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MASTER THESIS

SEX DISPARITIES IN THE EMOTIONAL IMPACT OF CHRONIC NON-CANCER PAIN USING HIERARCHICAL CLUSTERING AND MACHINE LEARNING TEMATICS

PRESENTED BY

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TUTOR'S DECLARATION

We, the undersigned, hereby declare that the Master's Thesis entitled *"Sex disparities in the emotional impact of chronic non cancer pain using hierarchical clustering and machine learning thematics*", submitted by **Hichem Allouti** in partial fulfillment of the requirements for the degree of Master in Biotechnology and Bioengineering , has been prepared under our supervision.

As the official tutor, I, **Dr. Ana María Peiró Peiró**, together with the co-tutor, **Ms. Noelia Serrano Gadea**, confirm that we have reviewed and guided the development of this work. We attest to the academic rigor, originality, and quality of the research conducted by the candidate.

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SUMMARY

Introduction: Chronic Non-Cancer Pain (CNCP) disproportionately affects women and men, not only in prevalence but also in emotional, social, and functional burden. Biological sex differences interact with gender roles and societal expectations. Women report higher emotional distress, sleep disturbances, and caregiving-related limitations, while men face higher work-related disability and underreport emotional suffering due to cultural norms of stoicism. These disparities result in unequal clinical presentations and treatment outcomes, highlighting the need for gender-sensitive categorization and management of CNCP.

Objectives: The primary objective was to identify sex-specific emotional impact profiles of CNCP patients through hierarchical clustering and machine learning.

Materials and Methods: This mixed-methods study included 216 CNCP patients (69% women) from a Spanish tertiary hospital. Data were collected via structured interviews conducted by four pain experts using clinical scales and the internally validated Gender-Pain Questionnaire. A team of three psychosocial researchers organized and thematically categorized the emotional impact data. Quantitative clustering analyses were conducted using hierarchical clustering (Ward.D2 with Euclidean distance and Gower's method for mixed data) and supported by machine learning thematic classification.

Results: 1/ Women were older, more likely to be homemakers or on work disability, and showed trends of higher anxiety. Men were more often prescribed morphine and antidepressants. **2/** Women reported higher reproductive role disruption, while men showed predominance in productive role impact. Mixed roles were more burdensome for women. **3/** For women, three clusters captured physical-emotional overload, psychosocial disconnection, and role-based distress. For men, three clusters highlighted emotional suppression, work-related loss, and social disintegration. **4/** Using weighted mixed data and thematic ML categorization, distinct emotional impact profiles by sex were found, with men clustering around emotional repression and productivity loss, and women around relational suffering and psychosocial vulnerability.

Conclusions: This thesis reveals robust sex-based differences in the emotional and functional impacts of CNCP. Women suffer a broader spectrum of emotional strain linked to caregiving and social expectations, while men exhibit underrecognized emotional distress tied to productivity and social withdrawal. Hierarchical clustering combined with ML proved effective in defining distinct emotional profiles, offering valuable insights for implementing gender-sensitive clinical and public health strategies in CNCP care.

Key words: Chronic non-cancer pain, Emotional impact, hierarchical clustering, Language machine learning models, Sex differences.

RESUMEN

Introducción: El dolor crónico no oncológico (DCNO) afecta de manera desproporcionada a mujeres y hombres, no sólo en términos de prevalencia sino también en la carga emocional, social y funcional. Las diferencias biológicas por sexo interactúan con los roles de género y las expectativas sociales. Las mujeres reportan mayor malestar emocional, alteraciones del sueño y limitaciones relacionadas con el cuidado, mientras que los hombres presentan una mayor discapacidad laboral y tienden a subreportar el sufrimiento emocional debido a normas culturales de estoicismo. Estas disparidades resultan en presentaciones clínicas y resultados terapéuticos desiguales, lo que subraya la necesidad de una categorización y manejo sensibles al género del DCNO.

Objetivos: El objetivo principal fue identificar perfiles de impacto emocional específicos por sexo en pacientes con DCNO mediante técnicas de agrupamiento jerárquico y aprendizaje automático.

Materiales y Métodos: Este estudio de métodos mixtos incluyó a 216 pacientes con DCNO (69 % mujeres) de un hospital terciario en España. Los datos fueron recolectados mediante entrevistas estructuradas utilizando escalas clínicas y el cuestionario Gender-Pain. Después se categorizaron los datos de impacto emocional. Los análisis de agrupamiento cuantitativo se realizaron mediante clustering jerárquico (Ward.D2 con distancia euclidiana y método de Gower para datos mixtos) y fueron complementados por una clasificación temática mediante aprendizaje automático.

Resultados: 1/ Las mujeres eran de mayor edad, más propensas a ser amas de casa o estar en situación de incapacidad laboral, y mostraron tendencias a mayor ansiedad. Los hombres recibieron con mayor frecuencia prescripción de morfina y antidepresivos. **2/** Las mujeres reportaron una mayor disrupción en los roles reproductivos, mientras que los hombres una predominancia en el impacto sobre los roles productivos. Los roles mixtos resultaron más gravosos para las mujeres. **3/** En mujeres, tres clústeres reflejaron sobrecarga físico-emocional, desconexión psicosocial y angustia basada en los roles. En hombres, los clústeres destacaron la supresión emocional, pérdida relacionada con el trabajo y desintegración social. **4/** Utilizando datos mixtos ponderados y categorización con aprendizaje automático, se identificaron perfiles emocionales diferenciados por sexo: los hombres se agruparon en torno a la represión emocional y la pérdida de productividad, mientras que las mujeres se centraron en el sufrimiento relacional y la vulnerabilidad psicosocial.

Conclusiones: Existen diferencias por sexo en los impactos emocionales y funcionales del DCNO. Las mujeres sufren un espectro más amplio de tensiones emocionales vinculadas al cuidado y las expectativas sociales, mientras que los hombres manifiestan un sufrimiento emocional subestimado, ligado a la productividad y al retraimiento social. El clustering jerárquico combinado con aprendizaje automático resultó eficaz para definir perfiles emocionales distintos, aportando conocimientos valiosos para implementar estrategias clínicas sensibles al género en el abordaje del DCNO.

Palabras clave: Dolor crónico no oncológico, Impacto emocional, ,Diferencias por sexo, Modelos de aprendizaje automático de lenguaje.

LIST OF ABBREVIATIONS

- **CNCP** - Chronic Non-Cancer Pain
- **DBI** - Davies-Bouldin Index
- **DSM-5** - Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
- **EQ-5D-3L** - EuroQol 5-Dimension 3-Level
- **HADS** - Hospital Anxiety and Depression Scale
- **IDF-R -** Impairment and Functioning Inventory Revised
- **IQR** - Interquartile Range
- **LMM** - Large Language Model
- **MEDD** - Morphine Equivalent Daily Dose
- **ML** - Machine Learning
- **MOS-SS** - Medical Outcome Study Sleep Scale
- **NSAIDs** - Non-steroidal anti-inflammatory drugs
- **OUD** - Opioid Use Disorder
- **PU** - Pain Unit
- **SD** - Standard Deviation
- **SF** - Short Form Health Survey
- **VAS** - Visual Analogue Scale

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1. Introduction and Background

Chronic non-cancer pain (CNCP) stands as a pervasive global health challenge, affecting ~20% of adults worldwide and ranking among the leading causes of disability [1]. Defined as persistent or recurring pain lasting beyond three months [2], CNCP transcends mere physical discomfort, casting a profound shadow over emotional well-being, social relationships, and economic stability. Its impact reverberates beyond the individual, straining familial networks and imposing significant costs on healthcare systems. In Spain, for instance, the annual economic burden of CNCP reaches €18.9 billion (~1.5-2% GDP), with 4.21% of the population reporting sick leave and 1.8% facing job loss due to the condition [3]. These disparities lay the groundwork for exploring CNCP's emotional toll through a sex and gender lens, with the goal of illuminating differences that could inform more equitable clinical practices and future research.

Central to this exploration are the emotional consequences of CNCP, which often manifest as heightened anxiety and depression, with women scoring higher on Hospital Anxiety and Depression Scale (HADS) [4], and disrupted sleep (e.g., 50% of CNCP patients report insomnia) eroding quality of life [5, 6]. These effects are not uniform across all individuals; mounting evidence suggests that sex and gender play critical roles in how pain is experienced and expressed. Women, in particular, appear to bear a heavier emotional burden, frequently reporting greater levels of psychological distress compared to men [7]. This disparity hints at a complex interplay of biological, psychological, and sociocultural factors that demand closer examination. Understanding these differences is not merely an academic exercise—it holds the potential to reshape pain management strategies, ensuring they address the unique needs of diverse populations.

Biologically, sex differences in pain perception are well-documented. Hormonal fluctuations, such as those involving estrogen, can amplify pain sensitivity in women, while genetic variations in pain pathways further distinguish female and male responses [8]. These physiological underpinnings are compounded by psychological factors, including distinct coping mechanisms. Research indicates that women often lean toward emotion-focused strategies—seeking social support or processing feelings—while men may favor stoicism or problem-focused approaches, such as distraction or physical activity [9]. Such patterns reflect broader societal norms that socialize boys to "tough it out" and girls to articulate discomfort, embedding gender-specific expectations into the pain experience from an early age [10] .

These gendered norms are not benign; they are reinforced by concepts like hegemonic masculinity, which valorizes traits such as strength and self-reliance as masculine ideals [10]. In contrast, feminine traits—expressivity, sensitivity, and interdependence—are often devalued, shaping how individuals report pain and seek care. This dynamic extends into healthcare settings, where andronormativity—the assumption that male experiences are the standard—can render women's pain less visible or prioritized [10]. For example, women with chronic conditions may face delays in diagnosis or receive treatments misaligned with their needs, while men's reluctance to disclose

emotional distress might mask underlying issues like depression [10]. All of them can affect pain management in real world patients.

This thesis aims to delve into these sex/gender roles disparities, focusing on the impact of CNCP as a critical lens. Inspired by emerging research, it seeks to explore how biological differences, coping strategies, and societal expectations converge to shape the lived experience of pain. Advanced analytical tools, such as hierarchical clustering and machine learning (ML), offer a promising avenue

for uncovering distinct emotional profiles that may differ by sex and gender [11]. By identifying these patterns, the research intends to move beyond surface-level observations, offering a nuanced understanding of how CNCP affects men and women differently.

1.1 Sex-differences in Pain Pathways

Pain perception is mediated by complex neurobiological pathways, with emerging evidence highlighting sex-specific differences that influence CNCP experiences. The nociceptive system—comprising peripheral receptors, spinal cord transmission, and brain processing—exhibits variations between men and women, driven by genetic, hormonal, and anatomical factors [12]. Women tend to have lower pain thresholds and higher sensitivity to experimental pain stimuli, such as thermal or pressure tests, a phenomenon linked to estrogen's modulation of nociceptive signaling [13] . Estrogen enhances the activity of transient receptor potential vanilloid 1 channels in sensory neurons, amplifying pain signals in females [13]. Conversely, testosterone in men may exert an analgesic effect by upregulating endogenous opioid systems, reducing pain perception in both animal models and humans [14, 15].

Genetic differences further delineate these pathways. For instance, the melanocortin-1 receptor gene, associated with red hair and fair skin, is more prevalent in women and correlates with increased analgesic response to kappa-opioid agonists, a sex-specific effect not observed in men [16]. Neuroimaging studies reveal that women exhibit greater activation in emotion-related brain regions (e.g., amygdala, prefrontal cortex) during pain processing, while men show more activity in sensory and motor areas (e.g., somatosensory cortex, insula), suggesting divergent central processing mechanisms [17, 18]. These biological disparities underpin the higher prevalence of CNCP conditions in women like chronic pelvic pain, migraine, oral pain, back pain, etc. (**Figure 1**) [12] , contrasting with men's higher rates of chronic tension-type headaches [19]. Sex differences also extend to conditions like osteoarthritis, where women report higher pain severity [20]. Understanding these pathways is crucial for tailoring CNCP interventions to sex-specific needs.

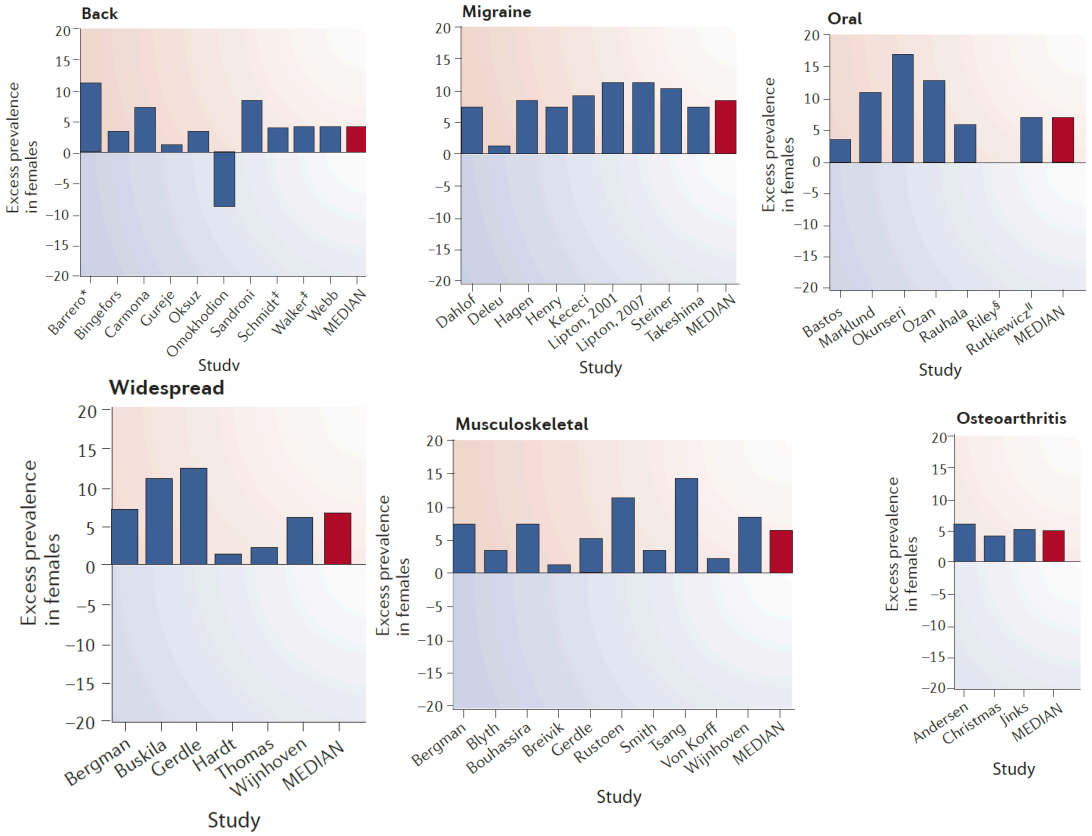


Figure 1. Sex differences in prevalence of chronic pain syndromes. Each blue bar represents the excess prevalence of the pain condition in women reported in a single epidemiological study; the red bar to the right represents the median excess prevalence within the category [12] .

1.2 Sex-differences in the Emotional Impact of CNCP

The impact of CNCP extends beyond physical sensation, affecting emotional, social, and functional domains differently across sexes. Women consistently report higher emotional distress, reflecting elevated anxiety and depression [21, 22, 23]. This aligns with their greater likelihood of experiencing sleep disturbances and feelings of hopelessness, eroding quality of life [6]. A Spanish study found that 47.6% of CNCP sufferers reported strained family dynamics, with women more affected due to overlapping domestic responsibilities, alongside higher sick leave (2.98% vs. 1.23%) and job loss rates (1.23% vs. 0.58%), reflecting a compounded burden tied to gender roles [3] (**Figure 2**).

Men, however, exhibit distinct impacts, often linked to societal expectations of stoicism. They report higher disability rates and opioid dependence, potentially due to delayed emotional disclosure and reliance on pharmacological relief [10]. Relational struggles, such as insecurity or fear of loneliness, with 25% higher prevalence in men, emerge as prominent emotional impacts, contrasting with women's pervasive mood-related difficulties [7]. Functionally, men experience greater interference in productive roles (e.g., 20% work disruption), while women face challenges in both productive and

reproductive domains (e.g., 30% childcare disruption) [19]. These differences, as shown in **Figure 2** and, highlight the need for gender-sensitive assessments of CNCP's multifaceted consequences, encompassing psychological health, social connections, and daily functioning.

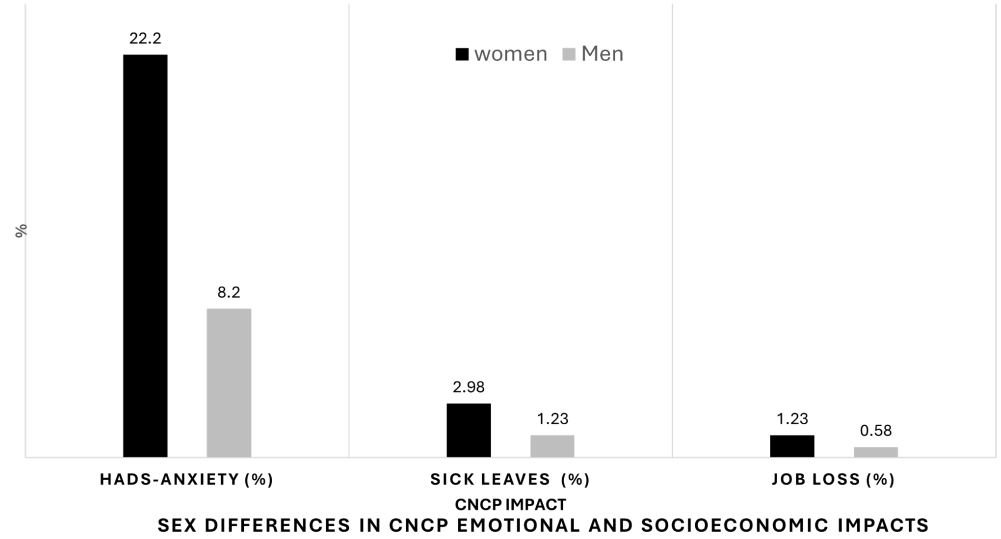


Figure 2. Bar chart illustrating sex differences in chronic non-cancer pain impact. HADS-Anxiety scores (women: 22.2, men: 8.2) are sourced from [21]. Sick leave (2.98% for women, 1.23% for men) and job loss (1.23% for women, 0.58% for men) data are sourced from [3].

1.2.1 Emotional and Functional Categorizations Focusing on Daily Life Disruptions

Historical and contemporary efforts to categorize the impacts of CNCP have varied in scope and methodology, often focusing on broad domains, specific conditions, functional disruptions, and emotional consequences. Early studies adopted broad categorizations, such as physical, emotional, and social domains, using standardized tools like the Short Form-36 (SF-36) health survey to quantify health-related quality of life [24]. The SF-36, for instance, measures subscales including physical functioning like mobility limitations, mental health like anxiety levels, and social functioning like role limitations due to emotional problems, providing a comprehensive framework to assess CNCP's multifaceted impact. Similarly, [3] Dueñas et al. (2016) categorized impacts into patient-level effects (e.g., pain intensity, emotional distress), social consequences (e.g., family strain, support networks), and systemic burdens (e.g., healthcare costs), revealing sex disparities such as women's higher healthcare utilization, with 15% more frequent medical visits compared to men.

Functional categorizations offer another perspective, focusing on daily life disruptions. The Impairment and Functioning Inventory (IDF), validated by [25] Ramirez-Maestre et al. (2022), divides

CNCP impact into household, independent, leisure, and social activities, capturing sex differences in functional interference. For example, women report 25% greater interference in household activities (e.g., cleaning, childcare) compared to men, reflecting the gendered distribution of domestic roles. This functional lens provides a practical framework for understanding how CNCP differentially affects men's and women's daily lives.

Emotional impact classifications have often relied on tools like the HADS. [22] McWilliams et al. (2004) used HADS to stratify CNCP patients into non-cases (scores 0-7), probable cases (scores 8-10), and definite cases (scores ≥11) of anxiety or depression, finding that women are overrepresented in higher severity groups, with 60% of definite cases being female compared to 40% male. However, these prior categorizations rarely integrated sex and gender as a primary axis of analysis, often treating them as covariates rather than core determinants. This approach overlooks critical interaction effects, such as how gender roles amplify women's emotional distress through increased domestic responsibilities, underscoring a significant gap in the literature.

This thesis aims to address this gap by developing a nuanced, sex-specific categorization of CNCP's emotional and functional toll. Leveraging advanced analytical techniques, such as hierarchical clustering and ML, this study seeks to uncover distinct impact profiles that account for sex and gender as central factors, moving beyond traditional covariate adjustments to inform more equitable pain management strategies.

1.3 CNCP Categorizations Using Clustering and Machine Learning

Research on clustering CNCP impacts remains limited, underscoring the need for advanced, sex-specific approaches. [11] Alter et al. (2024) applied hierarchical clustering to CNCP pain drawings, identifying fibromyalgia subgroups based on clinical features, but did not explore broader impacts, such as emotional or functional domains. [26] Lötsch and Ultsch (2018) used clustering on general pain data to identify patient subgroups by pain mechanisms, yet their study did not focus on CNCP-specific impacts.

ML has categorized CNCP impacts into domains such as functional, personal, social, and perception, laying a foundation for clustering studies [26]. A literature search (PubMed, Google Scholar, as of June 5, 2024) revealed no comprehensive studies categorizing CNCP impacts (e.g., emotional, functional, socioeconomic) using clustering, highlighting the innovative potential of sex-specific analyses. Clustering data separately for men and women can capture gender-specific profiles, addressing disparities in CNCP experiences [10]. For example, Bäckryd et al. (2018) [27] employed clustering algorithms on psychometric data to define four distinct CNCP profiles, revealing differences in emotional distress and coping strategies often overlooked by traditional diagnostics. Gálvez-Goicuría et al. (2022) [28] applied a "cluster-then-classify" ML model to real-time migraine pain curves, achieving high accuracy by analyzing pain episode dynamics. Santana et al. (2020) [29] demonstrated that combining patient questionnaires with quantitative sensory testing and ensemble

learning algorithms improved diagnostic sensitivity in chronic pain syndromes. These studies illustrate ML's potential to integrate emotional, physiological, and behavioral data for personalized pain management strategies.

ML has transformed medical research by enabling the identification of complex patterns in high-dimensional data, offering a robust approach to pain study categorization [30]. Techniques such as k-means clustering, decision trees, and neural networks have classified patients based on pain severity, treatment response, or associated risk factors [31]. For CNCP, ML provides a data-driven alternative to traditional statistical methods, excelling in thematic categorization, where qualitative data, such as patient narratives, are grouped into meaningful themes [32]. For instance, topic modeling, similar to Latent Dirichlet Allocation, has identified topics like emotional distress or coping strategies within chronic pain interview data [33].

1.4 Gender Roles in CNCP

CNCP, when viewed through a gender lens, reveals layered disparities that extend beyond biological differences. Women are more frequently affected and report greater emotional distress, often influenced by caregiving responsibilities, hormonal fluctuations, and societal expectations around emotional expression [34, 35]. Men, conversely, may under-report pain due to cultural norms of stoicism, leading to delayed diagnosis and undertreatment [34, 36]. These gender roles shape both the perception and communication of pain, with emotional suffering often overlooked in clinical settings.

The socioeconomic impact of CNCP is equally significant. It contributes to reduced workforce participation, increased healthcare costs, and a disproportionate burden on women, who frequently balance employment with unpaid caregiving [35, 36]. These inequities underscore the need for targeted policy briefs that translate scientific evidence into actionable recommendations. Such briefs can guide equitable healthcare strategies, promote gender-sensitive clinical protocols, and ensure that the emotional and social dimensions of pain are integrated into public health planning.

Our multidisciplinary research group, specializing in gender and health, developed the Gender-Pain Questionnaire [37], a novel tool designed to assess the influence of CNCP on gender identity and roles (see Annexes for the full questionnaire). This 10-item questionnaire, validated internally from an initial 15 items, captures patients' perceptions of how chronic pain impacts self-identity, relationships, and work through a gender lens. The development process followed established scale creation protocols outlined by [38], ensuring a robust methodological foundation.

The Gender-Pain Questionnaire addresses a critical gap in the literature by providing a quantitative tool to examine the interplay between chronic pain and gender. Its integration into clinical and research settings has the potential to inform gender-sensitive pain management strategies, contributing to more equitable healthcare interventions. Leveraging data from specific questions captured by the Gender-Pain Questionnaire, can provide valuable information about the distribution of

gender roles and their impact on CNCP patients, informing tailored interventions to address sex-specific disparities.

1.5 CNCP Sex-differences due to Socioeconomic Impact

Pain management practices reveal pharmacological inequities in CNCP. Women are more likely to be prescribed psychotropic medications, such as benzodiazepines, and report poorer drug tolerability, raising concerns about treatment appropriateness [39]. Men, conversely, may receive higher doses of certain analgesics, potentially reflecting assumptions about their pain tolerance or stoic presentation [40]. These patterns highlight a critical issue: conventional CNCP approaches often fail to address sex-specific needs, perpetuating disparities in care and quality of life.

To mitigate these inequities, implementing training programs for healthcare professionals can enhance awareness of sex differences in pain experiences, improving clinical care (Smith & Doe, 2020). Public awareness campaigns can also foster understanding and reduce stigma associated with pain in both women and men [41]. The socioeconomic impact of CNCP underscores the urgency of these interventions. In Spain, CNCP patients are absent from work 40% more frequently (20 days vs. 14 days annually) and 30% less productive (5 hours vs. 7 hours daily) than pain-free peers, with women more likely to report sick leave (2.98% vs. 1.23% for men) and job loss (1.23% vs. 0.58% for men) [3]. Emotionally, 47.6% of CNCP patients experience strained family dynamics, though 77% find solace in family support [3]. These findings suggest that women, who often balance reproductive and domestic roles with employment, face compounded burdens that amplify emotional distress [3].

Effective strategies include incorporating gender-specific criteria into clinical guidelines to ensure personalized and equitable interventions [42]. Policies promoting research on sex and gender interactions in CNCP can facilitate the development of targeted therapies [43]. Additionally, allocating resources for gender-differentiated care programs in health centers can reduce disparities in access and quality of care [44].

This exploration opens avenues for future inquiry. Intersecting factors, such as race, age, or socioeconomic status, may further modulate CNCP disparities, while healthcare provider biases could perpetuate inequities. This thesis builds on existing knowledge and lays a foundation for longitudinal and intersectional studies to refine our understanding of CNCP’s multifaceted impact.

2. Hypothesis and Objectives

2.1 Hypothesis

We hypothesize that sex and gender significantly shape the emotional impact of CNCP, with women experiencing greater emotional distress and men underreporting symptoms due to gender biases in pain reporting, where women are often perceived as “emotional” and men as “stoic” [34, 45]. These disparities, driven by neurobiological mechanisms and sociocultural expectations, result in distinct emotional and psychometric profiles that can be identified through hierarchical clustering and ML techniques, as demonstrated by clustering-based discriminant analysis of CNCP patients into four distinct groups [46]. Furthermore, the unequal emotional burden contributes to broader socioeconomic consequences, including reduced productivity, increased healthcare costs, and disproportionate caregiving responsibilities, particularly among women [3]. Addressing these inequities requires policy briefs that translate findings into actionable, gender-sensitive strategies for healthcare systems and public health planning. Integrating these insights into clinical practice would enable precise, empathetic, and effective pain management tailored to patients’ lived experiences.

2.2 Primary Objective

To explore the emotional impact of CNCP across sexes, integrating a gender-sensitive perspective, by employing hierarchical clustering and ML methods to identify distinct emotional response profiles.

2.3 Secondary Objectives

1. To describe the demographic, clinical, and pharmacological characteristics of the CNCP population, focusing on identifying sex-based differences.
2. To evaluate the broader socio-health and socioeconomic impact of CNCP, considering the interaction between sex and gender roles.
3. To analyze the frequency and distribution of emotional impact categories in CNCP among men and women, using hierarchical clustering and ML thematics, from a gender-informed perspective.
4. To collect evidence that could help shape recommendations for policymakers aimed at informing public health strategies and fostering gender-equitable healthcare policies.

3. Materials and Methods

3.1 Study Design and Participants

This investigation employed a mixed-methods study design conducted at the Pain Unit (PU) of the Alicante Health Department–Dr. Balmis General University Hospital in Spain, a tertiary care facility known for its specialized pain management services. The study enrolled 216 patients diagnosed with CNCP, a condition characterized by persistent or recurring pain lasting beyond three months, excluding pain from malignant origins [3]. Of these participants, 69% were women, reflecting the higher prevalence of CNCP among females observed in prior research [8]. Inclusion criteria stipulated that participants be adults (≥18 years) requiring opioid analgesic treatment and capable of providing signed informed consent, ensuring ethical participation and relevance to the study's focus on opioid-managed CNCP [47]. Exclusion criteria were carefully defined to enhance data integrity: patients with oncologic pain were excluded due to its distinct pathophysiology and treatment paradigms, while those with psychiatric disorders—specifically depression and anxiety severe enough to impair study participation—were omitted to minimize confounding effects on emotional outcome measures [23]. Additionally, chronic pain syndromes with unclear or opioid-resistant mechanisms, such as fibromyalgia, painful polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, and post-stroke pain, were excluded, aligning with clinical guidelines that discourage opioid use in these conditions due to limited efficacy and heightened risk profiles [48]. The study received ethical approval from the hospital's Institutional Review Board, adhering to the Declaration of Helsinki [47].

3.2 Procedure and Data Collection

A consecutive sampling method was utilized to recruit outpatients, a practical approach that ensures representation of the clinic's typical patient flow without randomization bias [49]. Researchers reviewed the PU's appointment schedule weekly, typically on Thursdays, to identify eligible participants, preparing questionnaires and informed consent forms in advance. Eligible patients were briefed by the PU healthcare team about the study's purpose—to explore sex/gender disparities in CNCP's emotional impact—and those expressing interest were approached by research staff for consent, a process adhering to ethical standards outlined in the Declaration of Helsinki [47]. Data collection encompassed both quantitative and qualitative dimensions, capturing a holistic view of participants' experiences. Clinical variables, including an opioid use disorder (OUD) diagnosis per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, were systematically recorded [50]. The DSM-5 framework, with its 11 diagnostic criteria (e.g., tolerance, withdrawal, unsuccessful efforts to cut down), provides a standardized, reliable method for identifying OUD, validated across diverse populations [50]. Where necessary, electronic health records supplemented data collection, offering a robust repository of medical diagnoses, treatment outcomes, and medication histories, thereby enhancing accuracy and completeness [51]. Of all the participants, 203 (142 women and 61 men) completed the Gender-Pain Questionnaire, and 193 had complete data for clustering analysis.

3.3 Clinical Variables

Demographic characteristics were meticulously documented, including age, sex (categorized as women, men, or non-binary, though no non-binary individuals were reported), and employment status (working, retired, work disability, unemployed, or homemaker). These variables provide critical context for understanding CNCP's socioeconomic impact, as employment status often correlates with pain-related disability [3]. Pain assessment relied on the Global Pain State questionnaire, a validated tool designed to evaluate pain intensity, relief, and quality of life during structured interviews [52]. Pain intensity and relief were measured using the Visual Analogue Scale (VAS), a widely adopted instrument consisting of a 100-mm horizontal line where patients mark their perceived pain level (0 = no pain, 100 = worst imaginable) or relief (0 = none, 100 = complete) [53]. The VAS's simplicity and sensitivity to change make it a gold standard in pain research, offering reliable, reproducible results across diverse populations [53].

Quality of life was assessed with the EuroQol-5D-3L (EQ-5D-3L), a comprehensive measure comprising a VAS (0 = worst imaginable health, 100 = best imaginable) and a descriptive system evaluating five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [52]. Each dimension offers three severity levels (no problems, some problems, extreme problems), yielding a health utility score (0 = death, 1 = perfect health) calculated via established algorithms [54]. The EQ-5D-3L's multidimensional approach and cross-cultural validation make it ideal for capturing CNCP's broad impact [54]. The Short Form Health Survey (SF)-12 further evaluated physical and mental health, condensing the SF-36 into a 12-item questionnaire yielding Physical Component Summary and Mental Component Summary scores (0-100, mean 50, SD 10 in the US general population) [55]. Its brevity and strong psychometric properties—demonstrated by high test-retest reliability—suit it for clinical settings with time constraints [55].

Psychological health was quantified using the HADS, a 14-item tool (7 items each for anxiety and depression) scored from 0-21, with thresholds of <7 (negative), 8-10 (doubt), and >11 (case) [23]. Validated for detecting clinically significant distress in medical populations, HADS avoids somatic symptoms that might overlap with CNCP, enhancing specificity [56]. Pain interference was measured with the 30-item Impairment and Functioning Inventory Revised (IDF-R), assessing four domains: Household Activities (11 items), Independent Function (7 items), Leisure Activities (4 items), and Social Activities (5 items) [57]. It generates two scores—Functionality Level (0-108, frequency of activities performed) and Impairment Level (0-27, binary yes/no)—offering a detailed, validated profile of pain's functional impact [57]. Sleep quality was evaluated using the nine-item Medical Outcomes Study Sleep Scale (MOS-SS), a self-administered tool completed in 2-3 minutes, with scores ranging from 0-100 (higher scores indicating worse sleep problems), except for sleep quantity (0-24) and adequacy (0-1) [58]. Its multidimensional structure—covering initiation, maintenance, and perceived adequacy—makes it a robust measure for CNCP-related sleep disturbances [58].

3.4 Pharmacology and Use of Hospital Resources

Pharmacological data included use (yes/no) of simple analgesics (e.g., paracetamol, metamizole), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids (e.g., tramadol, codeine, fentanyl, oxycodone, tapentadol, buprenorphine, morphine, hydromorphone, methadone), including immediate-release formulations [48]. For opioid combinations, the oral morphine equivalent daily dose (MEDD, mg/day) was calculated using standardized conversion factors, ensuring comparability across regimens [48]. This method, endorsed by international pain management consensus, accounts for potency differences, facilitating precise dosing analysis [48]. Adverse events were documented via a checklist of common analgesic side effects like nausea, constipation, dizziness, from product summaries, with an open field for additional reports, aligning with pharmacovigilance standards [59]. Healthcare utilization—hospital admissions, Attendance and Emergency visits, and prescription changes due to pain or other causes—was tracked, reflecting resource demands [60] . Diagnostic delay, the time from initial pain diagnosis to PU referral, was categorized (<1 year, 1-2 years, 2-5 years, >5 years), providing insight into care access disparities [60].

Spain's universal, free healthcare system contextualizes these data, though pharmaceutical copayments, introduced under Royal Decree Law 16/2012, vary: 40% for workers, 10% for chronically ill or HIV patients, and 0% for pensioners, disabled individuals, or those with work-related illnesses [60]. A 40% copayment threshold for incomes classified patients as low or high copayment, influencing medication adherence and outcomes [60].

3.5 Quantitative and Qualitative Gender Information

All participants self-identified as cisgender (women or men), with no non-binary individuals reported, and were assigned consecutive numbers for anonymity. Three trained interviewers conducted face-to-face interviews lasting 30-45 minutes, a duration balancing depth and participant burden [61]. The Gender-Pain Questionnaire underwent rigorous internal validation as part of a study involving 192 Spanish ambulatory CNCP patients, conducted at the Dr. Balmis General University Hospital in Alicante, Spain, from September 2020 to March 2022. Exploratory Factor Analysis identified a three-factor structure—Gender Self-Identity, Roles, and Chronic Pain Impact on Social, Familiar, Work, and Sexual Life. Internal consistency was evaluated using Cronbach's α and McDonald's ω, with values ranging from 0.63 to 0.74 across the factors, indicating acceptable to moderate reliability. These psychometric properties establish the Gender-Pain Questionnaire as a reliable and valid instrument for assessing gender-related impacts of CNCP within the studied population.

Currently, the Gender-Pain Questionnaire is in the process of external validation to further substantiate its applicability across diverse populations and settings. This ongoing effort aims to enhance the generalizability of the instrument, addressing limitations noted in the original study, such as the predominantly Caucasian, middle-aged, and cisgender sample. External validation will also explore the questionnaire's utility in capturing non-binary gender identities and additional sociocultural factors, thereby strengthening its relevance in global health research and clinical practice.

3.5. Emotional Impact Classification

A focused expert panel was convened to classify the emotional impact of CNCP. The group included four professionals (two women, two men), all recognized experts in pain: a tenured professor in clinical pharmacology, a predoctoral researcher in anesthesiology, and two pharmacy specialists—one holding a doctorate in bioengineering. Together, they conducted a qualitative analysis to group the emotional profiles of patients based on multidisciplinary insights.

Subsequently, a final classification was refined by a second expert team from the Miguel Hernández University, composed of two researchers in social psychology—a tenured female professor and a male predoctoral researcher. This second round added a psychosocial dimension to the categorization, reinforcing the gender-informed perspective of the emotional analysis.

3.6 Hierarchical Clustering Review

3.6.1 Overview of Hierarchical Clustering

Hierarchical clustering organizes similar entities, such as patients or data points, into groups based on shared characteristics, creating a tree-like structure or dendrograms that visually shows how groups are organised [62]. This method is widely used in medical research, particularly for CNCP, to identify distinct patient subgroups. For example, Alter et al. [11] used hierarchical clustering to group CNCP patients by pain intensity and anxiety levels, uncovering undiagnosed fibromyalgia subgroups.

Clustering usually operates in two forms: agglomerative and divisive. Agglomerative clustering starts with each entity as its own group and merges the most similar pairs into larger clusters, building the dendrogram from the bottom up. Divisive clustering begins with all entities in one group and splits them into smaller, less similar clusters, forming the dendrogram from the top down (**Figure 3**) [63, 64]. Similarity between entities and clusters is determined by linkage methods.

Common linkage methods include single linkage, which uses the closest pair of points between clusters, often creating elongated groups; complete linkage, which uses the farthest pair, forming compact clusters that reduce the impact of unusual pain reports in CNCP data; and average linkage , which calculates the average distance between all pairs, balancing cluster shapes [62, 63]. Ward's method aims to create uniform clusters by merging groups to keep data points as close as possible within each cluster, making it effective for identifying clear CNCP patient profiles, though it requires careful data preparation for mixed datasets like pain scores and categorical variables such as sex [65].

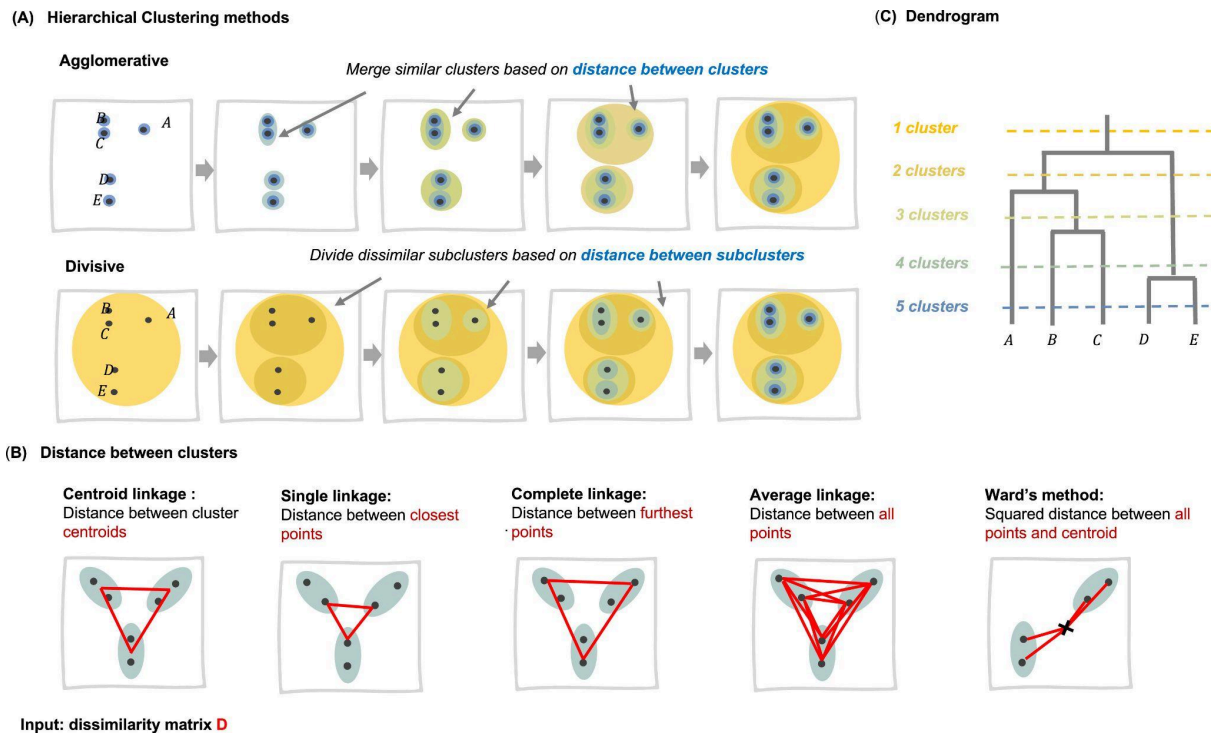


Figure 3. Hierarchical Clustering. (A) Agglomerative and divisive methods. (B) Distance between subclusters (linkage methods): centroid linkage, single linkage, complete linkage, average linkage and Ward's method. (C) Dendrogram generated after clustering allows users to slice the hierarchical structure into any number of clusters [63] .

3.6.2 Data Preparation for Clustering

Effective hierarchical clustering in CNCP research requires careful data preparation to manage the complexity of pain-related datasets, which often combine numeric and categorical variables. Key steps include **filtering**, **zero handling**, and **standardization**. Filtering removes incomplete data, such as missing pain scores or demographic details, to ensure reliable clustering results [66]. Missing data, common in CNCP studies, can skew groupings if not addressed properly. Zero handling addresses cases where certain variables, like rare pain impact categories, have no occurrences, often by adding a small value to avoid calculation issues [62] . Standardization adjusts numeric variables, such as pain intensity scores (0–10), to a common scale so that variables with larger ranges do not overly influence the clustering process. This is critical for CNCP datasets that include both numeric measures, like emotional scores, and categorical variables, like employment status, to ensure balanced analysis [65]. We also checked results with and without outliers removal and opted for no removal for two reasons not losing valuable data that could change the structure of the dendrogram -especially high frequencies impact- and using the ward D2 method that works well with outliers

3.6.3 Distance Metrics in Clustering

Distance metrics define how similarity is measured between entities in clustering, significantly affecting the results. Two key metrics in CNCP research are Euclidean distance and Gower's distance, each suited to different data types. Euclidean distance measures the straight-line distance between data points, making it suitable for numeric variables like pain scores. It works best when data is standardized to prevent variables with larger ranges, such as frequency counts, from dominating the results [62]. However, it struggles with mixed datasets that include categorical variables like pain impact assessment questionnaires, often requiring preprocessing to convert categories into numeric formats.

Gower's distance is designed for mixed datasets, making it ideal for CNCP studies that combine numeric (e.g., pain intensity) and categorical (e.g., sex) variables. It measures similarity by comparing numeric variables on a normalized scale and assigning matches or mismatches for categorical variables, producing a score that reflects overall dissimilarity. This approach ensures that diverse CNCP variables contribute equally to clustering without needing complex preprocessing. Gower's distance also allows researchers to assign different weights to variables, such as emphasizing pain-related factors over demographics, though care must be taken to avoid unintended bias [64]. For example, in CNCP research, Gower's distance can equitably handle variables like emotional scores and gender, improving the identification of patient subgroups [65].

3.6.4 Evaluating Clustering and Determining the Optimal Number of Clusters

Evaluating the quality of clustering ensures that the resulting groups are meaningful, especially for CNCP's complex datasets. Common evaluation methods assess how well-separated and cohesive the clusters are. **The Silhouette Score** measures how similar each data point is to its own cluster compared to others, with higher scores indicating well-defined clusters. **The Dunn Index** evaluates how far apart clusters are relative to their internal spread, where larger values suggest better separation. **The Davies-Bouldin Index** (DBI) compares the similarity between clusters, with lower values indicating clearer distinctions [66]. These methods are adaptable to mixed datasets using Gower's distance, ensuring robust evaluation of CNCP clusters, such as those separating male and female patients [65].

3.6.4.1 Silhouette Score

Determining the optimal number of clusters is a critical step, achievable before or after clustering. Before clustering, the gap statistic compares the compactness of clusters to a random distribution, selecting the number that maximizes this difference. After clustering, the elbow method examines a plot of cluster tightness against the number of clusters, identifying a point where adding more clusters offers little improvement. Dendrogram analysis involves visually inspecting the tree diagram for significant changes in cluster connections to choose the best number of groups [62]. These approaches help ensure that CNCP clusters, such as those reflecting distinct emotional or pain profiles by sex, are both statistically sound and clinically meaningful.

3.6.4.2 The Dunn Index

The Dunn Index was selected as an evaluation parameter for clustering CNCP data due to its ability to assess the compactness and separation of clusters by calculating the ratio of the minimum inter-cluster distance to the maximum intra-cluster diameter [67]. This metric is particularly valuable for identifying well-defined clusters, which is crucial when analyzing sex-specific emotional and functional impacts in CNCP patients. Its sensitivity to cluster separation ensures that distinct gender-related patterns, such as women's broader emotional burdens versus men's work-focused limitations, are reliably captured, supporting the development of targeted clinical interventions.

3.6.4.3 The Davies-Bouldin Index

The DBI was chosen as an evaluation parameter for clustering CNCP data because it measures the average similarity ratio between each cluster and its most similar cluster, based on intra-cluster scatter and inter-cluster separation, with lower values indicating better-defined clusters [68]. This index is ideal for validating the heterogeneity of emotional impact categories across sexes, ensuring that clusters reflecting men's stoicism or women's relational strains are distinct and interpretable. Its focus on minimizing within-cluster variation aligns with the need for precise segmentation to inform gender-sensitive pain management strategies.

3.6.4.4 Rationale for Using Silhouette Score, Dunn Index, and DBI Together

The Silhouette Score, Dunn Index, and DBI are used together to provide a comprehensive evaluation of CNCP clustering by combining complementary perspectives on cluster quality [62]. The Silhouette Score assesses overall cohesion and separation, the Dunn Index emphasizes inter-cluster separation and compactness, and the DBI focuses on the balance of intra-cluster scatter and inter-cluster distinctness. This triad ensures robust validation of sex-specific clusters, such as those highlighting women's emotional toll or men's functional losses, enhancing the reliability of findings for clinical and public health applications in a gender-informed context.

3.6.5. Application to CNCP Research

Hierarchical clustering, whether using Euclidean or Gower's distance, offers a powerful framework for CNCP research, particularly when focusing on sex and gender as central factors. Euclidean distance clustering, paired with Ward.D2, is effective for standardized numeric data (like emotional and physical impact frequencies), forming compact clusters that highlight CNCP patterns. Gower's distance clustering, however, excels with mixed CNCP datasets, integrating diverse variables like impact categories. By applying different weights to certain variables like frequency data over categories to achieve the best clustering quality, Gower's distance ensures clinically relevant patterns are captured, revealing distinct male and female emotional profiles. The resulting clusters can be evaluated using metrics like the Silhouette Score, Dunn Index, and DBI, with the optimal number of clusters determined as the configuration achieving the best scores for the chosen parametrics, ensuring robust and meaningful groupings to inform sex-specific pain management strategies.

3.7 Machine Learning (ML)

In this thesis, ML was applied to complement hierarchical clustering in categorizing the emotional impact of CNCP. The process began with the analysis of qualitative data derived from interviews conducted using Questionnaires. Due to the absence of predefined rules for generating indicators and categories, a comprehensive literature review was conducted, grounded in the state-of-the-art, to inform the categorization framework [69]. This review guided the restructuring of the initial categorization proposed by a team of psychologists, organizing categories into a hierarchical framework of main categories and subcategories (**Figure 4**). Redundant or overlapping themes were consolidated to enhance clarity and coherence, addressing the lack of explicit definitions and ensuring the framework was theoretically robust and clinically relevant [70].

The qualitative data, sourced from datasets, were preprocessed to prepare them for analysis by a custom-developed Large Language Model (LLM) tailored specifically for this project. The LLM was designed to process the restructured categorization framework, enabling the identification of patterns and themes within the interview data [71]). Supervised ML methods, such as support vector machines, have been used elsewhere to predict pain outcomes using labeled data (e.g., HADS scores), while unsupervised methods like hierarchical clustering paired with ML refine subgroup discovery without predefined categories [31, 72]. These approaches align well with metrics like Gower's distance for clustering mixed data types [73]. In mental health research, ML has successfully categorized depression subtypes, revealing sex-specific patterns, such as women's higher prevalence of somatic symptoms, which parallel the emotional impact observed in CNCP [74]. Despite these strengths, ML approaches face challenges, including the risk of overfitting and difficulties in interpretability, necessitating robust validation against clinical benchmarks [75].

The application of ML in this study enhances the precision of categorizing CNCP's emotional impact, particularly in identifying sex- and gender-specific patterns. By integrating qualitative insights from the Gender-Pain Questionnaire with advanced computational techniques, this approach contributes to a nuanced understanding of how chronic pain affects patients' daily lives, relationships, and self-identity [10]. Ongoing refinements to the LLM and categorization framework will further strengthen its utility, paving the way for more equitable and tailored pain management strategies [3].

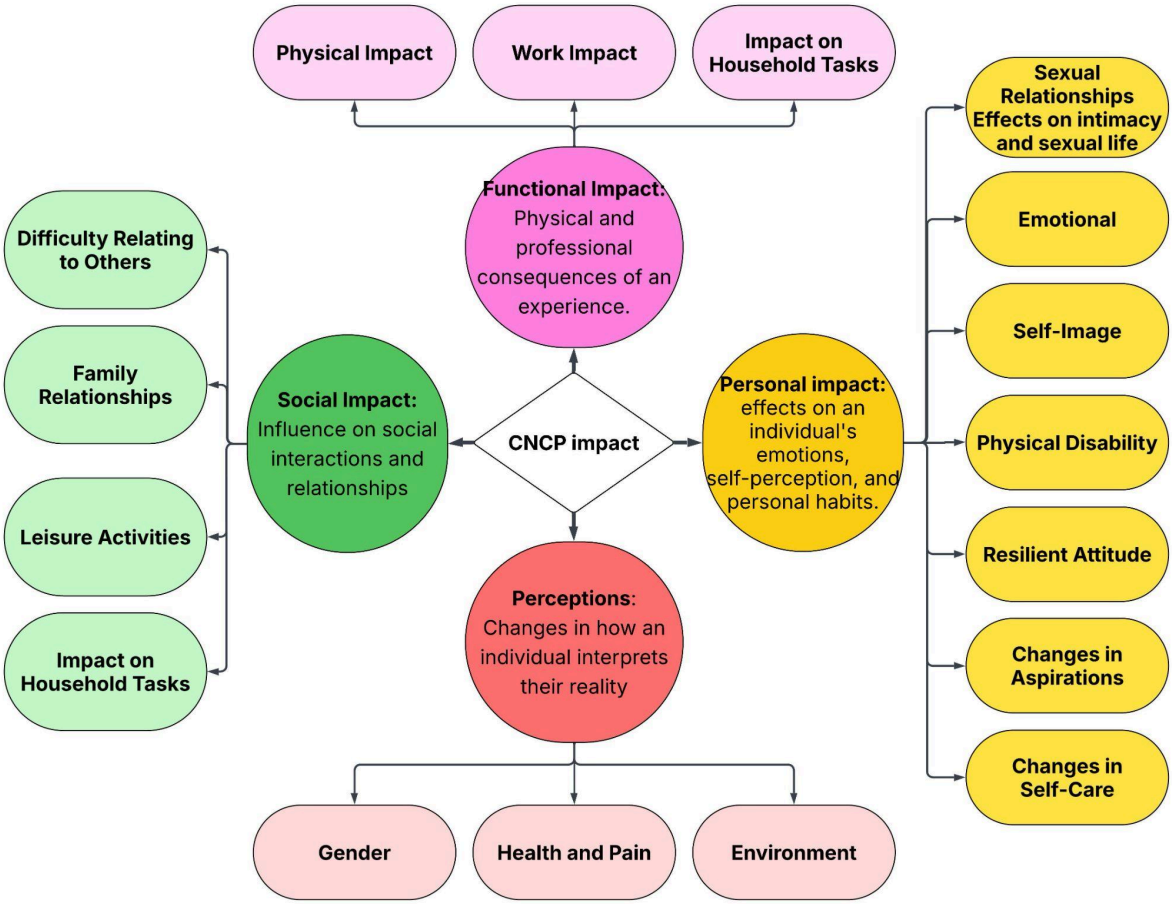


Figure 4. Machine learning thematic categorisation (showing categories and subcategories) for chronic non-cancer pain impact (personal scheme, Lucidspark flowchart).

3.8 Statistical Data Analysis

3.8.1. Statistical Analysis

The statistical methodology commenced with an assessment of data distribution using the Shapiro-Wilk test to determine normality, a robust method suitable for small to medium sample sizes [76]. Parametric data, assumed to follow a normal distribution, were summarized as mean ± standard deviation (SD) to provide a measure of central tendency and dispersion [76]. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests [77]. Non-parametric data, indicative of skewed distributions, were reported as median [interquartile range, IQR] to capture the central 50% of data variability [78]. Categorical variables, such as gender or role categories, were presented as percentages to reflect proportional representations within the study population [79]. Between-group comparisons were conducted using the t-test with Welch's correction to account for unequal variances in continuous parametric data, the Mann-Whitney U test for non-parametric continuous data, and Fisher's Exact test for categorical data with small expected frequencies, ensuring appropriate statistical power [80]. All analyses were performed using GraphPad Prism

(version 8.0.2), a validated software for biomedical research, with results interpreted at a significance level of $p < 0.05$ [87].

3.8.2 Gender Role Analysis

To investigate gender role differences, a suite of statistical tests was employed. The two-proportion z-test compared the prevalence of specific roles, such as the Productive Role, testing the null hypothesis implemented using R's prop.test() function with continuity correction for improved accuracy [82]. Additionally, the Chi-square test of independence evaluated the association between gender and role reporting, executed with R's chisq.test() function, with validity ensured by verifying that all expected cell counts were ≥5, adhering to Cochran's 1954 [83] guideline to maintain test reliability.

3.8.3 Clustering and Machine Learning Categorization

Data preparation was a foundational step to enable robust clustering and ML-based categorization. The process included filtering to remove rows with missing values, preserving data integrity by excluding incomplete records [66], handling zero frequency values by adding a small constant (1e-6) to prevent computational errors in distance calculations [31], and standardizing variables using z-score scaling via R's scale() function to normalize data across diverse measurement scales like pain scores vs. frequency counts [84]. The dataset, comprising mixed data types—categorical (categories, subcategories, observations) and numerical (frequencies)—was prepared for Gower distance computation to facilitate clustering by similarity, a method well-suited for heterogeneous data [73]. Clustering was performed separately for men and women to elucidate sex-specific emotional impact patterns, aligning with the study's gender-informed focus.

3.8.3.1. Hierarchical Clustering: The Ward.D2 method, which minimizes within-cluster variance, was applied using R's hclust() function to group impact categories based on frequency data [72, 85]. Clustering quality was assessed using the Silhouette Score (>0.5 indicating strong cohesion), Dunn Index (higher values reflecting better separation between clusters), and DBI (<1 indicating compact and well-separated clusters), calculated with established statistical packages and validated against theoretical benchmarks [63, 68, 86]. The optimal number of clusters (k) was determined by maximizing these metrics while ensuring practical interpretability, guided by visual and statistical evaluation.

3.8.3.2.1. Ward.D2 Distance Clustering: This approach utilized standardized emotional and physical impact frequencies, with clustering evaluated across k = 2 to 5. Quality metrics (Silhouette and Dunn Index) were computed using the cluster.stats function from the fpc package, while a custom function adapted the DBI to assess cluster compactness, drawing on prior methodologies [87].

3.8.3.2.2. Gower's Distance Clustering: This method integrated impact categories (Functional, Personal, Social, Perception) derived from a ML model, with distances calculated using the daisy() function to handle mixed data types. A weighting scheme of 1:1:1:2:2

(category:subcategory:observation:men's frequency:women's frequency) was applied to prioritize frequency data, reflecting the study's emphasis on sex-specific patterns. Clustering was assessed for k = 2 to 6 using Silhouette Score, Dunn Index, and an adapted DBI, with multiple weight combinations tested. The final configuration was selected based on optimized clustering performance, validated through iterative comparison of internal validity indices [73, 88].

4. Results

4.1 Demographic, Clinical, and Pharmacological Characteristics of the Study Population, Analyzing Sex-based Differences

The study included 216 patients with CNCP (**Table 1**), of whom 70% were women. The median age was 62 years [52–73], with women significantly older than men (66 [54–76] vs. 56 [49–69] years; *p*=0.002) (**Figure 5A**). Employment status differed significantly between genders (*p*=0.001): 39% of women vs. 33% of men were retired; 21% of women were homemakers compared to 0% of men; and 31% of women vs. 21% of men were on work disability (**Figure 5B**). Additionally, 76% of participants had low or no medication copayment (<40%), as defined by Spanish healthcare legislation.

Table 1. Sociodemographic characteristics of the Chronic Non-Cancer Pain patients by sex.

Med[IQR], n (%)	Total (n = 216)	Women (n = 151)	Men (n = 65)	p-value
Age	62 [52-73]	66 [54-76]**	56 [49-69]	0.002
Copayment				
<40	165 (76)	115 (76)	50 (77)	0.712
40	36 (17)	24 (16)	12 (19)	
>40	14 (7)	11 (7)	3 (5)	
NA	1 (1)	0	1 (1)	-
Income (€/month)				
<500	19 (9)	15 (10)	4 (6)	0.312
500-1000	101 (47)	75 (50)	26 (40)	
>1000	81 (38)	53 (35)	28 (43)	
NA	15 (7)	8 (5)	7 (11)	-
Employment status				
Active	37 (17)	25 (17)	12 (19)	0.001
Unemployed	12 (6)	8 (5)	4 (6)	
Retired	74 (34)	49 (33)	25 (39)	
Homemaker	31 (14)	31 (21)****	0	
Disability	52 (24)	32 (21)	20 (31)	
NA	10 (5)	6 (4)	0	-
Adverse events reported	2 [1-5]	3 [1-5]	2 [1-3]	0.098
Diagnostic delay				
3-12 months	53 (25)	35 (23)	18 (28)	0.549
12-24 months	36 (17)	23 (15)	13 (20)	
24 months-5 years	38 (18)	26 (17)	12 (19)	
More than 5 years	88 (41)	66 (44)	22 (34)	
NA	1 (1)	1 (1)	0	-

Med[IQR]: Median [Interquartile range]; NA: Not available.

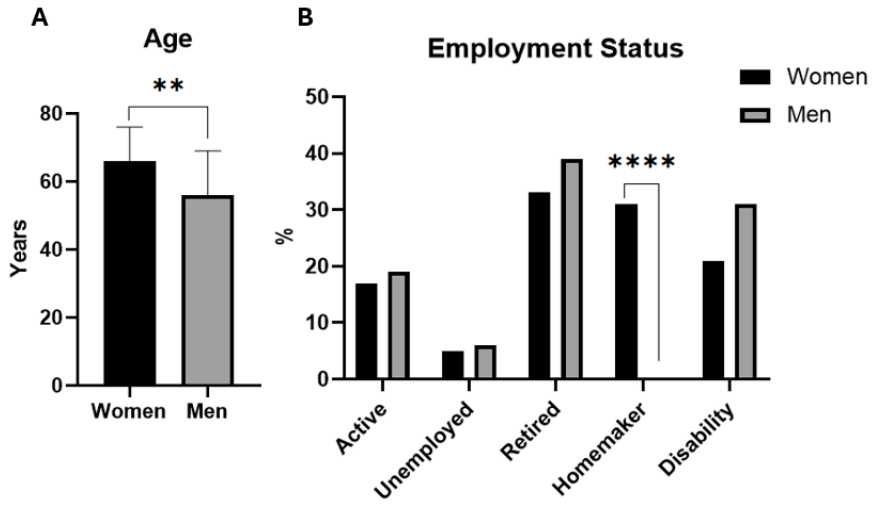


Figure 5. (A) Age and (B) employment disparities by sex in Chronic Non-Cancer Pain.

Clinical variables were generally similar across participants (**Table 2**). Pain intensity was severe (80 mm [50–90]) and pain relief was mild (40 mm [0–60]), as measured by the VAS. This was associated with a moderate perceived quality of life (50 mm [30–66]) and a health utility score of 0.254 [0.051–0.576]. Most participants were classified as non-cases for anxiety and depression according to the HADS, and reported similar levels of sleep disturbances.

Table 2. Clinical characteristics of the Chronic Non-Cancer Pain patients by sex.

Mean (SD), Med[IQR], n (%)	**Total (n = 216)**	**Women (n = 151)**	**Men (n = 65)**	**p-value**
Pain intensity (0-100mm)	80 [50-90]	80 [50-90]	80 [60-90]	0.773
Relief (0-100 mm)	40 [0-60]	42.5 [0-60]	30 [0-50]	0.113
Quality of Life (0-100 mm)	50 [30-66]	50 [30-60]	50 [30-70]	0.355
Health Utility Status (0-1)	0.254 [0.051-0.576]	0.247 [0.051-0.604]	0.256 [0.051-0.576]	0.611
SF 12 (0-100 scores)				
Physical health	26 [22-31]	26 [23-31]	25 [22-33]	0.767
Mental health	40 [32-51]	39 [32-50]	47 [34-56]	0.055
Sleep (MOS-SS, 0-100 scores)				
SLP6	40 [23-60]	40 [23-60]	40 [24-56]	0.827
SLP9	42 (22)	42 (21)	41 (22)	0.674
Anxiety (HADS, 0-21)	7 [5-11]	8 [5-11]	6 [4-9]	0.064
No case	83 (38)	55 (36)	28 (43)	0.139
Probable case	33 (15)	26 (17)	7 (11)	
Case	47 (22)	38 (25)	9 (14)	

NA	53 (25)	32 (21)	21 (32)	-
Depression (HADS, 0-21)	7 [4-10]	7 [4-10]	7 [3-10]	0.564
No case	98 (45)	70 (46)	28 (43)	
Probable case	30 (14)	25 (17)	5 (8)	0.351
Case	35 (16)	24 (16)	11 (17)	
NA	53 (25)	32 (21)	21 (32)	-
DSM-5 (TCOP) (%)	25 (12)	17 (11)	8 (12)	0.820

SD: Standard deviation; Med[IQR]: Median [Interquartile range]; SF12: Short Form Health Survey12; MOS-SS: Medical Outcomes Study Sleep Scale; SLP6: Sleep Problems Index I; SLP9: Sleep Problems Index II; HADS: Hospital Anxiety and Depression Scale; NA: Not available; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Pharmacological data are summarized in **Table 3**. All participants were prescribed opioid analgesics, with a median oral MEDD of 48 mg/day [20–81]. Notably, morphine was prescribed more frequently to men than to women (6% vs. 1%; p=0.03) (**Figure 6A**). Approximately half of the patients received additional coadjuvant medications, including neuromodulators and non-opioid analgesics. Among these, the use of antidepressants was significantly higher in women compared to men (59% vs. 38%; p=0.007) (**Figure 6B**).

Table 3. Pharmacological characteristics of the Chronic Non-Cancer Pain patients by sex.

Med[IQR], n (%)	**Total (n = 216)**	**Women (n = 151)**	**Men (n = 65)**	**p-value**
MEDD (mg/day)	48 [20-81]	60 [20-80]	40 [20-97]	0.481
Main Opioid				
Tramadol	64 (30)	43 (29)	22 (34)	0.425
Tapentadol	32 (15)	22 (15)	10 (15)	0.838
Buprenorphine	30 (14)	19 (13)	11 (17)	0.398
Fentanyl	28 (13)	24 (16)	4 (6)	0.075
Oxycodone	17 (8)	15 (10)	2 (3)	0.103
Morphine	5 (2)	1 (1)	4 (6)*	0.030
Pain co-adjuvants				
Analgesics	112 (52)	83 (55)	29 (45)	0.140
NSAIDs	107 (50)	35 (23)	10 (15)	0.206
Neuromodulators	117 (54)	76 (50)	41 (63)	0.135
Antidepressants	95 (44)	57 (38)	38 (59)**	0.007
Anxiolytics	45 (21)	76 (50)	31 (48)	0.766

Med[IQR]: Median [Interquartile range]; MEDD: Morphine Equivalent Daily Dose.

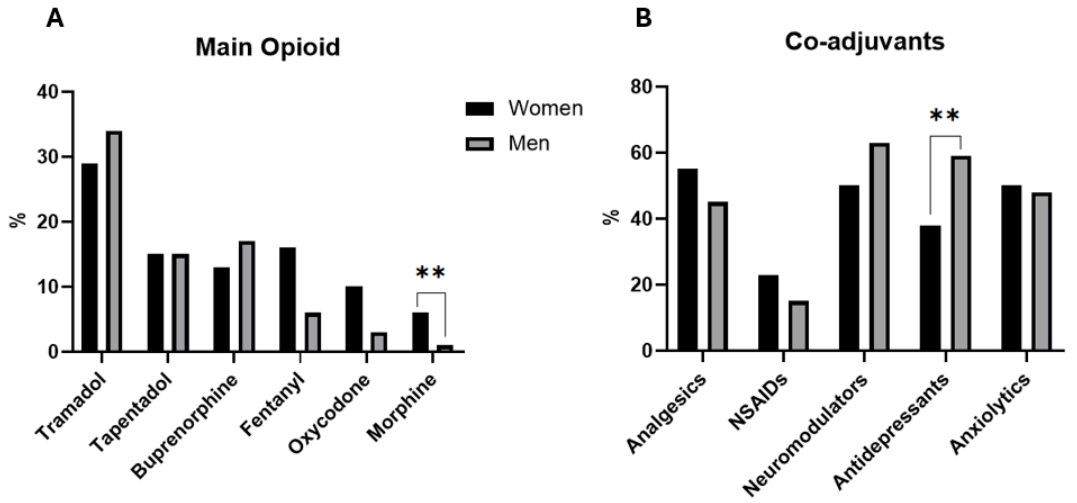


Figure 6. Pharmacological disparities in Chronic Non-Cancer Pain. (A) Opioid prescription. (B) Co-adjuvants prescription.

4.2 Socio-Health and Socioeconomic Impacts of CNCP with Respect to Sex and Gender Roles

The study assessed gender roles reporting among 203 respondents (142 women and 61 men), focusing on three role categories: the Productive Role (work-related tasks), the Reproductive Role (family and partner relationships), and Mixed Roles (a combination of productive and reproductive responsibilities). The distribution of these roles by gender is illustrated in **Figure 7**.

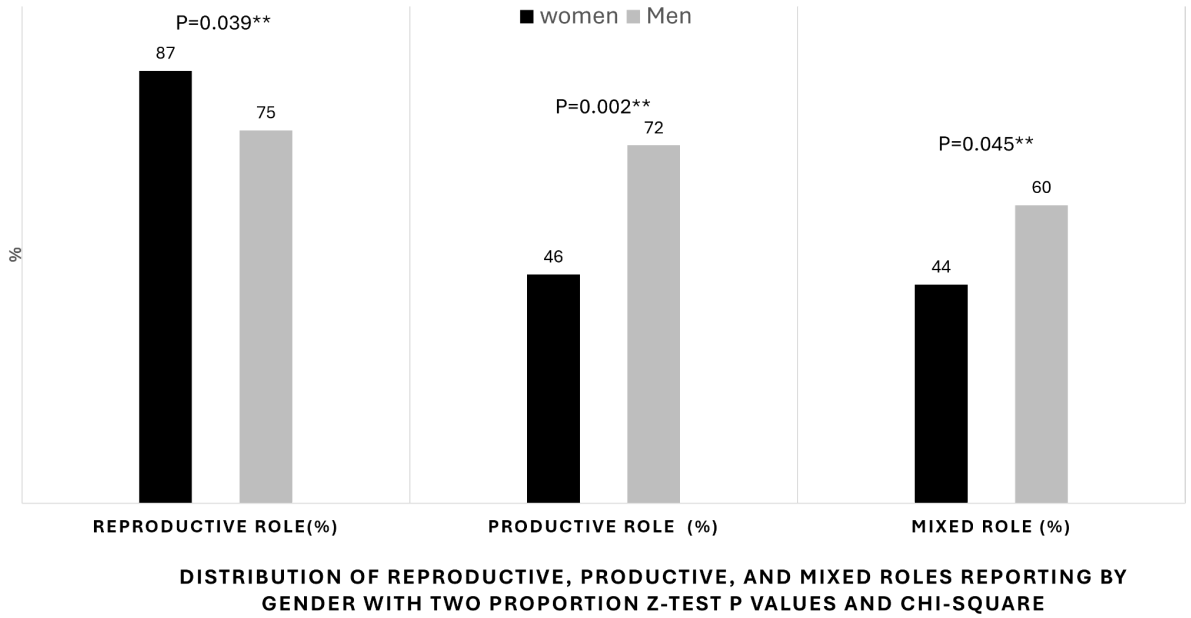


Figure 7. Distribution of Reproductive, Productive and mixed Roles in the study population by gender, with two proportion Z-test P-values and Chi-square.

4.3 Frequency of Emotional Impact Categories Related to CNCP among Men and Women

4.3.1 Hierarchical Clustering using Frequencies Euclidean Distance and Ward.D2

Selection of Number of Clusters (k)

The optimal number of clusters was determined by evaluating k values from 2 to 5 for both men and women, using the Silhouette Score, Dunn Index, and DBI). The results for each k value are summarized in **Tables 4 and 5**.

Table 4 . Clustering Quality Metrics for Women (Euclidean Distance, Ward.D2, k = 2 to 5).

Number of clusters (k)	Silhouette Score	Dunn Index	Davies-Bouldin Index	Cluster Sizes
2	0.6497247	0.03448276	0.5275318	29, 48
3	**0.7003837**	**0.07142857**	**0.4587806**	**20, 48, 9**
4	0.6656903	0.07692308	0.4562476	9, 48, 11, 9
5	0.678172	0.1428571	0.4288365	9, 48, 11, 5, 4

Table 5. Clustering Quality Metrics for Men (Euclidean Distance, Ward.D2, k = 2 to 5).

Number of clusters (K)	Silhouette Score	Dunn Index	Davies-Bouldin Index	Cluster Sizes
2	0.7269738	0.1428571	0.3327752	15, 62
3	**0.7277458**	**0.1428571**	**0.404689**	**15, 46, 16**
4	0.6896573	0.25	0.5152632	7, 46, 16, 8
5	0.6507579	0.25	0.5396756	7, 46, 9, 7, 8

The final clusters for women and men at k = 3 were extracted, and the categories assigned to each cluster are listed below (**Table 6**, **Figures 8** and **9**) with frequencies. This analysis revealed that the heterogeneity could be analyzed in three clusters identified to best describe the patients.

Table 6. Clustering results using frequencies Euclidean distance and Ward.D2.

	Women	Men
Cluster 1	**Physical limitations and emotional effects**	**Physical and emotional impacts**
Frequency	301	151
Categories	Limitation in traveling (115), Physical disability (51), Physical dependence (34), Low self-esteem (24), Abandonment of work (17), Negative self-concept (17), Anger (15), Decrease in sexual desire (14), Sexual pain (14), Decrease in activities with friends (13), Body changes (12), Discouragement (10), Pessimism (9), Decrease in family activities (8), Sexual disability (8), Change in personality (7), Frustration (7), Longing (6), Burden (2), Disinterest in leisure activities (1).	Limitation in leisure activities (15), Decrease in sexual desire (14), Decrease in family relationships (12), Inability for household tasks (12), Sadness (12), Decrease in social life (11), Physical dependence (11), Uselessness (11), Abandonment of work (10), Decrease in family activities (10), Anger (10), Physical disability (10), Low self-esteem (9), Sexual pain (4).
Cluster 2	**Emotional and psychological impacts**	**Emotional and social impacts**
Frequency	206	62

Categories	Family abandonment (35), Clumsiness (31), Insecurity (24), Inactivity (15), Quality of life (13), Limitation (12), Truncated life (10), Loss of enthusiasm (9), Argument (8), Anguish (6), Limitation of future plans (5), Neglect (5), Desolation (4), Decrease in activity (4), Divorce (4), Fear (4), Partner separation (4), Inability to do sports (3), Limitation in doing sports (3), Need for help with household tasks (3), Anxiety (2), Cowardice (2), Guilt (2), Weakness (2), Exhaustion (2), Aggressiveness (2), Job loss (2), Pretending well-being (2), Vulnerability (2), Daze (1), Pleasing others (1), Desperation (1), Hopelessness (1), Inability for leisure activities (1), Indifference from surroundings (1), Worry (1), Use of sexual companionship services (1).	Limitation (34), Divorce (5), Economic impact (2), Insecurity (2), Loss of enthusiasm (2), Pessimism (2), Family abandonment (1), Anxiety (1), Antipathy (1), Change in personality (1), Fatigue (1), Cowardice (1), Argument (1), Inactivity (1), Job uncertainty (1), Limitation in traveling (1), Nervousness (1), Job loss (1), Worry (1), Clumsiness (1), Use of sexual companionship services (1).
Cluster 3	**Personal and relational loss**	**Personal and Relational loss**
Frequency	168	48
Categories	Inability for household tasks (31), Sadness (31), Decrease in family relationships (26), Uselessness (24), Lack of understanding from surroundings (23), Decrease in social life (22), Neglecting personal care (11).	Limitation in doing sports (7), Negative self-concept (6), Absence of future plans (5), Hopelessness (5), Decrease in activities with friends (5), Partner separation (5), Weakness (4), Desolation (4), Sexual disability (4), Erectile dysfunction (3).

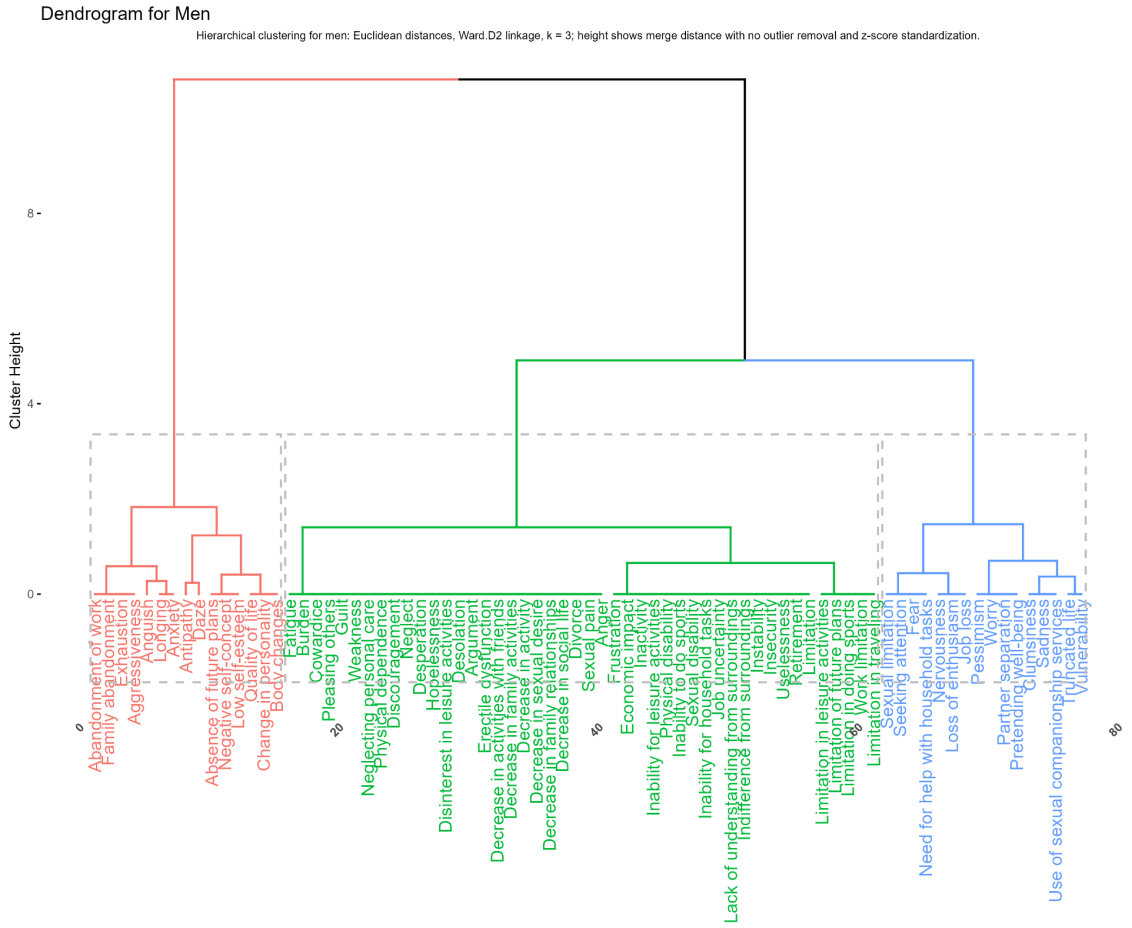
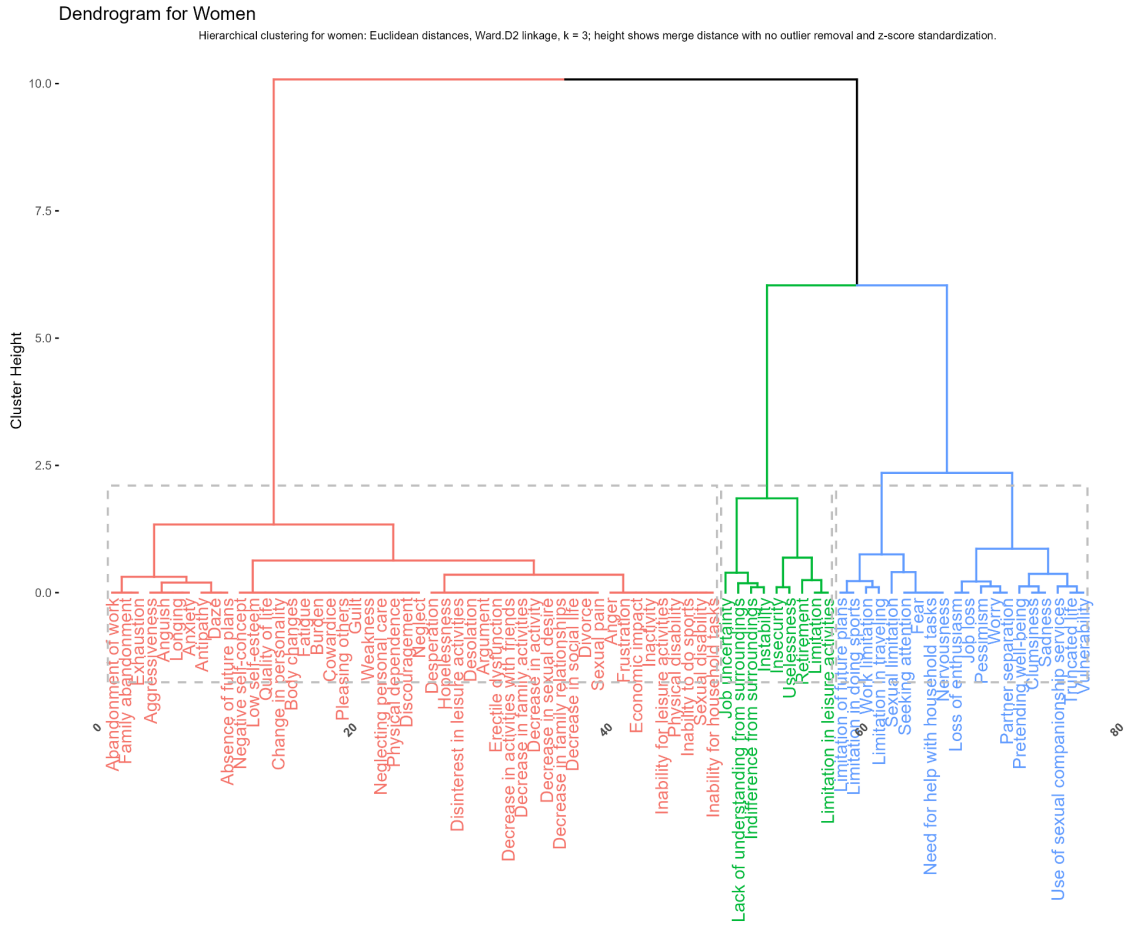


Figure 8. Dendrogram for men's hierarchical clustering euclidean distance Ward.D2, z score standardization and no outliers removal.

Figure 9. Dendrogram for women's hierarchical clustering euclidean distance Ward.D2, z score standardization and no outliers removal.



4.3.2 Hierarchical Clustering using Frequencies and ML Categorisation with Gower's Distance and Ward.D2 Method

Hierarchical clustering was performed on the dataset using Gower's [73] distance to handle the mixed data types (Categories, Subcategories, Observations, and Frequencies for men and women) and the Ward.D2 linkage method [89] to minimize within-cluster variance. The clustering was conducted separately for men and women to identify gender-specific patterns in emotional and physical impacts related to pain [90]. To balance the influence of variables, weights were assigned as 1:1:1:2:2 for Categories, Subcategories, Observations, Frequencies of men, and Frequencies of women, respectively. The optimal number of clusters (k) was determined by evaluating a range of k values and selecting the one that maximized clustering quality metrics.

Weight Optimization

Multiple weight combinations were tested to determine the optimal balance between categorical and numerical variables. The combinations included:

- Equal weights (1:1:1:1:1), giving equal importance to all variables.
- Categorical-heavy weights (2:2:2:1:1), prioritizing Categories, Subcategories, and Observations.
- Frequency-heavy weights (1:1:1:2:2), emphasizing Frequencies of men and women.

The equal weights (1:1:1:1:1) resulted in balanced but less cohesive clusters, with lower Silhouette Scores due to under-emphasizing frequency differences. The categorical-heavy weights (2:2:2:1:1) over-emphasized categorical variables, reducing the impact of frequency variations and leading to lower Dunn Indices, indicating poor inter-cluster separation. The frequency-heavy weights (1:1:1:2:2) improved Silhouette Scores and DBI by prioritizing frequency patterns while maintaining the influence of categorical variables, achieving the best overall clustering quality. Consequently, the weight combination of 1:1:1:2:2 was selected for the final clustering.

Selection of Number of Clusters (k)

The optimal number of clusters was determined by evaluating k values ranging from 2 to 6 for both men and women, using three clustering quality metrics: Silhouette Score [86] (Rousseeuw 1987), Dunn Index [67] (Dunn 1974), and DBI [68] (Davies 1979) (**Tables 7 and 8**).

Table 7. Clustering quality metrics for women (Gower's Distance, Ward.D2, k = 2 to 6).

Number of clusters (K)	Silhouette Score	Dunn Index	Davies-Bouldin Index	Cluster Sizes
2	0.3065	0.3125	1.2456	29, 48
3	0.3065	0.3567	1.0987	20, 48, 9
4	**0.3876**	**0.3892**	**0.9876**	**9, 48, 11, 9**
5	0.4006	0.4182	0.9377	7, 47, 2, 16, 7
6	0.3954	0.4012	0.9567	7, 45, 2, 16, 7, 2

Table 8. Clustering quality metrics for men (Gower's Distance, Ward.D2, k = 2 to 6).

Number of clusters (K)	Silhouette Score	Dunn Index	Davies-Bouldin Index	Cluster Sizes
2	0.2987	0.2876	1.2987	15, 62
3	0.3345	0.3012	1.1567	15, 46, 16
4	**0.3809**	**0.3286**	**1.1452**	**7, 12, 21, 15**
5	0.3765	0.3154	1.1678	7, 12, 19, 15, 2
6	0.3621	0.2987	1.1876	7, 12, 17, 15, 2, 2

The Silhouette Score measures cohesion and separation (higher values indicate better clustering, with >0.5 considered good) [86] (Rousseeuw 1987), the Dunn Index assesses cluster separation (higher values are better) [68], and the DBI evaluates the ratio of intra-cluster to inter-cluster distances (lower values are better, with <1 desirable). The results for each k value are summarized in the tables below [87] (Liu 2010). For women, k = 4 was selected as the optimal number of clusters, achieving a Silhouette Score of 0.3876, a Dunn Index of 0.3892, and a DBI of 0.9876, with cluster sizes of 9, 48,

11, and 9. This choice balanced cohesion and separation while avoiding over-segmentation, as higher k values (e.g., k = 5, Silhouette = 0.4006, Dunn = 0.4182371, DBI = 0.9377009) resulted in small clusters (e.g., size 2) that reduced interpretability. For men, k = 4 was confirmed as optimal, with a Silhouette Score of 0.3809, a Dunn Index of 0.3285687, and a DBI of 1.14519, with cluster sizes of 7, 12, 21, and 15, providing a good balance of cohesion, separation, and interpretability.

This analysis revealed that the heterogeneity could be analyzed in four clusters for men and for women identified to best describe the patients and compared to highlight sex differences (**Table 9**, **Figure 10**).

Tabla 9. Clustering results of Gower's distance in machine learning.

	Women	**Men**
Cluster 1 - Functional Impacts: Captures physical and work-related limitations due to pain.		
Frequency	144	64
Categories	Physical disability (51), Physical dependence (34), Inability for household tasks (31), Abandonment of work (17), Sexual disability (8), Limitation in doing sports (3)	Inability for household tasks (12), Physical dependence (11), Decrease in social life (11), Abandonment of work (10), Physical disability (10), Decrease in family activities (10)
Characteristics	Focuses on physical limitations, with a notable emphasis on household responsibilities.	Similar physical limitations, but with a stronger tilt toward work-related impacts.
Cluster 2 - Emotional Environment Impacts: Reflects emotional burdens tied to external or environmental factors.		
Frequency	206	10
Categories	Family abandonment (35), Clumsiness (31), Insecurity (24), Inactivity (15), Quality of life (13), Limitation (12), Truncated life (10), Loss of enthusiasm (9), Argument (8), Anguish (6), Limitation of future plans (5), Neglect (5), Divorce (4), Desolation (4), Decrease in activity (4), Partner separation (4), Fear (4), Inability to do sports (3), Need for help with household tasks (3), Exhaustion (2), Aggressiveness (2), Anxiety (2), Cowardice (2), Guilt (2), Weakness (2), Job loss (2), Pretending well-being (2), Vulnerability (2), Daze (1), Pleasing others (1), Desperation (1), Hopelessness (1), Inability for leisure activities (1), Indifference from surroundings (1), Worry (1)	Loss of enthusiasm (2), Economic impact (2), Worry (1), Anxiety (1), Job uncertainty (1), Job loss (1), Nervousness (1), Use of sexual companionship services (1)
Characteristics	Broad and diverse (48 categories), encompassing family-related stress and emotional strain.	Narrow (9 categories), focusing on limited emotional impacts, primarily economic or general stress.
Cluster 3 - Social and Emotional Impacts: Highlights personal emotional challenges for women and social limitations for men. but also include perception impact.		
Frequency	108	61
Categories	Low self-esteem (24), Negative self-concept (17), Decrease in activities with friends (13), Body changes (12), Discouragement (10), Pessimism (9), Change in personality (7), Frustration (7), Longing (6), Burden (2), Disinterest in leisure activities (1)	Limitation (34), Uselessness (11), Divorce (5), Desolation (4), Pessimism (2), Change in personality (1), Fatigue (1), Inactivity (1), Limitation in traveling (1), Clumsiness (1)
Characteristics	Centers on internal emotional states and self-perception.	Focuses on external social restrictions rather than internal emotions.

Cluster 4 - Personal and Social Losses (Women) vs. Personal and Sexual Impacts (Men): Reflects relational/mobility losses for women and personal/sexual challenges for men.		
Frequency	295	71
Categories	Limitation in traveling (115), Sadness (31), Decrease in family relationships (26), Uselessness (24), Lack of understanding from surroundings (23), Decrease in social life (22), Anger (15), Decrease in sexual desire (14), Sexual pain (14), Neglecting personal care (11)	Low self-esteem (9), Limitation in doing sports (7), Negative self-concept (6), Absence of future plans (5), Hopelessness (5), Decrease in activities with friends (5), Partner separation (5), Weakness (4), Sexual disability (4), Erectile dysfunction (3)
Characteristics	High-frequency mobility and relational impacts dominate.	Includes personal limitations and unique sexual impacts.

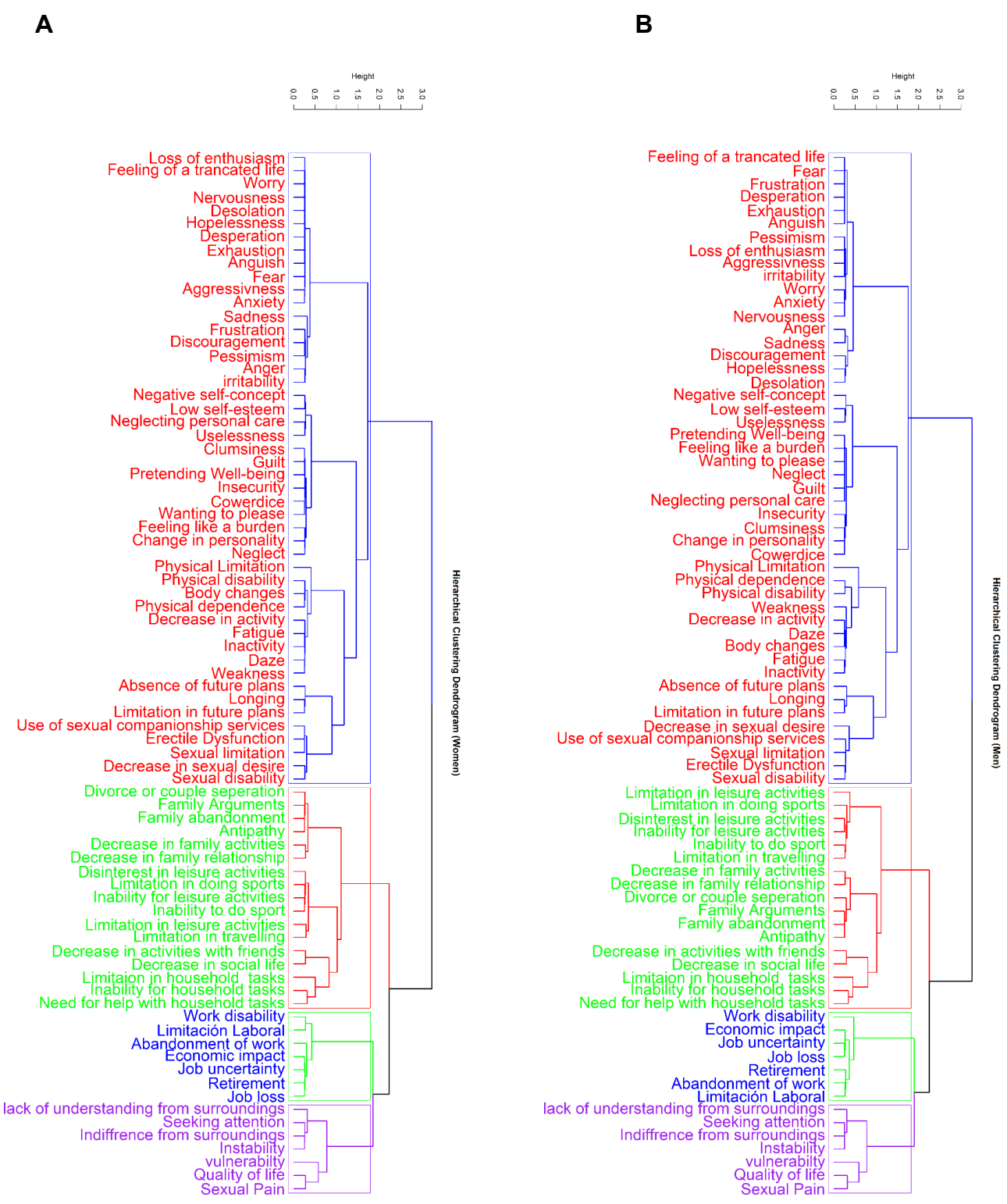


Figure 10. Dendrograms for women (A) and men (B) hierarchical clustering with machine learning thematics Gower's distance Ward.D2 (weights 2.2.1.1.1 for frequencies categories and subcategories).

5. Discussion

5.1 Sex-Based Differences in Age, Employment, and Pharmacological Patterns in CNCP Patients

This study's analysis of 216 CNCP patients (70% women) revealed significant sex-based differences in demographic, clinical, and pharmacological characteristics, underscoring the need for sex-sensitive pain management to enhance equity in care [19, 45]. Women were significantly older (median age: 66 years vs. 56 years for men, p=0.002), aligning with evidence that CNCP disproportionately affects older women [8, 34]. Employment status differed markedly (p=0.001), with women more likely to be homemakers (21% vs. 0%) or on work disability (31% vs. 21%), reflecting societal gender roles where women are tied to reproductive tasks, while men were more often retired (39% vs. 33%) or employed (19% vs. 17%), associated with productive roles [3, 61]. These disparities exacerbate socio-economic burdens, such as reduced income and workforce participation, particularly for women [34].

Clinically, pain intensity (VAS: 80 mm) and quality of life (EQ-5D-3L utility: 0.254) were comparable across sexes, suggesting similar physical impacts of CNCP. However, a trend toward higher anxiety in women (HADS: 8 [5–11] vs. 6 [4–9] for men, p=0.064) was observed, consistent with women's greater emotional vulnerability, including anxiety and mood disturbances [91, 92]. Although not statistically significant, this tendency warrants attention, as women's emotional expressivity may be undervalued clinically, necessitating targeted psychological interventions [52]. Pharmacologically, men were more likely to receive antidepressants (59% vs. 38%, p=0.007), potentially reflecting a higher prevalence of depression in this hospital cohort, which may be linked to less expressivity in chronic pain. This reduced expressivity, often tied to stoicism, could exacerbate psychological distress by limiting emotional outlet or social support, prompting clinicians to prescribe antidepressants to address this underlying need [37, 45]. Men were also prescribed morphine more frequently (6% vs. 1%, p=0.030), possibly due to perceptions of stoicism requiring stronger analgesics [40, 45]. These prescribing patterns highlight gender-biased treatment, challenging the one-size-fits-all approach to pain care [19].

The findings advocate for tailored interventions: psychological support for women to address emotional vulnerabilities and social connection strategies for men to mitigate stoic underreporting [40, 91]. Automated patient-reported outcome tools could reduce clinician bias, improving early detection of distress [92].

5.2 Predominance of Reproductive Roles in Women, Productive Roles in Men, and Socioeconomic Disparities in CNCP

The analysis of 203 CNCP patients (142 women, 61 men) using the Gender-Pain Questionnaire revealed distinct gender role distributions, underscoring the interplay of sex, gender, and socioeconomic impacts [34, 37]. Women predominantly reported reproductive roles (family and caregiving responsibilities), reflecting societal expectations that amplify their emotional distress and

unpaid labor burden [93]. Men, conversely, were more associated with productive roles (work-related tasks), consistent with cultural norms of stoicism that may mask pain and delay treatment [34, 45] . Mixed roles, combining productive and reproductive duties, were more common among men, suggesting greater overlap in work and home responsibilities within this cohort [94].

These gender role patterns significantly influence socioeconomic outcomes. Women's predominance in reproductive roles correlates with reduced workforce participation and increased financial strain, exacerbating CNCP's socioeconomic impact [10, 94]. Men's focus on productive roles, despite underreporting pain, may lead to prolonged work-related disability, contributing to healthcare costs and lost productivity [34]. The Gender-Pain Questionnaire, developed by our multidisciplinary gender and health research group and validated per Boateng et al. (2018), captured these disparities through items assessing identity, relationships, and work, providing a robust tool to quantify gender role influences [37]. For instance, responses to questions on work tasks and family relationships highlighted women's greater burden in balancing pain with caregiving, while men reported impacts on future plans tied to employment.

These findings align with literature emphasizing gender as a determinant of pain perception and socioeconomic burden, advocating for targeted interventions [34]. Policy briefs should leverage this evidence to promote gender-sensitive clinical protocols, ensuring emotional and social dimensions are addressed in public health planning [94]. The questionnaire's integration into clinical practice could guide tailored support, such as workplace accommodations for men and caregiving relief for women, fostering equitable pain management strategies.

5.3 Analysis of Emotional Impact Frequency and Distribution in CNCP: Three- and Four-Cluster Gender-Informed Insights

Using hierarchical clustering with Ward.D2 linkage and frequencies features, the optimal number of clusters for both sexes was found to be k = 3, supported by high Silhouette Scores (women, 0.700, Dunn = 0.071, DBI = 0.459; and men = 0.728, Dunn = 0.143, DBI = 0.405). These values indicate strong internal cohesion and compact cluster formation. Higher *k* values led to smaller, less interpretable clusters. Here, three-cluster solutions uncovered sex-specific themes being for women (broader and more intense impacts across physical, emotional, and relational domains) different than men (narrower themes focused on work, functional losses, and select emotional or sexual concerns).

In an expanded analysis incorporating both ML thematics and frequencies, Gower's distance and Ward.D2 linkage were employed to determine k = 4 as the optimal number of clusters for both men and women, a methodology validated in clinical data contexts by Liu P et al 2024 [95]. For women, the clustering yielded a Silhouette score of 0.3876, a Dunn index of 0.3892, and a DBI of 0.9876. For men, the corresponding metrics were a Silhouette score of 0.3809, a Dunn index of 0.3286, and a DBI of 1.1452. Despite the moderate scores, which reflect the inherent complexity of the data, the

application of frequency-heavy weighting (1:1:1:2:2) enhanced clustering performance by more effectively capturing variations in patient-reported frequencies [95].

For women, the clusters were interpreted as follows: **Cluster 1**, termed Functional Impacts, highlighted household limitations and a pronounced burden on daily functioning. **Cluster 2**, labeled Emotional Environment, was characterized by a substantial emotional burden, with a frequency of 227, and included emergent themes such as family abandonment. **Cluster 3**, Social & Emotional Toll, centered on internal struggles, including low self-esteem and mood disturbances. **Cluster 4**, Personal & Relational Losses, exhibited a high frequency of 295 and was marked by significant limitations in mobility and relationships.

For men, the cluster interpretations were distinct: **Cluster 1** focused on work abandonment and physical disability. **Cluster 2** showed sparse emotional reporting, with a frequency of 23, potentially attributable to stoicism. **Cluster 3** emphasized social limitations, particularly the loss of functionality. **Cluster 4** highlighted sexual dysfunction, with fewer relational themes compared to those observed in women.

This novel application of clustering chronic pain patients using Gower's distance demonstrated the relevance of Gower's distance in identifying patient segments and informing public health interventions using mixed-type health data.

The clustering analysis revealed pronounced gender differences in the experiences of CNCP across the identified clusters. In terms of emotional burden, women demonstrated extensive and multifaceted emotional responses, particularly evident in **Cluster 2** with a frequency of 227, reflecting significant emotional distress and themes such as family abandonment. Conversely, men exhibited limited and narrowly focused emotional reporting in **Cluster 2**, with a frequency of only 23, possibly due to socialized stoicism. Regarding functional impacts, women primarily highlighted household limitations, underscoring the disruption of domestic responsibilities, whereas men emphasized work-related impairments, reflecting a focus on occupational challenges. In the domain of mobility versus sexual health, women reported travel limitations and relational strain, indicating broader social and interpersonal difficulties, while men predominantly noted sexual dysfunction, such as erectile dysfunction, as a primary concern. Finally, coping mechanisms diverged distinctly: women displayed internal emotional responses, such as reduced self-esteem, while men focused on external constraints tied to social roles, aligning with societal expectations of masculinity.

5.4 Evidence-Based Recommendations for Gender-Equitable Public Health Strategies and Policymakers

Drawing from the previous sex-based disparities, gender role effects, emotional burden clustering, and pharmacological prescription of CNCP patients, we propose the following evidence-based and

multidimensional guidelines. These recommendations aim to guide public health institutions, clinicians, and policymakers towards more equitable and more effective care:

- Implement Gender-Sensitive Pain Management Programs Diagnose and manage the distinct emotional, functional, and relational components of CNCP in women and men. Clinical guidelines must include using Multidisciplinary teams that consist of mental health professionals that are particularly beneficial for women with emotional distress and caregiving burdens [20, 91]. and Vocational rehabilitation and sexual health counseling for men, particularly men who face role identity loss as a result of work disability and sexual dysfunction [19, 40]. Moreover, Custom communication approaches designed to address male stoicism and encourage emotional expression [96, 97].
- Train Healthcare Providers to be aware of Gender Variations in Pain Reporting To reduce delays in diagnosis -especially in women, whose pain is also widely attributed to psychological cause-, train clinicians in Implicit bias sensitivity and social expectation's impact on pain complaints [10, 45]. Gender-sensitive outcome measures, for example, the Gender-Pain Questionnaire, incorporate role-specific vulnerabilities and stressors [37, 38]. Fletcher et al. [92] advocate for the utilization of patient-reported outcome (PRO) measures, such as the EQ-5D-3L and HADS, to increase objectivity and minimize bias in symptom measurement.
- Expand Access to Mental Health Care, Particularly for Women: Women exhibited broader and more powerful emotional responses to CNCP, particularly in clusters involving family abandonment and low self-esteem. Policymakers should Provide psychological services in pain units and tailor them to the needs of women [52], Provide family-centered interventions to minimize the double burden of caregiving and pain [34, 93]. and Organize support groups or peer-facilitated therapy, which have been shown to work in managing chronic pain [98, 99].
- Address Risk of Opioid Dependence in Men Through Gender-Responsive Interventions Men's greater morphine use and lower emotional disclosure rates indicate a requirement for: Gender-specific opioid stewardship programs based on risk factors like underreporting of pain and heightened work-related injuries [100, 101], Greater reliance on non-pharmacologic interventions, including physical therapy and electronic Cognitive Behavioral Therapy—especially useful in engaging men via function-based storytelling [102]. Regular psychological evaluations in pain clinics, even in the presence of minimal self-reported distress, are necessitated to prevent delayed diagnoses resulting from stoic behavior.
- Promote mechanisms to enhance relational and social support for men. Men's clusters revealed social isolation and sexual dysfunction, which are required: Sexual health care as routine CNCP management among men [103], Community reintegration programs, including occupational therapy and structured social activities, are intended to counteract the loss of identity in the work role [94, 96] . and Public health campaigns to mitigate masculine norms that stifle emotional expression, promoting help-seeking behavior [97, 104].

- Integrate gender-responsive clustering tools into clinical practice. Hierarchical clustering using Gower's distance, weighted by frequency, has substantial practical application to: Individualized delivery of care, tailoring treatment according to the patient's prevailing cluster characteristics [95]. AI-powered clinical decision support systems aim to help clinicians identify emotional, functional, and relational vulnerabilities that are poorly communicated, especially by male patients. Risk stratification and optimization of resource use in overwhelmed health systems [105]. The development of a predictive risk model for pain: a mixed methods approach. and also Fund Longitudinal and Inclusive Gender Research in CNCP Effective public health response demands the ongoing generation and interpretation of data: Promote the incorporation of evidenced gender constructs within epidemiological research [106, 107]. Fund longitudinal studies to quantify the evolution of CNCP alongside changing gender roles, family life, and working conditions. Conduct empirical studies in practical environments to assess the efficacy of gender-sensitive protocols in various healthcare contexts [108].

6. Limitations, Implications and Future Directions

This study presents several methodological and conceptual limitations. First, the convenience sampling from a single hospital—comprising mostly white, middle-aged women—limits the generalizability of findings. Group size imbalance, with fewer male participants, reflects real-world prevalence but reduces statistical power for gender comparisons. There is narrative data variability, as some patients provided minimal qualitative input, constraining the clustering analysis. Furthermore, the gender questionnaire used requires broader validation across diverse populations, and many participants identified with multiple gender roles, complicating role-specific interpretations. Several uncontrolled variables—including pain duration, financial stress, and social support—may influence emotional outcomes but were not assessed. The older sample also skewed occupational role analysis, limiting insights into productivity-related gender differences. Additionally, biological contributors to sex-based differences were underexplored. Hormonal data (e.g., menstrual cycle phases, menopause) were not collected, though sex hormones influence nociception and emotional regulation [109]. Excluding non-binary participants further limits insights into the broader gender spectrum.

The findings of this study highlight the profound influence of early childhood socialization on gendered responses to CNCP, with boys socialized toward resilience and stoicism and girls encouraged to express sensitivity and verbalize discomfort, as noted by Myers et al. 2003 [110] and Gomes Nascimento et al. 2020 [111]. These gendered patterns underscore the necessity for targeted and nuanced approaches to pain management. To address these disparities effectively, interdisciplinary CNCP management is essential, tailoring interventions to account for both biological sex and gender identity to meet the unique needs of diverse patient populations [112]. Furthermore, the development of automated patient-reported outcome screening tools is critical to minimize bias and enable early intervention, ensuring timely and equitable care [113]. Additionally, leveraging modern natural language processing tools for qualitative text mining holds significant promise for uncovering nuanced narrative patterns in gendered pain experiences, offering deeper insights into patient perspectives. Finally, adopting intersectional approaches that consider factors such as education, income, and cultural background is vital to address compounded disparities. By integrating these strategies, future research and clinical practice can advance toward more equitable, effective, and personalized pain management, acknowledging the complex interplay of gender, socialization, and systemic factors in shaping CNCP experiences. Using hierarchical clustering combined with a large language model and including large pools of data is in the beginning of its development and could see further enhancements not only perfecting the methodology but also the validation which could allow a deep understanding for all the aspects of CNCP impact. This is what we aim to address in the future. The collaboration with Dr. Erica Briones, an expert in public health, could shape the intersectional and narrative-based framework utilized in this study. Her expertise could facilitate the integration of lived experiences, gender roles -through the validation and implementation of the Gender-Pain Questionnaire in the medical practice.

7. Conclusions

1- Sex differences have been shown due to the emotional and clinical landscape of CNCP. Women tend to experience a wide-ranging emotional and functional burden, encompassing psychological, social, and relational dimensions, while men exhibit more focused challenges, often centered on work, functionality, and sexual health, likely influenced by societal expectations like stoicism.

2- Clinical and pharmacological management sex-differences evidenced that women may face longer delays in accessing specialized care and report tendencies of higher anxiety, reflecting their expressive pain experiences. Men, on the other hand, appear to focus on functional toll and receive more antidepressant prescriptions, possibly due to less expressivity in pain contributing to underlying depression. This contrast in treatment approaches underscores the need for a nuanced understanding of sex/gender specific needs in pain management.

3- The sex-disparities in roles and in socioeconomic status showed that women were significantly householders compared to men and have a devastating effect on their pain experience and coping mechanisms as they tend to share their suffering and despair as high expressivity suggests. A key takeaway is the potential for these sex-related patterns to inform more equitable and personalized care strategies due a gender perspective.

4- By acknowledging women's broader emotional struggles and men's unique relational and functional challenges—potentially exacerbated by suppressed pain expression—public policy briefs should be implemented to develop targeted interventions. This approach, enriched by collaborative expertise in public health, advocates for care models that integrate lived experiences and social determinants, paving the way for improved outcomes in CNCP management for women and men.

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ANNEXES

I Code of Responsible Research

INFORME DE EVALUACIÓN DE INVESTIGACIÓN RESPONSABLE DE 2. TFM (Trabajo Fin de Máster)

Elche, a 6/06/2025

Nombre del tutor/a	ANA MARIA PEIRO PEIRO
Nombre del alumno/a	Hichem Allouti
Tipo de actividad	Adherido a un proyecto autorizado
Título del 2. TFM (Trabajo Fin de Máster)	Disparidades estereotipadas por sexo en el impacto emocional del dolor crónico: agrupamiento jerárquico y categorización temática utilizando aprendizaje automático
Evaluación de riesgos laborales	No solicitado/No procede
Evaluación ética humanos	No solicitado/No procede
Código provisional	250602010442
Código de autorización COIR	**TFM.MBB.AMPP.HA.250602**
Caducidad	2 años

Se considera que la presente actividad no supone riesgos laborales adicionales a los ya evaluados en el proyecto de investigación al que se adhiere. No obstante, es responsabilidad del tutor/a informar y/o formar al estudiante de los posibles riesgos laborales de la presente actividad.

La necesidad de evaluación ética del trabajo titulado: **Disparidades estereotipadas por sexo en el impacto emocional del dolor crónico: agrupamiento jerárquico y categorización temática utilizando aprendizaje automático** ha sido realizada en base a la información aportada en el formulario online: "TFG/TFM: Solicitud Código de Investigación Responsable (COIR)", habiéndose determinado que no requiere ninguna evaluación adicional. Es importante destacar que si la información aportada en dicho formulario no es correcta este informe no tiene validez.

Por todo lo anterior, **se autoriza** la realización de la presente actividad.

Atentamente,

Alberto Pastor Campos
Jefe de la Oficina de Investigación Responsable
Vicerrectorado de Investigación y Transferencia

II Ethics Committee Board Approvement

COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE - HOSPITAL GENERAL
C/. Pintor Baeza, 12 – 03010 Alicante
http://www.dep19.san.gva.es
Teléfono: 965-913-921
Correo electrónico: ceim_hgua@gva.es

Ref. CEIm: PI2023-021 -Ref. ISABIAL: 2023-0013

INFORME DEL COMITE DE ETICA PARA LA INVESTIGACION CON MEDICAMENTOS

Reunidos los miembros del Comité de Ética para la Investigación con medicamentos del Departamento de Salud de Alicante – Hospital General, en su sesión del día 23 de febrero de 2023 (Acta 2023-02), y una vez estudiada la documentación presentada por **Dña. Ana Mª Peiró Peiró** del Servicio de Farmacología Clínica del Hospital General Universitario Dr. Balmis, tiene bien a informar que el proyecto de investigación titulado **"Análisis text mining en la interacción sexo/género sobre la respuesta analgésica",** se ajusta a las normas deontológicas establecidas para tales casos. Se informa a su vez de que este estudio ha solicitado la exención del Consentimiento Informado.

Y para que conste a los efectos oportunos, firmo la presente en Alicante

Firmado por Luis Manuel Hernandez Blasco - 21424371D el 27/03/2023 08:38:50

Fdo. Dr. Luis Manuel Hernández Blasco
Secretario Técnico CEIm Departamento de Salud de Alicante – Hospital General

III Gender-Pain Questionnaire

Identity

1. Has your pain changed the way you are? Yes / No How?

2. Has the pain affected your self-esteem as a woman/man? Yes / No How?

3. Has the pain changed your image of yourself as a man/woman? Yes / No How?

4. Has the pain changed your masculinity or femininity? Yes / No How?

Relationships

5. Has the pain affected your relationships? Yes / No How?

6. Has the pain affected your sexual relationships? Yes / No How?

7. Has the pain affected your family relationships? Yes / No How?

Work

8. Has the pain affected your work tasks and/or responsibilities within your work environment? Yes / No How?

9. Has the pain affected your life project or your future plans? Yes / No How?

10. Do you think that your social, work or family position has worsened due to the pain? Yes / No How?

IV Master's Workflow Diagram