Investigating the Psychosocial Factors, Pain Characteristics, and Biological Markers for Opioid Use in Chronic Non-cancer Pain Patients

Azin Zare

Faculty of Faculty of Dental Medicine and Oral Health Sciences

McGill University

Montreal, Quebec, Canada

Jun 2022

Table of Contents

Abstract

Background Chronic pain has been identified as one of the ten most common reasons for primary care visits globally, being represented as a disease on its own. So far, opioid analgesics have been widely prescribed to patients suffering from chronic non-cancer pain (CNCP) due to their potential pain relief properties, particularly in the United States and Canada. However, the use of these medications in the context of CNCP has remained controversial, as there are concerns regarding reported public health challenges following long-term opioid therapy, such as opioid misuse and addiction. One major unanswered question is what makes a chronic pain patient more likely to be prescribed opioids among individuals recruited from the general population. Better understanding the characteristics of chronic non-cancer pain patients, determining prescribed opioid use, and opioid-related disorders will improve inform prescribing decisions on opioid analgesics.

Objective To estimate the extent to which biological, psychological, and social factors predict opioid use in a large cohort of CNCP patients.

Methods This population-based study used the prospective cohort of the UK Biobank. A machine learning approach was used to derive pain and pain-agnostic models predictive of opioid use. Models were developed using a sample of 178,763 CNCP patients from the baseline data (2006-2011) (i.e., train set) and validated using a left-out sample of 17,045 CNCP patients who have data available in a follow-up visit (6 to years later) (i.e., test set). Classification accuracy and correlation measures were used to evaluate the performance of the models. Regular prescription opioid use identified and confirmed at data collection visit was used as the outcome. Measures of C-reactive protein (CRP) collected from blood samples were assessed for their association with the predictive

models. Diagnosis on opioid-related disorders, as per ICD-10, were tested for the associations with the expression of the pain-agnostic model.

Results Of 195,808 CNCP patients included in the study, 110,712 (56.54%) were female and the mean (SD) age was 57.03 (8.02) years. 20,895 (11.7%) individuals from the train set, and 912 (5.4%) individuals from the test set used prescribed opioids. The pain and pain-agnostic models predicted opioid use with a good classification accuracy ($AUC_{pain} = 0.70$, $AUC_{pain\text{-}agnostic} = 0.75$). Models showed acceptable classification accuracy for predicting within-individual changes in opioid use between the baseline and follow-up visit. The pain-agnostic model was highly expressed in CNCP patients diagnosed with an opioid-related disorder. Levels of CRP were significantly associated with the expression of the pain-agnostic model ($r = 0.26$, $p<0.001$).

Conclusion Our results show a dissociation between opioid users and non-opioid users at two time points. This study suggests that a pattern of psychosocial risk factors associated with a biological marker of inflammation could be a common predictor for opioid use among chronic non-cancer pain patients. Identifying the associated characteristics in these individuals could help improve the assessment of risks and benefits of chronic opioid use in certain subpopulations and will be a step towards improving the safety and effectiveness of chronic pain treatment.

Résumé

Contexte La douleur chronique est l'une des dix raisons les plus courantes pourquoi les gens visitent leur médecin dans le monde. Les opioïdes sont de puissants analgésiques qui sont souvent prescrits aux patients souffrant de douleurs chroniques non cancéreuses (CNCP) en raison de leurs propriétés analgésiques. Cependant, la prescription d'opioïdes reste controversée, car leur utilisation est parfois associée aux abus et à la dépendance. Cette étude vise à mieux comprendre les caractéristiques de patients souffrant de douleur chronique susceptibles de se voir prescrire des opioïdes et de développer des troubles liés aux opioides.

Objectif Estimer dans quelle mesure les facteurs biologiques, psychologiques et sociaux prédisent l'utilisation d'opioïdes dans une grande cohorte de patients atteints de CNCP.

Méthodes Dans cette étude, nous avons utilisé la cohorte prospective du UK Biobank. Une approche d'apprentissage automatique a été implémentée pour dériver des modèles prédictifs basés sur les caractéristiques de la douleur ou sur des variables psychosociales (modèles agnostiques à la douleur) pour l'utilisation d'opioïdes. Ces modèles ont été développés à partir d'un échantillon de 178 763 patients CNCP et l'utilisation régulière d'opioïdes sur ordonnance fut confirmée lors de la visite initiale. De plus, des prélèvements sanguins ont été utilisés afin de mesurer les niveaux de protéine C-réactive (CRP). Ces marqueurs inflammatoires ont été corrélés avec les facteurs de risque identifié par nos modèles prédictifs. Les facteurs de risques identifiés par nos modèles prédictifs ont finalement été testés chez les participants avec un diagnostic des troubles liés aux opioïdes.

Résultats Sur 195 808 patients CNCP inclus dans l'étude, 110 712 (56,54 %) étaient des femmes et l'âge moyen était de 57,03 (STD : 8,02) ans. 20 895 (11,7 %) patients inclus dans l'échantillon

de découverte (training set) et 912 (5,4 %) patients dans le groupe de validation utilisaient des opioïdes prescrits par un médecin. Nos modèles basés sur les caractéristiques de douleur ou sur les facteurs psychosociaux ont tous deux prédit l'utilisation d'opioïdes avec une bonne classification (aire sous la courbe = 0.70-0.75). De plus, les modèles ont montré une précision de classification acceptable pour prédire les changements intra-individuels dans la consommation d'opioïdes entre la visite de référence et la visite de suivi. Le modèle agnostique de la douleur était plus fortement exprimé chez les patients CNCP diagnostiqués avec un trouble lié aux opioïdes. Finalement, les niveaux de CRP étaient significativement associés à l'expression du modèle agnostique de la douleur ($r = 0,26$, $p<0,001$).

Conclusion Cette étude identifie les facteurs de risque psychosociaux associés à la prescription d'opioïdes et au diagnostic du trouble liés aux opioïdes. L'identification des caractéristiques associées chez ces personnes pourrait aider à améliorer l'évaluation des risques et des avantages de l'utilisation chronique d'opioïdes dans certaines sous-populations et constituerait une étape vers l'amélioration de l'efficacité des traitements prescrits pour la douleur chronique.

Acknowledgement

I would like to express my most sincere gratitude to my supervisor, **Dr. Etienne Vachon-Presseau**, the kindest and most understanding mentor I could have asked for. Thanks for believing in me and granting me the opportunity to join your research team. You have always supported me in every possible way and provided encouragement while sharing your vast knowledge with me. I am forever grateful for all your empathy and invaluable guidance throughout my graduate program journey.

I would like to thank my thesis advisory committee, **Dr. Luda Diatchenko** and **Dr. Marc Martel**, for providing me with insightful comments and expert direction. I was extremely fortunate to receive their feedback in every step of my thesis. I am also grateful to **Dr. Mathieu Roy**, for his guidance during our journal club and lab meeting discussions.

I would also like to give thanks to my dearest lab mates, **Jax**, **Gianluca**, **Christophe, Matt**, and **Ronrick**, who became great friends of mine. Thanks for staying by my side and providing me with feedback on my project. Thanks for creating an exciting research environment and making me feel like home while being away from my home and family. Moreover, a special thanks to **Christophe**, without whose support the data preparation of this project was not possible. I am also thankful to **Ellen** for her kind assistance and contribution.

I am grateful to **Crystal Noronha** and **Despoina Moirakidou,** for their patience and prompt answers to my concerns throughout the program.

I cannot express enough thanks to my kind friend **Dana**. Thanks for continuously cheering me up, always being around, and being the one that I could constantly rely on. I would also like to

give special thanks to my dear friend, **Kimia**, who supported me before and throughout the journey.

I am deeply grateful to my parents, **Shahram** and **Ziba**, and my parent-in-laws, **Hossein** and **Manijeh**, for their unconditional love and support and keen interest for my academic achievements. None of my achievements throughout life could have been possible without them. Thanks to my amazing brother, **Armin**, my role model, for teaching me to dream big. Also, thanks to the kindest sister-in-law, **Kiana**, for being compassionate and believing in my confidence.

A final word of special thanks to my caring, loving, and supportive husband, **Kaveh**, who makes all the worries disappear. Thanks for being such an awesome person, encouraging and pushing me to thrive and grow further even at the expense of being far away.

Contribution of Authors

The MSc Candidate (**Azin Zare**) conducted the literature search, performed the data analysis, and wrote the initial draft of all sections of the present thesis and manuscript, under the guidance of the thesis supervisor **Dr. Etienne Vachon-Presseau**.

Dr. Etienne Vachon-Presseau designed and supervised this study and provided input on the manuscript preparation and revisions.

Co-authors on the manuscript include **Christophe Tanguay-Sabourin**, **Gianluca Guglietti**, **Matthew Fillingim**, **Jax Norman**, and **Ronrick Daano** who contributed to data organization and data visualization.

List of tables

List of figures

List of abbreviations

CNCP – Chronic Non-Cancer Pain

CRP – C-Reactive Protein

OR – Odds Ratio

AUC ROC – Area Under the Curve Receiver Operating Characteristic Curve

1. Introduction

Prescription opioids play a major role in the treatment of acute and chronic pain. While short-term opioid use has been strongly supported for severe acute pain, concerns remain regarding the long-term benefits of these drugs for chronic non-cancer pain (CNCP)[1, 2]. In addition, growing evidence suggests that long-term opioid therapy (i.e., more than 90 consecutive days) is associated with serious adverse effects, such as opioid misuse, opioid use disorder (OUD), and overdose-related mortality[3]. Recent medication guidelines have advised the usage of non-opioid interventions for CNCP to reduce opioid-related risks[4, 5]. However, non-opioid treatments seem to be associated with cost and accessibility-related barriers, and yet, opioids are considered as the basis of all treatment plans for CNCP patients over the world, especially in the United States and in Canada[6-8]. Given the high prevalence of chronic pain in these countries, the significant risks attributable to opioids remain a concern.

One major unanswered question is: in the general population, what makes a chronic pain patient more likely to use prescribed opioids. In order to reduce harms associated with pain management strategies, there is a need to better characterize prescribed opioid use among CNCP patients and to define the profile of patients who are at greatest risk of opioid use and misuse to inform pain management strategies of reducing harms. The overall goal of this study is to unravel the biological, psychological, and social contributors to opioid use in CNCP patients in the UK Biobank population.

Previous studies have identified a number of factors explaining the variations in opioid therapy initiation and its long-term use. Higher rates of prescription opioid use in CNCP patients have been found to be correlated with common sociodemographic and psychological factors such

as male gender, older age, lower income, lower education, unemployment, a history or a comorbidity of anxiety or depressive symptoms, and sleep disturbances[9-11]. Furthermore, in the context of pain management, a leading hypothesis is that opioids are prescribed to treat the general functioning of the patient, above and beyond the physical pain and include the treatment of social, systematic, and contextual factors[12]. In other words, findings from actual clinical studies have shown that opioids are often used to treat the total pain and distress of the patient rather than the sole physical aspect of the pain[13]. It is thus clear that patient characteristics besides pain-specific factors, such as pain severity, determine the physicians' attitudes towards prescribing opioids as well as the patients' decisions on continuing opioid use[14, 15]. However, pre-existing literature aiming at discriminating opioid use in CNCP patients has almost always either studied a limited number of risk factors or directed a certain subpopulation not necessarily representative of real-life patient populations. The identified predictors of opioid use have never been validated in out-of-sample patients and their capacities for predicting within-individual opioid use (start or discontinuation of opioids) remain to be demonstrated. A population-based study that outlines the psychosocial factors, pain characteristics, and biological markers of opioid use integrating the various contributions of an individual's identity and experience is therefore still lacking.

Here, our first aim is to derive two different multivariate models based on pain or pain-agnostic features that predict opioid use in CNCP patients in a large representative sample of the UK population. This will be done through a detailed examination of opioid medication records of individuals participating to the UK Biobank study. To further assess the causal relationship between the potential predictors and opioid use, the secondary aim of this study is to apply our predictive models to predict within-individual changes in opioid use at a 6 to 10-year follow-up timepoint. In addition, there is evidence that chronic pain patients who are at the greatest risk of

developing adverse opioid-related events are more likely to be prescribed opioids[12, 15]. Our third aim here is to test if our predictive models can predict opioid-related disorders as per ICD-10 in chronic pain patients currently using or not using opioids. Chronic pain is characterized by dysregulated stress-related system functioning, resulting in elevated levels of C-Reactive protein (CRP) – a common inflammatory marker that can be measured from blood draw[16, 17]. Additionally, an increase in CRP levels is shown to be associated with higher risks of psychological distress and depression which are frequent comorbid conditions among chronic pain patients[18]. Therefore, our fourth aim is to investigate if the biological levels of CRP are associated with opioid use and our risk scores for opioid use.

2. Literature Review

This part comprises three different sections. Section 2.1 summarizes the evidence on chronic pain and its treatment. Section 2.2. presents the evidence on opioid therapy for the management of chronic pain and risk factors associated with opioid use in these patients. Finally, section 2.3 presents the biological drivers of chronic pain and opioid use as a possible explanation related to opioid use.

2.1. Chronic pain

Based on the *International Association for the Study of Pain* (IASP), chronic pain is classified as "pain that persists or recurs for longer than 3 months"[19]. Chronic pain is often characterized by emotional distress, functional impairment, and limited social participation among patients[20]. Globally, chronic pain has been identified among the ten most common causes of burden of disease and seeking primary care as reported by both clinicians and patients[21, 22].

Worldwide estimates of chronic pain prevalence range from 11% to 40%[23]. A population-based study by the U.S. *Centers for Disease Control and Prevention* (CDC) estimated a point prevalence of 20.4% among U.S. adults in 2016, with significant subgroup differences[24]. In terms of newly diagnosed cases, an annual incidence rate of 8.3% with a recovery rate of 5.4% was found by a 4-year follow up study conducted in the UK[25]. The *World Health Organization (WHO)* puts the estimate equivalent to 1 out of 10 adults being diagnosed with chronic pain each year. In Canada, 1 in every 5 people suffers from chronic pain, two thirds of whom report moderate to severe pain, and almost half of whom live with their pain for more than 10 years[26].

The high prevalence of chronic pain translates to a significant economic cost imposed on the individuals as well as the society. Each year, in the U.S, an estimated amount of 560 to 635 billion dollars is spent on a combination of direct healthcare costs and indirect costs, i.e., costs related to loss of productivity as a consequence of chronic pain[27]. Based on the report issued by Health Canada, the total financial impact of chronic pain in Canada has been 38.2 to 40.3 billion dollars in 2019, and estimates predict an increase of 36.2% in the total cost by 2030[28].

Given its high prevalence and vast societal costs, chronic pain is considered as a public health priority requiring significant global attention[29]. Recently, chronic pain has been added to the 11th version of the *International Classification of Diseases* (ICD-11) to be recognized systematically as a health condition on its own [19, 30]. With the inclusion of chronic pain in the ICD-11, it is expected that an improved classification and a greater recognition of this condition as a disease, and thereby, a clearly defined treatment plan for these patients be provided. The ICD-11 classifies chronic pain as "chronic primary pain", where the condition could not be better explained by any other diagnoses, and "chronic secondary pain", following an underlying injury or a disease[31]. Chronic pain can be experienced at a specific body site, e.g., low back, neck, abdominal, head, knees, or in a combination of body sites, e.g., chronic widespread pain, which refers to diffuse musculoskeletal pain present in at least 4 or 5 body sites[31].

2.1.1. The biopsychosocial model of chronic pain

Over the past centuries, significant research has been conducted to better understand the underlying causes of chronic pain. The current influential framework for chronic pain uses a comprehensive approach known as the "biopsychosocial model". The biopsychosocial model was primarily introduced by George Engle[32]. This medical model suggests that as a medical illness

becomes chronic, apart from the biological abnormalities of the illness, psychological and sociocultural "layers" are crucial in considering the assessment and treatment. The proposed model was then applied to pain by John Loeser, 1982, and helped to develop the understanding of pain conditions[33]. In accordance with the ICD-11 classification in which chronic pain is accounted as a disease or a long-term condition, chronic pain is no longer treated as a traditional biomedical model. Rather, the characteristics of chronic pain are now widely accepted to be viewed as an interaction among the individuals' multiple dimensions involving biological, psychological, and social factors[34]. Chronic pain is not solely an aversive sensation, and one's subjective experience of chronic pain is influenced by a combination of the biopsychosocial traits that affects the whole individual [35]. Therefore, effective prevention and management of a patient suffering from chronic pain is subject to the consideration of all these predisposing factors contributing to this disease.

As discussed above, based on the heuristic biopsychosocial model, psychological, sociodemographic, and biological factors account for the observed differences in the subjective experience of pain[36]. Like other chronic illnesses, the distribution of chronic pain is not similar in all sub-populations. Numerous studies have reported that certain demographic factors as well as the parameters relevant to the social status contribute to chronic pain outcomes[24, 36, 37], with a higher prevalence observed in older adults, women, unemployed individuals, and those living in poverty or relative deprivation. In terms of age, chronic pain has an increasing trend in its prevalence rate from 14.3% in 18-25 years old to 62% in over 75 years old[25]. Research has also explored chronic pain disparities among different racial and ethnical groups, with higher rates of clinical pain, pain-related disability, and higher pain intensity scores among non-Caucasians compared to Caucasians[38, 39]. Possible explanations for this could be the differences in

socioeconomic status, such as disproportionate health care accessibility as well as the pain coping styles in different ethnic groups[40].

Moreover, mental health conditions influence the occurrence of chronic pain among individuals. Chronic pain is shown to be more common among patients suffering from comorbid depression [36]. Positive associations have also been found between chronic pain and anxiety, negative affect, catastrophizing beliefs, and accumulated stressful life events [41, 42].

2.1.2. Management of chronic non-cancer pain

Despite advances in understanding the mechanisms and the underlying factors of CNCP, many of the patients are not adequately responsive to the available treatments, and the treatment of these still remains challenging. Management of chronic pain involves a variety of pharmacological and/or non-pharmacological interventions. Some pharmacological approaches include prescribing opioid medications, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants [43-46]. However, relying solely on pharmacotherapy for a long duration has proved to be unsafe and ineffective in some cases. Moreover, the complex physiopathology of chronic pain calls for a non-pharmacological biopsychosocial-oriented treatment that addresses biological, psychological, and social issues of a patient[45, 47, 48]. Several non-pharmacological interventions, such as physical therapy[49-51], occupational therapy[52], and multidisciplinary pain management programs have been proposed for the management of pain in CNCP patients[53]. Psychological interventions have also emerged as multidisciplinary non-pharmacological treatments for patients living with chronic pain and are often based on cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT)[54-57].

Given the burden of chronic pain on a patient, aiming at pain intensity measurements for chronic pain treatment might not provide a beneficial treatment of the disease[12]. Many of the non-pharmacological treatments that create a more comprehensive treatment for the chronic pain patients favor the patients by addressing the suffering and disability aspect of the pain, rather than the severity of the pain. Despite the potential benefits of non-pharmacological treatments in improving chronic pain outcomes (e.g., pain reduction, improved functional status, as well as improvement in patients overall levels of quality of life and functioning), such interventions have shown to have barriers related to costs, access, and lack of knowledge about relief properties[6, 7]. So far, pharmacotherapy, including opioid therapy, tends to remain the basis of all treatment plans in chronic pain patients in the United States and Canada[58, 59].

2.2. Opioids

Opioids refer to all compounds that exert activity by attaching to opiate endogenous receptors. Exogenous opioids are classified as pure agonists (e.g., morphine, hydromorphone, and fentanyl), agonist/antagonists (e.g., nalorphine), and antagonists (e.g., naloxone), based on their action, showing varying degrees in their receptor binding affinity[60]. Another classification classifies opioids as semi-synthetic opiates, such as heroin and oxycodone, and fully synthetic opioids such as methadone, fentanyl, and propoxyphene[61]. In the process of pain modulation, either endogenous opioids or any kind of exogenous opioids (i.e., opioid drugs) act by binding to their receptors which are found in the central nervous system, the peripheral nervous system, and the immune system. Several types of opioid receptors exist (i.e., *mu, kappa, delta*). However, pain relieving opioid drugs mainly exert their analgesic effects by binding to *mu* receptors. Following binding, analgesia is produced by inhibiting the release of neurotransmitters form primary afferent nerves in the spinal cord as well as by activating the descending inhibitory control pathway in the

midbrain. Apart from the pain modulation pathways, *mu-opioid* receptors are also widely distributed in the mesolimbic reward system in the central nervous system[62]. By binding to these receptors, both endogenous opioids and exogenous opioids could stimulate the release of dopamine in these pathways. Dopamine release mediates mood outcomes, such as reward prediction and motivational value[63].

2.2.1. Opioid analgesics for the management of chronic non-cancer pain

Opioid analgesics are known as one of the most beneficial treatments for moderate-to-severe acute pain and chronic cancer pain in palliative care offering immediate and effective pain relief properties. Short-term use of opioids for severe and short-lived pain has been strongly supported by the International Association for the Study of Pain (IASP) for pain relief at all ages[2].

Moreover, opioid administration also has a long history in the treatment of chronic non-cancer pain. Survey data on the prescribing behaviors of physicians and their attitudes towards opioid therapy from the 19th century indicate that prescription of opioids for CNCP has been widespread, and a broad spectrum of practitioners prescribed opioids for non-cancer pain with the goal of symptom improvement and partial analgesia rather than functional improvement[64, 65]. More recently, a meta-analysis of diverse randomized trials have found that, compared to the placebo, opioid analgesics are superior in terms of pain alleviation and functional improvement outcomes in any type of chronic pain syndromes[66]. Treatment efficacy in these studies was assessed by the effect sizes of the standardized mean differences in pain intensity and functional outcomes comparing opioids with placebo (small effect size: <0.5, medium effect size: 0.5 – 0.8, large effect size: > 0.8). A medium effect size for pain and a small effect size for function was shown in favor of opioids. Similarly, another meta-analysis study on 96 randomized control trials, assessing the

efficacy of opioids on chronic non-cancer pain, has shown statistically significant but small improvements in pain and physical functioning. It has also shown small improvements in the social functioning following opioid therapy compared to the placebo treatment. However, none of the trials included in these studies followed up their patients for more than 6 months, and thus, evidence on longer-term effectiveness of opioid use as a treatment of chronic nonmalignant pain still remains limited. Despite these controversies and regardless of the purpose of opioid treatment (i.e., whether it is to improve pain or function), opioid drugs used for treating acute and cancer pain have been generalized to and widely prescribed for chronic non-cancer pain in primary care settings [1, 8, 67, 68].

Over the past decades, there has been an overall increase with a recent downward shift at some points in the consumption of medical opioids all over the world, including North America. Observed changes in the opioid prescription practices applied to the patients were partly due to the issuance of the CDC evidence-based guidelines in 2016 as well as the alternate prescribing recommendations pertaining to these guidelines[68-70]. These guidelines, which were issued as a result of the elevated risks of opioid-related harms, advise primary care clinicians on cautious opioid prescription for CNCP[71]. Reports on changes in the trends of opioid use from 1980 to 2000 in the US population have shown a two-fold increase in the opioid prescription in outpatient visits for chronic musculoskeletal pain patients[72]. Similarly, the findings of a huge 6-year observational study from 2000 to 2005 on two different populations of the US, showed a 29 % to 58% increase in the proportion of chronic non-cancer patients receiving opioid treatment. A 37% increase in the cumulative yearly dose of opioid use was also shown following the changes in the number of days patients have been administered opioids, rather than the daily opioid dose per se[73]. An increase in the opioid administration rates in the U.S continued until 2012, showing a dispensing rate of 81.3

prescriptions per 100 people by then. From 2012 to 2020 the declining trend resulted in an overall dispensing rate of around 43.3 prescriptions per 100 people[74]. In Canada, between 1999 and 2010, opioid prescription increased almost by 4-fold. From 2013 to 2018, the *Canadian Institute of Health Information (CIHI)* report indicates an 8% decrease in the number of people using opioids as well as a 9.6% decrease in the number of people initiating opioids[70]. Yet, in 2018, almost one out of every 8 Canadians was being prescribed opioids, and among them one in every 5 was being prescribed opioids on a long-term basis i.e., more than 90 consecutive days[70]. This makes Canada the second largest per capita opioid prescriber after the U.S.

2.2.2. Problems associated with prescription opioids in patients with chronic non-cancer pain

Chronic opioid use has been shown to be accompanied by deleterious side effects such as opioid misuse, addiction, and over-dose related mortality and morbidity[3]. Moreover, in contrast to the use of opioids for the treatment of chronic pain, chronic opioid usage increases disability and the subsequent healthcare costs, worsening the pain-related hazard[10]. These side effects have resulted in developing another global health crisis besides the crisis of chronic pain. Opioid misuse describes the use of opioid drugs in a way other than its prescribed description of usage. An example of misuse behaviors includes using opioids more than the prescribed dose regardless of the presence or absence of any pain. Individuals with chronic pain have been shown to be at higher risk prescribed opioids misuse[10]. Evidence from a systematic review indicates that an average rate of 20% to 29% of chronic pain patients who are prescribed long-term opioid therapy (LTOT) misuse their drugs[3]. Following opioid misuse, health-related challenges such as addiction may emerge, making it even more difficult to manage pain patients. Opioid addiction refers to a diagnosis of opioid use disorder (OUD) for a patient based on the *Psychiatric Association in the*

Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V)[75]. Previously, in the 1980s, it was falsely reported that the development of addiction is rare in prescription opioid therapy[76], which resulted in a dramatic increase in the rate of opioid prescription. However, it is now accepted through recent reviews that almost 8% to 12% of chronic pain patients with LTOT meet OUD diagnosis criteria[3].

Even though various interventions and strategies have been implemented focusing on the appropriate opioid prescription, opioid-related harms seem to remain high over time[77], and still these actions have not led to a measurable impact on the staggering proportions of the harms. As noted earlier, the number of opioid prescriptions has decreased in Canada since 2016. However, the dosage and duration of opioid therapy in opioid naïve patients (i.e., patients starting opioids) has remained stable[70]. The growing opioid crisis in Canada is driven by both non-pharmaceutical and prescription opioids. From 2016 to 2021, almost 24,626 opioid toxicity deaths (around 19 deaths each day) occurred in Canada[78]. Most of the reported deaths were caused by overdosing illicit opioids (e.g., illegally made Fentanyl), however, pharmaceutical opioids were involved in an average of 10% of these deaths which is yet a significant proportion of the rates. During the last five years in Canada, hospitalizations due to opioid-related poisoning have increased by 27%, with the COVID-19 pandemic contributing to the worsening of this crisis[79]. In the U.S, an estimate of 38 opioid-involved deaths per day was reported in 2019, summing up to a total of 14,000 deaths. Prescription opioids had an involvement rate of more than 28% in these deaths[80].

To reduce harms from opioid use among chronic pain patients, there is a need to find out who is at a greater risk of initiating, continuing and developing persistent opioid use, as well as developing problematic opioid use behaviors. By doing so, clinicians will be able to consider the

underlying factors associated with these behaviors prior to an opioid treatment initiation for CNCP patients. In other words, clinical decision making for opioid therapy could be better done based on an evaluation of the patients' clinical, societal, and functional situation.

2.2.3. Contributing factors to opioid prescription and long-term opioid use in chronic pain patients

Prescribing opioids in the context of CNCP management largely depends on the current recommended guidelines, and the attitudes of the prescribing physician towards opioids[67, 81, 82]. There are a number of pain-related factors that might be expected to influence the physicians' decisions on prescribing these drugs. Among chronic musculoskeletal (i.e., neck, shoulder, knee, low back) pain patients, multiple site pain and low back pain have been shown as potential risk factors for opioid prescription and chronic opioid use[83, 84]. Also, treatment planning may depend on the patients' complaints about how much pain is interfering with their daily activity. A four-fold increase in opioid use and dosage has been reported among those with high-impact chronic pain which is defined by substantial restrictions in work, and social and self-care, compared to the patients with lower pain intensity and lower activity restrictions[85].

In addition to the physical pain and its pathology, there might be a number of patient-specific characteristics that affect the clinical epidemiology of opioid use for CNCP. Sociodemographic characteristics have consistently been associated with a risk of increased opioid therapy among CNCP sufferers. Some studies have shown that potential sociodemographic predictors include younger age and male gender[86, 87], whereas other studies point to a greater probability of prescription opioid use in women and advanced ages[88-90]. Prescription opioid use is also associated with social classes, as low educational attainment and unemployment have been

pointed out as risk factors [91]. A recent study on an elderly population (aged over 65 years) used data from the peak period of U.S. opioid use between 2005 and 2006 to determine the sociodemographic risk factors associated with prescription opioid use[92]. The results of this study indicated low wealth as the strongest and most consistent predictor of opioid use. While pain level mediated the association (i.e., the poorest had an experience of more pain), it only explained less than half of the association, suggesting that other potential explanations might also have played a role. Additionally, lifestyle factors, such as a history of substance use, alcohol drinking, as well as heavy smoking have been recognized for their potential contributions to long-term opioid use and in some case opioid misuse behaviors[86]. Findings of a systematic review identifying patients at risk of problematic opioid use have reported a history of illicit drug and alcohol use as the strongest predictors[93]. Demographic differences, however, were not reported as consistent predictors for problematic opioid use among chronic pain patients in this study. Also, the association between race and prescription opioid use has been documented in studies. Whites have been shown to be receiving more opioid analgesics for the treatment of chronic pain compared to non-whites. This substantiates the role of race in the treatment decisions for chronic non-cancer pain patients[94].

As mentioned earlier, the close association between psychological disturbances with chronic pain has been well-documented in the literature, and psychiatric comorbidities are highly prevalent among chronic pain patients. This association is more likely a bidirectional relationship, meaning that not only chronic pain results in mental health problems, but also premorbid psychological problems may cause the development of chronic pain[95, 96]. Moreover, several studies indicate that CNCP patients with mental health disorders have an increased risk of harmful outcomes, such as misuse and opioid use disorder[10]. Therefore, decision making regarding opioid prescription in this subgroup of CNCP patients is complex. Studies have suggested that

psychological disturbances such as depression and anxiety, negative affect (i.e., the co-occurrence of depression and anxiety), as well as pain catastrophizing are associated with the initiation and continuation of prescription opioids in patients with chronic pain[97-99]. These factors seem to remain significant predictors of opioid use even after controlling for clinical and demographic variabilities[98]. Moreover, psychological distresses are incrementally associated with the duration of opioid use in CNCP patients[100]. A combination of age younger than 65 years old age, depression, use of psychotropic medications, and pain impairment has shown a significantly increased risk of opioid dependence among chronic pain patients on opioid therapy in a large healthcare system[101].

In one of the first prospective population-based studies, Sullivan et al. examined the association between common psychiatric disorders and regular opioid therapy, involving data from the nation-wide Health Care Communities (HCC) survey. Common mental health conditions in the past year, including major depression, dysthymia, generalized anxiety disorder, and panic disorder were assessed. It was reported that chronic pain patients with a comorbid mental health disorder are twice as likely to receive opioid therapy compared to those without any mental health disorders, even after adjusting for demographic and clinical features[98]. Later, studying the trends in the use of prescription opioids for CNCP, Edlund et al. reported that between 2000 and 2005, prescription opioid use was much higher and growing faster in CNCP patients with a mental health or substance use disorder[102].

Although current guidelines have emphasized that opioid therapy should be prescribed with a careful risk assessment and based on a careful selection basis, actual clinical studies have shown higher prescription rates in certain high-risk subpopulations. These findings point to opioids being prescribed to treat a "poorly differentiated state of mental and physical pain"[98]. It is argued that in the field of pain, opioids are prescribed to treat the general functioning of the patient, above and

beyond the physical pain and include the treatment of social, systematic, and contextual factors[98]. Both the physical pain and the comorbid psychological trauma contribute to the development of chronic pain, and higher intensity of pain has been reported in patients with greater current and past psychological disturbances. This has led to a pattern of *adverse selection* therapy termed by Sullivan et al, in which higher rates of opioids are prescribed to high-risk patients with higher rates of medical conditions and poorer outcomes[15]. It has been suggested that the reason why these high-risk patients are prescribed more opioids is that they tend to report the highest pain intensity levels, increased physical symptoms, and distress, but at the same time are the least likely to benefit by the analgesic effects of the opioids. This pattern of adverse selection takes place both at the initiation stage of opioid therapy as well as at the patients' decision on whether to continue their opioids or not.

2.3. Understanding the biological factors involved in chronic pain and opioid use

Apart from the risk factors mentioned above, which have led to an adverse selection for opioid therapy among chronic non-cancer pain patients, whether biological processes account for plausible links between chronic pain and opioid use remains unknown.

Persistence of pain is typically associated with peripheral and central inflammation. Peripheral inflammation is characterized by an increase in pro-inflammatory cytokines such as Interlukin-6 and C-reactive protein (CRP). Immune and inflammatory responses play a major role in several chronic diseases. The same happens in the situation of persistent pain. Inflammatory biomarkers have been shown to be linked to chronic multisite musculoskeletal pain, the development of neuropathic pain, and the severity of pain among chronic back pain patients[16, 103]. Higher levels of CRP have been shown to be relevant to higher pain sensitivity even in healthy individuals[104]. Also, elevated rates of CRP have been linked to psychological distress and

depression in the general population as a response to the stress-induced activation of the hypothalamic-pituitary-adrenocortical axis (HPA)[18, 105]. These findings suggest that an increase in the levels of CRP could be a consequence of the psychological factors in individuals, contributing to the maintenance of pain and the development of chronic pain. Immune stimulation and heightened rates of CRP have also been shown to be linked to opioid addiction[106], suggesting that the same biological mechanisms might also be associated with opioid use problems in patients with chronic pain. Peripheral inflammation causes inflammation in the central nervous system through disrupting the permeability of the blood-brain barrier. It is now clear that chronic pain and opioid use both involve inflammatory processes. This, subsequently, promotes common neuroinflammation in the limbic structure of the brain to be associated with the regulation of affective conditions[107].

3. Rationale

Opioid use, when it becomes chronic, is associated with substantial harm to chronic non-cancer pain patients. Understanding the factors determining opioid use in chronic non-cancer pain patients may help better recognize who and why individuals are using opioids, improving the assessment of risks and benefits of opioid use in this population. Despite findings from previous studies, questions remain concerning the potential risk factors of prescription opioid use among patients with chronic non-cancer pain. While several risk factors including sociodemographic factors, pain-related features, psychosocial factors, as well as psychopathological conditions have been described for prescription opioid use, it is not clear if a combination of these factors can predict opioid use in chronic pain patients in the general population[93]. Thus, calls have been made to better validate comprehensive and generalizable frameworks for probable risk factors affecting chronic pain patients. Also, no study has so far studied the relationship between the biological dimension of chronic pain and the likelihood of opioid use among these patients. Given the biological processes involved in both chronic pain, mood disorders, and addiction-related behaviors, there might be a reason to believe that inflammatory blood markers may be higher in opioid users and may be directly associated with the risk score for using opioids. In addition, previous research examining the potential risk factors for opioid use has mostly been targeting at certain sub-populations, including older adults[108, 109], databases from public drug plans, databases from outpatient clinics[110], and populations including small proportions of women and minority groups[93]. These study populations are not necessarily representative of the general population of chronic pain patients, representing a significant gap in the literature. Thus , there is a need for further research on nationally representative populations to assess the determinants of opioid use among chronic non-cancer pain patients[8]. Therefore, the overarching goal of this project is to

widely unravel the biological, psychological, and social contributors to opioid use in chronic non-cancer pain patients in a large population-based database. The results of this study will shed light on the different path by which opioids are prescribed to chronic non-cancer pain patients and would be a step towards improving the safety and effectiveness of chronic pain treatment.

4. Study objectives

The first objective of this study was to derive multivariate models explaining opioid use in chronic non-cancer pain patients using pain characteristics and pain-agnostic features. The second objective was to examine whether within-individual trends of opioid use could be predicted using our derived models. The third objective is to determine if a subgroup of chronic pain patients diagnosed with an opioid-related disorder score higher on the risk score derived from our pain-agnostic model. Finally, the third objective here was to examine whether C-reactive protein was associated with the risk of opioid use in chronic non-cancer pain patients.

5. Methods

5.1. UK Biobank population

This study used data from the UK Biobank. The UK Biobank is a large-scale, prospective, observational, on-going study on almost 500,000 adults with an inclusion age range of 40-69 years at initial visit who were invited through invitation letters from all around the United Kingdom. Baseline recruitment and data collection took place between 2006 and 2010 in 22 assessment centers in Scotland, England, and Wales. In the United Kingdom, the general population are registered in the UK National Health Service (NHS) with a general practitioner, and potential participants for this study were identified through this registry based on their age and their living within a reasonable distance from an assessment center. To recruit the intended sample size of around 500,000 participants, 5 million invitations were sent[111]. Throughout the study, collected data were recorded in a database. Data includes sociodemographic, lifestyle, psychosocial and health related factors, as well as medical history, medications, physical measurements, and biological sampling. A subset of approximately 50,000 participants underwent a follow-up visit 6 to 10 years after the initial visit.

Exclusion and inclusion criteria: For the purposes of the current study, data collected at both baseline and follow-up visits are used, and only patients classified as chronic non-cancer pain (CNCP) were included. In terms of pain condition, participants were first asked if they experienced any of the following-- including “headache”, “facial pain”, “neck or shoulder pain”, “back pain”, “stomach or abdominal pain”, “hip pain”, “knee pain”, “pain all over the body”, and “prefer not to answer”—in the last month that interfered with their usual activity (Data-field: 6159). Choosing “pain all over the body” was exclusive and no other options could be selected simultaneously. If

the answer to this question was positive, participants were then asked whether they had their reported pain for more than 3 months. According to the classification of chronic pain form the International Association for the Study of Pain (IASP)[19], those reporting having their pain for more than 3 months for at least one site were classified as "chronic pain" patients. Positive answers to the first question asking about experiencing pain at any of the 7 regional sites, but not reporting the pain for more than 3 months at that specific site were classified as "acute pain".

In terms of cancer illnesses, participants were asked if ever a doctor has told them they have cancer (Data-field: 2453). Those answering yes to this question were then directed to a trained nurse to go through a verbal interview to provide information on the number of their self-reported cancers (Data-field: 134). For this study, subjects reporting cancer were excluded from the analyses.

Training and testing population: A total of 195,808 chronic non-cancer pain participants were identified with complete data at baseline visit. This population was split into a training cohort population (n = 178,763) – those who did not participate the follow-up visit, from whom our models were derived from, and a testing cohort population (n = 17,045), including individuals with longitudinal data available at follow-up.

5.2. Measures and procedures

For the present study, analyses were conducted as part of the UK Biobank application No. 20802. At the assessment centers, prior to data collection, all participants were asked to provide electronically written consent through consent forms created based on the Ethics & Governance Council (ECG) advice and adhering to the Ethics & Governance Framework (EGF) guidelines (For further information regarding the consent procedure, see https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf).

To address our aims, data collected at the baseline and follow-up visit were included in this study. Each data-field refers to a fundamental block of data showing the results of a single question or a measurement in the UK Biobank repository. Here, a total of 95 variables were carefully selected based on previous literature reporting their relevance to opioid use. Among the selected variables, participants with more than 20% missing features were excluded. Also, participants with missing values on any of the chronic pain sites or answering, "prefer not to answer", were excluded from the data (i.e., <2.5% of the population).

5.2.1. Baseline assessment

Data collection included: i) a touch screen questionnaire, including data on sociodemographic, lifestyle, psychosocial factors (social support and mental health), and health and medical history, ii) a verbal interview with a nurse, including data on early life factors, employment, medical conditions, medications, and operations, iii) physical measurements and iv) biological sampling.

Sociodemographic

Age and sex: Study participants reported their age in years and their sex as a binary variable (male/female).

Household and economic status: Participants were asked to report the number of people living together in their household (Data-field: 709), and their relationship to them (Data-field: 6141), the number of vehicles they own (Data-field: 728), and their average total income in their household before tax, which included the following responses: less than 18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, do not know, and prefer not to answer (Data-field: 738).

Employment: Participants were asked about their current employment status (i.e., paid employment or self-employed, retired, looking after home/family, unable to work due to sickness or disability, unemployed, doing unpaid or voluntary work, full or part-time student) (Data-field: 6142).

Education: Information on qualifications were collected including response options of college/university degree, advanced levels (or equivalents), ordinary levels (or equivalents), certificated secondary education (or equivalents), practical carrier diploma, and other professional qualifications (e.g., nursing, teaching), and none. (Data-field: 6138)

Ethnicity: Participants were asked about their ethnic background. Response options included "White", "Mixed", "Asian or Asian British", "Black or Black British", and "other ethnic groups" (Data-field: 21000).

Lifestyle and environmental factors

Sleep: Participants were asked about their hours of sleep in every 24 hours (including naps) (Data-field: 1160). Values under 1 hour or over 23 hours were rejected, and confirmation of answer was required for responses below 3 hours or above 12 hours. Participants were also asked about if they have a nap during the day (i.e. never, sometimes, usually, prefer not to answer) (Data-field: 1190), how easy they find getting up in the morning (i.e., not at all easy, not very easy, fairly easy, very easy, do not know, prefer not to answer) (Data-field: 1170), their chronotype (a "morning" or "evening" person) (Data-field: 1180), sleeplessness and insomnia (i.e. never, sometimes, usually, prefer not to answer) (Data-field: 1200), daytime dozing or sleeping (narcolepsy) (i.e. never, sometimes, often, do not know, prefer not to answer, all of the time) (Data-field: 1220).

Smoking: Participants were asked about their smoking habits. Questions included if they have ever smoked (yes/ no) (Data-field: 20160), current and past tobacco smoking status (i.e., most or all days, occasionally, prefer not to answer) (Data-fields: 1239 and 1249), whether anyone smokes in their household (Data-field: 1259), hours per week of exposure to tobacco smoke at home (Data-field:1269).

Alcohol consumption: Participants reported their alcohol drinker status (i.e., current, past, never, prefer not to answer) (Data-field: 20117), their alcohol intake frequency (i.e., daily, 3 or 4 times per week, once or twice per week, one to three times per month, occasionally, prefer not to answer) (Data-field: 1558), their alcohol intake frequency compared to 10 years ago (i.e., more, less, same, prefer not to answer) (Data-field: 1628).

Mental health factors

Neuroticism: Participants were asked about the presence (i.e., yes/no/do not know/prefer not to answer) of twelve domains of neurotic behaviors linked to negative affect, i.e., mood swings, miserableness, irritability, sensitivity/hurt feelings, fed-up feelings, nervous feelings, worrier/anxious feelings, tense/"highly strung", worry too long after embarrassment, suffer from "nerves", loneliness/isolation, guilty feelings (Data-fields: 1920 – 2030). Neuroticism summary score was also derived from the number of 'yes' answers across these twelve questions, shown as an integer from 1-12 corresponding to the number of neurotic traits one has (Data-field: 20127[112]).

Risk Taking: Participants were asked how they describe themselves as someone who takes risk. Answers included "yes", "no", "do not Know", "prefer not to answer". (Data-field: 2040)

Mood: Participants were asked about the frequency of depressed mood, unenthusiasm/ disinterest, tenseness/ratelessness, and tiredness/lethargy in the last two weeks (Data-fields: 2050,

2060, 2070, & 2080) Also, participants were asked whether (i.e., yes/no/do not know/prefer not to answer) they sought help from a doctor (GP), or a psychiatrist for nerves, anxiety, tension, depression (Data-fields: 2090 & 2100). The two last questions are in line with examining depression using the "broad depression definition" suggested by Howard et al.

Trauma: Participants were asked about experiencing any serious illness, injury, or assault to themselves or their close relatives, experiencing death of a close relative, or their spouse/partner, or others, experiencing separation/divorce, and experiencing financial difficulties, in the last two years (Data-field: 6145).

Health and Medical history

Pain condition: We designated the total number of chronic pain sites by a cumulative score ranging from 0 to 7, showing a combined total of values from the pain dimensions as mentioned in the inclusion criteria. Also, groups of total number of chronic pain sites were designated by grouping individuals with chronic pain into 4 classes based on the number reported from 1 to 7 sites (i.e., 1, 2, 3, >4 sites, excluding widespread pain).

Cancer illnesses: As mentioned in the inclusion and exclusion criteria.

Medical conditions: Participants were asked in the touchscreens whether they have a history of any of a range of medical conditions, and their age if their diagnosis. This was followed by a verbal interview where the responses were amended by a trained nurse in case the participants were uncertain about their type of the medical condition they reported (Data-field: 20002).

Medication: Participants were asked if they regularly (i.e., most days of the week for the last 4 weeks) use any common prescription medications (Data-field: 2492). If they answered yes, they were interviewed by a trained nurse to provide the name of the medication they use (data-

field: 20003), and their medication was recorded by their generic or trade names by the nurse. This contains only regular medications taken, rather than short-term medications. Dosage, duration, and formulation of use was not recorded. Medications were classified by the UK Biobank into 6745 categories, among which 1809 were reported to be used by more than 10 participants. For our study, these highly reported medications were recoded to their corresponding active ingredient according to the online *Anatomical Therapeutical Chemical* (ATC) classification maintained by the *World Health Organization (WHO)* [113], as done by Wu et al [114]. For our analysis, all of the ATC codes referring to opioid medications were included.

Physical measures

Body Mass Index (BMI): BMI was calculated as weight divided by height squared (kg/m^2). BMI has previously been shown to be associated with experiences of pain and chronic widespread pain in large population-based studies [115, 116]. Besides these associations, studies have also shown that obesity could partially be responsible for the increased receipt of prescription opioids in the United States [117].

Biological samples (blood sample collection)

At baseline visit, blood samples were collected from participants for hematology analysis. A range of key biomarkers were selected for analysis in the UK Biobank, representing disease risk factors, clinical diagnostic measures or characterized phenotypes. Sampling was conducted through a sample selection algorithm to minimize introducing bias. Sample handling and storage procedures used by the UK Biobank have also been validated through a study done by Peakman and Elliott[118].

C-reactive protein: Serum C-reactive protein (CRP) level was measured by immunoturbidimetric high-sensitivity analysis on a Beckman Coulter AU5800 platform (Data-field: 30710). CRP is a useful inflammatory biomarker. As discussed in **section 2.3**, elevated levels of CRP have been observed to be associated with a number of chronic diseases, as well as with psychological distress and depression.

As the measured values of CRP (measurement unit: mg/L) were not normally distributed showing a positive skewness, logarithmic transformation was applied for the purpose of this study to improve normality.

5.2.2. Follow-up assessment visit

The subset of participants who were invited for a follow-up visit were assessed for the same measures as the baseline visit collected through touch-screen questionnaires, verbal interviews, and physical measurements as they did at their initial visit.

5.2.3. Hospital inpatient data

UK Biobank includes a category containing data on hospital inpatient admission (i.e., patients who have been admitted to a hospital). This data has been obtained from a range of external data records and does not consider participants' self-report information. Diagnosis have been coded as per the ICD version 10 (ICD-10) (Data-field: 41270), and used to identify participants with opioid-related disorders (F11- ICD10)

5.2.4. Predictors

For the purposes of our analyses, categorical features were converted into separate binary features. Two sets of independent variables were considered for the predictive models. "Pain

features" were selected based on 16 pain-related variables for each patient, including type of reported acute and chronic pain (i.e., headache, facial pain, neck or shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, and widespread pain). This set of predictors was used for our first model trained to predict opioid use from pain characteristics at baseline. "Pain-agnostic features" included 77 variables on sociodemographic (age, sex, ethnicity, household and economic status, employment, and education), lifestyle (sleep, smoking, and alcohol consumption), mental health (neuroticism, mood, and trauma), and physical measures (here, BMI). These features were entered in our second model trained to predict opioid use from features agnostic to pain. Features from both models were combined in a third model that included all 93 features to measure the additive effect of entering the Pain and the Pain agnostic features.

5.3. Statistical analysis

All statistical analyses were preformed using Python version 3.8.8 and R version 4.1.1. Descriptive statistics were performed to identify the main characteristics of the study sample. Continuous variables are presented by mean and standard deviations. For binary and categorical variables, percentages were calculated. Univariate associations between patients' characteristics of interest and our study outcome (i.e., opioid use) were assessed using odds ratios. The following steps describe the analysis performed to specifically address each objective. For all analyses, the alpha level of significance was considered 0.05.

Objective 1: Our primary goal was to predict opioid use at baseline visit in chronic non-cancer pain patients across various number of chronic pain sites. To this end, we derived two separate models. Our first model was the *pain* model, in which the outcome (i.e., opioid use) was modeled in the training population by entering the variables of "Pain features" as independent variables. Opioid use in our second model (i.e., *pain-agnostic*) was predicted using candidate

variables from "Pain-agnostic features". Combining Pain and Pain-agnostic features, a third model was derived (i.e., *combined*). All three models were modeled by a cross-validated Lasso regression *(Least Absolute Shrinkage and Selection Operator regression)* to avoid multicollinearity and enhance their generalizability[119]. In Lasso regression, both variable selection and regularization is performed, and the aim is to identify the variables and their corresponding regression coefficients resulting in a less complex model with the least prediction error. Variable selection is conducted through regularizing the sum of the absolute values by shrinking certain coefficients towards zero. The strength of the shrinkage is determined by a tuning parameter (i.e., alpha). Variables with coefficients forced towards zero are excluded from the predictive model considered as unnecessary variables, and the final models are trained on the remaining non-zero coefficient variables. Here, we performed a 10-fold cross-validated grid search in the training data to learn the optimal value for the alpha parameter. Lasso regression has been successfully used in a wide array of studies to predict clinical groups. Models were constructed using Python package scikit-learn[120].

Prediction performances were evaluated via an internal 10-fold cross-validation in the training dataset using area under the receiver operating characteristic curve (AUC-ROC curve)[121]. An AUC greater than 0.70 was considered as good performance. The trained models were finally tested in the independent testing dataset. Each model provided an individual "probability" risk score of being an opioid user.

Pearson correlation coefficients *(Pearson r)* were used to examine the relationship between opioid use risk scores and spreading of pain using the patients' total chronic pain sites as a continuum. In addition, differences in opioid risk scores between opioid users and non-users within each group of total chronic pain sites (i.e., 1, 2, 3, >4) were further measured with Cohen's d effect size (using pooled standard deviation due to unequal sample size).

Objective 2: Our secondary goal was to longitudinally predict opioid use at the 6-10-year follow-up visit in chronic non-cancer pain patients. All three derived models were applied to the testing population to predict the starting of opioid use and the discontinuation of opioid at the follow-up visit. Prediction performances were evaluated using AUC-ROC curves and Cohen's d effect sizes.

Objective 3: Our third goal was to examine the risk scores derived from our pain-agnostic model in a subgroup of chronic pain patients diagnosed with an opioid-related disorder as per ICD-10 diagnosis criteria. Cohen's d effect sizes were used to compare the risk scores of this subgroup with other chronic pain patients within groups of current opioid users and non-users.

Objective 4: Our fourth goal was to assess the association of the measures of the C-Reactive protein (CRP), with our predictive models among various numbers of chronic pain sites. Pearson correlation was used to measure the association between logarithmic values of CRP and opioid use risk scores in the testing population in each group of number of chronic pain sites (i.e., 1, 2, 3, >4).

5.4. Handling missing data and standardization of the variables

For each feature, coding values attributed to "prefer not to answer" and "do not know" answers from the questionnaire, were recoded as missing values. Individuals with more than 20% of missing values were excluded from the analyses. For individuals with less than 20% missing values, a data driven Bayesian ridge regression approach was applied to impute their missing data as a function of all other features in the model.

For the purposes of the regression analyses, features were standardized across the participants by centering mean to zero and scaling the variance to one unit. This will avoid our classifiers to be dominated by the magnitude of the variance of certain features. These processes

(exclusion followed by imputation for missing data and standardization) were applied separately for the training and the testing dataset to avoid data leakage.

6. Manuscript

A Pain-agnostic Model that Predicts Opioid Use, Opioid-related Disorders, and Elevated Levels of C-Reactive Protein among Chronic Non-cancer Pain Patients

Azin Zare[1], Christophe Tanguay Sabourin[2], Gianluca Guglietti[1], Jax Norman[1], Matthew Fillingim[3], Ronrick Daano[1], Etienne Vachon-Presseau[1]

[1] Faculty of Dental Medicine and Oral Health Sciences, McGill University (Montreal, Quebec, Canada)

[2] Faculty of Medicine, University of Montreal (Montreal, Quebec, Canada)

[3] Integrated Program in Neuroscience, McGill University (Montreal, Quebec, Canada)

Abstract

Importance Better understanding the characteristics of chronic non-cancer pain patients and determining prescribed opioid use and opioid-related disorders will improve prescribing decisions on opioid analgesics.

Objective To estimate the extent to which biological, psychological, and social factors predict opioid use in a large cohort of CNCP patients.

Design, Setting, and Participants This population-based study used the prospective cohort of the UK Biobank. A machine learning approach was used to derive pain and pain-agnostic models predictive of opioid use. Models were developed using a sample of 178,763 CNCP patients from the baseline data (2006-2011) (i.e., train set) and validated using a left-out sample of 17,045 CNCP patients who have data available in a follow-up visit (6 to years later) (i.e., test set). Classification accuracy and correlation measures were used to evaluate the performance of the models.

Exposures A total of 77 variables, including sociodemographic, lifestyle, mental health, mood, and anthropometric measures, and a total of 16 pain-related features, including type of acute and chronic pain reported were integrated in the models.

Main Outcome and Measures Regular prescription opioid use identified and confirmed at data collection visit was used as the outcome. Measures of C-reactive protein (CRP) collected from blood samples were assessed for their association with the predictive models. Diagnosis on opioid-related disorders, as per ICD-10, were tested for the associations with the expression of the pain-agnostic model.

Results Of 195,808 CNCP patients included in the study, 110,712 (56.54%) were female and the mean (SD) age was 57.03 (8.02) years. 20,895 (11.7%) individuals from the train set, and 912 (5.4%) individuals from the test set used prescribed opioids. The pain and pain-agnostic models predicted opioid use with a good classification accuracy ($AUC_{pain} = 0.70$, $AUC_{pain\text{-}agnostic} = 0.75$). Models showed acceptable classification accuracy for predicting within-individual changes in opioid use between the baseline and follow-up visit. The pain-agnostic model was highly expressed in CNCP patients diagnosed with an opioid-related disorder. Levels of CRP were significantly associated with the expression of the pain-agnostic model ($r = 0.26$, $p<0.001$).

Conclusions and Relevance Our results show a dissociation between opioid users and non-opioid users at two time points. This study suggests that a pattern of psychosocial risk factors associated with a biological marker of inflammation could be a common predictor for opioid use among chronic non-cancer pain patients. Identifying the associated characteristics in these individuals could help improve the assessment of risks and benefits of chronic opioid use in certain subpopulations and will be a step towards improving the safety and effectiveness of chronic pain treatment.

Introduction

Opioid prescriptions have remained quite common for the treatment of acute and chronic pain, and the well-known harms associated with their long-term use have raised serious concerns regarding their efficacy and safety[1-3]. Prescribing opioids in the context of chronic non-cancer pain (CNCP) management largely depends on the current recommended guidelines, attitudes and beliefs of the prescribing physician towards opioids, and patients' characteristics[4-7]. Since chronic pain is often associated with severe emotional distress and psychological disturbances, it has been argued that opioids might be prescribed as a psychiatric treatment to manage the emotional state of the patients[8]. Thus, a leading hypothesis in the field of pain is that opioids are used to treat the general functioning of the patient, above and beyond the sole physical pain[6, 8]. This has resulted in higher prescriptions in CNCP patients who also have psychiatric conditions and/or comorbid medical diagnoses [8, 9].

One major unanswered question is what chronic pain patients' characteristics make them more likely to use prescribed opioids. Previous studies addressing this question have either studied a limited number of risk factors, and ignored their interactions, or focused on a certain subpopulation of patients [10-13]. These studies show that certain sociodemographic factors[10, 14], common mental health conditions[15, 16], a history of substance use disorder[17], and pain severity[18] partly determine the prescription of opioids in CNCP patients. Yet, the challenge remains to identify the phenotypic characteristics of chronic pain patients that can formally predict individual use of prescribed opioids in an out-of-sample group of patients who are representative of the general population. The current study evaluated the extent to which biological, psychological, and social factors predict opioid use in a large cohort of CNCP patients from the UK Biobank.

The initial objective was to use machine learning to train models predicting opioid use from either pain measurements or pain-agnostic features. In an independent group of patients, we showed that prescribed opioid use was predicted with good accuracy using either the *pain* or *pain-agnostic model*. The strongest positive weights in the *pain-agnostic model* were unable to work, body mass index, and sleeplessness and the strongest negative weights were college education and household income. In the longitudinal data, the models showed acceptable accuracy for predicting the initiation or the discontinuation of prescribed opioid at a 6 to 10-year follow-up timepoint. Moreover, the derived *pain-agnostic* score was most strongly expressed in patients diagnosed with opioid-related disorders, as per ICD-10. Finally, we showed that levels of C-Reactive protein (CRP) – a common inflammatory marker [19, 20]- are higher in prescribed opioid users. Higher levels of CRP were associated with the expression of the *pain-agnostic* risk score but not with the use of opioids *per se*. Together, our findings suggest that prescribed opioid use, opioid-related disorders, and biological markers of inflammation are all associated with pain-agnostic characteristics that go beyond the physical pain experienced by the patients.

Materials and methods

UK Biobank cohort

The UK Biobank is a large-scale prospective study that recruited nearly half a million individuals (aged 40-69 years old at baseline) in the United Kingdom between 2006 and 2010. A subset of approximately 50,000 participants underwent a follow-up visit 6 to 10 years after baseline. In this study, we have used data from a total of 195,808 UK Biobank participants with self-reported CNCP that were split into a discovery set (n=178,763), used to train the predictive models, and a testing set (n=17,045), used to validate our predictive models. The testing set included only CNCP participants for whom longitudinal data about their opioid use were available

at both baseline and follow-up. CNCP was defined by the self-report of pain in at least one body site for at least three months. In specific, individuals were asked if they experienced any of the following that interfered with their usual activities in the past month: “headache”, “facial pain”, “neck or shoulder pain”, “back pain”, “stomach or abdominal pain”, “hip pain”, “knee pain”, “pain all over the body”, and “prefer not to answer” (data field: 6159). Choosing “pain all over the body” was exclusive and no other options could be selected simultaneously. To each positive answer, participants were asked whether they had had that pain for more than 3 months. Those who answered yes were classified as having 'chronic pain' and those who answered 'no' were classified as having “acute pain”. For the analysis on groups of total number of chronic pain sites, individuals with chronic pain were grouped into 4 classes based on the number of sites reported from 1 to 7 (i.e., 1, 2, 3, >4 sites). Self-reported medical conditions including non-cancer illnesses as well as cancer illnesses were recorded and confirmed through a verbal interview by a trained nurse (data field: 20001and 20002). For this study, patients classified as chronic non-cancer pain data at both initial and follow-up visits were included.

Opioid use

Participants were asked if they regularly (i.e., most days of the week for the last 4 weeks) use any common prescription medication (data field: 2492), and if so, they were interviewed by a trained nurse to record their medication by their generic or trade names (data field: 20003). Medications were classified by the UK Biobank into 6,745 categories. For this study, the highly reported medications were recoded to their corresponding active ingredient according to the online Anatomical Therapeutical Chemical (ATC) classification maintained by the World Health Organization (WHO)[22], as done by Wu et al[23], and only treatments containing opioids were considered.

Opioid-related disorders

We used the data containing a list of diagnoses coded as per the ICD version 10 (ICD-10) (Data-field: 41270). A subgroup of patients diagnosed with mental and behavioral disorders due to use of opioids (F11- ICD10) were included in our analysis.

Serum C-reactive protein (CRP) level

We used the serum CRP levels (measurement unit: mg/L) measured at the initial visit (data field: 30710). As the measured values were not normally distributed, we applied logarithmic transformation to improve normality.

Predictors

For the present study, a total of 95 variables were carefully selected based on previous literature reporting their relevance to opioid use. Of these variables, two sets of independent features were considered for the predictive models. "Pain features" were selected based on 16 pain-related variables for each patient, including type of reported acute and chronic pain. These features were entered in our first model trained to predict opioid use from pain characteristics at baseline. "pain-agnostic features" included 77 variables on sociodemographic (age, sex, ethnicity, household and economic status, employment, and education), lifestyle (sleep, smoking, and alcohol consumption), mental health (neuroticism, mood, and trauma), and anthropometric measures (body mass index). These features were entered in our second model trained to predict opioid use from features agnostic to pain. Features from both model were combined in a third model that included all 93 features to measure the additive effect of entering the pain and the pain-agnostic features. A full list of candidate features can be found in **Supplementary Table 1** and **2**.

Statistical analysis

Descriptive statistics were performed to identify the main characteristics of the study sample. Mean and standard deviations are reported for the continuous variables, and percentages are reported for the binary and categorical variables. Associations between opioid use and pain phenotypes (i.e., type and number of chronic pains reported) were described using odds ratio with 95% confidence intervals (95%CI). In addition, relationships between reported psychological and psychiatric conditions and opioid use, as well as associations between the total number of medical conditions with opioid use were described using odds ratio. The following steps describe the analysis performed to specifically address our objectives. For all analyses, the alpha level of significance was considered 0.05.

Predictive models

Two separate models were derived based on the sets of predictors. The first model was the *pain model*, in which opioid use was modeled in the training population by entering the "pain features" as independent variables. Opioid use in our second model (i.e., *pain-agnostic*) was predicted using candidate variables from "pain-agnostic features". Combining pain and pain-agnostic features, a third model was derived (i.e., *combined*). All three models were modeled by a cross-validated Lasso regression (Least Absolute Shrinkage and Selection Operator regression), in which both variable selection and regularization is performed to avoid multicollinearity[24]. Variables with coefficients forced towards zero are excluded from the predictive models considered as unnecessary variables, and the final models are trained on the remaining non-zero coefficient variables. Prediction performances were evaluated via an internal 10-fold cross-validation in the training dataset using area under the receiver operating characteristic curve (AUC-ROC curve)[25]. An AUC greater than 0.70 was considered as good performance. The trained models

were finally tested in the independent testing dataset. Each model provided an individual "probability" risk score of being an opioid user. Models were constructed using Python package scikit-learn[26].

We designated the total number of chronic pain sites by a cumulative score ranging from 1 to 7, showing a combined total of values from the pain dimensions. Pearson correlation coefficients (Pearson r) were used to examine the relationship between opioid use risk scores and spreading of pain using the patients' total chronic pain sites as a continuum. In addition, differences in opioid risk scores between opioid users and non-users within each group of total chronic pain sites (i.e., 1, 2, 3, >4) were further measured with Cohen's d effect sizes.

Longitudinal analysis

All three derived models were applied to the testing population to predict the starting of opioid use and the discontinuation of opioid use at the follow-up visit. Prediction performances were evaluated using AUC-ROC curves and Cohen's d effect sizes.

Risk scores in opioid-related disorder

Risk scores derived from our *pain-agnostic model* were assessed in a subgroup of chronic pain patients diagnosed with an opioid-related disorder. Cohen's d effect sizes were used to compare the risk scores of this subgroup with other chronic pain patients within groups of current opioid users and non-users.

Biological analysis

Pearson correlation coefficients were used to measure the association of the logarithmic values of CRP with the opioid use risk scores in the training and testing population.

Imputation and standardization

For each feature, coding values attributed to "prefer not to answer" and "do not know" answers from the questionnaire, were recoded as missing values. Individuals with more than 20% of missing values were excluded from the analyses. For individuals with less than 20% missing values, a data driven Bayesian ridge regression approach was applied to impute the missing data as a function of all other features in the model. For the purposes of our regression analyses, features were standardized across the participants by centering mean to zero and scaling the variance to one unit. These steps were applied separately for the training and testing set to avoid data leakage.

Ethics

For the current study, analyses were conducted as part of the UK Biobank application No. 20802. At the assessment centers, prior to data collection, all participants were asked to provide electronically written consent through consent forms created based on the Ethics & Governance Council (ECG) advice and adhering to the Ethics & Governance Framework (EGF) guidelines (For further information regarding the consent procedure, see https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf).

Results

Characteristics of opioid users in the UK Biobank:

Figure 1 shows the flowchart of the study. A total of 195,808 CNCP patients were identified in the UK Biobank. These patients were split into a discovery set (n=178,763) used to train the predictive models and a testing set (n=17,045) used to validate our models in an out-of-sample group of patients. The testing set only included the CNCP patients for whom longitudinal data about their opioid status were available as they came back for a follow-up visit 6 to 10-year later.

The CNCP patients regularly using prescribed opioids for over 4 weeks were identified as opioid users in the UK Biobank. These opioid users were identified in-person by a trained nurse at each visit. A total number of 20,895 CNCP patients used prescribed opioids in the training set (11.7%), and a total number of 912 CNCP patients used prescribed opioids in the testing set (5.4%). The percent of opioid users was lower in the longitudinal data as individuals participating the follow-up visits tend to be generally healthier[27]. These differences between the ratio of opioid users does not however compromise the sensitivity or the specificity of our model applied to the out of sample patients. The descriptive characteristics of the training and testing population in opioid users and non-users are displayed in **Table 1.** The frequency and the type of prescribed opioids are reported in **Table 2**. Univariate associations between all the candidate features and opioid use in the training and testing population are displayed in **Supplementary Table 1** and **Table 2**.

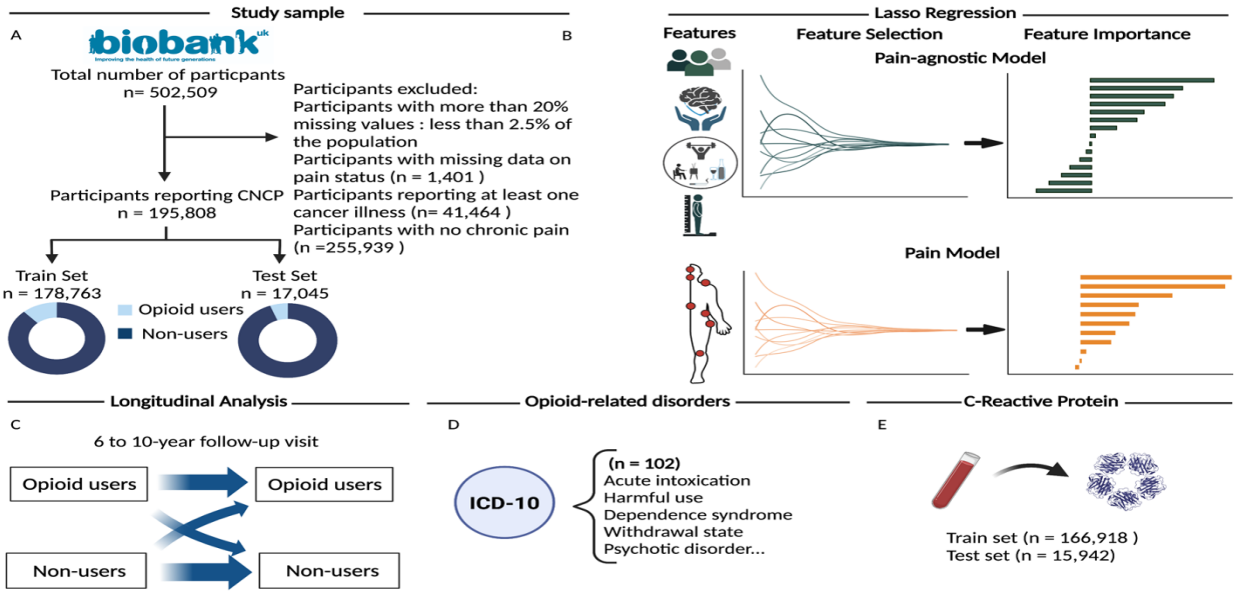

Figure 1 Study workflow. A) The study sample includes chronic non-cancer pain patients from the UK Biobank (n = 195,808). These patients were split into a train set (n=178,763 CNCP patients) and a testing set (n=17,045 CNCP patients). The testing set only included the CNCP patients for whom longitudinal data about their opioid status were available. B) The *pain-agnostic model* is derived integrating 77 variables on sociodemographic, lifestyle, mental health, and anthropometric measures, and the *pain model* is derived integrating 16 pain-related variables (i.e., types of chronic and acute pain). C) Derived models are applied to the test set to predict the opioid use status longitudinally at the follow-up visit. D) Data on ICD-10 diagnosis is used to validate opioid use risk scores in CNCP patients with an opioid-related disorder. E) Measures of C-reactive protein are investigated to assess their association with opioid use risk scores.

	Training population		*Testing population*	
	No opioid use (N=157868)	**Opioid users (N=20895)**	**No opioid use (N=16133)**	**Opioid users (N=912)**
Sex				
Female	88531 (56.1%)	12814 (61.3%)	8788 (54.5%)	579 (63.5%)
Male	69337 (43.9%)	8081 (38.7%)	7345 (45.5%)	333 (36.5%)
Age (years)				
Mean (SD)	57.0(8.08)	58.9(7.62)	55.3(7.48)	56.4(7.38)
Median [Min, Max]	58.1[39.9,73.7]	60.5[40.3,72.9]	55.7[40.3,70.4]	57.0[40.3,69.9]
Ethnicity				
White	147141 (94.5%)	19721 (95.6%)	15584 (97.4%)	878 (97.4%)
Black	3714 (2.39%)	435 (2.11%)	132 (0.825%)	11 (1.22%)
Asian	3653 (2.35%)	327 (1.59%)	198 (1.24%)	8 (0.888%)
Mixed	1063 (0.683%)	132 (0.640%)	86 (0.537%)	4 (0.444%)
Other	62 (0.0398%)	4 (0.0194%)	1 (0.00625%)	0 (0%)
Missing	2235 (1.4%)	276 (1.3%)	132 (0.8%)	11 (1.2%)
Education				
College/University	44327 (35.9%)	3154 (24.0%)	6852 (46.7%)	237 (30.6%)
Advanced level	16702 (13.5%)	1606 (12.2%)	2078 (14.2%)	104 (13.4%)
Ordinary level	33853 (27.4%)	4141 (31.6%)	3196 (21.8%)	245 (31.6%)
Certificate Secondary Education	9405 (7.61%)	1249 (9.52%)	783 (5.33%)	60 (7.74%)
Practical Career Diploma	11064 (8.95%)	1709 (13.0%)	927 (6.31%)	69 (8.90%)
Other Professional Qualification	8290 (6.70%)	1256 (9.58%)	849 (5.78%)	60 (7.74%)
Missing	34227 (21.7%)	7780 (37.2%)	1448 (9.0%)	137 (15.0%)
Employment				
Full/part-time student	438 (0.279%)	32 (0.154%)	49 (0.304%)	6 (0.659%)
Looking after home or family	4745 (3.02%)	533 (2.56%)	471 (2.93%)	23 (2.52%)
Unpaid voluntary work	719 (0.457%)	75 (0.360%)	81 (0.503%)	2 (0.220%)
Paid employment/self-employed	88825 (56.5%)	6085 (29.2%)	11027 (68.5%)	449 (49.3%)
Retired	51943 (33.0%)	9161 (44.0%)	3955 (24.6%)	295 (32.4%)
Unable to work due to sickness/disability	6613 (4.21%)	4510 (21.7%)	236 (1.47%)	122 (13.4%)
Unemployed	2936 (1.87%)	305 (1.47%)	193 (1.20%)	10 (1.10%)
None of the employments proposed	951 (0.605%)	105 (0.505%)	86 (0.534%)	4 (0.439%)
Missing	698 (0.4%)	89 (0.4%)	35 (0.2%)	1 (0.1%)
Household income (before tax)				
Less than 18,000	33921 (25.6%)	8225 (49.8%)	1885 (13.0%)	234 (29.1%)
18,000 to 30,999	34570 (26.1%)	4244 (25.7%)	3235 (22.3%)	233 (29.0%)
31,000 to 51,999	33491 (25.3%)	2703 (16.4%)	4376 (30.2%)	185 (23.0%)
52,000 to 100,000	24507 (18.5%)	1188 (7.19%)	3967 (27.4%)	132 (16.4%)
Greater than 100,000	6002 (4.53%)	171 (1.03%)	1026 (7.08%)	19 (2.37%)
Missing	25377 (16.1%)	4364 (20.9%)	1644 (10.2%)	109 (12.0%)
Chronic pain type				
Headaches	32420 (20.5%)	4640 (22.2%)	3822 (23.7%)	303 (33.2%)
Facial pain	2948 (1.87%)	580 (2.78%)	305 (1.89%)	33 (3.62%)
Neck or shoulder pain	56067 (35.5%)	8946 (42.8%)	5680 (35.2%)	404 (44.3%)
Stomach or abdominal pain	16441 (10.4%)	2889 (13.8%)	1579 (9.79%)	125 (13.7%)
Hip pain	28765 (18.2%)	6638 (31.8%)	2299 (14.3%)	248 (27.2%)
Back pain	60660 (38.4%)	11796 (56.5%)	5915 (36.7%)	507 (55.6%)
Knee pain	59536 (37.7%)	9504 (45.5%)	5564 (34.5%)	347 (38.0%)
Widespread pain	3781 (2.40%)	2192 (10.5%)	216 (1.34%)	78 (8.55%)

Table 1 Characteristics of the training and testing population. Mean, standard deviation (SD), and median are reported for the continuous variables (Age and BMI), and percentages are reported for categorical variables.

	Prescription opioids	Number	Percentage (%)
Weak opioids	Combined	13904	63.75
	Codeine	2020	9.26
	Dihydrocodeine	1444	6.62
	Dextropropoxyphene	314	1.43
	Meptazinol	61	0.28
	Pethidine	21	0.09
***Strong* opioids**	Tramadol	4646	21.3
	Morphine	360	1.65
	Buprenorphine	306	1.40
	Fentanyl	220	1
	Oxycodone	166	0.76

Table 2 Regular prescription opioids reported by the chronic non-cancer pain patients. Combined opioids comprise opioids in combination with a non-opioid analgesic.

The associations between chronic pain phenotypes and opioid use are displayed in **Figure 2A**. Individuals reporting chronic widespread pain, chronic hip pain, and chronic back pain were more likely to use opioids. Moreover, the likelihood of using opioids strongly linearly increased with the number of chronic pain sites (**Figure 2B**), psychiatric conditions (**Figure 2D**), and non-cancer illnesses (**Figure 2E**). These observations support the proposition that opioids are prescribed to high-risk patients showing widespread pain, comorbidities[122], and poor functioning [6, 13]. Thus, physical reported on a single site was not the main reason why opioids are prescribed in CNCP patients of the UK Biobank.

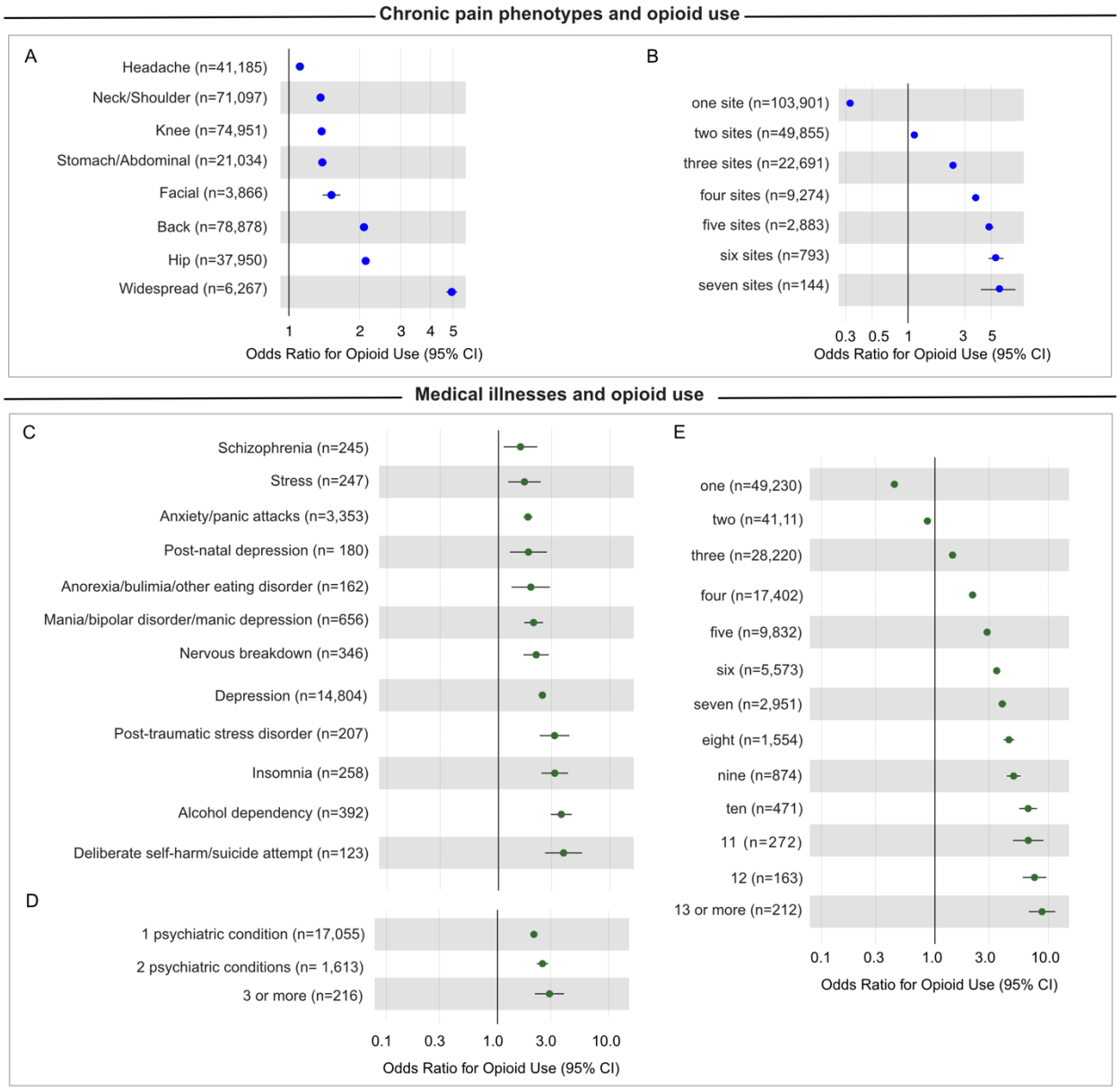

Figure 2 Characteristics of opioid users in the UK Biobank. A) Forest plot shows the associations between chronic pain sites and opioid use. Odds ratios are calculated between opioid use at each given pain site and opioid use at the other six pain sites. Among all types of chronic pain, widespread pain shows the greatest odds of using opioids, followed by hip and back pain. B) Associations between number of chronic pain sites and opioid use. Odd ratios are calculated between opioid use at each group of total number of pain sites and opioid use in the other groups. Odds of using opioids increases linearly with the number of pain sites. C) Associations between self-reported psychiatric illnesses and opioid use in CNCP patients. All psychiatric conditions show significant association with opioid use. D and E) Forest plots showing the associations between number of illnesses reported (psychiatric and non-cancer) and opioid use in CNCP patients. Odds of using opioids increases linearly with the number of psychiatric illnesses as well as non-cancer illnesses.

Predicting opioid use in CNCP patients:

We aimed to discriminate CNCP patients using opioids from the ones not using prescribed opioids based on the patients' characteristics. Three separate models were derived using either

pain features (*pain model)*, non-pain features (*pain-agnostic model)*, and the additive effect of all features included in both the *pain* and the *pain-agnostic models* (*combined model*). In the training set, the performance of the models predicting opioid use was estimated using a 10-folds cross-validation procedure. The *pain model* obtained an averaged AUC $_{pain}$ = 0.71, the *pain-agnostic model* obtained an averaged AUC $_{pain\text{-}agnostic}$ = 0.78, and the *combined model* obtained an averaged AUC $_{combined}$ = 0.80 (**Figure 3A**). The models applied to the test set obtained good performance in out of sample patients (AUC $_{pain}$ = 0.70, AUC $_{pain\text{-}agnostic}$ = 0.74, AUC $_{combined}$ = 0.78; **Figure 3A**). The models' performances show that prescribed opioid use can be predicted from either pain features or pain-agnostic features, and that combining all features added little value to the model performance. The models' features and their weights are presented in **Figure 3B**. In the *pain model*, chronic widespread pain and chronic back pain showed the strongest positive weights. In the *pain-agnostic model*, inability to work due to disability or sickness, body mass index and sleeplessness were among the strongest positive weights while household income and college education were the strongest negative weights. Altogether, our findings suggest that opioid use in chronic pain patients can be predicted solely from the patient's characteristics and without any information about the prescriber.

The probability of opioid use provided by our risk scores was then examined when accounting for the number of pain sites (**Figure 3C**). Near-to-medium effect sizes were found for the *pain-agnostic model*'s risk scores classifying opioid users and non-users within each number of pain site. The *pain model's* risk scores instead showed strong association with the number of pain sites, but only small effect sizes between opioid users and non-users within a given number of pain site (**Figure 5D)**. Our models therefore captured two different dimensions of prescribed opioid use; one most strongly depending on pain and the other on the general characteristic and

functioning of the patients regardless of the pain. In fact, the risk scores derived from both *pain* and *pain-agnostic models* were only weakly correlated together (r = 0.27, p < 0.0001).

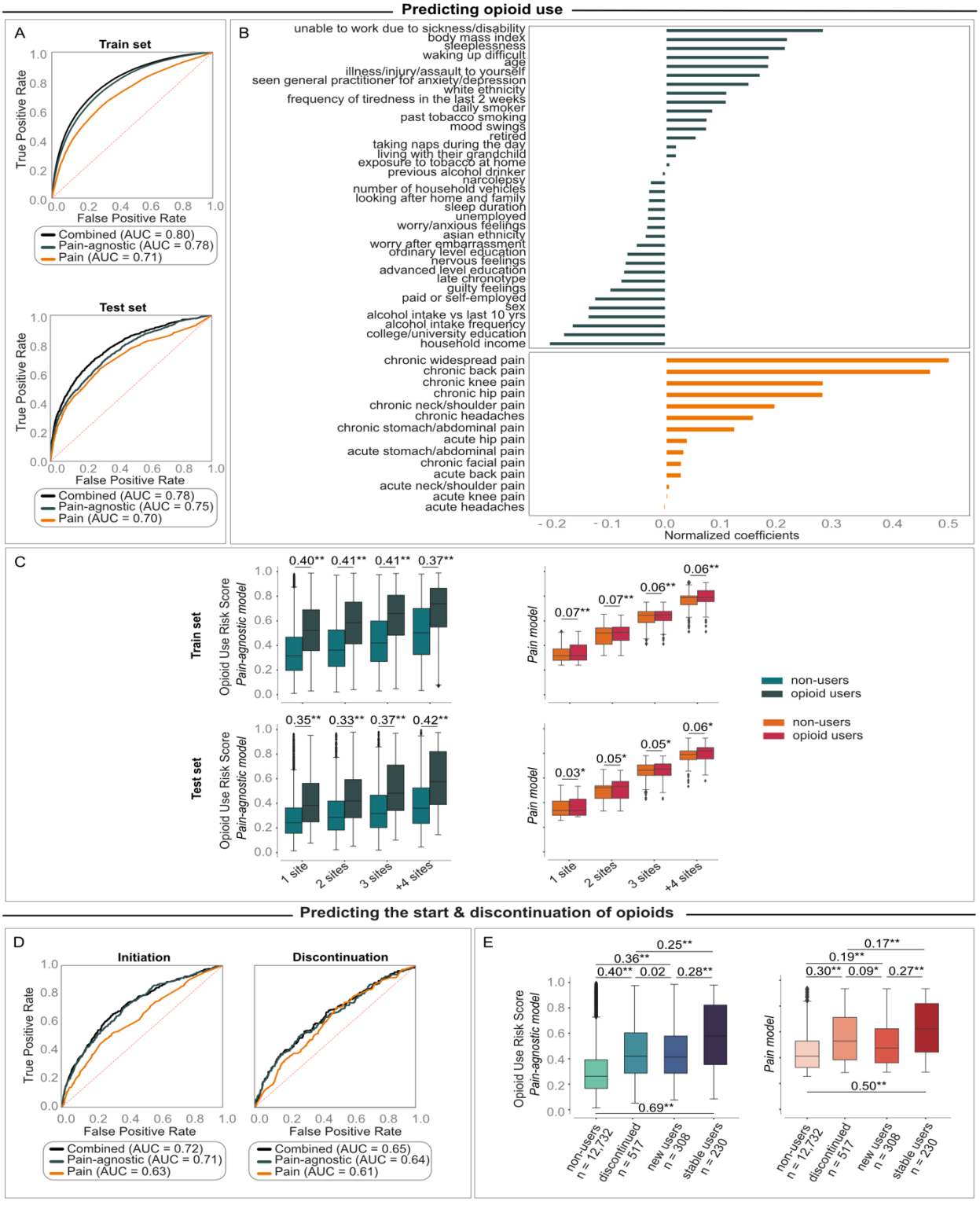

Figure 3 Pain and pain-agnostic models predicting opioid use at the baseline and follow-up visit in the UK Biobank. A) ROC-AUC curves showing classification accuracy of the three Lasso regression models (i.e., *combined*, *pain-agnostic*, and *pain*) in the train (top) and test set (below). All derived models obtained good performance in the test set. B) Normalized coefficients of selected features identified by the *pain-agnostic* (top) and *pain* (below) *models*. Features correspond to the most predictive variables with non-zero weights after penalization. Positive weights indicate positive correlation with opioid use, while negative weights indicate negative correlation with opioid use. C) Risk scores of opioid use in actual opioid users and non-users within various number of chronic pain sites in the train (top) and test (below) set. Box plots show the distribution of risk scores for the *pain-agnostic* (left) and *pain* (right) *model*. Cohen's d effect sizes between opioid users and non-users are provided (** = P-value <0.001, * = P-value<0.05). There are near-to-medium effect sizes between opioid users and non-users for the *pain-agnostic* opioid use risk scores, and small effect sizes for the *pain* opioid risk scores. D) ROC-AUC curves showing classification accuracy of the derived models in predicting the start (left) and the discontinuation (right) of opioid use at the follow-up visit (i.e., 6-10 years later). The *pain-agnostic model* shows an accuracy 0.71 AUC for predicting the start of opioid use, and the *pain model* shows an accuracy of 0.63. All three models show a poor-to-near-acceptable classification accuracy in predicting the discontinuation of opioid use. E) Box plots show the distribution of opioid use risk scores from the *pain-agnostic model* (left) and the *pain* (right) *model* in each opioid status at follow-up (i.e., non-users, discontinued, new-users, stable users). Y-axis shows the risk scores at baseline visit. Cohen's d effect sizes between each two groups (i.e., non-users, stable users, discontinued, and new users) are provided (** = P-value <0.001, * = P-value<0.05).

Predicting the start and the discontinuation of opioids:

Next, we sought to predict within-individual changes in opioid use between the two visits in the out-of-sample patients of the testing set. Here, the *pain* and *pain-agnostic models* were applied to predict CNCP patients that will start using prescribed opioids (compared to the ones that will not) and the ones that will discontinue prescribed opioids (compared to the ones that will still be using opioids). In the longitudinal analysis, the *pain-agnostic model* (AUC $_{pain\text{-}agnostic}$ = 0.71) and the *combined model* (AUC $_{combined}$ = 0.72) showed acceptable accuracies for predicting CNCP patients that started opioids (new users (n = 308) versus non-users (n=12,732)). The *pain model*, however, showed poor-to-near acceptable classification accuracy (AUC $_{pain}$ = 0.63). All three models represented a poor-to-near-acceptable classification accuracy in predicting the discontinuation of opioid use (stable users (n = 230) versus discontinued users (n = 517)); AUC $_{combined}$ = 0.65, AUC $_{pain\text{-}agonistic}$ = 0.64, and AUC $_{pain}$ = 0.61. In all cases, adding the characteristics of the pain to the pain-agnostic features did not improve the prediction accuracy. Receiver operating curve comparison of the three models for the longitudinal prediction are represented in **Figure 3D**, and **Figure 3E** represents the comparison of baseline opioid use risk scores among non-users, discontinued users, new users and stable users.

Opioid use risk scores in CNCP patients with an opioid-related disorder:

We next examined if the opioid use risk scores from the *pain agnostic model* were most strongly expressed in a subgroup of CNCP patients with an opioid-related disorder (ICD-10; n = 102). As shown in **Figure 4,** the risk scores were higher in CNCP patients with opioid-related disorders, with near-to-medium effect sizes. This finding suggests that *pain-agnostic* risk factors for using opioids contributed to opioid-related disorders in CNCP patients.

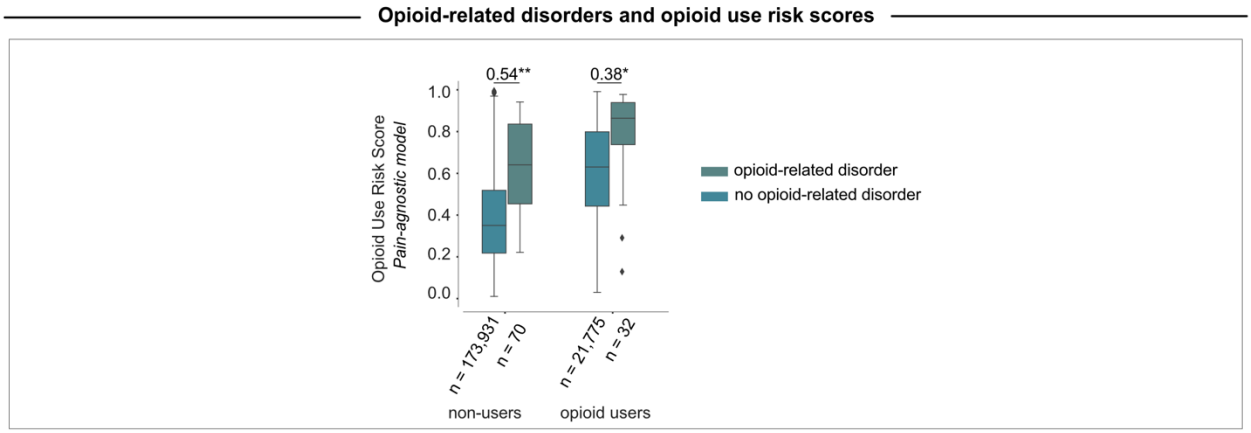

Figure 4 Pain-agnostic risk scores in opioid-related disorders. Risk scores were significantly higher in CNCP patients with a opioid-related disorder, regardless of opioid use. Cohen's d effect sizes are provided (** = P-value <0.001, * = P-value<0.05). In opioid non-users, medium effect size and in opioid users (d=0.54), near-to-medium effect size (d=0.38) are achieved (opioid-related disorder vs. no opioid-related disorder).

Association between C-reactive protein and opioid use risk scores:

Figure 5A shows that higher levels of C-reactive protein were observed in opioid users compared to non-users, even after matching the number of pain sites. The difference was observed in both the training and the testing set and at each number of pain site. These findings are consistent with the previous literature showing that opioid use can induce hormonal changes, such as testosterone deficiency, that may lead to an increased inflammation[28, 29].

Our opioid use risk scores indicated that higher levels of CRP (logarithmic values) are associated with the *pain-agnostic*-related risk scores (train set: r = 0.32, p <0.001, test set: r = 0.26,

p <0.001) (**Figure 5B**), The association between *pain-agnostic* risk scores and CRP remained significant after controlling for the *pain* risk scores (r =0.23, P-value <0.05), while the reverse was not true (r = 0.02, P-value > 0.05). Applying the *pain-agnostic model* to individuals who are not currently using opioids still showed a significant association with CRP, further supporting that the association between the risk factors and the inflammatory response was not determined by the actual use of opioids. These results suggest that a part of the inflammatory response observed in opioid users may be associated with pre-existing risk factors rather than with the consequences of the pain or prescribed opioid use.

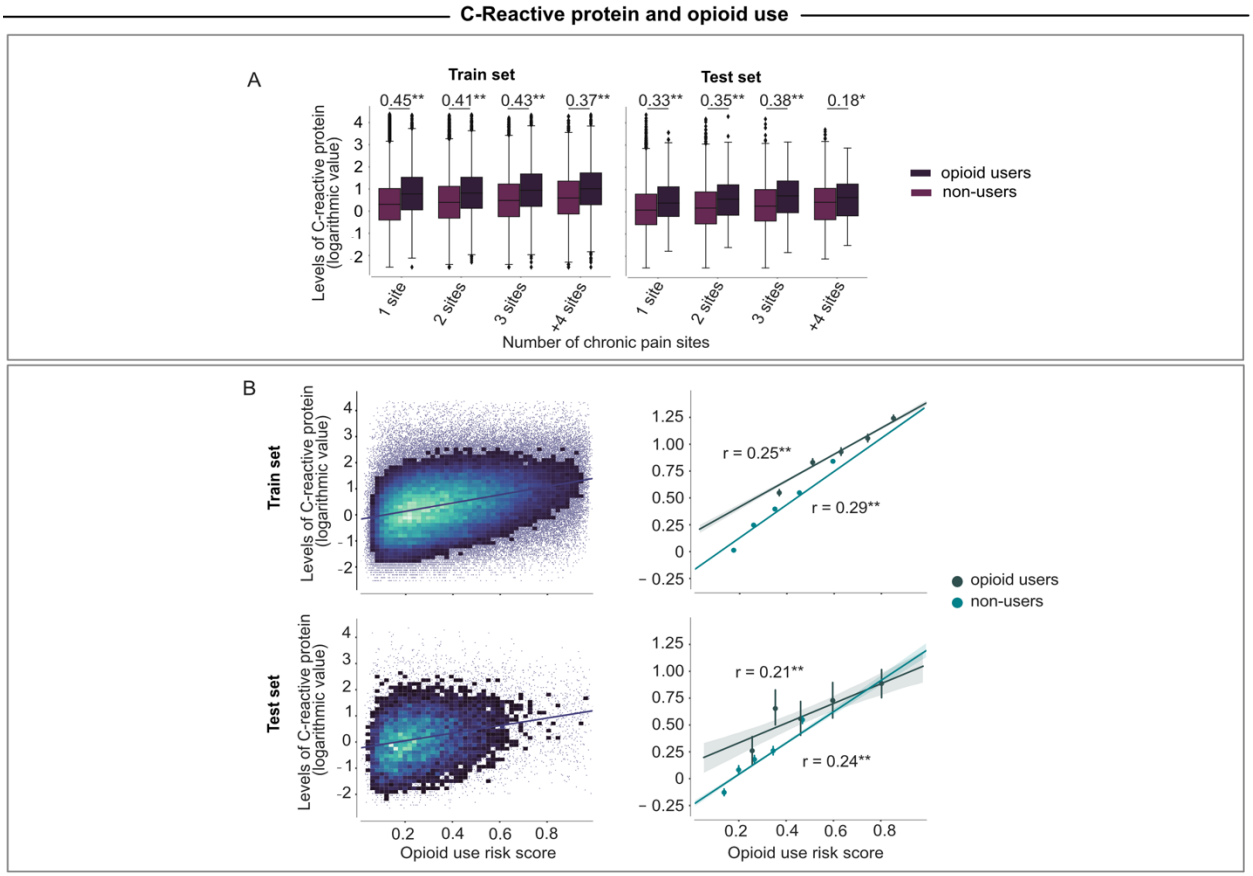

Figure 5 Association between levels of C-reactive protein with opioid use and opioid use risk scores. A) Comparison between levels of CRP (mg/L) (logarithmic values) in opioid users and opioid non-users at each number of pain sites (at both train set (left) and test set (right)). Higher levels of CRP in opioid users compared to non-users are shown regardless of number of pain sites. Cohen's-d effect sizes between opioid users and non-users are provided (** = P-value <0.001, * = P-value<0.05). B) Association between CRP and *pain-agnostic* risk scores in train (top) and test set (below). Higher values of CRP are associated with higher values of pain-agnostic risk score (left) (train set: r = 0.32**, test set: r = 0.26 **). After stratifying by opioid use (right), *pain-agnostic* risk scores show significant association with CRP in opioid non-users as well as opioid users. Pearson correlation values (r) are provided (** = P-value <0.001, * = P-value<0.05).

Discussion

In order to inform pain management strategies of reducing harms, there is a need to better characterize prescribed opioid use among CNCP patients and to define the profile of patients who are at greatest risk of opioid use and misuse. We initially showed that prescribed opioids were strongly associated with the number of chronic overlapping pain sites, with the number of psychiatric conditions, and with the number of non-cancer illnesses. We then showed that a biopsychosocial framework, based on the patient's characteristics, can predict prescribed opioid use in the cross-sectional data and the start/discontinuation of prescribed opioids in the longitudinal data. More specifically, the *pain agnostic* scores were most strongly associated with opioid-related disorders and with the inflammatory response measured with CRP. Overall, our results support the existing literature showing an adverse selection of high-risk patients for prescribed opioids in the setting of chronic pain management, as opioids are largely prescribed to treat the poorly functioning patients.

Previous studies have shown that prescribed opioids and opioid use disorders are more prevalent in the patients with overlapping pain conditions and higher pain intensity[30-33]. Here, we showed that regular use of prescribed opioids in the UK Biobank is associated with the type of chronic pain, as widespread, back and hip pain showed the highest probability of opioid use. Importantly, opioid use was more strongly associated with the number of pain sites than with the location of the pain on the body map, as prescribed opioid use increased monotonically with the number of chronic pain sites. This is in line with the evidence showing that higher rates of opioid use problems occur amongst chronic pain patients with multisite pain[30].

The associations between pain and opioid use are often confounded by psychological factors, such as distress and negative affect[34, 35], comorbidities, and poor functioning[6]. Here, we

showed that the prevalence of prescribed opioid use was significantly higher in patients suffering from a comorbid psychological/psychiatric problem, and greater numbers of comorbid conditions were associated with a higher propensity of opioid prescriptions. These findings are consistent with previous studies showing that patients who report a history of substance use disorder, post-traumatic stress disorder (PTSD), sleep disturbance, depression, and heightened anxiety are more likely to be prescribed opioid therapy and at a higher dose[36-39]. This so-called adverse selection of chronic pain management takes place both at the initiation of opioid therapy as well as the patients' decision making on the maintenance of opioids, contributing to problematic opioid use[8, 13]. Previous studies have shown that pain intensity and pain interferences are often higher in patients with psychiatric comorbidities, putting them at a greater risk of being prescribed opioids by the physicians[6]. These high-risk patients tend to show the worst clinical phenotypes, and opioid medications might be prescribed to them to treat a mutually inclusive emotional and physical pain[40]. Overall, our results support the proposition that opioids are prescribed for other factors that are not exclusive to the severity of the physical pain.

We next trained and validated machine learning algorithms entering either pain characteristics, pain agnostic features, or the combination of both to predict opioid use in CNCP patients. We trained Lasso regression algorithms with regularization to avoid multicollinearity and enhance generalizability in the out-of-sample patients of the testing set. Both *pain* and *pain-agnostic* models obtained an acceptable classification accuracy (AUC between 0.7-0.8), and the risk scores derived from the two models were weakly correlated one with another. Our findings stress that opioid use can be predicted with good accuracy without any prior information on the clinicians' clinical experience of non-cancer pain management and their attitudes towards opioid therapy.

In line with previous studies showing that chronic widespread pain and chronic back pain are the most common pain conditions treated with opioids[30, 32], chronic widespread pain, chronic back pain, and chronic hip pain showed the strongest weights in our *pain model* predicting opioid use. Other chronic pain conditions showed lower weights and acute pain conditions were mostly neutral. Our *pain-agnostic model* identified inability to work due to sickness or disability, body mass index (BMI), sleeplessness and difficulty waking up, age, self- illness or injury, and depression and anxiety as the strongest positive weighted predictors associated with higher likelihood of opioid use. On the other hand, higher income, college education, and lower alcohol intake were the strongest negative weighted predictors of opioid use (i.e., protective factors). The *pain-agnostic model* stresses the importance of day-to-day functioning improvement, anthropometric measurements, and socioeconomic status as determinants of opioid prescriptions for chronic pain. The evidence on the directionality of improved functioning by opioid therapy, however, remains unclear, as in some cases, it has been shown that opioids may be even associated with disability escalation[41].

We next used the longitudinal data to test if the *pain-agnostic* risk scores preceded opioid use. Here, both *pain* and *pain-agonistic models* were applied to predict within-individual changes in opioid use at a follow-up timepoint (i.e., after 6 to 10 years). The *pain-agnostic model* showed acceptable accuracy for classifying CNCP patients who will start prescribed opioid use. The discontinuation of prescribed opioid was harder to predict, as the models only obtained a near-to-acceptable classification accuracy. One explanation for the difficulty in predicting opioid discontinuation is that other factors such as the physicians' attitudes on long-term prescribing opioids may have been more important for the discontinuation of opioids.

So far, most studies have emphasized on the potential risk factors associated with opioid misuse and opioid use disorders[17, 42, 43]. The UK Biobank also comprises data on diagnoses made during hospital inpatient admissions which are coded according to the International Classification of Diseases (ICD-10). Using the ICD-10 data, we compared the *pain-agnostic* risk scores of opioid use in a subset of CNCP patients with opioid-related disorders and showed that risk scores were most strongly expressed in this subset of patients, regardless of their actual opioid use. We conclude that the *pain-agnostic* risk scores represent a general burden increasing the likelihood of receiving prescribed opioids and potentially leading to opioid-related disorders.

We finally showed that opioid use was associated with higher CRP when matching the pain patients based on their number of pain sites. Elevated levels of C-reactive protein have been observed in individuals with psychological distress, depression, and with a higher risk of developing persistent pain[19, 44, 45]. Opioid use has also been associated with lower testosterone and higher inflammatory blood markers[28, 29, 46]. Thus, higher measures of CRP could be a consequence of opioid use, or alternatively, a consequence of the biopsychosocial factors contributing to the poorly functioning of the individuals using prescribed opioids. In a follow-up analysis, levels of CRP were associated with the *pain-agnostic* risk scores, even after controlling for *pain* risk scores, in both opioid users and CNCP patients not using opioids. These findings suggest that the increase in the inflammatory blood marker observed in opioid users depends on the expression of the *pain-agnostic* risk score predisposing the patients to use prescribed opioids, rather than representing a consequence of opioid use.

Strengths and limitations

The strengths of our study include the use of the large, multistage, and prospective UK Biobank dataset. Conducting analysis on this nationally representative sample of the general

population avoids selection bias which happens in clinical trials and provides a more reproducible interpretation of the results. Moreover, the UK Biobank provides an extensive range of variables allowing a more comprehensive analysis on all potential factors contributing to the risk of prescription opioid use in CNCP patients. Our study has however a number of limitations. First, UK Biobank does not have measures of the pain intensity and pain interferences for all the CNCP patients, and we could not assess these variables as possible covariates associated with opioid use. Also, there is no information on the dosage and the period of use of opioid drugs in this dataset. Another limitation of this current study is the relatively long-time interval (i.e., around 9 years) between the baseline and the follow-up visit. Thus, the results should be interpreted carefully since there is no information on the fluctuations in chronic pain conditions and opioid use throughout this period. However, the fact that we could make use of this multistage data allowed us to predict opioid use in chronic non-cancer pain patients both cross-sectionally and longitudinally.

References

1. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448-60.
2. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.
3. IASP. International Association for the Study of Pain; 2018 [Available from: https://www.iasp-pain.org/advocacy/iasp-statements/opioids-for-pain-management/.
4. Henry SG, Matthias MS. Patient-Clinician Communication About Pain: A Conceptual Model and Narrative Review. Pain Medicine. 2018;19(11):2154-65.
5. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. The journal of pain. 2009;10(2):113-30.
6. Sullivan MD, Ballantyne JC. Must we reduce pain intensity to treat chronic pain? PAIN. 2016;157(1).
7. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? The Clinical journal of pain. 1997;13(4):330-6.

8. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. Gen Hosp Psychiatry. 2014;36(1):99-104.
9. Sullivan MD. Who gets high-dose opioid therapy for chronic non-cancer pain? PAIN. 2010;151(3).
10. Weissman JD, Russell D, Taylor J. Disparities in Opioid Prescribing for Long-Term Chronic and Short-Term Acute Pain: Findings from the 2019 National Health Interview Survey. J Behav Health Serv Res. 2022.
11. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. Pain physician. 2012;15(3 Suppl):ES67-ES92.
12. Quinn PD, Rickert ME, Franck J, Sariaslan A, Boersma K, Lichtenstein P, et al. Associations of mental health and family background with opioid analgesic therapy: a nationwide Swedish register-based study. PAIN. 2019;160(11):2464-72.
13. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. PAIN®. 2013;154:S94-S100.
14. Grol-Prokopczyk H. Use and Opinions of Prescription Opioids Among Older American Adults: Sociodemographic Predictors. The Journals of Gerontology: Series B. 2018;74(6):1009-19.
15. Quinn PD, Hur K, Chang Z, Krebs EE, Bair MJ, Scott EL, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial healthcare claims. Pain. 2017;158(1):140.
16. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Archives of internal medicine. 2006;166(19):2087-93.
17. Turk DC, Swanson KS, Gatchel RJ. Predicting Opioid Misuse by Chronic Pain Patients: A Systematic Review and Literature Synthesis. The Clinical Journal of Pain. 2008;24(6).
18. Svanberg M, Stålnacke BM, Quinn PD, Boersma K. Opioid Prescriptions in Chronic Pain Rehabilitation. A Prospective Study on the Prevalence and Association between Individual Patient Characteristics and Opioids. J Clin Med. 2021;10(10).
19. Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, et al. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. PAIN. 2014;155(8):1605-12.
20. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J Pain. 2008;9(2):122-45.
21. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015;12(3):e1001779.
22. Santos R, Ursu O, Gaulton A, Bento AP, Donadi RS, Bologa CG, et al. A comprehensive map of molecular drug targets. Nature reviews Drug discovery. 2017;16(1):19-34.
23. Wu Y, Byrne EM, Zheng Z, Kemper KE, Yengo L, Mallett AJ, et al. Genome-wide association study of medication-use and associated disease in the UK Biobank. Nature Communications. 2019;10(1):1891.
24. Tibshirani R. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society: Series B (Methodological). 1996;58(1):267-88.

25. Hanley AW, Garland EL. Salivary measurement and mindfulness-based modulation of prescription opioid cue-reactivity. Drug Alcohol Depend. 2020;217:108351.
26. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: Machine learning in Python. the Journal of machine Learning research. 2011;12:2825-30.
27. Lyall DM, Quinn T, Lyall LM, Ward J, Anderson JJ, Smith DJ, et al. Quantifying bias in psychological and physical health in the UK Biobank imaging sub-sample. Brain Communications. 2022;4(3):fcac119.
28. Mohamad N-V, Wong SK, Hasan WNW, Jolly JJ, Nur-Farhana MF, Ima-Nirwana S, et al. The relationship between circulating testosterone and inflammatory cytokines in men. The Aging Male. 2018.
29. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug and alcohol dependence. 2015;149:1-9.
30. Moshfegh J, George SZ, Sun E. Risk and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients With Newly Diagnosed Musculoskeletal Pain in the Neck, Shoulder, Knee, or Low Back. Annals of internal medicine. 2019;170(7):504-5.
31. Herman PM, Broten N, Lavelle TA, Sorbero ME, Coulter ID. Health Care Costs and Opioid Use Associated With High-impact Chronic Spinal Pain in the United States. Spine. 2019;44(16).
32. Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA. Opioids and the treatment of chronic pain in a primary care sample. Journal of pain and symptom management. 2001;22(3):791-6.
33. Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK biobank participants. EClinicalMedicine. 2020;21:100321.
34. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? Clin J Pain. 1997;13(4):330-6.
35. Martel MO, Edwards RR, Jamison RN. The relative contribution of pain and psychological factors to opioid misuse: A 6-month observational study. Am Psychol. 2020;75(6):772-83.
36. Martel MO, Bruneau A, Edwards RR. Mind-body approaches targeting the psychological aspects of opioid use problems in patients with chronic pain: evidence and opportunities. Transl Res. 2021;234:114-28.
37. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006;166(19):2087-93.
38. Dobscha SK, Morasco BJ, Duckart JP, Macey T, Deyo RA. Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clin J Pain. 2013;29(2):102-8.
39. López-Martínez AE, Reyes-Pérez Á, Serrano-Ibáñez ER, Esteve R, Ramírez-Maestre C. Chronic pain, posttraumatic stress disorder, and opioid intake: A systematic review. World Journal of Clinical Cases. 2019;7(24):4254.
40. Sullivan MD, Ballantyne JC. When physical and social pain coexist: insights into opioid therapy. The Annals of Family Medicine. 2021;19(1):79-82.
41. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. Pain Physician. 2012;15(3 Suppl):Es67-92.

42. Manchikanti L, Giordano J, Boswell MV, Fellows B, Rajeev Manchukonda B, Pampati V. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. Journal of opioid management. 2007;3(2):89-100.
43. Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC health services research. 2006;6(1):1-10.
44. Maria C. Pitharouli , M.Sc. ,, Saskia P. Hagenaars , Ph.D. ,, Kylie P. Glanville , Ph.D. ,, Jonathan R.I. Coleman , Ph.D. ,, Matthew Hotopf , Ph.D., F.R.C.Psych. ,, Cathryn M. Lewis , Ph.D. ,, et al. Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank. American Journal of Psychiatry. 2021;178(6):522-9.
45. Uher T, Bob P. Neuropathic Pain, Depressive Symptoms, and C-Reactive Protein in Sciatica Patients. International Journal of Neuroscience. 2013;123(3):204-8.
46. Reece AS. High-sensitivity CRP in opiate addiction: relative and age-dependent elevations. Cardiovasc Toxicol. 2012;12(2):149-57.

7. Discussion

A complex, yet insufficiently explored question in prescribing opioids for chronic pain is what factors predispose a patient to receive opioid therapy. In order to inform pain management strategies of reducing harms, there is a need to better characterize prescribed opioid use among CNCP patients and to define the profile of patients who are at greatest risk of opioid use and misuse. In general, our results suggested a biopsychosocial pattern associated with opioid use in CNCP patients.

The aims of this study were to first identify potential risk factors of opioid use by deriving multivariate models in chronic non-cancer pain patients based on the pain features as well as characteristics agnostic to pain. Second, we aimed to identify whether within-individual changes in the individuals' opioid use status at a follow-up timepoint could also be explained by the proposed features. Our third aim, here, was to test if our predictive models can predict opioid-related disorders as per ICD-10 in chronic pain patients currently using or not using opioids. Finally, our fourth aim was to assess the associations of the predictive features with an inflammatory marker (i.e., CRP) in chronic non-cancer pain patients. In the following sections I will discuss the main findings of my study in the context of the current literature. I will also discuss the limitations and the strengths of this study.

Overall, in this study we showed that prescribed opioids were strongly associated with the number of chronic pain sites, with the number of psychiatric conditions, and with the number of non-cancer illnesses. We also showed that a biopsychosocial framework, based on the patient's characteristics, can usefully predict prescribed opioid use in the cross-sectional data and the start/discontinuation of prescribed opioids in the longitudinal data. More specifically, the *pain*

agnostic scores were most strongly associated with opioid-related disorders and with the inflammatory response measured with CRP. Overall, our results support the existing literature

7.1. Associations between chronic pain phenotypes and medical illnesses with opioid use

Previous studies have shown that prescribed opioids and opioid use disorders are more prevalent in patients with overlapping pain conditions and higher pain intensity[83-85, 123]. In this study, we indicated that regular use of prescribed opioids in the UK Biobank is associated with the type of chronic pain, and across pain sites, widespread, back and hip pain showed the highest probability of opioid use. Importantly, opioid use was more strongly associated with the number of pain sites than with the location of the pain on the body map, as prescribed opioid use increased monotonically with the number of chronic pain sites. This is in line with the evidence showing that higher rates of opioid use problems occur amongst chronic pain patients with multisite pain[83].

Studies have shown that associations between pain and opioid use are often confounded by psychological factors, such as distress and negative affect[82, 124], comorbidities , and poor functioning[12]. Here, we showed that the prevalence of prescribed opioid use was significantly higher in patients suffering from a comorbid psychological/psychiatric problem, and greater numbers of comorbid conditions were associated with a higher propensity of opioid prescriptions. These findings are consistent with previous studies showing that patients who report a history of substance use disorder, post-traumatic stress disorder (PTSD), sleep disturbance, depression, and heightened anxiety are more likely to be prescribed opioids and at a higher dose[97, 98, 125, 126]. This so-called adverse selection of chronic pain management takes place both at the initiation of opioid therapy as well as the patients' decision making on the maintenance of opioids, contributing to problematic opioid use[14, 127]. Previous studies have shown that pain intensity and pain interferences are often higher in patients with psychiatric comorbidities, putting them at a greater risk of being

prescribed opioids by the physicians[12]. These high-risk patients tend to show the worst clinical phenotypes, and opioid medications might be prescribed to them to treat a mutually inclusive emotional and physical pain[13]. Overall, our results support the proposition that opioids are prescribed for other factors that are not exclusive to the severity of the physical pain.

7.2. *Pain* and *pain-agnostic models* predictive of opioid use in CNCP patients

Next, we trained and validated machine learning algorithms entering either pain characteristics, pain agnostic features, or the combination of both to predict opioid use in CNCP patients. Lasso regression was used to avoid multicollinearity and enhance generalizability. In Lasso regression modeling, both variable selection and regularization is performed, and the aim is to identify the variables and their corresponding regression coefficients resulting in a less complex model with the least prediction error[119]. Both *pain* and *pain-agnostic* models obtained an acceptable classification accuracy in predicting opioid use (AUC between 0.7-0.8), and the risk scores derived from the two models were weakly correlated one with another. Our findings stress that opioid use can be predicted with good accuracy without any prior information on the clinicians' clinical experience of non-cancer pain management and their attitudes towards opioid therapy.

In line with previous studies showing that chronic widespread pain and chronic back pain are the most common pain conditions treated with opioids[83, 84], chronic widespread pain, chronic back pain, and chronic hip pain showed the strongest weights in our *pain model* predicting opioid use. Other chronic pain conditions showed lower weights and acute pain conditions were mostly neutral. Our *pain-agnostic model* identified inability to work due to sickness or disability, body mass index (BMI), sleeplessness and difficulty waking up, age, self- illness or injury, and depression and anxiety as the strongest positive weighted predictors associated with higher

likelihood of opioid use. On the other hand, higher income, college education, and lower alcohol intake were the strongest negative weighted predictors of opioid use (i.e., protective factors). The *pain-agnostic model* stresses the importance of day-to-day functioning improvement, anthropometric measurements, and socioeconomic status as determinants of opioid prescriptions for chronic pain. The evidence on the directionality of improved functioning by opioid therapy, however, remains unclear, as in some cases, it has been shown that opioids may be even associated with disability escalation[10].

Opioid use was strongly associated with the *pain-agnostic* features after matching the number of chronic pain sites. However, higher numbers of chronic pain sites were associated with higher levels of the *pain model's* risk scores. This finding builds upon our results from the performances of our models suggesting that two separate aspect of a non-cancer pain patient, including the psychosocial and the pain characteristics determine their probability of opioid use.

7.3. Predicting the start and the discontinuation of opioid use at the follow-up visit

We next used the longitudinal data to test if the *pain-agnostic* risk scores preceded opioid use. Here, both *pain* and *pain-agonistic models* were applied to predict within-individual changes in opioid use at a follow-up timepoint (i.e., after 6 to 10 years). The *pain-agnostic model* showed acceptable accuracy for classifying CNCP patients who will start prescribed opioid use. The discontinuation of prescribed opioid was harder to predict, as the models only obtained a near-to-acceptable classification accuracy. One explanation for the difficulty in predicting opioid discontinuation is that other factors such as the physicians' attitudes on long-term prescribing opioids may have been more important for the discontinuation of opioids.

7.4. The expression of the *pain-agnostic model* in CNCP patients with opioid-related disorders

So far, most studies have emphasized on the potential risk factors associated with opioid misuse and opioid use disorders[93, 128, 129]. The UK Biobank also comprises data on the diagnoses made during hospital inpatient admissions which are coded according to the International Classification of Diseases (ICD-10). Using the ICD-10 data, we compared the *pain-agnostic* risk scores of opioid use in a subset of CNCP patients with opioid-related disorders and showed that risk scores were most strongly expressed in this subset of patients, regardless of their actual opioid use. We conclude that the *pain-agnostic* risk scores represent a general burden increasing the likelihood of receiving prescribed opioids and potentially leading to opioid-related disorders.

7.5. The association between inflammation and the expression of the *pain* and *pain-agnostic models*

We finally showed that opioid use was associated with higher CRP when matching the pain patients based on their number of pain sites. Elevated levels of C-reactive protein have been observed in individuals with psychological distress, depression, and with a higher risk of developing persistent pain[16, 103, 105]. Opioid use has also been associated with lower testosterone and higher inflammatory blood markers[106, 130, 131]. Thus, higher measures of CRP could be a consequence of opioid use, or alternatively, a consequence of the biopsychosocial factors contributing to the poorly functioning of the individuals using prescribed opioids. In a follow-up analysis, levels of CRP were associated with the *pain-agnostic* risk scores, even after controlling for *pain* risk scores, in both opioid users and CNCP patients not using opioids. These findings suggest that the increase in the inflammatory blood marker observed in opioid users depends on the expression of the *pain-agnostic* risk score predisposing the patients to use prescribed opioids, rather than representing a consequence of opioid use.

7.6. Strengths and limitations

The strengths of our study include the use of the large, multistage, and prospective UK Biobank dataset. Conducting analysis on this nationally representative sample of the general population avoids selection bias which happens in clinical trials and provides a more reproducible interpretation of the results. Moreover, the UK Biobank provides an extensive range of variables allowing a more comprehensive analysis on all potential factors contributing to the risk of prescription opioid use in CNCP patients.

Our study has a number of limitations. First, UK Biobank does not have measures of the pain intensity and pain interferences for all the CNCP patients, and we could not assess these variables as possible covariates associated with opioid use. Also, there is no information on the dosage and the period of use of opioid drugs in this dataset. Another limitation of this current study is the relatively long-time interval (i.e., around 9 years) between the baseline and the follow-up visit. Thus, the results should be interpreted carefully since there is no information on the fluctuations in chronic pain conditions and opioid use throughout this period. However, the fact that we could make use of this multistage data allowed us to predict opioid use in chronic non-cancer pain patients both cross-sectionally and longitudinally.

8. Conclusion

The present study provides new insights into our understanding of the potential risk factors associated with prescribed opioid use in chronic non-cancer pain patients.

- Prescribed opioid use are predictable by either pain or pain-agnostic characteristics of the CNCP patients.
- Pain-agnostic risk factors for using opioids strongly contribute to the opioid-related disorders in CNCP patients.
- A part of the inflammatory response observed in opioid users may be associated with pre-existing pain-agnostic risk factors rather than with the consequences of the pain or the prescribed opioid use.

In summary, our findings suggest that prescribed opioid use, opioid-related disorders, and biological markers of inflammation are all associated with pain-agnostic characteristics that go beyond the physical pain experienced by the patients. Understanding these associated factors in chronic non-cancer pain patients is a prerequisite for the assessment of risks and benefits of prescribed opioid use in certain subpopulations and will be a fundamental step towards improving the safety and effectiveness of chronic pain management.

9. References

1. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448-60.
2. IASP. International Association for the Study of Pain; 2018 [Available from: https://www.iasp-pain.org/advocacy/iasp-statements/opioids-for-pain-management/.
3. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.
4. Guy GP, Jr., Zhang K, Bohm MK, Losby J, Lewis B, Young R, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. MMWR Morb Mortal Wkly Rep. 2017;66(26):697-704.
5. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Cmaj. 2017;189(18):E659-E66.
6. Becker WC, Dorflinger L, Edmond SN, Islam L, Heapy AA, Fraenkel L. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. BMC Family Practice. 2017;18(1):41.
7. Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020;8(8):Cd007407.
8. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-86.
9. Weissman JD, Russell D, Taylor J. Disparities in Opioid Prescribing for Long-Term Chronic and Short-Term Acute Pain: Findings from the 2019 National Health Interview Survey. J Behav Health Serv Res. 2022.
10. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. Pain Physician. 2012;15(3 Suppl):Es67-92.
11. Quinn PD, Rickert ME, Franck J, Sariaslan A, Boersma K, Lichtenstein P, et al. Associations of mental health and family background with opioid analgesic therapy: a nationwide Swedish register-based study. PAIN. 2019;160(11):2464-72.
12. Sullivan MD, Ballantyne JC. Must we reduce pain intensity to treat chronic pain? PAIN. 2016;157(1).
13. Sullivan MD, Ballantyne JC. When physical and social pain coexist: insights into opioid therapy. The Annals of Family Medicine. 2021;19(1):79-82.
14. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. PAIN®. 2013;154:S94-S100.
15. Sullivan MD. Who gets high-dose opioid therapy for chronic non-cancer pain? PAIN. 2010;151(3).
16. Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, et al. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. PAIN. 2014;155(8):1605-12.
17. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J Pain. 2008;9(2):122-45.

18. Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-Reactive Protein Levels, Psychological Distress, and Depression in 73 131 Individuals. JAMA Psychiatry. 2013;70(2):176-84.
19. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.
20. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. Journal of pain research. 2016;9:457-67.
21. Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, et al. What are the most common conditions in primary care? Systematic review. Canadian family physician Medecin de famille canadien. 2018;64(11):832-40.
22. Murray CJ, Lopez AD. Measuring the global burden of disease. New England Journal of Medicine. 2013;369(5):448-57.
23. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-97.
24. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morbidity and mortality weekly report. 2018;67(36):1001-6.
25. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6(6):e010364.
26. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag. 2011;16(6):445-50.
27. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012;13(8):715-24.
28. Canadian Pain Task Force.Working Together to Better Understand,Prevent, and Manage Chronic Pain:
What We Heard: Health Canada; [cited 2020 October]. Available from: Canda.ca.
29. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health. 2011;11(1):770.
30. WHO. International Statistical Classification of Diseases and Related Health Problems (ICD) [Available from: https://www.who.int/standards/classifications/classification-of-diseases.
31. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. 2019;160(1):28-37.
32. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.
33. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. American Psychologist. 2004;59(8):795.
34. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.
35. Ojala T, Häkkinen A, Karppinen J, Sipilä K, Suutama T, Piirainen A. Chronic pain affects the whole person--a phenomenological study. Disabil Rehabil. 2015;37(4):363-71.

36. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. British journal of anaesthesia. 2019;123(2):e273-e83.
37. Poleshuck EL, Green CR. Socioeconomic disadvantage and pain. Pain. 2008;136(3):235.
38. Selim AJ, Fincke G, Ren XS, Deyo RA, Lee A, Skinner K, et al. Racial Differences in the Use of Lumbar Spine Radiographs: Results From the Veterans Health Study. Spine. 2001;26(12):1364-9.
39. Edwards RR, Doleys DM, Fillingim RB, Lowery D. Ethnic Differences in Pain Tolerance: Clinical Implications in a Chronic Pain Population. Psychosomatic Medicine. 2001;63(2):316-23.
40. Edwards CL, Fillingim RB, Keefe F. Race, ethnicity and pain. Pain. 2001;94(2):133-7.
41. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: Understanding the relationships between chronic pain and comorbidity in the general population. PAIN. 2012;153(2):293-304.
42. Boersma K, Linton SJ. Expectancy, fear and pain in the prediction of chronic pain and disability: A prospective analysis. European Journal of Pain. 2006;10(6):551-7.
43. Park HJ, Moon DE. Pharmacologic management of chronic pain. The Korean journal of pain. 2010;23(2):99.
44. Ashburn MA, Staats PS. Management of chronic pain. The Lancet. 1999;353(9167):1865-9.
45. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. Rheumatology international. 2017;37(1):29-42.
46. Fishman SM, Teichera D. Challenges and choices in drug therapy for chronic pain. Cleveland Clinic Journal of Medicine. 2003;70(2):119-38.
47. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford). 2008;47(5):670-8.
48. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. American psychologist. 2014;69(2):119.
49. Cherkin DC, Deyo RA, Battié M, Street J, Barlow W. A comparison of physical therapy, chiropractic manipulation, and provision of an educational booklet for the treatment of patients with low back pain. N Engl J Med. 1998;339(15):1021-9.
50. Ferreira ML, Ferreira PH, Latimer J, Herbert RD, Hodges PW, Jennings MD, et al. Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: A randomized trial. Pain. 2007;131(1-2):31-7.
51. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev. 2005(3):Cd000335.
52. Bosy D, Etlin D, Corey D, Lee JW. An interdisciplinary pain rehabilitation programme: description and evaluation of outcomes. Physiother Can. 2010;62(4):316-26.
53. Nees TA, Riewe E, Waschke D, Schiltenwolf M, Neubauer E, Wang H. Multidisciplinary Pain Management of Chronic Back Pain: Helpful Treatments from the Patients' Perspective. Journal of clinical medicine. 2020;9(1):145.
54. Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. Lancet. 2010;375(9718):916-23.

55. Kerns RD, Sellinger J, Goodin BR. Psychological treatment of chronic pain. Annu Rev Clin Psychol. 2011;7:411-34.
56. Hann KEJ, McCracken LM. A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy. Journal of Contextual Behavioral Science. 2014;3(4):217-27.
57. Hassett AL, Williams DA. Non-pharmacological treatment of chronic widespread musculoskeletal pain. Best Practice & Research Clinical Rheumatology. 2011;25(2):299-309.
58. Häuser W, Schug S, Furlan AD. The opioid epidemic and national guidelines for opioid therapy for chronic noncancer pain: a perspective from different continents. Pain Rep. 2017;2(3):e599.
59. Manchikanti L, Helm S, 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):Es9-38.
60. Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician. 2008;11(2 Suppl):S5-s62.
61. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Experimental and clinical psychopharmacology. 2008;16(5):405-16.
62. Volkow ND, Wang G-J, Fowler JS, Tomasi D. Addiction Circuitry in the Human Brain. Annual Review of Pharmacology and Toxicology. 2012;52(1):321-36.
63. Nummenmaa L, Saanijoki T, Tuominen L, Hirvonen J, Tuulari JJ, Nuutila P, et al. μ-opioid receptor system mediates reward processing in humans. Nature Communications. 2018;9(1):1500.
64. Turk DC, Brody MC, Okifuji AE. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. Pain. 1994;59(2):201-8.
65. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. Journal of Pain and Symptom Management. 1996;11(4):203-17.
66. Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A Comparison between Enriched and Nonenriched Enrollment Randomized Withdrawal Trials of Opioids for Chronic Noncancer Pain. Pain Research and Management. 2011;16:465281.
67. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. The journal of pain. 2009;10(2):113-30.
68. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA: Journal of the American Medical Association. 2016;315(15):1624-45.
69. Professional Standards and Guidelines: Safe Prescribing of Drugs with Potential for Misuse/Diversion: College of Physicians and Surgeons of British Columbia; 2016 [Available from: http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Publications/Epid/Other/09_CPSBC_Safe_Prescribing_of_Drugs_with_Potential_for_Misuse_Diversion.pdf.
70. Opioid Prescribing in Canada: How Are Practices Changing? Ottawa, ON: Canadian Institute for Health Information.

71. Goldstick JE, Guy GP, Losby JL, Baldwin G, Myers M, Bohnert ASB. Changes in Initial Opioid Prescribing Practices After the 2016 Release of the CDC Guideline for Prescribing Opioids for Chronic Pain. JAMA Network Open. 2021;4(7):e2116860-e.
72. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. Pain. 2004;109(3):514-9.
73. Sullivan MD, Edlund MJ, Fan M-Y, DeVries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000–2005 in Commercial and Medicaid insurance plans: The TROUP study. PAIN. 2008;138(2):440-9.
74. U.S. Opioid Dispensing Rate Maps: Centers for Disease Control and Prevention (CDC); [Available from: https://www.cdc.gov/drugoverdose/rxrate-maps/index.html.
75. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC.
76. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med. 1980;302(2):123.
77. Moride Y, Lemieux-Uresandi D, Castillon G, de Moura CS, Pilote L, Faure M, et al. A Systematic Review of Interventions and Programs Targeting Appropriate Prescribing of Opioids. Pain Physician. 2019;22(3):229-40.
78. Opioid- and Stimulant-related Harms in Canada: Government of Canada; 2022 [
79. Canadian Drug Summary: Prescription Opioids. Canadian Centre on Substance Use and Addiction; 2020.
80. Wide-ranging online data for epidemiologic research (WONDER) Atlanta, GA: CDC, National Center for Health Statistics; 2020 [Available from: http://wonder.cdc.gov.
81. Henry SG, Matthias MS. Patient-Clinician Communication About Pain: A Conceptual Model and Narrative Review. Pain Medicine. 2018;19(11):2154-65.
82. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? Clin J Pain. 1997;13(4):330-6.
83. Moshfegh J, George SZ, Sun E. Risk and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients With Newly Diagnosed Musculoskeletal Pain in the Neck, Shoulder, Knee, or Low Back. Annals of internal medicine. 2019;170(7):504-5.
84. Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA. Opioids and the treatment of chronic pain in a primary care sample. Journal of pain and symptom management. 2001;22(3):791-6.
85. Herman PM, Broten N, Lavelle TA, Sorbero ME, Coulter ID. Health Care Costs and Opioid Use Associated With High-impact Chronic Spinal Pain in the United States. Spine. 2019;44(16).
86. Turner JA, Saunders K, Shortreed SM, LeResche L, Riddell K, Rapp SE, et al. Chronic opioid therapy urine drug testing in primary care: prevalence and predictors of aberrant results. Journal of general internal medicine. 2014;29(12):1663-71.
87. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. PAIN. 2007;129(3):355-62.
88. Béliveau A, Castilloux AM, Tannenbaum C, Vincent P, de Moura CS, Bernatsky S, et al. Predictors of long-term use of prescription opioids in the community-dwelling population of adults without a cancer diagnosis: a retrospective cohort study. CMAJ Open. 2021;9(1):E96-e106.

89. Han H, Kass PH, Wilsey BL, Li CS. Age, gender, and earlier opioid requirement associations with the rate of dose escalation in long-term opioid therapy. J Opioid Manag. 2013;9(2):129-38.
90. Campbell CI, Weisner C, LeResche L, Ray GT, Saunders K, Sullivan MD, et al. Age and Gender Trends in Long-Term Opioid Analgesic Use for Noncancer Pain. American Journal of Public Health. 2010;100(12):2541-7.
91. Shiue KY, Dasgupta N, Naumann RB, Nelson AE, Golightly YM. Sociodemographic and Clinical Predictors of Prescription Opioid Use in a Longitudinal Community-Based Cohort Study of Middle-Aged and Older Adults. J Aging Health. 2021:8982643211039338.
92. Grol-Prokopczyk H. Use and Opinions of Prescription Opioids Among Older American Adults: Sociodemographic Predictors. J Gerontol B Psychol Sci Soc Sci. 2019;74(6):1009-19.
93. Turk DC, Swanson KS, Gatchel RJ. Predicting Opioid Misuse by Chronic Pain Patients: A Systematic Review and Literature Synthesis. The Clinical Journal of Pain. 2008;24(6).
94. Chen I, Kurz J, Pasanen M, Faselis C, Panda M, Staton LJ, et al. Racial differences in opioid use for chronic nonmalignant pain. J Gen Intern Med. 2005;20(7):593-8.
95. Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. Pain. 1991;45(2):111-21.
96. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain. 1994;56(3):289-97.
97. Dobscha SK, Morasco BJ, Duckart JP, Macey T, Deyo RA. Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clin J Pain. 2013;29(2):102-8.
98. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006;166(19):2087-93.
99. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. Journal of pain and symptom management. 2008;36(3):280-8.
100. Deyo RA, Smith DHM, Johnson ES, Donovan M, Tillotson CJ, Yang X, et al. Opioids for back pain patients: primary care prescribing patterns and use of services. Journal of the American Board of Family Medicine : JABFM. 2011;24(6):717-27.
101. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010;105(10):1776-82.
102. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. Clin J Pain. 2010;26(1):1-8.
103. Uher T, Bob P. Neuropathic Pain, Depressive Symptoms, and C-Reactive Protein in Sciatica Patients. International Journal of Neuroscience. 2013;123(3):204-8.
104. Afari N, Mostoufi S, Noonan C, Poeschla B, Succop A, Chopko L, et al. C-Reactive Protein and Pain Sensitivity: Findings from Female Twins. Annals of Behavioral Medicine. 2011;42(2):277-83.
105. Maria C. Pitharouli , M.Sc. ,, Saskia P. Hagenaars , Ph.D. ,, Kylie P. Glanville , Ph.D. ,, Jonathan R.I. Coleman , Ph.D. ,, Matthew Hotopf , Ph.D., F.R.C.Psych. ,, Cathryn M. Lewis , Ph.D.

,, et al. Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank. American Journal of Psychiatry. 2021;178(6):522-9.
106. Reece AS. High-sensitivity CRP in opiate addiction: relative and age-dependent elevations. Cardiovasc Toxicol. 2012;12(2):149-57.
107. Cahill CM, Taylor AM. Neuroinflammation—a co-occurring phenomenon linking chronic pain and opioid dependence. Current opinion in behavioral sciences. 2017;13:171-7.
108. Oh TK, Jeon YT, Choi JW. Trends in chronic opioid use and association with five-year survival in South Korea: a population-based cohort study. Br J Anaesth. 2019;123(5):655-63.
109. Shiue KY, Dasgupta N, Naumann RB, Nelson AE, Golightly YM. Sociodemographic and clinical predictors of prescription opioid use in a longitudinal community-based cohort study of middle-aged and older adults. Journal of aging and health. 2022;34(2):213-20.
110. Turk DC, Okifuji A. Psychological factors in chronic pain: evolution and revolution. Journal of consulting and clinical psychology. 2002;70(3):678.
111. UK Biobank: Protocol for a large-scale prospective epidemiological resource UK Biobank Coordinating Centre; 2007 [Available from: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf.
112. Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, et al. Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. PloS one. 2013;8(11):e75362.
113. Santos R, Ursu O, Gaulton A, Bento AP, Donadi RS, Bologa CG, et al. A comprehensive map of molecular drug targets. Nature reviews Drug discovery. 2017;16(1):19-34.
114. Wu Y, Byrne EM, Zheng Z, Kemper KE, Yengo L, Mallett AJ, et al. Genome-wide association study of medication-use and associated disease in the UK Biobank. Nature Communications. 2019;10(1):1891.
115. Slade GD, Sanders AE, By K. Role of Allostatic Load in Sociodemographic Patterns of Pain Prevalence in the U.S. Population. The Journal of Pain. 2012;13(7):666-75.
116. VanDenKerkhof EG, Macdonald HM, Jones GT, Power C, Macfarlane GJ. Diet, Lifestyle and Chronic Widespread Pain: Results from the 1958 British Birth Cohort Study. Pain Research and Management. 2011;16:727094.
117. Stokes A, Berry KM, Collins JM, Hsiao CW, Waggoner JR, Johnston SS, et al. The contribution of obesity to prescription opioid use in the United States. Pain. 2019;160(10):2255-62.
118. Peakman TC, Elliott P. The UK Biobank sample handling and storage validation studies. Int J Epidemiol. 2008;37 Suppl 1:i2-6.
119. Tibshirani R. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society: Series B (Methodological). 1996;58(1):267-88.
120. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: Machine learning in Python. the Journal of machine Learning research. 2011;12:2825-30.
121. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.
122. Oh G, Abner EL, Fardo DW, Freeman PR, Moga DC. Patterns and predictors of chronic opioid use in older adults: A retrospective cohort study. PloS one. 2019;14(1):e0210341.

123. Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK biobank participants. EClinicalMedicine. 2020;21:100321.
124. Martel MO, Edwards RR, Jamison RN. The relative contribution of pain and psychological factors to opioid misuse: A 6-month observational study. Am Psychol. 2020;75(6):772-83.
125. Martel MO, Bruneau A, Edwards RR. Mind-body approaches targeting the psychological aspects of opioid use problems in patients with chronic pain: evidence and opportunities. Transl Res. 2021;234:114-28.
126. López-Martínez AE, Reyes-Pérez Á, Serrano-Ibáñez ER, Esteve R, Ramírez-Maestre C. Chronic pain, posttraumatic stress disorder, and opioid intake: A systematic review. World Journal of Clinical Cases. 2019;7(24):4254.
127. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. Gen Hosp Psychiatry. 2014;36(1):99-104.
128. Manchikanti L, Giordano J, Boswell MV, Fellows B, Rajeev Manchukonda B, Pampati V. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. Journal of opioid management. 2007;3(2):89-100.
129. Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC health services research. 2006;6(1):1-10.
130. Mohamad N-V, Wong SK, Hasan WNW, Jolly JJ, Nur-Farhana MF, Ima-Nirwana S, et al. The relationship between circulating testosterone and inflammatory cytokines in men. The Aging Male. 2018.
131. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug and alcohol dependence. 2015;149:1-9.

10. Appendix

Supplementary Table 1 (part 1 of 4).

	Training population			Testing population		
	Non-users (N=157,868)	Opioid users (N=20,895)	OR(95%CI)	Non-users (N=16,133)	Opioid users (N=912)	OR(95%CI)
Sex						
Female	88,531 (56.1%)	12,814 (61.3%)	1.24(1.20,1.27)	8,788 (54.5%)	579 (63.5%)	1.45(1.26,1.66)
Male	69,337 (43.9%)	8,081 (38.7%)	0.80(0.78,0.83)	7,345 (45.5%)	333 (36.5%)	0.68(0.60,0.79)
Age (years)						
Mean(SD)	57.0(8.08)	58.9(7.62)	1.03(1.02,1.03)	55.3(7.48)	56.4(7.38)	1.02(1.01,1.03)
Median[Min, Max]	58.1[39.9,73.7]	60.5[40.3,72.9]		55.7[40.3,70.4]	57.0[40.3,69.9]	——
Ethnicity						
White	147,141 (94.5%)	19,721 (95.6%)	1.22(1.15,1.30)	15,584 (97.4%)	878 (97.4%)	0.91(0.63,1.29)
Black	3,714 (2.39%)	435 (2.11%)	0.88(0.79,0.97)	132 (0.825%)	11 (1.22%)	1.48(0.79,2.74)
Asian	3,653 (2.35%)	327 (1.59%)	0.67(0.59,0.75)	198 (1.24%)	8 (0.888%)	0.71(0.35,1.45)
Mixed	1,063 (0.683%)	132 (0.640%)	0.94(0.78,1.12)	86 (0.537%)	4 (0.444%)	0.82(0.30,2.24)
Other	62 (0.0398%)	4 (0.0194%)	0.49(0.18,1.34)	1 (0.00625%)	0 (0%)	——
Missing	2,235 (1.4%)	276 (1.3%)		132 (0.8%)	11 (1.2%)	
Education						
College/University	44,327 (35.9%)	3,154 (24.0%)	0.45(0.44,0.47)	6,852 (46.7%)	237 (30.6%)	0.47(0.40,0.55)
Advanced level	16,702 (13.5%)	1,606 (12.2%)	0.52(0.50,0.54)	2,078 (14.2%)	104 (13.4%)	0.62(0.53,0.72)
Ordinary level	33,853 (27.4%)	4,141 (31.6%)	0.63(0.61,0.65)	3,196 (21.8%)	245 (31.6%)	0.88(0.77,1.01)
Certificate Secondary Education	9,405 (7.61%)	1,249 (9.52%)	0.83(0.80,0.87)	783 (5.33%)	60 (7.74%)	1.05(0.88,1.26)
Practical Career Diploma	11,064 (8.95%)	1,709 (13.0%)	0.94(0.90,0.97)	927 (6.31%)	69 (8.90%)	1.22(1.04,1.43)
Other Professional Qualification	8,290 (6.70%)	1,256 (9.58%)	0.73(0.70,0.75)	849 (5.78%)	60 (7.74%)	0.81(0.70,0.94)
Missing	34,227 (21.7%)	7,780 (37.2%)		1,448 (9.0%)	137 (15.0%)	
Employment						
Full/part-time student	438 (0.279%)	32 (0.154%)	0.69(0.57,0.62)	49 (0.304%)	6 (0.659%)	1.62(0.96,2.71)
Looking after home or family	4,745 (3.02%)	533 (2.56%)	0.78(0.72,0.83)	471 (2.93%)	23 (2.52%)	0.86(0.63,1.17)
Unpaid voluntary work	719 (0.457%)	75 (0.360%)	1.00(0.93,1.08)	81 (0.503%)	2 (0.220%)	1.01(0.73,1.41)
Paid employment/self employed	88,825 (56.5%)	6,085 (29.2%)	0.32(0.31,0.33)	11,027 (68.5%)	449 (49.3%)	0.45(0.39,0.51)
Retired	51,943 (33.0%)	9,161 (44.0%)	1.54(1.50,1.59)	3,955 (24.6%)	295 (32.4%)	1.41(1.22,1.62)
Unable to work for sickness/disability	6,613 (4.21%)	4,510 (21.7%)	6.55(6.30,6.80)	236 (1.47%)	122 (13.4%)	9.17(7.41,11.35)
Unemployed	2,936 (1.87%)	305 (1.47%)	0.88(0.79,0.97)	193 (1.20%)	10 (1.10%)	0.97(0.54,1.74)
None of the employment proposed	951 (0.605%)	105 (0.505%)	0.83(0.68,1.01)	86 (0.534%)	4 (0.439%)	0.82(0.30,2.24)
Missing	698 (0.4%)	89 (0.4%)		35 (0.2%)	1 (0.1%)	
Number of people living in household						
Median[Min, Max]	2.00[1.00,100]	2.00[1.00,47.0]	0.80(0.79,0.82)	2.00[1.00,32.0]	2.00[1.00,10.0]	0.82(0.77,0.87)
Missing	1317 (0.8%)	289 (1.4%)		42 (0.3%)	1 (0.1%)	
Relationship to people in household						
Children	9,808 (7.68%)	1,485 (9.76%)	0.64(0.62,0.66)	862 (6.29%)	62 (8.36%)	0.68(0.60,0.79)
Grandchild	140 (0.110%)	63 (0.414%)	1.85(1.66,2.06)	8 (0.0583%)	1 (0.135%)	1.22(0.59,2.50)
Grandparents	8 (0.00627%)	0 (0%)	0.68(0.29,1.58)	0 (0%)	0 (0%)	——
Other related	281 (0.220%)	36 (0.237%)	0.96(0.81,1.14)	15 (0.109%)	1 (0.135%)	0.68(0.25,1.84)
Other unrelated	1,506 (1.18%)	217 (1.43%)	0.98(0.89,1.09)	119 (0.868%)	9 (1.21%)	0.94(0.55,1.58)
Parents	1,636 (1.28%)	242 (1.59%)	1.02(0.92,1.13)	164 (1.20%)	6 (0.809%)	0.88(0.52,1.48)
Partner	113,487 (88.9%)	13,046 (85.8%)	0.65(0.63,0.67)	12,496 (91.1%)	660 (88.9%)	0.76(0.65,0.88)
Siblings	788 (0.617%)	120 (0.789%)	1.02(0.86,1.22)	51 (0.372%)	3 (0.404%)	1.14(0.41,3.14)
Missing	30,214 (19.1%)	5,686 (27.2%)		2,418 (15.0%)	170 (18.6%)	
Number of vehicles in household						
Median[Min, Max]	2.00[1.00,5.00]	2.00[1.00,5.00]	0.66(0.65,0.68)	3.00[1.00,5.00]	2.00[1.00,5.00]	0.74(0.68,0.80)
Missing	1,274 (0.8%)	279 (1.3%)		48 (0.3%)	2 (0.2%)	
Household income (before tax)						
Less than 18,000	33,921 (25.6%)	8225 (49.8%)	2.37(2.30,2.44)	1,885 (13.0%)	234 (29.1%)	2.06(2.23,3.04)
18,000 to 30,999	34,570 (26.1%)	4,244 (25.7%)	0.90(0.87,0.94)	3,235 (22.3%)	233 (29.0%)	1.37(1.17,1.59)
31,000 to 51,999	33,491 (25.3%)	2,703 (16.4%)	0.55(0.53,0.57)	4,376 (30.2%)	185 (23.0%)	0.68(0.57,0.80)
52,000 to 100,000	24,507 (18.5%)	1,188 (7.19%)	0.33(0.31,0.35)	3,967 (27.4%)	132 (16.4%)	0.52(0.43,0.62)
Greater than 100,000	6,002 (4.53%)	171 (1.03%)	0.21(0.18,0.24)	1,026 (7.08%)	19 (2.37%)	0.31(0.20,0.49)
Missing	25,377 (16.1%)	4,364 (20.9%)		1,644 (10.2%)	109 (12.0%)	

Supplementary Table 1 (part 2 of 4).

	Training population			Testing population		
	Non-users (N=157,868)	Opioid users (N=20,895)	OR(95%CI)	Non-users (N=16,133)	Opioid users (N=912)	OR(95%CI)
Sleep duration (hours)						
Mean(SD)	7.10(1.18)	7.01(1.62)	0.93(0.94,0.95)	7.14(1.01)	7.07(1.45)	0.94(0.88,1.00)
Median[Min, Max]	7.00[1.00,23.0]	7.00[1.00,20.0]		7.00[2.00,14.0]	7.00[3.00,18.0]	
Missing	1128 (0.7%)	373 (1.8%)		29 (0.2%)	7 (0.8%)	
Taking naps during the day						
Never/rarely	84,450 (53.6%)	8,645 (41.5%)	0.61(0.59,0.63)	9,560 (59.3%)	482 (52.9%)	0.77(0.67,0.88)
Sometimes	63,737 (40.5%)	9,955 (47.7%)	1.34(1.30,1.38)	5,849 (36.3%)	346 (37.9%)	1.07(0.93,1.23)
Usually	9,362 (5.94%)	2,251 (10.8%)	0.91(1.82,2.01)	722 (4.48%)	84 (9.21%)	2.16(1.70,2.74)
Missing	319 (0.2%)	44 (0.2%)		2 (0.0%)	0 (0%)	
Getting up in the morning						
Difficult	33,988 (21.7%)	7,589 (36.8%)	2.07(2.01,2.14)	3,493 (22.0%)	299 (33.0%)	1.76(1.52,2.03)
Easy	122,446 (78.3%)	13,049 (63.2%)	0.48(0.46,0.49)	12,417 (78.0%)	607 (67.0%)	0.59(0.51,0.68)
Missing	1,434 (0.9%)	257 (1.2%)		223 (1.4%)	6 (0.7%)	
Chronotype						
Early	86,015 (61.0%)	10,823 (59.1%)	0.90(0.87,0.92)	8,603 (59.9%)	519 (62.9%)	1.15(1.01,1.32)
Late	55,056 (39.0%)	7,501 (40.9%)	1.04(1.01,1.08)	5,748 (40.1%)	306 (37.1%)	0.91(0.79,1.05)
Missing	16,797 (10.6%)	2,571 (12.3%)		1,782 (11.0%)	87 (9.5%)	
Sleeplessness						
Never	30,800 (19.5%)	2,150 (10.3%)	0.47(0.45,0.49)	3,621 (22.5%)	136 (14.9%)	0.60(0.50,0.73)
Sometimes	73,715 (46.7%)	7,950 (38.1%)	0.70(0.68,0.72)	7,674 (47.6%)	346 (37.9%)	0.67(0.58,0.77)
Usually	53,223 (33.7%)	10,781 (51.6%)	2.09(2.03,2.16)	4,833 (30.0%)	430 (47.1%)	2.08(1.82,2.38)
Missing	130 (0.1%)	14 (0.1%)		5 (0.0%)	0 (0%)	
Narcolepsy						
All of the time	20 (0.0127%)	5 (0.0242%)	1.89(0.71,5.03)	2 (0.0124%)	0 (0%)	———
Never	114,722 (73.1%)	12,944 (62.6%)	0.61(0.59,0.63)	12,436 (77.2%)	645 (70.9%)	0.61(0.59,0.63)
Often	5,500 (3.50%)	1,534 (7.42%)	2.19(2.07,2.32)	411 (2.55%)	43 (4.73%)	2.19(2.07,2.32)
Sometimes	36,724 (23.4%)	6,189 (29.9%)	1.39(1.34,1.43)	3,260 (20.2%)	222 (24.4%)	1.39(1.34,1.43)
Missing	902 (0.6%)	223 (1.1%)		24 (0.1%)	2 (0.2%)	
Current tobacco smoking status						
Daily	1,4218 (9.01%)	3,132 (15.0%)	1.78(1.71,1.86)	695 (4.31%)	68 (7.46%)	1.79(1.38,2.31)
No	138,980 (88.1%)	17,072 (81.8%)	0.60(0.58,0.63)	15,060 (93.4%)	823 (90.3%)	0.65(0.52,0.82)
Occasionally	4,563 (2.89%)	669 (3.21%)	1.11(1.02,1.20)	374 (2.32%)	20 (2.20%)	0.94(0.59,1.49)
Missing	107 (0.1%)	22 (0.1%)		4 (0.0%)	1 (0.1%)	
Past tobacco smoking status						
Never smoked	61,037 (42.7%)	7,016 (39.8%)	0.80(0.78,0.82)	6,638 (43.1%)	355 (42.3%)	0.91(0.79,1.04)
Mostly	39,966 (27.9%)	6,338 (35.9%)	1.28(1.24,1.32)	3,791 (24.6%)	245 (29.2%)	1.19(1.02,1.39)
Occasionally	20,575 (14.4%)	2,393 (13.6%)	0.86(0.82,0.90)	2,094 (13.6%)	114 (13.6%)	0.95(0.78,1.17)
Only tried once or twice	21,514 (15.0%)	1,884 (10.7%)	0.63(0.59,0.66)	2,885 (18.7%)	126 (15.0%)	0.73(0.60,0.89)
Missing	14,776 (9.4%)	3,264 (15.6%)		725 (4.5%)	72 (7.9%)	
Exposure to tobacco at home (hours per week)						
Mean(SD)	0.632(4.91)	1.08(6.47)	1.01(1.01,1.02)	0.501(4.61)	0.457(3.22)	0.99(0.98,1.01)
Median[Min, Max]	0[0,168]	0[0,144]		0[0,150]	0[0,45.0]	
Missing	18,069 (11.4%)	3,872 (18.5%)		866 (5.4%)	77 (8.4%)	
Alcohol drinker status						
Current	143,183 (90.8%)	17,241 (82.7%)	0.48(0.46,0.50)	15,321 (95.0%)	817 (89.7%)	0.45(0.36,0.57)
Never	7,976 (5.06%)	1,529 (7.34%)	1.48(1.40,1.57)	392 (2.43%)	31 (3.40%)	1.41(0.97,2.04)
Previous	6,531 (4.14%)	2,072 (9.94%)	2.55(2.42,2.68)	417 (2.59%)	63 (6.92%)	2.79(2.12,3.67)
Missing	178 (0.1%)	53 (0.3%)		3 (0.0%)	1 (0.1%)	
Alcohol intake frequency						
Almost daily	64,601 (41.0%)	5,350 (25.6%)	0.49(0.48,0.51)	7,842 (48.6%)	302 (33.2%)	0.52(0.45,0.60)
Never	14,549 (9.22%)	3,617 (17.3%)	2.06(1.98,2.14)	810 (5.02%)	94 (10.3%)	2.17(1.73,2.72)
Occasionally	78,582 (49.8%)	11,891 (57.0%)	1.33(1.29,1.37)	7,479 (46.4%)	515 (56.5%)	1.50(1.31,1.71)
Missing	136 (0.1%)	37 (0.2%)		2 (0.0%)	1 (0.1%)	

Supplementary Table 1 (part 3 of 4).

	Training population			Testing population		
	Non-users (N=157,868)	Opioid users (N=20,895)	OR(95%CI)	Non-users (N=16,133)	Opioid users (N=912)	OR(95%CI)
Alcohol intake frequency vs. the last 10 years						
Less	68,246 (48.0%)	10,446 (61.3%)	1.31(1.27,1.35)	6,522 (42.7%)	460 (56.7%)	1.50(1.31,1.71)
More	23,929 (16.8%)	1,856 (10.9%)	0.54(0.52,0.57)	2,913 (19.1%)	111 (13.7%)	0.63(0.51,0.77)
Same	49,886 (35.1%)	4,748 (27.8%)	0.63(0.61,0.66)	5,842 (38.2%)	241 (29.7%)	0.63(0.54,0.73)
Missing	15,807 (10.0%)	3,845 (18.4%)		856 (5.3%)	100 (11.0%)	
Neuroticism domains						
Mood swings	81,989 (51.9%)	13,080 (62.6%)	1.55(1.50,1.60)	7,737 (48.0%)	550 (60.3%)	1.64(1.43,1.89)
Miserableness	77,756 (49.3%)	12,004 (57.4%)	1.39(1.35,1.43)	7,736 (48.0%)	531 (58.2%)	1.51(1.32,1.73)
Irritability	49,032 (31.1%)	6,948 (33.3%)	1.10(1.07,1.14)	5,198 (32.2%)	302 (33.1%)	1.04(0.90,1.20)
Sensitivity/hurt feelings	93,060 (58.9%)	13,104 (62.7%)	1.17(1.13,1.20)	9,171 (56.8%)	571 (62.6%)	1.27(1.10,1.45)
Fed-up feelings	74,744 (47.3%)	12,394 (59.3%)	1.62(1.57,1.67)	6,883 (42.7%)	502 (55.0%)	1.64(1.43,1.88)
Nervous feelings	41,432 (26.2%)	6,096 (29.2%)	1.16(1.12,1.19)	3,653 (22.6%)	233 (25.5%)	1.17(1.00,1.36)
Worrier/anxious feelings	95,317 (60.4%)	13,137 (62.9%)	1.11(1.08,1.14)	9,212 (57.1%)	571 (62.6%)	1.25(1.09,1.44)
Tense/highly strung	33,346 (21.1%)	5,357 (25.6%)	1.29(1.24,1.33)	2,948 (18.3%)	198 (21.7%)	1.24(1.05,1.45)
Worry too long after embarrassment	79,053 (50.1%)	10,196 (48.8%)	0.95(0.92,0.97)	8,360 (51.8%)	483 (53.0%)	1.04(0.91,1.19)
Suffer from nerves	38,099 (24.1%)	6,108 (29.2%)	1.30(1.26,1.34)	3,450 (21.4%)	257 (28.2%)	1.44(1.26,1.67)
Loneliness/isolation	35,405 (22.4%)	6,620 (31.7%)	1.60(1.55,1.65)	2,940 (18.2%)	254 (27.9%)	1.73(1.49,2.01)
Guilty feelings	51,977 (32.9%)	7,215 (34.5%)	1.07(1.04,1.10)	5,271 (32.7%)	358 (39.3%)	1.33(1.16,1.52)
Risk taking						
No	108,586 (71.6%)	14,571 (73.0%)	1.24(1.20,1.28)	11,025 (70.3%)	630 (71.5%)	1.03(0.89,1.19)
Yes	43171 (28.4%)	5398 (27.0%)	0.93(0.90,0.96)	4,647 (29.7%)	251 (28.5%)	0.94(0.80,1.08)
Missing	6111 (3.9%)	926 (4.4%)		461 (2.9%)	31 (3.4%)	
Stress						
Financial difficulties	12,217 (16.2%)	1,977 (16.5%)	1.57(1.50,1.61)	963 (13.4%)	75 (14.6%)	1.99(1.68,2.36)
Death of spouse or partner	1,974 (2.62%)	370 (3.09%)	1.54(1.40,1.69)	145 (2.02%)	13 (2.53%)	2.16(1.39,3.34)
Death of close relatives	25,624 (34.0%)	3,226 (26.9%)	1.12(1.09,1.16)	2,468 (34.3%)	136 (26.5%)	1.22(1.05,1.43)
Serious illness/injury to a close relative	19,574 (25.9%)	2,527 (21.1%)	0.97(1.01,0.20)	2,373 (33.0%)	159 (31.0%)	1.22(1.02,1.46)
Serious illness/injury to yourself	12,797 (17.0%)	3,560 (29.7%)	2.44(2.35,2.53)	907 (12.6%)	120 (23.4%)	2.90(2.42,3.48)
Martial separation/divorce	3,278 (4.34%)	315 (2.63%)	0.99(0.91,1.06)	334 (4.65%)	10 (1.95%)	0.83(0.55,1.25)
Missing	82,404 (52.2%)	8,920 (42.7%)		8,943 (55.4%)	399 (43.8%)	
Seen a general practitioner for anxiety/depression						
No	95,349 (60.9%)	9,369 (45.3%)	0.53(0.51,0.54)	10,002 (62.3%)	392 (43.4%)	0.46(0.40,0.52)
Yes	61,153 (39.1%)	11,303 (54.7%)	1.88(1.82,1.93)	6,050 (37.7%)	511 (56.6%)	2.12(1.85,2.42)
Missing	1,366 (0.9%)	223 (1.1%)		81 (0.5%)	9 (1.0%)	
Seen a psychiatrist for anxiety/depression						
No	135,243 (86.1%)	15,983 (77.1%)	0.54(0.52,0.56)	14,274 (88.7%)	715 (78.8%)	0.47(0.40,0.56)
Yes	21,762 (13.9%)	4,746 (22.9%)	1.84(1.78,1.91)	1,817 (11.3%)	192 (21.2%)	2.10(1.78,2.48)
Missing	863 (0.5%)	166 (0.8%)		42 (0.3%)	5 (0.5%)	
Frequency of restlessness in the last 2 weeks						
More than half the days	5,729 (3.81%)	1,218 (6.19%)	1.64(1.54,1.75)	397 (2.53%)	44 (4.98%)	2.00(1.46,2.76)
Nearly every day	4,251 (2.82%)	1,256 (6.38%)	2.31(2.16,2.46)	249 (1.59%)	35 (3.96%)	2.54(1.77,3.65)
Never	99,961 (66.4%)	11,320 (57.5%)	0.68(0.66,0.70)	10,817 (69.0%)	532 (60.2%)	0.68(0.60,0.78)
Several days	40,592 (27.0%)	5,895 (29.9%)	1.13(1.09,1.17)	4,223 (26.9%)	272 (30.8%)	1.20(1.03,1.38)
Missing	7,335 (4.6%)	1,206 (5.8%)		447 (2.8%)	29 (3.2%)	
Frequency of depressed mood in the last 2 weeks						
More than half the days	6310 (4.22%)	1,387 (7.11%)	1.70(1.61,1.81)	416 (2.67%)	50 (5.64%)	2.19(1.62,2.96)
Nearly every day	4212 (2.81%)	1,283 (6.57%)	2.38(2.23,2.54)	285 (1.83%)	39 (4.40%)	2.48(1.76,3.49)
Never	105,000 (70.2%)	11,463 (58.7%)	0.61(0.59,0.63)	11552 (74.1%)	544 (61.4%)	0.58(0.51,0.67)
Several days	34,114 (22.8%)	5,388 (27.6%)	1.26(1.22,1.30)	3330 (21.4%)	253 (28.6%)	1.47(1.27,1.71)
Missing	8,232 (5.2%)	1,374 (6.6%)		550 (3.4%)	26 (2.9%)	

Supplementary Table 1 (part 4 of 4.)

	Training population			Testing population		
	Non-users (N=157,868)	Opioid users (N=20,895)	OR(95%CI)	Non-users (N=16,133)	Opioid users (N=912)	OR(95%CI)
Frequency of disinterest in the last 2 weeks						
More than half the days	6,061 (4.01%)	1,298 (6.59%)	1.65(1.56,1.76)	400 (2.54%)	48 (5.49%)	2.18(1.60,2.97)
Nearly every day	4,342 (2.87%)	1,162 (5.90%)	2.08(1.94,2.22)	286 (1.81%)	37 (4.23%)	2.34(1.65,3.32)
Never	109,564 (72.5%)	12,121 (61.6%)	0.61(0.59,0.63)	12,102 (76.8%)	556 (63.6%)	0.52(0.45,0.59)
Several days	31,178 (20.6%)	5,111 (26.0%)	1.31(1.27,1.36)	2,973 (18.9%)	233 (26.7%)	1.52(1.30,1.77)
Missing	6,723 (4.3%)	1,203 (5.8%)		372 (2.3%)	38 (4.2%)	
Frequency of tiredness in the last 2 weeks						
More than half the days	12,869 (8.41%)	2,368 (11.7%)	1.44(1.37,1.51)	1,084 (6.84%)	100 (11.1%)	1.70(1.37,2.12)
Nearly every day	14,169 (9.26%)	4,193 (20.8%)	2.54(2.45,2.64)	1,100 (6.94%)	175 (19.4%)	3.24(2.72,3.86)
Never	55,341 (36.2%)	4,448 (22.1%)	0.50(0.48,0.52)	6,282 (39.6%)	226 (25.1%)	0.51(0.44,0.60)
Several days	70,556 (46.1%)	9,151 (45.4%)	0.96(0.93,0.99)	7,388 (46.6%)	399 (44.3%)	0.92(0.80,1.05)
Missing	4,933 (3.1%)	735 (3.5%)		279 (1.7%)	12 (1.3%)	
Body mass index (BMI)						
Mean(SD)	28.0(5.00)	30.2(6.06)	1.08(1.07,1.08)	27.0(4.42)	28.9(5.54)	1.08(1.07,1.09)
Median[Min, Max]	27.3[12.8,68.4]	29.3[14.1,68.1]		26.4[15.7,63.6]	28.2[17.4,56.0]	
Missing	3,006 (1.9%)	845 (4.0%)		201 (1.2%)	16 (1.8%)	

Supplementary Table 1. Summary of all the predictors integrated in the pain-agnostic model and the characteristics of the training and testing populations. Mean, standard deviation (SD), and median are reported for continuous variables. Percentages are reported for categorical variables. Univariate associations between each predictor and opioid use are reported by odds ratio. (OR: Odds ratio, CI: confidence interval)

	Training population			*Testing population*		
	No opioid use (N=157,868)	Opioid users (N=20,895)	OR(95%CI)	No opioid use (N=16,133)	Opioid users (N=912)	OR(95%CI)
Chronic Pain						
Headache	32,420 (20.5%)	4,640 (22.2%)	1.10(1.06,1.14)	3,822 (23.7%)	303 (33.2%)	1.60(1.39,1.84)
Facial pain	2,948 (1.87%)	580 (2.78%)	1.50(1.37,1.64)	305 (1.89%)	33 (3.62%)	1.94(1.35,2.80)
Neck or shoulder pain	56,067 (35.5%)	8,946 (42.8%)	1.36(1.32,1.40)	5,680 (35.2%)	404 (44.3%)	1.46(1.28,1.67)
Stomach or abdominal pain	16,441 (10.4%)	2,889 (13.8%)	1.38(1.32,1.44)	1,579 (9.79%)	125 (13.7%)	1.46(1.20,1.78)
Hip pain	28,765 (18.2%)	6,638 (31.8%)	2.08(2.02,2.15)	2,299 (14.3%)	248 (27.2%)	2.24(1.93,2.62)
Back pain	60,660 (38.4%)	11,796 (56.5%)	2.07(2.01,2.13)	5,915 (36.7%)	507 (55.6%)	2.16(1.89,2.47)
Knee pain	59,536 (37.7%)	9,504 (45.5%)	1.37(1.34,1.42)	5,564 (34.5%)	347 (38.0%)	1.34(1.01,1.34)
Widespread pain	3,781 (2.40%)	2,192 (10.5%)	4.78(4.52,5.04)	216 (1.34%)	78 (8.55%)	6.89(5.27,9.01)
Acute pain						
Headache	19,280 (12.2%)	2,517 (12.0%)	0.98(0.94,1.03)	1,905 (11.8%)	108 (11.8%)	1.00(0.81,1.23)
Facial pain	1,928 (1.22%)	318 (1.52%)	1.25(1.10,1.40)	206 (1.28%)	21 (2.30%)	1.82(1.15,2.86)
Neck or shoulder pain	10,141 (6.42%)	1,117 (5.35%)	0.82(0.77,0.87)	1,023 (6.34%)	44 (4.82%)	0.75(0.55,1.02)
Stomach or abdominal pain	6,370 (4.04%)	941 (4.50%)	1.12(1.04,1.20)	647 (4.01%)	47 (5.15%)	1.30(0.96,1.76)
Hip pain	4,302 (2.73%)	583 (2.79%)	1.02(0.93,1.11)	403 (2.50%)	22 (2.41%)	0.96(0.62,1.49)
Back pain	9,365 (5.93%)	831 (3.98%)	0.65(0.61,0.70)	921 (5.71%)	37 (4.06%)	0.70(0.50,0.97)
Knee pain	5,461 (3.46%)	609 (2.91%)	0.83(0.76,0.91)	592 (3.67%)	22 (2.41%)	0.65(0.42,0.99)
Widespread pain	0 (0%)	0 (0%)	——	0 (0%)	0 (0%)	——

Supplementary Table 2. Summary of all the predictors integrated in the pain model. Mean, standard deviation (SD), and median are reported for continuous variables. Percentages are reported for categorical variables. Univariate associations between each predictor and opioid use are reported by odds ratio. (OR: Odds ratio, CI: confidence interval)