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Early View

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Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy

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Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy.

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"Take home" message: In a multicentre-based cohort of patients with mild-to-severe obstructive sleep apnoea, sustained and adherent CPAP therapy was not associated with a reduction in all-cancer incidence after a median follow-up time of 5.4 years.

Abstract

Background: Increasing evidence suggests that obstructive sleep apnoea (OSA) contributes to cancer risk; however, limited data are available on the impact of continuous positive airway pressure (CPAP) therapy on cancer incidence. We aimed to determine whether adherence to CPAP therapy is associated with a reduction in all-cancer incidence compared to non-adherent patients with OSA.

Methods: The study relied on the data collected by the multicentre study *Pays de la Loire Sleep Cohort,* linked to health administrative data, such as to identify new-onset cancer. We included patients who were prescribed CPAP for OSA, with no history of cancer before the diagnostic sleep study or during the first year of CPAP. Patients with documented CPAP use for at least 4h per night were defined as adherent. Those who discontinued or used CPAP less than 4h at night constituted the non-adherent group. A propensity-score inverse probability of treatment weighting analysis was performed to assess the effect of CPAP adherence on cancer risk.

Results: After a median [inter-quartile range] follow-up of 5.4 [3.1-8.0] years, 437 (9.7%) of 4,499 patients developed cancer, 194 (10.7%) in the non-adherent group (n=1,817) and 243 (9.1%) in adherent patients (n=2,682). The final weighted model showed no significant impact of CPAP adherence on all-cause cancer risk (sub distribution hazard ratio [95% confidence interval]): 0.94 [0.78; 1.14]).

Conclusions: Adherence to CPAP therapy in OSA patients was not associated with a reduction in all-cancer incidence. Whether adherent CPAP therapy of OSA might reduce the risk of specific cancer sites should be further evaluated.

Key words

Obstructive sleep apnoea, hypoxemia, cancer, continuous positive airway pressure

Introduction

With nearly 1 billion adults affected worldwide, obstructive sleep apnoea (OSA) is a highly prevalent disease characterized by recurrent episodes of complete or partial upper airway obstruction during sleep [1]. There is increasing evidence from population-and clinic-based cohort studies that the severity of OSA and sleep-related hypoxemia may adversely affect both overall cancer as well as selective cancers incidence [2–8]. Data from experimental studies using cell cultures or animal models suggest that intermittent hypoxia (IH) and sleep fragmentation (SF), the hallmark features of OSA, might promote oncogenesis as well as enhance tumour growth and metastasis. Several putative intermediate mechanisms invoked by OSA could link IH and SF to tumour growth, invasion and metastasis, and include sympathetic over-activity, systemic inflammation, oxidative stress, angiogenesis, and immunological alterations (see reference [9] for comprehensive review). Among the studies that have examined the links between specific cancer sites and OSA, cutaneous malignant melanoma has received the greatest attention, with most studies demonstrating a significant relationship between the prevalence, incidence, or aggressiveness of melanoma and OSA severity [10]. Limited by relatively small sample sizes and multiple comparisons, secondary analyses of large retrospective cohort studies have found significant associations of OSA and nocturnal hypoxia with common cancer sites such as lung, breast, colorectal, kidney, and smoking related cancer [7, 8, 11, 12]. A major piece of the puzzle that is yet to be addressed is whether continuous positive airway pressure (CPAP), the first line of therapy for OSA, will reduce cancer risk. The problem when trying to answer this questions lies in the fact that it is now impossible to perform an ethical randomized controlled trial of CPAP versus no treatment in patients with symptomatic OSA over a long period of time [13]. To circumvent this issue, propensity score matching of real-world observational data to estimate causal treatment effects represents a promising method for overcoming the sample selection biases described recently in randomized controlled trials of cardiovascular endpoints in the context of OSA [13].

We hypothesized that sustained and adherent CPAP therapy of OSA might be associated with a reduction in cancer risk. To address this question and properly account for confounders, we conducted a propensity-score inverse probability of treatment weighting (IPTW) analysis using observational data from the multicentre clinic-based *Pays de la Loire Sleep Cohort*.

Methods

The study relied on the data collected by the multicentre longitudinal study *Pays de la Loire Sleep Cohort*, which was further linked with data from the French administrative health care database (SNDS). The SNDS contains individualized, anonymous, and comprehensive data on healthcare spending reimbursements, and the linkage process between the *Pays de la Loire Sleep Cohort* and the SNDS database was conducted as previously reported (see references [8, 14] for details). All patients with newly diagnosed OSA (apnoea-hypopnea index of at least 5 events/h on Type 3 home sleep apnoea testing [HSAT] or in-lab polysomnography [PSG]) who were prescribed CPAP for at least one year, and who also had available SNDS data and were included in the cohort between May 15, 2007 and December 31, 2018, were eligible for inclusion the present study. Patients were excluded if they had been diagnosed with cancer at any time before the diagnostic sleep study or during the first year of CPAP therapy. Approval was obtained from the University of Angers Ethics Committee and the 'Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé' (CCTIRS ; 07.207bis). All patients had previously given their written informed consent to participate in research.

Baseline evaluation

Each patient enrolled in the *Pays de la Loire Sleep Cohort* completed surveys including anthropometric data, smoking habits, alcohol consumption, medical history, and medication use (see Table S1 for the definition of covariates). Patients were evaluated by either HSAT or PSG, according to pre-test clinical probability of OSA [15]. Respiratory events were scored manually using recommended criteria [16].

CPAP therapy initiation and follow-up

According to the criteria defined by the French National Health Insurance, CPAP therapy was prescribed in patients with severe OSA and in those with mild-to-moderate OSA and cardiovascular comorbidities or those with severe daytime sleepiness. As previously described, a single home respiratory care company (ASTEN Santé, Beaucouzé, France) was involved in CPAP device delivery and in the follow-up support program [17]. Follow-up visits with the sleep specialist took place at 5 months, at 12 months, and then at least annually. Objective daily PAP use was monitored at each follow-up visit based on the digital downloads from the CPAP devices and documented in the database.

Patients who had not discontinued CPAP and used it on average 4h or more per night during the entire follow-up period were assigned to the CPAP adherent group. Patients who stopped the use of CPAP, whatever the stoppage time was during the follow-up period, or those who used the device on average less than 4h per night, including patients with a zero or a near zero CPAP adherence, constituted the non-adherent group. To take into account the immortal time bias [18], a sensitivity analysis was performed by considering only the first year of treatment to define CPAP adherence or non-adherence.

Outcome definition

The primary outcome was defined as the first occurrence of an all-cause malignant neoplasm at any time between the end of the first year of CPAP therapy and the censor date. As described previously [8], the occurrence of cancer was identified based on the French Hospital Discharge database (Programme de Médicalisation des Systèmes d'Information [PMSI]), using an algorithm based on primary, related or associated PMSI diagnostic codes of malignancies (ICD-10: C00-C97, D00-D09, D37-D463). Patients who did not develop cancer were censored at the date of death or at the final follow-up date (December 31, 2019). Secondary analyses were conducted by considering the most frequent cancer types (lung, breast, colon, prostate) while all other tumour sites were considered together.

Statistical analyses

Variables were described by using number and percentage for qualitative variables and median and interquartile range for quantitative variables. Comparisons between groups (CPAP adherent *versus* non-adherent) were performed by using chi square test for qualitative variables and non-parametric Mann-Whitney test for quantitative variables.

Missing values were considered as occurring randomly, and therefore, multiple imputations were performed in 20 datasets for missing values that were introduced in the multivariable model. Fully conditional regression and Monte-Carlo Markov Chains were performed for variable imputations, and datasets were merged following Rubin's rules to obtain the final results (see Table S2 for the comparisons between imputed and non-imputed datasets).

The cancer incidence values were computed in person-years, and a Poisson estimation of the confidence interval was calculated.

To assess the effect of CPAP adherence on cancer risk, we used a causal inference method with IPTW estimator. This method has been extensively described elsewhere [19–21]. Briefly, the principle is to weigh each patient by the inverse of his/her probability of being exposed to the treatment (i.e. adherent CPAP therapy in our study). This probability is assessed by using a propensity score in which all measured confounders are considered. Weighing each patient in the final model by the inverse of the propensity score (IPTW) allows to constitute a pseudo-population in which each individual is his/her own control on the basis of measured confounders. Two steps were considered: the first one was to assess the probability of being CPAP adherent by using a non-parsimonious logistic regression. Variables introduced into the model were both related to CPAP adherence or to the outcome to avoid instrumental variables. The final logistic regression model is presented in Table S3. Weights were computed by using the inverse of the CPAP adherence probability, and stabilization was performed to limit the positivity assumption. Verifying weight distributions assessed the positivity assumption (Figure S1), and standardized differences were computed to control for balance for confounders after weighting (Figure S2). The second step aimed to assess the impact of CPAP adherence on the risk of

all-cause cancer. This was performed by using weighted patients in a Finn and Gray time-to-event model to account for death as competing risk [22]. An unadjusted weighted cumulative incidence function (CIF) was computed to illustrate the difference between groups for the primary objective and the log rank test was used to compare both CIF. The final result was the sub-distribution hazard ratio (sdHR). Sub-group analyses were considered to account for CPAP adherence threshold of 6 hours, OSA severity (categories of OSA severity (i.e., mild, moderate, severe), tertiles of 3% oxygen desaturation index [ODI] and quartiles of percent night-time with oxygen saturation <90% [T90]), categories of age and body mass index [BMI], and various cancer sites. The same method was applied for all secondary objectives, by computing new weights for each model. A sensitivity analysis was performed by introducing CPAP adherence as a continuous variable in the model. A threshold of 5% was considered as significant. Statistical analyses were performed using statistical software (SAS v9.4, SAS, Inc., New-York).

Results

Population description

Out of 6,803 eligible patients, 1,617 were not linked to SNDS dataset and 651 were diagnosed with cancer before the diagnostic sleep study was performed, or during the first year of CPAP therapy. In addition, 36 subjects died during the first treatment year (Figure 1). Thus, the final study sample comprised 4,499 patients with a median [interquartile range] age of 63 [54-72] years. As shown in Table 1, the study population consisted of typical patients with OSA (median AHI: 37 [27-52] events/h), predominantly male (69%), obese or overweight (median BMI: 31 [27-36] kg/m²), frequently presenting cardiovascular and metabolic comorbidities. During follow-up, the median CPAP adherence was 5.9 [4.1-7.2] hours/night (see Figure S3 for the distribution of CPAP adherence). In accordance with previous data from the *Pays de la Loire Sleep Cohort* [17], 2,682 patients (60%) were CPAP adherent, and 1,817 constituted the non-adherent group (median daily CPAP use: 6.7 [5.7-7.6] and 3.0 [2.1-3.6] hours respectively). Compared to the adherent group, non-adherent patients were younger,

had lower BMI, and less severe OSA. Significant intergroup differences were also observed for tobacco and alcohol consumption, socio-economic status and cardiovascular comorbidities (Table 1).

Cancer incidence during follow-up

After a median follow-up duration of 5.4 [3.1-8.0] years, 437 patients (9.7%) received a diagnosis of cancer, 194 (10.7%) in the non-adherent group and 243 (9.1%) among CPAP adherent patients (p=0.03). Overall, the all-cancer incidence rate was 16.4 cases by 1000 person-year (95%CI [14.8-18.0]), with an incidence of 17.5 [15.0-20.1] per 1000 person-year in the non-adherent group, and 15.6 [13.7-17.7] per 1000 person-year in the adherent group. Figure 2 shows the incidence of different cancer sites according to CPAP adherence.

Primary objective

The weighted cumulative incidence function is shown in Figure 3. The final weighted model (Table S4) showed the absence of any significant impact of CPAP adherence on all-cause cancer risk, with a sdHR [95% confidence interval] of 0.94 [0.78; 1.14], p=0.52. The un-weighted model showed a similar result. Sensitivity analysis considering CPAP adherence in the first year of follow-up showed a non-significant impact of CPAP adherence on the risk of cancer: sdHR: 1.13 [0.92; 1.38]. Sub-group analyses according to age, BMI and OSA severity revealed no significant effects of CPAP adherence on all-cause cancer (Figure 4). By comparing adherence ≥ 6 hours vs. <4h, there was no significant difference (sdHR: 1.04 [70.84; 1.30], p=0.71). However, there was a trend toward a significantly lower all-cancer incidence in CPAP adherent patients with more severe nocturnal hypoxemia during the diagnostic test (sdHR = 0.78 [0.58; 1.05] and 0.79 [0.60; 1.05] for the highest tertile of ODI and quartile of T90 respectively). By considering CPAP adherence as continuous variable, there was no significant effect of CPAP adherence on all-cause cancer risk: sdHR: 1.01 [0.97; 1.07], p=0.55.

Secondary objective

The analyses for specific cancers showed no significant association between CPAP adherence and specific cancer sites (Figure 5). However, there was a trend toward a significantly lower incidence of lung cancers in CPAP adherent patients (sdHR = 0.49 [0.22; 1.09]).

Discussion

Using IPTW estimations to control for confounding factors within a large multicentre clinic-based cohort of patients with OSA, we found that CPAP adherence did not reduce all-cancer incidence when compared to non-adherent patients. A borderline statistically significant reduction in lung cancer risk was observed in CPAP adherent patients.

Increasing evidence suggests that OSA and its nocturnal hypoxia-related consequences may contribute to the risk of cancer development and tumour progression [9]. However, limited data are available regarding the potential impact of CPAP therapy on cancer risk. Gharib et al. comprehensively profiled the circulating leukocyte bulk transcriptome of patients with severe OSA. Despite modest changes in global gene expression, the authors found that many of the perturbed pathways mapped to neoplasia-related gene pathways. Furthermore, effective CPAP therapy appeared to downregulate the coordinated expression patterns of these cancer-related pathways [23]. More recently, Hernández-Jiménez et al. demonstrated that patients with untreated OSA have altered immune cell phenotypes, particularly involving monocytes and natural killer cells. The impaired immune phenotypes did not persist in patients with OSA who had received at least 6 months of CPAP, implying the presence of a moderating role associated with effective OSA therapy [24]. To date, there is no clinical evidence that treatment with CPAP reduces the incidence or progression of cancer in patients with OSA. Most of the previous studies that have analysed the association between OSA and cancer incidence or mortality were not able to evaluate the impact of effective OSA therapy due to the lack or scarcity of data on CPAP prescription and usage [2, 3, 7, 11, 25–28]. Our recent study involving the *Pays de la Loire Sleep Cohort* showed an association between the severity of nocturnal hypoxemia and all-cancer incidence [8]. It is worth noting that the association appeared stronger when CPAP adherent patients were excluded from the analysis. Conversely, there was no association between nocturnal hypoxemia and cancer risk in patients receiving adequate CPAP therapy, raising the possibility of a protective effect afforded by adherent CPAP treatment. A similar finding was reported previously in cohort studies that evaluated the association of OSA and cancer mortality [2, 4]. However, CPAP adherence in the present

study was not associated with a significant reduction in all-cancer incidence, even though the association became stronger in sub-groups with more severe nocturnal oxygen desaturations as assessed by the ODI and the T90. This finding is consistent with previous studies showing that indices of nocturnal hypoxemia are stronger predictors of cancer incidence or mortality than the AHI [5, 8, 11]. However, indices of nocturnal hypoxemia, particularly T90, might be not only related to OSA but also to the effects of smoking and comorbid lung diseases. Several factors might explain the lack of effects of adherent CPAP therapy of OSA on all-cancer incidence. Being a chronic disease, it is likely that patients were exposed to intermittent hypoxia and other related consequences of OSA for many years before starting CPAP therapy. Furthermore, cancer causation is multifactorial and modelling studies have suggested that over 60% of tissue cancer burden may be due to factors that are intrinsic to human cell biology and thus, not modifiable [29].

Previous clinic-based cohort studies have demonstrated a significant association between sleep-related breathing disorders and the prevalence or incidence of smoking-related cancers [8, 11, 30]. Nocturnal hypoxemia may be a key variable linking OSA and lung cancer, although the patterns of hypoxia may elicit divergent responses among different lung tumour cell types [31], and therefore the predictability of such relationships may differ depending on the unique intrinsic characteristics of the tumours being evaluated. Lung tumour cell malignant properties were found to be enhanced *in vivo* by circulating exosomes released under IH conditions mimicking OSA [32]. Li et al. recently reported that OSA severity was a risk factor that contributed to short overall survival in patients with lung cancer. The authors identified molecular convergence between hypoxia and lung cancer that reflected their clinical profiles and revealed molecular pathways involved in hypoxic-induced lung cancer progression [33]. In the present study, secondary analyses for specific cancers found that the incidence of lung cancer was reduced by ~50% (95% CI, 0.22–1.09) under adequate CPAP therapy compared to non-adherent patients. Further studies are required to determine whether CPAP therapy of OSA with good adherence exerts a protective effect against lung cancer development, and which types of lung cancer appear to be susceptible to such effect.

The strength of the current study includes a multicentre design, a relatively large sample size, long and complete follow-up with access to comprehensive SNDS data and objective measurement of CPAP adherence. This study also has limitations, the most important being its observational design, which does not allow for definitive conclusions to be drawn regarding the impact of CPAP on cancer risk. Furthermore, partitioning of CPAP adherence to more sub-groups to assess for a dose-response to treatment was not possible, since the resultant cohort sizes would be insufficiently sized to derive meaningful deductions. The presence of potential unmeasured confounding factors cannot be excluded. Given the established benefits of CPAP and the danger sleepy individuals can present to themselves and others, it is no longer conceivable to ethically randomize excessively sleepy patients with OSA to no therapy for extended periods of time, as would be required for assessment of cancer incidence events [13]. However, the use of an exhaustive medical-administrative database combined with a clinical database can reasonably mitigate the risk of bias related to unmeasured confounders. Although observational data can lead to biases, the use of adequate approaches such as IPTW estimators are acknowledged to address confounding in real world studies when randomized clinical trials are not possible, as is the case here.

Conclusion

CPAP therapy of OSA with good adherence (defined as at least 4 hours/night) was not associated with a reduction in all-cause cancer incidence compared to non-adherent patients. Whether adequate CPAP therapy of OSA might reduce the risk specific cancer sites, particularly among those OSA patients with more severe nocturnal hypoxemia should be further evaluated.

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Figure Legends

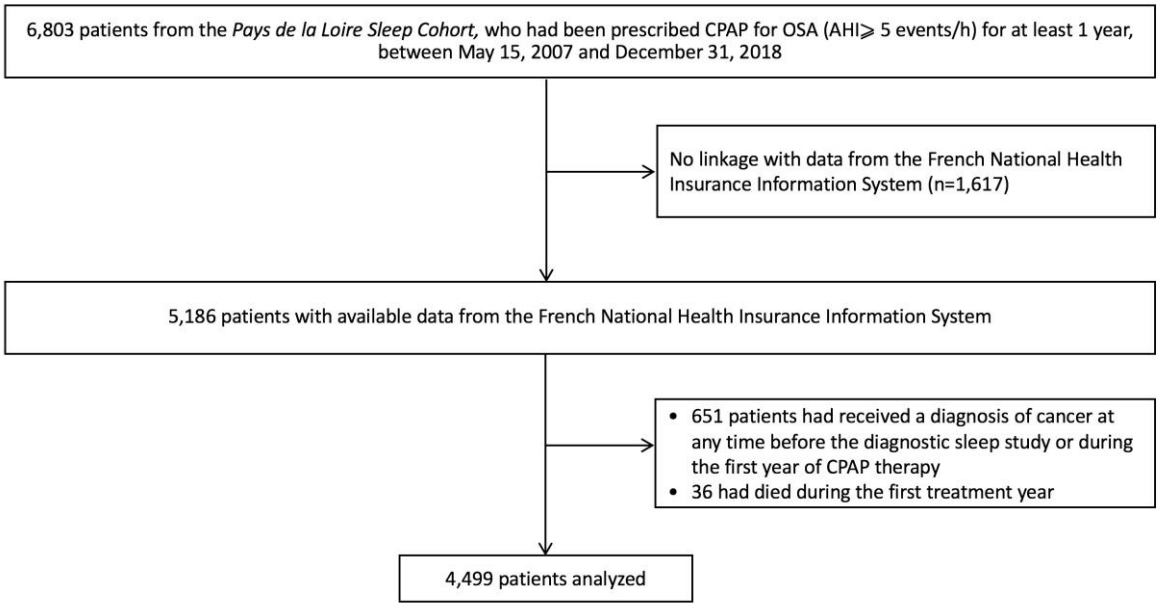

Figure 1: Flow diagram of the study subjects

Abbreviations: AHI, apnoea-hypopnea index; CPAP, continuous positive airway pressure, OSA, obstructive sleep apnoea

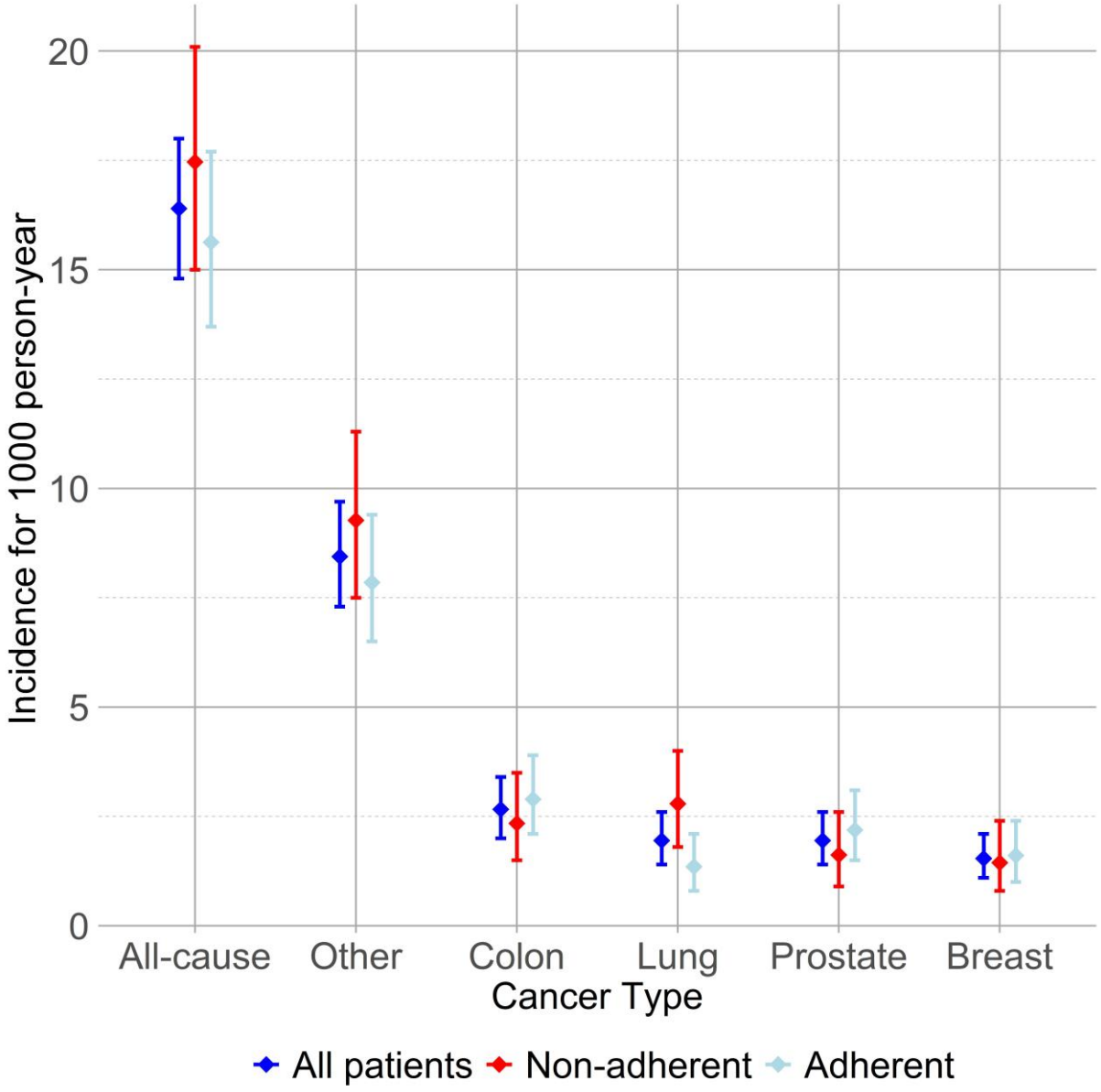

Figure 2: Incidence of different cancer sites according to CPAP adherence.

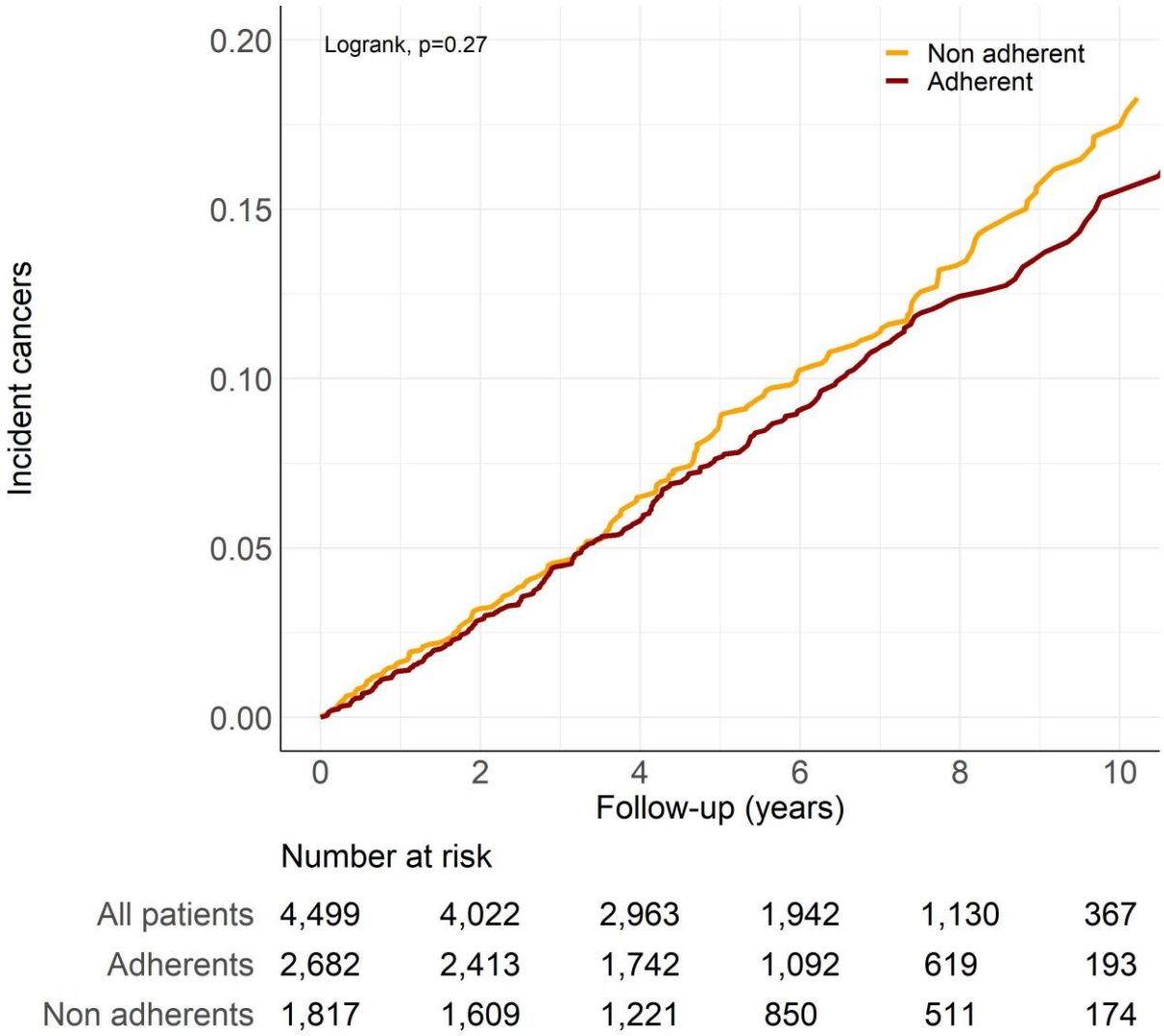

Figure 3: Weighted cumulative incidence function for all cause cancers according to CPAP adherence.

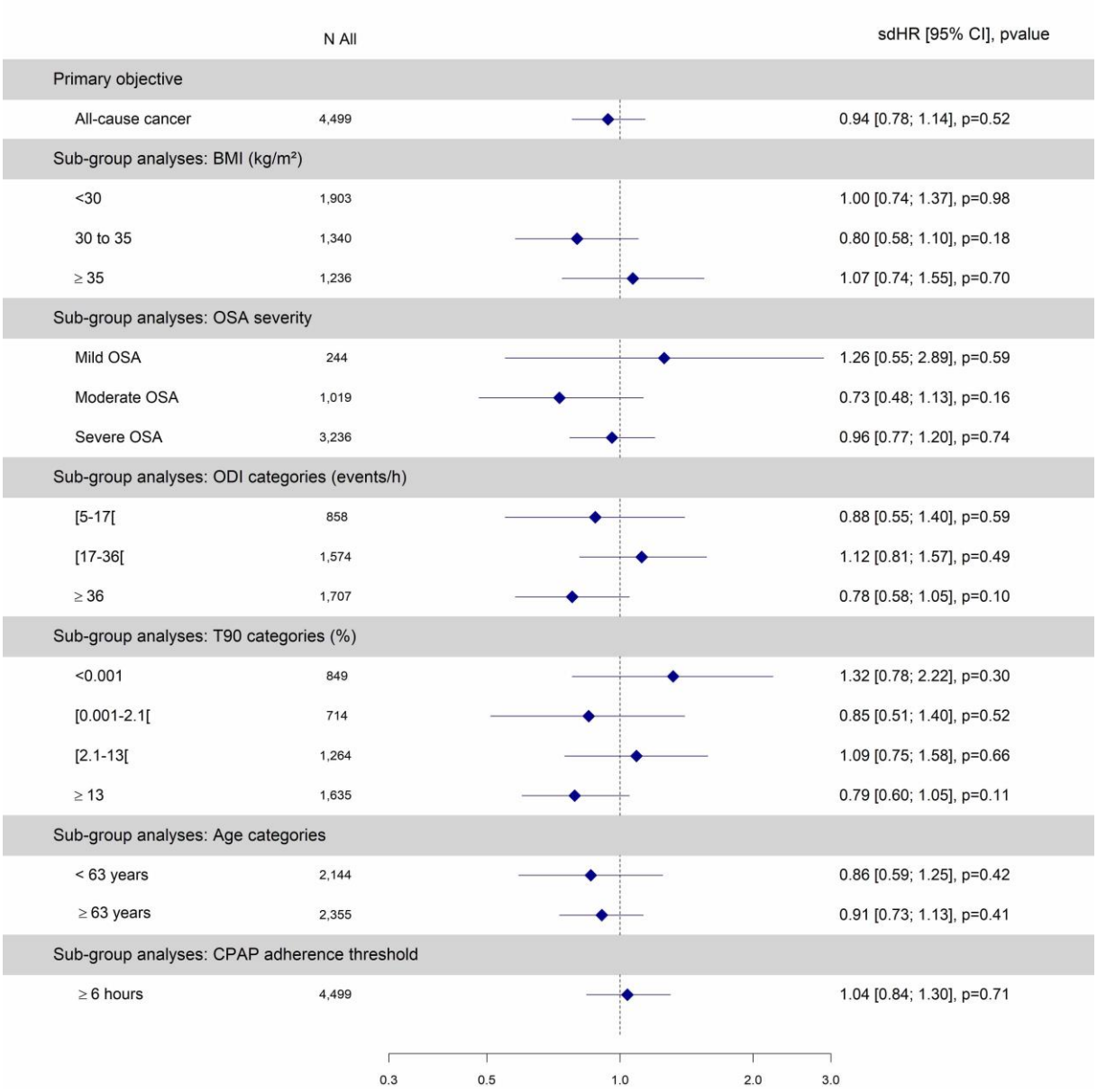

Figure 4: Summary of sub distribution hazard ratios (sdHR) for primary outcome

Abbreviations: CI, confidence interval; BMI, body mass index, ODI, 3% oxygen desaturation index; OSA obstructive sleep apnoea; T90, percentage of sleep time with oxygen saturation<90%.

The following commonly used cut-offs for apnoea-hypopnea index were used to define categories of OSA severity: <5 events/h (no OSA), 5 to <15 events/h (mild OSA), 15 to <30 events/h (moderate OSA), ≥30 events/h (severe OSA).

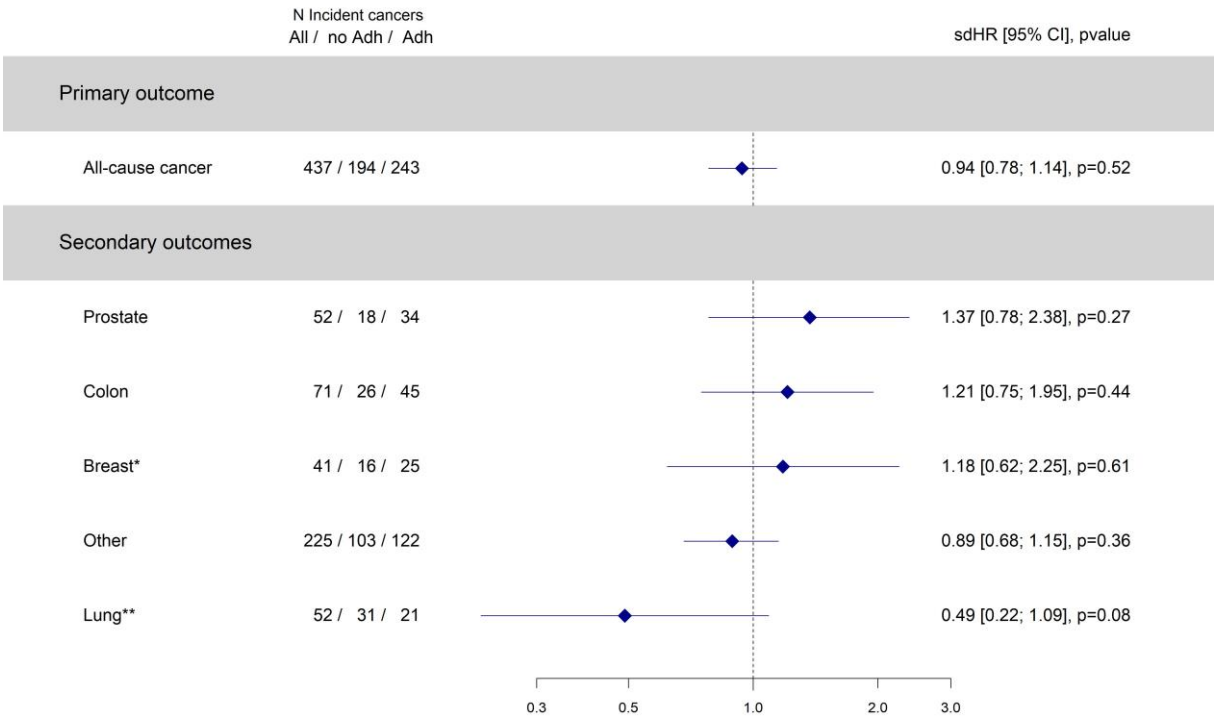

Figure 5: Summary of sub distribution hazard ratios (sdHR) for primary and secondary outcomes

Abbreviations: Adh, Adherent; CI, confidence interval

* Breast cancer model was not adjusted on gender; ** lung cancer model was adjusted for tobacco consumption

Table 1: Baseline characteristics of the entire population, CPAP non-adherent and adherent patients

	All patients	CPAP non-adherent	CPAP adherent	p value	Missing data
n	4,999	1,817	2,682		
Age; years	63 [54-72]	62 [52-72]	64 [55-72]	<0.01	0
Men	3112 (69.2)	1235 (68)	1877 (70)	0.15	0
Body mass index, kg/m²	31 [27-35.5]	30.5 [26.7-35.4]	31.4 [27.7-35.6]	<0.01	20
Alcohol intake	2014 (46.3)	772 (44)	1242 (47.8)	0.02	145
Smoking habits					
Former and current smokers	2628 (59.2)	1104 (61.6)	1524 (57.6)	<0.01	63
Non-smokers	1808 (40.8)	688 (38.4)	1120 (42.4)	.	.
Socio-professional category					
Farmer	190 (5)	75 (5)	115 (5.1)	0.21	727
Craftsman	411 (10.9)	181 (11.9)	230 (10.2)	.	.
Executive	616 (16.3)	261 (17.2)	355 (15.7)	.	.
Intermediate	754 (20)	304 (20.1)	450 (19.9)	.	.
Employee	682 (18.1)	274 (18.1)	408 (18.1)	.	.
Worker	1119 (29.7)	420 (27.7)	699 (31)	.	.
ESS	10 [7-14]	11 [7-14]	10 [7-14]	0.90	126
Prevalent diseases					
Depression	1246 (28)	560 (31.2)	686 (25.8)	<0.01	48
Diabetes	717 (17.7)	299 (18.3)	418 (17.2)	0.36	443
Hypertension	1600 (39.7)	608 (37.6)	992 (41.1)	0.02	470
Cardiac disease	787 (18.1)	327 (18.7)	460 (17.7)	0.41	161
Heart failure	214 (4.8)	101 (5.6)	113 (4.2)	0.04	0
CHD	252 (5.6)	108 (5.9)	144 (5.4)	0.41	0
Atrial fibrillation	374 (8.3)	171 (9.4)	203 (7.6)	0.03	0
Stroke	249 (5.5)	90 (5)	159 (5.9)	0.16	0
Indices of OSA severity					
AHI, events/h	37 [27-52]	34 [24-48]	38 [30-55]	<0.01	10
5-15	243 (5.4)	109 (6)	134 (5)	<0.01	10
15-30	1012 (22.5)	486 (26.9)	526 (19.6)	.	.
≥30	3234 (72)	1215 (67.1)	2019 (75.4)	.	.
ODI, events/h	30 [17-47]	27 [15-43]	32 [19-50]	<0.01	164
T90, %	6 [1-22]	5 [1-19]	7 [1.3-24]	<0.01	37
CPAP Adherence	5.9 [4.1-7.2]	3 [2.1-3.6]	6.7 [5.7-7.6]	<0.01	0
Follow-up, years	5.4 [3.2-8.1]	5.8 [3.2-8.3]	5.2 [3.1-7.8]	<0.01	0
Cancer incidence, n (%)	437 (9.7)	194 (10.7)	243 (9.1)	0.03	0

Data are expressed as median [interquartile range] or number (%).
Abbreviations: ESS, Epworth Sleepiness Score; CHD, coronary heart disease; OSA, obstructive sleep apnoea; AHI, apnoea-hypopnea index; ODI, 3% oxygen desaturation index; T90, percentage of sleep time with oxygen saturation<90%; CPAP, continuous positive airway pressure.
Comparisons between non-adherent and adherent patients were performed using Mann-Whitney test for quantitative variables or Chi square test for qualitative variables.

Online supplementary material

Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy.

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Table S1: definition of covariates

Variables	Definition
Obesity	According to the WHO definition, obesity was defined by a body mass index of at least 30 kg/m^2
Hypertension (HTN)	Blood pressure measurements taken in the sleep clinic were not used to diagnose HTN, as clinical blood pressure measured on only one occasion cannot be used as a reliable indicator for the definition of HTN. Only patients who were previously diagnosed as hypertensive based on data reported during baseline standardized health interview, and were taking antihypertensive medication were considered as having HTN [1].
Diabetes mellitus	Patients who were previously diagnosed with diabetes according to data from baseline standardized health interview, and use of oral hypoglycemic medications and/or insulin where considered as having diabetes mellitus [2].
Chronic obstructive pulmonary disease (COPD)	A COPD label was assigned for participants who were previously diagnosed with COPD, chronic bronchitis or emphysema, according to data from baseline standardized health interview [3] .
Cardiovascular diseases	Based on data reported by participants during the baseline standardized health interview, cardiovascular diseases were defined as history of physician-diagnosed angina, myocardial infarction, coronary revascularization procedure, heart failure, atrial fibrillation and/or stroke [4].
Smoking status	Never smokers were defined as people who had never smoked in their lifetime; former smokers were defined as people who had previously smoked but had stopped smoking for at least one year at the time of their diagnostic sleep study; a current smoker label was assigned if a patient was a smoker within the past year.
Excessive daytime sleepiness	Excessive daytime sleepiness was assessed using the Epworth Sleepiness Score [5, 6].
Depression	Patients who were previously diagnosed with depression according to data from baseline standardized health interview, and use of antidepressant medications where considered as depression [7].

Table S2: Comparison of imputed and non-imputed dataset

	Non imputed					Imputed				
	N	**Mean**	**Std**	**Min**	**Max**	**N**	**Mean**	**Std**	**Min**	**Max**
Body mass index	4479	32,1	6,7	15,3	69,3	89980	32,1	6,7	15,3	69,3
Epworth score	4373	10,5	5,0	0,0	24,0	89980	10,5	5,0	0,0	24,0
Apnea Hypopnea Index	4489	41,2	20,8	5,5	159,0	89980	41,1	20,8	5,5	159,0
Prevalent hypertension	4029	0,4	0,5	0,0	1,0	89980	0,4	0,5	0,0	1,0
Prevalent CV disease	4338	0,2	0,4	0,0	1,0	89980	0,2	0,4	0,0	1,0
Prevalent Diabetes	4056	0,2	0,4	0,0	1,0	89980	0,2	0,4	0,0	1,0

Abbreviations : N, number; Std, standard deviation; Min, minimum ; Max, Maximum ; CV, cardiovascular

Table S3: Logistic regression model to assess the probability of being CPAP adherent

Variable	Odds Ratio [95%CI]	p value
Age	1.01 [1 ; 1.01]	0.0038
Sex (male)	1.16 [1.02 ; 1.33]	0.0260
Epworth score ≥10	1.03 [0.91 ; 1.17]	0.6208
BMI categories, kg/m^2		0.0007
<25	0.76 [0.65 ; 0.89]	
25-30	1.07 [0.91 ; 1.26]	0.4253
>30	1 [. ; .]	.
Prevalent hypertension	1.14 [0.99 ; 1.32]	0.0732
Prevalent CV diseases	0.83 [0.7 ; 0.98]	0.0250
Prevalent Diabetes	0.81 [0.68 ; 0.96]	0.0181

Table S4: Primary outcome final model

Variable	OR [95%CI]	Pvalue
CPAP adherence	0.94 [0.78 ; 1.14]	0.5227
Epworth score ≥10	0.79 [0.65 ; 0.95]	0.0139
Age	1.04 [1.03 ; 1.05]	<.0001
Sex (male)	1.11 [0.9 ; 1.38]	0.3275
Body mass index (ref >30 kg/m^2)		
<25	0.91 [0.71 ; 1.17]	0.4678
25-30	1.08 [0.84 ; 1.38]	0.5630
Prevalent hypertension	0.81 [0.65 ; 1]	0.0520
Prevalent diabetes	1.23 [0.97 ; 1.58]	0.0920

Figure legends

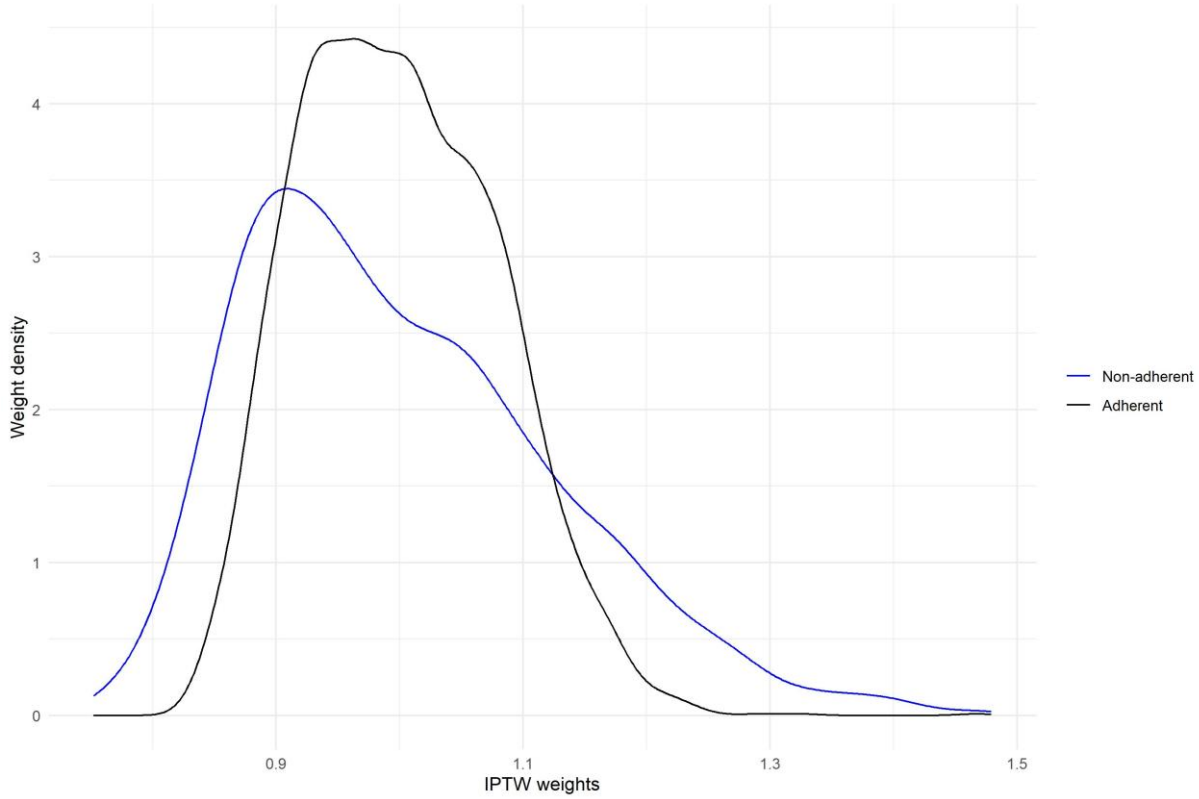

Figure S1: Distribution of weights according to the CPAP adherence group

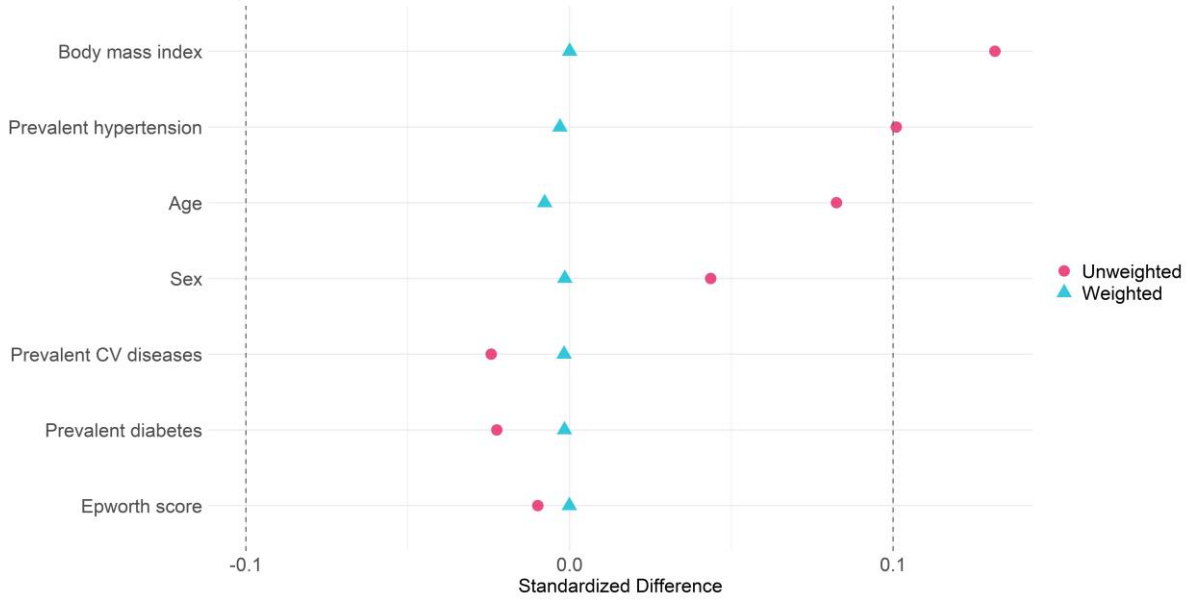

Figure S2: standardized differences according to weighting datasets

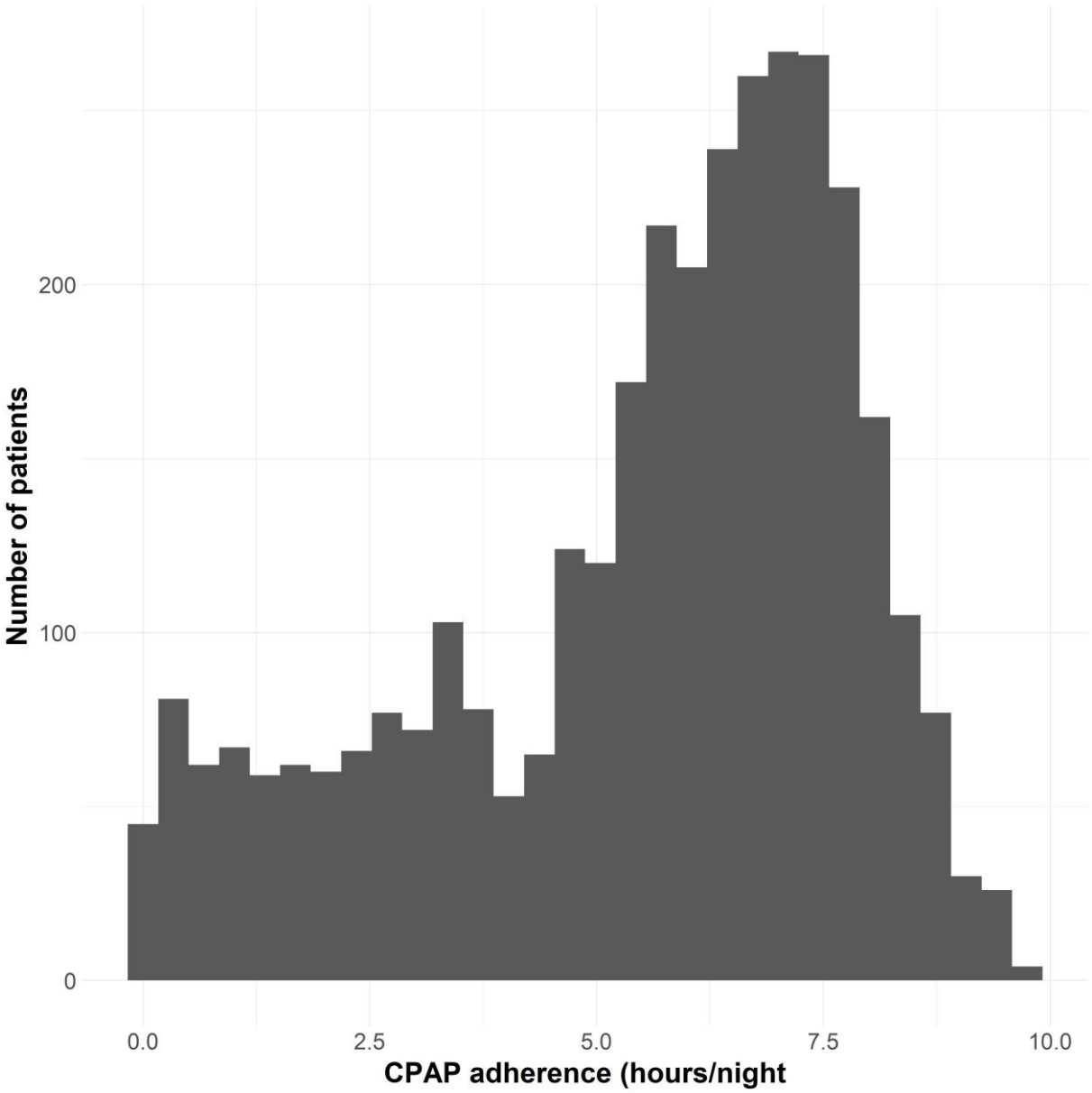

Figure S3: Histogram of the distribution of CPAP adherence

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