



Nocturnal oxygen resaturation parameters are associated with cardiorespiratory comorbidities

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ABSTRACT

Background: There are strong associations between oxygen desaturations and cardiovascular outcomes. Additionally, oxygen resaturation rates are linked to excessive daytime sleepiness independent of oxygen desaturation severity. No studies have yet looked at the independent effects of comorbidities or medications on resaturation parameters.

Methods: The Sleep Heart Health Study data was utilised to derive oxygen saturation parameters from 5804 participants. Participants with a history of comorbidities or medication usage were compared against healthy participants with no comorbidity/medication history.

Results: 4293 participants (50.4% female, median age 64 years) were included in the analysis. Females recorded significantly faster resaturation rates (mean 0.61%/s) than males (mean 0.57%/s, $p < 0.001$), regardless of comorbidities. After adjusting for demographics, sleep parameters, and desaturation parameters, resaturation rate was reduced with hypertension (-0.09 (95% CI -0.16, -0.03)), myocardial infarction (-0.13 (95% CI -0.21, -0.04)) and heart failure (-0.19 (95% CI -0.33, -0.05)), or when using anti-hypertensives (-0.10 (95% CI -0.17, -0.03)), mental health medications (-0.18 (95% CI -0.27, -0.08)) or anticoagulants (-0.41 (95% CI -0.56, -0.26)). Desaturation to Resaturation ratio for duration was decreased with mental health (-0.21 (95% CI -0.34, -0.08)) or diabetic medications (-0.24 (95% CI -0.41, -0.07)), and desaturation to resaturation ratio for area decreased with heart failure (-0.25 (95% CI -0.42, -0.08)).

Conclusions: Comorbidities and medications significantly affect nocturnal resaturation parameters, independent of desaturation parameters. However, the causal relationship remains unclear. Further research can enhance our knowledge and develop more precise and safer interventions for individuals affected by certain comorbidities.

1. Introduction

Nocturnal oxygen saturation parameters, representing states of intermittent hypoxaemia (IH), have shown significant associations with

both acute and chronic outcomes stemming from sleep-disordered breathing. The predictive capacity for IH parameters exceeds that of the traditional apnoea-hypopnoea index (AHI) for psychomotor vigilance tasks [1,2], daytime sleepiness [3,4], risk of road traffic accidents [5,6], and all-cause mortality [7,8]. Thus far, however, nocturnal

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Abbreviation list

ABOSA	Automatic blood oxygen saturation signal analysis software
AF	Atrial fibrillation
AHI	Apnoea-hypopnoea index
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
D:R	Desaturation to resaturation
EDF	European data format
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
FEV ₁	Forced expiratory volume in 1 s
FSH	Female sex hormones
FVC	Forced vital capacity
GLI	Global lung function initiative
HF	Heart failure
HTN	Hypertension
IH	Intermittent hypoxaemia
IQR	Interquartile range

LD	Lung disease
LLN	Lower limit of normal
MI	Myocardial infarction
MSLT	Multiple sleep latency test
NSAIDs	Non-steroidal anti-inflammatory drugs
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnoea
PSG	Polysomnography
REM	Rapid eye movement
RI	Resaturation index
RP	History of coronary Revascularisation procedure
SHHS	Sleep Heart Health Study
SpO ₂	Oxygen saturation
TRT	Total recording time
T90	Time under 90% oxygen saturation
ULN	Upper limit of normal
WASO	Wake after sleep onset
WHO	World Health Organization
WHR	Waist to hip ratio

oxygen saturation parameters have largely focused on the desaturation aspects alone or combined desaturation and resaturation information [9–11]. It has been suggested, however, that at least part of the mechanistic pathway linking IH and the aforementioned sequelae is the result of reperfusion injury [12]. Novel algorithms and software can assess both the desaturation and resaturation aspects of nocturnal oxygen saturation signals [13] which can have significant relevance in the context of cardiovascular and respiratory health. Identifying specific patterns of oxygen desaturation and resaturation can potentially aid clinicians and researchers in developing personalised and effective interventions to improve nocturnal oxygenation and prevent adverse cardiovascular events.

Cardiovascular and pulmonary diseases are known to impact oxygen resaturation dynamics through multiple mechanisms. Heart failure (HF) [14,15], chronic obstructive pulmonary disease (COPD) [16,17], and atrial fibrillation (AF) [18,19] are associated with significantly lower baseline levels of oxygen saturation and greater oxygen desaturation severity. In the case of cardiovascular disease, reduced stroke volume and impaired vascular function can significantly affect oxygen delivery and contribute to lower oxygen levels [14,15,20]. In some cases, this may be treated through the insertion of a pacemaker, though the varied pacemakers available work in different fashions and may thus display varied responses to reduced oxygen saturation. Similarly, pulmonary disease can alter oxygen intake and gas transfer dynamics, leading to reduced oxygen saturation levels [16,17]. Other chronic comorbidities such as hypertension and diabetes can affect the cardiovascular system by leading to alterations in the peripheral vasculature and autonomic regulation [20]. Furthermore, diabetic neuropathy may cause longer and deeper desaturation events and a higher AHI through its effects on upper airway and respiratory control [21]. While nocturnal desaturation parameters have been investigated consistently for several decades, nocturnal resaturation parameters are relatively novel. Thus, literature showing the effect of disease states and medications on these parameters is scarce. However, a previous study from our centre identified significant and independent associations between oxygen resaturation parameters and daytime sleepiness scored via multiple sleep latency test [22], while another showed significantly reduced resaturation rates among obstructive sleep apnoea (OSA) patients with a history of AF [19]. These studies hint at the potential utility of oxygen resaturation parameters in sleep research.

We hypothesise that nocturnal oxygen resaturation parameters,

including duration, depth, rate, and area will show significantly greater deficits among patients with comorbidities and/or medication usage compared to a healthy control group than the corresponding desaturation parameters. Furthermore, we hypothesise that oxygen resaturation rate will be positively correlated with subjective scores of daytime sleepiness. Therefore, in the current study, we set forth to define and assess 1) if, and to what extent, cardiorespiratory comorbidities and prescribed medication impact oxygen resaturation parameters 2) if this occurs independently of potential impacts on related oxygen desaturation parameters, and 3) if resaturation and desaturation parameters are related to subjective scores of daytime sleepiness.

2. Methods

2.1. Dataset

First-visit data from the Sleep Heart Health Study (SHHS) was utilised for this analysis. Further details regarding the setting, implementation, and outcomes of the SHHS are available via [23,24]. In brief 5804 participants from prospective cohort studies aged >40 years completed a baseline examination between 1995 and 1998. Participants provided information on clinical factors; smoking history, height, weight, body mass index (BMI – further classified as underweight <18.5 kg/m², normal weight 18.5–24.9 kg/m², overweight 25.0–29.9 kg/m², or obese ≥30.0 kg/m²), neck, waist, and hip circumference (waist to hip ratio (WHR), with the cut-off for central adiposity defined as per World Health Organisation (WHO) criteria ≥0.8 for females and ≥1.0 for males), and previous medical history and medication usage. In addition to this, several cohorts within the SHHS had lung function data via spirometry available (forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC)).

2.2. Comorbidities, medications, and daytime sleepiness

Comorbidities and medication usage were extracted from participants' self-reports. Full definitions are provided within [Supplement 1](#). In brief, comorbidities were defined under the following headings: lung disease (LD), hypertension (HTN), myocardial infarction (MI), heart failure (HF), presence of a pacemaker, history of coronary revascularisation procedure (RP), diabetes, and stroke. Medication usage was defined as per the existing SHHS medication categorisations under the

following headings: female sex hormones (FSH), anti-hypertensives, antiarrhythmics, lipid-lowering medications, mental health medication, diabetes medications, pulmonary medications, sympathomimetics, anticoagulants, and anti-inflammatory medications (including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and oral steroids). Daytime sleepiness was assessed via Epworth Sleepiness Scale (ESS) [25] and considered as both a continuous parameter and a dichotomous parameter, with excessive daytime sleepiness (EDS) defined as an ESS >10.

2.3. Data extraction and derivation

Due to the known data corruption issues in SHHS data [26] and updated respiratory event scoring rules, existing manual labels were not used. Instead, EDFs for patients were downloaded and blood oxygen saturation (SpO₂) data were analysed utilising the ABOSA open source research software [13,27], with minimum desaturation event duration set to 5 s, minimum transient drop to 4%, automated artefact removal, and total recording time (TRT) defined from sleep onset to offset. From the ABOSA outputs, the following parameters were extracted for analysis: number of desaturations, number of resaturations, the average duration of desaturations (seconds), the average duration of resaturations (seconds), average desaturation depth (percentile point change from pre-event baseline), the average resaturation height (percentile point change from nadir to new baseline), the average desaturation rate (desaturation depth/desaturation duration), the average resaturation rate (resaturation height/resaturation duration), the average desaturation area, the average resaturation area, the desaturation to resaturation ratios (D:R) for each. In addition to these parameters, TRT, wake after sleep onset (WASO), sleep latency, sleep efficiency, oxygen desaturation index (ODI), time under 90% oxygen saturation (t90) and desaturation severity (calculated as the total desaturation area normalised by TRT [3]) were also extracted.

Lung function parameters were assessed via Global Lung function Initiative (GLI) equations, with conversion to predicted and percent predicted values, and definition of upper and lower limits of normal (ULN & LLN, respectively) conducted via the online GLI batch calculator (<http://gli-calculator.ersnet.org/>). Participants for whom height was unavailable or below the limits used in the GLI were excluded from conversion. For Caucasian participants, the Caucasian reference ranges were utilised, for Black/African American patients the Black/African American reference ranges, and for Hispanic/not reported the other/mixed reference ranges were used. Lung function was assessed as a continuous parameter for FEV₁ and FVC percent predicted values, and FEV₁/FVC absolute values.

2.4. Ethics approval and data sharing

Initial ethical permissions for the data collection are presented elsewhere [23]. The data that support the findings of this study are available from the National Sleep Research Resource (NSRR). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from sleepdata.org with the permission of NSRR.

2.5. Study participant exclusion criteria

Participants were excluded if they had corrupted or missing nocturnal oximetry data ($n = 22$, 0.4%), a TRT <6 h ($n = 878$, 15.1%), or had <5 resaturation events ($n = 611$, 10.5%) (Fig. 1). Parameters with incomplete data (i.e., lung function, smoking history) were assessed only among participants with the relevant data available.

2.6. Statistical analysis

Demographic and oxygen saturation parameters were tested

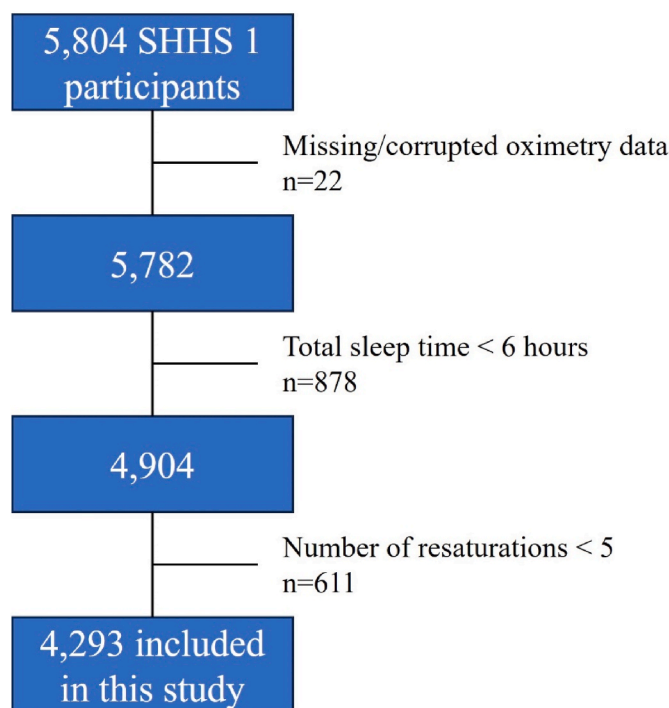


Fig. 1. Flow chart of participant exclusion for the current study.

between males and females, and between those with any comorbidity or medication and those without via the Kruskal Wallis Rank sum test. Following this, univariate analyses were conducted independently for each comorbidity and medication group using patients with no comorbidities or medications as the 'healthy baseline', and the dependent variable transformed to a z-score to allow equal comparison between effects on desaturations, resaturations, and D:R parameters.

In order to develop the multivariate model for the effects of comorbidities and medications on resaturation parameters, a stepwise regression was performed including demographic variables (age, sex, ethnicity), smoking status, anthropometric data (BMI, WHR), lung function parameters (FEV₁ % predicted, FVC % predicted and absolute FEV₁/FVC), polysomnography (PSG) variables (TRT, WASO, AHI (hypopnoeas defined with a 4% desaturation), sleep latency, sleep efficiency and REM sleep percentage (REM%)) and oxygen desaturation parameters (ODI, t90, average desaturation duration, desaturation area, desaturation depth, desaturation rate, and desaturation severity [13]). Variables within the model with a p -value >0.1 were excluded from further models. Following the stepwise regression exclusions our model contained age, sex, ethnicity, BMI, AHI, ODI, desaturation severity, t90, average desaturation duration, depth, area and rate, FEV₁%, FEV₁/FVC, TRT, and REM%. Given the potential for collinearity between the remaining predictor variables Pearson's pairwise correlation was assessed and predictors with a Pearson's $R^2 > 0.5$ were sequentially removed to determine which had the greatest effect on the model fit. The final model included age, sex, ethnicity, BMI, average desaturation duration, average desaturation depth, FEV₁%, FEV₁/FVC, t90, TRT, and REM%. This model was used as the basis to explore the adjusted effects of comorbidities and medications on resaturation parameters. The same model, but excluding average desaturation duration and average desaturation depth, was used to explore the adjusted effects of comorbidities and medications on average desaturation and D:R parameters. Participants for whom information was missing on parameters included in the multivariate models were excluded from the multivariate analyses.

Univariate quantile regression was used to explore the effect of average desaturation, resaturation, and D:R parameters on reported ESS, and logistic regression to explore the effect on EDS. Again, stepwise

regression was performed to determine the ideal model to explore the effects of saturation parameters on ESS ratings both as a continuous outcome and as a binary outcome. The multivariate models were developed in the same manner outlined above for both ESS and EDS, though additionally including a binary variable of ‘healthy’ (no reported comorbidities or medication) and ‘unhealthy’ (any reported comorbidity or medication) as an independent predictor. For the continuous

regression, the final model included presence of any comorbidity/medication, sex, BMI, sleep efficiency, sleep latency, and desaturation severity. For the logistic regression, the final model included presence of any comorbidity/medication, sex, BMI, WASO, sleep latency, TRT, and desaturation severity. Desaturation, resaturation, and D:R parameters were added to these models in order to explore if they had any additive effect.

Table 1

Oxygen saturation parameters for study participants.

Total study sample		Total (n = 4293)		
Desaturation	Age (years)	64 (56, 73)		
	BMI (kg/m ²)	27.82 (24.99, 31.01)		
	ESS (points)	7 (4,11)		
	Count	33 (16, 69)		
	ODI (Events/Hour)	4.46 (2.15, 9.47)		
	Rate (%/second)	0.28 (0.24, 0.35)		
	Duration (seconds)	27.4 (23.18, 31.93)		
Resaturation	Depth (% point change from baseline to nadir)	6.01 (5.52, 6.68)		
	Area (s%)	91.89 (76.57, 113.02)		
	Count	28 (13, 61)		
	RI (Events/hour)	3.82 (1.75, 8.43)		
	Rate (%/second)	0.57 (0.48, 0.67)		
	Duration (seconds)	13.4 (11.57, 15.61)		
	Height (% point change from nadir to baseline)	6.14 (5.47, 6.94)		
Desaturation/Resaturation	Area (s%)	41.23 (33.14, 50.83)		
	Rate	0.64 (0.53, 0.77)		
	Duration	2.50 (2.09, 2.96)		
	Depth	1.07 (1.00, 1.15)		
	Area	3.40 (2.81, 4.18)		
No comorbidities or medications		Female (n = 250)	Male (n = 345)	p-value
Desaturation	Age (years)	59 (49, 68)	58 (50, 66)	0.770
	BMI (kg/m ²)	26.93 (24.37, 31.44)	27.67 (25.33, 29.92)	0.435
	ESS (points)	6 (4,9)	7 (4,10)	0.605
	Count	24 (12,51)	34 (17, 78)	0.200
	ODI (Events/Hour)	3.17 (1.70, 6.62)	4.82 (2.39, 10.58)	0.103
	Rate (%/second)	0.31 (0.25, 0.41)	0.27 (0.23, 0.34)	0.031
	Duration (seconds)	25.92 (21.26, 30.63)	28.67 (24.13, 32.93)	0.060
Resaturation	Depth (% point change from baseline to nadir)	6.18 (5.63, 6.85)	5.93 (5.47, 6.65)	0.249
	Area (s%)	87.11 (73.41, 106.93)	97.36 (79.51, 115.57)	0.103
	Count	20 (10,46)	28 (14, 70)	0.245
	RI (Events/hour)	2.69 (1.33, 6.12)	3.98 (2.00, 9.41)	0.184
	Rate (%/second)	0.61 (0.52, 0.70)	0.55 (0.47, 0.66)	0.044
	Duration (seconds)	12.89 (10.67, 14.85)	13.39 (11.57, 15.37)	0.435
	Height (% point change from nadir to baseline)	6.29 (5.64, 6.98)	6.03 (5.36, 6.9)	0.256
Desaturation/Resaturation	Area (s%)	39.78 (31.71, 47.68)	40.59 (33.63, 50.45)	0.770
	Rate	0.67 (0.55, 0.79)	0.63 (0.52, 0.76)	0.300
	Duration	2.44 (2.05, 3.01)	2.59 (2.13, 3.09)	0.256
	Depth	1.06 (0.99, 1.15)	1.09 (1.02, 1.16)	0.435
	Area	3.26 (2.60, 4.09)	3.55 (2.87, 4.31)	0.256
Comorbidities or medications present		Female (n = 1912)	Male (n = 1786)	
Desaturation	Age (years)	65.5 (57, 74)	65 (57, 72)	1.000
	BMI (kg/m ²)	27.58 (24.43, 31.47)	28.09 (25.49, 30.90)	0.031
	ESS (points)	7 (4,10)	8 (5,12)	0.531
	Count	26 (13,53)	45.5 (20, 88)	0.001
	ODI (Events/Hour)	3.56 (1.79, 7.22)	6.27 (2.76, 12.44)	0.001
	Rate (%/second)	0.30 (0.25, 0.37)	0.27 (0.22, 0.32)	0.001
	Duration (seconds)	26.31 (22.14, 31.00)	28.53 (24.55, 33)	0.001
Resaturation	Depth (% point change from baseline to nadir)	6.01 (5.54, 6.67)	5.99 (5.49, 6.67)	0.880
	Area (s%)	86.89 (73.12, 106.81)	98.08 (80.88, 118.73)	0.001
	Count	22 (11,46)	38.5 (17, 79)	0.001
	RI (Events/hour)	2.96 (1.45, 6.37)	5.41 (2.34, 11.01)	0.001
	Rate (%/second)	0.58 (0.49, 0.69)	0.55 (0.46, 0.64)	0.001
	Duration (seconds)	13.18 (11.23, 15.46)	13.72 (11.95, 15.89)	0.003
	Height (% point change from nadir to baseline)	6.15 (5.51, 6.93)	6.11 (5.40, 6.94)	0.880
Desaturation/Resaturation	Area (s%)	39.97 (31.82, 49.55)	42.90 (34.90, 52.49)	0.003
	Rate	0.66 (0.54, 0.78)	0.62 (0.51, 0.74)	0.003
	Duration	2.43 (2.03, 2.92)	2.55 (2.16, 2.99)	0.003
	Depth	1.07 (0.99, 1.15)	1.08 (1.01, 1.15)	0.115
	Area	3.29 (2.66, 4.13)	3.51 (2.93, 4.22)	0.003

Data displayed as median (interquartile range).

p-value derived from quantile regression using Romano-Wolf adjustment for multiple comparisons and denotes the statistical significance between sexes.

Bolded p-values indicate statistical significance at a level of <0.05.

Abbreviations: BMI, Body mass index; ESS, Epworth sleepiness scale; ODI, Oxygen desaturation index; RI, Resaturation index.

Due to the number of hypotheses being tested, Romano-Wolf (R–W) correction was utilised in all analyses with 750 bootstrap replications. All analyses were conducted in STATA IC 15 (StataCorp, College Station, Texas) and alpha was set to $p = 0.05$ throughout.

3. Results

Following exclusion criteria, a total of 4293 participants were included for analysis. The majority of participants (86%) were Caucasian, with 50.4% females, and a median age of 64 years (IQR 56, 73) (Supplement 2). Participants were typically overweight (43%) or obese (32%), with central adiposity common (57%). Most participants reported at least one comorbidity (60%) or use of at least one medication (76%). Five hundred and ninety-five (13.9%) reported no comorbidities and no medication usage (hereafter referred to as ‘healthy participants’).

3.1. Baseline saturation parameters

Healthy females and males recorded a similar number of resaturation and desaturation events (Table 1). Healthy females recorded significantly faster desaturation and resaturation rates compared to healthy males, with no significant differences in other saturation parameters. Females with reported comorbidities or medication usage had a higher BMI and recorded significantly fewer desaturations and resaturations, and faster desaturation and resaturation rates compared to males with comorbidities/medications. Consequently the D:R parameters for rate, duration, and area also significantly differed between sexes with comorbidities/medications, with a greater D:R rate and reduced D:R duration and area present among females.

In comparison to healthy females, females with comorbidities/medications were older ($p = 0.033$), though with no statistically significant difference in BMI ($p = 0.816$), nor any saturation parameters. In comparison to healthy males, males with comorbidities/medications were older ($p = 0.001$), though with no difference in BMI ($p = 0.875$). Males with comorbidities/medications recorded significantly more

desaturation events ($p = 0.043$) and resaturation events ($p = 0.020$) compared to healthy males, though there were no significant differences in other saturation parameters.

3.2. Specific comorbidities and saturation parameters

Compared to healthy patients with no evidence of comorbidities or medication usage at baseline, specific comorbidities showed differing impacts between resaturation and desaturation parameters, and on rate, duration, depth, or area of de-/resaturation events (Fig. 2).

In multivariate models, HTN, MI, RP, stroke, HF, and the presence of a pacemaker all showed no significant effects on desaturation parameters. LD showed a reduction in desaturation area (-0.12 (95% CI -0.23 , -0.01)), while diabetes showed a reduced desaturation duration (-0.15 (95% CI -0.30 , 0.00)), however the significance of both were attenuated after R–W adjustment (Table 2).

After R–W adjustment participants with HTN showed borderline significantly reduced resaturation rates (-0.09 (95% CI -0.16 , -0.03)), borderline significantly increased resaturation areas (0.11 (95% CI 0.03 , 0.19)) and significantly increased resaturation durations (0.13 (95% CI 0.04 , 0.21)), alongside significantly reduced D:R duration (-0.14 (95% CI -0.24 , -0.04)).

Participants with MI showed significantly reduced resaturation rates (-0.13 (95% CI -0.21 , -0.04)), significantly increased resaturation durations (0.16 (95% CI 0.05 , 0.27)), and significantly increased resaturation areas (0.16 (95% CI 0.05 , 0.26)).

Participants with HF had significantly reduced D:R duration (-0.3 (95% CI -0.5 , -0.1)), and significantly reduced D:R area (-0.25 (95% CI -0.42 , -0.08)).

3.3. Specific medications and saturation parameters

In multivariate models, the only medications which showed any significant effect on desaturation parameters were female sex hormones, which were associated with a significantly reduced desaturation area

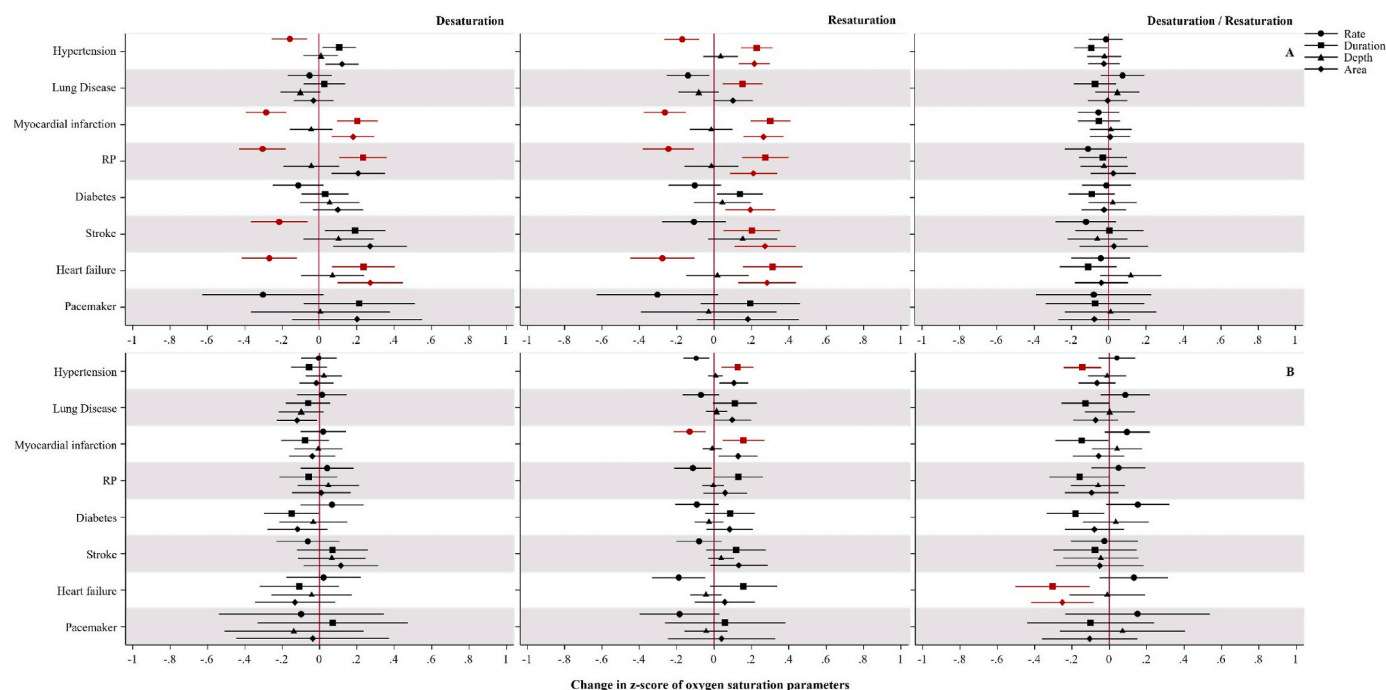


Fig. 2. Influence of specific comorbidities against healthy reference patients on oxygen saturation parameters showing univariate (Row A) and multivariate (Row B) models (adjusted for age, sex, ethnicity, BMI, FEV₁, FEV₁/FVC, t90, REM %, TRT with resaturation parameters additionally adjusted for average desaturation duration and average desaturation depth). Coloured lines represent those which retained significance after Romano-Wolf adjustment for multiple testing. Abbreviation: RP, Coronary revascularisation procedure.

Table 2
Influence of specific comorbidities against healthy reference patients on oxygen saturation parameters showing univariate and multivariate models (adjusted for age, sex, ethnicity, BMI, WHR, FVC, t90, TRT with resaturation parameters additionally adjusted for average desaturation duration and average desaturation depth).

	Desaturation			Resaturation			Desaturation:Resaturation ratio		
	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p
Univariate									
Rate									
Hypertension (n = 2152)	-0.16 (-0.25, -0.07)	0.001	0.017	-0.17 (-0.27, -0.08)	<0.001	0.005	-0.02 (-0.11, 0.08)	0.731	0.949
Lung disease (n = 591)	-0.05 (-0.17, 0.07)	0.391	0.418	-0.14 (-0.25, -0.03)	0.016	0.061	0.07 (-0.04, 0.19)	0.210	0.625
Myocardial infarction (n = 627)	-0.28 (-0.39, -0.18)	<0.001	0.003	-0.26 (-0.38, -0.15)	<0.001	0.003	-0.05 (-0.16, 0.05)	0.326	0.759
Coronary revascularisation procedure (n = 365)	-0.30 (-0.43, -0.18)	<0.001	0.003	-0.24 (-0.38, -0.11)	<0.001	0.007	-0.11 (-0.24, 0.01)	0.084	0.392
Diabetes (n = 353)	-0.11 (-0.25, 0.02)	0.107	0.220	-0.10 (-0.24, 0.04)	0.148	0.269	-0.01 (-0.14, 0.12)	0.851	0.949
Stroke (n = 194)	-0.21 (-0.37, -0.06)	0.006	0.039	-0.11 (-0.28, 0.06)	0.216	0.269	-0.12 (-0.29, 0.04)	0.142	0.547
Heart failure (n = 172)	-0.27 (-0.41, -0.12)	<0.001	0.013	-0.28 (-0.45, -0.10)	0.002	0.013	-0.04 (-0.20, 0.12)	0.598	0.949
Pacemaker (n = 44)	-0.30 (-0.63, 0.02)	0.070	0.220	-0.30 (-0.63, 0.02)	0.068	0.209	-0.08 (-0.39, 0.23)	0.611	0.949
Duration									
Hypertension (n = 2152)	0.11 (0.02, 0.20)	0.017	0.076	0.23 (0.14, 0.31)	<0.001	0.001	-0.09 (-0.18, 0.00)	0.043	0.256
Lung disease (n = 591)	0.03 (-0.08, 0.14)	0.632	0.834	0.15 (0.05, 0.26)	0.005	0.024	-0.07 (-0.19, 0.04)	0.207	0.611
Myocardial infarction (n = 627)	0.20 (0.09, 0.31)	<0.001	0.004	0.30 (0.19, 0.41)	<0.001	0.001	-0.05 (-0.17, 0.06)	0.366	0.802
Coronary revascularisation procedure (n = 365)	0.24 (0.11, 0.36)	<0.001	0.004	0.27 (0.15, 0.40)	<0.001	0.001	-0.03 (-0.16, 0.10)	0.631	0.935
Diabetes (n = 353)	0.03 (-0.10, 0.16)	0.630	0.834	0.14 (0.02, 0.26)	0.027	0.064	-0.09 (-0.21, 0.03)	0.147	0.563
Stroke (n = 194)	0.19 (0.03, 0.35)	0.020	0.076	0.20 (0.05, 0.35)	0.009	0.031	0.00 (-0.18, 0.19)	0.970	0.972
Heart failure (n = 172)	0.24 (0.07, 0.41)	0.006	0.032	0.31 (0.15, 0.47)	<0.001	0.001	-0.11 (-0.26, 0.04)	0.158	0.563
Pacemaker (n = 44)	0.21 (-0.08, 0.51)	0.160	0.382	0.19 (-0.07, 0.46)	0.153	0.176	-0.07 (-0.34, 0.19)	0.586	0.935
Depth									
Hypertension (n = 2152)	0.01 (-0.09, 0.10)	0.878	0.987	0.04 (-0.06, 0.13)	0.449	0.944	-0.02 (-0.11, 0.07)	0.618	0.972
Lung disease (n = 591)	-0.10 (-0.21, 0.01)	0.065	0.404	-0.08 (-0.19, 0.03)	0.134	0.526	0.05 (-0.07, 0.16)	0.444	0.945
Myocardial infarction (n = 627)	-0.04 (-0.16, 0.07)	0.461	0.916	-0.01 (-0.13, 0.10)	0.797	0.999	0.01 (-0.10, 0.12)	0.843	0.984
Coronary revascularisation procedure (n = 365)	-0.04 (-0.19, 0.11)	0.578	0.917	-0.01 (-0.16, 0.13)	0.845	0.999	-0.03 (-0.15, 0.10)	0.693	0.981
Diabetes (n = 353)	0.06 (-0.10, 0.22)	0.488	0.916	0.04 (-0.11, 0.20)	0.566	0.971	0.02 (-0.11, 0.15)	0.751	0.984
Stroke (n = 194)	0.10 (-0.09, 0.29)	0.284	0.838	0.15 (-0.03, 0.34)	0.102	0.463	-0.06 (-0.22, 0.10)	0.459	0.945
Heart failure (n = 172)	0.07 (-0.10, 0.24)	0.409	0.915	0.02 (-0.15, 0.18)	0.829	0.999	0.12 (-0.04, 0.28)	0.154	0.618
Pacemaker (n = 44)	0.01 (-0.37, 0.38)	0.973	0.987	-0.03 (-0.39, 0.33)	0.873	0.999	0.01 (-0.24, 0.26)	0.938	0.984
Area									
Hypertension (n = 2152)	0.12 (0.03, 0.21)	0.007	0.071	0.22 (0.13, 0.30)	<0.001	0.001	-0.03 (-0.11, 0.06)	0.546	0.992
Lung disease (n = 591)	-0.03 (-0.14, 0.08)	0.576	0.579	0.10 (0.00, 0.21)	0.061	0.105	-0.01 (-0.11, 0.10)	0.917	0.997
Myocardial infarction (n = 627)	0.18 (0.07, 0.30)	0.002	0.025	0.27 (0.16, 0.37)	<0.001	0.001	0.01 (-0.10, 0.12)	0.884	0.997
Coronary revascularisation procedure (n = 365)	0.21 (0.07, 0.35)	0.004	0.057	0.21 (0.08, 0.34)	0.001	0.008	0.02 (-0.10, 0.15)	0.696	0.997
Diabetes (n = 353)	0.10 (-0.04, 0.24)	0.146	0.380	0.19 (0.06, 0.33)	0.004	0.019	-0.03 (-0.15, 0.09)	0.677	0.997
Stroke (n = 194)	0.27 (0.07, 0.47)	0.007	0.071	0.27 (0.11, 0.44)	0.001	0.009	0.03 (-0.15, 0.21)	0.762	0.997
Heart failure (n = 172)	0.27 (0.10, 0.45)	0.002	0.033	0.28 (0.13, 0.44)	<0.001	0.005	-0.04 (-0.18, 0.10)	0.588	0.997
Pacemaker (n = 44)	0.20 (-0.15, 0.55)	0.253	0.443	0.18 (-0.09, 0.45)	0.194	0.214	-0.08 (-0.29, 0.12)	0.433	0.967
Multivariate									
Rate									
Hypertension (n = 1814)	-0.01 (-0.10, 0.09)	0.899	0.996	-0.09 (-0.16, -0.03)	0.008	0.059	0.04 (-0.06, 0.14)	0.411	0.855
Lung disease (n = 522)	0.01 (-0.12, 0.14)	0.863	0.996	-0.07 (-0.17, 0.03)	0.167	0.362	0.09 (-0.05, 0.22)	0.202	0.629
Myocardial infarction (n = 523)	0.02 (-0.10, 0.14)	0.768	0.991	-0.13 (-0.21, -0.04)	0.003	0.031	0.10 (-0.02, 0.22)	0.115	0.498
Coronary revascularisation procedure (n = 313)	0.04 (-0.10, 0.18)	0.591	0.988	-0.11 (-0.21, -0.01)	0.030	0.143	0.05 (-0.09, 0.20)	0.492	0.855
Diabetes (n = 291)	0.07 (-0.10, 0.23)	0.445	0.979	-0.09 (-0.21, 0.03)	0.130	0.362	0.15 (-0.01, 0.32)	0.074	0.390
Stroke (n = 159)	-0.06 (-0.23, 0.11)	0.462	0.979	-0.08 (-0.20, 0.04)	0.206	0.362	-0.03 (-0.20, 0.15)	0.780	0.855
Heart failure (n = 123)	0.02 (-0.18, 0.22)	0.844	0.996	-0.19 (-0.33, -0.05)	0.010	0.065	0.13 (-0.05, 0.31)	0.154	0.575
Pacemaker (n = 32)	-0.10 (-0.54, 0.34)	0.658	0.989	-0.18 (-0.40, 0.03)	0.095	0.353	0.15 (-0.24, 0.54)	0.441	0.855
Duration									
Hypertension (n = 1814)	-0.06 (-0.15, 0.04)	0.244	0.752	0.13 (0.04, 0.21)	0.004	0.032	-0.14 (-0.24, -0.04)	0.005	0.044
Lung disease (n = 522)	-0.06 (-0.18, 0.06)	0.305	0.796	0.11 (0.00, 0.23)	0.059	0.254	-0.13 (-0.25, 0.00)	0.054	0.201
Myocardial infarction (n = 523)	-0.08 (-0.21, 0.05)	0.225	0.726	0.16 (0.05, 0.27)	0.005	0.037	-0.15 (-0.29, 0.00)	0.045	0.201
Coronary revascularisation procedure (n = 313)	-0.06 (-0.21, 0.09)	0.441	0.803	0.13 (0.00, 0.26)	0.047	0.232	-0.16 (-0.32, 0.00)	0.055	0.201
Diabetes (n = 291)	-0.15 (-0.30, 0.00)	0.044	0.288	0.09 (-0.04, 0.22)	0.193	0.369	-0.18 (-0.33, -0.03)	0.022	0.133

(continued on next page)

Table 2 (continued)

	Desaturation			Resaturation			Desaturation:Resaturation ratio		
	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p
Stroke (n = 159)	0.07 (−0.12, 0.26)	0.482	0.803	0.12 (−0.04, 0.28)	0.140	0.369	−0.08 (−0.30, 0.15)	0.506	0.771
Heart failure (n = 123)	−0.11 (−0.32, 0.10)	0.309	0.796	0.16 (−0.02, 0.34)	0.081	0.290	−0.30 (−0.50, −0.10)	0.003	0.031
Pacemaker (n = 32)	0.07 (−0.33, 0.47)	0.736	0.803	0.06 (−0.26, 0.38)	0.710	0.695	−0.10 (−0.44, 0.24)	0.567	0.771
Depth									
Hypertension (n = 1814)	0.02 (−0.07, 0.12)	0.650	0.971	0.01 (−0.03, 0.05)	0.601	0.953	−0.01 (−0.11, 0.09)	0.840	0.997
Lung disease (n = 522)	−0.10 (−0.22, 0.02)	0.106	0.530	0.02 (−0.04, 0.07)	0.584	0.953	0.00 (−0.13, 0.14)	0.962	0.997
Myocardial infarction (n = 523)	−0.01 (−0.14, 0.12)	0.905	0.971	−0.01 (−0.06, 0.04)	0.790	0.953	0.04 (−0.09, 0.18)	0.528	0.991
Coronary revascularisation procedure (n = 313)	0.05 (−0.12, 0.21)	0.584	0.971	0.00 (−0.06, 0.06)	0.950	0.953	−0.06 (−0.20, 0.09)	0.421	0.963
Diabetes (n = 291)	−0.04 (−0.22, 0.15)	0.705	0.971	−0.02 (−0.10, 0.05)	0.528	0.953	0.04 (−0.14, 0.21)	0.686	0.997
Stroke (n = 159)	0.06 (−0.12, 0.25)	0.483	0.971	0.04 (−0.03, 0.11)	0.252	0.838	−0.04 (−0.25, 0.16)	0.665	0.997
Heart failure (n = 123)	−0.04 (−0.26, 0.17)	0.693	0.971	−0.04 (−0.13, 0.04)	0.336	0.900	−0.01 (−0.21, 0.19)	0.925	0.997
Pacemaker (n = 32)	−0.14 (−0.51, 0.23)	0.465	0.971	−0.04 (−0.16, 0.08)	0.492	0.953	0.07 (−0.26, 0.41)	0.674	0.997
Area									
Hypertension (n = 1814)	−0.02 (−0.11, 0.07)	0.694	0.965	0.11 (0.03, 0.19)	0.006	0.052	−0.07 (−0.16, 0.03)	0.194	0.723
Lung disease (n = 522)	−0.12 (−0.23, −0.01)	0.026	0.174	0.10 (0.00, 0.20)	0.052	0.240	−0.07 (−0.19, 0.05)	0.234	0.723
Myocardial infarction (n = 523)	−0.04 (−0.16, 0.08)	0.527	0.910	0.13 (0.03, 0.24)	0.014	0.093	−0.06 (−0.19, 0.08)	0.427	0.786
Coronary revascularisation procedure (n = 313)	0.01 (−0.15, 0.17)	0.919	0.980	0.06 (−0.06, 0.18)	0.300	0.655	−0.09 (−0.24, 0.05)	0.200	0.723
Diabetes (n = 291)	−0.12 (−0.28, 0.04)	0.144	0.573	0.09 (−0.04, 0.21)	0.174	0.511	−0.08 (−0.24, 0.08)	0.328	0.776
Stroke (n = 159)	0.11 (−0.09, 0.31)	0.267	0.707	0.13 (−0.02, 0.29)	0.084	0.328	−0.05 (−0.28, 0.18)	0.676	0.786
Heart failure (n = 123)	−0.13 (−0.35, 0.08)	0.224	0.696	0.06 (−0.10, 0.22)	0.467	0.719	−0.25 (−0.42, −0.08)	0.003	0.049
Pacemaker (n = 32)	−0.04 (−0.45, 0.37)	0.857	0.980	0.04 (−0.25, 0.33)	0.775	0.760	−0.10 (−0.36, 0.15)	0.424	0.786

Bold values indicate those with statistically significant differences compared to healthy participants after Romano-Wolf adjustment.

In univariate models 595 participants were considered as the 'healthy' reference group, while in multivariate models 514 'healthy' participants had all data available and were considered as the reference group. Numbers of participants in each comorbidity group for univariate and multivariate model are shown in the leftmost column.

(−0.15 (95% CI −0.28, −0.02)) although this was no longer significant after R–W adjustment (Fig. 3).

Participants reporting use of anti-hypertensives showed a significantly reduced rate of resaturation (−0.10 (95% CI −0.17, −0.03)), a significantly increased resaturation duration (0.13 (95% CI 0.04, 0.22)), and a significantly reduced D:R duration (−0.16 (95% CI −0.26, −0.06)) (Table 3).

Participants reporting use of anticoagulants showed a significantly reduced rate of resaturation (−0.41 (95% CI −0.56, −0.26)), an increased resaturation duration (0.51 (95% CI 0.28, 0.74)), and an increased resaturation area (0.33 (95% CI 0.11, 0.55)).

Participants reporting use of mental health medications also showed a significantly reduced rate of resaturation (−0.18 (95% CI −0.27, −0.08)), and D:R duration (−0.21 (95% CI −0.34, −0.08)) as did participants reporting use of diabetic medication (−0.24 (95% CI −0.41, −0.07)). Participants reporting use of sympathomimetics showed borderline increase in resaturation duration (0.34 (95% CI 0.10, 0.57) R–W $p = 0.051$) and decrease in D:R duration (−0.29 (95% CI −0.50, −0.08) R–W $p = 0.056$).

3.4. ESS and resaturation values

In univariate models, increasing desaturation depth (0.45 (95% CI 0.26, 0.64)) and area (0.40 (95% CI 0.22, 0.59)), and increasing resaturation depth (0.35 (95% CI 0.16, 0.54)) were significantly associated with higher ESS scores (Fig. 4). Each of these were also associated with significantly increased odds for EDS. Resaturation rate and D:R rate, though having no significant effect on ESS score as a continuous outcome, were also significantly associated with odds of EDS (resaturation rate OR 1.10 (95% CI 1.02, 1.17), D:R rate OR 0.92 (95% CI 0.85, 0.98)). In the multivariate models, however, average desaturation and resaturation parameters showed no significant associations with either ESS or EDS. Increasing desaturation severity however was significantly associated with both higher ESS scores and increased odds for EDS.

4. Discussion

In this study, we identified significant associations between several cardiovascular comorbidities and resaturation parameters, independent of desaturation parameters. Participants with a history of MI showed significant reductions and those with a history of HTN or HF borderline significant reductions in the rate of resaturation compared to healthy participants. Medications related to blood clotting or hypertension also showed significant reductions in resaturation rate, as did mental health medications (e.g., anti-depressants and benzodiazepines). Notably, however, the presence of comorbidities did not appear to have any association with oxygen desaturation parameters in the multivariate models. Yet D:R duration showed significant reductions in the presence of HTN and HF, as well as in the presence of antihypertensives, diabetic medications, mental health medications and anticoagulants.

In this study, we found that females experienced significantly faster desaturation and resaturation events compared to males, in both healthy and comorbid/medication groups with a mean difference of 0.03%/second. Though this finding was statistically significant, whether it is of clinical significance is uncertain, however it does represent a relative difference of 6% in resaturation rate between females and males. While the reason for this sex difference is unknown, several factors could contribute to it, such as differences in lung structure, function, or hormonal variations. Females typically have smaller lungs and airways than males, which can affect gas exchange and ventilation [16]. Hormonal differences, particularly estrogen and progesterone, which have been noted to have an effect on the development and progression of pulmonary diseases [28], may also play a role as evidenced by the increased D:R rate in regression models among those taking FSH. Additionally in univariate regressions, FSHs were associated with an increased desaturation rate and no change in desaturation depths. In the current study,

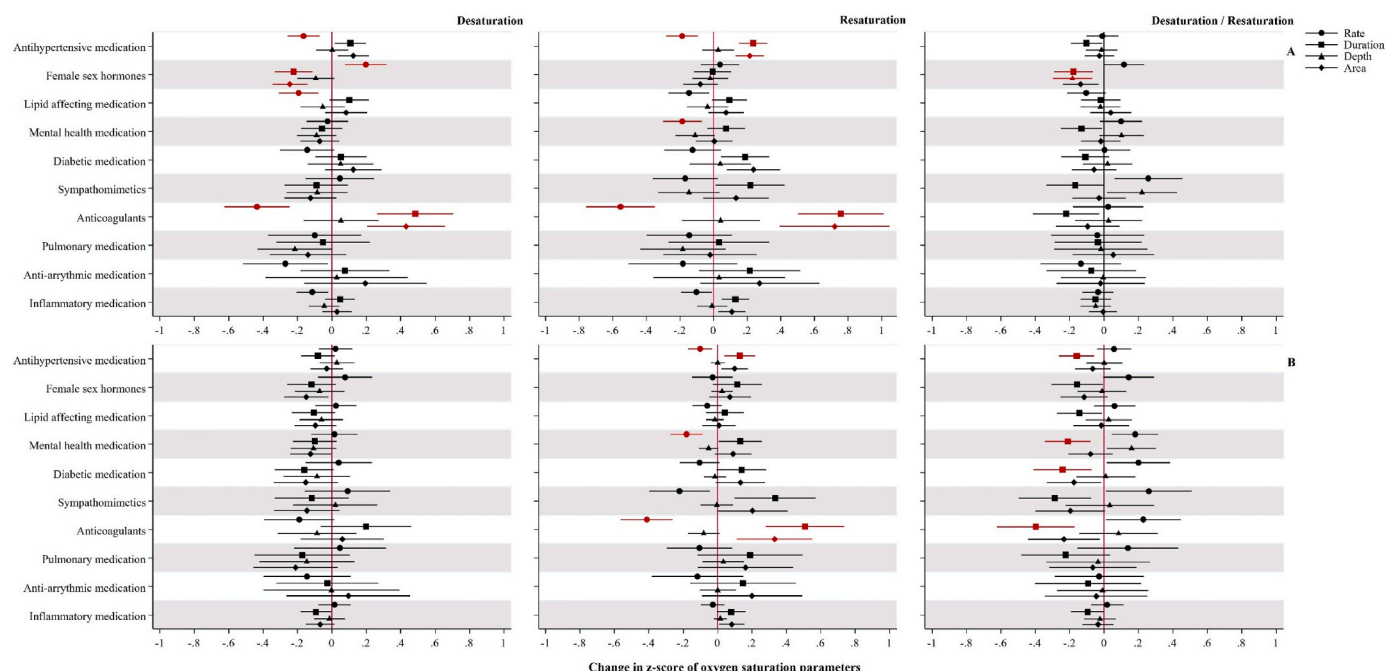


Fig. 3. Influence of specific medications against patients with no medications on oxygen saturation parameters showing univariate (Row A) and multivariate (Row B) models (adjusted for age, sex, ethnicity, BMI, FEV₁, FEV₁/FVC, REM %, t90, TRT with resaturation parameters additionally adjusted for average desaturation duration and average desaturation depth). Coloured lines represent those which retained significance after Romano-Wolf adjustment for multiple testing.

we did not have haemoglobin available to assess, however, females typically display lower haemoglobin levels than males [29], and lower haemoglobin concentrations have previously been linked to higher rates of and deeper desaturations [30,31]. Yet, previous research has indicated that estrogen use among post-menopausal women is associated with higher nocturnal oxygen saturation [32]. Furthermore, females are more commonly affected by asthma and their prognosis appears to be worse compared to males [28,33]. Alternatively, female OSA patients typically display a lower arousal threshold than males, and it may be that a greater proportion of desaturation events among females are thus linked to arousals, and as such the arousals are what is leading to a faster resaturation rate. This finding emphasizes the critical need to consider sex as a crucial factor during treatment planning and follow-up of patients, and when assessing the potential severity of the nocturnal hypoxic load [34–36].

Our study identified significantly impaired oxygen resaturation parameters among patients with lung disease, yet no significant differences in desaturation parameters. The association with resaturation parameters was attenuated in the multivariate models with the inclusion of BMI and lung function (FEV₁/FVC), however, it is notable that univariate effects were seen only in resaturation parameters. This may be due to the impairment in gas exchange that occurs in lung disease. In COPD, the pulmonary parenchyma is not normally ventilated due to the presence of bronchospasm and oedema, resulting in increased dead space and decreased gas exchange efficacy [17]. This may lead to an increase in respiratory muscle work, further increasing the oxygen demand [17] and making it difficult for oxygen to enter the bloodstream, leading to slower resaturations. In contrast, desaturation parameters may be more influenced by other factors, such as changes in breathing patterns or the oxygen capacity of the blood, which are less affected by lung disease [37,38].

Hypertension, MI, and HF were also shown to reduce the rate of resaturation and showed no significant differences in desaturation parameters after adjustment in the multivariate models. Furthermore, the reduction in D:R duration among patients with HF supports previous work showing a predictive relationship between reduced desaturation/resaturation time ratio and incident heart failure [39]. In each of these

comorbidities the heart's ability to efficiently pump blood throughout the body, including to the lungs, is impaired, though the underlying mechanisms leading to that impairment differ [14,15,20]. Pulmonary oedema, decreased lung compliance, and increased pulmonary vascular resistance can lead to a decrease in lung function in patients with HF [14]. Additionally, the release of stress hormones like adrenaline and norepinephrine due to HF may cause vasoconstriction further exacerbating the condition [40]. Furthermore, an increased rate of resaturation is associated with increased reperfusion injury [41,42], which may contribute to the development of HTN [12]. In possible contrast to our results, however, a previous study reported that a greater heart rate reaction which would theoretically be linked to an increased rate of resaturation was associated with an increased risk of MI [43]. This difference however may be temporal, as the current study used a history of MI (i.e., retrospective), while the previous study used incident MI (i.e., prospective), and it is plausible that heart rate reactions change following MI [44]. Furthermore, previous works have found the oxygen desaturation rate to be associated with hypertension [10], and higher scores on the ESS [11]. Yet in the current study, there was a significant reduction in desaturation rate among patients with hypertension in univariate models, and this was fully attenuated in multivariate models. The reduced rates of resaturation (and desaturation) recorded in patients with HTN in the current study may also be a marker of disease progression, and among patients with newly developing HTN, we may see higher rates of resaturation than among healthy patients or those with a longstanding diagnosis. Additionally, there was a high level of multimorbidity in the current cohort; half of the participants with HTN, 88% of patients with myocardial infarction, and 96% of patients with HF reported another comorbidity (Supplement 3). As such, there may well be compounding effects among those with multiple comorbidities.

The exact effect of medications upon oxygen saturation parameters however is difficult to ascertain, as the majority of participants taking medications have an underlying chronic condition. Therefore, there is an interactive effect between a medication and disease. However, similar to comorbidities, medications did show some significant effects on resaturation parameters, with desaturation parameters showing no significant changes. We identified significant reductions in the rate of

Table 3

Influence of specific medications against healthy reference patients on oxygen saturation parameters showing univariate and multivariate models (adjusted for age, sex, ethnicity, BMI, WHR, FVC, t90, TRT with resaturation parameters additionally adjusted for average desaturation duration and average desaturation depth).

	Desaturation			Resaturation			Desaturation:Resaturation ratio		
	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p
Univariate									
Rate									
Hypertension	−0.16 (−0.26, −0.07)	0.001	0.009	−0.19 (−0.28, −0.09)	<0.001	0.008	−0.01 (−0.10, 0.08)	0.838	0.996
Female sex hormones	0.20 (0.08, 0.32)	0.001	0.015	0.04 (−0.08, 0.15)	0.514	0.607	0.12 (0.00, 0.23)	0.051	0.298
Lipid affecting medication	−0.19 (−0.31, −0.08)	0.001	0.013	−0.15 (−0.27, −0.03)	0.018	0.116	−0.10 (−0.22, 0.01)	0.074	0.368
Mental health medication	−0.02 (−0.15, 0.10)	0.693	0.875	−0.19 (−0.30, −0.07)	0.002	0.016	0.10 (−0.02, 0.22)	0.114	0.489
Diabetes	−0.14 (−0.30, 0.01)	0.073	0.237	−0.13 (−0.29, 0.04)	0.142	0.455	0.00 (−0.15, 0.15)	0.975	0.996
Sympathomimetics	0.05 (−0.15, 0.25)	0.644	0.875	−0.17 (−0.36, 0.03)	0.089	0.356	0.26 (0.06, 0.46)	0.011	0.083
Anticoagulants	−0.43 (−0.62, −0.25)	<0.001	0.001	−0.55 (−0.76, −0.35)	<0.001	0.001	0.02 (−0.18, 0.23)	0.820	0.996
Pulmonary medications	−0.10 (−0.37, 0.17)	0.471	0.847	−0.14 (−0.40, 0.11)	0.266	0.607	−0.04 (−0.31, 0.23)	0.78	0.995
Anti-arrhythmics	−0.27 (−0.52, −0.02)	0.031	0.147	−0.18 (−0.51, 0.14)	0.271	0.607	−0.13 (−0.37, 0.10)	0.259	0.732
Anti-inflammatories	−0.11 (−0.21, −0.02)	0.015	0.115	−0.10 (−0.19, −0.01)	0.031	0.163	−0.03 (−0.13, 0.06)	0.449	0.902
Duration									
Hypertension	0.11 (0.02, 0.20)	0.019	0.125	0.24 (0.15, 0.32)	<0.001	0.001	−0.10 (−0.19, −0.01)	0.028	0.189
Female sex hormones	−0.22 (−0.33, −0.11)	<0.001	0.003	−0.01 (−0.12, 0.10)	0.924	0.961	−0.18 (−0.29, −0.06)	0.002	0.017
Lipid affecting medication	0.10 (−0.01, 0.22)	0.081	0.301	0.09 (−0.01, 0.20)	0.071	0.273	−0.02 (−0.13, 0.10)	0.743	0.937
Mental health medication	−0.06 (−0.18, 0.06)	0.348	0.772	0.07 (−0.04, 0.19)	0.187	0.527	−0.13 (−0.25, −0.01)	0.030	0.189
Diabetes	0.05 (−0.10, 0.20)	0.485	0.772	0.19 (0.04, 0.33)	0.010	0.085	−0.11 (−0.25, 0.03)	0.124	0.442
Sympathomimetics	−0.09 (−0.27, 0.09)	0.337	0.772	0.22 (0.01, 0.42)	0.037	0.189	−0.17 (−0.34, 0.00)	0.051	0.240
Anticoagulants	0.49 (0.26, 0.71)	<0.001	0.001	0.76 (0.50, 1.01)	<0.001	0.001	−0.22 (−0.41, −0.03)	0.026	0.189
Pulmonary medications	−0.05 (−0.32, 0.22)	0.713	0.772	0.03 (−0.27, 0.33)	0.834	0.961	−0.04 (−0.29, 0.22)	0.782	0.937
Anti-arrhythmics	0.08 (−0.18, 0.33)	0.565	0.161	0.22 (−0.08, 0.52)	0.159	0.602	−0.07 (−0.34, 0.19)	0.573	0.691
Anti-inflammatories	0.05 (−0.04, 0.13)	0.278	0.115	0.13 (0.05, 0.21)	0.002	0.184	−0.05 (−0.14, 0.04)	0.277	0.823
Depth									
Hypertension	0.00 (−0.09, 0.1)	0.952	0.952	0.03 (−0.07, 0.12)	0.572	0.963	−0.01 (−0.11, 0.08)	0.762	0.993
Female sex hormones	−0.09 (−0.20, 0.01)	0.088	0.431	−0.02 (−0.13, 0.09)	0.709	0.963	−0.18 (−0.30, −0.07)	0.002	0.032
Lipid affecting medication	−0.05 (−0.18, 0.08)	0.421	0.846	−0.04 (−0.16, 0.09)	0.580	0.963	−0.02 (−0.14, 0.09)	0.714	0.993
Mental health medication	−0.09 (−0.20, 0.03)	0.129	0.529	−0.11 (−0.23, 0.01)	0.064	0.388	0.10 (−0.03, 0.23)	0.121	0.581
Diabetes	0.05 (−0.14, 0.24)	0.597	0.923	0.04 (−0.14, 0.22)	0.671	0.963	0.02 (−0.12, 0.17)	0.781	0.993
Sympathomimetics	−0.09 (−0.26, 0.09)	0.346	0.846	−0.15 (−0.33, 0.04)	0.119	0.585	0.22 (0.02, 0.42)	0.034	0.250
Anticoagulants	0.05 (−0.16, 0.27)	0.631	0.923	0.04 (−0.19, 0.27)	0.718	0.963	0.03 (−0.17, 0.22)	0.794	0.993
Pulmonary medications	−0.21 (−0.43, 0.00)	0.053	0.314	−0.18 (−0.44, 0.07)	0.156	0.646	−0.02 (−0.29, 0.25)	0.893	0.993
Anti-arrhythmics	0.03 (−0.39, 0.44)	0.890	0.237	0.03 (−0.36, 0.42)	0.868	0.788	0.00 (−0.25, 0.24)	0.970	0.835
Anti-inflammatories	−0.04 (−0.13, 0.05)	0.346	0.160	−0.01 (−0.10, 0.08)	0.842	0.241	−0.05 (−0.14, 0.04)	0.282	0.948
Area									
Hypertension	0.13 (0.03, 0.22)	0.007	0.057	0.22 (0.13, 0.30)	<0.001	0.001	−0.03 (−0.11, 0.06)	0.537	0.949
Female sex hormones	−0.24 (−0.35, −0.14)	<0.001	0.001	−0.08 (−0.18, 0.02)	0.136	0.535	−0.14 (−0.24, −0.03)	0.010	0.096
Lipid affecting medication	0.08 (−0.04, 0.21)	0.182	0.437	0.07 (−0.03, 0.18)	0.167	0.563	0.04 (−0.08, 0.16)	0.521	0.949
Mental health medication	−0.07 (−0.18, 0.04)	0.224	0.437	0.00 (−0.11, 0.11)	0.932	0.993	−0.02 (−0.13, 0.10)	0.750	0.949
Diabetes	0.13 (−0.04, 0.29)	0.135	0.421	0.24 (0.08, 0.40)	0.003	0.032	−0.06 (−0.19, 0.07)	0.379	0.932
Sympathomimetics	−0.12 (−0.27, 0.03)	0.106	0.386	0.13 (−0.06, 0.33)	0.177	0.563	−0.03 (−0.18, 0.13)	0.718	0.949
Anticoagulants	0.43 (0.21, 0.66)	<0.001	0.007	0.72 (0.39, 1.05)	<0.001	0.004	−0.09 (−0.28, 0.09)	0.316	0.911
Pulmonary medications	−0.14 (−0.36, 0.08)	0.221	0.437	−0.02 (−0.30, 0.26)	0.884	0.993	0.05 (−0.18, 0.29)	0.657	0.949
Anti-arrhythmics	0.19 (−0.16, 0.55)	0.283	0.169	0.27 (−0.08, 0.63)	0.130	0.629	−0.02 (−0.28, 0.24)	0.876	0.884
Anti-inflammatories	0.03 (−0.06, 0.12)	0.489	0.107	0.11 (0.03, 0.19)	0.008	0.201	−0.01 (−0.09, 0.08)	0.892	0.940
Multivariate									
Rate									
Hypertension	0.02 (−0.08, 0.12)	0.665	0.997	−0.10 (−0.17, −0.03)	0.005	0.048	0.06 (−0.04, 0.16)	0.249	0.707
Female sex hormones	0.08 (−0.08, 0.24)	0.333	0.936	−0.03 (−0.15, 0.09)	0.644	0.744	0.14 (0.00, 0.29)	0.058	0.285
Lipid affecting medication	0.02 (−0.10, 0.14)	0.689	0.997	−0.06 (−0.14, 0.03)	0.172	0.585	0.06 (−0.06, 0.18)	0.316	0.768
Mental health medication	0.02 (−0.12, 0.15)	0.823	0.997	−0.18 (−0.27, −0.08)	<0.001	0.005	0.18 (0.05, 0.31)	0.008	0.095
Diabetes	0.04 (−0.15, 0.23)	0.678	0.997	−0.10 (−0.22, 0.01)	0.080	0.405	0.20 (0.02, 0.39)	0.034	0.248
Sympathomimetics	0.09 (−0.16, 0.34)	0.468	0.985	−0.22 (−0.40, −0.04)	0.014	0.116	0.26 (0.01, 0.51)	0.040	0.269
Anticoagulants	−0.19 (−0.39, 0.02)	0.070	0.469	−0.41 (−0.56, −0.26)	<0.001	0.001	0.23 (0.01, 0.45)	0.041	0.269
Pulmonary medications	0.05 (−0.22, 0.32)	0.727	0.997	−0.10 (−0.29, 0.08)	0.278	0.694	0.14 (−0.15, 0.43)	0.352	0.768
Anti-arrhythmics	−0.14 (−0.40, 0.11)	0.264	0.901	−0.12 (−0.38, 0.15)	0.393	0.744	−0.03 (−0.29, 0.23)	0.826	0.913
Anti-inflammatories	0.02 (−0.08, 0.11)	0.738	0.997	−0.03 (−0.09, 0.04)	0.451	0.744	0.02 (−0.08, 0.11)	0.709	0.913
Duration									
Hypertension	−0.08 (−0.18, 0.02)	0.108	0.523	0.13 (0.04, 0.22)	0.004	0.045	−0.16 (−0.26, −0.06)	0.002	0.029
Female sex hormones	−0.12 (−0.26, 0.02)	0.105	0.523	0.12 (−0.03, 0.26)	0.112	0.453	−0.16 (−0.31, −0.01)	0.040	0.152
Lipid affecting medication	−0.11 (−0.23, 0.02)	0.102	0.523	0.04 (−0.07, 0.15)	0.433	0.763	−0.14 (−0.27, −0.01)	0.032	0.152
Mental health medication	−0.10 (−0.23, 0.03)	0.126	0.531	0.13 (0.01, 0.26)	0.037	0.244	−0.21 (−0.34, −0.08)	0.002	0.025
Diabetes	−0.16 (−0.33, 0.01)	0.067	0.433	0.14 (0.00, 0.28)	0.057	0.308	−0.24 (−0.41, −0.07)	0.005	0.044
Sympathomimetics	−0.12 (−0.33, 0.10)	0.290	0.601	0.34 (0.10, 0.57)	0.005	0.051	−0.29 (−0.50, −0.08)	0.008	0.056
Anticoagulants	0.20 (−0.07, 0.46)	0.140	0.531	0.51 (0.28, 0.74)	<0.001	0.001	−0.40 (−0.62, −0.17)	0.001	0.016
Pulmonary medications	−0.17 (−0.45, 0.10)	0.222	0.586	0.19 (−0.11, 0.49)	0.222	0.642	−0.22 (−0.48, 0.04)	0.091	0.272
Anti-arrhythmics	−0.03 (−0.32, 0.27)	0.264	0.601	0.15 (−0.16, 0.46)	0.393	0.763	−0.09 (−0.40, 0.22)	0.826	0.913
Anti-inflammatories	−0.09 (−0.18, 0.00)	0.738	0.772	0.08 (0.00, 0.16)	0.451	0.763	−0.10 (−0.19, 0.00)	0.709	0.913
Depth									
Hypertension	0.03 (−0.07, 0.13)	0.554	0.924	0.00 (−0.04, 0.04)	0.897	0.989	0.00 (−0.10, 0.11)	0.984	1.000
Female sex hormones	−0.07 (−0.21, 0.07)	0.336	0.916	0.03 (−0.03, 0.09)	0.383	0.961	−0.01 (−0.15, 0.13)	0.883	1.000
Lipid affecting medication	−0.06 (−0.19, 0.07)	0.347	0.916	−0.01 (−0.07, 0.04)	0.583	0.969	0.03 (−0.11, 0.16)	0.695	1.000

(continued on next page)

Table 3 (continued)

	Desaturation			Resaturation			Desaturation:Resaturation ratio		
	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p	Beta (95% CI)	p-value	R-W p
Mental health medication	−0.11 (−0.24, 0.03)	0.115	0.658	−0.05 (−0.11, 0.00)	0.073	0.491	0.16 (0.02, 0.30)	0.027	0.236
Diabetes	−0.09 (−0.28, 0.11)	0.385	0.916	−0.01 (−0.08, 0.05)	0.662	0.969	0.01 (−0.16, 0.18)	0.912	1.000
Sympathomimetics	0.02 (−0.22, 0.27)	0.865	0.964	0.00 (−0.10, 0.09)	0.954	0.989	0.03 (−0.22, 0.29)	0.794	1.000
Anticoagulants	−0.09 (−0.32, 0.14)	0.464	0.920	−0.08 (−0.17, 0.01)	0.096	0.562	0.08 (−0.14, 0.31)	0.468	0.996
Pulmonary medications	−0.14 (−0.42, 0.13)	0.303	0.916	0.03 (−0.08, 0.15)	0.571	0.969	−0.03 (−0.33, 0.27)	0.821	1.000
Anti-arrythmics	0.00 (−0.4, 0.39)	0.264	0.900	0.00 (−0.10, 0.11)	0.393	0.961	−0.01 (−0.27, 0.26)	0.826	1.000
Anti-inflammatories	−0.01 (−0.10, 0.08)	0.738	0.964	0.02 (−0.02, 0.05)	0.451	0.961	−0.02 (−0.12, 0.07)	0.709	1.000
Area									
Hypertension	−0.03 (−0.12, 0.07)	0.550	0.901	0.10 (0.02, 0.18)	0.013	0.119	−0.07 (−0.17, 0.04)	0.217	0.771
Female sex hormones	−0.15 (−0.28, −0.02)	0.024	0.212	0.07 (−0.05, 0.19)	0.239	0.719	−0.12 (−0.25, 0.02)	0.099	0.449
Lipid affecting medication	−0.10 (−0.22, 0.03)	0.127	0.507	0.01 (−0.09, 0.11)	0.846	0.838	−0.02 (−0.18, 0.15)	0.847	0.984
Mental health medication	−0.12 (−0.24, 0.00)	0.045	0.313	0.09 (−0.02, 0.20)	0.093	0.455	−0.08 (−0.21, 0.05)	0.234	0.771
Diabetes	−0.15 (−0.34, 0.04)	0.113	0.507	0.13 (−0.01, 0.28)	0.066	0.384	−0.18 (−0.33, −0.02)	0.031	0.253
Sympathomimetics	−0.14 (−0.33, 0.05)	0.139	0.507	0.20 (0.00, 0.41)	0.049	0.341	−0.20 (−0.40, 0.01)	0.057	0.392
Anticoagulants	0.06 (−0.18, 0.30)	0.617	0.900	0.33 (0.11, 0.55)	0.003	0.043	−0.23 (−0.44, −0.03)	0.028	0.253
Pulmonary medications	−0.21 (−0.46, 0.03)	0.092	0.469	0.16 (−0.11, 0.44)	0.248	0.719	−0.07 (−0.32, 0.19)	0.612	0.984
Anti-arrythmics	0.10 (−0.26, 0.46)	0.264	0.700	0.20 (−0.09, 0.49)	0.393	0.766	−0.05 (−0.34, 0.25)	0.826	0.984
Anti-inflammatories	−0.07 (−0.15, 0.02)	0.738	0.900	0.08 (0.01, 0.16)	0.451	0.766	−0.03 (−0.12, 0.06)	0.709	0.984

Bold values indicate those with statistically significant differences compared to healthy participants after Romano-Wolf adjustment.

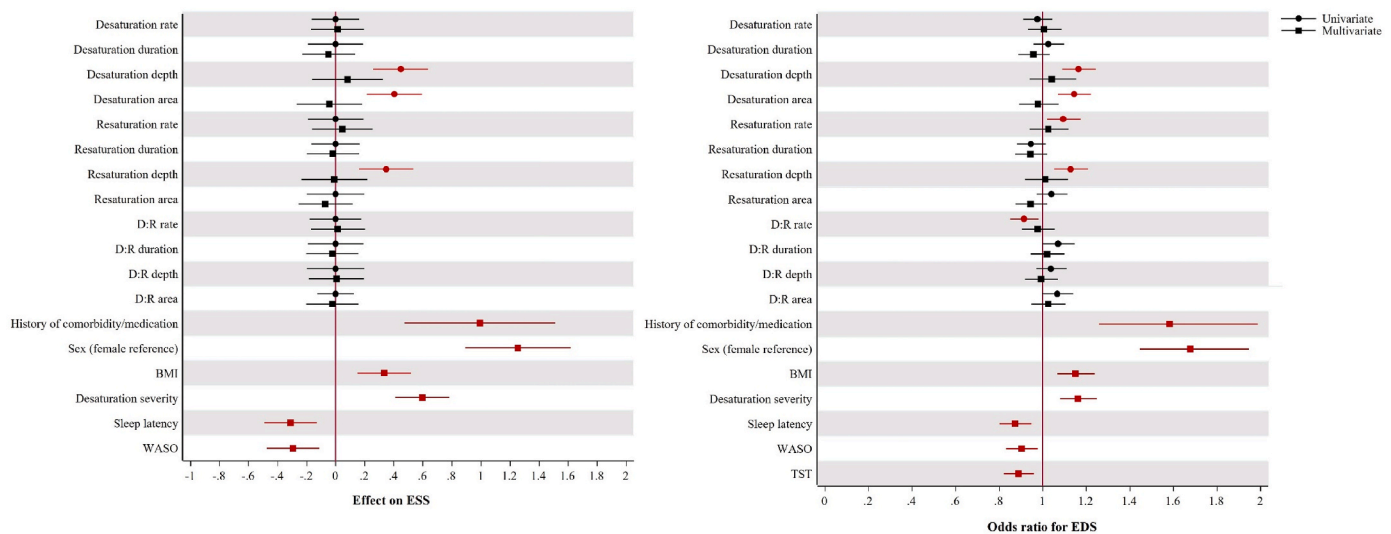


Fig. 4. Influence of oxygen saturation parameters on ESS and EDS (ESS >10) by univariate and multivariate analyses (Continuous regression model adjusted for presence of any comorbidity/medication, sex, BMI, WASO, sleep latency, and desaturation severity). Logistic regression model adjusted for presence of any comorbidity/medication sex, BMI, WASO, sleep latency, TRT, and desaturation severity). All continuous parameters were transformed to z-scores to estimate relative effects. Abbreviations: BMI, Body mass index; D:R, Desaturation:Resaturation ratio; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; TRT, Total recording time; WASO, Wake after sleep onset.

resaturation among patients using antihypertensive medications, mental health medications, and anticoagulants (warfarin/coumadin/anisindione). Beta-blockers (in this study grouped under the antihypertensive medication heading) are commonly used to treat high blood pressure and cardiovascular conditions. However, especially nonselective beta-blockers can also affect respiration, particularly in patients with pre-existing respiratory conditions such as asthma or COPD, due to beta receptors in the lungs which can result in airway restriction and impaired lung function [45]. Moreover, beta-blockers can reduce the ventilatory response to hypoxia, which can lead to an increased risk of respiratory failure in patients with COPD and other respiratory conditions. Beta-blockers may also decrease cardiac output, which can lead to decreased tissue perfusion and oxygen delivery [46]. Yet currently, of the antihypertensive medications angiotensin receptor blockers are the most common, and the prescription rate of beta blockers has fallen compared to the time when the SHHS data was first collected. There has been some speculation that benzodiazepines could reduce the number of arousals from sleep, reduce upper airway muscle tone, and decrease the

ventilatory response to hypoxia in patients with repetitive obstructive hypopnoeas [47,48]. They are also associated with a reduced heart rate, and these factors together may explain the reduction in the resaturation rate identified in this study. However, there may be alternative explanations for the effects of these medications on oxygen saturation, and further research is needed to fully understand their impact. Furthermore, in this study, the majority of participants taking medications were taking multiple medications (Supplement 4), and as such the effect of individual medications is difficult to tease out.

In contrast to a previous study from our centre, in the current study resaturation parameters were not independently associated with daytime sleepiness [22]. In univariate models, a faster resaturation rate increased the odds of EDS as assessed via ESS, as did an increased desaturation depth and area, and an increased resaturation depth. However, after adjustment of the oxygen saturation parameters, only total desaturation severity retained any significant association with EDS. Notably, a history of comorbidities or medication usage was associated with increased daytime sleepiness, and in the current study

comorbidities and medications were associated with a reduced rate of resaturation. However, in our previous study, a reduced rate of resaturation was protective against EDS [22]. This discrepancy may come from the different methods of assessing daytime sleepiness, with the current study using the ESS and the previous study utilising multiple sleep latency test (MSLT). MSLTs and the ESS measure different domains, with MSLTs validated for central hypersomnia, and the ESS a more general tool that may capture measures of fatigue as well as sleepiness [49–51]. Thus, it is not surprising that the results of our two studies differ. Furthermore, the ESS is known to have a male bias, with cultural differences evident across studies [52,53]. However, the ESS is a simple and cheap tool to use and thus widely utilised in sleep clinics and by general practitioners prior to referring patients to sleep specialists. It has also been noted to have greater generalisability as it measures sleep propensity across multiple situations and has been reported to have greater sensitivity and specificity for identifying EDS than the MSLT [54]. Yet given that comorbidities and medications affected resaturation parameters and not desaturation parameters in the current study, and that resaturation parameters were independently associated with daytime sleepiness in the previous study, it is clear that further research is warranted to elucidate further outcomes associated with nocturnal resaturation parameters.

4.1. Limitations

The current study was a retrospective study, with only a single night measure of oxygen saturation. This cross-sectionality and retrospective nature limits the ability to identify causation between comorbidities, medications, and desaturation or resaturation parameters. Furthermore, the data used in this study is now more than 20 years old, and in this time diagnosis and treatment guidelines for cardiorespiratory diseases have evolved. Due to the utilisation of self-reports for medication and comorbidity history, it is also plausible that there are recall errors. Moreover, within the SHHS dataset, several comorbidities such as hypertension are defined on the basis of using relevant medications, and therefore there is quite some overlap between ‘comorbidities’ and ‘medications’, meaning that we are largely unable to determine if it is the disease, or the medication leading to these results. Additionally, we utilised summary data from across the night and therefore do not have event wise information such as arousal status, event type, event duration or event baselines which could have impacted desaturation and resaturation parameters. Finally, the ABOSA software utilised is a new tool, and given that there are currently no standardised ways to score and define saturation events, it is plausible that differences in the underlying algorithms between ABOSA or over such programs could result in differences in desaturation and resaturation parameters.

5. Conclusion

The results of this study suggest that the presence of comorbidities, such as hypertension and heart failure, as well as usage of certain medications, can significantly affect resaturation parameters, independent of desaturation parameters. The rate of resaturations in particular appears to be most affected by comorbidities or medication usage. However, no significant association was seen between desaturation or resaturation parameters and subjective scores of daytime sleepiness. These findings highlight the importance of considering individual factors when managing sleep apnoea and optimizing treatment. Thus, it is vital to consider desaturation and resaturation parameters separately when assessing nocturnal oxygen saturation metrics – particularly in the presence of chronic disease.

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CRediT authorship contribution statement

Timothy P. Howarth: Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization, Writing – original draft, Writing – review & editing. **Saara Sillanmäki:** Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Tuomas Karhu:** Formal analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. **Marika Rissanen:** Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. **Anna Sigridur Islind:** Writing – review & editing. **Harald Hrubos-Strøm:** Funding acquisition, Writing – review & editing. **Philip de Chazal:** Writing – review & editing. **Juuso Huovila:** Writing – original draft, Writing – review & editing. **Samu Kainulainen:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Timo Leppänen:** Funding acquisition, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Timo Leppänen reports financial support was provided by Nordforsk. Timo Leppänen reports financial support was provided by Kuopio University Hospital. Saara Sillanmäki reports financial support was provided by Kuopio University Hospital. Marika Rissanen reports financial support was provided by Kuopio Area Respiratory Foundation. Harald Hrubos-Strøm reports financial support was provided by Nordforsk. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2024.03.047>.

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