Co-morbid insomnia and obstructive sleep apnoea is associated with all-cause mortality

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Take-Home Message:

Co-morbid insomnia and sleep apnoea is associated with a 47% increase in mortality risk compared to participants with no insomnia or obstructive sleep apnoea over 15 years of follow-up.

Abstract

Study Objectives: Increased mortality has been reported in people with insomnia and in those with obstructive sleep apnoea (OSA). However, these conditions commonly co-occur and the combined effect of co-morbid insomnia and sleep apnoea (COMISA) on mortality risk is unknown. This study used Sleep Heart Health Study (SHHS) data to assess associations between COMISA and all-cause mortality risk.

Methods: Insomnia was defined as difficulties falling asleep, maintaining sleep, and/or early morning awakenings from sleep ≥16 times a month and daytime impairment. OSA was defined as an apnoea-hypopnoea index ≥15 events/h sleep. COMISA was defined if both conditions were present. Multivariable adjusted Cox proportional hazard models were used to determine the association between COMISA and all-cause mortality (n = 1210) over 15 years of follow-up.

Results: 5236 participants were included. 2708 (52%) did not have insomnia/OSA (control), 170 (3%) had insomnia-alone, 2221 (42%) had OSA-alone, and 137 (3%) had COMISA. COMISA participants had a higher prevalence of hypertension (ORs [95%CI]; 2.00 [1.39, 2.90]) and cardiovascular disease compared to controls (1.70 [1.11, 2.61]). Insomnia-alone and OSA-alone were associated with higher risk of hypertension but not cardiovascular disease compared to controls. Compared to controls, COMISA was associated with a 47% (HR, 95% CI; 1.47 (1.06, 2.07)) increased risk of mortality. The association between COMISA and mortality was consistent across multiple definitions of OSA and insomnia.

Conclusions: Co-morbid insomnia and sleep apnoea was associated with higher rates of hypertension and cardiovascular disease at baseline, and an increased risk of all-cause mortality compared to no insomnia/OSA.

Introduction

Insomnia and obstructive sleep apnoea (OSA) are the two most common sleep disorders, each occurring in approximately 10 to 30% of the general population [1, 2]. Insomnia is characterised by frequent self-reported difficulties initiating sleep, maintaining sleep and/or undesired early morning awakenings from sleep, and daytime impairments such as reduced energy, concentration difficulties and feeling unrested [3]. OSA is characterised by frequent brief narrowing and partial or complete closure of the upper airway during sleep, resulting in transient reductions in oxygenation and hypercapnia, augmented but ineffectual breathing efforts, cortical arousals, blood pressure surges and daytime sleepiness and fatigue [3, 4].

Both insomnia and OSA are independently associated with increased risk of future psychiatric and medical conditions, reduced productivity and quality of life, and high healthcare utilisation [5-7]. In the Sleep Heart Health Study (SHHS) [8], a large US population-based cohort study designed to examine associations between sleep problems and adverse outcomes[9, 10], insomnia with objective short sleep duration was also associated with increased risk of cardiovascular disease (CVD) but not all-cause mortality [11]. SHHS participants with OSA showed an increased prevalence and incidence of CVD[10, 12-14]. Furthermore, participant with OSA (apnoea-hypopnoea index [AHI] $\geq$ 15 events/h sleep) and elevated daytime sleepiness showed greater risk of increased cardiovascular disease compared to asymptomatic OSA[15].

However, insomnia and OSA often co-occur within the same patient [16-20] and health outcomes are consistently worse when compared to individuals with neither condition or those with either condition alone. Co-morbid insomnia and sleep apnoea (COMISA) is associated with greater impairment of sleep [21], daytime function [22], mental health[17, 23, 24], and reduced productivity and quality of life [23, 25, 26], compared to individuals with either insomnia-alone or OSA-alone [17, 27].

Although COMISA is a prevalent and debilitating condition associated with greater morbidity compared to either insomnia-alone or OSA-alone, no population-based study has investigated the association of COMISA with all-cause mortality. Thus, the aim of this study was to use SHHS data to investigate associations between COMISA and all-cause mortality.

Methods

Study design and participants

The study design and methodology of the SHHS has been reported previously [28]. Full overnight sleep studies from 6,441 participants were pooled from different population-based studies, of which 5,804 are available through an open access dataset from the National Sleep Research Resource [29]; accessed in September 2019.

Participants undertook home-based polysomnography recordings in 1995-1998 (Compumedics P Series System; Abbotsford, Victoria, Australia). Polysomnography included two electroencephalograms (C4-M1, C3-M2), chin electromyogram, left and right electro-oculograms, electrocardiogram, nasal cannula, oro-nasal thermistor, two respiratory band signals (abdominal and thoracic), and finger pulse-oximetry. Sleep and electroencephalography arousals were scored according to the standard criteria at the time. Apnoeas were scored as a $\geq$ 75% reduction in breathing amplitude lasting at least 10 sec as recorded via the thermocouple signal. Hypopnoeas were identified if the breathing amplitude of the thermocouple or thoracic/abdominal band signals decreased by $\geq$ 30% for at least 10 sec in association with $\geq$ 3% reduction in oxygen saturation or an arousal [28]. The AHI was defined as the number of apnoeas and hypopnoeas per hour of sleep.

Insomnia, OSA and COMISA definitions

At the time of the polysomnography study, participants completed questionnaires assessing sleep habits and quality of life. Insomnia was defined according to the presence of self-reported nocturnal symptoms (difficulties falling asleep, waking up in the middle of the night and having difficulty returning to sleep, and/or waking up too early and being unable to resume sleep, on 16-30 times per month) *and* daytime impairments including having little to no energy in the past 4 weeks, and/or feeling unrested at least 5 times a month and/or feeling tired most/all of the time. Previous SHHS research has also used this nocturnal symptom frequency to define insomnia[11]. Alternative definitions of insomnia, such as insomnia symptom frequency reduced to ≥5 times a month and presence/absence of sleep medication use[24] were also explored in sensitivity analyses.

OSA was defined according to an AHI of ≥15 events/h sleep [12, 15]. Alternative definitions of OSA (≥ 4% reduction in oxygen saturation with and without arousal) and alternative AHI cut-offs (≥5, 10, and 20 events/h) were investigated in secondary analyses. COMISA was defined if both conditions were present. Participants who did not meet criteria for either insomnia or OSA were categorised with no insomnia/OSA and used as the reference group for comparisons of mortality risk.

Potential confounders

Questionnaires were used to determine baseline characteristics including socio-demographics (age, gender, race, educational and marital status), behavioural factors (smoking status) and body mass index (BMI; kg/m^2). Medical history (hypertension; CVD; chronic obstructive pulmonary disease (COPD); diabetes and medication intake) was determined during an examination no more than five years before the baseline polysomnography study. Medication

intake included benzodiazepines, any diuretics, tricyclic anti-depressants and any sleep medication intake more than 5 times a month. Pre-existing CVD cases were determined according to data provided by the parent study cohorts or by self-report at enrolment on the basis of physician reported angina, heart attack, heart failure, stroke, or if the participant ever underwent coronary bypass surgery and/or coronary angioplasty[8]. Polysomnography-defined total sleep time was also included as a potential confounder in the fully adjusted model.

Outcome assessment

Death from any cause, up until 2011, was identified using follow-up interviews, written annual questionnaires, telephone contact with study participants or next-of-kin, surveillance of local hospital records and community obituaries and linkage with the Social Security Administration Death Master File [12, 30].

Statistical analysis

Confounders and the statistical analyses closely followed previous SHHS reports [11, 12]. Distributions of covariates were summarised by sleep disorder group. Between-group differences in the prevalence of hypertension, CVD, and diabetes mellitus were investigated using logistic regression controlling for age, BMI, and gender. Between-group differences in the arousal index, AHI, total sleep time and percentage of time spent with less than 90% of oxygen were studied using linear regression controlling for age, BMI and gender.

Kaplan-Meier survival estimates, and log-rank tests were used for visual interpretation of the crude probability of mortality over time. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using Cox-regression models to compare risks in sleep disorder groups (insomnia-alone vs. OSA-alone vs. COMISA) and all-cause mortality risk relative to the

reference group (no insomnia/OSA). Proportional hazard assumptions for each variable were tested using Schoenfeld residuals. Five models were constructed to further explore the impact of potential confounders. The first model was unadjusted. The second model was adjusted for socio-demographics factors including age, race, gender, marital status and total number of years spent in education. The third model was additionally adjusted for smoking status and body mass index. The fourth model was additionally adjusted for pre-existing cardio-metabolic conditions, including diabetes, CVD, hypertension, lipid lowering medications and COPD. Finally, the last model was additionally adjusted for polysomnography-defined total sleep time, use of benzodiazepines within two weeks of the sleep study, tricyclic anti-depressants and a binary variable constructed to represent participants taking sleep medication more than 5 times a month.

Three *a-priori* interactions between sleep disorder groups with age, gender and total sleep time were tested given previous evidence that prevalence of OSA may be under-estimated among women, and that total sleep time may moderate cardiovascular risk in participants with insomnia [11, 31]. Given previous evidence of increased mortality risk for men with insomnia and short sleep duration[32], we tested for a 3-way interaction between sleep disorder group, sex and total sleep time.

In addition to sensitivity analyses with different insomnia and OSA definitions, two additional sensitivity analyses were conducted. In the first analysis, participants who died within the first two years were excluded to account for unidentified acute terminal illnesses that might have disrupted sleep (e.g. cancer). In the second sensitivity analysis, mortality risk for participants with OSA-alone and excessive daytime sleepiness (Epworth sleepiness scale > 10) was quantified and compared to mortality risk in the control group.

Results

Baseline characteristics

The analysis sample included 5236 participants (90.2% of 5804) after exclusion of 114 (1.9%), 452 (7.8%) and 2 (< 0.1%) participants due to missing information on nocturnal insomnia symptoms, daytime symptoms, and all-cause mortality, respectively. A complete case dataset (with no missing variables for the fully adjusted model) had 4433 participants (84.0 % of the analysis sample), with educational status (N = 443, 8.4%) and diabetes (N = 238, 4.5%) accounting for most missing data. Baseline characteristics of the analysis sample are reported in Table 1. Insomnia was present in 5.8% of participants with OSA, and 5.9% of participants without OSA ($\chi^2 = 0.02$, $p = 0.88$). OSA was present in 44.6% of participants with insomnia and 45.1% of participants without insomnia ($\chi^2 = 0.02$, $p = 0.88$).

Participants with COMISA had a higher prevalence of hypertension (ORs [95%CI]; 2.00 [1.39, 2.90]) and cardiovascular disease than control participants at baseline (1.70 [1.11, 2.61]; Supplementary Table S1) after adjusting for age, sex and BMI. Compared to the control group, insomnia alone and OSA alone were both associated with hypertension but not with CVD at baseline (Supplementary Table S1). The prevalence of diabetes was not different between any groups. The COMISA group had a 1.9-point greater (~ 6% increase) AHI compared to the OSA alone group (β [95%CI]; 1.93 [0.05, 3.81], p = 0.042). There was no significant difference in arousal index scores, or the percentage of total sleep time spent with less than 90% oxygen saturation between the COMISA and OSA alone groups (both p-values ≥ 0.09). Participants with COMISA had 12 min (-12.37 [-23.2, -1.5], p-value = 0.025) less total sleep time compared to OSA alone but showed no significant difference in total sleep time compared to the insomnia alone group (-2.3 [-16.6, 11.9], p-value = 0.74).

All-cause mortality

The median (IQR) follow-up period for all-cause mortality was 11.8 (10.4, 15.9) years, over which there were 1210 deaths (21.1% of the analysis sample). The crude mortality rates were 17.3, 19.3, 24.9 and 30.4 events per 1000 person-years for the reference, insomnia-alone, OSA-alone and COMISA groups, respectively. Kaplan-Meier curves are shown in Figure 1 and corresponding hazard ratios are reported in Table 2 and show that participants with COMISA had a lower survival probability than the other groups.

After adjusting for all pre-specified covariates (Table 2), COMISA was associated with an increase in all-cause mortality compared to the reference group, and OSA-alone group (p = 0.039), but not the insomnia-alone group (p = 0.348). In the fully adjusted model, there were no significant interactions of sleep disorder category with gender (p = 0.21), age (p = 0.58) or total sleep time (p = 0.82). The three-way interaction between sleep disorder group, gender and total sleep time was also not significant (*p-value* = 0.34).

The association between COMISA and all-cause mortality did not change after excluding 96 (1.8% of sample) participants who died within the first two years of follow-up (Supplementary Materials, Table S2). The increase in all-cause mortality risk in COMISA patients was also consistent across different definitions of OSA. Inclusion/exclusion of arousal for hypopnea scoring did not affect the association between COMISA and mortality risk, nor did the use of 3 vs 4% of oxygen saturation as a criterion (Table 3). The investigation of different AHI threshold to define OSA suggested an increased risk of mortality in participants with COMISA when OSA was defined according to an AHI of $\geq$ 10, 15 and 20 events per hour (Table 4).

COMISA was also associated with greater all-cause mortality risk compared to the reference group when insomnia was defined based on insomnia symptom frequency of at least 5 per month (Table 5). The inclusion/exclusion of sleeping medication intake in the definition of insomnia (as in Bertisch et al.[11]) did not change the main findings (Table 5). Finally, 606 (27%) of the participants with OSA alone had excessive daytime sleepiness. Compared to the control group, there was no significant difference in mortality risk in the group with OSA alone and daytime sleepiness (0.99 [0.82, 1.20]), or OSA alone without daytime sleepiness (0.99 [0.86, 1.14]) in the fully adjusted model.

Discussion

The main finding of this study is that COMISA is associated with increased risk of all-cause mortality compared to no insomnia or OSA. COMISA was also associated with higher rate of CVD and hypertension at baseline.

Our results are consistent with previous research demonstrating that COMISA is associated with worse physical and mental health compared to either insomnia-alone, or OSA-alone [17, 20, 21, 23, 33]. This is the first study to demonstrate that patients with COMISA are at increased risk of all-cause mortality, compared to patients with no insomnia/OSA. Although no previous study has investigated the association between COMISA and all-cause mortality, reports from the Sleep Heart Health Study and other cohort studies have shown decreased quality of life [34], and increased cardiovascular events in specific sub-groups of people with insomnia or OSA [11, 13, 15]. Our findings may also be consistent with previous SHHS reports investigating specific OSA sub-groups. Butler and colleagues [35] reported increased all-cause mortality in participants with short-duration apnoea events, which may be a marker of the low respiratory

arousal threshold phenotype [35]. Future research should investigate the co-occurrence of co-morbid insomnia and key physiological traits of OSA, and shared associations with all-cause mortality[36].

The clinical presentation, manifestations, and pathophysiology of OSA and response to treatment differs in women compared to men [31] . Earlier SHHS reports suggest that men with OSA are at higher risk of all-cause mortality (specifically men < 70 y) [12], incident coronary heart disease, heart failure [13] and stroke [14]. Consequently, when a fixed AHI threshold is used to define OSA, women with "OSA" are more likely to be undiagnosed, untreated, and experience treatment failure [37, 38]. While we did not find any significant interaction between sex and sleep disorder group on all-cause mortality risk, caution is warranted given the relatively low sample size for this comparison. Further work should assess adverse health effects of COMISA in women versus men using different measures of OSA presence and severity.

The associations between all-cause mortality and COMISA highlight the need for further research to investigate the mechanisms underpinning this relationship. It is possible that the association of COMISA with mortality may result from the high prevalence of additional medical/psychiatric co-morbidities and increased morbidity in participants with COMISA[23, 25, 26, 39], more complex interactions between the psychological and physiological mechanisms and manifestations of each disorder that may exacerbate the other and trigger worse physical and mental health, or other conditions/prodromal symptoms which were not identified or controlled within the available data[36]. It is also possible that the association of COMISA and mortality is mediated by an increased risk of cardiovascular disease. For example, Meira e Cruz and colleagues recently reported in a sample of 685 patients referred to a specialist sleep clinic, that

COMISA was associated with increased risks of diabetes and hypertension compared to OSA alone[33].

The lack of association between insomnia-alone and all-cause mortality is consistent with a recent meta-analysis[40]. The interaction of total sleep time and sleep-disorder group on mortality risk was investigated but no significant moderation effect was observed. This is somewhat surprising given that previous studies reported an increased risk of all-cause mortality in men for insomnia with short sleep (< 6 hours) but not normal sleep duration[32]. The lack of interaction in our study may have been due to a small number of participants in the insomnia alone group with short objective sleep duration. However, it is worth noting that the previously published evidence regarding increased mortality risk with insomnia and short sleep duration is based on only 12 deaths within 33 participants and has not been consistently found in other studies[11, 41, 42]. Indeed, a previous report of the Sleep Heart Health Study suggested that insomnia with objective short sleep duration was associated with increased risk of cardiovascular events but not all-cause mortality[11]. It will be important for future research to investigate the contribution of short sleep duration with both insomnia and COMISA on physical and mental health. Previous evidence indicates that people with COMISA experience worse sleep, including reduced objective sleep duration[21], compared to those with either insomnia or OSA alone[18]. Therefore, it is possible that the 'short sleep duration' component of COMISA contributed to the association with mortality. However, at baseline, there was no difference in sleep duration between the groups with COMISA versus insomnia-alone, after controlling for age, gender and BMI. Importantly, we also found that COMISA was associated with an increased risk of all-cause mortality independently of total sleep time, age and gender in the fully adjusted models.

The prevalence of COMISA was relatively small in the current sample (2.6%). This prevalence estimate is somewhat smaller than previous population-based studies, reporting a COMISA prevalence estimates of 5-7% when using PSG to define OSA[23, 43], and similar to estimates of 1-4% when using self-reported OSA symptoms or doctor diagnosis to define OSA[26, 27, 44, 45]. The low prevalence of COMISA in the current study may also reflect the conservative diagnostic criteria for insomnia[3]. Furthermore, there is evidence that insomnia prevalence has increased over time[46]. Given that SHHS baseline data were collected between 1995-1998, the current study may underestimate the prevalence of COMISA compared to more recent data. Given the older average age of SHHS participants, future studies should also investigate the prevalence and associations of COMISA and mortality in cohorts that include a more diverse age range. Patients with COMISA likely require tailored treatment approaches [17, 19]. For example, patients with OSA and co-morbid insomnia have lower acceptance and poorer compliance with continuous positive airway pressure (CPAP), compared to patients with OSA-alone [18]. Recent randomised controlled trials suggest that cognitive behavioural therapy for insomnia (CBTi) before commencing CPAP may increase CPAP adherence [17]. Future research should investigate the effect of single and combination treatment approaches for COMISA on markers of mortality risk.

Several limitations of the current study warrant consideration. Firstly, although both nocturnal and daytime insomnia symptoms were used to classify insomnia (as recommended in diagnostic criteria) and different sensitivity definitions were investigated, insufficient data were available to identify patients with 'chronic insomnia' persisting for ≥3 months[3]. Given sensitivity analyses supported robust associations of acute/chronic insomnia and mortality, it is possible an association between COMISA (and insomnia alone) with mortality may be underestimated

compared to insomnia defined according to *chronic* nocturnal and daytime symptoms. Indeed, Vgontzas and colleagues reported that men with chronic insomnia (occurring for at least 1 year) and short sleep duration demonstrated an increased mortality risk in men[32]. Similarly, we were not able to identify symptoms of acute insomnia that may have been attributable to other physical and mental health conditions[17]. However, it is rarely possible to identify patterns of 'secondary' versus 'co-morbid' insomnia based on pre-treatment symptoms alone. Furthermore, the association of COMISA and mortality remained after controlling for all available physical and mental health conditions. Secondly, SHHS participants were pooled from existing trials examining the effect of sleep-disordered breathing on cardiovascular complications. Thus, sampling and survival biases might contribute to these findings. Although diagnosed mental health condition data were not available, we controlled for mental health symptoms using anti-depressant medication use which will likely underestimate the burden of mental health conditions. Thus, residual confounding that may be present. Future research should examine the association of COMISA and mortality, controlling for treated and untreated mental health symptoms and doctor-diagnosed mental health conditions. Similarly, previous studies have reported high rates of COMISA in Veteran and military populations (who also have an increased prevalence of additional mental health issues), which may have contributed to the association between COMISA and mortality[17]. As these data were not available in the SHHS, future research should investigate longitudinal relationships between COMISA and health outcomes in Veteran and military personnel. Finally, post-hoc analysis of existing large trials is inherently problematic given that the Sleep Heart Health Study was not designed to answer specific questions regarding COMISA and all-cause mortality. Nevertheless, the present findings are robust across multiple

definitions of OSA and insomnia and support the need for future larger trials more specifically designed to answer these questions.

The association between all-cause mortality and OSA alone differs from some previous literature [12, 47, 48]. For example, some studies found an association between mortality and OSA in men < 70 years old[12], and some found an association with all-cause mortality only in severe OSA, and with a relatively low number of deaths (n = 12)[47]. In our study, we found no evidence of interaction effects of sex or age with sleep disorder group on mortality but lacked sufficient power to further dichotomize OSA by severity groups. It is possible that sub-categorizing OSA as OSA-alone and COMISA reduced the power necessary to detect interaction effects with age, which may explain the lack of association between OSA alone and all-cause mortality. Indeed, previous studies suggest that downstream effects of OSA on health may be stronger in younger participants and potentially influenced by hypoxic pre-conditioning effects[49-52]. Furthermore, previous studies that investigated associations between OSA and all-cause mortality did not control for insomnia. Consequently, it is possible that co-morbid insomnia symptoms contributed to the previous reported association between OSA and mortality in these previous studies[12, 47, 48]. Finally, as suggested in a recent study in a clinical cohort of 10,000 participants [53], it is possible that OSA severity as defined with AHI alone without consideration of hypoxia[54], sleep fragmentation[55, 56], insomnia or other co-morbidities[36] is not sufficiently discriminatory of underlying pathology and thus fails to predict all-cause mortality.

In summary, this study found that participants with co-morbid insomnia and sleep apnoea (COMISA) have showed increased mortality compared to participants with neither disorder. It is possible that the association of COMISA and mortality was driven by short sleep duration, worse cardiovascular health, and a higher AHI in the 'COMISA' group, although we controlled for each

of these variables. Future research should investigate the mechanisms underpinning the association between COMISA and mortality risk in population-based cohorts. It remains to be determined if these associations are causal and that treatment with CBTi, CPAP, or combination treatment can effectively decrease mortality risks in individuals with COMISA.

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Conflict of interest

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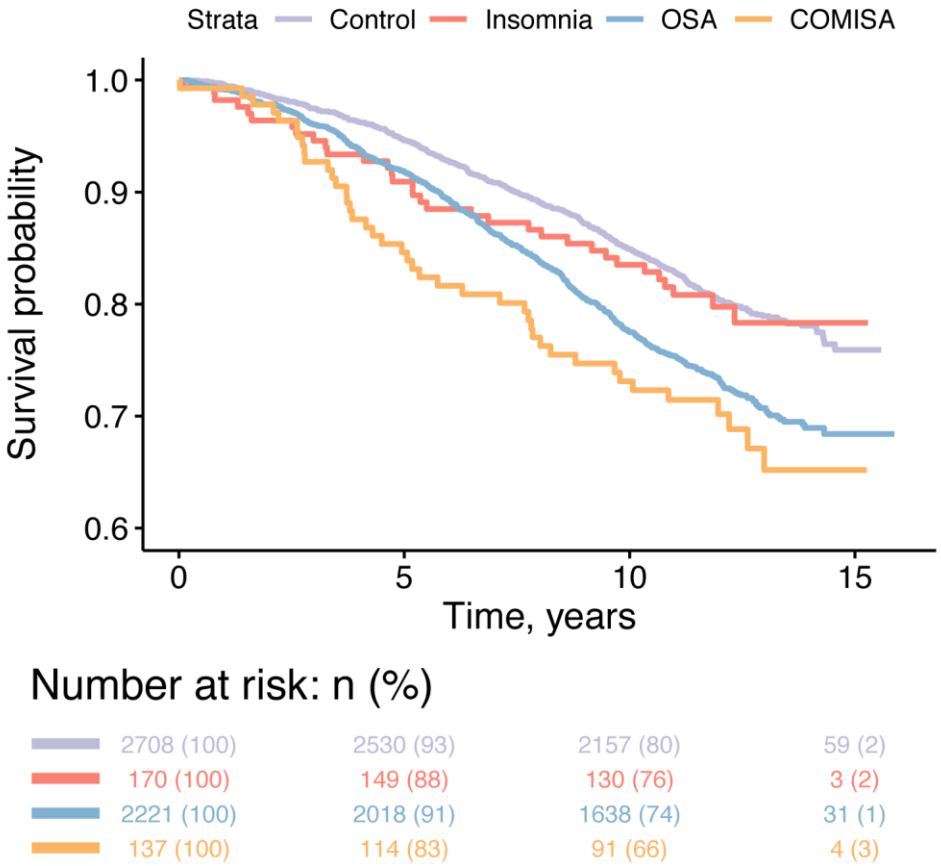

Figure 1: Unadjusted Kaplan-Meier's curve across sleep disorder categories for All-cause mortality. OSA = Obstructive sleep apnoea; COMISA = co-morbid insomnia and sleep apnoea.

Table 1: Participant baseline characteristics.

	Overall	Reference	Insomnia	OSA	COMISA
N (%)	5236 (100)	2708 (52)	170 (3)	2221 (42)	137 (3)
Socio-demographics					
Age, years	63 (11)	61 (11)	61 (12)	66 (11)	65 (11)
BMI, kg/m²	28 (5)	26.96 (4.62)	28 (5)	29 (5)	30 (6)
Gender: female, n (%)	2747 (52.5)	1738 (64.2)	136 (80.0)	814 (36.7)	59 (43.1)
Race, n (%)					
White	4418 (84)	2250 (83)	136 (80)	1920 (86)	112 (82)
Black	463 (9)	252 (9)	14 (8)	183 (9)	14 (10)
Other	355 (7)	206 (8)	20 (12)	118 (5)	11 (8)
Smoking status, n (%)					
Never	2471 (47.3)	1331 (49)	87 (52)	989 (45)	64 (47)
Current	497 (9.5)	306 (11)	24 (14)	154 (7)	13 (10)
Former	2251 (43.1)	1063 (40)	58 (34)	1072 (48)	58 (43)
Years spent in education, n (%)					
Less than 10 years	405 (8)	166 (7)	16 (11)	206 (10)	17 (14)
11 to 15 years	2484 (52)	1237 (51)	86 (58)	1096 (52)	65 (53)
16 to 20 years	1713 (36)	935 (38)	45 (30)	696 (33)	37 (30)
More than 20	191 (4)	93 (4)	2 (1)	93 (5)	3 (3)
Marital Status, n (%)					
Married	4013 (78)	2027 (76)	122 (72)	1770 (81)	94 (70)
Widowed	447 (9)	236 (9)	15 (10)	181 (8)	15 (12)
Divorced/Separated	511 (10)	301 (11)	19 (11)	171 (8)	20 (16)
Never Married	145 (3)	78 (4)	11 (7)	53 (3)	3 (2)
Cardio-metabolic conditions					
Hypertension, n (%)	2263 (43)	990 (37)	89 (52)	1101 (50)	83 (61)
Diabetes, n (%)	374 (7)	138 (5)	13 (8)	208 (9)	15 (12)
Baseline CVD, n (%)	855 (16)	351 (12)	20 (12)	450 (20)	34 (25)
Lipid lowering medication, n (%)	634 (12)	284 (10)	23 (14)	308 (14)	19 (14)
Chronic obstructive pulmonary disease, n (%)	59 (1)	34 (1)	2 (1)	21 (1)	2 (2)
Medication intake					
Sleeping pills > 5 times a month, n (%)	410 (8)	212 (8)	50 (29)	117 (5)	31 (23)
Benzodiazepines, n (%)	285 (5)	157 (6)	38 (22)	74 (3)	16 (12)
Tricyclic anti-depressants, n (%)	145 (3)	81 (3)	14 (7)	44 (2)	6 (4)
Diuretics, n (%)	844 (16)	361 (13)	38 (22.5)	416 (19)	29 (21)

Sleep related covariates					
AHI, events/hours	18.1 (15)	7.5 (3.9)	7.7 (4.2)	30.6 (15.9)	32.2 (17.7)
TST90, %	3.5 (10.3)	1.3 (6.3)	1.6 (7.5)	6.0 (12.9)	7.6 (14.2)
Total sleep time, min	360 (65)	361 (61)	360 (74)	351 (65)	343 (66)
Wake after sleep onset, min	62 (44)	54 (39)	59 (44)	69 (46)	79 (53)
Sleep efficiency, %	83 (11)	84 (9)	83 (11)	81 (11)	78 (12)
Sleep onset latency, min	14 (20)	14 (20)	16 (22)	14 (20)	16 (23)
Arousal index, events/hours	19 (11)	15 (7)	15 (7)	24 (12)	25 (13)
Outcomes					
Death, n (%)	1210 (23)	531 (20)	33 (20)	604 (27)	42 (31)

Data are reported as mean (SD) if continuous and n (%) if categorical

AHI = apnoea/hypopnea index/hr, BMI = body mass index, COMISA = co-morbid insomnia and sleep apnoea, CVD = Cardiovascular disease, OSA = obstructive sleep apnoea, TST90 = percent of total sleep time spent with less than 90% of oxygen saturation. * Composite cardiovascular endpoint in a community sample with and without prevalent cardiovascular disease

Table 2: Adjusted associations between sleep disorder group and all-cause mortality.

	N	N event	Insomnia	OSA	COMISA
Model 1	5236	1210	1.06 (0.75, 1.50)	1.47 (1.30, 1.65)	1.77 (1.29, 2.42)
Model 2	4752	1169	1.33 (0.94, 1.90)	1.01 (0.90, 1.15)	1.41 (1.02, 1.94)
Model 3	4730	1164	1.31 (0.92, 1.87)	1.03 (0.91, 1.17)	1.49 (1.08, 2.05)
Model 4	4439	1123	1.19 (0.82, 1.72)	1.02 (0.90, 1.16)	1.48 (1.07, 2.05)
Model 5	4433	1121	1.11 (0.77, 1.62)	1.01 (0.89, 1.15)	1.47 (1.06, 2.04)

Quoted values are Hazard ratios (and 95% CI) against the reference group. OSA = Obstructive sleep apnoea; COMISA = co-morbid insomnia and sleep apnoea.

Model 1: Unadjusted

Model 2: Age, gender, race, marital status and time spent in education

Model 3: Model 2 AND smoking status and BMI

Model 4: Model 3 AND diabetes, CVD, hypertension, lipid lowering medications and COPD

Model 5: Model 4 AND total sleep time, benzodiazepines use, tricyclic anti-depressants and sleep medication use more than 5 times per month, and diuretics medication

Table 3: Association between COMISA and all-cause mortality risk for different scoring criteria of the apnoea-hypopnea index.

OSA definition		COMISA prevalence	Insomnia	OSA	COMISA
Desaturation cut-off (%)	Arousals included in hypopnea criteria				
3	Yes	2.6%	1.11 (0.77, 1.62)	1.01 (0.89, 1.15)	1.47 (1.06, 2.04)
3	No	2.1%	1.16 (0.82, 1.63)	1.05 (0.92, 1.19)	1.53 (1.07, 2.18)
4	Yes	1.9%	1.05 (0.73, 1.50)	0.98 (0.86, 1.12)	1.57 (1.07, 2.32)
4	No	1.2%	1.28 (0.95, 1.70)	1.14 (0.99, 1.31)	1.51 (0.95, 2.41)

Quoted values are Hazard ratios (and 95% CI) against the reference group. OSA = Obstructive sleep apnoea; COMISA = co-morbid insomnia and sleep apnoea. Models are adjusted for age, gender, race, marital status, time spent in education, smoking status, BMI, diabetes, CVD, hypertension, lipid lowering medication, COPD, total sleep time, benzodiazepine use, tricyclic anti-depressant use and sleep medication use (> 5 times/month) and diuretics medications.

Table 4: Adjusted associations between sleep disorder group and all-cause mortality for different AHI cut-offs.

AHI cut offs	COMISA prevalence	Insomnia	OSA	COMISA
> 5	4.8%	0.83 (0.39, 1.79)	0.87 (0.72, 1.06)	1.20 (0.88, 1.64)
> 10	3.5%	1.21 (0.75, 1.95)	1.03 (0.90, 1.19)	1.37 (1.01, 1.85)
> 15	2.6%	1.12 (0.77, 1.63)	1.01 (0.89, 1.15)	1.48 (1.07, 2.06)
> 20	2.0%	1.23 (0.89, 1.71)	1.03 (0.90, 1.17)	1.42 (0.98, 2.06)

Quoted values are Hazard ratios (and 95% CI) against the reference group. OSA = Obstructive sleep apnoea; COMISA = co-morbid insomnia and sleep apnoea. Models are adjusted for age, gender, race, marital status, time spent in education, smoking status, BMI, diabetes, CVD, hypertension, lipid lowering medication, COPD, total sleep time, benzodiazepine use, tricyclic anti-depressant use and sleep medication use (> 5 times/month) and diuretics medications.

Table 5: Association between COMISA and all-cause mortality risk for different definitions of insomnia.

Insomnia definition		COMISA prevalence	Insomnia	OSA	COMISA
Minimum insomnia symptom Frequency/month	Sleeping medication use/month				
5	Not included in definition	6.3%	1.24 (0.97, 1.60)	1.01 (0.89, 1.16)	1.30 (1.04, 1.62)
15 *	Not included in definition	2.6%	1.12 (0.77, 1.62)	1.01 (0.89, 1.15)	1.47 (1.09, 2.04)
5	5	8.0%	1.05 (0.84, 1.32)	0.98 (0.85, 1.12)	1.30 (1.06, 1.60)
15	5	4.8%	0.98 (0.75, 1.27)	0.99 (0.87, 1.13)	1.32 (1.03, 1.69)
5	15	7.1%	1.07 (0.84, 1.35)	0.99 (0.87, 1.14)	1.26 (1.02, 1.57)
15	15	3.8%	0.97 (0.73, 1.29)	1.00 (0.88, 1.14)	1.27 (0.96, 1.67)

Quoted values are Hazard ratios (and 95% CI) against the reference group. OSA = Obstructive sleep apnoea; COMISA = co-morbid insomnia and sleep apnoea. Models are adjusted for age, gender, race, marital status, time spent in education, smoking status, BMI, diabetes, CVD, hypertension, lipid lowering medication, COPD, total sleep time, benzodiazepine use, tricyclic anti-depressant use and diuretics medication use.

*Primary definition (Hazard Ratio and CIs differ from primary analysis due to removal of ‘sleeping medicines’ from co-variates).

Supplementary material

Lechat et al. Co-morbid insomnia and obstructive sleep apnoea is associated with all-cause mortality.

Baseline characteristics

Table S1: Association between hypertension, diabetes and cardiovascular disease with sleep disorder group at baseline. Reported values are Odds Ratio and 95%CI. Models were controlled for age, BMI and gender.

Outcome	N	N event	Insomnia	OSA	COMISA
Hypertension	5205	2252	1.97 (1.42, 2.75)	1.23 (1.08, 1.40)	2.00 (1.39, 2.90)
Diabetes	4992	374	1.46 (0.79, 2.70)	1.18 (0.93, 1.50)	1.41 (0.79, 2.53)
Baseline CVD	5205	854	0.95 (0.57, 1.57)	1.15 (0.97, 1.37)	1.70 (1.11, 2.61)

Sensitivity analyses

Table S2: Adjusted associations between sleep disorder group and all-cause mortality, excluding participants that died within the first two years (N = 96).

	N	N event	Insomnia	OSA	COMISA
Model 1	5140	1114	0.94 (0.64, 1.38)	1.47 (1.30, 1.66)	1.79 (1.38, 2.17)
Model 2	4659	11076	1.19 (0.81, 1.76)	1.02 (0.90, 1.15)	1.44 (1.03, 2.00)
Model 3	4637	1071	1.18 (0.80, 1.74)	1.03 (0.90, 1.74)	1.52 (1.09, 2.13)
Model 4	4347	1031	1.03 (0.68, 1.56)	1.03 (0.90, 1.17)	1.53 (1.09, 2.16)
Model 5	4341	1029	0.98 (0.64, 1.49)	1.02 (0.89, 1.16)	1.53 (1.09, 2.16)

Quoted values are Hazard ratios (and 95% CI) against the reference group. OSA = Obstructive sleep apnea; COMISA = co-morbid insomnia and sleep apnoea.

Model 1: Unadjusted

Model 2: Age, gender, race, marital status and time spent in education

Model 3: Model 2 AND smoking status and BMI

Model 4: Model 3 AND diabetes, CVD, hypertension, lipid lowering medications and COPD

Model 5: Model 4 AND total sleep time, benzodiazepines use, tricyclic anti-depressants and sleep medication use more than 5 times per month, and diuretics medication