individual's age at study enrollment was defined as entry time, and exit time was defined as age at time of VTE, migration, death, or study end. The proportional hazards assumption was evaluated and verified on the basis of Schoenfeld residuals, and no statistical interaction between age and HGS was found. We performed complete case analysis, and HRs for all VTE events, and subgroups were estimated in sex- and multivariable-adjusted analyses. Adjustment model 1 included age (time scale) and sex only. In model 2, we also adjusted for height and BMI, and in model 3 we added adjustment for relevant comorbidities (previous cancer, CVD, and physical activity). The variables age, sex, height, BMI, CVD, and cancer all had less than 2% missing across all quartiles. For the physical activity index, the overall proportion of missing was 7.1%. We performed analyses comparing each quartile with the highest grip strength quartile (reference) and analyses in which the lowest grip strength quartile was compared with the remaining quartiles (reference). Analysis comparing the weakest quartile of HGS with the three higher quartiles combined was a post hoc analysis, as there seemed to be a threshold effect at the weakest quartile of HGS. We additionally performed subgroup analyses with DVT, PE, provoked VTE, and unprovoked VTE as outcomes, respectively. Due to the strong impact of sex and age on both HGS and VTE risk, we performed analyses stratified by men and women (using sex- and dynamometer-specific quartiles) and analyses restricted to those above and below age 75 years. For sensitivity purposes, we also performed analyses stratified by the dynamometer device (since two different devices were used in Tromsø4–6 and Tromsø7). To check for potential regression dilution bias, we also performed the analysis with follow-up restricted to 5 years from inclusion in the study.

2.6 | Ethics statement

This study was conducted in accordance with the 1964 Helsinki Declaration ethical standards.

3 | RESULTS

Study population characteristics are shown in Table 1. Mean age at study inclusion in quartile 1 versus quartile 4 was 69 years and 56 years, respectively (range, 25–89 years). The proportion of women decreased across quartiles from 82.2% women in quartile 1 to 24.5% in quartile 4. The average BMI was 26.5 kg/m^2 in quartile 1 and increased to 27.1 kg/m^2 in quartile 4. There was a higher prevalence of CVD among the participants in quartile 1 compared to the reference quartiles (23.5% in quartile 1 and 15.4% in quartile 4).

There were 545 recorded incident VTEs during a total of 173,905 person-years' follow-up. Median follow-up time was 6.5 years (range, 0.01–26.3 years). The average age at event was 74 ± 8.9 years, and the proportion of men was 45.1% (Table 2). With regard to localization of the VTE, 45.9% ($n = 250$) had a PE with or without concomitant DVT, and 54.1% ($n = 295$) had isolated DVT. Moreover, 59.6% ($n = 325$) of the events were classified as provoked, while 40.4% ($n = 220$) were unprovoked. The most common provoking factors were active cancer (25.9%), immobilization (21.1%), and surgery (15.8%).

Table 3 shows the crude IRs and HRs across quartiles of grip strength. For overall VTE, the crude IR per 1000 person-years was 4.52 (95% CI, 3.91–5.22) in the lowest grip strength quartile (i.e., quartile 1) and 2.30 (95% CI, 1.89–2.78) in the highest grip strength quartile (i.e., quartile 4). The age- and sex-adjusted HR for overall VTE was 1.13 (95% CI, 0.86–1.49) for those in the lowest versus the highest grip strength quartile. After further adjustment for height and BMI (model 2), the HR was 1.38 (95% CI, 1.04–1.83), and in model 3, after additional adjustment for multiple potential confounders (cancer, physical activity, and CVD), the HR was 1.32 (95% CI, 0.98–1.78). Subgroup analyses revealed that the association was particularly strong for unprovoked VTE and isolated DVT, with adjusted HRs for quartile 1 versus quartile 4 of 1.59 (95% CI, 0.97–2.61) and 1.64 (95% CI, 1.10–2.45), respectively.

As shown in Table 3, there was apparently a threshold effect for VTE risk at the lowest quartile of HGS. We therefore performed analyses comparing the lowest dynamometer specific quartile (quartile 1) with the three higher quartiles combined (quartiles 2–4) (Table 4). With this approach, the HR for overall VTE according to

TABLE 1 Study population characteristics across dynamometer-specific quartiles of hand grip strength

Variables	Quartile 1 (n = 5163)	Quartile 2 (n = 5145)	Quartile 3 (n = 5038)	Quartile 4 (n = 4757)
Age (years), mean ± SD	69 ± 9.1	64 ± 10.0	62 ± 10.6	56 ± 10.9
Sex, female, n (%)	4243 (82.2)	3739 (72.7)	2325 (46.2)	1166 (24.5)
BMI (kg/m^2), mean ± SD	26.5 ± 4.7	26.5 ± 4.4	26.7 ± 4.0	27.1 ± 3.9
Height (cm), mean ± SD	162 ± 7.8	166 ± 7.8	170 ± 8.5	175 ± 8.5
History of CVD, n (%)	1215 (23.5)	976 (19.0)	980 (19.5)	733 (15.4)
History of cancer, n (%)	1396 (27.0)	1417 (27.5)	1449 (28.8)	1108 (23.3)
Physical activity index, n (%)				
1	1441 (27.9)	1301 (25.3)	1281 (25.4)	1221 (25.7)
2	1081 (20.9)	1079 (21.0)	962 (19.1)	858 (18.0)
3	948 (18.4)	976 (19.0)	905 (18.0)	712 (15.0)
4	664 (12.9)	972 (18.9)	1062 (21.1)	1257 (26.4)
5	391 (7.8)	460 (8.9)	563 (11.2)	543 (11.4)

Note: A total of 13,704 unique individuals aged 25–89 participated in at least one of the Tromsø surveys, and this resulted in 20,109 observational periods.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease (history of cerebral stroke, myocardial infarction, or angina pectoris); SD, standard deviation.

TABLE 2 Characteristics of VTE events

	n (%)
Age, years (mean ± SD)	74 ± 8.9
Sex (male)	246 (45.1)
Clinical characteristics	
Pulmonary embolism	250 (45.9)
Deep vein thrombosis	295 (54.1)
Provoked	325 (59.6)
Unprovoked	220 (40.4)
Provoking factors	
Surgery	86 (15.8)
Trauma	45 (8.3)
Acute medical condition	67 (12.3)
Active cancer	141 (25.9)
Immobilization	58 (21.1)
Other	27 (5.0)

Abbreviations: SD, standard deviation; VTE, venous thromboembolism.

weak HGS was 1.27 (95% CI, 1.03–1.57) in the multivariable adjustment model (Table 4, model 3). The corresponding HRs were 1.22 (95% CI, 0.93–1.60) for provoked VTE, 1.35 (95% CI, 0.96–1.91) for unprovoked VTE, 1.02 (95% CI, 0.74.1.42) for PE and 1.52 (95% CI, 1.14–2.01) for DVT, respectively.

Similar results were found in analyses restricted to elderly participants (aged greater than 75 years) (Table S1), as well as in the sex-specific analyses (Table S3). Furthermore, sensitivity analyses restricted to HGS measured with the Martin Vigorimeter showed similar results (quartile 1 compared to quartiles 2–4, multivariable adjusted HR, 1.34; 95% CI, 1.09–1.66). When analysis was restricted to the first 5 years of follow-up after enrollment in the study, the fully adjusted HR for overall VTE was 1.38 (95% CI, 0.88–2.16) for the lowest HGS quartile (quartile 1) compared to the three other quartiles (quartiles 2–4).

4 | DISCUSSION

In this population-based cohort study, we found that weak HGS, defined as lowest hand grip quartile, was associated with a 27% increased risk of VTE. The association appeared to be particularly pronounced for unprovoked VTE and DVT, with a 35% and 52% increased relative risk, respectively. Analyses restricted to elderly participants (aged greater than 75 years) and sex-specific analyses yielded similar results, supporting the robustness of our findings. Moreover, the association between weak HGS and overall VTE was stronger when the analysis was restricted to the first 5 years of follow-up.

Few studies have investigated the association between HGS and risk of VTE, and they showed somewhat inconsistent results. In the AT-AGE study, a case–control study consisting of elderly individuals (aged greater than 70 years), weak HGS, defined as the lowest sex-specific 15th percentile, was associated with a 2.1-fold higher risk of VTE after adjustment for age, sex, study center, and BMI.[21] Furthermore, results from the Cardiovascular Health Study (CHS), a cohort of 4859 participants aged greater than 65 years followed for a median of 9.3 years, showed that frailty was associated with a 1.4-fold increased risk of VTE after adjustment for age, sex, race, BMI, diabetes, and physical activity. Weak grip strength, defined as the lowest sex- and BMI-specific quintile, was used to define frailty together with four other physical function measures, but, unfortunately, the association between grip strength and VTE was not investigated separately.[27] In contrast to our findings, the Kupio Ischemic Heart Disease study, a cohort of 864 men and women aged greater than 70 years in whom 58 developed VTE during a median of

TABLE 3 Crude IRs per 1000 person-years and HRs of VTE with 95% CIs across dynamometer-specific quartiles of hand grip strength

	Person-years	VTE	Crude IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Overall VTE						
Quartile 4	45,299	104	2.30 (1.89–2.78)	1	1	1
Quartile 3	44,726	124	2.77 (2.33–3.31)	0.91 (0.69–1.18)	1.01 (0.77–1.32)	1.03 (0.78–1.35)
Quartile 2	43,190	133	3.08 (2.60–3.65)	0.91 (0.70–1.20)	1.04 (0.79–1.37)	1.06 (0.80–1.42)
Quartile 1	40,692	184	4.52 (3.91–5.22)	1.13 (0.86–1.49)	1.38 (1.04–1.83)	1.32 (0.98–1.78)
Provoked VTE						
Quartile 4	45,299	68	1.50 (1.18–1.90)	1	1	1
Quartile 3	44,726	76	1.70 (1.36–2.13)	0.87 (0.62–1.21)	0.96 (0.68–1.34)	0.96 (0.68–1.36)
Quartile 2	43,190	78	1.81 (1.45–2.25)	0.85 (0.60–1.20)	0.96 (0.68–1.37)	0.97 (0.68–1.39)
Quartile 1	40,692	103	2.53 (2.09–3.07)	1.02 (0.72–1.45)	1.25 (0.87–1.79)	1.19 (0.82–1.73)
Unprovoked VTE						
Quartile 4	45,299	36	0.79 (0.57–1.10)	1	1	1
Quartile 3	44,726	48	1.07 (0.81–1.42)	0.98 (0.63–1.53)	1.09 (0.70–1.70)	1.16 (0.73–1.85)
Quartile 2	43,190	55	1.27 (0.98–1.66)	1.04 (0.66–1.62)	1.17 (0.75–1.85)	1.25 (0.78–2.02)
Quartile 1	40,692	81	1.99 (1.60–2.47)	1.33 (0.85–2.07)	1.62 (1.03–2.56)	1.59 (0.97–2.61)
Pulmonary embolism						
Quartile 4	45,299	48	1.06 (0.80–1.41)	1	1	1
Quartile 3	44,726	59	1.32 (1.02–1.70)	0.85 (0.58–1.26)	0.95 (0.64–1.40)	0.97 (0.65–1.45)
Quartile 2	43,190	63	1.46 (1.14–1.87)	0.84 (0.56–1.25)	0.96 (0.64–1.44)	0.99 (0.65–1.50)
Quartile 1	40,692	80	1.97 (1.58–2.45)	0.92 (0.61–1.37)	1.12 (0.74–1.70)	1.01 (0.65–1.57)
Deep vein thrombosis						
Quartile 4	45,299	56	1.24 (0.95–1.61)	1	1	1
Quartile 3	44,726	65	1.45 (1.14–1.85)	0.95 (0.66–1.36)	1.05 (0.73–1.51)	1.07 (0.73–1.57)
Quartile 2	43,190	70	1.62 (1.28–2.05)	0.98 (0.67–1.42)	1.09 (0.75–1.60)	1.12 (0.75–1.66)
Quartile 1	40,692	104	2.56 (2.11–3.10)	1.34 (0.92–1.95)	1.64 (1.12–2.42)	1.64 (1.10–2.45)

Note: Model 1: adjusted for age (as time scale) and sex. Model 2: adjusted for age (as time scale), sex, height, and BMI. Model 3: adjusted for age (as time scale), sex, height, BMI, physical activity, cancer, and CVD.Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IR, incidence rate; VTE, venous thromboembolism.

17.2 years of follow-up,[22] reported no association between tertiles of normalized HGS and risk of VTE. Of note, the long follow-up time with lack of repeated measures and few VTE events could have led to underestimation of the true association due to regression dilution, as muscle strength may vary in individuals over time. To minimize the chance of regression dilution in our study, we performed a time-varying analysis that allowed for updated grip strength measurements over time in participants attending repeated surveys. Still, with this approach, the median follow-up time in our study was 6.5 years. When we restricted our analyses to the first 5 years of follow-up after enrollment in the Tromsø study, the association was stronger, which might point toward some regression dilution also in our study.

In agreement with the AT-AGE study, which reported higher odds ratios (ORs) for DVT than for PE in subjects with weak HGS,[21] we also observed higher HRs for DVT than for PE in our study. Venous blood from the lower extremities returns to the heart by a venous pressure gradient created by the calf muscle pump.[8] Weak HGS correlates with lower-extremity strength and a weaker calf muscle pump in adults.[10–13,28] A weak calf muscle pump may lead to venous stasis and thereby increase the risk of thrombus formation in the deep veins. This is further supported by Houghton et al.,[8] who reported that reduced calf muscle pump function was associated with increased risk of DVT, but not with PE.

In the present study, risk estimates for unprovoked VTE were higher than for provoked VTE. This indicates that the association between weak HGS and VTE is independent of the presence of known predisposing factors for VTE (e.g., active cancer or immobilization) or frailty-induced comorbidities. Weak HGS was also associated with increased risk of unprovoked VTE in the AT-AGE study (OR, 1.8), but in contrast to our findings, the risk estimates for provoked VTE (OR, 2.8) were higher in AT-AGE.[21] In the CHS, frailty was associated with a 1.9-fold increased risk of unprovoked VTE after adjustment for age, sex, race, BMI, diabetes, and physical activity, while corresponding results for provoked VTE were not reported.[27] Taken together, these studies support that weak muscle strength may play a role in the

TABLE 4 Crude IRs per 1000 person-years and HRs of VTE with 95% CIs for weak grip strength (<25th percentile, quartile 1) compared to normal hand grip strength (≥25th percentile, quartiles 2–4)

	Person years	VTE	Crude IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Overall VTE						
Quartiles 2–4	133,214	361	2.71 (2.44–3.00)	1	1	1
Quartile 1	40,692	184	4.52 (3.91–5.22)	1.22 (1.00–1.48)	1.35 (1.11–1.65)	1.27 (1.03–1.56)
Provoked VTE						
Quartiles 2–4	133,214	222	1.67 (1.46–1.90)	1	1	1
Quartile 1	40,692	103	2.53 (2.09–3.07)	1.16 (0.90–1.49)	1.29 (1.00–1.67)	1.22 (0.93–1.60)
Unprovoked VTE						
Quartiles 2–4	133,214	139	1.04 (0.88–1.23)	1	1	1
Quartile 1	40,692	81	1.99 (1.60–2.47)	1.31 (0.97–1.77)	1.45 (1.07–1.97)	1.35 (0.96–1.91)
Pulmonary embolism						
Quartiles 2–4	133,214	170	1.28 (1.10–1.48)	1	1	1
Quartile 1	40,692	80	1.97 (1.58–2.45)	1.05 (0.79–1.40)	1.16 (0.87–1.55)	1.02 (0.74–1.42)
Deep vein thrombosis						
Quartiles 2–4	133,214	191	1.43 (1.24–1.65)	1	1	1
Quartile 1	40,692	104	2.56 (2.11–3.10)	1.38 (1.07–1.80)	1.55 (1.19–2.02)	1.52 (1.14–2.01)

Note: Model 1: adjusted for age (as time scale) and sex. Model 2: adjusted for age (as time scale), sex, height, and BMI. Model 3: adjusted for age (as time scale), sex, height, BMI, physical activity, cancer, and CVD. Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IR, incidence rate; VTE, venous thromboembolism.

pathogenesis of VTE regardless of other comorbidities and provoking factors.

It is well established that men have a higher grip strength than women and that HGS declines with increasing age.[29,30] Moreover, increasing BMI and body height have been shown to be independently correlated with a stronger hand grip.[29,31] Since overweight/obesity and taller height are associated with increased VTE risk,[7,32–35] and inversely associated with weak HGS, the HRs increased as expected when we adjusted for these confounders. Age is a particularly important confounder, as it is strongly related to both HGS and VTE risk. Therefore, age was used as time scale in the Cox models. To further explore whether the observed association could be confounded by a weak grip strength in the elderly, we conducted analyses restricted to participants aged greater than 75 years. The risk estimate for VTE according to weak HGS remained elevated also in this age group. Finally, weak muscle strength can be a consequence of physical inactivity, which is associated with VTE risk.[24] However, adjustment for physical activity only slightly attenuated the risk estimates in our study.

A weak HGS is associated with a variety of diseases and physical conditions[14–20] and is frequently used together with other components to assess frailty.[36,37] We therefore performed several adjustments and sensitivity analyses to try to account for potential confounding by comorbidities and frailty. In the main analysis, we adjusted for previous cancer, cardiovascular disease, and physical activity. Furthermore, we performed sensitivity analyses in which participants with major comorbidities for VTE (i.e., cancer and CVDs) were excluded, and we performed analyses restricted to those aged greater than 75 years to account for frailty by old age. However,

despite all these efforts to account for frailty and comorbidities, the presence of residual confounding cannot be completely ruled out, and the observed association between weak HGS and VTE could be rather a marker of a complex association between frailty, multimorbidity, and VTE.

Notable strengths of this study are the prospective cohort study design with a large number of participants selected from the general population and large number of adjudicated VTE events. The Tromsø study has an overall high attendance rate, and all hospital care and diagnostic workups for VTE in the region are provided by the same hospital, which facilitates a thorough outcome detection. All VTE events are well validated from hospital records, and detailed information on VTE subtypes and provoking factors was obtained.

Two different instruments were used to assess HGS, and this could potentially limit the precision of our results. In addition to applying device-specific quartiles, we also performed analyses restricted to participants measured with the Martin Vigorimeter in Tromsø4–6, and the results remained similar. Unfortunately, we did not have information on concomitant use of medications such as antiplatelet and anticoagulant therapy. However, lack of adjustment for these confounders would probably lead to an underestimation of the true association as the prevalence of antiplatelet and anticoagulant therapy is expected to be highest in the lowest grip strength quartile. The study population consisted of a predominantly Caucasian population, as the Tromsø study is based in Tromsø, a Norwegian city with relatively few immigrants. The findings might therefore not be generalizable across all ethnicities. Information about diseases and physical activity levels was

obtained through self-administered questionnaires, which could potentially introduce misclassification. The study population also varied a little between adjustment models 2 and 3, due to missing physical activity variables.

In conclusion, a weak HGS was associated with increased risk of overall VTE, and particularly DVT and unprovoked VTE. Our findings support the hypothesis that weak muscle strength may be a risk factor for VTE.

AUTHOR CONTRIBUTIONS

Conception and design: SKB, JBH, and VMM. Data collection: BHS, SKB, and JBH. Data analysis: OGL and SKB. Interpretation of results: OGL, SKB, VMM, JBH, and BHS. Manuscript draft: OGL and SKB. Critical revision of manuscript: VMM, JBH, and BHS. All authors read and approved the submitted version of the manuscript.

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RELATIONSHIP DISCLOSURE

The authors have no competing interests to declare.

CONSENT TO PARTICIPATE AND PUBLICATION

Written informed consent to participate in the Tromsø study was obtained from all individual participants included.

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