

All-Cause Mortality in People with Co-Occurring Insomnia Symptoms and Sleep Apnea: Analysis of the Wisconsin Sleep Cohort

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Purpose: Insomnia symptoms and sleep apnea frequently co-occur and are associated with worse sleep, daytime function, mental health and quality of life, compared to either insomnia or obstructive sleep apnea (OSA) alone. This study aimed to investigate the association of symptoms of co-morbid insomnia and sleep apnea (COMISA) with all-cause mortality.

Patients and Methods: Wisconsin Sleep Cohort data were analysed to assess potential associations between COMISA symptoms and all-cause mortality. Nocturnal insomnia symptoms were defined as difficulties initiating sleep, maintaining sleep, and/or early morning awakenings “often” or “almost always”, and/or regular sedative-hypnotic medicine use. OSA was defined as an apnea-hypopnea index ≥ 5 /hr sleep. Participants were classified as having neither insomnia symptoms nor OSA, insomnia symptoms alone, OSA alone, or COMISA symptoms. Associations between the four groups and all-cause mortality over 20 years of follow-up were examined via multivariable adjusted Cox regression models.

Results: Among 1115 adult participants (mean $\pm$ SD age 55 ± 8 years, 53% males), 19.1% had COMISA symptoms. After controlling for sociodemographic and behavioral factors, COMISA symptoms were associated with an increased risk of all-cause mortality compared to no insomnia symptoms or OSA (HR [95% CI]; 1.71 [1.00–2.93]). OSA alone (0.91 [0.53, 1.57]) and insomnia symptoms alone (1.04 [0.55, 1.97]) were not associated with increased mortality risk.

Conclusion: Co-morbid insomnia symptoms and sleep apnea is associated with increased all-cause mortality risk. Future research should investigate mechanisms underpinning COMISA and the effectiveness of different treatment approaches to reduce mortality risk for this common condition.

Keywords: sleep disordered breathing, Wisconsin Sleep Cohort, COMISA, obstructive, sleep apnea, insomnia, respiratory

Plain Language Summary

The co-occurrence of insomnia symptoms in people with obstructive sleep apnea (COMISA) is highly prevalent and is associated with poorer cardio-metabolic and mental health. This study investigated the association between COMISA and all-cause mortality over a 19-year follow-up in 1115 adult participants (number of deaths: 108). COMISA was associated with poorer cardiovascular and metabolic health at baseline, with higher prevalence of cardiovascular diseases, hypertension and diabetes compared to participants with neither sleep disorder. Participants with COMISA also had more depression and anxiety symptoms than participants with no sleep disorders. COMISA was also associated with a ~70% increased risk in all-cause mortality compared to control; further suggesting that people with insomnia symptoms and obstructive sleep apnea may be a specific group at higher risk of poor health.

Introduction

Obstructive sleep apnea (OSA) and insomnia are the two most common clinical sleep disorders, and frequently co-occur.^{1–3} OSA is characterized by brief closure (apnea) and narrowing (hypopnea) of the upper airway during sleep, which results in frequent cortical arousals from sleep, non-restorative sleep, worse physical/mental health, and reduced quality of life.^{2,4,5} It is estimated that 20% of people worldwide have OSA.⁶ Insomnia is characterized by difficulties initiating sleep, maintaining sleep or early morning awakenings from sleep, which results in daytime impairment.² Approximately 25–50% of the general adult population report infrequent or acute insomnia symptoms, and 6–20% experience chronic insomnia disorder (symptoms persisting for ≥ 3 months).^{7–11}

Co-morbid insomnia and sleep apnea (COMISA) is a prevalent condition that is associated with greater morbidity compared to either insomnia or sleep apnea alone.¹ For example, approximately 30–50% of people with OSA report insomnia symptoms, and 30–40% of people with insomnia symptoms have co-morbid OSA.¹² People with COMISA report worse sleep,¹³ daytime function,^{14,15} mental health^{16,17} and quality of life,⁵ compared to people with insomnia alone or OSA alone.¹⁸ Furthermore, people with COMISA have worse cardiovascular health compared to people with insomnia alone or neither insomnia nor sleep apnea.^{19–21} Associations between COMISA and morbidity have been reported using a wide range of diagnostic tools and severity/frequency criteria for both insomnia and OSA.¹ Even when COMISA is defined as mild/moderate OSA and less frequent insomnia symptoms (eg ≥ 5 nights/month), associations with worse mental/physical health persist.^{20,22–24}

Previous studies have investigated independent associations between insomnia and mortality^{25,26} as well as OSA and mortality^{27,28} and continuous positive airway pressure therapy and mortality.²⁹ To our knowledge, only two studies have investigated the association between COMISA and all-cause mortality. Using the Sleep Heart Health Study dataset, mortality risk was determined in people with insomnia-alone, OSA-alone, COMISA, or neither disorder, over 15 years of follow-up.³⁰ Insomnia was defined as difficulties initiating and/or maintaining sleep ≥ 16 nights/month and daytime impairment, and OSA was defined according to an apnea-hypopnea index (AHI) $15 \geq$ /hr sleep. COMISA was associated with a 47% increased risk of mortality compared to no insomnia/OSA after controlling for sociodemographic, behavioral factors and chronic conditions. Neither insomnia alone, nor OSA alone, were associated with mortality. However, a single study applying the traditional $p < 0.05$ threshold of significance should not be accepted as absolute truth of a probable relationship between COMISA and mortality.³¹ A recent study by Sweetman et al used the National Health and Nutrition Examination Survey to investigate the association of COMISA (co-morbid insomnia and high-risk OSA assessed with the STOP-Bang) and mortality, over 11 years of follow-up.³² Among 6877 participants, those in the COMISA group experienced a 56% increased risk of all-cause mortality compared to those with neither insomnia nor high-risk OSA, after controlling for sociodemographic factors, behavioral factors, chronic conditions, and potential mediators. Insomnia alone and OSA alone were not associated with increased mortality risk in fully adjusted models. Replication in independent samples, and with different insomnia and OSA threshold is critical to confirm a probable relationship, and to facilitate future systematic integration of cumulative evidence to inform health research and policy. Indeed, the mean age of the Sleep Heart Health cohort was ~ 65 years and it is therefore unclear if the previous findings are generalizable to other younger, healthier community samples. Thus, this study sought to determine the relative mortality risk over 19 years of follow-up in individuals with COMISA symptoms, OSA alone or insomnia symptoms alone compared to individuals with neither OSA nor insomnia symptoms in the Wisconsin Sleep Cohort.

Material and Methods

Study Design and Participants

This study used data from the Wisconsin Sleep Cohort (WSC), an ongoing longitudinal study of the consequences of sleep disorders.^{33–36} The WSC originally recruited ~ 1500 participants in 1988 from a random sample of employees aged 30–60 years from five Wisconsin state agencies. The data in the current study represent a sub-sample of the original WSC study ($n = 1123$), accessed through the National Sleep Research Resources³⁷ in September 2021. The protocol, including flow diagram, study design, as well as main results of the Wisconsin Sleep Cohort are available elsewhere.^{33–36} Accordingly, details below are restricted to those pertinent to the current study. Overnight in-laboratory

polysomnography recordings were undertaken by the participant at the University of Wisconsin–Madison Hospital and Clinics. Most sleep studies (88.1%) were conducted prior to 2005, however, a few participants (11.9%) had a sleep study between 2005 and 2014. This report uses de-identified data from a historical cohort study of participants that previously gave informed consent. Hence, this study was exempted from ethical approval (Paragraph 5.1.22 of the Australian National Statement on Ethical Conduct in Human Research).

Insomnia Symptoms Definition

Standardized interviews about sleep quality at the time of the polysomnography sleep study were administered by trained personnel. For the primary definition of insomnia, insomnia symptoms were defined either by 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; DIMS) at least “often” (≥ 5 nights/month) or “almost always” (≥ 16 nights/month); or self-reported regular use of sedative-hypnotic medicine use (yes/no). While a definition including chronic (≥ 3 months) nocturnal symptoms on at least 16 nights per month, and associated daytime impairments would most accurately reflect “chronic insomnia” criteria,² data on insomnia “chronicity” was unavailable and there were insufficient cases to reliably investigate associations with mortality when using more conservative symptom frequency criteria (See [Supplementary Table 2](#)). Importantly, our operationalization of insomnia symptoms is similar to previous studies investigating the prevalence and associations of COMISA symptoms in population-based and sleep clinic cohorts.^{20,22–24}

We also conducted several sensitivity analyses to investigate associations of COMISA symptoms and mortality according to more conservative definitions of insomnia symptoms including removal of the “sedative-hypnotic use” criterion, increasing the nocturnal insomnia symptom threshold to at least 16 nights per month, and defining insomnia according to the presence of both nocturnal and daytime impairments. Daytime impairment was considered present if the participant answered “often” or “almost always” to the question: “How often do you not feel rested during the day no matter how many hours of sleep you had?” (Never [Never], Rarely [Once a month], Sometimes [1–5 times a month], Often [5–15 times a month], or Almost always [16–30 times a month]). [Supplementary Table 2](#) includes the number of exposure cases and mortality events per group when using the primary and sensitivity definitions of insomnia symptoms.

Obstructive Sleep Apnea Definition

Sleep and respiratory events were scored according to standard criteria at the time of testing.³⁸ Apnea was defined as cessation of airflow for ≥ 10 seconds and hypopnea was defined as a discernible reduction in breathing with a reduction in oxyhemoglobin saturation $\geq 4\%$. The average number of apnea and hypopnea events per hour of sleep (apnea-hypopnea index, AHI) was calculated to define OSA according to an AHI of ≥ 5 events/h sleep. Alternative cut-offs (≥ 10 and 15 events per hour) were investigated in secondary analyses. In addition, OSA was characterized as “symptomatic” or “asymptomatic” based on self-reported daytime impairment (similar question used for insomnia). Percentage of total sleep time with less than 90% of oxygen saturation were also used to characterize nocturnal hypoxia.

COMISA Definition

COMISA was defined if both insomnia symptoms and OSA were present. Participants who did not meet criteria for either insomnia symptoms or OSA were categorized with no insomnia symptoms/OSA (control).

Outcome Assessment

Deaths from any cause, up until 2020, were identified by matching social security numbers with 2 death record sources: the US Social Security Death Index and the Wisconsin State Bureau of Health Information and Policy, Vital Records Section. More information on data matching is available elsewhere.³³ Only the year of death was available through the National Sleep Research Resources. The time to event was defined as the time difference between the sleep study and the date of death.

Covariates

At the time of the polysomnography study, participants were asked about lifestyle, sleep habits, and medical history. Weight, height, and blood pressure were assessed. A wide range of covariates were collected (all of which are available for browsing here: <https://sleepdata.org/datasets/wsc/variables>) during the initial study, and few covariates were retained for statistical analysis, based on previous literature.³⁰ The retained covariates and their definitions are presented in [Supplementary Table 1](#). Depression symptoms score were assessed using the Zung depression scale (score range from 20 to 100).³⁹ Anxiety symptoms score were assessed using the Trait Anxiety questionnaire (score range from 20 to 80).⁴⁰

Statistical Analysis

Distributions of covariates were summarized by sleep disorder group. Differences in covariates between sleep disorder groups were examined using unadjusted logistic or linear regression, as appropriate. Kaplan-Meier survival estimates were analysed for visual interpretation of the crude probability of mortality over time. Cox regression models were conducted to assess all-cause mortality risk of a sleep disorder group compared to control (absence of either sleep disorder). Results are summarized using hazard ratios (HRs) and 95% confidence intervals (CIs). Four models were constructed to further explore the impact of potential confounders. Models' confounders were chosen based on previous studies that investigated the association between COMISA and mortality,³⁰ OSA and mortality,^{27,33} and insomnia and mortality.²⁶ The first model was unadjusted. The second model was adjusted for socio-demographic factors, including age, race, sex, and the highest education level completed. The third model was additionally adjusted for body mass index, smoking status and alcohol intake. The fourth model was additionally adjusted for potential mediators including pre-existing cardio-metabolic conditions (diabetes, cardiovascular disease, hypertension), anti-depressant medication, and polysomnography-derived total sleep time. The fifth model additionally controlled for anxiety and depression symptoms. The main model of interest was Model 3, given that Models 4 and 5 adjusted for additional covariates that are potential mediators of sleep disorder group on mortality, which may have confounded effect estimates.

Sensitivity Analysis

Most sleep studies (~88%) were conducted before 2005, however, to further validate our findings and to account for different year of baseline sleep study, we conducted a sensitivity analysis by removing any participants with a baseline PSG after 2005 (N = 132). We conducted an additional sensitivity analysis removing participants that died within the first 3 years (N=18) of follow-up to minimize the influence of terminal illnesses and pre-existing conditions. We conducted a third sensitivity analysis that removed participants with sleep apnea treatment at baseline (N = 112). Finally, we conducted a fourth sensitivity analysis by further adjusting for percentage of total sleep time spent with less than 90% of oxygen saturation, to further control for potentially worse nocturnal hypoxia in participants with COMISA.

Results

Baseline Characteristics

A total of 1115 participants were available for the final analysis after exclusion of eight participants due to missing values for education status. The median of follow-up time was 19 years (range: 0 to 20 years). The baseline characteristics of participants with insomnia symptoms alone (17.2%), OSA alone (34.2%), COMISA (19.3%), and neither disorder (29.3%, control) are shown in [Table 1](#). A total of 52.2% of all participants with insomnia symptoms had co-morbid OSA, and 36% of all participants with OSA had co-morbid insomnia symptoms. Participants with COMISA or OSA alone had lower polysomnography total sleep time compared to the control group ([Table 1](#)), but there was no evidence of differences in total sleep time between the three sleep disorder groups (all *p*-values > 0.20).

Cardiometabolic and Mental Health Conditions

Cardiovascular disease was more common in participants with COMISA symptoms (ORs [95% CI]; 2.28 [1.28, 4.07]) and to some extent OSA alone (1.68 [0.98, 2.89]), but not insomnia symptoms alone (1.08 [0.54, 2.17]) compared to control (no OSA or insomnia symptoms). There was no evidence of a difference in cardiovascular disease prevalence

Table I Baseline Characteristics

	Control	Insomnia Symptoms Alone	OSA Alone	COMISA	p-value
n	327 (29.3%)	192 (17.2%)	381 (34.2%)	215 (19.3%)	
Age, years	54 (7)	56 (9)	58 (8)	57 (8)	<0.001
Sex (Male)	168 (51%)	76 (40%)	248 (65%)	111 (52%)	<0.001
BMI	29 (6)	29 (6)	34 (7)	34 (8)	<0.001
Smoker (%)					0.024
Never	179 (55%)	94 (49%)	184 (48%)	100 (46%)	
Past	110 (33%)	74 (38%)	170 (45%)	88 (41%)	
Current	39 (12%)	24 (13%)	27 (7%)	27 (13%)	
Alcohol intake (drinks per week)	3.6 (5.1)	3.4 (5.1)	3.9 (5.4)	3.5 (4.6)	0.716
Race					0.146
Asian	7 (2.1)	0 (0.0)	2 (0.5)	3 (1.4)	
Black	3 (0.9)	3 (1.6)	10 (2.6)	7 (3.3)	
Hispanic	3 (0.9)	1 (0.5)	4 (1.0)	5 (2.3)	
Native American	4 (1.2)	3 (1.6)	2 (0.5)	1 (0.5)	
White	310 (94.8)	185 (96.4)	363 (95.3)	199 (92.6)	
Total sleep time, min (self-report)	438 (54)	424 (62)	438 (55)	423 (70)	0.001
Total sleep time, min (polysomnography)	378 (59)	372 (60)	366 (59)	365 (58)	0.016
AHI	1.9 (1.4)	2.0 (1.4)	19.6 (15.8)	20.6 (18.2)	<0.001
TST 90%	0.9 (6.7)	1.0 (7.2)	3.7 (10.6)	4.8 (13.3)	<0.001
Cardiovascular disease (yes)	22 (7%)	14 (7%)	41 (11%)	30 (14%)	0.023
Hypertension (yes)	84 (26%)	45 (23%)	148 (39%)	89 (41%)	<0.001
Diabetes (yes)	21 (6%)	15 (8%)	51 (13%)	36 (17%)	<0.001
Use of anti-depressant	49 (15%)	60 (31%)	63 (17%)	58 (27%)	<0.001
Use of sedative medication	0 (0%)	46 (24%)	0 (0%)	45 (21%)	<0.001
Depression symptoms score (range 20 to 100)	38 (8)	43 (9)	39 (8)	44 (9)	<0.001
Anxiety symptoms score (range 20 to 80)	31 (8)	35 (9)	31 (8)	34 (9)	<0.001
Deaths	24	16	34	34	0.008
Crude mortality rate (deaths/1000 person-years)	4.0	4.6	5.2	9.2	0.001

Notes: Anxiety = State-Trait Anxiety Inventory, Trait scale; Depression = Zung depression scale.

Abbreviations: BMI, Body Mass Index; TST 90%, percent of sleep time with oxygen saturation below 90; AHI, apnea-hypopnea-index.

between participants with OSA alone and COMISA (p -value = 0.237). Both OSA alone and COMISA symptoms were associated with a greater prevalence of cardiovascular disease at baseline compared to insomnia symptoms alone (both p -values < 0.001). Compared to the control group, hypertension was more prevalent in participants with COMISA symptoms (2.04 [1.41, 2.96]) and OSA alone (1.85 [1.34, 2.56]). Diabetes was also more prevalent in COMISA symptoms (2.97 [1.68, 5.25]) and OSA alone (2.26 [1.33, 3.86]) compared to the control group.

Compared to the control group, participants with OSA alone did not have higher anxiety scores on the Trait scale (β [95% CI], 0.03 [−1.2, 1.3]) or depression scores on the Zung index (0.9 [−0.3, 2.1]). However, anxiety and depression symptoms scores were increased in both the insomnia symptoms alone (anxiety: 4.0 [2.5, 5.5], depression: 4.4 [3.0, 5.9]) and COMISA symptoms groups (anxiety: 2.8 [1.4, 4.3], depression: 5.5 [4.1, 6.9]), compared to the control group. Those with insomnia symptoms alone and COMISA symptoms had higher anxiety scores and higher depression scores, compared to participants with OSA alone (p -values <0.001).

All-Cause Mortality

The crude mortality rate was larger for the COMISA symptoms group (9.5 deaths/1000 participant years) compared to insomnia symptoms alone (4.5), OSA alone (5.2), or control groups (4.0). Kaplan-Meier curves also suggested a lower

survival probability for participants with COMISA symptoms compared to control, insomnia symptoms or OSA groups (Figure 1). In the unadjusted Cox-model, the COMISA group had a 2.3-fold increase in all-cause mortality risk compared to the control group (Table 2). COMISA symptoms were associated with increased risk of all-cause mortality compared to control after adjustment for socio-demographic factors (HR 95% CI; 1.89 [1.11, 3.20]), behavioral factors (1.71 [1.00, 2.93]; primary model of interest), and chronic conditions and potential mediators (1.71 [1.00, 2.97]), but not when additionally controlling for mental health symptoms (1.63 [0.94, 2.82]; Table 2). Neither insomnia symptoms alone nor OSA alone were associated with all-cause mortality compared to the control group in any crude or adjusted models. Furthermore, the COMISA symptoms group had an 89% (1.89 [1.17, 3.06]) increase in mortality risk compared to OSA-alone and a marginal 68% (1.68 [0.91, 3.10]) increase compared to insomnia symptoms alone in model 3 (primary model).

Increasing the AHI threshold to define OSA beyond 5 events/h did not change the main findings (Table 3). COMISA defined using an AHI cut-off of either ≥ 10 or ≥ 15 events/h was associated with a 1.86 (1.09, 3.19) and 1.86 (1.02, 3.41)-fold increase in mortality risk respectively compared to the control group (Table 3). However, insomnia symptoms defined without the sedative-hypnotic criterion reduced the apparent prevalence of insomnia symptoms and of COMISA, but only marginally attenuated the mortality risk in the COMISA symptoms group compared to the control group (1.66 [0.97, 2.83]). Other definitions of insomnia (inclusion of daytime impairments and increasing the frequency of nocturnal insomnia symptoms to at least 16/month) did not change the main findings (Table 3). More conservative definitions of

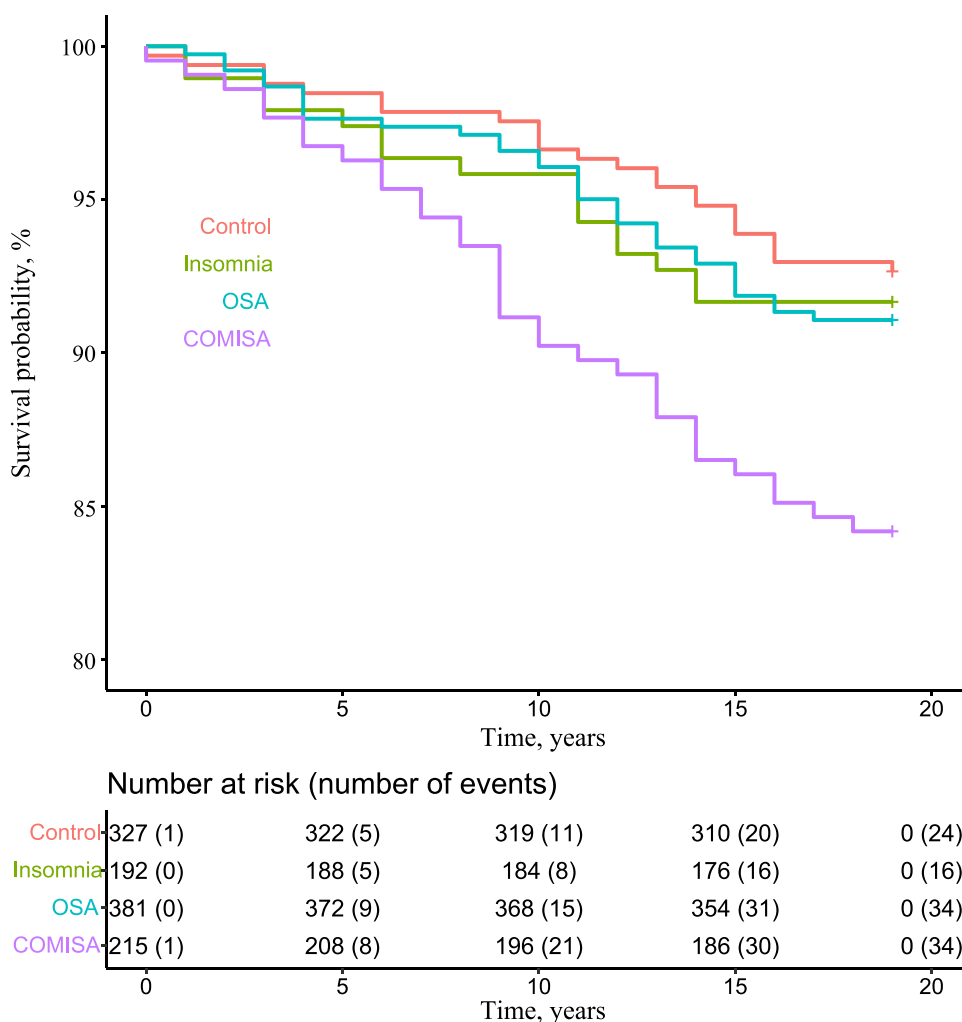


Figure 1 Unadjusted Kaplan-Meier curve across sleep disorder categories for all-cause mortality.
Abbreviations: OSA, Obstructive sleep apnea; COMISA, co-morbid insomnia and sleep apnea.

Table 2 Associations Between Sleep Disorder Group and All-Cause Mortality

	Insomnia Symptoms Alone	OSA Alone	COMISA
Model 1	1.16 (0.61, 2.17)	1.22 (0.73, 2.07)	2.27 (1.35, 3.83)
Model 2	1.01 (0.53, 1.92)	0.96 (0.56, 1.63)	1.89 (1.11, 3.20)
Model 3*	1.04 (0.55, 1.97)	0.91 (0.53, 1.57)	1.71 (1.00, 2.93)
Model 4	1.04 (0.55, 1.98)	0.91 (0.53, 1.58)	1.71 (1.00, 2.97)
Model 5	1.01 (0.53, 1.93)	0.91 (0.53, 1.58)	1.63 (0.94, 2.82)

Notes: Quoted values are Hazard Ratios (and 95% CI) against the reference control group with neither sleep disorders. Model 1: Unadjusted. Model 2: Age, sex and educational status. Model 3: Model 2 AND smoking status, alcohol intake and BMI. Model 4: Model 3 AND diabetes, previous CV event, hypertension, total sleep time, any anti-depressants. Model 5: Model 4 AND depression symptoms, anxiety symptoms.
*Primary model.

Abbreviations: OSA, Obstructive sleep apnea; COMISA, co-morbid insomnia and sleep apnea.

Table 3 Adjusted Associations Between Sleep Disorder Group and All-Cause Mortality

OSA Definition	Insomnia Symptoms Definition	Insomnia Symptoms Alone	OSA Alone		COMISA
AHI $\geq 5^*$	DIMS ≥ 5 /month, and/or SH use*	1.04 (0.55, 1.97)	0.91 (0.53, 1.57)		1.71 (1.00, 2.93)
AHI ≥ 10	DIMS ≥ 5 /month, and/or SH use*	1.18 (0.70, 2.00)	0.92 (0.54, 1.58)		1.86 (1.09, 3.19)
AHI ≥ 15	DIMS ≥ 5 /month, and/or SH use*	1.58 (0.98, 2.55)	1.34 (0.77, 2.31)		1.86 (1.02, 3.41)
AHI $\geq 5^*$	DIMS ≥ 5 /month AND daytime impairment, and/or SH use	1.10 (0.50, 2.41)	1.09 (0.68, 1.73)		1.82 (0.98, 3.36)
AHI $\geq 5^*$	DIMS ≥ 16 /month, and/or SH use	1.29 (0.57, 2.94)	1.13 (0.71, 1.78)		1.78 (0.94, 3.37)
AHI $\geq 5^*$	DIMS ≥ 5 /month	0.92 (0.47, 1.80)	0.91 (0.54, 1.52)		1.66 (0.97, 2.83)
AHI ≥ 10	DIMS ≥ 5 /month	0.99 (0.57, 1.72)	0.85 (0.51, 1.43)		1.86 (1.09, 3.15)
AHI ≥ 15	DIMS ≥ 5 /month	1.43 (0.88, 2.32)	1.25 (0.74, 2.13)		1.81 (0.98, 3.27)
AHI ≥ 5	DIMS ≥ 5 /month, and/or SH use*	1.04 (0.55, 1.97)	Asymptomatic	Symptomatic	1.71 (1.00, 2.93)
			0.84 (0.47, 1.49)	1.23 (0.54, 2.78)	

Notes: *Primary definition. Quoted values are Hazard Ratios (and 95% CI) against the reference control group with neither sleep disorder. Models are adjusted for age, sex, educational status, smoking status, alcohol intake and BMI.

Abbreviations: AHI, apnea-hypopnea index; COMISA, co-morbid insomnia and sleep apnea; DIMS, difficulties initiating and/or maintaining sleep; OSA, Obstructive sleep apnea; SH, sedative-hypnotic.

OSA and insomnia symptoms should be interpreted with caution, due to the lower number of deaths in the COMISA symptoms group for these secondary analyses ([Supplementary Table 2](#)). When OSA was further categorized as “symptomatic” and “asymptomatic”, no associations were observed with all-cause mortality compared to control ([Table 3](#)), although care should be taken in the interpretation of these findings given that there were only 71 patients with symptomatic OSA and 8 deaths ([Supplementary Table S2](#)). Further adjusting for % of total sleep time spent with less than 90% of oxygen in Model 4 did not change the main findings. In this model, COMISA remained associated with mortality (HR 95% CI: 1.73 [1.00, 3.00]). OSA (0.92 [0.53; 1.60]) and insomnia-alone (1.05 [0.55, 2.00]) were not associated with increased mortality risk. The findings remained the same in sensitivity analysis once the 132 participants (11.8%) who had a polysomnography after 2006 were removed ([Supplementary Table S3](#)). Similar results were also observed when participants that died within the first 3 years were excluded ([Supplementary Table S4](#)). The effect also

remained relatively similar when participants using sleep apnea treatment at baseline were excluded, although with wider 95% CIs ([Supplementary Table S5](#)).

Discussion

Co-morbid insomnia symptoms and sleep apnea (COMISA) at baseline was associated with increased risk of all-cause mortality over 19 years of follow-up compared to insomnia symptoms alone, OSA alone, and the absence of either disorder. The association between COMISA symptoms and mortality persisted after controlling for sociodemographic factors, behavioral factors, and chronic conditions, and remained quite consistent across multiple definitions of insomnia and OSA. These findings support previous reports that COMISA is associated with impaired sleep, mental health, physical health, quality of life and longevity.^{12,30}

The results of the current study are consistent with our recent work that indicated that COMISA is associated with a 47–56% increase in all-cause mortality risk compared to no insomnia/OSA^{30,32} in the Sleep Heart Health Study and National Health and Nutrition Examination Survey cohorts. Participants in the WSC sample were younger and relatively healthy at baseline compared to the Sleep Heart Health Study cohort, and slightly older than the National Health and Nutrition Examination Survey cohort. Furthermore, our previous analyses of mortality outcomes used definitions of insomnia that included both frequent nocturnal insomnia symptoms and daytime impairment, that may more closely reflect diagnostic criteria. This may explain the larger prevalence of COMISA symptoms in the current study compared to our earlier reports in the Sleep Heart Health Study and National Health and Nutrition Examination Survey data. Indeed, daytime impairments were not included in the primary definition of insomnia in the present study. However, sensitivity analyses suggested that inclusion of daytime impairment in the definition of insomnia did not substantially change the main findings. Taken together, these three studies suggest that COMISA is consistently associated with all-cause mortality with robust associations across multiple definitions of insomnia and OSA frequency and severity.

Previous cross-sectional studies have reported that COMISA is associated with increased rates of cardiovascular events compared to insomnia alone or controls.^{19–21,41} Indeed, we observed that the COMISA symptoms and OSA alone groups generally had higher rates of hypertension, diabetes, and cardiovascular events compared to the insomnia alone or control group. A recent paper by Lechat et al used the Sleep Heart Health Study cohort to investigate the association between COMISA with prevalent cardiovascular disease and incident cardiovascular events.²¹ COMISA was associated with increased odds of cardiovascular disease at baseline, and a two-fold increase in incident cardiovascular events over 11-years of follow-up, compared to participants with neither insomnia nor OSA. However, COMISA was not associated with incident cardiovascular events in fully controlled models. Furthermore, consistent with previous literature, we also observed more severe depression and anxiety symptoms in the COMISA, and insomnia symptoms alone groups compared to the OSA alone or control groups.^{16,19} It is likely that mental health symptoms mediate the relationship between COMISA and mortality.^{16,42} Insomnia and OSA are longitudinally associated with worse mental health, and treatment of sleep disorders improves mental health.^{42–44} Indeed, the association between COMISA and mortality was no longer significant in model 5 which additionally controlled for depression and anxiety symptoms as a potential mediator. Future research should investigate the effect of COMISA treatment including CBTi,⁴⁵ CPAP therapy,²⁹ and surgical interventions⁴⁶ on reducing potential mediators of mortality risk such as mental health symptoms.⁴⁷

OSA was defined according to several thresholds. Previous COMISA studies have adopted a range of AHI scoring criteria and thresholds to define OSA.¹ In this study, we found an association between COMISA and all-cause mortality with OSA defined as AHI ≥ 5 , 10, and 15 events per hour of sleep. Hypopneas were defined according to more stringent criteria in the current study ($\geq 4\%$ oxygen desaturation), compared the Sleep Heart Health Study report, which relied on the more recent $\geq 3\%$ desaturation (or arousal) criterion for defining hypopneas.²⁷ AHI calculated using a $\geq 4\%$ cut-off is usually between 5 to 10 events per hour lower than AHI calculated using a $\geq 3\%$ oxygen cut-off.⁴⁸ Therefore, our results are consistent with the previous study suggesting an increased mortality risk in participants with co-morbid insomnia and moderate OSA compared to control.³⁰ Our results that OSA-alone, with or without daytime impairment, is not associated with all-cause mortality is somewhat surprising given that previous studies, including from the WSC, have reported associations between OSA and all-cause mortality.^{27,33,49} However, these previous reports usually only found an association between moderate and severe OSA and all-cause mortality,^{33,49} and sometimes only in men.²⁷ In this

study, we did not have the power to further categorize OSA as moderate and severe and to test for a sex-interaction effect. Furthermore, these previous studies did not control for insomnia symptoms, and thus COMISA was not accounted for. It is possible that the association between COMISA and mortality may be partially explained by more severe OSA, through increased cardiovascular responses to apneic events,^{50,51} high levels of hypoxia,⁵² sleep fragmentation,^{53,54} or other co-morbidities. Future research trials should investigate the contribution of each to these OSA traits and clinical phenotypes to the increased mortality risk. Finally, the increase in mortality risk for people with COMISA, including in this study, has only been investigated in general population studies.^{30,32} Future studies should investigate association between COMISA and health outcomes in sleep clinic populations.

After removing 112 participants with positive airway pressure use at baseline, there was an association between COMISA and mortality in the unadjusted model, but not after adjusting for co-variables. As OSA treatment may be protective against mortality risk,⁵⁵ this is somewhat surprising. Attenuation of the relationship between COMISA and mortality may have been due to the reduction in sample size, or more complex relationships between rates of positive airway pressure therapy acceptance, use and rejection/survival between people with OSA alone and COMISA.¹ Future studies should investigate the effect of nightly positive airway pressure use, other OSA therapies, and insomnia treatment on the association of COMISA and mortality.

The findings of this study highlight the importance of routinely screening for insomnia symptoms in sleep clinics that current specialize in the diagnosis and management of OSA-alone, and to develop more effective and tailored treatment approaches for patients with COMISA. Current evidence suggests that combining targeted treatments for each disorder results in the best overall treatment outcomes in people with COMISA.^{1,56} Cognitive behavioral therapy for insomnia is the recommended “first line” treatment for insomnia,⁵⁷ is effective in the presence of un-treated OSA, and may improve subsequent acceptance and long-term use of positive airway pressure therapy.¹⁸ Positive airway pressure therapy is the most effective treatment for moderate and severe OSA, and improves co-morbid insomnia symptoms in a sub-sample of people with COMISA.¹² Future studies should investigate the potential effect of combination treatment approaches for COMISA on improving mental and physical health outcomes.

Limitations

This study should be interpreted in light of several limitations. Although a higher frequency of nocturnal insomnia symptoms, associated daytime impairments, and information about chronicity of insomnia symptoms would have reflected conservative diagnostic criteria for “chronic insomnia”, these data were either unavailable, or reduced the size of the COMISA group to the point where there were insufficient outcome cases available for reliable analysis and interpretation of associations with mortality. Furthermore, given previous COMISA literature reporting associations with worse physical and mental health when using less conservative insomnia criteria,^{20,22–24} we sought to determine if associations between COMISA and mortality were also present when defining insomnia according to different criteria and threshold. Consequently, a threshold of nocturnal insomnia symptoms on at least five nights per month (associated with a frequency descriptor of “Often”) and/or regular sedative-hypnotic use was selected as the primary definition of insomnia symptoms. In this study, associations with mortality persisted for several more conservative “insomnia symptom” definitions, however these were based on very few deaths (See [Table S2](#)).

Regular use of sedative-hypnotic medicines was used to define insomnia symptoms and ~20% of participants with COMISA/insomnia reported using sedative medication. Use of sleeping medication has also been used to define insomnia in a previous report from the Sleep Heart Health Study.²⁶ It is possible that some people in our study were using sedative or hypnotic medicines for indications other than insomnia (eg, anxiety, epilepsy, muscle spasms). A sensitivity analyses indicated that the association between COMISA and mortality was attenuated to non-significance after removing the “sedative hypnotic” criterion from the insomnia symptoms definition, likely due to a reduced number of participants (and deaths) in the COMISA group ([Table 2](#)).

Furthermore, OSA was defined based using an AHI measured on a single night. There is increased evidence that OSA is highly variable from night-to-night, which may have induced some noise in the association between COMISA, OSA-alone and all-cause mortality.^{6,58} Finally, racial-ethnic sleep disparities have been reported in others cohorts⁵⁹ and our results remain to be validated in a more diverse population than the one presented in this study.

Conclusions

This study found that people with co-morbid insomnia symptoms and sleep apnea are at increased risk of all-cause mortality compared to people without either sleep disorder. Insomnia symptoms alone and OSA alone were not associated with increased mortality risk. It is important to investigate mechanisms contributing to worse mental and physical health in people with COMISA, and to develop more effective treatments for this prevalent and debilitating condition.

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Author Contributions

All authors have contributed to the study design, data analysis and interpretation, and drafting of the manuscript. All authors have contributed and approved the final version of the manuscript. All authors agree to take responsibility and be accountable for the contents of the article.

Disclosure

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