Exploring the Patterns of Chronic Pain Locations and Their Associations with All-Cause Dementia: Results from UK Biobank

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Defense Date: March 25th, 2024

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Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the DKU Global Health Program in the Graduate School of Duke University
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ABSTRACT

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Abstract

Chronic pain is a widespread and intricate condition that affects a substantial portion of the global population. Its impact poses both societal and economic threats, exerting physical and psychological strains and becoming a genuine long-term public health concern. Emerging evidence suggests an association between chronic pain and cognitive decline, particularly in the context of Alzheimer's disease, vascular dementia, and other dementia-like symptoms.

While the conventional approach involves considering the count of locations and severity of pain in chronic pain research and clinical practice, this method may oversimplify the complexity of chronic pain experiences. Therefore, understanding the patterns of chronic pain locations and their associations with dementia is crucial for developing tailored and effective interventions as well as preventive strategies. This study aims to identify prevalent patterns of chronic pain locations and evaluate their associations with incident dementia among middle-aged and older adults in the UK.

This study leveraged medical data extracted from the UK Biobank, a large-scale prospective cohort study encompassing detailed health and genetic information from over 500,000 participants across the United Kingdom. The analysis involved a total of 445,530 participants, and incident dementia records were sourced from national health registers. Chronic pain location was self-reported, with respondents choosing from eight possible

options: headache, face, neck or shoulder, back, stomach or abdominal, hip, knee, or all over the body.

To identify the most prevalent patterns of chronic pain locations, the study calculated the incidence rates of all-cause dementia for the 20 most common combinations. Cox models were employed to examine the hazard of dementia for each of these 20 combinations in comparison to three groups: (i) participants without chronic pain, (ii) participants with only a single chronic pain location not included in the combination, and (iii) participants with only a single chronic pain location included in the combination.

The analysis unveiled that the size of the combinations of chronic pain locations varied, ranging from 6 to 8,207 persons. The three most prevalent combinations were neck and back (5.7%), back and knee (5.4%), and neck and knee (4.5%). Chronic pain in the back, neck, and knee was each present in over half of the 20 most prevalent combinations.

Notably, chronic pain in the back, neck, and knee was commonly found either individually or simultaneously in combinations linked to higher dementia rates compared to individuals without chronic pain. Furthermore, combinations involving back, neck, and knee were associated with greater dementia rates than groups with a single pain location not included in the combinations.

The findings of this study strongly indicate that chronic pain is not randomly distributed across body locations and that specific patterns of chronic pain locations may be linked to an elevated risk of dementia. The understanding of how different patterns of chronic pain locations relate to dementia offers fresh insights into dementia prevention strategies through effective pain relief. These results emphasize the significance of acknowledging the complexity of chronic pain experiences and their potential implications for cognitive health.

Further research is warranted to delve into the underlying mechanisms that connect chronic pain patterns to dementia. Additionally, exploring targeted interventions for dementia prevention through precise pain management would contribute to a more comprehensive understanding of the intricate relationship between chronic pain and cognitive health.

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1. Introduction

Dementia is widely considered as a progressing neurodegenerative condition characterized by a series of symptoms impairing brain function, frequently accompanied by alterations in social behaviors or motivation.[1] Previous researches exploring dementia-related conditions approximated present global prevalence at around 50 million, with an anticipated elevation to 63 million by the year 2030.[2,3] The burden of dementia extents beyond patients themselves, affecting their families, care givers, and social supporting systems.[4] Economic-wise, global expenditure in dementia care exceeded 800 billion dollar in 2015, and increased to one trillion dollar by 2018, posing majority financial impact towards developed countries.[5] On society level, elevated dementia prevalence imposed significant elevated pressure to medical systems with ongoing aging development.[6] To prevent these avoidable costs, researches in advancement of dementia prevention have become a spot-light point of inquiry. Notably, chronic pain has emerged as an increasingly recognized topic of concern, given that increased chronic pain prevalence had been reported among dementia population.[7] Therefore, it is imperative to comprehensively construct dementia prevention strategies by integrating chronic pain as a potential risk factor to enhance early detection process.

1.1 Dementia:

Specific classifications had been developed in dementia identification based on origins of the disease, burden, clinical manifestations, pathological characteristics, and

management strategies. Most common type of dementia diagnosed was Alzheimer's Disease (AD), causing cognitive disorder and potential memory loss by accumulating amyloid plaques and neurofibrillary tangles inside the brain tissue. On the other hand, vascular dementia presenting similar cognitive decline symptoms by compromising blood circulation to the brain, frequently caused by stroke or other small vessel disease. Other classifications of dementia were tied to a series of syndrome or disease, consisting of a number of causes including mixture of AD and vascular dementia, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and Parkinson-related dementia.[8-11]

1.1.1 Dementia: disease burden

The burden of dementia is a complex issue affecting patient's well-being both socially and economically. Various comorbibidities are correlated with dementia, cerebrovascular lesions have been recognized as an pivotal factor in the onset of dementia, particularly in the context of multi-infract dementia.[12] In addition, there is a correlation between the burden of hypertension and cognitive function, highlighting the cumulative effects of hypertension on the progression of dementia.[13] Furthermore, depression in persons with dementia has been identified as a significant factor afftecting both patients and their caregivers.[14] Apart from societal costs, the significant economic impact of dementia is well documented, emphasized by global estimates of an 818 billion dollars expenditure posing a substantial threat to patients, families, and healthcare systems.[15] Of which, informal care costs play a major role in amplifying economic burden of dementia, as studies propose a growing impact on dementia burden attributed

to the family caregivers' strain in providing both physically and psychologically care for dementia patients.[16,17] Moreover, the economic burden is particularly pronounced in low and middle income countries, where more than two thirds of population with dementia reside, leading to substantial economic strain in these settings.[18] This situation is exacerbated by elevated levels of health service utilization and adverse clinical outcomes when contrasted with older adults who do not bear dementia.[19]

1.1.2 Dementia: clinical manifestations

Historical researches had constructed clear classifications in advancing dementia detection process, however, current research focus in the field of dementia had furthered in detecting vulnerable population, early screening of social risky behaviors, and prevention of dementia incidence.[20] Vulnerable population, in particularly elder adults are of elevated risks in dementia incidence.[21] Previously documented epidemiological data have delineated the dementia prevalence, revealing incidence rates as one in fourteen for individuals age 65 and above, and one in six for individuals aged 80 and above.[22] Accompanied by the onset of aging population, dementia is causing increasing higher medical burden by accumulating vulnerable groups requiring high quality care and elevating mortality related to dementia in care centers and hospitals.[23,24]

1.1.3 Dementia: pathophysiology

The original study conducted in 1986 revealed dementia's potential correlation with various specific structural brain disease and systemic degenerations.[25] The pathophysiological process inducing dementia encompass a range of factors, including neurodegeneration, molecular mechanisms, vascular contributions.

The foundation of dementia pathophysiology is associated with progressive neurodegeneration, with studies emphasizing the pivotal roles played by the deposition of amyloid and tau proteins, as well as their genetic factors, in inducing dementia and the subsequent progression of cognitive decline.[26]

The significance of vascular contributions is highlighted through the exploration of potentially shared mechanisms between dementia and cerebrovasculature (CBVD), as well as cardiological diseases (CVD). The review of these three diseases proposed a stepwise increase in the odds ratio for Alzheimer's disease (AD) development with the severity of CBVD pathology, indicating that this pathology serves as a risk factor for AD development.[27]

The molecular mechanisms underlying the pathophysiology of dementia remain elusive to this day, presenting challenges in the development of effective disease modifiers.[28] The abnormal epigenetic process could be further complicated by the coexistence of other comorbid conditions, including hypertension, sleep disturbance, and

diabetes mellitus, respectively. In a literature review examining the association between sleep disorder and dementia, it was reported that over half of older adults suffer from sleeping disturbance. Among these, fractured sleep patterns, abnormal sleep duration, and difficulty falling asleep were listed as risk factors for the incidence of dementia.[29] In the context of hypertension, heightened systolic blood pressure is linked to diminished regional and total brain volumes, altered cerebral autoregulation, and impaired perfusion, impacting the brain's function to clear abnormal protein clusters in the brain. These affects coexists with other contributory mechanisms, including altered functional hyperemia, endothelial dysfunction, and oxidative stress.[30] Similar pathophysiological process was observed among diabetic patients, wherein cerebrovascular abnormalities, decreased brain volume, markers of white-matter injury were acknowledged as underlying cognitive impairing mechanisms. This is alongside the increasing presence of neurofibrillary tangles, neurotic plaques, fluid markers for gliosis, and progressing neurodegeneration.[31]

1.1.4 Dementia: treatment options

Current pharmacological modalities, exemplified by cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, afford only ephemeral mitigation of symptoms and lack the capacity to arrest the underlying disease progression.[32] In contrast, non-pharmacological interventions targeting pain in individuals with dementia have demonstrated promise in diminishing behavioral disturbances, highlighting the need for further investigations in this underdeveloped field.[33]

For Alzheimer's type dementia, the available treatment options are limited and predominantly involve acetyl-cholinesterase inhibitors and memantine. These treatments have shown varying degrees of success in addressing cognitive decline and functional impairment.[34] However, controversial results exist concerning Lewy Bodies syndrome and Parkinson’s disease, leading to unclear guidance for clinicians in prescribing effective pharmacological treatments.[35]

In the management of frontotemporal dementia, clinicians commonly prescribe cholinesterase inhibitors and memantine. Additionally, antidepressants and antipsychotic medications are often included in the therapeutic regimen, with the collective goal of improving patients' quality of life.[36] Among demented patients, the spectrum of psychological distress extends beyond depression and anxiety to encompass an escalating prevalence of pain, particularly in the form of chronic pain. As a measure to enhance well-being in individuals with moderate-to-severe dementia, acetaminophen is a commonly chosen clinical intervention to improve social interaction.[37]

1.1.5 Dementia: management strategies

To develop effective treatment strategy for dementia, it is essential to consider both pharmacological and non-pharmacological interventions. In a systematic review addressing the treatment of behavioral and psychological symptoms of dementia (BPSD), four pharmacological interventions were identified, comprising anticholinesterase inhibitors and pain-analgesics,

resulting in a significant decrease in the overall BPSD effect. While the evidence supporting the use of anticholinesterase inhibitors in treating cognitive decline symptoms was robust, it is noteworthy that the conclusion regarding pain management was solely derived from a single randomized controlled trial. Adverse events were reported across all pharmacological interventions, indicating an increased incidence of worsening mood with prolonged use of psychological medications. In contrast, pain-management medications reported a relatively lower incidence of adverse events.[38] On the other hand, exploration of non-pharmacological interventions, including cognitive interventions, has also been undertaken. Among five reviewed interventions consisting of psychological therapy, music therapy, cognitive stimulation, exercise, andfunctional analysis based interventions, only music therapy yield significantly reduced BPSD prevalence.[38]

In a pool of 17 randomized controlled trials addressing dementia management through diverse intervention strategies, non-pharmacological interventions were recommended as the primary approach, complemented by medication therapy. This recommendation stems from consistent findings suggesting that non-pharmacological methods were not associated with adverse events when compared to pharmacological interventions.[38]

1.2 Modifiable risks of dementia

Field of dementia research was called to identify modifiable risk factors to enhance early screening and develop preventive strategies as it is crucial to smooth the rocketing trend of dementia prevalence in the upcoming future.[39] Success in constructing effective clinical diagnosis of dementia comprises of multiple aspects includes

assessments at early stage of the disease, concise screening tool of precision, proper attitude and expertise knowledge from the medical staffs.[40] To date, previously identified factors contributing to dementia comprise a diverse array of risk elements, including lifestyle, social factors, environmental factors, and biological risk factors.[41]

1.2.1 Modifiable risk of dementia: lifestyle

Numerous contemporary studies have underscored that risky lifestyle factors, including obesity, sedentary behavior, insufficient sleep, physical inactivity, mental inactivity, and smoking, are identified as significant risk factors for dementia among general population.[42-44] The most recent "Lifestyle for BRAin health" (LIBRA) score, which evaluated ten modifiable risk factors for dementia in a sample of 7,460 individuals from the English Longitudinal Study of Aging, indicates a notable association between elevated LIBRA scores and individuals experiencing depression. This underscores the importance of developing interventions in mid-life to augment dementia prevention strategies.[42] Additionally, frailty has been recognized as a crucial risk factor for dementia in the older population. Specifically, individuals with both genetic risks and frailty conditions have been indicated to exhibit a higher risk of developing dementia compared to their counterparts with normal health conditions.[45]

1.2.2 Modifiable risk of dementia: social factors

In terms of public perception and understanding of dementia prevention, there is evidence indicating substantial gaps may exist between the general understanding and the latest scientific findings. A cross-sectional study based on a questionnaire, which involved 358 the recruitment of middle-aged and older adults in China, suggested that only one-third of the participants concurred with the notion that dementia can be prevented. Notably, those who reported contact with dementia patients, a relatively younger age, and higher educational attainment were observed to exhibit a heightened understanding of dementia prevention.[46]

Furthermore, beyond the level of understanding in dementia prevention, social engagement has been documented as a significant modifiable risk factor for dementia. Approximately 40% of healthy older individuals residing in the community actively engage in aerobic exercises, presenting an easily adoptable approach for preventing dementia in communities. A notable contrast emerges when comparing individuals aged 65 to 74 with those above 75 years old: the former group tends to participate in more social interactions and covers a broader range of exercises. Higher levels of social engagement within this age range were found to be associated with lower risks of dementia.[47]

Apart from social understanding and personal engagement, the influence of socioeconomic and geographical factors on dementia risks has been examined. A hierarchical Bayesian disease-mapping cohort study utilizing the Swedish Twin Registry brought to light an association between dementia and lower social class and birth weight.[48]

1.2.3 Modifiable risk of dementia: environmental factors

The relationships between environmental risk factors and dementia were not explicitly stated; however, existing evidence suggests a limited correlation. A comprehensive literature review scrutinized six major categories of environmental risk factors, including air quality, toxic heavy metals, other metals, mineral elements, occupational exposure, and other environmental hazards. Despite challenges arising from diverse methods employed across the included studies, the review successfully narrowed down environmental risk factors to specific elements. These identified factors include air pollution, aluminium, silicon, selenium, pesticides, vitamin D deficiency, and exposure to electric and magnetic fields.[49]

1.2.4 Modifiable risk of dementia: biological risk factors

Substantial body of current evidence highlights the biological risk factors for dementia, particularly focusing on cardiovascular risk factors. Cumulative counts of five factors, including hypertension, diabetes, coronary heart diseases, stroke, and smoking,

indicate elevated dementia hazards associated with an increased number of these risk factors.[50] Furthermore, studies have suggested that the oral environment and cerebral blood flow may contribute to the development of dementia. Factors such as the number of remaining teeth, occlusal force, denture use, and periodontal status have been associated with a decreased risk of developing dementia.[51]

However, recent development in dementia studies revealed chronic pain as a crucial independent risk factor for cognitive decline and dementia in middle aged and older adults.[52] Complex interactions have been postulated to exist between pain and dementia incidence, in particularly, potential mechanisms linking persistent pain and its treatment to the acceleration of dementia progression are under consideration.[52] Nevertheless, the specific mechanisms underlying the interplay between chronic pain and neurological disorders related to dementia are still yet to be detailed developed.[53]

1.3 Chronic pain

According to the latest International Association of the Study of Pain (IASP) definition, chronic pain has been clinically recognized as persistent or recurrence pain for a duration longer than three months.[54] This newest explication corresponds to a recently raised argument asserting that chronic pain should be regarded as a disease with a clinical course, rather than merely as a symptom.[55]

To date, the most recent systematic review and meta-analysis on chronic pain indicate a worldwide prevalence ranging from 10.1% to 55.5%, averaging at 35.5%.[56] The prevalence of chronic pain varies across different age groups, within the demographic of young adults, one in every nine individuals suffers from chronic pain experiences.[57] Notably, one latest study on chronic pain prevalence presents a notably higher global range, spanning from 25% to 85% within the elderly population.[58] Over various time trends and geological regions, analogous studies consistently support a heightened burden of chronic pain among the elderly. For instance, the Einstein Aging Study in 2008 reported a prevalence of 52% with slight variation between male and female (39.7% in male; 58.9% in female), while a parallel cross-sectional observation was derived from a study involving Chinese community-dwelling elderly in 2021.[59,60] One systematic review and meta-analysis conducted in the UK literature proposed a consistent elevation in the prevalence of chronic pain with age.[61] Likewise, this escalation is observed in individuals afflicted with chronic conditions.[62]

Correlated with various physical, social, and psychological characteristics impacting an individual's quality of life, chronic pain has predominantly been elucidated through pain-related parameters, encompassing factors such as the intensity of pain, duration of pain, and distribution across the body.[63,64] Specifically, chronic pain is recognized as a foremost contributor to diminishing quality of life, as persistent pain is associated with elevated rates of anxiety and depression compared to health individuals.[65] Moreover, clinical studies have unveiled a potential association between chronic pain and

sleeping disorder, as well as impaired psychological status.[66] Additionally, a number of research has suggested constraints on physical activities, social engagements, and recreational pursuits due to chronic pain.[67]

Evaluating chronic pain typically involves the measurement of pain intensity and duration. The intensity of pain is acknowledged as a pivotal parameter in both clinical and academic settings, frequently appraised using various measurements such as the Visual Analog Scale (VAS) and the Numerical Rating Scale (NRS).[68,69] Additionally, pain intensity has been linked to functional impairment, indicating its significance in assessing the influence of chronic pain on individual's lives.[70] Furthermore, heightened awareness has also been directed towards the duration of pain, with research indicating its association with impaired psychological conditions and augmented intensity of pain.[71] In contrast, although studies have addressed the significance of acquiring pain frequency, severity, and duration among individuals suffering from chronic pain, there is a shortage of literature specifically dedicated to the examination of pain location.[72]

Chronic pain could occur in different body locations, and its presence in multiple sites of the body is not uncommon. Research suggests persistent pain may manifest in various locations, encompassing low back pain, abdominal pain, joint pain and multi-site pain.[73] Multi-site pain or wide-spread pain is clinically defined as occurring in more than one anatomical site and is a prevalent phenomenon among adults worldwide.[74] The

diversity of bodily distribution of chronic pain can be caused by many different reasons, such as musculoskeletal, connective tissue, nerve system disease, injuries, and traumas.[75] Across the development of time trends in chronic pain screening, historical research in 1998 identified that at least one-third of patients experienced pain in multiple sites.[76] This conclusion aligns with recent findings where over half of chronic pain patients self-report experiencing pain at multiple locations, particularly among those with decreased body functioning status.[77,78]

1.4 Chronic pain and dementia: current research

Latest research focus in the field of chronic pain encompasses a board spectrum of topics, underscored by the diverse and dynamic nature of this domain. Within this realm, a crucial facet involves delving into the neuropsychological mechanisms associated with memory impairment among individuals suffering from chronic pain. This underscores the imperative demand to construct experimental intervention methods and leverage cognitive neuroscience approaches to address this issue.[79] Moreover, a burgeoning emphasis has recently emerged on exploring the intricate relationship between chronic pain and dementia. This highlights the necessity for more accurate estimations of chronic pain in older adults and elucidating the mechanisms underlying pain in the context of aging and dementia.[52]

The linkage between chronic pain and dementia-related conditions has been a topic of interest for public health studies in the context of general population,

emphasizing shared underlying mechanisms and identifying chronic pain as a risk factor for accelerated cognitive decline.[52] Furthermore, the potential underlying mechanisms connecting chronic pain and Alzheimer's disease find support in evidence from both animal and human studies.[80] The cognitive impairment resulting from chronic pain is notably more severe among aging individuals, particularly those with Alzheimer's disease.[81] Conversely, chronic pain among individuals with dementia poses a significant concern that is frequently under-diagnosed and under-treated.[53,82,83] Numerous studies consistently reveal a significant prevalence of chronic pain within the dementia patient population, underscoring the critical need for improved comprehension and effective management of this complex matter.[84-87]

Diverse intervention strategies have been scrutinized to address the confluence of chronic pain and dementia prevention, encompassing a spectrum of both pharmacological and non-pharmacological modalities. Non-pharmacological interventions, including music therapy, acupressure, and robot-assisted interventions, primarily target the enhancement of individual well-being and the improvement of overall quality of life, with their effectiveness often described as potentially impactful.[86,88,89] In contrast, pharmacological interventions predominantly involves the utilization of opioids, revealing an elevated risk of dementia progression undergoing pain-relief treatments.[90]

1.5 Chronic pain and dementia: gap

The paradoxical existence of pain-relief interventions proving ineffective and potentially exacerbating cognitive outcomes emphasizes the urgent need for a more comprehensive understanding of the intricate relationship between chronic pain and dementia. In the comprehensive landscape of chronic pain and dementia research, the intensity and duration of pain have been the predominant focal points. Recently, there has been a growing shift in attention towards the specific locations of pain.[52] However, in both clinical and academic research, the recognition of pain locations has predominantly centered on the count rather than detailed distributions. Individuals with the same pain burden, as quantified by a simple count approach, might represent clinically different groups with varying treatment strategies and therapeutic targets.

Latest studies are directing efforts towards identifying specific chronic pain locations associated with all-cause dementia. A clinical study, involving 98 chronic knee pain patients aged between 18 to 70 years old, revealed an elevated risks in dementia incidence among this cohort.[91] Similarly, knee pain was identified as a factor associated with increased dementia risks, along with low back pain, in a prospective study consisting of 14,627 older individuals with no prior history of stroke, cancer, injuries, depression, Parkinson's disease, or dementia.[92] Finally, a comprehensive systematic review and meta-analysis focusing on low back pain and dementia yielded consistent findings.[93]

Nevertheless, there is still a lack of understanding regarding the impact of different combinations of chronic pain locations on dementia. Comparing participants with specific chronic pain combinations to their healthy counterparts or individuals reporting pain in a single location holds clinical significance, yet these aspects have yet to be investigated adequately.

1.6 Research aim

The aim of this study is two-fold. First, we investigated the chronic pain patterns and identified the most popular patterns of chronic pain locations among a large nationwide sample of community-dwelling adults aged 40-70 years in the UK Biobank. Second, we determined the association between each set of chronic pain location combinations and all-cause dementia incidence relative to participants with no chronic pain location and those with a single chronic pain location (either included or excluded from the chronic pain locations involved in the combination).

2. Methods

2.1 Data source

We extracted research data from the UK Biobank, an ongoing nationwide prospective cohort study that includes more than half a million middle-aged and older participants (40-69 years) recruited between 2006 and 2010 from 22 assessment centers in England, Wales, and Scotland. The UK Biobank is a valuable resource for researchers due to its large sample size, comprehensive data collection methods, and long-term follow-up. The study follows standard procedures for data collection and participant assessment.[94]

At baseline, eligible participants were invited to attend the closest assessment center to complete a self-administered touch-screen questionnaire, a nurse-led interview, physical assessments, and bio-specimen sample collection. Additionally, follow-ups of medical and health-related records of the study participants were also available. All participants have signed informed consent for data collection, analysis, and linkage electronically. The ethical approval of the UK Biobank study was granted by the Northwest-Haydock Research Ethics Committee (REC reference: 16/NW/0274). Data access was provided under UK Biobank project 51450.

2.1.1 Analytic sample

We excluded participants who (i) had prevalent dementia at baseline (n=586), (ii) were outside the age range of 40-70 years (n=13), (iii) did not have sufficient data to identify chronic pain status (n=2,181), and (iv) had missing data in covariates (n=54,059). The final analytic sample included 445,530 participants (Figure S1).

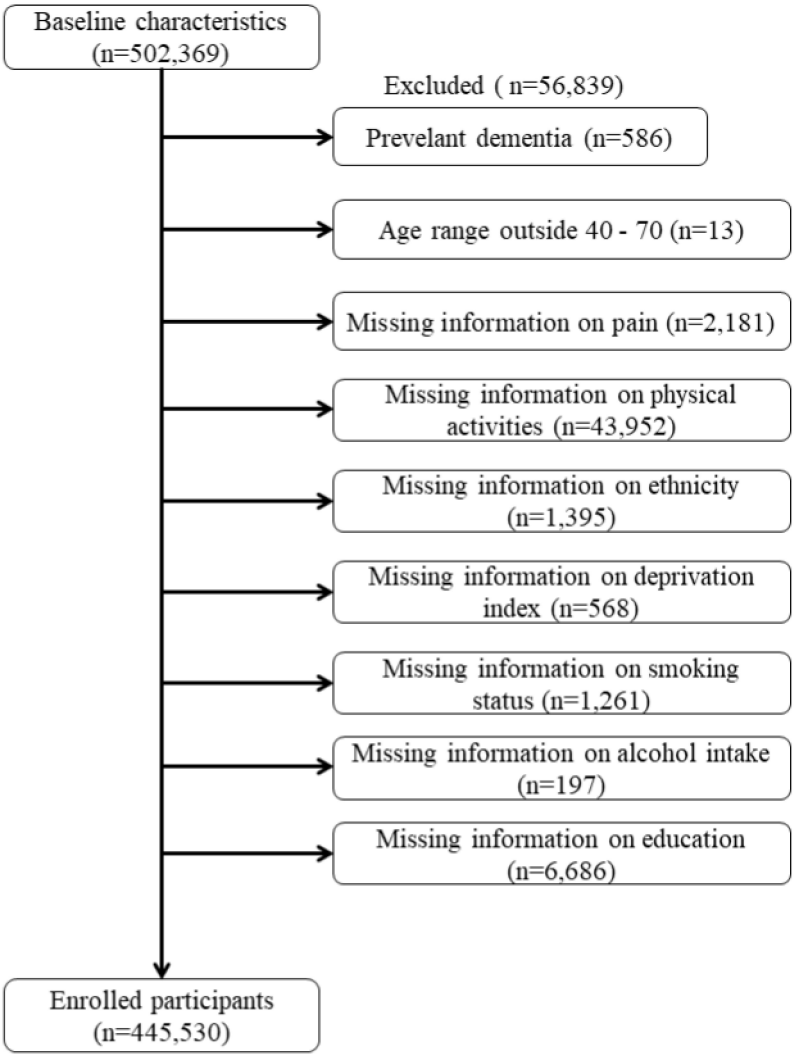

Figure S1. Flowchart of the number of persons dropped due to missing data.

2.2 Dementia

We included all three types of dementia available in the UK Biobank: all-cause dementia, vascular dementia, and Alzheimer's dementia. Diagnostic codes for the disease were derived from ICD9 and ICD10 (International Classification of Diseases, 9th and 10th revisions); data for these codes were registered from 1996 to 2016 February (gathered by Hospital Episode Statistics in England; for starting dates and sensory procedures from Scottish Morbidity Records and Patient Episode Database for Wales), and ICD10 codes on death status were registered between 2006.4 - 2016.2 (refer to Appendix 2 for detailed ICD codes). Data linkage, including permissions was managed by UK Biobank, and participant identifiers (NHS number, date of birth, sex, and postcode) were submitted to external organizations for secure mating to their respective secondary health care records. More details on primary and secondary diagnoses within hospital admissions and underlying and secondary causes of death from morbidity records are available elsewhere.[95]

2.3 Pain

Information on pain was collected using a touchscreen questionnaire. Participants were asked, "In the last month have you experienced any of the following that interfered with your usual activities?" They were then provided with a list of pain locations: headache, facial pain, neck or shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, and pain all over the body. Multiple responses were allowed. Participants

who reported having pain in any location were asked a follow-up question, “Have you experienced these pains for a duration exceeding three months?". Persons who answered positively were considered to have chronic pain.[94] Participants reporting pain all over the body were considered having chronic pain at each location. We created a sum score to count the number of locations with chronic pain and classified it into five categories: 0, 1, 2, 3, and 4 or more.

2.4 Covariates

Socio-demographics included age in years at recruitment (40-49.9 years, 50-59.9 years, and 60+ years), sex, self-reported ethnicity (Whites and Others; a common strategy to classify race/ethnicity in the UK Biobank study), education (college or above and below college), and the Townsend deprivation index. Lifestyle characteristics included smoking status (current, previous, and never), alcohol intake frequency (daily, three or four times a week, once or twice a week, one to three times a month, special occasion only, and never), physical activities (walking, moderate, and vigorous), comorbidity index (0, 1, and 2+).

2.5 Statistical analysis

In this study, we aimed to investigate the association between the pattern of chronic pain locations and the risk of all-cause dementia. The analysis involved describing the participants' baseline socio-demographic, lifestyle, and health characteristics based on the number of chronic pain locations, as well as examining the

frequency and relative frequency of combinations of two or more chronic pain locations. Furthermore, the study calculated the incidence rates of all-cause dementia by the 20 most prevalent combinations and conducted Cox models to examine the hazard of all-cause dementia among these combinations compared to three groups.

2.5.1 Participants' characteristics

We utilized means and standard deviations for continuous variables and counts and percentages for categorical variables to describe the baseline socio-demographic, lifestyle, and health characteristics of the participants based on the number of chronic pain locations (0, 1, 2, 3, and 4+). This approach allowed for a comprehensive understanding of the distribution of these characteristics across different chronic pain groups.

2.5.2 Characteristics across the count of chronic pain locations

To compare the characteristics of participants with different numbers of chronic pain locations, we employed the analysis of variance for continuous variables and the chi-squared test for categorical variables. These statistical tests are appropriate for assessing differences in means and proportions across multiple groups, providing valuable insights into the associations between chronic pain locations and various participant characteristics.

2.5.3 Chronic pain location patterns and dementia risk

Furthermore, we focused on examining the association between the pattern of chronic pain locations and the risk of all-cause dementia. This involved analyzing the frequency and relative frequency of combinations of two or more chronic pain locations, as well as calculating the incidence rates of all-cause dementia by the 20 most prevalent combinations. By exploring these patterns,we aimed to identify potential relationships between specific chronic pain location combinations and the risk of dementia.

2.5.4 Cox models for assessing dementia risk

To assess the hazard of all-cause dementia associated with different combinations of chronic pain locations,we employed Cox proportional hazards models. These models are widely used in survival analysis to evaluate the association between predictor variables and the timing of an event, making them suitable for investigating the risk of dementia in relation to chronic pain location patterns. The study considered 20 prevalent combinations of chronic pain locations and compared them to three reference groups, adjusting for various socio-demographic and lifestyle factors to account for potential confounding effects.

2.5.5 Statistical analysis and significance level

All statistical analyses were conducted using Stata 17.0, a widely used software package for statistical analysis. The choice of Stata for the analysis reflects its suitability

for handling complex data and conducting advanced statistical modeling. Additionally, the study set a significance level of $p < 0.05$, indicating that results with a p-value below this threshold were considered statistically significant. This approach ensures a rigorous assessment of the associations between chronic pain location patterns and the risk of all-cause dementia.

3. Results

3.1 Sample description

Table 1 displays the foundational characteristics of the studied group, focusing on the prevalence of chronic pain in different locations and various demographic and health-related factors. We extracted data from a large-scale study involving 445,530 participants, providing information on age, gender, ethnicity, Townsend deprivation index (TDI), education, smoking habits, alcohol consumption frequency, physical activity levels, and comorbidity index. Statistical significance across chronic pain locations is evaluated using appropriate tests such as analysis of variance for continuous variables and the chi-square test for categorical variables.

Of the 445,530 participants, 190,617 (42.8%) reported having chronic pain in at least one location (Table 1). Participants with chronic pain were older, more likely to be female, and had lower education and worse economic status than those without. In addition, persons with chronic pain had a lower level of physical activity and a higher number of chronic conditions than those without. Among persons with chronic pain, 71,676 (16.1%), 56,717 (12.7%), 33,174 (7.4%), and 29,050 (6.5%) reported having chronic pain in 1, 2, 3, and 4 or more locations, respectively. Participants with chronic pain in more locations were more likely to be female and non-white, had lower education attainment, and had more chronic conditions.

Table 1. Baseline characteristics of the analytic sample.

	Prevalence for the number of chronic pain locations						
	Total (n=445,530)	**0 (n=254,913)**	**1 (n=71,676)**	**2 (n=56,717)**	**3 (n=33,174)**	**4+ (n=29,050)**	**P value**
Age in years, mean (SD)	56.33 (8.08)	56.14 (8.14)	56.90 (8.00)	56.56 (8.04)	56.43 (8.04)	56.10 (7.89)	<0.001
Age in groups, n (%)							<0.001
40-49.9	107,400 (24.1%)	63,748 (25.0%)	15,730 (22.0%)	13,149 (23.2%)	7,822 (23.6%)	6,951 (23.9%)	
50-59.9	150,029 (33.7%)	85,328 (33.5%)	23,605 (32.9%)	19,060 (33.6%)	11,384 (34.3%)	10,652 (36.7%)	
60+	188,101 (42.2%)	105,837 (41.5%)	32,341 (45.1%)	24,508 (43.2%)	13,968 (42.1%)	11,447 (39.4%)	
Sex, n (%)							<0.001
Male	206,288 (46.3%)	123,841 (48.6%)	33,636 (46.9%)	24,548 (43.3%)	13,597 (41.0%)	10,666 (36.7%)	
Female	239,242 (53.7%)	131,072 (51.4%)	38,040 (53.1%)	32,169 (56.7%)	19,577 (59.0%)	18,384 (63.3%)	
Ethnicity, n (%)							<0.001
White	397,771 (89.3%)	228,394 (89.6%)	64,457 (89.9%)	50,773 (89.5%)	29,208 (88.0%)	24,939 (85.8%)	
Other	47,759 (10.7%)	26,519 (10.4%)	7,219 (10.1%)	5,944 (10.5%)	3,966 (12.0%)	4,111 (14.2%)	
TDI, mean (SD)	-1.41 (3.03)	-1.57 (2.93)	-1.48 (2.98)	-1.30 (3.08)	-1.04 (3.21)	-0.48 (3.41)	<0.001
Education, n (%)							<0.001
College	153,864 (34.5%)	96,497 (37.9%)	24,064 (33.6%)	17,434 (30.7%)	8,957 (27.0%)	6,912 (23.8%)	
Below College	291,666 (65.5%)	158,416 (62.1%)	47,612 (66.4%)	39,283 (69.3%)	24,217 (73.0%)	22,138 (76.2%)	
Smoking status, n (%)							<0.001
Current	45,171 (10.1%)	23,006 (9.0%)	7,194 (10.0%)	6,266 (11.0%)	4,196 (12.6%)	4,509 (15.5%)	
Previous	155,286 (34.9%)	85,520 (33.6%)	25,753 (36.0%)	20,863 (36.8%)	12,563 (37.9%)	10,587 (36.5%)	
Never	245,073 (55.0%)	146,387 (57.4%)	38,729 (54.0%)	29,588 (52.2%)	16,415 (49.5%)	13,954 (48.0%)	
Alcohol intake frequency, n (%)							<0.001
Daily or almost daily	93,762 (21.0%)	56,497 (22.2%)	15,592 (21.8%)	11,413 (20.1%)	6,067 (18.3%)	4,193 (14.4%)	
Three or four times a week	106,069 (23.8%)	64,654 (25.4%)	17,279 (24.1%)	12,728 (22.5%)	6,622 (20.0%)	4,786 (16.5%)	
Once or twice a week	115,320 (25.9%)	67,098 (26.3%)	18,559 (25.9%)	14,656 (25.8%)	8,343 (25.1%)	6,664 (22.9%)	
One to three times a month	49,512 (11.1%)	26,930 (10.6%)	7,804 (10.9%)	6,596 (11.6%)	4,298 (13.0%)	3,884 (13.4%)	
Special occasion only	48,416 (10.9%)	24,183 (9.5%)	7,398 (10.3%)	6,889 (12.2%)	4,698 (14.1%)	5,248 (18.1%)	
Never	32,451 (7.3%)	15,551 (6.0%)	5,044 (7.0%)	4,435 (7.8%)	3,146 (9.5%)	4,275 (14.7%)	
Physical activities days per week, mean (SD)							
Walking	5.37 (1.96)	5.42 (1.91)	5.38 (1.94)	5.32 (1.98)	5.27(2.04)	5.04 (2.27)	<0.001
Moderate activity	3.60 (2.33)	3.62 (2.31)	3.63 (2.32)	3.59 (2.34)	3.57 (2.39)	3.40 (2.53)	<0.001
Vigorous activity	1.86(1.96)	1.94 (1.94)	1.88 (1.96)	1.77 (1.93)	1.70 (1.98)	1.53 (2.01)	<0.001
Comorbidity index, n (%)							<0.001
0	391,630 (87.9%)	228,952 (89.8%)	63,235 (88.2%)	49,137 (86.6%)	27,827 (83.9%)	22,479 (77.4%)	
1	28,480 (6.4%)	13,032 (5.1%)	4,467 (6.2%)	4,167 (7.4%)	3,065 (9.2%)	3,749 (12.9%)	
2+	25,420 (5.7%)	12,929 (5.1%)	3,974 (5.6%)	3,413 (6.0%)	2,282 (6.9%)	2,822 (9.7%)	

Abbreviations: TDI, Townsend deprivation index.

Note: P values were obtained using analysis of variance for continuous variables and the chi-square test for categorical variables.

3.1.1 Pattern of chronic pain locations

We found 128 unique combinations of chronic pain locations with 6 to 8,207 persons per combination. We presented the 20 most prevalent combinations of chronic pain locations in Figure S2, ranked according to their prevalence. The most prevalent combination included neck and back, representing 5.7% of persons with multiple chronic pain locations. The second, third, fourth, and fifth most prevalent combination included back and knee, neck and knee, head and neck, all seven locations over body, and head and back, representing 5.4%, 4.5%, 4.5%, 4.1%, and 3.6% of persons with chronic pain in multiple locations, respectively. Back, neck, and knee were each presented 13, 12, and 12 times in the 20 most prevalent combinations of chronic pain locations, respectively, while face and stomach pain were each represented only once.

3.1.2 Associations between the pattern of chronic pain and dementia

Figure S2 presented the dementia rates of persons in each of the 20 most prevalent chronic pain locations, ranging from 0.73 to 2.95 per 1,000 PYs. Elevated dementia rates were consistently associated with a greater number of locations reporting chronic pain. Notably, the highest incidence rate of dementia (2.95 per 1,000 PYs) was observed in individuals experiencing chronic pain in the neck, back, hip, and knee. This was followed by a prevalence of 2.72 per 1,000 PYs for those reporting chronic pain throughout the body, and the combination of back, hip, and knee ranked third with an incidence rate of 2.62 per 1,000 PYs. Within the top three combinations associated with high dementia

prevalence, the presence of chronic pain in the back, hip, and knee concurrently was a consistent factor.

In contrast, the last three chronic pain combinations associated with dementia prevalence exhibited distinct patterns. The combination of head and stomach, representing 1.5% of the population with pain in multiple locations, showed a dementia incidence rate of 0.73 per 1,000 PYs. Following this, the combination of head and neck, encompassing 6,377 individuals (4.5% of the multiple-pain locations population), presented a dementia incidence rate of 0.74 per 1,000 PYs. Lastly, the combination of head and back, involving 5,206 individuals (3.5% of the multiple-pain locations population), exhibited a dementia incidence rate of 0.78 per 1,000 PYs.

Figure S2. The twenty most prevalent chronic pain combination groups and dementia incidence rates among 143,085 persons reporting chronic pain in multiple locations.

After multivariable adjustment, 10 out of 20 chronic pain combinations were associated with a significantly higher hazard of dementia than those with no chronic pain, with hazard ratios (HRs) ranging from 1.28 to 1.85 (Table 2). Persons with pain in all locations had the highest HR, followed by persons with pain in five locations (back, neck, knee, head, and hip; HR=1.73) and those with pain in four locations (back, neck, knee, and hip; HR=1.68). Back, neck, and knee was presented in nine, eight, and seven combinations significantly associated with a higher hazard of dementia, respectively; back and knee, back and neck, neck and knee were simultaneously presented in six, five, and five combinations, respectively; back, neck, and knee were simultaneously presented in four combinations.

Most of the ten combinations mentioned above remained to be associated with a significantly higher hazard of dementia than the group with a single location with chronic pain not included in the combination (e.g., back and neck vs. hip), except for the combination of neck and hip (Table 2). Fewer combinations were significantly associated with a higher hazard of dementia than the group with a single location with chronic pain within the combination (e.g., back and neck vs. back). The HRs for three combinations involving back, neck, or knee (back and neck, back and knee, and back, neck, and knee) reduced and were no longer significant.

Table 2. Unadjusted and adjusted cox regression of all-cause dementia on pain location group (N=445,530).

			Without chronic pain (N=254,913)		Single location pain			
					Outside combination		Inside combination	
Pain locations	Group rank	Prevalence N (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted[*] HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
2	Neck, back	8,207 (5.7%)	**1.47 (1.26, 1.72)**	**1.28 (1.09, 1.50)**	**1.35 (1.14, 1.61)**	**1.27 (1.07, 1.51)**	1.10 (0.93, 1.31)	1.08 (0.91, 1.29)
	Back, knee	7,664 (5.4%)	**1.67 (1.44, 1.95)**	**1.30 (1.12, 1.51)**	**1.63 (1.37, 1.93)**	**1.28 (1.08, 1.53)**	**1.22 (1.04, 1.45)**	1.13 (0.96, 1.34)
	Neck, knee	6,406 (4.5%)	**1.43 (1.20, 1.71)**	1.09 (0.91, 1.31)	**1.33 (1.09, 1.61)**	1.00 (0.83, 1.22)	1.07 (0.88, 1.29)	1.01 (0.83, 1.23)
	Head, neck	6,377 (4.5%)	0.68 (0.53, 0.88)	0.89 (0.69, 1.14)	0.51 (0.40, 0.67)	0.81 (0.62, 1.05)	0.70 (0.53, 0.92)	0.89 (0.67, 1.16)
	Head, back	5,206 (3.6%)	0.71 (0.54, 0.94)	0.93 (0.70, 1.22)	0.55 (0.41, 0.73)	0.89 (0.67, 1.19)	0.68 (0.51, 0.91)	0.83 (0.62, 1.11)
	Back, hip	3,860 (2.7%)	**1.53 (1.23, 1.91)**	1.11 (0.89, 1.38)	**1.34 (1.06, 1.69)**	1.08 (0.86, 1.36)	1.16 (0.91, 1.47)	0.93 (0.73, 1.19)
	Head, knee	3,843 (2.7%)	0.84 (0.63, 1.13)	0.98 (0.73, 1.31)	0.65 (0.48, 0.88)	0.87 (0.64, 1.17)	0.79 (0.58, 1.08)	1.02 (0.75, 1.38)
	Hip, knee	3,745 (2.6%)	**1.47 (1.17, 1.86)**	0.99 (0.78, 1.24)	**1.30 (1.02, 1.65)**	0.89 (0.70, 1.13)	1.11 (0.87, 1.42)	0.96 (0.75, 1.23)
	Head, stomach	2,123 (1.5%)	0.67 (0.43, 1.04)	1.02 (0.66, 1.59)	0.50 (0.32, 0.78)	0.93 (0.60, 1.45)	0.99 (0.62, 1.59)	1.12 (0.70, 1.80)
	Neck, hip	2,046 (1.4%)	**1.89 (1.44, 2.49)**	**1.38 (1.05, 1.82)**	**1.61 (1.22, 2.13)**	1.28 (0.97, 1.70)	**1.49 (1.11, 1.99)**	1.31 (0.98, 1.76)
3	Neck, back, knee	4,864 (3.4%)	**1.69 (1.40, 2.04)**	**1.23 (1.02, 1.48)**	**2.03 (1.62, 2.55)**	**1.29 (1.02, 1.62)**	**1.25 (1.03, 1.53)**	1.08 (0.89, 1.32)
	Head, neck, back	4,372 (3.1%)	0.92 (0.71, 1.20)	1.11 (0.85, 1.45)	0.71 (0.54, 0.93)	1.09 (0.83, 1.45)	0.81 (0.62, 1.07)	0.99 (0.75, 1.30)
	Back, hip, knee	3,324 (2.3%)	**2.47 (2.04, 2.99)**	**1.56 (1.29, 1.89)**	**2.47 (2.00, 3.05)**	**1.51 (1.22, 1.88)**	**1.83 (1.50, 2.24)**	**1.40 (1.14, 1.72)**
	Head, neck, knee	2,555 (1.8%)	**1.56 (1.19, 2.03)**	**1.63 (1.25, 2.13)**	1.20 (0.91, 1.59)	**1.40 (1.06, 1.86)**	**1.36 (1.04, 1.79)**	**1.62 (1.23, 2.14)**
	Neck, back, hip	2,412 (1.7%)	**2.14 (1.69, 2.72)**	**1.49 (1.17, 1.89)**	**1.99 (1.55, 2.57)**	**1.51 (1.17, 1.95)**	**1.63 (1.27, 2.08)**	**1.29 (1.01, 1.66)**
	Head, back, knee	2,410 (1.7%)	1.11 (0.80, 1.53)	1.13 (0.82, 1.56)	0.89 (0.63, 1.24)	1.07 (0.76, 1.50)	1.06 (0.65, 1.72)	1.00 (0.62, 1.63)
4	Neck, back, hip, knee	3,413 (2.4%)	**2.77 (2.31, 3.31)**	**1.68 (1.40, 2.01)**	**2.03 (1.66, 2.49)**	**1.62 (1.31, 2.00)**	**2.07 (1.72, 2.50)**	**1.51 (1.25, 1.82)**
	Head, neck, back, knee	2,761 (1.9%)	1.21 (0.90, 1.62)	1.19 (0.89, 1.59)	1.03 (0.74, 1.44)	1.18 (0.84, 1.66)	1.00 (0.75, 1.35)	1.08 (0.80, 1.45)
5	Head, neck, back, hip, knee	2,010 (1.4%)	**2.18 (1.68, 2.82)**	**1.73 (1.34, 2.24)**	**1.91 (1.33, 2.74)**	**1.56 (1.07, 2.28)**	**1.81 (1.39, 2.35)**	**1.59 (1.22, 2.08)**
7	Head, face, neck, back, stomach, hip, knee	5,859 (4.1%)	**2.56 (2.21, 2.95)**	**1.85 (1.59, 2.14)**	1.00	1.00	**2.13 (1.83, 2.47)**	**1.63 (1.39, 1.92)**

Abbreviations: HR, hazards ratio.

[a] Adjusted for age, sex, ethnicity, education, deprivation index, smoking, alcohol use, physical activities, and comorbidities.

4. Discussion

This study investigated the prevalence of chronic pain location combinations and their associations with all-cause dementia in a large, nationwide sample of middle-aged and older community-dwelling adults. The size of the combination of chronic pain locations varied hugely, ranging from 6 to 8,207 persons per combination. Pain is not randomly present in different body locations; chronic pain in back, neck, and knee was each present in over half of the 20 most prevalent combinations. The dementia rates were higher among combinations involving more locations of chronic pain. Chronic pain in back, neck, and knee was commonly present either individually or simultaneously (e.g., back and knee) in combinations significantly associated with higher dementia rates than persons with no chronic pain. The combinations involving back, neck and knee were also associated with greater dementia rates than groups with one pain location not included in the combination.

4.1 Decoding diverse chronic pain patterns

We identified 128 unique combinations of chronic pain locations; the combination size varied hugely from 6 to 8,207 persons. Chronic pain is not present uniformly across all body locations; chronic pain in back, neck, and knee was each present in over half of the 20 most prevalent combinations. This finding is consistent with several studies suggesting back, neck, and knee are the most common locations bearing chronic pain. The study by Takahashi provides insights into chronic pain patterns among community-

dwelling individuals aged between 40 to 74 years old, emphasizing the prevalence of chronic pain in the back and knee.[96] In parallel, a 12-year follow-up cohort study conducted within a general population context involving 214 participants identified pain among neck, back and knee.[97] Their results suggest that manifests simultaneously in various anatomical regions within individuals through intricate and non-random patterns, underscoring the imperative to transcend a simplistic count-based approach in both research and medical practice. Individuals exhibiting comparable pain burden, as assessed by a simple count of pain locations, might represent clinically distinct subgroups necessitating different treatment strategies.

4.2 Pain patterns and dementia risks

We found the dementia rates to be higher among combinations involving more locations of chronic pain. This result aligns with a study utilizing the same dataset from the UK Biobank, encompassing 356,383 participants without a prior diagnosis of dementia at baseline. It suggests that higher counts of chronic pain locations were associated with elevated dementia risks.[98]

The correlation between chronic pain and dementia has been rigorously investigated, and a plethora of studies consistently signify the discernible influence of chronic pain on cognitive decline, emphasizing the heightened risks associated with the development of dementia. Persistent pain is connected to accelerated memory decline and

an elevated likelihood of developing dementia.[90] Consistent conclusions were demonstrated in efforts exploring chronic pain and multimorbidities among older adults.[52]

The specific locations of chronic pain have been identified as influential factors. However, studies have encountered considerable challenges in identifying pain patterns and associated neuropsychiatric symptoms in patients with dementia. This difficulty arise primarily from the impaired condition of individuals within this population.[53,99] In particularly, the processing of pain involving areas of the medical pain system is impaired in patients with severe dementia, even though the pain stimulus itself is perceived adequately.[100]

In addition, the temporal relationships between pain intensity and pain interference with incident dementia were investigated, exploring the progression of pain and its potential association with dementia development. Among the 1,114 participants aged 70 years old included in the Einstein Aging Study (EAS), pain interference was significantly associated with the progression of dementia, rather than pain intensity.[101] In contrast, one research article in 2022 based on 498 older individuals from 12 nursing homes suggested no significant statistical association were found between chronic pain intensity and dementia incidence.[102]

These conflicting conclusions could potentially suggests lacking a comprehensive view in considering chronic pain's characteristics, our analysis revealed that among the

top 20 most prevalent combinations of chronic pain locations, half exhibited a heightened risk of dementia compared to those without chronic pain. Not all anatomical regions were uniformly represented within these ten combinations. Particularly noteworthy is the prominence of chronic pain in the back, neck, and knee, which emerged as frequently co-occurring either individually or concurrently within these patterns. Furthermore, our analysis of various chronic pain distributions indicates that numerous combinations are not strongly linked to higher dementia risks when compared to cases where chronic pain is isolated to a single location within the combination, suggesting that an increased presence of chronic pain locations does not necessarily lead to a significantly higher risk of dementia. These findings underscore the importance of prioritizing interventions targeting the concurrent presence of chronic pain in the back, neck, and knee.

4.3 Tailoring treatment

The complex and multifaceted nature of chronic pain management necessitates an individualized approach, as evidenced by previous studies revealing the varied manifestations of chronic pain among patients.[103,104] This emphasizes the vital meaning of tailored treatment plans to address the unique characteristics of each patient's experiences with chronic pain. Clinical guidelines for managing chronic pain recommend the inclusion of pain distribution information, along with pain location count, to form a comprehensive patient pain history, thereby enabling personalized treatment and ultimately improving cost-effectiveness and treatment outcomes.[105] However, within the framework of older individuals contending with cognitive impairment, a critical

exigency arises to address the existing lacunae in pain management. This particularly vulnerable demographic confronts issues encompassing pain-relief drug overdoses and a dearth of sufficient training for staffs and medicals students. These circumstances signifies the imperative for a thorough comprehension and integration of personalized strategies in the chronic pain management.[106,107]

Numerous investigations spanning the disciplines of chronic pain and dementia have collectively indicated potential underlying mechanisms, with a particular emphasis on neuroinflammation. Characterized by infiltration of immune cells, activation of glial cells, and generation of inflammatory mediators in both the peripheral and central nervous system, neuroinflammation plays a crucial role in the initiation and progression of chronic pain.[108] Furthermore, neuroinflammation has been associated with the pathogenesis of various neurodegenerative disease, encompassing Alzheimer's disease, Parkinson's disease, and Lewy body dementia where persistent inflammation is recognized as a contributor to neurodegeneration and cognitive impairment.[109,110] Despite these findings, our understanding of the intricate mechanisms linking chronic pain and dementia remains limited. Exploring specific combinations of chronic pain locations could provide valuable insights into identifying and intervening in cases of dementia.

The anatomical localization of chronic pain is acknowledged as a pivotal consideration in informing clinical decision-making procedures. The conventional gold standard for chronic pain measurement has historically relied on self-reporting, akin to

the methodologies employed in assessing depression. A scale was established to gather information on three self-efficacy elements related to pain, encompassing pain management, the capability to cope with symptoms, and physical functions.[111] While debates exist on this matter, the primary argument in favor of self-reporting measures posits that they are best suited for capturing the chronic pain experience from the patient's perspective.[112]

Recent advancements in pain location measurement, particularly through pain drawing, have significantly enhanced precision.[113-116] The utilization of pain drawing was initially introduced in the field of chronic pain in 1986, where a study involving 101 patients experiencing chronic pain required them to complete a drawing consists of 45 body areas. This approach yielded results that were highly comparable to the penalty point system widely approved at the time. However, it became evident that pain drawing accounted for a substantial portion of the variance in chronic pain distribution.[116] Subsequently, a reliability test conducted two years later further confirmed that self-reporting and pain drawing were reasonably stable and highly useful.[115] Several decades later, technological advancements facilitated the transition to a computerized self-reporting process. Its reliability was assessed across 117 bodily locations of pain, yielding a credible analysis of 52 graphical pain distributions with high reliability.[114] This technological development enhances the precision in detecting pain distribution, consequently contributing to the generation of research evidence characterized by increased accuracy and dependability. Such progress holds promise for advancing our

comprehension of the intricate relationship between chronic pain and dementia, with potential implications for the enhancement of patient care.

4.4 Implications

This study opened up new avenue in understanding chronic pain bodily distribution and corresponding association with dementia incidence. In clinical terms, revised definition of pain by the International Association for the Study of Pain (IASP) specifically classified chronic pain as an independent disease. The classification consist of chronic primary pain (CPP), chronic cancer related pain (CCRP), post traumatic pain (CPTP), chronic secondary musculoskeletal pain (CSMSP), chronic secondary visceral pain (CSVP), chronic neuropathic pain (CNP), chronic secondary headache or orofacial pain (CSH).[117]

Under the guidelines of this newly revised IASP classification of chronic pain, most popular pain locations identified were neck ,back, and knee. These common locations falls under the definition of chronic primary musculoskeletal pain(CPMP), which consists of neck, chest, low back, and limb. As prior research suggests CPMP as a potential risk factor for dementia incidence, however, it is worth analyzing specific combinations to aid the process of diagnosing dementia at a relatively early stage.[98] This study statistically suggested chronic pain commonly presents in combinations instead of single locations, in clinical process, patients could potentially experience combined risk instead of isolated in body parts. In particularly, patients report having chronic pain in

neck, back, and knee possess the highest priority in early stage dementia diagnostic. Furthermore, for dementia patients already experiencing chronic pain, certain combinations are of higher benefit for easing dementia progression while some other combinations with lower dementia risks might call for less aggressive pain-relief schemes to enhance pain treatment.

4.5 Strength and limitations

This study has advanced our understanding of multisite chronic pain combinations, and its robustness is underscored by several notable aspects. First, the study draws upon data from the UK Biobank, an ongoing cohort study comprising a large sample size of approximately 500,000 individuals aged between 40 and 69 years.[118] By employing a cross-sectional design, the research adeptly examines chronic pain prevalence and its potential connection to dementia outcomes. Third, this investigation contributes to the evolving chronic pain literature by meticulously identifying and comparing prevalent chronic pain combinations within a representative population. This methodology signifies a substantial progression beyond previous research endeavors that exclusively focused on predetermined pain locations or quantification of the number of chronic pain sites.[92,98,113,119,120] To the best of our knowledge, there is currently no prior research postulating the relationship between chronic pain combinations and the incidence of dementia. Thus, our study makes a substantial contribution to the existing literature by furnishing direct comparisons between prevalent chronic pain combination cohorts and their healthy counterparts, as well as individuals experiencing chronic pain in single

locations. This approach offers essential insights into identifying which chronic pain combinations present the most significant risks for dementia incidence.

We acknowledged several limitations. First, the chronic pain location was self-reported, potentially leading to misclassification bias. However, recent research supports self-reported chronic pain as the the gold standard for capturing this inherently personal and internal sensation.[113] Clinically, sensory intensity typically forms the cornerstone of chronic pain assessment, prompting the development of various tools, including numerical rating scales, visual analog scales, pain drawings, and electronic pain measures, catering to the demands of academic inquiry and clinical practice. Second, the results are based on a sample from the general population in the UK, raising concerns about generalizability of our findings to a global context. Future research using populations from other countries and regions is needed. Third, we focused on the chronic pain location in did not explicitly consider severity, a fundamental aspect frequently evaluated in chronic pain. Future investigations could incorporate additional dimensions such as pain intensity, distribution across the body, and temporal characteristics to enhance the precision of chronic pain assessment and augment clinical utility.[113] Lastly, the information on chronic pain might be susceptible to recall bias, which could lead to an underestimation of chronic pain prevalence.

5. Conclusion

In summary, chronic pain is not randomly present in body locations and the patterns of chronic pain locations are complex. Chronic pain in back, neck, and knee presents frequently either individually or simultaneously in combinations associated with increased dementia rates. This study has opened a new avenue for comprehending the association between chronic pain and dementia. Understanding how different patterns of chronic pain locations relate to dementia provide new insights into dementia prevention through pain relief.

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