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Lung Function, Respiratory Symptoms and Venous Thromboembolism Risk: the Atherosclerosis Risk in Communities Study

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Summary

Background—The evidence of the association between chronic obstructive pulmonary disease (COPD) and venous thromboembolism (VTE) is limited. There is no study investigating the association of restrictive lung disease (RLD) and respiratory symptoms with VTE.

Objectives—To investigate prospectively the association of lung function and respiratory symptoms with VTE.

Patients/Methods—In 1987–1989, we assessed lung function using spirometry and obtained information on respiratory symptoms (cough, phlegm and dyspnea) in 14 654 participants aged 45–64, without a history of VTE or anticoagulant use, and followed them through 2,011. Participants were classified into four mutually exclusive groups, ‘COPD’ [forced expiratory

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Addendum

All authors participated in the study design; A. R. Folsom acquired the data; Y Kubota and A. R. Folsom were involved with analysis, interpretation and writing of the manuscript; and all authors critically reviewed the manuscript.

Competing Interests

None.

volume in 1 second (FEV_1)/forced vital capacity (FVC)<lower limit of normal (LLN)], ‘RLD’ (FEV_1/FVC LLN and $FVC < LLN$), ‘respiratory symptoms with normal spirometry’ (without RLD or COPD), and ‘normal’ (without respiratory symptoms, RLD or COPD).

Results—We documented 639 VTEs [238 unprovoked and 401 provoked VTEs]. After adjustment for VTE risk factors, VTE risk was increased for individuals with either respiratory symptoms with normal spirometry [Hazard ratio, (95% confidence interval): 1.40 (1.12–1.73)] or COPD [1.33 (1.07–1.67)] but not for those with RLD [1.15 (0.82–1.60)]. These elevated risks of VTE were derived from both unprovoked and provoked VTE. Moreover, FEV_1 and FEV_1/FVC demonstrated dose-response relations with VTE. COPD was more strongly associated with pulmonary embolism than deep venous thrombosis.

Conclusions—Obstructive spirometric patterns were associated with an increased risk of VTE, suggesting that COPD may increase the risk of VTE. Respiratory symptoms may represent a novel risk marker for VTE.

Keywords

Venous thromboembolism; lung function; chronic obstructive pulmonary disease; restrictive lung disease; respiratory symptoms

INTRODUCTION

Several studies have reported that chronic obstructive pulmonary disease (COPD), especially an acute exacerbation of COPD, is a risk factor for venous thromboembolism (VTE) [1–4]. However, most information on the association of COPD with VTE risk in the general population relies on results from registry-based studies, with no validation of VTE diagnoses [5]. A recent prospective population-based cohort study investigated the association between COPD and validated VTE risk [5]. The results suggested that patients with severe COPD may have increased risk of “provoke” VTE, but the association was not statistically significant [5]. In addition, this population-based study used the fixed 0.70 cut-off of forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) [5]. Using a fixed cut-off leads to underdiagnosis in young adults and overdiagnosis of airway obstruction in adults aged over 40 years, and as a result using the the 5th percentile of distribution as the lower limit of normal (LLN) is recommended [6, 7]. Thus, evidence for a relation between COPD and VTE remains limited.

Although potential mechanisms by which COPD might cause VTE remain unclear, hypercoagulability, inflammation, immobilization, and pulmonary hypertension with venous stasis due to impaired lung function and hypoxia are candidate risk mediators [1]. Other respiratory impairments, such as restrictive lung diseases (RLD), may also increase the risk of VTE via similar mechanisms, but to the best of our knowledge no epidemiological study has reported the prospective association between VTE and respiratory impairments other than COPD.

Here, using two important markers for respiratory impairment, lung function measured by spirometry and respiratory symptoms, we prospectively investigated whether respiratory

impairments (lung restriction, airway obstruction, and others) defined by the LLN are related to the risk of VTE in a population-based study in the U.S.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing population-based prospective study of cardiovascular diseases [8]. The ARIC Study recruited and examined 15 792 mostly Caucasian or African American men and women aged 45–64 from 4 U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); and suburbs of Minneapolis, Minnesota) in 1987–1989 (visit 1). The institutional review boards of the collaborating institutions approved the study protocol, and each participant provided written informed consent.

For the present analyses, we excluded participants who reported a history of VTE or were taking anticoagulants at baseline survey (n=349), participants whose data on main exposure (n=188) or any covariates (n=837) were missing. We further excluded non-white participants in Washington County or Minneapolis or non-white/black participants in Forsyth County (n=54) in order to allow multivariable adjustment for race and study site [9]. After exclusions, 14 364 participants were included in the present analyses.

Main Exposure: Lung Function and Respiratory Symptoms

Spirometry was conducted at baseline using a water-sealed Collins Survey II volume displacement spirometer (Collins Survey II; Collins Medical; Braintree, MA) and Pulmo-Screen II software (Pulmo-Screen; PDS Healthcare Products; Louisville, CO). At least 3 acceptable spirometers were sought from a minimum of 5 forced expirations. The best single spirogram was identified by a computer and confirmed by a technician according to American Thoracic Society guidelines, using a standardized protocol [10]. Quality control was conducted carefully throughout the study [10]. FEV₁ as a percentage of predicted value (FEV₁ % predicted), FVC as a percentage of predicted value (FVC % predicted), and LLN were calculated using the Hankinson 1999 equations [11]. Bronchodilator (beta-agonist) response was not evaluated at visit 1.

Assessment of respiratory symptoms was based on responses to a standardized self-administered questionnaire adopted from the Epidemiology Standardization Project [12]. We chose three representative respiratory symptoms (cough, phlegm and dyspnea) based on GOLD report [13] and COPD Foundation Guide [14]. Participants were considered as having respiratory symptoms if they responded positively to any of the following questions: ‘Do you usually have a cough?’ (defined here as ‘cough’); ‘Do you usually bring up phlegm from your chest?’ (defined here as ‘phlegm’); and ‘Do you have to walk slower than people of your age on the level because of breathlessness?’ or ‘Are you too breathless to leave the house or breathless on dressing or undressing?’ (yes to either, defined here as ‘dyspnea’).

We classified participants into 4 categories, ‘normal’ was defined as those with FEV₁/FVC LLN, FVC LLN and no respiratory symptoms, ‘respiratory symptoms with normal spirometry’ as those with respiratory symptoms but FEV₁/FVC LLN and FVC LLN,

‘restrictive lung disease pattern’ as FEV_1/FVC LLN and $FVC < LLN$, and ‘COPD pattern’ as $FEV_1/FVC < LLN$ [7]. We included ‘respiratory symptoms with normal spirometry’ in the present analysis because others have documented adverse health outcomes among people in this category [15], and this category may reflect lung diseases with preserved lung function or borderline RLD or COPD.

Potential Confounding Factors

We evaluated a number of potential confounding factors, assessed at baseline, for the association of respiratory impairments with VTE. They included age (continuous), sex, race/ARIC field center (whites in Washington County, Forsyth County, or Minneapolis, or African Americans in Jackson or Forsyth County), body mass index (BMI) calculated as weight (kg)/height (m)² (continuous), prevalent diabetes, smoking status (current, former or never), pack-years of cigarettes smoked (continuous), estimated glomerular filtration rate (eGFR) (continuous), sport index (continuous) and steroid inhaler use. We included steroid inhaler use as a potential confounding factor because some patients with lung diseases receive steroid inhaler treatments, and several previous reports have suggested a positive association between steroid use and VTE risk [16, 17]. Prevalent diabetes was defined as a fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. Pack-years of cigarettes smoked was calculated as the average number of cigarettes smoked per day times the number of years of smoking divided by 20 (the number of cigarettes in a pack). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18, 19]. Sport index was assessed using the Baecke sports questionnaire, with scores ranging from 1 (low) to 5 (high) [20].

Confirmation of Venous Thromboembolism

ARIC contacted participants annually or semi-annually by phone to ask about all hospitalizations in the previous year. Using standard criteria, two physicians validated possible VTEs using hospital records of possible VTE cases reported through 2011 [21]. Secondary VTEs associated with cancer, major trauma, surgery or marked immobility were classified as ‘provoked VTE’ while all others were classified as ‘unprovoked VTE’. Pulmonary embolism (PE) or deep venous thrombosis (DVT) was diagnosed using imaging tests.

Statistical Analysis

The person-years of follow-up for each participant were calculated from the baseline (1987–1989) to the first endpoint: VTE, death, loss to follow-up, or the end of follow-up (2011). Hazard ratios (HRs) and their 95% confidence intervals (CIs) of VTE occurrence were calculated after adjustment for potential confounding factors using Cox proportional hazard models. Model 1 adjusted for age, sex, and race/ARIC field center; Model 2 additionally for body mass index, prevalent diabetes, smoking status, pack-years of cigarettes smoked, eGFR, sport index, and steroid inhaler use. We constructed cubic spline graphs with 3 knots at 25, 50 and 75 percentiles in order to examine dose-response relationships between FEV_1 % predicted, FVC % predicted or FEV_1/FVC and VTE risk.

For sensitivity analyses, we further adjusted Model 2 for (i) self-reported diagnosis of bronchitis, emphysema and asthma, prevalent heart failure and coronary heart disease, or (ii) competing risks of death from underlying causes other than VTE or (iii) competing risks of arterial vascular diseases (coronary heart disease, heart failure, atrial fibrillation and stroke) which may require antithrombotic treatments [22]. We also (iv) ran models using shorter-follow-up time for VTE (5 years from baseline).

The proportional hazards assumption in Cox regression was tested using risk factor-by-time interactions and was not violated. Since we found no statistical interactions between sex or race and main exposures in relation to VTE risk, an analysis pooled across sex and race was conducted. SAS version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All statistical tests were two-tailed and P values < 0.05 were regarded as significant.

RESULTS

Baseline Characteristics According to Lung Function Categories

Among the 14 364 ARIC participants included in the analysis, the mean age was 54.1 years, 54.9% were female, and 25.7% were African Americans. The prevalences of normal, respiratory symptoms with normal spirometry, RLD pattern, and COPD pattern were 63.8%, 13.2%, 5.9%, and 17.4%, respectively. As shown in Table 1, those with respiratory symptoms or any of the abnormal spirometric patterns were more likely to be older, current smokers, have more pack-years and lower sports indices, and have reported diagnosis of bronchitis, emphysema or asthma, and history of coronary heart disease and heart failure than those with normal spirometry and no respiratory symptoms. Those with the RLD pattern were more likely to be obese and diabetic than the other categories.

Associations of Respiratory Categories with Venous Thromboembolism

During 284 969 person-years of follow-up, over a median of 22.5 years, we documented 639 incident cases of VTE (238 unprovoked and 401 provoked) (Table 2). In the age, sex, and race-adjusted model (Model 1), participants with respiratory symptoms and normal spirometry, with the RLD pattern, or with the COPD pattern had a higher risk of VTE than those with normal spirometric results and no respiratory symptoms. After adjustment for the other risk factors (Model 2), participants with respiratory symptoms and normal spirometry had significantly increased risks of total VTE [HR (95% CI): 1.40 (1.12–1.73)], deriving from both unprovoked VTE [1.33 (0.93–1.91)] and provoked VTE [1.44 (1.10–1.89)], and both PE [1.33 (0.97–1.83)] and DVT [1.47 (1.09–1.97)]. Those with the RLD pattern had an elevated risk of unprovoked VTE [1.52 (0.93–2.49)] that was not statistically significant. Those with the COPD pattern had increased risk of total VTE [1.35 (1.08–1.68)]—both unprovoked [1.50 (1.05–2.14)] and provoked VTE [1.25 (0.94–1.67)], and were more likely to have increased risk of PE [1.49 (1.09–2.05)] than DVT [1.20 (0.87–1.65)]. No significantly increased risk of cancer-related VTE was observed among those with respiratory symptoms and normal spirometry [1.28 (0.85–1.93)], with the RLD pattern [0.67 (0.31–1.46)], or with the COPD pattern [1.30 (0.87–1.96)] (not shown in Table 2).

Dose-response Relations between Spirometry Measurements and Venous Thromboembolism

In order to examine how the degree of lung restriction or airway obstruction was associated with VTE risk, the continuous relations of FEV₁ % predicted, FVC % predicted, and FEV₁/FVC with VTE incidence were plotted using restricted cubic splines (Figure). Dose-response relations were generally observed, with lower levels of FEV₁/FVC and FEV₁ significantly associated with elevated risks of total VTE.

Sensitivity Analyses

For sensitivity analyses, first we further adjusted for self-reported diagnoses of bronchitis, emphysema and asthma, prevalent heart failure or coronary heart disease (data not shown), competing risks of death from underlying causes other than VTE (Model 3 in Table 2), or competing risks of arterial vascular diseases (data not shown) and found almost identical associations between lung function and VTE risk. Next, we ran models using shorter follow-up intervals (within 5 years from baseline). Similar trends were observed although the analyses were less likely to be statistically significant, due to the smaller number of VTE events (49 cases for 5 years follow-up) (Supplementary Table and Figures).

DISCUSSION

In this prospective population-based cohort study, participants with respiratory symptoms but normal spirometric pattern and obstructive spirometric patterns had increased risk of VTE. The previous study reported elevated risk of only provoked VTE among those with obstructive spirometric pattern [5], but in the present study, we found they had increased risks of not only provoked but also unprovoked (not secondary) VTE. In addition, lower FEV₁ % predicted and FEV₁/FVC, indices of airway obstruction, were associated with elevated risk of VTE. To the best of our knowledge, this is the first prospective population-based cohort study to investigate the association of lung function and respiratory symptoms with VTE occurrence, and to suggest that respiratory symptoms may be a risk marker for VTE. Furthermore, we provided further evidence on that COPD may increase the risk of VTE.

COPD involves pulmonary and systemic inflammation [23, 24]. Inflammation induced hypercoagulability, hypoxia, pulmonary hypertension, and venous stasis from immobility all might increase risk of VTE [1]. In the present study, those with COPD pattern had increased risk of unprovoked VTE, which may be explained by these mechanisms. As previous registry-based studies have suggested, our study also showed COPD pattern was associated with PE rather than DVT [5]. This may be partially because COPD patients often may be given CT scans, and thus be more likely to be diagnosed with PE (referral bias). In addition, cubic spline graphs suggested inverse dose-response relationships of FEV₁ % predicted and FEV₁/FVC with VTE. COPD is characterized by reduced FEV₁/FVC [25]. Thus, these results support the hypothesis that COPD may increase the risk of VTE.

Those with the RLD pattern also had increased risk of unprovoked VTE, but the association was not significant. Possible reasons for this may be that the number of participants with the

RLD pattern (n=847 versus 2499 with COPD pattern) was insufficient, and perhaps the RLD pattern was also closely related to comorbidities, such as obesity and diabetes [26, 27]. Thus, a further study will be needed on the association between RLD and VTE risk.

Participants with respiratory symptoms and a normal spirometric pattern also had increased risk of VTE, particularly provoked VTE (Model 3 in Table 2). We speculate that their increased risk of VTE may be mainly due to immobility, cancer, heart failure, borderline COPD, or other comorbidities. Of course, respiratory symptoms would not be a causal risk factor for VTE but a marker for such comorbidities. Although our further adjustment for prevalent heart failure did not change the result, we cannot negate bias from undiagnosed heart failure (residual confounding) as heart failure with preserved ejection fraction is hard to diagnose [28]. In addition, those with respiratory symptoms and a normal spirometric pattern had an increased risk of cancer-related VTE (HR 1.28), although the association was not significant. In any case, respiratory symptoms may be a noteworthy marker of increased risk of VTE.

Although several previous studies have demonstrated associations of reduced spirometry measurements with increased risks of cardiovascular diseases, such as coronary heart disease [29], heart failure [30], stroke [31], or atrial fibrillation [32], no study has shown a relation of lung function with VTE risk. These previous studies have reported that FEV₁ was associated with increased risk of cardiovascular diseases, but FEV₁/FVC was not. Thus, VTE might be more strongly associated with airway obstruction than are other cardiovascular diseases.

The strengths of our study include its prospective design, a long follow-up, and validated VTE events. In addition, we used the LLN spirometry measurements, not fixed cut-offs, to define RLD and COPD, which theoretically reduced misclassification of exposures.

Nonetheless, some limitations need to be addressed. First, although we assumed the obstructive spirometric pattern was mainly COPD, as in other epidemiological studies [5, 15, 33, 34], only pre-bronchodilator measurements were available. Thus, some participants without lung disease might have been included in the obstructive category, but this misclassification would tend to bias the results toward the null and do not readily explain the observed associations. In addition, we did not have data on total lung capacity, which is needed to meet the strict definition of restrictive lung disease [35]. Next, our follow-up was quite long and the lung function values and symptoms at baseline certainly would have changed during follow-up. Although both results from long and short-term (5 years) follow-ups showed similar trends, we cannot negate the possibility of exposure misclassification especially among participants with respiratory symptoms and a normal spirometry because respiratory symptoms are subjective unlike spirometry. Some of participants' symptoms might have stopped over time, while others might have developed COPD. The former case could have led to an overestimation of the risk of VTE and the latter, an underestimation. Those with a COPD or RLD pattern might have returned to normal lung function over time because of e.g. treatment, and this would led to an underestimation of the risk of VTE. Finally, the possibility of residual confounding of the observed associations cannot be

negated, although the extent of potential bias is likely small given our detailed adjustment for many known confounders.

In conclusion, in the prospective population-based ARIC cohort, obstructive spirometric patterns (COPD pattern, low FEV₁ and low FEV₁/FVC) were associated with an elevated risk of VTE, suggesting that COPD may increase the risk of VTE. Furthermore, the presence of respiratory symptoms might be a novel risk marker for VTE. Those with the RLD pattern also had an increased risk of VTE, but the association was not significant, perhaps because it is closely related to comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Essentials

- The association of lung function with venous thromboembolism (VTE) is unclear.
- Chronic obstructive pulmonary disease (COPD) pattern were associated with a higher risk of VTE.
- Symptoms were also associated with a higher risk of VTE, but a restrictive pattern was not.
- COPD may increase the risk of VTE. Respiratory symptoms may be a novel risk marker for VTE.

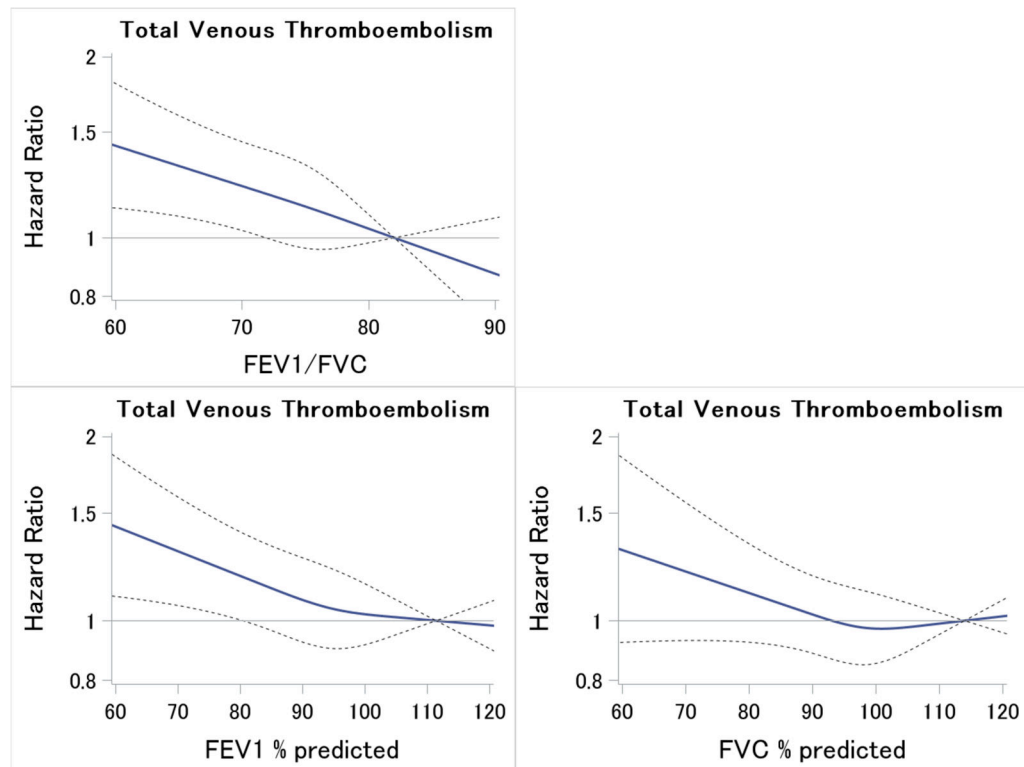


Figure.

Multivariable adjusted (Model 2) associations of FEV₁ as a percentage of predicted value (FEV₁ % predicted), FVC as a percentage of predicted value (FVC % predicted), or FEV₁/FVC with total VTE. Solid and dashed lines represent hazard ratios and 95% confidence interval, respectively. The reference value was the median value of the fourth quartile (87.5th percentile).

Table 1
Baseline Characteristics of Participants According to Lung Function Impairment, ARIC, 1987–89 (n=14 364).

	Normal	Respiratory symptoms with normal spirometry	Restrictive lung disease pattern	COPD pattern
No. at risk	9162	1892	847	2499
Venous Thromboembolism Risk factors				
Age, years	53.8±5.7	54.2±5.7	54.5±5.7	55.0±5.6
Female, %	56.1	57.5	51.1	50.0
African American, %	26.3	29.8	20.8	22.0
Body mass index, kg/m ²	27.6±5.0	28.7±5.8	30.2±6.4	26.0±4.8
Diabetes mellitus, %	10.5	15.4	23.8	9.0
Smoking				
Pack-years	11.1±17.4	18.8±23.3	20.7±23.1	30.0±26.0
Current	16.0	37.3	35.1	49.4
Former	34.1	24.4	30.6	30.3
Never	49.9	38.3	34.4	20.3
eGFR, ml/min/1.73m ²	103±15	103±17	102±17	102±16
Sports index	2.5	2.3	2.3	2.4
Steroid inhaler use, %	0.1	0.7	0.1	1.7
Respiratory measures				
FEV ₁ % predicted	100±12	97±12	73±8	75±18
FVC % predicted	101±12	99±12	73±7	94±18
FEV ₁ /FVC, %	77±5	77±5	78±6	62±8
Cough, %	0	50.3	16.7	26.3
Phlegm, %	0	52.0	14.9	24.1
Dyspnea, %	0	27.8	12.0	10.8
Self-reported diagnosis of bronchitis, %	4.9	14.6	10.5	15.8
Self-reported diagnosis of emphysema, %	0.5	1.7	1.4	5.8
Self-reported diagnosis of asthma, %	3.3	8.0	5.1	13.1
Prevalent cardiovascular disease				
Coronary heart disease, %	3.3	5.9	10.7	6.3
Heart failure, %	1.7	12.3	8.6	7.0

ARIC, Atherosclerosis Risk in Communities Study; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal.

Using spirometry done without bronchodilator: Normal was defined as FEV₁/FVC LLN and FVC LLN, respiratory symptoms with normal spirometry as those with respiratory symptoms but FEV₁/FVC LLN and FVC LLN, restrictive lung disease pattern as FEV₁/FVC LLN and FVC < LLN, and COPD pattern as FEV₁/FVC < LLN.

Values are mean ± standard deviation for continuous variables and % for categorical variables.

Table 2

Hazard Ratios and 95% Confidence Intervals for Venous Thromboembolism According to Respiratory Impairment, ARIC, 1987–2011 (n=14 364).

	Normal	Respiratory symptoms with normal spirometry	Restrictive lung disease pattern	COPD pattern
No. at risk	9162	1892	847	2499
Person-years	187 704	36 345	15 436	45 485
Crude death rates per 1000 person-years (95% CI)	12.5 (12.0–13.0)	18.2 (16.8–19.8)	23.5 (21.1–26.2)	25.3 (23.8–26.8)
Total Venous Thromboembolism, cases	373	112	40	114
Crude incidence rates per 1000 person-years (95% CI)	1.99 (1.88–2.10)	3.08 (2.78–3.42)	2.59 (2.18–3.08)	2.51 (2.26–2.78)
Model 1	1	1.57 (1.27–1.94)	1.41 (1.02–1.95)	1.35 (1.09–1.66)
Model 2	1	1.40 (1.12–1.73)	1.15 (0.82–1.60)	1.33 (1.07–1.67)
Model 3	1	1.36 (1.08–1.72)	1.01 (0.71–1.45)	1.27 (1.00–1.62)
Unprovoked Venous Thromboembolism, cases	133	39	19	47
Crude incidence rates per 1000 person-years (95% CI)	0.72 (0.68–0.77)	1.11 (0.98–1.25)	1.26 (1.05–1.50)	1.06 (0.94–1.18)
Model 1	1	1.52 (1.06–2.17)	1.87 (1.15–3.03)	1.52 (1.09–2.13)
Model 2	1	1.33 (0.93–1.92)	1.52 (0.93–2.49)	1.50 (1.05–2.14)
Model 3	1	1.18 (0.78–1.77)	1.37 (0.81–2.32)	1.51 (1.02–2.23)
Provoked Venous Thromboembolism, cases	240	73	21	67
Crude incidence rates per 1000 person-years (95% CI)	1.29 (1.22–1.37)	2.04 (1.83–2.27)	1.38 (1.13–1.69)	1.50 (1.34–1.68)
Model 1	1	1.62 (1.25–2.11)	1.15 (0.74–1.80)	1.25 (0.95–1.64)
Model 2	1	1.44 (1.10–1.89)	0.94 (0.60–1.48)	1.25 (0.94–1.67)
Model 3	1	1.48 (1.11–1.96)	0.81 (0.50–1.33)	1.16 (0.85–1.56)
Pulmonary Embolism, cases	240	73	21	67
Crude incidence rates per 1000 person-years (95% CI)	0.97 (0.91–1.03)	1.44 (1.28–1.61)	1.25 (1.04–1.52)	1.32 (1.18–1.47)
Model 1	1	1.52 (1.11–2.07)	1.44 (0.90–2.32)	1.51 (1.12–2.03)
Model 2	1	1.33 (0.97–1.83)	1.17 (0.72–1.90)	1.49 (1.09–2.05)
Model 3	1	1.35 (0.97–1.88)	1.14 (0.70–1.85)	1.41 (1.01–1.96)
Deep Venous Thrombosis, cases	194	61	21	55
Crude incidence rates per 1000 person-years (95% CI)	1.05 (0.99–1.12)	1.72 (1.53–1.92)	1.39 (1.14–1.68)	1.24 (1.10–1.39)
Model 1	1	1.64 (1.23–2.19)	1.37 (0.87–2.16)	1.20 (0.89–1.63)
Model 2	1	1.47 (1.09–1.97)	1.12 (0.71–1.78)	1.20 (0.87–1.65)
Model 3	1	1.39 (1.01–1.93)	0.89 (0.52–1.52)	1.16 (0.82–1.64)

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Model 1: Adjusted for age, sex, and race/ARIC field center.

Model 2: Adjusted for Model 1 + body mass index, diabetes mellitus, eGFR, pack-years, smoking status, sports index and steroid inhaler use.

Model 3: Adjusted for Model 2 + competing risks of death from underlying causes other than venous thromboembolism.