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Witnessed sleep apneas together with elevated plasma glucose are predictors of COPD exacerbations

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ABSTRACT

Objective: Sleep apnea and elevated plasma glucose associates with inflammation which associates with the risk of COPD exacerbations. We investigated the risk of exacerbations in individuals with COPD, witnessed sleep apneas, and elevated plasma glucose.

Methods: From the Copenhagen City Heart Study cohort, we identified 564 individuals with COPD (forced expiratory volume in 1 sec divided by forced vital capacity, $FEV_1/FVC<0.70$), no asthma, above 40 years of age, and more than 10 pack-years of smoking history, with information on witnessed apneas and levels of plasma glucose. We prospectively recorded hospital admissions with COPD exacerbations during maximum available follow-up (26.3 years; mean 10.7 years). Cox-regression analyses were used to analyze the risk of COPD exacerbations.

Results: We identified 74 (13%) individuals with sleep apnea without elevated plasma glucose, 70 (12%) had elevated plasma glucose (above 6.9 mM (>125 mg/dL)) without sleep apnea and 11 individuals had the presence of both conditions. In univariable analysis, witnessed apneas together with elevated plasma glucose had a high risk of exacerbations, hazard ratio (HR) = 5.81 (2.34–14.4, $p = 0.0001$) compared to those without sleep apnea and without elevated plasma glucose. Multivariable analysis, adjusting for several risk factors of exacerbations, showed a similar result, HR = 3.45 (1.13–10.5, $p = 0.03$). Both presence of sleep apnea without elevated plasma glucose and the presence of elevated plasma glucose without sleep apnea showed no associations with the risk of exacerbations.

Conclusions: Witnessed sleep apneas in COPD are associated with increased risk of exacerbations, but only among those with elevated plasma glucose.

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Introduction

Chronic obstructive pulmonary disease is one of the most prevalent diseases in the world and estimated to be the third leading cause of death [1]. COPD is characterized by chronic inflammation in the airways and in a substantial proportion of these patients, there are also signs of systemic inflammation [2,3]. Obstructive sleep apnea is also a prevalent disease associated with increased morbidity [4] and mortality [5], and is recognized as a common comorbidity for COPD patients [6]. The presence of both conditions, sometimes referred to as an overlap syndrome, is estimated to coexist in around 1% of the adult general population [7], and in a study of patients with COPD undergoing an inpatient pulmonary rehabilitation program the overlap prevalence was 45% [8]. Importantly, the presence of sleep apnea in COPD has been linked with an increased risk of exacerbations requiring admission to the hospital [9].

Sleep apnea is also associated with metabolic syndrome and elevated plasma glucose and seems to have an inflammatory component [10,11]. Furthermore, it has been shown that elevated plasma glucose in COPD patients with acute exacerbations associates with prolonged admissions and increased mortality [12]. Although some studies have not been able to replicate these findings [13], there is emerging evidence of the importance of glucose metabolism and insulin resistance in patients with COPD. A causal role for hyperglycemia in the human immune activation has been suggested probably mediated by increasing circulating cytokine concentrations [14], and it is acknowledged that there is a close link between metabolism and immunity [15]. Studies in mice have

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shown that chronic inflammation exacerbates glucose metabolism [16] and that chronic hyperglycemia has an effect on the innate immune system with an exaggeration of the inflammatory response [17]. Impaired immune mechanisms and inflammation are also common features of individuals with COPD [3,18], and it could be postulated that sleep apnea and elevated plasma glucose may have a synergistic effect on inflammation and risk of exacerbations in COPD.

Nevertheless, to our knowledge previous studies have not assessed a possible interaction between the presence of sleep apnea and elevated plasma glucose levels; i.e. whether the risk of COPD exacerbations associated with sleep apnea is different in individuals with or without elevated glucose levels.

We hypothesized that elevated plasma glucose in individuals with COPD and witnessed sleep apneas associates with an increased risk of COPD exacerbations and investigated this theory by performing a prospective analysis of data from the Copenhagen City Heart Study (CCHS).

Materials and methods

Participants

Among individuals with COPD in the third examination of the Copenhagen City Heart Study (examined 1991–1994) [19], defined by pre-bronchodilator forced expiratory volume in 1 sec (FEV_1) divided by forced vital capacity (FVC), $FEV_1/FVC<0.7$, no asthma, age above 40 years, more than 10 pack-years of smoking history, and no history of admissions with severe COPD exacerbations, we identified 571 individuals with or without sleep apnea reported by their spouses. Of these, 564 (98.9%) had data on baseline plasma glucose levels and comprised our study population.

Sleep apnea

Presence of witnessed apneas observed by spouses was reported as seldom/never, sometimes, and often/always. In the present analyses, we defined seldom/never as no witnessed apneas and sometimes/often/always as an indication of the presence of witnessed apneas (details in Supplementary Table 1) [19].

Elevated plasma glucose

Plasma glucose level at baseline was measured in mmol/L (mM). In our main analysis, we used a non-fasting plasma glucose above 6.9 mM (>125 mg/dL) to define elevated plasma glucose (Supplementary Table 1).

Admissions

Data on hospitalizations were available from the national Danish Patient Registry [20,21], from 1977 until April 2018. Prospectively, severe COPD exacerbations were recorded as the first admission with a discharge diagnosis of COPD and time to first admission (ICD-8: 491.00–492.09 and ICD-10: DJ41.0-DJ44.9; ICD-9 was never used in Denmark where ICD-8 was used until 1994 and hereafter shifted directly to ICD-10).

Statistical analysis

For demographics, continuous variables and categorical variables were compared using analysis of variance and chi-square tests as appropriate.

The Kaplan–Meier estimator was used to estimate the percentage of events during follow-up after the initial examination, accounting for censoring of data, and percentages presented are 100% minus the Kaplan–Meier estimate of being event-free. Kaplan–Meier curves were included to describe the clinical prognosis for groups of individuals with COPD with or without sleep apnea and with or without elevated plasma glucose. Interaction between the presence of sleep apnea and elevated plasma glucose was tested by analysis of variance (ANOVA) using a likelihood ratio test.

To estimate the confounder adjusted risks of COPD hospital admissions we used a Cox-regression model. In multivariable modeling we included the following variables: age at examination, sex, FEV_1 in % of predicted value, breathlessness (a score on the modified medical research council scale, mMRC ≥2), night-time dyspnoea, body mass index (BMI) categories, pack-years, elevated C-reactive protein (CRP) (>3 mg/L), elevated systolic blood pressure (>140 mmHg) and elevated total cholesterol (>6.2 mM (>240 mg/dL)), lowered HDL cholesterol (<1.03 mM (<40 mg/dL)), and elevated triglycerides (>1.7 mM (>150 mg/dL)). In the third examination of the Copenhagen City Heart Study, we also had data on self-reported regular use (reported daily or almost daily use) of asthma/bronchitis medication, diuretics, cholesterol-lowering medication, and blood pressure medication as yes/no variables. These were also included in multivariable analyses, except cholesterol-lowering medication since no individuals with COPD reported regular use of these drugs at the baseline examination. Supplementary Table 1 shows details of all variables included in our analyses.

The assumption of proportionality in the Cox-regression models was tested with the Lin, Wei, and Ying score process test [22]. All analyses were performed with R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) [23].

Sensitivity analysis

We chose our main glucose cut-point (>125 mg/dL or >6.9 mM) in correspondence with the established cut-point for a diagnosis of diabetes in fasting individuals. However, as we only had non-fasting glucose levels, we also chose to analyze the cut-point corresponding to an impaired glucose tolerance in an oral glucose tolerance test (>140 mg/dL or >7.8 mM). In addition, we wished to assess a possible dose–response relation with plasma glucose levels. Therefore, in our sensitivity analysis, we defined elevated plasma glucose by plasma glucose above 7.8 mM (>140 mg/dl) at the baseline examination. Univariable and multivariable sensitivity analyses were done as described above.

Results

Demographics

Among 564 individuals with COPD, 85 (15%) reported witnessed apneas. We identified 11 (2%) individuals with COPD, sleep apnea, and elevated plasma glucose above 6.9 mM (>125 mg/dL), and five individuals with COPD, sleep apnea, and elevated plasma glucose above 7.8 mM (>140 mg/dL). Furthermore, 74 (13%) individuals had sleep apnea without elevated plasma glucose and 70 (12%) individuals had elevated plasma glucose without sleep apnea. Table 1 shows baseline characteristics of individuals with COPD with or without sleep apnea and with or without elevated plasma glucose. Individuals with sleep apnea and elevated plasma glucose were mainly men with poorer lung function, more breathlessness, night-time dyspnoea and obesity, and a higher number of pack-years, slightly more with elevated CRP, and more with lowered HDL-cholesterol. The use of asthma/bronchitis medication and blood pressure medication was not significantly different at baseline, but the use of diuretics was higher among those with witnessed apneas and elevated plasma glucose.

We observed a highly significant interaction between reported witnessed apneas and baseline plasma glucose level, $p = 0.0004$.

Admissions with severe exacerbations

During an average follow-up of 10.7 years (maximum: 26.4 years), among the 564 individuals with COPD, 196 (35%) individuals had severe exacerbations and we prospectively analyzed the first admission with a COPD exacerbation (these 196 individuals had at least one hospital admission due to a COPD exacerbation during follow-up).

Figure 1 shows Kaplan–Meier curves (with Log-rank test) for individuals with COPD with or without witnessed apneas and with or without elevated plasma glucose and the prospective risk of being free of COPD exacerbations during maximum available follow-up.

In univariable Cox-regression analysis, sleep apnea with elevated plasma glucose associated with increased risk of exacerbations, hazard ratio (HR) = 5.81 (2.34–14.4, $p = 0.0001$) compared to individuals without sleep apnea and without elevated plasma glucose. Sleep apnea alone without elevated plasma glucose and elevated plasma

Table 1. Characteristics of 564 individuals with chronic obstructive pulmonary disease (COPD) in the third examination of the Copenhagen City Heart Study, with or without sleep apnea and with or without elevated plasma glucose above 6.9 mM (>125 mg/dL).

Characteristics	No sleep apnea and not elevated glucose (*N* = 409)	Sleep apnea but not elevated glucose (*N* = 74)	No sleep apnea but elevated glucose (*N* = 70)	Sleep apnea and elevated glucose (*N* = 11)	*P* Value
Age at examination – mean (SD)	66.0 (9.5)	63.2 (8.9)	67.8 (8.5)	67.1 (8.4)	0.02
Males – % (No.)	60.4 (247)	77.0 (57)	67.1 (47)	90.9 (10)	0.009
FEV_1 in % of predicted value – mean (SD)	74.3 (19.5)	69.0 (19.8)	66.8 (16.7)	64.0 (14.9)	0.002
Pack-years – mean (SD)	39.7 (20.5)	48.6 (25.3)	42.0 (15.4)	53.7 (24.0)	0.002
Breathlessness* – % (No.)	15.9 (65)	33.8 (25)	27.1 (19)	63.6 (7)	<0.001
Night-time dyspnoea – (% (No.)	2.9 (12)	14.9 (11)	2.9 (2)	18.2 (2)	<0.001
Normal weight[a] – % (No.)	54.8 (224)	51.4 (38)	47.1 (33)	45.5 (5)	0.06
Underweight[b] – % (No.)	3.7 (15)	2.7 (2)	2.9 (2)	0.0 (0)	
Overweight[c] – % (No.)	33.7 (138)	29.7 (22)	40.0 (28)	18.2 (2)	
Obese[d] – % (No.)	7.8 (32)	16.2 (12)	10.0 (7)	36.4 (4)	
C-reactive protein – (> 3 mg/L) – % (No.)	25.8 (91)	35.8 (24)	45.5 (30)	30.0 (3)	0.009
Systolic blood pressure – mean (SD)	143.6 (21.7)	143.7 (19.1)	142.1 (21.2)	137.8 (25.4)	0.79
Total cholesterol >6.2 mM (> 240 mg/dL) – % (No.)	48.9 (200)	45.9 (34)	40.0 (28)	18.2 (2)	0.13
HDL cholesterol <1.03 mM (<40 mg/dL) – % (No.)	9.5 (39)	21.6 (16)	25.7 (18)	63.6 (7)	<0.001
Triglycerides >1.7 mM (>150 mg/dL) – % (No.)	43.5 (177)	51.4 (38)	57.1 (40)	63.6 (7)	0.08
Asthma or bronchitis medication – % (No.)	3.4 (14)	6.8 (5)	1.4 (1)	9.1 (1)	0.27
Blood pressure medication – % (No.)	11.6 (47)	16.4 (12)	15.7 (11)	9.1 (1)	0.55
Diuretics – % (No.)	7.4 (30)	9.6 (7)	14.3 (10)	45.5 (5)	<0.001

*A score on the Modified Medical Research Council Scale equal to or larger than two; SD: Standard Deviation. [a]Normal weight: 18.5 kg/m^2≤ BMI<25.0 kg/m^2; [b]Underweight: BMI<18.0 kg/m^2; [c]Overweight: 25 kg/m^2≤ BMI<30.0 kg/m^2; [d]Obese: BMI≥30.0 kg/m^2.

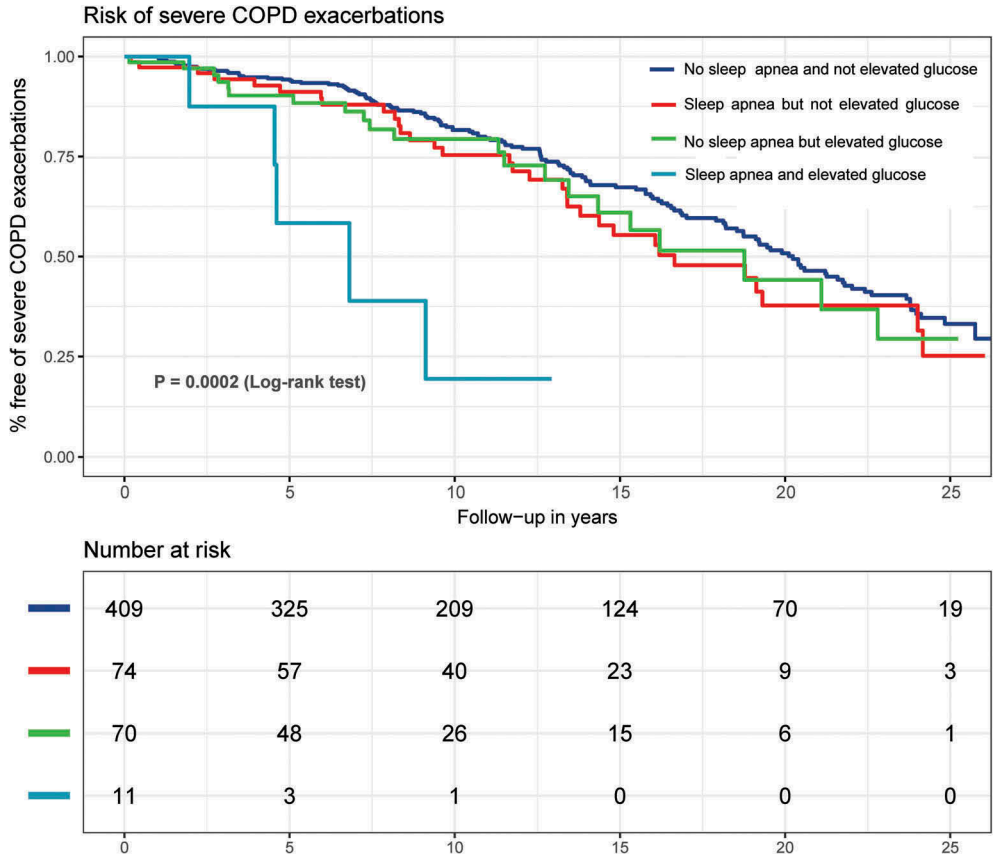

Figure 1. Kaplan–Meier curves showing associations between individuals with COPD with or without reported witnessed apneas and with or without elevated plasma glucose above 6.9 mM (>125 mg/dL) at baseline and risk of being free of COPD exacerbations during follow-up in the Copenhagen City Heart Study.

glucose alone without sleep apnea showed a numerically slightly higher risk, which did not reach statistical significance, HR = 1.31 (0.89–1.92, p = 0.17) and HR = 1.27 (0.80–2.01, p = 0.30), respectively.

In multivariable analyses, sleep apnea with elevated plasma glucose associated with increased risk of exacerbations, HR = 3.45 (1.13–10.5, p = 0.03). Sleep apnea without elevated plasma glucose and elevated plasma glucose without sleep apnea showed no associations with risk of exacerbations, HR = 0.92 (0.58–1.45, p = 0.72) and HR = 0.83 (0.50–1.36, p = 0.45), respectively. Table 2 shows the results for all variables included in the multivariable analysis.

Sensitivity analysis

We identified five individuals with COPD, sleep apnea, and plasma glucose above 7.8 mM (>140 mg/dL); characteristics shown in Supplementary Table 2. In our univariable sensitivity analysis, we observed that sleep apnea with this elevation of plasma glucose was associated with an even higher risk of exacerbations, HR = 11.0 (4.00–30.3, p = 0.000003).

In our multivariable sensitivity analysis, we observed a similar significant association for sleep apnea with elevated plasma glucose, HR = 5.71 (1.42–23.0, p = 0.01) compared to those without sleep apnea and without elevated plasma glucose. Similar to our main analysis, sleep apnea without elevated plasma glucose and elevated plasma glucose without sleep apnea showed no associations with risk of COPD admissions, HR = 0.92 (0.59–1.44, p = 0.70) and HR = 0.54 (0.24–1.20, p = 0.13), respectively. Supplementary Table 3 shows results for all variables included in the multivariable sensitivity analysis.

Discussion

In this prospective cohort study, we observed that among individuals with COPD those who had reported witnessed apneas and elevated plasma glucose at baseline had a threefold increased risk of severe COPD exacerbations requiring hospital admission compared to those without sleep apnea and without elevated plasma glucose. Furthermore, individuals with sleep apnea without elevated plasma glucose and those with elevated plasma glucose

Table 2. Multivariable associations between all variables included in multivariable Cox-regression analysis and prospective risk of severe COPD exacerbations requiring hospital admission. Elevated plasma glucose defined by a plasma glucose level above 6.9 mM (>125 mg/dL).

Characteristics	Hazard ratio (95% CI)	*P* Value
Sleep apnea and not elevated glucose[a]	0.92 (0.58–1.45)	0.72
No sleep apnea but elevated glucose[a]	0.83 (0.50–1.36)	0.45
Sleep apnea and elevated glucose[a]	3.45 (1.13–10.5)	0.03
Age (per year increase)	1.03 (1.01–1.05)	0.003
Males (reference females)	1.02 (0.70–1.48)	0.92
FEV_1 in % of predicted value (per % increase)	0.96 (0.95–0.97)	<0.0001
Overweight[b]	0.67 (0.46–0.97)	0.03
Obese[b]	0.35 (0.19–0.64)	0.0008
Underweight[b]	1.43 (0.69–2.99)	0.34
Breathlessness[c]	1.49 (0.97–2.29)	0.07
Night-time dyspnoea	1.50 (0.76–2.97)	0.24
C-reactive protein (> 3 mg/L)	1.09 (0.73–1.61)	0.68
Total cholesterol >6.2 mM (>240 mg/dL)	1.12 (0.81–1.56)	0.48
HDL-cholesterol <1.03 mM (<40 mg/dL)	1.03 (0.66–1.62)	0.89
Triglycerides >1.7 mM (>150 mg/dL)	0.88 (0.64–1.22)	0.45
Systolic blood pressure elevated (>140 mmHg)	0.58 (0.42–0.82)	0.002
Pack-years (per one year increase)	1.01 (1.00–1.02)	0.01
Asthma or bronchitis medication	1.82 (0.91–3.65)	0.09
Blood pressure medication	1.32 (0.79–2.20)	0.29
Diuretics	0.98 (0.51–1.85)	0.94

FEV_1: Forced expiratory volume in 1 sec; [a]No sleep apnea and not elevated plasma glucose as reference; [b]Normal weight as reference group; [c]A score on the modified medical research council scale, mMRC ≥2.

without sleep apnea did not have an increased risk of exacerbations.

To our knowledge, this is the first study showing an interaction between sleep apnea and plasma glucose levels in individuals with COPD affecting the future risk of severe exacerbations.

Our findings are novel and seem biologically plausible. In a study of 96 individuals with or without sleep apnea, Cizza et al. found that sleep apnea associated with impaired glucose metabolism [24]. Similarly, in a larger study by Bakker et al. the authors found that sleep apnea associated with metabolic dysfunction and increased plasma glucose levels [25]. Elevated plasma glucose is a part of the metabolic syndrome which is prevalent in COPD [26]. A study of 29 individuals with metabolic syndrome and 77 controls showed a significant correlation between the presence of metabolic syndrome and COPD exacerbation frequency [27], and the explanation for our findings could be a hypermetabolic state caused by an interaction between sleep apnea and plasma glucose thereby increasing inflammation and risk of exacerbations. In our study, we were able to include several variables describing metabolic syndrome such as total cholesterol, HDL cholesterol, and systolic blood pressure. Surprisingly, of these variables only HDL cholesterol was associated with the presence of sleep apnea with elevated plasma glucose in COPD at baseline, and all these variables were included in multivariable analyses without affecting our conclusions.

Previous research has shown that the measurement of biomarker combinations including C-reactive protein could be useful in identifying individuals with obstructive sleep apnea [28]. In another study of 15 individuals with impaired glucose tolerance, the authors found higher plasma levels of the cytokines IL-6 and TNF-α compared to 20 controls [14]. This could be particularly important in COPD patients that are characterized by systemic inflammation and elevated inflammatory biomarkers [3]. In our study, we observed slightly more with an elevated CRP level in those with sleep apnea with or without elevated plasma glucose. CRP elevation could represent systemic inflammation in individuals with sleep apnea but, importantly, including CRP in multivariable analyses did not change our conclusions. This, of course, does not rule out the involvement of other inflammatory pathways. Similarly, the difference in pack-years across groups at baseline could have an effect on systemic inflammation and confound univariable analyses, but the multivariable estimates were also significant and robust towards adjustments for this variable.

Sleep apnea and metabolic syndrome are associated with obesity and we observed a higher prevalence of obesity in individuals with sleep apnea and elevated plasma glucose. Nevertheless, our results remained similar after adjustment for BMI categories and, in fact, overweight and obesity *per se* associated with reduced risk of severe exacerbations requiring hospital admissions, which is in line with previous findings [29], and in line with our observation that hypertension was associated with reduced risk of exacerbations [30], but future studies on the associations between BMI, hypertension, sleep apnea, and COPD exacerbations are warranted.

A major limitation to our study was the sample size with only 11 individuals with sleep apnea and elevated plasma glucose above 6.9 mM (>125 mg/dL) and five individuals in our sensitivity analysis with sleep apnea and plasma glucose above 7.8 mM (>140 mg/dL) at baseline, which increase the likelihood of false-positive findings. However, we believe that our conclusion that sleep apnea in COPD only associates with exacerbations in those with elevated plasma glucose is supported by the observed null associations between sleep apnea without elevated plasma glucose and elevated plasma glucose without sleep apnea, which we also believe are novel findings. These subgroups were quite large comprising 74 and 70 individuals, respectively. Furthermore, our main significant findings are based mostly on a sample of males which is an important potential limitation to the generalisability of our results, although most individuals with both COPD and sleep apnea are males. Another major limitation to our study is the assessment of sleep

apnea by self-report. Although witnessed apnea events are a good predictor of obstructive sleep apnea they do not predict severity and are not diagnostic [31]. Inclusion of information on overnight monitoring demonstrating obstructed breathing events [31] would make our study more reliable; however, such data are not available in the Copenhagen City Heart Study. As we cannot assess the severity of sleep apnea in the present study, we speculate that another explanation for our findings could be that the elevation of plasma glucose levels reflects more severe sleep apnea. As such, the association with exacerbations observed in individuals with sleep apnea and elevated plasma glucose could simply reflect a marker of disease severity and not represent an inflammatory synergism which is somewhat supported by the observed only slightly increased levels of CRP.

Similarly, individuals with COPD and increased glucose levels and witnessed apneas had the lowest FEV_1, highest number of pack-years, highest proportion of breathlessness, and nocturnal dyspnea suggesting more severe COPD. Although we adjusted our analyses for all these variables, confounding from COPD severity and residual confounding might still be present.

Therefore, our results must be interpreted with caution, and of course, only provides associations and does not address causality on the effect of sleep apnea and elevated plasma glucose in COPD.

Unfortunately, the Copenhagen City Heart Study does not hold data on other symptoms of sleep apnea, but as a major strength to our study included information of several baseline characteristics associated with COPD, exacerbations, and metabolic syndrome. Inclusion of all these variables in multivariable modeling produced robust and significant associations between witnessed apneas with elevated plasma glucose and the risk of severe exacerbations in COPD. Further strengths include recording of severe COPD exacerbations requiring admission to hospital in the all-covering national admission registry with a validated positive predictive value of 92% [32].

As another potential limitation to our study, regular use of diuretics was higher among those with witnessed apneas and elevated plasma glucose which suggests comorbid heart failure. Heart failure could provoke nocturnal dyspnea and irregular breathing which could be interpreted as apneas, and in addition, diuretics could contribute to elevated plasma glucose levels. Furthermore, decompensated heart failure despite diuretic treatment could cause fluid shift during night-time leading to worsening of obstructive sleep apnea and perhaps thereby increase the risk of exacerbations in COPD. However, for this study, we did not have data on comorbid cardiovascular disease, but multivariable analyses remained significant after adjustment for regular use of diuretics. Similarly, another potential limitation was that the third examination of the Copenhagen City Heart Study does not hold information on the type of antidiabetic medication used by the participants.

A further important limitation to our study is that we did not have data on how many patients had a diagnosis of obstructive sleep apnea with or without treatment. A meta-analysis found that continuous positive airway pressure (CPAP) treatment significantly improved insulin resistance in non-diabetic patients with obstructive sleep apnea, although the meta-analysis did not detect a change in glycaemic control [33]. In a large study of 718 patients with sleep apnea treated with CPAP, those who were most adherent to treatment had a significant improvement in glucose levels [34]. Furthermore, CPAP treatment in patients with COPD and sleep apnea reduces the risk of severe exacerbations [9]. Therefore, it would be interesting to assess whether CPAP treatment in patients with COPD, sleep apnea, and elevation of plasma glucose has a particularly beneficial effect on future risk of exacerbations.

In conclusion, we observed that among individuals with COPD, those who had witnessed sleep apneas and elevated plasma glucose had a threefold increased risk of severe COPD exacerbations compared to those without sleep apnea and without elevated plasma glucose. Furthermore, individuals with COPD and sleep apnea without elevated plasma glucose, and those with COPD and elevated plasma glucose without sleep apnea did not have an increased risk of exacerbations.

Author contributions

Study concept and design: TSI, PL; Acquisition of data: PL, JLM; Analysis and interpretation of data: TSI, PL; First drafting of the manuscript: TSI, PL; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: TSI; Obtained funding: PL; Administrative, technical, and material support: PL, JLM; Study supervision: PL.

Data access and responsibility

Dr. Truls Sylvan Ingebrigtsen had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

Disclosure statement

Truls Sylvan Ingebrigtsen: has received fee for speaking from AstraZeneca, not related to the topic of this study.

Jacob Louis Marott: none to declare.
Peter Lange has received research grants from Astra Zeneca, Boehringer Ingelheim and GlaxoSmithKline; received fee for speaking from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithCline, Novartis, Teva; received fee for consulting from AstraZeneca, Boehringer Ingelheim, GlaxoSmithCline, Novartis and Teva.

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Notes on contributors

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References

[1] Lundbäck B, Bakke P, Ingebrigtsen TS, et al. Chronic obstructive pulmonary disease. In: Annesi-Maesona I, Lundbäck B, Viegi G, editors. Respiratory epidemiology. European Respiratory Society Publications; 2014; Chapter 1: 1–17.
[2] Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–582. .
[3] Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA. 2013;309(22):2353–2361. .
[4] Robichaud-Halle L, Beaudry M, Fortin M. Obstructive sleep apnea and multimorbidity. BMC Pulm Med. 2012;12:60.
[5] Marshall NS, Wong KK, Liu PY, et al. Sleep apnea as an independent risk factor for all-cause mortality: the busselton health study. Sleep. 2008;31(8):1079–1085.
[6] Soler X, Gaio E, Powell FL, et al. High prevalence of obstructive sleep apnea in patients with moderate to severe chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2015;12(8):1219–1225.
[7] McNicholas WT. COPD-OSA overlap syndrome: evolving evidence regarding epidemiology, clinical consequences, and management. Chest. 2017;152(6):1318–1326.
[8] Schreiber A, Cemmi F, Ambrosino N, et al. Prevalence and predictors of obstructive sleep apnea in patients with chronic obstructive pulmonary disease undergoing inpatient pulmonary rehabilitation. COPD. 2018;15(3):265–270.
[9] Marin JM, Soriano JB, Carrizo SJ, et al. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182(3):325–331.
[10] Kent BD, Grote L, Bonsignore MR, et al. Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study. Eur Respir J. 2014;44(1):130–139.
[11] Calvin AD, Albuquerque FN, Lopez-Jimenez F, et al. Obstructive sleep apnea, inflammation, and the metabolic syndrome. Metab Syndr Relat Disord. 2009;7(4):271–278.
[12] Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006;61(4):284–289.
[13] Islam EA, Limsuwat C, Nantsupawat T, et al. The association between glucose levels and hospital outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease. Ann Thorac Med. 2015;10(2):94–99.
[14] Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002;106(16):2067–2072.
[15] Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005;115(5):1111–1119.
[16] Wu Y, Wu T, Wu J, et al. Chronic inflammation exacerbates glucose metabolism disorders in C57BL/6J mice fed with high-fat diet. J Endocrinol. 2013;219(3):195–204.
[17] Gyurko R, Siqueira CC, Caldon N, et al. Chronic hyperglycemia predisposes to exaggerated inflammatory response and leukocyte dysfunction in Akita mice. J Immunol. 2006;177(10):7250–7256.
[18] Bhat TA, Panzica L, Kalathil SG, et al. Immune dysfunction in patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2015;12(Suppl 2):S169–75.
[19] Schnohr P, Jensen G, Lange P, et al. The copenhagen city heart study - Østerbroundersøgelsen. Tables with data from the third examination 1991-1994. Eur Heart J. 2001;3(supplH):H1–H83.
[20] Andersen TF, Madsen M, Jorgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999;46(3):263–268.
[21] Lynge E, Sandegaard JL, Rebolj M. The danish national patient register. Scand J Public Health. 2011;39(7 Suppl):30–33.
[22] Lin DY, Wei LJ, Ying Z. Checking the cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80(3):557–572.
[23] R Core Team. R: A language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing. [cited 2020 Apr 27]. Available from: www.R-project.org.
[24] Cizza G, Piaggi P, Lucassen EA, et al. Obstructive sleep apnea is a predictor of abnormal glucose metabolism in chronically sleep deprived obese adults. PLoS One. 2013;8(5):e65400. .

[25] Bakker JP, Weng J, Wang R, et al. Associations between obstructive sleep apnea, sleep duration, and abnormal fasting glucose. The multi-ethnic study of atherosclerosis. Am J Respir Crit Care Med. 2015;192(6):745–753.
[26] Cebron Lipovec N, Beijers RJ, van den Borst B, et al. The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. COPD. 2016;13(3):399–406.
[27] Kupeli E, Ulubay G, Ulasli SS, et al. Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. Endocrine. 2010;38(1):76–82.
[28] Fleming WE, Holty JC, Bogan RK, et al. Use of blood biomarkers to screen for obstructive sleep apnea. Nat Sci Sleep. 2018;10:159–167.
[29] Wei YF, Tsai YH, Wang CC, et al. Impact of overweight and obesity on acute exacerbations of COPD - subgroup analysis of the Taiwan obstructive lung disease cohort. Int J Chron Obstruct Pulmon Dis. 2017;12:2723–2729.
[30] Julius S, Valentini M, Palatini P. Overweight and hypertension: a 2-way street? Hypertension. 2000;35(3):807–813.
[31] McNicholas WT. Diagnosis of obstructive sleep apnea in adults. Proc Am Thorac Soc. 2008;5(2):154–160.
[32] Thomsen RW, Lange P, Hellquist B, et al. Validity and underrecording of diagnosis of COPD in the danish national patient registry. Respir Med. 2011;105(7):1063–1068. .
[33] Yang D, Liu Z, Yang H, et al. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath. 2013;17(1):33–38.
[34] Loachimescu OC, Anthony J Jr., Constantin T, et al. VAMONOS (Veterans affairs' metabolism, obstructed and non-obstructed sleep) study: effects of CPAP therapy on glucose metabolism in patients with obstructive sleep apnea. J Clin Sleep Med. 2017;13(3):455–466.