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Association of co-morbid insomnia and sleep apnoea symptoms with all-cause mortality: Analysis of the NHANES 2005-2008 data.

Alexander Sweetman[a,b,*], Bastien Lechat[a], Sarah Appleton[a], Amy Reynolds[a], Robert Adams[a,b], Yohannes Adama Melaku[a,c]

[a] The Adelaide Institute for Sleep Health, Flinders Health and Medical Research Institute: Sleep Health, College of Medicine and Public Health, Flinders University, Australia
[b] National Centre for Sleep Health Services Research: A NHMRC Centre of Research Excellence, Flinders University, Adelaide, South Australia
[c] Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Victoria

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ABSTRACT

Background: Co-morbid insomnia and sleep apnoea (COMISA) is a highly prevalent condition associated with negative health outcomes. This population-based study aimed to investigate the association between COMISA and all-cause mortality.

Methods: Sleep data in 6,877 participants (Age median [IQR]=45 [33,57], 50.1% male) were drawn from the National Health and Nutrition Examination Survey (2005-2008). Insomnia was defined as difficulties initiating sleep, long awakenings, and/or early morning awakenings on ≥16 nights/month, with daytime impairment. The STOP-Bang questionnaire was used to identify participants at high risk of obstructive sleep apnoea (OSA). COMISA was defined if participants met criteria for insomnia and high risk OSA. The median (IQR) follow-up for mortality was 8.6 (7.8, 9.8) years. Cox regression models were used to determine the association between COMISA and all-cause mortality, controlling for socio-demographic characteristics, behavioural factors and chronic conditions.

Results: The prevalence of no insomnia/OSA, insomnia-alone, OSA-alone, and COMISA were 73.5, 3.0, 20.1, and 3.3%, respectively, and 6.7% of participants died by 11-year follow-up. Compared to participants with no insomnia/OSA, higher mortality risk was observed in participants with COMISA (HR=1.9; 95%CI=1.3-2.8) and insomnia alone (HR=1.5; 95%CI=1.0-2.3) after adjusting for socio-demographic characteristics, and behavioural factors. The relationship between COMISA and mortality persisted after additionally controlling for chronic conditions, sleep duration and sleeping pill use (HR=1.6; 95%CI=1.1-2.3), but the relationship between insomnia-alone and mortality did not (HR=1.4; 95%CI=0.9-2.3).

Conclusion: Co-morbid insomnia and high-risk OSA is associated with increased risk of all-cause mortality. More research is needed to identify effective treatments for COMISA.

1. Introduction

Insomnia and obstructive sleep apnoea (OSA) are the two most common sleep disorders, each occurring in 10-30% of the general population [1–6]. Insomnia is defined by frequent self-reported difficulties initiating sleep, maintaining sleep, and/or undesired early morning awakenings, and associated daytime impairments including fatigue, concentration difficulties, poor mood, and impaired workplace/social functioning [3]. OSA is characterised by frequent narrowing (hypopnoea) and closure (apnoea) of the upper airway during sleep, resulting in reduced oxygen saturation, cortical arousals from sleep, and daytime impairments [3]. Both untreated insomnia and OSA are independently associated with reduced quality of life, worse physical and mental health and high healthcare use [7–13].

Insomnia and OSA frequently co-occur [14]. Co-morbid insomnia and sleep apnoea (COMISA) is a highly prevalent and debilitating condition that is associated with greater morbidity compared to insomnia or OSA alone [14]. For example, approximately 40-50% of people with OSA have clinically significant insomnia, and 30-40% of people with chronic insomnia have co-morbid OSA [15]. People with COMISA have

Abbreviations: AHI, Apnoea-hypopnoea index; BMI, Body mass index; CBTi, Cognitive behavioral therapy for insomnia; COMISA, Co-morbid insomnia and sleep apnoea; CPAP, Continuous positive airway pressure; CVD, Cardiovascular disease; HR, Hazard ratio; NHANES, National health and nutrition examination survey; OSA, Obstructive sleep apnoea.

* Corresponding author at: The Adelaide Institute for Sleep Health, Level 2A, Mark Oliphant Building, 5 Laffer Drive, Bedford Park, Flinders University, South Australia, Australia.

E-mail address: alexander.sweetman@flinders.edu.au (A. Sweetman).

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worse sleep [16], daytime function [17,18], mental health [19], productivity [20], quality of life [21,22], and greater rates of cardiovascular disease (CVD) [23] compared to people with insomnia alone, OSA alone, or neither disorder [24]. Previous population-based studies have reported associations of self-reported OSA symptoms (e.g. frequent snoring, daytime sleepiness, witnessed apnoea events) and co-morbid insomnia with reduced health and productivity [20,25,26].

Research has independently investigated the association of insomnia and mortality [27], and OSA and mortality [28], however only one study to date has investigated the association between COMISA and mortality. Lechat and colleagues recently used the Sleep Heart Health Study data to investigate the association of COMISA and all-cause mortality over 15 years of follow-up [29]. Participants with COMISA had a 47% increased risk of mortality, compared to participants with neither insomnia nor OSA. This study defined OSA using polysomnography, which is costly and often has long-waiting times. Polysomnography defined OSA also fails to account for clinical presentation and symptoms (ie. symptomatic OSA), which may have important associations with health consequences. It is currently unclear whether self-report measures of co-morbid insomnia and OSA symptoms are associated with mortality. Determining this is important, as if these self-report measures are reliable, this will allow greater investigation of COMISA, health and safety in populations where polysomnography is not feasible. This study aimed to investigate the association of self-reported COMISA symptoms and mortality, to inform simple and widely accessible tools to screen for COMISA and its associated health risk.

2. Methods

2.1. Study design and participants

This study used data from two cycles of the National health and Nutrition Examination Survey (NHANES) 2005-2008 waves [30]. NHANES is US-based ongoing nationally representative study including adults and children. 20,497 people participated in the 2005-2008 waves. After excluding participants less than 20 years of age (N=9,583), pregnant women (N=372), and those with missing data on exposure (N=3,135), outcome (N=4) and covariates (n=526), 6,877 participants were included in this study. No ethics approval was required for this study.

2.2. Definitions of insomnia, sleep apnoea, and COMISA

Probable insomnia was defined as at least one nocturnal symptom (trouble falling asleep, and/or frequent awakenings from sleep, and/or early morning awakenings from sleep) on at least 16 nights per month, *and* at least one daytime symptoms (feeling unrested during the day more than half the time, or at least moderate difficulties with; concentration, memory, tiredness or low energy, work difficulties because of tiredness, or engaging in hobbies due to tiredness). This definition follows diagnostic criteria for insomnia, which specifies that at least one frequent nocturnal symptom and one daytime impairment must be present [3].

High-risk OSA was defined according to a high-risk score on the STOP-Bang [31]. The STOP-Bang includes 8 self-report items with a yes-no response option (Snoring, Tired, Observed apnoea [snort], Pressure [high blood pressure], Body Mass Index [BMI], Age, Neck [waist circumference], and Gender; see **Supplementary Materials**). Scores range from 0 (negative response to all items) to 8 (positive response to all items). High risk OSA was defined as a score of ≥5 on the STOP-Bang, or a score of ≥2 on the STOP in addition to at least one of; male, BMI >35, high waist circumference threshold. Sensitivity analyses were also performed with different definitions of OSA. First, OSA was defined as intermediate-risk or high-risk on the STOP-Bang (≥3 on STOP-Bang, or ≥2 on STOP and at least one of male, BMI >35, or high waist circumference threshold). Secondly, OSA was defined as a score of ≥2 on the STOP [31] (i.e. same as high-risk sub-criteria without BMI, age, waist circumference or gender). Previous population-based studies of COMISA have used similar self-report measures to define high-risk OSA [20,22,25,26]. COMISA was defined if both conditions were present. The reference group included participants with neither insomnia nor OSA.

2.3. Mortality assessment

NHANES data are linked with the US mortality registry dataset using a probabilistic record linkage [National Health and Nutrition Examination Survey (1999–2014) Linked mortality files. [Accessed: June 23, 2019]. Available: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/datalinkage/linked_mortality/]. We combined the two datasets using sequence numbers. The registry contains participants' unique number, mortality status, cause of death, and age at death. In the analyses, we considered all-cause mortality. Mortality data were updated to 2015 for NHANES 1999/-2000 – 2013/-14 waves.

2.4. Covariates

We constructed incremental models to control for socio-demographic characteristics (age, sex, BMI, educational status, marital status, family poverty income ratio, and race), behavioural factors (smoking, physical activity level and alcohol consumption), chronic conditions (diabetes, cancer and cardiovascular disease), and potential mediators, sleep-related symptoms and treatments (sleep duration, sleep medicine use, depression and health insurance status). Information about assessment of covariates is available in the **Supplement**.

2.5. Statistical analyses

Cox regression models were used to compare mortality risk between participants with no insomnia/OSA, insomnia alone, OSA alone and COMISA. Hazard ratios (HRs) and 95% Confidence Intervals (CIs) are reported. HRs represent the ratio of events over time in an exposure (or intervention) group relative to a control group (HR = hazard in exposure group/hazard in control group). For this analysis, HRs above 1 represent increased risk of mortality over time in the COMISA group relative to the control group, while HRs less than 1 represent reduced risk of mortality over time in the COMISA group relative to the control group. In addition to unadjusted analyses, we used 4 models to investigate the association of COMISA and mortality. Model 1 was adjusted for age, sex, BMI, educational status, marital status, family poverty income ratio, and race. Model 2 additionally adjusted for smoking, physical activity level and alcohol consumption. Model 3 additionally adjusted for diabetes, cancer and cardiovascular disease. Finally, model 4 additionally adjusted for sleep duration, sleep medicine use, depression and health insurance status. Analyses were performed using STATA 16.0 and R (R Foundation for Statistical Computing; Vienna, Austria).

Age and sex may moderate the effect of sleep disorder status on mortality [29,32,33]. Therefore, we conducted subgroup analysis stratified by age (≤48, vs >48 years; median age of COMISA group) and sex to investigate the association of COMISA and mortality. We also assessed an interaction between COMISA and other covariates in predicting mortality risk using multiplicative terms.

In addition to two sensitivity analyses with different OSA definitions, two additional sensitivity analyses were performed. Firstly, participants with chronic conditions at baseline were removed (diabetes, cancer, and cardiovascular disease). Secondly, mortality risk was compared between participants with COMISA, versus no COMISA (ie. collapsing groups with; insomnia alone, OSA alone, and neither insomnia/OSA).

3. Results

3.1. Baseline characteristics

The prevalence and baseline characteristics of the no insomnia or OSA (reference), insomnia alone, high-risk OSA alone, and COMISA

Table 1
Baseline characteristics of groups with no insomnia or OSA (reference), insomnia alone, OSA alone, and COMISA.

		Overall	No insomnia or OSA	Insomnia alone	High-risk OSA	COMISA
%			73.5	3.0	20.1	3.3
Age in years, median; interquartile		45 (33, 57)	43 (31, 54)	41 (29, 51)	54 (43, 64)	48 (39, 57)
Age category						
	≤48 years	58.0	62.9	72.3	39.1	51.4
	>48 years	42.0	37.1	27.7	60.9	48.6
Males		50.1	48.3	31.2	60.3	45.8
Educational status						
	Less Than High School	17.5	16.0	22.0	20.9	25.9
	School Diploma (including GED)	24.7	23.1	31.9	28.2	32.0
	More Than High School	57.8	60.9	46.1	50.9	42.2
Cohabitating						
	Yes	69.2	68.8	63.4	72.5	64.3
	No	30.8	31.2	36.7	27.5	28.3
Race						
	Mexican American	7.4	8.0	5.0	5.9	4.8
	Other Hispanic	4.0	4.1	3.1	3.8	5.1
	Non-Hispanic White	73.1	72.5	76.7	75.4	71.4
	Non-Hispanic Black	10.4	10.3	8.1	11.0	13.6
	Other Race (Inc. Multi-Racial)	5.0	5.2	7.1	3.9	5.2
Family poverty to income ratio (mean, SD)		3.2 (1.6)	3.2 (1.6)	2.5 (1.7)	3.1 (1.7)	2.4 (1.8)
Smoking						
	Never smoked	51.5	55.1	32.9	44.2	33.4
	Former smoker	25.2	23.3	24.8	31.4	28.7
	Smoker	23.3	21.6	42.3	24.4	37.8
Physical activity level (MET-minutes/week)						
	Low (<600)	35.4	32.1	46.3	42.8	53.1
	Moderate (≥600 - <1200)	13.7	14.1	8.5	13.7	9.2
	High (≥1200)	50.9	53.8	45.2	43.4	37.7
Alcohol intake						
	Non-drinker	10.0	10.5	6.0	9.2	8.6
	Drank rarely	14.1	13.1	16.5	15.3	27.6
	Drinker	75.9	76.4	77.5	75.5	63.8
Sleep duration (mean, SD)		6.9 (1.3)	7.0 (1.2)	5.9 (1.8)	6.7 (1.5)	5.4 (1.7)
BMI, mean (SD)		28.5 (6.5)	27.3 (5.6)	26.6 (5.5)	32.4 (7.3)	32.9 (8.9)
Diabetes		11.6	8.0	7.6	23.0	25.4
Cancer		8.0	6.8	12.2	11.2	11.4
Cardiovascular disease		7.6	4.9	8.1	15.3	20.3
Depression		16.5	10.0	63.5	24.5	70.6
Hypertension		30.4	19.0	9.5	68.7	67.9
Used sleep medications		8.8	6.9	27.1	10.0	27.0
Had health insurance		81.7	81.5	73.5	84.7	75.1
Intermediate and high-risk sleep (STOP-Bang)		46.6				
High-risk sleep apnoea (STOP only)		24.8				
Death (%)		6.7	5.4	7.4	10.1	14.0

Reference group = no insomnia or high-risk OSA. BMI = body mass index, COMISA = co-morbid insomnia and sleep apnoea, CVD = cardiovascular disease, MET = metabolic equivalent of task, OSA = obstructive sleep apnoea. Numbers indicate proportions unless specified.

groups are reported in Table 1. The prevalence of insomnia was higher among participants with high-risk OSA (14.2%; 95% CI: 12.0-16.7) compared to those without (4.0%; 95% CI: 3.0-4.6;). The prevalence of high-risk OSA was higher among participants with insomnia (52.2%; 95% CI: 45.1-59.3), compared to those without (21.5%; 95% CI: 20.0-23.1). Self-reported sleep duration in the COMISA group was shorter (5.4 hours) compared to the other three groups. The COMISA group had lower levels of physical activity, and a higher prevalence of depression and CVD than other groups (Table 1).

3.2. COMISA and Mortality

The median (IQR) follow-up period for all-cause mortality was 8.6 (7.8, 9.8) years. In total, 730 (6.7%) participants died by 11-year follow-up. Mortality rate per 1000 person-years was 6.1, 8.4, 11.5, and 16.7 in the reference, insomnia alone, OSA alone, and COMISA groups, respectively (**Supplementary Materials, Table S3**). Compared to the reference group, COMISA was associated with increased risk of all-cause mortality in the unadjusted model (HR = 2.79, CI = 1.82-429; Fig. 1; Table S3). COMISA was also associated with a higher risk of mortality compared to the reference group, after adjusting for socio-demographic characteristics (HR = 2.03, CI = 1.37-3.02; Model 1), behavioural factors (HR = 1.87, CI = 1.27-2.75; Model 2), chronic conditions (HR = 1.64, CI = 1.11-2.41; Model 3), and potential mediators and moderators (HR = 1.56, CI = 1.06-2.30; Model 4). Insomnia alone was also associated with increased mortality risk compared to the reference group, after controlling for socio-demographic and behavioural factors (Model 2) but high-risk OSA alone was not (Fig. 1; Table S3). Insomnia was no longer associated with increased mortality risk after additionally controlling for chronic conditions and potential mediators and moderators (Fig. 1; Table S3). Unadjusted survival curves are shown in Fig. 2.

Compared to the insomnia alone group, COMISA was associated with increased mortality risk in the unadjusted model (HR = 2.00, CI = 1.02-3.95), but not after adjustment for socio-demographic characteristics (HR = 1.18, CI = 0.69-2.03), behavioural factors (HR = 1.23, CI = 0.72-2.09), chronic conditions (HR = 1.13, CI = 0.66-1.94), or potential mediators and moderators (HR = 1.12, CI = 0.65-1.92). Compared to the high-risk OSA alone group, COMISA was not associated with increased mortality risk in the unadjusted model (HR = 1.46, CI = 0.96-2.23), but was associated with significantly increased mortality risk after adjustment for socio-demographic characteristics (HR = 1.79, CI = 1.18-2.72), behavioural factors (HR = 1.73, CI = 1.16-2.57), chronic conditions

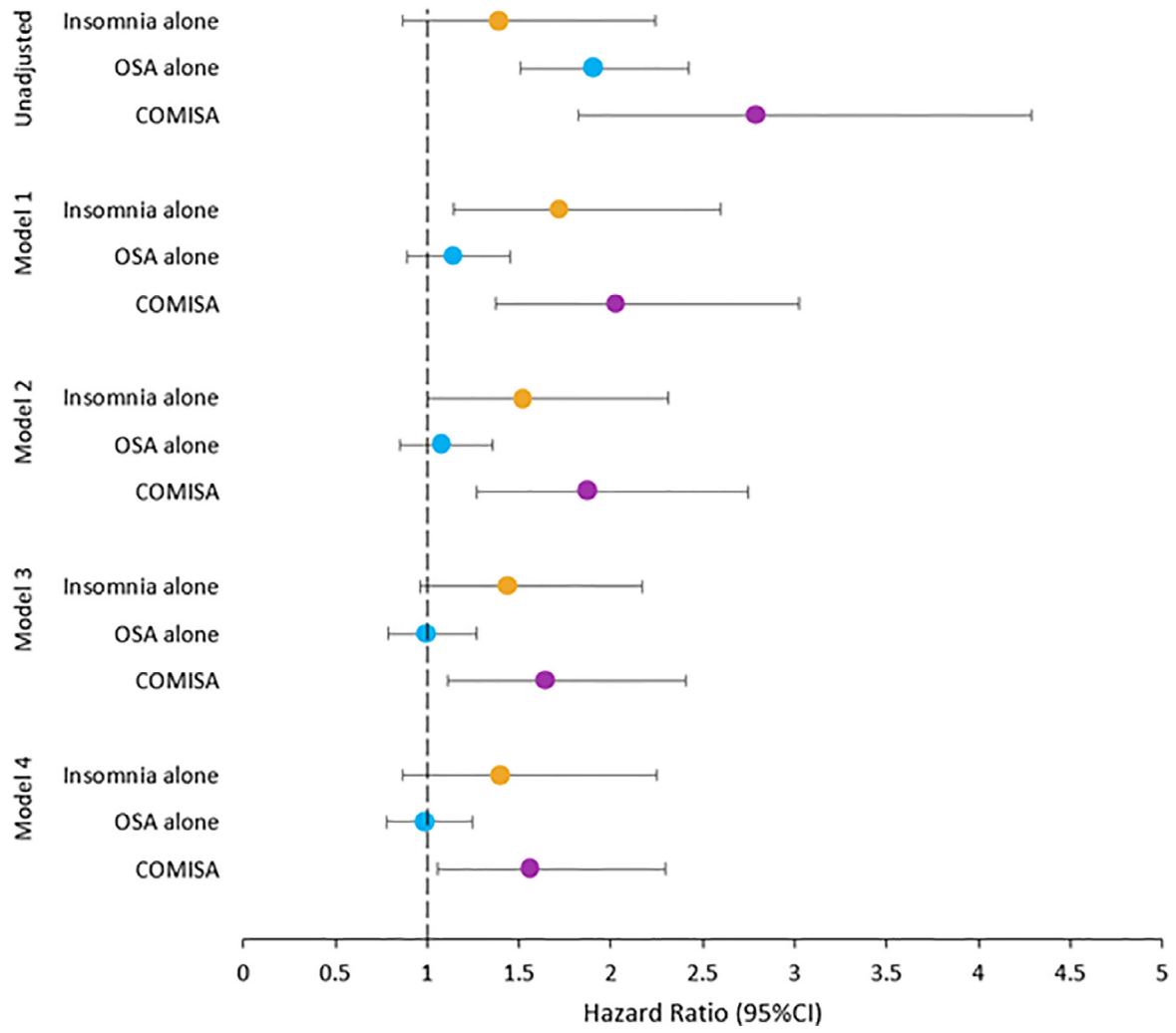

Fig. 1. Relationship between sleep disorder group and all-cause mortality for unadjusted and adjusted models (HRs; 95%CIs).
COMISA = co-morbid insomnia and sleep apnoea, OSA = obstructive sleep apnoea.
Model 1 adjusted for age, sex, BMI, educational status, marital status, family poverty income ratio, race.
Model 2 adjusted for factors in Model 1 + smoking, physical activity level and alcohol consumption.
Model 3 adjusted for factors in Model 1 + 2 + diabetes cancer and cardiovascular disease.
Model 4 adjusted for factors in Model 1 + 2 + 3 + sleep duration, sleep medicine use, depression and health insurance status.

(HR = 1.63, CI = 1.11-2.40), and potential mediators and moderators (HR = 1.58, CI = 1.06-2.36).

3.3. Sub-group analyses

Compared to the reference group, there was no significant difference in the effect of COMISA on mortality risk between males (HR = 1.89, CI = 1.08-3.30) and females (HR = 1.95, CI = 1.16-3.29), after controlling for socio-demographic and behavioural factors (See **Supplementary Materials**, Table S4). Similarly, there was no significant interaction effect between COMISA and age (≤48 versus >48 years) on mortality risk (p for interaction = 0.1185; See **Supplementary Materials**, Table S5).

3.4. Sensitivity analyses

Sensitivity analyses were performed to investigate the association of COMISA and mortality using different definitions of OSA, and after excluding participants with chronic conditions at baseline. When defining OSA according to an intermediate-risk or high-risk score on the STOP-Bang questionnaire (≥3 on STOP-Bang, or ≥2 on STOP and at least on of; male, BMI >35, high waist circumference threshold; see **Supplementary Materials**), the association of COMISA and mortality persisted in model 2 (HR = 1.93, CI = 1.23-3.01), and after further adjustment for potential moderators and mediators in model 4 (HR = 1.64, CI = 1.04-2.61; **Supplementary Materials, Table S6**). When high-risk OSA was defined according to a score of ≥2 on the STOP sub-scale (snoring, tired, observed breathing pauses, high blood pressure), the association of COMISA and mortality was observed in model 2 (HR = 1.83, CI = 1.25-2.68), and after controlling for additional co-variates in model 3 and model 4 (HR = 1.54, CI = 1.03-2.29; **Supplementary Materials, Table S7**). A sensitivity analysis was performed after removing participants with chronic conditions at baseline (diabetes 11.6%, cancer 8.0%, and cardiovascular disease 7.6%). There was a significant association of COMISA and mortality in the unadjusted model, but not in any of the subsequent models which controlled for covariates (**Supplementary Materials, Table S8**). Finally, compared to participants with no COMISA (i.e. collapsing the groups with insomnia alone, OSA alone and neither disorder), COMISA was associated with an increased risk of mortality in model 2 (HR = 1.59, CI = 1.05-2.40), and after controlling for additional co-variates in models 3 and 4 (HR = 1.46, CI = 1.00-2.12; **Supplementary Materials, Table S9**).

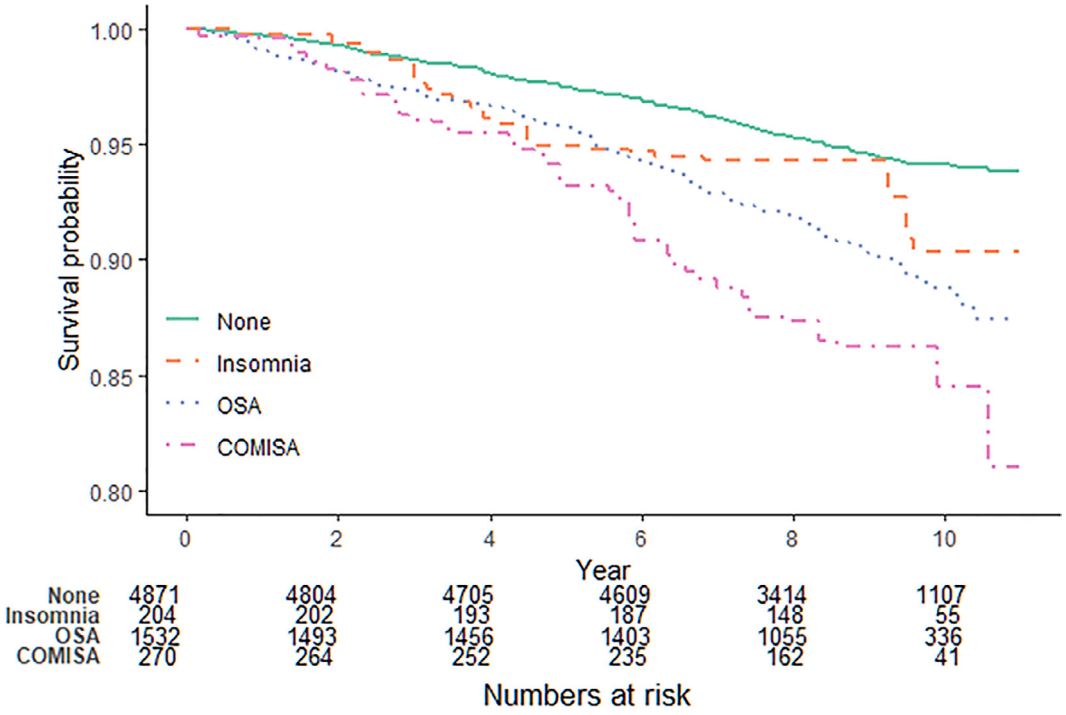

Fig. 2. Unadjusted Kaplan-Meier's curve across sleep disorder group for all-cause mortality. OSA = high-risk obstructive sleep apnoea, COMISA = Co-morbid insomnia and high-risk sleep apnoea.

4. Discussion

The main finding of this study is that self-reported symptoms of co-morbid insomnia and sleep apnoea (COMISA) are associated with an increased risk of all-cause mortality after controlling for socio-demographic factors, behavioural factors, chronic conditions, sleep duration, sleeping pill use and depression. This association was consistent across several sensitivity definitions of OSA. This directly addressed our study aim of determining the association between self-reported symptoms of COMISA and risk of all-cause mortality. Importantly, these results suggest that self-reported insomnia symptoms combined with the validated STOP-Bang questionnaire can be used to identify people with probable COMISA at risk of adverse health outcomes. This is important given the limited availability and long wait times to access polysomnography to identify OSA. These results are consistent with a previous study reporting an association of COMISA and all-cause mortality [29], and cross-sectional studies reporting that COMISA is associated with worse daytime function, quality of life, depression, CVD, and sleep compared to insomnia alone or OSA alone [15,24,34].

Previous studies have investigated associations between insomnia and mortality [27,33], and OSA and mortality [35,36], however only one previous study has investigated the association between COMISA and mortality [29]. The present results are consistent with a recent report using the Sleep Heart Health Study data, which reported that COMISA was associated with a 47% increased risk of all-cause mortality compared to no insomnia/OSA [29]. Like this previous study, we also found that compared to the no insomnia/OSA group, neither the insomnia alone, nor high-risk OSA alone groups were associated with increased mortality risk in the fully controlled model. Although similar insomnia criteria were used in these two studies, the previous study defined OSA according to an Apnoea-Hypopnoea Index (AHI) of at least 15 events/hr sleep from overnight polysomnography data, without consideration of symptoms. Taken together, these two reports indicate that the association of COMISA and mortality persists regardless of whether OSA is defined according to a single night of polysomnography, or validated self-report measures of high-risk OSA. In both studies, a range of sensitivity analyses for OSA were investigated, which did not substantially attenuate the association of COMISA and mortality. Taken together, our findings suggest that the combination of the STOP-Bang and a simple insomnia questionnaire may be an efficient tool to assess at scale the risk of adverse health outcomes in people with probable COMISA.

In the fully adjusted model, COMISA was associated with increased risk of mortality compared to high-risk OSA alone, but not compared to insomnia alone. These results are consistent with Lechat and colleagues [29], who also observed increased mortality risk among people with COMISA compared to those with OSA alone, but not insomnia alone in adjusted models. This may indicate that insomnia symptoms are the more important component of COMISA associated with mortality. Future studies should investigate the association of specific symptoms/markers of COMISA with reduced physical and mental health, and mediators between specific COMISA symptoms and mortality to understand the mechanisms underpinning this relationship (e.g. nocturnal and daytime insomnia symptoms and increased risk of depression, suicide, cardiovascular disease, etc.)[37,38].

These results are consistent with previous studies that have reported associations between specific subgroups of OSA and mortality. For example, Butler and colleagues [35] recently reported an association of short apnoea event duration and mortality risk in the Sleep Heart Health Study. Shorter respiratory events may be a marker of the low respiratory arousal threshold phenotype of OSA, which is suggested to be an important mechanism in the co-morbidity of insomnia and OSA [15,39]. Characteristics of insomnia including pre-sleep anxiety and a conditioned physiological/cognitive arousal responses to the bedroom environment may contribute to an increased propensity to arouse to environmental and internal physiological stimuli during the night, thereby reinforcing the low arousal threshold. Future studies should investigate the prevalence and associations of the low arousal threshold phenotype in people with COMISA and OSA alone, to guide understanding of COMISA development and treatment [15,40].

A relatively small number of participants in this study had both insomnia and high-risk OSA (3.3%). This prevalence estimate is similar to previous population-based research which has reported that between 1-

7% of people have COMISA [19,20,22,25,29,41]. Like other studies, we found that the prevalence of insomnia was higher among participants with high-risk OSA, compared to those without, and that the prevalence of high-risk OSA was higher among participants with insomnia, compared to those without [15]. This suggests that the combination of STOP-Bang and an insomnia questionnaire may provide an accurate estimate of COMISA risk.

Like previous cross-sectional COMISA research, we found that participants in the COMISA group generally had the highest rates of depression [19,42], CVD [22,23] and shorter average sleep duration [16,29], compared to the other groups. It is possible that additive effects of the two sleep disorders, or interactions between the mechanisms or manifestations of COMISA contribute to worse sleep, physical and mental health, versus either disorder alone. Although these factors could mediate the relationship between COMISA and mortality, we found that the relationship persisted even after controlling for these factors. Previous research has reported an increased risk of mortality associated with OSA in younger male adults [32]. There was no interaction effect of sleep disorder category and age on mortality risk. Similarly, there was no sex by COMISA interaction on mortality risk.

Future research should investigate the effect of treatment on reduction of mortality risk factors in people with COMISA. The recommended first-line treatment for moderate and severe OSA is continuous positive airway pressure (CPAP) therapy [43]. Although CPAP stabilises breathing and improves daytime symptoms of untreated OSA [10], poor acceptance and use of CPAP remain a significant barrier to its effectiveness. Importantly, people with COMISA are less likely to initially accept CPAP, and use CPAP for fewer hours per night compared to people with OSA alone [14,44,45]. Cognitive behavioral therapy for insomnia (CBTi) is the recommended 'first line' treatment for insomnia [46,47]. CBTi is effective [18] and safe [48] in people with COMISA, and may improve subsequent acceptance and use of CPAP therapy [49,50]. Future studies should investigate the effect of single and combination treatment approaches for COMISA on improving mental and physical health.

4.1. Limitations

Although this study has several strengths including a large sample size, robust measures of health and socio-demographic factors, a standardised measure of high-risk OSA, and a long-term follow-up of mortality data, it should be interpreted in light of several limitations.

Firstly, OSA was defined according to a high-risk score on the STOP-Bang questionnaire, rather than polysomnography data. Polysomnography is costly, time-consuming, and rarely accessible in rural and remote settings [51]. Furthermore, identifying OSA presence according to a single night of polysomnography introduces risk of mis-classification due to night-to-night variability in OSA severity [6], and standard polysomnography metrics such as the AHI do not capture features of OSA that may be associated with worse health outcomes (e.g. daytime sleepiness, sleep fragmentation, respiratory event duration) [35,52,53]. Consequently, we used a concise screening tool of OSA risk factors and symptoms that was developed and validated to facilitate widespread screening and identification of high-risk of OSA [31]. The sensitivity and specificity of the STOP-Bang in identifying people with OSA depends on the STOP-Bang threshold, and OSA severity threshold that are used (mild, moderate, or severe) [31,54]. Generally, the STOP-Bang has adequate sensitivity but moderate specificity to identify people with OSA [31].

This study defined high-risk OSA according to the 'two-step' STOP-Bang scoring strategy recommend by Chung and colleagues [31]. A recent meta-analysis of STOP-Bang validation studies in sleep clinic settings reported that a score of ≥5 had a sensitivity value 77.2%, and specificity of 54.5% in identifying patients with severe OSA [55]. The use of high-risk STOP-Bang scores to define OSA may have resulted in a number of false-positives in the 'OSA alone' and 'COMISA' groups. Consequently, the association of sleep disorder group and mortality may be under-estimated, given the potential for some false-positive cases included in these groups. We also defined OSA according to an intermediate-risk score (≥3) on the STOP-Bang [31,54]. In the Sleep Heart Health Study, a STOP-Bang score of ≥3 had a sensitivity of 87% and specificity of 43% in identifying moderate-to-severe OSA, and a sensitivity of 70.4% and specificity of 59.5% in identifying severe OSA [54]. Given the potential association of mortality and demographic variables included in the 'Bang' sub-scale that may artificially increase the measured association between mortality and high-risk OSA (blood pressure, age, neck [waist] circumference, male gender), we also defined high-risk OSA as a score of ≥2 on the STOP sub-scale. Silva and colleagues [54] reported that a STOP score ≥2 had 62% and 68.8% sensitivity, and 56.3% and 59.5% specificity in identifying moderate-to-severe, and severe OSA in the Sleep Heart Health Study, respectively. The association between COMISA and mortality persisted across all scoring methods. Previous population-based studies investigating associations of COMISA/OSA and health outcomes have also defined OSA according to the STOP-Bang [26], and other self-reported OSA symptoms including; snoring, tiredness and witnessed apnoea events [20,22,25].

Secondly, no data on chronicity of insomnia symptoms were available to identify participants with 'chronic insomnia' [3]. Therefore, the insomnia and COMISA groups may have included participants with both acute (<3 months) and chronic insomnia symptoms (≥3 months) [3]. It is possible that the association between COMISA (and insomnia) with mortality may be even stronger for individuals with 'chronic' insomnia.

Finally, no data were available on access to insomnia and OSA treatments over later follow-up occasions. The association between COMISA and mortality persisted after controlling for baseline sleep medication use. However, it is possible that additional treatments for insomnia and OSA that were commenced after baseline may have moderated mortality risk in people with insomnia, OSA, and COMISA. Consequently, this may have reduced the associations of sleep disorder groups and mortality risk.

4.2. Conclusion

Symptoms of co-morbid insomnia and sleep apnoea (COMISA) are associated with a 56% increased risk of all-cause mortality in the general population after controlling for sociodemographic factors, behavioural factors, chronic conditions and potential mediators and moderators. Clinicians can screen patients for COMISA symptoms with existing validated self-report questionnaires. It is important to develop more effective and tailored management approaches for COMISA, and to investigate the effect of COMISA treatment on reduction of mortality risk.

Potential conflicts of interest

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sleepe.2022.100043.

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