Impact of respiratory symptoms and oxygen saturation on the risk of incident venous thromboembolism—the Tromsø study

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Funding information
KG Jebsen TREC is supported by an independent grant from Stiftelsen Kristian Gerhard Jebsen.

Handling Editor: Suzanne Cannegieter

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is associated with risk of venous thromboembolism (VTE). It remains unknown whether individual respiratory symptoms and lowered oxygen saturation (SpO₂), individually and in combination with COPD, affect the risk of VTE.

Objectives: To investigate whether measures of respiratory impairments including respiratory symptoms and SpO₂, individually and combined with COPD, were associated with an increased risk of VTE.

Methods: Spirometry, SpO₂, and self-reported respiratory symptoms were collected in 8686 participants from the fifth (2001-2002) and sixth (2007-2008) surveys of the Tromsø Study. Incident VTE events were registered from the date of inclusion to December 31, 2016. Cox regression models with exposures and confounders as time-varying covariates (for repeated measurements) were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE.

Results: During a median follow-up of 9.1 years, 330 participants developed incident VTE. Subjects with SpO₂ ≤ 96% (lowest 20th percentile) had a 1.5-fold higher risk of VTE (adjusted HR, 1.48; 95% CI, 1.13-1.93) compared with those with SpO₂ ≥ 98%. Severe respiratory symptoms (dyspnea, cough, and phlegm) were associated with a 1.4- to 2.0-fold higher risk of VTE compared with no such symptoms. COPD, combined with respiratory symptoms or lowered SpO₂, had an additive effect on the VTE risk.

Conclusions: Lowered SpO₂ and severe respiratory symptoms were associated with increased VTE risk. COPD combined with respiratory impairments had an additive effect on VTE risk, and may suggest particular attention on VTE preventive strategies in COPD patients with respiratory impairments.

Keywords
chronic obstructive pulmonary disease, oxygen saturation, respiratory symptoms, risk, venous thromboembolism
1 | INTRODUCTION

The global prevalence of chronic obstructive pulmonary disease (COPD) has increased substantially during the past decades and represents a major challenge to health care systems. COPD is associated with frequent hospitalizations, grave morbidities, and a high mortality rate. Around 5%–10% of patients hospitalized for acute COPD exacerbation die during the hospital stay, and 20% die during the first year after hospital discharge.

Results from registry-based studies have reported that COPD is associated with a 2- to 5-fold increased risk of venous thromboembolism (VTE), and the prevalence of acute pulmonary embolism (PE) is high (15%–30%) in patients with COPD hospitalized with suspected acute exacerbation. Recent population-based cohorts, with respiratory function assessed by spirometry and validated evaluation of confounding factors and VTE events, confirmed that COPD was associated with a moderately increased risk of VTE and showed that the VTE risk increased with the severity of COPD. Furthermore, respiratory symptoms (eg, cough, phlegm, and dyspnea) were associated with VTE risk, even in subjects with normal spirometry measurements, suggesting that respiratory symptoms may represent risk markers for VTE.

Although the mechanism by which COPD causes VTE remains unknown, COPD-related complications such as lower respiratory tract infections, repeated hospitalizations, and immobilization are potential mediators. Moreover, impaired lung function and hypoxemia may result in pulmonary hypertension and systemic inflammation, which contribute to increase the risk. Patients with COPD with hypoxemia have been shown to have a larger mean platelet volume and increased platelet aggregation compared with those with normal oxygen saturation. In addition, COPD patients had higher coagulation activation than age- and sex-matched controls and exposure to short-term hypoxia further augmented coagulation activation. Severe hypoxia was also shown to increase the incidence and size of thrombi in the inferior vena cava stenosis model in mice.

To the best of our knowledge, no study has investigated the association between oxygen saturation and future risk of VTE. The aims of the present study were to investigate whether measures of respiratory impairments, such as respiratory symptoms and oxygen saturation, individually and combined with COPD, were associated with increased risk of VTE.

2 | METHODS

2.1 | Study population

Study participants were derived from the fifth (2001-2002) and sixth (2007-2008) surveys of the Tromsø Study. To these surveys, fractions of the population aged ≥30 years living in the municipality of Tromsø, Norway, were invited to participate in an extensive screening where measurements of oxygen saturation and spirometry were included. A detailed description of study participation in the Tromsø study has been published elsewhere.

Overall, 9577 unique individuals aged 32 to 89 years participated in ≥1 of the surveys. All subjects gave their written consent to participate, and the study was approved by the regional committee of medical and health research ethics. We excluded subjects who had officially moved out of Tromsø before the date of study enrollment (n = 7), subjects with VTE before baseline (n = 111), and subjects with missing values for SpO₂ (n = 773). Consequently, 8686 subjects were included in the study and were followed from the date of inclusion until the end of follow-up (December 31, 2016). Of these, 2752 participated in both surveys, while 2328 participated only in Tromsø 5 and 3606 participated only in Tromsø 6.

2.2 | Measurement of peripheral capillary SpO₂

SpO₂ values were measured at baseline with a digital handheld pulse oximeter (Onyx II, model 9550, Nonin Medical, Inc, Plymouth, MN, USA). The participants rested at least 15 minutes before the measurement, and the best of 3 measurements were recorded.

2.3 | Respiratory symptoms

At baseline, the participants completed a questionnaire with questions about respiratory symptoms, including presence of dyspnea in various situations, daily cough for periods of the year, chronic cough (ie, cough with continuous duration of more than 3 months during the past 2 years), and productive cough (ie, phlegm) for periods of the year. Dyspnea was categorized into “none,” “dyspnea when walking calmly or flat or when washing and dressing,” and “dyspnea at rest.” Cough was categorized into “none,” “daily cough for periods of the year,” and “chronic cough for periods of the year” (ie, periods of daily cough lasting continuously for more than 3 months in the past 2 years). Phlegm was categorized as “none” and “productive cough for periods of the year.”
spirometry testing were followed. Population Registry of Norway.

2.4 | Chronic obstructive pulmonary disease

 Spirometry was assessed at enrollment in the Tromsø study, as previously described in detail. The American Thoracic Society’s criteria for spirometry testing were followed. Current drug therapy was not interrupted before the test, and reversibility testing was not performed. The equations proposed by Langhammer et al were used to calculate predicted values of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. Those with FEV1/FVC < 0.7 or predicted FEV1 < 80% were excluded from the analyses if peak expiratory flow (PEF) was < 3× forced expiratory flow when 75% of the air had been expired (PEF < 3× FEF25). The subjects were allocated into groups based on lung function according to the Global Initiative of Chronic Obstructive Lung Disease guidelines.

2.5 | Other measurements

Height and weight were measured at enrollment in the Tromsø study, with subjects wearing light clothes and no shoes, and body mass index (BMI) was calculated (kg/m²). Information on smoking status (current, former, never) and history of cardiovascular disease (CVD; ie, myocardial infarction, stroke, or angina pectoris), was collected from a self-administered questionnaire.

2.6 | Venous thromboembolism

All incident VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway as previously described. VTE events were adjudicated by thorough review of medical records, and the adjudication criteria included clinical signs and symptoms of deep vein thrombosis or PE combined with objective confirmation tests (imaging or autopsy), which resulted in a VTE diagnosis that required treatment. Information on date of death was obtained from the National Population Registry of Norway.

2.7 | Statistical analysis

Statistical analyses were performed with STATA version 13.0 (Stata Corporation, College Station, TX, USA). For each participant, person-years for follow-up were accrued from the date of enrollment (in Tromsø 5 or 6) to the date a VTE was diagnosed, the date the participant died or officially moved from the municipality of Tromsø, or to the end of the study period (December 31, 2016). We used a time-varying analysis, which allowed for update of exposure and covariates in participants who were re-measured in Tromsø 6 (n = 2752). Thus, 8686 individuals contributed, with 11 438 observational periods. Subjects who died (n = 1706) or moved from Tromsø (n = 501) during follow-up were censored at the date of migration or death.

3 | RESULTS

During a median follow-up of 9.1 years, 330 participants developed an incident VTE (overall IR, 3.5; 95% CI, 2.3-3.2). Baseline characteristics according to categories of SpO2 are shown in Table 1. The mean age, the mean BMI levels, and the proportion of men increased over decreasing levels of SpO2. As expected, the proportion of subjects with COPD and respiratory symptoms increased over decreasing levels of SpO2 (Table 1).

The risk of VTE according to categories of SpO2 and respiratory symptoms are shown in Table 2. The IR of VTE was 2.7 per 1000 person-years in those with SpO2 ≤ 98% and 5.3 per 1000 person-years in those with SpO2 ≤ 96%, with a corresponding age and sex-adjusted HR of 1.58 (95% CI, 1.22-2.05) for SpO2 ≤ 96% vs. SpO2 ≥ 98% (reference category). Further adjustment for BMI, CVD, and history of cancer only slightly attenuated the HR. The risk of VTE increased according to the degree of dyspnea. Those who reported dyspnea when performing light activities (walking calmly, washing, or dressing) had a 1.5-fold increased risk of VTE, while those with dyspnea at rest had a 2-fold higher risk of VTE (HR, 2.18; 95% CI, 1.22-3.88) compared with those without dyspnea. Chronic cough and phlegm were both associated with a 1.4-fold higher risk of VTE (Table 2 and Figure 1). Subgroup analyses revealed that the associations between respiratory symptoms and VTE were mainly driven by an increased risk of PE (Figure 1).

Information on COPD status, assessed by spirometry, was available in 8129 subjects (contributing with 10 849 observation periods) in whom 315 VTEs occurred during follow-up. Overall, 2493 participants had COPD, and COPD was associated with an 18% increased risk of VTE (HR, 1.18; 95% CI, 0.92-1.50) compared to those with airflow without obstruction in a model adjusted for age and sex. However, the risk of VTE was substantially higher in those with severe COPD. The HR of VTE was 1.09 (95% CI, 0.85-1.42) in those with stage I to II COPD, and 1.92 (95% CI, 1.15-3.21) in those with stage III to IV COPD, compared to those with airflow without obstruction. Table 3 shows the risk of VTE according to categories of SpO2 and respiratory symptoms in subjects with and without COPD. SpO2 ≤ 96% was associated with increased risk...
TABLE 1  Baseline characteristics according to categories of oxygen saturation

| Oxygen saturation level (%) | ≥98 | 97 | ≤96 |
|-----------------------------|-----|----|-----|
| Observation periods         | 6169 (53.9) | 2951 (28.8) | 2318 (20.3) |
| Age (y)                     | 63.1 (9.7) | 65.7 (8.9) | 67.1 (8.3) |
| Sex (male)                  | 2386 (38.6) | 1435 (48.6) | 1136 (49.0) |
| Daily smoking               | 1288 (21.1) | 612 (21.0) | 558 (24.3) |
| Body mass index (kg/m²)     | 26.0 (3.8) | 27.7 (4.0) | 28.5 (4.7) |
| History of CVD              | 768 (12.5) | 472 (16.0) | 465 (20.1) |
| History of cancer           | 480 (7.8) | 264 (9.0) | 212 (9.2) |
| COPD stages                 |       |     |     |
| Airflow without obstruction | 4744 (80.9) | 2127 (75.8) | 1483 (68.0) |
| Stage I-II                  | 1066 (18.2) | 607 (21.7) | 555 (25.4) |
| Stage III-IV                | 52 (0.9) | 69 (2.5) | 144 (6.6) |
| Dyspnea when walking calmly | 131 (2.1) | 95 (3.2) | 130 (5.6) |
| Dyspnea while washing and dressing | 150 (2.4) | 120 (4.1) | 183 (7.9) |
| Dyspnea at rest             | 96 (1.6) | 53 (1.8) | 56 (2.4) |
| Cough daily in periods of the year | 965 (15.6) | 554 (18.8) | 564 (24.3) |
| Chronic cough               | 580 (9.4) | 361 (12.2) | 405 (17.5) |
| Productive cough (in periods of the year) | 649 (10.5) | 379 (12.8) | 435 (18.8) |

Note: Values are n (%) or mean ± SD.
Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

of VTE both in subjects with airflow without obstruction and in subjects with COPD. The degree of dyspnea was associated with increased risk of VTE in subjects with airflow without obstruction, and particularly among those with COPD. Subjects with COPD and dyspnea at rest had a >3-fold higher risk of VTE (multivariable HR, 3.30; 95% CI, 1.35-8.04) compared with those with airflow without obstruction and no dyspnea. Chronic cough with phlegm was associated with VTE only in subjects with concomitant COPD (Table 3).

4 | DISCUSSION

In the present study, we investigated how individual respiratory symptoms (ie, dyspnea, cough, and phlegm) and oxygen saturation, alone and in combination with COPD, affected the VTE risk. We found that subjects with SpO₂ ≤96% (lowest 20th percentile) had a 1.5-fold higher risk of VTE than subjects with SpO₂ ≥98% (highest 40th percentile). In addition, severe manifestations of individual respiratory symptoms were associated with a 1.4 to 2.0-fold higher risk of VTE compared with those without such symptoms. COPD combined with severe respiratory symptoms or lowered SpO₂ had an additive effect on the VTE risk, suggesting that COPD patients with severe respiratory symptoms or lowered SpO₂ should attract particular attention with regard to prevention strategies for VTE.

In the present study, we observed that moderately lowered oxygen saturation was associated with a higher risk of VTE among subjects recruited from the general population. There are several conditions that could lead to lowered SpO₂, such as obesity,26 heart failure,28 COPD,14,27 and cancers affecting the cardiorespiratory system.29 These conditions are all associated with VTE risk,11,12,30,32 and may act as confounders for the relationship between lowered SpO₂ and VTE risk. However, the risk estimates for VTE by categories of SpO₂ were only marginally affected in the multivariable model taking obesity, history of CVD, and cancer into account. Moreover, SpO₂ was associated with increased risk of VTE in analyses restricted to subjects with airflow without obstruction. This suggest that a skewed distribution of obesity, CVD, COPD and cancer between subjects with high and low SpO₂ does not explain the apparent association between low SpO₂ and VTE risk. Even though the underlying mechanism(s) are unknown, several lines of evidence support a direct relationship between hypoxia or hypoxemia and VTE risk. First, hypoxia induces secretion of Weibel-Palade bodies in endothelial cells,33 with subsequent expression at the cell surface and release of von Willebrand factor and P-selectin,34 both of which are associated with VTE risk. Second, hypoxia is reported to affect key components in the pathogenesis of thrombus formation. Hypoxia increases platelet reactivity40 and, though controversial, hypoxia has been shown to increase coagulation activation in some40 but not all studies.41 Third, systemic hypoxia has been shown to accelerate thromboembolic events in mice through induction of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 inflammasome complex.42 Fourth, severe hypoxia is also reported to increase the incidence and size of thrombi in the inferior vena cava stenosis model in mice.20

In coherence with previous cohort studies,11,12 COPD was found to be associated with a moderately higher risk of VTE that increased with the severity of COPD. In the present study, we additionally found that the combination of COPD and lowered SpO₂ had an additive effect on the risk of VTE. Patients with COPD with hypoxemia are known to have larger mean platelet volume (MPV)15 and increased platelet reactivity16 compared to those with normal oxygen saturation. High MPV has been identified as a biomarker of increased VTE risk,53 and the protective effect of antiplatelet drugs strongly suggests that platelet reactivity plays an important role in the pathogenesis of VTE.44 Furthermore, patients with COPD have higher coagulation activation than age- and sex-matched controls,17,18 and exposure to short-term hypoxia further augments coagulation activation.19 In light of these latter findings, it is pertinent to speculate that the additive effect of COPD and
TABLE 2  Risk of VTE according to oxygen saturation and respiratory symptoms

| Oxygen saturation (SpO₂) | Person-years | Events | IR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|--------------------------|--------------|--------|-------------|---------------------|---------------------|
| SpO₂ ≥ 98%               | 50,450       | 137    | 2.72 (2.30-3.21) | Reference           | Reference           |
| SpO₂ 97%                 | 23,778       | 93     | 3.91 (3.19-4.79) | 1.26 (0.97-1.65)    | 1.19 (0.91-1.56)    |
| SpO₂ ≤ 96%               | 18,835       | 100    | 5.31 (4.36-6.46) | 1.58 (1.22-2.05)    | 1.48 (1.13-1.93)    |

| Dyspnea                  |              |        |             |                     |                     |
|--------------------------|--------------|--------|-------------|---------------------|---------------------|
| None                     | 86,989       | 290    | 3.33 (2.97-3.74) | Reference           | Reference           |
| Dyspnea when walking calmly, washing or dressing | 4439 | 28 | 6.31 (4.36-9.13) | 1.49 (1.00-2.20) | 1.37 (0.92-2.04) |
| Dyspnea at rest          | 1636         | 12     | 7.33 (4.17-12.9) | 2.18 (1.22-3.88)    | 2.04 (1.14-3.66)    |

| Cough                    |              |        |             |                     |                     |
|--------------------------|--------------|--------|-------------|---------------------|---------------------|
| None                     | 75,678       | 251    | 3.32 (2.93-3.75) | Reference           | Reference           |
| Cough daily (in periods of the year) | 6800 | 27 | 3.97 (2.72-5.79) | 1.21 (0.81-1.80)    | 1.21 (0.81-1.80)    |
| Chronic cougha           | 10,585       | 52     | 4.91 (3.74-6.44) | 1.39 (1.03-1.87)    | 1.39 (1.03-1.88)    |

| Phlegm                   |              |        |             |                     |                     |
|--------------------------|--------------|--------|-------------|---------------------|---------------------|
| None                     | 81,638       | 271    | 3.32 (2.95-3.74) | Reference           | Reference           |
| Productive cough (in periods of the year) | 11,426 | 59 | 5.16 (4.00-6.66) | 1.40 (1.05-1.85)    | 1.39 (1.04-1.85)    |

Note: Model 1: adjusted for age (time scale) and sex. Model 2: adjusted for age (time scale), sex, body mass index, history of cardiovascular disease, and history of cancer.

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1000 person-years; VTE, venous thromboembolism.

aCough daily >3 months past 2 years.

FIGURE 1  Risk of venous thromboembolism (A), pulmonary embolism (B), and deep vein thrombosis (C), according to oxygen saturation and respiratory symptoms. Hazard ratios (HRs) with 95% confidence intervals (CIs) adjusted for age (time scale), sex, BMI, history of CVD, and history of cancer.BMI, body mass index; CVD, cardiovascular disease.
lowered SpO\textsubscript{2} on VTE risk is mediated by the same pathophysiological mechanism.

Previously, Kubota et al\textsuperscript{11} reported that the presence of any respiratory symptom (dyspnea, cough, and phlegm) was associated with 1.4-fold higher VTE risk in subjects with normal spirometry compared to those without respiratory symptoms. In the present study, we extended the knowledge by showing that all respiratory symptoms (dyspnea, cough, and phlegm) were individually associated with VTE risk, and that the VTE risk increased with the severity of the dyspnea and cough. Even though the mechanism for the association between respiratory symptoms and VTE risk is unknown, it is obvious that these respiratory symptoms merely are markers rather than mediators of the VTE risk. It could be speculated that the VTE risk by respiratory symptoms is attributed to associated

### TABLE 3  Risk of VTE according to oxygen saturation and categories of COPD

| Oxygen saturation (SpO\textsubscript{2}) | Person-years | Events | IR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|----------------------------------------|--------------|--------|-------------|---------------------|---------------------|
| **Airflow without obstruction**        |              |        |             |                     |                     |
| SpO\textsubscript{2} ≥ 98%             | 38 847       | 100    | 2.57 (2.12-3.13) | Reference           | Reference           |
| SpO\textsubscript{2} 97%               | 17 322       | 60     | 3.46 (2.69-4.46) | 1.20 (0.87-1.65)    | 1.12 (0.81-1.55)    |
| SpO\textsubscript{2} ≤ 96%             | 12 270       | 60     | 4.88 (3.79-6.30) | 1.54 (1.12-2.13)    | 1.40 (1.01-1.96)    |
| **COPD**                               |              |        |             |                     |                     |
| SpO\textsubscript{2} ≥ 98%             | 9039         | 31     | 3.43 (2.41-4.89) | 1.03 (0.70-1.55)    | 1.06 (0.70-1.60)    |
| SpO\textsubscript{2} 97%               | 5249         | 30     | 5.71 (4.00-8.17) | 1.52 (1.00-2.30)    | 1.51 (0.99-2.29)    |
| SpO\textsubscript{2} ≤ 96%             | 5446         | 36     | 6.61 (4.77-9.16) | 1.77 (1.20-2.61)    | 1.72 (1.17-2.54)    |
| **Dyspnea**                            |              |        |             |                     |                     |
| Airflow without obstruction            |              |        |             |                     |                     |
| None                                   | 64 777       | 200    | 3.09 (2.69-3.55) | Reference           | Reference           |
| Dypsnea when walking calmly, washing or dressing | 2585       | 14     | 5.42 (3.21-9.15) | 1.39 (0.81-2.40)    | 1.25 (0.72-2.18)    |
| Dypsnea at rest                        | 1077         | 6      | 5.57 (2.50-12.4) | 1.75 (0.78-3.95)    | 1.59 (0.70-3.59)    |
| COPD                                   |              |        |             |                     |                     |
| None                                   | 17 687       | 79     | 4.47 (3.58-5.57) | 1.12 (0.86-1.45)    | 1.18 (0.90-1.54)    |
| Dypsnea when walking calmly, washing or dressing | 1631       | 13     | 7.97 (4.63-13.7) | 1.76 (1.00-3.10)    | 1.66 (0.94-2.93)    |
| Dypsnea at rest                        | 417          | 5      | 12.0 (5.00-28.8) | 3.12 (1.28-7.58)    | 3.30 (1.35-8.04)    |
| **Cough**                              |              |        |             |                     |                     |
| Airflow without obstruction            |              |        |             |                     |                     |
| None                                   | 57 540       | 179    | 3.11 (2.69-3.60) | Reference           | Reference           |
| Cough daily (in periods of the year)   | 4411         | 18     | 4.08 (2.57-6.48) | 1.33 (0.82-2.16)    | 1.30 (0.80-2.11)    |
| Cough daily > 3 months last two years  | 6489         | 23     | 3.54 (2.35-5.33) | 1.08 (0.70-1.67)    | 1.06 (0.69-1.64)    |
| COPD                                   |              |        |             |                     |                     |
| None                                   | 14 043       | 63     | 4.49 (3.50-5.74) | 1.09 (0.82-1.46)    | 1.14 (0.85-1.54)    |
| Cough daily (in periods of the year)   | 2092         | 6      | 2.87 (1.29-6.38) | 0.76 (0.34-1.72)    | 0.81 (0.36-1.82)    |
| Cough daily > 3 months last two years  | 3599         | 28     | 7.78 (5.37-11.3) | 1.95 (1.30-2.91)    | 2.08 (1.39-1.53)    |
| **Phlegm**                             |              |        |             |                     |                     |
| Airflow without obstruction            |              |        |             |                     |                     |
| None                                   | 61 833       | 195    | 3.15 (2.74-3.63) | Reference           | Reference           |
| Productive cough (in periods of the year) | 6606        | 25     | 3.78 (2.55-5.60) | 1.11 (0.73-1.68)    | 1.08 (0.71-1.64)    |
| COPD                                   |              |        |             |                     |                     |
| None                                   | 15 431       | 66     | 4.28 (3.36-5.44) | 1.04 (0.79-1.38)    | 1.10 (0.82-1.46)    |
| Productive cough (in periods of the year) | 4303        | 31     | 7.20 (5.06-10.2) | 1.73 (1.17-2.53)    | 1.82 (1.24-2.69)    |

Note: Model 1: adjusted for age (time scale) and sex. Model 2: adjusted for age (time scale), sex, body mass index, history of cardiovascular disease, and history of cancer. Information on COPD was available in 8129 subjects in whom 315 VTEs occurred during follow-up.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence rate per 1000 person-years; VTE, venous thromboembolism.
comorbidities, such as immobility, cancer, heart failure, and others. The risk estimates for VTE by respiratory symptoms, however, remained unchanged after adjustments for BMI, cancer, and CVD. However, we cannot rule out the possibility of residual confounding, in particular by heart failure, as we only adjusted for CVD in general.

Our findings revealed an additive impact of COPD and other measures of respiratory impairments on the risk of VTE. Both severe respiratory symptoms (cough, dyspnea, and phlegm) and lowered SpO\textsubscript{2} had a detrimental effect on the VTE risk in patients with COPD. This may imply a need for close monitoring and consideration of VTE-preventing strategies in patients with COPD with severe respiratory symptoms or decreased SpO\textsubscript{2}.

Recruitment of participants from a general population, long-term follow-up with repeated measurements of exposure and confounders, temporal sequence between exposure and outcome, and thorough adjudication of outcomes are major strengths of our study. Objective methods were used to assess COPD and SpO\textsubscript{2}, as spirometry was used for measurement of airflow patterns, and SpO\textsubscript{2} was measured by a digital handheld pulse oximeter. The personnel who performed outcome adjudication were blinded to the baseline variable, and potential exposure misclassification would likely be non-differential (ie, not related to the outcome). The study also had some limitations. Unfortunately, the statistical power was too low to perform subgroup analyses. For some estimates, the CIs were wide, and our findings should therefore be interpreted with caution. Moreover, participants with asthma could potentially have been misclassified as having COPD, as spirometry was performed without reversibility testing. Presence of respiratory symptoms was registered on a self-administered questionnaire and this could lead to nondifferential misclassification, which could bias our estimates toward null.

In conclusion, lowered SpO\textsubscript{2} and individual respiratory symptoms (dyspnea, cough, and phlegm) were associated with an increased risk of VTE. COPD combined with severe respiratory symptoms or lowered SpO\textsubscript{2} had an additive effect on the VTE risk. Our findings may suggest that particular attention with regard to VTE preventive strategies should be considered for patients with COPD with severe respiratory symptoms or lowered SpO\textsubscript{2}.

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**RELATIONSHIP DISCLOSURE**

The authors report nothing to disclose.

**AUTHOR CONTRIBUTIONS**

Conception and design: JBH. Data collection: TB, LE, SKB, HM, and JBH. Statistical analyses: TB and SKB. Draft of manuscript: TB, JBH. Interpretation of results: TB, LE, WMM, HM, SKB, and JBH. Critical revision of manuscript: LE, WMM, HM, SKB, and JBH.

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How to cite this article: Børvik T, Evensen LH, Morelli VM, Melbye H, Braekkan SK, Hansen J-B. Impact of respiratory symptoms and oxygen saturation on the risk of incident venous thromboembolism—the Tromsø study. Res Pract Thromb Haemost. 2020;4:255–262. https://doi.org/10.1002/rth2.12299