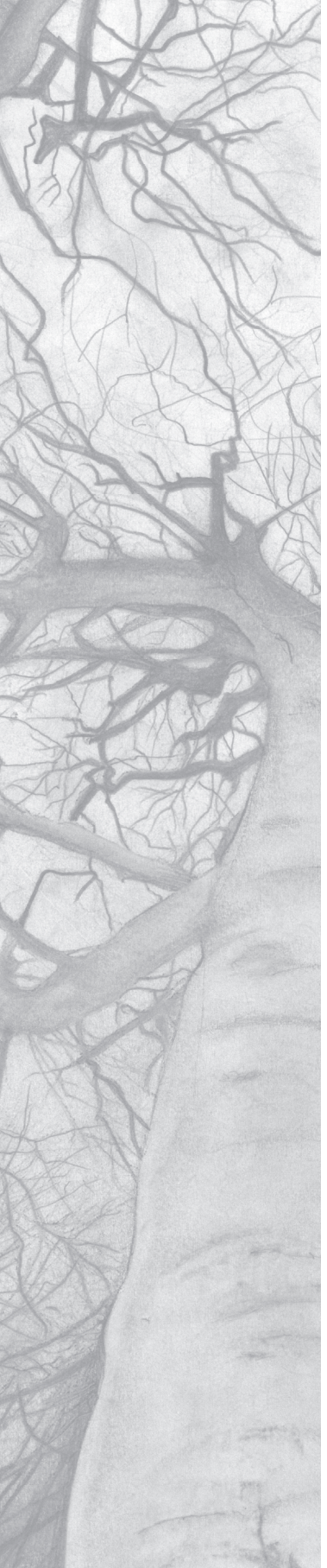

CHAPTER 6

Functional impairment and risk of venous thrombosis in older people

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Submitted

ABSTRACT

Background

Venous thrombosis incidence increases with age. The role of age-specific risk factors in thrombosis etiology at older age, such as functional impairment, is unclear.

Objective

Assess the thrombotic risk associated with functional impairment, defined as impaired activities of daily living (ADL), impaired mobility, sedentary lifestyle, and low handgrip strength.

Methods

The AT-AGE study is a two-centre case-control study conducted in the Netherlands and the USA (2008-2011). Consecutive cases (n=401) aged 70 years and older with a first-time deep venous thrombosis in the leg or pulmonary embolism and control subjects ≥70 years (n=431) without a history of thrombosis were included. Exclusion criteria were active malignancy and severe cognitive disorders. Estimations of the risk of thrombosis associated with two or more impaired Katz ADL items, inability to walk outside for 15 minutes, sedentary life style (>20 hours per day) and low handgrip strength (<15%) were performed. Odds ratios (ORs) adjusted for age, sex, and study centre with 95% confidence intervals (CI95) and population attributable risks (PAR) were calculated.

Results

Impaired ADL was associated with a 2.9-fold (CI95 1.6-5.3) increased risk of venous thrombosis, impaired mobility with a 3-fold (OR 3.0 (CI95 1.9-4.7)), a sedentary lifestyle with a 4-fold (OR 4.0 (CI95 2.5-6.3)) and low handgrip strength with a 2.3-fold (CI95 1.5-3.4) increased risk of thrombosis. The PARs for ADL disability, inability to walk outside for 15 minutes, sedentary lifestyle, and low hand grip strength were 8%, 13% 29%, and 13%, respectively.

Conclusion

In those over 70 years of age, functional impairments are major risk factors for venous thrombosis. Findings may have important implications for awareness of venous thrombosis risk by providers caring for older people.

INTRODUCTION

The incidence of venous thrombosis increases steeply with age. [1] The oldest old have a 100-fold increased risk of venous thrombosis compared with young people, thus age is one of the most important risk factors. It is unclear why ageing leads to an increased incidence of thrombosis, and it is remarkable that few data are available on risk factors that are almost exclusively present in older individuals, i.e., age-specific risk factors. [2] With ageing a decline in physiological functioning occurs with an increased susceptibility to functional impairments. Functional impairment predisposes to adverse health outcomes including death. [3-5] Functional impairment is associated with an inflammatory state, which promotes pro-coagulation [6], so functional impairment associated with ageing could result in an increased risk of venous thrombosis. Functional impairment is also associated with reduced mobility [3] An increased risk of thrombosis with mobility impairment would be expected based on the detrimental effects on muscular pump function and subsequent stasis of blood flow in the lower extremities. [6]

To study whether impaired functional status is an age-specific risk factor for venous thrombosis, we evaluated the associations between impaired functional status, expressed as disability of activities of daily living (ADL), impairment of mobility, sedentary lifestyle, and impaired hand grip muscle strength, and the occurrence of venous thrombosis in individuals aged 70 years and older.

METHODS

A detailed description of the Age and Thrombosis - Acquired and Genetic risk factors in the Elderly (AT-AGE) study has been published previously. [7] In brief, AT-AGE is a two-centre population-based case-control study among individuals aged 70 years and older to determine risk factors for venous thrombosis in the older population. Individuals aged 70 years and older with a first occurrence of deep vein thrombosis of the leg (DVT) and/or pulmonary embolism (PE) were enrolled in the Leiden area (the Netherlands) and Burlington (Vermont, United States). Control subjects were randomly selected from several primary care practices in the same geographical area as the cases. For both the cases and the control subjects, exclusion criteria were the presence of an active malignancy and psychiatric or cognitive disorders that hindered communication during the first contact. All participants provided written informed consent and gave permission to obtain information about their medical history. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre and by the Committee of Human Research of the University of Vermont. In Leiden, 504 cases were invited and 341 (68%) participated. In Burlington, 115 cases were invited and 62 (54%) participated. Of

the 407 invited control subjects in Leiden, 306 (75%) participated, while in Burlington 127 (65%) of the 196 invited control subjects participated. [7] The index date for the cases was defined as the date of diagnosis of the thrombotic event and for control subjects, this was the date of completing the interview. At enrollment, a structured detailed interview took place at the participant's home. The median duration between the index date and the home visit for the cases was 5 weeks (range 1–44 weeks), 75% were visited within 7 weeks, and 90% were visited within 10 weeks.

We used four instruments during the home visit to ascertain functional status prior to the index date. For ADLs we used the Katz Index [8] which includes questions on whether the participant was independent in six daily activities by yes/no answers: bathing, dressing, toilet use, transferring in and out of bed, eating, and presence of urinary or bowel incontinence. The range of the impairment score can be 0 of 6 (no ADL impairment) to 6 of 6 (fully ADL impaired). We used two items of the Barthel index to assess impairment of mobility; ability to walk outside for 15 minutes and ability to climb stairs. [9] We also estimated sedentary lifestyle by querying participants about the percentage of time spent sleeping and sitting per day during the two weeks before the index date. [10,11] Measurement of hand grip strength was performed twice in the dominant hand using a Jamar dynamometer, with the highest result used. [12] Weight was measured with a calibrated scale and height was measured. Body-mass index was calculated in kg per m^2. We also obtained information about the presence of other diseases such as a history of myocardial infarction and chronic obstructive pulmonary disease, and about other risk factors for venous thrombosis including recent hospitalisation, surgery, fracture, plaster cast or splint use, and minor injury or immobilisation. [7] A provoked event was defined when one of the following conditions was present in the three months before the thrombotic event: recent hospitalisation, surgery, fracture, plaster cast or splint use, minor injury or immobilisation in the home situation.

Analyses

We included cases and control subjects who completed the interview (401 of the 403 cases and 431 of the 433 control subjects). Characteristics of the control subjects were tabulated by study centre. We estimated the risk of venous thrombosis associated with the following expressions of the Katz ADL instrument: 'yes' versus 'no' to each of the 6 items of the Katz score, ADL disability present, defined as ≥ two impaired Katz ADL items compared to no impairment and for ≥ 3 impairments versus none. Impairment of mobility was present if an individual was not able to walk outside for 15 minutes. [9] Impairment of mobility was also separately analysed measured by the ability to climb stairs. A sedentary lifestyle was analysed by comparing individuals who spent 14 hours or less sleeping or sitting (20^{th} percentile in the control subjects) with individuals who spent 20 hours or more sleeping or sitting (80^{th} percentile in the control subjects). We

also considered tertiles of the hours of sedentary time, with the lowest tertile as the reference category. As handgrip strength is sex dependent, we assessed risk by comparing participants below versus above the sex-specific 15th percentile hand grip strength in the control group (<26 kg in men, and <16 kg in women). [13,14] We also assessed handgrip strength in sex specific tertiles based on the distribution in control subjects.

For all analyses, multivariable logistic regression models were used to estimate the odds ratios (ORs) and their 95% confidence intervals (CI95s) as estimates of the relative risk. All odds ratios were adjusted for the pre- defined potential confounders, age (continuous), sex and study centre. As weight loss is seen as an important marker of functional status, [3] further adjustments were made for BMI in three categories, <25kg/m2, 25-30 kg/m2 and >30kg/m2). Also adjustments were performed for the presence of co-morbidities (a history of myocardial infarction, transient ischemic attack, stroke, heart failure, or chronic obstructive pulmonary disease). To assess whether the association of functional impairment and thrombosis varied within the three BMI groups, we performed stratified analyses for all four functional impairments within the three BMI groups. The risk associated with an impaired functional state was calculated for provoked and unprovoked venous thrombosis and DVT and PE separately. To investigate whether an accumulation of functional impairments would influence the risk of thrombosis, we calculated the risk of thrombosis associated with the number of impairments present (1-4).

To obtain insight into the contribution of impaired functional state to the incidence of venous thrombosis in the older population we estimated the population attributable risk (PAR) for each of the four functional state entities. The PAR was calculated by *pd* (OR-1)/(OR). In which *pd* is the prevalence of the risk factor among cases, and OR is the adjusted OR. All statistical analyses were performed using SPSS 20 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

Median age was similar for control subjects in the Netherlands (76 years (range 70-94) and the United States (76 years, range 70-96). Distributions of sex and BMI (kg.m^{-2}) were also similar between the two centres (Table 1). The prevalence of impaired functional status by each of the four measures was low among controls, with sedentary lifestyle being the most prevalent. Since no major differences in other variables were observed, we combined data from the two centres for all analyses.

The separate Katz ADL items were each associated with venous thrombosis. The adjusted ORs for impairment of bathing, getting dressed, toilet use, eating, transferring in and out of bed (or chair) and the presence of urinary or bowel incontinence were respectively: 2.0 (CI95 1.2-3.2), 3.9 (CI95 1.9-8.2), 16.1 (CI95 2.1-124.9), 5.7 (CI95 0.6-51.1)

Table 1. Characteristics of control subjects by center

	Controls NL	Controls US
Number of Participants	306	125
Male sex (%)	147 (48)	62 (50)
Median Age (Range)	76 (70-94)	76 (70-96)
70-75 years (%)	126 (41)	49 (39)
75-80 years (%)	90 (29)	39 (31)
80-85 years (%)	61 (20)	24 (19)
>85 years (%)	29 (10)	13 (11)
Median BMI* (range)	26 (17-42)	27 (19-49)
Number of KATZ ADL disability		
0 (%)	253 (86.9)	117 (95.1)
1 (%)	38 (13)	6 (6)
2 (%)	8 (3)	2 (2)
≥ 3 (%)	6 (2)	0 (0)
Inability to walk outside 15 min (%)	23 (8)	9 (7)
Sedentary lifestyle (>20 h/24 h) (%)	138 (12)	18 (14)
Impaired hand grip strength (%)	25 (8)	19 (15)

NL= Netherlands, US= United States
* BMI = Body Mass Index kg.m-2;

13.9 (CI95 1.8-109.5), and 1.5 (CI95 1.0-2.3). In table 2, the associations of four functional impairment entities with venous thrombosis are presented. The risk of thrombosis increased 3-fold (OR 2.9; CI95 1.6-5.3) when two or more impairments were present on the ADL score compared with no impairments. Impairment of mobility was associated with a 3-fold (CI95 1.9-4.7) increased risk. The risk of thrombosis was up to 4-fold higher in individuals with a sedentary lifestyle defined as ≥20 hours of sitting/sleeping than in the group of ≤14 hours (OR 4.0; CI95 2.5-6.3). A gradually increasing risk of thrombosis was also found across tertiles of hours of sedentary time. Low handgrip strength was associated with a 2.3-fold (CI95 1.5-3.4) increased risk of thrombosis.

Functional impairment entities were associated with BMI in the control subjects. Impairment on the ADL score was lowest in the middle BMI group (1.7%) and 3.9% in the low, 4.3% in the high BMI group. Impairment of mobility was highest (10.6%) in the high BMI group. Impairment of mobility was present in 4.5% in the low BMI group, and 6.9% in the middle BMI group. A sedentary lifestyle was present in 17.2% in the low BMI group, 17.5% in the middle BMI group, and 29.0% in the high BMI group. There was no association between BMI and low hand grip strength (low: 13.5%, middle: 10.9%, high: 11.6%).

Additional adjustment for BMI did not alter the associations of any of the four functional impairment measures with thrombosis risk. Stratified analyses by BMI group for all four functional impairment entities showed that functional impairment was associated with thrombosis in each group. In the lowest BMI group, impairment of the ADL score was associated with a 1.9 fold (CI95 0.6-5.4) increased risk, in the middle BMI group and

the high BMI group, a risk of 5.9 (CI95 1.7-20.8) and 2.4 (CI95 0.7-8.1) was found. Corresponding ORs for impairment of mobility for the three BMI groups were 3.7 (CI95 1.5-9.1), 3.1 (CI95 1.5-6.5) and 2.2 (CI95 0.9-5.4). For a sedentary lifestyle these ORs were 3.7 (CI95 2.0-6.6), 3.6 (CI95 2.1-6.2) and 2.8 (CI95 0.9-3.3). A low handgrip strength increased the risk of thrombosis in the low BMI group 2.2 fold (CI95 1.0-4.5), 1.6 fold (CI95 0.8-3.3) in the middle group, and 2.9 (CI95 1.2-7.0) in the high BMI group.

Associations between the impairments and thrombosis risk were similarly present after adjustments for the presence of co-morbidities. (table 2) Functional impairment was associated with an increased risk of both DVT and PE. Presence of two or more im-

Table 2. Associations of functional impairment with venous thrombosis

Functional Impairment Type□	Cases	Controls	OR crude (CI95)	OR adj* (CI95)	OR adj** (CI95)	OR adj*** (CI95)
ADL disability						
0 vs ≥ 2 disabilities	50 (14.6)	16 (4.1)	4.0 (2.2-7.1)	2.9 (1.6-5.3)	2.9 (1.5-5.6)	2.7 (1.5-5.2)
Number of disabilities						
0 (%)	292 (84.1)	370 (89.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1 (%)	55 (15.9)	44 (10.6)	1.6 (1.0-2.4)	1.3 (0.8-2.0)	1.3 (0.8-2.1)	1.2 (0.7-1.9)
2 (%)	23 (7.3)	10 (2.6)	2.9 (1.4-6.2)	2.1 (1.0-4.7)	2.6 (1.1-6.1)	1.7 (0.7-3.9)
≥ 3 (%)	27 (8.5)	6 (1.6)	5.7 (2.3-14.0)	3.9 (1.5-9.8)	3.1(1.1-8.7)	3.9 (1.5-10.3)
Impairment of mobility						
Walk outside, not able (%)	78 (19.5)	32 (7.4)	3.0 (2.0-4.7)	3.0 (1.9-4.7)	2.9 (1.8-4.7)	2.8 (1.7-4.6)
Climbing stairs, not able (%)	72 (18.0)	29 (6.7)	3.0 (1.9-4.8)	2.4 (1.5-3.9)	2.2 (1.3-3.7)	2.1 (1.3-3.5)
Sedentary lifestyle						
20th percentile (≤14 h)	42 (10.6)	92 (23.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
80th percentile (≥20h)	173 (43.6)	90 (22.7)	4.2 (2.7-6.6)	4.0 (2.5-6.3)	4.4 (2.7-7.2)	4.0 (2.4-6.8)
Tertiles						
< 16 h	68 (17.4)	133 (31.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
16-18 h	115 (29.5)	156 (37.0)	1.4 (1.0-2.1)	1.4 (0.9-2.0)	1.3 (0.9-2.0)	1.3 (0.9-2.0)
>18 h	207 (53.1)	133 (31.5)	3.0 (2.1-4.4)	2.8 (1.9-4.1)	2.8 (1.9-4.1)	2.7 (1.8-4.0)
Low hand grip strength						
<15%	92 (23.2)	50 (11.6)	2.3 (1.6-3.3)	2.3 (1.5-3.4)	2.1 (1.4-3.2)	1.7 (1.1-2.6)
>15%	305 (76.8)	380 (88.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Tertiles						
<33%	222 (55.9)	161 (37.4)	2.1 (1.5-2.9)	2.2 (1.5-3.2)	2.0 (1.4-3.0)	2.1 (1.4-3.1)
33-66%	90 (22.7)	142 (33.0)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	1.6 (0.7-1.5)	1.0 (0.7-1.5)
> 66%	85 (21.4)	127 (29.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

*adj for age, sex and study center **adj for age, sex, study center and BMI ***adj for age, sex, study center and co-morbidities

□ ADL missing cases 4; missing control subjects 1; Impairment of mobility: missing cases 1 missing control subjects 1; Sedentary lifestyle: missing cases: 11 missing control subjects 9; Low handgrip strength: missing cases: 4 missing control subjects: 1

pairments on the ADL score was associated with a 3.8 fold (CI95 1.9-7.6), increased risk of DVT and of 2.3 fold (CI95 1.1-4.5) increased risk of PE. Impairment of mobility had an odds ratio for DVT of 3.2 (CI95 1.9-5.4), and of PE of 2.6 (CI95 1.6-4.4). Sedentary lifestyle increased the risk for both DVT and PE (OR DVT 2.6; CI95 1.8-3.9, OR PE 3.1; CI95 2.2-4.5). Unlike the other measures, low handgrip strength was mainly associated with DVT; OR 3.1 (CI95 1.8-5.3) for DVT and 1.7 (CI95 1.1-2.8) for PE. Of the 401 cases, 182 (45.4%) had a provoked venous thrombotic event. In general, the functional measures were more strongly associated with provoked events. For unprovoked thrombosis, two or more impairments on the ADL score was associated with a 1.8 fold (CI95 0.9-3.7) increased risk, impaired mobility was associated with an odds ratio of 2.4 (CI95 1.4-4.1), sedentary life style had an odds ratio of 1.7 (CI95 1.1-2.4), and low handgrip strength had an odds ratio of 1.8 (CI95 1.1-2.9). For the provoked events the odds ratio of thrombosis was 4.9 (CI95 2.3-8.7) when two or more impairments on the ADL score were present, while this was 3.6 (CI95 2.1-5.9) for impaired mobility, 5.4 (CI95 3.6-8.1) for sedentary lifestyle and 2.8 (CI95 1.7-4.7) for impaired handgrip strength.

Table 3 shows that the number of functional impairment entities was positively associated with risk of venous thrombosis. The prevalence of at least one functional impairment was 56.5% in the cases (221 of 391) and 28.7% the control subjects (121 of 422). Compared with those with no impairments, the OR of thrombosis increased from 3.0 (CI95 2.1-4.3) when one impairment was present, up to 25.1 (CI95 3.2-195.0) when four impairments were present.

Population attributable risk estimates the proportion of a disease attributable to a risk factor under the assumption of causality. The PARs for sedentary lifestyle, ADL disability, inability to walk outside for 15 minutes and low hand grip strength were 29%, 8%, 13% and 13%, respectively.

Table 3. Association of accumulation of functional impairments with venous thrombosis

Functional Impairment	Cases	Controls	OR crude (95%CI)	OR adj* (95%CI)	OR adj** (95%CI)	ORadj*** (95%CI)
n= 0	170 (43.5)	301 (71.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
n= 1	121 (30.9)	72 (17.1)	3.0 (2.1-4.2)	3.0 (2.1-4.3)	3.2 (2.2-4.6)	2.9 (2.0-4.3)
n= 2	50 (12.8)	34 (8.1)	2.6 (1.6-4.2)	2.8 (1.7-4.5)	2.8 (1.7-4.7)	2.4 (1.4-4.0)
n= 3	34 (8.7)	14 (3.3)	4.3 (2.2-8.2)	4.4 (2.2-8.6)	4.1 (2.0-8.3)	3.0 (1.5-6.3)
n= 4	16 (4.1)	1 (0.2)	28.3 (3.7-215.5)	25.1 (3.2-195.0)	18.8 (2.4-148.1)	22.9 (2.8-186.1)

*adj for age, sex and study center

**adj for age, sex, study center and BMI

***adj for age, sex, study center and co-morbidities

DISCUSSION

In a two-centre population-based study of people over age 70, comprising 401 patients with thrombosis and 431 control subjects, we showed that functional impairment defined as an impaired ADL, impaired mobility, sedentary life style, and low handgrip strength were associated with an increased risk of venous thrombosis. These four manifestations of functional impairment each were associated with a 2- to 4-fold increased risk of thrombosis. Further, an increasing number of functional impairments was also associated with risk of thrombosis. The overall relative contribution of each functional impairment entity to the thrombotic risk, based on the PAR, varied from 8% to 29%. Furthermore, all functional impairment entities were also associated with unprovoked thrombosis, which suggests that the associations were not explained by the provoking factors for venous thrombosis. The associations of functional impairment with venous thrombosis were also present in the provoked thrombosis group, indicating that when other major risk factors are present in this older age group, functional impairment is also important.

Our findings are in line with previous reports that showed that functional impairment is associated with the risk of thrombosis. A cross-sectional analysis of older in-hospital patients illustrated that a decreased Katz ADL score was associated with 2-fold increased risk of asymptomatic thrombosis. [15] Furthermore, Folsom et al reported a 1.5- to 2-fold increased risk of future thrombosis with frailty, also a measure of functional status, in those 65 years and older. [16] Having a sedentary lifestyle or transient immobility have been previously reported as risk factors in both young and older populations. [7,17,18] In this study, the number of functional impairment markers was positively associated with the risk of venous thrombosis, indicating that impairment on several aspects, which likely reflects the severity, influences the risk of thrombosis.

Various causal mechanisms regarding the association of impaired functional status and venous thrombosis can be hypothesised. [16,19] Biological age is related with the functional status of an individual. [20] Age-related alterations of the venous vessel wall are postulated to provoke thrombus formation. [21,22] Low hand grip strength reflects loss of overall muscle mass and strength. A decline of leg muscle strength, and specifically calf muscles could result into stasis of the blood flow in the legs, and subsequently venous hypertension could induce a pro-thrombotic environment. [6] Furthermore, functional impairment with ageing is associated with inflammation and procoagulation. [23,24] Thrombosis might occur more easily in older, impaired individuals due to deregulation of the blood coagulation system by increased inflammation and higher levels of D-dimer, factor VIII and von Willebrand factor [25], all of which are related to risk of venous thrombosis. [16,26]

Strengths and limitations of this study require discussion. We performed home-visits, thereby allowing functionally impaired individuals to participate. This resulted in a high participation rate and minimised selection bias. [7] However, we cannot completely rule out that participation was related to the presence of functional impairment which would, if different in cases and controls, lead to biased estimates. If at all present, this would most likely have affected controls, with those with impairments participating less readily than those with. If this bias was present, the reported risks are an overestimation. Recall bias may have been present for the self-reported measures, but not for the handgrip assessment. Handgrip strength could have been influenced by conditions associated with the venous thrombosis event, such as recent hospitalisation or surgery, but presence of associations in both unprovoked and provoked thrombosis suggests a minimal impact on interpretation of results. Despite the use of standardised questionnaires for both the cases and control subjects, we cannot rule out differential recall of functional status by case control status.

Functional impairment may be the result of disorders affecting the risk of thrombosis, leading to confounding. However, the risk of thrombosis remained clearly elevated also after adjustment for several diseases, such as myocardial infarction and pulmonary disorders. BMI was not a confounder in the association of functional impairment and venous thrombosis, although weight loss is seen as an important marker of functional status [3], and higher BMI is a risk factor of thrombosis in the middle aged population.

In conclusion, functional impairment is a risk factor for venous thrombosis in older people and the contribution of functional impairment to the overall incidence of venous thrombosis is high. The risk of thrombosis is increased in older individuals with functional impairments, also when other major risk factors are present. Moreover, accumulation of multiple functional impairments signified substantial risk. Our findings have important implications for awareness of venous thrombosis risk by providers caring for older people.

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