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Handgrip strength is not associated with risk of venous thromboembolism: a prospective cohort study

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ABSTRACT

Objectives. Consistent evidence suggests an inverse and independent association between handgrip strength and arterial thrombotic disease. However, whether handgrip strength is related to future risk of venous thromboembolism (VTE) is uncertain. We sought to assess the prospective association between handgrip strength and VTE risk. *Design.* Handgrip strength was assessed using a hand dynamometer in a population-based sample of 864 men and women aged 61-74 years without a history of VTE at baseline in the Kuopio Ischemic Heart Disease prospective cohort study. Handgrip strength was allometrically scaled to account for the effect of body weight (handgrip strength/body weight$^{2/3}$) and to normalize the data. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for VTE. *Results.* During a median (interquartile range) follow-up of 17.2 (12.1-18.3) years, 58 VTE events were recorded. The risk of VTE did not significantly decrease per 1 standard deviation increase in normalized handgrip strength in age- and sex-adjusted analysis (HR 0.89; 95% CI 0.65–1.22). The association remained similar in analyses adjusted for several established and emerging risk factors (HR 0.90; 95% CI 0.65–1.25). The corresponding adjusted HRs were 1.10 (95% CI: 0.56-2.18) and 1.15 (95% CI: 0.57-2.34) respectively, when comparing the extreme tertiles of normalized handgrip strength values. *Conclusions.* Normalized handgrip strength is not associated with future VTE risk in an older Caucasian population. Large-scale studies in other populations and age-groups are warranted to generalize these findings.

KEYWORDS

handgrip strength; venous thromboembolism; cohort study

Introduction

The role of physical activity in the prevention of atherosclerotic vascular disease and mortality is well established [1]. Physical activity has also been recently shown to be associated with reduced risk of venous thromboembolism (VTE) [2]. Venous thromboembolism which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE), constitutes a significant public health burden, given its substantial morbidity, premature mortality, as well as high costs to health systems [3,4]. Venous thromboembolism and atherosclerotic cardiovascular disease (CVD) are closely related disease conditions and they seem to share common risk factors such as obesity and cigarette smoking [5-7]. Evidence suggests they share common pathophysiological mechanisms such as coagulation, platelet activation and dyslipidaemia [8]. Physical fitness is a strong predictor of future health status[9] with its main components being cardiorespiratory fitness (CRF) and muscular fitness [10]. The inverse and independent relationship between CRF and vascular diseases is well established [9]. Limited but emerging evidence suggests CRF may also be linked to VTE risk [11-14]. The main components of muscular fitness include muscular strength, muscular endurance and muscular power [10]. Among these, muscular strength has been the most widely studied in terms of its relationship to health outcomes. Handgrip strength has commonly been used as a typical measure of muscular strength. The emerging evidence on the inverse and independent relationship between handgrip strength and atherosclerotic CVD is consistent [15,16]. Given the overall evidence and inter-relationship between physical fitness, atherosclerotic CVD, and VTE, we hypothesized that handgrip strength may be linked to the risk of VTE. A previous evaluation of the association between handgrip strength and VTE risk in individuals aged 70 years and older by Engbers and colleagues demonstrated that low handgrip strength (<15th percentile) was associated with a 2.3 times higher risk of VTE compared to high handgrip strength ((>15th percentile) [17]; however, this evaluation was limited by the use of a case-control design which is characterised by lack of temporality.

In this context, we sought to assess the prospective association between handgrip strength and VTE risk in a general population-based cohort of Finnish men and women. We accounted for the effect of body weight on handgrip strength using allometric scaling to normalize the data.

Methods

Study design and population

This study was reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Material 1**).[18] Participants in the current analyses were part of the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a prospective population-based cohort study designed to investigate risk factors for vascular disease and other chronic disease outcomes. The study recruitment methods, blood sample collection procedures and examinations have been described previously [19]. The initial cohort comprised a representative sample of men randomly recruited from the city of Kuopio and surrounding rural communities in eastern Finland using a population register. These participants underwent re-examinations at 4 years, 11 years and 20 years after study entry. In the 11-year follow-up re-examinations, women were invited to join the study and they formed part of the cohort employed for this analysis. A total of 2,358 participants (1,007 men and 1,351 women) aged 53 to 74 years at baseline were initially recruited [19]. Of the 2,072 participants found to be potentially eligible, 193 did not agree to participate, 66 did not respond to the invitation and 39 declined to provide informed consent, which left 1,774 participants (**Supplementary Material 2**) [19]. The current analysis is based on 864 men and women with complete information on handgrip strength, relevant covariates, and VTE events, who had baseline examinations conducted from March 1998 to December 2001. The research protocol was approved by institutional review board of the University of Kuopio and Kuopio University Hospital, Kuopio, Finland (License

number 143/97). Written informed consent was obtained from all participants and all study procedures were conducted according to the Declaration of Helsinki.

Assessment of handgrip strength, risk markers and outcome

Handgrip strength of the dominant hand for each participant was measured by a hand dynamometer (in kPa; Martin-Balloon-Vigorimeter; Gebrüder Martin, Tuttlingen, Germany). The MartinVigorimeter is known for its high reliability and accuracy, especially in older patients [20]. Two measurements were taken and the mean of both values was used for analysis. The dynamometers were calibrated at the beginning of each test and there was a one-minute resting gap between both handgrip measurements. Absolute values of handgrip strength were allometrically scaled to account for the influence of body weight and to normalize the data (normalized handgrip strength = handgrip strength/body weight$^{2/3}$) [21]. All results were multiplied by 100 for easier readability.

All first lifetime VTE events that occurred from study enrollment through to 2017 were included. The diagnosis of DVT or PE required positive imaging tests and they were identified by computer linkage to the National Hospital Discharge Registry data maintained by the Finnish Institute for Health and Welfare. The medical documents for each potential VTE case were cross-checked in detail and VTE events were validated by two physicians who were blinded to the exposures. The ICD 10 codes (I26, I80 and I82) were used to code and classify each potential VTE case.

Statistical analysis

Using descriptive analyses, baseline characteristics were presented as means (standard deviation, SD) or medians (interquartile range, IQR) for continuous variables and percentages for categorical variables. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard

models after confirming no substantial departure from the assumptions of proportionality of hazards [22]. Normalized handgrip strength was modeled as both continuous [per SD increase] and categorical (tertiles) exposures. In a subsidiary analysis, normalized handgrip strength was also modelled as percentiles ($\geq 15^{th}$ percentile versus $< 15^{th}$ percentile) to maintain consistency with a previous study [17]. Hazard ratios were adjusted for in three models: (1) unadjusted; (2) age and sex; and (3) plus body height, smoking status, prevalent coronary heart disease (CHD), history of diabetes mellitus, use of lipid medication, physical activity, and prevalent cancer. All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

The overall mean (SD) age of study participants at study entry was 69 (3) years and 47.2% were males. The mean (SD) values of normalized handgrip strength and weight were 0.48 (0.22) $kPa/kg^{2/3}$ and 75.5 (12.9) kg respectively (**Table 1**). During a median (IQR) follow-up of 17.2 (12.1-18.3) years, a total of 58 VTE cases (annual rate 4.54/1,000 person-years at risk; 95% CI: 3.51 to 5.87) occurred. The high VTE event rate potentially reflects the older age, high body mass and high prevalence of CHD in the study sample (**Table 1**); these are all established risk factors for VTE [23]. The HR for VTE per 1 SD increase in normalized handgrip strength in unadjusted analysis was 0.91 (95% CI: 0.67 to 1.22), which remained similar when adjusted for age and sex 0.89 (95% CI: 0.65 to 1.22) and further adjustment for established risk factors and other potential confounders (body height, smoking status, prevalent CHD, history of type 2 diabetes, use of lipid medication, physical activity, and prevalent cancer) 0.90 (95% CI: 0.65 to 1.25) (**Table 2**). The corresponding adjusted HRs were 1.13 (95% CI: 0.58 to 2.17), 1.10 (95% CI: 0.56 to 2.18), and 1.15 (95% CI: 0.57 to 2.34) respectively, when comparing the top versus bottom tertiles of normalized handgrip strength. The non-significant association remained when the risk was assessed by

comparing participants above the 15th percentile normalized handgrip strength with those below below (**Supplementary material 3**).

Discussion

Summary of main findings

Previous prospective observational data on the inverse and independent association between handgrip strength (a measure of muscular strength) and arterial thrombotic disease is plentiful [15,16]. Muscular strength has also been demonstrated to be inversely associated with cardiometabolic conditions such as type 2 diabetes and metabolic syndrome [24,25]. In this first study to evaluate the prospective association between normalized handgrip strength and risk of VTE in a general population-based cohort of older Caucasian men and women, we found no evidence of an association. These findings may seem unexpected given that a previous study based on a case-control design showed that weak handgrip strength was associated with an increased risk of VTE in individuals aged 70 years and older [17]. However, because of the lack of temporality in the study design, the findings were prone to reverse causation bias. Furthermore, our findings were unexpected given the close inter-relationship between atherosclerotic CVD, VTE and physical fitness and also the fact that handgrip strength is a measure of whole-body muscle strength, correlated with leg strength, provides a valid index of overall limb muscle strength, and characterizes physical capability [26].

Possible explanations for findings

Pathways postulated to underlie the protective effect of higher muscular strength (handgrip strength) on vascular disease have included reduction in incidence of weight gain, abdominal adiposity, insulin resistance, metabolic syndrome, and inflammation [10,27]. There is a possibility that the null association

observed in our study may reflect important pathophysiologic differences between arterial thrombotic disease and VTE. There is still uncertainty as to whether arterial thrombotic disease (comprising of CHD, stroke, and peripheral artery disease) is related to VTE. It has been suggested that atherosclerotic CVD is an underlying condition and precedes the development of VTE [28]; however, evidence on the contrary also suggests this is not the case [29,30]. There is controversy as to whether any relationship between atherosclerotic CVD and VTE may reflect shared risk factors. Whereas some studies have demonstrated significant associations between traditional CVD risk factors and VTE risk [5,7], others have not [6,31]. Atherosclerotic CVD and VTE have historically been viewed as two distinct diseases [32] and based on findings that traditional risk factors for VTE and arterial thrombotic disease are not similar, it is generally believed that their pathogenesis differ [33]. On the contrary, the absence of evidence of an association could also be related to study design factors and population characteristics such as (i) low statistical power due to the low number of VTE events; (ii) regression dilution bias due to the long follow-up duration; (iii) residual confounding; and (iv) age, sex, or genetic background of the population. Given the absence of previous prospective evaluations of the associations, large-scale studies are warranted to confirm or refute these findings.

Strengths and limitations

The notable strengths of this study include the novelty (prospective cohort design), the general population-based sample of men and women with no history of pre-existing VTE at study entry, employment of the Martin Vigorimeter for measuring grip strength, long and complete follow-up of participants, and reliable data on a comprehensive panel of lifestyle factors which allowed adjustment for potential confounding. Limitations which merit mention include (i) the relatively low number of VTE events, which also precluded the ability to investigate sex-specific associations; (ii) potential residual

confounding due to unmeasured confounding; (iii) inability to generalise the findings to other populations; (iv) inability to correct for regression dilution bias due to absence of repeat measurements of handgrip strength; and (v) data was available on only total VTEs which precluded the ability to evaluate specific VTE outcomes (DVT or PE).

Conclusions

Normalized handgrip strength is not associated with future VTE risk in an older Caucasian population. Large-scale studies in other populations and age-groups are warranted to generalize these findings.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017 Dec 16;390(10113):2643-2654.

2. Kunutsor SK, Makikallio TH, Seidu S, et al. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. Eur J Epidemiol. 2019 Nov 14.

3. Douketis JD, Gu CS, Schulman S, et al. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med. 2007 Dec 4;147(11):766-74.

4. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007 Oct;98(4):756-64.

5. Ageno W, Becattini C, Brighton T, et al. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008 Jan 1;117(1):93-102.

6. Mahmoodi BK, Cushman M, Anne Naess I, et al. Association of Traditional Cardiovascular Risk Factors With Venous Thromboembolism: An Individual Participant Data Meta-Analysis of Prospective Studies. Circulation. 2017 Jan 3;135(1):7-16.

7. Gregson J, Kaptoge S, Bolton T, et al. Cardiovascular Risk Factors Associated With Venous Thromboembolism. JAMA Cardiol. 2019 Feb 1;4(2):163-173.

8. Ray JG. Dyslipidemia, statins, and venous thromboembolism: a potential risk factor and a potential treatment. Curr Opin Pulm Med. 2003 Sep;9(5):378-84.

9. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis [Meta-Analysis. Jama. 2009 May 20;301(19):2024-35.

10. Artero EG, Lee DC, Lavie CJ, et al. Effects of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev. 2012 Nov-Dec;32(6):351-8.

11. Kunutsor SK, Laukkanen JA. Does cardiorespiratory fitness really influence venous thromboembolism risk? Journal of thrombosis and haemostasis : JTH. 2019 Dec;17(12):2220-2222.

12. Kunutsor SK, Makikallio TH, Araujo CGS, et al. Cardiorespiratory fitness is not associated with risk of venous thromboembolism: a cohort study. Scand Cardiovasc J. 2019 Jun 20:1-4.

13. Kunutsor SK, Makikallio TH, Laukkanen JA. Response to letter by Peng-Wu and Ma on: the relationship of cardiorespiratory fitness and venous thromboembolism: yes or no? Scand Cardiovasc J. 2019 Nov 9:1-2.

14. Evensen LH, Isaksen T, Braekkan SK, et al. Cardiorespiratory fitness and future risk of venous thromboembolism. Journal of thrombosis and haemostasis : JTH. 2019 Aug 25.

15. Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. BMJ. 2018 May 8;361:k1651.

16. Andersen K, Rasmussen F, Held C, et al. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. BMJ. 2015 Sep 16;351:h4543.

17. Engbers MJ, Blom JW, Cushman M, et al. Functional Impairment and Risk of Venous Thrombosis in Older Adults. J Am Geriatr Soc. 2017 Sep;65(9):2003-2008.

18. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [Research Support, Non-U.S. Gov't]. Journal of clinical epidemiology. 2008 Apr;61(4):344-9.

19. Kunutsor SK, Blom AW, Whitehouse MR, et al. Renin-angiotensin system inhibitors and risk of fractures: a prospective cohort study and meta-analysis of published observational cohort studies. Eur J Epidemiol. 2017 Nov;32(11):947-959.

20. Sipers WM, Verdijk LB, Sipers SJ, et al. The Martin Vigorimeter Represents a Reliable and More Practical Tool Than the Jamar Dynamometer to Assess Handgrip Strength in the Geriatric Patient. J Am Med Dir Assoc. 2016 May 1;17(5):466 e1-7.

21. Jacobson BH, Thompson BJ, Conchola EC, et al. A Comparison of Absolute, Ratio and Allometric Scaling Methods for Normalizing Strength in Elite American Football Players. J Athl Enhancement. 2013;2(2).

22. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. New York, NY: Springer; 2000.

23. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.

24. Wang Y, Lee DC, Brellenthin AG, et al. Association of Muscular Strength and Incidence of Type 2 Diabetes. Mayo Clin Proc. 2019 Apr;94(4):643-651.

25. Hong S. Association of Relative Handgrip Strength and Metabolic Syndrome in Korean Older Adults: Korea National Health and Nutrition Examination Survey VII-1. J Obes Metab Syndr. 2019 Mar;28(1):53-60.

26. Araujo CGS, Castro CLB, Franca JFC, et al. Sitting-rising test: Sex- and age-reference scores derived from 6141 adults. Eur J Prev Cardiol. 2019 May 1:2047487319847004.

27. Andersen K, Pedersen BK. The role of inflammation in vascular insulin resistance with focus on IL-6. Horm Metab Res. 2008 Sep;40(9):635-9.

28. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med. 2003 Apr 10;348(15):1435-41.

29. Reich LM, Folsom AR, Key NS, et al. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. Journal of thrombosis and haemostasis : JTH. 2006 Sep;4(9):1909-13.

30. van der Hagen PB, Folsom AR, Jenny NS, et al. Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study. Journal of thrombosis and haemostasis : JTH. 2006 Sep;4(9):1903-8.

31. 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 Sep;108(3):508-15.

32. Prandoni P. Venous thromboembolism and atherosclerosis: is there a link? Journal of thrombosis and haemostasis : JTH. 2007 Jul;5 Suppl 1:270-5.

33. Tsai AW, Cushman M, Rosamond WD, et al. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002 May 27;162(10):1182-9.

Table 1. Baseline participant characteristics

		Normalized handgrip strength exposure		
	Overall (N=864)	**Tertile 1 (N=288)**	**Tertile 2 (N=288)**	**Tertile 3 (N=288)**
	Mean (SD), median (IQR), or n (%)	**Mean (SD), median (IQR), or n (%)**	**Mean (SD), median (IQR), or n (%)**	**Mean (SD), median (IQR), or n (%)**
Normalized handgrip strength ($kPa/kg^{2/3}$)	0.48 (0.22)	0.30 (0.06)	0.45 (0.04)	0.70 (0.25)
Questionnaire/Prevalent conditions				
Age at survey (years)	69 (3)	69 (3)	69 (3)	68 (3)
Males	408 (47.2)	176 (61.1)	153 (53.1)	79 (27.4)
History of type 2 diabetes	83 (9.6)	32 (11.1)	28 (9.7)	23 (8.0)
Current smokers	81 (9.4)	23 (8.0)	27 (9.4)	31 (10.8)
History of CHD	308 (35.7)	126 (43.8)	103 (35.8)	79 (27.4)
History of cancer	89 (10.3)	26 (9.0)	30 (10.4)	33 (11.5)
Use of cholesterol medication	54 (6.3)	23 (8.0)	16 (5.6)	15 (5.2)
Physical measurements				
Weight (kg)	75.5 (12.9)	86.5 (10.8)	76.5 (7.5)	63.3 (2.9)
Height (cm)	164.2 (9.0)	167.3 (9.1)	165.1 (8.3)	160.3 (8.1)
BMI (kg/m^2)	28.0 (4.3)	31.0 (4.1)	28.2 (3.2)	24.7 (2.9)
SBP (mmHg)	138 (18)	138 (18)	140 (17)	137 (18)
DBP (mmHg)	80 (9)	81 (18)	80 (8)	78 (9)
Energy expenditure of total LTPA (kcal/day)	378 (226-649)	387 (246-614)	411 (239-703)	343 (197-584)
Blood-based markers				
Total cholesterol (mmol/l)	5.44 (0.94)	5.34 (0.89)	5.46 (1.00)	5.54 (0.93)
HDL-C (mmol/l)	1.24 (0.32)	1.15 (0.28)	1.22 (0.31)	1.35 (0.33)

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LTPA, leisure-time physical activity; SD, standard deviation; SBP, systolic blood pressure

Table 2. Association between normalized handgrip strength and risk of venous thromboembolism

Normalized handgrip strength (kPa/kg$^{2/3}$)	**Events/ Total**	**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	58 / 864	0.91 (0.67 to 1.22)	0.52	0.89 (0.65 to 1.22)	0.47	0.90 (0.65 to 1.25)	0.53
T1 (0.12-0.38)	16 / 288	ref		ref		ref	
T2 (0.39-0.52)	22 / 288	1.32 (0.69 to 2.50)	0.40	1.31 (0.69 to 2.49)	0.42	1.36 (0.70 to 2.62)	0.36
T3 (0.53-4.03)	20 / 288	1.13 (0.58 to 2.17)	0.72	1.10 (0.56 to 2.18)	0.78	1.15 (0.57 to 2.34)	0.70

CI, confidence interval; HR, hazard ratio; ref, reference; SD, standard deviation; T, tertile

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Model 2 plus body height, smoking status, prevalent coronary heart disease, history of type 2 diabetes, use of lipid medication, physical activity, and prevalent cancer

Supplementary Material

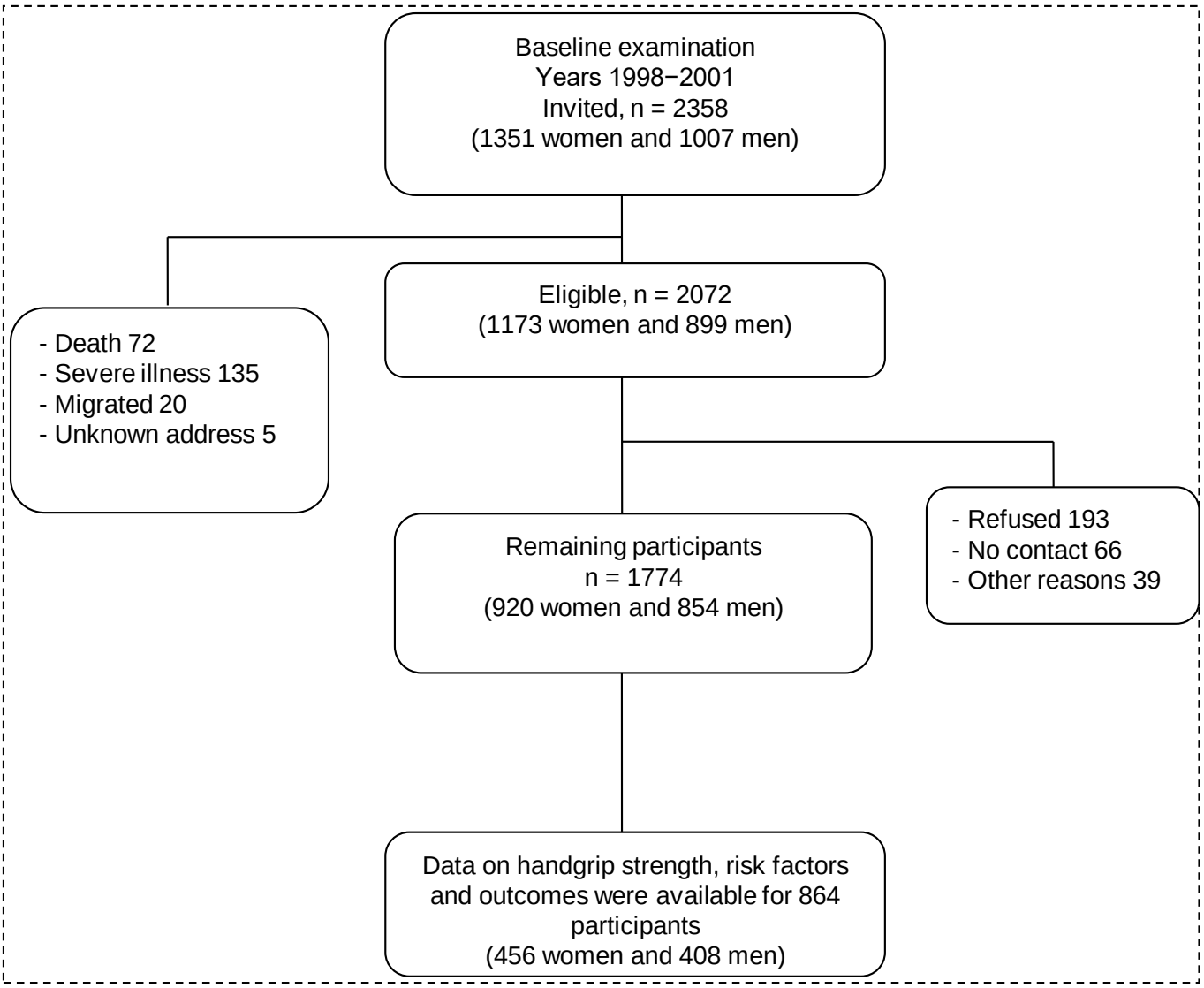
Supplementary material 1	STROBE 2007 Statement—Checklist of items that should be included in reports of cohort studies
Supplementary material 2	Participant flow
Supplementary material 3	Association of normalized handgrip strength with venous thromboembolism by percentile cutoffs of normalized handgrip strength

Supplementary material 1: STROBE 2007 Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Study design and population
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study design and population
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Study design and population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Study design and population
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Assessment of handgrip strength, risk markers and outcome
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Assessment of handgrip strength, risk markers and outcome
Bias	9	Describe any efforts to address potential sources of bias	Statistical analysis
Study size	10	Explain how the study size was arrived at	Statistical analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical analysis
		(*c*) Explain how missing data were addressed	Not applicable

		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Statistical analysis
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary material 3
		(b) Give reasons for non-participation at each stage	Supplementary material 3
		(c) Consider use of a flow diagram	Supplementary material 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Results; Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion - Summary of main findings
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgement

Supplementary material 2: Participant flow



Supplementary material 3: Association of normalized handgrip strength with venous thromboembolism by percentile cutoffs of normalized handgrip strength

Normalized handgrip strength (kPa/kg$^{2/3}$)	**Events/ Total**	**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
< 15th percentile	6 / 118	ref		ref		ref	
≥ 15th percentile	52 / 746	1.20 (0.51 to 2.79)	0.68	1.19 (0.51 to 2.80)	0.69	1.27 (0.53 to 3.04)	0.60

CI, confidence interval; HR, hazard ratio; ref, reference

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Model 2 plus body height, smoking status, prevalent coronary heart disease, history of type 2 diabetes, use of lipid medication, physical activity, and prevalent cancer