Universidade de Lisboa
Faculdade de Medicina

INSOMNIA AND PSYCHOSOCIAL STRESS IN PATIENTS WITH PAIN IN THE OROFACIAL REGION

Bárbara Patrícia Guerra Nobre

Supervisor: Professor Isabel Rocha

Co-supervisor: Dr. Miguel Meira e Cruz

Dissertation especially designed to obtain Master's degree in Neurosciences

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All statements made in this document are the sole responsibility of the author.

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Contents

List of Tables

List of Figures

List of Abbreviations

ARAS – Ascending Reticular Activating System

BDD – Body Dysmorphic Disorder

BMI – Body Mass Index

BP – Blood Pressure

BZ – Benzodiazepine

CBT-I – Cognitive Behavioural Therapy for Insomnia

CKD – Chronic Kidney Diseases

CO – Cut-off value

COPD – Chronic Obstructive Pulmonary Disease

CRSWDs – Circadian Rhythm Sleep-Wake Disorders

CVD – Cardiovascular Disease

DCQ – Dysmorphic Concern Questionnaire

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders-4th edition (1994)

EEG – Electroencephalogram

FIRST – Ford Insomnia Response to Stress Test

GABA - γ-aminobutyric acid

GAD-2 – Generalized Anxiety Disorder 2-item scale

GAD-7 – Generalized Anxiety Disorder 7-item scale

HBRA – Hypnotic Benzodiazepine Receptor Agonists

HPA – Hypothalamic-Pituitary-Adrenal Axis

HR – Heart Rate

ICD-10 – International Classification of Diseases-10th edition (1992)

ICSD-1 – International Classification of Sleep Disorders-1st Edition (1990)

ICSD-2 – International Classification of Sleep Disorders-2nd Edition (2005)

ICSD-3 – International Classification of Sleep Disorders-3rd Edition (2014)

IEQ – Injustice Experience Questionnaire

IHS – International Headache Society

IPQ – Illness Perception Questionnaire

ISI – Insomnia Severity Index

NRS – Numeric Rating Scale

OFP – Orofacial Pain

OFR – Pain in the Orofacial Region

p – p-value (level of significance)

PCS – Pain Catastrophizing Scale

PHQ-2 – The 2-item Patient Health Questionnaire

PHQ-4 – The 4-item Patient Health Questionnaire

PHQ-9 – The 9-item Patient Health Questionnaire

PHQ-Str – Patient Health Questionnaire for Stress

PI – Pain Intensity

PRIME-MD – Primary Care Evaluation of Mental Disorders

PTSD – Post-Traumatic Stress Disorder

REM – Rapid Eye Movement

RLS – Restless Legs Syndrome

r_s – Spearman's rank correlation coefficient

TMD – Temporomandibular Disorder

WISE – Web-based Interdisciplinary Symptom Evaluation

Authorship

The results presented in this Master thesis are or will be supporting the following manuscripts:

1) Nobre B, Rocha I, Morin C, Meira e Cruz M (2020). Insomnia and circadian misalignment: an underexplored interaction towards cardiometabolic risk. Sleep Science, DOI: 10.5935/1984-0063.20200025 in press [Q2].
   Available from: https://cdn.publisher.gn1.link/sleepscience.org.br/pdf/aop419.pdf

2) Meira e Cruz M, Nobre B, Ettlin D, Rocha I. Psychosocial stress and insomnia in pain in the orofacial region (in preparation).

Abstract

Insomnia, the most common sleep disorder, is highly prevalent and causes clinically significant functional distress or impairment, both at physical and psychological levels. Sleep complaints are present in a large majority of pain disorders and individuals with insomnia often suffer from pain. Pain in the orofacial region (OFR) includes the pain arising from the regions above the neck, in front of the ears, and below the orbitomeatal line, the oral cavity itself, and might be also associated with temporomandibular disorders. Few studies have been evaluating the relationship between OFR and insomnia but failed to address the triad OFR, insomnia, and associated psychosocial factors which was the purpose of the present study. For that, anonymized data of 184 adult patients with OFR, both sexes (71.2% women), aged 45.8±16.4 years were extracted from the self-screening WISE platform (Web-based Interdisciplinary Symptom Evaluation). Significant medical or psychiatric conditions, shift working, or drug treatments that may cause insomnia were exclusion criteria. Prevalence data for insomnia (ISI), stratified by severity grade, and psychometric measures (DCQ, GAD-7, IPQ, PCS, PHQ-4, PHQ-9, IEQ, and PHQstr) assessing the dysmorphic concern, anxiety, illness perception, pain-related catastrophizing and disability, distress, depression, injustice experience, and psychosocial stress were performed. The correlations of psychometric scores with insomnia grades having gender, age, and employment status as putative confounders were analysed. Globally, patients had a normal weight or were pre-obese, being most of them light smokers and active workers. From the recruited patients, 34.8% reported insomnia symptoms, with 16.3% of them reaching moderate to severe insomnia which is clinically relevant. Pain intensities, psychosocial burden, and sleep disturbances were higher in women than men. Severe depression, anxiety, and distress were the most frequent symptoms (18.5-23.9%), while clinically relevant stress and dysmorphic concern were the least (5.40% and 3.80%, respectively). The results of correlation analysis of the psychometric measures and insomnia scores were as follows: DCQ, GAD-7, IPQ, PCS, PHQ-4, and PHQ-9 had moderate and strong associations ($r_s > 0.300$) with ISI scores of all respondents and women (unlike the male group). The IEQ scores were strongly correlated with ISI scores between 8 and 21 ($-0.608 < r_s < 0.626$). The association between PHQstr and ISI scores was only found in patients unable to work. Patients aged between 30 and 39 years had the greatest number of statistically significant correlations between the variables, while the seniors (>70 years) had none. The active workers constitute the employment status with the highest number of associations between sleep

problems and impaired well-being (anxiety, pain catastrophizing, distress, and depression), followed by the retired ones. Despite the small number of data, that should be increased in the future, we may conclude that insomnia and psychosocial stressors biunivocal influence each other, with different weights, in OFR patients. Due to the high incidence of clinically relevant insomnia in OFR patients, these patients should always be screened for insomnia, at least, with a self-assessed questionnaire and appropriately counselled. In addition, our study shows how an easy-to-use self-assessment instrument, when used judiciously by the patient, can be useful in clinical practice by promoting a more complete assessment of the patient, his personalized treatment, and the strengthening of the doctor-patient relationship.

Keywords: sleep, insomnia, pain in the orofacial region, well-being, psychosocial factors, self-screening

Sumário

A insónia, o distúrbio do sono mais comum, é altamente prevalente e causa um sofrimento ou défice funcional clinicamente significativo, tanto a nível físico quanto psicológico. As queixas de sono estão presentes na grande maioria das patologias que cursam com dor e os indivíduos com insónia, em muitas circunstâncias, também têm dor. A dor na região orofacial (DROF) pode ser definida como uma dor localizada na região acima do pescoço, junto ao pavilhão auricular e abaixo da linha orbitomeatal, bem como na cavidade oral ou associada à patologia temporomandibular. Muitas doenças podem levar a síndromes de dor orofacial que atualmente são classificadas em vários subgrupos. Frequentemente, tratamentos cirúrgicos inadequados levam a um ciclo vicioso que cria uma situação de dor persistente, portanto, uma abordagem de tratamento multimodal é essencial para evitar o agravamento da dor de forma a que se não torne crónica. No entanto, atualmente, o controlo da dor orofacial permanece desafiante. De acordo com a *International Headache Society* existe uma diferenciação entre síndromes de dor na região orofacial e outras condições dolorosas. Alguns estudos já avaliaram a relação entre dor na região orofacial e insónia, mas ainda não abordaram a tríade dor na região orofacial, insónia e fatores psicossociais associados. Este foi o objetivo do presente estudo. Para isso, dados previamente anonimizados de 184 doentes adultos com DROF, de ambos os sexos (71.2% mulheres), com idade de 45.8 ± 16.4 anos, foram extraídos da plataforma de autoavaliação de sintomas WISE. Condições médicas ou psiquiátricas, trabalho por turnos ou tratamentos com fármacos que possam causar insónia constituíram os critérios de exclusão. Foram realizados estudos de prevalência de insónia (ISI) estratificada por grau de gravidade, bem como estudos de avaliação psicométrica (DCQ, GAD-7, IPQ, PCS, PHQ-4, PHQ-9, IEQ e PHQstr), analisando a preocupação dismórfica, ansiedade, perceção da doença, catastrofização e incapacidade relacionadas com a dor, angústia, depressão, experiência de injustiça e stress psicossocial. A correlação dos resultados psicométricos com os graus de insónia, considerando como fatores confundidores o sexo, idade e empregabilidade foi, também, efetuada. Globalmente, os doentes apresentavam peso normal ou eram pré-obesos, sendo a maioria fumadores leves e trabalhadores ativos. Dos doentes recrutados, 34.8% deles relataram sintomas de insónia e 16.3% apresentavam insónia moderada e grave, que são os dois tipos de insónia clinicamente relevantes. A intensidade da dor, a carga psicossocial e os distúrbios do sono foram superiores nas mulheres. Depressão, ansiedade e angústia severas foram os sintomas mais frequentes (18.5-23.9%), enquanto o stress e a preocupação dismórfica

clinicamente relevantes foram os menos frequentes (5.40% e 3.80%, respetivamente). A correlação das medidas psicométricas com os estádios de insónia foram os seguintes: DCQ, GAD-7, IPQ, PCS, PHQ-4 e PHQ-9 tiveram associações moderadas e fortes ($r_s > 0.300$) com os valores obtidos pelo ISI para todos as doentes, mas não para o grupo de doentes masculinos. Os valores do IEQ foram fortemente correlacionados com os valores do ISI entre 8 e 21 ($-0.608 < r_s < 0.626$). A associação entre os valores do PHQstr e do ISI foi encontrada apenas em doentes com incapacidade para o trabalho. Doentes com idade compreendida entre os 30 e 39 anos apresentaram o maior número de correlações estatisticamente significativas entre as variáveis, ao contrário dos doentes com mais 70 anos para os quais não se encontrou nenhuma. Os trabalhadores ativos constituíram o estatuto profissional com o maior número de associações entre problemas de sono e alterações de bem-estar como ansiedade, catastrofização da dor, angústia e depressão, sendo seguidos pelos doentes reformados. Assim, em doentes com dor orofacial, a insónia e fatores de stress psicossocial influenciam-se mutuamente de forma biunívoca embora com pesos diferentes. Em conclusão, este trabalho, apesar de baseado numa pequena coorte de pacientes que deverá ser futuramente aumentada, enfatiza a interconexão entre DROF, insónia e carga psicológica, bem como a relevância de avaliar, em ambientes clínicos, comorbidades somáticas e psicológicas que podem interromper o sono. As mulheres, os trabalhadores ativos e os doentes jovens e de meia-idade tiveram um predomínio de resultados mais expressivos, ou seja, as pontuações do ISI correlacionaram-se mais fortemente com as medidas do eixo II, representando os grupos que devem ser acompanhados de perto. Para além disso, o nosso estudo demonstra como um instrumento de autoavaliação de fácil utilização, quando usado de forma criteriosa pelo doente, pode ser útil na prática clínica, promovendo uma avaliação mais completa do doente, bem como o seu tratamento personalizado e o fortalecimento da relação médico-doente.

Palavras-chave: sono, insónia, dor na região orofacial, bem-estar, fatores psicossociais, autoavaliação

1. Introduction

1.1. Insomnia

1.1.1. Definition

Insomnia is defined as a persistent difficulty with sleep initiation, duration, and consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and, results in some form of daytime impairment (ICSD-3, 2014) (Sateia, 2014). This disorder differs from sleep deprivation, a condition related to insufficient sleep, by the persistent difficulty in sleeping despite having the adequate opportunity and circumstances for that (Levenson, Kay, & Buysse, 2015). Despite the higher prevalence of mixed symptom phenotypes, sleep-onset insomnia is more common in younger adults, whereas sleep-maintenance difficulties are more frequent in middle-aged and older adults. Subjects with this problem are dissatisfied with their sleep, and experience one or more of the following symptoms: fatigue, excessive daytime sleepiness, decreased energy, difficulty concentrating, mood disturbances, and decreased performance at work or school; and, these, are required criteria to diagnose insomnia disorder (Morin et al., 2015; Riemann et al., 2017; Sateia, 2014) (see **Table 1**).

Since 1990, diagnostic algorithms have been developed to categorize insomnia given its duration, etiology, and pathophysiology. Over the years, the insomnia subtypes were critically discussed and updated with the growth of new documented evidence. Some previously used terms, such as ‘non-organic insomnia’ vs ‘organic insomnia’ (ICD-10, 1992) and ‘primary insomnia’ vs ‘secondary insomnia’, were therefore removed (ICSD-1, 1990; ICSD-2, 2005 and DSM-IV, 1994). The 3rd version of the International Classification of Sleep Disorders (ICSD-3) includes an important distinction between short-term insomnia disorder, characterized by insomnia symptoms that typically last a few days or weeks, and chronic insomnia disorder (clinically relevant disorder), which tends to be persistent and often remains for months or years. The diagnosis of chronic insomnia requires the presence of sleep difficulties more than 3 times per week during a period of, at least, 3 months (Morin et al., 2015; Sateia, 2014; Schutte-Rodin et al., 2017).

Table 1 | Insomnia diagnostic criteria according to ICSD-3

[a] specific diagnostic criterion for chronic insomnia. ICSD-3, International Classification of Sleep Disorders – 3rd Edition, 2014.

A | Night-time symptoms
1. Difficulty initiating sleep
2. Difficulty maintaining sleep
3. Waking up earlier than desired
4. Resistance to going to bed on appropriate schedule
5. Difficulty sleeping without parent or caregiver intervention
B | Daytime symptoms
1. Fatigue/malaise
2. Attention, concentration, or memory impairment
3. Impaired social, family, occupational, or academic performance
4. Mood disturbances
5. Daytime sleepiness
6. Behavioural problems (e.g., hyperactivity, impulsivity, aggression)
7. ↓ motivation/energy/initiative
8. Proneness for errors/accidents
9. Concerns about or dissatisfaction with sleep**.**
C
The reported sleep/wake complaints cannot be explained purely by an inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.
D[a]
The sleep disturbance and associated daytime symptoms occur, at least, 3 times per week.
E[a]
The sleep disturbance and associated daytime symptoms have been present for, at least, 3 months.
F
The sleep/wake difficulty is not better explained by another sleep disorder

A: The patient reports, or the patient's parent or caregiver observes, one or more of the following.
B: The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the night-time sleep difficulty.

In clinical practice, the diagnostic management of insomnia is crucial. It involves a clinical patient interview with a detailed sleep history (e.g., sleep habits, hygiene behaviours, work schedules, circadian factors), being highly recommended the use of sleep diaries and sleep questionnaires (Mai & Buysse, 2008; Riemann et al., 2017). The most widely used instrument and the gold standard to evaluate the severity of both night-time and daytime components of insomnia and its consequences is the Insomnia Severity Index (ISI) (for details see Methods) (Bastien, Vallières, & Morin, 2001). Additionally, physical examination together with blood analysis and polysomnography (the gold standard method to quantify sleep time, to differentiate sleep stages, and do evaluate sleep fragmentation (Rundo & Downey, 2019)), can be performed to improve the diagnose and also to search for other sleep disorders (Mai & Buysse, 2008; Riemann et al., 2017).

1.1.2. Epidemiology

Insomnia is the most reported sleep problem worldwide, with high prevalence rates depending on the methodological procedure and diagnostic criteria used (Kalmbach, Anderson, & Drake, 2018; Mai & Buysse, 2008; Mellor et al., 2019; Morin et al., 2015; Riemann et al., 2017). Among the world population, 10-50% of subjects, of all ages, acknowledge having insomnia symptoms, and 5-15% suffer from chronic insomnia, a declared sleep disorder (Choueiry et al., 2016; Mai & Buysse, 2008; Meira e Cruz et al., 2019; Morin et al., 2015; Tobaldini et al., 2019). Considering only the adult population affected by insomnia disorder, its prevalence is about 6% to 20% across studies (Kalmbach, Anderson, et al., 2018; Riemann et al., 2017). In ten European countries, a study on insomnia diagnosis and treatment revealed a prevalence of chronic insomnia ranging from 5.7% in Germany to 19% in France (Riemann et al., 2017) (**Table 2**). Epidemiological studies about sleep disturbances in Portugal have not been a major goal in scientific research. Nevertheless, the very few studies show an estimated prevalence of insomnia symptoms between 17.7% and 28.1% in the Portuguese adult population (Ohayon & Paiva, 2005; Pereira, Almeida, Veiga, & Amaral, 2014) and of 21.4% among the Portuguese adolescents with 8.3% of them having daytime consequences (Amaral, De Figueiredo Pereira, Martins, De Serpa, & Sakellarides, 2013). Besides, the prevalence of insomnia was higher in female subjects, corroborating gender as a risk factor for the disease (Amaral et al., 2013; Ohayon & Paiva, 2005; Pereira et al., 2014).

Table 2 | Prevalence of insomnia disorder in ten European countries. Adapted from Riemann et al., 2017

Country	Author (year)	Sample size	% Insomnia disorder
England	Calem *et al.* (2012)	20 503	5.8%
Finland	Ohayon & Partinen (2002)	982	11.7%
France	Léger *et al.* (2000)	12 778	19%
Germany	Schlack *et al.* (2013)	7988	5.7%
Hungary	Novak *et al.* (2004)	12 643	9%
Italy	Ohayon & Smirne (2002)	3970	7%
Norway	Pallesen *et al.* (2001, 2014)	2000	15.5%
Romania	Voinescu & Szentágotai (2013)	588	15.8%
Spain	Ohayon & Sagales (2010)	4065	6.4%
Sweden	Mallon *et al.* (2014)	1550	10.5%

It is well-established in the literature that insomnia affects women and men differently (Carmel & Bernstein, 2003; Kret & De Gelder, 2012; Shaefer, Khawaja, & Bavia, 2018; Suh, Cho, & Zhang, 2018) being ~1.5-2 times more preponderant in women (Léger & Bayon, 2010; Meira e Cruz et al., 2019; Morin et al., 2015; Roth, 2007) who, together with additional complaints and distress, have a 2-fold higher likelihood of looking for help from health care professionals (Suh et al., 2018). Underlying sex differences are the female reproductive hormones (progesterone and oestrogen) that affect sleep in women during the menstrual cycle. Progesterone reduces arousals while oestrogen enhances plasmatic norepinephrine leading to an increase in REM sleep duration and decreasing in REM sleep latency. Typically, insomnia becomes more frequent in female puberty, getting worse during menopause transition or after it due to a decrease in melatonin synthesis and secretion, in line with the decline of female reproductive hormones which compromises a good sleep quality (Fang & Fishbein, 1996; Morin et al., 2015; Suh et al., 2018). Moreover, insomnia might persist for an average duration of 3 years (Morin et al., 2015), with 50-70% of patients reporting symptoms at 1-year follow-up and 46% after three years (Morin et al., 2015; Riemann et al., 2017). The annual incidence of the disease is, indeed, remarkably high, varying between 5% and 15% (Kalmbach, Anderson, et al., 2018; Morin et al., 2015; Perlis et al., 2019).

1.1.3. Risk factors

Despite the heterogeneity of the disorder, the ICSD-3 classification only includes one diagnosis covering all forms of chronic insomnia (Sateia, 2014; Zucconi & Ferri, 2014). The severity of the disease is influenced, to different degrees, by various factors. These risk factors include 1) *predisposing factors*, that make individuals more vulnerable to developing the disorder (demographic, biological, psychological, and social factors); 2) *precipitating factors*, which are the real trigger of an acute episode of insomnia (stressful life events or medical conditions that may disrupt sleep); and 3) *perpetuating factors*, which potentiate sleep disturbances even after the initial trigger has been removed (behavioural or cognitive changes like excessive worrying about sleep loss and its effects). In chronic insomnia, the perpetuating factors have a stronger contribution to the maintenance than the onset of the disorder (Morin et al., 2015; D. Patel, Steinberg, & Patel, 2018). The various risk factors that influence insomnia are shown in **Table 3**.

1.1.4. Pathophysiology

At the pathophysiological level, insomnia can be characterized as two distinct phenomena that are summarized in **Table 4** and **Figure 1**. On one hand, insomnia is a psychological phenomenon due to the cognitive components involved, such as worries, negative thoughts, and rumination about sleep efficiency and associated daytime consequences (Harvey, 2002; Morin et al., 2015) and also behavioural aspects (classic conditioning) (Harvey, 2002; Molen, Carvalho, Prado, & Prado, 2014; Riemann et al., 2017). On the other hand, it can be defined as a neurophysiologic phenomenon, i.e., a state of cerebral hyperexcitability or hyperarousal represented by the hyperarousal model (Grandner & Perlis, 2013; Mai & Buysse, 2008; Riemann, 2019; Riemann et al., 2017). Hyperarousal results from an elevated whole-body metabolic rate during sleep and wakefulness, increased cortisol secretion during the early sleep period, reduced parasympathetic activity (D. Patel et al., 2018), continuous sympathetic hyperactivation, and increased heart rate, and temperature (Levenson et al., 2015; Molen et al., 2014).

Table 3 | Insomnia risk factors: predisposing, precipitating and perpetuating factors

Predisposing	
Psychological	- Personality traits: neuroticism, sensitivity to anxiety symptoms, tendency to internalize problems
Demographic and biological	- Female sex - Older adults - Race and ethnicity (e.g., African Americans are more likely to develop insomnia than Caucasians) - Lower level of education - Positive family history - Sleep reactivity, hyperarousal and higher scores on the FIRST, the Ford Insomnia Response to Stress Test (see Drake et al., 2004 for the whole instrument)
Social	- Unemployed / lower socioeconomic status - Shift work/work schedules - Divorced - Smoking and alcohol use - Reduced physical activity
Precipitating	
- Stressful life events - Medical conditions (especially respiratory, chronic pain, neurological disorders) - Medications: beta-blockers, glucocorticoids, etc	
Perpetuating	
- Maladaptive cognitions and behaviours: excessive time in bed; frequent naps; increased anxiety before sleep onset - Excessive worrying about sleep loss and its consequences	

Adapted from Kalmbach, Cuamatzi-Castelan, et al., 2018; Morin et al., 2015; D. Patel et al., 2018; S. R. Patel, 2007; Sateia, 2014; Schutte-Rodin et al., 2017; Wolińska, 2020.

Table 4 | Insomnia associated symptoms and pathophysiological mechanisms

Psychological	Physiological
- Worries and rumination - ↓ cognitive functions: impaired attention, concentration, and memory - ↑ emotional reactivity - ↑ arousal levels in the cognitive and emotional domains - Unrealistic expectations concerning sleep duration and daytime functioning - EEG: ↑ β activity; ↓δ activity	- ↑ sympathetic activity (hyperarousal model) → ↑ BP and ↑HR - HPA axis dysregulation and ↑ nocturnal cortisol - ↑ ghrelin and ↓ leptin (↑appetite) - Immune (↑ pro-inflammatory cytokines) and endocrine systems dysregulation

↑, increased; ↓, reduced; EEG, Electroencephalogram; BP, Blood Pressure; HR, Heart Rate; HPA, Hypothalamic Pituitary Adrenal Axis. Adapted from D'Aurea et al., 2015; Hirotsu, Tufik, & Andersen, 2015; Jarrin, Ivers, et al., 2018; Kalmbach, Cuamatzi-Castelan, et al., 2018; Mai & Buysse, 2008; Morin et al., 2015; Riemann et al., 2017; Vargas et al., 2018.

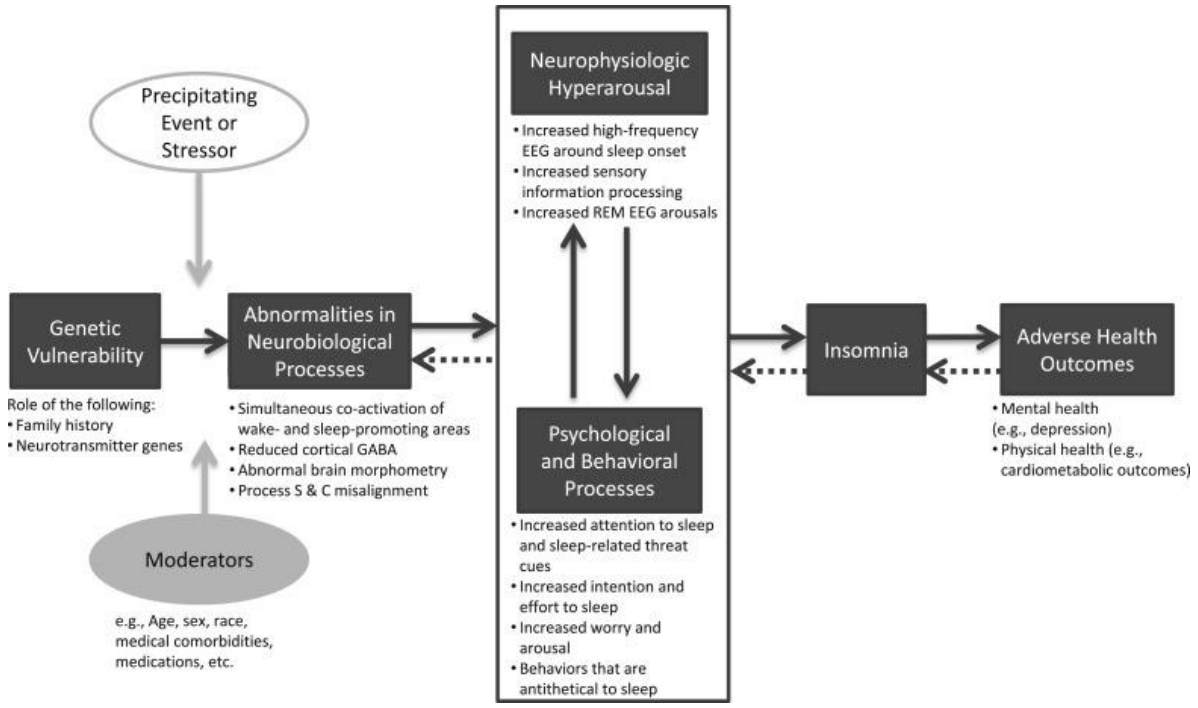

Figure 1 | Model of the pathophysiology of insomnia. GABA = γ-aminobutyric acid; EEG, Electroencephalogram; REM, Rapid Eye Movement. Process S (homeostatic sleep drive) and Process C (circadian rhythm) are two independent and interrelated biological mechanisms that promote sleep regulation. Adapted from Levenson et al., 2015.

1.1.5. Comorbidities

Given the importance of good sleep, either in quantity or quality, it's not surprising that sleep disturbances may be a risk factor for impaired daytime functioning and other medical conditions (Grandner & Perlis, 2019), contributing to the development of adverse physical and psychological health outcomes. In fact, 85-90% of insomnia is comorbid with other disorders (Reddy & Chakrabarty, 2011). Some negative sequelae and comorbidities of insomnia are described in **Table 5**.

Table 5 | Insomnia negative sequelae and comorbidities

Negative Sequelae	
Psychological	**Physiological**
- Cognitive impairment - Emotional distress	- Obesity - Type 2 diabetes - Hypertension - ↑ gastrointestinal and urinary difficulties - Metabolic dysfunction - ↑ mortality

Comorbidities				
Psychiatric	**Other medical conditions**	**Neurological**	**Sleep Disorders**	**Substance use**
- Depression and depressive disorders - Bipolar disorders - GAD - Panic Disorder - PTSD - Schizophrenia	- Chronic pain - COPD - CKD - HIV infection - Malignancy - Rheumatic disorders - CVD	- Neurodegenerative disorders - Fatal familial insomnia - Multiple sclerosis	- Sleep apnea - RLS - CRSWDs - Parasomnias - REM sleep behaviour disorder	- Alcohol - Nicotine, caffeine, marijuana - Opioids - Designer drugs, cocaine, amphetamine

GAD, Generalized Anxiety Disorder; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Diseases; CVD, Cardiovascular Disease (congestive heart failure, arrhythmia, coronary artery disease); PTSD, Posttraumatic Stress Disorder; RLS, Restless Legs Syndrome; CRSWDs, Circadian Rhythm Sleep-Wake Disorders; REM, Rapid Eye Movement. Adapted from Fernandez-Mendoza & Vgontzas, 2013; Hirotsu et al., 2015; Leblanc, Smith, Nichols, Allison, & Clarke, 2018; Mai & Buysse, 2008; Morin et al., 2015; Riemann et al., 2017; Schutte-Rodin et al., 2017; Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013; Zucconi & Ferri, 2014.

A wide range of evidence supports that both short-term and chronic insomnia have been associated with adverse long-term health consequences, overall increasing cardiovascular and associated metabolic risk (D'Aurea et al., 2015; Grandner & Perlis, 2013; Jarrin, Alvaro, et al., 2018; Leblanc et al., 2018; Schiller, Söderström, Lekander, Rajaleid, & Kecklund, 2018; Sørengaard et al., 2019; Tobaldini et al., 2019; Vgontzas et al., 2013). Cardiometabolic risk can be defined as a cluster of metabolic and cardiovascular abnormalities leading to obesity, insulin resistance, hypertension, and atherosclerosis (Knutson, 2010; Vargas et al., 2018). Insomnia is also linked to psychiatric issues such as anxiety, depression, distress, and burnout, although sometimes it is difficult to understand this cause-and-effect relationship, and its mechanistic pathways (Khurshid, 2018; Riemann, 2019; Schiller et al., 2018; Schutte-Rodin et al., 2017; Sørengaard et al., 2019). Thus, when insomnia is not an independent condition and co-occurs with another disorder, two diagnostic procedures might be used (Riemann et al., 2017; Zucconi & Ferri, 2014).

Insomnia also constitutes a risk factor for professionals by increasing by 7 times the rate of occupational accidents and by promoting absenteeism, its most frequent consequence (Léger & Bayon, 2010; Metlaine, Leger, & Choudat, 2005), which reduces workability, productivity, worker satisfaction, and performance (Daley, Morin, LeBlanc, Grégoire, Savard, et al., 2009; Léger & Bayon, 2010; Metlaine et al., 2005; Riemann et al., 2017). Overall, understanding the causes, factors, and mechanisms that perpetuate insomnia is considered a major public concern.

1.1.6. Economical costs

The socioeconomic impact of insomnia is massive and estimates of total costs range from 35 to 107.5 billion USD per year (Chilcott & Shapiro, 1996; Daley, Morin, LeBlanc, Grégoire, & Savard, 2009; Léger & Bayon, 2010; Wade, 2011). These costs include three components: 1) *direct costs* (~2.1 to 15.4 billion USD per year (Chilcott & Shapiro, 1996; Metlaine et al., 2005)), encompassing medications, self-treatment, visits to healthcare professionals or hospital services, and institutionalization for the treatment of the disease supported by patients, government, organized health care providers and insurance companies; 2) *indirect costs* (~41.1 to 56.02 billion USD per year (Léger & Bayon, 2010; Metlaine et al., 2005)) due to illness-related morbidity and mortality borne by the patient and the employer; and, 3) *related costs*, which are those derived from the treatment of a disease associated with the onset of insomnia (Chilcott & Shapiro, 1996; Daley, Morin, LeBlanc, Grégoire, & Savard, 2009; Léger & Bayon, 2010; Wade, 2011). Interestingly, it has been suggested that 76% of total costs are attributed to

insomnia-related work absences and decreased productivity (Daley, Morin, LeBlanc, Grégoire, & Savard, 2009). In Europe, it was estimated an amount of 35 billion euros per year related to insomnia costs, excluding its indirect costs. Additionally, the weighted mean of costs per patient suffering from sleep disorders, per year, by prevalence in each European country was 790 euros. In Portugal, this cost was about 599 euros per year, per person (Gustavsson et al., 2011).

1.1.7. Therapeutic approaches

Therapeutic options, pharmacological or of other nature, have been developed to help insomniacs get back to healthy sleep patterns (Frase, Nissen, Riemann, & Spiegelhalder, 2018; Mellor et al., 2019). However, the relapse rates are high and the field is struggling to develop preventive measures acting on specific and easily identified stressors with interaction with shortened and disturbed sleep (Han, Kim, & Shim, 2012; Kalmbach, Anderson, et al., 2018; Morin et al., 2009).

Cognitive Behavioural Therapy for Insomnia (CBT-I) is the gold standard for treating insomnia. It is an effective and safe non-pharmacological treatment (Mellor et al., 2019) that eliminates insomnia perpetuating risk factors and then targets the precipitating components (Molen et al., 2014). CBT-I consists of 6 to 10 sessions with a therapist, focused on patients' cognitive beliefs and behaviours that might compromise sleep (D. Patel et al., 2018). For long-term effects, this psychological treatment is highly recommended, because patients change habits, behaviours, and beliefs, overall improving their life quality (Mellor et al., 2019; Molen et al., 2014). CBT-I is usually preferred by patients over medications and this is another advantage of this therapeutics (Mellor et al., 2019).

Pharmacotherapy is sometimes required in clinical care when CBT-I is not available or not effective (Frase et al., 2018). It includes substances that target the ascending reticular activating system (ARAS), by modulating GABAergic transmission and, subsequently, inhibiting this system. ARAS is responsible for wakefulness and hyperarousal. Benzodiazepines (BZ) and hypnotic benzodiazepine receptor agonists (HBRA) are used to promote a sedative effect and improve sleep (Frase et al., 2018; Riemann et al., 2017). However, long-term use of BZ or HBRA is not recommended, because it can have additive effects and lead to dependence, cognitive impairment, residual daytime sedation, and increased risk of work accidents (D. Patel et al., 2018; Riemann et al., 2017). Other possible pharmacological interventions include melatonin and melatonin receptor agonists, sedating antidepressants, antipsychotics, and antihistamines. Nevertheless, all these options are less advised based on very low-, low- or

moderate-quality evidence (Riemann et al., 2017). Although with a weak recommendation and low-quality evidence, light therapy, exercise, and alternative medicine (e.g. acupuncture, aromatherapy, relaxation techniques, yoga) are options to complementary treat insomnia disorder (Molen et al., 2014; D. Patel et al., 2018; Riemann et al., 2017).

1.2. Relationship between sleep, psychosocial well-being, and pain

Despite recent developments, the relationship between insomnia and psychological symptoms is still quite unexplored even if they influence each other and, anxiety and depressive symptoms are still interpreted by many authors in terms of comorbidity of sleep disorders. On the other side, some studies have found that subclinical symptoms of mood changes and anxiety play a significant role in sleep disorders. In fact, insomnia can be an anticipatory symptom of mood changes and some studies showed cognitive-emotional hyperexcitation as a predictor of insomnia as well as a common genetic and neurobiological substrate, cognitive patterns, and regulation of emotions with psychiatric disorders (Alföldi, Wiklund, & Gerdle, 2014).

Furthermore, sleep appears to also have a protective role against pain as during sleep there seems to be a deactivation of the pain matrix in the brain together with a deactivation of the arousal ascending system, while the lack of sleep appears to be related to the opposite events (Alföldi et al., 2014). Some studies have shown that insomnia has a greater impact on the sensation of pain than the effect of pain on sleep quality because poor sleep in individuals increases the risk for chronic pain whereas good sleep quality has been associated with a better long-term prognosis in subjects with pain such as tension headache or chronic musculoskeletal pain (Broberg, Karjalainen, & Ollila, 2021). Thus, a relationship between poor sleep quality and the sensation of pain has been suggested, as observed in sleep deprivation studies in which sleep interruption for 3 consecutive nights increased the perception of pain (Finan et al, 2013). Previous studies have also shown a high prevalence of clinical insomnia in chronic pain in which 23% of patients reporting, at least, insomnia symptoms while 40% of insomniacs report, at least, one type of pain (Alföldi et al., 2014; Ohayon, 2005). Confirming these observations, some systematic reviews have shown an association between pain and insomnia as pain increases the risk of insomnia and vice versa (Kelly, Blake, Power, Okeeffe, & Fullen, 2011; Smith & Haythornthwaite, 2004).

Besides, both conditions, insomnia, and chronic pain, negatively affect the well-being and quality of life of patients (Dragioti, Levin, Bernfort, Larsson, & Gerdle, 2017). Furthermore, pain and insomnia have comorbidities that are common such as obesity, type 2 diabetes, and

depression (Finan, Goodin, & Smith, 2013; Heo, Allison, Faith, Zhu, & Fontaine, 2003; Knutson, Ryden, Mander, & Van Cauter, 2006), and high cost of living (Bernfort, Gerdle, Rahmqvist, Husberg, & Levin, 2015). In healthy individuals, studies have shown that sleep disturbances reduce the threshold for pain whereas chronic pain and insomnia frequently co-exist (Dragioti, Bernfort, Larsson, Gerdle, & Levin, 2018).

To date, not many studies have studied how chronic pain and insomnia affect the quality of life and well-being of individuals, and, in particular, we are not aware of any study that relates insomnia, well-being, and pain in the orofacial region.

1.2.1. WISE (Web-based Interdisciplinary Symptom Evaluation)

In clinical practice, various paper and computer-based tools are widely used to capture data for optimal clinical management and research. Recently (2016), a new modular, universally accessible, web-based interdisciplinary symptom evaluation was designed, constructed, and technically implemented for subject-tailored assessment of OFR and temporomandibular disorders (TMD) before clinical interviews. The WISE is easy to administer, and electronic data are store securely. This tool helps to clarify case complexity and referral need, based on symptom burden and response. It provides single-case summary reports from a biopsychosocial perspective and includes graphical symptom maps. The WISE symptom burden checklist was thematically aligned with available questionnaires commonly addressing these diverse symptom domains. This tool enables personalized medicine, facilitates interprofessional education and collaboration, and allows for multicentre patient-reported outcomes research (see Ettlin et al., 2016 for the full instrument).

1.3. Thesis Rationale and Objectives

Sleep, which is affected by lifestyle and health, might be considered as a restorative process and has a major influence on protein synthesis and hormone release (Whitesell, Obi, Tamanna, & Sumner, 2018). Its importance is easily understood as human subjects, among other species, spend a third of their time sleeping, and the productivity of the other two-thirds depends on the quality of sleep they have (Shamim, Warriach, Tariq, Rana, & Haider, 2019). Adequate duration and quality of sleep improve alertness, mood, and performance, besides long-term health benefits (Gamaldo, Chung, Kang, & Salas, 2014). In fact, around the world, insufficient sleep is prevalent across the population, being a public health epidemic that is often undiagnosed, under-reported, and which is related to a high economic burden (Chattu et al., 2018).

Pain is a physical and emotional signal, apparently, without biological value, that becomes chronic when it persists beyond 3 months, the considered normal tissue healing time (Finan et al., 2013; Mayer et al., 2019). Chronic pain affects about 50 to 80 million people in the United States (Ong, Zautra, & Reid, 2010) and 12% to 30% of the Europeans (Mayer et al., 2019), with a higher prevalence among the elderly (Larsson, Hansson, Sundquist, & Jakobsson, 2017; Mayer et al., 2019; Ong et al., 2010) and female gender (Shaefer et al., 2018). In general, pain in the orofacial region can be defined as "pain localized to the region above the neck, in front of the ears and below the orbitomeatal line, as well as pain within the oral cavity" (Racich, 2018). Many diseases can lead to orofacial pain (OFP) syndromes that are currently classified into several subgroups: temporomandibular disorders, persistent idiopathic facial pain and atypical odontalgia. Often, inadequate surgical treatments may lead to a vicious cycle that creates a situation of persistent pain, so a multimodal treatment approach is essential to avoid worsening pain as the management of chronic orofacial pain remains difficult (Galli, Ettlin, Palla, Ehlert, & Gaab, 2010). In accordance to the International Headache Society (IHS), a differentiation exists between orofacial pain syndromes and other painful conditions (Galli et al., 2010). Pain-related disability can be considered a psychosocial stressor that negatively impacts individuals' daily activity and potentially accentuates psychological burdens (M. J. L. Sullivan, Sullivan, & Adams, 2002). The importance of considering the patient's social and environmental context, besides the genetic susceptibility, as determinants of pain-related disability has been emphasized in previous research (M. J. L. Sullivan et al., 2002). Therefore, the presence of pain in the orofacial region may negatively affect social interactions and life

quality, contributing to significant emotional distress, morbidity, and sleep problems (Hester & Tang, 2008; Palermo, Wilson, Lewandowski, Toliver-Sokol, & Murray, 2011). Compromised emotional and cognitive functioning may alter pain perception as well as appropriate pain responses. In turn, distressing persistent pain may overwhelm psychological resilience (Ong et al., 2010).

Given the dynamic relationship between sleep, pain, and psychosocial burden, and knowing that patients with pain are more likely to develop sleep problems and mental health issues, the hypothesis underlying the present work is that insomnia impacts the psychosocial condition of patients with pain in the orofacial region leading to stress and anxiety. Thus, we sought to investigate the correlation between insomnia and psychosocial well-being factors measured by eight psychosocial variables through anonymous data collected by the WISE platform, a patient's self-screening tool, applied to a population with pain in the orofacial region. To address this main purpose, the following specific objectives have been drawn:

1) To investigate the prevalence of clinically relevant insomnia in the studied population.
2) To analyse insomnia relationship with psychosocial factors such as stress and anxiety, considering the influence of putative confounders such as age, gender, and employment status.

2. Methods

2.1. Subjects and data collection

Anonymized data of adult patients, both sexes, with a broad variety of orofacial pain conditions who attended the Interdisciplinary Orofacial Pain Unit of the Centre of Dental Medicine, University of Zurich (Switzerland) between January and May 2019 were used. The presence of other significant medical or psychiatric conditions, shift working, or drug treatments that may cause insomnia were considered as exclusion criteria. Data were extracted from the WISE (Web-based Interdisciplinary Symptom Evaluation) platform that patients completed before their first medical appointment. In short, upon a referral by a medical doctor, the patient was registered in a database. Login information was, then, generated and sent to the patient to allow access to the WISE platform where information about the purpose of the questionnaires, the survey duration, and privacy protection details was given. After the reception of the survey responses, a medical appointment was scheduled. For questionnaires to be analysed, patients must have clicked a checkbox indicating their consent for the usage of their data for research purposes after a process of anonymization which ensured that the probability of assigning a correct identity to a record in a dataset is not possible. According to Swiss and Portuguese laws, the analysis of strictly anonymized data does not require approval by an ethics committee. Only the fully completed WISE datasets were evaluated in this work.

2.2. The WISE platform

As previously mentioned, the WISE, which was conceived to assist clinical decision-making, combines a symptom-oriented checklist with validated questionnaires to provide an in-depth analysis of the burdening somatic and psychological symptoms by a targeted expert, either a clinician or a psychologist. At the WISE platform oral pain features are represented by an interactive pain map of the head and neck where patients will select the area where they feel pain both at rest and upon movement for the 4 weeks before access WISE. At this time, patients also report pain features and intensities through the NRS- numeric rating scale. NRS is one of the most used pain scales and it is the numeric version with 11 points of the visual analogue scale. It is labelled from zero to ten, with zero meaning no pain and ten being the worst pain

possible. From the NRS, PI-max, the maximal experienced pain intensity of the main complaint, was also extracted.

The questionnaires evaluating various psychometric domains are presented when the checklist scores exceed threshold values and, thus, indicate a burden related to the screened item. Several psychometric instruments are integrated, beyond pain measures, providing summary reports from a biopsychosocial perspective. Based on the publicly available and already validated questionnaires for the Swiss population used in the construction of WISE and respective assessed psychosocial domains (Ettlin et al., 2016), the key variables for the present study are represented in **Table 6**.

Table 6 | Validated questionnaires used in the construction of the WISE and respective psychosocial domain evaluated

Psychosocial domain	**Questionnaire (Abbreviation)**
Sleep	Insomnia Severity Index (ISI)
Dysmorphic concern	Dysmorphic Concern Questionnaire (DCQ)
Anxiety	General Anxiety Disorder Questionnaire 7 (GAD-7) General Anxiety Disorder Questionnaire 2 (GAD-2)
Illness perception	Brief Illness Perception Questionnaire (B-IPQ)
Injustice experience	Injustice Experience Questionnaire (IEQ)
Pain catastrophizing	Pain Catastrophizing Scale (PCS)
Distress (anxiety + depression)	Patient Health Questionnaire 4 (PHQ-4)
Depression	Patient Health Questionnaire 9 (PHQ-9) Patient Health Questionnaire 2 (PHQ-2)
Stress	Patient Health Questionnaire-Stress (PHQ-Stress)

In this study, we used the following questionnaires from the WISE datasets.

2.2.1. Insomnia Severity Index

The Insomnia Severity Index (ISI) (Bastien et al., 2001; Ettlin et al., 2016) is a brief self-report instrument that targets the subjective symptoms and consequences of insomnia, as well as the degree of concerns/distress caused by those difficulties. It consists of 7 items (5 questions) assessing the a) severity of sleep-onset (initial), b) sleep maintenance (middle) and c) nocturnal and early morning awakening problems over the past 2 weeks on a scale of none

(=0), mild (=1), moderate (=2), severe (=3), and very severe (=4); d) satisfaction with current sleep pattern on a scale from 'very satisfied' (=0), 'satisfied' (=1), 'moderately satisfied' (=2), 'dissatisfied' (=3), to 'very dissatisfied' (=4); and e) interference with daily functioning, f) noticeability of impairment attributed to the sleep problem, and g) degree of distress or concern caused by the sleep problem on a scale from 'not at all' (=0), 'a little' (=1), 'somewhat' (=2), 'much' (=3), to 'very much' (=4). The maximum score is 28, with insomnia scales of 'none' (ISI = 0–7), 'subthreshold' (ISI = 8–14), 'moderate' (ISI = 15–21), or 'severe' (ISI > 21). A cut-off score of 15 indicates insomnia at a clinically relevant level. For full details see Appendix I.

2.2.2. Dysmorphic Concern Questionnaire

The Dysmorphic Concern Questionnaire (DCQ) (Ettlin et al., 2016; Mancuso, Knoesen, & Castle, 2010; Oosthuizen, Lambert, & Castle, 1998) is a valid-self report measure for body dysmorphic disorder (BDD) through the assessment of a person's degree of excessive preoccupation or concern with imagined or actual, minimal defects in appearance that is associated with a significant impact on psychosocial functioning. Dysmorphic concern is a symptom found across several clinical disorders (e.g., eating disorders, depression, social anxiety, delusional disorder: somatic type, obsessive-compulsive disorder, trichotillomania). On the other side, BDD is a term later retained in DSM-IV, with a focus on a dysmorphic concern as a manifestation of a disorder, rather than a symptom, contributing to clinically significant distress and/or impairment of social and/or occupational functioning of the individuals. The questionnaire consists of 7 items assessing cognitive and behavioural aspects of dysmorphic concern, to capture the essence of the problem (e.g., concern about physical appearance, considering oneself misshapen), and past attempts to deal with the problem (e.g. consulting a plastic surgeon, covering up supposed defects). Each item is rated on an ordinal scale ranging from 0 'not at all' to 3 'much more than most people', resulting in a maximum sum score of 21. A cut-off score of 9 indicates a possible BDD. For full details see Appendix II.

2.2.3. General Anxiety Disorder 7

The General Anxiety Disorder 7 (GAD-7) (Ettlin et al., 2016; Löwe et al., 2008; Ruiz et al., 2011; Spitzer, Kroenke, Williams, & Löwe, 2006) is a valid screening tool and symptom

severity measure for the four most common anxiety disorders in primary care patients: Generalized Anxiety Disorder, Panic Disorder, Social Anxiety Disorder, and Posttraumatic Stress Disorder. It consists of 7 items covering different aspects of general anxiety, with higher scores correlated with a disability and functional impairment, in a measure such as work productivity and health care utilization. For the question 'Over the last 2 weeks, how often have you been bothered by the following problems?', items are scored on a 4-point ordinal scale ranging from 'not at all' (=0), 'several days' (=1), 'half of the days' (=2) to 'nearly every day' (=3). Summary scores range from 0–21 and indicate anxiety levels of 'none/minimal' (0–4), 'mild' (5–9), 'moderate' (10–14), or 'severe' (>14). A cut-off score of 10 indicates anxiety at a clinically relevant level. For full details on GAD-7 see Appendix III.

2.2.4. Short form of General Anxiety Disorder

The Short form of General Anxiety Disorder **(**GAD-2) (Appendix III and Appendix VII) (Ettlin et al., 2016; Kujanpää et al., 2014; Plummer, Manea, Trepel, & McMillan, 2016; Spitzer et al., 2006) is a short version of the previous screening tool comprising of the first two items of GAD-7. These first two items represent core anxiety symptoms and can be useful when an ultra-brief screening tool is desired. The questionnaire is also a subscale of the PHQ-4. Similarly to GAD-7, this questionnaire is also valid and useful to perform initial screening for the other common anxiety disorders among primary health care patients, in addition to Generalized Anxiety Disorder. The maximum score is 6.

As the operating characteristics (sensitivity, specificity, and positive likelihood ratio) of the GAD-7 and the GAD-2 are remarkably similar, it is suggested that both versions may be equally effective for screening purposes. Therefore, GAD-2 can be used when screening for anxiety disorders in clinical practice, followed by the other five items of the GAD-7 for patients with positive results (scores ≥ 3).

2.2.5. Brief Illness Perception Questionnaire

The Brief Illness Perception Questionnaire (IPQ) (Broadbent, Petrie, Main, & Weinman, 2006; Ettlin et al., 2016; Morgan, Villiers-Tuthill, Barker, & McGee, 2014) assesses cognitive and emotional representations of illness. The relationship between beliefs about illness and health-related outcomes has been well established, namely when investigating the antecedents of depression. The questionnaire consists of 8 items rated on a numeric scale ranging from 0-

10. The 8 questions cover different aspects of illness perception with a maximum score of 80. No cut-off value has been reported for this questionnaire. For a detailed view of IPQ see Appendix IV.

2.2.6. Injustice Experience Questionnaire

The Injustice Experience Questionnaire (IEQ) (Ettlin et al., 2016; M. J. L. Sullivan, 2008; M. J. L. Sullivan et al., 2008) is a self-report that assesses injustice experience due to accidents, injuries, or maltreatment. The questionnaire was first developed to measure perceived injustice associated with musculoskeletal injury. It consists of 12 items that reflect the frequency of thoughts, beliefs, and emotions associated with an injury. Each item is rated on a 5-point ordinal scale from 'never' (=0), 'rarely' (=1), 'sometimes' (=2), 'often' (=3), to 'all the time' (=4) and the total score ranges from 0 to 48. Scores ≥18 indicate the need for a professional evaluation. For details on IEQ see Appendix V.

2.2.7. Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) (Ettlin et al., 2016; M. J. L. Sullivan, Bishop, & Pivik, 1995; M. J. L. Sullivan et al., 2002) assesses catastrophizing thoughts, feelings, and corresponding behaviour that individuals experience when they are in pain. 13 items are scored on a 5-point ordinal scale from 'not at all' (=0), 'to a slight degree' (=1), 'to a moderate degree' (=2), 'to a great degree' (=3) to 'all the time' (=4). Higher scores suggest a more intense level of pain behaviour, disability, depression, and anxiety, in addition to increased consumption of analgesic medication and more prolonged stays in the hospital. The PCS yields three subscales by summing the responses of the items 8, 9, 10, 11 for rumination scores; the items 6, 7, 13 for magnification scores; and the items 1, 2, 3, 4, 5, 12 for helplessness scores. The maximum score for the entire questionnaire is 52. A total score of 30 (cut-off value) represents clinically relevant pain catastrophizing and the corresponding cut-off values are 13 for rumination, 5 for maximizing, and 13 for helplessness. For details on PCS see Appendix VI.

2.2.8. Patient Health Questionnaire 4

The Patient Health Questionnaire 4 (PHQ-4) (Ettlin et al., 2016; Kroenke, Spitzer, Williams, & Löwe, 2009; Löwe et al., 2010) (Appendix VII) is an ultra-brief self-report questionnaire that assesses depression and anxiety (distress). This questionnaire includes two

subscales: the PHQ-2, a depression screener (items 1 and 2 of PHQ-9), and the GAD-2, an anxiety screener (items 1 and 2 of the GAD-7). Therefore, these 2-item measures are combined into a composite 4-item ordinal scale ranging from 0-3, using the labels 'not at all' (=0), 'several days' (=1), 'more than half of the days' (=2) or 'nearly every day' (=3) to answer the question "Over the last 2 weeks, how often have you been bothered by the following problems?". The overall score ranges from 0 to 12 with a cut-off score ≥ 6, indicating expert evaluation referral. Scores can also be calculated for the two subscales individually (maximum score = 6) with a cut-off value of 3.

2.2.9. Patient Health Questionnaire 9

The Patient Health Questionnaire (PHQ-9) (Ettlin et al., 2016; Kroenke, Spitzer, & Williams, 2001) assesses the severity of depression. The questionnaire consists of 9 items covering different aspects of depression. For the question "Over the last 2 weeks, how often have you been bothered by the following problems?", items are scored on an ordinal scale ranging from 'not at all' (=0), 'several days' (=1), 'more than half of the days' (=2) to 'nearly every day' (=3). Summary scores range from 0–27 and indicate depression levels of 'none/minimal' (0–4), 'mild' (5–9), 'moderate' (10–14), 'moderately severe' (15-19) or 'severe' (>19). A cut-off score of 10 indicates depression at a clinically relevant level. For details on PHQ-9 see Appendix VIII.

2.2.10. Patient Health Questionnaire 2

The Patient Health Questionnaire 2 (PHQ-2) (Brewster, 2008; Ettlin et al., 2016; Löwe et al., 2010) (Appendix VII and Appendix VIII) is the short version of the PHQ-9 (first 2 items), being the most validated two-item screener for depression. The questionnaire is also a subscale of the PHQ-4, as mentioned before. Summary scores range from 0-6 and scores ≥ 3 suggest possible cut-off points and probable cases of depression. One approach would be to use the PHQ-2 when screening for depression in a "first step", followed by the other 7 items of the PHQ-9 for the patients with positive results on screening. An interesting difference between PHQ-9 and PHQ-2 is that PHQ-9 has a 61 percent sensitivity and 94 percent specificity in adults whereas PHQ-2 has a 97 percent sensitivity and 67 percent specificity in adults.

2.2.11. Patient Health Questionnaire for Stress

The Patient Health Questionnaire for Stress (PHQstr) (Adams et al., 2015; Ettlin et al., 2016; Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000) is a subscale of the Primary Care Evaluation of Mental Disorders (PRIME-MD), an instrument validated to diagnose common types of mental disorders (depressive, anxiety, somatoform, alcohol, and eating disorders), that addresses burden by psychosocial stress. This patient health questionnaire consists of 10 items, each scored on an ordinal scale ranging from 'not at all' (=0), 'a little' (=1), to 'a lot' (=2). Individuals rate the extent to which they have been bothered by each psychosocial stressor (worries about health, difficulties with relationships, work-related stress, financial problems, etc). The maximum score is 20, with scales of 'none/minimal' (0-4), 'mild' (5-9), 'medium' (10-14) and, 'severe' (≥14) indicating the degree of psychosocial stress burden. A cut-off score range of 8-11 indicates the need for a professional evaluation. For details on PHQstr see Appendix IX.

All the above-mentioned questionnaires use Likert scales - one of the most popular ordinal rating scales - to measure respondents' opinions, perceptions, and behaviours (Likert, 1932). An ordinal scale indicates that the responses of each question of each survey can be rated or ranked, but the distance between values is not measurable, i.e, not presumed to be equal (G. M. Sullivan & Artino, 2013; Sung & Wu, 2018). A Likert scale uses a series of questions with response alternatives (typically a 5 or 7-point scale) that ranges from one extreme attitude to another, with a neutral option between (strongly agree, agree, neutral, disagree, and strongly disagree). Then, the items obtained from the series of questions are combined to create a single score/variable and, subsequently, to provide a quantitative measure. Individual questions are not analysed. This way, Likert scales have advantages compared to binary questions, since they offer more detailed information/feedback about persons' complaints and beliefs (Boone & Boone, 2012).

2.3. Statistical Analysis

All analyses were conducted using IBM SPSS version 26, and the results of the descriptive statistics – univariate and multivariate- of the data are presented. As the data was ordinal (sum of Likert scale items) and, at some stages of the study, it was not normally distributed or the sample size was small (with less than 5-10 observations per group), certain parametric assumptions were violated. Therefore, it was chosen to use non-parametric tests to compare groups and to conduct correlation analyses (McCrum-Gardner, 2008; G. M. Sullivan & Artino, 2013). Gender differences were investigated with the Mann-Whitney test. Kruskal-Wallis test, with a Bonferroni correction for multiple comparisons, was applied to examine the differences of psychosocial domains between ISI categories, age decades, and employment status. Spearman rank correlations were used for correlation analysis between ISI scores and other questionnaire scores. For the different association levels, correlation coefficients (r_s) at intervals of ≤ 0.100; $0.100 – 0.300$; $0.300 – 0.500$, and ≥ 0.500 demarcate very small, small, moderate, and strong effect size (Gignac & Szodorai, 2016). Categorical variables are given as frequencies and percentage of patients and continuous variables are shown as mean ± SD. A level of *p*-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Demographics variables and health behaviours

A group of 184 adult patients, both sexes (71.2% women; N=131) with a mean age of 45.8±16.4 years (range: 18-81 years) and experiencing pain in the orofacial region were included in this study. Regarding employment, patients were either active workers, trainees, retired persons, or persons without a job. Patients incapable of work given their disability were also included. Specific patients' demographics are detailed in **Table 7** and **Figure 2**. Globally, patients had a normal weight or were pre-obese (mean weight = 67.4±13.2 kg; mean BMI = 23.8±4.32 kg/m^2) and most of them being light smokers (12.0% women, 5.43% men). Interestingly, two aged between 30-39 years old (both sexes), two male patients with 41 and 61 years old and one female patient with 55 years old showed a score on the CAGE questionnaire suggestive of heavy alcohol use or alcohol use disorder (see **Table 8** for details).

All patients the included patients were experiencing pain in, at least one, of these three regions: mouth, face, and head. Our data show that most of the patients referred as a main complaint pain in the face and head, independently of the age and with a maximum pain intensity score of 7.29±2.61 (see **Table 9**).

Due to the WISE matrix, which depending on the patients answer to the screening questions drives the patient for the adequate questionnaire, the number of patients who completed one of the questionnaires ranged from 23 (DCQ) to 184 (PHQ-4), being PHQ-4 a very brief but accurate way of measuring depression and anxiety, data indicate that all patients answered to it. Also, the prevalence of patients reaching a clinically relevant score (above cut-off) in descending order was: PHQ-9 (23.9%), PHQ-4 (21.2%), GAD-7 (18.5%), PCS (17.4%), ISI (16.3%), IEQ (10.9%), PHQstr (5.40%) and DCQ (3.80%). Within the domain itself, this percentage ranged from 17.7% (PCS) to 78.6% (PHQ-9). For IPQ, no cut-off value has been reported (Ettlin et al., 2016). In all questionnaires, and despite the gender unbalance of our sample, the maximum and the highest mean scores were from female patients, and the percentage of women who reached a clinically relevant score for each of the evaluated psychosocial domain was always higher than the male percentage (see **Table 10**).

Table 7 | Patients' demographics with the distribution by the decade of age and employment status

		Total subjects (number of women)	% individuals/sample
Age group	**18-29**	32 (21W)	17.4%
	30-39	41 (26W)	22.3%
	40-49	39 (31W)	21.2%
	50-59	32 (26W)	17.4%
	60-69	20 (12W)	10.9%
	70-79	18 (15W)	9.80%
	80-89	2 (0W)	1.10%
Employment status (current or latest occupation)	**Training**	15 (9W)	8.20%
	Working	127 (90W)	69.0%
	Retired	26 (19W)	14.1%
	Unable to work	11 (9W)	6.00%
	No job	5 (4W)	2.70%

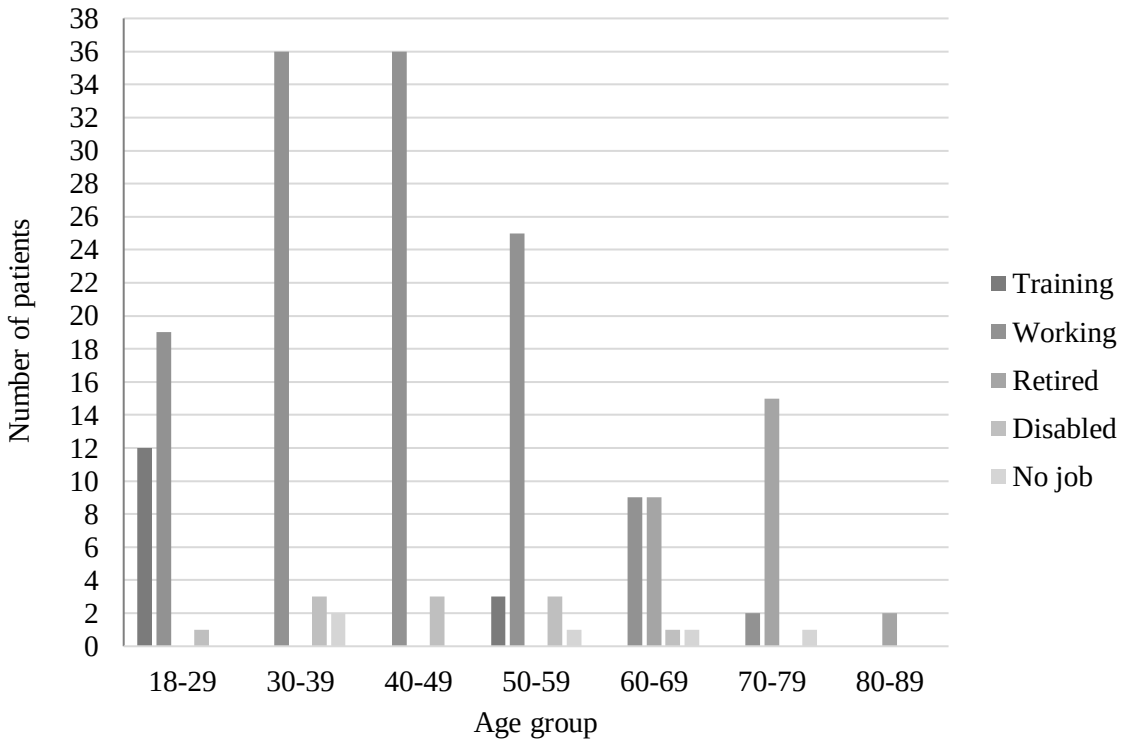

Figure 2 | Age decades and employment status distribution of the global sample of patients (N=184).

Table 8 | Descriptive of weight, height, body mass index (BMI), tobacco, and alcohol of the 184 participants stratified by age decade, and gender (W=women, M=men) statistics. Data shown as mean ± SD

[1]The CAGE questionnaire is the most popular alcohol screening questionnaire, that consists of 4 questions: 1) Have you ever felt you should cut down on your drinking?; 2) Have people annoyed you by criticizing your drinking?; 3) Have you ever felt bad or guilty about drinking?; 4) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)? Each item score 0 for 'no' and 1 for 'yes', resulting in a maximum sum score of 4. A cut-off score of 2 indicates a clinically significant level ("screening positive") and a 90% sensitivity for diagnoses of alcohol disorders (Williams, 2014).

			Weight (kg)	Height (m)	BMI (kg/m^2)	Cigarettes per day (n smokers)	CAGE scores (n subjects screening positive)[1]
Age group	**18-29**	**W (N=21)**	60.8±8.15	1.67±6.82	21.8±2.91	4.67±4.73 (3)	n.a.
		M (N=11)	70.9±10.7	1.78±5.59	22.4±2.51	12.5±6.46 (4)	.000 (0)
	30-39	**W (N=26)**	62.0±9.73	1.64±7.19	23.1±3.88	7.33±4.16 (3)	2.00 (1)
		M (N=15)	75.7±8.04	1.78±6.22	23.9±2.85	12.5±5.00 (4)	2.00 (1)
	40-49	**W (N=31)**	65.3±10.7	1.65±6.09	23.9±4.23	13.0±9.80 (7)	.500±.707 (0)
		M (N=8)	78.6±12.1	1.75±6.40	25.6±2.72	22.5±3.54 (2)	1.50±2.12 (1)
	50-59	**W (N=26)**	63.9±16.0	1.64±6.15	23.5±5.14	15.0±3.54 (5)	2.00 (1)
		M (N=6)	82.2±16.9	1.81±6.56	24.9±4.52	0	n.a.
	60-69	**W (N=12)**	62.9±12.8	1.64±7.00	23.4±4.13	11.7±2.89 (3)	.000 (0)
		M (N=8)	84.8±13.2	1.72±7.43	28.6±5.11	0	1.50±2.12 (1)
	70-79	**W (N=15)**	65.5±12.5	1.62±6.52	25.0±5.51	4.00 (1)	.500±.707 (0)
		M (N=3)	76.0±8.54	1.76±9.61	24.6±.195	0	.000±.000 (0)
	80-89	**M (N=2)**	72.5±.707	1.77±6.36	23.3±1.91	0	.000 (0)

n.a.: non-available.

Table 9 | Patients' pain features assessed with the WISE, stratified by age decade, and gender (W=women, M=men): chief complaints reported by patients, onset date, and pain intensity during the last 4 weeks. Prevalence of pain in the different regions of the head (ear pain, ear pressure, tinnitus (e.g., ringing noise) and headache), face (pain/tightness in the jaw or face), and mouth (toothache / oral pain (e.g., tongue, gums)). Categorical variables shown as % of patients and continuous variables as mean ± SD

			Chief complaints (% individuals/N in each category)			Onset date of complaints	PI-max (Max) (Mean)
			Mouth	Face	Head		
Age group	18-29	W (N=21)	7 33.3%	19 90.5%	19 90.5%	1982-2019	10/10 8.32±1.70
		M (N=11)	5 45.5	10 90.9%	11 100%		10/10 7.45±1.37
	30-39	W (N=26)	17 65.4%	23 88.5%	21 80.8%		10/10 7.84±2. 73
		M (N=15)	8 53.3%	13 86.7%	13 86.7%		9/10 6.40±2.10
	40-49	W (N=31)	17 54.8%	29 93.5%	25 80.6%		10/10 7.68±2.52
		M (N=8)	4 50.0%	7 87.5%	7 87.5%		10/10 5.75±3.85
	50-59	W (N=26)	16 61.5%	23 88.5%	20 76.9%		10/10 6.96±2.80
		M (N=6)	4 66.7%	6 100%	4 66.7%		10/10 8.50±1.38
	60-69	W (N=12)	7 58.3	11 91.7%	8 66.7%		10/10 7.25±2.99
		M (N=8)	3 37.5%	6 75.0%	5 62.5%		10/10 6.29±3.15
	70-79	W (N=15)	8 53.3%	12 80.0%	10 66.7%		10/10 7.13±2.72
		M (N=3)	2 66.7%	1 33.3%	1 33.3%		8/10 6.00±1.73
	80-89	M (N=2)	0	1 50.0%	1 50.0%		7/10 3.50±4.95

PI-max, Maximum pain intensity; Max = maximum score obtained/maximum score possible to obtain.

Table 10 | Descriptive statistics and frequencies of ISI scores (sleep measures) and axis II psychometric measures. Note that ≥ cut-off score (CO) indicates clinical relevance.

WISE Questionnaires		N_{domain}	Max	Mean	SD	≥ cut-off score (CO)			
						CO	N_{CO}	% domain	% of study sample
ISI	Total	64	27/28	15.2	5.24	15	30	46.9	16.3
	W	48	27/28	15.3	5.62		24	50.0	18.3
	M	16	22/28	14.8	4.01		6	37.5	11.3

DCQ	Total	23	17/21	6.30	4.79	9	7	30.4	3.80
	W	20	17/21	6.50	5.03		7	35.0	5.30
	M	3	8/21	5.00	3.00		0	0.00	0.00
GAD-7	Total	60	20/21	10.5	3.74	10	34	56.7	18.5
	W	47	20/21	11.0	3.83		29	61.7	22.1
	M	13	14/21	8.77	2.95		5	38.5	9.40
IPQ	Total	156	76/80	44.5	10.8	n.a.	n.a.	n.a.	n.a.
	W	144	76/80	45.0	11.1				
	M	42	62/80	43.2	9.81				
IEQ	Total	59	46/48	14.8	11.3	18	20	33.9	10.9
	W	47	46/48	14.9	12.0		16	34.0	12.2
	M	12	28/48	14.5	8.15		4	33.3	7.50
PCS	Total	181	49/52	16.7	12.7	30	32	17.7	17.4
	W	129	49/52	17.7	13.2		27	20.9	20.6
	M	52	43/52	14.0	11.0		5	9.60	9.40
PHQ-4	Total	184	12/12	3.32	3.16	6	39	21.2	21.2
	W	131	12/12	3.67	3.37		34	26.0	26.0
	M	53	9/12	2.45	2.38		5	9.40	9.40
PHQ-9	Total	56	25/27	12.4	5.39	10	44	78.6	23.9
	W	45	25/27	13.0	5.54		37	82.2	28.2
	M	11	16/27	10.1	4.13		7	63.6	13.2
PHQ-Str	Total	52	18/20	6.62	4.05	10	10	19.2	5.40
	W	44	18/20	7.00	4.06		9	20.5	6.90
	M	8	10/20	4.50	3.55		1	12.5	1.90

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; SD, Standard Deviation; W, women; M, Men; n.a.: non-available.

N_{domain} = number of respondents in each domain (total respondents, women respondents, men respondents)

Max = Maximum score obtained / Maximum score possible to obtain in each questionnaire

N_{CO} = number of respondents that obtained scores above cut-off value, in each domain

% domain = $\frac{N_{CO}}{N_{domain}}$%; % of study sample (total) = $\frac{N_{CO\ (total)}}{184}$%; % of study sample (women) = $\frac{N_{CO\ (women)}}{131}$%; % of study sample (total) = $\frac{N_{CO\ (men)}}{53}$%

3.2. Insomnia prevalence and severity

Insomnia was evaluated through the ISI questionnaire. From the 184 patients evaluated, only 64 of them (34.8%) with a mean age of 45.1±15.6 years reported "trouble falling or staying asleep or sleeping too much" on the WISE screening questionnaire.

Among all patients reporting insomnia, moderate and severe grades were expressed by 46.9% of them (37.5% women), representing a combined prevalence of ~ 50% in the sample of 64 patients who completed the ISI questionnaire and of 16.3% of the global patients' sample. This means that one in six patients suffered from clinically relevant insomnia expressed by ISI scores ≥ 15. Almost the same number reached a score related to subthreshold insomnia (**Table 10**, **Table 11**, **Figure 3**).

The distribution of ISI scores between genders was not statistically different but women showed a tendency to score higher (15.3±5.62; N=48) than men (14.8±4.00; N=16) despite the imbalance between both gender samples size. In addition, while men scored between 8 and 22, the women group included patients with the highest scores (>22 points) (**Table 12**, **Figure 4A**, **Figure 5A**). Age also interferes with the distribution of ISI categories, despite the differences among age groups have not been statistically significant (**Table 12**, **Figure 4B**). In fact, severe insomnia was not reported by younger patients (<30 years). The second insomnia category was prevalent in the 2nd, 3rd, and 5th decade of age but the number of patients decreases as the insomnia severity increases. Furthermore, the number of patients of 50-59 and 70-79 years old was the same in all categories when ISI scores ≥ 8 (**Figure 5B**).

Employment status seems to also influence the sleep-wake cycle. In fact, trainees, patients unable to work or retirees had higher ISI scores than active workers, independently of their gender, whereas patients with no job revealed the lowest ISI scores (for details see **Table 12** and **Figure 4C**). In particular, active workers showed the highest prevalence in all categories, namely in subthreshold insomnia, which gradually declined with the increase of insomnia severity. Patients who are unable to work and experience some form of pain, by contrast, have a relatively homogeneous distribution in the three ISI categories with scores > 8 and none of the unemployed have reached a moderate or severe degree of severity (**Figure 5C**). Interesting is the observation that the maximum and minimum ISI scores were both reached by two women, with 68 and 39 years, the first a retiree and the second an unemployed person.

Table 11 | Patients (pts) number (N) and prevalence (%) of insomnia distributed by the Insomnia Severity Index (ISI) categories: no clinically significant insomnia (scores 0-7), subthreshold insomnia (scores 8-14), and clinical insomnia – moderate (scores 15-21) and severe (scores 22-28)

			N	% study sample (184 pts)	% domain (64 pts)
ISI categories	**Clinically relevant**	**Severe (22-28)**	9	4.89	14.1
		Moderate severity (15-21)	21	11.4	32.8
	No clinically relevant	**Subthreshold (8-14)**	31	16.8	48.4
		No clinically significant (0-7)	3	1.63	4.69
		Total	64	34.8	100

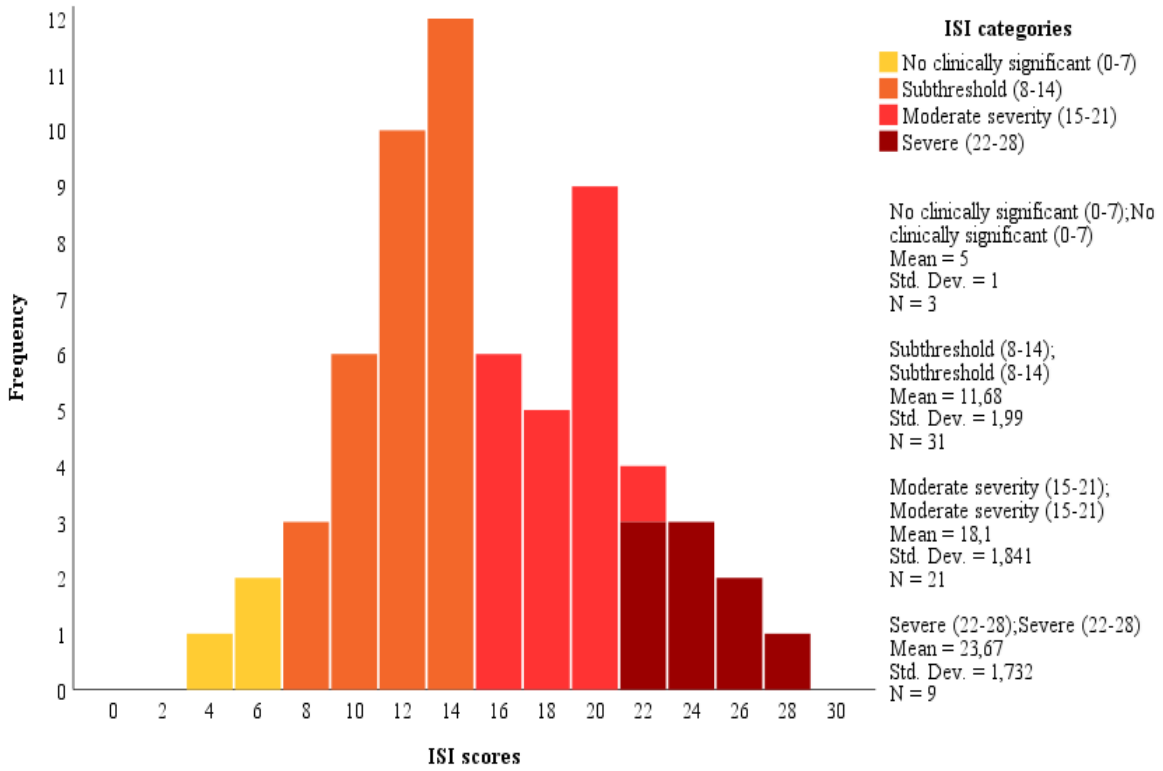

Figure 3 | Stacked Histogram of the Insomnia Severity Index (ISI) scores by ISI categories of the sample of 64 patients. Yellow, orange, light red, and dark red bars represent the four insomnia severity grades: no clinically significant insomnia, subthreshold insomnia, moderate clinical insomnia, and severe clinical insomnia, respectively. Mean, standard deviation, and the number of participants (N) in each category are also displayed.

Table 12 | Descriptive statistics of the Insomnia Severity Index (ISI) scores, considering the 3 confounders: age, sex (W=women, M=men), and employment status

			ISI scores		
			Mean ± SD	**Median**	**Mean rank**
Age group	**18-29**	**Total (N=10)**	15.7±5.20	17.5	36.0
		W (N=7)	14.7±5.74	16.0	23.8
		M (N=3)	18.0±3.46	20.0	12.5
	30-39	**Total (N=16)**	13.6±5.22	13.0	26.7
		W (N=11)	13.5±6.04	12.0	19.7
		M (N=5)	13.8±3.27	14.0	7.40
	40-49	**Total (N=14)**	15.6±4.31	15.0	34.3
		W (N=13)	15.9±4.41	16.0	26.1
		M (N=1)	13.0	13.0	5.50
	50-59	**Total (N=10)**	15.7±6.52	15.5	34.5
		W (N=9)	15.8±6.91	16.0	25.7
		M (N=1)	15.0	15.0	11.0
	60-69	**Total (N=10)**	15.3±5.96	14.0	31.7
		W (N=5)	16.2±6.72	14.0	25.6
		M (N=5)	14.4±5.73	14.0	7.90
	70-79	**W (N=3)**	18.0±5.29	20.0	42.8
	80-89	**M (N=1)**	13.0	13.0	24.5
Employment Status	**Training**	**Total (N=5)**	18.6±4.39	19.0	43.3
		W (N=4)	19.5±4.51	19.5	35.3
		M (N=1)	15.0	15.0	11.0
	Working	**Total (N=42)**	14.2±4.84	14.0	29.3
		W (N=31)	14.1±5.13	14.0	21.5
		M (N=11)	14.6±4.13	14.0	8.32
	Retired	**Total (N=7)**	17.7±5.74	18.0	40.1
		W (N=6)	18.5±5.86	19.0	31.8
		M (N=1)	13.0	13.0	5.50
	Disabled	**Total (N=7)**	17.9±5.27	17.0	41.6
		W (N=5)	18.4±5.03	17.0	32.4
		M (N=2)	16.5±7.78	16.5	9.38
	No job	**Total (N=3)**	10.0±5.29	12.0	17.0
		W (N=2)	8.00±5.66	8.00	8.25
		M (N=1)	14.0	14.0	8.50

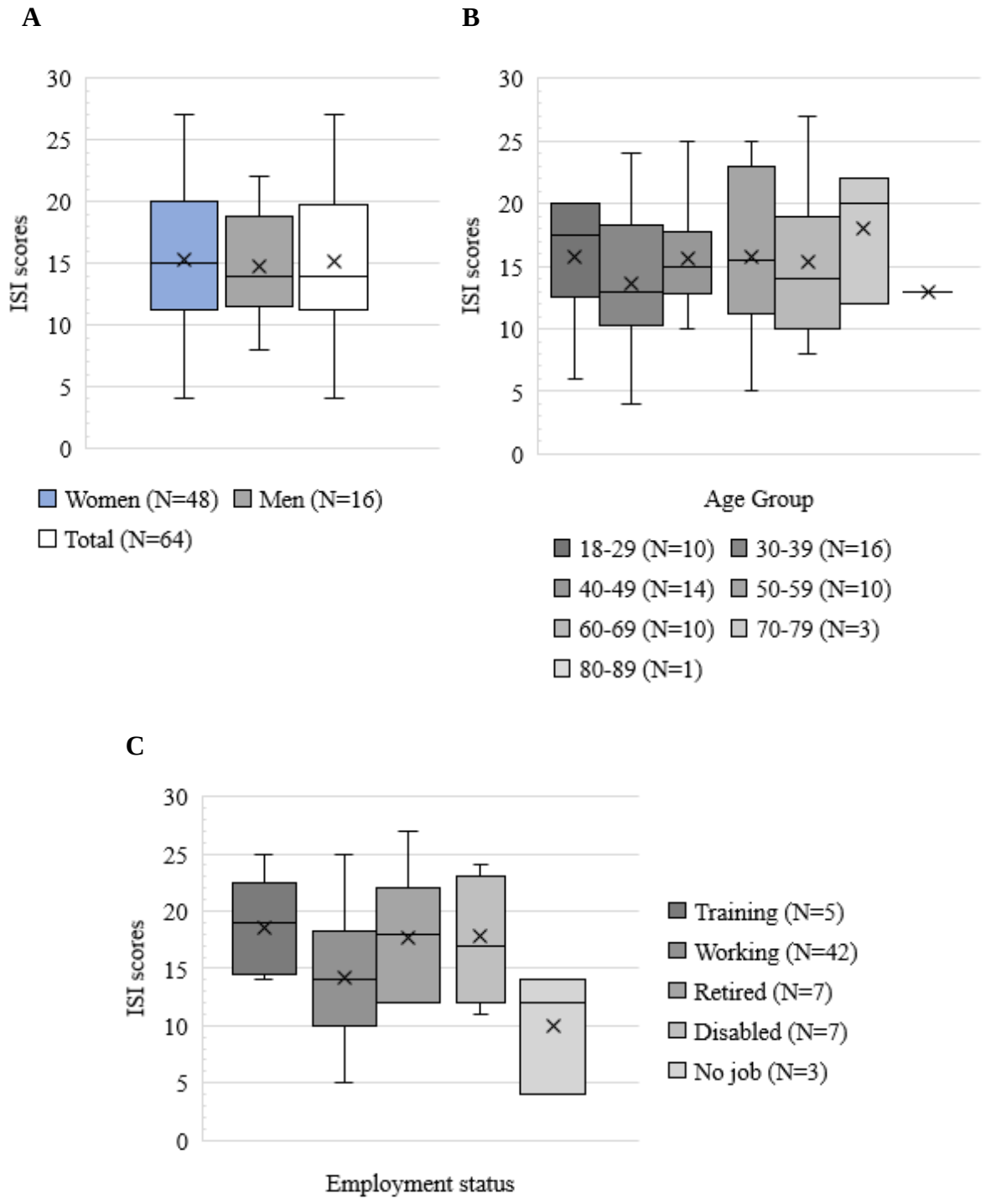

Figure 4 | Boxplots representing the distribution of the Insomnia Severity Index (ISI) scores of the 64 patients who reported "trouble falling or staying asleep or sleeping too much" **(A)** by gender (48 women, 16 men); **(B)** by age group (10 in the 1st group, 16 in the 2nd, 14 in the 3rd, 10 in the 4th, 10 in the 5th, 3 in the 6th and 1 in the 7th) and **(C)** by employment status (5 trainees, 42 workers, 7 retired people, 7 disabled people and 3 with no job). X indicates the sample ISI means scores.

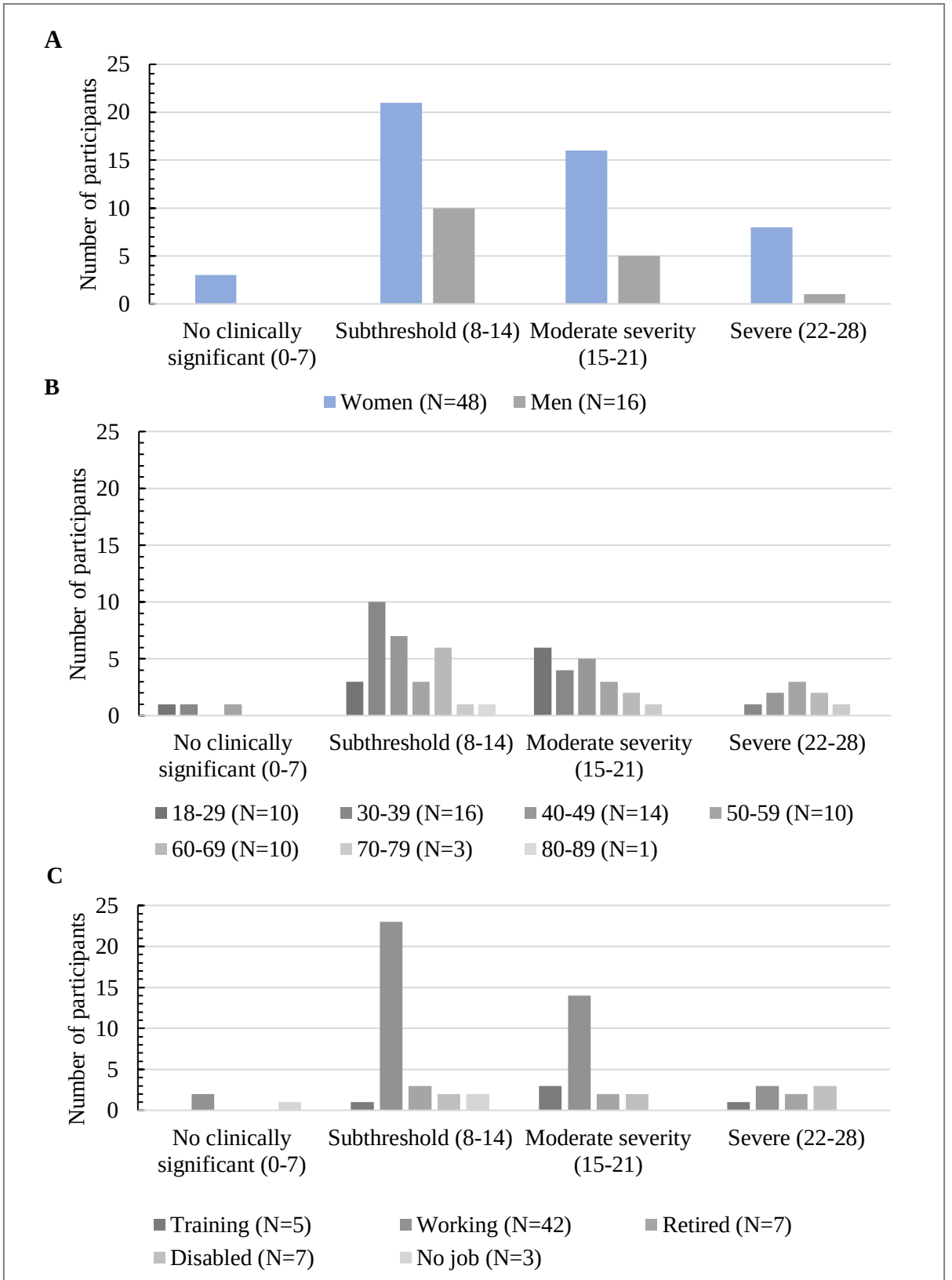

Figure 5 | Insomnia severity grades (ISI categories) distribution **(A)** by gender; **(B)** by age decade and **(C)** by employment status of the 64 patients who reported "trouble falling or staying asleep or sleeping too much".

3.3. Associations between insomnia and psychosocial domains

The number of patients who completed both ISI and one of the other questionnaires ranged from 10 (ISI + DCQ) to 64 (ISI + PCS and ISI + PHQ-4) (**Table 13** and **Table 14**).

The influence of insomnia severity grades and confounders on the mean rank of the assessed psychosocial domains was determined (**Table 13** and **Table 15 - Appendix X**, respectively) firstly by examining the differences in each axis II measures according to the ISI score and, secondly, by studying the behaviour of gender, age, and employment status.

Regarding the comparison between the various questionnaires, there was a statistically significant difference in IPQ and PHQ-4 scores among the four insomnia categories, namely between subthreshold and clinical severe insomnia. No differences among the categories of insomnia were found for the other questionnaires. Overall, as the clinical relevance of insomnia was increasing the mean rank scores were higher except for DCQ, IPQ, and PHQ-stress (**Table 13**).

In our study, neither gender, age, nor employment status had a significant effect on the axis II domain scores ($p>0.05$) (for details see **Table 15**). Although the differences were not statistically significant, a similar trend was observed for almost all axis II measures in two of the confounders: gender and employment status, whereas age influenced the psychosocial variables differently. Women and disabled patients had the highest mean rank scores in all questionnaires, except in DCQ, and men had in IPQ and IEQ. The lowest mean rank scores occurred in jobless patients, leaving out the PCS, PHQ-9, and PHQ-stress, in which trainees, and retired reported the lowest values.

Associations between insomnia and psychosocial variables were also quantified. A significant relation between insomnia (scores ≥ 15) and the patient's beliefs and feelings about their illness given by the IPQ questionnaire was found as is shown in **Table 14**.

From **Table 14A** when correlations analyses were performed between all scores, the following six axis II measures showed moderate or strong positive correlations with ISI scores: DCQ (N=10; $r > 0.500$; $p \leq 0.01$), GAD-7 (N=34; $0.300 < r_s < 0.500$; $p \leq 0.05$), IPQ (N=58; $0.300 < r_s < 0.500$; $p \leq 0.01$), PCS (N=64; $0.300 < r_s < 0.500$; $p \leq 0.01$), PHQ-4 (N=64; $0.300 < r_s < 0.500$; $p \leq 0.01$) and PHQ-9 (N=46; $0.300 < r_s < 0.500$; $p \leq 0.05$).

Focusing on the association between ISI scores grouped by insomnia severity grade and psychosocial variables, IEQ scores significantly correlated with the second and third insomnia severity grades, i.e subthreshold insomnia and moderate clinical insomnia. Nevertheless, the

results showed that lower levels of injustice experience were associated with higher subthreshold insomnia scores (N=11; $r_s < -0.500$; $p \leq 0.05$), possibly contributing to the weak positive and no statistically significant correlation between all scores of both questionnaires. Beyond the strong and significant correlation between injustice experience and insomnia when considering ISI scores between 15 and 21 (N=11; $r_s > 0.500$; $p \leq 0.05$), pain catastrophizing was also strongly associated with insomnia (N=21; $r_s > 0.500$; $p \leq 0.01$) in this ISI category. There were no significant associations for the other psychometric measures (**Table 14A, ISI categories**).

To investigate if gender influence the relationship between insomnia and psychosocial variables, correlations between ISI and axis II scores were performed by gender. The same six questionnaires which showed a moderate/strong correlation between the two variables (ISI total scores vs axis II measures total scores) exhibited a moderate or strong positive association between the scores only when patients were female: DCQ (N=9; $r_s >0.500$; $p \leq 0.01$), GAD-7 (N=27; $0.300 < r_s < 0.500$; $p \leq 0.05$), IPQ (N=43; $0.300 < r_s < 0.500$; $p \leq 0.01$), PCS (N=48; $r_s > 0.500$; $p \leq 0.01$), PHQ-4 (N=48; $0.300 < r_s < 0.500$; $p \leq 0.01$) and PHQ-9 (N=36; $0.300 < r_s < 0.500$; $p < 0.05$) (**Table 14A**, **Gender**).

For the correlations between scores clustered by patients' age, the results were quite different. We found that patients under 50 years old obtained ISI scores significantly correlated with scores of four questionnaires: 1) ISI with IEQ for the age range 18-29: strong positive correlation (N=6; $r_s > 0.500$; $p \leq 0.01$); 2) ISI with GAD-7 (N=11), PCS (N=16) and PHQ-4 (N=16) for the decade 30-39: strong positive correlation ($r_s > 0.500$; $p \leq 0.05$); 3) ISI with PCS (N=14) and PHQ-4 (N=14) for the decade 40-49: strong positive correlation ($r_s > 0.500$; $p \leq 0.05$). Moreover, patients aged 60-69 years who answered IPQ, in addition to ISI, obtained a strong positive association between ISI scores and the respective axis II measure (N=8; $r_s > 0.500$, $p \leq 0.05$). Overall, the age decade of 30-39 had the greatest number of correlations between insomnia and psychosocial measures (**Table 14A**, **Age group**).

Finally, regarding employment status, GAD-7 (N=22), PCS (N=42), PHQ-4 (N=42), and PHQ-9 (N=29) scores reported a moderate or strong correlation with ISI scores in working patients ($r_s > 0.300$; $p \leq 0.05$). Retired patients also obtained ISI scores significantly correlated with PCS (N=7) and PHQ-9 (N=6) scores ($r_s > 0.500$; $p \leq 0.05$), contrarily to trainees and unemployed patients. The PHQ-stress had only one correlation with ISI scores. High levels of

insomnia were strongly associated with high-stress levels in respondents incapable of work given their disability (N=5; $r_s \approx 1.00$; $p \leq 0.05$) (**Table 14A**, **Employment status**).

As mentioned, the PCS and PHQ-4 can be divided into three and two subscales, respectively, assessing different domains: rumination, magnification, and helplessness in the first questionnaire; and depression and anxiety in the PHQ-4 (**Table 14B**). For PCS subscales, helplessness and magnification showed a positive correlation (N=64; $0.300 < r_s < 0.500$; $p \leq 0.05$) with insomnia symptoms. Rumination did not relate to ISI scores. Both PHQ-4 subscales had a similar result: anxiety and depression scales showed moderate positive correlation effects with scores of the insomnia questionnaire (N=64; $0.300 < r_s < 0.500$; $p \leq 0.01$).

From **Table 14C** to **Table 14H** information about the correlation analysis after dichotomizing questionnaires scores into above and below cut-off values are exhibited: correlations between ISI total scores and axis II scores above and below cut-off values (**Table 14C** and **Table 14D**, respectively), correlations between ISI scores ≥ 15 and axis II total scores and axis II scores above cut-off value (**Table 14E** and **Table 14F**, respectively) and correlations between ISI scores < 15 and axis II total scores and axis II scores below cut-off value (**Table 14G** and **Table 14H**, respectively).

We found that the ISI scores not only correlated significantly with the total scores of PCS, PHQ-4, and PHQ-9 but also with the scores of these questionnaires above the cut-off value (N=20; N=28 and N=36, respectively). For PHQ-9 the association was even stronger ($r_s > 0.300$; $p \leq 0.05$; **Table 14C**). By contrast, PHQ-str scores were not correlated with ISI scores in **Table 14A-Total Scores**, but when considering PHQ-strs scores below 10, the results showed a moderately negative correlation with ISI scores (N=23; $-0.500 < r_s < -0.300$; $p \leq 0.05$; **Table 14D**). **Table 14E**, which presents the correlations between clinically relevant insomnia and axis II measures, enhances four of the positive and moderate associations found in **Table 14A-Total Scores** but considering ISI scores ≥ 15 ($r_s > 0.300$; $p \leq 0.05$): correlation with IPQ (N=28), PCS (N=30), PHQ-4 (N=30), and PHQ-9 (N=26). Interestingly, a new strong relationship was observed between IEQ and ISI scores (N=17; $r_s > 0.500$; $p \leq 0.05$) when insomnia disorder was at a higher severity level. Comparing these results with those in **Table 14A-ISI Categories**, we elucidate that the association of IEQ and PCS scores with ISI scores ≥15 was due to moderate clinical insomnia, as the correlation between the variables weakened when ISI scores > 21 were additionally considered. IPQ, PHQ-4, and PHQ-9 scores only exhibited a statistically significant correlation with ISI scores indicative of a clinically relevant

level when the entire range was considered. Still considering ISI scores ≥ 15, and now, adding axis II scores above cut-off values (**Table 14F**), only PCS scores ≥ 30 (N=15) and PHQ-9 ≥ 10 (N=21) significantly correlated with ISI scores (r_s > 0500; $p \leq 0.05$). Finally, for not clinically relevant or subthreshold insomnia (ISI scores < 15), neither axis II total scores nor axis II scores below cut-off value were associated with ISI scores (**Table 14G** and **Table 14H**). It should be noted that the only patient who completed both the ISI and the IEQ, with no clinically relevant insomnia (**Table 14A-ISI Categories**), made the association between ISI scores < 15 and perceived injustice become statistically non-significant.

For DCQ and GAD-7 no correlations were found with ISI scores after dichotomizing the scores into above and below cut-off values.

Table 13 | Analysis of variance (Kruskal-Wallis test) between insomnia severity grades (no clinically significant insomnia, subthreshold insomnia, moderate clinical insomnia, severe clinical insomnia) and axis II measures. Axis II measures shown as median and mean ± SD

		Insomnia severity grades (ISI categories)					
Axis II Measures (N in common with ISI)		**No clinically significant (0-7)**	**Subthreshold insomnia (8-14)**	**Moderate severity (15-21)**	**Severe insomnia (22-28)**	**Axis II Median**	**Axis II Mean±SD**
DCQ (N = 10)	**Mean rank**	1.00	4.75	4.00	9.00	4.50	5.10±4.20
	p		ns				
GAD-7 (N = 34)	**Mean rank**	n.a.	13.9	17.0	26.5	12.0	12.1±3.84
	p		ns				
IPQ (N = 58)	**Mean rank**	23.2	23.1	32.6	45.7	50.0	50.3±9.57
	p			|----------**----------|(B)			
IEQ (N = 29)	**Mean rank**	1.50	14.1	14.3	20.3	17.0	19.1±11.8
	p		ns				
PCS (N = 64)	**Mean rank**	25.2	26.1	38.6	43.0	24.0	23.8±12.8
	p		ns				
PHQ-4 (N = 64)	**Mean rank**	21.2	26.4	37.7	45.1	5.00	5.36±3.64
	p			|----------*----------|(B)			
PHQ-9 (N = 46)	**Mean rank**	16.5	19.6	23.4	33.2	13.0	12.9±5.66
	p		ns				
PHQstr (N = 33)	**Mean rank**	17.0	15.1	16.6	22.7	7.00	7.85±4.21
	p		ns				
Analysis of variance post hoc tests with Bonferroni(B) correction ns *p*>0.05 * *p* ≤ 0.05 ** *p* ≤0.01							

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; ns: non-significant; n.a.: non-available; *p* = p-value.

Table 14 | Correlations between ISI scores and scores of axis II measures. Effect sizes: very small (< 0.100), small (0.100 ≤ r_s < 0.300), moderate (0.300 ≤ r_s < 0.500) and strong (r_s ≥ 0.500); Spearman's rho non-significant (ns) $p > 0.05$; * $p \leq 0.05$; ** $p \leq 0.01$; orange and red marked fields represent moderate and strong correlation of statistical significance, respectively; r_s = Spearman's rank correlation coefficient

A) Correlations between ISI and axis II measures: all scores and scores grouped by insomnia severity grade, sex, age group, and employment status.

				Axis II measures							
				DCQ (N = 23)	**GAD-7 (N = 60)**	**IPQ (N = 156)**	**IEQ (N = 59)**	**PCS (N = 181)**	**PHQ-4 (N = 184)**	**PHQ-9 (N = 56)**	**PHQstr (N = 52)**
ISI (N = 64)	**Total scores**		**N**	**10**	**34**	**58**	**29**	**64**	**64**	**46**	**33**
			% of study sample	5.43%	18.5%	31.5%	15.8%	34.8%	34.8%	25.0%	17.9%
			r_s	.796**	.380*	.380**	.304^{ns}	.392**	.409**	.364*	.159^{ns}
	ISI categories	**No clinically insomnia (0-7)**	**N**	1		3	1	3	3	2	2
			% of study sample	.543%	0	1.63%	.543%	1.63%	1.63%	1.09%	1.09%
			Valid %	10.0%		5.17%	3.45%	4.69%	4.69%	4.35%	6.06%
			r_s	n.a.	n.a.	n.a. (-.500)	n.a.	n.a. (.866)	n.a. (1.00**)	n.a. (-1.00)	n.a. (1.00)
		Subthreshold (8-14)	**N**	4	13	27	11	31	31	18	16
			% of study sample	2.17%	7.07%	14.7%	5.98%	16.8%	16.8%	9.78%	8.70%
			Valid %	40.0%	38.2%	46.6%	37.9%	48.4%	48.4%	39.1%	48.5%
			r_s	.544^{ns}	.191^{ns}	-.352^{ns}	-.608*	-.0886^{ns}	-.0265^{ns}	-.0976^{ns}	-.214^{ns}
		Moderate severity (15-21)	**N**	2	15	20	11	21	21	17	9
			% of study sample	1.09%	8.15%	10.9%	5.98%	11.4%	11.4%	9.24%	4.89%
			Valid %	20.0%	44.1%	34.5%	37.9%	32.8%	32.8%	37.0%	27.3%
			r_s	n.a. (1.00**)	-.0547^{ns}	.403^{ns}	.626*	.570**	.320^{ns}	.221^{ns}	-.064^{ns}

ISI (N=64)		Severe (22-28)	N	3	6	8	6	9	9	9	6
			% of study sample	1.63%	3.26%	4.35%	3.26%	4.89%	4.89%	4.89%	3.26%
			Valid %	30.0%	17.6%	13.8%	20.7%	14.1%	14.1%	19.6%	18.2%
			r_s	n.a. (.00**)	-.522^{ns}	.209^{ns}	.294^{ns}	.474^{ns}	.254^{ns}	.240^{ns}	-.403^{ns}
	Gender	Women	N	9	27	43	23	48	48	36	28
			% of study sample	4.89%	14.7%	23.4%	12.5%	26.1%	26.1%	19.6%	15.2%
			Valid %	90.0%	79.4%	74.1%	79.3%	75.0%	75.0%	78.3%	84.8%
			r_s	.834**	.414*	.416**	.407^{ns}	.552**	.485**	.414*	.155^{ns}
		Men	N	1	7	15	6	16	16	10	5
			% of study sample	.543%	3.80%	8.15%	3.26%	8.70%	8.70%	5.43%	2.72%
			Valid %	10.0%	20.6%	25.9%	20.7%	25.0%	25.0%	21.7%	15.2%
			r_s	n.a.	-.0360^{ns}	.247^{ns}	-.213^{ns}	-.235^{ns}	.0867^{ns}	.0462^{ns}	.289^{ns}
	Age group	18-29	N	0	5	9	6	10	10	8	7
			% of study sample		2.72%	4.89%	3.26%	5.43%	5.43%	4.35%	3.80%
			Valid %		14.7%	15.5%	20.7%	15.6%	15.6%	17.4%	21.2%
			r_s	n.a.	-.177^{ns}	.538^{ns}	.924**	.476^{ns}	.502^{ns}	.155^{ns}	.209^{ns}
		30-39	N	2	11	16	7	16	16	8	7
			% of study sample	1.09%	5.98%	8.70%	3.80%	8.70%	8.70%	4.35%	3.80%
			Valid %	20.0%	32.4%	27.6%	24.1%	25.0%	25.0%	17.4%	21.2%
			r_s	n.a. (1.00**)	.807**	.366^{ns}	0	.608*	.633**	.661^{ns}	-.0818^{ns}
		40-49	N	3	10	13	9	14	14	11	9
			% of study sample	1.63%	5.43%	7.07%	4.89%	7.61%	7.61%	5.99%	4.89%
			Valid %	30.0%	29.4%	22.4%	31.0%	21.9%	21.9%	23.9%	27.3%
			r_s	n.a. (1.00**)	.110^{ns}	.423^{ns}	.148^{ns}	.653*	.575*	.533^{ns}	.640^{ns}

ISI (N=64)	**50-59**	**N**	3	4	8	5	10	10	8	5
		% of study sample	1.63%	2.17%	4.35%	2.72%	5.43%	5.43%	4.35%	2.72%
		Valid %	30.0%	11.8%	13.8%	17.2%	15.6%	15.6%	17.4%	15.2%
		r_s	n.a. (.866)	0	.108^{ns}	.316^{ns}	.190^{ns}	.109^{ns}	-.252^{ns}	.738^{ns}
	60-69	**N**	1	4	8	1	10	10	8	4
		% of study sample	.543%	2.17%	4.35%	.543%	5.43%	5.43%	4.35%	2.17%
		Valid %	10.0%	11.8%	13.8%	3.45%	15.6%	15.6%	17.4%	12.1%
		r_s	n.a.	.833^{ns}	.711*	n.a.	.0644^{ns}	.167^{ns}	.303^{ns}	.316^{ns}
	70-79	**N**	1		3	1	3	3	3	1
		% of study sample	.543%	0	1.63%	.543%	1.63%	1.63%	1.63%	.543%
		Valid %	10.0%		5.17%	3.45%	4.69%	4.69%	6.52%	3.03%
		r_s	n.a.	n.a.	.500^{ns}	n.a.	n.a. (.500)	n.a. (.500)	n.a. (1.00**)	n.a. (1.00)
	80-89	**N**			1		1	1		
		% of study sample	0	0	.543%	0	.543%	.543%	0	0
		Valid %			1.72%		1.56%	1.56%		
		r_s	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n. a
Employment status	**Training**	**N**		3	5	2	5	5	5	2
		% of study sample	0	1.63%	2.72%	1.09%	2.72%	2.72%	2.72%	1.09%
		Valid %		8.82%	8.62%	6.90%	7.81%	7.81%	10.9%	6.06%
		r_s	n.a.	0	-.300^{ns}	n.a. (1.00**)	-.205	-.600^{ns}	-.600^{ns}	n.a. 1.00**
	Working	**N**	5	22	37	18	42	42	29	22
		% of study sample	2.72%	12.0%	20.1%	9.78%	22.8%	22.8%	15.8%	12.0%
		Valid %	50.0%	64.7%	63.8%	62.1%	65.6%	65.6%	63.0%	66.7%

	r_s	.667^{ns}	.423*	.287^{ns}	.308^{ns}	.413**	.513**	.436*	.179^{ns}
Retired	**N**	2	2	6	1	7	7	6	3
	% of study sample	1.09%	1.09%	3.26%	.543%	3.80%	3.80%	3.26%	1.63%
	Valid %	20.0%	5.88%	10.3%	3.45%	10.9%	10.9%	13.0%	9.09%
	r_s	n.a. (1.00**)	n.a. (1.00**)	.600^{ns}	n.a.	.775*	.631^{ns}	.821*	-.866^{ns}
Unable to work	**N**	1	6	7	6	7	7	6	5
	% of study sample	.543%	3.26%	3.80%	3.26%	3.80%	3.80%	3.26%	2.72%
	Valid %	10.0%	17.6%	12.1%	20.7%	10.9%	10.9%	13.0%	15.2%
	r_s	n.a.	.348^{ns}	.750^{ns}	.486^{ns}	.429^{ns}	.491^{ns}	.551^{ns}	.949*
No job	**N**	2	1	3	2	3	3		1
	% of study sample	1.09%	.543%	1.63%	1.09%	1.63%	1.63%	0	.543%
	Valid %	20.0%	2.94%	5.17%	6.90%	4.69%	4.69%		3.03%
	r_s	n.a. (1.00**)	n.a.	n.a. (-1.00**)	n.a. (-1.00**)	n.a. (.866)	n.a. (-.500)	n.a.	n.a.

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; n.a.: non-available.

% of study sample = $\frac{N_{\text{each category}}}{184}$ %; Valid % = $\frac{N_{\text{each category}}}{N_{\text{total scores}}}$ %

B) Correlations between ISI scores and axis II measures subscales' total scores (PCS and PHQ-4)

	PCS subscales			PHQ-4 subscales	
	Magnification	**Rumination**	**Helplessness**	**Anxiety (GAD-2)**	**Depression (PHQ-2)**
ISI scores	.307*	.192^{ns}	.403**	.428**	.341**
N		64		64	

PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; GAD-2, Generalized Anxiety Disorder 2-item scale; PHQ-4, 4-item Patient Health Questionnaire.

C) Correlations between ISI total scores and axis II measures *above* clinical relevance

	DCQ	**GAD-7**	**IPQ**	**IEQ**	**PCS**	**PHQ-4**	**PHQ-9**	**PHQstr**
ISI scores	n.a. (-1.00**)	.121^{ns}	n.a.	.0892^{ns}	.474*	.391*	.569**	.325^{ns}
N	2	25	n.a.	14	20	28	36	10

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; n.a.: non-available.

D) Correlations between ISI total scores and axis II measures *below* clinical relevance

	DCQ	**GAD-7**	**IPQ**	**IEQ**	**PCS**	**PHQ-4**	**PHQ-9**	**PHQstr**
ISI scores	.638^{ns}	.0601^{ns}	n.a.	.182^{ns}	.149^{ns}	-.0278^{ns}	-.0356^{ns}	-.451*
N	8	9	n.a.	15	44	36	10	23

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; n.a.: non-available.

E) Correlations between ISI scores *above* clinical relevance and axis II measures

	DCQ	**GAD-7**	**IPQ**	**IEQ**	**PCS**	**PHQ-4**	**PHQ-9**	**PHQstr**
ISI scores	.821^{ns}	.326^{ns}	.504**	.542*	.429*	.389*	.444*	.233^{ns}
N	5	21	28	17	30	30	26	15

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress.

F) Correlations between scores *above* clinical relevance of both ISI and axis II measures

	DCQ	GAD-7	IPQ	IEQ	PCS	PHQ-4	PHQ-9	PHQstr
ISI scores	n.a. (-1.00**)	.250^{ns}	n.a.	.336^{ns}	.579*	.415^{ns}	.556**	.420^{ns}
N	2	18	n.a.	10	15	19	21	8

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; n.a.: non-available.

G) Correlations between ISI scores *below* clinical relevance and axis II measures

	DCQ	GAD-7	IPQ	IEQ	PCS	PHQ-4	PHQ-9	PHQstr
ISI scores	.803^{ns}	.191^{ns}	-.313^{ns}	-.222^{ns}	-.0739^{ns}	.0130^{ns}	-.0641^{ns}	-.203^{ns}
N	5	13	30	12	34	34	20	18

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress.

H) Correlations between scores *below* clinical relevance of ISI and axis II measures

	DCQ	GAD-7	IPQ	IEQ	PCS	PHQ-4	PHQ-9	PHQstr
ISI scores	.803^{ns}	.000	n.a.	.115^{ns}	-.0430^{ns}	-.157^{ns}	.304^{ns}	-.168^{ns}
N	5	6	n.a.	8	29	25	5	16

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress. n.a.: non-available.

4. Discussion

The present work was able to establish a correlation between pain in the orofacial region, insomnia, and psychosocial factors showing how this triad of elements and their interactions affects patients' overall well-being. A novel finding elicited from our study is that the levels of dysmorphic concern, anxiety, perceived-injustice experience, pain catastrophizing, depression, and psychosocial stress were similar regardless of insomnia severity reported but female patients are predominantly affected. In addition, reinforces the role of sleep management in patients with pain and shows the relevance of the self-screening tools in particular groups of patients, in our case patients with pain in the orofacial region, to detect sleep disturbances that will guide the medical doctor towards a more precise diagnosis and integrated treatment of orofacial pain and sleep disturbances.

As stated before, insomnia is one of the most common sleep disorders worldwide (Choueiry et al., 2016; Meira e Cruz et al., 2019), with a well-established bidirectional relationship with the development of psychological illnesses and poor well-being (Bluestein, Rutledge, & Healey, 2010). About 40% of insomniacs also have a comorbid psychiatric condition (Mai & Buysse, 2008) and, at least, 50% of the subjects who report sleep problems (Finan et al., 2013) are those who are more disabled and suffer from chronic pain (Hester & Tang, 2008; Palermo et al., 2011). Given the role of psychosocial factors either in the onset and maintenance of OFP (Buscemi, Chang, Liston, McAuley, & Schabrun, 2019; Goldthorpe et al., 2017), as well as in chronic insomnia (Hsieh, Lu, & Yen, 2019; Palermo et al., 2011; Sing & Wong, 2011), our study aimed to understand the relationship between insomnia and psychosocial domains in OFP patients. As women, older adults, unemployed and disabled individuals seem to have an increased risk for continuous sleep disturbances together with mental/psychological problems, age, gender, and patients' current or latest occupation (employment status) were considered as putative confounders. Therefore, correlations between ISI scores and the axis II psychometric measures were overall analysed and then, subdivided concerning each confounder.

4.1. Clinically relevant insomnia, psychosocial factors, and psychological burden

Our data revealed that around one-third of patients, most of them females and active workers, reported a sleep disturbance in the form of insomnia and/or excessive sleepiness, and from those, approximately one in six patients experienced insomnia at a clinically relevant level

– moderate severity and severe with ISI scores equal or above 15. These results are in line with other studies showing that adults above 30 years old present the most significant insomnia severity grades and that older adults are at increased risk of insomnia (Meira e Cruz et al., 2019; D. Patel et al., 2018). Besides, in our population, the levels of moderate and severe insomnia are higher than in the general population which is stated that insomnia reaches around 5-15% of individuals (Choueiry et al., 2016; Mai & Buysse, 2008; Meira e Cruz et al., 2019; Morin et al., 2015; Tobaldini et al., 2019), suggesting that our patients have other factors/conditions that are potentiating sleep disturbances. One of these factors appears to be the patients' underlying primary condition - pain in the orofacial region - but patients' psychological distress expressed under various emotional responses, - e.g., anxiety, perceived injustice - derived from the primary condition might be involved in insomnia development. Furthermore, the levels of subthreshold insomnia are significantly higher than those of moderate to severe insomnia in the 2nd, 3rd, and 5th decades of age indicating that these patients might be at risk of developing a clinically relevant condition, thus, needing close surveillance of their sleep profile. In our population, insomnia severity is increasing with age, but we cannot exclude that the duration and level of pain might eventually be the same among individuals of various ages. Thus, we might suggest that pain is modulating insomnia in the youngest patients but, in the older ones, age needs to be accounted for as, it is well known, that the deterioration in central nervous system function can disrupt circadian rhythms, directly influencing when the person feels tired and alert. Interestingly, unemployed patients did not achieve a significant level of insomnia probably because, even if they have a disturbed sleep profile, they can mask it throughout the day. In this situation, the subject's perception regarding his sleep profile is not so negative as it would be in a working patient. Being originated from a prosperous country, we might speculate that the lack of economical stressors might also positively influence the psychosocial well-being of these unemployed patients. However, this was not evaluated in our work.

Various studies have shown that the subjective beliefs – e.g., own ideas about the disease and its cause, disease evolution over time and its consequences, treatment options, emotional responses to the illness - related to the own condition of patients with chronic diseases are strongly associated with various outcomes such as pain, physical and mental health status (Buscemi et al., 2019; Ohrbach & Durham, 2017; Selvam, VK, SV, & JM, 2018; M. J. L. Sullivan et al., 2008). Also, catastrophizing, an increasingly recognized factor influencing pain outcomes may alter physical and mental status due to its relation to a persistently negative

cognitive-affective behaviour which induces, among others, sleep disturbances including insomnia (Bryson, Read, Bush, & Edwards, 2014). In our study, illness perception, catastrophizing, and the observed distress - maladaptive anxiety and depression - together with the perceived injustice of the pain experience are significantly associated with insomnia, in particular to its severity. Nevertheless, it is difficult from our study to understand which is the cause and which is the consequence as, in our opinion, these elements are part of a positive feedback loop that perpetuates their manifestation unless broken by an external factor (e.g., pain resolutive treatment). Moreover, the correlation between insomnia severity grades and psychosocial factors brought into conclusion that insomnia of moderate severity is significantly associated with patients' level of perceived injustice (severity of loss consequent to injury, blame, a sense of unfairness or irreparability of loss) and pain catastrophizing, whereas subthreshold insomnia had a negative relationship with illness perceptions. Patients with sub-clinical insomnia do not have the perception of the problem itself, so a linear and positive relationship of their symptoms with the feeling of injustice was not expected. Thus, the more severe insomnia, the greater the impact on the sense of injury-related injustice (and vice-versa), which exacerbates insomnia symptoms and, consequently, pain disability and/or intensity (insomnia modulating pain through psychosocial stress factors) (Bryson et al., 2014; M. J. L. Sullivan et al., 2008). And, this psychological maladjustment may compromise the patient's capacity to manage his medical condition by influencing both help-seeking behaviour and treatment outcomes but also having an impact on patients' daily activities and social and family environments (Galli et al., 2010; Selvam et al., 2018) and needs to be subjected to early detection.

A multitude of interactive biological, psychological, and social mechanisms has been proposed to explain the insomnia-anxiety-depression relationship (Blake, Trinder, & Allen, 2018; Choueiry et al., 2016) and they might also be applied to the interpretation of our results. In fact, biological mechanisms such as genetic influences, dysregulation in shared neural regions, pathways or neuronal neurochemistry, inflammatory conditions linked to an excess of cytokines are among processes that may influence and be influenced by psychological and social/environmental factors (Blake et al., 2018). A common symptom reported by patients who suffered from insomnia is the difficulty of falling asleep (Mai & Buysse, 2008) which might be linked with anxiety and depression as the increased wakefulness in bed might increase negative cognitions and, hence, anxiety and depression symptoms. From the social perspective, insomnia

may decrease the likelihood of experiencing positive social contexts, compromising restorative processes and executive function. Therefore, it becomes more difficult to solve interpersonal conflicts and deal with challenging social situations (Blake et al., 2018).

Despite the fewer studies focused on the relationship between insomnia and dysmorphic concern, their association was expected since the dysmorphic concern is a symptom found across other clinical disorders, including depression and anxiety (Bjornsson, Didie, & Phillips, 2010; Oosthuizen et al., 1998) and, when it becomes a clinical relevant as body dysmorphic disorder (BDD), an overall reduced life quality may occur. In fact, results from another study indicate that young patients with clinically relevant insomnia had significantly higher self-reported BDD symptoms' severity, besides psychological maladjustment (Sevilla-Cermeño et al., 2019), which is in line with our results.

Interestingly, from our work, insomnia was significantly related to psychosocial stress just in patients unable to work given their disease. It has previously been verified that several types of stressors increase the risk of insomnia episodes across different cultures and age groups (Bernert, Merrill, Braithwaite, Van Orden, & Joiner, 2007; Kim et al., 2011; Linton, 2004). Behind this connection is a range of bodily reactions induced by stress in the nervous (mainly sympathoexcitation), endocrine (through the activation of the hypothalamic-pituitary-adrenal axis), and immune systems, as well as a persistent state of hyperarousal, common among insomniacs which might be due to maladaptive positive feedback mechanisms (Antoni & Dhabhar, 2019; Fernandez-Mendoza & Vgontzas, 2013; Hirotsu et al., 2015; Kogler et al., 2015). Simultaneously, insomnia can exacerbate stress by creating a new stressor (sleeping disturbances) which leads to additional time to think, reinforcing the state of hyperarousal (Kalmbach, Cuamatzi-Castelan, et al., 2018). Nevertheless, there are a few suggestions for the reason why the association between stress and poor sleep outcomes was poor in this study. First, the patients were not all exposed to the same stressors, so the nature of stress may impact differently. Second, even when facing the same stressor, individuals can respond in different ways and psychological resilience, the ability to adapt after stressful episodes and move forward healthily might apply to some patients (Schneiderman, Ironson, & Siegel, 2005; Zaidel, Musich, Karl, Kraemer, & Yeh, 2021). And third, we are reasoning about data extracted from a self-screening tool which is emphasizing patients' perceptions rather than dealing with objective clinical measures.

4.2. Sex, age, and employment status

Studies on the sex impact on the perception of orofacial pain indicate that female patients have a higher pain sensitivity, rating a higher severity when compared to male patients, and also suffer a severe impairment (Dahlhamer et al., 2018; Dragioti et al., 2017; Suh et al., 2018). Also, when sex by age cohort comparisons is made the significant differences in pain categories are found within the 45 to 64-year-old group and not older group above 65 years old despite general studies refer that the prevalence of insomnia increases with higher age. Various mechanisms have been suggested to explain this sex difference such as the effect of sex hormones, differences in endogenous opioid function and opioid receptors, cognitive/affective influences, coping patterns, and contributions of social factors such as stereotypic gender roles (Kret & De Gelder, 2012; Shaefer et al., 2018; Suh et al., 2018). Our results corroborate with this previous evidence with ISI scores being only significantly associated with axis II measures in female patients, elucidating that women are indeed the most affected by both insomnia and chronic pain, potentiating this vicious cycle.

Another key point in our results is that adults aged between 30 and 39 years old displayed more psychosocial issues (anxiety, pain catastrophizing, distress, and depression) associated with insomnia symptoms which suggests that this age range had a stronger contribution to the overall positive correlation between the variables. Patients in young and middle adulthood tend to overrate the problem, as they have less life experience, psychological resilience and may experience physical problems for the first time. By contrast, the older patients, having a shorter life expectancy and a greater capacity to adjust in the face of chronically occurring circumstances, are more concerned if the disease will actually lead to their death (Anasuri, 2016; McGinnis, 2018).

Finally, it is noteworthy that an unhealthy and harmful workplace result in work-related stress and occupational stress is one of the most dangerous health risks for employees. Active workers are, therefore, more likely to develop emotional distress and insomnia symptoms (Kim et al., 2011; Rafferty, Restubog, & Jimmieson, 2010; Schiller et al., 2018; Wolińska, 2020). In our study, a significant correlation between poor sleep outcomes and axis II measures was firstly found in those patients and then in the retired ones. For elderly status, retirement represents for some individuals also an additional psychosocial stressor, due to a variety of factors such as financial matters, social and individual roles, relationships, self-esteem, or use of time. (Kagamimori, Nasermoaddeli, & Wang, 2004). Interestingly, a study published last

year showed that retirement can be associated with improvements in mental health, since individuals, especially in the 3 years following retirement, settle into a stability phase which indicates that interrelation between retirement and mental health is dependent on the social and economic context individuals retire from (Fleischmann, Xue, & Head, 2020).

Despite our best effort in this study, we are aware of some limitations. First, data from the WISE questionnaire do not allow to divide patients with chronic or acute pain or distinguish patients with orofacial pain from those with referred orofacial pain. This remains to be further explored as both acute and chronic pain as well as the pain origin stand on different pathophysiological mechanisms impacting medical management of the patient's condition. Second, all questionnaires use Likert scales, which have some inherent disadvantages that prevent the accurate identification of respondents' traits. Disadvantages include response styles, ambiguous numbers of response categories, and the fact that Likert scales produce ordinal data. Sometimes, respondents misread the questions or adulterate responses to keep privacy, giving wrong feedbacks. Therefore, responses can negatively affect statistical analysis and then, the results. To avoid this interference, parametric tests, which are usually more powerful and flexible, were not used. A third limitation concerns the available data on sample size, which has a disparity between women and men. Insufficient sample size for statistical measurement in some stages of the study also reinforce the choice of non-parametric tests for our data analyses. Finally, to validate our results which are based on a self-screening tool, polysomnographic studies – the gold standard method to evaluate sleep disturbances- should have been prospectively performed as well as the application of specific instruments to monitor mental well-being.

In conclusion, this work, despite based on a small cohort of orofacial pain patients, emphasizes the interconnectedness between pain, insomnia, and psychological burden, as well as the relevance of assessing in clinical settings both somatic and psychological comorbidities that might disrupt sleep. Women, active workers, and young/middle-aged patients had a predominance in more expressive results (ISI scores more correlated with axis II measures), representing a group to be closely followed-up. As the correlations between insomnia symptoms and psychological burdens - namely dysmorphic concern, illness perception, injustice experience, and pain catastrophizing - in patients suffering from chronic pain have not previously been reported, this warrants further investigations. Our work also highlights the

important role of a good sleep hygiene to complement pain management strategies. Additionally, this study elucidates how a user-friendly self-assessment tool, when used judiciously by the patient, can be useful in the current medical practice, favouring a more complete patient assessment and its personalized treatment.

5. References

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6. Supplemental Material

Appendix I – The Insomnia Severity Index (full item)

Adapted from Bastien et al., 2001.

Screening items and thresholds for further evaluation by ISI (Ettlin et al., 2016): third item of PHQ-9 > 1 (trouble falling or staying asleep, or sleeping too much; see Appendix VIII).

Name: _____ **Date:** _____

1. Please rate the current (i.e., last 2 weeks) **SEVERITY** of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

5. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add scores for all seven items (1a+1b+1c+ 2+3+4+5) = _____
Total score ranges from 0-28
- 0-7 = No clinically significant insomnia
- 8-14 = Subthreshold insomnia
- 15-21 = Clinical insomnia (moderate severity)
- 22-28 = Clinical insomnia (severe)

Appendix II – The Dysmorphic Concern Questionnaire (full item)

Adapted from Oosthuizen et al., 1998.

Screening items and thresholds for further evaluation by DCQ (Ettlin et al., 2016): tooth/jaw position (e.g., bite is incorrect) / physical appearance (a lot).

These questions are designed to screen for people with certain concerns that are: (i) often difficult or embarrassing to talk about with their doctor/family/friends; and (ii) often difficult to find the right help for.

Please read the following questions carefully and answer them by circling the answer which you think is most appropriate for your specific situation:

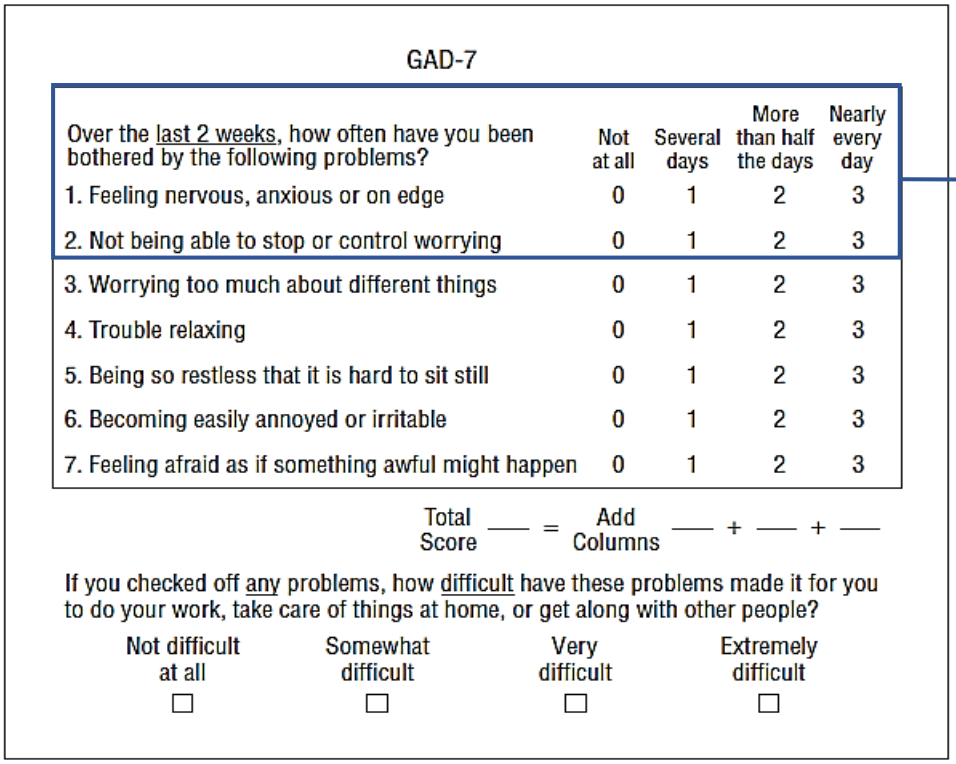
Have you ever:	**0**	**1**	**2**	**3**
1. Been very concerned about some aspect of your physical appearance	Not at all	Same as most people	More than most people	Much more than most people
2. Considered yourself misformed or misshapen in some way (e.g. nose/hair/skin/sexual organs/ overall body build)	Not at all	Same as most people	More than most people	Much more than most people
3. Considered your body to be malfunctional in some way (e.g. excessive body odour, flatulence, sweating)	Not at all	Same as most people	More than most people	Much more than most people
4. Consulted or felt you needed to consult a plastic surgeon/dermatologist/physician about these concerns	Not at all	Same as most people	More than most people	Much more than most people
5. Been told by others/doctor that you are normal in spite of you strongly believing that something is wrong with your appearance or bodily functioning	Not at all	Same as most people	More than most people	Much more than most people
6. Spent a lot of time worrying about a defect in your appearance/bodily functioning	Not at all	Same as most people	More than most people	Much more than most people
7. Spent a lot of time covering up defects in your appearance/bodily functioning	Not at all	Same as most people	More than most people	Much more than most people

Appendix III – The Generalized Anxiety Disorder 7-item scale (full item)

Adapted from Spitzer et al., 2006.

Note that GAD-2 only incorporates the first 2 items of GAD-7.

Screening items and thresholds for further evaluation by GAD-7 (Ettlin et al., 2016): the sum of GAD-2 items > 2.



GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

GAD-2

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Appendix IV – The Brief Illness Perception Questionnaire (full item)

Adapted from Broadbent et al., 2006.

Screening items and thresholds for further evaluation by IPQ (Ettlin et al., 2016): worries about my chief complaints (a lot); are you concerned about being a burden to others? (yes).

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?

0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life

How long do you think your illness will continue?

0	1	2	3	4	5	6	7	8	9	10
a very short time										forever

How much control do you feel you have over your illness?

0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control

How much do you think your treatment can help your illness?

0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful

How much do you experience symptoms from your illness?

0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms

How concerned are you about your illness?

0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned

How well do you feel you understand your illness?

0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly

How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused your illness.
The most important causes for me:-

1. _____
2. _____
3. _____

Appendix V – The Injustice Experience Questionnaire (full item)

Adapted from M. J. L. Sullivan, 2008.

Screening items and thresholds for further evaluation by IEQ (Ettlin et al., 2016): different opinions of different caregivers/not been taken seriously (a lot); did you experience injustice concerning your chief complaints (e.g., misinformation, mistreatment, undue expense, etc.)? (yes).

Name: _____ Age: _____ Gender: _____ Date: _____

When injuries happen, they can have profound effects on our lives. This scale was designed to assess how your injury has affected your life.

Listed below are twelve statements describing different thoughts and feelings that you may experience when you think about your injury. Using the following scale, please indicate how frequently you experience these thoughts and feelings when you think about your injury.

0 – never **1** – rarely **2** – sometimes **3** – often **4** – all the time

1 ☐	Most people don't understand how severe my condition is.
2 ☐	My life will never be the same.
3 ☐	I am suffering because of someone else's negligence.
4 ☐	No one should have to live this way.
5 ☐	I just want to have my life back.
6 ☐	I feel that this has affected me in a permanent way.
7 ☐	It all seems so unfair.
8 ☐	I worry that my condition is not being taken seriously.
9 ☐	Nothing will ever make up for all that I have gone through.
10 ☐	I feel as if I have been robbed of something very precious.
11 ☐	I am troubled by fears that I may never achieve my dreams.
12 ☐	I can't believe this has happened to me.

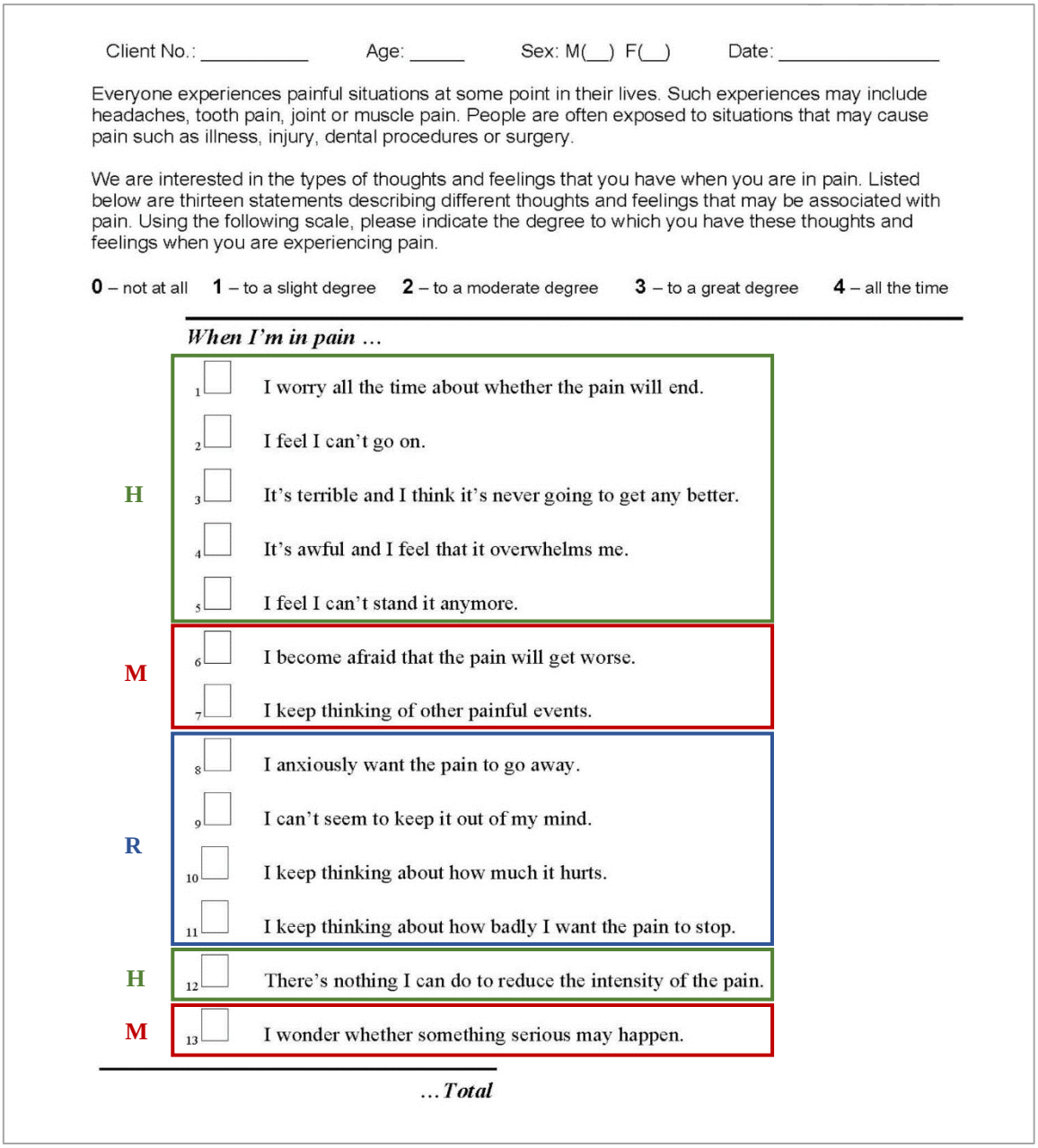
…Total

Appendix VI – The Pain Catastrophizing Scale (full item)

Adapted from M. J. L. Sullivan et al., 1995; PCS English Version Manual (Adult)

The items of PCS subscales (**rumination - R**, **magnification - M**, and **helplessness - H**) are marked in the figure.

Screening items and thresholds for further evaluation by PCS (Ettlin et al., 2016): worries about my chief complaints (a lot).



Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

	When I'm in pain …	
	1 ☐	I worry all the time about whether the pain will end.
	2 ☐	I feel I can't go on.
H	3 ☐	It's terrible and I think it's never going to get any better.
	4 ☐	It's awful and I feel that it overwhelms me.
	5 ☐	I feel I can't stand it anymore.
M	6 ☐	I become afraid that the pain will get worse.
	7 ☐	I keep thinking of other painful events.
	8 ☐	I anxiously want the pain to go away.
	9 ☐	I can't seem to keep it out of my mind.
R	10 ☐	I keep thinking about how much it hurts.
	11 ☐	I keep thinking about how badly I want the pain to stop.
H	12 ☐	There's nothing I can do to reduce the intensity of the pain.
M	13 ☐	I wonder whether something serious may happen.
		…Total

Appendix VII – The Patient Health Questionnaire – 4 (full item)

Adapted from Kroenke et al., 2009.

The items of PHQ-4 subscales (**anxiety: items of GAD-2** and **depression: items of PHQ-2**) are marked in the figure.

Over the <u>last 2 weeks</u>, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

GAD-2

PHQ-2

Appendix VIII – The Patient Health Questionnaire – 9 (full item)

Adapted from Kroenke et al., 2001.

Screening items and thresholds for further evaluation by PHQ-9 (Ettlin et al., 2016): increased fatigue/loss of energy/unintentional weight loss or gain (a lot); the sum of PHQ-2 items > 2.

PHQ-2

ISI screening item (score>1)

Nine-symptom Checklist

Name _____ Date _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

(For office coding: Total Score _____ = _____ + _____ + _____)

If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet BW Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at *rls8@columbia.edu*. PRIME-MD is a trademark of Pfizer Inc. Copyright 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Appendix IX – The Patient Health Questionnaire for Stress (full item)

Adapted from Spitzer et al., 2000.

Screening items and thresholds for further evaluation by PHQ-str (Ettlin et al., 2016): dizziness/nausea/fainting spells/shortness of breath/feeling your heart pound or race/indigestion (a lot); lack of time/work-related stress/caring responsibilities/finances (a lot); lack of support/interpersonal conflicts/loneliness (a lot); stressful life events (something bad that happened recently or in the past with corresponding thoughts/dreams/feelings) (a lot).

In the last 4 weeks, how much have you been bothered by any of the following problems?	**Not at all (0)**	**A little (1)**	**A lot (2)**
a. Worrying about your health……	☐	☐	☐
b. Your weight or how you look……	☐	☐	☐
c. Little or no sexual desire or pleasure during sex……	☐	☐	☐
d. Difficulties with husband/wife, partner/lover or boyfriend/girlfriend……	☐	☐	☐
e. The stress of taking care of children, parents, or other family members……	☐	☐	☐
f. Stress at work outside of the home or at school……	☐	☐	☐
g. Financial problems or worries……	☐	☐	☐
h. Having no one to turn to when you have a problem……	☐	☐	☐
i. Something bad that happened recently……	☐	☐	☐
j. Thinking or dreaming about something terrible that happened to you in the past - like your house being destroyed, a severe accident, being hit or assaulted, or being forced to commit a sexual act……	☐	☐	☐

Appendix X – Influence of confounders on axis II measures (Table)

Table 15 | Analysis of variance (Mann-Whitney and Kruskal-Wallis tests) between sex, age group, employment status, and axis II measures, considering the number of participants who also replied to ISI

Axis II Measures (N in common with ISI)		Gender		Age group							Employment status				
		Women	Men	18-29	30-39	40-49	50-59	60-69	70-79	80-89	Training	Working	Retired	Disabled	No job
DCQ	**Mean rank**	5.39	6.50	n.a.	3.75	5.67	5.83	3.00	10.0	n.a.	n.a.	7.00	6.50	4.00	1.50
(N = 10)	***p***	ns					ns						ns		
GAD-7	**Mean rank**	18.9	12.1	12.0	14.1	23.7	24.3	11.5	n.a.	n.a.	14.0	17.0	14.3	22.9	12.5
(N = 34)	***p***	ns					ns						ns		
IPQ	**Mean rank**	29.4	29.9	31.7	29.4	26.9	30.9	32.8	28.0	12.0	33.3	27.3	31.6	44.0	12.8
(N = 58)	***p***	ns					ns						ns		
IEQ	**Mean rank**	15.0	15.2	11.9	12.4	18.8	17.8	8.00	10.5	n.a.	11.8	14.9	10.5	19.1	9.25
(N = 29)	***p***	ns					ns						ns		
PCS	**Mean rank**	34.2	27.4	31.8	36.8	35.7	25.3	30.2	36.7	8.50	23.4	32.6	34.6	39.8	24.3
(N = 64)	***p***	ns					ns						ns		
PHQ-4	**Mean rank**	34.7	26.1	33.0	33.1	42.2	28.4	26.6	17.7	28.0	30.5	32.1	29.1	45.4	18.7
(N = 64)	***p***	ns					ns						ns		
PHQ-9	**Mean rank**	25.3	16.9	22.8	25.6	29.7	22.2	18.8	13.2	n.a.	18.7	23.9	20.2	28.8	n.a.
(N = 46)	***p***	ns					ns						ns		
PHQstr	**Mean rank**	17.7	13.1	16.6	13.9	20.4	25.4	7.50	6.50	n.a.	18.8	16.4	7.33	23.8	22.0
(N = 33)	***p***	ns					ns						ns		
Analysis of variance post hoc tests with Bonferroni[(B)] correction									**ns *p* > 0.05**		*** *p* ≤ 0.05**		**** *p* ≤ 0.01**		

ISI, Insomnia Severity Index; DCQ, Dysmorphic Concern Questionnaire; GAD-7, General Anxiety Disorder; IPQ, Illness Perception Questionnaire; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; PHQ-4, Patient Health Questionnaire 4; PHQ-9, Patient Health Questionnaire 9; PHQstr, Patient Health Questionnaire Stress; ns: non-significant; n.a.: non-available; *p* = p-value.