





Dual-Site Pain in the Low Back and Knee as a Risk Factor for Dementia: A Population-Based Cohort Study

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Purpose: Chronic pain is a major public health concern and has been linked to cognitive decline. However, the effect of pain occurring simultaneously in two musculoskeletal sites on dementia risk remains unclear. In this study, we aimed to examine whether dual-site pain (DSP; in this study defined as cooccurring chronic low back and knee pain) is associated with an increased risk of dementia in community-dwelling older adults.

Patients and Methods: We analyzed data from 2060 participants aged ≥ 65 years in the Locomotive Syndrome and Health Outcomes in the Aizu Cohort Study. DSP was defined as the presence of both chronic low back and knee pain lasting >3 months. Participants without DSP served as the reference group. Incident dementia was identified from long-term care insurance certification records, and Cox proportional hazards models were used to estimate hazard ratios (HRs) adjusting for demographic and vascular risk factors, depressive symptoms, and physical activity.

Results: Over 6 years, 197 participants (9.6%) developed dementia. The incidence was higher in the DSP group (16.5%, 26/158) than in the control group (9.0%, 171/1902). After adjustment, DSP remained significantly associated with dementia (HR = 1.57, 95% CI: 1.02–2.42).

Conclusion: Dual-site pain involving the low back and knee is a significant risk factor for dementia among older adults. Early identification and management of DSP may help preserve cognitive health, highlighting the need for integrated strategies addressing both musculoskeletal and cognitive well-being.

Keywords: dual-site pain, dementia, epidemiology, cohort study

Introduction

The global population is aging rapidly, with no indications of this trend slowing down.¹ With the aging population, the incidence of dementia increases. In 2019, the global economic burden of dementia was estimated at USD 1.3 trillion globally, a figure projected to increase in the coming years.² Therefore, preventing dementia and extending healthy life expectancy are critical. Although various preventive measures against dementia have been proposed, identifying new insights that can contribute to its prevention remains a primary focus.

Chronic pain is defined as pain that persists for > 3 months and has been reported to accelerate memory loss and increase the risk of dementia.³ Notably, chronic pain affects $>30\%$ of the global population, imposing substantial economic and healthcare burdens.⁴ With an aging society, the prevalence of multisite chronic pain (MCP) is expected to increase further. Consequently, in orthopedic clinics, patients who have cooccurring chronic low back and knee pain are commonly encountered globally.^{5,6} Recent evidence has suggested an association between musculoskeletal disorders

and cognitive function,^{7–9} suggesting that appropriate treatment may help prevent cognitive decline. However, the mechanisms underlying this association remain unclear. Notably, a Japanese prospective cohort study reported that the coexistence of chronic low back and knee pain was associated with an increased risk of dementia, highlighting the potential importance of pain affecting these two sites.¹⁰ However, in that study, pain was not restricted to chronic conditions, and it remains unclear whether persistent dual-site pain confers a higher risk of dementia than single-site pain.

We therefore hypothesized that dual-site pain (DSP; in this study, defined as cooccurring chronic low back and knee pain) may serve as a risk factor for dementia development.¹¹ Accordingly, the present study aimed to evaluate whether DSP increases the risk of dementia in community-dwelling older adults. Understanding the links between musculoskeletal health and neurological disorders could not only inform strategies to alleviate chronic pain but also improve cognitive function, enabling early interventions that enhance the quality of life of older adults.

Materials and Methods

Study Design

This study used data from the Locomotive Syndrome and Health Outcomes in the Aizu Cohort Study (LOHAS), a population-based prospective cohort study investigating the risk factors for cardiovascular disease, quality of life, medical costs, and mortality attributable to locomotor dysfunction. LOHAS also provides epidemiological information required for policymaking regarding locomotor dysfunction detection. Participants in the LOHAS were residents of Minamiaizu and Tadami in Fukushima Prefecture, Japan, who underwent regular health examinations conducted by the municipalities in 2009 and opted for locomotor health examinations. All examinations were performed simultaneously. Details of the study design have been previously described.¹² Inclusion criteria were age ≥ 65 years and completion of a questionnaire on chronic low back and knee pain.

For indicating low back pain, a diagram of the lower back was provided, and participants were asked to indicate if they experienced pain in the illustrated area. The duration of pain was categorized as <1 , 1–3, >3 months. No diagram was provided for knee pain; however, the same duration options were used. In both cases, pain lasting >3 months was classified as chronic pain. We excluded participants with missing data, those with dementia at baseline, and those who had passed away or relocated. Additionally, we used data from long-term care insurance certification (LTCI) in Japan to identify participants requiring care. Specifically, this care refers to the support and services provided to individuals certified as needing long-term care, including assistance with daily activities, physical rehabilitation, and other forms of support tailored to their level of care needs.

Previous studies from our group have examined the associations between lumbar spinal stenosis or radiographic knee osteoarthritis and dementia risk within the same regional framework. However, the present analysis is distinct in that it focuses on self-reported dual-site chronic pain in the low back and knee, based on questionnaire data from a different recruitment phase of the LOHAS cohort.^{7,8}

All participants provided written informed consent for the use of their data before participating in the study, which included consent for the future use of administrative data, including LTCI certification data obtained from municipal governments for research purposes. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Fukushima Medical University, Japan (approval No. 673). All participants provided written informed consent at enrollment in the Locomotive Syndrome and Health Outcomes in the Aizu Cohort Study (LOHAS), which included permission for the use of their questionnaire data and linkage with relevant administrative health data, such as Long-Term Care Insurance (LTCI) records. Therefore, additional consent to review medical or administrative records was not required by the Research Ethics Committee of Fukushima Medical University. All data were anonymized prior to analysis to ensure participant confidentiality.

Definition of DSP

The DSP group was operationally defined as those who answered “yes” to both “low back pain lasting more than 3 months” and “knee pain lasting more than 3 months” in the questionnaire. Those who did not meet these criteria were categorized into the control group.

Outcome Measures and Definition of Dementia

The primary outcome was the incidence of newly diagnosed dementia identified through the Japanese LTCI system, classified as class II or higher according to the criteria for dementia. Class II dementia is defined as follows:

They can be independent if someone pays attention to them, even if they show some symptoms/behaviors or communication difficulties that interfere with their daily lives.¹³

This definition has been widely used in previous Japanese epidemiological studies based on LTCI records to identify dementia.^{14,15} The diagnosis of dementia was based on opinion statements submitted by the attending physicians to the municipality and standardized in-home assessments conducted by trained personnel as part of the LTCI certification process. The date of LTCI certification was used as the date of dementia onset in the survival analyses. Using the official LTCI data, we comprehensively investigated the incidence of dementia in community-dwelling older adults.

Measurement of Confounding Factors

Based on current evidence, we included age, sex, and vascular risk factors, such as diabetes, hypertension, dyslipidemia,^{16,17} depressive symptoms,^{18,19} and daily activity.^{20,21} Diabetes mellitus was defined as a random glucose concentration ≥ 200 mg/dL, a fasting glucose concentration ≥ 126 mg/dL, a glycosylated hemoglobin level $\geq 6.5\%$, or the use of hypoglycemic medication. Hypertension was defined as systolic blood pressure >130 mmHg, diastolic blood pressure >85 mmHg, or antihypertensive medication use. Dyslipidemia was defined as a fasting blood count of low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, triglyceride level ≥ 150 mg/dL, or use of dyslipidemia medication.

Depressive symptoms were identified using the Center for Epidemiologic Studies Depression Scale (CES-D), which comprises 20 items. The CES-D is a self-reported questionnaire where participants evaluate their mood and behavior over the past week. A score of ≥ 10 was defined as having depressive symptoms.²²

Daily activity was defined as “moderate-intensity walking or exercise at least once a week” based on the rating chart devised by the International Physical Activity Questionnaire (IPAQ).²³ Moderate-intensity exercise was defined as exercise accompanied by light sweating (3.0–5.9 metabolic equivalents; METs).²⁴ In the present study, exercise below this level (<3.0 METs) was assessed as a low activity level.

Statistical Analysis

All investigated factors were compared across groups using *t*-tests and chi-squared tests. Demographic characteristics, main exposure (DSP), and outcomes (dementia development) were described as appropriate indices. The effect measures included *p*-values from the Log rank test and hazard ratios (HRs) derived from the Cox proportional hazards model adjusted for similar confounders. The proportional hazards assumption of the Cox model was tested using Schoenfeld residuals, and no violations were detected in the global test ($p = 0.149$).

Statistical analyses were performed using JMP Pro version 16.0.0 (SAS Institute Inc., Cary, NY, USA). A *p*-value of <0.05 was considered significant.

Sensitivity Analysis

To assess the robustness of the primary findings, we conducted a sensitivity analysis using an alternative exposure definition. Participants were categorized into four groups based on their baseline pain status: pain-free, knee pain only, low back pain only, and DSP. Cox proportional hazards models, adjusted for the same confounders as in the primary analysis, were used to estimate hazard ratios for incident dementia, with the pain-free group serving as the reference category.

Results

Study Participants and Outcome Data

Of the 3790 participants from the LOHAS in 2009, 2514 remained after excluding those with missing data or aged <65 years. Among these, 19 had dementia at baseline, 97 died during the follow-up, and 338 relocated. After these exclusions, a total of 2060 participants were included in the final analysis (Figure 1).

Baseline Characteristics of Participants

Table 1 summarizes the baseline characteristics of the participants. The mean age was 72.5 years, and 59.5% were women. The DSP group included 158 participants, whereas the control group included 1902 participants. The DSP group had a significantly higher proportion of women (72.8% vs 58.1%), more individuals with depressive symptoms (18.4% vs 7.8%), and lower levels of daily activity (62.0% vs 50.9%) than those in the control group ($p < 0.001$).

Study Outcome: Dementia

All participants were included in the final analysis. Among the 2060 participants, 197 (9.6%) developed dementia in 2015, including 26 (16.5%) and 171 (9.0%) participants in the DSP and control groups, respectively. The DSP group exhibited a significantly higher incidence of newly diagnosed dementia compared with the control group ($p < 0.001$).

Over the 6-year follow-up period, Kaplan–Meier curves were used to depict the cumulative incidence of dementia development between the two groups. The curve demonstrated significant divergence, as supported by the Log rank test ($p < 0.001$; **Figure 2**).

Risk Factors for the Development of Dementia

Cox regression analysis indicated a higher rate of dementia development in the DSP group than in the control group after adjusting for confounding factors (HR = 1.57, 95% confidence interval; 1.02–2.42) (**Table 2**).

Pain Status and the Risk of Dementia

In a sensitivity analysis using an alternative four-category pain classification, only participants with DSP showed a significantly higher risk of development of dementia compared with pain-free group, whereas knee pain only and low back pain only were not significantly associated with development of dementia (**Table 3**).

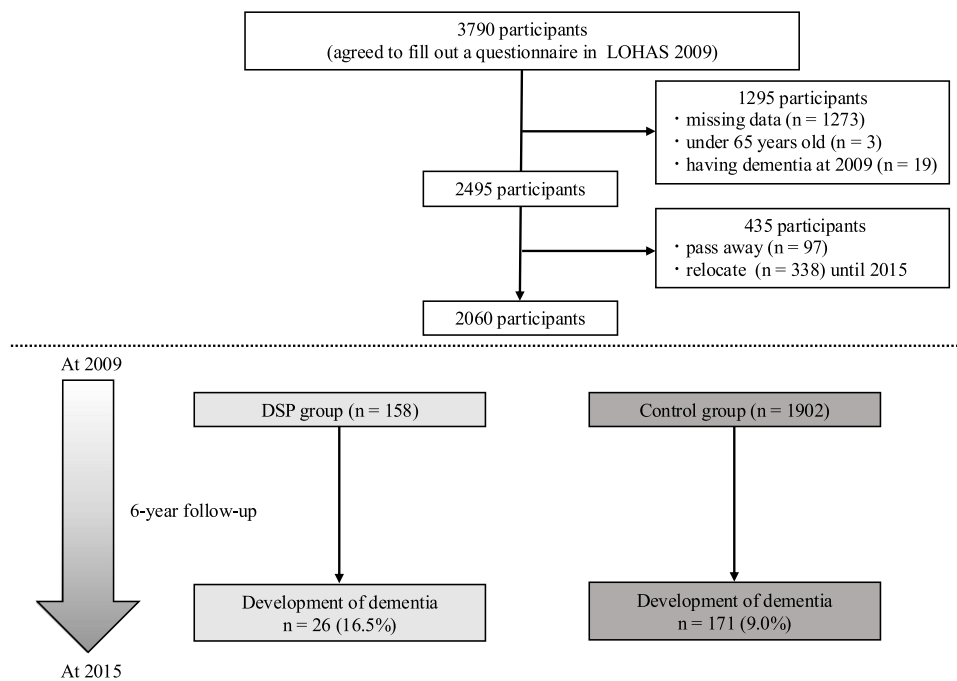


Figure 1 Flowchart of participant selection and follow-up. This flowchart illustrates the selection process of the study cohort and follow-up outcomes from 2009 to 2015. It presents the initial number of participants, exclusion criteria (age, pre-existing conditions, death, or relocation), and outcomes. Of the 3790 eligible participants, 2060 were followed up for >6 years, and data on dementia incidence were collected.

Abbreviation: LOHAS, Locomotive Syndrome and Health Outcomes in the Aizu Cohort Study.

Table 1 The Demographic Data of Participants in the DSP Group and Control Group

	Total N = 2060	DSP Group n = 158	Control Group n = 1902
Age (average \pm SD)	72.5 \pm 4.4	72.6 \pm 4.1	72.5 \pm 4.1
Sex (female)	1221 (59.5%)	115 (72.8%)*	1106 (58.1%)
Hypertension	1529 (74.2%)	123 (77.8%)	1406 (73.9%)
Diabetes	735 (35.7%)	58 (36.7%)	677 (35.6%)
Dyslipidemia	1107 (53.7%)	84 (53.2%)	1023 (53.8%)
CES-D \geq 10	177 (8.6%)	29 (18.4%) *	148 (7.8%)
Low Daily Activity	1066 (51.7%)	98 (62.0%) *	968 (50.9%)

Notes: Daily activity: Defined by the rating chart devised by the IPAQ (International Physical Activity Questionnaire) as "moderate-intensity walking or exercise at least once a week". *Statistically significant difference between the DSP group and the Control group ($p < 0.05$).

Abbreviations: DSP, Dual site pain; SD, Standard Deviation; CES-D, the Center for Epidemiologic Studies Depression scale.

Discussion

This study demonstrated that participants with cooccurring chronic low back and knee pain (DSP) had a significantly higher risk of developing dementia over a 6-year follow-up period, even after adjusting for age, sex, diabetes, hypertension, dyslipidemia, depressive symptoms, and daily activity. These findings highlight DSP as an independent risk factor for dementia in community-dwelling older adults.

Our findings are consistent with previous studies reporting an association between chronic pain at multiple sites and the risk of dementia, demonstrating that dementia risk increases with the number of chronic pain sites, suggesting a cumulative effect of multisite pain on cognitive decline.²⁵ In a Japanese prospective cohort¹¹ also reported that the coexistence of knee pain and low back pain was associated with a higher risk of dementia. Extending these findings, our study showed that DSP involving the low back and knee, but not single-site pain, was independently associated with the development of dementia after comprehensive adjustment for confounding factors.

Several biological pathways may explain the association between DSP and dementia. Central sensitization may promote the transition from localized to more widespread pain, lowering the pain threshold and producing hypersensitivity.²⁶ Chronic pain can also spread to additional body regions through altered gait and biomechanical changes,^{27–29} which might increase

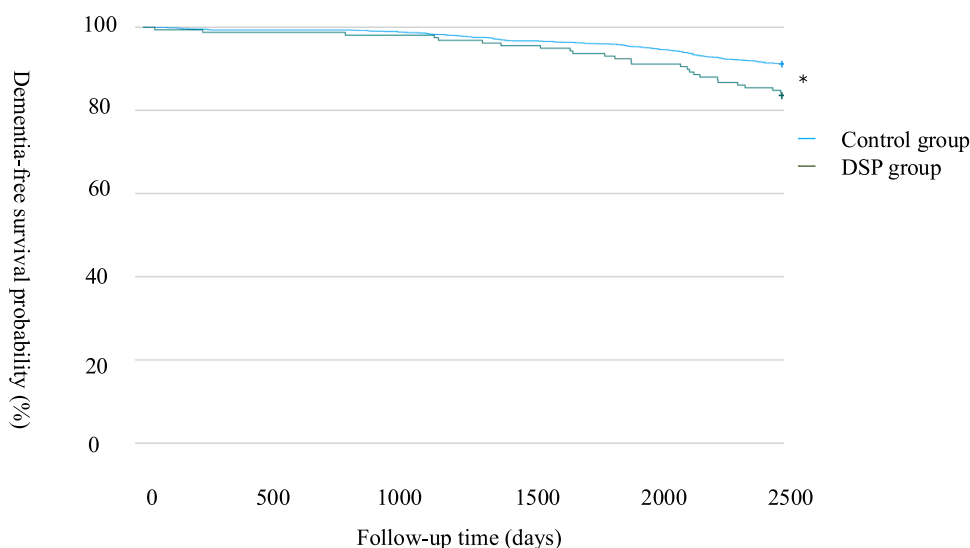


Figure 2 Cumulative Incidence of Dementia: Kaplan–Meier Analysis. Kaplan–Meier curves illustrate the cumulative incidence of dementia development between the two groups, exhibiting significant divergence, as evidenced by the Log rank test ($p < 0.001$). * $p < 0.001$.

Abbreviation: DSP, Dual-site pain.

Table 2 Association Between DSP and the Development of Dementia Using Cox Proportional Hazards Model

Variable	HR (CI)	p value
DSP	1.57 (1.02–2.42)	0.039
Age (per year)	1.19 (1.15–1.23)	< 0.001
Sex (female)	1.12 (0.82–1.52)	0.466
Hypertension	0.87 (0.61–1.24)	0.435
Diabetes	1.17 (0.85–1.60)	0.333
Dyslipidemia	0.84 (0.62–1.15)	0.277
CES-D \geq 10	1.56 (1.00–2.42)	0.523
Daily Activity	0.85 (0.52–1.39)	0.050

Abbreviations: DSP: Dual site pain. HR: Hazard Ratio. CI: Confidence Interval. CES-D: the Center for Epidemiologic Studies Depression scale.

Table 3 Sensitivity Analysis of the Association Between Pain Status and the Development of Dementia

Pain Status	Number of Subjects	Development of Dementia	HR (CI)	p value
Pain-free	1495	133 (8.9%)	Reference	-
Low back pain only	198	18 (9.1%)	0.95 (0.59–1.54)	0.85
Knee pain only	209	20 (9.6%)	0.99 (0.61–1.60)	0.95
DSP group	158	26 (16.5%)	1.56 (1.01–2.43)	0.047

Abbreviations: DSP, Dual site pain; HR, Hazard Ratio; CI, Confidence Interval.

the overall burden of pain and its effect on cognitive function. Chronic pain has additionally been linked to hippocampal atrophy¹⁷ and microglial activation, which may induce neuronal apoptosis and contribute to brain atrophy and cognitive decline.^{3,30} Furthermore, DSP may indirectly increase dementia risk through reduced physical activity and comorbid depression, both of which are well-established risk factors for cognitive impairment.^{18,21,31}

A major strength of this study was the use of a population-based prospective cohort with a 6-year follow-up, allowing for the temporal assessment of pain and dementia onset. However, several limitations should be acknowledged. First, dementia diagnosis was based on opinion forms for long-term care certification rather than internationally standardized diagnostic tools (eg, ICD or DSM), and participants without certification were presumed to be dementia-free. In addition, the date of LTCI certification was used as the date of dementia onset, which may not exactly reflect the true clinical onset and could result in temporal misclassification. Second, the study was limited to rural older adults, and dementia outcomes were identified only among individuals who applied for LTCI certification, which may affect generalizability. Third, we lacked information on pain severity, duration, or treatment during follow-up, and we were unable to capture pain at sites other than the low back and knee. Fourth, although we observed significant differences, the relatively small size of the DSP group may have limited the statistical power. Finally, the “pain-free” category may have included individuals with pain at other sites; therefore, we cannot definitively conclude that single-site pain is unrelated to dementia.

These findings highlight the importance of comprehensive pain management strategies, including physical therapy, psychological support, and routine monitoring of chronic pain, as potential interventions to delay dementia onset. From a research perspective, future studies should incorporate standardized dementia diagnostic tools, detailed pain assessments (including severity and treatment), and resilience factors that may protect against cognitive decline even in individuals with DSP. Larger, more diverse cohorts are warranted to confirm these findings and to further clarify the mechanisms linking musculoskeletal pain and dementia.

Conclusion

This population-based prospective study demonstrated that cooccurring chronic low back and knee pain are significant risk factors for the development of dementia in older adults. These findings suggested that identifying and managing DSP may contribute to delaying dementia onset and improving quality of life in aging populations. Comprehensive pain management strategies, including physical therapy, psychological support, and routine monitoring, should be considered as part of integrated approaches to preserve cognitive health. Future studies using standardized dementia diagnostics, detailed assessment of pain characteristics, and inclusion of other pain sites are warranted to confirm and extend these findings.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available at this time. However, the data can be made available on reasonable request from the corresponding authors.

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Disclosure

The authors report no conflicts of interest in this work.

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