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ORIGINAL RESEARCH

# Low $FEV_1$, smoking history, and obesity are factors associated with oxygen saturation decrease in an adult population cohort

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**Background:** Worsening of pulmonary diseases is associated with a decrease in oxygen saturation ($SpO_2$). Such a decrease in $SpO_2$ and associated factors has not been previously evaluated in a general adult population.

**Aim:** We sought to describe $SpO_2$ in a sample of adults, at baseline and after 6.3 years, to determine whether factors predicting low $SpO_2$ in a cross-sectional study were also associated with a decrease in $SpO_2$ in this cohort.

**Methods:** As part of the Tromsø Study, 2,822 participants were examined with pulse oximetry in Tromsø 5 (2001/2002) and Tromsø 6 (2007/2008). Low $SpO_2$ by pulse oximetry was defined as an $SpO_2$ ≤95%, and $SpO_2$ decrease was defined as a ≥2% decrease from baseline to below 96%.

**Results:** A total of 139 (4.9%) subjects had a decrease in $SpO_2$. Forced expiratory volume in 1 second ($FEV_1$) <50% of the predicted value and current smoking with a history of ≥10 pack-years were the baseline characteristics most strongly associated with an $SpO_2$ decrease in multivariable logistic regression (odds ratio 3.55 [95% confidence interval (CI) 1.60–7.89] and 2.48 [95% CI 1.48–4.15], respectively). Male sex, age, former smoking with a history of ≥10 pack-years, body mass index ≥30 kg/m$^2$, and C-reactive protein ≥5 mg/L were also significantly associated with an $SpO_2$ decrease. A significant decrease in $FEV_1$ and a new diagnosis of asthma or chronic obstructive pulmonary disease during the observation period most strongly predicted a fall in $SpO_2$. A lower $SpO_2$ decrease was observed in those who quit smoking and those who lost weight, but these tendencies were not statistically significant.

**Conclusion:** A decrease in $SpO_2$ was most strongly associated with severe airflow limitation and a history of smoking. Smoking cessation and reducing obesity seem to be important measures to target for avoiding $SpO_2$ decreases in the general population.

**Keywords:** pulse oximetry, lung function, cohort study, general population

## Introduction

Pulse oximetry is an inexpensive, noninvasive method for measuring oxygen saturation ($SpO_2$). Pulse oximetry has a wide range of use both in primary pulmonary care and critical care medicine. Low $SpO_2$/hypoxemia have been associated with conditions or diseases causing ventilation–perfusion mismatch in the lungs, hypoventilation, right-to-left shunts, reduced diffusion capacity, and reduced oxygen partial pressure in inspired air. Decrease in $SpO_2$/desaturation has been associated with the worsening of preexisting pulmonary diseases.[1–3]

There is no clear cutoff point for abnormal $SpO_2$, but $SpO_2$ ≤95% is used in most adult studies. In their blood gas reference values for sea level, Crapo et al found mean

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arterial oxygen saturation ($SaO_2$) to be 95.5%–96.9% (standard deviation [SD] 0.4%–1.4%), depending on age.[4] Resting $SpO_2$ ≤95% has been found to predict oxygen desaturation during sleep, exercise, and flights, in chronic obstructive pulmonary disease (COPD) patients.[5–7] $SpO_2$ ≤95% has also been identified as a risk factor for postoperative pulmonary complications.[8] The limit of 96% therefore seems a reasonable cutoff value. A cutoff value of ≤92% has been used when screening for respiratory failure in COPD.[9]

In a previous cross-sectional study, we have shown that body mass index (BMI) and the forced expiratory volume in 1 second ($FEV_1$) as a percentage of the predicted value ($FEV_1$ % predicted) are the most important predictors of low $SpO_2$ in the general adult population.[10] Other predictors for low $SpO_2$ are former and current smoking, C-reactive protein (CRP) ≥5 mg/L, age, male sex, elevated hemoglobin, and respiratory symptoms.

The role of inflammation in lung function decline is not clearly understood. CRP and other biomarkers have, in COPD, been associated with progression of the disease and decline in lung function.[11–13] Systemic inflammation in COPD might play a role in the development of extrapulmonary comorbid conditions.[14,15] Elevated CRP levels have previously been found to be associated with cardiovascular disease (CVD), metabolic syndrome, and obesity. In sleep apnea, elevated CRP has been associated with hypoxemia.[16,17] Sleep apnea is associated with obesity and metabolic syndrome, both characterized by systemic inflammation and comorbidities.[18] In some studies, elevated CRP has been associated with hypoxemia in COPD patients.[19,20]

Lung function decline in adult population cohorts has been evaluated by spirometry, but decrease in $SpO_2$ has not been studied. We wanted to investigate changes in $SpO_2$ in an adult population cohort to determine whether parameters predicting low $SpO_2$ in a cross-sectional study were also associated with a decrease in $SpO_2$ in a cohort study.

# Material and methods

## Subjects

A cohort of the adult population in Tromsø, Norway has been followed in the Tromsø Study since 1974. Tromsø is a university city in northern Norway, with approximately 70,000 inhabitants. To date, the Tromsø Study has consisted of six cross-sectional studies. Participant selection in Tromsø 4 (1994/1995) has influenced later studies as described in the cohort profile (Figure 1).[21] In the fourth study, all inhabitants of Tromsø 55–74 years of age, and 5%–10% of the samples in the other cohorts aged 25–84 years were asked to take part in an extra, more extended medical examination; a total of 7,916 (77%) participated. All participants who had this second visit in Tromsø 4 were invited to the Tromsø 5 Study[21] and were again eligible for a second, extended, medical examination. As part of the fifth Tromsø Study (2001/2002), 5,152 subjects were examined with pulse oximetry. Of these, 3,453 (67.0%) participants also took part in Tromsø 6 (2007/2008),[21] and 3,127 (60.7%) attended the extended examination. Figure 2 shows the flow chart of participants from Tromsø 5 to 6.

A total of 9.8% of the participants were not examined with pulse oximetry and spirometry due to absence of staff or drop out related to wait time for lung function testing. $SpO_2$ values of 2,822 participants were measured in both Tromsø 5 and Tromsø 6. The mean time between measurements was 6.3 years (SD 0.4 years).

## Examinations

In both Tromsø 5 and Tromsø 6, a questionnaire including medical history and smoking habits was enclosed in the invitation to participate. Participants who reported suffering from angina pectoris, myocardial infarction, or cerebral stroke were classified as "self-reported CVD". "Pack-years" of cigarette use was calculated by multiplying the average number of cigarettes smoked daily by the number of years smoked and dividing the product by 20. Subjects who attended the assessment received an additional questionnaire about dyspnea, cough, and sputum. Examinations at the first visit included height and weight, and BMI ($kg/m^2$) was calculated.

Pulse oximetry and spirometry were included at the second visit for both Tromsø 5 and Tromsø 6. $SpO_2$ values were measured with a digital handheld pulse oximeter (Onyx II® 9550; Nonin Medical, Inc., Plymouth, MN, USA). Participants rested at least 15 minutes before examination. The best of three measurements was recorded. The manufacturer's testing has shown that only values between 70% and 100% are accurate to within ±2%, and values below 70% are regarded as invalid. None of the participants received supplemental oxygen.

Spirometry was carried out using a SensorMedics Vmax™ Legacy 20® (VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA) in Tromsø 5, and the Vmax Encore 20® (VIASYS Healthcare Respiratory Technologies) in Tromsø 6. American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for spirometry testing were followed.[22] Norwegian reference values for prebronchodilator spirometry were used because reversibility testing was not performed.[23] Three trained technicians conducted the spirometry.

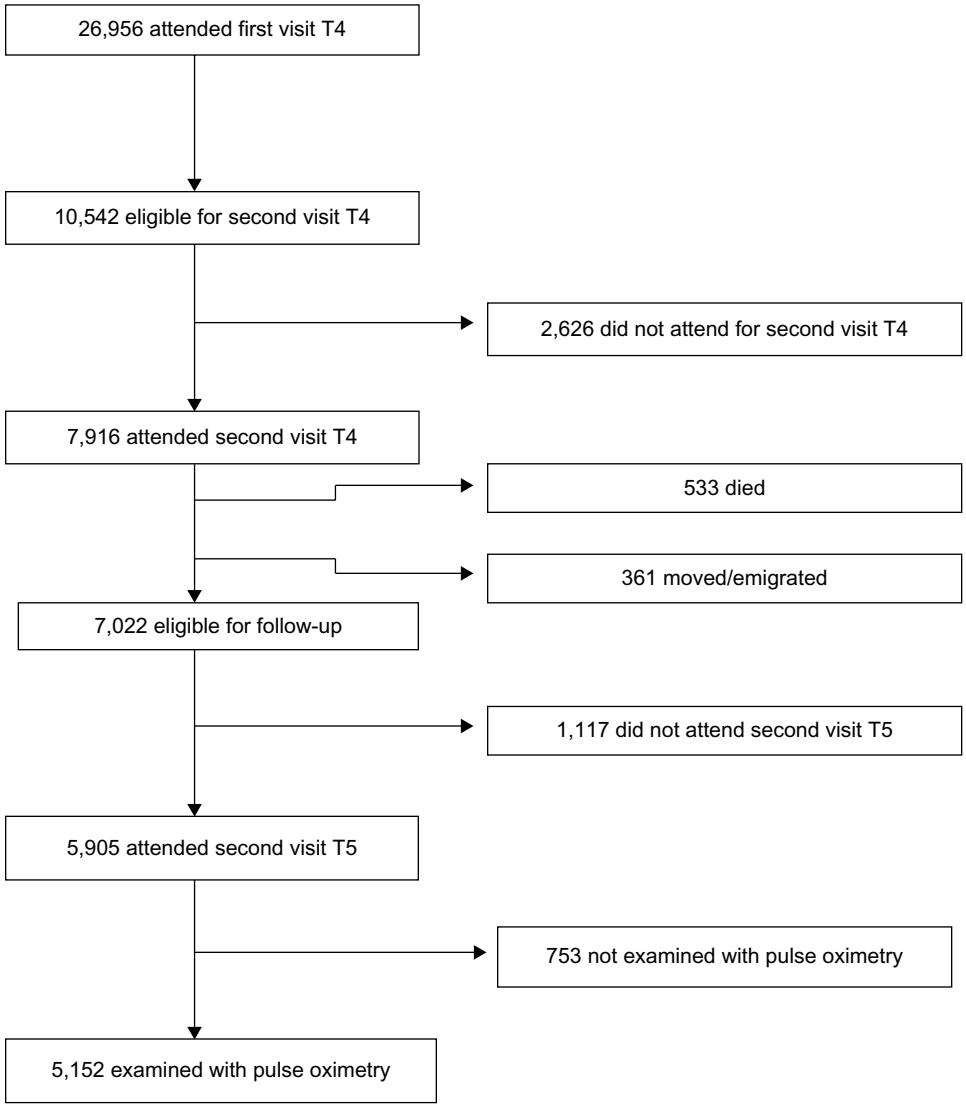


**Figure 1** Participation from Tromsø 4 (T4) to Tromsø 5 (T5).

## Adjustment of spirometry results

The mean annual $FEV_1$ decline of 14 mL/year (standard error [SE] 0.8) was lower than expected. The lowest mean decline recorded, in samples of women who never smoked, was 17.6 mL/year, but higher values, depending on sex, age, and history of smoking, are usually found.[24,25] We therefore considered potential sources of bias. The use of two different spirometers in Tromsø 5 and 6 was a likely source. The Norwegian supplier confirmed that the Vmax Legacy used in Tromsø 5 probably provided values that were too low and that this was not the case for Vmax Encore used in Tromsø 6, but no documentation could be provided. Küenzli et al have demonstrated that using different spirometers in longitudinal studies is a source of bias.[26] We therefore tested 48 subjects, 24 patients and 24 voluntary employees using both spirometers. The mean $FEV_1$ value found with the Vmax Legacy was 2.5% (66 mL [SE 14 mL]) lower than that measured by the Vmax Encore. We therefore chose to correct the $FEV_1$ values in Tromsø 5 by adding 2.5%. Likewise, forced vital capacity (FVC), was 5.2% (188 mL [SE 25 mL]) lower when the Vmax Legacy was used compared with the Vmax Encore.

## Laboratory samples

Blood was drawn for high-sensitivity CRP, fibrinogen, and uric acid analyses (also biomarkers of inflammation). For 3 consecutive days, albumin and creatinine were measured in urine, and the albumin:creatinine ratio (ACR) was estimated for each day. Mean values were used in the analysis, and an ACR between 3.0 and 30.0 mg/mmol was used as an indication of microalbuminuria.

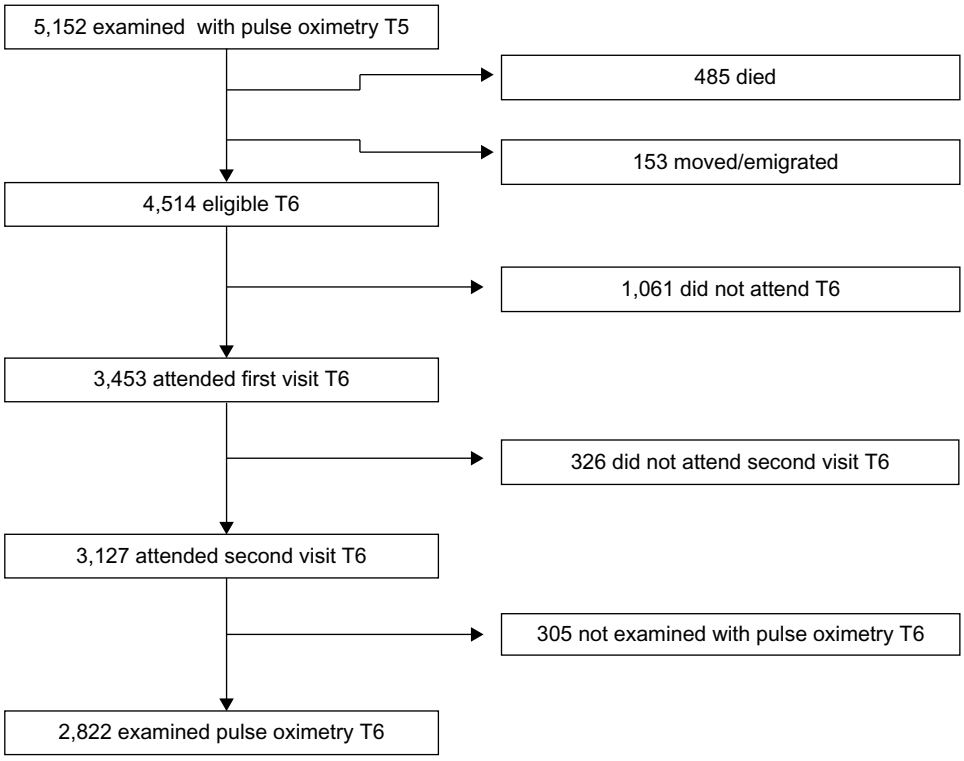


**Figure 2** Participation from Tromsø 5 (T5) to Tromsø 6 (T6).

## Statistical analysis

Low $SpO_2$ was defined by $SpO_2 \leq 95\%$, and $SpO_2$ decrease was defined by ≥2% decrease from baseline to <96%. Differences in continuous variables between subgroups at baseline (Tromsø 5) were explored using the Mann–Whitney *U* test, and differences found between baseline and after 6.3 years were explored using the Wilcoxon signed-rank test. Frequency of $SpO_2$ decrease was analyzed by sex, age, smoking habit, spirometry, BMI, CRP, fibrinogen, uric acid, ACR, self-reported health and diseases, and pulmonary symptoms. Continuous variables (age, BMI, $FEV_1$, fibrinogen, uric acid, ACR, and CRP) were categorized, and the statistical significance of differences was analyzed by chi-square test. Predictors of $SpO_2$ decrease with a statistical significance of <5% were entered into a multivariable binary logistic regression and excluded by backward stepwise elimination. Only predictors with $P<0.05$ were kept in the final model. Changes from baseline variables other than $SpO_2$ were registered and continuous variables categorized, based on one standard deviation. The associations with $SpO_2$ decrease were analyzed by chi-square test. IBM SPSS Statistics for Windows, Version 21 (IBM Corp, Armonk, NY, USA) was used.

The Regional Committee for Medical and Health Research Ethics in North Norway approved the Tromsø 5 and 6 surveys. All participants gave written, informed consent.

# Results

Among the 2,822 participants who had $SpO_2$ measured in both studies, 241 (8.5%) and 213 (7.5%) had an $SpO_2 \leq 95\%$ in Tromsø 5 and Tromsø 6, respectively. Fifty-six (2.0%) had $SpO_2 \leq 95\%$ in both studies. Sixteen (0.6%) in Tromsø 5 and 25 (0.9%) participants in Tromsø 6 had $SpO_2 \leq 92\%$. $SpO_2$ decrease was seen in 139 (4.9%) participants. Mean age at baseline of the 2,822 participants was 63.2 (SD 8.9) years, range 32–81 years. No significant difference was seen between mean $SpO_2$ at baseline (97.4%) and that found after 6.3 years (97.3%). Self-reported diseases were more frequently reported in Tromsø 6 than in Tromsø 5, but the frequency of current smoking dropped from 23.7 to 15.2 (Table 1). Valid spirometry was found in 2,728 participants, for both baseline and after 6.3 years. Mean $FEV_1$ % predicted increased significantly, from 88.7% to 90.8% ($P<0.001$). There was no significant change in mean BMI, but in those with BMI ≥30 kg/m$^2$ at baseline, the BMI decreased significantly, from 32.8 to 32.4 ($P<0.001$).

Table 2 displays frequency of $SpO_2$ decrease by baseline characteristics. Age, male sex, self-reported CVD, obesity (BMI ≥30 kg/m$^2$), $FEV_1$ % predicted, chronic cough with sputum, and smoking were all significantly associated with a $SpO_2$ decrease in univariable analysis, as were the biomarkers CRP, fibrinogen, and uric acid.

**Table 1** Characteristics of 2,822 participants in Tromsø 5 (baseline) and Tromsø 6 (6.3 years later)

| | Tromsø 5 | | Tromsø 6 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Sex | | | | |
| Female | 1,625 | (57.6) | | |
| Male | 1,197 | (42.4) | | |
| Age (years) | | | | |
| <70 | 2,162 | (76.6) | 1,346 | (47.7) |
| ≥70 | 660 | (23.4) | 1,476 | (53.3) |
| Self-reported diseases | | | | |
| CVD | 348 | (12.3) | 541 | (19.2) |
| Asthma | 218 | (7.7) | 288 | (10.2) |
| COPD | 115 | (4.1) | 178 | (6.3) |
| Diabetes | 87 | (3.1) | 198 | (7.0) |
| Hypertension | 571 | (20.2) | 1,018 | (36.1) |
| Smoking history | | | | |
| Never smoked | 1,010 | (35.8) | 1,008 | (35.7) |
| Former smoker | 1,143 | (40.5) | 1,386 | (49.1) |
| ≥10 pack-years | 630 | (22.3) | 816 | (28.9) |
| Current smoker | 669 | (23.7) | 428 | (15.2) |
| ≥10 pack-years | 558 | (19.8) | 387 | (13.7) |
| Dyspnea[a] | | | | |
| 0 | 1,557 | (55.2) | 1,335 | (47.3) |
| 1 | 1,120 | (39.7) | 1,266 | (44.9) |
| ≥2 | 145 | (5.1) | 221 | (7.8) |
| Chronic cough with sputum | | | | |
| No | 2,646 | (93.8) | 2,637 | (93.4) |
| Yes | 176 | (6.2) | 185 | (6.6) |
| BMI (kg/m$^2$) | | | | |
| <20 | 57 | (2.0) | 75 | (2.7) |
| 20–30 | 2,171 | (76.9) | 2,163 | (76.7) |
| ≥30 | 585 | (20.8) | 583 | (20.7) |
| $FEV_1$ % predicted | | | | |
| ≥80 | 2,018 | (71.5) | 2,089 | (74.0) |
| 50–80 | 708 | (25.1) | 614 | (21.8) |
| <50 | 48 | (1.7) | 65 | (2.3) |
| $FEV_1$/FVC ratio | | | | |
| <70 | 631 | (23.1) | 805 | (29.5) |
| ≥70 | 2,097 | (76.9) | 1,923 | (70.5) |
| Spirometry pattern | | | | |
| Normal | 1,923 | (70.5) | 1,775 | (65.1) |
| Obstructive | 631 | (23.1) | 805 | (29.5) |
| Restrictive | 174 | (6.4) | 148 | (5.4) |
| CRP (mg/L) | | | | |
| <5 | 2,426 | (86.0) | 2,438 | (86.4) |
| ≥5 | 357 | (12.7) | 340 | (12.0) |
| Hemoglobin (g/dL)[b] | | | | |
| ≤Upper limits | 2,546 | (90.2) | 2,741 | (97.1) |
| >Upper limits | 8 | (0.3) | 37 | (1.3) |
| Fibrinogen (g/L) | | | | |
| <4 | 2,304 | (81.6) | 1,943 | (68.9) |
| ≥4 | 312 | (11.1) | 834 | (29.6) |
| Uric acid (μmol/L)[c] | | | | |
| ≤Upper limits | 2,547 | (90.3) | 2,601 | (92.2) |
| >Upper limits | 110 | (3.9) | 177 | (6.3) |
| Albumin:creatinine ratio (mg/mmol) | | | | |
| <3 | 2,606 | (92.3) | 2,475 | (87.7) |
| ≥3 | 127 | (4.5) | 231 | (8.2) |
| $SpO_2$ | | | | |
| ≥96 | 2,581 | (91.5) | 2,609 | (92.5) |
| 93–95 | 225 | (8.0) | 188 | (6.7) |
| ≤92 | 16 | (0.6) | 25 | (0.9) |

**Notes:** "Pack-years" were obtained by multiplying the average number of cigarettes smoked daily by the number of years smoked and dividing the product by 20. [a]dyspnea: 0= no dyspnea, 1= dyspnea walking rapidly on level ground or up a moderate slope, and ≥2= dyspnea walking calmly on level ground, washing or dressing, or at rest; [b]upper limits: men 17 g/dL, women 16 g/dL; [c]upper limits: men 480 μmol/L, women 18–49 years 350 μmol/L, women ≥50 years 400 μmol/L.

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; $SpO_2$, arterial oxygen saturation as measured by pulse oximetry.

Table 3 shows the results of the multivariable logistic regression. In the final multivariable analysis, 2,682 subjects were included. Current smoking with pack-years ≥10 and $FEV_1$ % predicted <50 had the highest odds ratio (OR), 2.48 (1.48–4.15) and 3.55 (1.60–7.89), respectively. In addition age, male sex, former smoking with pack-years ≥10, increased CRP, and high BMI were significant predictors in the multivariable analysis. We did not find any significant interactions. Assumptions for logistic regression were met, and we did not find any multicollinearity.

When $FEV_1$/FVC ratio, as a dichotomous (with a threshold of 0.7 or lower) or as a continuous variable, was added to the multivariable model that included $FEV_1$ % predicted, no significant association with $SpO_2$ decrease was found; 91.7% of $FEV_1$ % predicted <50 had $FEV_1$/FVC ratio <0.7.

Frequency of $SpO_2$ decrease by changes from baseline of other variables (across Tromsø 5 and Tromsø 6) is shown in Table 4. Participants who had been diagnosed with asthma, COPD, or diabetes between the two time points had a significantly higher incidence of $SpO_2$ decrease. These participants had significantly decreased $FEV_1$ % predicted at baseline, of 81.1, 71.5, and 82.8, respectively, ($P<0.001$). In addition, $FEV_1$ % predicted decrease/year and CRP increase were associated with $SpO_2$ decrease. As BMI increased, the frequency of decline in $SpO_2$ increased. The opposite was the case when BMI dropped. This trend was not statistically significant. Smoking cessation between the time points was associated with a lower frequency of $SpO_2$ decrease than was continued smoking, but this finding was not statistically significant.

## Discussion

$SpO_2$ decrease was associated with smoking history ≥10 pack-years, lung function (by $FEV_1$ % predicted <50),

**Table 2** Frequency of $SpO_2$ decrease by subjects' characteristics among 2,822 study participants

| | $SpO_2$ decrease (n) | (%) | *P*-value[a] |
|---|---|---|---|
| Total numbers | 139 | (4.9) | |
| Sex | | | |
| Female | 59 | (3.6) | <0.001 |
| Male | 80 | (6.7) | |
| Age (years) | | | |
| <70 | 96 | (4.4) | 0.031 |
| ≥70 | 43 | (6.5) | |
| Self-reported diseases | | | |
| CVD | 27 | (7.8) | 0.009 |
| Asthma | 12 | (5.5) | 0.7 |
| COPD | 9 | (7.8) | 0.1 |
| Diabetes | 7 | (8.0) | 0.2 |
| Hypertension | 28 | (4.9) | 1.0 |
| Smoking history | | | |
| Never smoking | 30 | (3.0) | |
| Former smoking | 65 | (5.7) | 0.002 |
| <10 pack-years | 21 | (4.1) | 0.2 |
| ≥10 pack-years | 44 | (7.0) | <0.001 |
| Smoking | 44 | (6.6) | <0.001 |
| <10 pack-years | 2 | (1.8) | 0.8 |
| ≥10 pack-years | 42 | (7.5) | <0.001 |
| Dyspnea[b] | | | |
| 0 | 68 | (4.4) | 0.3 |
| 1 | 62 | (5.5) | |
| ≥2 | 9 | (6.2) | |
| Chronic cough with sputum | | | |
| No | 122 | (4.6) | 0.003 |
| Yes | 17 | (9.7) | |
| BMI ($kg/m^2$) | | | |
| <20 | 3 | (5.3) | 0.033 |
| 20–30 | 95 | (4.4) | |
| ≥30 | 41 | (7.0) | |
| $FEV_1$ % predicted | | | |
| ≥80 | 84 | (4.2) | <0.001 |
| 50–80 | 44 | (6.2) | |
| <50 | 9 | (18.8) | |
| $FEV_1$/FVC ratio | | | |
| <70 | 39 | (6.2) | 0.08 |
| ≥70 | 94 | (4.5) | |
| Spirometry pattern | | | |
| Normal | 78 | (4.1) | 0.001 |
| Obstructive | 39 | (6.2) | |
| Restrictive | 16 | (9.2) | |
| CRP (mg/L) | | | |
| <5 | 107 | (4.4) | <0.001 |
| ≥5 | 32 | (9.0) | |
| Hemoglobin (g/dL)[c] | | | |
| ≤Upper limits | 126 | (4.9) | 0.7[d] |
| >Upper limits | 0 | (0.0) | |
| Fibrinogen (g/L) | | | |
| <4 | 107 | (4.6) | 0.011 |
| ≥4 | 25 | (8.0) | |
| Uric acid (μmol/L)[e] | | | |
| ≤Upper limits | 122 | (4.8) | 0.014 |
| >Upper limits | 11 | (10.3) | |
| Albumin:creatinine ratio (mg/mmol) | | | |
| <3 | 127 | (4.9) | 0.06 |
| ≥3 | 11 | (8.7) | |

**Notes:** "Pack-years" were obtained by multiplying the average number of cigarettes smoked daily by the number of years smoked and dividing the product by 20. [a]*P*-values by chi-square; for smoking compared with never smoking, for others by trend; [b]dyspnea: 0= no dyspnea, 1= dyspnea walking rapidly on level ground or up a moderate slope, and ≥2= dyspnea walking calmly on level ground, washing or dressing, or at rest; [c]upper limits men 17 g/dL, women 16 g/dL; [d]Fischer's exact test; [e]upper limits men 480 μmol/L, women 18–49 years 350 μmol/L, women ≥50 years 400 μmol/L.

**Abbreviations:** BMI, body mass index; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; $SpO_2$, arterial oxygen saturation as measured by pulse oximetry.

BMI ≥30 $kg/m^2$, CRP ≥5 mg/L, male sex, and age, in multivariable logistic regression. Decrease in $FEV_1$ % predicted was significantly associated with decrease in $SpO_2$, and a tendency, although not statistically significant, for less frequent $SpO_2$ decrease with BMI decrease and smoking cessation were also observed.

**Table 3** Factors associated with arterial oxygen saturation ($SpO_2$) decrease in multivariable logistic regression

| | OR | 95% CI | *P*-value |
|---|---|---|---|
| Sex | | | |
| Male | 1.68 | 1.15–2.45 | 0.008 |
| Age (years) | 1.03 | 1.01–1.06 | 0.008 |
| Smoking history | | | |
| Never smoking | 1 | | |
| Former smoking | | | |
| <10 pack-years | 1.14 | 0.62–2.09 | 0.7 |
| ≥10 pack-years | 1.74 | 1.04–2.92 | 0.035 |
| Smoking | | | |
| <10 pack-years | 0.71 | 0.17–3.04 | 0.6 |
| ≥10 pack-years | 2.48 | 1.48–4.15 | 0.001 |
| BMI ($kg/m^2$) | | | |
| <30 | 1 | | |
| ≥30 | 1.72 | 1.15–2.57 | 0.008 |
| $FEV_1$ % predicted | | | |
| ≥80 | 1 | | |
| 50–80 | 1.18 | 0.79–1.75 | 0.4 |
| <50 | 3.55 | 1.60–7.89 | 0.002 |
| CRP (mg/L) | | | |
| ≥5 | 1.74 | 1.12–2.71 | 0.013 |

**Notes:** N=2,682 subjects. Pack-years were obtained by multiplying the average number of cigarettes smoked daily by the number of years smoked and dividing the product by 20.

**Abbreviations:** BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; $FEV_1$, forced expiratory volume in 1 second; OR, odds ratio.

**Table 4** Frequency of $SpO_2$ decrease and associations to changes from baseline characteristics

| | Total (n) | $SpO_2$ decrease (n) | (%) | *P*-value |
|---|---|---|---|---|
| | 2,822 | 139 | (4.9) | |
| Self-reported diseases, new | | | | |
| CVD | 225 | 7 | (3.1) | 0.2 |
| Asthma | 104 | 14 | (13.5) | <0.001 |
| COPD | 117 | 16 | (13.7) | <0.001 |
| Diabetes | 113 | 10 | (8.8) | 0.049 |
| Hypertension | 512 | 28 | (5.5) | 0.5 |
| Smoking history T5–T6 | | | | 0.3 |
| Quit smoking | 266 | 14 | (5.3) | |
| Continued smoking | 399 | 30 | (7.5) | |
| BMI (kg/m$^2$) | | | | |
| All | | | | 0.09 |
| ≥2↑ | 302 | 22 | (7.3) | |
| 2↑–2↓ | 2,201 | 106 | (4.8) | |
| ≥2↓ | 309 | 11 | (3.6) | |
| ≥30 | | | | 0.1 |
| ≥2↑ | 60 | 7 | (11.5) | |
| 2↑–2↓ | 407 | 29 | (7.1) | |
| ≥2↓ | 115 | 4 | (3.5) | |
| $FEV_1$ % predicted/year[a] | | | | |
| ≥2↓ | 168 | 18 | (10.7) | <0.001 |
| CRP (mg/L) | | | | |
| ≥5↑ | 142 | 13 | (9.2) | 0.020 |
| Fibrinogen (g/L) | | | | |
| ≥1↑ | 593 | 33 | (5.6) | 0.6 |
| Uric acid (μmol/L) | | | | |
| ≥60↑ | 293 | 15 | (5.1) | 0.9 |
| Albumin:creatinine ratio (mg/mmol) | | | | |
| ≥3↑ | 142 | 8 | (5.6) | 0.7 |

**Notes:** [a]Decrease divided by years between examinations. Upward arrows indicate an increase, downward arrows indicate a decrease.

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; $FEV_1$, forced expiratory volume in 1 second; $SpO_2$, arterial oxygen saturation as measured by pulse oximetry; T5, Tromsø 5; T6, Tromsø 6.

## Comparison with previous studies

This study complements our previous cross-sectional study showing that smoking, $FEV_1$ % predicted, and obesity are the most important predictors of low $SpO_2$.[10] The findings from a longitudinal cohort provide stronger indications of a causal relationship than can be determined using a cross-sectional study.[27]

The association between male sex and a fall in $SpO_2$ was consistent with our previous findings. More men had previously smoked and had also smoked for more pack-years. CVD was also more common in men.

The impact of age was also consistent with the cross-sectional study. Aging means physiological changes and increasing comorbidity, and the summation of risk factors might accelerate an $SpO_2$ decrease.

We found a significant association between $SpO_2$ decrease and self-reported CVD in univariable analysis. CVD contributes to heart failure, which may affect pulmonary function and thus lower $SpO_2$. This association was not shown in multivariable analysis. One reason for this might be that CVD is strongly associated with both age and male sex.

Low $SpO_2$ and partial pressure of oxygen in arterial blood ($PaO_2$) in smokers have been shown in previous studies.[28,29] Even when correcting for lung function by $FEV_1$ % predicted, this association was clearly demonstrated.

More than 90% of the group with a $FEV_1$ % predicted <50 had an $FEV_1$/FVC ratio <0.7. Even though an $FEV_1$/FVC ratio <0.7 was not significant in univariate analysis, severe airflow limitation seems to be associated with an $SpO_2$ decrease.

We found that baseline CRP ≥5 mg/L was associated with an $SpO_2$ decrease in both uni- and multivariable analysis, and the associations with CVD and other chronic diseases probably contributed to increased OR in the multivariable analysis. Other biomarkers, such as fibrinogen, uric acid, and microalbuminuria (expressed by the albumin:creatinine ratio), were significant in univariable, but not multivariable, analyses. Microalbuminuria has been found to be associated with hypoxia (defined as $SpO_2$ ≤92%) in COPD.[30,31] In our study, less than 1% of participants had $SpO_2$ ≤92%, which may be a reason for not finding this association. CRP might also be a better marker of inflammation associated with $SpO_2$ decrease than microalbuminuria, fibrinogen, and uric acid.

BMI ≥30 kg/m$^2$ was, as expected, associated with $SpO_2$ decrease. Among other disorders, this group is at risk for sleep apnea and obesity hypoventilation, which is known to lead to low daytime $SpO_2$.[32–34]

Baseline hemoglobin above the upper limit was not associated with $SpO_2$ decrease. This was expected since a high hemoglobin value is usually a consequence of, rather than a reason for, a decrease in $SpO_2$.

A new diagnosis of asthma or COPD between the time points was associated with a decrease in $SpO_2$. Subjects with such a new diagnosis had decreased $FEV_1$ % predicted at baseline. COPD is frequently underdiagnosed, which may be linked to less help-seeking among smokers.[35] It is not unexpected that subjects recently diagnosed with COPD or asthma had troubling symptoms and increased risk of decreased $SpO_2$.

## Strength and limitation

The subjects in this study were a subgroup of participants in the cross-sectional study on $SpO_2$ from the sixth Tromsø Study.[10] This study would have provided stronger supplemental evidence if the subjects had been recruited from a separate population sample. Of the original group examined with lung function tests in Tromsø 5, only 54.8% were reexamined in Tromsø 6. We know that almost 10% died between these time points. Those with severe health problems and increased risk of low $SpO_2$ probably participated to a lesser degree than others. We found that almost 10% quit smoking, mean $FEV_1$ % predicted increased, and those in the obese category lost weight. A healthy survivor effect and a decreased representation of those with poor health may have led to a healthier sample. This may explain why aging did not lead to decreased $SpO_2$.

Smoking may have been a difficult topic for some participants, and thus there may have been some bias in categorizing smokers, former smokers, and never smokers. Yet previous studies have showed that self-reports of smoking are usually accurate.[36,37] The pack-years calculated might be uncertain, because of recall bias, especially among former smokers. Only seven out of 256 participants who quit smoking between Tromsø 5 and 6 had valid data on the question, "How long has it been since you stopped?" Some participants may have stopped smoking recently, and the effect of smoking cessation on $SpO_2$ may not have been measurable yet, thereby weakening the associations.

Pulse oximetry has some limitations; among others, high carboxyhemoglobin might have given falsely elevated $SpO_2$ in smokers and thus, diminished the association between $SpO_2$ and smoking.[38]

$SpO_2$ decrease may be imprecise since the accuracy of the device is within ±2%. By using three measurements, categorizing in groups, and excluding values that fell within the normal range ($SpO_2$ >95%), we tried to decrease this influence.

The $FEV_1$ % predicted values in Tromsø 6 increased. Reasons for this might be selection bias and a healthier sample. Using two different spirometers may also have contributed to the difference, even though we attempted to correct for this. Using age in whole years as of December 31 in calculating $FEV_1$ % predicted may have resulted in a systematic bias, since the mean years between analyses were 6.3, not 6.0;[39] however, this is likely to have underestimated the increase in predicted values. Due to the high number of subjects aged 75 years or older, a limitation in the validity of the reference values, when applied in the oldest age groups, might also have played a role.

## Clinical implications

This study describes associations between unhealthy lifestyle and decreased $SpO_2$. Smoking stands out as an important cause, and not only through its deteriorating effect on lung function. Obesity is another modifiable risk factor for decreased $SpO_2$. It is promising that the findings in this study indicate that subjects who stop smoking or lose weight may have a decreased risk of decreased $SpO_2$. It may be possible to stabilize $SpO_2$ with a healthier lifestyle.

# Conclusion

A decrease in $SpO_2$ was most strongly associated with low $FEV_1$ % predicted and a history of smoking. It was also associated with higher BMI. This is in accordance with the findings of our previous cross-sectional study. Smoking cessation and reducing obesity are important measures that may help avoid $SpO_2$ decrease in the general population.

# Author contributions

All authors participated in concept and design of the study. HM performed data collection, and MLV and HM performed data analysis and interpretation. MLV and HM drafted the manuscript. All authors participated in revision and gave final approval of the manuscript.

# Disclosure

The authors report no conflict of interest in this work.

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