Nocturnal hypoxemic burden and micro- and macrovascular disease in patients with type 2 diabetes

Sarah Driendl[1*], Stefan Stadler[1], Michael Arzt[1], Florian Zeman[2], Iris M. Heid[3] and Mathias Baumert[4]

Abstract

Background Micro- and macrovascular diseases are common in patients with type 2 diabetes mellitus (T2D) and may be partly caused by nocturnal hypoxemia. The study aimed to characterize the composition of nocturnal hypoxemic burden and to assess its association with micro- and macrovascular disease in patients with T2D.

Methods This cross-sectional analysis includes overnight oximetry from 1247 patients with T2D enrolled in the DIACORE (DIAbetes COhoRtE) study. Night-time spent below a peripheral oxygen saturation of 90% (T90) as well as T90 associated with non-specific drifts in oxygen saturation ($T90_{non-specific}$), T90 associated with acute oxygen desaturation ($T90_{desaturation}$) and desaturation depths were assessed. Binary logistic regression analyses adjusted for known risk factors (age, sex, smoking status, waist-hip ratio, duration of T2D, HbA1c, pulse pressure, low-density lipoprotein, use of statins, and use of renin-angiotensin-aldosterone system inhibitors) were used to assess the associations of such parameters of hypoxemic burden with chronic kidney disease (CKD) as a manifestation of microvascular disease and a composite of cardiovascular diseases (CVD) reflecting macrovascular disease.

Results Patients with long T90 were significantly more often affected by CKD and CVD than patients with a lower hypoxemic burden (CKD 38% vs. 28%, $p < 0.001$; CVD 30% vs. 21%, $p < 0.001$). Continuous $T90_{desaturation}$ and desaturation depth were associated with CKD (adjusted OR 1.01 per unit, 95% CI [1.00; 1.01], $p = 0.008$ and OR 1.30, 95% CI [1.06; 1.61], $p = 0.013$, respectively) independently of other known risk factors for CKD. For CVD there was a thresholdeffect, and only severly and very severly increased $T90_{non-specific}$ was associated with CVD ([Q3;Q4] versus [Q1;Q2], adjusted OR 1.51, 95% CI [1.12; 2.05], $p = 0.008$) independently of other known risk factors for CVD.

Conclusion While hypoxemic burden due to oxygen desaturations and the magnitude of desaturation depth were significantly associated with CKD, only severe hypoxemic burden due to non-specific drifts was associated with CVD. Specific types of hypoxemic burden may be related to micro- and macrovascular disease.

Keywords Hypoxia, Hypoxemic burden, Cardiovascular disease, Chronic kidney disease, Type 2 diabetes

*Correspondence:
Sarah Driendl
sarah-maria.driendl@ukr.de
[1]Department of Internal Medicine II, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
[2]Centre of Clinical Studies, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
[3]Department of Genetic Epidemiology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
[4]Discipline of Biomedical Engineering, School of Electrical and Mechanical Engineering, University of Adelaide, North Terrace, Adelaide, SA 5000, Australia

Driendl *et al. Cardiovascular Diabetology*   (2024) 23:195

Page 2 of 11

Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive apneas and hypopneas during sleep, leading to intermittent hypoxemia and recurrent arousals from sleep. It is common in patients with diabetes mellitus type 2 (T2D), and both diabetes and SDB are associated with micro- and macrovascular damage [1–4]. Indeed, SDB and T2D are each likely to contribute to the development of the other [5], showing high coincidences [5, 6]. Chronic kidney disease (CKD), characterized by reduced glomerular filtration rate (GFR) and elevated urine albumin excretion, is a consequence of microvascular damage. Importantly, the prevalence of CKD and mortality has globally increased by 29% and 42%, respectively, since 1990 [7]. About 50–60% of patients wih CKD also suffer from SDB [8] and have an increased risk of end-stage renal disease [9]. A recent meta-analysis demonstrated that the co-existence between sleep apnea and advanced CKD doubled overall mortality [10].

SDB has been linked to hypertension [11], increased risk for incident stroke [12] and increased incidence of total cardiovascular disease (CVD) [13] in meta-analyses in the general population. CVD affects approximately one-third of all patients with T2D [2], but data on the association between SDB and CVD in these patients is sparse. CVD is the primary cause of mortality in patients with T2D, accounting for up to 52% of deaths [14]. The economic burden of CVD in these patients substantially impacts direct medical costs at both the patient and population levels [15].

The above named pathophysiological mechanisms of SDB are central in CVD processes through activation of various intermediate pathways including sympathetic activation, inflammation, oxidative stress, metabolic dysregulation, and mechanical stress [16–19]. SDB is diagnosed by an elevated apnea-hypopnea index (AHI, number of hypopneas and apneas per hour of sleep). But it encompasses a broad variation in nocturnal hypoxemia [20, 21] that may not be reflected in AHI, as this parameter does not distinguish between brief or sustained changes in peripheral oxygen saturation (SpO_2) or the depth of desaturations or the baseline SpO_2 level from which they occur. These cumulative effects may be clinically important [22] as recent studies suggest that nocturnal hypoxemic burden is an independent predictor of cardiovascular mortality [23] and all-cause mortality in stable chronic heart failure [24] and is more strongly associated with adverse cardiovascular outcomes than the AHI [25]. Also, factors other than SDB may contribute to nocturnal hypoxemic burden, such as COPD or heart failure, and contribute to micro- and macrovascular damage [26].

The present study aimed to characterize the composition of nocturnal hypoxemic burden in patients with T2D and to assess its association with micro- and macrovascular disease. We hypothesized that specific oximetry-derived parameters of nocturnal hypoxemic burden are associated with chronic kidney disease and cardiovascular disease in patients with T2D.

Patients and methods

Study population

We investigated participants of the DIACORE (DIAbetes COhoRtE)-SDB (sleep-disordered breathing) sub-study [27]. DIACORE is a prospective, longitudinal, two-center cohort study of 3000 T2D patients of European descent in the cities and counties of Regensburg and Speyer [28]. DIACORE participants of the Regensburg study center who did not use a positive airway pressure device were invited to participate in the DIACORE-SDB sub-study. Patients with chronic obstructive pulmonary disease (COPD) were not excluded. A total of 1491 patients agreed to participate in the sub-study; the baseline survey was conducted between 2010 and 2014 [27]. The protocol, the data protection strategy, and the study procedures were approved by the Ethics Committees of the participating institutions and were in accordance with the Declaration of Helsinki.

Quantification and characterization of nocturnal hypoxemic burden

Hypoxemic burden was assessed using a validated 2-channel ambulatory monitoring device [29] recording nasal flow and pulse oximetry (ApneaLink®, ResMed) as described previously [27]. Participants were instructed how to use the device by trained personnel in a standardized manner [27]. Oximetry signals were extracted for further processing using a fully automated and custom-made computer algorithm programmed in MATLAB® (MathWorks®, Natick, MA, USA), as described previously [30]. Signal artifacts were automatically detected and excluded based on a set of empirical criteria (e.g. instantaneous changes in $SpO_2 > 5\%$) [30].

Nocturnal hypoxemic burden was defined as analyzed recording time spent at SpO_2 levels below 90% (T90) in minutes. To further characterize the composition of nocturnal hypoxemic burden, we quantified the component of T90 associated with non-specific and non-cyclic drifts in SpO_2 or incomplete resaturation ($T90_{non-specific}$) versus T90 associated with acute oxygen desaturation events accompanied by resaturation ($T90_{desaturation}$) [23, 30]. Acute desaturations were defined as episodic, monotonic drops in oxygen saturation by at least 4% from any prior level that was followed by a resaturation to at least two-thirds of the oxygen saturation level observed before desaturation within 150 s starting from the onset of desaturation [23]. Oxygen desaturation index (ODI) measured the mean number of respiratory events per

hour where blood oxygen level dropped by 4% compared to immediately preceding basal value. We measured the desaturation depth as the average SpO_2 reduction throughout acute events (in %) and obtained the median value across all desaturation events. Apnea-hypopnea index (AHI) was calculated as the mean number of apnea and hypopnea events per hour of recording time.

Assessment of macro—and microvascular disease

The participants completed a standardized online questionnaire and underwent physical examination [28]. Arterial blood pressure was determined via repeated measurement: three measures were performed, and the last two were averaged [28]. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Whole blood samples were drawn after the patients had rested in a seated position for at least 15 min [28]. Estimated GFR was calculated using the CKD-EPI equation from 2009 [28]. Microvascular disease was assessed via serum creatinine, GFR, and urine albumin-creatinine ratio (uACR) as surrogates for renal function. CKD was defined as elevated urine albumin excretion (uACR > 30 mg/g), reduced eGFR (< 60 ml/min per 1.73 m^2), or both, following current KDIGO guidelines [31]. CVD was determined as a composite of peripheral artery disease (PAD), coronary artery disease (CAD), or stroke. PAD and CAD were ascertained by self-reported history of surgical or interventional therapy of PAD or CAD or myocardial infarction and validated from medical records and direct contact with local physicians [32]. Stroke was defined as a self-reported history of at least one ischemic or embolic stroke ascertained by a review of a physician's record, including cerebral imaging. The stroke definition did not include the diagnosis of carotid stenosis, transient ischemic attacks, or intracerebral bleeding [32]. The wording of the questions asked in the questionnaire can be found in the online supplement (S1).

Statistical analysis

Descriptive data are presented as mean (±standard deviation) for normally distributed variables and median [interquartile range] otherwise. Group comparisons of continuous variables were performed by t-test for normally distributed data, Mann-Whitney-U-test for non-normally distributed variables, and Chi-square test for categorical variables. We used logistic regression to analyze the association between hypoxemic burden and CKD and CVD. Known confounders for atherosclerosis and chronic renal disease, such as sex, age, waist-hip ratio (WHR), pulse pressure, duration of T2D, HbA1c, low-density lipoprotein (LDL), smoking status (current or former vs. never smokers), use of statins, and use of renin-angiotensin-aldosterone system inhibitors were included as covariates. Results are presented as odds ratio (OR) estimates with a 95% confidence interval (CI). We performed a Bonferroni correction for two independent tests and a stricter level of significance was considered statistically significant, i.e. P values < 0.05/2 = 0.025. Data were analyzed using the SPSS statistical software package (SPSS 28.0 IBM SPSS Statistics, Armonk, New York, USA).

Results

Patient characteristics

Complete data were available for 1247 patients (83.6%) of the 1491 DIACORE-SDB sub-study participants. 244 (16.4%) patients were excluded from the final analysis due to incomplete polygraphy data, loss to follow-up or withdrawal of consent (Fig. 1). Characteristics of the analyzed cohort are summarized in Table 1. The median T90, $T90_{desaturation}$, and $T90_{non-specific}$ were 16.0 [2.1; 57.4] min,
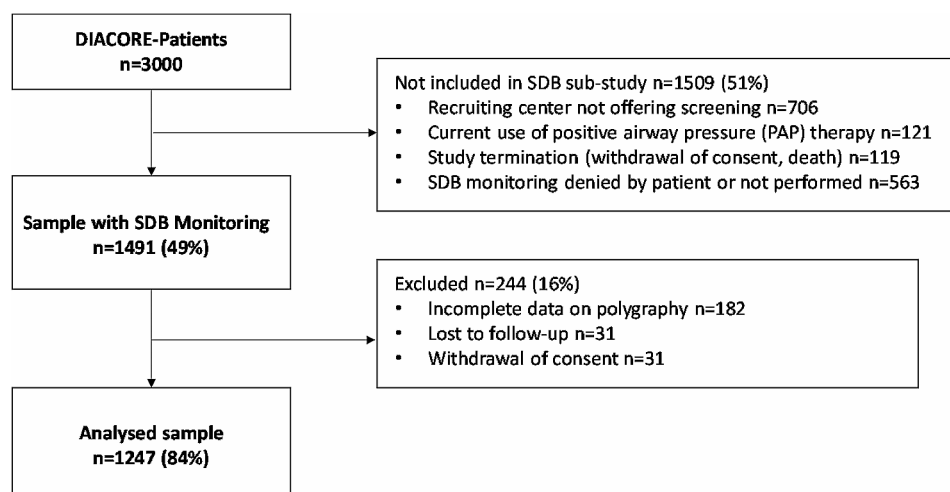

Fig. 1 Study flow chart

Table 1 Baseline characteristics of the 1247 patients, overall and according to the severity of the hypoxemic burden

Variables	Entire cohort	T90 Q1-2 [0–16.0 min]	T90 Q3–4 [> 16.0 min]	*P* value	$T90_{non-specific}$ Q1-2 [0–3.5 min]	$T90_{non-specific}$ Q3-4 [> 3.5 min]	*P* value	$T90_{desaturation}$ Q1-2 [0–6.5 min]	$T90_{desaturation}$ Q3-4 [> 6.5 min]	*P* value
n (%)	1247	623 (50)	624 (50)		622 (50)	625 (50)		622 (50)	625 (50)	
Age [years]	67 ± 9	65 ± 9	68 ± 8	< 0.001	65 ± 9	68 ± 8	< 0.001	65 ± 9	68 ± 8	< 0.001
Sex (female), n (%)	514 (41.2)	288 (46.2)	226 (36.2)	< 0.001	275 (44.2)	239 (38.2)	0.032	284 (45.7)	230 (36.8)	0.001
BMI [kg/m²]	30.9 ± 5.4	29.6 ± 5.1	32.2 ± 5.4	< 0.001	30.0 ± 5.2	31.9 ± 5.4	< 0.001	29.7 ± 5.1	32.2 ± 5.4	< 0.001
Waist-hip ratio	0.95 ± 0.08	0.93 ± 0.08	0.97 ± 0.08	< 0.001	0.94 ± 0.08	0.97 ± 0.08	< 0.001	0.94 ± 0.08	0.97 ± 0.08	< 0.001
Former or current smokers, n (%)	704 (56.5)	323 (51.8)	381 (61.1)	< 0.001	337 (54.2)	367 (58.7)	0.106	319 (51.3)	385 (61.6)	< 0.001
High alcohol intake, n (%)	358 (28.7)	171 (47.8)	187 (52.2)	0.325	164 (26.4)	194 (31.0)	0.068	155 (24.9)	203 (32.5)	0.003
Physical inactivity, n (%)	701 (56.2)	317 (45.2)	384 (54.8)	< 0.001	319 (51.3)	382 (61.1)	< 0.001	321 (51.6)	380 (60.8)	0.001
HbA1c [mmol/mol]	54 ± 16	48 [43; 54]	50 [43; 57]	0.020	48 [43; 54]	49 [43; 56]	0.070	48 [43; 54]	50 [44; 56]	0.010
T2D duration [years]	8.0 [3.9; 14.0]	7.5 [3.4; 13.7]	8.7 [4.3; 14.9]	0.015	7.7 [3.6; 13.8]	8.2 [4.2; 14.7]	0.125	7.3 [3.6; 13.2]	8.9 [4.2; 15.2]	0.003
Systolic BP [mmHg]	138 ± 18	137 ± 18	140 ± 18	0.002	138 ± 18	140 ± 18	0.048	137 ± 17	140 ± 18	0.001
Diastolic BP [mmHg]	75 ± 10	76 ± 10	76 ± 10	0.493	76 ± 10	76 ± 10	0.673	75 ± 10	76 ± 10	0.381
Pulse pressure [mmHg]	63 ± 15	61 ± 15	64 ± 15	0.002	62 ± 16	64 ± 15	0.011	62 ± 15	64 ± 16	0.001
RAAS inhibition use	813 (65.2)	372 (59.7)	441 (70.1)	< 0.001	369 (59.3)	444 (71.0)	< 0.001	379 (60.9)	434 (69.4)	0.002
Hypertension, n (%)	545 (43.7)	250 (40.1)	295 (47.4)	0.009	261 (42.0)	284 (45.6)	0.197	247 (39.8)	298 (47.8)	0.005
Serum creatinine [mg/dl]	0.88 [0.75; 1.05]	0.85 [0.73; 1.02]	0.90 [0.78; 1.08]	< 0.001	0.87 [0.73; 1.02]	0.89 [0.78; 1.07]	0.003	0.86 [0.73; 1.02]	0.90 [0.78; 1.08]	< 0.001
eGFR-CDKepi [ml/min/1,73 m²]	83 [67; 93]	85 [70; 95]	80 [65; 92]	< 0.001	86 [70; 95]	81 [66; 92]	< 0.001	85 [70; 95]	80 [66; 92]	< 0.001
uACR [mg/g]	9.0 [4.5; 26.6]	8.1 [4.2; 20.9]	10.5 [4.8; 36.5]	< 0.001	7.9 [4.0; 19.6]	10.6 [5.0; 35.9]	< 0.001	8.0 [4.2; 19.5]	10.9 [4.8; 35.9]	< 0.001
LDL [mg/dl]	119 ± 37	122 ± 35	116 ± 38	0.005	121 ± 36	116 ± 37	0.004	122 ± 36	117 ± 37	0.023
HDL [mg/dl]	54 ± 16	55 ± 15	52 ± 16	0.003	55 ± 15	53 ± 16	0.046	55 ± 16	53 ± 15	0.075
Statin use, n (%)	560 (44.9)	245 (40.8)	306 (49.0)	0.003	244 (39.2)	316 (50.6)	< 0.001	264 (42.4)	296 (47.4)	0.081
Mean SpO₂ [%]	92.4 ± 2.0	93.6 ± 1.2	91.3 ± 1.6	< 0.001	94 ± 1	91 ± 2	< 0.001	93 ± 1	91 ± 2	< 0.001
Min SpO₂ [%]	81 [78; 83]	82 [81; 86]	80 [76; 82]	< 0.001	82 [80; 85]	80 [76; 82]	< 0.001	82 [81; 86]	79 [76; 82]	< 0.001
Sleep efficiency [%]	0.98 [0.88; 1.00]	0.99 [0.88; 1.00]	0.98 [0.88; 1.00]	0.322	0.98 [0.88; 1.00]	0.98 [0.88; 1.00]	0.066	0.98 [0.88; 1.00]	0.98 [0.88; 1.00]	0.857
T90 [min]	16.0 [2.1; 57.4]	2.1 [0.4; 6.5]	57.3 [28.9; 140.8]	< 0.001	2.1 [0.4; 7.6]	55.7 [25.1; 139.3]	< 0.001	2.1 [0.4; 6.5]	49.5 [21.4; 132.8]	< 0.001
$T90_{non-specific}$ [min]	3.5 [0.2; 34.1]	0.2 [0.0; 1.5]	33.7 [10.0; 98.6]	< 0.001	0.2 [0.0; 0.8]	33.3 [10.9; 98.1]	< 0.001	0.3 [0.0; 3.6]	19.1 [3.5; 84.0]	< 0.001
$T90_{desaturation}$ [min]	6.5 [1.1; 21.1]	1.4 [0.3; 4.3]	21.1 [11.2; 40.8]	< 0.001	1.5 [0.3; 6.5]	16.8 [6.4; 37.7]	< 0.001	1.1 [0.2; 3.1]	21.1 [12.2; 40.7]	< 0.001
Desaturation depth [%]	2.7 [2.5; 3.1]	2.6 [2.4; 2.8]	2.9 [2.6; 3.4]	< 0.001	2.6 [2.4; 2.9]	2.8 [2.5; 3.2]	< 0.001	2.5 [2.3; 2.7]	3.0 [2.7; 3.4]	< 0.001
ODI [events/h]	9 [5; 18]	7 [4; 12]	15 [8; 26]	< 0.001	8 [4; 16]	11 [6; 21]	< 0.001	3 [1; 6]	14 [8; 22]	< 0.001

Table 1 (continued)

Variables	Entire cohort	T90 Q1-2 [0–16.0 min]	T90 Q3–4 [>16.0 min]	P value	T90$_{non-specific}$ Q1-2 [0–3.5 min]	T90$_{non-specific}$ Q3-4 [>3.5 min]	P value	T90$_{desaturation}$ Q1-2 [0–6.5 min]	T90$_{desaturation}$ Q3-4 [>6.5 min]	P value
AHI [events/h]	10 [5; 18]	6 [3; 10]	15 [7; 25]	<0.001	7 [4; 14]	11 [6; 21]	<0.001	5 [3; 9]	16 [10; 26]	<0.001
Excessive daytime sleepiness, n (%)	89 (7.1)	40 (8.0)	49 (7.9)	0.334	44 (6.2)	45 (8.4)	0.334	40 (6.4)	49 (7.9)	0.326

Results are provided as mean±standard deviation for normally distributed and as median [interquartile range] for non-normally distributed variables. High alcohol intake defined as ≥3/drinks per week; excessive daytime sleepiness defined as Epworth Sleepiness Scale≥11; physical inactivity defined as light activity≤2 times/week; hypertension defined as blood pressure≥140/90 mmHg; sleep efficiency: sleeping time per time in bed

RAAS Renin-angiotensin-aldosterone system, *AHI* apnoea-hypopnoea index, *BMI* body-mass index, *BP* blood pressure, *eGFR-CDKepi* estimated glomerular filtration rate calculated using the CKD-EPI equation, *HbA1c* hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *ODI* oxygen-desaturation index, *SpO$_2$* arterial oxygen saturation, *T90* night-time spent with oxygen saturation<90%, *T90$_{desaturation}$* T90 associated with acute oxygen desaturation events accompanied by resaturation, *T90$_{non-specific}$* T90 associated with non-specific and non-cyclic drifts in SpO$_2$ or incomplete resaturation, *uACR:* urine albumin-creatinine ratio, *Q* quartile

3.5 [0.2; 34.1] min and 6.5 [1.1; 21.1] min, respectively. The median ODI was 6.6/h [2.7; 14.9] and the median desaturation depth was 2.7% [2.5; 3.1].

Patients with T90 above the median were predominantly male, older, and more often obese than patients with T90 below the median. They were also more often current or former smokers and more often physically inactive. Diabetes duration, HbA1c, and systolic blood pressure were significantly higher in these patients. LDL, however, was significantly lower. When we analyzed patient characteristics separately for hypoxemic burden due to acute oxygen desaturation events accompanied by resaturation (T90$_{desaturation}$), we observed results similar to T90 (Table 1). For hypoxemic burden due to non-specific drifts (T90$_{non-specific}$), there was no difference in diabetes duration, HbA1c, hypertension, and smoking status between groups (Table 1).

As expected, patients with T90 above the median exhibited significantly higher AHI and ODI values. When analyzing these parameters separately for T90$_{non-specific}$ and T90$_{desaturation}$, results were similar (Table 1). For all hypoxemic burden parameters, patients above the median exhibited significantly higher desaturation depth values than patients in the lowest two quartiles. Patients with ODI≥15/h had similar characteristics to the patients with T90 above the median, but there was no difference between LDL, HbA1c, and uACR for patients with ODI </≥ 15/h (Table S2). For patients with desaturation depth above the median there was no difference with regards to age, smoking status, and physical activity compared to desaturation depth below the median (Table S2).

Association of hypoxemic burden and chronic kidney disease
Patients with T90 above the median had significantly higher serum creatinine levels, lower GFR, and higher uACR (Table 1). In total, 409 (32.8%) patients had CKD; the prevalence was higher in patients with T90 above versus below the median (234 (37.5%) vs. 175 (28.1%), *p*<0.001). Similar results were obtained when

decomposing T90 into T90$_{non-specific}$ and T90$_{desaturation}$. CKD prevalence, serum creatinine levels and uACR were higher and GFR lower in patients above the median for T90$_{non-specific}$ and T90$_{desaturation}$ (Table 1; Fig. 2). The prevalence of CKD also was significantly higher in patients with ODI≥15/h than in patients with ODI<15/h (40.6% vs. 30.2%, *p*<0.001) and in patients with desaturation depth above the median versus below the median (35.8% vs. 29.5%, *p*=0.021).

In univariable logistic regression models, high hypoxemic burden was consistently associated with CKD, considering continuous and dichotomized T90 variables as well as ODI and desaturation depth. To further analyze the elevated odds, we assessed the association between hypoxemic burden and CKD by adjusting the regression models for known risk factors for CKD: age, sex, WHR, smoking status, pulse pressure, duration of T2D, Hb1Ac, use of statins, and use of renin-angiotensin-aldosterone system inhibitors. In the adjusted model, continuous T90$_{desaturation}$ remained significantly associated with CKD but not T90 or T90$_{non-specific}$ (Table 2). We also observed significant associations between hypoxemic burden variables and serum creatinine, GFR, and uACR separately with linear regression models (Table S3). Continuous ODI was associated with CKD in univariable logistic regression, but not in the multivariable model (Table 2). Desaturation depth was significantly associated with CKD independently of the above-named risk factors (Table 2). We adjusted for WHR in the multivariable analyses because it is a better measure of abdominal adiposity. However, when adjusting for body-mass index instead of WHR results were similar (data not shown).

Association of hypoxemic burden and cardiovascular disease
A total of 318 (25.5%) patients reported a history of CVD, including 244 (19.6%) cases of CAD, 45 (3.6%) cases of PAD, and 77 (6.2%) cases of stroke. CVD was more frequent in patients with T90 above the median (190 (30.4%) vs. 128 (20.5%) patients, *p*<0.001). Similarly,
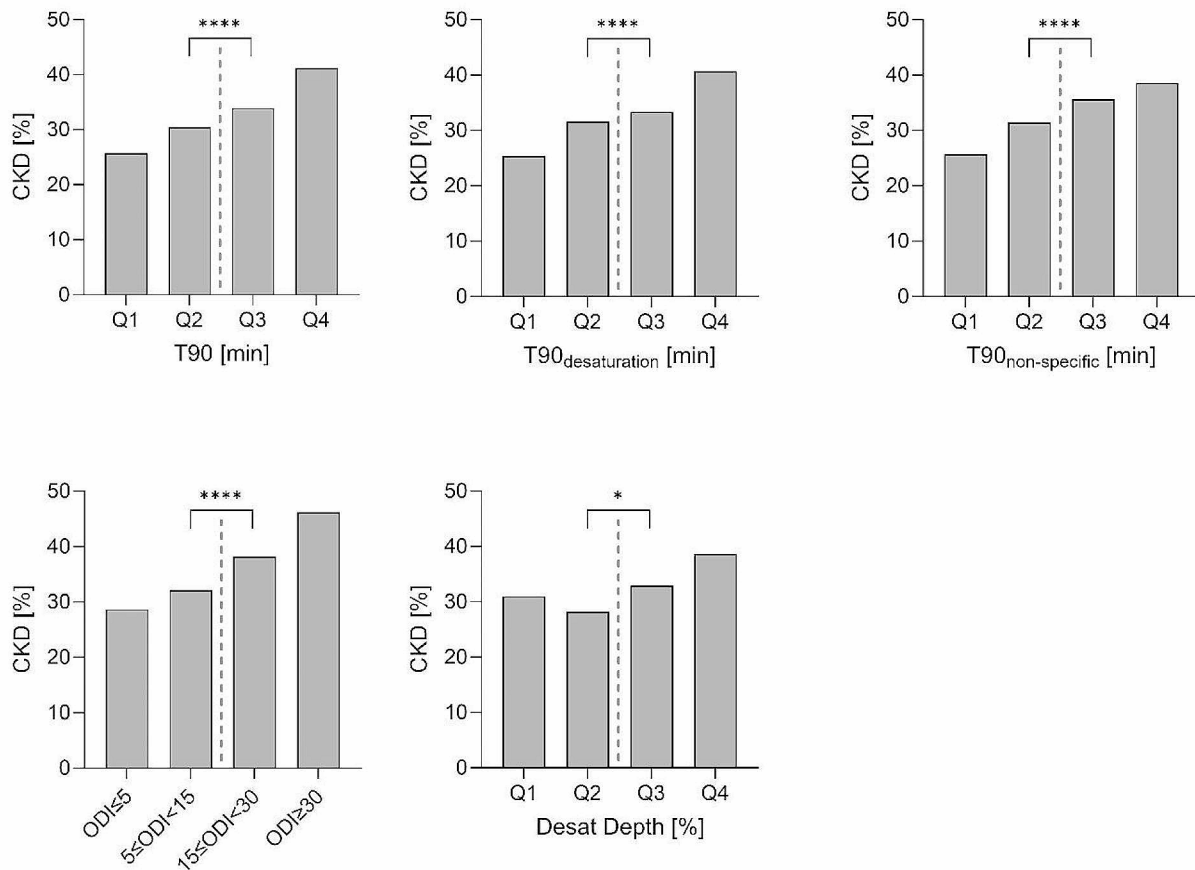
Fig. 2 Prevalence of chronic kidney disease according to the presence of hypoxemic burden for T90, T90$_{non-specific}$ and T90$_{desaturation}$, ODI, and desaturation depth. *CKD* chronic kidney disease, *Desat Depth* Desaturation depth, *ODI* oxygen desaturation index, *T90* night-time spent with oxygen saturation < 90%, *T90 desaturation* T90 associated with acute oxygen desaturation events accompanied by resaturation, *T90 non-specific* T90 associated with non-specific and non-cyclic drifts in SpO2 or incomplete resaturation, *Q* quartile. * $p < 0.05$, **** $p < 0.0001$

CVD was more common in patients with T90$_{non-specific}$ above the median (178 (33.1%) vs. 140 (19.7%) patients, $p < 0.001$) and with T90$_{desaturation}$ above the median (211 (28.1%) vs. 107 (21.6%) patients, $p = 0.011$, Fig. 3). There was no significant difference in CVD prevalence between patients with ODI ≥ vs. < 15/h (91 (29.4%) vs. 227 (24.2%), $p = 0.073$) and between patients with desaturation depth above vs. below the median (158 (26.3%) vs. 149 (24.2%), $p = 0.399$).

Univariable logistic regression analysis showed an association between all hypoxemic burden variables and CVD. After adjusting the models for known risk factors for CVD, namely age, sex, WHR, smoking status, duration of T2D, HbA1c, pulse pressure, LDL, use of statins, and use of renin-angiotensin-aldosterone system inhibitors, there was an independent association between dichotomized T90$_{non-specific}$ and CVD.

Discussion

This cross-sectional analysis of a large cohort of T2D patients showed an association between nocturnal hypoxemic burden and micro- and macrovascular diseases. The prevalence of CKD and CVD was significantly higher in patients with a high nocturnal hypoxemic burden than in those with a lower hypoxemic burden. T90$_{desaturation}$ and desaturation depth were associated with CKD, T90$_{non-specific}$ was associated with CVD. The characteristics of hypoxemic burden may differ between CKD and CVD.

Association of hypoxemic burden and chronic kidney disease

In our study cohort, nocturnal SpO2 dropped under 90% in 1014 patients (81%) and 310 of the patients had an ODI ≥ 15/h, showing that nocturnal hypoxemic burden is highly prevalent in T2D. The prevalence of CKD in

Driendl *et al. Cardiovascular Diabetology* (2024) 23:195

Page 7 of 11

Table 2 Multivariate logistic regression models for the association between hypoxemic burden parameters and chronic kidney disease

Variable	Odds ratio (95% CI), multivariate	P value
T90 cont.	1.00 (1.00; 1.00)	0.246
T90 Q12 vs. Q34	1.15 (0.89; 1.50)	0.284
$T90_{non-specific}$ cont.	1.00 (1.00; 1.00)	0.688
$T90_{non-specific}$ Q12 vs. Q34	1.15 (0.89; 1.49)	0.295
$T90_{desaturation}$ cont.	1.01 (1.00; 1.01)	**0.008**
$T90_{desaturation}$ Q12 vs. Q34	1.10 (0.85; 1.43)	0.472
Desaturation depth cont.	1.30 (1.06; 1.61)	**0.013**
Desaturation depth Q12 vs. 34	1.18 (0.91; 1.53)	0.202
ODI cont.	1.01 (1.00; 1.02)	0.044
ODI < vs. ≥ 15/h	1.29 (0.97; 1.71)	0.085
ODI < vs. ≥ 30/h	1.40 (0.89; 2.21)	0.144

ODI oxygen-desaturation index, *T90* night-time spent with oxygen saturation < 90%, $T90_{desaturation}$ T90 associated with acute oxygen desaturation events accompanied by resaturation, $T90_{non-specific}$ T90 associated with non-specific and non-cyclic drifts in SpO_2 or incomplete resaturation, *Q* quartile

[a]Multivariate analyses adjusted for age, sex, waist-hip ratio, smoking status, HbA1c, diabetes duration, pulse pressure, statin use, and renin-angiotensin-aldosterone system inhibitor use

Bold values statistically significant

Table 3 Multivariate logistic regression models for the association between hypoxemic burden parameters and cardiovascular disease

Variable	Odds ratio (95% CI), multivariate[a]	P value
T90 cont.	1.00 (1.00; 1.00)	0.439
T90 Q12 vs. Q34	1.20 (0.89; 1.63)	0.238
$T90_{non-specific}$ cont.	1.00 (1.00; 1.00)	0.683
$T90_{non-specific}$ Q12 vs. Q34	1.51 (1.12; 2.05)	**0.008**
$T90_{desaturation}$ cont.	1.00 (1.00; 1.01)	0.356
$T90_{desaturation}$ Q12 vs. Q34	0.86 (0.63; 1.16)	0.315
Desaturation depth cont.	0.91 (0.70; 1.16)	0.438
Desaturation depth Q12 vs. 34	0.90 (0.68; 1.20)	0.479
ODI cont.	1.00 (0.99; 1.01)	0.947
ODI < vs. ≥ 15/h	0.96 (0.68; 1.34)	0.795
ODI < vs. ≥ 30/h	1.20 (0.72; 2.02)	0.480

HbA1c hemoglobin A1c, *LDL* low density lipoprotein, T90: night-time spent with oxygen saturation < 90%, $T90_{desaturation}$ T90 associated with acute oxygen desaturation events accompanied by resaturation, $T90_{non-specific}$ T90 associated with non-specific and non-cyclic drifts in SpO_2 or incomplete resaturation, Q quartile

[a]Multivariate analyses adjusted for age, sex, smoking status, waist-hip ratio, HbA1c, diabetes duration, pulse pressure, LDL, statin use, and renin-angiotensin-aldosterone system inhibitor use

Bold values statistically significant

the present study (32.8%) is comparable to other studies including T2D patients of similar age [33, 34].

Different pathophysiological mechanisms by which hypoxemia could exacerbate the risk of developing and worsening CKD have been proposed. Decreased partial oxygen pressure in renal tissue drives renal inflammation, oxidative stress, fibrosis, and subsequent declines in kidney function [35]. Nocturnal hypoxemia contributes to the development of CKD by hypoxia itself and glomerular hypertension/hyperfiltration, increased activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [36, 37]. In a mouse model, chronic intermittent hypoxia contributed to renal damage and dysfunction by promoting persistent renal hypoperfusion and tissue hypoxia during wakefulness and sleep [38]. GFR was decreased in a study of rats exposed to long-term chronic intermittent hypoxia [39].

In the present study, the hypoxemic burden due to acute, sleep apnea related desaturations expressed by $T90_{desaturation}$ and desaturation depth were associated with CKD independently of known risk factors for CKD. Previous studies observed an association between SDB and CKD. A meta-analysis of seven studies of patients with T2D demonstrated an association between obstructive sleep apnea (OSA), assessed using either AHI or ODI and diabetic kidney disease (pooled OR 1.59, 95% CI [1.16; 2.18]) [40]. Another meta-analysis of six clinical trials and observational studies comprising 29% T2D patients also found an association between sleep apnea and CKD (pooled adjusted OR 2.088 [1.78–2.45] [41].

Considering T90, Marrone et al. found that GFR ≥ 60 ml/min was less prevalent in patients with high hypoxemic burden (T90 > 12%) than in patients with GFR < 60 ml/min [42]. A recent study of 1,295 adults with suspected SDB (comprising 18.5% of patients with T2D) observed an increased risk of CKD progression in patients with severe OSA compared to those with no or mild OSA (OR 2.96 [2.04; 4.30]) [43]. Neither eGFR nor uACR was significantly associated with T90.

In a study by Sakaguchi et al., T90 was an independent predictor of a rapid decline in kidney function in 120 patients [44]. Both severe and moderate hypoxemia were associated with greater glomerular pressure, a sign of increased renal risk [36] and severe hypoxemia was associated with greater renal renin-angiotensin-aldosterone system activity [37]. The question arises as to why, in the present study, only $T90_{desaturation}$ and not T90 was associated with CKD. Studies suggest that as a response to continuous hypoxia, coordinated upregulation of HIF-1 and HIF-2 mediates adaptive responses in the systemic circulation, whereas chronic intermittent hypoxia triggers an imbalance between HIF-1 and HIF-2 activity that leads to oxidative stress, resulting in maladaptive responses [45]. Furthermore, hypertension is one of the main reasons for CKD [31], and SDB can cause hypertension [11]. While the overall T90 was not independently associated with CKD in our study, the component related to acute desaturation events was, suggesting that SDB is the primary driver affecting kidney function rather than other causes of hypoxemic burden, such as obesity and COPD. Supporting this view, the desaturation depth was independently associated with CKD.
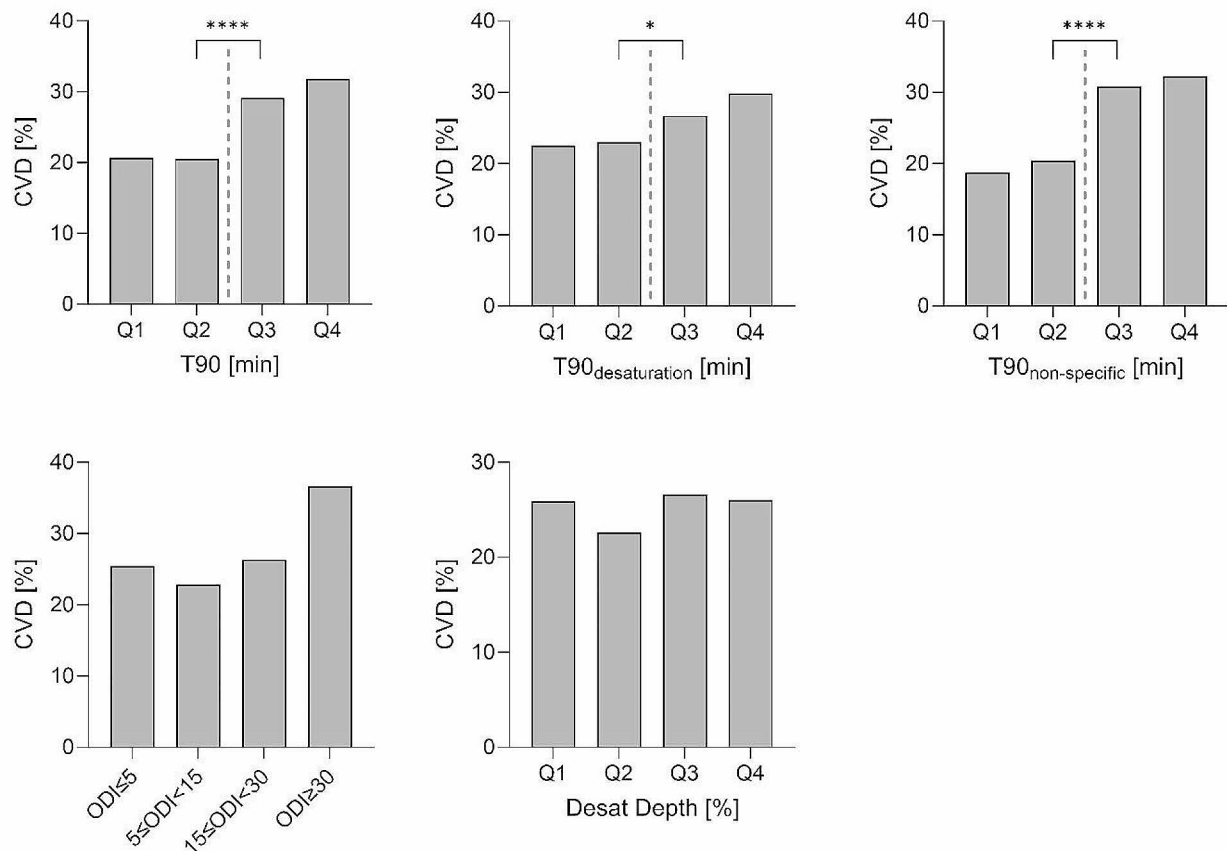
Fig. 3 Prevalence of cardiovascular disease according to the presence of hypoxemic burden for T90, $T90_{non-specific}$ and $T90_{desaturation}$, ODI, and desaturation depth. *CVD* cardiovascular disease, *Desat Depth* Desaturation depth, *ODI* oxygen desaturation index, *T90* night-time spent with oxygen saturation <90%, *T90 desaturation* T90 associated with acute oxygen desaturation events accompanied by resaturation, *T90 non-specific* T90 associated with non-specific and non-cyclic drifts in SpO_2 or incomplete resaturation, *Q* quartile. * $p<0.05$, **** $p<0.0001$

As SBD likely contributes to CKD, continuous positive airway pressure (CPAP) therapy may reduce its impact. In a non-randomized study, CPAP treatment significantly reduced the rate of eGFR decline after 12 months, especially in patients with moderate and severe OSA [46]. However, in another randomized controlled trial involving 57 patients, CPAP therapy did not significantly slow the decline in eGFR or reduce albuminuria over 12 months [47]. Yet some improvement in eGFR occurred with CPAP therapy in patients with a lower risk of CKD progression, but this did not reach statistical significance [47]. Larger longitudinal trials investigating the effect of CPAP on CKD are warranted.

Association of hypoxemic burden and cardiovascular disease

In the present study, 25.5% of the patients reported a history of CVD comparable to other studies on patients with T2D [1, 2]. In the present study, T90 due to non-specific drifts was significantly and independently associated with

prevalent CVD. Contrary to CKD, where we observed a dose-response relationship (Fig. 2), for CVD there was a thresholdeffect and only severly and very severly increased hypoxemic burden due to non-specific drifts was associated with CVD (Fig. 3). While the association between the different compositions of hypoxemic burden and the prevalence of cardiovascular disease has not been investigated previously, recent studies have shown that T90 was an independent predictor of all-cause death in patients with stable chronic heart failure [24] and was associated with an increased incidence of cardiovascular death and fatal stroke [23, 48].

On the contrary, Adderley et al. have shown that in a study with 14,117 patients with T2D, those patients who develop OSA (diagnosed by relevant diagnostic clinical code) were at increased risk of cardiovascular disease (adjusted hazard ratio 1.54, 95% CI [1.32, 1.79]) [49]. Also, Strausz et al. observed in a longitudinal population-based study of three cohorts with a cumulative 36,963 individuals that OSA (diagnosed by ICD codes) increased

the risk for coronary heart disease independently of other risk factors in patients with T2D (hazard ratio 1.36, 95% CI [1.05 to 1.76]) [50]. In the present cross-sectional study, for T90 due to acute oxygen desaturation events there was no association with CVD. ODI and desaturation depth were also not associated with CVD in the adjusted models.

Our findings did not verify a previous analysis of a smaller DIACORE-SDB sub-study set, including 679 patients, where AHI was associated with CVD independently of other known risk factors [32]. The smaller cohort size may have suffered from sample bias. Also, in contrast to CKD, in the present analysis, the prevalence of CVD did not show a linear dose-response relationship. As the DIACORE patients exhibit many comorbidities that contribute to hypoxemia beyond SDB such as COPD and obesity [26], in the present, larger cohort other comorbidities and cardiovascular risk factors like age, obesity, high LDL levels, and smoking history predominate. In the present study, we have observed elevated odds for $T90_{desaturation}$ in the univariable but not in the adjusted analyses.

Strengths and limitations

Strengths of our study include the large sample size and the detailed phenotyping, providing comprehensive information about the participants' lifestyle factors, and enabling adjustment for the main known risk factors for chronic kidney and cardiovascular disease.

The present study is subject to some limitations. First, our cross-sectional analysis cannot establish causal relationships between hypoxemic burden and CKD or CVD. Longitudinal data are required to establish causality and the potential predictive value of hypoxemic burden. Second, while we adjusted for many potential confounders, we cannot exclude the possibility of unmeasured confounders. Third, the study relied on physician-validated self-reported CVD diagnosis; thus, some cases of CVD may have been missed, and the potential association between nocturnal hypoxemic burden and CVD may have been underestimated. Fourth, the DIACORE study did not collect information about lung disease or chest X-rays; the non-specific hypoxemic burden observed in our study may partly reflect lung disease, pulmonary congestion, or ventilation-perfusion mismatches [26]. Lastly, our study was only conducted on patients with Caucasian ethnicity. Therefore, generalizability and extrapolation to other populations with T2D is limited.

Conclusion

In summary, while hypoxemic burden due to oxygen desaturations and the magnitude of desaturation depth was significantly associated with CKD in a dose-response relationship, for CVD we observed a thresholdeffect and

only severely and very severely increased hypoxemic burden due to non-specific drifts was associated with CVD. Thus, specific types of hypoxemic burden may differently be related to micro- and macrovascular disease. For CVD, concomitant risk factors and comorbidities, highly prevalent in patients with T2D and with SDB, seem to remain the predominant determinants for cardiovascular events and thus deserve intensive management. Yet, these findings emphasize the necessity to investigate whether there are causal mechanisms underlying the association between hypoxemic burden and CKD/CVD and how T2D influences this association. Further studies on the effect of CPAP therapy on microvascular disease are warranted. If longitudinal studies demonstrate causal relationships, the different compositions of nocturnal hypoxemic burden derived from overnight oximetry and quantified using a fully automated computer algorithm could be used as a simplified diagnostic and/or prognostic tool in patients with T2D for micro- and macrovascular diseases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02289-w.

> Supplementary material 1. Table S1. Excerpt of the online questionnaire asked at the baseline visit and translated into English. Table S2: Baseline characteristics of the 1247 patients according to the severity of oxygen desaturation index and desaturation depth. Table S3. Univariate linear regression models for the association between hypoxemic burden parameters and serum creatinine, urine albumin-creatinine ratio and eGFR.

Author contributions

S.D., M.B., M.A., and S.S. were involved in the conception, hypotheses delineation, and design of the study, the analysis and interpretation of such information, the writing of the article, and its revision prior to submission. I.M.H. was involved in the design of this sub-study, the acquisition and interpretation of the data, and the critical revision of the article prior to submission. F.Z. was involved in statistical data analysis. S.D. is the guarantor of this work and, as such, had full access to all data of the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The protocol, the data protection strategy, and the study procedures were approved by the Ethics Committees of the participating institutions and were in accordance with the Declaration of Helsinki. The study is registered at the German Clinical Trials Register (https://drks.de/; identifier number DRKS00010498) and at the International Clinical Trials Registry Platform of the World Health Organization.

Consent for publication
Not applicable.

Competing interests
M.A. reports grants from the Else-Kröner Fresenius Foundation, the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) the German Academic Exchange Service (Deutscher Akademischer Austauschdienst, DAAD) and the Resmed Foundation, grants and personal fees from Philips Respironics and ResMed, and personal fees from Inspire, outside the submitted work. S.D., S.S., F.Z., I.M.H. and M.B. have nothing to disclose.

References

1. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72. https://doi.org/10.1056/NEJMoa0802987.
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17:83. https://doi.org/10.1186/s12933-018-0728-6.
3. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010;182:269–77. https://doi.org/10.1164/rccm.200911-1746OC.
4. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122:352–60. https://doi.org/10.1161/CIRCULATIONAHA.109.901801.
5. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. Lancet Respiratory Med. 2013;1:329–38. https://doi.org/10.1016/S2213-2600(13)70039-0.
6. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, et al. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care. 2003;26:702–9. https://doi.org/10.2337/diacare.26.3.702.
7. Global regional, national burden of chronic kidney disease. 1990–2017: a systematic analysis for the global burden of Disease Study 2017. Lancet. 2020;395:709–33. https://doi.org/10.1016/S0140-6736(20)30045-3.
8. Huang H-C, Walters G, Talaulikar G, Figurski D, Carroll A, Hurwitz M, et al. Sleep apnea prevalence in chronic kidney disease - association with total body water and symptoms. BMC Nephrol. 2017;18:125. https://doi.org/10.1186/s12882-017-0544-3.
9. Lee Y-C, Hung S-Y, Wang H-K, Lin C-W, Wang H-H, Chen S-W, et al. Sleep apnea and the risk of chronic kidney disease: a nationwide population-based cohort study. Sleep. 2015;38:213–21. https://doi.org/10.5665/sleep.4400.
10. Puthenpura MM, Hansrivijit P, Ghahramani N, Thongprayoon C, Cheung-pasitporn W. Chronic kidney disease and concomitant sleep apnea are associated with increased overall mortality: a meta-analysis. Int Urol Nephrol. 2020;52:2337–43. https://doi.org/10.1007/s11255-020-02583-y.
11. Xia W, Huang Y, Peng B, Zhang X, Wu Q, Sang Y, et al. Relationship between obstructive sleep apnoea syndrome and essential hypertension: a dose-response meta-analysis. Sleep Med. 2018;47:11–8. https://doi.org/10.1016/j.sleep.2018.03.016.
12. Li M, Hou W-S, Zhang X-W, Tang Z-Y. Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. Int J Cardiol. 2014;172:466–9. https://doi.org/10.1016/j.ijcard.2013.12.230.
13. Dong J-Y, Zhang Y-H, Qin L-Q. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. Atherosclerosis. 2013;229:489–95. https://doi.org/10.1016/j.atherosclerosis.2013.04.026.
14. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of Vascular Disease in Diabetes. Diabetologia. 2001;44(Suppl 2):S14-21. https://doi.org/10.1007/pl00002934.
15. Einarson TR, Acs A, Ludwig C, Panton UH. Economic Burden of Cardiovascular Disease in Type 2 diabetes: a systematic review. Value Health. 2018;21:881–90. https://doi.org/10.1016/j.jval.2017.12.019.
16. McNicholas WT. Obstructive sleep apnea and inflammation. Prog Cardiovasc Dis. 2009;51:392–9. https://doi.org/10.1016/j.pcad.2008.10.005.
17. Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T, Kimura H. Oxidative stress in obstructive sleep apnea. Chest. 2005;127:1674–9. https://doi.org/10.1378/chest.127.5.1674.
18. Malhotra A, White DP. Obstructive sleep apnoea. Lancet. 2002;360:237–45. https://doi.org/10.1016/S0140-6736(02)09464-3.
19. Ryan S. Mechanisms of cardiovascular disease in obstructive sleep apnoea. J Thorac Dis. 2018;10:S4201–11. https://doi.org/10.21037/jtd.2018.08.56.
20. Linz D, Baumert M, Catcheside P, Floras J, Sanders P, Lévy P, et al. Assessment and interpretation of sleep disordered breathing severity in cardiology: clinical implications and perspectives. Int J Cardiol. 2018;271:281–8. https://doi.org/10.1016/j.ijcard.2018.04.076.
21. Linz D, Colling S, Nußstein W, Debl K, Hohl M, Fellner C, et al. Nocturnal hypoxemic burden is associated with epicardial fat volume in patients with acute myocardial infarction. Sleep Breath. 2018;22:703–11. https://doi.org/10.1007/s11325-017-1616-0.
22. Linz D, Loffler KA, Sanders P, Catcheside P, Anderson CS, Zheng D, et al. Low prognostic value of Novel Nocturnal Metrics in patients with OSA and High Cardiovascular Event Risk: Post Hoc analyses of the SAVE Study. Chest. 2020;158:2621–31. https://doi.org/10.1016/j.chest.2020.06.072.
23. Baumert M, Immanuel SA, Stone KL, Litwack Harrison S, Redline S, Mariani S, et al. Composition of nocturnal hypoxaemic burden and its prognostic value for cardiovascular mortality in older community-dwelling men. Eur Heart J. 2020;41:533–41. https://doi.org/10.1093/eurheartj/ehy838.
24. Oldenburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J. 2016;37:1695–703. https://doi.org/10.1093/eurheartj/ehv624.
25. Azarbarzin A, Sands SA, Taranto-Montemurro L, Vena D, Sofer T, Kim S-W, et al. The Sleep Apnea-Specific Hypoxic Burden Predicts Incident Heart failure. Chest. 2020;158:739–50. https://doi.org/10.1016/j.chest.2020.03.053.
26. Tafelmeier M, Blagoeva V-G, Trum M, Hegner P, Floerchinger B, Camboni D, et al. Predictors of Nocturnal Hypoxemic Burden in patients undergoing elective coronary artery bypass grafting surgery. Biomedicines. 2023;11:2665. https://doi.org/10.3390/biomedicines11102665.
27. Stadler S, Zimmermann T, Franke F, Rheinberger M, Heid IM, Böger CA, Arzt M. Association of sleep-disordered breathing with diabetes-associated kidney disease. Ann Med. 2017;49:487–95. https://doi.org/10.1080/07853890.2017.1306100.
28. Dörhöfer L, Lammert A, Krane V, Gorski M, Banas B, Wanner C, et al. Study design of DIACORE (DIAbetes COhoRtE) - a cohort study of patients with diabetes mellitus type 2. BMC Med Genet. 2013;14:25. https://doi.org/10.1186/1471-2350-14-25.
29. Erman MK, Stewart D, Einhorn D, Gordon N, Casal E. Validation of the ApneaLink™ for the screening of Sleep Apnea: a novel and simple single-Channel Recording device. J Clin Sleep Med. 2007;3:387–92.
30. Linz D, Malfertheiner MV, Werner N, Lerzer C, Gfüllner F, Linz B, et al. Nocturnal hypoxemic burden during positive airway pressure treatment across different central sleep apnea etiologies. Sleep Med. 2021;79:62–70. https://doi.org/10.1016/j.sleep.2021.01.007.

31. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102:S1–127. https://doi.org/10.1016/j.kint.2022.06.008.

32. Stadler S, Jalili S, Schreib A, Jung B, Zeman F, Böger CA, et al. Association of sleep-disordered breathing with severe chronic vascular disease in patients with type 2 diabetes. Sleep Med. 2018;48:53–60. https://doi.org/10.1016/j.sleep.2018.05.001.

33. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf Q-A, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. Diabetes Care. 2013;36:3718–25. https://doi.org/10.2337/dc13-0450.

34. Xue P, Covassin N, Ran X, Zhou J, Zhang X, Yan D, et al. Association of parameters of nocturnal hypoxemia with diabetic microvascular complications: a cross-sectional study. Diabetes Res Clin Pract. 2020;170:108484. https://doi.org/10.1016/j.diabres.2020.108484.

35. Wang B, Li Z-L, Zhang Y-L, Wen Y, Gao Y-M, Liu B-C. Hypoxia and chronic kidney disease. EBioMedicine. 2022;77:103942. https://doi.org/10.1016/j.ebiom.2022.103942.

36. Lin C-H, Lurie RC, Lyons OD. Sleep apnea and chronic kidney disease: a state-of-the-art review. Chest. 2020;157:673–85. https://doi.org/10.1016/j.chest.2019.09.004.

37. Zalucky AA, Nicholl DDM, Hanly PJ, Poulin MJ, Turin TC, Walji S, et al. Nocturnal hypoxemia severity and renin-angiotensin system activity in obstructive sleep apnea. Am J Respir Crit Care Med. 2015;192:873–80. https://doi.org/10.1164/rccm.201502-0383OC.

38. Kious KW, Savage KA, Twohey SCE, Highum AF, Philipose A, Díaz HS, et al. Chronic intermittent hypoxia promotes glomerular hyperfiltration and potentiates hypoxia-evoked decreases in renal perfusion and PO2. Front Physiol. 2023;14:1235289. https://doi.org/10.3389/fphys.2023.1235289.

39. O'Neill J, Jasionek G, Drummond SE, Brett O, Lucking EF, Abdulla MA, O'Halloran KD. Renal cortical oxygen tension is decreased following exposure to long-term but not short-term intermittent hypoxia in the rat. Am J Physiol Ren Physiol. 2019;316:F635–45. https://doi.org/10.1152/ajprenal.00254.2018.

40. Leong WB, Jadhakhan F, Taheri S, Thomas GN, Adab P. The Association between Obstructive Sleep Apnea on Diabetic kidney disease: a systematic review and Meta-analysis. Sleep. 2016;39:301–8. https://doi.org/10.5665/sleep.5432.

41. Hansrivijit P, Puthenpura MM, Ghahramani N, Thongprayoon C, Cheungpasitporn W. Bidirectional association between chronic kidney disease and sleep apnea: a systematic review and meta-analysis. Int Urol Nephrol. 2021;53:1209–22. https://doi.org/10.1007/s11255-020-02699-1.

42. Marrone O, Battaglia S, Steiropoulos P, Basoglu OK, Kvamme JA, Ryan S, et al. Chronic kidney disease in European patients with obstructive sleep apnea: the ESADA cohort study. J Sleep Res. 2016;25:739–45. https://doi.org/10.1111/jsr.12426.

43. Beaudin AE, Raneri JK, Ahmed SB, Hirsch Allen AJM, Nocon A, Gomes T, et al. Risk of chronic kidney disease in patients with obstructive sleep apnea. Sleep. 2022. https://doi.org/10.1093/sleep/zsab267.

44. Sakaguchi Y, Hatta T, Hayashi T, Shoji T, Suzuki A, Tomida K, et al. Association of nocturnal hypoxemia with progression of CKD. Clin J Am Soc Nephrol. 2013;8:1502–7. https://doi.org/10.2215/CJN.11931112.

45. Prabhakar NR, Semenza GL. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by Hypoxia-Inducible factors 1 and 2. Physiol Rev. 2012;92:967–1003. https://doi.org/10.1152/physrev.00030.2011.

46. Li X, Liu C, Zhang H, Zhang J, Zhao M, Sun D, et al. Effect of 12-month nasal continuous positive airway pressure therapy for obstructive sleep apnea on progression of chronic kidney disease. Med (Baltim). 2019;98:e14545. https://doi.org/10.1097/MD.0000000000014545.

47. Rimke AN, Ahmed SB, Turin TC, Pendharkar SR, Raneri JK, Lynch EJ, Hanly PJ. Effect of CPAP therapy on kidney function in patients with chronic kidney disease: a pilot randomized controlled trial. Chest. 2021;159:2008–19. https://doi.org/10.1016/j.chest.2020.11.052.

48. Stone KL, Blackwell TL, Ancoli-Israel S, Barrett-Connor E, Bauer DC, Cauley JA, et al. Sleep disordered breathing and risk of stroke in Older Community-Dwelling men. Sleep. 2016;39:531–40. https://doi.org/10.5665/sleep.5520.

49. Adderley NJ, Subramanian A, Toulis K, Gokhale K, Taverner T, Hanif W, et al. Obstructive sleep apnea, a risk factor for Cardiovascular and Microvascular Disease in patients with type 2 diabetes: findings from a Population-based Cohort Study. Diabetes Care. 2020;43:1868–77. https://doi.org/10.2337/dc19-2116.

50. Strausz S, Havulinna AS, Tuomi T, Bachour A, Groop L, Mäkitie A, et al. Obstructive sleep apnoea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland. BMJ Open. 2018;8:e022752. https://doi.org/10.1136/bmjopen-2018-022752.

Publisher's Note