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The association between self-rated health, health-related quality of life, and risk of venous thromboembolism

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ABSTRACT

Poor self-rated health (SRH) is associated with various adverse health outcomes, including cardiovascular disease. Little is known about SRH and health-related quality of life (HRQoL) as predictors of first-time venous thromboembolism (VTE). Our aim was to investigate the association between SRH, HRQoL, and risk of VTE in a whole cohort, as well as in women and men separately.

A total of 108,025 middle-aged inhabitants (51 % women) of Västerbotten, Sweden, participated in a health examination between 1985 and 2014. Data on SRH, HRQoL, and potential confounders were collected by questionnaire. Participants were followed as a cohort and validated first-time VTE events were registered. The mean follow-up time was 13.9 years, during which 2054 participants experienced a first-time VTE. Overall, 27 % of participants reported their health as very good, 46 % as good, 20 % as average, 5 % as somewhat bad, and 1 % as bad. In a multivariable analysis, compared with participants who self-rated as having very good SRH, hazard ratios (95 % confidence intervals) for VTE were 1.17 (1.02–1.33) with good SRH, 1.27 (1.09–1.47) with average SRH, and 1.48 (1.00–2.18) with bad SRH. The risk of VTE increased with lower SRH for both men (p for trend 0.02) and women (p for trend 0.04). In a fully adjusted model, we also found significant associations between four aspects of HRQoL (general health, bodily pain, vitality, emotional well-being) and VTE risk.

In conclusion, lower perceived health is associated with an increased risk of VTE in both men and women.

1. Introduction

Venous thromboembolism (VTE) is a complex disease associated with major mortality and morbidity worldwide and most frequently manifested as lower extremity deep vein thrombosis and pulmonary embolism (Heit, 2005; Khan et al., 2021). Its incidence is around 1–2 per 1000 person-years (Heit, 2005; Johansson et al., 2014), and 30-day mortality rates are estimated at 9.7 % for pulmonary embolism and 4.6 % for deep vein thrombosis (Naess et al., 2007). Individuals who have suffered a VTE event often have a lower quality of life than the unaffected population (Ljungqvist et al., 2018; Lutsey et al., 2020; Erickson et al., 2019; Tavoly et al., 2016).

Risk factors for VTE include recent surgery, active cancer, trauma, immobilization, and hospitalization (Khan et al., 2021; Heit et al., 2000). Lifestyle and metabolic factors such as obesity, smoking, low physical activity, and a high alcohol intake also have been suggested to be associated with VTE risk (Mahmoodi et al., 2017; Cheng et al., 2013; Johansson et al., 2019 Jul; Johansson et al., 2019 Jun). Several models to predict the risk of recurrent VTE have been published, but there is less evidence related to the prediction of first-time VTE (Ensor et al., 2016). Sex-based differences in risk markers for VTE have been reported (Johansson et al., 2019 Jul; Johansson et al., 2019 Jun), so that it is important to include both sexes in relevant studies and to conduct separate analyses of associations in men and women.

Self-rated health (SRH) is widely used to measure an individual's perception of their own health and has a good test–retest reliability (DeSalvo et al., 2005; Lundberg and Manderbacka, 1996). Poor SRH is a predictor for mortality and is associated with increased levels of serum inflammatory markers and with various conditions, including cardiovascular disease, diabetes, and dementia (DeSalvo et al., 2005; Sundquist and Johansson, 1997; Lorem et al., 2020; Christian et al., 2011; van der Linde et al., 2013; Naess et al., 2005; Stephan et al., 2021). A

Abbreviations: VTE, venous thromboembolism; SRH, self-rated health; HRQoL, health-related quality of life; VEINS, Venous thromboEmbolism In Northern Sweden; VIP, Västerbotten Intervention Programme; BMI, Body mass index; ICD, International Classification of Diseases; HR, Hazard ratio; CI, confidence interval; MPP, Malmö Preventive Program.

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previous study of the association between SRH and risk of VTE in middle-aged women showed no statistically significant increased risk of incident VTE in those with poor SRH (Nymberg et al., 2020). Another study that included both men and women, however, measured SRH with a dichotomous question and showed an association between poor SRH and VTE risk in women but not in men (Nymberg et al., 2022).

Knowledge about how different aspects of self-rated health-related quality of life (HRQoL) are associated with VTE risk also is insufficient. A Norwegian study that focused on the association between different emotional states and risk of VTE showed that self-reported emotional states characterized by happiness/optimism were associated with a lower risk, whereas states characterized by depression/loneliness were associated with a higher risk (Enga et al., 2012). The analyses in that study were not stratified by sex.

Currently, the association between SRH, HRQoL, and risk of VTE is unclear, with limited research covering SRH and HRQoL and possible sex differences in VTE risk. The aim of this study was to investigate the association between perceived health and risk of first-time VTE in men and women separately. Our hypothesis was that a poor SRH would be independently associated with increased risk of incident VTE in both men and women.

2. Methods

2.1. Study population

This analysis is based on the Venous thromboEmbolism In Northern Sweden (VEINS) cohort study with 108,025 participants, conducted between 1985 and 2014 (Johansson et al., 2018). Västerbotten County inhabitants were invited at ages 30, 40, 50, and 60 years (from 1996, at ages 40, 50, and 60 years) to partake in the population-based Västerbotten Intervention Programme (VIP) (Hays and Morales, 2001). The program encompassed a health examination and a questionnaire. Participants also received health-related lifestyle advice from a trained nurse. Persons with a diagnosis of VTE registered before the date of the VIP health examination were excluded from the present study (Hays and Morales, 2001). Participants were followed as a cohort until a first-time VTE event, death, migration from the study area, or the end of the study on September 5, 2014.

2.2. SRH and HRQoL

To assess SRH, study participants completing the VIP health questionnaire answered the question: “What has your health been like during the last year?”, with five possible responses: “Very good”, “Good”, “Average”, “Somewhat bad”, and “Bad”. Data on HRQoL were collected using the RAND-36 questionnaire (Öhman et al., 2018), which is commonly used to assess HRQoL and evaluates eight aspects of health: physical functioning, role limitations due to physical health, role limitations due to emotional problems, general health, vitality, emotional well-being, social functioning, and bodily pain. Questionnaires are scored from 0 to 100, with a higher score indicating better health. The RAND-36 questionnaire was included in the VIP from 2003 to 2014 so that a smaller proportion of the cohort provided data on HRQoL compared with SRH (Supplementary Material Fig. 1).

2.3. Adjustment variables

Body mass index (BMI) was calculated from the weight and height measured at the VIP health examinations. Data on smoking was derived from the VIP questionnaire and participants were dichotomized into ever smokers, including active smokers and previous smokers, and never smokers. Blood pressure was measured at the VIP health examination. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or self-reported treatment with antihypertensive medication in the VIP questionnaire. Fasting plasma glucose was measured in all participants. An oral glucose tolerance test was performed in participants without known diabetes and with a fasting plasma glucose $<$ 7.0 mmol/L. Diabetes was defined as self-reported diabetes, self-reported treatment with oral antidiabetics or insulin, a fasting plasma glucose $\geq$ 7.0 mmol/L, or an oral glucose tolerance test two-hour plasma glucose of $\geq$ 12.2 mmol/L. Data on education level was derived from the VIP questionnaire and was dichotomized into up to secondary school education and more than secondary school education. Data on alcohol intake was extracted from the VIP questionnaire where a food frequency questionnaire was used to assess alcohol consumption. The participants were asked to report how often they consumed five different alcoholic beverages (light beer, medium strong beer, strong beer, wine, and spirits). These consumption frequencies where then used to calculate weekly alcohol intake in standard drinks as has been previously described (Johansson et al., 2019 Jul). One standard drink was defined as containing 12 g of ethanol. Data on physical activity was collected from the VIP questionnaire. The participants answered the question: ”How often have you trained or exercised in training clothes during the last 3 months to improve your fitness and/or to feel healthy?”. We then dichotomized leisure time physical activity using leisure time physical activity at least once a week as a cut-off. Data on cancer diagnoses in study participants were collected from the Swedish Cancer Registry.

2.4. VTE events

All first-time VTE events were identified by conducting a search for International Classification of Diseases (ICD) diagnosis codes that could represent potential VTE events. A search for ICD-8, ICD-9, and ICD-10 diagnosis codes was made in registries for both outpatient and inpatient care in Västerbotten as well as in the Cause of Death register. A complete list of the ICD-codes used can be found in a previous publication (Johansson et al., 2018). All diagnoses were validated by evaluation of medical records, radiology reports, and autopsy reports. Only objectively verified first-ever VTE events were included.

2.5. Statistical methods

We described the baseline characteristics of the study population using median and 1st and 3rd quartile boundaries for continuous variables and numbers and proportions for categorical variables. Differences between groups were tested using the chi-squared test for categorical variables. For continuous variables, the Mann–Whitney *U* test was used for comparisons between two groups and the Kruskal–Wallis test was used for comparisons between more than two groups. Cox proportional hazards regression was used to investigate the association among SRH, HRQoL, and risk of VTE. SRH was treated as a categorical variable. Originally, the eight aspects of HRQoL were continuous variables scored from 0 to 100, but as they were not normally distributed, each aspect was categorized in tertiles. For two aspects (role limitations due to physical health and role limitations due to emotional problems), only two categories were formed (100 and $<$100) because both the highest and middle tertile boundaries were located at a score of 100. Hazard ratios (HRs) with 95 % confidence intervals (CIs) and *p* for trend were calculated. A p-value $<$ 0.05 was considered statistically significant. Analyses were performed for the whole cohort and for women and men separately. Three models were created: Model 1 – univariable; Model 2 – adjusted for age and sex; and Model 3 – adjusted for age, sex, cancer, hypertension, education level, smoking, BMI, alcohol consumption, physical activity, and diabetes. The groups who rated their health as very good or belonged to the highest category of each aspect of HRQoL were used as reference. In a sensitivity analysis, participants with a diagnosis of cancer before or within 2 years after the health examination were excluded. Correlations between SRH and HRQoL were tested using Spearman’s rank order correlation. A power calculation showed that with a sample size of 108,000 participants (54,000 men and 54,000

women), a cumulative incidence of VTE of 1.9 % during the study period, a power of 80 %, and a significance level of 0.05 (two-sided), we could detect an HR of 1.3 for an increased risk of VTE in the 25 % of women or men with the lowest SRH when analyzing women and men separately. Analyses were performed using IBM SPSS Statistics, Version 28.0 (IBM Corp, Armonk, NY).

When describing the baseline characteristics of the study population, we found missing data for the following variables: BMI (n = 1173), smoking (n = 2035), hypertension (n = 1773), diabetes (n = 1582), education level (n = 1904), alcohol consumption (n = 10,226), and physical activity (n = 7280). Of the entire cohort, data on SRH were missing for 5952. Participants with missing data were excluded from analyses containing that variable. Overall, there were 33,833 (role limitations due to emotional problems) and 33,992 (physical functioning) participants with data on the different aspects of HRQoL.

2.6. Ethics

The study was approved by the Regional Ethics Review Board, Umeå (Dnr 06–162 M §157/06, 2006–12-05), with later amendments. All study participants provided informed consent when attending the VIP health examination. Later, all living participants with VTE were sent a letter with information about the study and the option to decline participation. All the institution's guidelines for protection of human subjects concerning their safety and privacy were met.

3. Results

3.1. Baseline characteristics

The VEINS cohort included 108,025 middle-aged participants, with 54,632 women (51 %). The median follow-up time was 15.5 years (range 0.0–28.8 years). During follow-up, 2054 participants (944 women and 1110 men) had an objectively verified first-time VTE event, and 1848 of this group had data on SRH. A participant flow chart is presented in Supplementary Material Fig. 1. The median age at baseline was 41.7 years (Table 1). Of all participants, 72.2 % had an education level below university, 2.6 % had a cancer diagnosis before or within 2 years of the health examination, 73.2 % rated their health as good or very good, and 6.5 % rated their health as somewhat bad or bad. Men rated their health higher than women (Table 1).

Lower SRH ratings were more often given by women, older participants, smokers, those with diabetes, hypertension, or cancer, and those with lower education, lower physical activity level, and lower alcohol intake (Supplementary Material Table 1).

3.2. SRH and VTE

Table 2 and Fig. 1 show the associations between SRH and risk of VTE. Poor SRH was associated with VTE risk, and the significance remained after adjustment for possible confounders. In the unadjusted model for all study participants and in comparison with very good SRH, all categories of lower SRH from good to bad were associated with an increased risk of VTE. Persons who rated their health as bad had a doubled risk of VTE (HR 2.14 [95 % CI 1.52–2.99]) compared with those reporting very good SRH.

In the multivariable model, in comparison with a very good SRH, a good, an average or a bad SRH was significantly associated with risk of first-time VTE. Persons with a bad SRH had a HR of 1.48 (95 % CI 1.00–2.18, $p = 0.048$) for first-time VTE. The p for trend was 0.002 over categories of SRH in the multivariable analysis, confirming a statistically significant increased risk for VTE with lower SRH after adjustment for possible confounders. In a sensitivity analysis, participants with a diagnosis of cancer before or within 2 years after the health examination were excluded. In this analysis, HRs for associations between SRH and risk of VTE were similar to those of the main analysis (p for trend 0.002), although not statistically significant for all categories of SRH (data not shown).

We also analysed data for men and women separately (Table 2 and Supplementary Material Fig. 2). In a univariable model, men who rated their health as good to somewhat bad had a significantly increased risk of first-time VTE compared with men reporting very good SRH; men with bad SRH did not have a significantly increased risk of VTE. In women, risk of first-time VTE was increased for all levels below very good health, with an almost three-fold increased risk for those with bad SRH (HR 2.87 [95 % CI 1.90–4.34]). Over categories of SRH, the p for trend for increased risk of VTE was < 0.001 for both women and men in the univariable model. In a multivariable model, compared with very good SRH, ratings of good, average, and somewhat bad SRH were significantly associated with risk of first-time VTE in men. In women, compared with very good SRH, average or bad SRH was significantly associated with risk of VTE in a multivariable model. For men, the p for trend for increased risk of VTE over categories of SRH was 0.02; for women, it was 0.04.

3.3. HRQoL and VTE

Table 3 shows the HRQoL ratings of the study population. All eight aspects of HRQoL were correlated with SRH, most strongly so with general health (correlation coefficient 0.68; Supplementary Material Table 2). In a fully adjusted model, we found significant associations

Table 1
Health examination and cancer data in a Västerbotten County cohort: Sweden, 1985 to 2014.

		All (N = 108,025)	Men (n = 53,393)	Women (n = 54,632)	*P*
Age, years		41.7 (40.0–50.4)	48.8 (40.0–50.4)	41.1 (40.0–50.3)	0.69
Self-rated health	Very good	27,328 (26.8)	13,977 (27.7)	13,351 (25.9)	
	Good	47,418 (46.5)	23,913 (47.4)	23,505 (45.5)	
	Average	20,719 (20.3)	9942 (19.7)	10,777 (20.9)	<0.001
	Somewhat bad	5162 (5.1)	2047 (4.1)	3115 (6.0)	
	Bad	1446 (1.4)	588 (1.2)	858 (1.7)	
BMI, kg/m^2		25.2 (22.9–28.0)	25.8 (23.8–28.2)	24.5 (22.2–27.6)	<0.001
Ever smoker		53,871 (50.8)	26,860 (51.4)	27,011 (50.3)	<0.001
Hypertension		30,388 (28.6)	16,522 (31.4)	13,866 (25.8)	<0.001
Diabetes		4490 (4.2)	2585 (4.9)	1905 (3.5)	<0.001
Education level below university		76,630 (72.2)	40,117 (76.4)	36,513 (68.1)	<0.001
Alcohol intake, standard drinks weekly		1.8 (0.3–3.5)	2.8 (0.9–4.8)	1.1 (0.1–2.1)	<0.001
Physical activity < 1 time/week		65,299 (64.8)	32,839 (66.0)	32,460 (63.7)	<0.001
Cancer		2762 (2.6)	1001 (1.9)	1761 (3.2)	<0.001

Characteristics are given as median (1st–3rd quartiles) for continuous variables and number (percentage) for categorical variable.
BMI, body mass index.

Table 2
Self-rated health and risk of venous thromboembolism in a Västerbotten County cohort: Sweden, 1985 to 2014.

	Self-rated health	Events/ participants (n)	Model 1[a]	*p* for trend	Model 2[b]	*p* for trend	Model 3[c]	*p* for trend
All	Very good	389/27,328	1 (ref.)		1 (ref.)		1 (ref.)	
	Good	832/47,418	1.25 (1.11–1.41)		1.20 (1.06–1.35)		1.17 (1.02–1.33)	
	Average	479/20,719	1.68 (1.47–1.92)	<0.001	1.43 (1.25–1.63)	<0.001	1.27 (1.09–1.47)	0.002
	Somewhat bad	111/5162	1.67 (1.35–2.06)		1.46 (1.18–1.80)		1.21 (0.96–1.53)	
	Bad	37/1446	2.14 (1.52–2.99)		1.92 (1.37–2.69)		1.48 (1.00–2.18)	
Men	Very good	220/13,977	1 (ref.)		1 (ref.)		1 (ref.)	
	Good	474/23,913	1.27 (1.08–1.49)		1.25 (1.06–1.46)		1.24 (1.04–1.47)	
	Average	244/9942	1.60 (1.33–1.92)	<0.001	1.38 (1.15–1.65)	<0.001	1.27 (1.03–1.55)	0.02
	Somewhat bad	55/2047	1.84 (1.37–2.47)		1.58 (1.18–2.13)		1.42 (1.03–1.97)	
	Bad	11/588	1.43 (0.78–2.62)		1.27 (0.70–2.34)		1.11 (0.57–2.18)	
Women	Very good	169/13,351	1 (ref.)		1 (ref.)		1 (ref.)	
	Good	358/23,505	1.23 (1.03–1.48)		1.14 (0.95–1.37)		1.09 (0.89–1.32)	
	Average	235/10,777	1.81 (1.49–2.21)	<0.001	1.48 (1.21–1.81)	<0.001	1.27 (1.02–1.58)	0.04
	Somewhat bad	56/3115	1.62 (1.20–2.20)		1.35 (0.997–1.83)		1.04 (0.74–1.45)	
	Bad	26/858	2.87 (1.90–4.34)		2.43 (1.61–3.68)		1.75 (1.08–2.83)	

Associations are shown as hazard ratios with 95 % confidence intervals. Only participants with data on self-rated health (n = 102,073) are presented in the table.
[a] Univariable model.
[b] Model adjusted for age. Analysis of all participants also adjusted for sex.
[c] Model adjusted for age, cancer, hypertension, education level, smoking, body mass index, alcohol consumption, physical activity, and diabetes. Analysis of all participants also adjusted for sex.

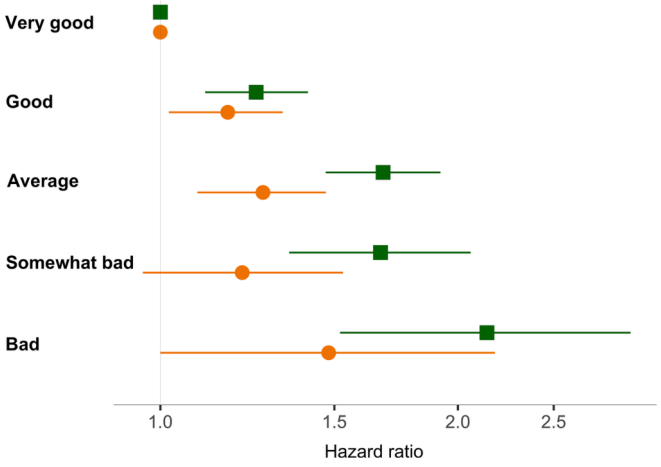

Fig. 1. Associations between self-rated health and venous thromboembolism in a Västerbotten County cohort: Sweden, 1985 to 2014. Univariable (green squares) and multivariable (orange circles) associations are shown as hazard ratios with 95% confidence intervals. The multivariable model was adjusted for age, sex, cancer, hypertension, education level, smoking, body mass index, alcohol consumption, physical activity, and diabetes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

between four of the eight studied aspects of HRQoL and risk of VTE (Table 4). Compared with the highest scoring group for each aspect, risk for VTE was increased in participants with scores in the lowest tertile for general health (HR 1.85 [95 % CI 1.25–2.75]), bodily pain (HR 1.57 [95 % CI 1.07–2.32]), vitality (HR 1.54 [95 % CI 1.05–2.25]), and emotional well-being (HR 1.68 [95 % CI 1.15–2.45]). The other four HRQoL aspects (physical functioning, social functioning, role limitations due to physical health, and role limitations due to emotional problems) were not significantly associated with increased VTE risk in the fully adjusted model. In our analyses of men and women separately, men with the lowest general health, lowest vitality, and lowest emotional well-being had an increased risk of VTE in a fully adjusted model. In women, bodily pain and role limitations due to physical health were associated with increased risk of VTE.

Table 3
Health-related quality of life in a Västerbotten County cohort: Sweden, 2003 to 2014.

	All (n = 34,178)	Men (n = 17,701)	Women (n = 16,477)	*P*
General health	75.0 (60.0–90.0)	75.0 (65.0–90.0)	75.0 (60.0–90.0)	<0.001
Physical functioning	95.0 (90.0–100.0)	100.0 (90.0–100.0)	95.0 (85.0–100.0)	<0.001
Bodily pain	90.0 (57.5–100.0)	90.0 (67.5–100.0)	80.0 (57.5–100.0)	<0.001
Vitality	70.0 (50.0–80.0)	70.0 (55.0–85.0)	65.0 (45.0–80.0)	<0.001
Social functioning	100.0 (87.5–100.0)	100.0 (87.5–100.0)	100.0 (75.0–100.0)	<0.001
Emotional well-being	84.0 (72.0–92.0)	88.0 (76.0–92.0)	84.0 (72.0–92.0)	<0.001
Role limitations due to physical health	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (75.0–100.0)	<0.001
Role limitations due to emotional problems	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	<0.001

Characteristics are given as median (1st–3rd quartiles). Only participants with data on at least one aspect of health-related quality of life are presented in the table.

4. Discussion

We found that lower perceived health was associated with an increased risk of first-time VTE in both middle-aged men and women. Among the eight studied aspects of HRQoL, low general health, more bodily pain, less vitality, and less emotional well-being were associated with increased risk of future VTE.

Our results differ somewhat from previously reported findings. In a prospective cohort study of 5626 middle-aged women (ages 50–65 years), 220 women experienced a VTE event during the study (Nymberg et al., 2020), with no significant associations found between SRH and VTE after adjustment for lifestyle-related variables. The relatively small size of that study could partly explain the lack of association, as could a difference in age distribution between participants in our study and

Table 4
Associations between different aspects of health-related quality of life and risk of venous thromboembolism in a Västerbotten County cohort: Sweden, 2003 to 2014.

Health-related quality of life	All Events/ participants (n)	HR (95 % CI)	Men Events/ participants (n)	HR (95 % CI)	Women Events/ participants (n)	HR (95 % CI)
General health						
≥85	40/12,480	1 (ref.)	26/6503	1 (ref.)	14/5977	1 (ref.)
70–84	46/10,354	1.20 (0.78–1.84)	32/5680	1.28 (0.76–2.18)	14/4674	1.02 (0.48–2.16)
<70	86/11,003	1.85 (1.25–2.75)	49/5336	1.92 (1.17–3.17)	37/5667	1.77 (0.93–3.37)
Physical functioning						
100	58/16,118	1 (ref.)	43/9267	1 (ref.)	15/6851	1 (ref.)
95–99	37/7219	1.14 (0.74–1.74)	26/3810	1.20 (0.72–1.99)	11/3409	1.05 (0.48–2.31)
<95	77/10,655	1.24 (0.84– 1.83)	38/4500	1.15 (0.70–1.88)	39/6155	1.39 (0.71–2.70)
Bodily pain						
100	49/12,653	1 (ref.)	38/7293	1 (ref.)	11/5360	1 (ref.)
67.5–99	54/12,242	1.16 (0.78–1.72)	35/6302	1.09 (0.68–1.75)	19/5940	1.40 (0.67–2.95)
<67.5	68/9062	1.57 (1.07–2.32)	34/3989	1.29 (0.79–2.10)	34/5073	2.23 (1.11–4.49)
Vitality						
≥80	54/11,742	1 (ref.)	37/6864	1 (ref.)	17/4878	1 (ref.)
55–79	56/12,794	1.04 (0.71–1.53)	34/6758	1.04 (0.64–1.68)	22/6036	1.08 (0.57–2.04)
<55	62/9410	1.54 (1.05–2.25)	36/3938	1.82 (1.13–2.94)	26/5472	1.24 (0.66–2.32)
Social functioning						
100	111/22,546	1 (ref.)	75/12,631	1 (ref.)	36/9915	1 (ref.)
87.5–99	17/3475	1.01 (0.59–1.70)	14/1719	1.43 (0.79–2.60)	3/1756	0.49 (0.15–1.60)
<87.5	44/7959	1.10 (0.76–1.58)	18/3236	0.89 (0.52–1.52)	26/4723	1.30 (0.78–2.18)
Emotional well-being						
≥92	51/12,045	1 (ref.)	32/7012	1 (ref.)	19/5033	1 (ref.)
80–91	54/10,937	1.39 (0.94–2.06)	32/5616	1.45 (0.88–2.41)	22/5321	1.23 (0.67–2.29)
<80	67/10,973	1.68 (1.15–2.45)	43/4938	2.18 (1.35–3.50)	24/6035	1.11 (0.60–2.04)
Role limitations due to physical health						
100	115/25,882	1 (ref.)	82/14,013	1 (ref.)	33/11,869	1 (ref.)
<100	57/7998	1.32 (0.95–1.84)	25/3533	0.98 (0.61–1.56)	32/4465	1.97 (1.19–3.25)
Role limitations due to emotional problems						
100	135/27,950	1 (ref.)	89/14,999	1 (ref.)	46/12,951	1 (ref.)
<100	37/5883	1.32 (0.91–1.93)	18/2528	1.19 (0.71–2.01)	19/3355	1.53 (0.89–2.65)

Note: The different aspects of health-related quality of life have been categorized into tertiles. A higher value indicates a better health-related quality of life. Only participants with data on at least one aspect of health-related quality of life are presented in the table.
Associations are shown as hazard ratios with 95% confidence intervals and are adjusted for age, cancer, hypertension, education level, smoking, body mass index, alcohol consumption, physical activity, and diabetes. Analysis of all participants also adjusted for sex.

theirs. It is not implausible that the association between SRH and VTE risk varies with age. In a recently published study, the prospective population-based Malmö Preventive Program (MPP) study (Nymberg et al., 2022), an analysis of associations between SRH and VTE separately in men and women showed a significant association between good SRH and lower VTE risk in women but not in men. That population was larger and participants tended to be younger compared with those in the study of middle-aged women. The larger study is similar to ours in many respects, but the results still diverged from ours, as we found a significant association between worse SRH and higher risk of VTE among men (p for trend 0.02 in a fully adjusted model) and they did not. We used a five-point scale to assess SRH as opposed to using a binary "good" vs "poor" response, as in the MPP study, and we believe that our approach is the more sensitive method. Having more options when self-rating health can yield more detailed information. As also discussed in the MPP, however, we have found no studies comparing different methods of assessing SRH. Furthermore, the MPP study used diagnosis codes in the Swedish National Patient Registry as a proxy for VTE events. For deep venous thromboembolism, in particular, the positive predictive value of a diagnosis code in this registry is low (Norberg et al., 2010). The possible inclusion of false-positive VTE events as outcomes could lead to both type 1 and type 2 errors.

Enga et al. investigated the association between self-reported emotional states and risk of VTE in a prospective cohort study (Enga et al., 2012). They found that persons who often felt happy/optimistic had a 40 % decreased risk of VTE compared to those who did not feel happy/optimistic, whereas persons who often felt depressed/lonely had a more than 60 % increased risk of VTE compared to those who did not feel depressed/lonely. Their results indirectly support our findings. As a further indication that emotional states can be related to VTE risk, a prospective study of 6958 middle-aged men showed a link between persistent stress and an increased risk of pulmonary embolism (Rosengren et al., 2008). It is reasonable to infer that persistent stress, SRH, and HRQoL are closely related.

Cancer is a known risk factor for VTE, and we hypothesized that persons with cancer in general would have a low SRH. To address this potential confounder, we performed a sensitivity analysis that excluded participants with a cancer diagnosis before or within 2 years after the baseline health examination. The purpose was to determine whether the results are applicable to people without cancer, and we found that the HRs for the association between SRH and risk of VTE in the sensitivity analyses were similar to those for all participants. This increases the generalizability of our results. Other pre-existing conditions could also influence the association between SRH and VTE risk. However, we think that the proportion of health examination participants with underlying serious medical conditions was low. For example, the percentage of participants that reported a history of myocardial infarction in the VIP questionnaire was below 1 %.

To our knowledge, this study represents the first investigation of associations of SRH, HRQoL, and risk of VTE, with separate analyses for men and women. Its other strengths are a population-based design with a large number of participants (N = 108,025), including a similar number of women and men in relevant age groups. Furthermore, the data on SRH and adjustment variables were collected before the VTE, VTE events were validated, and the follow-up time was lengthy.

One main limitation of this study is that participants rated their health only at baseline and in connection with the VIP health examination. During the long follow-up period, they might have experienced changes in health status or other factors that would have affected our results.

The ethnic homogeneity in the study population, with most participants being of western European ancestry, might affect the applicability of our results to other groups. For example, self-perception of health status varies among different ethnic groups, as does the incidence of VTE (Bombak and Bruce, 2012; White and Keenan, 2009; Beckman et al., 2010). In addition, VTE incidence and risk factors vary among age groups (Heit, 2005; Beckman et al., 2010; Anderson and Spencer, 2003), and whether our results can be applied to persons outside the studied age range is not clear.

5. Conclusions

In conclusion, we found an independent association between self-perceived health in middle-aged persons and risk of future first-time VTE. Our findings underline that SRH is a simple, quick, and inexpensive measure that could be useful in the process of identifying individuals at increased risk of future somatic illness including VTE.

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CRediT authorship contribution statement

Otto Nylund: Writing – original draft, Formal analysis. **Lars Johansson:** Conceptualization, Writing – review & editing. **Marcus M Lind:** Conceptualization, Writing – review & editing. **Magdalena Johansson:** Conceptualization, Validation, Investigation, Writing – review & editing, Funding acquisition, Visualization, Data curation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102434.

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