

Supplementary Online Content

Chang S-L, Huang Y-L, Lee M-C, et al. Association of varicose veins with incident venous thromboembolism and peripheral artery disease. *JAMA*. doi:10.1001/jama.2018.0246

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Methods

Data Source

The NHI program is a single-payer system with mandatory enrollment, providing comprehensive coverage to all residents of Taiwan. Of the NHI beneficiaries, 98% are Taiwanese residents, who are predominately ethnic Chinese. A computerized database was created from the claims data, comprising registry files of the beneficiaries, hospital admissions, ambulatory care and emergency room visits.

Validation of a diagnosis of varicose veins

We requested outpatient medical records with ICD-9-CM codes 454.xx in any one of the three outpatient diagnosis code fields between 2000 and 2014 from three branches of Chang-Gung Memorial Hospital. Medical records for a random sample of 239 patients were obtained and reviewed by a dermatologist as part of this external validation. Diagnosis codes were validated using the CEAP classification, a duplex ultrasound examination report, or an operation or treatment report. Of the 239 patients, 39 were excluded due to incomplete or unidentifiable medical records. The validation criterion was met in 196 of the 200 remaining patients. Thus in our validation cohort, code 454 in outpatient records had a positive predictive value of 98%. Among the 196 patients with varicose veins, 12 were classified as C1 (telangiectasias or reticular veins, 6.1%), 81 as C2 (varicose veins, 41.3%), 32 as C3 (edema, 16.3%), 45 as C4 (pigmentation, eczema, lipodermatosclerosis, or atrophie blanche, 22.9%), four as C5 (healed venous ulcer, 2.0%), and 16 as C6 (active venous ulcer, 8.2%). Six patients (3.1%) could not be classified due to insufficient information in their medical records; however, the duplex ultrasound reports and/or operation records confirmed their diagnosis of varicose veins.

Analysis of the potential effect of unmeasured confounders

We used the methods of Greenland et al.¹ to perform the external adjustment for smoking and estimate the strength of the association between smoking and varicose veins that is required to remove most of the observed associations with DVT, PE and PAD.

A previous meta-analysis revealed that the relative risk in association with current smoking was 1.39 for DVT and 1.38 for PE.² Another meta-analyses showed that the odds ratio (relative risks were treated as equivalent to odds ratio) of PAD associated with current smoking was 3.08 in general populations.³ The prevalence of smoking in control group was estimated to be 21.1%, which was inferred from previous studies of general adult population in Taiwan.⁴ In patients with varicose veins, we used hypothesized values with smoking prevalence of 30%, 50%, and 70%, corresponding to an

odds ratio of 1.60, 3.74 and 8.73 for the association between smoking and varicose veins.

Hypothetical scenarios with a relative risk of 5 for the associations of smoking with DVT, PE and PAD were also used in the sensitivity analyses.

Results

Taking the smoking prevalence of 30% in varicose veins group, the RRs were 5.15 for DVT, 1.68 for PE, and 1.53 for PAD after external adjustment for smoking; taking a smoking prevalence of 70% in the varicose veins group, the adjusted RRs were 4.52 for DVT, 1.48 for PE, and 1.01 for PAD. In the sensitivity analyses, we used a hypothetical scenario with a RR of 5 for the associations between smoking and DVT, PE and PAD. Taking smoking prevalence of 30% in varicose veins group, the externally smoking-adjusted RRs were 4.45 for DVT, 1.45 for PE, and 1.45 for PAD. When taking smoking prevalence of 50% in the varicose veins group, the adjusted RRs were 3.26 for DVT, 1.06 for PE, and 1.06 for PAD. When taking the smoking prevalence of 70% in the varicose veins group, the adjusted RR reduced substantially to 2.58 for DVT, 0.84 for PE, and 0.84 for PAD.

References

1. Greenland S, Lash TL. Analysis of unmeasured confounders – external adjustment, in *Modern Epidemiology*, 3rd ed. Edited by Rothman KJ, Greenland S, Lash TL. Philadelphia, Lippincott Williams & Wilkins, 2008, pp 348–351.
2. Cheng YJ, Liu ZH, Yao FJ, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Med*. 2013;10(9):e1001515.
3. Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. *Heart*. 2014;100(5):414-23.
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eTable 1. Diagnosis codes

Name	ICD-9-CM code
Deep vein thrombosis	451.1 Phlebitis & thrombophlebitis of deep veins of lower extremities
	451.11 Phlebitis & thrombophlebitis, of deep veins lower extremities, femoral vein
	451.19 Phlebitis & thrombophlebitis, of deep veins of lower extremities, other
	451.2 Phlebitis & thrombophlebitis, of lower extremities, unspecified
	451.81 Phlebitis & thrombophlebitis, of other sites, iliac vein
	451.89 Phlebitis & thrombophlebitis of other sites
	451.9 Phlebitis & thrombophlebitis, of unspecified site
	Deep vein thrombosis, not of upper extremity:
	453.2 Other venous embolism & thrombosis, of vena cava
	453.4 Acute venous embolism & thrombosis of deep vessels of lower extremity
	453.41 Venous embolism & thrombosis of deep vessels of proximal lower extremity
	453.42 Venous embolism & thrombosis of deep vessels of distal lower extremity
	453.8 Other venous embolism & thrombosis, of other specified veins
	453.89 Acute venous embolism & thrombosis of other specified veins
	453.9 Other venous embolism & thrombosis, of unspecified site
	Pulmonary embolism
415.12 Septic pulmonary embolism	
415.19 Other	
Peripheral artery disease	440.0x Atherosclerosis of aorta
	440.2x Atherosclerosis of native arteries of the extremities
	440.8x Atherosclerosis of other specified arteries
	440.9x Generalized and unspecified atherosclerosis

	443.9x Peripheral vascular disease, unspecified
	444.0x Arterial embolism and thrombosis of abdominal aorta
	444.2x Arterial embolism and thrombosis of arteries of the extremities
	444.8x Arterial embolism and thrombosis of other specified artery
	447.8x Other specified disorders of arteries and arterioles
	447.9x Unspecified disorders of arteries and arterioles
Hypertension	401.xx-405.xx
Diabetes	250.xx
Chronic obstructive pulmonary disease	490.xx, 491.xx, 492.xx, 493.xx, 494.xx, 495.xx, 496.xx
Hyperlipidemia	272.xx
Malignancy	140.xx-208.xx
Atrial fibrillation	427.31
Heart failure	428.xx
Ischemic heart disease	410.xx-414.xx
Chronic renal insufficiency	403.xx, 404.xx, 582.xx, 585.xx-588.xx
Stroke	434.0x-434.9x, 436.xx, 430.xx-432.9x

Abbreviation: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

eTable 2. Associations between varicose veins and subsequent risk of deep vein thrombosis, pulmonary embolism and peripheral artery disease by duration of follow-up

Duration of follow-up, years	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
Deep vein thrombosis											
All	212984	10360	1581446	6.55 (6.42-6.68)	851936	6942	6440345	1.08 (1.05-1.10)	5.47(5.34-5.60)	6.06 (5.88-6.25)	5.39 (5.22-5.56)
>1	208648	6060	1371818	4.42 (4.31-4.53)	847026	5488	5591184	0.98 (0.96-1.01)	3.44(3.33-3.55)	4.50 (4.34-4.67)	3.99 (3.84-4.14)
>2	190590	4941	1172684	4.21 (4.10-4.33)	774771	4558	4782143	0.95 (0.93-0.98)	3.26(3.14-3.38)	4.42 (4.25-4.60)	3.92 (3.76-3.38)
>5	144383	2585	672578	3.84 (3.70-3.99)	588693	2469	2746103	0.90 (0.86-0.93)	2.94(2.79-3.09)	4.28 (4.05-4.52)	3.82 (3.61-4.04)
Pulmonary embolism											
All	212984	793	1639174	0.48 (0.45-0.52)	851936	1521	6469344	0.24 (0.22-0.25)	0.24(0.20-0.28)	2.06 (1.89-2.24)	1.75 (1.60-1.91)
>1	212785	631	1426296	0.44 (0.41-0.48)	848237	1278	5619429	0.23 (0.21-0.24)	0.21(0.17-0.25)	1.95 (1.77-2.14)	1.68 (1.52-1.85)
>2	195394	545	1222657	0.45 (0.41-0.48)	776640	1108	4808825	0.2 (0.22-0.2)	0.22(0.18-0.26)	1.93 (1.75-2.14)	1.6 (1.52-1.87)

eTable 2. Associations between varicose veins and subsequent risk of deep vein thrombosis, pulmonary embolism and peripheral artery disease by duration of follow-up

Duration of follow-up, years	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
>5	149935	326	706675	0.46 (0.41-0.51)	591566	619	2765458	0.2 (0.21-0.24)	0.24(0.19-0.29)	2.06 (1.80-2.36)	1.8 (1.60-2.10)
Peripheral artery disease											
All	212984	16615	1547861	10.7 (10.57-10.39)	851936	32725	6296328	5.2 (5.14-5.20)	5.53(5.36-5.70)	2.06 (2.02-2.10)	1.7 (1.72-1.79)
>1	208119	11784	1338123	8.81 (8.65-8.97)	840180	24425	5451739	4.4 (4.42-4.58)	4.33(4.16-4.50)	1.96 (1.92-2.01)	1.6 (1.66-1.73)
>2	189028	9620	1140068	8.44 (8.27-8.61)	765158	20097	4650998	4.3 (4.26-4.32)	4.12(3.94-4.30)	1.95 (1.91-2.00)	1.6 (1.65-1.74)
>5	141003	4888	647852	7.54 (7.33-7.76)	574547	10534	2651990	3.9 (3.90-4.07)	3.57(3.35-3.79)	1.90 (1.84-1.96)	1.6 (1.62-1.73)

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

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^eModels were adjusted for sex, age, index year, and comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, heart failure, ischemic heart disease, stroke, and chronic renal insufficiency, and the number of outpatient visits in the year before the index date.

eTable 3. Incidence rates and hazard ratios for deep vein thrombosis in patients with varicose veins vs. propensity score-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on propensity score				Absolute risk difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		
Overall	212984	10360	1581446	6.55 (6.43-6.68)	212984	1980	1605243	1.23 (1.18-1.29)	5.32 (5.18-5.46)	5.30 (5.05-5.56)
Sex ^c										
Men	65341	3998	486377	8.22 (7.97-8.48)	63352	651	489104	1.33 (1.23-1.44)	6.89 (6.62-7.16)	6.11 (5.63-6.64)
Women	147643	6362	1095069	5.81 (5.67-5.95)	149632	1329	1116139	1.19 (1.13-1.26)	4.62 (4.46-4.78)	4.88 (4.60-5.18)
Age at diagnosis ^d , years										
20-34	26797	521	199083	2.62 (2.40-2.85)	26810	37	200667	0.18 (0.13-0.25)	2.44 (2.21-2.67)	14.17 (10.15-19.78)
35-44	32457	977	251769	3.88 (3.64-4.13)	32235	124	252207	0.49 (0.41-0.59)	3.39 (3.13-3.65)	7.88 (6.54-9.50)
45-54	47791	2079	360883	5.76 (5.52-6.01)	48054	271	367497	0.74 (0.65-0.83)	5.02 (4.76-5.28)	7.80 (6.87-8.85)
55-64	43720	2473	310383	7.97 (7.66-8.29)	44711	454	322251	1.41 (1.28-1.54)	6.56 (6.22-6.90)	5.64 (5.11-6.24)
65-74	36714	2514	276120	9.10 (8.75-9.47)	37901	670	289656	2.31 (2.14-2.50)	6.79 (6.39-7.19)	3.93 (3.61-4.28)
≥75	25505	1796	183208	9.80 (9.35-10.27)	23273	424	172964	2.45 (2.22-2.70)	7.35 (6.84-7.86)	3.96 (3.56-4.40)

Abbreviations: CI, confidence interval; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cInteraction between sex and varicose veins, p<0.001

^dInteraction between age and varicose veins, p<0.001

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eTable 4. Incidence rates and hazard ratios for deep vein thrombosis in patients with varicose veins vs. propensity score-matched controls presented overall and by sex and age at diagnosis of varicose veins in analysis restricted to a length of follow-up of at least one year

	Patients with varicose veins				Control group matched on propensity score				Absolute risk difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		
Overall	208648	6060	1371818	4.42 (4.31-4.53)	211403	1545	1393182	1.11 (1.05-1.17)	3.31(3.19-3.43)	3.98(3.77-4.21)
Sex ^c										
Men	63594	2263	422405	5.36 (5.14-5.58)	62920	495	488923	1.16 (1.06-1.27)	4.20(3.96-4.44)	4.60(4.17-5.70)
Women	145054	3797	949413	4.00 (3.87-4.13)	148483	1050	1115662	1.09 (1.02-1.15)	2.91(2.77-3.05)	3.69(3.44-3.95)
Age at diagnosis ^d , years										
20-34	26546	274	172476	1.59 (1.41-1.79)	26760	31	173884	0.18 (0.12-0.25)	1.41 (1.21-1.61)	8.91(6.15-12.92)
35-44	32032	556	219646	2.53 (2.33-2.75)	32093	101	220055	0.46 (0.37-0.56)	2.07 (1.85-2.29)	5.52(4.46-6.82)
45-54	46943	1239	313760	3.95 (3.73-4.18)	47745	221	319627	0.69 (0.60-0.79)	3.26 (3.03-3.49)	5.71(4.95-6.59)
55-64	42681	1441	267474	5.39 (5.11-5.67)	44319	348	277770	1.25 (1.12-1.39)	4.14 (3.84-4.44)	4.30(3.83-4.83)
65-74	35739	1548	240150	6.45 (6.13-6.78)	37463	533	251999	2.12 (1.94-2.30)	4.33 (3.97-4.69)	3.05(2.76-3.36)
≥75	24707	1002	158311	6.33 (5.94-6.73)	23023	311	149848	2.08 (1.85-2.32)	4.25 (3.81-4.69)	3.04(2.67-3.45)

Abbreviations: CI, confidence interval; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cInteraction between sex and varicose veins, p<0.001

^dInteraction between age and varicose veins, p<0.001

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eTable 5. Incidence rates and hazard ratios for pulmonary embolism in patients with varicose veins vs. propensity score-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on propensity score				Absolute risk difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		
Overall	212984	793	1639174	0.48 (0.45-0.52)	212984	451	1613354	0.28 (0.25-0.31)	0.20(0.16-0.24)	1.73 (1.54-1.94)
Sex ^c										
Men	65341	298	509210	0.59 (0.52-0.66)	63352	155	491919	0.32 (0.27-0.37)	0.27(0.19-0.35)	1.86 (1.53-2.26)
Women	147643	495	1129961	0.44 (0.40-0.48)	149632	296	1121435	0.26 (0.23-0.30)	0.18(0.13-0.23)	1.66 (1.44-1.92)
Age at diagnosis ^d , years										
20-34	26797	18	202145	0.09 (0.05-0.14)	26810	7	200774	0.03 (0.01-0.07)	0.06(0.01-0.11)	2.56 (1.07-6.12)
35-44	32457	49	257551	0.19 (0.14-0.25)	32235	20	252721	0.08 (0.05-0.12)	0.11(0.05-0.17)	2.40 (1.43-4.04)
45-54	47791	107	372794	0.29 (0.24-0.35)	48054	59	368539	0.16 (0.12-0.21)	0.13(0.06-0.20)	1.79 (1.31-2.47)
55-64	43720	153	324057	0.47 (0.40-0.55)	44711	96	324196	0.30 (0.24-0.36)	0.17(0.07-0.27)	1.59 (1.23-2.05)
65-74	36714	258	289906	0.89 (0.78-1.01)	37901	151	292525	0.52 (0.44-0.61)	0.37(0.23-0.51)	1.72 (1.41-2.11)
≥75	25505	208	192721	1.08 (0.94-1.24)	23273	118	174599	0.68 (0.56-0.81)	0.40(0.21-0.59)	1.60 (1.27-2.00)

Abbreviations: CI, confidence interval; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cInteraction between sex and varicose veins, p=0.36

^dInteraction between age and varicose veins, p=0.62

eTable 6. Incidence rates and hazard ratios for deep vein thrombosis in patients with varicose veins vs. age-, sex-, calendar year-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
Overall	212984	10360	1581446	6.55 (6.42-6.68)	851936	6942	6440345	1.08 (1.05-1.10)	5.47(5.34-5.60)	6.06 (5.88-6.25)	5.39 (5.22-5.56)
Sex ^d											
Men	65341	3998	486377	8.22 (7.97-8.47)	261364	2137	2011187	1.06 (1.02-1.11)	7.16(6.90-7.42)	7.68 (7.29-8.10)	6.50 (6.16-6.86)
Women	147643	6362	1095069	5.81 (5.67-5.95)	590572	4805	4429158	1.08 (1.05-1.12)	4.73(4.58-4.88)	5.35 (5.15-5.55)	4.88 (4.70-5.07)
Age at diagnosis ^e , years											
20-34	26797	521	199083	2.62 (2.39-2.84)	10704	150	803266	0.19 (0.16-0.22)	2.43(2.20-2.66)	13.93 (11.66-16.77)	12.86 (10.67-15.49)
35-44	32457	977	251769	3.88 (3.64-4.12)	129983	391	1018306	0.38 (0.35-0.42)	3.50(3.25-3.75)	10.09 (8.98-11.35)	8.86 (7.85-9.99)
45-54	47791	2079	360883	5.76 (5.51-6.01)	191572	1016	1469880	0.69 (0.65-0.73)	5.07(4.82-5.32)	8.32 (7.71-8.96)	7.55 (6.99-8.15)
55-64	43720	2473	310383	7.97 (7.65-8.28)	174503	1659	1259519	1.32 (1.25-1.38)	6.65(6.33-6.97)	6.04 (5.67-6.43)	5.63 (5.29-6.00)
65-74	36714	2514	276120	9.10 (8.75-9.46)	146616	2304	1128854	2.04 (1.96-2.12)	7.06(6.69-7.43)	4.45 (4.20-4.70)	4.06 (3.83-4.30)
≥75	25505	1796	183208	9.80 (9.35-10.26)	102188	1422	760519	1.87 (1.77-1.97)	7.93(7.47-8.39)	5.20 (4.85-5.57)	4.09 (3.80-4.39)

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cModels were adjusted for sex, age, index year, and comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, heart failure, ischemic heart disease, stroke, and chronic renal insufficiency, and the number of outpatient visits in the year before the index date.

^dInteraction between sex and varicose veins, p<0.001

^eInteraction between age and varicose veins, p<0.001

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eTable 7. Incidence rates and hazard ratios for deep vein thrombosis in patients with varicose veins vs. age-, sex-, calendar year-matched controls presented overall and by sex and age at diagnosis of varicose veins in analysis restricted to a length of follow-up of at least one year

	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
Overall	208648	6060	1371818	4.42 (4.31-4.53)	847026	5488	5591184	0.98 (0.96-1.01)	3.44(3.33-3.55)	4.50 (4.34-4.67)	3.99 (3.84-4.14)
Sex ^d											
Men	63594	2263	422405	5.36 (5.14-5.58)	260125	1669	1750514	0.95 (0.91-1.00)	4.41(4.18-4.64)	5.61 (5.26-5.97)	4.71 (4.42-5.03)
Women	145054	3797	949413	4.00 (3.87-4.13)	586901	3819	3840669	0.99 (0.96-1.03)	3.01(2.88-3.14)	4.02 (3.85-4.21)	3.66 (3.49-3.83)
Age at diagnosis ^e , years											
20-34	26546	274	172476	1.59 (1.40-1.78)	106918	127	696268	0.18 (0.15-0.21)	1.41(1.22-1.60)	8.71 (7.08-10.75)	7.92 (6.37-9.84)
35-44	32032	556	219646	2.53 (2.32-2.74)	129549	328	888568	0.37 (0.33-0.41)	2.16(1.95-2.37)	6.86 (5.98-7.86)	6.03 (5.24-6.94)
45-54	46943	1239	313760	3.95 (3.73-4.17)	190589	845	1278859	0.66 (0.62-0.71)	3.29(3.07-3.51)	5.98 (5.48-6.52)	5.43 (4.96-5.94)
55-64	42681	1441	267474	5.39 (5.11-5.67)	173249	1343	1085730	1.24 (1.17-1.30)	4.15(3.86-4.44)	4.36 (4.04-4.69)	4.07 (3.78-4.39)
65-74	35739	1548	240150	6.45 (6.12-6.77)	145275	1806	982998	1.84 (1.75-1.92)	4.61(4.28-4.94)	3.51 (3.28-3.75)	3.18 (2.97-3.41)
≥75	24707	1002	158311	6.33 (5.94-6.72)	101446	1039	658761	1.58 (1.48-1.67)	4.75(4.35-5.15)	4.00 (3.67-4.36)	3.13 (2.86-3.42)

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cModels were adjusted for sex, age, index year, and comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, heart failure, ischemic heart disease, stroke, and chronic renal insufficiency, and the number of outpatient visits in the year before the index date.

^dInteraction between sex and varicose veins, p<0.001

^eInteraction between age and varicose veins, p<0.001

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eTable 8. Incidence rates and hazard ratios for pulmonary embolism in patients with varicose veins vs. age-, sex-, calendar year-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
Overall	212984	793	1639174	0.48 (0.45-0.52)	851936	1521	6469344	0.24 (0.22-0.25)	0.24(0.20-0.28)	2.06 (1.89-2.24)	1.75 (1.60-1.91)
Sex ^d											
Men	65341	298	509210	0.59 (0.52-0.65)	261364	527	2020381	0.26 (0.24-0.28)	0.33(0.26-0.40)	2.25 (1.95-2.59)	1.79 (1.55-2.07)
Women	147643	495	1129964	0.44 (0.40-0.48)	590572	994	4448963	0.22 (0.21-0.24)	0.22(0.18-0.26)	1.96 (1.76-2.18)	1.73 (1.55-1.93)
Age at diagnosis ^e , years											
20-34	26797	18	202145	0.09 (0.05-0.13)	10704	28	803816	0.03 (0.02-0.05)	0.06 (0.02-0.10)	2.56 (1.41-4.62)	2.45 (1.33-4.54)
35-44	32457	49	257551	0.19 (0.14-0.24)	129983	74	1019936	0.07 (0.06-0.09)	0.12 (0.06-0.18)	2.62 (1.83-3.76)	2.17 (1.49-3.14)
45-54	47791	107	372794	0.29 (0.23-0.34)	191572	176	1474229	0.12 (0.10-0.14)	0.17 (0.11-0.23)	2.41 (1.89-3.06)	2.13 (1.67-2.72)
55-64	43720	153	324057	0.47 (0.40-0.55)	174503	320	1266495	0.25 (0.22-0.28)	0.22 (0.14-0.30)	1.87 (1.54-2.26)	1.65 (1.36-2.00)
65-74	36714	258	289906	0.89 (0.78-1.00)	146616	520	1138764	0.46 (0.42-0.50)	0.43 (0.31-0.55)	1.95 (1.68-2.26)	1.75 (1.51-2.04)
≥75	25505	208	192721	1.08 (0.93-1.23)	102188	403	766104	0.53 (0.47-0.58)	0.55 (0.39-0.71)	2.05 (1.74-2.43)	1.60 (1.35-1.90)

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cModels were adjusted for sex, age, index year, and comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, heart failure, ischemic heart disease, stroke, and chronic renal insufficiency, and the number of outpatient visits in the year before the index date.

^dInteraction between sex and varicose veins, p=0.14

^eInteraction between age and varicose veins, p=0.38

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eTable 9. Incidence rates and hazard ratios for peripheral artery disease in patients with varicose veins vs. propensity score-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on propensity score				Absolute risk difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}		
Overall	212984	16615	1547861	10.73 (10.57-10.90)	212984	9709	1561421	6.22 (6.09-6.34)	4.51(4.31-4.71)	1.7 2 (1.68-1.77)
Sex ^c										
Men	65341	6767	470235	14.39 (14.05-14.74)	63352	3511	472271	7.43 (7.19-7.68)	6.96(6.54-7.38)	1.9 2 (1.84-2.00)
Women	147643	9848	1077626	9.14 (8.96-9.32)	149632	6198	1089150	5.69 (5.55-5.83)	3.45(3.22-3.68)	1.6 1 (1.56-1.66)
Age at diagnosis ^d , years										
20-34	26797	359	200197	1.79 (1.61-1.99)	26810	119	200188	0.59 (0.49-0.71)	1.20(0.99-1.41)	3.0 2 (2.45-3.71)
35-44	32457	1051	251975	4.17 (3.92-4.43)	32235	479	250350	1.91 (1.75-2.09)	2.26(1.96-2.56)	2.1 8 (1.96-2.43)
45-54	47791	2703	358523	7.54 (7.26-7.83)	48054	1504	360713	4.17 (3.96-4.39)	3.37(3.02-3.72)	1.8 1 (1.70-1.93)
55-64	43720	3878	303552	12.78 (12.38-13.18)	44711	2410	311424	7.74 (7.43-8.05)	5.04(4.53-5.55)	1.6 (1.57-1.74)

65-74	36714	4815	262792	18.32 (17.81-18.85)	37901	3087	275820	11.19 (10.80-11.59)	7.13(6.48-7.78)	1.6 3	5 (1.56-1.71)
≥75	25505	3809	170821	22.30 (21.60-23.02)	23273	2110	162925	12.95 (12.40-13.52)	9.35(8.45-10.25)	1.7 0	(1.61-1.79)

Abbreviations: CI, confidence interval; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

^cInteraction between sex and varicose veins, p<0.001

^dInteraction between age and varicose veins, p<0.001

eTable 10. Incidence rates and hazard ratios for peripheral artery disease in patients with varicose veins vs. age-, sex-, calendar year-matched controls presented overall and by sex and age at diagnosis of varicose veins

	Patients with varicose veins				Control group matched on age, sex and calendar year				Absolute risk difference (95% CI) per 1000 person-years	Patients with varicose veins vs. control group	
	(n=212984)				(n=851936)					Unadjusted HR (95%CI)	Adjusted ^c HR (95%CI)
	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}	No. of patients	No. of cases	Number of PY	Incidence (95% CI) ^{a,b}			
Overall	212984	16615	1547861	10.73 (10.57-10.90)	851936	32725	6296328	5.20 (5.14-5.25)	5.53(5.36-5.70)	2.06 (2.02-2.10)	1.76 (1.72-1.79)
Sex ^d											
Men	65341	6767	470235	14.39 (14.05-14.73)	261364	11361	1958174	5.80 (5.70-5.91)	8.59(8.23-8.95)	2.46 (2.39-2.54)	1.95 (1.89-2.01)
Women	147643	9848	1077626	9.14 (8.96-9.32)	590572	21364	4338154	4.92 (4.86-4.99)	4.22(4.03-4.41)	1.85 (1.81-1.90)	1.64 (1.60-1.68)
Age at diagnosis ^e , years											
20-34	26797	359	200197	1.79 (1.61-1.98)	10704	408	802029	0.51 (0.46-0.56)	1.28(1.09-1.47)	3.52 (3.06-4.06)	2.90 (2.51-3.56)
35-44	32457	1051	251975	4.17 (3.92-4.42)	129983	1448	1013074	1.43 (1.36-1.50)	2.74(2.48-3.00)	2.92 (2.70-3.16)	2.41 (2.23-2.62)
45-54	47791	2703	358523	7.54 (7.26-7.82)	191572	5142	1448043	3.55 (3.45-3.65)	3.99(3.69-4.29)	2.12 (2.03-2.22)	1.84 (1.76-1.93)
55-64	43720	3878	303552	12.78 (12.37-13.18)	174503	8334	1223119	6.81 (6.67-6.96)	5.97(5.54-6.40)	1.87 (1.80-1.95)	1.69 (1.63-1.76)
65-74	36714	4815	262792	18.32 (17.80-18.84)	146616	10629	1080741	9.83 (9.65-10.02)	8.49(7.94-9.04)	1.85 (1.79-1.92)	1.66 (1.60-1.72)
≥75	25505	3809	170821	22.30 (21.59-23.01)	102188	6764	729322	9.27 (9.05-9.50)	13.03(12.29-13.77)	2.36 (2.27-2.45)	1.78 (1.71-1.85)

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

^aper 1,000 person-years

^bExact confidence intervals for Poisson distribution

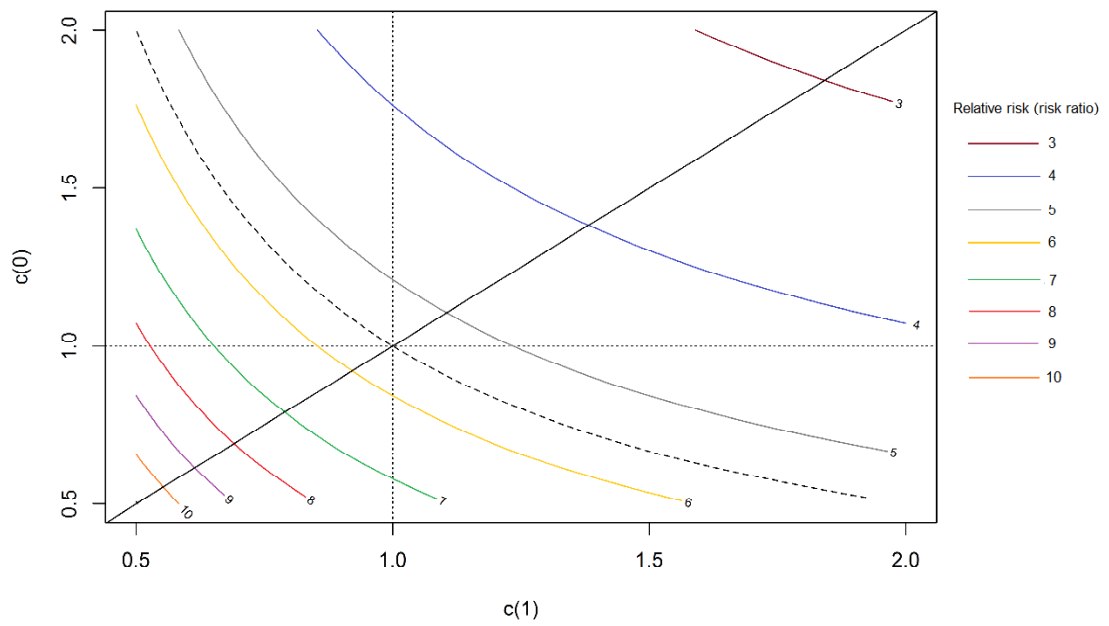
^cModels were adjusted for sex, age, index year, and comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, heart failure, ischemic heart disease, stroke, and chronic renal insufficiency, and the number of outpatient visits in the year before the index date.

^dInteraction between sex and varicose veins, p<0.001

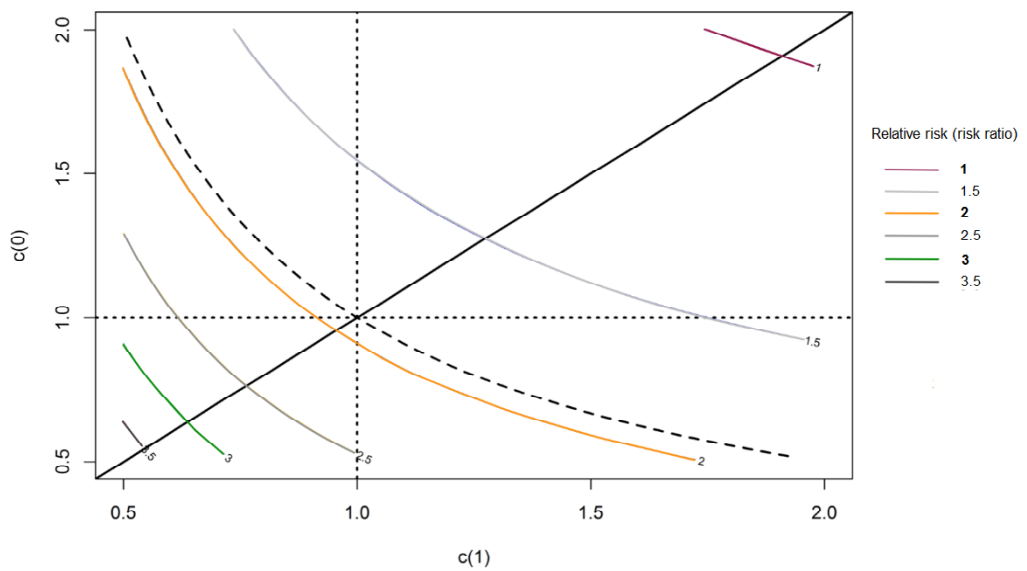
^eInteraction between age and varicose veins, p<0.001

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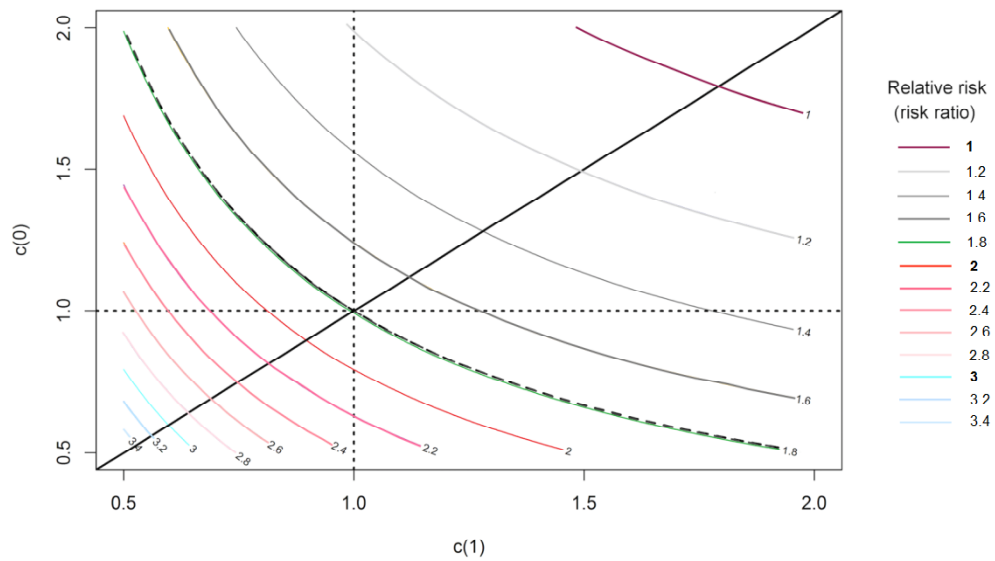
(a) Deep vein thrombosis (DVT)



(b) Pulmonary embolism (PE)



(c) peripheral artery disease (PAD)



eFigure. Sensitivity analysis for the relative risk (RR) of DVT, PE and PAD calculated using inverse probability of treatment weighting (IPTW). The marginal RRs obtained from IPTW were corrected for various values of confounding functions, $c(0)$ and $c(1)$. These parameters are counterfactual, where $c(1)$ represents a hypothetical RR of the outcome (DVT, PE, or PAD) comparing those who actually did or did not have varicose veins, but assuming all had varicose veins. The values of $c(0)$ and $c(1)$ were then varied to estimate the effect of unmeasured confounding required to give an adjusted RR. For example, $c(0)=c(1)$ denotes the assumption that there were no unmeasured effect modifiers, and $c(0)>1$ and $c(1)>1$ implies that the exposed participants would have had a greater risk of the potential outcome than unexposed participants, had they had the same exposure status. The solid straight line indicates $c(0)=c(1)$. When $c(0)=c(1)=1$, the relative risk unadjusted for unmeasured confounding is (a) 5.52 for deep vein thrombosis; (b) 1.91 for pulmonary embolism, and (3) 1.79 for peripheral artery disease. The dashed curve indicates the value of $c(0)$ and (1) required to give a relative risk of (a) 5.52 for deep vein thrombosis; (b) 1.91 for pulmonary embolism, and (3) 1.79 for peripheral artery disease.