# Aging and chronic pain: exploring predictors and prevalence of chronic pain sites in a cross-sectional study; insights from the United Kingdom Biobank

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# Abstract

**Background**: Chronic pain is a prevalent issue affecting a significant proportion of the population, with its prevalence increasing with age. Understanding the complex relationship between bio-psycho-social (BPS) predictors and chronic pain (CP) is crucial, particularly in relation to age and pain type. We hypothesized that the prevalence of CP changes with age, and BPS predictors play a significant role in predicting CP in different body sites and age groups.

**Aims**: This study aims to: 1) Evaluate the association of CP with age in different body sites males and females; 2) Describe predictor models for CP in various body sites based on BPS predictors and age; 3) Assess the strength of the relationship between BPS predictors in different pain types and age groups.

**Methods**: Data from more than 500,000 individuals aged 37-73 in the UK Biobank dataset were analyzed. Baseline data from participants reporting pain lasting over 3 months were used. Missing data were imputed using the median. Line graphs were used to illustrate the prevalence of CP sites by age and sex. The odds ratio was calculated by dividing the odds of having a specific CP site in a specific age group by the odds in a reference group. The data were normalized, divided into a train-test set; grouped into age windows, and analyzed using a sliding window approach. For each age window and for each pain type, we analyzed 100 features using logistic regression to predict CP. These features were grouped into ten categories (mood, neuroticism, trauma, sleep, physiological, health, substance use, physical activity, socioeconomic, and occupational) using

feature aggregation. The absolute mean coefficients of each category were used to determine the importance of categories per pain considering the age.

**Results**: The prevalence of chronic musculoskeletal pain increased with age, while chronic stomach-abdominal and headache pain decreased. Women had a higher prevalence of almost all types of pain. The likelihood of experiencing chronic musculoskeletal, such as hip and knee pain, was higher in older age groups, with females having a 2.5 times likelihood and males having a 3 and 1.5 times likelihood, respectively. Chronic back pain showed a 30% higher likelihood in older age groups for females but remained consistent in males. The likelihood of chronic multi-site pain was 40% higher in older age groups. BPS predictors, such as neuroticism and socioeconomic factors, emerged as important predictors for most pain types and age groups. Trauma was a stronger predictor for CP in younger individuals. The area under the curve (AUC) scores ranged from 0.70 to 0.94, with widespread pain showing the highest AUC.

**Conclusion**: This study provides insights into the relationship between BPS predictors and CP, taking into account age and pain type. The findings have implications for pain prevention and management, informing public health policies aimed at reducing the burden of CP on society. Understanding the role of BPS predictors can aid in developing targeted interventions and personalized approaches for CP management across different age groups.

**Keywords**: chronic pain, biopsychosocial predictors, age, prevalence, UK Biobank

# Abrégé

**Contexte**: La douleur chronique est un problème prévalent qui affecte une proportion significative de la population, sa prévalence augmentant avec l'âge. Comprendre la relation complexe entre les prédicteurs biopsychosociaux (BPS) et la douleur chronique (DC) est crucial, en particulier en ce qui concerne l'âge et le type de douleur. Nous avons émis l'hypothèse que la prévalence de la DC change avec l'âge et que les prédicteurs BPS jouent un rôle significatif dans la prédiction de la DC dans différents sites corporels et groupes d'âge.

**Objectifs**: Cette étude vise à : 1) Évaluer l'association de la DC avec l'âge dans différents sites corporels pour les hommes et les femmes ; 2) Décrire des modèles de prédicteurs pour la DC dans différents sites corporels en se basant sur des prédicteurs BPS et l'âge ; 3) Évaluer la force de la relation entre les prédicteurs BPS, les différents types de douleur et les groupes d'âge.

**Méthodes**: Les données de plus de 500 000 individus âgés de 37 à 73 ans dans l'ensemble de données UK Biobank ont été analysées. Les données de base des participants signalant une douleur persistante depuis plus de 3 mois ont été utilisées. Les données manquantes ont été complétées en utilisant la médiane. Des graphiques linéaires ont été utilisés pour illustrer la prévalence des sites de DC en fonction de l'âge et du sexe. Le rapport de cotes a été calculé en divisant les chances de présenter un site spécifique de DC dans un groupe d'âge spécifique par les chances dans un groupe de référence. Les données ont été normalisées, divisées en ensembles d'entraînement et de test, regroupées en fenêtres d'âge et analysées à l'aide d'une approche de fenêtre glissante. Pour

chaque fenêtre d'âge et pour chaque type de douleur, nous avons analysé 100 caractéristiques à l'aide de la régression logistique pour prédire la DC. Ces caractéristiques ont été regroupées en dix catégories (humeur, névrosisme, traumatisme, sommeil, physiologie, santé, consommation de substances, activité physique, facteurs socio-économiques et professionnels) à l'aide de l'agrégation des caractéristiques. Les coefficients moyens absolus de chaque catégorie ont été utilisés pour déterminer l'importance des catégories par type de douleur en fonction de l'âge.

**Résultats**: La prévalence de la douleur musculosquelettique chronique augmentait avec l'âge, tandis que la douleur abdominale et la douleur de tête diminuaient. Les femmes présentaient une prévalence plus élevée de presque tous les types de douleur. La probabilité de souffrir de douleurs musculosquelettiques chroniques, telles que la hanche et les genoux, était plus élevée dans les groupes d'âge plus avancés, les femmes présentant une probabilité 2,5 fois plus élevée et les hommes une probabilité 3 et 1,5 fois plus élevée, respectivement. La douleur chronique du dos présentait une probabilité 30% plus élevée dans les groupes d'âge plus avancés pour les femmes, mais restait stable chez les hommes. La probabilité de douleur multisite chronique était 40% plus élevée dans les groupes d'âge plus avancés. Les prédicteurs BPS, tels que le névrosisme et les facteurs socio-économiques, sont apparus comme des prédicteurs importants pour la plupart des types de douleur et groupes d'âge. Le score de la surface sous la courbe (AUC) variait de 0,70 à 0,94, avec la douleur généralisée présentant le plus haut AUC.

**Conclusion**: Cette étude fournit des informations sur la relation entre les prédicteurs BPS et la DC, en tenant compte de l'âge et du type de douleur. Les résultats ont des implications pour la prévention et la gestion de la douleur, en informant les politiques de santé publique visant à réduire le fardeau de la DC sur la société. Comprendre le rôle des prédicteurs BPS peut aider à développer des interventions ciblées et des approches personnalisées pour la gestion de la DC dans différents groupes d'âge.

**Mots-clés**: douleur chronique, prédicteurs biopsychosociaux, âge, prévalence, UK Biobank

# Contribution of Authors

Rayehehossadat Rezvaninejad is the primary author of this thesis and took responsibility for the overall preparation of the document, conducted the analysis, and was responsible for the writing and visualization. Dr. Etienne Vachon-Presseau provided valuable guidance, offering revisions that enhanced the quality of the thesis. Gianluca V. Guglietti provided guidance for the research process.

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# List of Abbreviations

| | |
|---|---|
| CP | Chronic Pain |
| BPS | Bio-Psycho-Social |
| MSP | MusculoSkeletal Pain |
| OR | Odds Ratio |
| SES | Socioeconomic Status |
| CWP | Chronic Widespread Pain |
| AUC | Area Under Curve |
| ROC | Receiver Operating Characteristic |
| CEPP | Category Exclusion for Pain Prediction |

# Chapter 1

# Introduction and Literature Review

## 1.1 Background

Pain, being a subjective sensation, holds a crucial role in our survival, but it can also give rise to numerous complexities, such as the emergence of CP [1]. CP, a prevalent condition, is widely acknowledged as a significant contributor to global disability, impacting both individuals and societies [2, 3, 4]. Notably, the prevalence of CP tends to rise with age.

A study conducted by [5] revealed that half of the elderly population that experience CP are suffering from movement-related problems underscoring the significance of accurately diagnosing patients, particularly among older individuals with cognitive impairments and long-term sufferers and who are at risk of under-diagnosis [6]. Additionally, understanding the risk factors associated with CP is crucial for the development of effective prevention and treatment strategies.

The etiology of CP varies among individuals experiencing this condition, and several models have been developed to explore its underlying causes [7, 8]. Among these models, the BPS model of pain stands out as the most comprehensive and explanatory [9]. This model encompasses a multidimensional approach, considering biological, psychological, and societal factors

in understanding and managing CP [9, 10]. By taking into account all these aspects, researchers and healthcare professionals can gain a holistic understanding of CP and develop more effective strategies.

Numerous studies have been conducted to identify predictors and risk factors associated with CP, aiming to distinguish patients with CP from healthy individuals within a society. However, these studies have faced certain challenges that have hindered the development of a comprehensive methodology for differentiating between various CP conditions. One significant obstacle has been the limited sample sizes available, which have often restricted the generalizability of the findings. Additionally, the existing research has often failed to encompass a comprehensive range of predictors, including biological, psychological, and social factors that are relevant across different types of pain [7].

## 1.2 Rational

While a substantial body of research has investigated the prevalence, predictors, and impact of chronic pain, there are several notable gaps in the current literature that this study seeks to address. Despite the well-documented association between chronic pain and various factors such as age, sex, biological conditions, psychological states, and societal influences, limited research has comprehensively examined the interplay of these factors within the framework of the biopsychosocial (BPS) model. Furthermore, existing literature often suffers from limitations like small sample sizes and incomplete inclusion of risk factors across various chronic pain sites. Additionally, existing studies often focus on specific pain types or specific age groups, potentially overlooking valuable insights into the broader patterns of chronic pain occurrence.

While some studies have explored the relationship between individual factors and chronic pain, there remains a need for a holistic approach that captures the synergistic effects of these factors across diverse pain types and age groups. Besides, despite the growing recognition of the importance of personalized medicine, limited research has examined how these predictors of chronic pain may vary across different age groups. It is especially important since as the population ages, it becomes increasingly important to identify age-specific risk factors and patterns of chronic pain.

Addressing these research gaps, the current study focuses on developing an inclusive approach that includes all relevant risk factors to accurately predict and differentiate patients with CP from healthy individuals. By incorporating comprehensive methods that consider the BPS aspects of pain, as well as age and sex groups this research aims to provide a robust framework for pain prediction across different age groups and pain sites. By filling this research gap, the study contributes to improving the accuracy of diagnosing CP, enhancing the understanding of its etiology, and facilitating more targeted and effective interventions for pain management.

In summary, the presence and impact of CP necessitate an in-depth exploration of its predictors, risk factors, and diagnostic approaches. By addressing these gaps and utilizing the extensive data set available in the UK Biobank, which provides information on over 100 pain-related risk factors, this study aims to overcome previous limitations and contribute to the advancement of pain prediction and the accurate differentiation of patients with CP from healthy individuals, and the advancement of both research and clinical practice in this field.

## 1.3 Literature Review

### 1.3.1 Chronic Pain

Pain is a subjective experience that is universally experienced and essential for survival. However, when the pain becomes chronic, it can lead to various complications and is now recognized as a distinct disease rather than a syndrome [1]. Imaging studies have revealed that CP induces changes in brain function, structure, and chemistry, further supporting its classification as a disease [11, 12]. The International Association for the Study of Pain (IASP) provides a specific definition of CP as lasting or recurring pain that persists exceeding the normal healing time or persists for more than three months [13, 14]. CP is characterized by its long-lasting and persistent nature, setting it apart from acute pain [14].

The effects of CP on both individuals and societies are profound. Extensive research, such as the studies conducted by [2, 3, 15, 16, 17], consistently highlight CP as a major contributor to global disability. The burden of CP is not only experienced by individuals but also has substantial societal consequences. Inadequate pain management contributes to this burden and results in high healthcare expenditures [18]. In fact, the projected annual healthcare costs for pain management in the United States alone ranged from $261 billion to $293 billion in 2010, with total costs estimated between $560 billion and $635 billion [19]. These staggering figures underscore the urgent need for effective pain management strategies.

### 1.3.2 Epidemiology of Chronic Pain

The field of epidemiology plays a crucial role in understanding the occurrence, distribution, and impact of health-related events and processes within specific populations. Within the realm of CP, epidemiological studies play a pivotal role in determining the prevalence, which refers to the pro-

portion of individuals within a population affected by this condition. This information is crucial for understanding the burdens associated with CP on the societal and healthcare system and guiding diagnostic and preventive measures [20]. High prevalence, relative complications, the costly nature, and current inadequate pain care, underline the importance of epidemiological studies to identify the related risk factors for CP in the general population. Such studies are essential for informing prevention strategies and improving pain management approaches [21].

Different studies have presented varying prevalence rates of CP due to differences in how it is defined and measured [22]. For example, the Centers for Disease Control and Prevention (CDC) documented a point prevalence of 20.4% among the U.S. population [23]. Likewise, a Canadian study discovered that 18.9% of adults in Canada reported suffering from CP [24]. However, it is important to note that prevalence estimates may vary depending on the criteria used to define CP [22]. In a telephone survey conducted by [25], 19% of participants reported CP, when a duration of more than 6 months served as the defining criterion. In a national health survey conducted in England, the estimated prevalence of CP was reported to be 34% [26]. A systematic review conducted by [25] reported prevalence estimates ranging from 35% to 51% in the adult population. These variations in prevalence rates highlight the importance of standardized definitions and measurement approaches as well as consistent criteria to accurately assess the burden of CP to facilitate international comparisons and epidemiological studies. By understanding the epidemiology of CP, healthcare professionals and policymakers can develop targeted interventions and improve the overall management of this prevalent condition.

### 1.3.3 Prevalence of Chronic Pain sites

CP can affect any region of the body, and it can be localized to one site, such as the low back, or knees, or it can affect multiple sites at once, such as diffuse musculoskeletal pain (chronic

widespread pain) [27]. The annual incidence of CP was calculated to be 8.3%, with a recovery rate of 5.4% [28].

**Headache:** Chronic headaches can affect individuals of all ages, with the frequency and intensity varying based on the specific type of headache, individual characteristics, and age [29, 30, 31]. Migraines are recognized as a highly debilitating condition, especially for women, and are considered one of the leading causes of disability worldwide [4, 32]. The occurrence of migraines and tension-type headaches is influenced by various factors, including age and gender being more prevalent among younger individuals and women [32, 33, 34]. Biological factors such as menopause in women could play a role in the frequency of migraines [35, 36]. Some studies suggest that the frequency of migraines may increase just before menopause but decline afterward [35, 37, 38]. Additionally, lifestyle elements like stress and inadequate sleep could be other potential causes of chronic headaches [36, 39, 40]. Moreover, some studies demonstrated that the development of headaches was linked to psychological elements like worry and restlessness [36, 39, 40]. It is proposed that proper sleep habits and engaging in stress-reducing activities may lessen headache frequency and intensity [36, 39, 40]

**Facial Pain:** The prevalence of Facial Pain (FP) varies based on the studies due to a lack of clear definition. In a cross-sectional study of [41] using data from the UK Biobank, the reported prevalence of FP was 1.9%, with 48% classified as chronic. FP was found to be most common in the younger age groups [41]. In another study, 11.16% of elderly individuals reported having orofacial pain [42]. According to several research, women are more likely than males to experience orofacial pain [41, 42]. According to [41], the prevalence of FP was twice as common in women as it was in men . In a cross-sectional study conducted by [42], it was observed that among the elderly population, the prevalent causes of orofacial discomfort included burning mouth syndrome, temporomandibular disorders, and trigeminal neuralgia.

**Musculoskeletal pain:** Musculoskeletal pain, including low back pain, neck-shoulder pain, knee and hip pain, has a significant impact on individuals of all ages, and according to findings from the Ontario Health Survey, a significant portion of chronic conditions (40%) and long-term disabilities (54%) can be attributed to musculoskeletal issues [43]. According to [44, 45, 46], the prevalence of low back pain is estimated to be around 40%, while the prevalence of shoulder pain is approximately 10%. Additionally, [4] state in their research that low back pain and shoulder pain are leading causes of disability. Their findings highlight the substantial impact these conditions have on individuals' functional abilities and overall well-being. The prevalence of regional musculoskeletal pain has been reported to vary in different studies, ranging from 23.9% to 47% [47, 48]. The World Health Organization (WHO) estimates that approximately 20-33% of the global population is affected by musculoskeletal pain [49] and it changes with age [50]. While musculoskeletal pain can affect individuals of any age, its prevalence tends to rise with advancing age, making it a prominent cause of disability among older adults [24, 47, 48, 50]. In a cross-sectional study of the prevalence of CP sites, the low back, neck, shoulder, and knee sites were the most common areas affected [51]. In the study of [24], conducted in Canada, the lower back is commonly reported as the most affected site of chronic musculoskeletal pain.

**Widspread pain:** Chronic Widespread Pain (CWP) refers to persistent discomfort affecting the axial skeleton for at least three months, with symmetrical involvement on both sides of the body, including regions above and below the waist [52]. The definition of CWP was established by the American College of Rheumatology (ACR) in 1990 [52]. CWP affects 11.4% to 24% of the population [47, 53, 54]. Women and people in the age group of the forties and fifties are at an increased risk of developing CWP [55, 54]. Other determinants include a lower socioeconomic and educational level [54, 55]. Life stressors, such as immigration, have been suggested to contribute to the development of CWP, as demonstrated in the study by [47]. Individuals with CWP often experience comorbid conditions such as depression and weakness and face greater functional diffi-

culties compared to those with localized pain [54, 56]. Patients with CWP reported poor life quality and lifestyle [27, 57]. In [27, 57] authors claimed that these individuals often face challenges such as increased disability, disturbances in sleep patterns, and a higher prevalence of mental health disorders like anxiety and depression as well as medical issues including obesity, and high blood pressure, as a result, higher rates of complexity, hospitalization, and mortality.

### 1.3.4 The Association of Chronic Pain with Age and Sex

Research suggests that CP is more commonly observed among older individuals, the prevalence of CP tends to increase with age, and older people are more likely to experience pain in multiple sites with higher severity [25, 58]. This association can be attributed to various factors, including age-related physiological changes [59].

**Age:** Several studies have investigated the relationship between age and CP, although findings have been inconsistent. A systematic review [25], concluded that the prevalence of moderate-to-severely disabling CP tends to increase with age. They reported that individuals aged 75 and above have approximately four times higher rates of CP compared to those in the 18 to 25 age group. [58] found that while only 11% of adults under the age of 60 had CP, the prevalence ranged from 25% to 40% for those over 60. Although the overall relationship between age and CP is not consistently supported, certain age-related patterns have been observed. [60] did not find a direct correlation between age and the type of CP; however, they did identify age-related differences in the distribution of site-specific CP.

[51] found that shoulder and lower back pain are most common among individuals aged 55 to 64. Knee and hip pain tends to increase with age and peaked in those aged 75 and older [51]. Headaches, on the other hand, remained relatively consistent between the age group of 18 and 54 and decreased with age [33, 34]. Abdominal pain similarly decreased with age [51]. [51] revealed

no correlation between aging and upper back, neck, or chest pain. Furthermore, age has been identified as a significant predictor of CP in the study by [18], along with gender, housing ownership, and occupational status. It is important to note that the relationship between age and CP is complex and influenced by various factors, and further research is needed to gain a comprehensive understanding.

**Sex:** Epidemiological and clinical investigations have consistently shown sex differences in the development of CP, with a higher prevalence among women [61, 62, 63]. For instance, according to the Canadian Community Health Survey, 14% of men and 18% of women in Canada reported having CP [64].

These sex disparities in CP have been explained by a number of different processes, for example, biological factors play a role, including differences in the distribution of sex hormones, lower pain thresholds associated with the menstrual cycle, and sex-related cortical differences [65, 66, 67]. Psychological factors such as pain coping strategies, pain catastrophizing, and early-life environmental stress exposure also contribute to the disparities [68, 69, 70, 71]. Additionally, social factors related to gender roles and femininity have been implicated, although the specific contributions are not yet fully understood [62, 65, 72, 73, 74, 75]. Furthermore, males and females exhibit differences in pain ratings and responses to pain interventions. Women generally report lower pain tolerance and threshold, higher pain ratings, and a higher likelihood of experiencing clinical pain [75, 76]. According to [51], the prevalence of CP is significantly correlated with sex, educational attainment, occupational status, and social class; being female and belonging to a lower socioeconomic class are risk factors. It is important to consider gender differences in CP to ensure appropriate assessment, management, and treatment approaches that address the unique needs of both men and women.

### 1.3.5 The BPS Model and Predictors of Chronic Pain

The exploration of pain perception and its underlying mechanisms has led to the evolution of various theories. Descartes' theory of pain dualism proposed that physical and psychological injuries resulted in distinct and separate pain experiences [77]. Subsequent to this, the biological model of disease, including the Specificity Theory, explained the pain in terms of the relationship between tissue damage and pain perception [78]. Specificity Theory proposed that specific sensory receptors in the periphery transmit pain signals to the spinal cord and then to the brain [78]. An alternative perspective, the pattern theory of pain was introduced by psychologist John Paul Nafe. The pattern theory of pain suggests that sensations reach the brain via distinct signal patterns, in contrast to the Specificity theory. Subsequent identification of unique receptors for different sensations, however, invalidated this theory's accuracy [79, 80].

The Gate Control Theory, which incorporates insights from the Specificity Theory and pattern response, challenges the notion that pain is solely tied to tissue damage [81, 82]. This theory introduces a mind-body perspective on pain perception, proposing that pain signals are regulated by a spinal cord "gate" that reacts to stimulus intensity and psychological factors, emphasizing the interplay of physical and psychological elements in pain experience [83, 82, 84].

Subsequently, Ronald Melzack's Neuromatrix Model accentuated the central nervous system's involvement in orchestrating pain perception, redirecting attention from mere physical injury to intricate interactions within the central nervous system [79, 85]. The model identifies neural components, within the central nervous system that collectively creates a "neurosignature" responsible for pain perception [79, 85]. This acknowledges the influence of cognitive, emotional, and physical factors on pain perception, yet it falls short of encompassing the entirety of pain's complexity, necessitating further theories for a comprehensive understanding [79, 80, 85, 9].

Recognizing the limitations of these dualistic views in explaining the complex nature of health and illness, including pain, the BPS model emerged as a comprehensive framework [9]. The BPS model considers both objective and subjective aspects of disease and illness [9]. It emphasizes the interaction of biological, psychological, and sociological factors in understanding pain perception [9].

In the context of CP, the BPS model highlights the importance of considering not only biological factors such as genetics and noxious signals but also psychological and sociological factors [9, 86]. Psychological factors encompass cognitive processes, emotions, beliefs, coping mechanisms, and individual differences in pain perception and response. Sociological factors include social support, socioeconomic status, cultural influences, and the impact of the social environment on pain experience [10, 87, 86]. This model encourages a holistic approach to pain management that addresses not only biological aspects but also psychological and social factors, ultimately leading to more effective and patient-centered care.

**Biological Backgrounds:**

The impact of obesity on CP has been extensively studied. The study, conducted on adults aged 70 and above as part of the Einstein Aging Study, revealed that obese and severely obese individuals had approximately twice and 4.5 times higher odds of experiencing CP, respectively, compared to those of normal weight [88]. The most commonly reported sites of pain among individuals with CP include the head, neck or shoulder, back, legs or feet, and abdomen or pelvis [88]. Moreover, a study conducted in the UK by [89] found a significant association between obesity and a higher prevalence of spinal pain. [90] examined the relationship between BMI and pain in older Americans and found that the prevalence of knee, hip, and back pain increased with higher BMI. [89] further demonstrated that higher BMI was a strong predictor of chronic, intense, and disabling pain in individuals with back pain. Additionally, higher total body obesity has been

linked to an increased prevalence of migraines [91]. [88] conducted a study in the Journal of the American Geriatrics Society, revealing a positive association between obesity and the prevalence of CP. Furthermore, their findings indicated that individuals experiencing CP were more likely to report depression [88]. Also, female sex, depression, and anxiety were connected to CP [88], suggesting a bi-directional association between obesity and its psychosocial effects [92]. [92] proposed that obesity may contribute to psychosocial consequences, while simultaneously being influenced by these effects.

In another study focusing on the link between weight and pain, it is found that after weight loss and exercise the frequency of musculoskeletal symptoms dropped significantly, from 100% to 23%, at the majority of sites [93]. [94] conducted a longitudinal study that showed a reduced risk of developing symptomatic knee osteoarthritis in women who underwent weight loss. Similarly, [95] found that weight loss contributed to improved function in individuals with knee osteoarthritis. Physical activity and exercise have also been recognized as potential interventions for CP management [96]. A systematic review conducted by [96] demonstrated that physical activity and exercise interventions can improve pain severity, function, and overall quality of life in individuals with CP. These findings align with the recommendations provided by the National Institute for Health and Care Excellence and the Scottish Intercollegiate Guideline Network, which advise the incorporation of exercise and exercise therapy in the management of CP [97].

Another factor that has been evaluated is Vitamin D level. Nearly half of the world's population has hypovitaminosis D, which is characterized by low vitamin D levels [98]. The immune system and bone health are both influenced by vitamin D[99, 98]. Increasing evidence points to a possible connection between a vitamin D deficiency and the emergence of CP, including diseases like osteoarthritis (OA), widespread pain (WP), and lower back pain [100]. However, the precise mechanism underlying this association remains unclear. Several studies have explored the rela-

tionship between vitamin D and CP. Other studies, such as those conducted by [101, 102, 103], have also examined the role of deficiency in vitamin D in muscle pain.

Another significant biological factor to consider is substance use. While the overall smoking rate in the general population has been declining [104], it remains higher among individuals with CP [105, 106, 107]. Smokers have higher levels of pain intensity and more CP sites [108, 109]. Moreover, long-term smoking has been linked to a higher likelihood of developing CP conditions like back pain and headache [110, 111]. There is often a mutually reinforcing relationship between CP and smoking, where they worsen each other's effects [112, 113, 114]. Moreover, pain can act as both a drive for smoking and a deterrent for quitting [115, 116]. However, a study by [117] found that smoking cessation was associated with a decrease in the prevalence of CP among the study population.

A critical component of preserving both physical and mental health is sleep, which is a fundamental biological activity. However, sleep problems and disruptions are common in many populations including CP [118, 119]. According to a survey study conducted in Quebec, approximately one-third of the general population reported experiencing insomnia symptoms, making it one of the most prevalent conditions associated with sleep impairment [119]. Among the participants, 9.5% met the criteria for insomnia, and 13% sought medical advice for their sleep issues [119]. Research suggests a reciprocal relationship between sleep disorders and CP, indicating that managing sleep can significantly benefit individuals with CP [118, 120]. It has been reported that 50% to 88% of CP patients experience significant sleep problems [121, 122]. Sleep deprivation can contribute to pain by lowering pain thresholds [120, 123, 124]. According to a study by the National Sleep Foundation on a sample of 2000 US residents, back pain, and headaches, were the most prevalent types of discomfort at night [120]. In a prospective analysis of the Nord-Trøndelag Health Study, it was found that individuals with insomnia at baseline had an increased risk of developing

headaches, with a relative risk of 1.4 over the long term [125]. A longitudinal study focusing on the Norwegian female population revealed a link between sleep problems and the development of fibromyalgia (FM), with a relative risk of 3.43 for those experiencing sleep problems, particularly among middle-aged and older women [126]. This bi-directional association sheds light on the importance of sleep management as an integral component of comprehensive CP care [118, 120].

**Psychological Background:**

The implications of persistence and CP extend beyond the physical domain, with significant emotional tangle [127]. Neuroticism is characterized by negative emotions, such as concern, irritability, and anxiety [128, 129, 130]. Evidence points to a possible connection between neuroticism and CP [131]. High neuroticism has been associated with an increased likelihood of experiencing frequent headaches (odds ratio of 1.4) and stomachaches (odds ratio of 1.5) [130, 132]. Neuroticism has also been identified as a predictor of fibromyalgia symptoms [131].

Furthermore, there is evidence to suggest a bidirectional relationship between CP, mood disturbances, and neuroticism [130]. According to some studies, people with CP may be more likely to have depression, anxiety and greater degrees of neuroticism [128, 129, 130]. CP can negatively affect mood by increasing neuroticism and acting as a stressor; Another theory contends that low mood and increased neuroticism interfere with pain coping, [130, 133, 134]. In the study of [133] higher neuroticism was associated with more severe pain and a worse mood in rheumatoid arthritis patients, although daily mood was only slightly correlated with daily pain. Neuroticism can be viewed as a vulnerability factor, lowering the pain threshold and contributing to the development of catastrophic thoughts about pain [135]. It has been observed that women tend to exhibit higher levels of neuroticism compared to men [135]. CP can affect normal life, and be considered as a source of stress [136], which highlights the importance of combination therapy and considering

sleep management, and physical and emotional factors in CP management. (if possible add about depression)

**Societal Background:**

The psychological and biological factors can have social effects, leading to changes in relationships and a decline in overall quality of life [127].

Socioeconomic disadvantage (SED) is determined by considering the combined score of income, occupational status, and educational level, and serves as an indicator of an individual's socioeconomic status (SES) [56]. SES, as defined by Mueller and Parcel in 1981, refers to the positioning of individuals, families, households, or other groups in terms of their ability to produce or consume goods valued in society [137, 138]. Lower SES has been associated consistently with various aspects of health including having higher morbidity, lower life expectancy, and higher risk of developing pain such as musculoskeletal pain [139, 140, 141]. Several factors have been identified in population-based studies as predictors of pain [142]. For example, gender, education, and long-term health issues have been found to contribute to the prediction of pain [142]. Another population-based observational study found a substantial correlation between CP and gender, age, marital status, and occupational status. Women, older individuals, those who are separated, and individuals working part-time were more likely to report CP in this study [143].

Furthermore, the relationship between social class and CP has been explored, with findings indicating that manual labourers have a higher likelihood of reporting CP [144]. Additionally, 13% of the cohort studies reported reduced functional capacity associated with their pain [144]. These findings demonstrate how socioeconomic factors affect how people experience pain and imply that those from lower socioeconomic origins may be more susceptible to CP and its functional impacts [143, 144].

### 1.3.6 Chronic Pain Management and Treatment

The World Health Organization (WHO) predicts that by 2030, unipolar depression, coronary heart disease, cerebrovascular disease, and road traffic accidents will have a substantial impact on the global burden of disease [3, 145]. It is important to note that CP is closely associated and often manifests as comorbidity with these conditions [12]. A systematic analysis of the Global Burden of Disease revealed that low back pain, headache, and dietary iron deficiency were the primary causes of years lived with disability (YLDs) in 1990. However, in 2017, low back pain, headache, and depressive disorders took precedence as the leading causes [127], illustrating the evolving landscape of CP and its impact on individuals' well-being.

The negative consequences of CP on physical function, quality of life, and overall health are particularly pronounced in older individuals [146]. CP, in turn, can disrupt daily life, act as a significant stressor, and negatively impact sleep quality and overall well-being [136]. Aging populations are more vulnerable to the detrimental effects of CP, which can result in reduced mobility, social isolation, and an increased risk of falls [146, 147, 148]. However, due to the complexity of pain in this population and the possibility of negative side effects of some pain management techniques, managing CP in older persons can be difficult [148, 149, 150]. It is crucial for healthcare professionals to employ a multi-modal approach to both pharmaceutical and non-pharmacological therapies for addressing CP in older persons and adopting a comprehensive approach to CP management that takes into account sleep management, physical factors, and emotional well-being [148, 149, 150].

Valuable information provided by epidemiology studies regarding the prevalence and predisposing factors for CP aids pain prevention and management and reduces its consequences such as severity and disability in CP patients [12]. Taken together, to be able to design therapeutic inter-

ventions and preventative strategies in a society, the associated CP risk markers, such as biological, psychological, and social should be comprehended in the context of the BPS model [74].

Research has indicated that weight loss can have a positive impact on CP management [94]. [94] conducted a longitudinal study demonstrating a reduced risk of developing symptomatic knee osteoarthritis in women who underwent weight loss. Similarly, [95] found that weight loss contributed to improved function in individuals with knee osteoarthritis. Physical activity and exercise have also been recognized as potential interventions for CP management [96]. A systematic review conducted by [96] demonstrated that physical activity and exercise interventions can improve pain severity, function, and overall quality of life in individuals with CP.

Orofacial pain has a significant impact on an individual's quality of life and is associated with a higher risk of disability [151, 152]. However, it is surprising that only 46% of individuals experiencing orofacial pain actively seek treatment for their condition [151, 152, 153, 154]. Moreover, [42] demonstrated that women are more likely than males to feel orofacial discomfort, and in the study of [41], the prevalence of FP was twice as high in women as in males. Also, it seems that women are more likely to look for pain treatment [42]. To effectively manage orofacial pain, a comprehensive BPS approach is recommended. This approach includes a combination of exercise and relaxation techniques, pharmacotherapy, and psychological treatments [155]. By addressing the biological, psychological, and social factors contributing to orofacial pain, individuals can experience improved pain management and a better overall quality of life.

Valuable information provided by Epidemiology studies regarding the prevalence and predisposing factors for CP aids pain prevention and management and reduces its consequences such as severity and disability in CP patients [12]. Taken together, to be able to design therapeutic interventions and preventative strategies in a society, the associated CP risk markers, such as biological, psychological, and social should be comprehended in the context of the BPS model [74].

## 1.4 Study Goals and Objectives:

This project aims to investigate and accomplish the following objectives:

**Objective 1:** To explore the association of CP with age and the likelihood of experiencing CP in specific body sites, including widespread, neck-shoulder, hip, back, stomach-abdominal, knee, headaches, facial, and multi-site pain, as a function of age in females, and males. Additionally, this objective aims to identify any discernible age-related patterns or trends.

**Objective 2:** To develop predictive models for different types of CP by incorporating BPS predictors and age as variables. The objective also involves assessing the predictive strength of these models across distinct pain types and age groups.

**Objective 3:** To compare the relative strength and variability of BPS pain predictors (biological, psychological, and social factors) in relation to the presence of CP, and assess how these relationships vary across different age groups. Also how the exclusion of one category will impact the performance of the model.

# Chapter 2

# Methods

## 2.1 Research Design:

This study utilizes a retrospective observational design to explore the prevalence and predictors of CP across different body sites within distinct age groups. The dataset used for analysis is sourced from the publicly available United Kingdom (UK) Biobank, which offers comprehensive information on physical, psychological, and sociodemographic factors. Leveraging this dataset enables the examination of associations between CP and various pertinent variables.

## 2.2 Participants:

The UK Biobank dataset encompasses a population of over 500,000 individuals aged 37-73 years. Baseline participants were recruited from multiple centers in Scotland, England, and Wales between 2006 and 2010. During the baseline assessment, participants completed detailed questionnaires that encompassed demographic, psychological, and social information. Furthermore, physical, medical, and biological data, including blood samples, were collected. Notably, a subset of 40,000 individuals also underwent magnetic resonance imaging (MRI) for brain imaging purposes.

The overarching goal of the UK Biobank initiative is to enhance disease prevention, diagnosis, and treatment strategies while investigating the interplay of genetic, environmental, and behavioural factors that impact overall health and disease progression.

## 2.3 Data Collection:

The recruitment procedure was designed to include a diverse spectrum of people to provide a broad representation of the UK population. Approximately 5 million invitation letters were issued throughout the United Kingdom to accomplish this. The National Health Service (NHS) database was utilized to identify potential participants based on their age and living location. UK Biobank's website was provided for interested individuals to obtain more information and submit an online consent form. Before data collection, all participants were required to provide electronically written consent, utilizing consent forms developed by the advice of the Ethics & Governance Council (ECG) and adhering to the Ethics & Governance Framework (EGF) guidelines. Further information can be found at [156].

Following that, participants were instructed to visit assessment centers located in various regions including Scotland, Wales, and England. At these centers, a comprehensive data collection process was carried out, which involved the collection of biological samples such as blood, urine, and saliva. In addition, various physical measurements including height, weight, and blood pressure were taken from the participants. Additionally, participants completed comprehensive questionnaires that encompassed sociodemographic, psychosocial, health, lifestyle, and economic measurements. All collected information was meticulously recorded in a dedicated database. Each data field within the UK Biobank repository represents a fundamental unit of data, reflecting the results of a specific question or measurement. These data fields were documented and stored within the UK Biobank database.

To examine the relationship between age and CP, participants from the baseline data, 2006 to 2010, were included. The study population consisted of 502,368 participants who attended the initial assessment. The age of participants at the time of recruitment was determined by subtracting their date of birth from the initial assessment date at the center. The calculated ages ranged from 37 to 73 years, with a median age of 58 years (data-field 21022).

The collected data include a wide range of information related to the physical, mental, and sociodemographic status of the participants as well as information related to CP. The UK Biobank questionnaire incorporated queries regarding pain experienced in the previous month, including pain duration, frequency, and intensity. Participants were asked to rate their pain on a scale ranging from 0 to 10. Furthermore, participants were inquired about any potential interference with their regular activities from a provided set of options (data-field 6159). These responses were utilized to categorize participants into specific pain sites, such as ”headache”, ”facial pain”, ”neck or shoulder pain”, ”back pain”, ”stomach or abdominal pain”, ”hip pain”, and ”knee pain”, which were coded from 1 to 7, respectively (data-field 6159). Selections such as ”Pain all over the body”, ”None of the above”, or ”Prefer not to answer” were coded as 8, -7, or -3, respectively, with no further selections allowed (data-field 6159). Participants reporting ”Pain all over the body” were considered as widespread pain. In accordance with the criteria outlined by the International Association for the Study of Pain (IASP), individuals who reported experiencing any of these types of pain for more than three months were classified as having CP. In cases where individuals reported pain in a single location or multiple locations, it was categorized as single-site or multi-site pain, respectively.

## 2.4 Variables and Measures:

Drawing upon the work of [157, 158], this study incorporated 100 pain-related variables extracted from the UK Biobank dataset, along with information on CP and age obtained from the respective data fields. These variables were then categorized into ten groups: *Mood, Neuroticism, Traumas, Sleep, Physiological, Health, Substance Use, Physical Activity, Socioeconomic, and Occupational*. Later, they were further classified into three domains: *physical, mental, and societal health*, providing a comprehensive assessment of various aspects related to CP.

### 2.4.1 Mental Health:

**Mood:** Mood-related variables were collected through a touchscreen questionnaire administered to participants. The following questions were included:

- *Frequency of tiredness/lethargy in the last two weeks:* Participants were asked to rate the frequency of feeling tired or experiencing low energy over the past two weeks (Data-Coding 100484).

- *Frequency of depressed mood in the last two weeks:* Participants indicated how often they felt down, depressed, or hopeless during the past two weeks (data-field 2050).

- *Frequency of tenseness/restlessness in last 2 weeks:* Additionally, participants were asked to report the frequency of feeling tense, fidgety, or restless over the past two weeks (data-field 2070). This variable was included as part of the mood-related assessment to capture participants' experiences of inner tension and restlessness during the specified timeframe.

- *Frequency of unenthusiasm/disinterest in the last two weeks:* Participants were queried about the frequency of experiencing little interest or pleasure in doing things over the past two weeks (data-field 2060).

- *Consultation with a general practitioner (GP) for nerves, anxiety, tension, or depression:* Participants were asked if they had ever sought medical attention from a GP for nerves, anxiety, tension, or depression (data-field 2090).

- *Consultation with a psychiatrist for nerves, anxiety, tension, or depression:* Participants were asked if they had ever seen a psychiatrist for nerves, anxiety, tension, or depression (data-field 2100).

- *Risk-taking:* Participants were assessed on their self-perceived tendency to take risks (data-field 2040).

**Neuroticism:** Participants engaged with a touchscreen questionnaire to provide their responses on various aspects related to neuroticism. The questions included:

- *Mood swings:* "Does your mood often go up and down?" (data-field 1920).

- *Fed up:* "Do you often feel 'fed-up'?" (data-field 1960).

- *Miserableness:* "Do you ever feel 'just miserable' for no reason?" (data-field 1930).

- *Loneliness and isolation:* "Do you often feel lonely?" (data-field 2020).

- *Guilty feelings:* "Are you often troubled by feelings of guilt?" (data-field 2030).

- *Tense / 'highly strung':* "Would you call yourself tense or 'highly strung'?" (data-field 1990).

- *Worrier / anxious feelings:* "Are you a worrier?" (data-field 1980).

- *Suffer from 'nerves':* "Do you suffer from 'nerves'?" (data-field 2010).

- *Irritability:* "Are you an irritable person?" (data-field 1940).

- *Sensitivity / hurt feelings:* "Are your feelings easily hurt?" (data-field 1950).

- *Worry too long after embarrassment:* "Do you worry too long after an embarrassing experience?" (data-field 2000).

- *Nervous feelings:* "Would you call yourself a nervous person?" (data-field 1970).

- *Total Neuroticism:* This derived data field, provided by Professor Jill Pell [159]from the University of Glasgow, represents an externally derived summary score of neuroticism. It is based on the responses to the aforementioned twelve questions from the touchscreen questionnaire administered during the baseline assessment. The total neuroticism score is an integer value that indicates the number of "Yes" responses across these twelve questions for each participant, with a mean value of 4.11875 (data-field 20127). The derived data field, comprising the total neuroticism score, offers an assessment of neurotic behaviour within the study population, providing insights into the participants' tendencies towards mood swings, irritability, and worries.

**Traumas**: Participants' responses to the question "In the last 2 years, have you experienced any of the following?" (data-field 6145) were categorized into different groups based on their selections:

- *Illness, Injury, or Assault to Self:* Participants who selected "Serious illness, injury, or assault to yourself" were grouped under this category.

- *Illness, Injury, or Assault of a Close Relative:* Participants who selected "Serious illness, injury, or assault of a close relative" were grouped under this category.

- *Death of a Spouse or Partner:* Participants who selected "Death of a spouse or partner" were categorized into this group.

- *Death of a Close Relative:* Participants who selected "Death of a close relative" were grouped under this category.

- *Marital Separation/Divorce:* Participants who selected ”Marital separation/divorce” were categorized into this group.

- *Financial Difficulties:* Participants who selected ”Financial difficulties” were grouped under this category.

By grouping the participants based on their selected options, we can examine the association between these life events and the variables of interest in the study. This categorization allows for a comprehensive analysis of the impact of serious illness, injury, assault, death, separation/divorce, and financial difficulties on the study outcomes.

### 2.4.2 Physical Health:

**Sleep**: Participants completed a touchscreen questionnaire to provide information on various aspects of their sleep patterns.

- *Sleeplessness/Insomnia* (data-field 1200): Participants were asked, ”Do you have trouble falling asleep at night or do you wake up in the middle of the night?” The responses were recorded to assess the presence of sleeplessness or insomnia.

- *Nap During the Day* (data-field 1190): Participants were asked, ”Do you have a nap during the day?” An ’x’ was considered as the threshold to identify individuals who reported taking naps during the day and the response, then was binarized

- *Late Chronotype* (data-field 1180): Participants were answered: ”Do you consider yourself to be?”. The options ranged from ”Definitely a ’morning’ person” coded (1) to ”Definitely an ’evening’ person” coded (4). A ’y’ response was considered as the threshold to identify individuals with a late chronotype.

- *Difficulty Waking Up* (data-field 1170): Participants were asked to rate the ease of getting up in the morning on an average day. Their responses were recorded to assess the level of difficulty in waking up. A 'z' response was considered as the threshold to identify individuals who reported difficulty waking up.

- *Narcolepsy* (data-field 1220): Participants were asked, "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading, or driving)". Their responses were used to evaluate the likelihood of narcolepsy.

- *Sleep Duration* (data-field 1160): Participants were asked, "About how many hours of sleep do you get in every 24 hours? (please include naps)". Answers less than 1 or more than 23 hours were excluded. If the response was less than 3 or more than 12 hours, participants were asked to confirm the accuracy of their response.

**Physiological**: Physiological information was collected through various measurements and assessments.

- *Body Mass Index:* (data-field 21001): Body Mass Index (BMI) was determined by measuring the height and weight of participants during the baseline assessment.

- *Weight:* Weight values were recorded in kilograms (data-field 21002).

- *Weight Changes*: Information on weight changes was obtained using the touchscreen questionnaire. Participants were asked to answer "Compared with one year ago, has your weight changed?" (data-field 2306). This data was coded "0" for "No - weigh about the same", "2" "Yes - gained weight", and "3" for "Yes - lost weight further" and categorized into three groups: *"Lost Weight," "Gained Weight," and "No_Weight Change,"* representing participants who reported losing weight, gaining weight, or experiencing weight changes within one year of the baseline assessment.

- *Pulse Rate* (data-field 102): The pulse rate was measured by automated blood pressure readings.

- *Blood Pressure*: Diastolic and systolic blood pressure values were obtained through automated readings taken at the baseline assessment. Two measurements were taken a few moments apart to ensure accuracy. The mean values for Diastolic Blood Pressure (data-field 4079) and Systolic Blood Pressure (data-field 4080) were recorded as having means of 81.8042 and 138.131 respectively.

- *Fractured/Broken Bones in the Last 5 Years* (data-field 2463): Participants were asked if they had experienced any fractured or broken bones within the past 5 years. This information was collected through a touchscreen questionnaire.

**Health:** The "Health" category included information obtained through blood biochemistry sampling, specifically focusing on Vitamin D and C-reactive protein levels.

- *Vitamin D:* Vitamin D levels were measured using CLIA analysis on a DiaSorin Ltd. LIASON XL instrument. The median value of Vitamin D was 46.8 nmol/L, with a range between 10 nmol/L and 36 nmol/L2 (data-field 30890).

- *C-reactive protein*: C-reactive protein levels were measured using immunoturbidimetric high-sensitivity analysis on a Beckman Coulter AU5800 instrument. The median value of C-reactive protein was 1.33 mg/L, with a range between 0.08 mg/L and 79.96 mg/L (data-field 30710).

**Substance Use:** The Substance Use category in our study focuses on gathering information about participants' smoking and alcohol consumption habits. We collected data on various aspects, including:

- *Smoking Status:* The information on smoking status was collected using data field 20116 and categorized into three groups: Never Smoker, Previous Smoker, and Current Smoker.

- *Alcohol Intake Frequency:* The information on alcohol intake frequency was obtained by asking participants the question "About how often do you drink alcohol?" This data was categorized into values representing *Alcohol Daily Drinker, Alcohol Intake Weekly Drinker, Alcohol Occasional Drinker, and Never Drank Alcohol* (data-field 1558).

- *Alcohol Intake Compared to 10 Years Ago:* Information on alcohol intake compared to 10 years ago was gathered through a questionnaire. Participants were asked if their alcohol consumption had changed compared to a decade ago (data-field 1628).

- *Alcohol Use Status*: data-field 20117 provided information on current alcohol use and was categorized into *Never Drank, Previous Drinker, and Current Drinker*.

- *Current Tobacco Smoking:* Current tobacco smoking status was assessed by asking participants "Do you smoke tobacco now?" The responses were divided into two groups: Daily Smokers and Occasional Smokers (data-field 1239).

- *Past Tobacco Smoking:* Information on past tobacco smoking habits was collected by asking participants how often they had smoked tobacco in the past. The responses were categorized into binary values representing Past *Daily Smoker, Past Occasional Smoker, Past Tried Once or Twice, and Past Never Smoked* (data-field 1249).

- *Ever Smoked:* Current tobacco smoking status (data-field 1239) and past tobacco smoking status (data-field 1249) was used to create the variable 'Ever Smoked' (data-field 20160). Individuals were classified as Ever Smoker if they were currently smoking most days or occasionally, or if they had smoked most days, occasionally, or tried once or twice in the past.

- *Smoking in the Household*: Participants were asked the question "Does anyone in your household smoke?" to gather information on smoking within their household. The responses were used to create the variable 'Smoking Household' (data-field 1259).

- *Exposure to Tobacco at Home*: Participants were asked to estimate the number of hours per week they were exposed to other people's tobacco smoke at home. Checks were performed on the responses, and if the answer was less than 0 or greater than 168, it was rejected. If the answer was greater than 100, participants were asked to confirm. This information was used to categorize the variable 'Hours of Exposure to Tobacco at Home' (data-field 1269).

**PhysicalActivity**: Collected data related to participants' physical activity levels and their adherence to recommended guidelines. The following measures and variables were used to assess physical activity:

- *IPAQ Activity Group* (data-field 20220): This variable was classified into three categories based on the International Physical Activity Questionnaire (IPAQ): *LowIPAQActivityGroup, ModerateIPAQActivityGroup, and HighIPAQActivityGroup,* representing participants' levels of physical activity.

- *Metabolic Equivalent Task (MET) Minutes per Week for Walking* (data-field 22037): This measure quantified the number of minutes per week participants engaged in walking activities with different metabolic intensities.

- *Minutes of Metabolic Equivalent Task (MET) per Week for Moderate Activity* (Field 22038): This captured the total time in minutes per week that participants engaged in moderate-intensity physical activities, as measured by MET.

- *METVigorousActivity* (data-field 22039): This measure assessed the number of MET minutes per week participants devoted to vigorous-intensity activities.

- *Above Moderate/Vigorous/Walking Recommendation* (data-field 22035): This variable indicated whether participants met the 2017 UK Physical Activity Guidelines.

- *Summed Day's Activity* (data-field 22033): This measure captured the total number of days per week participants engaged in walking, moderate, and vigorous activities

- *Attending a Sports Club or Gym* (data-field 6160): Participants were queried about their regular attendance at specific activities. They were asked, "Which of the following do you attend once a week or more often?" If participants indicated their attendance at sports clubs or gyms at least once a week or more often, a code of 1 was assigned to signify their selection in the response. This variable allows us to identify individuals who engage in regular physical activity at sports clubs or gyms as part of their routine.

- *Hand Grip Strength*: Hand Grip Strength: Hand grip strength was examined by measuring the grip strength of both the right (data-field 46) and left (data-field 47) hands. The mean grip strength values from both hands were recorded at the end.

These variables provide insights into participants' physical activity levels, their adherence to recommended guidelines, and their involvement in sports clubs or gyms. The data collected in this category will help us evaluate the impact of physical activity on various health outcomes.

### 2.4.3 Societal and Economic:

**Socioeconomic**: In this section of the methodology, we will introduce the socioeconomic variables that were used for analysis in this study. These factors provide valuable insights into participants' educational backgrounds, employment status, household characteristics, and income.

- *Certificate Secondary Education:* (data-field 6138): Participants were asked about their educational qualifications by responding to the question, "Which of the following qualifications

do you have?" The qualifications were classified into the *Certificate of Secondary Education, College/ University, Advanced Level, Practical Career Diploma, Ordinary Level, and Other Professional Qualifications*. This variable provides information about the participant's educational background.

- *Current Employment Status:* (data-field 6142) The current employment status of participants was determined by their response to the question, "Which of the following best describes your current situation? *'LookAfterHomeFamily,' 'Unemployed,' 'FullPartTimeStudent,' 'NoneOfEmploymentProposed,' 'UnpaidVoluntaryWork,' 'Retired,' and 'PaidEmploymentSelfEmployed'* were among the responses. This data field was used to calculate the total number of employees reported.

- *Number of Vehicles in Household* (data-field 728): The number of vehicles present in the participants' households was collected using this data field. It indicates the level of vehicle ownership in the households.

- *Household Income Before Taxes* (data-field 738): Information about household income before taxes was derived from this data field. It provides insights into the participants' income level at the household level.

**Occupational**: In this section of the methodology, we will discuss several key variables related to participants' work, social interactions, and living arrangements. These factors play an important role in understanding individuals' daily activities, social connections, and overall living conditions. By examining these variables, we can gain insights into different aspects of participants' lives.

- *JobWalkingStanding:* (data-field 806): Participants were asked the question "Does your work involve walking or standing for most of the time?" to gather information on their

job-related activity. This variable indicates whether participants' work primarily requires walking or standing.

- *Frequency of Friend/Family Visits:* (data-field 1031): The variable was divided into two categories: *WeeklyMonthlyFriendFamilyVisits* and *RareOrNoFriendsFamilyVisits*. Participants' responses to the question "How frequently do you visit friends or family?" were used to classify their visit frequency. Participants who reported visiting friends or family less than five times were categorized as having rare or no visits, while those who visited at least five times were classified as having weekly or monthly visits.

- *Job Involving Heavy Manual or Physical Work:* Information on whether participants' jobs involve heavy manual or physical work was collected using a touchscreen question (data-field 816).

- *Relationship with people living in household:* The question "How are the other people who live with you related to you?" was used to collect information on participants' living information ((data-field 6141)). The responses were divided into various categories, including *Living with a grandchild*, *Live with children*, *Live with other related individuals*, *Live with other unrelated individuals*, *Live with parents*, *Live with siblings*, *Live with grandparents*, and *Live with partners*.

- *Number of People in Household* (data-field 709): Participants were asked to indicate the number of people living together in their household, including themselves. This variable provides information on the size of participants' households.

- *Ability to Confide in Someone Close* (data-field 2110): The variable captures participants' ability to confide in someone close to them. Participants were asked the question "How often

are you able to confide in someone close to you?" to assess their level of emotional support and confidante availability.

By incorporating these variables into the study, we aim to explore aspects related to participants' work conditions, social connections, and household characteristics.

In addition to the above features, Age (data-field 21003), and Sex (data-field 31) was added for the purpose of the study, and the following steps were taken to address each of the mentioned objectives.

## 2.5 Data Preparation and Statistical Analysis:

To achieve the previously mentioned objectives, this study utilized Python programming language version *3.9.13* and R programming language version *4.1.1*. Here we provide a specific methodology to achieve each objective:

***Objective 1:*** In the first part of the study, for calculating the prevalence of CP in different body sites across ages, we addressed missing data by replacing them with the median value, which is less influenced by outliers compared to the mean. Subsequently, the dataset was stratified based on sex, with females assigned a code of 0 (n = 273,302) and males assigned a code of 1 (n = 229,069). The goal was to assess the prevalence of CP in various body sites, namely *headache, facial, stomach-abdominal, neck-shoulder, hip, back, knee, and widespread pain*, by considering age as a linear input.

To quantify the prevalence of pain, the descriptive measure was employed to estimate the proportion of individuals within a population that have CP in specific body sites across age groups. For this purpose, the "Numpy" (1.23.4) and "Pandas" (1.4.3) libraries were used. For each age

point, we computed the average prevalence of pain in each body site by aggregating the number of participants who reported experiencing a particular type of pain in that site at that age point and dividing it by the total population. Furthermore, the standard error is calculated while accounting for gender and age group stratification. This technique assists in quantifying the range in prevalence estimates while accounting for various demographic factors. To visually illustrate the relationship between age and the prevalence of CP across different body sites, we created line graphs using the "matplotlib" library (3.5.2). These graphs allow for a clear visualization of how the prevalence of pain varies with age for each specific body site, providing valuable insights into the age-related patterns of CP and its association with sex. This information contributes to the overall comprehension of the burden of CP and provides a basis for further investigations into its underlying causes and potential interventions.

Next, the focus was on examining the association between CP and age in different body sites. The body sites considered were headache, facial, stomach-abdominal, neck-shoulder, hip, back, knee, and widespread pain. To investigate this association, odds ratios were calculated.

To start, contingency tables were constructed to illustrate the distribution of CP across various age groups and body sites using the "Schifer" library. These tables provided a clear representation of the number of individuals experiencing pain in specific body sites within each age group. The contingency table consisted of rows representing different age groups spanning from 37 to 73, while the columns represented different categories of CP. Each cell within the table represents the odds ratios corresponding to the specific intersection of a particular age group and CP category. We divided the overall population into 10 age groups, each containing approximately 50,000 individuals. The odds ratios were then calculated to assess the likelihood of experiencing pain in specific body sites for each age group, comparing them to a reference group. In this study, the first age group served as the reference group, against which the subsequent age groups were compared.

By comparing the odds of pain in different body sites across different age groups, the analysis aimed to identify any age-related changes in CP. Then, the study population was stratified by sex, allowing for a comparison of age-related changes in CP between males and females. This approach provided insights into potential differences in the age-related prevalence and patterns of CP across the sexes. Statistical significance was determined using a significance level of 0.05, indicating that results with p-values less than 0.05 were considered statistically significant. Additionally, confidence intervals provided an estimate of the precision for the odds ratio estimates. Overall, this part of the study aimed to explore the association between CP and age in different body sites, considering both sexes.

***Objective 2:*** In this part, we discuss the data preparation steps undertaken to utilize pain-related variables to build predictive models. Using various libraries such as "Numpy" (1.23.4) and "Scikit-learn" (1.0.2). We focused on a comprehensive set of 100 pain-related variables obtained from the UK Biobank dataset, in addition to these pain-related features information on CP, sex, and age was collected. Before proceeding with the analysis, we performed crucial data preprocessing steps to ensure the reliability and accuracy of the results.

First, we standardized continuous variables using z-scores, which transformed the data into a common scale, enabling meaningful comparisons between different variables. Categorical variables were encoded using one-hot encoding, which created binary variables for each category.

Age, being a key factor in our investigation, underwent normalization as well, using a z-score. It was also saved as a continuous variable, allowing us to capture the age-related changes of CP accurately. To handle missing or invalid values, negative values were treated as null, then null and missing values were appropriately handled. Furthermore, participants with more than 20% missing pain-related variables or missing data on any acute or CP sites were excluded from the analysis, ensuring data integrity and reliability which was less than 2.5% of the population. To address

missing values, we applied specific imputation techniques. For binary and categorical values, missing entries were replaced while preserving the original distribution of values. Continuous values were imputed using the mean, enhancing precision and minimizing potential biases.

We conducted descriptive statistical analysis on the preprocessed datasets to explore the relationships between CP, age, and various factors derived from the pain-related variables. Specifically, we calculated Spearman correlation coefficients to examine the strength and direction of these relationships. This analysis provided valuable insights into the associations between CP, age, and the identified factors, helping us better understand their interconnections and potential influences.

To evaluate the performance of our models, assess their generalizability, and mitigate the risk of overfitting, we employed a combination of techniques. Firstly, we divided the dataset into training (80%) and testing sets (20%) to be able to train the models on a subset of the data while evaluating their performance on unseen data. By doing so, we ensured robustness and minimized the potential for overfitting.

Additionally, we incorporated 10-fold cross-validation into our evaluation process. This technique involved partitioning the training set into 10 equal-sized subsets or folds. During each iteration, we trained the models on 9 folds and used the remaining fold for validation. By repeating this process 10 times, with each fold serving as the validation set once, we obtained a more comprehensive assessment of the models' performance and generalization across different subsets of the training data.

In the first step, we incorporated 9 predictor models using the 100 pain-related features as our independent variables, and 9 CP types as our dependent variables. We reported Area Under Curve (AUC) and visualize it using Receiver Operating Characteristic (ROC) curve by plotting the true positive rate (sensitivity) against the false positive rate (1 - specificity) to be able to assess the performance of the prediction models.

To account for the non-normal distribution of age, we employed a sliding window analysis approach to analyze the relationship between CP, age, and various pain-related predictors. This method involved creating age windows of 5 years each, with a 3-year overlap. By utilizing this approach, we aimed to capture potential changes and trends in CP over time and to gain insights into the dynamic nature of CP allowing for a comprehensive understanding of its relationship with age and other predictors.

Logistic regression models were employed within each age window to predict specific types of pain, utilizing 100 pain predictors as independent variables. The objective was to evaluate the likelihood of experiencing a particular type of pain based on the corresponding age group. The models were trained using the training dataset and subsequently tested on an independent testing dataset.

Several performance metrics were reported to assess the performance of the prediction models AUC, f-score, and p-value, for each model at different body sites and age groups. The AUC provided insights into the overall discriminatory power of the models, while the f-score represented the balance between precision and recall. Additionally, the p-value indicated the statistical significance of the associations between the predictors and pain types and accurately reflected the overall correctness of the model's predictions. These metrics provided valuable insights into the model's predictive ability and the statistical significance of the associations.

To visually represent the variation in predictive performance across ages, line graphs were utilized to display the AUC curves for each pain type at different age groups. This graphical representation facilitated the understanding of how the models performed in predicting specific pain types across different age ranges. An AUC value greater than 0.70 was considered indicative of good performance, indicating that the model had a relatively high ability to distinguish between positive and negative instances of the pain type being predicted.

***Objective 3:*** Following the development of predictor models for each pain type and age group, we utilized the coefficients (weights) of the 100 features in the models to categorize them into ten pre-defined categories. These groups encompassed various aspects such as *mood, neuroticism, trauma, sleep, physiological factors, health, substance use, physical activity, socioeconomic status, and occupational factors*. This feature aggregation was created by computing the absolute means of features related to each category which enabled us to evaluate the importance of each category per pain type and age group. To visually represent the data, we employed line plots to demonstrate the strength of each category for each pain type across different age groups. These plots helped identify the influential factors within each category and their variations across age groups.

In the next phase, we implemented a process using a technique we refer to as "Category Exclusion for Pain Prediction" (CEPP), in which the data set was retrained iteratively by dropping one category at a time while keeping the other categories intact and assessing the result on predictive performance. Sliding window analysis and logistic regression models were utilized to predict specific types of pain within each age window using the modified dataset resulting in 1350 pain models. The AUCs from 1350 models were reported for each model at different body sites and age groups to evaluate the impact of category exclusion. The CEPP technique allowed us to compare the impact of removing specific categories on the prediction of different pain types across age groups. Line graphs were used to visualize the AUC curve across age groups for each pain type to compare the importance and contribution of different categories in pain prediction after implementing the CEPP.

By using this comprehensive approach of sliding window analysis, logistic regression modelling, feature aggregation, CEPP and performance evaluation, we aimed to gain a deeper understanding of the relationship between CP, age, and various factors derived from pain-related variables.

# Chapter 3

# Results

In this section, we will discuss the results obtained from our analysis of the prevalence, age association, and predictive factors of chronic pain. We will first present the overall prevalence rates of chronic pain across different body sites. Subsequently, we will explore the relationship between age and chronic pain, considering potential variations by sex. Finally, we will delve into the predictive models developed to identify the coefficients of experiencing specific types of chronic pain based on pain-related variables, age, and sex. Through these analyses, we aim to shed light on the patterns and factors associated with chronic pain, providing insights that can inform clinical management and improve the well-being of individuals affected by chronic pain.

Table 3.1 provides an overview of the study population's characteristics, specifically focusing on continuous variables for the whole population at the baseline which is over 500,000 individuals. The mean age of the participants was calculated to be 57.03 years, reflecting the age distribution within the sample.

**Table 3.1: Characteristics of the Study Population**. Mean (M), standard deviation (STD), and median [min, max] are reported for the continuous variables.

| Continuous Variables | Mean (STD) | Median [Min, Max] |
|---|---|---|
| Age | 57.03 (8.09) | 58.25 [38.83, 73.67] |
| Total Neuroticism | 4.14 (3.2) | 4.0 [0.0, 12.0] |
| Sleep Duration | 7.15 (1.11) | 7.0 [1.0, 23.0] |
| BMI | 27.43 (4.74) | 26.9 [12.8, 68.4] |
| Weight | 78.04 (15.74) | 76.8 [30.1, 197.7] |
| Pulse Rate | 69.35 (10.92) | 69.0 [30.5, 174.0] |
| Diastolic Blood Pressure | 82.22 (9.85) | 82.22 [32.0, 147.5] |
| Systolic Blood Pressure | 137.83 (18.12) | 137.5 [65.0, 268.0] |
| Vitamin D | 48.63 (19.95) | 48.63 [10.0, 340.0] |
| CRP | 2.6 (4.21) | 1.47 [0.08, 79.96] |
| MET Walking | 28.17 (14.05) | 28.17 [0.0, 64.48] |
| MET Moderate Activity | 24.2 (16.72) | 24.2 [0.0, 70.99] |
| MET Vigorous Activity | 17.52 (17.22) | 17.52 [0.0, 100.4] |
| Summed Days Activity | 3.14 (0.8) | 3.14 [0.0, 4.58] |
| Hand Grip | 30.61 (11.01) | 29.0 [0.0, 85.0] |
| Number Employment | 1.08 (0.35) | 1.0 [0.0, 7.0] |
| Number In Household | 2.43 (1.32) | 2.0 [1.0, 100.0] |

## 3.1 Objective 1: Association Between Chronic Pain and Age in Different Body Sites

**1. Prevalence of Chronic Pain in Different Body Sites Across Ages:** To assess the prevalence of CP in different body sites across ages, we analyzed a dataset from the UK Biobank study. The dataset consisted of responses from a total of 502,371 participants, including 273,302 females and 229,069 males.

Within the UK Biobank, CP affects 43.7% of individuals. Among those with CP, 47% experience overlapping CP, while among acute pain patients, 29.53% experience the co-occurrence of acute pain. We also calculated the prevalence of CP in various body sites, namely headache, facial, stomach-abdominal, neck-shoulder, hip, back, knee, widespread pain, and single-site and multi-

site pain. Table 3.2 displays the prevalence of pain in different body sites for acute and CP. The prevalence of CP varied across body sites. The highest prevalence was observed for chronic single and Multi-sites pain. Chronic back pain (17.57%), followed by knee pain (16.7%) and neck-shoulder pain (15.85%) are the most common types of pain. However, for acute pain, the most prevalent type of pain was single-site (20.5%), headaches (11.45%), and multi-site pain (8.59%). In both acute and CP, the least common types of pain were widespread and facial pain. All types of CP are more common than acute except, for facial and headaches.

We examined the prevalence of CP among females and males across different age groups. Figure 3.1 shows the age-related patterns of CP in different body sites for females and males. It demonstrates that the prevalence of CP generally increases with age, with some variations across body sites. The mean prevalence for chronic back pain and neck-shoulder pain remained high across ages. The prevalence of other body site-specific pain varied across different age ranges. Chronic widespread and facial pain remained the lowest in both sex groups.

Analyzing the prevalence of each type of CP in relation to age, we observed that the prevalence of chronic hip pain, chronic knee pain, chronic back pain, and chronic neck-shoulder pain tends to increase with age. Specifically, the prevalence of chronic hip and knee pain is approximately three and two times higher, respectively, in individuals aged 70 compared to those aged 40, particularly among females. Chronic headaches in both sex groups are approximately constant till the age of 50, and then it decreases. Chronic headaches were twice as common in females as in males, and three times more prevalent at the age of 40 compared to 70.

At the age of 40, chronic neck and shoulder pain, headaches, and back pain were found to be the most common among females. The prevalence of chronic stomach and abdominal pain showed a slight decrease with age in females while remaining relatively constant among males. Multi-site pain, experienced by 62,834 females and 40,215 males in the sample population, increased with

age. Interestingly, after initial growth, there was a decrease in the prevalence of CWP among both females and males, in the age group of 55, and this decrease continued until the age of 62 for females, and until 70 for both females and males. Females tended to have slightly higher prevalence rates compared to males for most body sites except chronic knee pain in the age groups of 40-50.

**Table 3.2: Prevalence of Chronic and Acute Pain in Different Body Sites at Baseline.**

| Chronic Pain | Prevalence (%) |
|---|---|
| Overlapping | 47.22 |
| Sinle-Site | 22.92 |
| Multi-Site | 20.59 |
| Back | 17.57 |
| Knee | 16.7 |
| Neck Shoulder | 15.85 |
| Headaches | 9.04 |
| Hip | 8.59 |
| Stomach Abdominal | 4.78 |
| Widespread | 1.42 |
| Facial | 0.88 |

| Acute Pain | Prevalence (%) |
|---|---|
| Overlapping | 29.53 |
| Single-Site | 20.5 |
| Headaches | 11.45 |
| Multi-Site | 8.59 |
| Back | 8.32 |
| Neck Shoulder | 7.43 |
| Knee | 4.82 |
| Stomach Abdominal | 3.98 |
| Hip | 2.61 |
| Facial | 0.98 |
| Widespread | 0.34 |

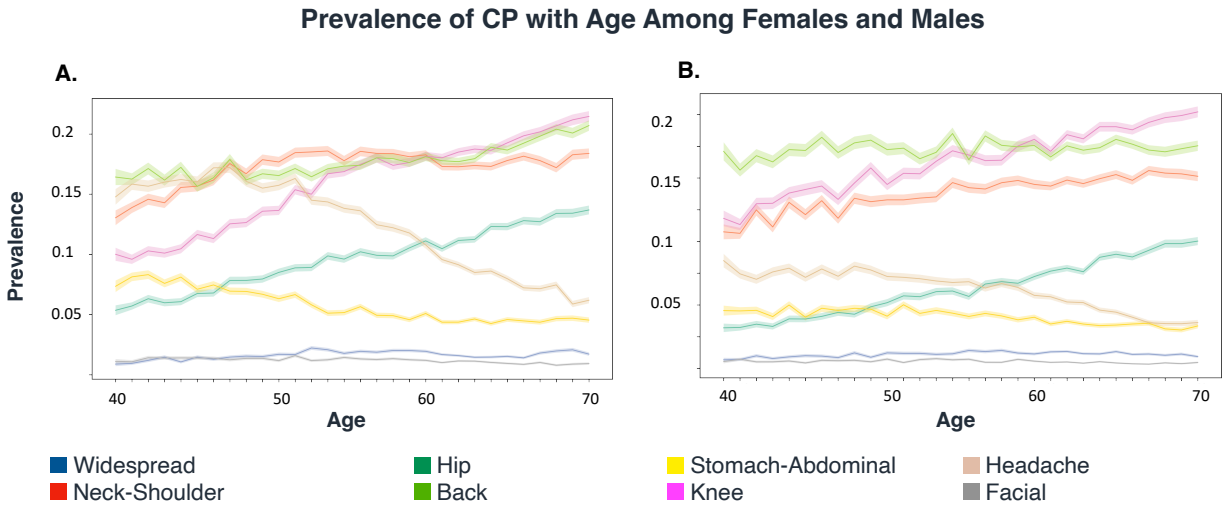


**Figure 3.1: Prevalence of 8 CP Sites with Age in Females and Males.** The x-axis represents ages from 40 to 70. The y-axis shows the prevalence of CP and the standard error of the mean. A. corresponds to the female and B. to the male.

Table 3.3 displays the percentages of individuals with overlapping pain, categorized by different chronic pain sites. Overlapping pain refers to individuals who experience a specific chronic pain site along with at least one additional pain site. The data is based on a subset of patients with chronic pain, comprising a total of 219,086 individuals. The table ranks the chronic pain sites by their corresponding overlapping pain percentages in descending order. Notably, "Chronic Multi-Site Pain" shows the highest percentage at 47.22%, followed by "Chronic Back Pain" at 27.75%. The findings offer valuable insights into the prevalence of overlapping pain patterns across various chronic pain sites.

**Table 3.3: Overlapping Pain Percentages for Different Chronic Pain Sites**

| CP | Overlapping Pain Percentage |
|---|---|
| Chronic Multi-Site Pain | 47.22% |
| Chronic Back Pain | 27.75% |
| Chronic Neck Shoulder Pain | 25.47% |
| Chronic Knee Pain | 23.37% |
| Chronic Hip Pain | 15.67% |
| Chronic Headaches Pain | 13.70% |
| Chronic Stomach Abdominal Pain | 8.11% |
| Chronic Widespread Pain | 3.25% |
| Chronic Facial Pain | 1.71% |

**2. The likelihood of having different pain sites across ages:** To examine the association between CP and age in different body sites, we calculated odds ratios to assess the likelihood of experiencing pain in specific body sites for different age groups. The odds ratios were compared to a reference group (the first age group) to identify age-related changes in CP. Contingency tables were constructed to illustrate the distribution of CP across various age groups and body sites. The odds ratios indicated that the likelihood of experiencing pain in different body sites generally increased with age. However, the magnitude of the increase varied across body sites, which has illustrated in Figure 3.2.

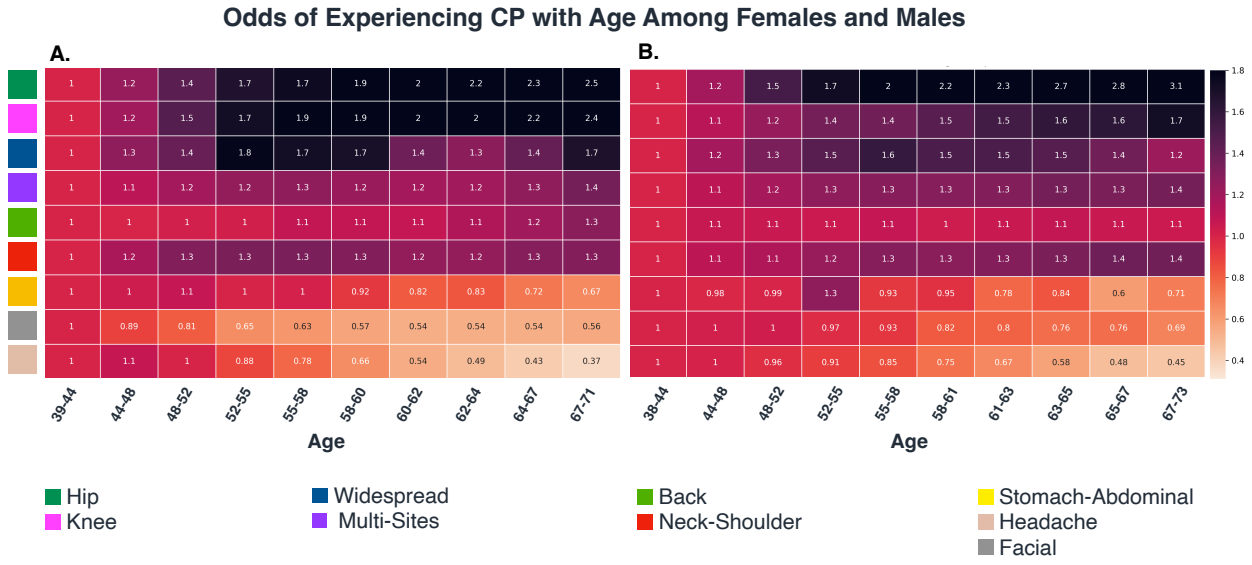


**Figure 3.2: Odds of Developing CP Sites with Age in Females and Males.** The x-axes represent the age range. The y axes correspond to the type of CP. A. corresponds to the female and B. corresponds to the male.

For females, the likelihood of chronic musculoskeletal pain including neck-shoulder, hip and knee pain, in the older age group was higher compared to the reference group. This increase was particularly evident in chronic musculoskeletal pain such as hip and knee pain. Similarly, males in the older age group exhibited a higher likelihood of chronic musculoskeletal pain, with odds ratios of 3 and 1.7 compared to the reference group for hip and knee pain, respectively in the age group

of [67 - 73]. Furthermore, chronic neck-shoulder pain was also found to be more likely in the older age group for both males and females. Females and males exhibited a 30-40% higher likelihood of chronic neck-shoulder pain in the oldest age group compared to the reference group.

In the case of chronic back pain, females in the older age group had a 30% higher likelihood compared to the first age group. Interestingly, this difference remained consistent across different age groups in males. The likelihood of developing CWP also increased with age for both genders. Females exhibited a 70% higher likelihood of developing CWP in the older age group, while males showed a 20% higher likelihood compared to the reference group. The age groups of 52-60 for females and 55-63 for males had the highest odds of developing CWP, with odds ratios of 1.8 and 1.5, respectively, compared to the reference group. Moreover, the likelihood of developing chronic multi-site pain was 40% higher in both age groups, indicating a consistent trend across genders.

However, the odds of developing chronic headaches and facial pain decreased with age. In the last age group, females exhibited a 63% lower likelihood of chronic headache and a 33% lower likelihood of facial pain compared to the first age group. Similarly, males showed a 55% lower likelihood of chronic headache and a 29% lower likelihood of facial pain in the last age group compared to the reference group. Lastly, the odds of experiencing chronic stomach abdominal pain were significantly lower in both genders, with females having a likelihood of 0.56 times and males having a likelihood of 0.69 times compared to the reference group.

Overall, the results indicate that the likelihood of chronic musculoskeletal pain varies across age groups and genders, with an increased likelihood observed in older age groups for several pain types. These results demonstrate the association between CP and age in different body sites and highlight the importance of considering sex as a factor when examining this association.

## 3.2 Objective 2: Predictive Models for Chronic Pain Based on Pain-Related Variables and Age

We developed predictive models for CP using 100 pain-related variables obtained from the UK Biobank dataset. These models aimed to predict the likelihood of experiencing specific types of pain based on pain-related variables, age, and sex.

In the first step, we examined the association between pain-related features, including age and sex, with different CP sites across the body. To assess this association, we calculated the Spearman correlation coefficient, which takes into account the rank order of variables, and visualized the results in Figure 3.3. The heat map in Figure 3.3 displays the strength and direction of the association between the pain-related features and CP sites. The intensity of the colour indicates the magnitude of the correlation, with darker colours representing stronger correlations. This analysis provides insights into the relationships between the variables. There was a positive association between, neuroticism, mood and sleeplessness and chronic multi-site pain, hand grips had a negative association with chronic widespread, neck-shoulder, hip pain, headache, and multi-site pain. SES has a negative association with most types of pain, suggesting lower SES is correlated with higher pain. Age and sex were also negatively correlated to the headache.

In the next step, we divided the population into train and test datasets to evaluate the performance of our predictive models. Table 3.4 presents the prevalence of different CP sites in both the train and test datasets. This table demonstrates that the distribution of pain types is approximately equal between the two groups, ensuring a balanced representation of CP cases in the model training and evaluation stages. Table 3.5 presents the characteristics of continuous variables in both the train and test populations. The mean age in both groups is 57.03, indicating a similar age distribu-

tion. Additionally, the table displays the mean values of other continuous variables, namely sleep duration, BMI, and CRP.


**Figure 3.3: Spearman Correlation Coefficient for CP Sites** The colour-coded matrix depicts the strength and direction of correlations, with blue shades indicating stronger associations.

**Table 3.4: Prevalence of CP in Train and Test Datasets.** The table presents the percentage of CP for different types of pain in the train and test datasets. The values highlighted in blue represent the maximum prevalence in each column.

| CP | Train | Test |
|---|---|---|
| Chronic Widespread Pain | 1.42% | 1.42% |
| Chronic Neck Shoulder Pain | 15.97% | 15.76% |
| Chronic Hip Pain | 8.63% | 8.57% |
| Chronic Back Pain | 17.67% | 17.60% |
| Chronic Stomach Abdominal Pain | 4.78% | 4.84% |
| Chronic Knee Pain | 16.78% | 16.72% |
| Chronic Headaches | 9.11% | 9.06% |
| Chronic Facial Pain | 0.89% | 0.83% |
| Chronic MultiSite Pain | 20.64% | 20.59% |

**Table 3.5: Table: Characteristics of continuous variables in train and test populations**. Mean (M), standard deviation (STD), and median [min, max] are reported for the continuous variables.

| Continuous Variables | Train (N = 401110) | | Test (N = 100278) | |
|---|---|---|---|---|
| | Mean (STD) | Median [Min, Max] | Mean (STD) | Median [Min, Max] |
| **Age** | 57.03 (8.09) | 58.25 [38.83, 73.67] | 57.05 (8.1) | 58.33 [39.67, 72.08] |
| **Total Neuroticism** | 4.14 (3.2) | 4.0 [0.0, 12.0] | 4.13 (3.2) | 4.0 [0.0, 12.0] |
| **Sleep Duration** | 7.15 (1.11) | 7.0 [1.0, 23.0] | 7.16 (1.11) | 7.0 [1.0, 20.0] |
| **BMI** | 27.43 (4.74) | 26.9 [12.8, 68.1] | 27.41 (4.73) | 26.8 [15.0, 68.4] |
| **Weight** | 78.04 (15.74) | 76.8 [30.1, 195.0] | 78.0 (15.75) | 76.8 [34.0, 197.7] |
| **Pulse Rate** | 69.36 (10.93) | 69.0 [30.5, 173.0] | 69.32 (10.89) | 69.0 [30.5, 174.0] |
| **Diastolic Blood Pressure** | 82.22 (9.84) | 82.22 [36.5, 147.5] | 82.19 (9.89) | 82.22 [32.0, 147.5] |
| **Systolic Blood Pressure** | 137.84 (18.13) | 137.5 [65.0, 253.5] | 137.78 (18.08) | 137.5 [82.0, 268.0] |
| **Vitamin D** | 48.62 (19.95) | 48.63 [10.0, 335.0] | 48.68 (19.91) | 48.63 [10.0, 340.0] |
| **CRP** | 2.6 (4.22) | 1.47 [0.08, 79.96] | 2.58 (4.17) | 1.45 [0.08, 79.44] |
| **MET Walking** | 28.17 (14.05) | 28.17 [0.0, 64.48] | 28.17 (14.06) | 28.17 [0.0, 64.48] |
| **MET Moderate Activity** | 24.18 (16.71) | 24.2 [0.0, 70.99] | 24.28 (16.74) | 24.2 [0.0, 70.99] |
| **MET Vigorous Activity** | 17.51 (17.21) | 17.52 [0.0, 100.4] | 17.59 (17.29) | 17.52 [0.0, 100.4] |
| **Summed Days Activity** | 3.14 (0.8) | 3.14 [0.0, 4.58] | 3.14 (0.8) | 3.14 [0.0, 4.58] |
| **Hand Grip** | 30.61 (11.01) | 29.0 [0.0, 85.0] | 30.6 (10.97) | 29.0 [0.0, 77.5] |
| **Number Employment** | 1.08 (0.35) | 1.0 [0.0, 7.0] | 1.08 (0.35) | 1.0 [0.0, 5.0] |
| **Number In Household** | 2.43 (1.32) | 2.0 [1.0, 100.0] | 2.43 (1.34) | 2.0 [1.0, 72.0] |

The study utilized multivariate logistic regression models to predict various CP sites, taking into account pain-related features, sex, and age to control for potential confounding factors. The AUC was calculated as a measure of the model's predictive accuracy and discriminative power in distinguishing between positive and negative instances.

The AUC values for the different pain types ranged from 0.68 to 0.88. The highest AUC values were observed for CWP (0.88) and other pain types such as Chronic facial pain, stomach-abdominal pain, and multi-site pain (0.74). These high AUC values indicate that the model effectively identifies individuals with these specific CP conditions. To visually represent the model's performance, Receiver Operating Characteristic (ROC) curves were plotted, illustrating the AUC values across different threshold settings. Figure 3.4 depicts the ROC curves for the various pain types, providing a graphical representation of the model's discriminative power.

In summary, the AUC values and ROC curves demonstrate the predictive accuracy of the multivariable logistic regression model for different CP sites. Higher AUC values signify better discrimination between positive and negative cases, indicating the model's effectiveness in identifying specific types of CP. In our study, the AUC values obtained for the multivariable logistic regression model ranged from 0.68 to 0.94, indicating a good to excellent discriminatory ability in identifying different chronic pain sites.

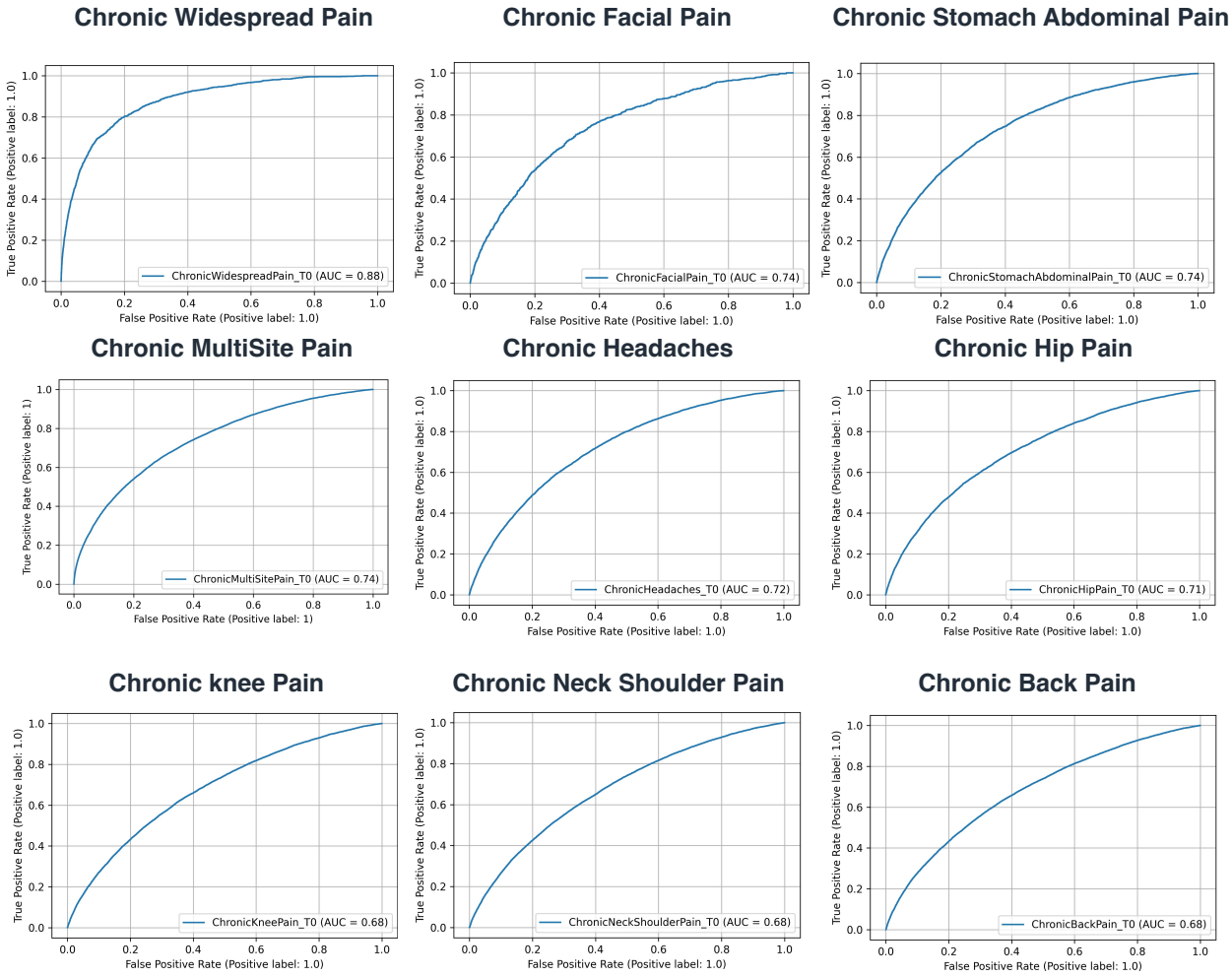


**Figure 3.4: ROC Curves and AUC Values for Different CP Types.** The figure displays the ROC curves and corresponding AUC values for the multivariable logistic regression model predicting various CP types. Each ROC curve represents the model's performance in distinguishing between positive and negative instances for a specific pain type.

To assess the performance of the predictor model across different age groups, multivariate logistic regression models were adjusted using a sliding window analysis approach. This approach involved dividing the age variable into intervals of 5 years with a 3-year overlap. Age was considered a linear factor in the analysis. The AUC values were calculated for each age group, and these values were plotted in Figure 3.5. The results showed that the highest AUC values were observed for CWP, ranging from 0.88 to 0.95 across different age groups. However, it is worth mentioning

that the AUC values for CWP showed a decrease with increasing age. This suggests that the model has an excellent discriminative ability for CWP, particularly in the younger age groups. The next highest AUC values were observed for chronic facial pain, ranging from 0.76 to 0.79. Chronic multi-site pain and stomach-abdominal pain exhibited consistent AUC values of 0.75 across age groups. Chronic facial pain, multi-site, knee and stomach-abdominal pain also exhibited relatively high AUC values across age groups. This suggests that the model has good discriminative ability for these pain types, regardless of age. On the other hand, chronic neck-shoulder, knee, and back pain had the lowest AUC values, ranging from 0.67 to 0.70. These findings suggest that the predictive accuracy of the model varies across different pain types and age groups. It is enabling us to understand the performance of the model for different CP types in relation to age. This information can help researchers and clinicians gain insights into the predictive accuracy of the model and its applicability in different age-related pain conditions.

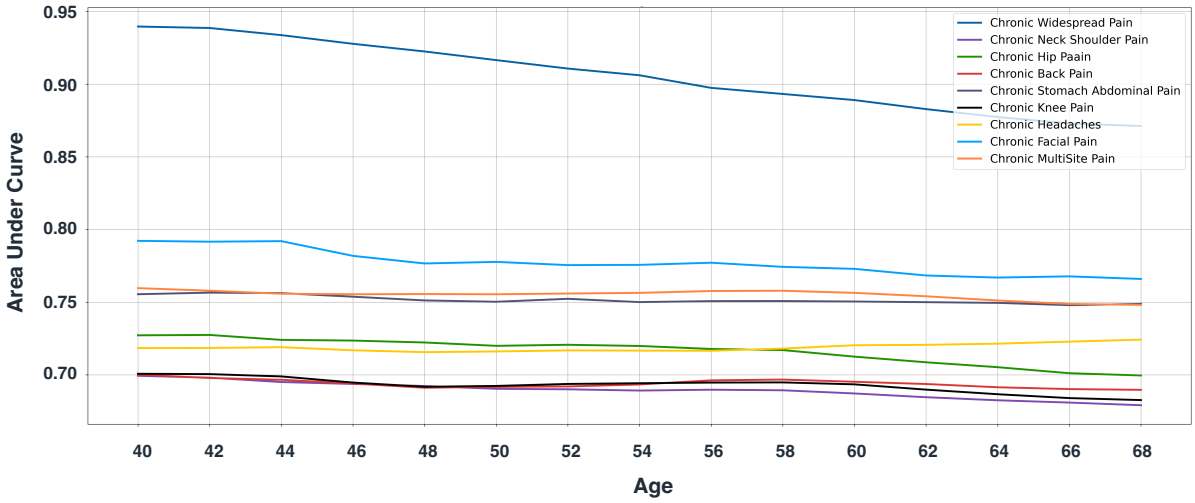


**Figure 3.5: This plot represents the AUC values across age groups.** The plot shows the age range on the x-axis and the mean average coefficient values for different categories on the y-axis. This graph allows us to observe the trends and patterns of AUC values across different age groups.

## 3.3 Objective 3: Compare the Relative Strength and Variability of Bio-Psycho-Social Pain Predictors in Different Pain Types, and Age Groups

Following the development of predictor models for each pain type and age group, we utilized the coefficients (weights) of the 100 features in the models to categorize them into ten pre-defined categories. These groups encompassed various aspects such as mood, neuroticism, trauma, sleep, physiological factors, health, substance use, physical activity, socioeconomic status, and occupational factors. This feature aggregation was created by computing the absolute means of features related to each category which enabled us to evaluate the importance of each category per pain type and age group.

Figure 3.6 visually represents the strength of each category for each pain type across different age groups using line plots. These plots provide insights into the influential factors within each category and how they vary across age groups. In the case of CWP, SES and neuroticism exhibit the highest strength, and their strength increases with age. Health and occupational factors have the lowest strength, while substance use and sleep show relatively high strength. For chronic headaches and facial pain, neuroticism and substance use are the most influential factors. Emotional trauma also shows high strength initially but decreases with age. Health is the lowest predictor in this case. In chronic stomach-abdominal pain, neuroticism, emotional trauma, and substance use exhibit the highest strength, and their effects increase with age. In chronic multi-site and hip pain, SES has the strongest influence, reaching a value of 0.4. However, the strength of other factors remains low. For chronic knee, neck-shoulder, and back pain, SES is the most influential factor, with the highest value occurring at age 56 for knee pain and age 60 for back and neck-shoulder pain. Trauma is

strong in younger age groups but decreases with age in back and knee pain. The lowest predictor in these cases is health and physical activity.

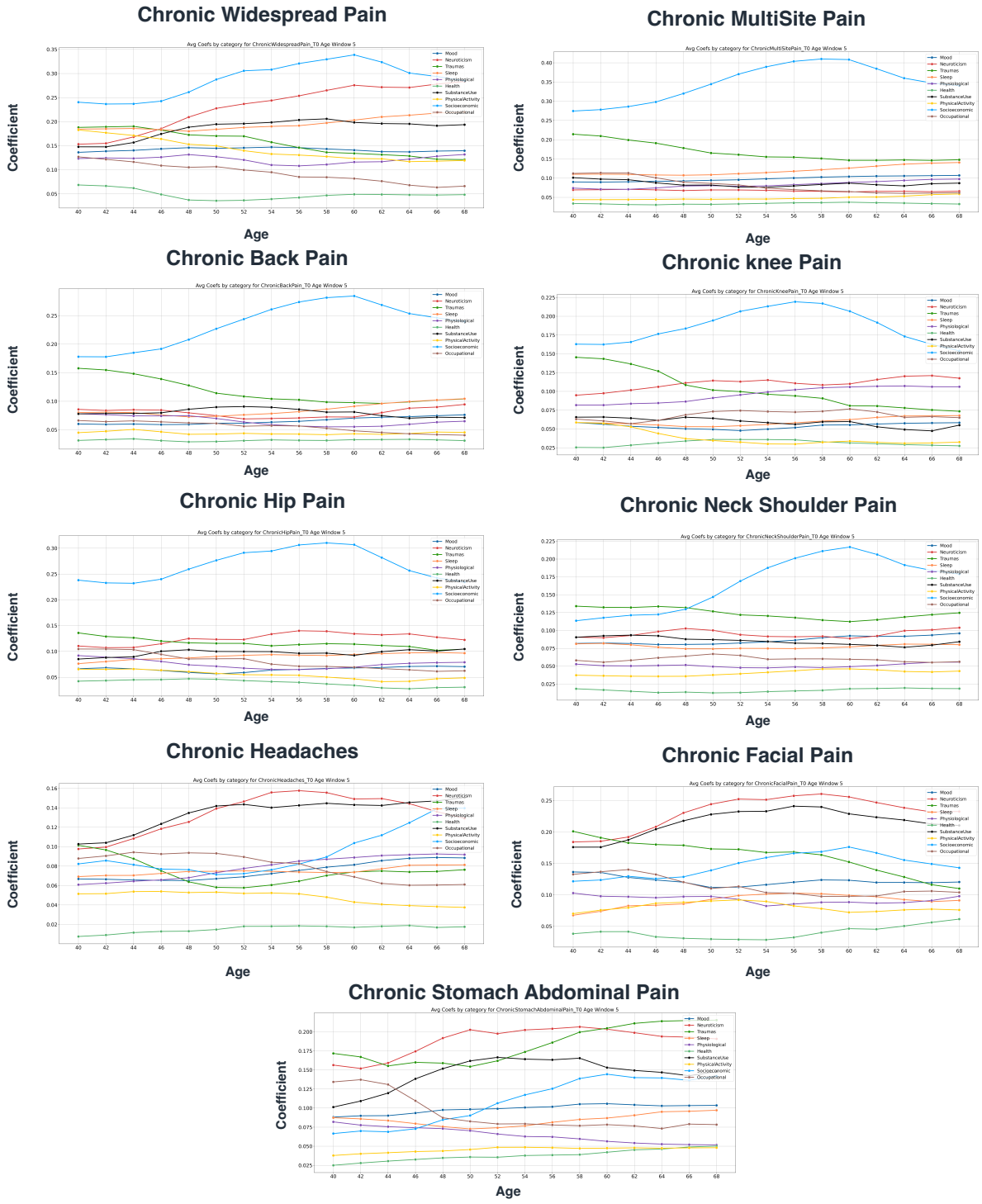


**Figure 3.6: Strength of Predictor Categories for Different Pain Types and Age Groups.** The y-axis represents the mean average coefficient values, indicating the relative importance of each predictor category. The x-axis represents the age groups under consideration.

In the next step, the analysis of the CEPP technique revealed that the exclusion of specific categories did not lead to a significant change in the AUC values, indicating that the predictive performance of the pain prediction models remained relatively stable. Figure 3.7 shows the AUCs for different pain types after removing each category per time across age groups. This lack of observable differences can be attributed to several factors. Firstly, the removed categories may have contained information that overlapped or was redundant with the remaining categories, resulting in minimal impact on the prediction performance. Lastly, it is possible that the pain prediction models relied more heavily on other factors or interactions between features, rendering the exclusion of individual categories less influential. These findings suggest that the remaining categories, even without the excluded ones, are sufficient for accurate pain prediction in this particular analysis.

Through the utilization of a comprehensive methodology encompassing sliding window analysis, logistic regression modelling, feature aggregation, and performance evaluation, our study aimed to unravel the intricate relationship between chronic pain, age, and a myriad of factors derived from pain-related variables. By doing so, we have enhanced our understanding of the complex nature of chronic pain and its associated factors, paving the way for more targeted interventions and personalized management strategies.

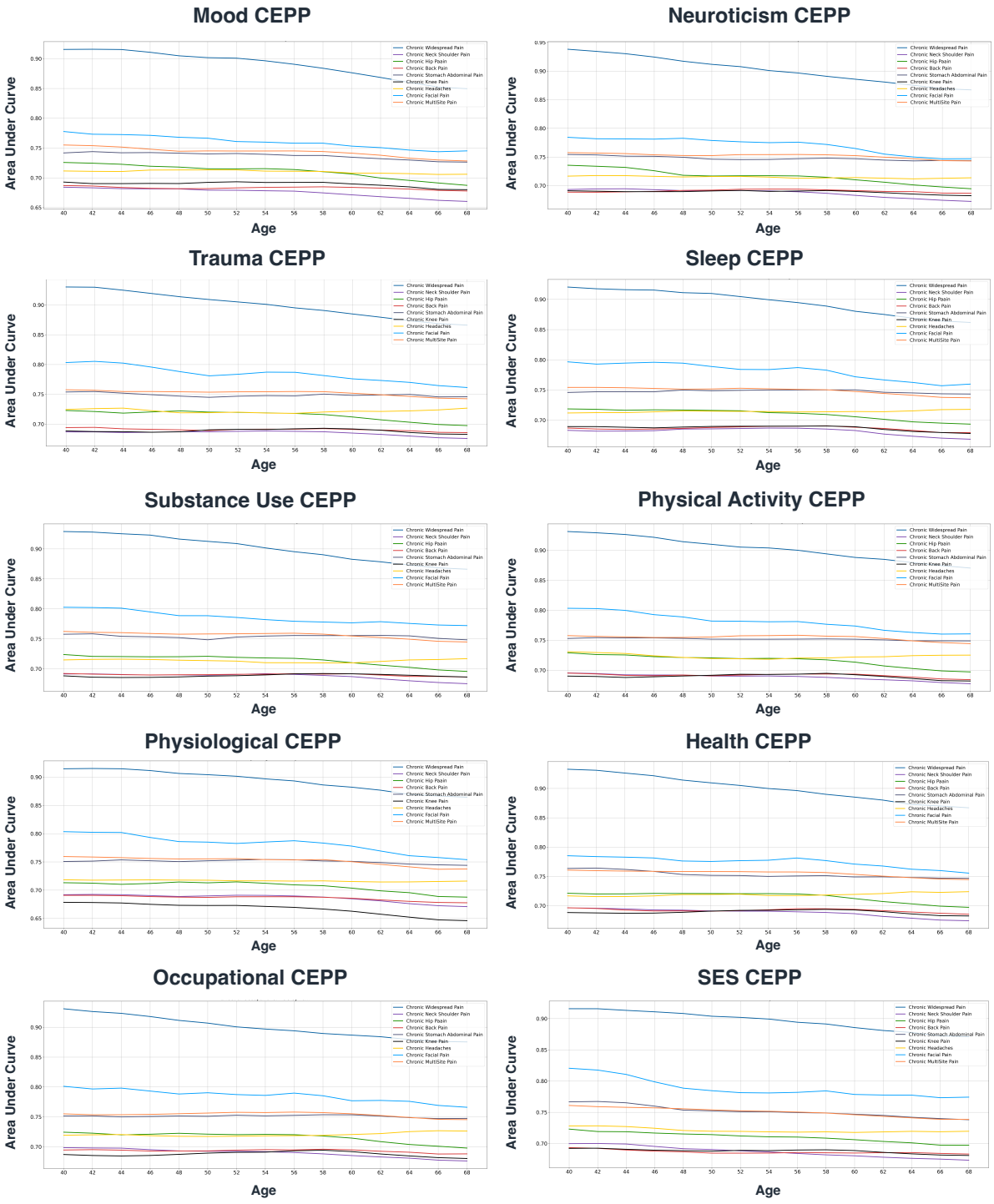


**Figure 3.7: Category Exclusion For Pain Prediction (CEPP).** The y-axis represents the Area Under the Curve of the model after removing each category per time. The x-axis represents the age groups under consideration.

# Chapter 4

# Discussion

In this study, our main objectives were to investigate the prevalence of CP across various body sites within a population, explore its variations in relation to age, develop predictive models for different types of CP by incorporating BPS predictors, sex and age, and compare the relative strength and variability of BPS pain predictors in relation to the presence of CP across different age groups.

When examining the prevalence of CP among females and males, across different age groups, it was observed that there are age-associated trends in the prevalence of CP which varies based on the different types of pain. The association between CP and age in different body sites was further examined using odds ratios. The odds ratios indicated that the likelihood of experiencing pain in different body sites generally increased with age, but the magnitude of the increase varied across body sites. Chronic musculoskeletal pain, such as chronic hip pain, knee pain, and neck-shoulder pain, showed an increasing trend with age. Chronic headaches exhibited a relatively constant prevalence until the age of 50 and then decreased. Females tended to have slightly higher prevalence rates compared to males for most body sites, except for chronic knee pain in the age groups of 40-50.

Our study findings align with existing research on the prevalence of chronic headaches and facial pain, which are more common among younger individuals and more prevalent among women [33, 34, 41, 55]. Musculoskeletal pain can affect individuals of any age but generally becomes more prevalent as people get older, becoming a leading cause of disability in the elderly population [48, 4, 24, 47, 50]. Chronic back pain, as the most prevalent form of CP, also demonstrates an increase in frequency with age [4, 24]. Additionally, our study indicates that individuals in their fifties are at a heightened risk of developing CWP [55, 54]. These results further emphasize the significance of addressing and preparing for the growing burden of CP, and the need for more populational studies [160]. Population-based studies play a key role in patient care and guiding strategies for the prevention and management of CP [161, 160]. In light of the established and validated sample handling and protocol by UK Biobank, our study benefits from the quality assurance and robustness of the methods employed [162]. Moreover, within the context of our research conducted using UK Biobank, our findings demonstrate the comparability of pain prevalence estimates with previous large-scale studies as it is mentioned by [163].

Objective 3 focused on the development of predictive models for different types of CP by incorporating BPS predictors and age as variables. We utilized the Spearman correlation coefficient to examine the relationship between pain-related features, age, and sex with CP sites. To display these associations, we employed a heatmap visualization (Figure 3.3). Our findings revealed correlations between various factors and specific CP sites. For example, for chronic multi-site pain, we observed positive correlations with mood category, total neuroticism 2.4.1, sleeplessness 2.4.2, and negative correlations with hand grip strength 2.4.2, employment status, and income household 2.4.3. The hand grip 2.4.2 has also a negative correlation with CWP, neck-shoulder, hip, headaches, and multi-site pain. Furthermore, chronic knee pain exhibited negative correlations with education level and employment status 2.4.3, while showing a positive correlation with BMI and weight 2.4.2. Age was also positively correlated to systolic blood pressure 2.4.2 as well as

retirement 2.4.3. These results indicate that certain pain-related features may play a significant role in developing specific CP sites.

Next, we constructed multivariable logistic regression models for different types of pain and then by incorporating pain-related features, age, and sex to predict different CP sites. The models demonstrated varying degrees of predictive accuracy, as indicated by the AUC values ranging from 0.68 to 0.88. The highest AUCs were observed for CWP, chronic facial pain, stomach-abdominal pain, and multi-site pain, suggesting that our models have a good discriminative ability for these particular pain types. The ROC curves (Figure 3.4) further supported the models' performance in distinguishing between positive and negative instances for different CP sites. Our analysis revealed that the inclusion of BPS predictors, such as biological, psychological, and social factors, along with age significantly improved the predictive accuracy of the models. These findings underscore the multifactorial nature of CP and emphasize the importance of considering a comprehensive set of variables in predictive modelling.

Lastly, Objective 4 aimed to compare the relative strength and variability of BPS pain predictors in relation to the presence of CP across different age groups. Our analysis revealed interesting patterns, with certain BPS predictors showing stronger associations with CP in specific age groups. These findings highlight the importance of considering age as a potential effect modifier in the relationships between BPS predictors and CP. Lastly, the CEPP 3.7)approach was incorporated and showed that their pain predictors are highly correlated and common risk factors exist between them.

In a study conducted by [36], the association between various factors such as alcohol consumption, physical activity, sleep, smoking, and stress with headaches was examined. The findings revealed significant associations between headaches and sleep, alcohol consumption, stress, and mental health. Similarly, our study identified neuroticism factors, such as loneliness-isolation, and

substance use as strong predictors of chronic headaches, while health and physical activity were found to be less important predictors.

These results are consistent with the findings of [41], who analyzed data from the UK Biobank and reported a significant association between income and facial pain, with the highest prevalence observed among individuals with the lowest income. They also found associations with unhappiness, depression, sleep, smoking, and alcohol consumption. These findings align well with our strength evaluation graphs, which indicate that neuroticism, substance use and Socioeconomic factors are significant predictors of facial pain. In our study, the predictor model's AUC ranged from 0.76 to 0.79 across different age groups.

Regarding chronic musculoskeletal pain (MSK), the study by [47] examined the associations between life stressors such as immigration, SES, manual jobs, and chronic MSK pain. They found that CWP was particularly associated with these factors. In our study, we observed that SES had the highest strength as a predictor for chronic back, neck-shoulder, knee, and hip pain across all age groups, with its effects generally increasing and peaking after the age of 55. The impact of life stressors, particularly the trauma category, was also high in younger individuals while it decreased with age.

Occupational categories, such as manual jobs, did not show significant strength, as indicated by absolute mean coefficients below 0.1. The AUC for knee, neck-shoulder, and back pain were approximately 0.7 while chronic hip pain had a 73% AUC, which decreased to 0.7 in the oldest age group.

The findings indicate that certain factors, such as SES, neuroticism, and substance use, consistently emerge as influential predictors across different pain types and age groups. The results also suggest that the strength and impact of these factors may vary with age, with some factors showing

increasing or decreasing trends as individuals grow older. It emphasizes the need for a multidimensional approach when studying CP and highlights the potential implications for developing targeted interventions and personalized treatment strategies.

Our study provides valuable insights into the prevalence, age-related patterns, and predictive modelling of CP across different body sites, and underscores the complex interplay between BPS factors, age, and the presence of CP. However, it is essential to acknowledge the limitations of our study, such as 4.1. Future research should address these limitations and further investigate the underlying mechanisms of CP to inform more effective prevention and management strategies.

## 4.1 Strengths and limitations

Our study's strengths lie in the utilization of the UK Biobank dataset, which provides a large population-based sample and enhances the generalizability of our findings [162]. The rigorous sampling and storage protocol implemented by UK Biobank ensures the reliability, quality assurance, and validity of our study methods. Moreover, our study makes a significant contribution to the existing literature by incorporating a comprehensive range of predictors and pain types. By considering the inclusivity of pain predictors and types, as well as accounting for the dynamic nature of age and its impact on chronic pain (CP), we have gained a more holistic understanding of this complex phenomenon. While studies like [7, 164] focused on older adults and incorporated a machine learning approach, their analysis was limited to the evaluation of movement and sleep hours as predictors of chronic pain. In contrast, we conducted a comprehensive analysis by incorporating BPS predictors, sex, and age, which allowed us to capture a more holistic understanding of CP patterns and their relationships with age and sex. Our study examined over 100 pain features across nine CP sites in different age and sex groups, providing extensive insights into the prevalence and associations of CP. Population-based studies like ours are crucial for informing

patient care and guiding strategies for the prevention and management of CP, making our findings highly relevant in addressing the burden of CP in the population. Furthermore, our study's findings are comparable to previous large-scale studies, indicating the reliability and external validity of pain prevalence estimates obtained from the UK Biobank. This highlights the potential of the UK Biobank for investigating novel exposure-pain relationships. Our study also has real-life applications for chronic pain

While UK Biobank has a lot to offer [165] considering the potential selection bias resulting from a low response rate during recruitment, it is important to be cautious when estimating the comorbidity of diseases from the UK Biobank [166]. Although our analysis focused on nine CP sites, there are other potential pain sites that were not included, limiting the comprehensiveness of our study. Additionally, the voluntary nature of participation in the UK Biobank introduces the potential for self-selection bias, while the use of self-reported questionnaires increases the risk of recall bias. Furthermore, the questionnaire does not provide information on the onset of the pain. Despite our efforts to control for confounding variables, there is still the possibility of unmeasured or residual confounding, which may influence the observed associations. Factors such as genetic predisposition and specific environmental exposures, which were not included in our analysis, could also contribute to CP outcomes.

## 4.2 Future Directions:

In future research, several avenues can enhance our understanding of CP. The application of residualization techniques can be considered to account for potential confounding factors and further enhance the analysis of the relationship between pain prediction, age, and other relevant variables. Incorporating deep learning techniques can capture complex relationships and improve predictive accuracy. External validation using diverse populations will ensure the robustness and generaliz-

ability of findings. Additionally, exploring dental-related factors can shed light on their associations with chronic headaches and facial pain. These efforts will contribute to improved diagnostics, interventions, and patient care for CP. headache and facial pain.

# Chapter 5

# Conclusion

In conclusion, our study investigated the prevalence, age-related patterns, and predictive modelling of CP across different body sites. We found that CP exhibited varying trends with age, with musculoskeletal pain increasing in prevalence as individuals grew older. Females generally had higher CP prevalence rates compared to males for almost all types of pain. By incorporating biological, psychological, and social predictors (BPS), along with age and sex, we developed predictive models for different types of CP. These models demonstrated good discriminative ability, with the highest accuracy observed for CWP, chronic facial pain, stomach-abdominal pain, and multi-site pain.

The inclusion of BPS predictors significantly improved the predictive accuracy of the models, highlighting the multifactorial nature of CP. Our findings revealed significant correlations between pain-related features, age, and sex with specific CP sites. Factors such as mood, neuroticism, sleeplessness, sleep duration, hand grip strength, alcohol intake, employment status, income, education level, BMI, and weight showed associations with various CP sites. We also identified age-specific associations between BPS predictors and CP, emphasizing the importance of considering age as an effect modifier in these relationships.

The implications of this study are significant for both research and clinical practice. By identifying the predictors and patterns of chronic pain, our findings provide valuable insights for the development of targeted interventions and personalized treatment strategies. The comprehensive analysis of a large population-based sample from the UK Biobank enhances the generalizability and reliability of our findings. Our study has the potential to identify key risk factors for chronic pain in the general population, offering valuable supplemental tools for physicians. Specifically, it can aid in the prognostic decision-making process for chronic pain in elderly individuals with cognitive impairments like Alzheimer's disease, as well as those who have been experiencing prolonged pain. Additionally, our findings can contribute to assessing the risk of chronic pain in individuals scheduled for surgery, enabling proactive measures to manage pain and improve postoperative outcomes.

It is important to acknowledge the limitations of our study, including potential selection bias, self-reported data, and the possibility of unmeasured confounding variables. Future research should address these limitations and further investigate the underlying mechanisms of chronic pain to inform more effective prevention and management strategies.

In conclusion, our study contributes to the understanding of CP by highlighting its prevalence, age-related patterns, and the importance of BPS predictors in predictive modelling. Despite the limitations, our findings emphasize the need for a multidimensional approach to studying CP and provide insights that can inform targeted interventions and personalized treatment strategies. Future research should address the limitations and further investigate the underlying mechanisms of CP to improve prevention and management strategies.

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