



# Sleep apnoea and incident malignancy in type 2 diabetes

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## ABSTRACT

**Background:** Sleep apnoea and type 2 diabetes (T2D) have been linked to malignancy. The aim of the present study was to evaluate the association between sleep apnoea and incidence of malignancy in patients with T2D.

**Methods:** The DIACORE (DIAbetes COHoRtE) study is a prospective, population-based cohort study in T2D patients. In the sleep disordered breathing substudy, the apnoea-hypopnoea index (AHI), oxygen desaturation index (ODI) and percentage of night-time spent with a peripheral oxygen saturation of <90% ( $t_{\text{sat}90\%}$ ) were assessed using a two-channel ambulatory monitoring device. Malignancy diagnoses were gathered using self-reported medical history data validated by medical records. Hazard ratios (HRs) for incident malignancy were derived by Cox regression adjusting for sex, age, body mass index, smoking status, alcohol intake, socioeconomic status and HbA1c.

**Results:** Of 1239 patients with T2D (mean age 67 years, 41% female, mean body mass index 30.9 kg·m<sup>-2</sup>), 79 (6.4%) were first-time diagnosed with a malignancy within a median follow-up period of 2.7 years (interquartile range 2.2–4.5 years). AHI, ODI and  $t_{\text{sat}90\%}$  were not associated with incident malignancy. In subgroup analysis, females showed increased cancer risk per AHI unit (adjusted HR 1.03 per AHI unit, 95% CI 1.00–1.06;  $p=0.028$ ) and severe sleep apnoea (defined as AHI  $\geq 30$  events·h<sup>-1</sup>; adjusted HR 4.19, 95% CI 1.39–12.77;  $p=0.012$ ). This was not seen in males, and a significant interaction was observed (interaction terms  $p=0.048$  and  $p=0.033$ , respectively).

**Conclusion:** Sleep apnoea was not associated with incident malignancy in T2D patients. However, stratified analysis revealed a significant association between sleep apnoea and incident malignancy in females, but not in males.



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In patients with type 2 diabetes, sleep apnoea is not associated with the incidence of malignancy. However, stratified analysis shows that sleep apnoea is associated with incident malignancy in females, but not in males. <https://bit.ly/37RAK8V>

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## Introduction

Sleep apnoea is a highly prevalent disorder characterised by repetitive apnoeas and hypopnoeas and arousals from sleep. The prevalence of moderate-to-severe sleep apnoea (defined as apnoea-hypopnoea index (AHI)  $\geq 15$  events·h<sup>-1</sup>) is up to 49% in males and 23% in females, and it has increased substantially over the past two decades [1, 2]. Sleep apnoea is strongly associated with cardiovascular and metabolic morbidity and mortality [3, 4]. Sleep apnoea leads to intermittent hypoxaemia and sleep fragmentation, and causes sympathetic nervous system activation, oxidative stress and systemic inflammation [5–8]. Sleep apnoea and intermittent hypoxaemia have been linked to an increased incidence [9–12], growth, angiogenesis, chemoresistance and radioresistance in tumours [13–16]. Experimental studies have shown that intermittent hypoxaemia can lead to a faster and more invasive tumour growth as well as metastasis in animal studies [17–19]. There was an association between sleep apnoea and increased tumour mortality in clinical studies [20]. Until now, clinical studies investigating the association between sleep apnoea and incidence of malignancy have shown inconsistent results [21, 22]. When such evidence is documented in cohort studies where incident cancer is assessed, this could point to new paths of cancer prevention through early diagnosis and treatment of sleep apnoea or nocturnal hypoxaemia.

Type 2 diabetes mellitus (T2D) is an important hazard, with prevalence rates rising worldwide [23, 24]. T2D and sleep apnoea are each likely to contribute to the development of the other [25] and show high co-occurrence rates [26–29]. T2D has also been linked to an increased risk of incident malignancies [30]. This is the first study to evaluate the association between sleep apnoea and incidence of malignancy in a sample of patients with T2D.

## Methods

### Study design

The investigated patients were participants of the DIACORE (DIAbetes COHoRtE)-SDB (sleep disordered breathing) substudy [31]. DIACORE is a two-centre prospective and longitudinal cohort study of T2D patients of European descent [32]. The DIACORE study was originally designed to determine incident micro- and macrovascular T2D complications, malignancy and hospitalisation [32]. As the substudy was conducted only at the Regensburg Clinical Study Centre (Regensburg, Germany), all participants from the Regensburg centre were invited to take part in the DIACORE-SDB substudy. 492 (16%) patients did not agree to participate. Other patients did not participate for the following reasons: recruiting centre not offering SDB monitoring, current use of positive airway pressure (PAP) therapy, study termination and SDB monitoring not performed (figure 1).

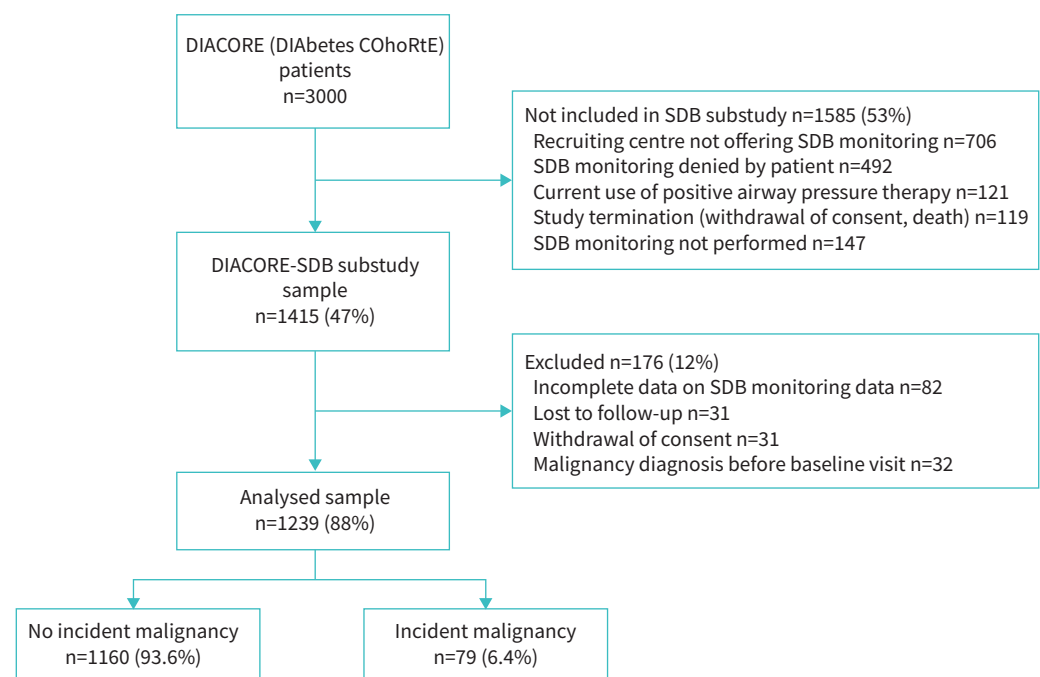


FIGURE 1 Study flow chart. SDB: sleep disordered breathing.

The participants were subjected to a standardised online questionnaire, blood sampling and physical examination, and were invited to re-examinations every 2 years. Assessment of sleep apnoea was performed using a two-channel ambulatory monitoring device (ApneaLink; ResMed, Sydney, Australia). The DIACORE-SDB substudy started in November 2011 and patients were followed-up every 2 years until April 2018.

The protocol, data protection strategy and study procedures were approved by the ethics committees of the participating institutions and in accordance with the Declaration of Helsinki. Patients participated in the DIACORE study only after providing written consent. The study protocol has been described previously [32]. 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.

### *Study population*

All T2D patients living in the regions around Regensburg and Speyer were eligible for participation in the DIACORE study (figure 1) [32]. The recruitment process has been described previously [32]. Further inclusion criteria were as follows: ability to fully understand the study information; ability to give written informed consent; age  $\geq 18$  years; and self-reported Caucasian ethnicity [32]. Exclusion criteria included a history of active malignancy within the past 5 years (prostatic cancer within the past 2 years); haemochromatosis; history of pancreoprivic or self-reported type 1 diabetes mellitus; acute infection or fever; pregnancy; chronic viral hepatitis or HIV infection; presence of autoimmune disease potentially affecting kidney function; and chronic renal replacement therapy [32]. For the DIACORE-SDB substudy, participants were included if they consented to perform sleep apnoea monitoring and excluded if they currently used PAP therapy [31].

Alcohol intake (number of drinks per week), smoking status (current, former or never), socioeconomic status (according to the Robert Koch Institute, Germany [33], subdivided into four groups ranging from 1 (lowest) to 4 (highest) and including educational level, professional qualification and income) and physical activity (defined as light activity at least three times per week) were evaluated by standardised questionnaires. Subjective daytime sleepiness was assessed using the validated Epworth Sleepiness Scale. Patients were asked to rank how likely it was for them to fall asleep in various common situations [31]. Scores range from 0 (least sleepy) to 24 (sleepiest). Excessive daytime sleepiness is defined as a score of  $\geq 11$ .

### *Assessment of sleep apnoea*

Ambulatory sleep apnoea monitoring was conducted using a validated device [34, 35] (ApneaLink), as described previously [31]. The participants were instructed on the use of the device by trained personnel in a standardised manner [31]. Nasal flow and pulse oximetry were measured. AHI was calculated as the mean number of apnoea and hypopnoea events per hour of recording time. Oxygen desaturation index (ODI) measured the mean number of respiratory events per hour where blood oxygen level dropped by 4% in comparison with immediately preceding basal value. The percentage of the total recording time with a peripheral oxygen saturation below 90% ( $t_{\text{sat}90\%}$ ) was documented. The standard settings of the monitoring device were used for the definitions of apnoea, hypopnoea and desaturation [36]. Due to the lack of a chest band, it was not possible to differentiate between obstructive and central apnoea.

All patients were informed about the results of sleep apnoea monitoring, but further diagnosis and treatment was not part of the protocol of DIACORE. Use of PAP treatment during follow-up was evaluated by standardised questionnaires as part of the protocol of DIACORE. PAP treatment status was available in 1133 patients.

### *Assessment of incident malignancy*

The incidence of a malignancy, defined as the first diagnosis of a malignant neoplasm at any time between the sleep apnoea monitoring (starting November 2011) and the last performed DIACORE follow-up visit (April 2018), was assessed by medical history and medical records at every visit by the DIACORE end-point committee [32]. Medical documentation was requested up to three times from the patients' treating physicians and validated by an experienced physician. If a patient-reported end-point could not be confirmed by available documentation or if adequate medical documentation was not available, then that end-point was coded as "not validated" and analysed as "no cancer" [32]. Basal cell carcinomas were excluded from the analysis, as these tumours rarely metastasise and have low mortality.

### *Statistical analysis*

Descriptive data are presented as mean $\pm$ SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Continuous variables were compared by t-test

and categorical variables by Chi-squared test. AHI, ODI and  $t_{\text{sat}90\%}$  were used as surrogates of sleep apnoea severity, all as continuous variables and in categories. Sleep apnoea severity categories according to the AHI were defined as  $<5$  events·h<sup>-1</sup>, no sleep apnoea;  $5-<15$  events·h<sup>-1</sup>, mild sleep apnoea;  $15-<30$  events·h<sup>-1</sup>, moderate sleep apnoea; and  $\geq 30$  events·h<sup>-1</sup>, severe sleep apnoea. As there is no clinically established cut-off,  $t_{\text{sat}90\%}$  was dichotomised by the median. Cox proportional hazard regression models were used to analyse the association between sleep apnoea parameters as well as for severe sleep apnoea and the incidence of malignancy. Known risk factors for cancer development such as age, sex, body mass index (BMI), smoking status, alcohol intake and socioeconomic status were included as covariates, as well as HbA1c as a surrogate of T2D severity. Sex- and age-specific associations between sleep apnoea and incidence of malignancy were analysed. The results are presented as hazard ratios (HR) with 95% confidence intervals. Cumulative hazards of the multivariable analyses were analysed and visualised in figures. p-values  $<0.05$  were considered significant, except in the subgroup analyses by sex and high versus low age, where we performed a Bonferroni correction for two independent tests and used a stricter level of significance, *i.e.*  $p < 0.05/2 = 0.025$ . Data were analysed using the SPSS statistical software package (SPSS 25.0; IBM SPSS Statistics, Armonk, NY, USA).

## Results

### Patient characteristics

Of the 1415 patients monitored for sleep apnoea, 176 (12.4%) could not be included in the final analysis due to incomplete polygraphy data, loss to follow-up, withdrawal of consent or history of cancer at baseline assessment (figure 1). Of the analysed sample (n=1239), 292 (23.3%) patients had no sleep apnoea, 521 (42.1%) had mild sleep apnoea, 298 (24.1%) had moderate sleep apnoea and 128 (10.3%) had severe sleep apnoea. Patients with severe sleep apnoea were predominantly male, significantly more likely to be obese and exhibited a significantly higher  $t_{\text{sat}90\%}$  (table 1). The median (interquartile range) follow-up time was 2.7 (2.2–4.5) years.

### Sleep apnoea and incidence of malignancy

During the observation period, 79 (6.4%) patients received the diagnosis of an incident malignant tumour. The most frequent diagnoses were skin tumours, followed by prostate cancer, colorectal carcinoma and pancreatic cancer (table 2).

Sleep apnoea was described using event-driven parameters (such as AHI and ODI) as well as with measures of cyclic and noncyclic nocturnal hypoxaemia ( $t_{\text{sat}90\%}$ ). The rates of incident malignancies were 6.3%, 5.4% and 9.4% in the groups of no or mild, moderate and severe sleep apnoea (Chi-squared test

TABLE 1 Baseline characteristics of the 1239 patients overall and according to severity of sleep disordered breathing

	Entire cohort	AHI $<30$ events·h <sup>-1</sup>	AHI $\geq 30$ events·h <sup>-1</sup>
<b>Patients</b>	1239	1111 (89.7)	128 (10.3)
<b>Age years</b>	67±9	66±9	68±8
<b>Female</b>	511 (41.2)	482 (43.4)	29 (22.7)
<b>BMI kg·m<sup>-2</sup></b>	30.9±5.3	30.5±5.2	33.6±5.9
<b>Waist-hip ratio</b>	0.95±0.08	0.95±0.08	1.00±0.08
<b>Obesity</b>	622 (50.2)	533 (48.0)	89 (69.5)
<b>HbA1c mmol·mol<sup>-1</sup></b>	51±11	51±12	50±9
<b>Former or current smokers</b>	701 (56.6)	624 (56.2)	77 (60.2)
<b>High alcohol intake<sup>#</sup></b>	353 (28.5)	309 (27.8)	44 (34.4)
<b>Socioeconomic status<sup>¶</sup></b>	2 (1–2)	2 (1–2)	2 (2–2)
<b>Physical inactivity<sup>*</sup></b>	699 (56.4)	620 (55.8)	79 (61.7)
<b>Follow-up time years</b>	2.7 (2.2–4.5)	2.8 (2.2–4.5)	2.4 (2.1–4.5)
<b>Excessive daytime sleepiness<sup>§</sup></b>	87 (7.1)	77 (7.0)	10 (7.8)
<b>AHI events·h<sup>-1</sup></b>	10 (5–19)	9 (4–15)	44 (36–52)
<b>ODI events·h<sup>-1</sup></b>	9 (5–19)	8 (5–15)	39 (33–49)
<b><math>t_{\text{sat}90\%}</math></b>	10.4 (2.5–30.6)	8.8 (2.1–28.4)	23.5 (13.7–45.4)

Data are presented as n, mean±sd, n (%) or median (interquartile range). AHI: apnoea-hypopnoea index; BMI: body mass index; ODI: oxygen-desaturation index;  $t_{\text{sat}90\%}$ : percentage of night-time spent with oxygen saturation  $<90\%$ . <sup>#</sup>:  $\geq 3$  drinks per week; <sup>¶</sup>: according to Robert Koch Institute (Germany) [37] subdivided into four groups ranging from 1 [lowest] to 4 [highest] and including educational level, professional qualification and income; <sup>\*</sup>: light activity  $\leq 2$  times per week; <sup>§</sup>: Epworth Sleepiness Scale  $\geq 11$ .

TABLE 2 Tumour entities

<b>Total sample</b>	1239
Skin tumours <sup>#</sup>	20 (25.3)
Prostate carcinoma	9 (11.5)
Colorectal carcinoma	7 (8.9)
Pancreatic carcinoma	7 (8.9)
Breast cancer	5 (6.3)
Pulmonary carcinoma	5 (6.3)
Malignancy of the haematopoietic and lymphatic system	5 (6.3)
Malignancy of the female genital organ	5 (6.3)
Malignancy of the urinary organ	5 (6.3)
Others <sup>¶</sup>	11 (13.9)
Total	79 (100)
<b>Males</b>	728
Skin tumours <sup>#</sup>	15 (28.3)
Prostate carcinoma	9 (17.0)
Colorectal carcinoma	7 (13.2)
Malignancy of the urinary organ	5 (9.4)
Pulmonary carcinoma	4 (7.5)
Pancreatic carcinoma	3 (5.7)
Malignancy of the haematopoietic and lymphatic system	2 (3.8)
Others <sup>¶</sup>	8 (15.1)
Total	53 (100)
<b>Females</b>	511
Skin tumours <sup>#</sup>	5 (19.2)
Breast cancer	5 (19.2)
Malignancy of the female genital organ	5 (19.2)
Pancreatic carcinoma	4 (15.4)
Malignancy of the haematopoietic and lymphatic system	3 (11.6)
Pulmonary carcinoma	1 (3.8)
Others <sup>¶</sup>	3 (11.6)
Total	26 (100)

Data are presented as n or n (%). #: malignant melanomas, squamous cell carcinomas and lentiginous melanomas (basal cell carcinomas were excluded); ¶: cancer types observed only in few or single persons, e.g. liver tumour, parotid tumour, meningioma.

$p=0.294$ ), respectively. Hazard ratios for the incidence of a malignancy in dependency on continuous and dichotomised sleep apnoea parameters are given in tables 3 and 4; all analyses were adjusted for potential confounders such as age, sex, BMI, smoking status, alcohol intake, socioeconomic status and HbA1c. There was no association between any of the six sleep apnoea parameters and incident cancer in the entire

TABLE 3 Adjusted hazard ratios (HRs) for the incidence of malignancy in 1239 patients with type 2 diabetes during a median follow-up of 2.7 years (number of events 79)

	Adjusted HR (95% CI) <sup>#</sup>	p-value
<b>AHI events·h<sup>-1</sup></b>		
AHI (continuous)	1.01 [0.99–1.03]	0.416
AHI $\geq 30$	1.30 [0.64–2.62]	0.473
<b>ODI events·h<sup>-1</sup></b>		
ODI (continuous)	1.00 [0.98–1.02]	0.799
ODI $\geq 30$	1.24 [0.57–2.68]	0.584
<b><math>t_{\text{sat}90\%}</math></b>		
$t_{\text{sat}90\%}$ (continuous)	1.00 [1.00–1.01]	0.395
$t_{\text{sat}90\%} \geq 10.4\%$	1.59 [0.94–2.68]	0.085

HRs calculated using Cox proportional hazards regression analysis. The multivariable analyses were adjusted for sex, age, body mass index, smoking status, alcohol intake, socioeconomic status and HbA1c. AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index;  $t_{\text{sat}90\%}$ : percentage of night-time spent with oxygen saturation  $<90\%$ .

TABLE 4 Adjusted hazard ratios (HRs) for the incidence of malignancy in 1239 patients with type 2 diabetes during a median follow-up of 2.7 years stratified by sex and age

	Males		Females		≥70 years		<70 years	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Patients n	728		511		472		767	
Events n	53		26		43		36	
<b>AHI events·h<sup>-1</sup></b>								
AHI (continuous)	1.00 [0.97–1.02]	0.659	1.03 [1.00–1.06]	0.028	1.00 [0.98–1.03]	0.751	1.01 [0.98–1.03]	0.538
AHI ≥30	0.76 [0.31–1.87]	0.550	4.19 [1.38–12.77]	0.012	1.21 [0.48–3.09]	0.686	1.28 [0.44–3.78]	0.651
<b>ODI events·h<sup>-1</sup></b>								
ODI (continuous)	0.99 [0.96–1.01]	0.357	1.04 [1.00–1.07]	0.032	1.00 [0.97–1.03]	0.933	1.00 [0.97–1.03]	0.972
ODI ≥30	0.62 [0.22–1.79]	0.380	5.64 [1.78–17.90]	0.003	1.34 [0.53–3.36]	0.539	0.88 [0.20–3.83]	0.863
<b>t<sub>sat90%</sub></b>								
t <sub>sat90%</sub> (continuous)	1.00 [0.99–1.01]	0.670	1.02 [1.00–1.03]	0.035	1.00 [0.99–1.01]	0.912	1.01 [1.00–1.02]	0.236
t <sub>sat90%</sub> ≥10.4%	1.28 [0.66–2.46]	0.467	2.57 [1.03–6.41]	0.043	0.91 [0.51–2.11]	0.913	2.43 [1.09–5.42]	0.030

HRs calculated by Cox proportional hazards regression analysis. The multivariable analyses were adjusted for sex, age, body mass index, smoking status, alcohol intake, socioeconomic status and HbA1c. AHI: apnoea-hypopnoea index; ODI: oxygen desaturation index; t<sub>sat90%</sub>: percentage of night-time spent with oxygen saturation <90%.

cohort (table 3). For patients with severe sleep apnoea there was no significantly elevated cumulative hazard (figure 2).

In subanalyses, we stratified the data by sex and high *versus* low age (≥70 years *versus* <70 years). In females, all six sleep apnoea parameters were associated with incident malignancy: continuous AHI, ODI and t<sub>sat90%</sub>, as well as their dichotomisation to reflect severe sleep apnoea (AHI ≥30 events·h<sup>-1</sup>, ODI ≥30 events·h<sup>-1</sup> or t<sub>sat90%</sub> above the median of 10.4%) (table 4, figure 3). Severe sleep apnoea (defined as AHI ≥30 events·h<sup>-1</sup> or ODI ≥30 events·h<sup>-1</sup>) was significantly associated with incident malignancy on a Bonferroni-corrected significance level of 0.05/2=0.025. Still, the other parameters showed consistent results (table 4). The hazard ratio estimates for severe sleep apnoea ranged from 2.57 to 4.19 and thus indicated a substantially increased risk of incident malignancy.

No association between the severity of sleep apnoea or severe sleep apnoea with incident malignancy was found in males (table 4, figure 3). The associations were significantly different between females and males for most parameters: continuous AHI (interaction term 0.049), AHI ≥30 events·h<sup>-1</sup> (interaction term 0.033) and ODI ≥30 events·h<sup>-1</sup> (interaction term 0.009), but not for continuous ODI (interaction term 0.060) or continuous and dichotomised t<sub>sat90%</sub> (interaction terms p=0.097 and p=0.320, respectively).

When HbA1c was treated as an effect modifier and the cohort was stratified by HbA1c (HbA1c <6.5% *versus* HbA1c ≥6.5%), there was no significant difference between the groups regarding the association between sleep apnoea and the incidence of malignancy.

In the subgroup analyses by high *versus* low age with the cut-off at 70 years, we found no significant association of any of the six parameters at the significance level of 0.05/2=0.025 (table 4). When including an interaction term, we found no significantly different association between the groups of patients aged ≥70 years *versus* <70 years.

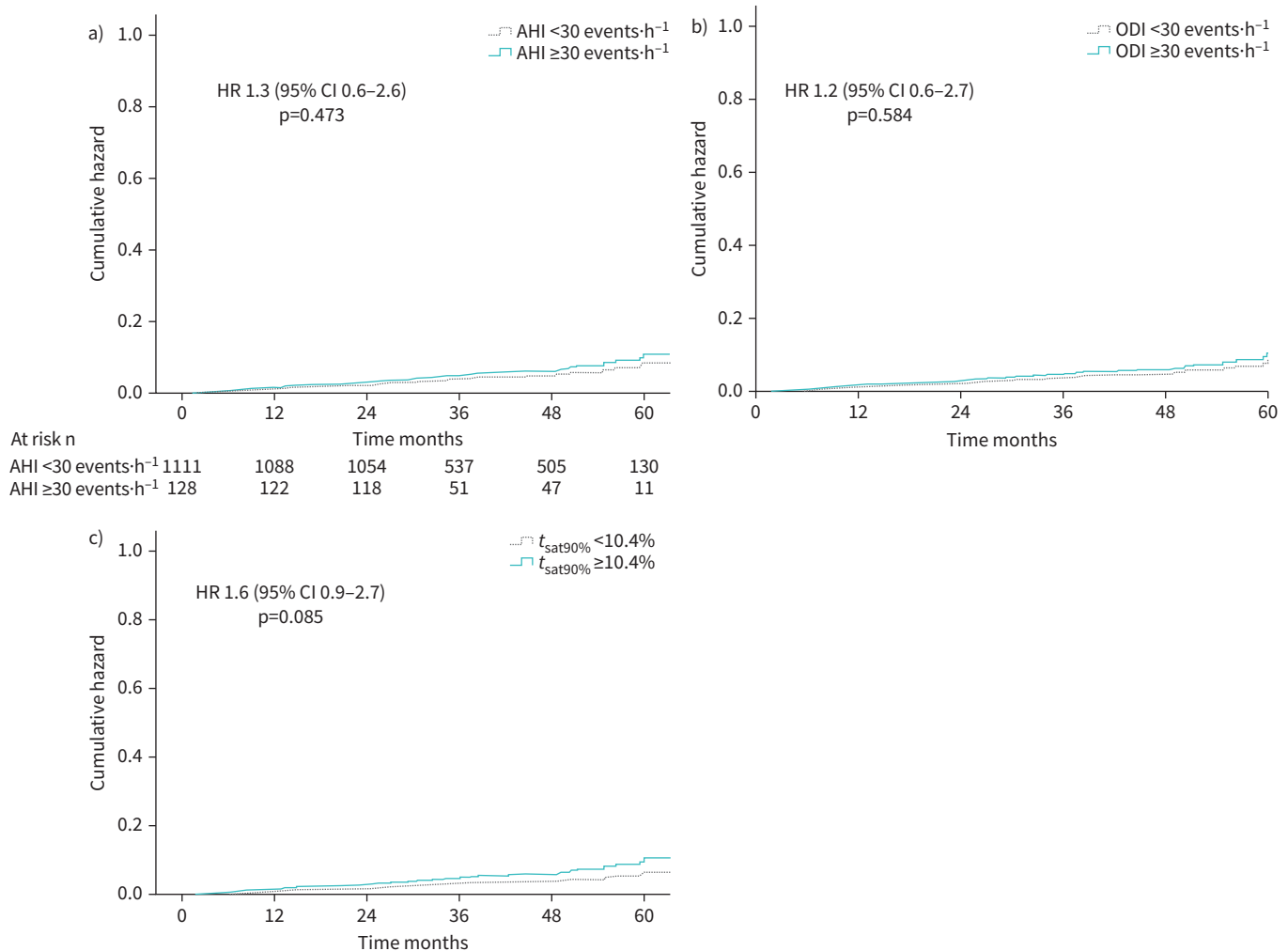
In the present study, there were no associations between the mean and minimal peripheral oxygen saturation, excessive daytime sleepiness, daytime napping, duration of night's sleep or sleep efficiency (hours of sleep per hours in bed) and the incidence of a malignancy (p-values ranging from 0.090 to 0.993).

#### PAP treatment and incidence of malignancy

During follow-up, 74 patients initiated PAP treatment within their clinical routine, of whom 30 had severe sleep apnoea. Of the 72 patients with newly started PAP therapy who had at least mild sleep apnoea at DIACORE-SDB monitoring, 6.9% had an incident malignancy compared to 5.3% of the 799 patients with at least mild sleep apnoea without PAP treatment.

#### Discussion

In this prospective cohort study of T2D patients, we investigated the association between sleep apnoea and the incidence of malignancy. Sleep apnoea at baseline was not significantly associated with the incidence

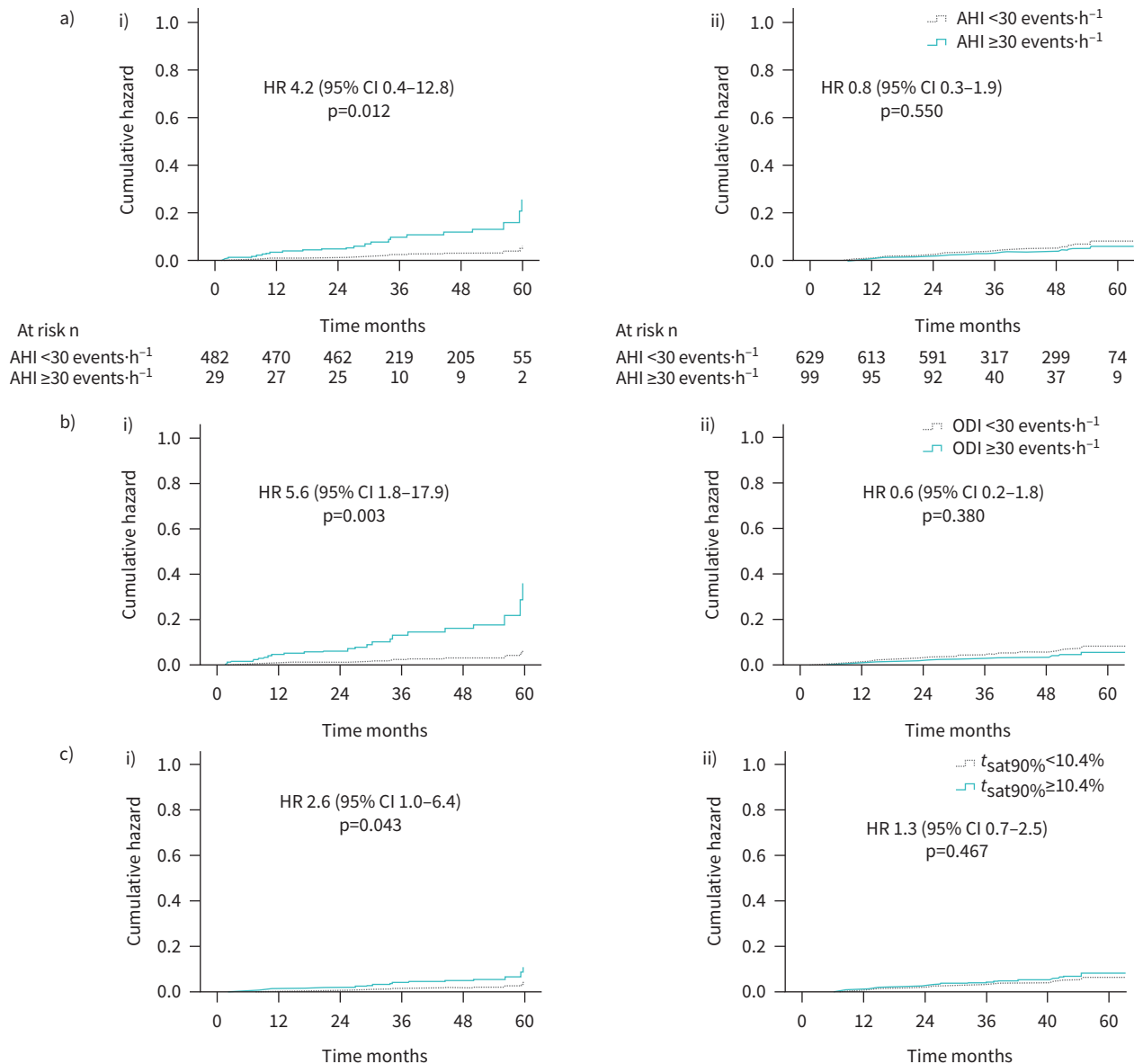


**FIGURE 2** Cumulative adjusted hazard for incident malignancy in 1239 patients with diabetes mellitus type 2 and a) apnoea–hypopnoea index (AHI) <30 events·h<sup>-1</sup> versus ≥30 events·h<sup>-1</sup>; b) oxygen desaturation index (ODI) <30 events·h<sup>-1</sup> versus ≥30 events·h<sup>-1</sup>; and c) percentage of night-time spent with oxygen saturation <90% ( $t_{\text{sat}90\%}$ ) <10.4% versus ≥10.4%.

of malignancy during follow-up. However, stratified analysis showed that, in females only, sleep apnoea was associated with incident malignancy. This finding was independent of other known risk factors such as age, sex, BMI, smoking status, alcohol intake, socioeconomic status and HbA1c as a surrogate for diabetes severity. Females had a 3% increased risk per unit increase of AHI and HR 4.2 for incident malignancy in case of severe sleep apnoea. There was no increased risk of malignancy with any sleep apnoea parameter in males. The incidence rate of malignancy was 1.9% per year compared to 1.1% in the German general population, including ~7–8% of patients with T2D [37, 38].

This is the first study to investigate the association of sleep apnoea and the incidence of malignancy among T2D patients. Thus, results are compared to both sleep clinic and community cohorts with a proportion of T2D patients ranging between 3% and 22% (table 5).

In the present study, severity of sleep apnoea was not associated with the incidence of malignancy when males and females were combined. This result is consistent with two clinical cohort studies [10, 41]. In contrast to the present study, CAMPOS-RODRIGUEZ *et al.* [9] found that nocturnal hypoxaemia ( $t_{\text{sat}90\%} >12\%$ ) was significantly associated with an increased risk of tumour incidence in a retrospective clinical cohort study on patients with suspected obstructive sleep apnoea (OSA). Several aspects of our study differ from the CAMPOS-RODRIGUEZ *et al.* study: first, CAMPOS-RODRIGUEZ *et al.* [9] did not indicate interaction terms, so it remains unclear whether the detected association was significantly different between males and females. Second, there are differences in the sample composition: the present study focused on patients with T2D, while CAMPOS-RODRIGUEZ *et al.* [9] included all patients from a sleep clinic with a focus on symptomatic patients documented by the high proportion of PAP treatment (57.9%). Third, the DIACORE study found



**FIGURE 3** Cumulative adjusted hazard for incident malignancy in i) 511 females and ii) 728 males with a) apnoea-hypopnoea index (AHI) <math><30\text{ events}\cdot\text{h}^{-1}</math> versus

significant associations between sleep apnoea and incident malignancy in females for event-driven measures (AHI, ODI) as well as cyclic and continuous nocturnal hypoxaemia ( $t_{\text{sat}90\%}$ ), while CAMPOS-RODRIGUEZ *et al.* [9] only found an association for nocturnal hypoxaemia. Although patients with daytime respiratory failure were excluded in the study of CAMPOS-RODRIGUEZ *et al.* [9], the aetiology of nocturnal hypoxaemia remained unclear. In contrast to OSA, for example, obesity and pulmonary disease cannot be ruled out. In addition, the ODI, a specific marker of intermittent hypoxaemia to rule out effects from continuous hypoxaemia, was not available [9].

In the present study,  $t_{\text{sat}90\%}$  showed a trend in the total sample (HR 1.59, 95% CI 0.94–2.68;  $p=0.085$ ), suggesting a similarity with the CAMPOS-RODRIGUEZ *et al.* [9] study. However, this was not statistically significant and possibly due to limited power. In addition, females showed an increased risk for higher  $t_{\text{sat}90\%}$ , but this association did not differ between males and females.

In a recent cross-sectional analysis of the European Sleep Apnea Database (ESADA) including 19 556 patients, cancer prevalence was higher in females with sleep apnoea and nocturnal hypoxaemia, but not in males [42]. The only prospective cohort study investigating the association between sleep apnoea and cancer incidence, the community sample Busselton Health Study Cohort [39], with 390 individuals and



TABLE 5 Association of sleep apnoea and incidence<sup>#</sup> of malignancy, comparison of existing studies

First author (year) [ref.]	Population n (% female)	T2D %	Study design	Follow-up years	Sleep apnoea diagnosis	Main outcomes	Main findings	Key limitations
<b>Sleep apnoea diagnosis with PSG or PG</b>								
Prospective								
DRIENDL (2020; present study)	1239 (41)	100	Prospective cohort study	2.7	PG	Cancer incidence (n=79)	Association between AHI $\geq 30$ events-h <sup>-1</sup> and cancer incidence in females	Use of PG
MARSHALL (2014) [39]	390 (26)	3	Prospective cohort study	20	PG	Cancer incidence (n=125)	Association between elevated RDI ( $\geq 15$ events-h <sup>-1</sup> ) and cancer incidence	Small population Lack of control of some cancer risk factors Lack of information on PAP therapy
Retrospective								
JUSTEAU (2020) [40]	8748 (36)	15	Retrospective cohort study, multicentre	5.8	PSG, PG	Cancer incidence (n=718)	Association between nocturnal hypoxaemia ( $t_{\text{sat}90\%} > 13\%$ ) and cancer incidence	Lack of control of some cancer risk factors Partial use of PG
CAMPOS-RODRIGUEZ (2013) [9]	4910 (33)	n/s	Retrospective cohort study, multicentre	4.5	PSG (32%), PG (68%)	Cancer incidence (n=261)	Association between severe OSA ( $t_{\text{sat}90\%} > 12\%$ ) and cancer incidence, limited to male patients <65 years	Lack of control of some cancer risk factors Major use of PG
BRENNER (2019) [10]	5243 (26)	n/s	Retrospective cohort study	5.9	PSG	Cancer incidence (n=265)	Association between AHI $> 57$ events-h <sup>-1</sup> and cancer incidence for patients <45 years	Lack of control of some cancer risk factors Lack of information on PAP therapy
KENDZERSKA (2014) [41]	10 149 (38)	14	Retrospective cohort study, multicentre	7.8	PSG	Cancer incidence (n=627)	No association between OSA and cancer incidence	
Cross-sectional								
PATAKA (2019) [42]	19 556 (29)	n/s	Cross-sectional analysis, multicentre		PSG, PG	Cancer prevalence (n=388)	Association between cancer prevalence and OSA and nocturnal hypoxaemia in females	Lack of control of some cancer risk factors Lack of information on PAP therapy

Continued

TABLE 5 Continued

First author (year) [ref.]	Population n (% female)	T2D %	Study design	Follow-up years	Sleep apnoea diagnosis	Main outcomes	Main findings	Key limitations
Meta-analysis SHANTHA (2015) [21]	112 228 (26–100)	4–22	Meta-analysis, five studies	4.5–20	PSG, PG	Cancer incidence (n=864)	Patients with SDB had a nearly 50% greater overall cancer risk compared with patients without SDB OSA was not independently associated with cancer incidence	
ZHANG (2017) [22]	86 460 (26–38)	n/s	Meta-analysis, six studies	4.5–20	PSG, PG	Cancer incidence (n=965)		
<b>OSA diagnosed according to ICD-9 or symptoms</b>								
Prospective CHRISTENSEN (2013) [43]	8783 (55)	n/s	Prospective cohort study	13	Symptoms of OSA	Cancer incidence (n=1985)	No association between symptoms of OSA and cancer incidence	OSA diagnosis based on symptoms Lack of information on PAP therapy
Retrospective GOZAL (2016) [11]	5.6 million (50)	14 in OSA-group	Retrospective cohort study	3.2–3.9	According to ICD-9-CM	Cancer incidence (n=167 022)	Elevated risk for malignant melanoma and kidney and pancreatic cancer for patients with OSA Lower risk for colorectal, breast and prostate cancer for patients with OSA	Potential bias by use of administrative claims database Lack of control of some cancer risk factors
SILLAH (2018) [12]	34 402 (43)	n/s	Retrospective cohort study	5.3	According to ICD-9-CM	Cancer incidence (n=1575)	Elevated risk for malignant melanoma and kidney, uterine and breast cancer for patients with OSA Lower risk for colorectal and lung cancer for patients with OSA	Lack of control of some cancer risk factors Lack of information on PAP therapy

T2D: type 2 diabetes mellitus; PSG: polysomnography; PG: polygraphy; OSA: obstructive sleep apnoea; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; AHI: apnoea–hypopnoea index; RDI: respiratory disturbance index; n/s: not specified; PAP: positive airway pressure; SDB: sleep disordered breathing;  $t_{\text{sat} < 90\%}$ : percentage of night-time spent with oxygen saturation <90%. #: prevalence shown for PATAKA *et al.* [42].

125 events observed during a follow-up time of 20 years, showed that participants with moderate to severe sleep apnoea had a 2.5-fold elevated risk of an incident malignancy, but there were no differences between males and females. However, hazard ratios for females were elevated but not statistically significant, probably because of a small sample size, as the analysis had only five females in the moderate-to-severe OSA group [39].

Even meta-analyses found inconsistent results when investigating the association between sleep apnoea and the incidence of malignancy. Whereas SHANTHA *et al.* [21] found a 50% greater overall cancer risk compared to patients without sleep apnoea, ZHANG *et al.* [22] found that sleep apnoea was not associated with incidence of malignancy (table 5). Other studies examining overall malignancy and site-specific cancer observed that sleep apnoea was only associated with specific cancer types such as malignant melanoma, kidney, pancreatic, uterine and breast cancer [11, 12] (table 5). Reasons for the inconsistency of these studies could be limited study power, retrospective design, poor control of cancer risk factors and potential bias by use of administrative claims database (table 5).

Different pathophysiological mechanisms were suggested to explain the association between sleep apnoea and incident malignancy, such as intermittent hypoxaemia and sleep fragmentation resulting in oxidative stress, systemic inflammation and immunodeficiency [16, 44]. These mechanisms can contribute to changes in tumour biology, accelerated tumour growth and progression of existing tumours including metastasis [16]. We found an association of sleep apnoea and incident malignancy only in females, but not in males. One reason could be that females are more likely to have regular physician's visits and therefore are more likely to receive a malignancy diagnosis [45, 46].

In our study, skin tumours were the most common malignancy (n=20, 25% of all neoplasms). This observation differs from the expected distribution of tumours, in which prostate, breast, lung and colorectal cancer would be the most frequent tumours [37]. Studies found a hypoxic microenvironment of the skin contributing to melanocyte transformation [47] and a significantly higher incidence of melanomas in patients with sleep apnoea [11, 12]. However, we lacked statistical power to examine this association. Sensitivity analyses of the association between measures of sleep apnoea and incidence of malignancy without nonmelanotic skin cancers show similarly increased hazard ratios in females (supplementary tables S1 and S2).

There is evidence that PAP treatment may have a moderating role in patients with sleep apnoea and in neoplasm-related pathways [48–50]. In the present study, there was no difference in malignancy incidence between patients with and without PAP therapy among patients with at least mild sleep apnoea, nor among patients with moderate-to-severe sleep apnoea. This should not be interpreted as a lack of efficacy in PAP therapy, as the number of events in the PAP therapy group was very low (n=5 in both analyses). Furthermore, because we consider sleep apnoea to be a chronic disease with intermittent hypoxaemia and other consequences of the disorder likely to have been present for several years before, recent treatment would probably not immediately affect the outcome.

Strengths of our study include the prospective study design and detailed phenotyping at baseline, which ensures wide and complete information about lifestyle and socioeconomic factors of the participants, enabling adjustment for the primary known cancer-related risk factors. Furthermore, we only validated cancer diagnoses when the self-reported diagnosis could be validated by a medical report.

The present study has the following limitations and thus cannot rule out an association of sleep apnoea and incidence of malignancy. First, we used a portable respiratory device to diagnose sleep apnoea. Even though the usage of a home sleep apnoea monitoring device is well established and validated for assessment of sleep apnoea [35, 51], due to the missing chest band, we could not distinguish between obstructive and central sleep apnoea. As a result, it is possible that the association we found is only valid for one of the two forms of sleep apnoea. Nonetheless, as we consider OSA to be the main pathophysiology linking sleep apnoea and incident malignancy, not excluding central sleep apnoea from the analysis would most likely confer a conservative bias towards the null, *i.e.* underestimate the association between sleep apnoea and the incidence of malignancy. Moreover, in previous studies of patients with T2D, 99% of the sleep apnoea was obstructive [26, 27]. Furthermore, inaccurate measurement of the AHI could result from the use of ApneaLink as a monitoring device, which could decrease the potential association between sleep apnoea and incidence of malignancy. Second, we lacked the statistical power to examine site-specific malignancies. Thus, we cannot rule out an association between sleep apnoea and site-specific malignancies such as malignant melanoma [11, 12]. Third, the median follow-up time of the study is ~2.7 years, which is a rather short period of time for evaluating the incidence of malignancies and could decrease the potential association between sleep apnoea and incidence of malignancy. However, we detected an overall cumulative tumour incidence of 6.4%, which is largely comparable to previous studies investigating the association between sleep apnoea and incident

malignancy [9, 10, 41]. It cannot be ruled out that some malignancies were already present at baseline, but not yet diagnosed. Fourth, the diagnosis of a malignancy was only possible when reported by the participants in follow-up visits, after which a medical report was obtained to validate the self-reported diagnosis, potentially introducing bias. Fifth, investigation of patients with T2D could lead to referral bias. Sixth, the use of Bonferroni-corrected p-values for the female and age-stratified analyses constitutes a conservative statistical approach. Last, similar to most previous studies evaluating the association of sleep apnoea and cancer, the present study was not prospectively designed for this research question. Prospective studies on this topic are warranted.

In summary, there was no association between sleep apnoea and incident malignancy in this sample of patients with T2D. However, stratified analysis revealed a significant association of sleep apnoea with incident malignancy in females, but not in males. These findings emphasise the necessity to further investigate whether there are groups at higher risk for an incident malignancy associated with sleep apnoea and how T2D influences this association. Therefore, further research including longitudinal analyses and intervention studies is required to enhance the understanding of the underlying pathophysiological mechanisms of sleep apnoea on the incidence of malignancies.

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