ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Interactions between Insomnia, Sleep Disordered Breathing and Cardiometabolic Risk in Patients Complaining of Pain in the Orofacial Region

Interações entre Insónia, Distúrbios Respiratórios do Sono e Risco Cardiometabólico em Doentes com Dor Orofacial

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Acta Med Port 2025 Jan;38(1):37-41 ▪ https://doi.org/10.20344/amp.22350

ABSTRACT

The existence of intersected pathways between the mechanisms of insomnia, sleep-disordered breathing and persistent/chronic pain has been documented. Such concurrence will eventually contribute to a higher burden of cardiometabolic diseases, a main cause of death worldwide. The aim of this study was to evaluate the interactions between insomnia, sleep-disordered breathing, cardiometabolic risk, and psychosocial stress in patients seeking care at an orofacial pain clinic. Anonymized data of 1236 patients seeking care at the orofacial pain unit of the University of Zurich were analysed. Prevalence data was estimated for insomnia, sleep disordered breathing/sleep apnea and increased risk of a combination of insomnia and sleep disordered breathing/sleep apnea, both regarding demographics and cardiometabolic risk factors. Psychosocial stress factors acting as additional cardiometabolic risk factors were assessed. Among patients with persistent orofacial pain, increased risk of combination of insomnia and sleep disordered breathing/sleep apnea was present in 11.5% of cases, and it was likely to increase psychosocial stress as an aditional independent risk factor for cardiometabolic disorder.
Keywords: Cardiometabolic Risk Factors; Facial Pain; Sleep Apnea Syndromes; Sleep Initiation and Maintenance Disorders

RESUMO

A existência de vias interligadas entre os mecanismos da insónia, distúrbios respiratórios do sono e dor persistente/crónica tem sido documentada. Esta convergência contribuirá eventualmente para um maior fardo de doenças cardiometabólicas, uma das principais causas de morte em todo o mundo. O objetivo deste trabalho foi avaliar as interações entre insónia, distúrbios respiratórios do sono, risco cardiometabólico e *stress* psicossocial em doentes que procuram cuidados numa clínica de dor orofacial. Foram analisados dados anonimizados de 1236 indivíduos que procuraram atendimento na unidade de dor orofacial da Universidade de Zurique. Foram estimados os dados de prevalência de insónia, distúrbios respiratórios do sono e alto risco para a combinação da insónia e distúrbios respiratórios do sono/apneia do sono, tanto em relação a fatores demográficos como a fatores de risco cardiometabólico. Foram avaliados fatores de *stress* psicossocial que atuam como fatores de risco cardiometabólico adicionais. Em doentes com dor orofacial persistente, o alto risco para combinação da insónia e distúrbios respiratórios do sono/apneia do sono foi confirmado em 11,5% dos casos e associou-se a um aumento do *stress* psicossocial, um fator de risco adicional e independente para doença cardiometabólica.
Palavras-chave: Dor Facial; Factores de Risco Cardiometabólico; Perturbações da Iniciação e Manutenção do Sono; Síndromes de Apneia do Sono

INTRODUCTION

Insomnia and sleep disordered breathing (SDB), particularly sleep apnea, are the most prevalent sleep disorders and both have a significant impact on health. When they co-occur, the term comorbid insomnia and sleep apnea (COMISA) has been established and may be associated with an increased risk of comorbidities. In fact, cardiovascular and metabolic disorders (CMD) are often linked to both insomnia and SDB when occurring in isolation, and their interaction appears to enhance cardiometabolic complications.[1] Interestingly, painful conditions may also eventually compromise cardiometabolic function.[2] In particular, chronic pain has been associated with an increased risk of CMD either by affecting intrinsic factors such as autonomic sympathetic hyperactivation[3] or via indirect pathways involved in the pathogenesis of CMD, such as anxiety, depression, fragmented sleep and stress.[4] The latter may not only aggravate the burden of pain, but also negatively impact general health and well-being. Therefore, we aimed to evaluate interactions between insomnia, SDB, cardiometabolic risk factors (CMRF), and psychometric measures in patients seeking care at an orofacial pain clinic.

METHODS

This study analyzed anonymized data from 1236 patients who sought care at the Orofacial Pain Unit of the University of Zurich. The data from consecutive patients assessed between January 2017 and January 2023 were extracted from the web-based interdisciplinary symptoms evaluation (WISE) self-screening platform, as previously described (Ettlin *et al*, 2016).[5] Psychometric measures assessed pain-related catastrophizing and disability, illness perception, distress, anxiety, depression, injustice

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Recebido/*Received*: 23/09/2024 - **Aceite/*Accepted*:** 18/11/2024 - **Publicado/*Published*:** 02/01/2025

experience, dysmorphic concerns, SDB, and insomnia. The objective was to evaluate the interactions between insomnia, SDB, and psychosocial stress dimensions as surrogates of CMRF, with a focus on identifying the influence of psychosocial stressors and demographic variables on these conditions.

Dependent variables

Given the uncertainty of SDB diagnosis (lacking polysomnographic assessment) the attribute "increased risk for COMISA" was used in detriment of COMISA. The primary dependent variables were insomnia, SDB, and increased risk of COMISA. Moreover, because it was not possible to assure whether association between insomnia and sleep apnea apply to such sample, for the purpose of the present paper, the authors preferred to use the term COMISA as the combination of insomnia and SDB. Insomnia was assessed using the Insomnia Severity Index (ISI),[6] with a score greater than 8 indicating significant insomnia. Sleep disordered breathing was identified based on self-reported complaints of snoring and/or apneas.

Independent variables

The independent variables were the demographic factors (age, sex), CMRF, and psychosocial stress factors. Cardiometabolic risk factors included body mass index (BMI), smoking history, and alcohol consumption history. Psychosocial stress factors were assessed using psychometric tests: anxiety was measured by the Generalized Anxiety Disorder scale (GAD-7),[7] and depression was assessed using both the Patient Health Questionnaire-4 (PHQ-4),[8] and the PHQ-Stress (PHQ-Str)[9] as a stress subscale derived from the PHQ commonly used in clinical settings to assess psychological distress.

Analytic approach

Descriptive statistics were used to estimate the prevalence of insomnia, SDB, and COMISA across the sample, with breakdowns by demographic and CMRF variables. As the WISE platform allows to proceed to the next question only after all fields are completed, participants are automatically alerted when a field has been missed and, therefore, for the present study all the questions were fully completed with no loss of data. To assess the relationships between the dependent and independent variables, analyses of variance (ANOVA) were conducted. Furthermore, multiple regression models were applied to determine the strength and significance of associations between the sleep conditions (insomnia, SDB, and COMISA) and the explanatory factors (demographics, CMRF, and psychosocial stress). Statistical significance was set at $p \leq 0.05$.

RESULTS

From the global sample (69.1% women, age range 10 to 89 years), 384 patients (31.1%) had insomnia, either subclinical (n = 184; 40.1%) or clinical (n = 200; 43.6%) as defined by an ISI score between 8 and 14 or >15, respectively. Regarding SDB, 310 patients (25.0%) acknowledged to snore or to have sleep apnoea. One hundred and forty-two patients (11.5%) had increased risk of COMISA. The BMI of patients with COMISA (25.3 ± 3.1) was higher compared to those with isolated insomnia (23.3 ± 2.5; $p = 0.001$) but not different from those with isolated SDB (25.1 ± 3.3; $p = 0.972$). Smoking history was more frequent ($p = 0.007$) among patients at increased risk of COMISA (23.9%) than in patients with isolated conditions (12.0% for insomnia and 22.0% for SDB). Alcohol consumption was more frequent ($p = 0.007$) in SDB (16.1%) and in patients at increased risk of COMISA (14.1%) compared to patients with insomnia (7.0%) (Fig. 1). Regarding psychometric measures scores from questionnaires measuring anxiety, depression, pain catastrophizing, and stress were significantly higher for patients with high-risk for COMISA compared with patients with any of the two isolated conditions (Fig. 2).

DISCUSSION

To the best of our knowledge, this is the first study reporting on insomnia, SDB, and cardiometabolic risk in a large sample seeking care at an orofacial pain clinic.

A significant interaction between increased risk of COMISA and psychosocial stress factors, such as anxiety and depression, was observed in this study. Patients at increased risk of COMISA exhibited considerably higher levels of anxiety (GAD-7) and depression (PHQ-4) scores when compared to patients with isolated insomnia or sleep-disordered breathing. These findings align with previous literature indicating that psychosocial stress – especially anxiety and depression – is a recognized CMRF[10] persisting in patients with chronic pain conditions and therefore interacting with them, particularly when sleep disorders like insomnia[11] and SDB are present.[12] Such interaction has been recently discussed in the literature under distinct perspectives and is shown to be clinically relevant.[13]

Additionally, the increased risk of COMISA group of our sample demonstrated higher BMI and a greater prevalence of smoking habits, both of which are well-established CMRF. Since COMISA and persistent pain are highly prevalent conditions, they likely co-occur and may independently or jointly contribute to CMD risk, the latter being a well-known cause of morbidity and mortality. Furthermore, although the emerging interest on COMISA has prompted several studies on adult and pediatric populations regarding possible interactions with distinct aspects of systemic health, this is the first assessment examining the prevalence and

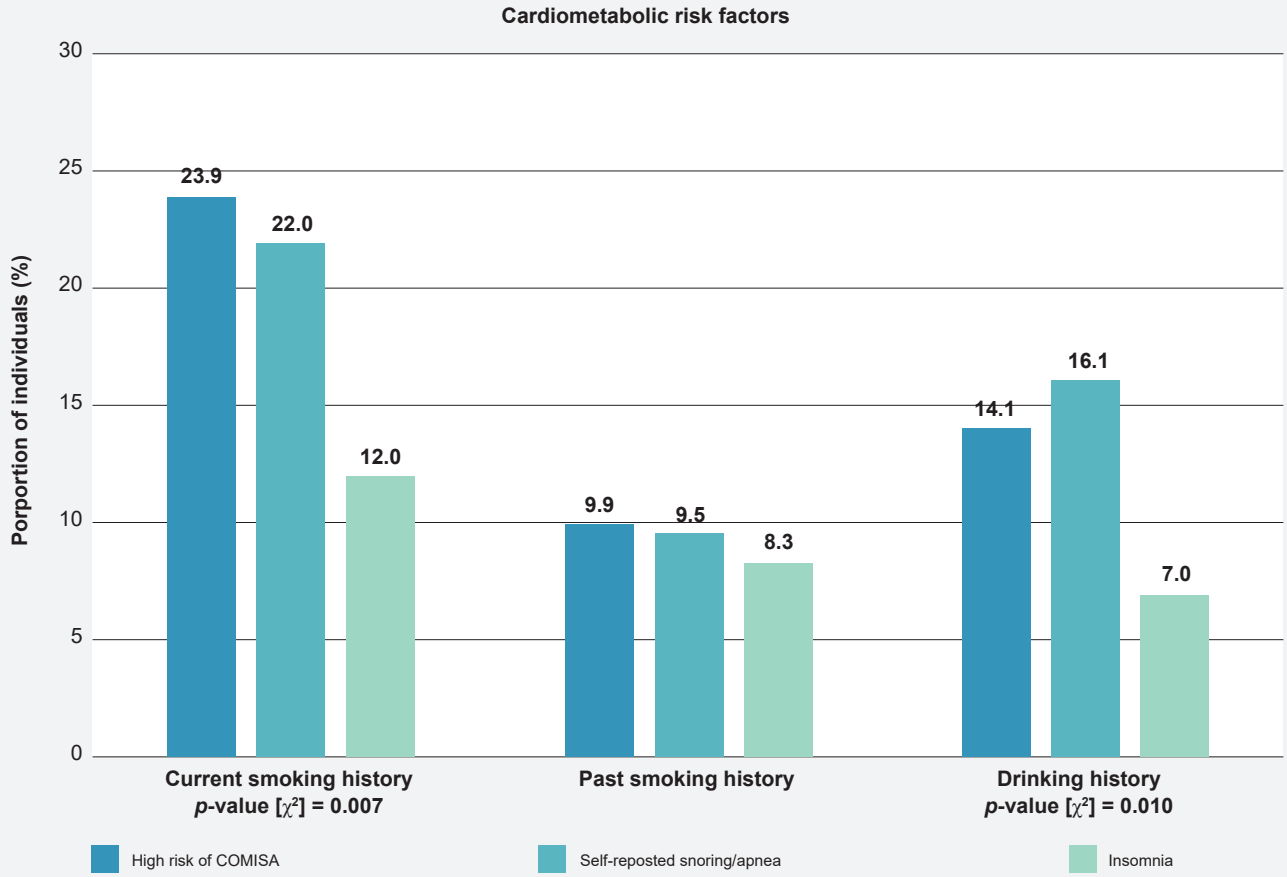

Figure 1 – Sample distribution by classical cardiometabolic risk factors (smoking and drinking)
The percentage of the affected sample is presented in relation to current smoking history, past smoking history and drinking history as established cardiometabolic risk factors

potential downstream consequences of COMISA in patients with chronic pain. The relationships between COMISA and CMRF have been quite extensively explored in some recent papers.[1,14,15] Furthermore, increasing evidence points to the role of pain on CMRF. For example, results from a recent study showed that increased pain intensity in white women may have a negative impact on cardiovascular and associated metabolic regulatory mechanisms related to BMI and smoking status.[16]

Our analysis also indicated that alcohol consumption as a surrogate of cardiometabolic risk was more frequent in both SDB and putative COMISA patients. Previous research has suggested that systemic inflammation, microvascular changes, sympathetic nervous system maladaptive responses, and genetic predisposition to both chronic pain and cardiometabolic disfunction may be causal mechanisms for this crosstalk which may be potentiated by social determinants of disease (e.g., loneliness and perceived insufficiency of social support).[17] Although the present study did not address these issues, it is plausible that COMISA could potentiate chronic pain-related effects on CMD. The multiple regression analysis revealed that increased risk of COMISA was a significant predictor of increased psychosocial stress ($p < 0.05$), which, in turn, may further influence cardiometabolic parameters like BMI and smoking history.

Other findings relying on self-reports corroborate that pain may significantly contribute to additional cardiometabolic risk factors such as sedentarism. Rodriguez-Sánchez *et al* argued that, along with increased tobacco use, a reduction in physical activity comprises a self-imposed strategy for pain management.[17] In their five-year follow up study of patients without prior cardiovascular disease, a 7.7% cumulative risk emerged along with decreased levels of exercise, increased psychological distress, poor sleep quality and worse quality of diet, all of which are CMRF. Similarly, the current findings point towards an important role of conventional CMRF, such as tobacco history as a modulator of cardiometabolic risk. Overall, this

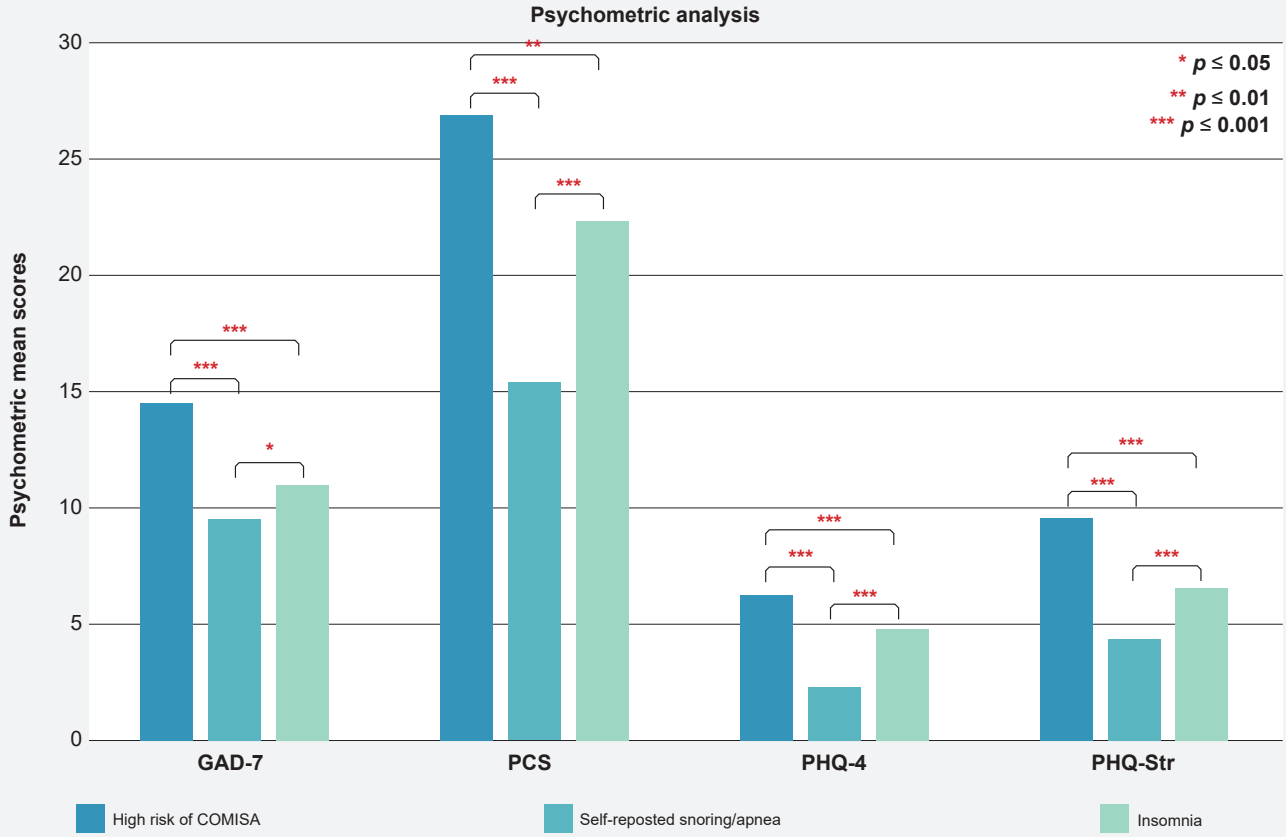

Figure 2 – Sample distribution by psychosocial stress dimensions
Presented psychometric mean score refer to GAD-7: Generalized Anxiety Disorder scale; PCS: Pain Catastrophysing scale; PHQ-4: Patient Health questionnaire; and Stress subscale of the Patients Health questionnaire.

supports our findings that anxiety and depression may be key modulators of cardiometabolic risk in COMISA patients. Likewise, in the present study, anxiety, depression, and stress were significantly higher in COMISA patients compared to isolated conditions. Therefore, psychosocial stress seems to be a common pathway for CMD burden observed in this sample. These factors would probably have major clinical implications since adequate management targeting those contributors may enable clinically relevant impact on cardiometabolic health and prevention of future CMD.[17] Despite some limitations observed in the present study – like the undefined comorbid conditions and the lack of analyses of associations between factors like age, BMI and other cardiometabolic risk factors – our findings revealed critical aspects warranting further exploration in the future steps of the WISE project.

In conclusion, 11.5% of patients complaining from persistent pain in the orofacial region were shown to present with both insomnia and SDB. Those with symptoms corresponding to the likely presence of COMISA seemed to be at increased risk of CMD compared with those with insomnia or SDB alone. Furthermore, in addition to classical risk factors such as BMI, smoking and alcohol drinking, additional psychosocial stress dimensions may also significantly contribute to enhance CMD risk in patients with orofacial pain.

AKNOWLEDGMENTS

To Inês Santos, for her statistical analysis support for this paper.

AUTHOR CONTRIBUTIONS

MMC: Study design, data collection, analysis and interpretation, writing of the manuscript.

DG, CS, IR: Data interpretation and writing of the manuscript.

DE: Data collection and interpretation, writing of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical

Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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