Venous thromboembolism associated with severe dyspnoea and asthma in 102 792 adults

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Individuals with venous thromboembolism have increased risks of severe dyspnoea and asthma, and may account for 3.5% and 3.0% of people with severe dyspnoea and asthma in the general population, respectively https://bit.ly/48pt7nV

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Abstract

Background The most recent guideline on acute pulmonary embolism (PE) indicates possible long-term sequelae such as dyspnoea and chronic thromboembolic pulmonary hypertension after a PE event. However, effects on lung function or asthma risk have not been evaluated in the general population.

Methods We tested whether individuals with a venous thromboembolism (VTE) encompassing PE and deep vein thrombosis (DVT) have reduced lung function, or greater risks of dyspnoea and asthma using data from 102 792 adults from the Copenhagen General Population Study. Diagnoses of PE, DVT and asthma were collected from the national Danish Patient Registry. Factor V Leiden and prothrombin G20210A gene variants were determined using TaqMan assays.

Results Prevalences of PE, DVT and VTE were 2.2%, 3.6% and 5.2%, respectively. Individuals with VTE had forced expiratory volume in 1 s of 92% predicted compared with 96% pred in individuals without VTE ($p<0.001$). Individuals with VTE *versus* those without had adjusted OR (95% CI) for light, moderate and severe dyspnoea of 1.4 (1.2–1.6), 1.6 (1.4–1.8) and 1.7 (1.5–1.9), respectively. Individuals with VTE *versus* those without had an adjusted OR for asthma of 1.6 (95% CI 1.4–1.8). Factor V Leiden and prothrombin G20210A genotype also associated with increased risk of asthma (p for trend=0.002). Population-attributable fractions of severe dyspnoea and asthma due to VTE were 3.5% and 3.0%, respectively, in the population.

Conclusion Individuals with VTE have worse lung function and higher risks of severe dyspnoea and asthma, and may account for 3.5% and 3.0% of people with severe dyspnoea and asthma, respectively, in the general population.

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with increased mortality within the first 30 days after an event, especially after an acute PE [1]. VTE can generally be viewed as a clinical continuum of DVT, thrombus in transit, acute PE and long-term sequelae [2]. The best known long-term complications after a PE include dyspnoea and chronic thromboembolic pulmonary hypertension (CTEPH) [3, 4], but other less known long-term sequelae are also seen, *e.g.* exercise intolerance and impaired functional or mental status [5, 6].

A previous study showed factor V Leiden homozygotes who are predisposed to VTE have a lower lung function and higher risk of severe dyspnoea [7]. The authors suggested that factor V Leiden homozygotes perhaps experience repeated peripheral venous thrombi that dislodge and result in small, clinically

unrecognised pulmonary thromboemboli causing lower lung function and susceptibility to severe dyspnoea. In the current study we seek to extend these findings from factor V Leiden homozygotes to individuals with an overt clinical VTE in the Danish population. Because factor V Leiden mutations and VTE may also be related to asthma [8, 9], we also examined for association between VTE and increased susceptibility to asthma.

We tested the hypothesis that individuals with VTE have worse lung function, or greater risks of severe dyspnoea and asthma using data from 102 792 random adults from the Danish Copenhagen General Population Study (CGPS).

Materials and methods

Study design and population

The CGPS is a prospective population-based cohort study of >102 000 Danish adults performed since 2003 with continuous recruitment until 2015 [10, 11]. All individuals in Denmark are assigned a unique identification number at birth/immigration and recorded in the national Danish Civil Registration System. By using this unique number, individuals aged 20–100 years were randomly selected and invited from the national Danish Civil Registration System to reflect the adult Danish population. All participants completed a comprehensive questionnaire, underwent a physical health examination and gave blood for biochemical and genetic analyses. Questionnaires were reviewed on the day of attendance by a healthcare professional together with the participant. The study was approved by the institutional review board at Herlev–Gentofte Hospital (Herlev, Denmark) and Danish ethics committees (H-KF-01–144/01) and was conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Definitions of DVT and PE

DVT (International Classification of Diseases (ICD)-8: 451.00, 451.08–09, 451.90, 451.92, 671.01–03, 671.08–09; ICD-10: I80.1–3, O22.3, O87.1) and PE (ICD-8: 450.99, 673.99; ICD-10: I26.0, I26.9, O88.2) were defined as hospital admissions or acute emergency department visits according to the national Danish Patient Registry, which is a complete register of all public and private hospital contacts in Denmark. VTE was defined as having either DVT or PE.

Genotyping

The prothrombin G20210A (rs1799963) and factor V Leiden (rs6025) alleles were genotyped using TaqMan-based assays (Applied Biosystems) as described previously [12]. Genotype frequencies did not differ significantly from those predicted by the Hardy–Weinberg equilibrium (factor V Leiden p=0.05, prothrombin G20210A p=0.75).

Clinical outcomes

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured pre-bronchodilator as described in detail elsewhere [10, 13]. Dyspnoea was graded according to a slightly modified version of the British Medical Research Council questionnaire's breathlessness scale grade II–IV, as described previously [7]. Light dyspnoea was an affirmative answer to the question "Do you get shortness of breath when you walk at an ordinary pace on a level road alongside someone your own age?", moderate dyspnoea was an affirmative answer to the question "Do you have to stop once in a while in order to catch your breath when walking at your own pace?" and severe dyspnoea was an affirmative answer to the question "Do you get shortness of breath during morning toilette or when you get dressed?". Asthma (ICD-8: 493; ICD-10: J45–J46) was defined as hospital admissions or acute emergency department visits according to the national Danish Patient Registry, as in previous studies [14, 15]. This definition may underestimate the true asthma burden, as not all patients with asthma require hospital contact. However, it represents a well-characterised asthma definition, typically confirmed by objective measures in accordance with current hospital guidelines. The specificity of asthma diagnosis in the national Danish Patient Registry was found to be 0.98 in adults, validating its use in epidemiological studies [14, 16]. Body mass index (BMI) was measured weight in kilograms divided by measured height in metres squared. Ever-smoking was defined as current or former tobacco smoking.

Statistical analysis

VTE and asthma were collected from the national Danish Patient Registry from 1993 to 2018, while dyspnoea, lung function and smoking, *etc*. were assessed at the CGPS examination from 2003 to 2015. These data were analysed cross-sectionally using STATA/SE 12.1 for Windows (StataCorp). To compare individuals with VTE *versus* control subjects we used the t-test for continuous data and the Pearson Chi-squared test for categorical data. Prior to the *post hoc* t-test in figure 1 we used ANOVA analysis to examine whether lung function values differed by VTE status overall. Logistic regression adjusting for sex,

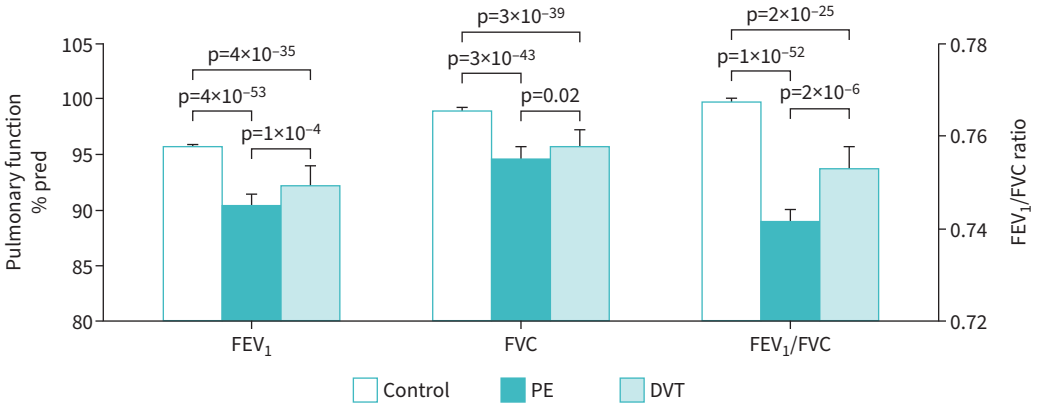

FIGURE 1 Pulmonary function in individuals with venous thromboembolism (VTE) in the general population. Data are presented as mean±SEM. p-values are derived from Welch-corrected t-tests. p<0.001 for comparing lung function values and VTE status overall on ANOVA. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PE: pulmonary embolism; DVT: deep vein thrombosis.

age, smoking and BMI was used to assess dyspnoea and asthma risks in individuals with VTE. Population-attributable fractions (PAFs) were calculated to estimate the fraction of severe dyspnoea and asthma cases attributable to VTE in the study sample: PAF=f(OR−1)/1+f(OR−1), where f is the prevalence of VTE in the study sample.

Results

Prevalence of PE, DVT and VTE in the CGPS were 2.2%, 3.6% and 5.2%, respectively (table 1). Individuals who had PE or DVT were older and more often males and ever-smokers with a higher BMI as compared with individuals without any VTE episodes (table 1).

Pulmonary function

Individuals with PE or DVT had reduced FEV_1 of 90% pred and 92% pred, respectively, compared with 96% pred in individuals without any VTE (figure 1). Corresponding values for FVC were 95% pred and 96% pred *versus* 99% pred, respectively, and for FEV_1/FVC 0.74 and 0.75 *versus* 0.77, respectively.

Dyspnoea

Individuals with PE or DVT experienced more dyspnoea compared with individuals without any VTE (table 2). 8.2%, 8.3% and 10.5% of individuals with PE and 6.3%, 5.3% and 6.6% of individuals with DVT had light, moderate or severe dyspnoea compared with 3.2%, 2.2% and 2.8%, respectively, in individuals without VTE. Sex- and age-adjusted odds ratios for light, moderate and severe dyspnoea in individuals with PE *versus* those without VTE were 2.1 (95% CI 1.7–2.4), 2.4 (2.0–2.8) and 2.8 (2.4–3.3), respectively (table 2). A similar pattern could be observed in individuals with DVT and VTE. After adjustment for sex, age, smoking and BMI, the elevated odds ratios for light, moderate and severe dyspnoea remained statistically significant (table 2). With increasing age, the frequency of dyspnoea increased in the three study groups ($p \leqslant 0.0001$; figure 2). The increase with age was more pronounced in

TABLE 1 Characteristics of individuals with venous thromboembolism (VTE)[#] in the general population

	No VTE	PE[¶]	DVT[+]	VTE
Men/women	43 542/53 846	1131/1142***	1836/1882***	2635/2769***
Age, years	57±13	66±12***	64±13***	65±12***
BMI, kg·m^{-2}	26±4.2	28±4.8***	28±4.9***	28±4.8***
Ever-smoking	55 187 (57)	1474 (67)***	2268 (63)***	3372 (65)***

Data are presented as n, mean±SD or n (%). PE: pulmonary embolism; DVT: deep vein thrombosis; BMI: body mass index. [#]: either PE or DVT; [¶]: International Classification of Diseases (ICD)-8: 450.99, 673.99; ICD-10: I26.0, I26.9, O88.2; [+]: ICD-8: 451.00, 451.08–09, 451.90, 451.92, 671.01–03, 671.08–09; ICD-10: I80.1–3, O22.3, O87.1. ***: p<0.001 *versus* individuals without VTE by Pearson's Chi-squared test or t-test, as appropriate.

TABLE 2 Risk of dyspnoea in individuals with venous thromboembolism (VTE)[#] in the general population

	No VTE (n=97 388)	VTE	p-value[¶]	Adjusted OR (95% CI)[+]	Adjusted OR (95% CI)[§]
PE[f]		n=2273			
Light dyspnoea	3.2±0.1	8.2±0.6	<0.001	2.1 (1.7–2.4)	1.6 (1.4–2.0)
Moderate dyspnoea	2.2±0.0	8.3±0.6	<0.001	2.4 (2.0–2.8)	2.1 (1.8–2.5)
Severe dyspnoea	2.8±0.1	10.5±0.7	<0.001	2.8 (2.4–3.3)	2.4 (2.0–2.8)
DVT[##]		n=3718			
Light dyspnoea	3.2±0.1	6.3±0.4	0.007	1.6 (1.4–1.9)	1.2 (1.05–1.4)
Moderate dyspnoea	2.2±0.0	5.3±0.4	0.001	1.6 (1.4–1.9)	1.3 (1.1–1.6)
Severe dyspnoea	2.8±0.1	6.6±0.4	<0.001	1.8 (1.5–2.1)	1.3 (1.2–1.6)
VTE		n=5404			
Light dyspnoea	3.2±0.1	7.0±0.4	<0.001	1.8 (1.6–2.0)	1.4 (1.2–1.6)
Moderate dyspnoea	2.2±0.0	6.1±0.3	<0.001	1.8 (1.6–2.1)	1.6 (1.4–1.8)
Severe dyspnoea	2.8±0.1	7.7±0.4	<0.001	2.1 (1.9–2.4)	1.7 (1.5–1.9)

Values are presented as mean±SEM, unless otherwise stated. PE: pulmonary embolism; DVT: deep vein thrombosis. [#]: either PE or DVT; [¶]: p-values for comparison with individuals without VTE on Pearson's Chi-squared test; [+]: adjusted for sex and age; [§]: adjusted for sex, age, smoking and body mass index; [f]: International Classification of Diseases (ICD)-8: 450.99, 673.99; ICD-10: I26.0, I26.9, O88.2; [##]: ICD-8: 451.00, 451.08–09, 451.90, 451.92, 671.01–03, 671.08–09; ICD-10: I80.1–3, O22.3, O87.1.

individuals with PE and DVT than in individuals without any VTE. Population-attributable fractions of severe dyspnoea in individuals with PE, DVT or VTE were 3.0%, 1.1% and 3.5%, respectively.

Asthma

Prevalence of asthma was 8.8% in individuals with PE, 7.4% in individuals with DVT and 7.9% in individuals with VTE compared with 4.9% in individuals without VTE (table 3). Multiple adjusted odds ratios (95% CI) for asthma were 1.8 (1.5–2.1) in individuals with PE, 1.5 (1.3–1.6) in individuals with DVT and 1.6 (1.4–1.8) in individuals with VTE compared to individuals without VTE. Population-attributable fractions of asthma in individuals with PE, DVT or VTE were 1.7%, 1.8% and 3.0%, respectively.

The risk of asthma was increased stepwise with factor V Leiden and prothrombin G20210A prothrombotic genotypes (p for trend=0.002; table 4): individuals homozygous or compound heterozygous for the two

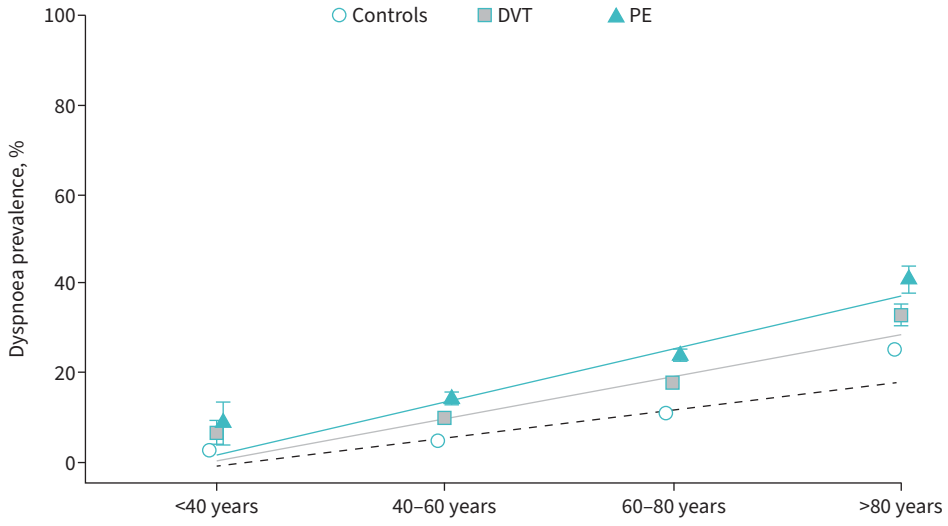

FIGURE 2 Prevalence of dyspnoea in individuals with venous thromboembolism according to age groups. Data are presented as mean±SE. p-values for Wald testing for equality of logistic regression coefficients for age was $<1\times10^{-10}$ for pulmonary embolism (PE) *versus* control subjects and $<1\times10^{-10}$ for deep vein thrombosis (DVT) *versus* control subjects.

TABLE 3 Risk of asthma in individuals with venous thromboembolism (VTE)[#] in the general population

	No VTE (n=97 388)	VTE	p-value[¶]	Adjusted OR (95% CI)[+]	p-value[¶]	Adjusted OR (95% CI)[§]	p-value[¶]
PE[f]		n=2273					
Asthma[##]	4.9±0.1	8.8±0.6	<0.001	1.9 (1.6–2.2)	<0.001	1.8 (1.5–2.1)	<0.001
DVT[¶¶]		n=3718					
Asthma[##]	4.9±0.1	7.4±0.4	<0.001	1.6 (1.4–1.8)	<0.001	1.5 (1.3–1.6)	<0.001
VTE		n=5404					
Asthma[##]	4.9±0.1	7.9±0.4	<0.001	1.7 (1.6–1.9)	<0.001	1.6 (1.4–1.8)	<0.001

Data are presented as prevalence of asthma±SD, unless otherwise stated. PE: pulmonary embolism; DVT: deep vein thrombosis. [#]: either PE or DVT; [¶]: p-values for comparison with individuals without VTE on Pearson's Chi-squared test or logistic regression analysis; [+]: adjusted for sex and age; [§]: adjusted for sex, age, smoking and body mass index; [f]: International Classification of Diseases (ICD)-8: 450.99, 673.99; ICD-10: I26.0, I26.9, O88.2; [##]: ICD-8: 493; ICD-10: J45-J46; [¶¶]: ICD-8: 451.00, 451.08–09, 451.90, 451.92, 671.01–03, 671.08–09; ICD-10: I80.1–3, O22.3, O87.1.

gene variants, and individuals heterozygous for either of the gene variants had multiple adjusted odds ratios for asthma of 1.2 (0.8–1.9) and 1.1 (1.0–1.3), respectively, compared with noncarriers. When stratifying the analysis by individual factor V Leiden and prothrombin G20210A genotypes similar results to those presented were seen (supplementary table E1). There was no association between factor V Leiden and prothrombin G20210A genotype, and dyspnoea (p for trend ⩾0.31).

Discussion

In this study of 102 792 adults from the Danish population we evaluated lung function and susceptibility to severe dyspnoea and asthma in individuals with VTE compared to individuals without any VTE. The results revealed that individuals with VTE have markedly lower lung function and higher risks for severe dyspnoea and asthma. The findings were more pronounced in individuals with PE than in individuals with DVT, and the asthma results were confirmed in a sample of individuals with factor V Leiden and prothrombin genotypes. Population-attributable fractions indicated that VTE accounted for 3.5% and 3.0% of people with severe dyspnoea and asthma, respectively, in the general population.

The genetic part of the study represents a Mendelian randomisation design, which is typically free from influence from confounders and reverse causation supporting causality if a positive association exists [17, 18]. The concept of Mendelian randomisation builds on the random segregation of alleles from parent to offspring, thereby constituting a naturally determined randomised controlled trial in which two random allocated groups are divided on the basis of genetic variants comparable to treatment and placebo groups [17–19]. Hence, the genetic results in the current study support that VTE is causally related to increased risk of asthma. Causality of this relationship is also supported by a recent study by Ghouse *et al*. ([20]; figure 3 therein) showing that a polygenic risk score for VTE is significantly associated with higher risk for asthma. Most previous studies examined the opposite whether asthma is observationally associated with higher risk of VTE [21, 22]. This relationship is not contradictory to the present findings, as both may be present in the clinical setting. However, future Mendelian randomisation studies or randomised trials are needed to conclusively determine whether asthma is causally related to increased risk of VTE.

Previous follow-ups of patients with acute PE have shown abnormal exercise capacity of cardiopulmonary origin in up to 50% and severe cardiopulmonary limitation in up to 15% of the patients [23, 24]. A few

TABLE 4 Risk of asthma by factor V Leiden and prothrombin G20210A genotype

	Subjects	Asthma[#]	Adjusted OR (95% CI)[¶]	p-trend	Adjusted OR (95% CI)[+]	p-trend
No mutation	91 439	5.0±0.2		0.002		0.002
Heterozygotes	9981	5.7±0.2**	1.1 (1.0–1.3)**		1.1 (1.0–1.3)**	
Homozygotes/compound heterozygotes	388	6.2±0.2	1.3 (0.8–1.9)		1.2 (0.8–1.9)	

Values are presented as n or prevalence±SD, unless otherwise stated. [#]: International Classification of Diseases (ICD)-8: 493; ICD-10: J45–J46; [¶]: adjusted for sex and age; [+]: adjusted for sex, age, smoking and body mass index. **: p<0.01 for comparison with individuals without mutations on Pearson's Chi-squared test or logistic regression analysis.

studies also suggested that acute PE and repeated PEs over a longer time can lead to episodes of shortness of breath and be diagnosed and/or treated as asthma [9, 25–29]. In our study we cannot provide any underlying pathophysiological "causative" explanation of our findings as no cardiopulmonary exercise testing or other detailed examinations were performed. We suggest that the asthma phenotype in PE patients is examined in further detail with regard to, for example, cardiopulmonary exercise testing, biochemical markers, mucus production and response to therapy.

Individuals with VTE had reduced FEV_1 % pred and, to a lesser degree, reduced FVC % pred in the current study, supporting the presence of an obstructive pulmonary phenotype such as asthma. This novel finding is an extension of previous results by Juul *et al.* [7] who showed that factor V Leiden homozygotes had markedly reduced FEV_1 % pred and, to a lesser extent, reduced FVC % pred. Recently, Yanagisawa *et al.* [30] also found reduced FEV_1, but increased FVC in patients with CTEPH, supporting that pulmonary embolisms over time can lead to pulmonary function deficits such as reduced FEV_1.

CTEPH is a rare complication of VTE with an estimated 10-year cumulative incidence of 3.3% for PE and 1.3% for DVT [31], accounting for relatively few possible CTEPH cases among people with VTE in the current study (2.2%). It therefore seems unlikely that unrecognised CTEPH in individuals with VTE could explain our findings of increased risks of dyspnoea and asthma in individuals with VTE. However, it could be that milder pulmonary impairments not leading to overt CTEPH may lead to less severe lung disease in individuals with VTE in line with previous studies [23, 24], and the observed higher dyspnoea and asthma prevalences in individuals with VTE in the present study.

The fact that patients frequently report dyspnoea after VTE (especially PE) has repeatedly been published and confirmed, and it is also included in current guidelines [3, 6]. In line with Juul *et al.* [7], who found that factor V Leiden homozygotes had more severe dyspnoea than control subjects, we observed increased risks for severe dyspnoea in people with VTE in the current study, but not in people with factor V Leiden homozygosity. Participation rate in the CGPS (49.3%) is lower than in the population studied by Juul *et al.* [7] (61.2%), and it could be that some of the individuals with the most severe types of VTE, genetic thrombophilia and lung disease may not have attended the physical examination and participated in the study. This could theoretically lead to bias toward the null and cause us to underestimate some of the associations observed and/or the possible association between factor V Leiden and severe dyspnoea.

Strengths of our study include a randomly chosen sample of the general population with the possibility of adjustments for confounders and additional analysis of individuals with factor V Leiden and prothrombin genotypes. The analysis showed that factor V Leiden and prothrombin genotype was associated with risk of asthma overall, while *post hoc* tests showed an increased risk for asthma in heterozygotes, but not in homozygotes/compound heterozygotes. This could be due to lower statistical power for the analysis in homozygotes/compound heterozygotes. A possible limitation is that although ICD codes should be accurate, in the real-life clinical setting sometimes patients with cough or dyspnoea get an ICD code of asthma. However, the specificity value of 0.98 for adult asthma (and 0.99 for childhood asthma) in the national Danish Patient Registry [16] indicate that misclassification of asthma is unlikely to have substantially influenced our results. In the present study, patients with DVT frequently reported dyspnoea or were diagnosed with asthma, and we cannot totally exclude that PE may have been underdiagnosed or unrecognised among the patients with DVT. However, if the analysis was restricted to patients with DVT but without PE (n=3131), the multiple adjusted odds ratios (95% CI) were similar to those presented (1.2, 1.03–1.5 for severe dyspnoea; 1.5, 1.3–1.7 for asthma). Because 99.9% of the individuals studied were of white Caucasian descent, the generalisability of our findings may be constrained. That said, we are not aware of results suggesting that our findings are not relevant to individuals of all races.

Interpretation

In conclusion, individuals with VTE compared to individuals without VTE have worse lung function and higher risks of severe dyspnoea and asthma in the general population. These findings were more pronounced among individuals with PE than in individuals with DVT, and the asthma results were confirmed among individuals with genetic predisposition to VTE. The genetic part of the study supports that the relationship between VTE and susceptibility to asthma most likely is causal. Population-attributable fractions showed that VTE accounted for 3.5% and 3.0% of people with severe dyspnoea and asthma, respectively, in the population.

Provenance: Submitted article, peer reviewed.

Ethics statement: The study was approved by the institutional review board at Herlev and Gentofte Hospital, and Danish ethics committees (H-KF-01-144/01); and was conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Author contributions: K.F. Nilausen, E.M. Landt, S. Al-Shuweli, B.G. Nordestgaard, U. Bødtger and M. Dahl contributed to the study concept and design, and collected, analysed or interpreted the data. K.F. Nilausen, E.M. Landt and M. Dahl wrote the draft manuscript and performed the statistical analyses. All authors were involved in revising the manuscript for important intellectual content.

Conflict of interest: None declared.

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