INTERNATIONAL DOCTORAL
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Roya
Karimi

PhD Thesis

LIFESTYLE AND PSYCHOLOGIC FACTORS, AND PAIN: A META-ANALYSIS AND COHORT STUDY

Santiago de Compostela, 2023

Doctoral Programme in Epidemiology and Public Health

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Título de la tesis: **Lifestyle and psychologic factors, and pain: a meta-analysis and cohort study**

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This thesis is dedicated to the memory of Mahsa Amini …

ABSTRACT

Chronic pain is one of the leading causes of healthcare seeking. Chronic pain is the main contributor to years lived with disability (YLDs) worldwide and represents a considerable economic burden due to healthcare expenses and lost productivity. However, chronic pain has long been considered a symptom of other diseases and not an independent pathological condition. This has contributed to the undervaluation of this entity by health professionals. Recently, an International Association for the Study of Pain (IASP) Task Force was instrumented to add a code for chronic pain to the ICD-11, to support the fact that chronic pain is a disease entity "in its own right". Therefore, in this thesis, we decided to assess the role of lifestyle and psychological factors in the incidence of chronic pain among the young population.

In this thesis, we used dose-response meta-analysis techniques to answer the question of whether alcohol intake is related to chronic pain occurrence. We analyzed three case-control and thirteen cohort studies that were eligible to be included in the meta-analysis. The results showed a decreased risk of chronic pain among people who drank alcohol. In addition, we found a non-linear association between alcohol consumption and chronic pain in the dose-response meta-analysis.

Also, we evaluated the direct and indirect effects of depression on pain through sleep disturbance using a two-stage meta-analytic structural equation modeling. With a comprehensive search strategy, we found sixty-four case-control and cohort studies eligible for the meta-analysis. The results showed a partial mediation effect of sleep disturbance on the relationship between depression and pain among some subgroups, including chronic pain outcomes, cohort design, studies carried out in the general population, and high-quality studies.

We conducted a cohort study on the students of the University of Santiago de Compostela to evaluate the effect of health-related quality of life or well-being as a biopsychosocial factor on chronic pain incidence. In the first part of this cohort study, we assessed the association between physical and mental components of health-related quality of life (well-being) on chronic pain incidence. High scores of physical health-related quality of life were related to a decrease in chronic pain incidence; however, no association was observed between mental health-related quality of life and chronic pain. In the second part of this cohort study, we assessed the causal role of covariates in the association between physical well-being and chronic pain. We applied mediation analysis to find potential mediators and stratum-specific techniques to find and distinguish potential confounders from interactors. The results showed that perceived stress had a mediation role, physical activity and alcohol drinking had a significant role as interactors, and smoking was a potential confounder and interactor of the association between physical well-being and chronic pain.

The different biological mechanisms can explain the results of these findings; however, we considered some concepts as alternative explanations in our interpretation, such as reverse causality and misclassification.

RESUMEN

El dolor crónico es una de las principales causas de búsqueda de atención médica. El dolor crónico es el principal contribuyente en el mundo a los años vividos con discapacidad (YLD) y representa una carga económica considerable debido a los gastos de atención médica y la pérdida de productividad. Sin embargo, durante mucho tiempo el dolor crónico se consideró un síntoma de otras enfermedades y no una condición patológica independiente. Esto ha contribuido a la infravaloración de esta entidad por parte de los profesionales de la salud. Recientemente, un grupo de trabajo de la Asociación Internacional para el Estudio del Dolor (IASP, por sus siglas en inglés) fue requerido para agregar un código para el dolor crónico a la CIE-11, para respaldar el hecho de que el dolor crónico es una entidad de enfermedad "por derecho propio". Por lo tanto, en esta tesis, decidimos evaluar el papel del estilo de vida y de los factores psicológicos en la incidencia del dolor crónico en población joven.

En esta tesis, usamos técnicas de metanálisis de dosis-respuesta para responder a la pregunta de si la ingesta de alcohol está relacionada con la aparición de dolor crónico. Analizamos tres estudios de casos y controles y trece estudios de cohortes elegibles para ser incluidos en el metanálisis. Los resultados mostraron una disminución del riesgo de dolor crónico en las personas que beben alcohol. Además, encontramos una asociación no lineal entre el consumo de alcohol y el dolor crónico en el metanálisis de dosis-respuesta.

Además, evaluamos los efectos directos e indirectos de la depresión sobre el dolor a través de la alteración del sueño, utilizando un modelo de ecuaciones estructurales de metaanálisis de dos etapas. Con una estrategia de búsqueda exhaustiva, encontramos sesenta y cuatro estudios de casos y controles y de cohortes elegibles para el metanálisis. Los resultados mostraron un efecto de mediación parcial de la alteración del sueño en la relación entre la depresión y el dolor en algunos subgrupos: el grupo específico de dolor crónico, el de diseño de cohortes, el de los estudios realizados en población general y el que corresponde a estudios de alta calidad.

Realizamos un estudio de cohortes en estudiantes de la Universidad de Santiago de Compostela para evaluar el efecto de la calidad de vida relacionada con la salud como factor biopsicosocial en la incidencia del dolor crónico. En la primera parte de este estudio de cohorte, evaluamos la asociación entre los componentes físicos y mentales de la calidad de vida (bienestar) relacionada con la salud y la incidencia del dolor crónico. Unos altos niveles de calidad de vida relacionada con la salud física se asociaron con una disminución de la incidencia de dolor crónico; sin embargo, no se observó asociación entre calidad de vida relacionada con la salud mental y el dolor crónico. En la segunda parte de este estudio de cohortes, evaluamos el papel causal de las covariables en la asociación entre el bienestar físico y el dolor crónico. Aplicamos análisis de mediación para encontrar posibles mediadores y técnicas específicas de estratificación para hallar y distinguir posibles factores de confusión de interactores. Los resultados mostraron que el estrés percibido tenía un papel de mediador, la actividad física y el consumo de alcohol un papel significativo como interactores, y el consumo de tabaco un papel de factor de confusión y de interacción en la asociación entre ebienestar físico y dolor crónico.

Los diferentes mecanismos biológicos pueden explicar los resultados de estos hallazgos; sin embargo, barajamos explicaciones alternativas, como causalidad inversa y clasificación errónea, en nuestras interpretaciones.

RESUMO

A dor crónica é unha das principais causas de busca de asistencia sanitaria. A dor crónica é o principal contribuínte aos anos vividos con discapacidade (YLD) en todo o mundo e representa unha carga económica considerable debido aos gastos sanitarios e á perda de produtividade. Non obstante, a dor crónica considerouse un síntoma doutras enfermidades e non unha condición patolóxica independente. Isto contribuíu á infravaloración desta entidade por parte dos profesionais sanitarios. Recentemente, un grupo de traballo da Asociación Internacional para o Estudo da Dor (IASP) foi instrumentado para engadir un código para a dor crónica á CIE-11, para apoiar o feito de que a dor crónica é unha entidade de enfermidade "por dereito propio". Por iso nesta tese decidimos valorar o papel do estilo de vida e dos factores psicolóxicos na incidencia da dor crónica entre a poboación nova.

Nesta tese, realizamos técnicas de metaanálise dose-resposta para responder á pregunta de se a inxestión de alcol está relacionada coa aparición de dor crónica. Analizamos tres estudos de casos e controles e trece estudos de cohortes que eran elixibles para incluírse na metaanálise. Os resultados mostraron unha diminución do risco de dor crónica entre as persoas que beben alcohol. Ademais, atopamos unha asociación non lineal entre o consumo de alcohol e a dor crónica na metaanálise dose-resposta.

Ademais, avaliamos os efectos directos e indirectos da depresión sobre a dor a través da alteración do sono mediante un modelado de ecuacións estruturais metaanalíticas en dúas etapas. Cunha estratexia de busca completa, atopamos sesenta e catro estudos de casos-control e cohortes para a metaanálise. Os resultados mostraron un efecto de mediación parcial da alteración do sono na relación entre a depresión e a dor entre algúns subgrupos, incluíndo os resultados da dor crónica, o deseño de cohortes, os estudos realizados na poboación xeral e os estudos de alta calidade.

Realizamos un estudo de cohorte sobre estudantes da Universidade de Santiago de Compostela para avaliar o efecto da calidade de vida ou o benestar relacionados coa saúde como factor biopsicosocial na incidencia da dor crónica. Na primeira parte deste estudo de cohortes, avaliamos a asociación entre os compoñentes físicos e mentais da calidade de vida relacionada coa saúde (benestar) na incidencia da dor crónica. As puntuacións altas de calidade de vida relacionada coa saúde física relacionáronse coa diminución da incidencia da dor crónica; con todo, non se observou ningunha asociación entre a calidade de vida relacionada coa saúde mental e a dor crónica. Na segunda parte deste estudo de cohortes, avaliamos o papel causal das covariables na asociación entre o benestar físico e a dor crónica. Aplicamos a análise de mediación para atopar os potenciais mediadores e técnicas específicas de estrato para atopar e distinguir os potenciais confusores dos interactores. Os resultados mostraron que o estrés percibido tiña un papel de mediación, a actividade física e o consumo de alcohol tiñan un papel importante como interactores e o tabaquismo era un posible factor de confusión e interacción da asociación entre o benestar físico e a dor crónica.

Os diferentes mecanismos biolóxicos poden explicar os resultados destes achados; porén, consideramos algúns conceptos, como a causalidade inversa e a clasificación errónea, nas nosas interpretacións.

ABBREVIATIONS

ACC: Anterior Cingulate Cortex
ACE: Adverse childhood experiences
ACR: American College Of Rheumatology
AIM: African Index Medicus
AP: Attributable Proportion
BCTQ: Boston Carpal Tunnel Questionnaire
BDI: Beck Depression Inventory
BMI: Body Mass Index
BSI: Brief Symptom Inventory
CBT: Cognitive Behavioural Therapy
CES-D, Center For Epidemiologic Studies Depression Scale
CI: Confidence Interval
CIE: Clasificación Internacional de Enfermidades
CNS: Central Nervous System
CPG: Chronic Pain Grade
CPGQ: Chronic Pain Grade Questionnaire
CWMSC: Chronic Widespread Musculoskeletal Complaints
CWP: Chronic Widespread Pain
CWP: Dor crónica xeneralizada (Chronic Widespread Pain)
DAG: Diagrama de Gráficos Acíclicos
DALYs: Disability-Adjusted Life Years
DNIC: Diffuse Noxious Inhibitory Controls
DSM: Diagnostic And Statistical Manual Of Mental Disorders
DSS: Depressive Symptoms Score
EDS: Excessive Daytime Sleepiness
EI: Extracranial/Bodily Injury
EPND: Edinburgh Postnatal Depression Score
FIML: Full Information Maximum Likelihood
GABA: gamma-aminobutyric acid
GIM: WHO Global Index Medicus
GMS: Geriatric Mental State Diagnostic Schedule
GWAS: Genome-wide association study
GWBS: General Well-Being Schedule
HADS: Hospital Anxiety And Depression Scale
HAMD: Hamilton Depression Scale
HFHS: High-Fat High-Sugar
HPA: Hypothalamic Pituitary Adrenal
HRQOL: Health-Related Quality of Life
IASP: International Association for the Study of Pain

ICD-11: International Classification of Diseases 11th Revision
ICR: Interaction Contrast Ratio
IMEMR: Index Medicus for the Eastern Mediterranean Region,
IMSEAR: Index Medicus for the South-East Asia Region,
IPAQ-SF: International Physical Activity Questionnaires
IPW: Inverse-probability weighting
IRR: Incidence Rate Ratio
IRS: Insomnia Rating Scale
ISI: Insomnia Severity Index
LBP: Low Back Pain
LBP: Lower-back pain
LILACS: Latin America and the Caribbean Literature on Health Sciences
MASEM: Structural Equation Modeling
MCS: Mental Component Summary
MDD: Major Depressive Disorder
MHI: Mental Health Inventory
MHQ: Middle-Sex Hospital Questionnaire
MI: multiple imputations
MICE: Multiple Imputation by Chained Equations
MIDAS: Migraine Disability Assessment
MPQ: Mcgill Pain Questionnaire
non-steroidal anti-inflammatory drugs (NSAIDs)
NRS: Numeric Rating Scale
NRS: Numerical Rating Scale
OA: Osteoarthritis
OATD: Open Access Theses and Dissertations
OR: Odds Ratio
PBPI: Pain Behavior And Perception Inventory
PCS: Pain Catastrophizing Scale
PCS: Physical Component Subgroup
PHQ: Patient Health Questionnaire
PHQ-9: Patient Health Questionnaire 9
PSG: Polysomnography
PSQI: Petersburg Sleep Quality Index
PSQI: Pittsburgh Sleep Quality Index;
PSS: Perceived Stress Scale
QOL: Quality Of Life
QST: Quantitative Sensory Testing
RA: Rheumatoid Arthritis
RERI: Relative Excess Risk due to Interaction
S: Synergy index
SAQ: Seattle Angina Questionnaire
SCL-90: Symptom Checklist-90
SD: Standard Deviation
SDQ: Shoulder Disability Questionnaire
SDS: Zung Self-Rating Depression Scale
SDSC: Sleep Disturbance Scale For Children
SF-12: Short-Form 12-Item Health Survey

SF-36: Health Survey Short Form – 36
SF-MPQ-2: Short-Form McGill Pain Questionnaire-2
SLBP: Subacute Low Back Pain
SNQ: Standardized Nordic Questionnaire
SPIKE: Structured Psychopathological Interview And Rating Of The Social Consequences For Epidemiology
SQS: Sleep Quality Scale
ST-DEP: State-Trait Depression Questionnaire
TBI: Traumatic Brain Injury
TLRs: Toll-like receptors
TMD: Temporomandibular Disorder
TMD: Temporomandibular Joint Disorders
TQTFSD: The Quebec Task Force On Spinal Disorders
USI: Uppsala Sleep Inventory
VAS: Visual Analogue Scale
WHO: World Health Organisation
YLDs: Years lived with disability

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1 INTRODUCTION

1.1 BACKGROUND

Chronic pain is one of the leading causes of healthcare seeking (1). It represents a considerable economic burden due to healthcare expenses and lost productivity (2,3). Chronic pain may cause physical impairment, such as disabilities and restrictions in daily activities, and psychological implications, such as anxiety and depression(4). Approximately half of the chronic pain patients meet the criteria for depression and experience depressed mood in a subclinical class(5). Furthermore, chronic pain interferes with social life and reduces the quality of life (6,7).

Pain is a psychophysiological perception in which somatosensory inputs convert into the physiological, cognitive, affective, and functional responses identified as pain (8). Identifying individual differences that contribute to the development and persistence of chronic pain and taking them into account, improves pain control and is, therefore, a high priority (9).

The International Association of Pain (IASP) estimates that up to 20 % of the European population suffers from chronic pain (10). Furthermore, one in every nine young adults experiences some type of chronic pain (11).

1.2 DEFINITION

Chronic pain is not a mere extension of acute pain. Instead, it may happen due to lack of the warning function of the physiological nociception system and maintains even when the initial pathogenetic and physical causes are gone; it can be explained by changes in central sensitization, altered pain modulation, glial activation, and neuroimmune signaling (12,13).

Chronic pain can be described as a negative emotional experience that is influenced by a combination of psychological factors through various inhibitory procedures.(14)

Until recently, chronic pain was defined by the International Association for the Study of Pain (IASP) (15) as pain persisting more than the normal healing time, which is an average of three months. "Normal healing time" can vary widely depending on the condition causing the pain; therefore, it is hard to ascertain a standard length of time for healing time. Another concern with this definition is that chronic pain, as the main symptom of many disorders, never reaches complete healing. For instance, rheumatoid arthritis is involved with long-term persistent pain because of continued tissue damage and deterioration. Chronic pain can appear where there is no existing or detectable pathology or damaged tissue (e.g., fibromyalgia). These issues led to an arbitrary

agreement between clinicians and researchers on the window of three months as the standard cut-off point, more than which the existing pain is considered chronic or persistent. Recently, an IASP Task Force was instrumented to add a code for chronic pain to the ICD-11 (WHO International Classification of Diseases 11th edition), to support the fact that chronic pain is a disease entity "in its own right"(15,16). Also, the IASP definition of pain itself was recently edited (in July 2020) (17), to state that pain is defined as: "An aversive sensory and emotional experience typically caused by, or resembling that caused by actual or potential tissue injury." The current version uses the term "aversive," instead of "unpleasant" to introduce a better image of subjectivity and personal experience of pain.

1.3 EPIDEMIOLOGY OF CHRONIC PAIN

Prevalence and incidence

Chronic pain is a major healthcare problem worldwide, impacting 19% of Europeans (18) and 20.4% of US adults (19). Globally, it has been estimated that 20% (ranging from 12% to 30%) of the population suffers from chronic pain 6,10. More specifically one in every nine young adults experience some type of chronic pain in life (11). A more recent study reported that age- and sex-standardized prevalence of pain was estimated to be 27.5% (ranging from 9.9% to 50.3%) worldwide (20).

A meta-analysis in the UK estimated the prevalence of chronic pain to range between 38.4% and 48.6%, with severely disabling pain affecting 10.4% to 14.3% of the adult population (21).

A National Health Interview Survey among US adults reported the prevalence of chronic pain and high-impact chronic pain (chronic pain that frequently limits life or work activities) to be 20.4% and 8%, respectively (19).

The prevalence of chronic pain was estimated to be 24.3% in the general population in Spain (22). However, other studies reported a prevalence ranging from 12% to 17.2% in this population (6,23). A more recent study showed that the prevalence is 16.6%, with higher figures in women and older participants (4). Another study compared 19 European countries and showed that the prevalence of chronic pain in Spain is 40.96%, 25.92%, and 26.31% for the back, upper, and lower parts of the body, respectively (24).

It is challenging to accurately determine the incidence of chronic pain because of a lack of longitudinal studies. However, it is estimated that approximately 1 in 10 adults are newly diagnosed with chronic pain yearly (25). In one region of the UK, the annual incidence of chronic pain has been estimated to be 8% per year in the older adult population (26). While in the older population in the Netherlands, this figure is 5.4% (27). However, in some specific subsamples, such as cancerous patients, the incidence of chronic pain was estimated to range from 13% to 28% during a 6-month follow-up period (28).

Impact of chronic pain

The impact of chronic pain can be devastating. More than 100 million adult Americans suffer from chronic pain, which is more than the population with diabetes, heart disease, and cancer altogether (29). Three main chronic pain conditions (back pain, musculoskeletal disorders, and neck pain) are among the four leading causes of years lost due to disability (30). Also, in 2017, the Global Burden of Disease report concluded that, among non-communicable diseases,

musculoskeletal pain is the third cause of disability-adjusted life years (DALYs) worldwide (31,32), while low back pain and neck pain are the second leading cause of years lived with disability (YLD) among young adults in all European countries (33).

The total national cost of back pain ranges between $71.6 billion in Germany and $259 million in Sweden each year, with indirect costs that include productivity loss and absenteeism, representing up to 92% of the total cost (34). Acute pain can help the individual to rest and take necessary care to prevent further damage to the body. However, it becomes of little evolutionary value if it transitions to chronic pain and persists (30). Pain is no longer just a symptom of injury or condition but has become an independent medical issue (35).

1.4 ETIOLOGY OF CHRONIC PAIN

The etiology of chronic pain is not entirely comprehended, and unlike acute pain, it does not have a protective role following evolutionary responses by warning of bodily harm (36). Chronic pain may arise after acute injuries, as part of degenerative diseases, or as a primary condition (e.g., migraine and fibromyalgia). However, there is general agreement that chronic pain is a multidimensional experience affected by biological, physiological, psychological, social, and contextual factors (37).

Pathophysiology

Pain can be modulated at the periphery or spinal cord level or from supraspinal areas. Two peripheral fibers transmit the pain signal to the spinal cord (A-delta and C fibers). There are two pathways transmitting signals from the spinal cord to the supraspinal area of the brain, which has a key role in pain processing: 1) the sensory pathway from lamina V, the neck of the dorsal horn of the spinal cord, to the hypothalamus and somatosensory cortex; and 2) the affective pathway from lamina I (also called the marginal zone) in the dorsal horn of the spinal cord to the hypothalamus, amygdala (responsible for the emotional-affective dimension of pain and pain modulation), and anterior cingulate cortex (ACC) (38–40).

Chronic pain may arise due to maladaptive changes in peripheral and central pain sensitization pathways, along with alterations in various important neurotransmitters, including dopamine, norepinephrine, and serotonin (41).

Factors influencing chronic pain:

1.4.2.1 Age

The prevalence of chronic pain, especially pain due to musculoskeletal causes, increases with age (31). The number of people living with chronic pain worldwide will increase as life expectancy and the likelihood of having harmful stimuli or injury that can trigger chronic pain increase. Common pain syndromes in older people include arthritis, lumbar spinal stenosis, and osteoporosis with fractures. However, chronic pain is not limited to older age groups; it can affect up to around 30% of the 18 to 39 years-old population (42).

1.4.2.2 Gender

Age-adjusted prevalence of chronic pain is higher in women (43,44). Men are less likely to experience or report chronic pain than women, and women report more severe and more anatomical

locations than men (43,45). Lower pain thresholds and tolerance in women than in men(46), different sensitivities to analgesia among women (47), the role of estrogens (48), and sex-specific genetic differences (49) can be the explanations for this difference suggested by research.

1.4.2.3 Genetic factors

It is still unclear why some individuals develop chronic pain while some do not and why pain becomes chronic only in some individuals. Genetic vulnerability to pain is a possible answer.

A review shows that genes can affect pain through overexpression or elimination of a gene that modulates the individual sensitivity to pain (10). A recent study concluded that genetic factors increase the risk of chronic pain regardless of the pain area (50). More genome-wide association studies (GWAS) are needed to understand the genetic basis of chronic pain.

1.4.2.4 Pregnancy

Opioid prescriptions in the first trimester of pregnancy increased by one-third from 1995 to 2009 for non-cancer pain diagnoses, indicating that pain syndromes during pregnancy are increasing(51).

It has been shown that low back pain is a frequent condition during pregnancy that starts between the fifth and the seventh month of pregnancy, and that low back pain and pelvic pain occur in 72% of pregnancies (52). Back pain during pregnancy is regarded as lumbar pain, pelvic pain, or a combination of both. Hip and foot pain are also typical during the perinatal period but are not been well investigated so far (53).

1.4.2.5 Race/ethnicity/culture

Ethnic differences in pain perception have been documented in a variety of clinical pain conditions, generally indicating that, for persistent pain complaints, African–Americans report greater pain and more pain-related disability when compared to Caucasians (54,55).

Physiological pain sensitivity in minority classes has been suggested as a contributing factor that might clarify the observed ethnic dissimilarities in clinical pain reports(56). Also, the prevalence of chronic pain and its related disabilities is higher in developing countries than in developed countries (57).

1.4.2.6 Occupation

Some occupations, such as healthcare workers, heavy manual workers, and occupations involving long-standing, physical weight loading, repetitive motion, and vibration, are associated with an increased risk of chronic back pain (58–60).

Myofascial chronic pain is more prevalent among office workers, musicians, and dentists, who conduct sustained low-level movements (61). Chronic pain has also been shown to be prevalent in soldiers, which is mostly related to deployment effects, including injuries, combat exposure, and mental health conditions (62).

Unemployed people who are not able to work because of health issues or disabilities are more at risk of having chronic pain than those who are employed (42).

1.4.2.7 Socio-economic status

The prevalence of chronic pain and its related disabilities is reported to be twice as high in low and middle-income countries as in high-income countries (63). Also, people with deprived socio-economic status (who have low levels of education, perceived income inequalities, and high levels of neighborhood deprivation) are more likely to experience chronic pain and report more severe pain and a greater level of pain-related disability than people from more affluent neighborhoods (64).

1.4.2.8 Smoking

Both current and former smokers have a higher prevalence and incidence of low back pain than never-smokers, and there is evidence of a dose-response relation between the number of cigarettes smoked per day and low back pain (65). Disc degeneration can justify this association via malnutrition of spinal disc cells by producing carboxyhemoglobin and hypoxia or vascular disease (66). In addition, smokers who experience chronic pain are more likely to be dependent on tobacco, smoke more cigarettes, and have more difficulty ceasing smoking than those who do not experience chronic pain (67).

1.4.2.9 Alcohol

The associations between alcohol consumption and pain have been considered curvilinear(68). Heavy alcohol consumption may be associated with an increase in the risk of chronic pain; however, low-to-moderate alcohol consumption may be associated with a lowered likelihood of developing chronic pain (69). In addition, evidence demonstrates that patients affected by fibromyalgia with low-to-moderate alcohol consumption had a better quality of life and physical functioning, fewer fibromyalgia symptoms, and fewer sick leaves from work than teetotalers (70).

Higher levels of pain perception among heavy drinkers might be related to maladaptive changes in the brain's reward systemthus reducing the pain threshold and enhancing nociceptive pain among them (71,72).

1.4.2.10 Physical activity

Moderate exercise and physical activity levels can prevent chronic pain by improving quality of life and physical functioning and by modulating physiological changes in the central nervous system (73). Moderate physical activity was associated with less frequent back pain than physical inactivity; however, a high intensity of physical activity is associated with a higher incidence of back pain when compared to moderate physical activity (74,75).

Policies for including physical activity in treatment programs for chronic pain management have formed to feature in national and international care guidelines (76). In a review, the authors concluded that aerobic exercise opposes the deconditioning cycle and is crucial in treating chronic pain because aerobic exercise induces analgesia. This analgesia effect was found to last up to 30 min after the individual had exercised at an intensity of more than 75% maximal oxygen uptake for 30 min (77).

1.4.2.11 Obesity

Obesity (a Body Mass Index > 30) is one of the independent risk factors of chronic pain. Obesity may increase the risk of chronic pain by inducing pressure on weight-bearing joints and conditioning lifestyle-related factors such as reducing physical activity (78). Also, obesity is potentially a marker of functional and psychological complications of chronic pain (79).

A survey in the USA demonstrated a linear growth in chronic pain cases as BMI increases. In that study, compared with normal-weight subjects, overweight subjects reported 20% higher rates of chronic pain (80). Obesity is mainly associated with low back pain, headaches, fibromyalgia/chronic widespread pain, and abdominal pain (81). Obesity appears to be related to daily consumption of palliatives, and obese patients were more likely to be taking opioids than normal-weight patients (82). Longitudinal studies revealed that obesity was a considerable risk factor (OR =2.5, 95% CI, 1.0–6.0) for developing chronic widespread pain, whereas normal-weight was associated with decreasing the prevalence of multisite pain (OR =3.7, 95% CI, 1.1–12.7) (82).

1.4.2.12 Sleep quality

There is a potentially complex reciprocal sleep-pain relationship across chronic pain disorders(83). However, recent studies indicate that sleep disturbance may contribute more tohe experience, development, continuation, and perception of chronic pain than *vice versa* (84).

Sleep disorders have been shown to affect 67-88% of chronic pain disorders (85,86), and at least 50% of patients with chronic pain had clinical insomnia (the most commonly diagnosed disorder of sleep impairment) (87). Sleep quality has been shown to predict chronic widespread pain symptoms over 15 months of follow-up (88).

Sleep disturbance changes μ and δ opioid receptor function in mesolimbic circuits (89), diminishes endogenous opioid levels and impairs the regulation of central opioid receptors (90). Also, poor sleep may alter central pain mechanisms, the process of the pain experience, and the pathophysiology of chronic pain, and influences not just the biological but also the behavioral and psychological mechanisms that may perpetuate the pain perception (91,92). Additionally, recent evidence suggests that improving sleep quality may alleviate the pain experience and consequently improve health outcomes and quality of life for those living with chronic pain conditions (92).

1.4.2.13 Depression and anxiety

The role of negative emotions in pain perception is well-documented. Negative emotional responses, such as anger or depression, can worsen the pain experience. Chronic anxiety has been shown to provoke a vicious cycle, which can complicate the experience of chronic pain(93).

The prevalence of severe depressive symptoms or mood disorders overreaches 50% in patients with chronic pain disorders, including fibromyalgia, chronic joint pain, chronic spinal pain, and chronic abdominal pain (94–97). Also, the prevalence of depression overreaches 20% in patients with arthritis, migraine headache, and pelvic pain (98,99).

The frequent co-existence of chronic pain and depression suggests the presence of shared pathways and risk factors in these two disorders (100). An indirect relationship between pain and depression through the influence of biopsychosocial factors should be considered(101). In a 6–12-month follow-up study of healthy subjects, neck or back pain incidence increased by 4% for every 1-point increase in the severity of depressive symptoms (102). This increase can be explained by increased activation within the ventral insula for processing emotions in depressed patients, shifting toward another insular region associated with processing pain stimuli (103,104).

The partial overlap of the symptoms of chronic pain and depression renders the distinction between these entities difficult. For example, subjects with chronic pain generally report fatigue(105), and fatigue is included as a symptom of depression, complicating the diagnosis of depression in chronic pain patients (106). Additionally, an expression of depression or depressive symptoms could be misclassified as chronic pain. For example, men often consider depression symptoms to indicate physical illness (107). In general, many people with depression seek treatment for somatic symptoms, including pain (108). Chronic pain and depression also share many risk factors, including female sex and low socioeconomic status.

Similarly, as explained above on depression, there is a bidirectional relationship between chronic pain and anxiety. Subjects with anxiety disorders are twice as likely to develop migraine headaches than individuals without such disorders (109). The neuroimaging studies suggest an overlap in the mechanism of anxiety and pain in the thalamus area of the brain, which gets activated by both chronic pain and anxiety (110,111).

1.4.2.14 Stress

Stress and chronic pain have a bidirectional relationship, in which chronic pain is influenced by stress, and also represents a stressor itself, causing poor functioning (112).

Among young adults, perceived stress is known to be associated with neck pain and headaches (113). Also, individuals with higher perceived stress related to their occupation have a higher risk of developing chronic neck, shoulder, and back pain (114–116). In addition, emotional distress (114) and early life stressors, such as child abuse, are associated with developing fibromyalgia and other chronic pain disorders (117,118). Subjects who reported stress for more than seven days in the past 12 months had a 60% higher risk of developing chronic pain (119).

Chronic stress reactivates this stress response repeatedly and might eventually trigger cortisol dysfunction (120). As cortisol is a critical anti-inflammatory hormone, this dysfunction results in the impairment of the inflammatory response (121,122). This can lead to systemic tissue degeneration and various symptoms, including chronic pain (120,123).

Adverse childhood experiences (ACEs) include physical, sexual, and emotional abuse, neglect, and household dysfunction early in life (124) and are associated with cognitive, social, and emotional impairment and chronic pain (125–127). Such physical or psychological traumas are one of the underlying mechanisms that increase Hypothalamic Pituitary Adrenal (HPA) activity due to increased stress (128,129), which has been observed in chronic pain patients and may impact pain responsivity (130). Cortisol is responsible for forming a rapid response to threats by maintaining high glucose levels. High levels of cortisol, which could be caused by chronic stress, have been associated with fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome (131).

1.4.2.15 Diet

Diet can influence pain sensitivity by modulating inflammatory processes (132). The western world, particularly that with lower socioeconomic status, consumes an excessive amount of unhealthy fats and sugars, which may produce serious health complications (133,134). The high-fat, high-sugar (HFHS) diet, which is known as the "Western Diet," results in reduced synaptic plasticity in the prefrontal cortex, impaired function in the amygdala and Hypothalamic Pituitary Adrenal axis, and may induce hyperalgesia (135,136). HFHS diets also have an imbalance of omega-6: omega-3 fatty acids. Omega-6 fatty acids increase prostaglandin synthesis and can activate Toll-like receptors (TLRs) (137,138). TLRs activate the immune system and sustain the

production of proinflammatory mediators (139), leading to sensitization of the central nervous system and contributing to hyperalgesia (140). On the other hand, omega-3 fatty acids inhibit TLRs, thus desensitizing the central nervous system and providing analgesic effects (138).

The ketogenic diet is suggested to induce analgesia (132), with the switch to ketone metabolism reducing reactive oxygen species (141,142) and increasing central adenosine and GABA, which are essential inhibitory neurotransmitters of the central nervous system. (143,144) Anti-inflammatory, calorie-restricted, and soy diets also induce hypoalgesia (145,146).

1.5 BIOPSYCHOLOGICAL MODEL FOR CHRONIC PAIN

Most chronic pain syndromes lack any physical explanation. Moreover, there is extensive evidence that psychosocial factors may be the main contributors to the progression of chronic pain. This suggests a Biopsychosocial Model that forms a paradigm for understanding chronic pain (6,10).

The biopsychosocial model is very useful for conceptualizing individual differences in pain and achieving personalized pain treatment. According to this model, an individual's experience of pain is formed by biological (e.g., genetic susceptibility, nutrition, and physiological functions), psychological (e.g., emotions, experiences, and personality), and social (e.g., environment, culture, interpersonal relationships, and socioeconomics) factors (147). The dynamic interactions between such factors lead to a unique scenery of how pain is stimulated, modified, and maintained in each individual (148). Understanding this scenery is essential for optimizing personalized treatment for the individual.

Overall, the biopsychosocial approach represents pain as a multidimensional, dynamic interaction among physiological, psychological, and social factors that reciprocally affect one another, resulting in chronic pain syndromes (29,149). In other words, the biopsychosocial model emphasizes 1) the pathophysiology involved in the initiation of nociception, 2) the involvement of the patient's cognitive and emotional state or psychological vulnerability (i.e., susceptibility to undesirable outcomes)(150), and 3) the conditioned responses that influence their pain experiences and subsequent behavior. From this perspective, examination, diagnosis, prognosis, and treatment of the patient with chronic pain require a comprehensive strategy that concerns and incorporates a broad range of psychosocial and behavioral factors in addition to the biomedical ones (151).

1.6 QUALITY OF LIFE AND CHRONIC PAIN

Definition of Quality of Life

The very old definition of quality of life (QOL) is presented by Lawton (152). He presented a comprehensive definition of QOL and called it the "good life" and stated that it was formed by "behavior competence, psychological well-being, perceived quality of life, and the objective environment." Katschnig was more explicit than Lawton 153. He remarked that QOL is "a loosely related body of work on psychological well-being, social and emotional functioning, health status, functional performance, life satisfaction, social support, and standard of living, whereby normative, objective and subjective indicators of physical, social and emotional functioning are all used." Harper and Power suggested a definition used by the World Health Organization (WHO) (154). They stated, "Quality of Life is the individual's perception of their position in life in the context of

culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns". These definitions give researchers a general insight into QOL; however, they do not clarify how the various factors mentioned within the QOL definition relate to each other.

Well-being is a closely connected and integral subjective part of QOL(155). The WHO QoL frame draws a comprehensive conception of well-being (156). Well-being, quality of life and health-related quality of life (HRQOL) are terms used in this thesis interchangeably, but they cover the same topic.

Quality of life measures

In quality of life (QOL) research, two objective and subjective measures are defined for quality of life. Objective measures refer to variables such as income, physical functioning, and the frequency of social relationships and can be measured by someone other than the participant. Subjective measures refer to cognitive determinations such as satisfaction in various life areas and can be answered by the participant only 157.

The QOL concept was first used in medicine in order to take into consideration aspects that are beyond the patients' disease. Medicine concentrates on health-related quality of life (HRQOL), which usually links to the effects of disease and somatic symptoms more than other aspects such as liberty, social support, and economic resources 158. Moreover, QOL is more connected to the definition of happiness and subjective life satisfaction than to objective situations such as bodily function. As Diener et al. (159) state: "People react differently to the same circumstances, and they evaluate conditions based on their unique expectations, values, and previous experiences." This perception is compatible with the results showing that the factorial structure of the WHOQOL was somewhat consistent across 15 countries with different cultural and economic backgrounds (160).

Quality of life and pain-related outcomes

Quality of life is a complex and multidimensional concept. Factors such as life satisfaction (161), social Support (162), affective experience (163), spirituality (164), financial stability (165), and physical functioning (166) work together to represent an overall judgment of QOL. From a multidimensional perspective, the psychological, social, and cognitive dimensions of quality of life and the interaction between them generate a metavariable that acts as a preventive factor for health and illness, which can be understood as an explanatory health factor beyond the absence or presence of disease (167).

Although there are many studies on the effect of chronic pain of quality of life and well-being, there is not much evidence on the effect of quality of life on chronic pain. However, it has been shown that positive well-being is associated with a reduced risk of physical illness and prolonged survival (168). Also, a better quality of life and well-being is relevant to the experience of chronic pain. On the other hand, pr well-being has been implicated in worse pain among patients with systematic sclerosis (169).

Well-being is a highly subjective concept; this fact highlights a mistaken belief that health can be correlated with the absence of illness and that well-being is equal to a lack of distress. Also, several studies have shown that psychological distress and well-being are better interpreted as different and independent dimensions (170).

1.7 MANAGEMENT OF CHRONIC PAIN

Based on the biopsychosocial model of health (171), the biopsychosocial approach is recommended as the best practice for managing chronic pain in all ages (172).

As mentioned, the biopsychosocial approach forms a complex and interrelated concept of biological, sociocultural, psychological, and cognitive factors that frame an individual's pain perception (see section 1.4). Therefore, the treatments are tailored based on an interdisciplinary clinical formulation for each individual (172).

IASP introduces interdisciplinary, multi-modal treatment that works towards the same biopsychosocial treatment goals (173). Healthcare professionals, including physicians, psychologists, physical therapists, and co-discipliners (e.g., nurses), should be involved in this chronic pain treatment approach (174).

Psychological treatments

The role of psychology in treating chronic pain is embedded in the biopsychosocial model for chronic pain. Although chronic pain has cognitive and affective consequences, psychological aspects can also influence the social and physical characteristics of pain.

Cognitive Behavioral Therapy (CBT) is the most commonly used psychological treatment (175) for chronic pain among young subjects (176). CBT aims to provide new cognitive and behavioral coping skills for chronic pain patients (149). This therapy is usually composite and can be associated with interrelated variables, including thoughts, emotions, behaviors, and bodily sensations (175). CBT typically includes a combination of relaxation exercises, behavioral activation, problem-solving, cognitive restructuring, and training coping skills (177), and also contains instructing self-management techniques, such as being focused on the goals, and sleep hygiene (178). Other psychological therapies include mindfulness, hypnotism, biofeedback (actively monitoring physiological activity) techniques, and acceptance and commitment therapy (ACT) (179). However, due to conflicting evidence, biofeedback is no longer recommended as the primary treatment of chronic pain for young people over 16 years old (180).

Pain education is essential in improving an individual's insight regarding persistent pain experience that does not indicate a dangerous situation for the body. Pain education can be considered part of CBT, as physical sensation is connected with the thoughts, emotions, and behaviors that contribute to the overall experience of pain (181).

Pharmacological treatments

Although pharmacological treatment is not recommended as an independent treatment for chronic pain (182), it is still required in pain management programs. This is because pharmacological medications reduce the pain intensity short term and enable patients to engage better with psychological and physiotherapy interventions.

Some medications used in other illnesses are effective in chronic pain, such as antidepressants and epilepsy medications. Still, even the most potent medications relieve pain by up to 35% for half of the users, indicating that exclusive use of medications can rarely relieve chronic pain (182). Depending on the etiology, the pharmacological management of pain can be different. For example, antidepressants (e.g., tricyclics or serotonin and norepinephrine reuptake inhibitors (SNRIs)) can be used for treating neuropathic pain (183). On the other hand, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (183) can be used to treat non-neuropathic pain. Other

medication may be helpful in some instances to help mitigate other symptoms of pain, specific to an individual; for example, melatonin may be used as a sleep assistance and can improve chronic pain indirectly (184).

Pharmacological protocol for treating chronic pain in young adults has been recently updated and states that medication management is not recommended except for antidepressants (185).
It has also been shown that those who misuse or overdose on medications are more at risk of distress (186). In addition, analgesic medications are inadequate for long-term intake, are addictive, and have severe adverse effects, which result in more pain (182).

2 OBJECTIVES

The relationship between chronic pain and some risk factors is ambiguous due to its bidirectional association. Alcohol consumption, quality of life or well-being, sleep quality, and depression are some of these factors that can be a consequence and a cause of health outcomes because of their multidimensional nature and their interrelations. Consequently, we conducted two systematic reviews and meta-analyses, as well as a prospective cohort study with the following objectives:

1. To determine, through a meta-analysis, the role of alcohol consumption in chronic pain occurrence.
2. To assess, through a meta-analysis, the role of sleep disturbance in the relationship between depression and the incidence of chronic pain
3. To assess the relationship between quality of life and chronic pain occurrence in a cohort study.
4. To assess, in a cohort study, the relationship between physical well-being, the following covariates: physical activity, sleep quality, perceived stress, smoking, and drinking, and chronic pain occurrence, and, in particular, to assess the role of mediator, confounder or interactor of each of the cited covariates.

3 METHODS

This chapter presents the contents of the following articles:

1) Association between alcohol consumption and chronic pain: A systematic review and meta-analysis (see section 3.1)

   Karimi R, Mallah N, Nedjat S, Beasley MJ, Takkouche B. Association between alcohol consumption and chronic pain: a systematic review and meta-analysis. Br J Anaesth. 2022;129(3):355-365.

2) Sleep Quality as a mediator of the relation between depression and pain: a systematic review and meta-analysis (see section 3.2).

   Karimi R, Mallah N, Scherer R, Rodríguez-Cano R, Takkouche B. Sleep quality as a mediator of the relation between depression and pain: Aa systematic review and meta-analysis. Br J Anaesth 2023. Accepted for publication on 15 January 2023

3) Quality of life and chronic pain: a cohort study among Spanish university students (see section 3.3)

   Karimi R, Mallah N, Prego-Domínguez J, Takkouche B. Quality of life and chronic pain: a cohort study among Spanish university students. Submitted to Affective Disorder on 29 September 2022

4) Causal variables, mediators, interactors and confounders of the association between physical well-being and chronic pain: results from a Spanish cohort study (see section 3.4)

   Karimi R, Prego-Domínguez J, Takkouche B. Causal variables, mediators, interactors and confounders of the association between physical well-being and chronic pain: results from a Spanish cohort study. Submitted to Am J Prev Med on 29 November 2022

SYSTEMATIC REVIEW AND META-ANALYSIS:

3.1 ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND CHRONIC PAIN

In this paper, using the PECO (Population, Exposure, Comparison, Outcome) framework, we sought to answer through a meta-analysis the question of whether men and women who drink alcoholic beverages, compared with teetotalers or occasional drinkers, are at increased risk for chronic pain.

We registered the protocol of this meta-analysis in The International Database of Prospectively Registered Systematic Reviews (PROSPERO), protocol number CRD42020166386. We carried it out according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (187).

Search strategy

We localized related studies by searching Medline, Embase, Conference Proceedings Citation Index - Science (CPCI-S), Open Access Theses and Dissertations (OATD), CINAHL, and the WHO Global Index Medicus (GIM) with its different regional databases - LILACS, AIM, IMEMR, IMSEAR, WPRIM - since inception until April 2021. In Medline, we used the search syntax: ((("chronic pain"[MeSH Terms]) OR ("fibromyalgia"[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR ("osteoarthritis"[Title/ Abstract]) OR ("migraine"[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract]) OR ("ankylosing spondylitis" [Title/ Abstract]) OR ("systemic lupus" [Title/Abstract]) OR ("headache"[Title/Abstract]) OR ("widespread chronic pain"[Title/ Abstract])) AND ((alcohol*[MeSH Terms]) OR (ethanol[MeSH Terms])) AND ((cohort) OR (prospective) OR (retrospective) OR (longitudinal) OR (case-control)).

We completed our search with free-text words, using broad concepts such as 'pain' and 'alcohol'. The search strategy was adapted to each of the other databases.

To supplement the search, we manually reviewed the reference lists of each study retrieved from the databases and those of related reviews (68,71). When necessary, authors of published studies were contacted for clarification or request for additional data (188,189).

This meta-analysis was carried out by 3 authors. The search was developed by all authors and was completed by two of them. One of the authors subsequently reviewed the strategy and the results were compared. Duplicates were removed.

Eligibility criteria

We included cohort and case-control studies that measured the association between chronic pain and alcohol consumption and provided effect measures (odds ratios [ORs] or incidence rate ratios [IRRs]) and their corresponding 95% confidence intervals (95% CIs) or sufficient data for their calculation. Participants were aged 18 years or above, with no age limit. Participants should have been exposed or non-exposed to alcohol consumption. Studies were included if the outcome was chronic pain conditions for at least three months with a clinical diagnosis or self-report. We included studies regardless of their publication date or language. Studies whose primary focus was an acute presentation of pain were excluded. Letters, commentaries, editorials, opinion pieces, cross-sectional, and *in vitro* or studies on nonhuman subjects were not further considered.

Data extraction and collection

Two authors independently screened the titles and abstracts obtained through electronic and manual search, selected studies for full-text review, reviewed those selected studies and extracted the data from eligible studies. Disagreements on the eligibility of the articles were resolved by consensus or with the help of a third author. Extracted data included author, year of publication, study location, study design, sample size, outcome, exposure measurement details, effect measures (OR or RR) and their 95% CIs, and adjustment, restriction, or matching factors. When adjusted effect measures were not available, we used crude effect measures.

Risk of bias in individual studies

To measure the risk of bias, we used those elements of the Newcastle-Ottawa scale that applied to our setting (190). Two authors performed the quality assessment independently. The detailed quality assessment scoring is presented in Table 3.1. Agreement between the two reviewers was assessed using Bland-Altman analysis.

We evaluated the following criteria. (1) Exposure ascertainment: if the alcohol consumption levels were described either quantitatively or by definite categories (1 point), else or unspecified (0 point). (2) Outcome ascertainment: chronic pain was determined using objective measures such as clinical evidence, report, or examination (1 point), else or unspecified measures (0 point). (3) Comparison group: (a) for case-control studies: subjects of the control group were representative of the source population from which the cases have been selected (1 point), else (0 point); (b) for cohort studies, the unexposed group was drawn from the same source population as that of individuals who consumed alcohol (1 point), else (0 point). (4) Participation rate: (a) for case-control studies: the participation rate was at least 80% for cases and controls (1 point), else (< 80% or unreported, 0 point). (5) Comparability: adjustment, matching, or restriction for age, sex, and smoking (1 point), else (incomplete control for the three variables or uncontrolled measurement) (0 point). The points attributed to each criterion were summed to obtain a quality score of a maximum of 5 points. The quality score variable was subsequently dichotomized into high quality (>3 points) and low quality (≤3 points).

Table 3.1 Quality assessment scoring of included studies in the association between alcohol and chronic pain meta-analysis

	Exposure assessment		Outcome assessment		Comparison group assessment		Participation assessment		Confounding assessment		Sum score		Mean score
	Rater1	Rater 2	Rater1	Rater2	Rater1	Rater2	Rater1	Rater2	Rater1	Rater2	Rater1	Rater2	
Beasley et al, 2016	1	1	0	0	1	1	0	1	1	1	3	4	**3.5**
Bergman et al, 2002	1	1	1	0	1	1	1	1	1	1	5	4	**4.5**
Ang et al, 2006	0	0	1	1	1	1	1	1	0	0	3	3	**3**
Wöber et al, 2007	0	0	0	0	1	1	1	1	1	1	3	3	**3**
Daoust et al, 2018	0	0	1	1	1	1	1	1	0	0	3	3	**3**
Hestbaek et al, 2006	0	0	0	0	1	1	1	1	1	1	3	3	**3**
Mundala et al, 2014	1	1	0	0	1	1	1	1	0	0	3	3	**3**
Muraki et al, 2012	0	0	0	0	1	1	1	1	0	0	2	2	**2**
Rivara et al, 2008	1	1	0	0	1	1	1	1	0	0	3	3	**3**
Skillgate et al, 2009	1	1	1	0	1	1	1	1	1	1	5	4	**4.5**
Parreira et al, 2017	0	0	0	0	1	1	1	1	0	0	2	2	**2**
McBeth et al, 2014	1	1	0	0	1	1	1	1	1	1	4	4	**4**
O'conner et al, 1992	1	1	0	0	1	1	1	1	0	0	3	3	**3**
Allaf et al, 2003	0	0	1	1	1	1	0	1	0	0	2	3	**2.5**
Boisset et al, 1995	0	0	1	1	1	1	0	0	0	0	2	2	**2**
Ryden et al, 1988	0	0	1	0	1	1	0	0	0	0	2	1	**1.5**

Statistical analysis

Pooled ORs and their 95% CIs were estimated by weighting the log ORs in case-control studies and log incidence rate ratios in cohort studies by the inverse of their variance. OR was considered an unbiased estimate of incidence rate ratio (191).

We calculated ORs for any intake, moderate intake, and high intake of alcohol. To compute an estimate for the category 'any intake' for a given study, we pooled the ORs of the categories moderate intake and high intake of this study whenever they were available.

The estimates of studies that did not provide data for different levels of alcohol intake but assessed alcohol intake on a yes/no basis were included in the 'any intake' group. Following the CDC definition, we considered the consumption of ≥15 drinks (a standard drink equal to 14 g pure alcohol) or more per week for men and eight drinks or more per week for women as heavy drinking (192). 'Alcoholism' (193), 'hazardous' drinking (194), and alcohol 'abuse' (195) were considered heavy drinking. Consumptions between 1 and 14 drinks per week for men and between 1 and 7 drinks per week for women formed the category of moderate drinking. When needed, we used the following category mid-points: no drinking, 0 drink per week; moderate drinking for males, 7 drinks per week; moderate drinking for females, 3.5 drinks per week; heavy drinking for males, 22 drinks per week; heavy drinking for females, 11 drinks per week.

Dose-response analysis

We quantified the dose-response association between alcohol consumption and chronic pain occurrence. In our setting, 'dose' represents the units of alcohol consumed per week. We undertook a dose-response meta-analysis using a one-stage mixed-effects model that considers heterogeneity across studies(196). First, we flexibly modeled the dose, using restricted cubic splines with three knots fixed at the distribution's 10th, 50th, and 90th centiles, and examined the departure of the second spline from linearity. We then transformed the dose into quartiles of alcohol doses and estimated the ORs and their 95% CIs using the first quartile as a referent.

Heterogeneity and random-effects model

Assessing the heterogeneity in meta-analysis is essential because the true heterogeneity (between studies variability) can affect the statistical model the author decides to apply to analyze the meta-analytic database. Therefore, when the studies' results only vary by the sampling error (non-heterogeneous case), a fixed-effects model can be applied to compute an average effect size. On the contrary, if the study results vary by more than the sampling error (heterogeneous case), then the author can apply a random-effects model to take into account both within- and between-studies variability or can decide to search for the source of heterogeneity through subgroup analysis (197,198). A random-effects model assumes the existence of measurement error beyond that due to sampling. When there is no heterogeneity (i.e. Ri or $I^2 < 50\%$), fixed-effects and random-effects models produce the same results (199).

Heterogeneity was checked using DerSimonian and Laird's Q test and quantified by calculating the proportion of the total variance attributable to between-study variance (Ri) (200). We computed both fixed- and random-effects models but used the latter in case of large heterogeneity. Heterogeneity was considered substantial if Ri >0.75. We investigated the source of heterogeneity by performing various subgroup analyses by study design, sex, pain location, and

geographic regions defined previously (197). Subgroup analysis was planned before the initiation of the meta-analysis.

Assessment of publication bias

We evaluated publication bias visually using a funnel plot (with the effect size on the horizontal axis and the standard error on the vertical axis) and, more formally, using Egger's regression test (201) and the trim-and-fill method (202). In a funnel plot, Small studies will appear towards the bottom of the graph and tend to be spread across a broader value of ranges, and large studies appear at the top and are closest to the mean effect; thus, the pattern forms a funnel shape. Furthermore, we conducted a sensitivity analysis assuming that the results of case-control studies are less likely to be published when they present no effect. Therefore, we recalculated the pooled OR under the following extreme assumptions: (1) the case-control studies obtained in our search represent only half of the studies ever conducted, (2) the unpublished studies found a null association (OR=1) between alcohol consumption and chronic pain, and (3) the average number of cases and control is similar in published and unpublished studies.

We conducted the analyses using the software HEpiMA version 2.1.3,35 and STATA version 15 (Stata Corp., College Station, TX, USA).

3.2 SLEEP QUALITY AS A MEDIATOR OF THE RELATION BETWEEN DEPRESSION AND PAIN

The present paper synthesizes the indirect effect of depression on pain via sleep disturbance. Specifically, we conducted a meta-analysis of longitudinal studies (i.e., non-cross-sectional studies). Using the PECO framework (Population, Exposure, Comparison and Outcome), we formulated our research question as follows: To what extent does sleep disturbance, self-reported or measured by a validated questionnaire, act as a mediator of the relation between exposure to depression and the outcome chronic pain, defined as pain in any site of the body that persists or recurs for longer than 3 months in a population of any age?

We registered this meta-analysis at Prospero (CRD42022338201) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines(187).

Search strategy

To identify relevant primary studies, we searched the following databases: MEDLINE, PsycInfo, Scopus, Conference Proceedings Citation Index (Web of Science), Open Access Theses and Dissertations (OATD), and WHO Global Index Medicus (GIM) with its five databases: African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), and Latin America and the Caribbean Literature on Health Sciences (LILACS). The general search strategy in Medline was: ((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) AND ((“sleep disorders”[Title/Abstract]) OR (“dyssomnias”[Title/Abstract]) OR (“insomnia”[Title/Abstract]) OR (“sleep apnea”[Title/Abstract]) OR (“narcolepsy”[Title/Abstract])) Filter: Observational studies. Similar strategies were used for the other databases. Table 3.2 shows the detailed search strategy. Each database was searched up until 21 May 2022. The search was not confined to specific countries or languages; reference lists from relevant articles were manually explored.

In case of queries regarding the data, the authors of published studies were contacted for clarification or additional data requests. The search was independently completed by two authors (RK and NM), one of the authors subsequently reviewed the strategy (BT), and the results were compared. Duplicates were removed.

Table 3.2 Search history (Status: updated on 21 May 2022)

Step	Databases	Search Strategy (Pubmed)	Results
1	**Search engines**		
	MEDLINE	**Depression-sleep disturbance-pain:** ((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) AND ((“sleep disorders”[Title/Abstract]) OR (“dyssomnias”[Title/Abstract]) OR (“insomnia”[Title/Abstract]) OR (“sleep apnea”[Title/Abstract]) OR (“narcolepsy”[Title/Abstract])) Filter: Observational studies	1227
	PsycInfo		1705
	Scopus		1047
	Global Index Medicus		107
		Sleep disturbance-pain: ((“sleep disorders”[Title/Abstract]) OR (“dyssomnias”[Title/Abstract]) OR (“insomnia”[Title/Abstract]) OR (“sleep apnea”[Title/Abstract]) OR (“narcolepsy”[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) Filter: Observational studies	
		Depression-pain:	

		((depress*[Title/Abstract]) OR (depression[Title/Abstract]) OR ("depressive disorder"[Title/Abstract]) OR ("mood disorder"[Title/Abstract]) OR ("depressive neuroses"[Title/Abstract]) OR (melancholia[Title/Abstract])) AND ((pain[Title/Abstract]) OR (fibromyalgia[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR (osteoarthritis[Title/Abstract]) OR (migraine[Title/Abstract]) OR (headache[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract])) Filter: Observational studies	
2	**Congress papers**		
	Conference Proceedings Citation Index (Web of Science)		75
3	**Dissertations**		
	Open Access Theses and Dissertations (OATD)		268

Eligibility criteria

The search was filtered for longitudinal studies only, and articles were screened based on their title, abstract, and full text. We included cohort and case-control studies that measured at least one of the associations between depression, pain and sleep disturbance on the condition that sleep disturbance and depression preceded pain. The included studies had to provide association measures [e.g., odds ratios (ORs) or incidence rate ratios (IRRs), Cohen's *d* or Hedges' *g*, or correlation coefficients such as Pearson's *r*], their corresponding 95% confidence intervals (95% CIs) or standard errors, or sufficient data for their calculation. Letters, commentaries, editorials, opinion pieces, *in vitro* studies, or studies on nonhuman subjects were excluded. Due to the impossibility of ensuring that exposure and mediation factors preceded the pain outcome, cross-sectional studies were excluded.

Subsequently, we performed a restricted analysis in which we excluded studies that assessed the relation between depression and sleep disturbance but did not assess pain.

Data extraction and collection

Two authors screened the titles and abstracts obtained through electronic and manual search, selected studies for full-text review, reviewed those selected studies and extracted the data from eligible studies independently. Discrepancies on the eligibility of the articles were resolved by consensus. Extracted data included the first author's last name, year of publication, study location (i.e., country), sample size (*N*), study design (i.e., cohort vs. case-control study), type of relation (i.e., depression-sleep disturbance, sleep-pain, or depression-pain), correlation coefficient *r*, outcome measurement tool, exposure measurement tools, and adjustment, restriction, or matching factors. When adjusted association measures were not available, we used crude association measures. When a single study provided estimates for different depression/sleep/pain variables, we used each estimate separately. We transformed all association measures to Pearson's correlation coefficient *r*.

Risk of bias (quality) assessment

The quality of eligible papers was independently evaluated by two authors, using an adapted version of the critical appraisal tool developed by Lee et al (203). and standard guidelines(204,205). As a result, a checklist of eight items, coded as 0=No or 1=Yes, was obtained (Table 3.3). The items were as follows: 1) a clear description of the objectives, 2) appropriate study design, 3) a representative sample, 4) psychometric characteristics of the mediator and outcome variables reported, 5) whether changes in the mediating variable preceded changes in the outcome variable, 6) whether changes in the predictor variable preceded changes in the mediator variable and outcome variable, 7) findings clearly described, and, 8) control for at least two main potential confounders (age and sex). Disagreements between reviewers were resolved by consensus, with the participation of a third reviewer when necessary. We categorized studies into low-quality (scores ≤ 6) and high-quality studies (scores > 6) for the subsequent subgroup analyses.

Table 3.3 Assessment of primary quality of studies included in the mediation effect of sleep disturbance on depression and pain meta-analysis

The following questions indicate different aspects of primary study quality and are coded with binary labels (*0=no, 1=yes*).

Q1= Is the hypothesis/aim/objective of the study clearly described? (i.e., objectives are formulated precisely, clearly, and comprehensively)?

Q2 = Is the study design appropriate to achieve the objectives?

Q3 = Is the study sample representative (i.e., participants are recruited from a representative setting that relates to the study's aims and hypotheses)?

Q4 = Were the psychometric characteristics of the mediator and outcome variables reported? (e.g., psychometric characteristics, such as reliability estimates or validity evidence, computed from the present study or a reference provided)

Q5 = Were statistically appropriate/acceptable methods of data analysis used?

Q6 = Did the study ascertain whether changes in the predictor or mediating variable preceded changes in the outcome variable?

Q7 = Are the main findings of the study clearly described? (Note: Simple outcome data should be reported for all major findings so that the reader can check the major analysis and conclusions.)

Q8 = Did the study control for possible confounding factors (i.e., variables that may impact results are identified and controlled for in the statistical analysis)?

Author/Year	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Sum score**
Bigatti et al. 2008	1	1	0	1	1	1	1	0	6
Riley et al. 2001	1	1	1	1	1	0	1	0	6
Toprak et al. 2019	1	1	0	1	1	0	1	0	6
Affleck et al. 1996	1	1	0	0	0	1	1	0	4
Agargun et al. 1999	1	1	0	1	1	0	1	0	5
Aili et al. 2018	1	1	1	0	1	1	1	1	7
Boardman et al. 2006	1	1	1	1	1	1	1	1	8
Breslau et al. 1996	1	1	1	1	1	1	1	1	8
Ediz et al. 2013	1	1	0	1	1	1	1	0	6
Edwards et al. 2008	1	1	0	1	1	1	1	1	7
Edwards et al. 2009	1	1	1	0	1	1	1	1	7
Ford et al. 1989	1	1	1	0	1	1	1	0	6
Generaal et al. 2017	1	1	1	1	1	1	1	1	8
Gupta et al. 2006	1	1	1	1	1	1	1	1	8
Halser et al. 2004	1	1	1	1	1	1	1	0	7
Jansson-Fröjmark et al. 2007	1	1	1	1	1	1	1	0	7
Kaila-Kangas et al. 2006	1	1	1	0	1	1	1	1	7
Kim et al. 2009	1	1	1	1	1	1	1	0	7
Kundermann et al. 2004	1	1	0	1	1	1	1	1	7
Lin et al. 2017	1	1	1	0	1	1	1	1	7

Magni et al. 1994	1	1	1	0	1	1	1	1	7
Mork et al. 2012	1	1	1	0	1	1	1	1	7
Morphy et al. 2007	1	1	1	1	1	0	1	0	6
Nitter et al. 2012	1	1	1	1	1	0	1	1	7
Pilowsky et al. 1985	1	1	1	1	1	0	1	0	6
Quartana et al. 2010	1	1	0	1	1	0	1	0	5
Rasmussen et al. 2014	1	1	1	1	1	0	1	1	7
Sanders et al. 2016	1	1	1	1	1	1	1	1	8
Sayer et al. 2002	1	1	1	1	1	0	1	0	6
Skarpsono et al. 2021	1	1	1	1	1	1	1	1	8
Smith et al. 2008	1	1	1	1	1	0	1	1	7
Strutz et al. 2019	1	1	1	1	1	0	1	1	7
Uhlig et al. 2018	1	1	1	1	1	1	1	1	8
Walton et al. 2016	1	1	0	1	1	0	1	0	5
Wiklund et al. 2019	1	1	1	1	1	0	1	1	7
Yabe et al. 2021	1	1	1	1	1	0	1	1	7
Brander et al. 2003	1	1	1	1	1	1	1	1	8
Carroll et al. 2004	1	1	1	1	1	1	1	1	8
Daly et al. 2017	1	1	1	1	1	1	1	0	7
Datema et al. 2018	1	1	1	1	1	0	1	1	7
Kim et al. 2011	1	1	0	1	1	1	1	1	7
Kroff et al. 1993	1	1	1	1	1	0	1	1	7
Larson et al. 2004	1	1	1	1	1	0	1	1	7
Lautenbacher et al. 1999	1	1	0	1	1	1	1	0	6
Leino et al. 1993	1	1	1	1	1	0	1	1	7
Lopez et al. 2017	1	1	0	1	1	1	1	0	6
Mommersteeg et al. 2016	1	1	1	0	1	1	1	1	7
Palomo-Lopez et al. 2019	1	1	1	1	1	0	1	1	7
Peker et al. 2021	1	1	1	1	1	0	1	1	7
Pietri-Taleb et al. 1994	1	1	1	1	1	0	1	1	7
Pinheiro et al. 2017	1	1	1	1	1	1	1	1	8
San-Antolin et al. 2020	1	1	0	1	1	0	1	1	6
Sinikallio et al. 2007	1	1	1	1	1	0	1	0	6
Suffeda et al. 2016	1	1	1	1	1	0	1	0	6
Suri et al. 2016	1	1	0	1	1	0	1	1	6
Vranceanu et al. 2010	1	1	1	1	1	0	1	1	7
Wolfe et al. 2020	1	1	1	1	1	0	1	1	7
Young et al. 2008	1	1	0	1	1	1	1	1	7
Zautra et al. 2001	1	1	1	1	1	0	1	0	6
Mannion et al. 1996	1	1	1	1	1	1	1	0	7

Data analysis

For a long time, meta-analysis has been focused on representing single effects, and this practice had “severely limited its capacity to contribute to one of the most fundamental tasks of science --- the development of explanatory theories.” (206). It has been suggested that researchers should conduct “causal mediating modeling“ (using path analysis techniques and structural equation modeling (SEM) techniques) to address this issue.

As a general description of these techniques, Cheung and Chan(207,208) used the term “Meta-analytic Structural Equation Modeling (MASEM)”. Usually, there are two steps involved in MASEM: the first step is the synthesis of correlation coefficients across studies; the second step is to apply structural equation modeling techniques to explore the relationship among variables using the pooled correlation matrix (208). Cheung and Chan called this method the “Two-stage Structural Equation Modeling“ (TSSEM) approach. When there are incomplete data, they are handled by the use of the full information maximum likelihood (FIML) in the analysis which has been shown to produce unbiased parameter estimates and standard errors under MAR and MCAR (209).

To synthesize the correlation matrices across studies and perform structural equation modeling, we used a TSSEM approach (210). In stage one, we pooled the correlation matrices using a multivariate random-effects model with maximum-likelihood estimation, accounting for the dependence between multiple correlations within studies (207,211). In stage two, we specified and estimated a structural equation model using the pooled correlation matrix and the total sample size as input. This model quantified the indirect effect of sleep disturbance, along with all possible direct effects.

Figure 3.1 displays the proposed mediation model. The corresponding path coefficients are labelled as "a" (depression and sleep disturbance), "b" (sleep disturbance and pain), and "c" (the direct effect of depression on pain). The direct, indirect (path a*b), and total (c + a*b) effects were obtained from the output of TSSEM in stage 2. In case of partial mediation and the same sign of direct and indirect effects, the variance accounted for by the indirect effect (*VAF*) represents the ratio of the indirect effect of depression on pain via sleep disturbance and the total effect of depression on pain (212):

$$VAF = \frac{\text{Indirect effect}}{\text{Total effect}}$$

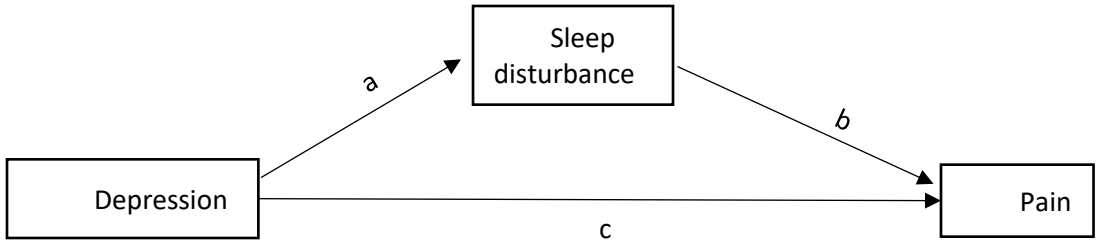

Figure 3.1 Hypothesized mediation model.
Note. Path "a" = Effect of depression on sleep disturbance; path "b" = Effect of sleep disturbance on pain; path "c" = Direct effect of depression on pain controlling for sleep disturbance.

We estimated the I^2 statistic and performed the heterogeneity test based on the Q statistic to quantify heterogeneity in correlations(197). Finally, we evaluate the potential sources of any significant heterogeneity, conducting subgroup analyses based on extracted covariates (213). To test the robustness of our findings, we further restricted the analysis to the studies that presented data on pain and excluded studies that presented data on sleep disturbance and depression only (214–220) .

We performed TSSEM using the R package "metaSEM" version 1.2.3 (221), and assumed that missing correlation coefficients within studies were missing at random (MAR). TSSEM handles these missing coefficients via the full-information maximum-likelihood procedure under MAR(222). However, researchers suggested that missing not at random data affects the precision of the correlations and the model parameters at the second stage of MASEM (223).

We used STATA version 14.0 (StataCorp, 2015) to check for publication bias using the funnel plot and Egger's regression test. The R codes used for this meta-analysis is available at osf.io/9ekwg.

Certainty of evidence

The assessment of the certainty of the evidence was conducted under the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines (Table 4.6) (224). With this approach, evidence can be rated down due to the risk of bias, indirectness, imprecision, inconsistency, or publication bias. We considered measures of association between depression-sleep disturbance, depression-pain, and sleep disturbance-pain to be imprecise when the majority of studies´ effect measure and confidence interval included 0 for risk difference measures or 1 for risk ratio measures. We considered evidence to be indirect if more than 20% of contributing studies did not measure exactly depression, sleep disturbance, or pain lasting more than three months and instead measured alternatives. If there were considerable heterogeneity, the consistency was rated down. The risk of bias was evaluated based on the quality appraisals of the studies; if the majority of the studies had low quality, the grade was down rated. If both inconsistency and imprecision were present, we only rated down the certainty of evidence one level. We followed the GRADE guidance for communicating our findings.

COHORT STUDIES PART 1 AND 2:

STUDY SAMPLE AND PROCEDURE

This work is part of the ongoing Online Pain, Lifestyle, and Diet Multicenter cohort project, a web-based study aiming to identify risk factors for chronic pain in a young population that involves Spanish, Iranian, and Moroccan university students.

The present work focuses on the students at the University of Santiago de Compostela, Spain, home to approximately 25,000 students. From February 2019 through April 2020, the participants completed a baseline questionnaire on demographic measures, such as age, sex, marital status, height, and weight; lifestyle factors such as sleep quality, physical activity, and diet; medical factors such as current comorbidities or history of diseases; psychological factors such as perceived stress, social readjustment rating, core self-evaluation; quality of life or well-being as a biopsychosocial factor; and dietetic aspects, as well as pain measurements. Quality of life or well-being has been considered the main exposure *(Exposure assessment)* in the cohort study and the rest of the variables were considered as the covariates (*Covariate assessment)*. All participants were asked about pain at a range of bodily sites that lasted more than three months, at baseline and follow-up assessment *(Outcome assessment).* Subsequently, the participants were followed up every four months for one year.

The web-based baseline and follow-up questionnaires were previously validated in the Spanish population. In addition, the baseline questionnaire was pilot-tested in the study population before the study initiation. Those individuals who participated in the pilot test did not form part of the cohort study.

The data obtained from each student were anonymous, and the various questionnaires answered by the same participant were linked to each other using the ID number specified to each email address they provided. Informed consent was obtained from all individual participants included in the study. The University of Santiago de Compostela institutional review board approved this study (reference BT-RDC-2017-01).

Two-thousands university students, contacted through their academic email addresses, were invited to participate in the study. The sample size was estimated using the following assumptions: power of 0.90, Incidence Rate Ratio (IRR) of chronic pain to be detected = 1.5, type 1 error rate of 0.05, and an expected probability of the event in the unexposed population of 0.10.

EXPOSURE ASSESSMENT

We used the short-form 12-item health survey (SF-12) to evaluate Health-Related Quality of Life (HRQoL) in the past four weeks of the baseline. SF-12 generates two 0–100 component scores: physical component subgroup (PCS) and mental component summary (MCS). The reliability and validity of the SF-12 in the Spanish population have been well documented (225) , and its internal consistency coefficients were close to 0.9 (226) . Participants completed the SF-12 at baseline, and PCS-12 and MCS-12 scores were calculated using algorithms and recommended coefficients developed by Ware et al. (227). Scores between 0 and 100 were generated, with higher PCS and MCS scores indicating better quality of life or well-being.

In the first part of the Pain Study Online Cohort, we considered PCS and MCS as the main exposures and categorized then in four quartiles. However, in the second part of this cohort study we considered only the PCS as the main exposure, which is known as physical well-being in this

thesis. For the purposes of that part we transformed the calculated scores into a binary variable, lower/higher than the first quartile.

OUTCOME ASSESSMENT

We instructed participants to record on a calendar any episode of pain they might suffer. In the follow-up questionnaires sent every four months, students were asked to report whether they had had recurrent pain for at least three months in the past four months. The outcome was defined, using the International Association for the Study of Pain (IASP) definition (228), as pain at any part of the body that lasts more than three months, and was assessed by the question: "In the past four months, did you have pain that lasted for more than three months?". If the answer was "yes" participants had to specify which part of their body was concerned with chronic pain, and answer the validated Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) (229). This questionnaire consists of 22 pain descriptors that participants score on a 0–10 numerical scale according to the severity of their pain episode. SF-MPQ-2 has been validated in the general population in Spain and had a correlation coefficient higher than 0.9 between scale and rank values (229).

The baseline was formed by subjects without any regular pain for more than three months who were followed for one year.

COVARIATE ASSESSMENT

We collected covariate information at baseline. In the first part the covariables included age, sex, height, weight, comorbidities, smoking status, alcohol consumption status, sleep quality, perceived stress, and physical activity. In the second part, we considered age, sex, smoking status, alcohol consumption status, sleep quality, perceived stress, and physical activity as the covariables.

Demographic characteristics (age and sex) and lifestyle habits were collected at baseline using a self-administered and validated questionnaire.

Smoking status was divided into three categories: current smokers (subjects who smoked more than one cigarette per week in the past six months), former smokers (subjects who previously smoked at least one cigarette per week but had quit more than six months ago), and non-smokers (subjects who have not smoked any cigarette). In the first part we used the variable with three categories current smokers, former smokers, and non-smokers. In second part, we combined non-smokers and former smokers into one binary variable with the categories: "non-current smokers" and "current smokers".

We calculated the daily alcohol consumption from the food frequency questionnaire administered to the participants (230). Based on the categorization used by the Centers for Disease Control and Prevention, low- or non-drinkers were subjects who drank alcohol less than once a day for women and less than twice a day for men. Moderate drinkers were those who drank alcohol once a day for women and twice a day for men, and heavy drinkers were those who drank alcohol more than once a day for women and more than twice a day for men(192) . Subjects with an intake higher than moderate were exceptional in our population (10 subjects only) and, therefore, were excluded them from the second part.

Sleep quality was assessed using the Petersburg Sleep Quality Index (PSQI). The calculated scores, ranging from 0 to 21, with lower scores indicating higher sleep quality. Sleep Quality was divided into two categories, using the suggested cut-off value of 5 in the first part. In the second part, it was divided into two categories, using the cut-off value of 6, the median score of the sample (231).

A score of physical activity was obtained using the short form of the International Physical Activity Questionnaires (IPAQ-SF) to define low, moderate, and high level of physical activity based on pre-established algorithms (232). However, in the second part we combined moderate and high groups to have a dichotomous variable of low and high activity.

In both part, the level of perceived stress was considered a dichotomous variable, either lower or higher than 8, the median score obtained from the Perceived Stress Scale questionnaire (PSS-4) (233).

Body Mass Index (BMI) was used in the first part calculated as weight (kilograms) divided by height (meters) squared.

3.3 COHORT STUDY PART 1: QUALITY OF LIFE AND CHRONIC PAIN

Statistical analysis

Person-time was calculated from the date of completion of the baseline questionnaire until the occurrence of the chronic pain episode, loss to follow-up, or end of the study, whichever occurred first. We assumed a constant incidence of chronic pain between follow-ups.

We used Poisson regression models to estimate the IRR of the association of chronic pain with physical and mental components of QoL in each quartile and their 95% confidence intervals (CIs). We used a directed acyclic graph to identify the role of covariates and potential confounders (234). We assumed QoL to be a relatively stable factor over time, and some variables were treated as mediators (Figure *3.2*). Covariates that changed the original IRR estimates of the association between chronic pain with MCS and PCS by more than 10% when they were introduced in the model were assumed to be confounders and were kept in the final model (235).

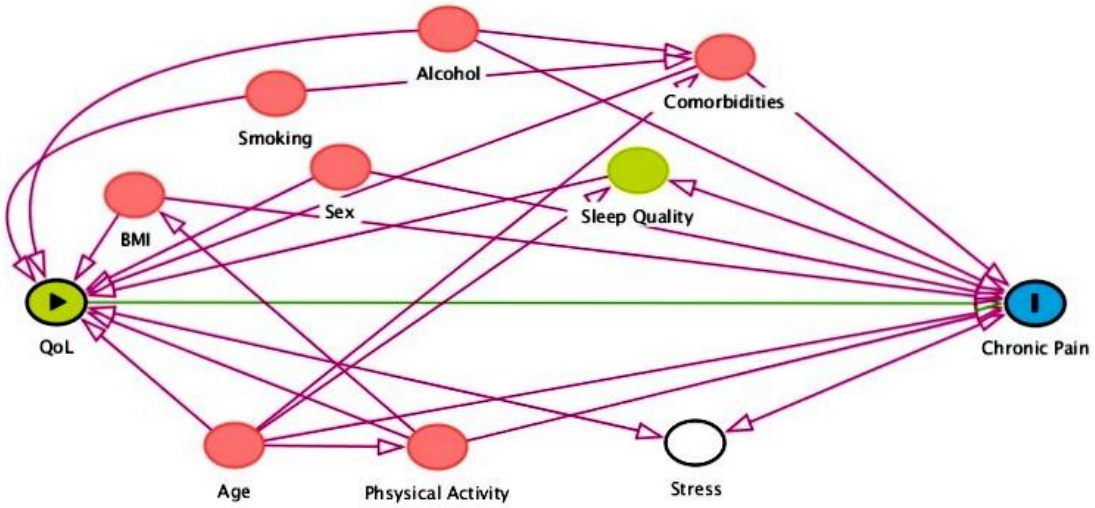

Figure 3.2 Directed Acyclic Graph of the Relation Between Quality of Life and Pain Incidence, Pain Study Online, Spain, 2019-2020.

Furthermore, we used restricted cubic spline analyses to assess the relation between MCS and PCS continuous scores and pain incidence. The reference level for this analysis was the minimum score of each subgroup (MCS score: 7.75, PCS score: 31.72). We set 4 knots at the 10th, 25th, 75th, and 90th percentiles.

All analyses were performed with STATA/MP software version 15.1 (Stata Corp LLC, Tx, USA).

Sensitivity analysis:

We generated 40 imputation data sets using multiple imputations by chained equations (MICE) to impute missing values in exposure, covariate, and outcome variables. We then repeated each Poisson regression analysis carried out on the complete-case analysis(236).

Furthermore, we used Inverse-probability weighting (IPW) to recalculate the estimates, correcting any possible differential attrition during follow-up. We used a combined method of multiple imputations (MI) and IPW (MI/IPW) developed by Seaman et al.(237). First, study continuation was defined as a binary variable in which participants who had not completed the follow-up period and had not reported any episodes of pain during the study were considered to be lost to follow-up. Second, missing values of the dataset were multiply imputed. Third, a logistic regression model was applied with baseline variables to calculate the predicted probability of study continuation as the dependent binary variable. Finally, we used the inverse of the predicted probabilities as a weight in a subsequent Poisson regression model(238).

In addition to MI and IPW analyses, we recalculated the IRRs in two extreme scenarios as another method to address loss to follow-up. We first assumed that all participants lost to follow-up developed chronic pain, and then, we assumed that none of those participants developed the disease.

3.4 COHORT STUDY PART 2: CAUSAL VARIABLES, MEDIATORS, INTERACTORS AND CONFOUNDERS OF THE ASSOCIATION BETWEEN PHYSICAL WELL-BEING AND CHRONIC PAIN

This part of the thesis is a continuation of the Pain Study Online cohort with a focus on the physical component subgroup of quality of life known as physical well-being and the role of covariates in its effect on chronic pain incidence.

The details of study sample and procedure of cohort study is explained in *COHORT STUDIES PART 1 AND 2*:.

Measures of association

Person-time was calculated as the time elapsed from the date of filling out the baseline questionnaire until the onset of a chronic pain episode, loss to follow-up, or end of the study, whichever appeared first. Cases of chronic pain were allocated half of the period between the last follow-up and the onset of the episode, assuming constant incidence during that period.

To examine the relation between physical well-being and chronic pain occurrence, incidence rate ratios (IRR) and their 95% confidence intervals (95% CI) were estimated by Poisson regression.

We used Directed acyclic graphs (DAGs) to represent our hypothesis and assumptions regarding the causal relationship between physical well-being and chronic pain (Figure *3.3*). Two

types of covariates that are considered in our models are confounders (variables that shared causes of the exposure and outcome), and mediators (variables that transmit some of the effect of interest through an indirect pathway). Colliders (variables that are caused by the outcome and the exposure) were not considered further due to the longitudinal design of our study that forces exposure and covariates to precede outcome. We also represented interaction covariates (also known as interactors or moderators), which are variables that interact with exposure to affect the outcome. Since DAGs are nonparametric representations, interactors/moderators are depicted in the same way as confounders, however we distinguished the interactors from confounders when we translated the DAG into a statistical model, using stratum-specific analysis (see section 0).

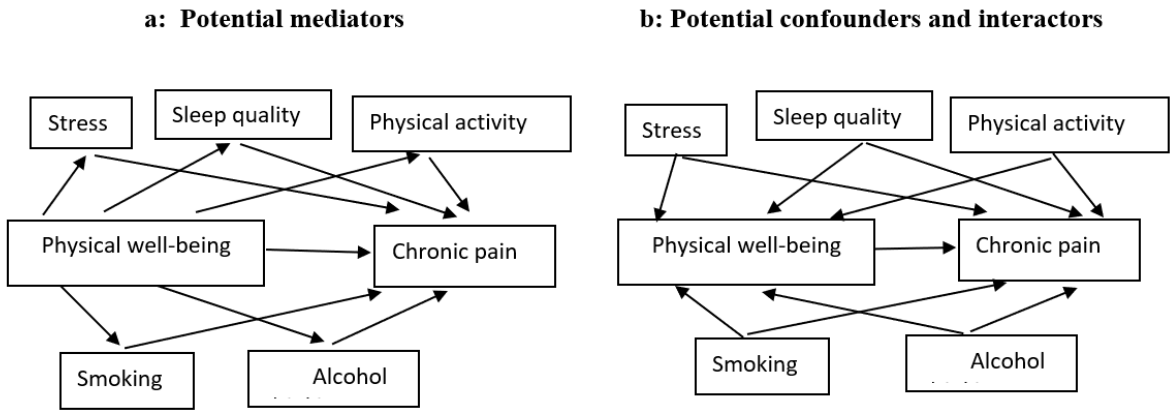

Figure 3.3 A hypothesized causal diagram of the model with covariates of the association between physical well-being and chronic pain.

Mediation analysis

We used General Structural Equation Modeling (GSEM) to test whether the potential mediators (physical activity, perceived stress, sleep quality, smoking status, and alcohol consumption) may represent indirect causal paths between physical well-being (main exposure) and chronic pain (Figure 3.3 a.). We first estimated the model parameters and causal effects, including Natural Direct Effect (NDE), Natural Indirect effect (NIE), and Total Effect (TE): The indirect effects were generated by multiplying the estimated regression coefficient of physical well-being on each mediator by the regression coefficient of each mediator on chronic pain (239). The direct effects were generated by the regressions of the association between physical well-being and pain perception. Finally, the total effects comprised a sum of direct and indirect effects captured in the GSEM analysis (240). We calculated the proportion mediated as $(IRR_{NDE} \times [IRR_{NIE} - 1])/(IRR_{NDE} \times IRR_{NIE} - 1)$.

Stratum-specific analysis

In order to distinguish confounding from interaction (Figure *3.3* b.), we measured the relation between physical well-being and pain in the different strata of each covariate separately (perceived stress, smoking, alcohol consumption, and sleep quality). If the crude overall estimate and the stratum-specific estimates were similar, the covariate was considered neither a confounder nor an interactor. If the stratum-specific measures of association were *similar* to each other, but differed from the overall crude estimate by 10% or more (235), we considered this covariate as a confounder. If the stratum-specific estimates *differ* from each other, we consider this covariate as an interactor. There is both confounding and interaction if 1) the stratum-specific estimates vary from each other and ***both*** have higher or lower values than the crude estimate, or 2) the stratum-specific estimates differ from each other, and the crude estimate is *between* the two stratum-specific estimates. In the latter case, we adjusted the Poisson regression estimate for the covariate to find out whether the adjusted estimate differs in more than 10% from the crude estimate. Those covariates that changed crude IRR estimates by more than 10% were considered both confounders (235) and interactors. If the crude estimate did not differ by more than 10%, we considered the covariate to be only an interactor.

Interaction analysis

After performing the stratum-specific analysis and deciding on the confounding and interactional nature of the covariates, we performed an additive interaction analysis for the variables that were not potentially eligible as confounders of the association between physical well-being and chronic pain.

Additive interaction analyses between physical well-being and each covariate were performed to measure the joint effects of the combination of two potential risk factors (241). For each physical well-being–covariate relation, we computed the adjusted Relative Excess Risk due to Interaction (RERI), also named Interaction Contrast Ratio (ICR), the Attributable Proportion (AP), and the Synergy index (S) along with their 95% CIs (241,242).

RERI is interpreted as the additional risk due to interaction added to the total risk expected by summing the risks of each exposure separately. The AP is interpreted as the proportion of the outcome due to the interaction of both exposures. Accordingly, a RERI and AP >0 imply a deviation from additivity and provide evidence that the exposure and the covariate may have a joint effect in causing the outcome (243). The low-risk groups were considered as the reference category. However, since moderate alcohol consumption is known to exert analgesic effects (69), in this study, we considered moderate alcohol consumption as the reference category. The joint effect analyses were adjusted for age and sex. We used Poisson regression to estimate IRRs of chronic pain and their 95% CIs for interaction analysis.

All the analyses were conducted on multiply imputed data. In this study, to generate more precise estimates, we imputed the missing data first, and then performed the analysis and bootstrapping as explained hereafter (244). Ten imputed data sets were generated via Multiple Imputation by Chained Equations (MICE), and a fitted conditional imputation model was obtained for each variable used for imputation. The analysis was replicated for each multiply-imputed data set, and the estimates were pooled from the ten imputed data sets(245). We used bootstrap resampling to calculate the mean point estimate for the parameters by repeating the mediation analysis across 1000 bootstrapped data sets (246). Bias-corrected and accelerated 95% CIs were calculated to assess skewness in the confidence interval obtained from mediation analysis (247).

All analyses were performed with STATA/MP software version 15.1 (Stata Corp LLC, Tx, USA).

4 RESULTS

4.1 ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND CHRONIC PAIN

Study characteristics

The process of study localization is summarized in Table 4.1. Sixteen studies, 13 cohort studies (189,193,194,248–257) and 3 case-control studies (195,258,259), examined the association of alcohol consumption with chronic pain and met the inclusion criteria of this meta-analysis (Table 4.1 and Figure 4.1) The study by Beasley et al. included a cross- sectional analysis carried out within a well-defined cohort study (249). This study was then considered as a cohort study. In a secondary analysis, this study was excluded to check whether it represented an influential point.

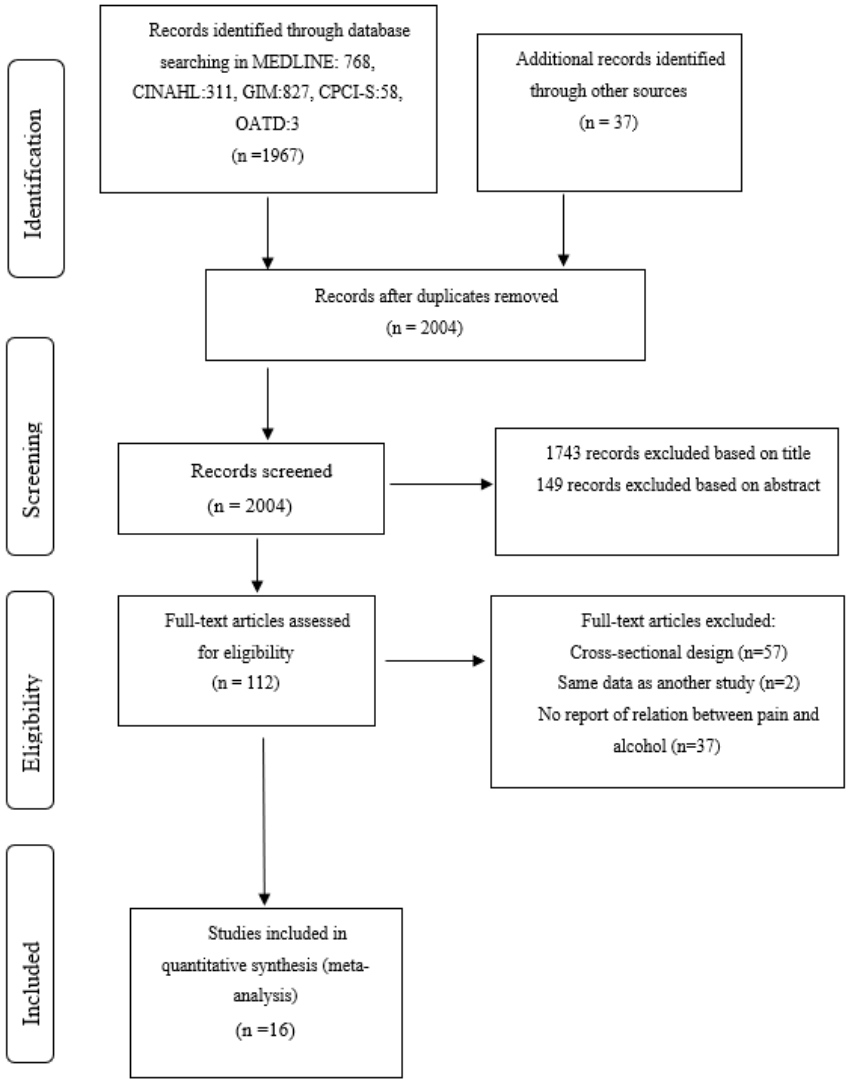

Figure 4.1 Flow diagram of the selection of studies of alcohol consumption and chronic pain

Table 4.1 Main characteristics and odds ratios of any drinking, moderate drinking, and heavy drinking of included studies

Author, Year	Country	Setting	Study size or #cases/#controls	Any drinking OR (95%CI)	Moderate drinking OR (95%CI)	Heavy drinking OR (95%CI)	Adjustment, restriction, or matching variables	Outcome
Cohort studies								
Daoust et al, 2018	Canada	Adults from trauma center	95134	1.41 (1.18–1.69)	--	1.41 (1.18–1.69)	Age, health insurance, follow-up duration	Post injury pain
Parreira et al, 2017	Australia	General male population > 70yrs	1685	1.00 (0.30-3.37)	1.00 (0.32-3.58)	1.00 (0.03-60.48)	Sex, socio-demographic and lifestyle factors, comorbidities	LBP
Beasley et al, 2016	UK	General population 40-69yrs	500000	0.45 (0.43-0.48)	0.50 (0.46-0.56)	0.44 (0.42-0.47)	Age, sex, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status	CWP
McBeth et al, 2014	UK	General population > 50yrs	4326	0.98 (0.93-1.02)	0.75 (0.63-0.88)	1.00 (0.91–1.05)	Age, sex, education, social networks, smoking, anxiety, BMI, health impairments	CWP
Mundal et al, 2014	Norway	General population > 20yrs	19192	0.85 (0.77-0.94)	--	--	Age, sex, marital status, education, exercise, chronic disease at baseline	CWP
Muraki et al, 2012	Japan	General population 23-95yrs	2262	0.91 (0.73–1.14)	--	--	Unadjusted	Knee pain
Skillgate et al, 2009	Sweden	Occupational population	6532	0.76 (0.57-1.02)	0.76 (0.57-1.02)	--	Age, sex, pain intensity, SES, quality of life, other diseases, exercise, sleep, BMI, snuff use, geographical area	LBP
Rivara et al, 2008	USA	Subjects with injuries 28-84yrs	3047	0.74 (0.61-0.89)	0.85 (0.67-1.09)	0.60 (0.44- 0.81)	Age, sex, ethnicity, education, preinjury health, comorbidity, illicit drug use, depression, activities of daily living, injury characteristics	Post injury pain

Continue of the Table 4.1

Author, Year	Country	Setting	Study size or #cases/ #controls	Any drinking OR (95%CI)	Moderate drinking OR (95%CI)	Heavy drinking OR (95%CI)	Adjustment, restriction, or matching variables	Outcome
Wöber et al, 2007	Austria	Migraineurs >18yrs	327	0.62 (0.57-0.67)	--	--	Age, sex, marital status, number of children, education, occupation, comorbidity, lifestyle, smoking, nutrition	Headache
Ang et al, 2006	USA	Gulf war veterans	370	0.20 (0.10-0.60)	--	--	Age, sex, race, marital status, income, military status	LBP
Hestbaek et al, 2006	Denmark	Twin registry 12-22yrs	6554	0.82 (0.61-1.10)	0.87 (0.61–1.23)	1.25 (0.76–2.06)	Age, sex, smoking, BMI	CWP
Bergman et al, 2002	Sweden	General population 20-74yrs	2425	0.65 (0.43–0.98)	0.81 (0.49–1.35)	0.42 (0.21–0.85)	Age, sex, SES, education, emigrant status, smoking, family history of chronic pain	LBP
O'Connor et al, 1992	USA	Men newly enlisted in the Army.	160	1.23 (0.57-2.63)	0.99 (0.40-2.41)	2.21 (0.46-9.56)	Sex	CWP
Case-control studies								
Al-Allaf et al, 2003	UK	Hospital	40/37	0.10 (0.03-0.29)	0.10 (0.03-0.29)	--	Age, sex	Fibromyalgia
Boisset-Pioro et al, 1995	Canada	Hospital and private office	83/161	1.64 (0.74-3.64)	--	1.64 (0.74 - 3.64)	Sex	Fibromyalgia
Ryden et al, 1988	USA	Hospital employees	84/168	1.13 (0.92-2.86)	--	--	Age, sex, place of work	LBP

The studies were published between 1988 and 2018, originated from 9 countries and involved a total population of 642,587 individuals. The studies evaluated the association of alcohol intake with several pain conditions including chronic widespread pain, fibromyalgia, headache, knee pain, low back pain and post-injury pain.

The study by Parreira et al.(256) provided effect measures corresponding to one additional alcoholic drink per week. Therefore, we calculated the OR and 95%CI corresponding to moderate intake and heavy intake, using the mid-point of each category.

Synthesis of results

Overall, any alcohol drinking is associated with 24% lower odds of chronic pain episodes (OR= 0.76, 95% CI: 0.61–0.95) (Figure 4.2 and Table 4.2). The association was observed in cohort studies (OR= 0.77; 95%CI: 0.61-0.98) but not in case-control studies (OR= 0.59; 95%CI: 0.12-2.94) (Table 4.2). The association of high alcohol intake with pain was not significant (OR=0.89, 95% CI: 0.58-1.36) (Table 4.2).

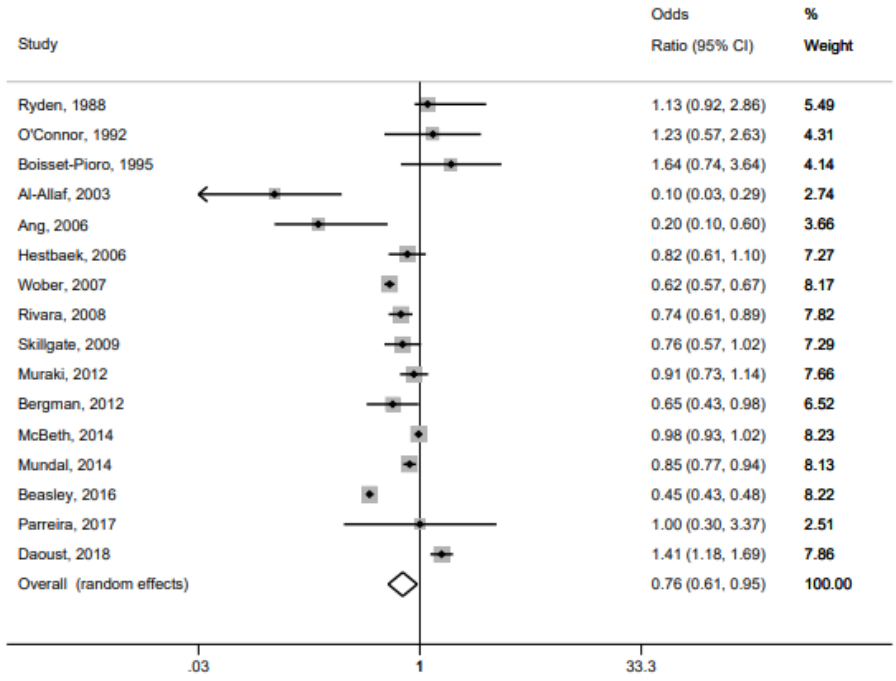

Figure 4.2 Forest plot of study-specific and random-effect pooled OR of any alcohol consumption and chronic pain of meta-analysis of alcohol consumption and chronic pain.

Table 4.2 Pooled odds ratios and 95% confidence intervals of alcohol consumption and chronic pain

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	R_i†	Q test p-value
Alcohol consumption					
Any alcohol consumption	16	0.78 (0.76-0.80)	0.76 (0.61-0.95)	0.98	0.00001
Moderate intake	9	0.62 (0.58-0.68)	0.69 (0.54-0.89)	0.86	0.00001
Heavy intake	9	0.77 (0.74-0.80)	0.89 (0.58-1.36)	0.99	0.00001
Study design					
Cohort	13	0.78 (0.76-0.80)	0.77 (0.61-0.98)	0.98	0.00001
Case-Control	3	0.74 (0.43-1.24)	0.59 (0.12-2.94)	0.89	0.00001
Pain location					
Chronic widespread pain	5	0.80 (0.77-0.82)	0.79 (0.52- 1.21)	0.99	<0.0001
Fibromyalgia	2	1.40 (0.76-2.56)	1.40 (0.76-2.56)	0.00	0.55
Low back pain	5	0.71 (0.57-0.89)	0.69 (0.48-0.98)	0.49	0.15
Post injury	2	1.03 (0.90-1.17)	1.02 (0.54-1.92)	0.96	<0.0001
Geographical location					
European	8	0.77 (0.74-0.79)	0.65 (0.48-0.87)	0.99	<0.0001
Non-European	8	1.00 (0.89-1.11)	0.97 (0.70-1.33)	0.83	<0.0001
Sex					
Male	3	0.48 (0.46-0.51)	0.75 (0.36-1.55)	0.99	0.03
Female	3	0.45 (0.42-0.49)	0.44 (0.14-1.37)	0.99	0.0001
Adjustment					
Not adjusted or unspecified	10	0.91 (0.84-0.97)	0.85 (0.65-1.11)	0.88	<0.0001
Adjusted	6	0.76 (0.74-0.78)	0.69 (0.48-0.99)	0.99	<0.0001
Quality Score					
High score	11	0.78 (0.76-0.80)	0.76 (0.59-0.97)	0.98	<0.0001
Low score	5	0.88 (0.72-1.08)	0.74 (0.36-1.54)	0.90	0.0009

†: Proportion of total variance due to between-study variance

Both males and females who drink alcohol are at lower odds of presenting chronic pain when compared to teetotalers. However, the confidence intervals of the estimates for these categories are wide due to the limited number of studies that provided association measures by sex. The magnitude of the negative association is stronger in females than in males ($OR_{females}$=0.44; 95%CI: 0.14-1.37 and OR_{males}=0.75; 95%CI: 0.36-1.55).

European individuals who consume alcohol are at lower odds of suffering chronic pain than those who do not consume alcohol (OR= 0.65; 95%CI: 0.48-0.87). Conversely, alcohol intake was no associated with chronic pain in non-European populations (OR= 0.97; 95%CI: 0.70-1.33) (Table 4.2).

Stratifying the studies by pain location showed lower odds of lower back pain in subjects consuming alcohol than in those who do not drink alcohol (OR= 0.69; 95% CI: 0.48– 0.98), with moderate heterogeneity (Table 4.2). The rest of pain syndromes did not show significant association with alcohol consumption.

Dose–response meta-analysis

Four publications provided enough data for dose-response analysis, and a fifth report included data for men and women independently, making a total of six studies included in the dose-response analysis. The six studies encompassed 403,521 individuals and 7,343 pain episodes (249,252,253,255,257). We observed a nonlinear association between alcohol consumption and the occurrence of chronic pain (P-value for non-linearity <0.001) (Figure 4.3).

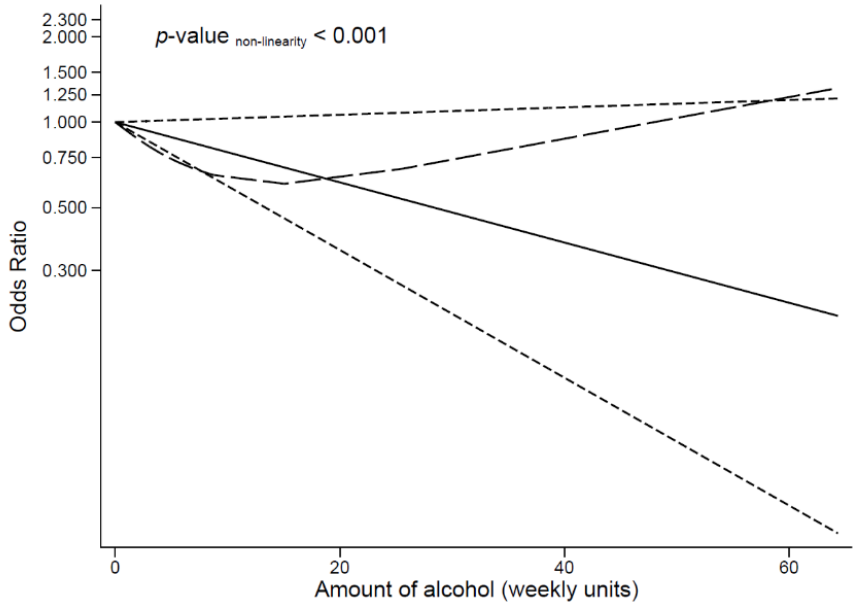

Figure 4.3 Dose-response analysis of the association between alcohol consumption and pain occurrence of the meta-analysis of the alcohol consumption and chronic pain.

Solid line represents summary odds ratios. Short-dashed lines represent the lower and upper bounds of confidence intervals. The long-dashed line represents summary odds ratios using non-linear assumption

The results by quartile of distribution, using the quartile with lower intake as a reference, were as follows: OR $_{2nd\ quartile}$=0.74; 95%CI: 0.64-0.87, OR $_{3rd\ quartile}$=0.67; 95%CI: 0.53-0.86 and OR $_{4th\ quartile}$= 0.75; 95%CI: 0.50-1.14.

Quality rating

The Bland-Altman agreement analysis showed that the quality rating by the two reviewers falls within the accepted limits of agreement. The average disagreement between the two raters was close to zero (T= 0; 95% CI: -0.23, 0.23), and the proportional bias was not statistically significant (T= 0.87; 95% CI: -0.15, 0.37), indicating that scoring was similar between raters. Eleven of the 16 studies scored more than 3 points in the quality assessment and were classified as high-quality studies. The magnitude of association was similar in low quality and high-quality studies (OR $_{low\text{-}quality}$= 0.74; 95%CI= 0.36-1.54 and OR $_{high\text{-}quality}$= 0.76; 95%CI: 0.59-0.97).

Six studies adjusted for age, sex, and smoking. The association between alcohol intake and chronic pain was significant for adjusted studies, but not for unadjusted studies (OR $_{adjusted\ studies}$= 0.69; 95%CI: 0.48-0.99) (Table 4.2).

No evidence of publication bias was observed as revealed by the globally symmetric shape of the funnel plot (Figure 4.4) and Egger's regression test (p-value= 0.78). The Trim and Fill method suggested the addition of three studies, but the corrected OR confirmed the presence of a negative association, even stronger than that observed initially, between alcohol exposure a chronic pain (OR=0.67; 95% CI: 0.54-0.84).

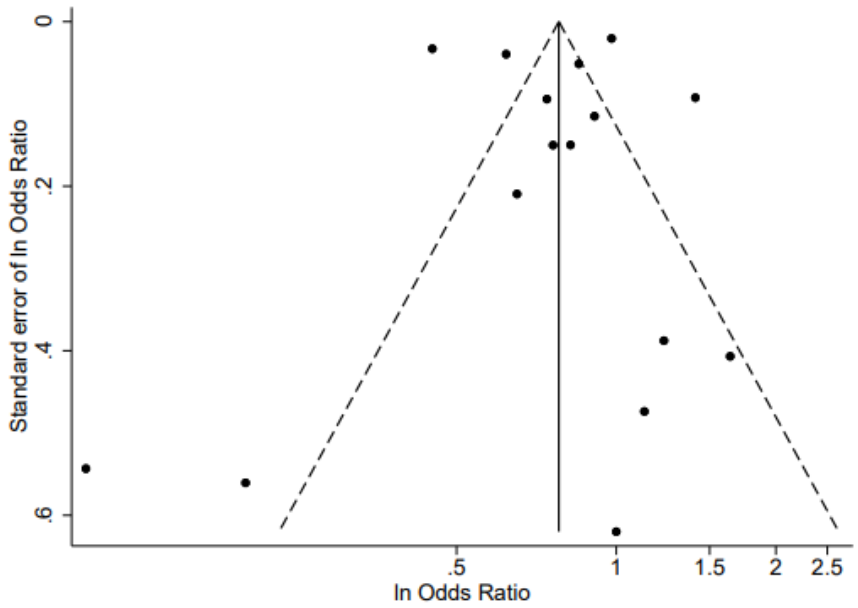

Figure 4.4 Funnel plot of log OR versus standard error of log OR of alcohol consumption and chronic pain of the meta-analysis of alcohol consumption and chronic pain.

The association between alcohol intake and chronic pain held under our sensitivity analysis extreme assumptions (OR= 0.79; 95% CI: 0.64–0.97).

Furthermore, the association between alcohol intake and chronic pain was not meaningfully modified after exclusion of the study by Beasley et al. (249). The random-effects pooled measures were as follows: $OR_{\text{moderate intake}}$= 0.76; 95% CI: 0.63–0.93, $OR_{\text{heavy intake}}$= 0.99; 95% CI: 0.75–1.30, $OR_{\text{any intake}}$= 0.82; 95% CI: 0.69–0.97.

4.2 SLEEP QUALITY AS A MEDIATOR OF THE RELATION BETWEEN DEPRESSION AND PAIN

Synthesis of results

Table 4.5 summarizes the results of different stages of the systematic search strategy. Initially, a total of 4467 records were selected as eligible to be screened by title and abstract; after duplication removal, 171 were retrieved as potential relevant full-text and screened to determine eligibility. Among them, 107 did not meet the inclusion criteria and were excluded. Finally, 64 different study units, published in 60 articles, met the inclusion criteria and were included in the meta-analysis (27,102,215–220,260–310). Nine studies were excluded from the restricted analysis as they reported the association between depression and sleep only without including pain.

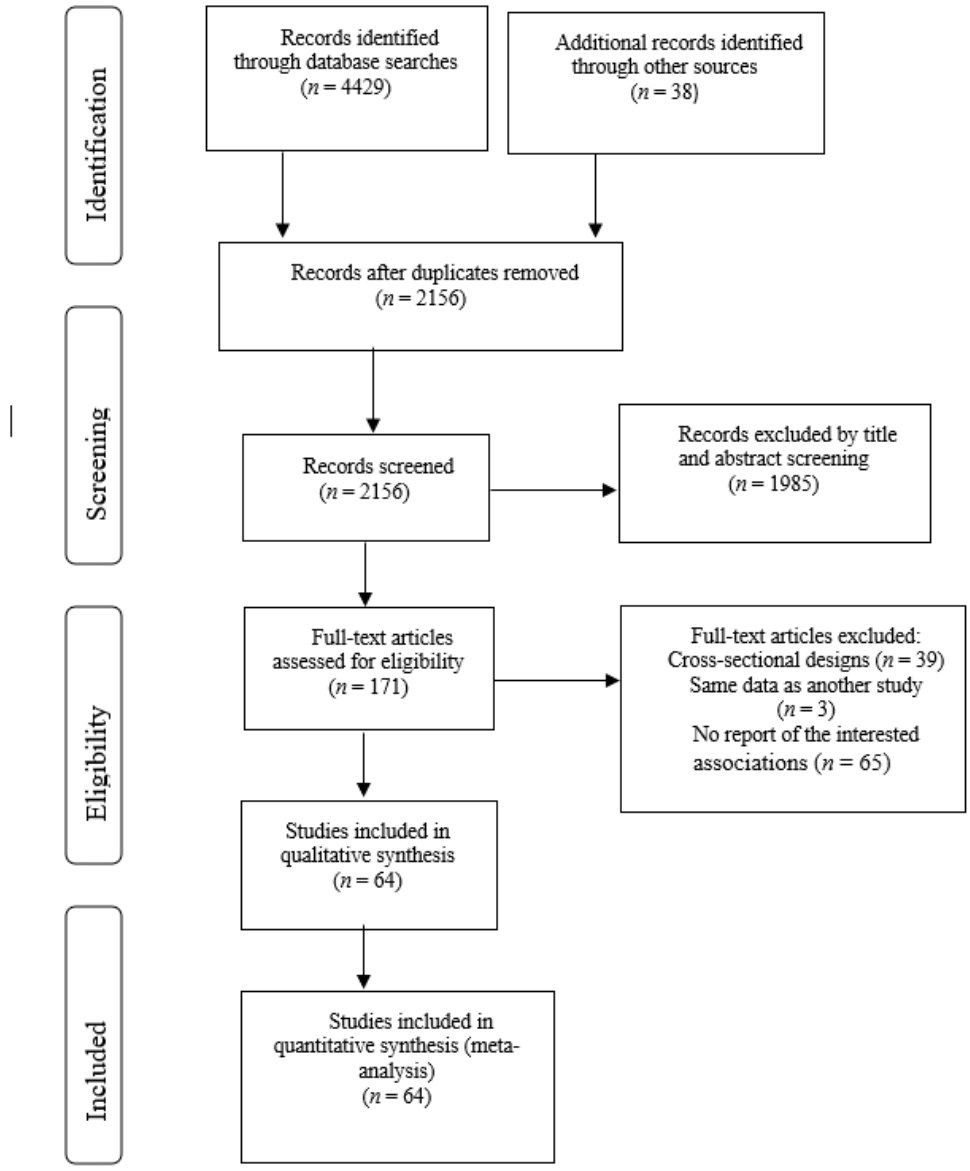

Figure 4.5 PRISMA flow chart of literature inclusion.

Description of the primary studies

Study characteristics are summarized in Table 4.3. Participants were predominantly female (75.8%); six studies included only women, while one employed only men. The average age of participants within studies ranged from 16 to 103 years. Eight studies used a case-control design, and 56 had a cohort design. Sample sizes ranged from 16 to 35248 participants, and the overall sample size in our meta-analysis was 139684. Participants with depression were mainly diagnosed using the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), the Centre for Epidemiologic Studies Depression (CES-D) scale, or did not report any criteria. Furthermore, pain and sleep disturbance were assessed using various self-report measures. The quality assessment scores ranged between 4 and 8 (Table 4.3).

Table 4.3 Characteristics of the included studies.

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Cohort studies										
Pilowsky et al. (214) **1985**	Hospital patients (average age 43.5 yrs)	100	Australia	0.12	-	-	Crude	Depression/SDS	Sleep disturbance/ Researcher made questionnaire	-
Ford et al. (215) **1989**	General population (18-65+ yrs)	7954	USA	0.55	-	-	Sex, age, socioeconomic status, race, and marital status	Major depression/DSM-III	Hypersomnia/ DSM-III	-
Korff et al. (275) **1993**	General population (18-44 yrs)	1016	USA	-	-	-0.18	Age, sex and education	Depression/SCL 90	-	Back pain/Self reported
Leino et al.(278)**1993**	Industry employees (40-68 yrs)	607	Finland	-	-	0.13	Age, baseline depression, stress scores	Depressive symptoms/DSS	-	Musculoskeletal pain/Self report
Magni et al. (281) **1994**	General population (25-74 yrs)	2324	USA	-	0.06	0.006	Crude	Depression/CES-D	Restless sleep/Self report	Chronic musculoskeletal pain/Health records
Pietri-Taleb et al. (289) **1994**	Industry employees (25-49 yrs)	1015	France	-	-	0.01	Age, marital status, smoking and physical exercise	Depression/MHQ	-	Neck trouble/Self report

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Affleck et al. (260) **1996**	Hospital patients (average age 43.8 yrs)	50	USA	-	-0.28	-	Between-persons variation and autocorrelation	-	Mean sleep quality ratings/Researcher made questionnaire	Fibromyalgia/ Clinical diagnosis
Breslau et al. (216) **1996**	General population (21-30 yrs)	1007	USA	0.61	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/Diagnostic interview	Insomnia/Diagnostic interview	-
Breslau et al. (216) **1996**	General population (21-30 yrs)	1007	USA	0.57	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/Diagnostic interview	Hypersomnia/ Diagnostic interview	-
Breslau et al. (216) **1996**	General population (21-30 yrs)	1007	USA	0.71	-	-	Sex, nicotine dependence, insomnia, hypersomnia	Major depression/Diagnostic interview	Insomnia and Hypersomnia/ Diagnostic interview	-
Mannion et al. (282)**1996**	Healthcare workers (18-39 yrs)	403	UK	-	-	0.01	Crude	Depressive symptoms/SDS	-	Back pain/Self report
Agargun et al. (261)**1999**	Hospital patients (average age 30.3 yrs)	16	Turkey	-	-0.58	-	Crude	-	Sleep quality/PSQI	Fibromyalgia/ Algometers
Riley et al. (293) **2001**	Hospital patients (18-85 yrs)	128	USA	0.07	0.05	0.10	Crude	Depression/BDI	Sleep quality/ Researcher made questionnaire	Orofacial pain/MPQ

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Zautra et al. (310) **2001**	Postmenopausal women (42-76 yrs)	188	USA	-	-	0.93	Age	Depressive symptoms/MHI	-	RA/Self report
Zautra et al. (310) **2001**	Postmenopausal women (42-76 yrs)	188	USA	-	-	0.91	Age	Depressive symptoms/MHI	-	OA/Self report
Brander et al. (265) **2003**	Hospital patients (36-85 yrs)	116	USA	-	-	0.43	Crude	Depression/BDI	-	Knee pain/MPQ
Carroll et al. (102) **2004**	At risk general population (20-69 yrs)	1131	Canada	-	-	0.02	Education, age	Depression/CES-D	-	Neck and low back pain/CPGQ
Hasler et al. (218) **2005**	General population (19-40 yrs)	499	Switzerland	0.10	-	-	Sex, age, baseline psychopathology, trouble falling asleep, impaired sleep quality, awakenings during sleep period, waking up too early, and trouble getting up in the morning	Major depression/SPIKE	EDS/SPIKE	-
Larson et al. (27)**2004**	General population (18-65< yrs)	4349	USA	-	-	0.34	Sex, age, education and income	Depressive disorder/ CES-D	-	Back pain/Self reported

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Boardman et al. (264) **2006**	General population (18-90 yrs)	1589	UK	-	0.19	0.24	Age, sex, and headache disability level	Depression /HADS	Sleep problem/Jenkins et al. questionnaire	Headache/Self report
Gupta et al. (272) **2007**	General population (25-65 yrs)	3185	UK	-	0.26	0.22	Age and sex	Depression /HADS	Sleep problems/SQS	CWP/ACR criteria
Kaila-Kangas et al. (273) **2006**	Factory employees (24-41 yrs)	902	Finland	-	0.24	-	Age, sex, and occupational class	-	Sleep disturbances/ Researcher made questionnaire	Back pain/Self report
Jansson-Fröjmark et al. (219) **2008**	General population (20-60 yrs)	1273	Sweden	0.32	-	-	Crude	Depression/HADS	Insomnia/DSM	-
Morphy et al. (285) **2007**	General population (18-98 yrs)	2662	UK	0.05	0.20	-	Age, sex, social class, anxiety, depression, and pain areas	Depression/HADS	Insomnia/Researcher made questionnaire	Widespread pain/Self report
Sinikallio et al. (296) **2007**	Hospital patients (average age 61.7 yrs)	99	Finland	-	-	0.03	Crude	Depression/BDI	-	Back and leg pain/Self report

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Bigatti et al. (263) **2008**	Hospital patients (average age 54 yrs)	492	USA	0.36	0.27	0.36	Crude	Depression/CES-D	Sleep quality/PSQI	Fibromyalgia /MPQ
Edwards et al. (269) **2008**	General population (average age 47 yrs)	1031	USA	-	-0.03	-	Age, sex, BMI, number of chronic conditions, use of prescription medications, chronic sleep difficulties, the presence of an emotional disorder, and the presence of a persistent pain condition	-	Sleep duration/Self reported	Daily pain/Self report
Smith et al. (298) **2008**	Hospital patients (average age 40.9 yrs)	333	USA	-	0.80	-	Crude	-	Insomnia/BSI	Arthritis Pain/SF-36
Young et al. (309) **2007**	Hospital patients (average age 46.9 yrs)	84	USA	-	-	0.07	Crude	Depressive symptoms/CES-D	-	Back pain/PBPI

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Edwards et al. (270) **2009**	Hospital patients (average age 34 yrs)	53	USA	-	0.07	-	Crude	-	Sleep efficiency/PSG	Overall pain/DNIC
Kim et al. (220) **2009**	Elderly population (20-41 yrs)	83	Korea	0.23	-	-	Age, sex, education, housing, past occupation, current employment, living area, life events, social deficit, physical activity, anxiety, and daily drinking	Depression/GMS	Insomnia/Researcher made questionnaire	-
Quartana et al. (291) **2010**	Hospital patients (average age 33.7 yrs)	53	USA	-	0.08	-	Crude	-	Insomnia/ISI	TMD/BPI
Vranceanu et al. (304) **2010**	Hospital patients (18-86 yrs)	120	USA	-	-	0.50	Crude	Depression /PHQ	-	Shoulder pain/VAS
Kim et al. (274) **2010**	Hospital patients (32-78 yrs)	83	South Korea	-	-	0.12	Crude	Depression/CES-D	-	Scar pain/BCTQ

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Mork et al. (284) **2012**	General population (20-70 yrs)	12350	Norway	-	0.25	-	Age	-	Sleep problems/Self report	Fibromyalgia/Clinical diagnosis
Nitter et al. (286) **2012**	General population (20-50 yrs)	2498	Norway	-	0.20	-	Age	-	Sleep disturbance/Self report	Chronic regional pain/Researcher made questionnaire
Rasmussen-Barr et al. (292) **2014**	Hospital patients (18-84 yrs)	6979	Sweden	-	0.17	-	Socioeconomic class, workload, and economic stress	-	Sleep disturbance/Self report	Neck, shoulder, and arm pain/Self report
Mommerstee g et al. (283)**2015**	Hospital patients (average age 61.4 yrs)	523	The Netherlands	-	-	0.03	Age and sex	Depression /HADS	-	Chest pain/SAQ
Sanders et al. (295) **2016**	General population (18-44 yrs)	2453	USA	-	0.10	-	Age, sex, study site, and race/ethnicity.	-	Sleep quality/PSQI	Painful TMD/QST

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Suffeda et al. (300) **2016**	Hospital patient (18-84 yrs)	82	Germany	-	-	0.07	Crude	Depression/PHQ	-	
Suri et al. (301) **2017**	General population (average age 41 yrs)	971	USA	-	-	0.15	Crude	Depression/Self report	-	Postoperative pain/NRS
Walton et al. (305) **2016**	Hospital patients (18-68 yrs)	276	Canada	-	0.21	0.05	Crude	Depression /HADS	Sleep disturbance/Self report	Uncontrolled Pain/PCS
Daly et al. (266) **2017**	Pregnant women (average age 31.4 yrs)	186	UK	-	-	0.04	Anxiety, deprivation score, and presence of preoperative pain	Dperession/EPND	-	Persistent pain/VAS
Generaal et al. (271) **2017**	General population (18-65 yrs)	1860	The Netherlands	-	0.12	-	Sex, age, years of education, BMI, smoking, alcohol intake, physical activity, and number of chronic diseases	-	Insomnia/IRS	Multisite musculoskeletal pain/CPG

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Lin et al. (279) **2017**	General population (20-65 yrs)	7895	Taiwan	-	0.18	-	Age, sex, monthly income, urbanization, and comorbidities	-	Insomnia/Health records	Myofacial pain/Clinical diagnosis
Pinheiro et al. (290) **2017**	General population of twins (43-71 yrs)	1098	Spain	-	-	0.10	Age and sex	Depression/ST-Dep	-	LBP/Self report
Aili et al. (262) **2018**	General population (20-74 yrs)	1249	Sweden	-	0.24	-	Age and sex	-	Initiating sleep disturbance/USI	CWP/ACR criteria
Aili et al. (262) **2018**	General population (20-74 yrs)	1249	Sweden	-	0.26	-	Age and sex	-	Maintaining sleep disturbance/USI	CWP/ACR criteria
Datema et al. (267) **2018**	Hospital patients (49-73 yrs)	227	The Netherlands	-	-	0.01	Crude	Depression/CES-D	-	Palmar pain/BCTQ
Uhlig et al. (303)**2018**	General population (20-70 yrs)	13429	Norway	-	0.17	-	Age, education, smoking, physical activity	-	Insomnia/DSM-IV	CWMSC/ACR criteria

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Strutz et al. (299) **2019**	Hospital patients (>18 yrs)	1441	USA	-	0.003	0.01	Age, sex, BMI, type of surgery, Charlson comorbidity index, procedural cardiac risk, physical status, alcohol use, intra-operative midazolam dose, volatile anesthetic concentration, intra-operative ketamine dose, opioid dose	Depression/Clinical diagnosis	Obstructive sleep apnoea risk/Clinical diagnosis	Postoperative pain/VAS
Wiklund et al. (306) **2020**	General population (16-85 yrs)	959	Sweden	-	0.19	-0.006	Age, sex, education, depressive symptoms, anxiety symptoms, level of pain catastrophizing, and pain intensity	Depression /GWBS	Insomnia/ISI	Local pain/PCS
Wolfe et al. (307) **2022**	Hospital patients (21-103 yrs)	35248	USA	-	-	0.09	Age, sex	Depression/Self report	-	Local pain/PCS
Peker et al. (288) **2021**	Hospital patients (average age 47.5 yrs)	362	Turkey	-	-	0.06	Crude	Depression/BDI	-	Headache/VAS

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Skarpsno et al. (297) **2021**	General population (average age 54.7 yrs)	6033	Norway	-	0.07	-	Age, sex, education, BMI, relative change in body weight, leisure time, physical activity, and smoking status	-	Sleep quality/Self report	CWP/SNQ
Yabe et al. (308) **2021**	General population and natural disaster survivors (18-65 yrs)	2059	Japan	-	0.14	-	Sex, age, body mass index, living area, smoking habits, drinking habits, comorbid conditions, working status, walking time, living status, subjective economic condition, psychological distress, and social isolation	-	Sleep disturbance/Self report	Low Back Pain/Self report
Case-control studies										
Lautenbacher et al. (277) **1999**	Hospital patients (average age 32.3 yrs)	26/13	Germany	-	-	0.42	Crude	MDD/HAMD	-	Pain threshold/ VAS

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Sayar et al. (217) **2002**	Cases: hospital patient; Controls: general healthy population (average age 36.7)	40/40	Turkey	0.6	-	-	Age, sex, pain duration, disability, pain intensity, anxiety	Depression/BDI	Sleep quality/PSQI	-
Kunderman n et al. (276) **2004**	General population (20-45 yrs)	10/10	Germany	-	0.20	-	Thermal detection thresholds	-	Sleep quality/Hemm eter et al. questionnaire	Cold pain threshold/Rese archer made questionnaire
Ediz et al. (268)**2013**	General population (18-65 yrs)	40/43	Turkey	-	0.49	-	Age, sex, educational status and BMI	-	Sleep quality/PSQI	Shoulder pain/SDQ
López-López et al. (280) **2017**	Hospital patients vs. general population (19-65 yrs)	82/82	Spain	-	-	0.06	Age and sex	Depression/BDI	-	SLBP/ TQTFSD

Continue of Table 4.3

Author, Year	Sample type	Study size or #cases/ #controls	Country	*r* Dep-Sl	*r* Sl-Pa	*r* Dep-Pa	Adjustment variables	Exposure/ Measurement tool	Mediator/ Measurement tool	Outcome/ Measurement tool
Palomo-López et al. (287) **2019**	Hospital women patients vs. general population healthy women (19-94 yrs)	100/100	Spain	-	-	0.56	Crude	Depression/BDI	-	Fibromyalgia/Clinical diagnosis
Toprak et al. (302)**2019**	Cases: hospital patient; Controls: general healthy population (18-65 yrs)	76/72	Turkey	0.22	-0.14	-0.05	Crude	Depression/BDI	Sleep quality/PSQI	Shoulder pain/VAS
San-Antolín et al. (294) **2020**	Hospital athletes, patients vs. healthy athelets (18-65 yrs)	25/25	Spain	-	-	0.35	Crude	Depression/BDI	-	Gastrocnemius myofascial pain/Self report

Note. r, correlation coefficient; Dep, depression; Sl, sleep disturbance; Pa, pain; BMI, body mass index; MDD, major depressive disorder; GWBS. general well-being schedule; HADS, hospital anxiety and depression scale; PHQ, patient health questionnaire; BDI, beck depression inventory; SDS, Zung self-rating depression scale; CES-D, center for epidemiologic studies depression scale;

MHI, mental health inventory; MHQ, middle-sex hospital questionnaire; DSS, Depressive symptoms score; HAMD, Hamilton depression scale; ST-DEP, state-trait depression questionnaire; SCL-90, symptom checklist-90; EPND, Edinburgh postnatal depression score; ISI, insomnia severity index; DSM, diagnostic and statistical manual of mental disorders; BSI, brief symptom inventory; PSQI, Pittsburgh sleep quality index; SQS, Sleep Quality Scale; IRS, insomnia rating scale; SDSC, sleep disturbance scale for children; PSG, Polysomnography; USI, Uppsala sleep inventory; GMS, geriatric mental state diagnostic schedule; SPIKE, structured psychopathological interview and rating of the social consequences for epidemiology; EDS, excessive daytime sleepiness; ACR, American college of rheumatology; CWP, chronic widespread pain; RA, rheumatoid arthritis; OA, osteoarthritis; SDQ, shoulder disability questionnaire; DNIC, diffuse noxious inhibitory controls; TBI, traumatic brain injury; EI, extracranial/bodily injury; CPG, chronic pain grade; TMD, temporomandibular joint disorders; LBP, low back pain; SLBP, subacute low back pain; MPQ, McGill pain questionnaire; QST, quantitative sensory testing; TMD, temporomandibular disorder; SNQ, Standardized Nordic questionnaire; SF-36, health survey short form – 36; VAS, visual analogue scale; CWMSC, chronic widespread musculoskeletal complaints; PCS, pain catastrophizing scale; MIDAS, Migraine disability assessment; CPGQ, chronic pain grade questionnaire; BCTQ, Boston carpal tunnel questionnaire; NRS, numeric rating scale; TQTFSD, the Quebec task force on spinal disorders; SAQ, Seattle angina questionnaire; PBPI, pain behavior and perception inventory

Publication bias

Study characteristics for articles reporting the associations are summarized in Table 4.3. Egger's test yielded non-significant test statistics for the correlations between depression-pain (p=0.19), sleep disturbance-pain (p=0.44), and depression-sleep disturbance-pain (p=0.61), and the funnel plots showed some dispersion but no evidence of asymmetry (Figure 4.6).

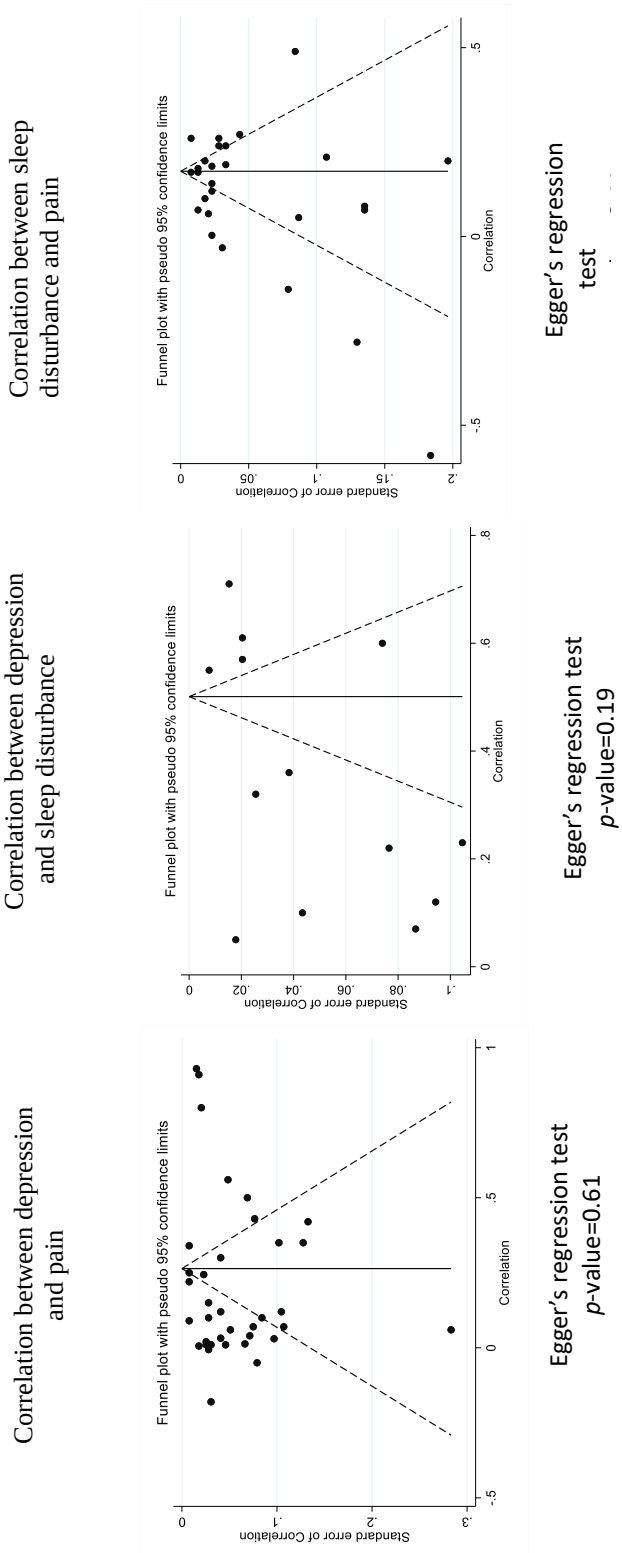

Figure 4.6 Funnel plots of the correlations

To further evaluate the possibility that our results could be due to publication bias, we recalculated the pooled estimates of correlations under the following extreme assumptions: (a) published studies represent only half of the studies identifying any of the correlations between depression, sleep disturbance, and pain; (b) all unpublished studies found a zero correlation; and (c) the unpublished studies have a sample size equal to the average sample size of the published studies. Under these extreme assumptions, the pooled correlation between depression and sleep disturbance (0.26; 95% CI [0.09, 0.42]), sleep disturbance and pain (0.18; 95% CI [0.07. 0.29]), and depression and pain (0.25; 95% CI [0.10, 0.35]) were still significant. These analyses do not provide evidence for publication bias in the three correlations.

Meta-analytic structural equation modelling

Table 4.4 provides the pooled correlation matrix that resulted from stage 1 of TSSEM. The pooled correlations between depression and sleep disturbance, sleep disturbance and pain, and depression and pain were 0.24 (95% CI [0.10, 0.38]), 0.15 (95% CI [0.10. 0.20]), and 0.20 (95% CI [0.10, 0.29]) respectively, and indicated small positive associations among the variables. The I^2 statistic (94-99%) and the results of the *Q* tests indicated large heterogeneity for the overall sample (Table 4.4). Heterogeneity was similarly high for the different subgroups of studies as well as for the restricted analysis in which we excluded studies that assessed the relation between depression and sleep disturbance, but did not assess pain (Table 4.5).

Table 4.4 Pooled correlation coefficients ($\bar{r}$).

	k	**Sample size (*N*)**	$\bar{r}$	**95% confidence interval**		I^2	***p*-value *Q* test**
				Lower limit	**Upper limit**		
Depression-Pain	34	59091	0.20	0.10	0.29	99%	< 0.001
Sleep disturbance-Pain	30	71137	0.15	0.10	0.20	96%	< 0.001
Depression-Sleep disturbance	13	768	0.24	0.10	0.38	94%	< 0.001

Note. k = Number of primary studies, $\bar{r}$ = Pooled correlation coefficient.

Table 4.5 Direct, indirect, and total effects in the meta-analytic mediation models.

	Main analyses					Restricted analyses[#]				
	k	**Direct effect (95% CI)**	**Indirect effect (95% CI)**	**Total effect (95% CI)**	**VAF (%)**	***k***	**Direct effect (95% CI)**	**Indirect effect (95% CI)**	**Total effect (95% CI)**	**VAF (%)**
All studies	64	0.17 (0.07-0.27)	0.03 (0.01-0.05)	0.20 (0.10-0.29)	15.0	54	0.17 (0.07-0.28)	0.02 (0.01-0.05)	0.20 (0.10-0.29)	10.0
Subgroup analysis										
Type of pain										
Chronic pain	50	0.20 (0.05-0.35)	0.02 (0.01-0.04)	0.22 (0.07-0.36)	9.1	47	0.20 (0.07-0.32)	0.02 (0.005-0.04)	0.22 (0.10-0.34)	9.1
Non chronic or undetermined pain	14	0.13 (0.03-0.22)	0.01 (-0.02-0.04)	0.14 (0.05-0.23)	7.1	-	-	-	-	-
Region										
European	29	0.11 (-0.01-0.22)	0.04 (0.02-0.08)	0.15 (0.05-0.25)	26.6	-	-	-	-	-
Non-European	35	0.26 (0.09-0.44)	-0.005 (-0.06-0.03)	0.26 (0.10-0.41)	-	28	0.25 (0.10-0.43)	0.001 (-0.04-0.03)	0.26 (0.12-0.39)	0.4
USA	23	0.35 (0.11-0.60)	-0.02 (-0.14-0.03)	0.33 (0.12-0.52)	-	19	0.34 (0.11-0.58)	-0.005 (-0.07-0.02)	0.335 (0.13-0.52)	-

Continue of Table 4.5

	Main analysis					Restricted analysis				
	k	**Direct effect (95% CI)**	**Indirect effect (95% CI)**	**Total effect (95% CI)**	**VAF (%)**	***k***	**Direct effect (95% CI)**	**Indirect effect (95% CI)**	**Total effect (95% CI)**	**VAF (%)**
Study design										
Cohort	56	0.15 (0.04-0.26)	0.02 (0.01-0.04)	0.17 (0.08-0.27)	11.7	51	0.14 (0.05-0.24)	0.03 (0.007-0.05)	0.17 (0.08-0.27)	17.6
Case-control	8	0.29 (0.08-0.45)	0.02 (-0.22-0.23)	0.31 (0.07-0.55)	6.4	-	-	-	-	-
Adjustment										
Unadjusted	24	0.34 (0.15-0.52)	0.01 (-0.02-0.05)	0.35 (0.18-0.51)	2.8	22	0.33 (0.15-0.52)	0.02 (-0.01-0.05)	0.35 (0.18-0.51)	2.8
Adjusted	40	0.05 (-0.05-0.15)	0.04 (0.02-0.09)	0.10 (0.02-0.18)	40.0	-	-	-	-	-
Quality assessment score										
Low	19	0.36 (0.12-0.62)	-0.03 (-0.16-0.04)	0.32 (0.11-0.53)	-	15	0.34 (0.12-0.56)	-0.01 (-0.08-0.03)	0.32 (0.11-0.53)	-
High	45	0.10 (0.01-0.21)	0.04 (0.02-0.07)	0.14 (0.04-0.24)	28.5	-	-	-	-	-

Note. *k* = Number of primary studies, 95% CI = 95% confidence interval, VAF = Variance accounted for by the indirect effect. The VAF is only reported for partial mediation models with the same sign of the direct and indirect effects. [#] The primary studies excluded from these analyses did not measure pain and only measured the association between depression and sleep disturbance.

The meta-analytic estimates of the direct, indirect, and total effects, along with their confidence intervals, and VAF values are presented in Table 4.5. For both the main analysis and the restricted analysis we observed a partial mediation effect of sleep disturbance on the association between depression and pain. Overall, 15% of the total effect of depression on pain was explained by the indirect effect of sleep disturbance. The indirect effect explained 9% of the total effect when we excluded the acute pain outcomes and analysed only those studies with chronic pain outcomes.

In the subgroup analyses we observed a significant indirect effect among chronic pain outcomes, cohort design, and high-quality studies in both main and restricted analyses. Significant indirect effect among adjusted studies was observed in the main analysis only. For studies conducted in Europe, about 27% of the total effect was due to the mediation effect via sleep disturbance. For non-European studies, no mediation was evident. Concerning the study designs, the percentage of the total effect explained by the indirect effect was 12% among cohort studies and 6% among the case-control studies. For studies with incomplete adjustment for confounders, no mediation was evident; in contrast, about 40% of the total effect could be explained by the indirect effect for studies adjusting for at least age and sex. For high-quality studies, the VAF was 18.5%, and the mediation effect for low-quality studies was non-significant.

Certainty of evidence

GRADE assessment was implemented for the meta-analysis. The certainty of the evidence was rated for meta-analytic outcomes as Moderate (⨁⨁⨁◯) which means the team is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (Table 4.6).

Table 4.6 GRADE criterio for the meta-analysis of the indirect association of sleep disturbance on the relationship between depression and chronic pain

GRADE Domain	Criteria used in the review
Risk of Bias	Low risk (+1) In general, the included studies had a low risk of bias when applying tools for evaluation.
Inconsistency	High risk (-1) A substantial heterogeneity was present (I^2 value >50%).
Indirectness	Low risk (+1) Studies used the depression and sleep disturbances as the exposure and the pain that lasts more than three months as the outcome, and directly answer the result raised in the PECO question.
Imprecision	Low risk (+1) Studies have sufficient sample size. Studies met Optimal Information Size (OIS).
Publication Bias	Low risk (+1) There is no evidence of asymmetry in the funnel plots, or statistical evidence ($p<0.05$) from Egger's test.

COHORT STUDIES PART 1 AND 2:

The characteristics of the study population is the same in both parts. In the first part (4.3) we used both PCS and MCS as the main exposures. We used the quartiles to categorize them in different levels. However, in the second part (4.4) we only used PCS (physical well-being) as the main exposure and we categorized it into two groups lower/higher than the first quartile.

CHARACTERISTICS OF THE STUDY POPULATION

Out of 2,000 invited students, 1,842 completed the baseline questionnaire. We excluded participants aged >50 (n = 57) and those who did not provide any ID number to link with the previous records, or were duplicated (n = 168). Subjects reporting pain at baseline (n= 593) were also excluded from the follow-up. Therefore, a total of 1,024 students were free of pain at the beginning of the study. Of the 1,024 students, 73 were lost to follow-up, and 951 students were then included in the final analysis (Figure 4.7).

We observed a total of 223.2 years at risk among 1,024 students. During the follow-up, we identified 584 new pain cases, with a total of 106.4 years at risk, which yielded an overall incidence rate of 5.4 year^{-1}. These cases were distributed as follows: back pain: 310 (53%), headache: 124 (21%), upper and lower extremities pain: 118 (20%), and other types of pain: 32 (6%).

The baseline characteristics of the study population for PCS and MCS quartiles in the first part are presented in Table 4.7. The population was evenly distributed across sex and age groups, with a mean age of 25.29±5.7 and 24.31±6.3 years for men and women, respectively. Women had slightly higher baseline MCS scores than men (mean = 41.4 and 40.8, respectively), and the baseline PCS scores were similar in women and men (mean = 55.7 and 55.1, respectively).

Higher MCS scores among students were inversely associated with comorbidities, current smoking and directly associated with sleep quality and physical activity (Table 4.7). Higher PCS scores were inversely associated with comorbidities and perceived stress and directly associated with physical activity (Table 4.7). The remaining variables were not meaningfully associated with exposure variables. The MCS and PCS scores of students were negatively correlated (Pearson correlation coefficient = -0.19).

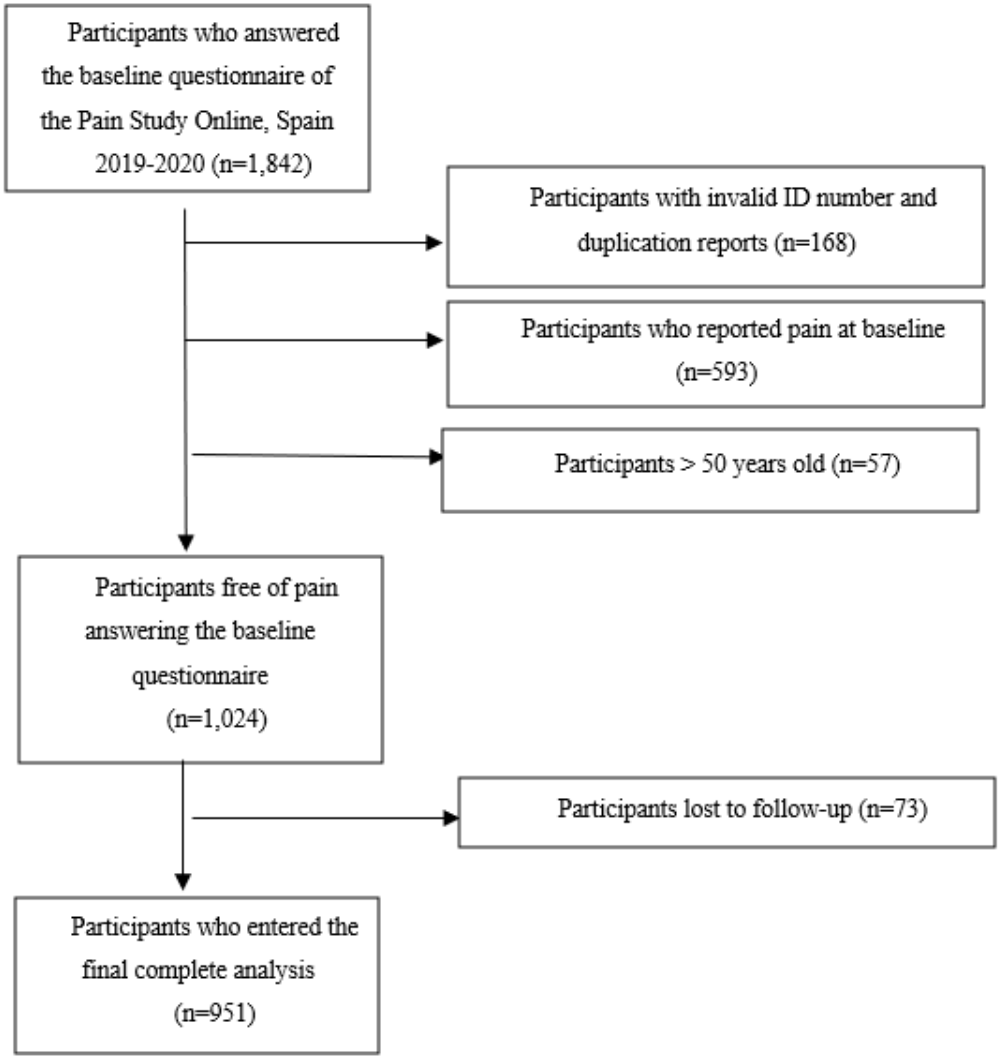

Figure 4.7 Flow diagram of Pain Study Online, Spain, 2019-2020.

Table 4.7 Baseline Characteristics of 1,024 Students for MCS and PCS quartiles, Pain Study Online, Spain, 2019

Exposure	Mean age (years)	Female		Single		Normal BMI (18.5-25)		Good Sleep Quality (<5)		Low Perceived Stress (<8)		Non-drinkers		Non-smokers		High physical activity		No-comorbidity	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mental component summary																			
1st quartile (median=29.74)	23.99	114	76.00	128	85.91	111	75.51	28	21.71	113	82.48	24	40.00	88	57.14	24	16.78	82	54.67
2nd quartile (median=37.79)	24.71	118	77.63	118	79.19	116	78.38	58	47.54	111	77.62	31	49.21	96	62.75	46	31.29	108	71.05
3rd quartile (median=45.39)	25.48	122	79.74	123	82.00	114	77.03	68	56.20	109	76.76	20	36.36	119	77.27	43	29.25	125	81.70
4th quartile (median=54.11)	24.57	120	80.54	127	85.81	109	75.69	101	73.72	118	80.82	22	39.29	119	77.78	56	37.09	117	78.52
Physical component summary																			
1st quartile (median=49.57)	24.94	114	75.50	127	85.23	108	75.00	48	45.28	98	75.97	25	45.45	94	61.04	34	23.94	94	62.25
2nd quartile (median=54.86)	24.43	115	77.18	119	80.95	116	77.85	60	47.62	110	76.39	24	42.11	101	66.01	37	25.34	103	69.13
3rd quartile (median=57.76)	24.83	124	81.58	130	86.67	113	76.35	74	65.22	116	80.00	26	42.62	117	75.97	43	28.67	121	79.61
4th quartile (median=61.33)	24.55	121	79.61	120	80.00	113	77.94	73	51.05	127	84.67	22	36.07	110	71.90	47	31.33	114	75.00

Table 4.8 presents the study second part´s population's descriptive results by physical well-being status for all variables. The mean score of physical well-being was 55.63 (SD: 5.44), and the population was evenly distributed across sex and age groups, with a mean age of 25.29±5.7 and 24.31±6.3 years for men and women, respectively. In addition, the baseline physical well-being scores were similar in women and men (mean = 55.7 and 55.1, respectively).

Table 4.8 Baseline characteristics of 1,024 Students in different levels of dichotomized physical well-being variable, Pain Study Online, Spain, 2019-2020

Exposure	**Physical well-being (Physical Component Summary)**	
	Low **Mean=48.4 (n=154)**	**High** **Mean=58.07 (n=460)**
Age; Mean (SD)	24.95 (6.2)	24.61 (6.1)
Sex; n (%)		
Male	37 (24.50)	93 (20.53)
Female	114 (75.50)	360 (79.47)
Physical activity; n (%)		
High	34 (21.12)	127 (78.88)
Low	108 (25.29)	319 (74.71)
Perceived stress; n (%)		
High (>8)	88 (26.91)	239 (73.09)
Low (<8)	41 (17.01)	200 (82.99)
Smoking; n (%)		
Non-current smokers	112 (22.72)	381 (77.28)
Current smokers	42 (34.71)	79 (65.29)
Alcohol consumption; n (%)		
Abstainers/low drinkers	25 (25.77)	72 (74.23)
Moderate drinkers	30 (21.90)	107 (78.10)
Sleep quality; n (%)		
Low >5	56 (52.83)	149 (36.97)
High <5	50 (47.17)	254 3.03)

4.3 COHORT STUDY PART 1: QUALITY OF LIFE AND CHRONIC PAIN

Analytical analysis

After adjusting for confounders, we observed an inverse association between PCS and pain incidence (Table 4.9). A PCS score higher than 50 is associated with up to a 36% decrease in the incidence of chronic pain. Compared with the first quartile, students of the second, third and fourth quartiles of PCS presented IRRs of 0.64 (95% CI: 0.45, 0.92), 0.66 (95% CI: 0.46, 0.94), and 0.64 (95% CI: 0.45, 0.91) adjusted for age, sex and sleep quality. On the contrary, no association was observed between MCS and chronic pain. Compared with the first quartile, students of the second, third and fourth quartiles of PCS presented IRRs of 1.19 (95% CI: 0.84, 1.69), 0.93 (95% CI:0.64, 1.35), and 0.76 (95% CI: 0.50, 1.13). The results of the main analyses are shown in Table 4.9.

Table 4.9. Incidence Rate Ratios (IRR) of Quality of Life and pain, Pain Study Online, Spain, 2019-2020

Exposure		Unadjusted IRR		Adjusted IRR	
		IRR	**95% CI**	**IRR***	**95% CI**
Mental component summary	**1st quartile (median=29.74)**	1	Referent	1	Referent
	2nd quartile (median=37.79)	1.14	0.84, 1.55	1.19	0.84, 1.69
	3rd quartile (median=45.39)	0.99	0.72, 1.36	0.93	0.64, 1.35
	4th quartile (median=54.11)	0.72	0.51, 1.01	0.76	0.50, 1.13
Physical component summary	**1st quartile (median=49.57)**	1	Referent	1	Referent
	2nd quartile (median=54.86)	0.64	0.47, 0.87	0.64	0.45, 0.92
	3rd quartile (median=57.76)	0.60	0.44, 0.82	0.66	0.46, 0.94
	4th quartile (median=61.33)	0.58	0.42, 0.80	0.64	0.45, 0.91

*Adjusted for age, sex, sleep quality

Restricted cubic spline analyses presented a general nonlinear tendency for MCS and PCS association with chronic pain (Figure 4.8). In addition, we observed a tendency to have an S-type association between PCS and pain incidence since the risk of pain incidence increases slightly as the PCS score increases. Still, at higher scores, the growth gradually slowed (PCS = 48).

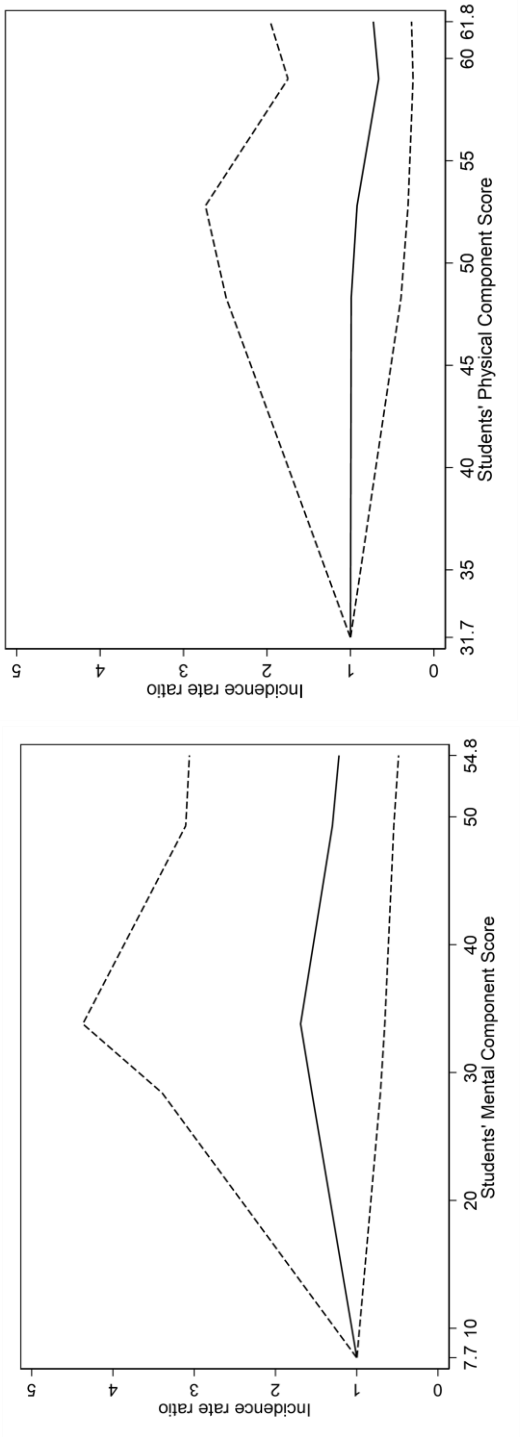

Figure 4.8 Restricted cubic splines of the association between baseline Mental and Physical Component Scores and chronic pain incidence rate ratios (IRR)

In the assessment of attrition, the results from the robustness analyses did not differ meaningfully from those obtained in the original analyses, which indicated that losses to follow-up did not introduce bias in our estimates. None of the point estimates in the Inverse Probability Weighting and the Multiple Imputation methods showed a deviation ≥ 20% from the uncorrected point estimates (Table 4.10 and Table 4.11). Furthermore, the results of the analysis of the two extreme scenarios did not show any noticeable change compared to those of the main analysis.

Table 4.10 Multiple Imputation Analysis of Quality of Life, Mental Well-being and Pain Incidence Rate Ratios (IRR) among students, Pain Study Online, Spain, 2019-2020

Exposure		Unadjusted IRR		Adjusted IRR	
		IRR	**95% CI**	**IRR***	**95% CI**
Mental component summary	**1st quartile (median=29.74)**	1	Referent	1	Referent
	2nd quartile (median=37.79)	1.13	0.83, 1.53	1.20	0.85, 1.69
	3rd quartile (median=45.39)	1.00	0.73, 1.36	0.92	0.64, 1.34
	4th quartile (median=54.11)	0.72	0.52, 1.01	0.75	0.50, 1.13
Physical component summary	**1st quartile (median=49.57)**	1	Referent	1	Referent
	2nd quartile (median=54.86)	0.64	0.47, 0.86	0.65	0.45, 0.92
	3rd quartile (median=57.76)	0.59	0.44, 0.81	0.66	0.46, 0.94
	4th quartile (median=61.33)	0.57	0.41, 0.77	0.64	0.45, 0.91

*Adjusted for age, sex, sleep quality

Table 4.11 Inverse Probability Weighting analysis of Quality of Life and pain Incidence Rate Ratios (IRR) among students, Pain Study Online, Spain, 2019-2020

Exposure		Unadjusted IRR		Adjusted IRR	
		IRR	**95% CI**	**IRR***	**95% CI**
Mental component summary	**1st quartile (median=29.74)**	1	Referent	1	Referent
	2nd quartile (median=37.79)	1.21	0.87, 1.68	1.27	0.92, 1.77
	3rd quartile (median=45.39)	0.95	0.67, 1.34	1.00	0.70, 1.43
	4th quartile (median=54.11)	0.71	0.49, 1.03	0.82	0.55, 1.24
Physical component summary	**1st quartile (median=49.57)**	1	Referent	1	Referent
	2nd quartile (median=54.86)	0.64	0.46, 0.90	0.67	0.47, 0.95
	3rd quartile (median=57.76)	0.58	0.41, 0.81	0.61	0.43, 0.85
	4th quartile (median=61.33)	0.57	0.41, 0.80	0.59	0.42, 0.82

*Adjusted for age, sex, sleep quality

4.4 COHORT STUDY PART 2: CAUSAL VARIABLES, MEDIATORS, INTERACTORS AND CONFOUNDERS OF THE ASSOCIATION BETWEEN PHYSICAL WELL-BEING AND CHRONIC PAIN

Mediation analysis

Mediation analysis was conducted separately for all potential mediators. Figure 3.3 a. displays our hypothesized relations, and the estimated total causal effect, as well as the direct and indirect effects of physical well-being on chronic pain, are shown in Table 4.12.

The GSEM analysis revealed that, compared to low physical well-being, high physical well-being is related to a large decrease in the risk of chronic pain ($IRR^{\text{Total Effect}} = 0.58$; 95%CI 0.50-0.81), and that the indirect effect of perceived stress of that relation was $IRR^{\text{Natural Indirect Effect}} = 0.92$; 95%CI 0.89-1.00. Perceived stress mediates 12.5% of the total effect of physical well-being on chronic pain (Table 4.12). Other potential mediators, including physical activity, smoking, drinking, and sleep quality showed a 6.4%, 4.8%, and 3.4% mediation proportion of the association between physical well-being and chronic pain.

Table 4.12 Natural Direct and Indirect Effects of physical well-being on chronic pain incidence among students, Pain Study Online, Spain, 2019-2020

Mediator	Unadjusted				Adjusted			
	Natural Indirect Effect	Natural Direct Effect	Natural Total Effect	Proportion Mediated, %	Natural Indirect Effect	Natural Direct Effect	Natural Total Effect	Proportion Mediated, %
	IRR (95% CI)	**IRR (95% CI)**	**IRR (95% CI)**		**IRR[a] (95% CI)**	**IRR[a] (95% CI)**	**IRR[a] (95% CI)**	
Physical activity ***(Low vs. High)***	0.97 (0.87, 1.07)	0.64 (0.45, 0.79)	0.60 (0.44, 0.81)	5.1	0.96 (0.85, 1.09)	0.63 (0.50, 0.82)	0.59 (0.49, 0.82)	6.4
Perceived stress ***(Low vs. High)***	0.94 (0.91, 1.03)	0.63 (0.45, 0.77)	0.59 (0.46, 0.92)	9.3	0.92 (0.89, 1.00)	0.64 (0.48, 0.81)	0.58 (0.50, 0.81)	12.5
Smoking ***(non-current vs. current)***	0.98 (0.89, 1.05)	0.62 (0.45, 0.80)	0.60 (0.44, 0.80)	3.2	0.97 (0.84, 1.07)	0.63 (0.49, 0.79)	0.60 (0.50, 0.78)	4.8
Drinking ***(abstainers/low vs moderate)***	1.02 (0.86, 1.15)	0.63 (0.44, 0.80)	0.60 (0.48, 0.82)	-3.5	1.03 (0.83, 1.16)	0.63 (0.48, 0.78)	0.65 (0.50, 0.79)	-5.3
Sleep quality ***(Good vs. poor)***	0.98 (0.84, 1.10)	0.63 (0.48, 0.81)	0.61 (0.47, 0.80)	3.3	0.98 0.93, 1.07)	0.64 (0.48, 0.84)	0.62 (0.49, 0.85)	3.4

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

[a] Adjusted for age and sex.

Stratum-specific analysis

Table 4.13 shows the results of the stratum-specific analysis. The crude estimate value (IRR=1.49; 95% CI: 1.24-1.80) was between the low physical activity value (IRR=1.76; 95% CI: 1.28-2.36) and the high physical activity value (IRR=1.20; 95% CI: 1.06-1.45), and the adjusted estimate did not change the crude estimate by more than 10% (IRR=1.51; 95% CI: 1.20-1.90), indicating that the physical activity could be an interactor but not a confounder. We observed the same pattern for perceived stress and drinking. However, the stratum-specific IRRs of smokers (IRR=1.80; 95% CI: 1.05-2.81) and non-smokers (IRR=1.52; 95% CI: 1.35-1.62) were different from each other and both were larger than the crude estimate, which indicates that smoking can be both a confounder and an interactor in the association between physical well-being and chronic pain. The IRR of the association between physical well-being and chronic pain changed slightly less than 10% when it was adjusted for smoking (IRR=1.59; 95% CI: 1.39-1.62), which favors the explanation that smoking is not a strong confounder of this association. Furthermore, the magnitude of the association between physical well-being and chronic pain in low sleep quality (IRR=1.54, 95% CI: 1.01-2.26) is not different from that in high sleep quality (IRR=1.52, 95% CI: 0.97-2.20). The crude estimate of this association and the stratum-specific estimates are similar, indicating that sleep quality is neither a confounder nor an interactor in the association between sleep quality and chronic pain.

Table 4.13 Stratum-specific Incidence Rate Ratios of the association between physical well-being and chronic pain among students, Pain Study Online, Spain, 2019-2020

Covariates	Stratum-specific IRR	IRR crude	IRR pooled
Low physical activity	1.76 (1.28, 2.36)	1.49 (1.24, 1.80)	1.51 (1.20, 1.90)
High physical activity	1.20 (1.06, 1.45)		
Low stress	1.27 (1.30, 1.79)	1.49 (1.24, 1.80)	1.47 (1.16, 1.86)
High stress	1.68 (1.22, 2.32)		
Non-current smokers	1.80 (1.05, 2.81)	1.49 (1.24, 1.80)	1.59 (1.39, 1.62)
Current smokers	1.52 (1.35, 1.62)		
Low/non-drinkers	1.59 (1.19, 2.75)	1.49 (1.24, 1.80)	1.44 (1.22, 1.58)
Moderate drinkers	1.44 (1.10, 1.58)		
Low sleep quality	1.54 (1.01, 2.26)	1.49 (1.24, 1.80)	1.50 (1.13, 1.98)
High sleep quality	1.52 (0.97, 2.20)		

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

Interaction analysis

Interaction analyses (

Table *4.14*) showed that the RERI of physical well-being and physical activity on pain was 0.25 (95% CI: 0.13-0.60), which indicates that the joint effect on the additive scale of physical activity and physical well-being together was greater than the sum of the effects of physical activity alone and physical well-being alone. Also, we found that low physical well-being, when it is present together with no alcohol consumption, shows an excess risk of pain (RERI= 0.11; 95% CI: 0.06-0.36).

The interaction results did not show any indication of departure from additivity of effects in other covariates. AP and synergy index gave results that were consistent with those shown by RERI.

Table 4.14 Measures of additive interaction between covariates and physical well-being among students in the occurrence of chronic pain, Pain Study Online, Spain, 2019-2020

Interaction	Adjusted[a] Chronic pain IRR (95% CI)	Univariate RERI (95% CI)	Adjusted RERI[a] (95% CI)	AP (95% CI)	S (95% CI)
Physical activity/Physical well-being		0.25(0.13, 0.60)	0.27 (0.12, 0.51)	0.19 (0.13, 0.58)	3.79 (1.29, 7.84)
High activity, high well-being	1(ref)				
Low activity, high well-being	0.89 (0.77, 1.04)				
High activity, low well-being	1.20 (1.06, 1.45)				
Low activity, low well-being	1.34 (1.07, 1.59)				
Perceived stress/Physical well-being		0.02 (-0.89, 0.16)	0.01(-0.92, 0.17)	0.02(-0.83, 0.23)	1.07 (0.59, 1.27)
Low stress, high well-being	1(ref)				
High stress, high well-being	1.03 (0.73, 1.09)				
Low stress, low well-being	1.27 (1.30, 1.79)				
High stress, low well-being	1.37 (0.79, 1.10)				
Smoking status/Physical well-being		-0.07(-0.15, 0.01)	-0.04(-0.24, 0.10)	-0.08(-0.10, 0.11)	0.64(0.32, 0.70)
Non-current smokers, high well-being	1(ref)				
Smokers, high well-being	0.74 (0.45, 1.30)				
Non-current smokers, low well-being	1.52 (1.35, 1.62)				
Smokers, low well-being	1.17 (0.92, 1.26)				
Drinking status/Physical well-being		0.11(0.06, 0.36)	0.09(0.04, 0.28)	0.08(0.05, 0.30)	1.81(1.51, 2.12)
Moderate drinkers, high well-being	1(ref)				
Abstainer, high well-being	0.68 (0.56, 0.81)				
Moderate drinkers, low well-being	1.44 (1.10, 1.58)				
Abstainer, low well-being	1.24 (1.12, 1.36)				

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

[a] Adjusted for age and sex.

5 DISCUSSION

5.1 ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND CHRONIC PAIN

This meta-analysis suggests that alcohol drinking is associated with a moderate decrease in the risk of chronic pain. The dose-response analysis showed that the relation could be curvilinear with low doses associated with lower pain occurrence and high doses indicating a global absence of association.

One possible explanation of these results could be that the expectations about the effectiveness of pain relievers affect pain perception. Since alcohol is known as a substance with analgesic effects, expecting a reduction in pain among patients after alcohol consumption can manipulate and increase the primary effect of alcohol on pain (311).

The association observed is likely to be confounded by psychological factors such as depression. On the one hand, some of the perceived pain episodes are caused by depression without any other neurological cause. On the other hand, drinking is frequent in people with depression. Since alcohol consumption improves the general mood of depressed people temporarily, drinkers are likely to cope with pain due to mood improvement after consuming alcohol, not due to alcohol itself (312,313).

In this meta-analysis, the protective association of alcohol and pain was observed in studies carried out in Europe only. The effect of alcohol drinking on pain may vary in different parts of the world, due to different patterns of drinking. In Europe, alcohol is integrated into routine life and is consumed daily (wet culture), while in the U.S., alcohol is less regularly consumed, but more often in massive amounts related to intoxication (dry culture) (314). It is then likely that frequent alcohol intoxication and withdrawal experiences that are more probable in non-European countries dysregulate the function of brain stress and reward circuits, and causes deficiency in the activity of the endogenous opioid peptide system, inducing hyperalgesia, a characteristic symptom of alcohol withdrawal (315,316). On the other side, routine alcohol consumption lowers the pain threshold; in other words, routine alcohol consumers, such as European drinkers, are more sensitive to the analgesic effects of alcohol. Alcohol may help European drinkers endure the pain for a more extended period (317). These differences between associations between European and non-European populations may also be due to the differing relations of confounders, such as smoking habits, with alcohol consumption.

Animal studies showed that alcohol could partially block pain receptors (318). The same effect was observed in humans (319). Another plausible mechanism is that ethanol mimics the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain, which binds to GABA receptors and inhibits neural signaling (320). Another research suggested that alcohol consumption produces a dose-related release of the endogenous opioid ligands, which reduces the transmission of pain signals to the central nervous system (CNS) (321). Alcohol affects various neurotransmitter mechanisms, including serotonin (72). Serotonin plays a role in improving mood, sleep, and pain; alcohol increases the nervous system's serotonin release (322). People experiencing pain may take related medications to manage the pain; alcohol can synergistically enhance the medication's effects that operate through the CNS (323).

Although some part of the observed association might be explained by known but unmeasured confounders (324), most of the studies of this meta-analysis controlled for primary socio-demographic factors (e.g., age or sex). Although smoking is a potential confounder of the association between alcohol and pain, our results show the magnitude of the pooled estimates did not differ much between studies that adjusted for smoking and studies that did not. However, residual confounding due to unknown factors may have distorted our results, as in any meta-analysis of observational studies. Although, so far, no genetic polymorphism has been shown to play the role of confounder of the relation of alcohol with chronic pain, we cannot rule out the existence of such a factor. However, the existence of such an unidentified factor, genetic or environmental, associated with both alcohol intake and pain, that could explain a high proportion of the observed association, is highly improbable. Even if this unidentified confounder could double the odds of chronic pain among individuals exposed to it (OR confounder-disease = 2) and, simultaneously, this factor happened to be twice more frequent among drinkers than among teetotalers (OR confounder-exposure = 2), the adjusted OR of the relation between alcohol and pain would still be 0.85 for any intake, and 0.78 for moderate intake, but 1.00 for heavy drinking (assuming one-third of people are exposed to this unknown factor) (235).

Pain, as a subjective and highly personal experience, is a very challenging outcome to measure. Most of the studies assessed pain through self-report only; therefore, the specificity and sensitivity of the self-report tests are probably lower than that of clinical tests. This may lead to the misclassified assignment of outcome to a different category than the one they should be in. In addition, misclassification of pain is considered independent of exposure, i.e. misclassification is similar in teetotalers and drinkers. This non-differential misclassification yields to an underestimation of the magnitude of the association (325).

Our findings show that the association of alcohol consumption with pain is stronger in women than in men. This finding may be related to the fact that women have higher pain sensitivity than men, including a lower pain threshold (the minimum stimulus intensity required to produce pain) (326). In addition, the different distributions of confounders, considering that some of the studies restricted for men or women were unadjusted for other factors, might explain the difference in results between men and women.

Potential publication bias is unlikely to explain our results, as the strength of association between alcohol consumption and pain was not meaningfully modified under extreme assumptions. Likewise, the funnel plot and Egger's asymmetry test confirmed the low possibility of publication bias in our results. Besides, although the Trim-and-Fill method imputed three additional studies, the corrected OR was even stronger the one we obtained initially.

We also found considerable effect heterogeneity between studies in many subgroup analyses. We, therefore, interpreted the results based on random effects estimates as recommended (197). Meta-analysis experts emphasize that no degree of heterogeneity is unacceptable if the data are correct (198), and that heterogeneity, due to the fact that data are collected using different methods in different populations, should be viewed as the "expectation, rather than the exception" (327).

Our meta-analysis shows that moderate alcohol consumption is associated with lower occurrence of pain. The results are compatible with plausible biologic mechanisms. Future studies should reduce measurement errors by 1) considering essential confounders such as smoking and depression, as well as the pattern of drinking beside the socio-demographic factors, 2) discovering whether there is a threshold for the preventive effects of alcohol consumption on pain. Furthermore, since a randomized controlled trial of alcohol use is not ethically feasible, the Mendelian randomization design could represent a good alternative (328). These studies can assess the association between alcohol and pain using genetic variants for enzymes involved in alcohol metabolism (329).

5.2 SLEEP QUALITY AS A MEDIATOR OF THE RELATION BETWEEN DEPRESSION AND PAIN

The present study explored the mediating role of sleep disturbance in the association between depression and pain. It confirmed that depression is correlated with worse sleep disturbance and pain and revealed that sleep disturbance may emerge as a mediating factor in the relationship between depression and pain. The mediation effect of sleep disturbance in the association between depression and pain was observed among studies of chronic pain outcomes and cohort design. However, the indirect effect of sleep disturbance was not observed in all study contexts; in fact, the mediation effect was non-significant in non-European, unadjusted, and low-quality studies.

The non-European subgroup is comprised of many different countries all over the world. Therefore, the impact of ethnic and/or cultural differences in depression and pain perceptions (42) could contribute to the lack of a significant indirect effect of sleep disturbance in the association between depression and pain in this subgroup. When we restricted our analysis to the studies carried out in the USA, no substantial change in the results was observed. There could be a stronger association between depression and pain in ethnic groups such as African Americans than among Caucasians (329) as the former group is more frequently subject to a variety of adverse psychosocial outcomes due to its increased levels of distress (330). In this case, the direct effect of depression on pain in the non-European subgroup, including the US population is so strong that the indirect effect via sleep disturbance is small. In other words, the direct relationship rather than the indirect mechanism dominates.

The relation between depression on pain found in our study is consistent with previous studies which have reported emotional distress as a risk factor of chronic pain (331,332). Moreover, our findings support the overall relation between sleep disturbance and pain, yet with small effect sizes and variation across study subgroups. Previous studies have reported that sleep quality predicts pain, which might be due to the fact that low sleep quality can exaggerate pain sensation (333) and weaken the ability to disengage from painful stimuli (334).

As mentioned earlier, our meta-analysis supports the hypothesis that sleep disturbance mediates the association between depression and pain. However, prior research has documented different directions of the relations among the three constructs (335–337). The interrelation between these variables explains the inconsistencies in the literature regarding these pathways. Studies have previously focused on depression as a mediator between pain and sleep (338,339). Also, pain can contribute to sleep and mood disturbance independently, suggesting that pain may affect sleep fragmentation and nightly awakenings, leading to reduced sleep quality (340) and depression over time (341). Although our study was restricted to longitudinal designs, the aforementioned reciprocal interactions could prove the possibility of reverse causation between the observed associations in this study.

A plausible pathobiological mechanism that could explain these associations is that pain, sleep, and depression share common neurobiological pathways, and alterations in these pathways could explain the observed association. Serotonin, for example, has long been recognized as a critical regulatory neurotransmitter in the sleeping and wakening cycle (342). Serotonin is also believed to play an essential role in the pathobiology of depression (343) and has been involved in pain

modulation (344). Therefore, some studies have suggested serotonergic signaling dysfunction as the underlying mechanism connecting pain, sleep dysfunction, and depression (345).

Furthermore, sleep disturbance may also serve as a moderator, with good sleep quality attenuating the effect of depression on pain, and poor sleep quality amplifying the effect of depression on pain. Sleep disturbance has been broadly associated with depression through common biochemical pathways and genetic factors (346). The interaction between depression and sleep disturbance could worsen pain perception (347).

To the best of our knowledge, this is the first meta-analysis assessing the indirect effect of a range of common sleep disorders in the association between depressive disorders and pain syndromes in the clinical and subclinical samples at any age. This study is particularly robust as we included longitudinal studies only. This knowledge represents a novelty in pain research and allows the design of better assessments and interventions. Nevertheless, our results should be interpreted in light of several limitations. First, although the findings from the restricted analyses largely agreed with the main analyses, publication bias may still influence the model parameters and effects. Second, most studies in this meta-analysis used self-report measures to assess depression, pain, and sleep. These measures may not reflect the symptoms as accurately as objective measures (348). However, all three factors are subjective in essence and it is their perception by the subject that takes a toll on the subjects' health. Third, between-study heterogeneity in the pooled effects was high in this meta-analysis and did not subside after stratification. This heterogeneity can be partially explained by differences in population characteristics and possibly unmeasured variables (349). In our meta-analysis, we interpreted the results based on random-effects estimates as recommended (196). Meta-analysis experts emphasize the fact that no degree of heterogeneity is unacceptable if the data are correct (197), and that heterogeneity, because data are collected using different methods in different populations, should be viewed as the 'expectation, rather than the exception' (326). Fourth, given the design of some of the primary studies, strict causal inference cannot be drawn. Future studies should prospectively explore the mediating mechanisms by implementing designs that ascertain the precedence of the independent variable (depression) on the mediator (sleep disturbance) and the mediator on the dependent variable (pain).

Understanding the nature and dynamics of the relations between depression, sleep disturbance, and pain can help develop an effective model for pain management. The evidence on the mediation effect may guide clinicians in the development and administration of interventions that focus not only on depression but also on sleep quality and disorders, in order to explore better therapeutic outcomes for pain management.

5.3 COHORT STUDY PART 1: QUALITY OF LIFE AND CHRONIC PAIN

To the best of our knowledge, this cohort study is the first to uncover the association between physical and mental health and chronic pain. We found that a higher PCS is associated with an important decrease in chronic pain incidence among young adults. However, the mental component summary score in our settings was not related to chronic pain occurrence. The sensitivity analyses confirmed our findings. Results were similar regardless of how the data were analyzed (complete case analysis, multiple imputations, or combined method of multiple imputation and inverse probability weighting).

Higher levels of physical well-being influence the function of endogenous pain inhibitory systems by releasing serotonin and endogenous opioids in the central nervous system, which decreases pain perception (351). Moreover, physical well-being may increase the endogenous analgesia capacity during the conditioned pain modulation process in healthy adults, resulting in reduced pain perception (352).

Additionally, in our study, almost three-fourths of students with the highest PCS scores had low-stress levels when they enrolled in the study. Low levels of perceived stress decrease the release of neurotransmitters, such as epinephrine, at sympathetic nerve terminals, which can reduce hyperalgesia and increase the pain threshold in nociceptors (353). Also, higher perceived stress may contribute to stress-system dysregulation and may increase the risk of chronic pain perception(354).

Students with higher physical and mental well-being reported higher physical activity and fewer comorbidities in this study. Previous studies have shown that more physically active individuals have a lower risk of developing chronic pain (75,355) and that individuals with comorbid conditions are more prone to report chronic pain(356).

Students with lower mental well-being may have insufficient personal coping resources and poor social network support(357), leading to a lack of reporting of their health problems, including chronic pain(358). Therefore, a differential misclassification may have biased our findings by increasing false-negative outcomes among students with lower MCS. This may explain the lack of association between MCS and chronic pain incidence in our results.

Accordingly, pain perception is an intrapersonal and interpersonal factor affected by personified expectations and lifestyle patterns and does not necessarily correspond to health conditions(359).

Chronic pain often occurs with an episodic pattern, alternating painful bouts with remission intervals(360). Therefore, some students may have previously experienced chronic pain and were in the remission interval at the beginning of the study. Yet, they were labeled as pain-free at baseline. In addition, these students may have low physical well-being resulting from previous chronic pain experiences that lasted until the study's beginning(361). Therefore, although students included in the analysis were pain-free for at least three months before the start of the study, some degree of reverse causation in our results cannot be ruled out if previous undetermined bouts of chronic pain existed.

Our analyses are adjusted for a wide range of demographic, lifestyle, and dietary variables; nonetheless, residual confounding from unknown variables, as in any observational study, might still be present.

The present study has further limitations. Pain perception can be modified by lifestyle, emotional, social, and cognitive changes(362). In our study, exposure, Health-Related QoL, was measured at baseline only, as continuous monitoring was not feasible in our settings. Therefore, some participants might have changed their exposure category during the follow-up. In addition, it has been discussed that health-related QoL is a subjective comparison between people's expectations and experiences and represents a concept beyond the physical and mental health status only(363). For example, the absence of mental problems does not forcedly indicate the presence of mental well-being(364), and patients suffering from severe diseases do not necessarily state having a poor health-related quality of life(365). The absence of measurement of genetic factors and personality traits (326) due to the online-based and self-report design represents another limitation of this study. Genetic factors could modify the relation between quality of life and pain occurrence. Previous studies showed that individuals with a low quality of life are less likely to respond to research studies and may leave the study during follow-up more frequently(366), a feature that may increase the risk of selection bias. However, this was unlikely to occur in our study as individuals who left the study after baseline assessment and those who completed the follow-up questionnaires had similar levels of MCS and PCS scores. Another limitation of our study is that the loss to follow-up in our study, although limited to 10% of the population, may have reduced the number of pain onsets during the follow-up, which may have decreased the statistical power of some of the assessed associations.

In conclusion, in this prospective cohort study, physical health-related QoL among university students was inversely associated with pain incidence. Part of the association might be due to the effect exerted by mediation factors such as stress level and physical activity, a hypothesis that needs further research. Multiple social, environmental, and emotional factors are responsible for chronic pain perception, no matter how clear-cut the etiology is. These factors also contribute to the quality of life. Therefore, the association between quality of life and chronic pain should be considered multidimensional. The aforementioned psychosocial factors are valued as modifiable factors. Consequently, it is important to consider patients' quality of life in the prevention and prognosis of chronic pain and integrate the appropriate interventions, especially on physical health-related quality of life, with pain-reducing strategies.

5.4 COHORT STUDY PART 2: CAUSAL VARIABLES, MEDIATORS, INTERACTORS AND CONFOUNDERS OF THE ASSOCIATION BETWEEN PHYSICAL WELL-BEING AND CHRONIC PAIN

To our knowledge, this was the first prospective cohort study to specifically examine the potential mediators, interactors, and confounders in the association between physical well-being and chronic pain occurrence.

In this study, perceived stress played an important role in mediating the effect of physical well-being on chronic pain onset. We showed that, approximately, one-seventh of the total effect of physical well-being on chronic pain development was mediated by perceived stress.

The role of mediator played by perceived stress may relate to the fact that students with higher physical well-being levels have better social support and a greater sense of individual cohesion to overcome stressors and life changes (367). Lower physical well-being is then expected to increase these individuals' stress levels. Higher stress levels induce lower thresholds of pain perception due to impaired dopaminergic activity in the nucleus accumbens and, consequently, may cause hyperalgesia(368–370). Moreover, the level of perceived stress in our study population was rather low, and it is plausible that higher levels of stress could reveal a stronger indirect effect between physical well-being and chronic pain through perceived stress.

Due to the physiological overlap that pain has with stress (371) and physical well-being (372), it would be reasonable to suspect that students who perceived more stress or lower physical well-being at baseline might have had chronic pain before starting the study; this may have caused potential reverse causation in our research. In addition, perceived stress could represent both a cause and a consequence of low physical well-being (373). This bidirectional association between physical well-being and stress can create a vicious cycle by promoting pain perception in students. Although our design was longitudinal, the aforementioned reciprocal inter-relation could be compatible with a reverse causation procedure between mediator and exposure since they were both collected at baseline.

Furthermore, our results suggest that physical activity interacts with physical well-being, and that students with low physical well-being and low physical activity levels had a higher incidence of chronic pain. Physical activity and exercise reduce the excessive sensitivity of central neurons by altering the neuroimmune signals in the central nervous system and increasing the release of endogenous opioids and serotonin in the brainstem pain inhibitory pathways(374–376).

Also, in this study, abstainer/low drinkers who had low physical well-being experienced more chronic pain than other subgroups. The analgesic effects of alcohol, described in previous studies, could explain this feature. Consuming a moderate amount of alcohol can increase the level of neurotransmitters in the central nervous system responsible for reducing the activity of neurons and decreasing pain experience(68,69,72).

The stratum-specific analysis showed that, in our study, smoking could be both a confounder and an interactor of the association between physical well-being and chronic pain. However, both interaction and confounding analysis showed that the impact of smoking in this association is so small that it can be dismissed.

The interrelation between psychosocial factors may also explain the results of this study. For example, low physical well-being among those with smoking or drinking profiles will deteriorate

stress coping skills by limiting adaptive coping strategies (377,378). As we showed, higher perceived stress can be responsible for part of the total effect between physical well-being and chronic pain.

The longitudinal character of the study supports the belief that the direct and indirect (through perceived stress) association between physical well-being and chronic pain may be causal. However, our results should be interpreted while considering some limitations. First, we should consider that pain status was assessed using a self-report questionnaire. Although the perception of pain is not clinically measurable, it is possible that using an active clinical examination for measuring the outcome could lead to other potential associations. Second, other potential confounder variables, such as personality traits and depression that could give a broader vision of the biopsychosocial model approach were not included. Finally, this longitudinal study measured exposure and mediators at baseline without lapses, and the temporal ambiguity between exposure (physical well-being) and mediator (perceived stress) cannot be disregarded.

Knowing the role of covariates in the relation between subjective exposures and outcomes is of paramount importance. For example, adjusting a mediator variable can block a causal path and distinguishing a confounder from an interactor provides a more accurate interpretation of the results.

In conclusion, perceived stress, as an emotional state, plays a relevant role in the relation between physical well-being and pain and might be regarded as an intermediate outcome for evaluating interventions aimed at reducing chronic pain in students. If perceived stress is elected as a high-priority intervention in pain management, physical well-being should be acknowledged as one of the determinants of perceived stress. Furthermore, these findings may enable professionals to distinguish high-risk from low-risk subgroups, focusing their interventions on subjects with lower physical well-being and levels of physical activity.

6 CONCLUSIONS

1. Alcohol drinking is associated with a moderate decrease in the risk of chronic pain. The dose-response meta-analysis showed that the relation could be curvilinear with low doses associated with lower pain occurrence and high doses indicating a global absence of association.
2. Depression is correlated with a higher probability of sleep disturbance and pain occurrence. Sleep disturbance emerges as a mediating factor in the relationship between depression and pain.
3. A higher degree of the physical component subgroup of health-related quality of life is associated with an important decrease in chronic pain incidence among young adults. However, the mental component summary score was not related to chronic pain occurrence.
4. Perceived stress is a *mediator* of the effect of physical well-being on chronic pain onset. Approximately, one-seventh of the total effect of physical well-being on chronic pain development was mediated by perceived stress.
   Physical activity *interacts* with physical well-being, and students with low physical well-being and low physical activity levels are at a higher risk of chronic pain. Likewise, abstainer/low drinkers who had low physical well-being experience more chronic pain than other subgroups.
   Smoking is both a *confounder* and an *interactor* of the association between physical well-being and chronic pain.

CONCLUSIONES

1. El consumo de alcohol se asocia con una disminución moderada del riesgo de dolor crónico. El metanálisis de dosis-respuesta mostró que la relación podría ser curvilínea con dosis bajas asociadas con menor aparición de dolor y dosis altas indicando una ausencia global de asociación.
2. La depresión se relaciona con una mayor probabilidad de alteración del sueño y aparición de dolor. La alteración del sueño parece ser un factor mediador en la relación entre depresión y dolor.
3. Un mayor grado del subgrupo del componente físico de la calidad de vida relacionada con la salud se asocia con una disminución importante en la incidencia de dolor crónico entre los adultos jóvenes. Sin embargo, el grado del componente mental no se relacionó con la aparición de dolor crónico.
4. El estrés percibido es un *mediador* del efecto del bienestar físico sobre la aparición del dolor crónico. Aproximadamente, una séptima parte del efecto total del bienestar físico sobre el desarrollo del dolor crónico es mediada por el estrés percibido. La actividad física es un factor de *interacción* con el bienestar físico, y los estudiantes con bajo bienestar físico y bajos niveles de actividad física tienen un mayor riesgo de dolor crónico. Del mismo modo, los abstemios/consumidores de baja cantidad de alcohol con grado de bienestar físico bajo experimentan más dolor crónico que otros subgrupos.

   El consumo de tabaco es un factor de *confusión* además de un factor de *interacción* en la relación entre bienestar físico y dolor crónico.

RESUMEN DE LA TESIS DOCTORAL

A dor crónica é un dos principais motivos para buscar atención médica. Representa unha carga económica considerable debido aos gastos sanitarios e á perda de produtividade. Así mesmo, a dor crónica pode provocar un deterioro físico, por causas como discapacidades e restricións nas actividades diarias, e implicacións psicolóxicas, como ansiedade e depresión. Ata hai pouco, a Asociación Internacional para o Estudo da Dor (IASP) definía a dor crónica como unha dor que persiste máis aló do tempo de curación normal, que se considerou de tres meses. Recentemente, solicitouse a un grupo de traballo do IASP que engada un código específico para a dor crónica á CIE-11 (Clasificación Internacional de Enfermidades da OMS, 11ª edición), para apoiar o feito de que a dor crónica é unha enfermidade de entidade "por dereito propio".

A dor crónica é un importante problema de saúde en todo o mundo, que afecta ao 19% dos europeos e ao 20,4% dos adultos estadounidenses. A nivel mundial, estímase que o 20% (que vai do 12% ao 30%) da poboación sofre dor crónica. Máis concretamente, un de cada nove adultos novos experimenta dor crónica ao longo da súa vida. Un estudo recente descubriu que a prevalencia da dor estandarizada por idade e sexo estimouse nun 27,5% (rango de 9,9% a 50,3%) en todo o mundo. A prevalencia da dor crónica estimouse nun 24,3% na poboación xeral en España.

Un estudo máis recente mostrou que a prevalencia é de 16,6. %, con maiores cifras en mulleres e participantes maiores. Estímase que aproximadamente 1 de cada 10 adultos recibe un novo diagnóstico de dor crónica cada ano.

Nos Estados Unidos, máis de 100 millóns de adultos sofren dor crónica, que é máis que a poboación total con diabetes, enfermidades cardíacas e cancro. Tres principais afeccións de dor crónica (dor de costas, trastornos musculoesqueléticos e dor de pescozo) están entre as catro principais causas de anos perdidos debido á discapacidade. Ademais, en 2017, o informe Global Burden of Disease concluíu que, entre as enfermidades non transmisibles, a dor musculoesquelética é a terceira causa de anos de vida axustados por discapacidade (DALY) en todo o mundo.

A dor crónica é un evento multidimensional afectado por factores biolóxicos, fisiolóxicos, psicolóxicos e sociais. Polo tanto, suxírese un modelo biopsicosocial como paradigma para comprender a dor crónica. Segundo este modelo, a experiencia da dor dun individuo está configurada por factores que son biolóxicos (por exemplo, susceptibilidade xenética, nutrición e funcións fisiolóxicas), psicolóxicos (por exemplo, emocións, experiencias e personalidade), sociais (por exemplo, ., ambiente, etc.). cultura, relacións interpersoais) e factores socioeconómicos.

Aínda que os efectos nocivos do consumo excesivo de alcohol se observan tanto en enfermidades transmisibles como non transmisibles, algúns estudos mencionan de forma controvertida os efectos positivos do consumo "non prexudicial" nalgúns resultados, como a diabetes tipo 2, os accidentes cerebrovasculares, as enfermidades cardiovasculares e as funcións cognitivas. función. Recentemente, dúas revisións de estudos experimentais demostraron que o alcohol podería exercer efectos analxésicos entre as persoas que xa sofren dor. Ademais, algúns estudos individuais demostraron que o consumo de alcohol pode estar fortemente asociado cun menor risco de dor. Ao mesmo tempo, outros estudos indicaron unha asociación cun maior risco de dor. Non obstante, a pesar da existencia de numerosos estudos, ata a data ningunha metaanálise resumira o efecto do consumo de alcohol na dor crónica. A través dunha metaanálise, avaliamos se os homes e mulleres que beben bebidas alcohólicas, en comparación cos abstemios ou os bebedores lixeiros, teñen un maior risco de sufrir dor crónica.

Incluíronse estudos de cohortes e de casos e controles que mediron a asociación entre a dor crónica e o consumo de alcohol e proporcionaron medidas de efecto e os seus correspondentes intervalos de confianza do 95% ou datos suficientes para o seu cálculo. Dezaseis estudos foron elixibles, cunha poboación total de 642.587 individuos. Para medir o risco de sesgo, utilizamos

a escala Newcastle-Ottawa aplicada ao noso contexto. As estimacións agrupadas de efectos fixos e aleatorios obtivéronse ponderando os ratios de probabilidades logarítmicas (OR) nos estudos de casos e controis e os ratios de taxas de incidencia logarítmica nos estudos de cohortes pola inversa da súa varianza. Calculamos os OR agrupados para calquera inxestión, inxestión moderada e alta inxestión de alcol. Para calcular unha estimación para a categoría "calquera inxestión" para un estudo determinado, agrupamos os OR para a inxestión moderada e a categoría de alta inxestión deste estudo sempre que estivesen dispoñibles. Cuantificamos a asociación dose-resposta entre o consumo de alcohol e a aparición de dor crónica. Realizamos unha metaanálise dose-resposta utilizando un modelo de efectos mixtos. Probouse a heteroxeneidade mediante a proba Q de DerSimonian e Laird e cuantificouse calculando a proporción da varianza total atribuíble á varianza entre estudos (Ri). Calculáronse modelos de efectos fixos e aleatorios, pero utilizouse o modelo de efectos aleatorios en caso de gran heteroxeneidade. A fonte de heteroxeneidade foi investigada mediante a realización de varias análises de subgrupos. Avaliamos o sesgo de publicación visualmente mediante un gráfico en funil e, máis formalmente, mediante a proba de regresión de Egger e o método Trim and Fill.

O consumo de alcohol está asociado a unha diminución do 24% da probabilidade de episodios de dor crónica (OR = 0,76, IC do 95%: 0,61-0,95). A asociación da alta inxestión de alcol coa dor non foi significativa (OR=0,89, IC 95%: 0,58-1,36). A magnitude da asociación negativa é máis forte nas mulleres que nos homes (OR mulleres=0,44; IC 95%: 0,14-1,37 e OR homes=0,75; IC 95%: 0,36-1,55). Observamos unha asociación non lineal entre o consumo de alcohol e a aparición de dor crónica (valor P para a non linealidade <0,001). Os OR por cuartil de dose de alcol foron os seguintes: OR2o cuartil=0,74; IC 95 %, 0,64-0,87; OR3o cuartil=0,67; IC 95%, 0,53-0,86; e OR4o cuartil=0,75; IC 95%, 0,50-1,14. Esta asociación observouse só para estudos de cohortes (OR = 0,77; IC 95%, 0,61-0,98) e estudos europeos (OR = 0,65; IC 95%, 0,48-0, 87). Os estudos con axuste completo para factores de confusión mostraron unha relación máis forte que aqueles con axuste incompleto (OR=0,69; IC 95%, 0,48-0,99 e OR=0,85; IC 95%, 0,65-1,11, respectivamente). Non se observou ningunha evidencia de sesgo de publicación, como o revela a forma simétrica global do gráfico de funil e a proba de regresión de Egger (valor de p = 0,78). O método Trim and Fill suxeriu a adición de tres estudos, pero o OR corrixido confirmou a presenza dunha asociación negativa, aínda máis forte da observada inicialmente, entre a exposición ao alcohol e a dor crónica (OR=0,67; IC 95 %, 0,54-0,84).

O consumo de alcohol presenta unha asociación inversa non lineal coa aparición de dor crónica. Unha posible explicación para estes resultados podería ser que as expectativas sobre a eficacia do alcohol como analxésico afectan a percepción da dor. Non obstante, mecanismos plausibles, como o bloqueo dos receptores da dor e a produción de ligandos opioides endóxenos, que reducen a transmisión do sinal de dor ao sistema nervioso central (SNC), poderían explicar este efecto protector do alcohol. Tamén son probables outras explicacións, incluíndo o efecto de confusión dos factores psicolóxicos sobre a asociación entre o consumo de alcohol e a dor crónica. As diferenzas nas asociacións entre poboacións europeas e non europeas pódense atribuír a diferentes culturas de consumo de bebidas e á diferente relación dos factores de confusión, como os hábitos de fumar, co consumo de alcohol.

A dor e a depresión representan dous problemas de saúde global con importantes consecuencias económicas. Non obstante, aínda que a literatura existente proporciona información sobre a relación entre a depresión e as condicións de dor, non hai evidencias de metaanálise que apoien o papel mediador da alteración do sono na asociación entre depresión e dor. Por iso, formulamos a nosa pregunta de investigación do seguinte xeito: En que medida a alteración do sono media na relación entre a depresión e a dor crónica, definida como a dor en calquera parte do corpo que persiste ou se repite durante máis de tres meses?

Buscamos de forma sistemática en Medline e noutras bases de datos relevantes artigos e identificamos estudos de cohortes e casos-control sobre a depresión, os trastornos do sono e a dor a condición de que os trastornos do sono e a depresión precedesen á dor. Sesenta e catro estudos foron elixibles, cunha poboación total de 139.684 individuos. Obtivemos coeficientes de relación directa e indirecta mediante o modelo de ecuacións estruturais metaanalíticas en dúas etapas (TSSEM). Agrupamos as matrices de correlación na etapa 1 usando un modelo multivariado de efectos aleatorios con estimación de máxima verosimilitud. Especificamos e estimamos un modelo de ecuación estrutural na etapa 2 usando a matriz de correlación agrupada e o tamaño total da mostra como entrada. Examinamos a heteroxeneidade mediante a análise de subgrupos e avaliamos a calidade dos estudos primarios mediante a escala de Lee et al (2015).

Atopamos un efecto de mediación parcial se importancia dos trastornos do sono na relación entre depresión e dor. O estatístico I2 (94-99%) e os resultados da proba Q indicaron unha gran heteroxeneidade na mostra global. Nas análises de subgrupos, observamos un efecto de contaxio significativo entre os resultados da dor crónica, o deseño de cohortes, os estudos realizados na poboación xeral e os estudos de alta calidade. O coeficiente agrupado de efecto indirecto foi de 0,03 (IC do 95% 0,01-0,05) e representou o 11% do efecto total da depresión sobre a dor. Este efecto indirecto tamén existía para estudos de cohortes (coeff. = 0,04, IC 95%: 0,02-0,06), estudos europeos (coeff. = 0,03, IC 95%: 0,01 -0,05) e estudos que se axustaron por factores de confusión (coeff. = 0,04, IC 95%: 0,02-0,09). O efecto mediador da alteración do soño na asociación entre a depresión e a dor crónica en países europeos, estudos de cohortes, estudos axustados e estudos con puntuacións de calidade altas foi do 27%, 6%, 40% e 18,5%, respectivamente.

Os trastornos do sono median parcialmente a asociación entre depresión e dor. Non obstante, o efecto de mediación non foi significativo en estudos non europeos de baixa calidade, non axustados. A disfunción da sinalización serotoninérxica pode ser o mecanismo subxacente que conecta a depresión, os trastornos do sono e a dor. A serotonina, que regula o ciclo sono-vixilia, pode desempeñar un papel esencial na patobioloxía da depresión e estivo implicada na modulación da dor. Ademais, a interacción entre a depresión e os trastornos do soño poden empeorar a percepción da dor, polo que os trastornos do sono tamén poden ser un factor moderador, cunha boa calidade do soño que atenúa o efecto da depresión sobre a dor e unha mala calidade do sono que amplifica este efecto. Non obstante, a interrelación recíproca entre a dor, a depresión e os trastornos do sono podería suxerir a posibilidade de causalidade inversa entre as asociacións observadas neste estudo.

A calidade de vida relacionada coa saúde engloba a saúde física, a disposición psicolóxica, a autosuficiencia, as relacións persoais, o apoio social real e o apoio social percibido nun contexto particular ou ambiente habitual. A calidade de vida demostrou ser un forte predictor de varios resultados relacionados coa saúde. Non obstante, ata a data ningún estudo examinou a asociación entre a calidade de vida como predictor e a dor crónica como resultado. Polo tanto, neste estudo de cohorte prospectivo, o noso obxectivo foi investigar a asociación entre os compoñentes físicos e mentais da calidade de vida e o risco de dor crónica entre os estudantes universitarios en España.

Este traballo forma parte do proxecto de cohorte multicéntrico Online Pain, Lifestyle and Diet, un estudo en liña no que participan estudantes universitarios españois, iranianos e marroquís. Esta parte da tese céntrase nun estudo de cohorte prospectivo realizado entre estudantes da Universidade de Santiago de Compostela, entre febreiro de 2019 e abril de 2020, no que participaron 1.842 universitarios. Os cuestionarios iniciais e de seguimento foron previamente validados na poboación española. Posteriormente, os participantes foron seguidos cada catro meses durante un ano para a aparición de episodios de dor crónica, definidos como dor recorrente durante máis de tres meses. O tempo de seguimento calculouse desde a data de finalización do cuestionario inicial ata o inicio do episodio de dor crónica, a perda do seguimento ou o final do estudo, o que ocorrese primeiro. Usamos modelos de regresión de Poisson para estimar o índice de incidencia (IRR) da asociación da dor crónica cos compoñentes físicos e mentais da calidade de vida en cada cuartil e os seus intervalos de confianza (IC) do 95%. Utilizouse un gráfico acíclico dirixido (DAG) para avaliar a relación entre exposición e resultado con factores de confusión e mediadores. Ademais, utilizamos análises de spline cúbica restrinxida para avaliar a relación entre as puntuacións continuas do subgrupo de compoñente mental e do subgrupo de compoñentes físicos e a incidencia da dor. Realizáronse análises de sensibilidade; utilizamos un método combinado de imputación múltiple e ponderación de probabilidade inversa (MI/IPW) para corrixir calquera posible sesgo diferencial no seguimento.

Un total de 1024 estudantes non tiñan dor ao inicio do estudo e formaron a nosa mostra. Observamos un total de 223,2 anos en risco entre 1.024 estudantes. Durante o seguimento, identificamos 584 novos casos de dor, cun total de 106,4 anos de risco, o que dá unha taxa de incidencia global de 5,4 ano-1. Despois de axustar por factores de confusión, observamos unha inversa entre o subgrupo do compoñente físico e a incidencia da dor. Un subgrupo de compoñentes físicos con puntuacións superiores a 50 asóciase cunha diminución de ata un 36% na incidencia de dor crónica. En comparación co primeiro cuartil, os estudantes do segundo, terceiro e cuarto cuartiles do subgrupo de compoñentes físicos tiveron unha TIR de 0,64 (IC 95%: 0,45, 0,92), 0,66 (IC 95%: 0,46, 0,94) e 0,64 (IC 95%: 0,46; 0,94). % IC: 0,45, 0,91) axustado por idade, sexo e calidade do sono. En cambio, non se observou ningunha asociación entre o subgrupo de compoñente mental e a dor crónica. As análises de spline cúbica restrinxidas mostraron unha tendencia xeral non lineal para a asociación de MCS e PCS con dor crónica. Na avaliación do sesgo de seguimento, os resultados das análises de robustez non

diferían significativamente dos obtidos nas análises orixinais, o que indica que as perdas durante o seguimento non sesgaron as nosas estimacións.

Descubrimos que un alto nivel do compoñente físico está asociado cunha diminución significativa da incidencia de dor crónica entre os adultos novos. Non obstante, a puntuación total do compoñente mental non estivo relacionada coa aparición de dor crónica. Os altos niveis do compoñente físico inflúen na función dos sistemas inhibidores da dor endóxenos mediante a liberación de serotonina e opioides endóxenos no sistema nervioso central, o que diminúe a percepción da dor. Os estudantes con baixo compoñente mental de calidade de vida poden ter recursos persoais de afrontamento insuficientes e un apoio deficiente das redes sociais, o que fai que non se informen dos seus problemas de saúde, incluída a dor crónica. Polo tanto, a clasificación errónea diferencial pode ter sesgado os nosos descubrimentos ao aumentar os resultados falsos negativos entre os estudantes con niveis de compoñente mentais máis baixos. Isto pode explicar a falta de asociación nos nosos resultados entre o compoñente mental e a incidencia da dor crónica. Aínda que os estudantes incluídos na análise estiveron libres de dor durante polo menos tres meses antes do inicio do estudo, non se pode descartar algún grao de causalidade inversa nos nosos resultados se houbo episodios previos de dor crónica non diagnosticados.

O benestar físico é un concepto multidimensional que abarca dimensións física, mental, social, cultural e cognitiva. A relación entre o benestar físico e a dor crónica é complexa e implica varias covariables subxectivas e obxectivas. Esta relación está mediada por factores que están presentes na vía causal (efecto indirecto) ou poden ser non mediados (efecto directo). Outros factores tamén poden desempeñar o papel de factores de confusión ou de interacción na relación entre o benestar e a dor. Para avaliar o papel mediador, de confusión ou de interacción que desempeñan as variables da calidade do sono, a actividade física, o estrés percibido, o tabaquismo e o consumo de alcohol na relación entre o benestar físico e a dor crónica, analizamos os datos dun estudo de cohorte prospectivo realizado. entre os estudantes universitarios.

Usamos a regresión de Poisson para obter índices de incidencia (IRR) para a asociación entre o benestar físico e a dor crónica. Usamos o Modelado de ecuacións estruturais xerais (GSEM) para descubrir se os potenciais mediadores (actividade física, estrés percibido, calidade do sono,

tabaquismo e consumo de alcohol) poden representar factores causais indirectos entre o benestar físico (exposición principal) e a dor crónica. Usamos a análise de estratos específicos para diferenciar o fenómeno de confusión do fenómeno de interacción. Despois de realizar a análise específica do estrato e decidir sobre a natureza de confusión e interacción das covariables, realizamos unha análise de interacción aditiva para as variables que non eran potencialmente elixibles como factores de confusión da asociación entre o benestar físico e a dor crónica. Calculamos o exceso de risco relativo axustado debido á interacción (RERI), a proporción atribuíble (AP) e a relación de sinerxía (S) para medir a interacción aditiva.

Un alto benestar físico está relacionado cunha gran diminución do risco de dor crónica (IRR Total Effect= 0,58; IC 95% 0,50-0,81). A análise da mediación revelou que o efecto indirecto do estrés percibido nesa relación foi: TIR do efecto directo natural = 0,92; IC do 95% 0,89-1,00 e que o estrés percibido media o 12,5% do efecto total do benestar físico sobre a dor crónica. Os IRR específicos do estrato dos fumadores actuais (IRR = 1,80; IC 95%: 1,05-2,81) e dos non fumadores (IRR = 1,52; IC 95%: 1,35-1,62) foron diferentes entre si, e ambos foron superiores aos TIR bruta, o que indica que o tabaquismo pode ser tanto un factor de confusión como un factor de interacción.

Ademais, a magnitude da asociación entre o benestar físico e a dor crónica no sono de baixa calidade (IRR = 1,54, IC 95%: 1,01-2,26) non é diferente da que ocorre no sono de alta calidade (IRR = 1,52, 2,26). IC 95%: 0,97-2,20). A estimación bruta desta asociación e as estimacións específicas do estrato son similares, o que indica que a calidade do sono non confunde nin interactúa na asociación entre a calidade do soño e a dor crónica. O RERI de benestar físico e actividade física sobre a dor foi de 0,25 (IC 95%: 0,13-0,60), o que indica que o efecto na escala aditiva da actividade física e o benestar físico xuntos foi maior que a suma dos efectos individuais. por separado. Así mesmo, comprobamos que o baixo benestar físico, cando se asocia coa ausencia de consumo de alcol, mostra un exceso de risco de dor (RERI = 0,11; IC 95%: 0,06-0,36).

Descubrimos que aproximadamente un sétimo do efecto total do benestar físico sobre o desenvolvemento da dor crónica estaba mediado pola percepción de estrés. Non obstante, debido á superposición fisiolóxica que a dor ten co estrés e o benestar físico, sería razoable

sospeitar que os estudantes que percibían máis estrés ou menos benestar físico na liña de base poderían ter dor crónica antes de comezar o estudo. Ademais, o estrés percibido pode representar tanto unha causa como unha consecuencia do baixo benestar físico. Aínda que o noso deseño foi lonxitudinal, a mencionada interrelación recíproca podería ser compatible cun procedemento de causalidade inversa nesta investigación. Por outra banda, a interacción observada entre o benestar físico e a actividade física pódese explicar polo aumento da liberación de opioides endóxenos e serotonina despois do exercicio. A interacción entre o consumo de alcohol e o benestar físico pódese explicar polos efectos analxésicos do alcohol, descritos en estudos anteriores.

Os nosos descubrimentos poden resultar útiles para distinguir os grupos de alto risco dos de baixo risco nas intervencións dirixidas a reducir a dor crónica.

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LIST OF PUBLICATION

PUBLICATIONS INCLUDED IN THIS DOCTORAL THESIS

Chapters 3, 4, 5: Karimi R, Mallah N, Nedjat S, Beasley MJ, Takkouche B. Association between alcohol consumption and chronic pain: a systematic review and meta-analysis. Br J Anaesth. 2022;129(3):355-365. ISSN: 0007-0912; DOI: 10.1016/j.bja.2022.03.010
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Chapters 3, 4, 5: Karimi R, Mallah N, Scherer R, Rodríguez-Cano R, Takkouche B. Sleep quality as a mediator of the relation between depression and pain: A systematic review and meta-analysis. Accepted for publication in Br J Anaesth on 15 January, 2023. (2021 Impact factor: 11.719; Position: First decile (D1), 2/35 journals).

Chapters 3, 4, 5: Karimi R, Mallah N, Prego-Domínguez J, Takkouche B. Quality of life and chronic pain: a cohort study among Spanish university students. Submitted to Affective Disorder on 29 September, 2022.

Chapters 3, 4, 5: Karimi R, Prego-Domínguez J, Takkouche B. Causal variables, mediators, interactors and confounders of the association between physical well-being and chronic pain: results from a Spanish cohort study. Submitted to American Journal of Preventive Medicine on 29 November, 2022.

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Roya Karimi´s contribution in the articles: Concept, data gathering, analyses, interpretation, and drafting the published and pending articles.

Conflict of interest:
The doctoral candidate declares no conflicts of interest related to her thesis..

APPENDIX 1: ARTICLE OF THE ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND CHRONIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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REVIEW ARTICLE

Association between alcohol consumption and chronic pain: a systematic review and meta-analysis

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Abstract

Introduction: Chronic pain represents a global health problem with a considerable economic burden. The relation of alcohol intake and chronic pain conditions was assessed in several studies with conflicting results. We used dose–response meta-analysis techniques to answer the question of whether alcohol intake is related to chronic pain occurrence.

Methods: We searched MEDLINE, Embase, and other databases to identify cohort and case-control studies on alcohol consumption and chronic pain. Sixteen studies were eligible with a total population of 642 587 individuals. Fixed-effects and random-effects pooled estimates were obtained by weighting log odds ratios (ORs) in case-control studies and log incidence rate ratios in cohort studies by the inverse of their variance. A heterogeneity assessment and a dose–response analysis were carried out. Quality scoring was also performed.

Results: Our results show that any alcohol consumption was related to lower odds of chronic pain (pooled OR=0.76; 95% confidence interval [CI], 0.61–0.95). The association was non-linear. The ORs by quartile of alcohol doses were as follows: $OR_{2nd\ quartile}$=0.74; 95% CI, 0.64–0.87; $OR_{3rd\ quartile}$=0.67; 95% CI, 0.53–0.86; and OR_{4th} quartile=0.75; 95% CI, 0.50–1.14. This association was observed for cohort studies (OR=0.77; 95% CI, 0.61–0.98) and European studies (OR=0.65; 95% CI, 0.48–0.87) only. Studies with complete adjustment for confounding factors showed a stronger relation than those with incomplete adjustment (OR=0.69; 95% CI, 0.48–0.99 and OR=0.85; 95% CI, 0.65–1.11, respectively).

Conclusion: Alcohol consumption presents a non-linear inverse association with the occurrence of chronic pain. Although plausible mechanisms could explain this protective effect, other explanations, including reverse causation, are probable.

Keywords: alcohol; chronic pain; dose–response; drinking; meta-analysis

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Editor's key points

- The relationship between alcohol intake and chronic pain conditions has been considered in several studies but results have been conflicting.
- Using meta-analytical techniques, the authors found that alcohol consumption has a non-linear inverse association with the occurrence of chronic pain. This association may be real, or it could represent inverse causation.
- Future research should assess the impact of potential confounders including smoking, depression, and drinking patterns.

Until recently, pain was considered a symptom of other diseases and not an independent pathological condition. This has contributed to the undervaluation of this entity by health professionals.[1] The International Association for the Study of Pain (IASP) and the WHO developed a new classification of chronic pain syndrome for the International Classification of Diseases, 11th Revision (ICD-11), in which persistent or recurrent pain lasting more than 3 months is defined as 'chronic pain'.[2]

Chronic pain is the leading contributor to years lived with disability (YLDs) worldwide.[3] In the USA, the prevalence of chronic pain is about 20% among adults, and 8% of them experience 'high-impact chronic pain' (i.e. chronic pain that frequently limits life or work activities).[4] The prevalence in the UK varies between 35% and 51%.[5]

More than 5% of all deaths and disability-adjusted life years (DALYs) are attributed to alcohol consumption.[6] In 2016, alcohol consumption was the seventh leading risk factor for both death and global disease burden, especially in Eastern Europe, most of Latin America, and southern sub-Saharan Africa.[7,8] In the USA, 86.3% of the adult population reported drinking alcohol at some point during their lifetime.[9]

Although harmful effects of heavy drinking are observed in both non-communicable and communicable diseases,[10,11] some studies mention the positive effects of 'nonharmful' drinking on some health-related outcomes, including type 2 diabetes,[12] stroke,[13] cardiovascular disease,[14] cognitive function,[15] and physical function.[16]

Recently, two reviews of experimental studies showed that alcohol may exert analgesic effects among people who already suffer from pain.[17,18] Some individual studies showed that alcohol consumption may be strongly related to a lowered risk of pain,[19] whereas other studies indicated a relation with an increased risk of pain.[20] However, despite the existence of numerous studies, no meta-analysis has summarised the effect so far. Using the PECO (Population, Exposure, Comparison, Outcome) framework, we sought to answer through a meta-analysis the question of whether men and women who drink alcoholic beverages, compared with teetotalers or occasional drinkers, are at increased risk for chronic pain.

Methods

We registered the protocol of this meta-analysis in The International Database of Prospectively Registered Systematic Reviews (PROSPERO), protocol number CRD42020166386, and carried it out according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[21]

Eligibility criteria

We included cohort and case-control studies that measured the association between chronic pain and alcohol consumption and provided effect measures (odds ratios [ORs] or incidence rate ratios [RRs]) and their corresponding 95% confidence intervals (95% CIs) or sufficient data for their calculation. We included studies regardless of their publication date or language. Letters, commentaries, editorials, opinion pieces, cross-sectional, and *in vitro* or studies on non-human subjects were not further considered.

Search strategy

We localised related studies by searching Medline, Embase, Conference Proceedings Citation Index – Science (CPCI-S), Open Access Theses and Dissertations (OATD), CINAHL, and the WHO Global Index Medicus (GIM) with its different regional databases – LILACS, AIM, IMEMR, IMSEAR, WPRIM – since inception until April 2021.

In Medline, we used the search syntax: (("chronic pain"[MeSH Terms]) OR ("fibromyalgia"[Title/Abstract]) OR ("rheumatoid arthritis"[Title/Abstract]) OR ("osteoarthritis"[Title/Abstract]) OR ("migraine"[Title/Abstract]) OR ("psoriatic arthritis"[Title/Abstract]) OR ("ankylosing spondylitis" [Title/Abstract]) OR ("systemic lupus" [Title/Abstract]) OR ("headache"[Title/Abstract]) OR ("widespread chronic pain"[Title/Abstract])) AND ((alcohol*[MeSH Terms]) OR (ethanol[MeSH Terms])) AND ((cohort) OR (prospective) OR (retrospective) OR (longitudinal) OR (case-control)).

We completed our search with free-text words, using broad concepts such as 'pain' and 'alcohol'. The search strategy was adapted to each of the other databases. To supplement the search, we reviewed manually the reference lists of each study retrieved from the databases and those of related reviews.[18,22]

When necessary, authors of published studies were contacted for clarification or the request of additional data.[23,24]

The search was developed by all authors and was completed by two of them (RK and NM). One of the authors subsequently reviewed the strategy (BT), and the results were compared. Duplicates were removed.

Data extraction and collection

Two authors (RK and SN) independently screened the titles and abstracts obtained through electronic and manual search, selected studies for full-text review, reviewed those selected studies, and extracted the data from studies deemed eligible. Disagreements on the eligibility of the articles were resolved by consensus or with the help of a third author (BT). Extracted data included author, year of publication, study location, study design, sample size, outcome, exposure measurement details, effect measures (OR or RR) and their 95% CIs, and adjustment, restriction, or matching factors. When adjusted effect measures were not available, we used crude effect measures.

Risk of bias in individual studies

To measure the risk of bias, we used those elements of the Newcastle–Ottawa scale that were applicable to our setting.[25] Two authors (RK and SN) performed the quality assessment independently. The detailed quality assessment scoring is presented in the Supplementary Table S1. Agreement between the two reviewers was assessed using Bland–Altman analysis.

We evaluated the following criteria. (1) Exposure ascertainment: if the alcohol consumption levels were described either quantitatively or by definite categories (1 point), else or unspecified (0 point). (2) Outcome ascertainment: pain was determined using objective measures such as clinical evidence, report, or examination (1 point), else or unspecified measures (0 point). (3) Comparison group: (a) for case-control studies: subjects of the control group were representative of the source population from which the cases have been selected (1 point), else (0 point); (b) for cohort studies, the unexposed group was drawn from the same source population as that of individuals who consumed alcohol (1 point), else (0 point). (4) Participation rate: (a) for case-control studies: the participation rate was at least 80% for cases and controls (1 point), else (<80% or unreported) (0 point); (b) for cohort studies, the rate of dropouts or losses to follow-up was less than 70% (1 point), else (>70% or unreported, 0 point). (5) Comparability: adjustment, matching, or restriction for age, sex, and smoking (1 point), else (incomplete control for the three variables or uncontrolled measurement) (0 point).

The points attributed to each criterion were summed to obtain a quality score of a maximum of 5 points. The quality score variable was subsequently dichotomised into high quality (>3 points) and low quality (≤3 points).

Statistical analysis

Pooled ORs and their 95% CIs were estimated by weighting the log ORs in case-control studies and log incidence rate ratios in cohort studies by the inverse of their variance. OR was considered an unbiased estimate of incidence rate ratio.[26] Heterogeneity was checked using DerSimonian and Laird's Q test and quantified by calculating the proportion of the total variance attributable to between-study variance (R_i).[27] We computed both fixed- and random-effects models but used the latter in case of large heterogeneity. Heterogeneity was considered substantial if $R_i \geq 0.75$. We investigated the source of heterogeneity by performing various subgroup analyses by study design, sex, pain location, and geographic regions, defined previously.[28] Subgroup analysis was planned before the initiation of the meta-analysis.

We calculated ORs for any intake, moderate intake, and high intake of alcohol. To compute an estimate for the category 'any drinking' for a given study, we pooled the ORs of the categories moderate intake and high intake of this study, whenever they were available.

The estimates of studies that did not provide data for different levels of alcohol intake but, instead, assessed alcohol intake on a yes/no basis, were included in the 'any intake' group. Following the CDC definition, we considered consumptions ≥15 drinks (a standard drink is equal to 14 g pure alcohol) or more per week for men and ≥8 drinks or more per week for women as heavy drinking.[29] 'Alcoholism',[20] 'hazardous' drinking,[30] and alcohol 'abuse'[31] were considered heavy drinking. Consumptions between 1 and 14 drinks week^{-1} for men and between 1 and 7 drinks week^{-1} for women formed the category of moderate drinking. When needed, we used the following category mid-points: no drinking, 0 drink week^{-1}; moderate drinking for males, 7 drinks week^{-1}; moderate drinking for females, 3.5 drinks week^{-1}; heavy drinking for males, 22 drinks week^{-1}; heavy drinking for females, 11 drinks week^{-1}.

Furthermore, we quantified the dose–response association between alcohol consumption and pain occurrence. In our setting, 'dose' represents the units of alcohol consumed per week. We undertook a dose–response meta-analysis using a one-stage mixed-effects model which takes heterogeneity across studies into account.[32] We flexibly modelled the dose, using restricted cubic splines with three knots fixed at 10th, 50th and 90th centiles of the distribution, and examined departure of the second spline from linearity. We then transformed the dose into quartiles of alcohol doses and estimated the ORs and their 95% CIs using the first quartile as a referent.

Assessment of publication bias

We evaluated publication bias visually using a funnel plot and then, more formally, using Egger's regression test[33] and the trim-and-fill method.[34]

Furthermore, we conducted a sensitivity analysis assuming that the results of case-control studies are less likely to be published when they present no effect. Therefore, we recalculated the pooled OR under the following extreme assumptions: (1) the case-control studies obtained in our search represent only half of the studies ever conducted, (2) the unpublished studies found a null association (OR=1) between alcohol consumption and pain, and (3) the average number of cases and control is similar in published and unpublished studies.

We carried out the analyses using the software HEpiMA version 2.1.3,[35] and STATA version 15 (Stata Corp., College Station, TX, USA).

Results

Study characteristics

The process of study localisation is summarised in Fig 1. A total of 16 studies – 13 cohort studies[19,20,24,30,36–44] and three case-control studies[31,45,46] – examined the association of alcohol consumption with pain and met the inclusion criteria of this meta-analysis (Table 1 and Fig 1). The study by Beasley and colleagues[19] included a cross-sectional analysis carried out within a well-defined cohort study. This study was then considered a cohort study. In a secondary analysis, this study was excluded to check whether it represented an influential point. Thanks to the authors' collaboration, we managed to include unpublished data from one study.[24] We excluded two articles from the analysis as the precedence of drinking over chronic pain was not met in the first one,[47] whereas the second study was concerned with drinking reduction in subjects who were all problem drinkers.[48]

The studies were published between 1988 and 2018, originated from nine countries and involved a total population of 642 587 individuals. The studies evaluated the association of alcohol intake with several pain conditions including chronic widespread pain, fibromyalgia, headache, knee pain, low back pain, and post-injury pain.

The study by Parreira and colleagues[37] provided effect measures corresponding to one additional alcoholic drink per week. Therefore, we calculated the OR and 95% CI corresponding to moderate intake and heavy intake, using the midpoint of each category.

Synthesis of results

Overall, any alcohol drinking is associated with 24% lower odds of chronic pain episodes (OR=0.76; 95% CI, 0.61–0.95) (Table 2 and Fig 2). The association was observed in cohort

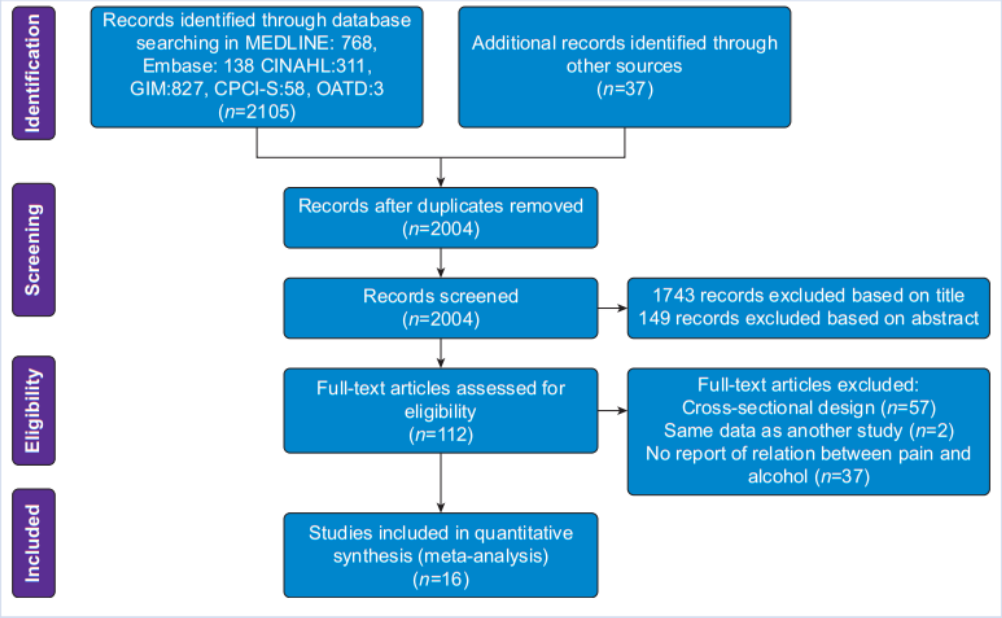

Fig 1. Flow diagram of the selection of studies of alcohol consumption and chronic pain.

studies (OR=0.77; 95% CI, 0.61–0.98) but not in case-control studies (OR=0.59; 95% CI, 0.12–2.94) (Table 2). The association of high alcohol intake with pain was not statistically significant (OR=0.89; 95% CI, 0.58–1.36) (Table 2).

Both males and females who drink alcohol are at lower odds of presenting chronic pain when compared with teetotalers. However, the CIs of the estimates for these categories are wide owing to the limited number of studies that provided association measures stratified by sex. Although not statistically significant, the magnitude of the negative association between alcohol drinking and occurrence of chronic pain is stronger in females than in males ($OR_{females}$=0.44; 95% CI, 0.14–1.37; OR_{males}=0.75; 95% CI, 0.36–1.55).

European individuals who consume alcohol are at lower odds of suffering chronic pain than those who do not consume alcohol (OR=0.65; 95% CI. 0.48–0.87). Conversely, alcohol intake was no associated with chronic pain in non-European populations (OR=0.97; 95% CI, 0.70–1.33) (Table 2).

Stratifying the studies by pain location showed lower odds of lower back pain in subjects consuming alcohol than in those who do not drink alcohol (OR=0.69; 95% CI, 0.48–0.98) (Table 2). The rest of pain syndromes did not show significant association with alcohol consumption.

Dose–response meta-analysis

Four publications provided enough data for dose–response analysis, and a fifth report included data for men and women independently, making a total of six studies included in the dose–response analysis. The six studies encompassed 403 521 individuals and 7343 pain episodes.[19,38,41,42,44] We observed a non-linear association between alcohol consumption and the occurrence of chronic pain (P-value for non-linearity <0.001) (Fig 3).

The results by quartile of distribution, using the quartile with lower intake as a reference, were as follows: $OR_{2nd\ quartile}$=0.74 (95% CI, 0.64–0.87); $OR_{3rd\ quartile}$=0.67 (95% CI, 0.53–0.86); and $OR_{4th\ quartile}$=0.75 (95% CI, 0.50–1.14).

Quality rating

The Bland–Altman agreement analysis showed that the quality rating by the two reviewers fell within the accepted limits of agreement. The average disagreement between the two raters was close to zero (T=0; 95% CI, −0.23 to 0.23), and the proportional bias was not statistically significant (T=0.87; 95% CI, −0.15 to 0.37), indicating that scoring was similar between raters. Eleven of the 16 studies scored more than 3 points in the quality assessment and were classified as high-quality studies. The magnitude of association was similar in low quality and high-quality studies ($OR_{low\text{-}quality}$=0.74; 95% CI, 0.36–1.54 and $OR_{high\text{-}quality}$=0.76; 95% CI, 0.59–0.97).

Six studies adjusted for age, sex, and smoking. The association between alcohol intake and chronic pain was significant for adjusted studies, but not for unadjusted studies ($OR_{adjusted\ studies}$=0.69; 95% CI, 0.48–0.99) (Table 2).

Only two studies adjusted for mental health disorders such as depression.[30,41] We carried out an additional analysis on any drinking which excludes those studies. The random-effects pooled estimate was OR=0.75 (95% CI, 0.59–0.95), almost identical to those of the original analysis.

Table 1 Main characteristics and odds ratios of any drinking, moderate drinking, and heavy drinking of alcohol in included studies. 95% CI, 95% confidence interval; CWP, chronic widespread pain; LBP, low back pain; OR, odds ratio; SES, socio-economic status

Authors, year	Country	Setting	Study size or #cases/ #controls	Any drinking OR (95% CI)	Moderate drinking OR (95% CI)	Heavy drinking OR (95% CI)	Adjustment, restriction, or matching variables	Outcome
Cohort studies								
Daoust and colleagues,[20] 2018	Canada	Patients from trauma centre	95 134	1.41 (1.18–1.69)	–	1.41 (1.18–1.69)	Age, health insurance, follow-up duration	Post-injury pain
Parreira and colleagues,[37] 2017	Australia	General male population >70 yr	1685	1.00 (0.30–3.37)	1.00 (0.32–3.58)	1.00 (0.03–60.48)	Sex, socio-demographic and lifestyle factors, comorbidities	LBP
Beasley and colleagues,[19] 2016	UK	General population 40–69 yr from UK biobank	500 000	0.45 (0.43–0.48)	0.50 (0.46–0.56)	0.44 (0.42–0.47)	Age, sex, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status	CWP
McBeth and colleagues,[41] 2014	UK	General population >50 yr from a general practice)	4326	0.98 (0.93–1.02)	0.75 (0.63–0.88)	1.00 (0.91–1.05)	Age, sex, education, social networks, smoking, anxiety, BMI, health impairments	CWP
Mundal and colleagues,[42] 2014	Norway	General population >20 yr)	19 192	0.85 (0.77–0.94)	–	–	Age, sex, marital status, education, exercise, chronic disease at baseline	CWP
Muraki and colleagues,[43] 2012	Japan	General population 23–95 yr	2262	0.91 (0.73–1.14)	–	–	Unadjusted	Knee pain
Skillgate and colleagues,[44] 2009	Sweden	Employees of the public sector	6532	0.76 (0.57–1.02)	0.76 (0.57–1.02)	–	Age, sex, pain intensity, SES, quality of life, other diseases, exercise, sleep, BMI, snuff use, geographical area	LBP
Rivara and colleagues,[30] 2008	USA	Patients 28–84 yr from trauma centres	3047	0.74 (0.61–0.89)	0.85 (0.67–1.09)	0.60 (0.44–0.81)	Age, sex, ethnicity, education, preinjury health, comorbidity, illicit drug use, depression, activities of daily living, injury characteristics	Post-injury pain
Wober and colleagues,[24] 2007	Austria	Migraineurs >18 yr	327	0.62 (0.57–0.67)	–	–	Age, sex, marital status, number of children, education, occupation, comorbidity, lifestyle, smoking, nutrition	Headache
Ang and colleagues,[36] 2006	USA	Gulf War veterans	370	0.20 (0.10–0.60)	–	–	Age, sex, race, marital status, income, military status	LBP
Hestbaek and colleagues,[40] 2006	Denmark	Subjects from twin registry 12–22 yr	6554	0.82 (0.61–1.10)	0.87 (0.61–1.23)	1.25 (0.76–2.06)	Age, sex, smoking, BMI	CWP

Continued

Table 1 Continued

Authors, year	Country	Setting	Study size or #cases/ #controls	Any drinking OR (95% CI)	Moderate drinking OR (95% CI)	Heavy drinking OR (95% CI)	Adjustment, restriction, or matching variables	Outcome
Bergman and colleagues,[39] 2002	Sweden	General population 20–74 yr	2425	0.65 (0.43–0.98)	0.81 (0.49–1.35)	0.42 (0.21–0.85)	Age, sex, SES, education, emigrant status, smoking, family history of chronic pain	LBP
O'Connor and colleagues,[38] 1992	USA	Newly enlisted in the Army	160	1.23 (0.57–2.63)	0.99 (0.40–2.41)	2.21 (0.46–9.56)	Sex	CWP
Case-control studies								
Al-Allaf and colleagues,[45] 2003	UK	Hospital fibromyalgia patients	40/37	0.10 (0.03–0.29)	0.10 (0.03–0.29)	–	Age, sex	Fibromyalgia
Boisset-Pioro and colleagues,[31] 1995	Canada	Hospital patients with rheumatic diseases	83/161	1.64 (0.74–3.64)	–	1.64 (0.74–3.64)	Sex	Fibromyalgia
Ryden and colleagues,[46] 1989	USA	Hospital employees	84/168	1.13 (0.92–2.86)	–	–	Age, sex, place of work	LBP

No evidence of publication bias was observed as revealed by the globally symmetrical shape of the funnel plot (Fig 4) and Egger's regression test (P=0.78). The Trim and Fill method suggested the addition of three studies, but the corrected OR confirmed the presence of a negative association, even stronger than that observed initially, between alcohol exposure and chronic pain (OR=0.67; 95% CI, 0.54–0.84).

The association between alcohol intake and chronic pain held under our sensitivity analysis with extreme assumptions (OR=0.79; 95% CI, 0.64–0.97).

Furthermore, the association between alcohol intake and chronic pain was not meaningfully modified after exclusion of the study by Beasley and colleagues.[19] The random-effects pooled measures, after excluding this study, were as follows: $OR_{moderate\ intake}$=0.76 (95% CI, 0.63–0.93); $OR_{heavy\ intake}$=0.99 (95% CI, 0.75–1.30); $OR_{any\ intake}$=0.82 (95% CI, 0.69–0.97).

Discussion

This meta-analysis suggests that alcohol drinking is associated with a moderate decrease in the risk of chronic pain. The dose–response analysis showed that the relation could be curvilinear with low doses associated with lower pain occurrence and high doses indicating a global absence of association.

One possible explanation of these results could be that the expectations about the effectiveness of pain relievers affect pain perception. As alcohol is known as a substance with analgesic effects, expecting a reduction in pain among patients after alcohol consumption can manipulate and increase the primary effect of alcohol on pain.[49]

The association observed is likely to be confounded by psychological factors such as depression. On the one hand, some of the perceived pain episodes are caused by depression without any other neurological cause. On the other hand, drinking is frequent in people with depression. As alcohol consumption improves the general mood of depressed people temporarily, drinkers are likely to cope with pain because of mood improvement after consuming alcohol, not because of alcohol itself.[50,51] However, in our meta-analysis, the results obtained after exclusion of the two studies that adjusted for mental disorders were almost identical to those of the complete analysis.

In this meta-analysis, the protective association of alcohol and pain was observed in studies carried out in Europe only. The effect of alcohol drinking on pain may vary in different parts of the world, owing to different patterns of drinking. In Europe, alcohol is integrated into routine life and is consumed daily (wet culture), whereas in the USA, alcohol is less regularly consumed, but more often in massive amounts related to intoxication (dry culture).[52] It is then likely that frequent alcohol intoxication and withdrawal experiences, which are more probable in non-European countries, dysregulate the function of brain stress and reward circuits, and cause deficiency in the activity of the endogenous opioid peptide system, inducing hyperalgesia, a characteristic symptom of alcohol withdrawal.[53,54] On the other side, routine alcohol consumption lowers the pain threshold; in other words, routine alcohol consumers, such as European drinkers, are more sensitive to the analgesic effects of alcohol. Alcohol may help European drinkers endure the pain for a more extended period.[55] These differences of associations between European and non-European populations may also be attributable to the differing relation of confounders, such as smoking habits, with alcohol consumption. Additional factors such as genetic

Table 2 Pooled odds ratios (OR) and 95% confidence intervals (CIs) of alcohol consumption and chronic pain. *Proportion of total variance attributable to between-study variance

	Number of studies	OR (95% CI) fixed effects	OR (95% CI) Random effects	R_I^*	Q test P-value
Alcohol consumption					
Any alcohol consumption	16	0.78 (0.76–0.80)	0.76 (0.61–0.95)	0.98	0.00001
Moderate intake	9	0.62 (0.58–0.68)	0.69 (0.54–0.89)	0.86	0.00001
Heavy intake	9	0.77 (0.74–0.80)	0.89 (0.58–1.36)	0.99	0.00001
Study design					
Cohort	13	0.78 (0.76–0.80)	0.77 (0.61–0.98)	0.98	0.00001
Case control	3	0.74 (0.43–1.24)	0.59 (0.12–2.94)	0.89	0.00001
Pain location					
Chronic widespread pain	5	0.80 (0.77–0.82)	0.79 (0.52–1.21)	0.99	<0.0001
Fibromyalgia	2	1.40 (0.76–2.56)	1.40 (0.76–2.56)	0.00	0.35
Low back pain	5	0.71 (0.57–0.89)	0.69 (0.48–0.98)	0.49	0.15
Post injury	2	1.03 (0.90–1.17)	1.02 (0.54–1.92)	0.96	<0.0001
Geographical location					
European	8	0.77 (0.74–0.79)	0.65 (0.48–0.87)	0.99	<0.0001
Non-European	8	1.00 (0.89–1.11)	0.97 (0.70–1.33)	0.83	<0.0001
Sex					
Male	3	0.48 (0.46–0.51)	0.75 (0.36–1.55)	0.99	0.03
Female	3	0.45 (0.42–0.49)	0.44 (0.14–1.37)	0.99	0.0001
Adjustment					
Not adjusted or unspecified	10	0.91 (0.84–0.97)	0.85 (0.65–1.11)	0.88	<0.0001
Adjusted	6	0.76 (0.74–0.78)	0.69 (0.48–0.99)	0.99	<0.0001
Quality score					
High score	11	0.78 (0.76–0.80)	0.76 (0.59–0.97)	0.98	<0.0001
Low score	5	0.88 (0.72–1.08)	0.74 (0.36–1.54)	0.90	0.0009

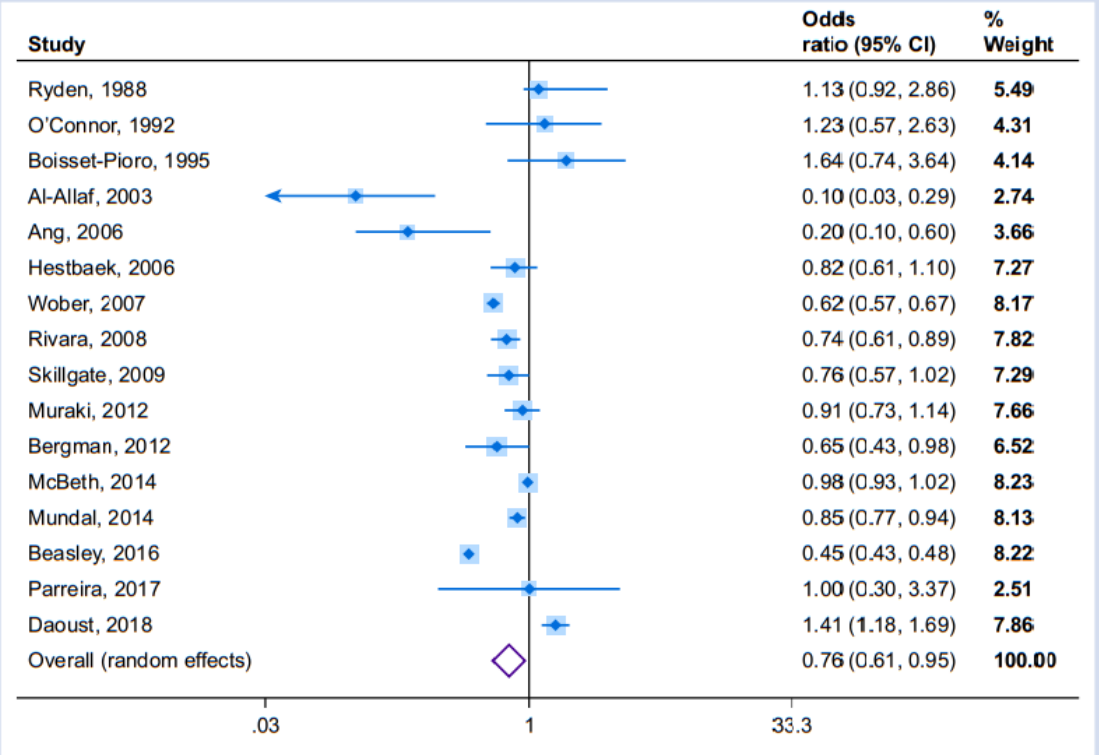

Fig 2. Forest plot of study-specific and random effect pooled OR of alcohol consumption and chronic pain. CI, confidence interval; OR, odds ratio.

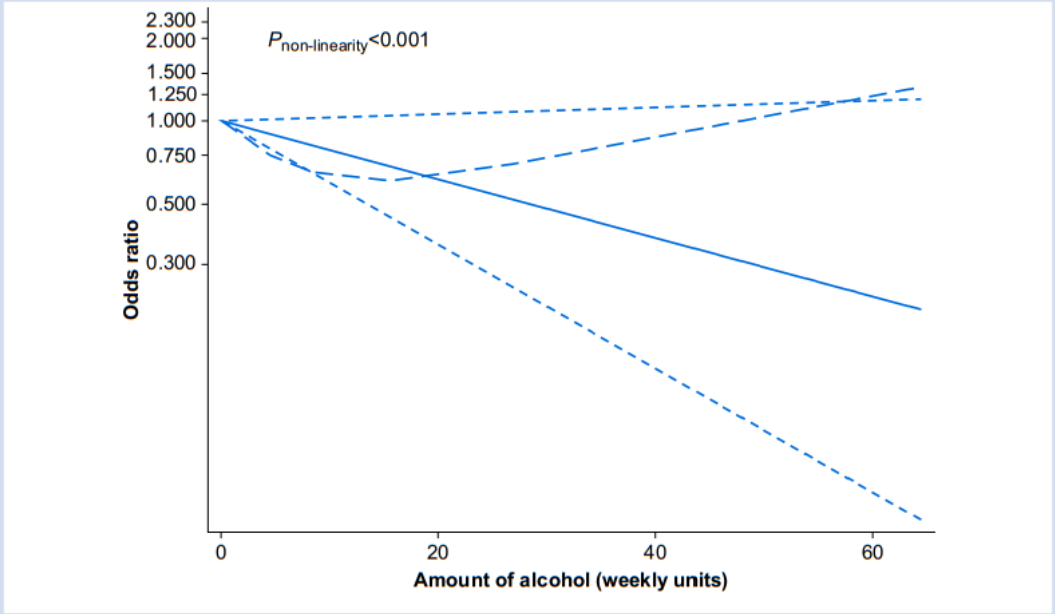

Fig 3. Dose–response analysis of the association between alcohol consumption and pain. Solid line represents summary odds ratios. Short-dashed lines represent the lower and upper bounds of confidence intervals. The long-dashed line represents summary odds ratios using non-linear assumption.

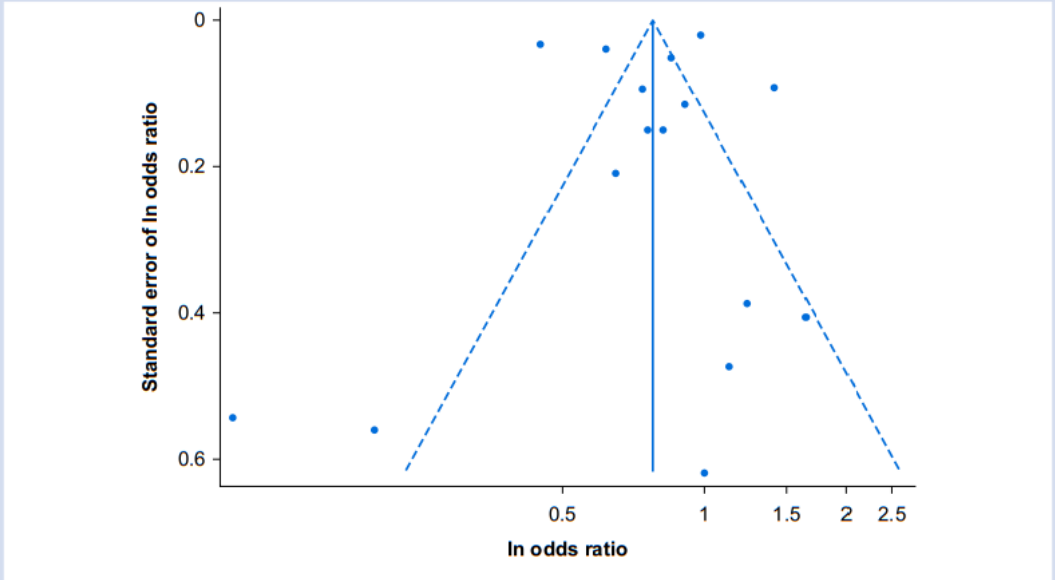

Fig 4. Funnel plot of log odds ratio (OR) vs standard error of log OR of alcohol consumption and chronic pain.

factors may also play a role of effect modifiers. It is known that several genetic factors from immune, inflammatory, and stress-related pathways are associated to chronic pain.[56] The distribution of these genes may present differences between Europe and the USA.

Animal studies showed that alcohol could partially block pain receptors.[57] The same effect was observed in humans.[58] Another plausible mechanism is that ethanol mimics the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain, which binds to GABA receptors and inhibits neural signalling.[59] Another research suggested that alcohol consumption produces a dose-related release of the endogenous opioid ligands, which reduces the transmission of pain signals to the CNS.[60] Alcohol affects various neurotransmitter mechanisms, including serotonin.[61] Serotonin plays a role in improving mood, sleep, and pain; moreover, alcohol increases the nervous system's serotonin release.[62] People experiencing pain may take related medications to manage this disorder, and alcohol can increase the effects of the medication that operate through the CNS.[63]

Although some part of the observed association might be explained by known but unmeasured confounders,[64] most of the studies of this meta-analysis controlled for primary socio-demographic factors (e.g. age or sex). Although smoking is a potential confounder of the association between alcohol and pain, our results show the magnitude of the pooled estimates did not differ much between studies that adjusted for smoking and studies that did not. However, residual confounding attributable to unknown factors may have distorted our results, as in any meta-analysis of observational studies. Although, so far, no genetic polymorphism has been shown to play the role of confounder of the relation of alcohol with chronic pain, we cannot rule out the existence of such a factor. However, the existence of such an unidentified factor, genetic or environmental, associated with both alcohol intake and pain, that could explain a high proportion of the observed association, is highly improbable. Even if this unidentified confounder could double the odds of chronic pain among individuals exposed to it (OR confounder-disease=2) and, simultaneously, this factor happened to be twice more frequent among drinkers than among teetotalers (OR confounder-exposure=2), the adjusted OR of the relation between alcohol and pain would still be 0.85 for any intake, and 0.78 for moderate intake, but 1.00 for heavy drinking (assuming one-third of people are exposed to this unknown factor).[65]

Pain, as a subjective and highly personal experience, is a very challenging outcome to measure. Most of the studies assessed pain through self-report only; therefore, the specificity and sensitivity of the self-report tests are probably lower than that of clinical tests. This may lead to the misclassified assignment of the outcome. In addition, misclassification of pain is considered independent of exposure, that is misclassification is similar in teetotalers and drinkers. This non-differential misclassification leads to an underestimation of the magnitude of the association.[26]

Our findings show that the association of alcohol consumption with pain is stronger in women than in men. This finding may be related to the fact that women have higher pain sensitivity than men, including a lower pain threshold (the minimum stimulus intensity required to produce pain).[66] In addition, the different distributions of confounders, considering that some of the studies restricted for men or women were unadjusted for other factors, might explain the difference in results between men and women.

Potential publication bias is unlikely to explain our results, as the strength of association between alcohol consumption and pain was not meaningfully modified under extreme assumptions. Likewise, the funnel plot and Egger's asymmetry test confirmed the low possibility of publication bias in our results. Besides, although the trim-and-fill method imputed three additional studies, the corrected OR was even stronger than the one we obtained initially.

We also found considerable effect heterogeneity between studies in many subgroup analyses. We, therefore, interpreted the results based on random-effects estimates as recommended.[28] Meta-analysis experts emphasise that no degree of heterogeneity is unacceptable if the data are correct,[67] and that heterogeneity, because data are collected using different methods in different populations, should be viewed as the 'expectation, rather than the exception'.[68]

Our meta-analysis shows that moderate alcohol consumption is associated with lower occurrence of pain. The results are compatible with plausible biologic mechanisms. Future studies should reduce measurement errors by (1) considering essential confounders such as smoking and depression, and the pattern of drinking beside the socio-demographic factors, and (2) discovering whether there is a threshold for the preventive effects of alcohol consumption on pain. Furthermore, because a randomised controlled trial of alcohol use is not ethically feasible, the Mendelian randomisation design could represent a good alternative.[69] These studies can assess the association between alcohol and pain using genetic variants for enzymes involved in alcohol metabolism.[70]

Authors' contributions

Conception of research idea: BT
Study design: BT
Supervision of data analysis and interpretation: BT
Data analysis and interpretation: NM, RK
Data extraction: RK, SN
Literature review: BT
Drafting of the manuscript: BT
Critical review and revision of the manuscript: NM, MJB
All authors reviewed the manuscript and approved it for publication.

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Declarations of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.03.010.

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Handling editor: Jonathan Hardman

De: BJA <em@editorialmanager.com>
Fecha: dom., 15 ene. 2023 19:46
Para: MALLAH NARMEEN <narmeen.mallah@usc.es>
Asunto: Decision on submission to British Journal of Anaesthesia

Manuscript Number: BJA-D-22-01574R2
Sleep Quality as a mediator of the relation between depression and pain: a systematic review and meta-analysis

Dear Dr Mallah,

I have now received our expert reviewers' reports on this manuscript submitted for consideration by the *British Journal of Anaesthesia*. I am pleased to inform you that I am prepared, in principle, to accept this manuscript for publication in the journal once minor revisions have been made. The revision will need to be submitted within 90 days (or 30 days for Editorials).

Please include a detailed, point-by-point explanation of how you have responded to each of the points raised by the reviewers. Please make sure that you highlight the changes made in your manuscript using track changes or red font (not red background). Please consult the instructions to the authors for submitting your detailed point-by-point response to the reviewers' comments; do not include these in the cover letter. Please also ensure that you have taken into consideration all the editorial requirements (detailed below); failure to adhere to these requirements is likely to delay processing your manuscript and may necessitate further revision.

Your manuscript must be submitted as a revision.

To submit your revised manuscript, please log in as an author at *British Journal of Anaesthesia*, and navigate to the "Submissions Needing Revision" folder under the Author Main Menu.

NOTE: For additional details regarding acceptable file formats, please refer to the Guide for Authors at: http://www.elsevier.com/journals/bja/0007-0912/guide-for-authors

Kind regards,

Jonathan G Hardman
Editor
British Journal of Anaesthesia

Reviewer 2: I agree with the revisions made on the second revised version of this manuscript and have no further comment.

APPENDIX 2: QUESTIONNAIRES

DATOS XERAIS

Sexo

Home
Muller

Ano de nacemento **…….**

Altura en centimetro **…….**
Peso en quilogramos **…….**

Nivel de estudios dos seus país

Pai:

Ningun
Estudos primarios
Estudos secundarios
Estudos profesionais de grao medio
Estudos profesionais de grao superior
Estudos universitarios

Nai:

Ningun
Estudos primarios
Estudos secundarios
Estudos profesionais de grao medio
Estudos profesionais de grao superior
Estudos universitarios

¿Cal é a súa situación laboral actual?

Desempregado/perceptor de renda básica (RISGA ou similar)
Desempregado con prestación por desemprego
Traballador en activo
Estudante a tempo completo
Pensionista/xubilado

ENFERMIDADES DIAGNOSTICADAS

Marque, se ten algunha, as enfermedades diagnosticadas por un médico que padeza. Pode marcar varias á vez.

Artrite (Artrite Reumatoide e Osteoartrite)
Osteoporose
Asma
EPOC, Bronquite crónica, ou Enfisema
Anxina de peito
Insuficiencia ou arritmia cardiaca
Infarto de miocardio
Enfermidades neurolóxicas (tales como Parkinson ou Esclerose múltiple)
Accidente cerebrovascular
Insuficiencia vascular perférica
Diabetes (tipo I ou II)
Enfermidade gastrointestinal (úlcera, refluxo ou hernia de hiato)
Depresión
Ansiedade
Déficits visuais (tales coma cataratas, glaucoma ou dexeneración macular)
Déficits auditivos (sordeira severa, incluso con aparatos)
Enfermidades dexenerativas da columna vertebral (hernia discal, estenose medular ou dor de espalda crónica)

CONSUMO DE TABACO

Vostede...

Non fuma nin fumou nunca
Non fuma agora
Fuma ocasionalmente
Fuma diariamente

¿Fumou máis de 100 cigarrillos en total na súa vida?

Sí
Non

Número de cigarrillos ó día (en número) …….

¿Cantos anos leva fumando?

<2
2-5
6-15
15-25
>25

Se é ex-fumador, ¿cantos anos fumou?

<2
2-5
6-15
15-25
>25

¿Canto tempo hai que o deixou?

<6 meses
6 meses - 1 ano
1-5 anos
6-10 anos
11-20 anos
>20 anos

¿Cantos pitillos adoitaba fumar Ó DÍA? …….

¿Cantos pitillos fuman agora en total ó día na súa casa, excluído vostede? ..….

CONSUMO DE ALCOHOL

Viño branco (copas ou vasos) …….

Viño tinto (copas ou vasos) …….

Cervexa (xerras, latas ou botellas) …….

Licores, sós ou incluíndo os combinados con refrescos (copas ou vasos) ……..

CALIDADE DE VIDA

En xeral, vostede diría que a súa saúde é

Excelente
Moi boa
Boa
Regular
Mala

As seguintes preguntas refírense a actividades ou cousas que vostede podería facer nun día normal. A súa saúde actual, ¿limítao para facer estas actividades ou cousas? Se é así, ¿cánto?

	Sí, limítame moito	*Sí, limítame un pouco*	*Non, non me limita nada*
Esforzos moderados, como mover unha mesa, pasar a aspiradora, xogar ós bolos ou camiñar unha hora			
Subir varios pisos pola escaleira			

Durante as 4 últimas semanas, ¿con qué frecuencia tivo algún dos seguintes problemas no seu traballo ou nas súas actividades cotidianas, a causa da súa saúde física?

	Sempre	*Case sempre*	*Algunhas veces*	*Case nunca*	*Nunca*
¿Fixo menos do que quixera ter feito?					
¿Estivo limitado no traballo ou outras actividades?					

Durante as 4 últimas semanas, ¿con qué frecuencia tivo algún dos seguintes problemas no seu traballo ou nas súas actividades cotiás, a causa dalgún problema emocional (como estar triste, deprimido ou nervioso)?

	Sempre	*Case sempre*	*Algunhas veces*	*Case nunca*	*Nunca*
¿Fixo menos do que quixera ter feito?					
¿Fixo o seu traballo ou outras actividades cotiás menos coidadosamente ca de costume?					

Durante as 4 últimas semanas, ¿ata qué punto a dor lle dificultou o seu traballo habitual (incluído o traballo fóra da casa e as tarefas domésticas)?

Nada
Un pouco
Regular
Bastante
Moitísimo

As seguintes preguntas refírense a cómo se sentiu e cómo lle foron as cousas durante as 4 últimas semanas. En cada pregunta responda o que se pareza máis a cómo se sentiu vostede. Durante as 4 últimas semanas, ¿con qué frecuencia.

	Sempre	*Case sempre*	*Moitas veces*	*Algunhas veces*	*Case nunca*	*Nunca*
...se sentiu calmado e tranquilo?						
...tivo moita enerxía?						
...se sentiu esanimado e deprimido?						

Durante as 4 últimas semanas, ¿con qué frecuencia a saúde física ou os problemas emocionais lle dificultaron as súas actividades sociais (como visitar ós amigos e familiares)?

Sempre
Case sempre
Algunhas veces
Case nunca
Nunca

ACTIVIDADE FÍSICA

Durante os últimos 7 días, ¿en cántos realizou actividades físicas intensas tales como levantar pesos pesados, cavar, facer exercicios aeróbicos ou andar rápido en bicicleta?

0
1
2
3
4
5
6
7

Habitualmente, ¿cánto tempo en total adicou a unha actividade física intensa nun deses días?

Menos de 15 minutos
Entre 15 e 30 minutos
De 30 minutos a 1 hora
Máis dunha hora
Non sabe/non está seguro

Durante os últimos 7 días, ¿en cántos realizou actividades físicas moderadas tales como transportar pesos liviáns, ou andar en bicicleta a velocidade regular? Non inclúa camiñar

0
1
2
3
4
5
6
7

Habitualmente, ¿cánto tempo en total adicou a unha actividade física moderada nun deses días?

Menos de 15 minutos
Entre 15 e 30 minutos
De 30 minutos a 1 hora
Máis dunha hora
Non sabe/non está seguro

Durante os últimos 7 días, ¿en cantos camiñou polo menos 10 minutos seguidos?

0
1
2
3
4
5
6
7

Habitualmente, ¿cánto tempo en total adicou a camiñar nun deses días?

Menos de 15 minutos
Entre 15 e 30 minutos
De 30 minutos a 1 hora
Máis dunha hora
Non sabe/non está seguro

Durante os últimos 7 días, ¿cánto tempo pasou sentado durante un día hábil (indique horas e/ou minutos)?

Menos de 1 hora
Entre 1 e 2 horas
De 2 a 4 horas
Máis de 4 horas
Non sabe/non está seguro

ESTRÉS PERCIBIDO

Puntuando de 0 (nada) a 4 (moito), durante os últimos 3 meses globalmente vostede diría que se sentiu...

	Nada	*Algo*	*Regular*	*Bastante*	*Moito*
Incapaz de controlar cousas importantes na súa vida					
Sen confianza para manexar os seus problemas persoais					
Que as cousas non lle van ben					
Con tantos problemas que se sentiu sobrepasado					

CALIDADE DO SONO

As seguintes preguntas refírense á forma en que normalmente durmiu durante o último mes. As súas respostas intentarán axustarse da maneira máis exacta ó acontecido durante a maior parte dos días e noites do último mes.

Durante o último mes...

¿Cal foi, normalmente, a súa hora de deitarse? .....

¿A que hora se levantou habitualmente pola mañá? .....

¿Cánto tempo tardou en quedar a durmir?

0-15 minutos
16-30 minutos
31-60 minutos
Máis dunha hora

¿Cántas horas calcula que terá durmido verdadeiramente cada noite durante o último mes? (o tempo pode ser diferente do que pasou na cama) .....

Para cada unha das seguintes preguntas, escolla a resposta que máis se axuste ó seu caso. Intente contestar a TODAS as preguntas.

Durante o último mes, cántas veces tivo vostede problemas para durmir a causa de:

	Ningunha vez no último mes	***Menos dunha vez por semana***	***Unha ou dúas veces por semana***	***Tres ou máis veces por semana***
Non poder conciliar o sono na primeira media hora				
Espertarse durante a noite ou de madrugada				
Ter que levantarse ó servicio				
Non poder respirar ben				
Tusir ou roncar ruidosamente				

Sentir frío				
Sentir demasiada calor				
Ter pesadelos ou malos somos				
Sufrir dolores				
Outros				

Durante o último mes, ¿cómo valoraría, en conxunto, a calidade do seu sono?

Bastante boa
Boa
Mala
Bastante mala

Durante o último mes:

	Ningunha vez no último mes	***Menos dunha vez por semana***	***Unha ou dúas veces por semana***	***Tres ou máis veces por semana***
¿Cántas veces terá tomado mediciñas (pola súa conta ou receitadas polo médico) para durmir?				
¿Cántas veces sentiu somnolencia mentres conducía, comía ou desenrolaba outra actividade?				

Durante o último mes, ¿representou para vostede moito problema o ter ánimos para realizar algunha das actividades detalladas na pregunta anterior (conducir, comer, outras)?

Ningún problema
Só un leve problema
Un problema
Un grave problema

PRESENCIA DE DOR

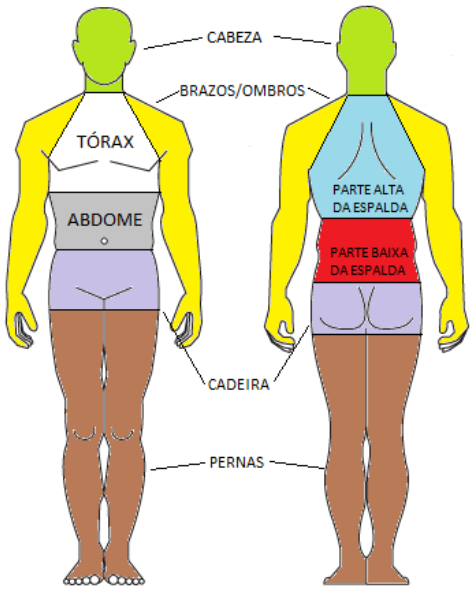
¿Tivo dor de forma persistente (contínua ou intermitentemente) nalgunha parte do seu corpo durante os últimos tres meses?

Sí
No

Indique a zona ou zonas do corpo nas que tivo dor (pode marcar varias á vez)

Cabeza
Parte alta da espalda
Parte baixa da espalda
Pernas
Brazos e/ou ombros
Tórax
Abdome
Cadeira

Partes do corpo descritas na pregunta:



¿Con qué frecuencia tivo dor nalgunha desas partes?

Menos dunha vez por mes
Entre 1 e 3 veces por mes
1 vez por semana
2-4 veces por semana
Diariamente

¿Cando ten dor, soe tomar analxésicos (paracetamol, ibuprofeno, etc..) para calmalo?

Sí
No

CARACTERÍSTICAS DEL DOLOR

Marque aquellos números que describen mejor la intensidad del dolor y los síntomas relacionados que sintió durante la semana pasada. Utilice el 0 si la palabra no describe el dolor o los síntomas relacionados (cuestionario en castellano por motivos de derechos de autor).

0= sin dolor / 10= el peor dolor posible (Valor por defecto 0)

Dolor como pulsaciones	1 2 3 4 5 6 7 8 9 10
Dolor como una sacudida	1 2 3 4 5 6 7 8 9 10
Dolor como una puñalada	1 2 3 4 5 6 7 8 9 10
Dolor agudo	1 2 3 4 5 6 7 8 9 10
Dolor como un calambre	1 2 3 4 5 6 7 8 9 10
Dolor que corroe	1 2 3 4 5 6 7 8 9 10
Dolor ardiente	1 2 3 4 5 6 7 8 9 10
Dolor sordo	1 2 3 4 5 6 7 8 9 10
Dolor aplastante	1 2 3 4 5 6 7 8 9 10
Sensibilidad al tacto	1 2 3 4 5 6 7 8 9 10
Dolor como un desgarro	1 2 3 4 5 6 7 8 9 10
Agotador, extenuante	1 2 3 4 5 6 7 8 9 10
Que marea	1 2 3 4 5 6 7 8 9 10
Angustioso	1 2 3 4 5 6 7 8 9 10
Cruel, que atormenta	1 2 3 4 5 6 7 8 9 10
Dolor como una descarga eléctrica	1 2 3 4 5 6 7 8 9 10
Dolor helado	1 2 3 4 5 6 7 8 9 10
Punzante	1 2 3 4 5 6 7 8 9 10
Dolor causado por un leve roce	1 2 3 4 5 6 7 8 9 10
Picor	1 2 3 4 5 6 7 8 9 10
Cosquilleo u hormigueo	1 2 3 4 5 6 7 8 9 10
Entumecimiento	1 2 3 4 5 6 7 8 9 10

INTERNATIONAL THESIS DOCUMENTS

PROGRAMA DE DOUTORAMENTO EN
Epidemioloxía e Saúde Pública
pd.epidemioloxia@usc.es

AUTORIZACIÓN DA CAPD DA MOBILIDADE DE ESTUDANTES DE DOUTORAMENTO

A Comisión Académica do Programa de Doutoramento en Epidemioloxía e Saúde Pública, na súa reunión do 10/12/2021 acordou autorizar a mobilidade da estudante **R o y a K a r i m i** para realizar unha estadía de investigación no marco do Programa ERASMUS+ Prácticas na Universidade de Oslo, desde o 04/02/2022 ata o 07/05/2022.

En Santiago de Compostela, a 10 de decembro de 2021

O Coordinador do PD e presidente da CAPD

MONTES MARTINEZ AGUSTIN - 76804086W

Firmado digitalmente por MONTES MARTINEZ AGUSTIN - 76804086W
Nombre de reconocimiento (DN): c=ES, serialNumber=IDCES-76804086W, givenName=AGUSTIN, sn=MONTES MARTINEZ, cn=MONTES MARTINEZ AGUSTIN - 76804086W
Fecha: 2021.12.11 22:08:12 +01'00'

Agustín Montes Martínez

ç

UNIVERSIDADE DE SANTIAGO DE COMPOSTELA
OFICINA DE MOBILIDADE
Pavillón Estudiantil, 1º Andar
Campus Vida
15782-Santiago de Compostela
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D. Victor Arce Vázquez, Vicerrector de Estudiantes y Proyección Internacional de la Universidad de Santiago de Compostela expide la siguiente:

CREDENCIAL DE ESTUDIANTE DE INTERCAMBIO ERASMUS+

A favor de **Roya Karimi [Y7670599K]** estudiante de la **E SANTIAG01 - UNIVERSIDAD DE SANTIAGO DE COMPOSTELA**, que realizará una movilidad Erasmus+ Prácticas para estudiantes de Doctorado en la **N OSLO01 - Universitetet i Oslo** (España) al amparo del programa de intercambio Erasmus+ existente entre ambas instituciones durante el curso académico 2021/2022

Duración del Intercambio: **14/03/2022 – 13/06/2022**

Y para que así conste a petición del interesado/a, firmo la presente en Santiago de Compostela, a 10/03/2022.

El Vicerrector de Estudiantes e Internacionalización

Vicerrector de Estudiantes e Internacionalización
Víctor Arce Vázquez

Víctor Arce Vázquez

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SUPERVISOR REPORT / INFORME DEL TUTOR
Erasmus+ Traineeship PhD / Prácticas de doctorado

I. STUDENT

Student's name: ***Roya Karimi***
DNI/NIE: ***Y7670599K***
Home University: ***Universidade de Santiago de Compostela - E SANTIAG01***
Host institution: ***University of Oslo***
Academic year: 2021-2022

II. PERFORMANCE REPORT

As a supervisor, please report briefly how the performance of the doctoral student was during his/her research stay:

The performance of Roya Karimi was excellent. She carried out a substantial work in project proposed for this research stay. In addition, she attended actively to different research and training seminars at the Department of Psychology at the University of Oslo.

Please select the overall performance of the doctoral student:

Qualitative assessment	Please, select with a X which one corresponds
EXCELENT	x
VERY GOOD	
GOOD	
POOR	
VERY POOR	

III. RESPONSIBLE PERSON IN THE RECEIVING INSTITUTION

Name: ***Rubén Rodríguez Cano.***
Function (please select): ***Primary mentor during the stay.***
E-mail: ***r.r.cano@psykologi.uio.no***

Fdo.: Rubén Rodríguez Cano.

Signature
In, 13 of 06 of 2022

Copy of the favourable report

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral Técnica

Secretaría Técnica
Comité Autonómico de Ética da Investigación de Galicia
Secretaría Xeral. Consellería de Sanidade
Edificio Administrativo San Lázaro
15703 SANTIAGO DE COMPOSTELA
Tel: 881546425. Correo-e: ceic@sergas.es

galicia

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN DE SANTIAGO-LUGO

Guillermo José Prada Ramallal, Secretario del Comité de Ética de la Investigación de Santiago-Lugo,

CERTIFICA:

Que este Comité evaluó en su reunión del día 26 de octubre de 2017 el estudio:

Título: Estudo sobre os factores de risco da dor crónica
Promotor: Bahi Takkouche
Tipo de estudio: Outros
Versión: v2
Código del Promotor: BT-RDC-2017-01
Código de Registro: 2017/452

Y, tomando en consideración las siguientes cuestiones:

- La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los requisitos legales aplicables, y en particular la Ley 14/2007, de investigación biomédica, el Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humana, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica, la ORDEN SAS/3470/2009, de 16 de diciembre, por la que se publican las Directrices sobre estudios Postautorización de Tipo Observacional para medicamentos de uso humano, y la Circular nº 07/2004, de investigaciones clínicas con productos sanitarios.
- La idoneidad del protocolo en relación con los objetivos del estudio, justificación de los riesgos y molestias previsibles para el sujeto, así como los beneficios esperados.
- Los principios éticos da Declaración de Helsinki vigente.
- Los Procedimientos Normalizados de Trabajo del Comité.

Emite un dictamen **FAVORABLE** para la realización del estudio **por el/la investigador/a del centro**:

Centros	**Investigadores Principales**
C.H. Universitario de Santiago	Jesús Prego Domínguez

En Santiago de Compostela, a 3 de noviembre 2017.

El Secretario del Comité Territorial de Ética de la Investigación de Santiago Lugo,

XUNTA DE GALICIA SECRETARÍA XERAL TÉCNICA COMITÉS DE ÉTICA DA INVESTIGACIÓN CONSELLERÍA DE SANIDADE

guillermo.jose.prada.ramallal@sergas.es
2017.11.02 14:59:03 +02'00'

Guillermo José Prada Ramallal

XUNTA DE GALICIA
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Secretaría Técnica
Comité Autonómico de Ética da Investigación de Galicia
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Guillermo José Prada Ramallal, Secretario del Comité de Ética de la Investigación de Santiago-Lugo,

HACE CONSTAR QUE:

1.- El Comité Territorial de Ética de la Investigación de Santiago-Lugo cumple tanto en su composición como en sus PNTs los requisitos legales vigentes (RD 1090/2015 de ensayos clínicos, y la Ley 14/2007 de Investigación Biomédica).

2.- La composición actual del Comité Territorial de Ética de la Investigación de Santiago-Lugo es:

- **Juan Manuel Vázquez Lago (Presidente).** Médico especialista en Medicina Preventiva y Salud Pública. Área de Gestión Integrada de Santiago.
- **Pilar Rodríguez Ledo (Vicepresidenta).** Médico especialista en Medicina Familiar y Comunitaria. Área de Gestión Integrada de Lugo.
- **Guillermo José Prada Ramallal (Secretario).** Médico especialista en Farmacología Clínica. Área de Gestión Integrada de Santiago. Fundación Ramón Domínguez.
- **Lorenzo Armenteros del Olmo (Vicesecretario).** Médico especialista en Medicina Familiar y Comunitaria. Área de Gestión Integrada de Lugo.
- **Francisco Campos Pérez.** Biólogo. Instituto de Investigación Sanitaria de Santiago de Compostela.
- **Rosana Castelo Domínguez.** Farmacéutica de Atención Primaria. Área de Gestión Integrada de Santiago.
- **Ricardo García Martínez.** Licenciado en Derecho. Área de Gestión Integrada de Lugo.
- **Jaime Gulín Dávila**. Farmacéutico especialista en Farmacia Hospitalaria. Área de Gestión Integrada de Lugo.
- **Victor Herrán Carreira.** Paciente. ADIL-Asociación de Diabéticos Lucense.
- **María Jesús Lamas Díaz.** Farmacéutica especialista en Farmacia Hospitalaria. Área de Gestión Integrada de Santiago.
- **Carlos Rodríguez Moreno.** Médico especialista en Farmacología Clínica. Área de Gestión Integrada de Santiago.
- **Rafael Carlos Vidal Pérez.** Médico especialista en Cardiología. Área de Gestión Integrada de Lugo.
- **María Jesús Wandosell Picatoste.** Enfermera. Área de Gestión Integrada de Santiago.

Para que conste donde proceda, y a petición del promotor/investigador, en Santiago de Compostela, a 3 de noviembre de 2017.

El Secretario del Comité Territorial de Ética de la Investigación de Santiago Lugo,

XUNTA DE GALICIA SECRETARÍA XERAL TÉCNICA COMITÉS DE ÉTICA DA INVESTIGACIÓN CONSELLERÍA DE SANIDADE

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Guillermo José Prada Ramallal

Chronic pain is one of the leading causes of healthcare seeking. It is a multidimensional experience affected by biological, physiological, psychological, social, and contextual factors. In this doctoral thesis, we conducted a dose-response meta-analysis to assess the effect of alcohol consumption on chronic pain. Also, we evaluated the direct and indirect effects of depression on pain through sleep disturbance using a two-stage meta-analytic structural equation modeling. Furthermore, we conducted a cohort study to assess the impact of the health-related quality of life (well-being) on chronic pain incidence. Finally, we evaluated the causal role of covariates in the association between physical well-being and chronic pain through mediation analysis and stratum-specific analysis.