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REVIEW ARTICLE

Co-morbid insomnia and sleep apnea and cardiovascular consequences: is the whole greater than each part?

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Abstract

Recently, the sleep field has adopted the term co-morbid insomnia and sleep apnea (COMISA) to describe patients who present these two important sleep disorders. There is no novelty in the fact that a considerable number of patients may present not only one sleep disturbance but also a combination of them. In this scenario, it is reasonable to speculate that co-morbid sleep disturbances (e.g., COMISA) may have myriad consequences beyond each condition. While intuitive, this argument may sound simplistic because the impact of each sleep disturbance may not have the same "weight" across domains, making it fair to argue that one sleep disturbance may mitigate the effects of the other, thereby not imposing any "additional" effect. Fortunately, the traditional view in the literature of studying one sleep disturbance at a time has recently changed. In this review, we will summarize the current evidence on the cardiovascular effects of COMISA compared with each condition alone.

Keywords: *Insomnia. Sleep apnea. Co-morbid insomnia and sleep apnea. Hypertension. Diabetes. Cardiovascular disease.*

Introduction

Chronic insomnia and obstructive sleep apnea (OSA) are probably the main actors in the sleep field in terms not only of the high prevalence[1,2] but also in promoting a myriad of consequences, including cardiometabolic complications[3,4]. While insomnia relies on the difficulty initiating sleep and/or maintaining sleep and/or waking up earlier than desired, despite adequate opportunity to sleep[5], OSA has a hallmark in promoting repetitive upper airway obstructions and related phenomena, such as intermittent hypoxia, intrathoracic swings, and sleep fragmentation[6]. Although they present quite distinct characteristics, these two major sleep disturbances trigger a considerable overlap of downstream mechanisms, such as sympathetic activation, inflammation, endothelial dysfunction, and hypothalamic-pituitary axis dysregulation, among others[3,4].

In the past decades, we have observed considerable evidence evaluating the impact of insomnia and OSA as isolated entities, largely due to the failure to systematically evaluate insomnia in studies involving OSA and vice versa[7]. Considerable challenges regarding the relatively small sample observed in several investigations may also explain this "compartmentalization" scenario[7]. However, it is important to mention that the concept as a co-morbid condition comprising insomnia and OSA is not new: in 1973, Guilleminault, Eldridge and Dement reported at that time a "new syndrome" in two patients with insomnia who presented symptoms of OSA and insomnia[8]. They described sleep architecture, respiratory, and cardiovascular particularities that caught their attention in supporting the relevance

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of this combination. The term COMISA was formally adopted by Sweetman et al[9]. in 2017 to describe this co-morbidity, leading not only to a surge in research under this specific acronym but also to the need for specific treatment recommendations (for instance, combining cognitive behavior therapy for insomnia, and continuous positive airway pressure)[10]. In terms of prevalence, initial studies by Lichstein et al.[11] and Krakow et al.[12] highlighted that 30-50% of people with insomnia have OSA, and vice versa. More recently, population-based studies revealed that the prevalence of COMISA seems to be lower (1.7-11.4%) than observed in sleep clinics[13].

Given the arguments, it is intuitive and plausible that COMISA may add more prognostic value than each condition alone. This is an evolving research area attracting growing interest from sleep experts. In this review, we summarized the present evidence discussing whether COMISA promotes higher cardiometabolic consequences, such as hypertension, metabolic syndrome, diabetes, myocardial infarction, and mortality.

COMISA and hypertension

Compelling evidence from independent studies has shown that insomnia and OSA are associated with prevalent and incident hypertension[14-20]. More recently, the impact of COMISA on hypertension has been reported in the literature using both cross-sectional and longitudinal study designs.

Cross-sectional studies

In a cross-sectional analysis of a longitudinal study, Lechat et al.[21] reported that, among 5236 participants, 2708 (52%) did not have insomnia/OSA (reference group), 170 (3%) had insomnia-alone, 2221 (42%) had OSA-alone, and 137 (3%) had COMISA. COMISA participants had a higher prevalence of hypertension (odds ratio [OR] 2.00, 95% confidence interval [CI] 1.39-2.90) compared with the reference group. Interestingly, insomnia-alone and OSA-alone were associated with a higher risk of hypertension[21].

Data from three population-based cohorts from Benin (Benin Sleep Apnea Study [BeSAS], n = 1733), Switzerland (HypnoLaus, n = 1999), and India (BhopaL Epidemiological Sleep Study [BLESS], n = 958) revealed a significant heterogeneity in the association of COMISA with hypertension[13]: in the HypnoLaus cohort, COMISA showed a trend toward an association with hypertension (OR: 1.34, p = 0.09), which was statistically significant when insomnia was defined by sleep initiation difficulties. In BLESS, COMISA was significantly associated with hypertension (OR: 3.30). However, no significant association was observed in BeSAS, suggesting that differences in sample sizes, definitions, and regional particularities may explain these discrepancies.

Regarding the association of COMISA with uncontrolled hypertension, Wu and Guo[22] evaluated 326 patients with co-morbid OSA and hypertension, investigating the association of insomnia symptoms with uncontrolled blood pressure (BP) and apparent resistant hypertension (RH). After adjustment for confounders, participants experiencing COMISA had 3 times higher odds of RH but no association with uncontrolled BP. More recently, Kobayashi Frisk et al.[23] investigated the relationship between COMISA (defined as an apnea-hypopnea index (AHI) > 10 events/h and an insomnia severity index [ISI] score ≥ 15) and uncontrolled hypertension in the Swedish cardiopulmonary bioimage study. Uncontrolled hypertension was found in 4.4%, 4.5%, 7.9% and 10.2% of the control group, insomnia-only, OSA-only, and COMISA groups, respectively ($p < 0.001$). Compared to the control group, the OSA-only group was independently associated with uncontrolled hypertension (OR 1.31 [1.05-1.64]) and the COMISA group (OR 1.88 [1.23-2.89]). Of note, the severity of OSA was comparable between OSA-only and COMISA patients (AHI: 18 ± 9 vs. 19 ± 9 events/h, $p = 0.86$)[22].

It is important to note that the phenotype of COMISA may influence the association with hypertension and other endpoints. For instance, in a clinical sample of 101 adults with mild-to-moderate OSA and insomnia symptoms, hypertension was significantly more common in the objective short sleep duration group (OR = 3.88, 95% CI = 1.26-11.95) than in the insomnia with normal sleep duration group[24]. Considerable limitations of this study, including the small sample size, will require further analysis for identifying the real utility in phenotyping COMISA in this scenario.

Longitudinal studies

In longitudinal studies, data from 11,623 Hispanic/Latino participants in the Hispanic Community Health Study/Study of Latinos (visit 1, 2008-2011; visit 2, 2014-2017) revealed that OSA was associated with 1.54 times higher adjusted odds of incident hypertension. Consistently, insomnia was associated with incident hypertension (OR, 1.37), but COMISA provided the highest odds (2.09)[25].

Gaffey et al.[26] performed a retrospective analysis to examine whether COMISA is associated with incident hypertension in younger men and women who enrolled

in Veterans Health Administration care from 2001 to 2021 (n = 937,598). Greater hypertension risk was observed overall (adjusted hazard ratio [aHR]: 2.43, 95% CI: 2.36-2.50), for men (aHR: 2.09, 95% CI: 2.02-2.16) and women with COMISA (aHR: 2.20, 95% CI: 2.00-2.42), insomnia only (aHRs: 1.27-1.44), and OSA only (aHRs: 2.00-2.26) versus no sleep disorder.

More recently, investigators from the Penn State adult cohort examined whether the increased hypertension risk associated with COMISA is driven by the insomnia short sleep duration phenotype[27]. After a 7.5 years of follow-up, the highest risk of incident hypertension was in the COMISA with insomnia short sleep duration phenotype (OR = 4.25, 95% CI = 1.52-11.90), followed by OSA-alone (OR = 3.31, 95% CI = 1.85-5.92) and insomnia short sleep duration alone (OR = 2.27, 95% CI = 1.29-4). Interestingly, the insomnia with normal sleep duration phenotype alone or with OSA (COMISA) was not significantly associated with incident hypertension[27].

In terms of uncontrolled hypertension and apparent RH, Wu and Guo[28] evaluated 301 patients with OSA and hypertension. In this very short-term study (5 months of follow-up), these authors showed that participants with insomnia was associated 2-fold higher risk of RH.

In summary, the available evidence is consistent in showing that COMISA is independently associated with prevalent and incident hypertension. These results seem to be more pronounced than OSA or insomnia alone, although this comparison is not so clear and consistent for OSA-alone. Cross-sectional and longitudinal analyses suggested that phenotyping COMISA by sleep duration might add value to the risk of hypertension.

COMISA, metabolic syndrome, and diabetes

Neither OSA nor insomnia alone is formally considered a risk factor for metabolic syndrome and diabetes despite the biological plausibility and availability of prospective studies suggesting that both sleep disorders are independently related to metabolic syndrome and diabetes incidence[29-32]. Here, we summarized the evidence in the context of COMISA.

Cross-sectional studies

The aforementioned joined cohorts from Benin, Switzerland, and India also evaluated the association between COMISA and metabolic syndrome[13]. Similar to that observed for hypertension, a significant heterogeneity in the association of COMISA with metabolic syndrome was observed: in the HypnoLaus cohort, COMISA showed a trend toward an association with metabolic syndrome (OR: 1.39, p = 0.09), which was statistically significant when insomnia was defined by sleep initiation difficulties. In BLESS, COMISA was significantly associated with metabolic syndrome (OR: 1.71). In the diabetes scenario, Liu et al. reported that compared to insomnia alone, COMISA patients suffered from more than twice the risk of prevalent diabetes[33].

Longitudinal studies

In the Hispanic Community Health Study/Study of Latinos, revealed that OSA was associated with 1.33 higher odds of incident diabetes (95% CI, 1.05-1.67) compared with no OSA after 6 years of follow-up. In contrast, insomnia alone was not associated with incident diabetes[25]. COMISA was associated with a marginal effect on the incident diabetes (OR 1.41, 95% CI, 1.00-1.99). The same cohort evaluated the impact of COMISA on the incidence of metabolic syndrome[34]. OSA was significantly associated with incident metabolic syndrome (hazard ratio [HR] 1.31, 95% CI 1.10-1.56), and COMISA was associated with a numerically higher risk of incident MS (HR 1.40, 95% CI 1.14-1.72), whereas insomnia alone showed no significant association. Both results suggest that OSA is the main driver of metabolic dysregulation in COMISA. In the MrOS (osteoporotic fractures in men) study[35], the authors tested the hypothesis that a COMISA phenotype based on comorbid insomnia and the sleep breathing impairment index predicts incident diabetes and compared this association with an AHI-based definition of COMISA. The rationale for this comparison was that although the AHI is currently the diagnostic criterion for assessing OSA severity, it has not consistently predicted incident diabetes. Individually, OSA and insomnia were not associated with incident diabetes after a median follow-up of 10 years. However, participants with COMISA-sleep breathing impairment index had a higher risk of incident diabetes (HR, 1.82; 95% CI, 1.15-2.89) than those without sleep disorders. COMISA, based on AHI, was not associated with this endpoint.

COMISA, cardiovascular events and mortality

Independent studies have shown that OSA and insomnia were associated with increased cardiovascular events[36,37]. One of the first studies to evaluate the cardiovascular impact of COMISA on cardiovascular

events was conducted by Lechat et al.[38] In contrast to the initial hypothesis, the authors did not find a significant association between COMISA and incident cardiovascular events after a 11-year follow-up of 5803 participants from the Sleep Heart Health Study. In the unadjusted model, COMISA was associated with a 2-fold increase in the risk of cardiovascular events, but the results were not sustained after full adjustment. Further study by Fang et al.[39] yielded mixed results, assessing the cardiovascular impact of COMISA in 181 elderly patients. The multivariate Cox regression analysis showed that COMISA increased the incidence of major adverse cardiac events (MACE) (HR = 2.328, 95% CI: 1.349-4.018, p = 0.002), hospitalization for unstable angina (HR = 2.915, 95% CI: 1.397-6.081, p = 0.004), and the combination of all events (HR = 2.301, 95% CI: 1.393-3.803, p = 0.001). However, there were no significant differences in cardiovascular death, all-cause mortality, myocardial infarction, or hospitalized heart failure in patients with COMISA after a 43-month follow-up[39]. Unfortunately, no detailed data on the impact of OSA and insomnia alone were available in this analysis.

In a retrospective analysis of electronic medical records data from patients with clinical encounters at sleep medicine centers to identify patients with COMISA, Luyster et al.[40] showed that COMISA was associated with a significantly higher risk of developing MACE (HR 3.60, 95% CI: 2.33-5.91) as compared to controls in unadjusted analyses. The relationship between COMISA and MACE remained after adjustment for demographic and behavioral factors, but not after further adjustment for comorbidities. In this study, neither OSA nor insomnia was independently associated with MACE.

A nationwide cohort analysis of nearly 1 million of Veterans revealed that COMISA was independently associated with a 3-fold increase in cardiovascular disease incidence[26]. The magnitude of the effects has clearly higher in COMISA (HR: 3.81; 3.64-3.99) and OSA alone (HR: 3.32; 3.21-3.43) as compared to insomnia alone HR: 1.37, 1.32-1.41), but any definitive conclusion about a potential additive effect of COMISA versus OSA alone should be interpreted with caution. Interestingly enough, the results were consistent in men and women[26]. Recently, a prospective analysis from the HypnoLaus cohort showed that COMISA, but not OSA or insomnia alone, was associated with increased incident cardiovascular events (myocardial infarction, stroke, or cardiovascular death) over a median follow-up period of 7.8 years[41].

Regarding total mortality, Lechat et al.[21] analyzed 5.236 middle-aged adult participants from the Sleep Heart Health Study cohort, with an average follow-up of 11.8 years. The crude mortality rates (deaths/1.000 participant-years) were 17.3 for the control group, 19.3 for the insomnia-only group, 24.9 for the OSA-only group, and 30.4 for the COMISA group. The COMISA group was associated with a 47% increase in the risk of all-cause mortality (HR: 1.47 [95% CI: 1.06-2.04]), while no association was found for the insomnia-only (HR: 1.11 [0.77-1.62]) or OSA-only (HR: 1.01 [0.89-1.15]) groups in the fully adjusted model.

A study conducted within the Wisconsin sleep cohort aimed to assess the relative risk of mortality over 19 years of follow-up among individuals with symptoms of COMISA, OSA alone, or insomnia, compared to those without OSA or insomnia[42]. The crude mortality rate for participants with COMISA was 9.5 deaths/1.000 participant-years, compared to 4.5 for those with insomnia, 5.2 for those with OSA alone, and 4.0 for the control group. The Cox regression analysis, adjusted for age, sex, education, smoking status, alcohol consumption, BMI, diabetes, previous cardiovascular events, hypertension, total sleep time, and antidepressant use, showed that the COMISA group had a higher risk of all-cause mortality (HR: 1.71 [95% CI: 1.00-2.97]). No association was found for those with OSA only (HR: 0.91 [95% CI: 0.53-1.58]) or insomnia only (HR: 1.04 [95% CI: 0.55-1.98]). However, in the fully adjusted model, which also included symptoms of depression and anxiety, no associations were found between OSA, insomnia, or COMISA and all-cause mortality risk[42]. Sweetman et al.[43] followed 6.877 participants from the National Health and Nutrition Examination Survey over 11 years to analyze the association between COMISA (insomnia and OSA assessed using the STOP-Bang questionnaire) and mortality. The COMISA group showed a 56% higher risk of all-cause mortality compared to those without insomnia or OSA. Insomnia alone and OSA alone were not associated with increased mortality risk in fully adjusted models.

Based on the aforementioned evidence, it is not entirely clear whether COMISA is at a heightened risk of cardiovascular events and mortality, and this uncertainty is partially explained by methodological differences across the studies. For instance, several definitions of insomnia were used: International Classification of Sleep Disorders, 3rd Edition, The Pittsburgh Sleep Quality Index, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR, DSM-5, and ISI. Similarly, the OSA status was defined by different polygraph types, respiratory event criteria, and use of self-report or medical record diagnostics. In this scenario, it remains necessary to continue investigating this association and its effects.

Table 1. Gaps in the literature

Research gaps	Comments
The impact of COMISA on several endpoints are not clear: heart failure, arrhythmias, endothelial function, atherosclerosis, etc., are uncertain	Standard definitions for both COMISA and cardiovascular endpoints (for instance: heart failure with preserved versus reduced ejection fraction) are crucial
It is unclear whether COMISA has a higher impact on the 24-h blood pressure control than each condition in isolation	Systematic evaluation of 24-h ambulatory blood pressure monitoring may provide additional insights on dipping pattern, nocturnal hypertension, etc.
OSA seems to have a higher cardiovascular impact than insomnia and may drive most of the COMISA data. Present data are insufficient to address this issue	Several papers claimed that the OR and HR are higher in COMISA than each condition in isolation, but the respective 95% CI frequently overlapped (especially for OSA). Strong need of refining these comparisons with appropriate sample sizes
Despite some suggestions that short sleep duration modulates the cardiovascular risk of COMISA, more research are needed	Phenotyping COMISA may be challenging and requires large sample sizes due to multiple combinations
There is a paucity of data on the cardiovascular impact of COMISA stratified by gender, ethnicity, and comorbidities	Additional analysis stratifying for gender, ethnicity, and comorbidities will be quite helpful to understand the potential heterogeneity of COMISA on cardiovascular endpoints
Intervention studies approaching the cardiovascular impact of COMISA treatment are lacking.	The present evidence focused on CPAP adherence, quality of sleep, and quality of life

COMISA: co-morbid insomnia and sleep apnea; OSA: obstructive sleep apnea; OR: odds ratio; HR: hazard ratio; CPAP: continuous positive airway pressure.

Research agenda

Despite the advancements in this important research area, considerable gaps in the literature highlight the need for additional investigations. Some of the crucial topics are summarized in the table 1.

Conclusion

Growing evidence suggests that COMISA may act synergistically, meaning that the combination of OSA and insomnia has a greater negative impact on cardiovascular health than either condition on its own. The relative impact seems to be more pronounced for OSA than for insomnia, suggesting that OSA may drive most of the cardiovascular impact of COMISA. However, there is still a lack of convincing data to confirm the greater impact of COMISA over each of the components.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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