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RESEARCH ARTICLE

Does obstructive sleep apnea increase the risk of cancer and cancer mortality in combined community-based cohorts?

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Summary

Obstructive sleep apnea (OSA) has been linked to cancer in several clinical and community-based cohorts. The effect in community-based studies free of clinical referral bias needs to be replicated. In this observational prospective cohort study, we pooled data from three community-based prospective cohorts (Uppsala Sleep and Health in Men cohort [UMEN]; Sleep and health in women [SHE]; Men Androgen Inflammation Lifestyle Environment and Stress Cohort [MAILES]; $n_{Total} = 1467$). All cohorts had objective data on obstructive sleep apnea and registry linkage data on cancer and cancer mortality. Analyses for different obstructive sleep apnea measures (apnea–hypopnea index [AHI], oxygen desaturation index [ODI], and minimal saturation) as risk factors for cancer incidence (all cancers) were performed using Cox proportional hazards models (follow-up 5–16 years). We did not find an overall increased risk of cancer after adjustment for age, sex, and BMI (HR_{AHI} [95% CI] = 1.00 [0.98; 1.01] and HR_{ODI} [95% CI] = 0.99 [0.97; 1.01]). Stratifying by daytime sleepiness did not influence the association. Cancer mortality was not significantly associated with obstructive sleep apnea. Taken together, we did not observe an overall increased risk of cancer or cancer mortality in relation to obstructive sleep apnea, however, our confidence limits remain wide for important diagnostic categories of sleep apnea severity. The relationship between obstructive sleep apnea and cancer needs further investigation in a comprehensive multi-cohort approach with greater statistical precision. For future studies we may need to find and then combine every community-based cohort study that can provide a definitive answer to the question on the risk of cancer from obstructive sleep apnea in the general population.

KEYWORDS
cancer, obstructive sleep apnea, population-based, registry

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder in the general population, with important neurocognitive, metabolic, and cardiovascular effects such as daytime sleepiness, diabetes, stroke, and hypertension (Punjabi, 2008). It is characterised by recurrent episodes of total (apnea) or partial (hypopnea) obstruction of the upper airway, due to muscle collapse in the pharynx during sleep, resulting in hypoxia, arousals (i.e., disrupted sleep), and snoring (Eckert & Malhotra, 2008).

Previous studies suggest that OSA is related to an increased risk of cancer incidence and mortality (Campos-Rodriguez et al., 2013; Chang et al., 2014; Gozal et al., 2015; Kendzerska et al., 2014; Marshall et al., 2014; Nieto et al., 2012). Animal models show that intermittent hypoxaemia, mimicking OSA, can enhance cancer growth and/or metastases by promoting angiogenesis, changes in immune function, or inflammatory changes, and oxidative stress (Almendros et al., 2013; Almendros & Gozal, 2018). In addition, in humans both OSA and some cancers (such as breast, colon, kidney, pancreas, and oesophagus) are linked with a higher body mass index (BMI) (Gallagher & LeRoith, 2015; Gozal et al., 2015). However, given the emerging data on OSA and cancer there is the possibility that OSA itself, independent of BMI, affects cancer development through the cycles of peripheral oxygenation changes (Almendros et al., 2013; Almendros & Gozal, 2018; Campos-Rodriguez et al., 2013; Chang et al., 2014; Hunyor & Cook, 2018; Kendzerska et al., 2014; Kendzerska et al., 2021; Marshall et al., 2014; Nieto et al., 2012). From previous cohorts, the risks of different types of cancers have been assessed, such as melanomas (Martinez-Garcia, Martorell-Calatayud, et al., 2014) because of their sensitivity to hypoxia and the ease of study in animal models, whereas others have studied breast, prostate, and central nervous system (CNS) cancers (Chang et al., 2014; Chen & Hwang, 2014; Lee et al., 2021). Nonetheless, there are also studies where no relationship between OSA and cancer has been found (Justeau et al., 2022; McEvoy et al., 2016; Sillah et al., 2019). As the true incidence of both OSA and cancer is increasing (Bhaskaran et al., 2014; Steele et al., 2017), there is a pressing public health and clinical need to study the relationship further.

Clinic-based studies unavoidably suffer from clinical referral biases (i.e., those referred for sleep studies may suffer from clusters of conditions which are not causally related in reality) and therefore community-based studies present an advantage (Young, 2009). Research in samples free from clinical referral bias (i.e., conducted in people recruited because of community affiliation and not health system interactions) could therefore give further clarification as to whether or not OSA increases the risk of cancer in the general population. This could be particularly important for some cancers that may be diagnosed earlier, because of the way sleep apnea symptoms present to the clinicians who diagnose and treat sleep apnea. Two simple examples of this are that the need to urinate nocturnally could lead to an investigation for prostate cancer, or early lung cancers may be detected by pulmonologists because they are trained to detect them. However, longitudinal community-based cohorts where OSA is properly phenotyped and then linked to cancer outcomes are extremely rare because of the considerable cost of performing overnight sleep studies (Marshall et al., 2014). This means that when analysed alone, our existing community-based cohorts are too small to assess a true effect in the population. Our current study has therefore pooled three population-based cohorts, all including objectively measured OSA data, and also cancer data from their local registries, with the aim to investigate whether the previously seen increased risk of cancer in OSA in selected cohorts is also true in the general population.

MATERIALS AND METHODS

Cohort description

We had access to data from four population-based cohorts, all of which contained objectively measured OSA data (including the number of respiratory events, measures of hypoxia) and also cancer data (all cancers and cancer types) from linked registry data (Figure 1). Within the main analysis we used the cohorts from the Sleep and Health in men (UMEN) study, the Sleep and HEalth in women (SHE) study, and the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study, including all participants with data on objectively measured OSA and registry data on cancer events and mortality. After we began analysis of the dataset we decided not to include the Busselton (BSN) study in the main analyses as it was one of the cohorts that has already reported a positive association, and including it would introduce a form of confirmation bias. We nonetheless included Busselton data in a sensitivity analysis because it includes male and female people, controls for some addition confounders, and facilitates some of the stratifications (Marshall et al., 2014).

Sleep and health in men (UMEN)

The sleep and health in men cohort was recruited via a postal questionnaire sent out to randomly selected men living in the City of Uppsala in 1994 ($n = 3201$). In 1996, 230 men (aged ≥43 years) underwent whole-night polysomnography (Elmasry et al., 2001; Elmasry et al., 2002). In addition, anthropometric measures and fasting bloods were collected. In 2012, register data for diagnosis of cancer, heart failure, diabetes, stroke, myocardial infarction, and cardiovascular disease, and all-cause mortality were collected.

Uppsala Sleep and HEalth (SHE) in women cohort

The Uppsala SHE cohort was first recruited in 2000 where 7051 women (aged ≥20 years) answered a questionnaire on sleep and health, including anthropometric measures. In 2002–2004, a one-

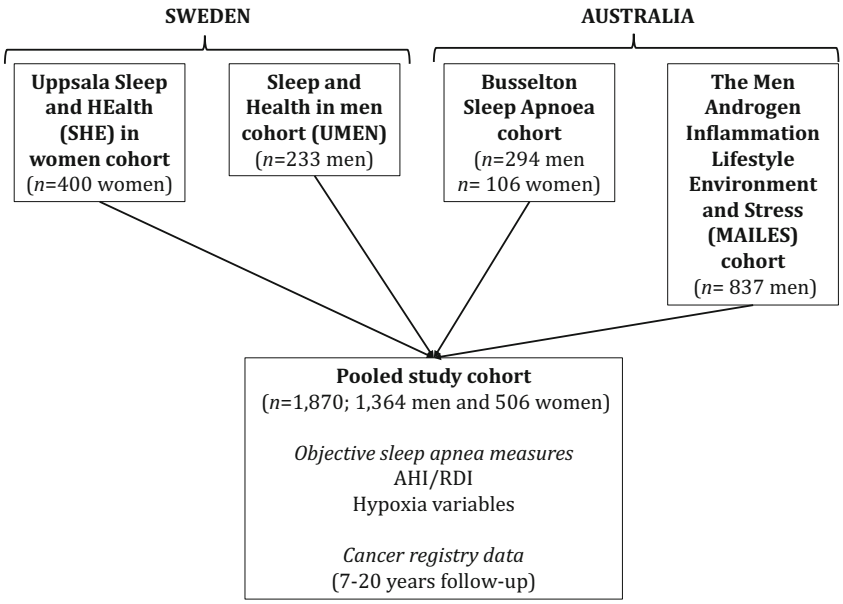

FIGURE 1 Overview of the project and the study population. Numbers presented for the main analysis cohort. Dashed lined cohort included in the sensitivity analysis.

night level 2 polysomnography was conducted in a subsample of 400 women, recording sleep and wake variables as well as breathing, movement, and snoring, and fasting blood samples were taken (Theorell-Haglow et al., 2008; Theorell-Haglow et al., 2010; Theorell-Haglow et al., 2011). Register data for diagnosis of cancer from the Swedish Cancer register and information on mortality from the Swedish National Death register were obtained in 2012.

The men androgen inflammation lifestyle environment and stress (MAILES) cohort

The MAILES cohort was recruited in 2002 and is a prospectively community-based cohort of men ($n = 2563$; aged 35–80 years) (Grant et al., 2014). The study collects ongoing information on chronic medical conditions, risk factors, overall health status, quality of life, measured anthropometric values, and hypertension, and demographic, psychosocial, and economic factors, as well as fasting blood samples. In a sub-study ($n = 837$), a home-based polysomnography for the assessment of OSA was conducted between 2010 and 2011 (MAILES4) and the ESS was administered. Data linkage with the Australian National Death Index register was performed in 2015 and provided cause-of-death and cancer information (cancer events and cancer mortality).

Busselton sleep apnea cohort (BSN)

The Busselton sleep apnea cohort was a community-based sample of men and women (40–65 years) recruited in 1990. At baseline, 486 men and 537 women responded to a postal questionnaire and an overnight sleep study was conducted in 294 men and 106 women for whom there was matched follow-up data in 1994/95 (Bearpark et al., 1995; Marshall et al., 2014). Anthropometric variables were measured, and fasting blood samples were collected. Information on hospital admission, cancer registration and death records for Busselton health survey participants were available from 1981 to 2010. An analysis of this dataset (up to the same date) for the same question has already been published (Marshall et al., 2014).

Public involvement statement

The current study pooled data from studies that were started and data collected prior to the concept of Patient and Public Involvement was launched broadly within the research community. Therefore, the public was not involved in study design and conduct, dissemination of results, and evaluation of studies.

Questionnaire data

All cohorts collected age and gender. Smoking status was available in all cohorts, however, in the MAILES cohort information on smoking was collected in MAILES2 (M2) which was performed prior to MAILES4 (Md = 25 months; IQR 5–51 months), where the sleep recording was performed. Information on alcohol consumption (in g/week) was available for SHE and BSN. In UMEN, SHE, and MAILES, information on daytime sleepiness was collected using the Epworth sleepiness scale (ESS) (Johns, 1991). For all cohorts there was information on cancer history (self-reported or from cancer registry) and self-reported information on somatic disease such as hypertension, and diabetes. In UMEN, SHE, and BSN information on history of CVD, MI, and stroke was also available.

Anthropometric measures and blood sampling

For all cohorts, information on height, weight, and BMI was available. For UMEN, SHE, and BSN there was also information on blood pressure, and blood sampling (glucose, insulin, lipids, triglycerides, CRP) at the time for when the sleep recording was available. For the MAILES cohort, blood sampling was performed in MAILES2 which was collected in the 4 years preceding PSG studies prior to MAILES4, when the sleep recording was performed.

Objective sleep measurements

In the SHE and MAILES studies, level 2 polysomnography (SHE: EMBLA, Flaga Inc., Reykjavik, Iceland; MAILES: Embletta X100, Embla Systems, Broomfield, CO, USA) was performed. As the studies were performed at different time points different scoring criteria were applied. Within the SHE study, the Chicago criteria (American Academy of Sleep Medicine, 1999) for scoring respiratory events were used and within the MAILES the AASM 2007 alternate criteria were used (Iber et al., 2007). Nonetheless, both cohorts contained the following variables: apnea–hypopnea index (AHI), oxygen desaturation index at 3% (ODI3%), mean and minimal oxygen saturation, position, sleep stages, sleep latency, and total sleep time (TST).

Within the UMEN cohort and the BSN cohort, respectively, a level 3 device was used (UMEN: Eden Tec model 3711 Eden Trace, II multichannel recording system; Eden Tec Corp, Eden Prairie, MN, USA [Redline et al., 1991], and BSN: MESAM IV device; Madaus Medizin-Elektronik, Freiburg, Germany [Stoohs & Guilleminault, 1992; Penzel et al., 1990]). At the time for both UMEN and BSN studies AASM criteria for scoring were not in place. Nonetheless, for both cohorts mean and minimal oxygen saturation were available, and for the sleep and health in men cohort AHI and ODI (3%) were also available, whereas the Busselton cohort recorded a respiratory disturbance index (RDI) (Bearpark et al., 1995; Marshall et al., 2014).

For the current study only OSA related variables that were available in all cohorts (AHI, ODI, and minimal oxygen saturation) were used as risk factors in the analysis.

Registry data

All studies included data on cancer diagnosis (date of diagnosis, cancer type, cancer history). For the individual studies cancer registry linkage was performed as described above, giving a follow-up time of 5–16 years for cohorts included in the main analyses and 5–20 years for all four cohorts. The number of cancer events in each study is shown in Table **S1**.

Statistical analyses

A descriptive analysis was performed to produce tables describing pooled and individual cohorts. Data are presented as *n* (%) or mean ± SD.

The severity of OSA was described both using AHI and ODI, respectively, as AHI describes the number of respiratory events, whereas ODI is a measure of intermittent hypoxia. Both variables were used as continuous and categorical variables. For both AHI and ODI, four categories were created using standard clinical cut points (American Academy of Sleep Medicine, 1999). The following categories were used: none (0–4.9 events/h), mild (5–14.9 events/h), moderate (15–29.9 events/h), and severe (≥30 events/h). The "no sleep apnea" group served as the reference category.

Analyses for different measures of OSA (AHI, ODI, and minimal saturation) as risk factors for cancer incidence (all cancers) as well as cancer mortality (all cancers) were performed using Cox proportional hazards models. For the analysis of cancer incidence and also cancer mortality, we included participants with no cancer diagnosis at the time of the sleep recording ($n = 1376$). Time-to-event (cancer diagnosis and cancer death, respectively) was calculated in years. Time was censored at the time of the cancer registry linkage for each individual study if no cancer event or cancer death, respectively, had occurred.

First univariate associations between measures of OSA and time-to-event outcomes were investigated using Kaplan Meier and associated rank sum test, and analysis was further adjusted for age, sex, BMI, and cohort using Cox regression. We further adjusted for smoking and hypertension. Kaplan–Meier curves were used to produce graphs. In addition, we further assessed a curvilinear shape of the association between OSA severity (AHI and ODI, respectively) and cancer incidence, by performing the analysis using restricted cubic splines (Durrleman & Simon, 1989), with three knots, instead of the linear term for OSA severity.

To further test the effect of age and BMI we also performed age-, and BMI- stratified analyses using Cox proportional hazards modelling. We could not perform a stratified analysis for sex, as the cohorts for the main analysis were either all male or all female, however, we compared the two all-male study with the all-female study. We also explored the addition of daytime sleepiness as this is a common problem in OSA patients and several previous studies within OSA patient cohorts have shown an increased risk of cancer. These analyses were performed using data from SHE and MAILES where there was information on daytime sleepiness (measured as ESS) was available.

Sensitivity analysis

The Busselton cohort has shown previously an increased risk of cancer in moderate to severe OSA (Marshall et al., 2014) and we were able to replicate the results (Table S4). To reduce the risk of the Busselton cohort data driving the results in the direction of an association, we did not include this cohort in the main analysis. However, we performed a sensitivity analysis including the Busselton data. Within this analysis the OSA categories "none" (AHI <5/h), "mild" (AHI 5- < 15/h), and "moderate to severe" (AHI≥15/h) were used as there were few participants within the BSN with severe OSA. Unadjusted and age, sex, BMI, and cohort adjusted models were calculated.

We further performed age, BMI, and sex stratified analyses for cancer development within the pooled cohort.

To further assess the potential effect of cohort and possibly different scoring criteria, and as different cut-offs for AHI in epidemiological studies (i.e., AHI < 10/h as no OSA and AHI = 10–19.9/h as mild OSA) have been suggested (Ruehland et al., 2009), we also performed analysis using restricted cubic splines for each cohort (UMEN, SHE, and MAILES) assessing the effect of AHI and ODI along the full spectrum, respectively, on cancer incidence and cancer mortality.

For all analyses, a value of $p < 0.05$ was considered significant.

Ethical approval

In all studies, the participants had given their informed consent and the Ethics Committees at each site had approved the studies, respectively. The UMEN study and the SHE study and the registry linkage in these studies were approved by the Ethics Board (Etikprövningsnämnden) in Uppsala (Dnr 67/94, decision date 1994-03-16; Dnr 2009/379, decision date 2009-12-16; Dnr 2012/008, decision date 2012-06-29). Approval for the MAILES study was obtained from the Human Research Ethics Committees of the North West Adelaide Health Service /Approval no. 2010054). The Busselton cohort study was approved by the Human Research Ethics Committee of the Health Department of Western Australia (Project no. 2011/60).

The Ethics Board (Etikprövningsnämnden) in Uppsala (Dnr 2020–03564, decision date 2020-09-09) approved the current study.

RESULTS

Table 1 describes the pooled cohort as well as the individual cohorts. The cohort comprised 1067 (63%) men and 400 (27%) women with a mean age of 58.0 (±11.0 SD) years and BMI of 27.9 (±4.5 SD) kg/m^2. Female participants were younger and less overweight compared with participants in the two other studies comprising only men. Overall, the participants mainly had mild to moderate sleep apnea, and the AHI ranged from 0 to 116/h. Approximately 11% had severe sleep apnea (AHI ≥30/h). The two cohorts comprising only men had the highest prevalence of history of hypertension.

OSA and cancer incidence

Within the three pooled cohorts there were a total of 124 cancer events. The most common cancer types were breast ($n = 13$) and gynaecological ($n = 8$) within the female cohort, and prostate ($n_{Total} = 36$) and skin cancers (including melanomas; $n_{Total} = 14$) within the male cohorts. The Kaplan–Meier curve using AHI as the measure of OSA severity is plotted across four commonly used severity levels (Figure 2a). Figure 2b uses the ODI as the exposure variable in four categories instead (Figure 2b). For both measures the relationship was non-significant. Figure 3a,b depicts the results from the splined analysis showing hazard ratios for cancer incidence along the full range of AHI and ODI, respectively. From the analysis of hypoxia measures there was an increased risk of cancer if having a minimal saturation <85%, however, this relationship did not remain after adjusting for confounders (Table 2). Having mild sleep apnea measured as ODI 5–<15/h showed a decreased risk of cancer after adjusting for confounders including smoking and hypertension (Table 2).

OSA and cancer mortality

Within the pooled cohort there were 36 cancer deaths. After adjusting for age, BMI, and sex there was a decreased risk of cancer mortality in people with mild OSA, however, this did not remain after adjusting for smoking and hypertension (Table 3).

Sub-analysis: Effect of age, BMI, sex, and daytime sleepiness and cancer risk in OSA

Overall, we did not observe an increased risk of cancer in any age group for any of the OSA related variables (Table S2.) In the oldest age group (age ≥70 years) there was a decreased risk of cancer in the group with moderate OSA (AHI), however, this relationship did not remain after adjusting for confounders (Table S4).

Table S3 shows the risk of cancer by BMI groups. There was an increased risk of cancer with increasing AHI (as a linear term) in the obese group (BMI ≥30 kg/m^2) which remained significant after adjusting for confounders. Severe OSA was associated with a *decreased* risk in the overweight group after adjusting for confounders. We did not observe any relationship between OSA and cancer incidence in the normal weight group (Table S3).

In the unadjusted analysis there was an increased cancer risk with low minimal saturation in men, however, this relationship did not remain after also adjusting for confounders. There was a decreased HR for cancer development in men with mild OSA (AHI) after adjusting for age and BMI but not in the fully adjusted model. We did not observe any significant effect of OSA on cancer incidence in women (Table S4).

In a stratified analysis we assessed the risk of cancer in those with severe or moderate to severe OSA (AHI ≥30/h and ≥15/h, respectively), with and without daytime sleepiness, and also compared with participants with AHI <30/h or <15/h, respectively. However, we did not see a statistically significant effect of daytime sleepiness (Figure 4a,b).

Sensitivity analysis

Overall, the sensitivity analysis (i.e., including also data from the BSN cohort) showed similar results to the main analysis. Table S5 describes the whole cohort as well as the individual cohorts, when the BSN cohort was also added. The mean age and sex ratio, when also adding

TABLE 1 Description of the study population.

	All studies $n = 1467$ Mean (SD) or n (%)	UMEN $n = 230$ Mean (SD) or n (%)	SHE $n = 400$ Mean (SD) or n (%)	MAILES $n = 837$ Mean (SD) or n (%)
Age (years)	58.0 (11.0)	60.8 (9.5)	50.1 (11.3)	61.0 (11.0)
Sex (% female)	400 (27.0)	0 (0)	400 (100)	0 (0)
BMI (kg/m^2)	27.9 (4.6)	27.5 (4.1)	26.6 (5.0)	28.6 (4.3)
Smoking*				
Never	609 (42.8)	103 (44.8)	189 (47.2)	317 (39.9)#
Ex	586 (41.2)	97 (42.2)	128 (32.0)	361 (45.5)#
Current	229 (16.0)	30 (13.0)	83 (20.8)	116 (14.6)#
Alcohol consumption (g/w)*	55.2 (58.2)†	N/A	55.2 (58.2)	N/A
ESS*	6.8 (4.1)	6.8 (4.0)	8.6 (4.1)	6.0 (3.8)
HDL cholesterol (mmol/L)*	1.4 (0.4)	1.2 (0.3)	1.6 (0.4)	1.3 (0.3)#
Total cholesterol (mmol/L)*	5.4 (1.9)	5.6 (1.0)	5.7 (3.1)	5.2 (1.1)#
Triglycerides (mmol/L)*	1.6 (1.4)	1.5 (1.0)	1.2 (0.7)	1.8 (1.6)#
Glucose (mmol/L)*	5.4 (1.3)	5.2 (1.4)	5.5 (1.1)	5.5 (1.4)#
History of				
Cancer (all types)**	91 (6.2)	16 (7.0)	30 (7.5)	45 (5.4)
Hypertension*	482 (32.9)	113 (49.1)	62 (15.5)	307 (36.7)
Stroke*	8 (1.3)†	6 (2.6)	2 (0.5)	N/A
Angina*	68 (4.7)	25 (10.9)	10 (2.5)	33 (4.0)#
Myocardial infarction*	15 (2.4)†	12 (5.2)	3 (0.8)	N/A
Diabetes*	89 (7.2)†	N/A	18 (4.5)	71 (8.5)
AHI (/h)	14.0 (14.3)	9.2 (10.7)	13.5 (15.4)	15.6 (14.4)
AHI categories				
<5 (/h)	413 (28.2)	104 (45.2)	134 (33.5)	175 (20.9)
5–14.9 (/h)	561 (38.2)	86 (37.4)	131 (32.8)	344 (41.1)
15–29.9 (/h)	330 (22.5)	22 (9.6)	93 (23.2)	215 (25.7)
≥30 (/h)	163 (11.1)	18 (7.8)	42 (10.5)	103 (12.3)
ODI3% (/h)*	11.1 (13.2)	7.0 (9.5)	10.0 (14.1)	12.7 (13.3)
ODI3% categories				
<5 (/h)	595 (40.6)	135 (58.7)	192 (48.1)	268 (32.1)
5–14.9 (/h)	507 (34.6)	64 (27.8)	117 (29.3)	326 (39.0)
15–29.9 (/h)	242 (16.5)	22 (9.6)	57 (14.3)	163 (19.5)
≥30 (/h)	121 (8.3)	9 (3.9)	33 (8.3)	79 (8.4)
Minimal saturation (%)	84.7 (9.3)	83.5 (6.8)	87.6 (6.1)	83.7 (10.8)
T90 (%)*,†	3.8 (9.8)†	N/A	1.8 (5.8)	4.7 (11.0)

Note: Data are described for the whole study population as well as for each individual study, for all participants with data on AHI. Data are presented as mean with standard deviation (SD) or percent (%).

Abbreviations: AHI, apnea–hypopnea index; BSN, Busselton cohort; BMI, body mass index; ESS, Epworth sleepiness scale; HDL, high density lipoprotein; MAILES, Men Androgen Inflammation Lifestyle Environment and Stress Cohort; ODI, oxygen desaturation index; SHE, Sleep and health in women; T90, percent of night with oxygen saturation < 90%; UMEN, Uppsala Sleep and Health in Men cohort.

*For the current study history of diabetes and T90 was not available for UMEN, history of stroke and myocardial infarction was not available for MAILES, and alcohol consumption was not available in UMEN and MAILES.

**Cancer history based on cancer diagnosis date in relation to study entry date.

#From MAILES2 data.

†Calculated from available data.

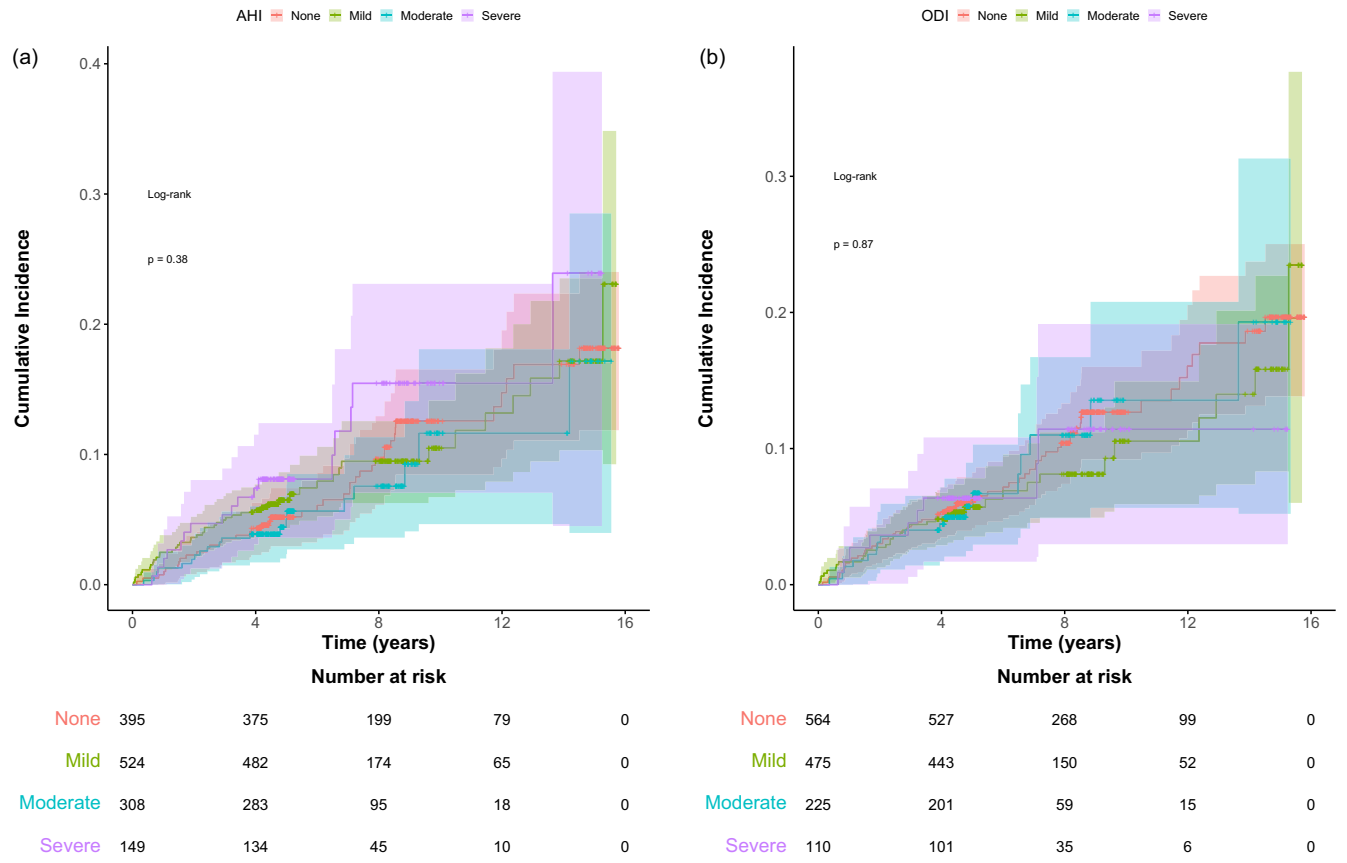

FIGURE 2 (a) OSA severity, according to AHI groups, in relation to cancer incidence, in the pooled cohort (UMEN, SHE, and MAILES). Results from Cox regression modelling. AHI, apnea–hypopnea index; 'none' indicates AHI <5/h, 'mild' indicates AHI 5–14.9/h, 'moderate' indicates AHI 15–29.9/h, and 'severe' indicates AHI ≥30/h. (b) OSA severity, according to ODI groups, in relation to cancer incidence, in the pooled cohort (UMEN, SHE, and MAILES). Results from Cox regression modelling. ODI, oxygen desaturation index; 'none' indicates ODI <5/h, 'mild' indicates ODI 5–14.9/h, 'moderate' indicates ODI 15–29.9/h, and "severe" indicates ODI ≥30/h.

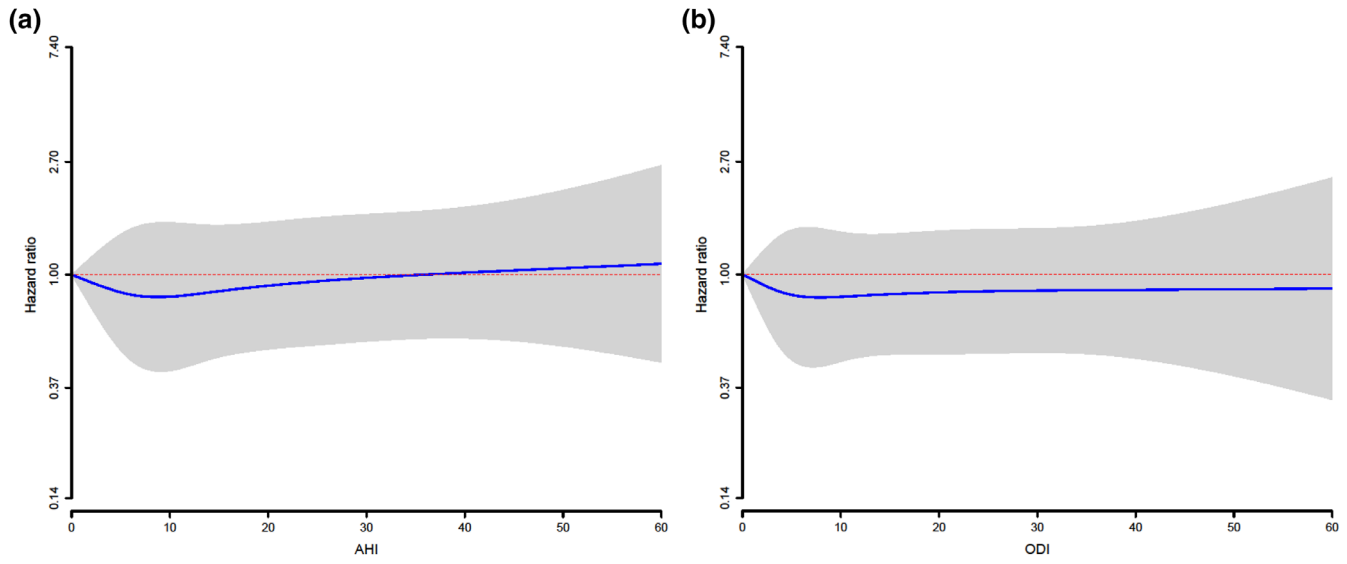

FIGURE 3 (a) Hazard ratio of cancer incidence for AHI using AHI = 0 as the reference, in the pooled cohort (UMEN, SHE, and MAILES). Results from the restricted cubic splined analysis of AHI and cancer incidence. AHI, apnea–hypopnea index. (b) Hazard ratio of cancer incidence for ODI using ODI = 0 as the reference, in the pooled cohort (UMEN, SHE, and MAILES). Results from the restricted cubic splined analysis of AHI and cancer incidence. ODI, oxygen–desaturation index.

TABLE 2 OSA measures and risk of cancer.

	Model 1		Model 2		Model 3	
	Unadjusted		Adjusted for age, sex, and BMI, and cohort		Adjusted for age, sex, BMI, cohort, smoking, and hypertension	
	n = 1374		*n* = 1364		*n* = 1324	
	n (events) = 124		*n* (events) = 123		*n* (events) = 124	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
AHI (events/h)	1.00 (0.99; 1.02)	0.61	1.00 (0.98; 1.01)	0.80	1.00 (0.98; 1.01)	0.78
ODI (events/h)	0.998 (0.99; 1.01)	0.85	0.99 (0.97; 1.01)	0.32	0.99 (0.97; 1.01)	0.29
Sleep apnea severity according to AHI						
No sleep apnea (AHI <5/h)	REF		REF		REF	
Mild sleep apnea (AHI 5–<15/h)	1.03 (0.68; 1.58)	0.88	0.82 (0.53; 1.27)	0.38	0.85 (0.55; 1.32)	0.48
Moderate sleep apnea (AHI 15–<30/h)	0.82 (0.48; 1.40)	0.47	0.62 (0.35; 1.11)	0.11	0.64 (0.36; 1.14)	0.13
Severe sleep apnea (AHI ≥30/h)	1.44 (0.82; 2.55)	0.21	1.01 (0.55; 1.32)	0.98	0.99 (0.54; 1.85)	0.99
Sleep apnea severity according to ODI						
No sleep apnea (ODI <5/h)	REF		REF		REF	
Mild sleep apnea (ODI 5–<15/h)	0.84 (0.55; 1.27)	0.40	0.63 (0.41; 0.97)	0.03	0.63 (0.41; 0.98)	0.04
Moderate sleep apnea (ODI 15–<30/h)	0.95 (0.56; 1.67)	0.86	0.67 (0.38; 1.18)	0.15	0.68 (0.39; 1.20)	0.19
Severe sleep apnea (ODI ≥30/h)	0.95 (0.47; 1.92)	0.89	0.69 (0.33; 1.44)	0.32	0.66 (0.31; 1.38)	0.27
Minimum saturation <85%	1.53 (1.08; 2.19)	0.02	1.05 (0.72; 1.54)	0.79	1.05 (0.72; 1.54)	0.80

Note: Results from regression modelling and adjusting for potential confounders. Results are presented as hazard ratio (HR) with 95% confidence intervals (CI) and *p*-values for the pooled cohort.

TABLE 3 OSA measures and cancer mortality.

	Model 1		Model 2		Model 3	
	Unadjusted		Adjusted for age, sex, and BMI, and cohort		Adjusted for age, sex, BMI, cohort, smoking, and hypertension	
	n = 1465		*n* = 1455		*n* = 1412	
	n (events) = 36		*n* (events) = 36		*n* (events) = 36	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
AHI (events/h)	0.997 (0.97; 1.02)	0.85	0.996 (0.97; 1.03)	0.79	0.997 (0.97; 1.03)	0.85
ODI (events/h)	0.98 (0.95; 1.02)	0.33	0.98 (0.94; 1.02)	0.24	0.98 (0.94; 1.02)	0.26
Sleep apnea severity according to AHI						
No sleep apnea (AHI <5/h)	REF		REF		REF	
Mild sleep apnea (AHI 5–<15/h)	0.55 (0.24; 1.26)	0.16	0.42 (0.18; 0.94)	0.04	0.44 (0.19; 1.02)	0.06
Moderate sleep apnea (AHI 15–<30/h)	0.95 (0.38; 2.34)	0.90	0.83 (0.33; 2.17)	0.72	0.91 (0.35; 2.35)	0.84
Severe sleep apnea (AHI ≥30/h)	1.08 (0.36; 3.27)	0.89	0.87 (0.27; 2.79)	0.81	0.91 (0.28; 2.94)	0.87
Sleep apnea severity according to ODI						
No sleep apnea (ODI <5/h)	REF		REF		REF	
Mild sleep apnea (ODI 5–<15/h)	0.61 (0.27; 1.39)	0.24	0.45 (0.20; 1.04)	0.06	0.45 (0.19; 1.02)	0.06
Moderate sleep apnea (ODI 15–<30/h)	1.20 (0.48; 3.02)	0.70	0.97 (0.37; 2.58)	0.96	1.02 (0.38; 2.73)	0.97
Severe sleep apnea (ODI ≥30/h)	0.36 (0.05; 2.72)	0.33	0.34 (0.04; 2.64)	0.30	0.34 (0.04; 2.65)	0.30
Minimum saturation <85%	1.63 (0.85; 3.15)	0.14	0.76 (0.38; 1.53)	0.44	0.73 (0.36; 1.49)	0.39

Note: Results from regression modelling and adjusting for potential confounders. Results are presented as hazard ratio (HR) with 95% confidence intervals (CI) and *p*-values for the pooled cohort.

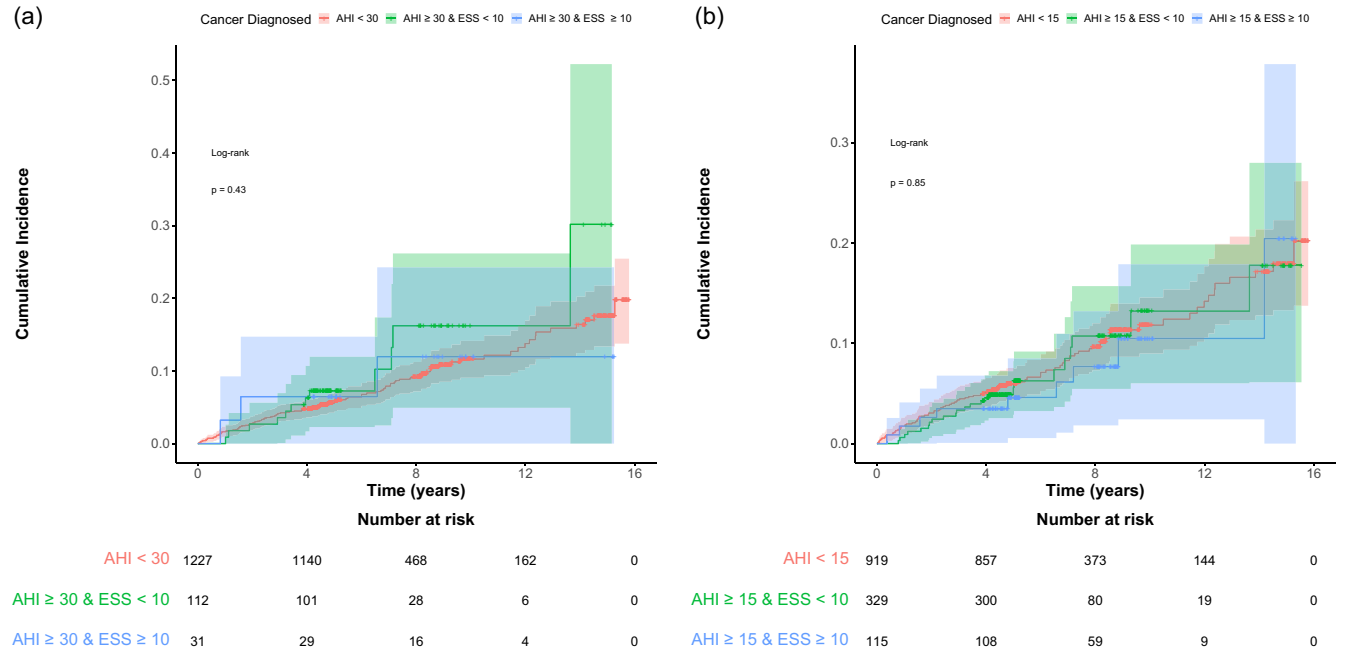

FIGURE 4 (a) Severe OSA with and without daytime sleepiness (ESS), in relation to cancer incidence, in the pooled cohort (UMEN, SHE, and MAILES). Results from Kaplan–Meier estimate. (b) Moderate to severe OSA with and without daytime sleepiness (ESS), in relation to cancer incidence, in the pooled cohort (UMEN, SHE, and MAILES). Results from Kaplan–Meier estimate.

the BSN cohort, were similar to the results from main analysis. Participants in the BSN cohort as in the SHE study were somewhat younger and less overweight compared with participants in the two other studies. Overall, the participants mainly had mild to moderate sleep apnea, and within the cohort ~9% had severe sleep apnea (Table S5).

A numerically increased number of cancer events was seen in the moderate to severe OSA group, however, the increased risk was not significant (Figure S1). There was an increased risk of cancer if having a minimal saturation <85%, however, this relationship did not remain after adjusting for confounders (Table S6).

We assessed the effect of cohort on the relationship between derived measures of OSA and cancer risk. As shown previously (Marshall et al., 2014) there was a significant increase cancer risk in the Busselton cohort, if having moderate to severe OSA, not only when adjusting for age, BMI, smoking, and alcohol but also other confounders (including several medical conditions and blood samples). This was not observed for the other cohorts in unadjusted or (age, sex, and BMI) adjusted analysis (Table S7). Within the pooled cohort there was a significantly increased HR for cancer in the unadjusted analysis for minimal saturation <85%, however, this was not significant in the unadjusted analysis. Adjusting also for study site did not change the results from the adjusted analysis for any of the OSA variables (Table S7). The effect of AHI and ODI along the full spectrum, respectively, on cancer incidence and cancer mortality, for each individual cohort (UMEN, SHE, and MAILES) showed wide confidence intervals in all cohorts (Figures S2–S5).

We did not observe an effect of age (Table S8), however, for BMI there was a significantly increased risk of cancer with increasing AHI in the obese group (BMI ≥30 kg/m^2) also when adjusting for age and sex (Table S9). In addition, moderate to severe OSA and also minimal saturation <85% was associated with an increased cancer risk in the obese group in the unadjusted analysis but not after adjusting for age and sex. In the overweight group there was a significantly decreased cancer risk with increasing ODI (Table S9). This was not seen in the normal weight or obese group. We did not find any relationship between OSA and cancer incidence in the normal weight group. Within males, there was an increased cancer risk with increased OSA severity (AHI) in the unadjusted analysis, however, this relationship did not remain after also adjusting for age and BMI (Table S10). We did not observe any relationships in women (Table S10).

DISCUSSION

This pooled, community based prospective cohort data did not demonstrate an overall clear pattern at a univariate or multivariate level to suggest that sleep apnea increases the risk of cancer incidence or mortality in cohorts free from clinical referral bias. However, our confidence intervals remain wide, meaning that we have also not shown conclusively that a sleep apnea does not have some small effect on cancer. Investigating OSA subtypes, we did not find the posited effect in phenotypically "sleepy" patients. In the obese group, AHI was associated with an increased risk of cancer. This observation must be considered in the context of sub-analyses where, for instance, we saw that having a high ODI in overweight patients was associated with a notably lowered cancer risk. We did not see an increased cancer risk in sex or age stratified analysis after adjustments.

Previous studies on OSA and cancer have been conducted mainly in clinical cohorts of patients diagnosed with OSA, or have been animal studies mimicking OSA as sleep fragmentation or intermittent hypoxia (Almendros et al., 2013; Campos-Rodriguez et al., 2013; Chen & Hwang, 2014; Kendzerska et al., 2014; Martinez-Garcia, Campos-Rodriguez, et al., 2014; Nieto et al., 2012). One of the first studies on the relationship between sleep-disordered breathing and cancer was from the Wisconsin Sleep Cohort Study (WSC) in which a population of 30–60-year-old men and women living in south-central Wisconsin were selected from payroll records of several Wisconsin state agencies with job titles ranging from unskilled to professional (Nieto et al., 2012). Within the WSC study a significant trend for increased cancer mortality (at 22 years follow-up) was seen with the highest risk for participants with severe SDB (~4% of the participants) both for respiratory events and hypoxia measures (Nieto et al., 2012). Nonetheless, the confidence intervals were very wide (HR ~2–13 and 2.5–28) indicating a large uncertainty within the measurement.

In our current study, increased OSA, as measured by AHI or ODI, was not associated with an increased risk of cancer either in unadjusted or adjusted analyses. In addition, we did not demonstrate an increased risk of cancer mortality for any of the measured OSA variables. In line with our findings, some previous studies also show no relationship between OSA and cancer (Justeau et al., 2022; McEvoy et al., 2016; Sillah et al., 2019). Nonetheless, one possible explanation for the discrepancies between previous studies (Campos-Rodriguez et al., 2013; Chang et al., 2014; Chen & Hwang, 2014; Kendzerska et al., 2021; Pataka et al., 2019) and the current results, is that the existing literature is predominantly drawn from clinical cohorts. Patient cohorts differ from population or community cohorts, as seen in this study, as patient cohorts include people who have sought health care. Within the current study, in an attempt to mimic patient cohorts, we tested the association between OSA and cancer incidence with and without daytime sleepiness, as this is a common complaint in OSA patients. We did not observe an increased risk in sleepy OSA participants. On the other hand, compared with the results from Kendzerska et al. (2021), it is possible, given our confidence limits for severe OSA, that there may be an increased risk of cancer which would align with existing findings in patient cohorts, but that our community-based cohort is too small. We had a much lower baseline prevalence of severe OSA, which may also explain why we did not detect this association. The increased risk seen previously in patient cohorts (Campos-Rodriguez et al., 2013; Chang et al., 2014; Chen & Hwang, 2014) might indicate that treating OSA effectively could reduce cancer incidence. However, emergent studies of CPAP use in such cohorts indicate no increase or decrease in cancer risk in people treated with CPAP (Justeau et al., 2022). Careful reading of the supplements of the SAVE study also indicates that there was no change in the risk of neoplasms caused by CPAP treatment (McEvoy et al., 2016) (Supplementary Appendix).

There was an indication, within the current study, that mild intermittent hypoxia (as measured by ODI) decreases the risk of cancer and mild intermittent hypoxia was also associated with a decreased risk of cancer in the overweight group after adjustments, whereas this was not seen in the normal weight group. In adjusted analysis, mild to moderate OSA (as measured by AHI) was also associated with decreased cancer incidence. Some earlier studies have reasoned around the protective effects of OSA or traits of OSA (Chen et al., 2021), as OSA patients have been shown to have increased coronary collateral circulation (Lavie & Lavie, 2010; Steiner et al., 2010), and to upregulate cardioprotective pathways (Aronson et al., 2018; Sanchez-de-la-Torre et al., 2018). Further, some studies show OSA patients to be less likely to have a poor outcome for subarachnoid haemorrhage compared with non-OSA patients, despite having several comorbidities (Kaculini et al., 2020). In line with this, a question that arises is whether the decreased risk of cancer in the mild to moderate OSA group is indicative of a protective mechanism that possibly is negated by weight gain. This warrants further investigation in studies specifically targeted to this question, and the association between OSA hypoxia and cancer development needs further investigation in large population-based and patient cohorts. The need to further investigate the risk of cancer and cancer mortality in OSA in large cohorts is further supported by the wide confidence intervals for both AHI and ODI, respectively, depicted in the splined analysis in each of the pooled cohorts in the current study.

We could not see any clear overall effect of age or sex on the risk of cancer for any of the OSA variables after adjustments. In unadjusted analysis low minimal saturation (sat <85%) was shown as a risk factor for cancer in men, however, this did not remain when adjusting for confounders. We could not show an increased risk in women in the main analysis and although the sensitivity analysis yielded borderline significant relationships for AHI in women, the relationship did not remain after adjustments. In previous studies in patient cohorts a higher prevalence of cancer has been shown in female OSA patients (Pataka et al., 2019) and in their Spanish patient population Campos-Rodriguez et al. showed increased cancer incidence in men but not women with increasing hypoxia (Campos-Rodriguez et al., 2013). In this study the authors state that as >60% of the entire cohort were men, and some of the most common cancers were sex-dependent, it could not be excluded that the sex differences in cancer incidence reflected a lack of statistical power for women or the particular profile of our cohort (Campos-Rodriguez et al., 2013). Some patient cohorts have shown an increased cancer mortality in OSA patients in younger patients (<65 years) (Martinez-Garcia, Campos-Rodriguez, et al., 2014). In the current study there was no overall increased cancer risk in any age groups and no increased cancer mortality. Future population-based or patient cohort studies need to further assess the possible risk of cancer from OSA based on age.

One previous population-based study shows that OSA symptoms, that is, snoring, were not associated with an increased risk of cancer (Christensen et al., 2013). However, after the addition of daytime sleepiness to the model there was an increased risk (Christensen et al., 2013). This may be the reason why selected cohorts, such as patient cohorts, have shown an increased risk of cancer in OSA. In addition, sleep duration and sleep fragmentation, respectively, have

also been linked to an increased cancer risk or cancer development in humans (Lv et al., 2022; Peeri et al., 2022) and in animal models (Almendros et al., 2013; Cao et al., 2015). Within the current study we could not show an increased cancer risk when comparing individuals with severe OSA (AHI ≥30/h), with and without daytime sleepiness, and individuals with AHI <30/h.

This is the first community-based study using pooled data from international cohorts where objectively measured OSA from a randomly selected population is available. Within our main pooled cohort, we had ~11% with severe OSA, which might have left us somewhat underpowered. Previous clinical cohorts of newly diagnosed OSA patients or cohorts with OSA patients treated with CPAP, have a higher prevalence of severe OSA as well as obesity (Campos-Rodriguez et al., 2013; Kendzerska et al., 2014; Martinez-Garcia, Campos-Rodriguez, et al., 2014; Pataka et al., 2019). This difference in prevalence of severe OSA within cohorts may account for the shown relationships between OSA and cancer in the previous studies, if it is indeed real, and not caused by clinical referral bias or selective reporting. It is also important to acknowledge that patients with OSA are likely not the same type of cohort as participants randomly selected and included in a population-based study, as the cohorts included in the present study, and this may account for the difference in results compared with previous studies. In an attempt to simulate a more clinical cohort, that is, adding daytime sleepiness to the factor of severe OSA in a stratified analysis, we could however, not yield results similar to patient cohort results.

Our study strengths include a large cohort of population-based randomly recruited participants and the objective assessment of OSA. Cancer was assessed through registry-linkage using national registries with high quality data. We also had the possibility of adjusting for obesity and smoking status in addition to age and sex. Nonetheless, there are several limitations when interpreting our results. First, the range of the follow-up times for the individual studies is fairly wide. As cancer takes time to develop, it is possible that the overall follow-up time was too short, even with a large cohort. Second, although the cohort comprised more than 1400 individuals (and in the sensitivity analysis nearly 1800 individuals) we had few cancer events and also deaths. This also prevents us from a possible lead time between OSA diagnosis and cancer event or mortality. It is likely that we would need an even larger community-based cohort to truly see the effect of OSA on cancer risk and cancer mortality. Globally, there are to date likely no more than 10 population or community-based cohort studies with comprehensive sleep measurement to allow for this, and future research needs to address this issue. Third, we pooled data from Swedish and Australian cohorts, which may to some extent limit generalisability. Fourth, although OSA was objectively measured in all studies, due to the fact that the individual studies were conducted at different points in time different types of recording devices were used. In addition, scoring criteria for the scoring of sleep apnea events have changed over time (Penzel et al., 2015) leading to a risk of changing definitions affecting diagnostic specificity depending on when a study was performed and recordings scored. Unfortunately, to date there are too few population-based studies with objectively measured OSA and data on cancer events and cancer mortality, to firmly assess trends in results relating to different scoring criteria. In the current study ODI3% was used as this was available for all pooled cohorts. It is possible that the cancer risk could be more visible with 4% desaturation criteria or the time with saturation <90% (T90), however, we did not have that for all cohorts.

In conclusion, within this combined cohort of individuals selected into community-based studies in different sites, we did not see a significant association between OSA and incident cancers or in specific age or sex groups. There was a small increased risk of cancer in the subsample of obese individuals which may to some extent explain the previously shown association between OSA and cancer in patient populations but this observation should be treated with caution. However, the confidence limits in our analyses remain wide. For future studies we may need to find and then combine every community-based cohort study that can answer the question to provide a definitive answer to question on risk of cancer from OSA in the general population.

AUTHOR CONTRIBUTIONS

Jenny Theorell-Haglöw: Conceptualization; methodology; data curation; visualization; funding acquisition; writing – original draft; writing – review and editing; validation; investigation; formal analysis; resources. **Xingwu Zhou:** Formal analysis; writing – review and editing; visualization. **Gary Wittert:** Writing – review and editing; resources; data curation; methodology; investigation. **Robert Adams:** Writing – review and editing; resources; data curation; methodology; investigation. **Sarah Appleton:** Investigation; methodology; data curation; resources; writing – review and editing. **Amy Reynolds:** Writing – review and editing; resources; methodology; data curation; investigation. **Mirjam Ljunggren:** Investigation; methodology; data curation; resources; writing – review and editing. **Nathaniel Marshall:** Conceptualization; investigation; writing – review and editing; resources; methodology; data curation; validation.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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