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Research Article

Beyond pain presence: the impact of multisite pain and pain interference on cognitive functioning among middle-aged and older adults

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Abstract

Objectives: This study investigates the relationship between chronic pain and cognitive function in the U.S. middle-aged and older population, focusing on the impact of the number of pain sites. It also explores whether pain interference mediates the association between pain sites and cognition.

Methods: Data were drawn from the 2004–2006 and 2013–2017 waves of the Midlife in the United States Study (MIDUS 2 and MIDUS 3, $N = 2,219$). We fit inverse-probability-weighted models to examine the associations between pain status, number of pain sites (none vs. 1–2 vs. 3+ sites), and cognitive function in MIDUS 3, controlling for confounders from MIDUS 2. The Sobel–Goodman mediation test with Bonferroni-adjusted significance level was applied to assess the mediating role of pain interference in five domains: activities, mood, relationships, sleep, and enjoyment.

Results: Among those with chronic pain, 40% report pain in three or more sites. There was no significant difference in cognitive function between individuals with and without chronic pain. However, individuals with pain in 3+ sites had significantly poorer cognitive function than those with no pain or pain in 1–2 sites. Pain interference significantly mediated over 50% of this association, with social relations being the strongest mediator, followed by mood.

Discussion: The mere presence of chronic pain may not significantly affect cognitive function, but having multi-site pain could be a risk factor for cognitive decline in later life. Addressing multi-site pain and/or pain interference in psychosocial dimensions may help protect cognitive health.

Keywords: Cognitive function, Chronic pain, Inverse-probability-weighted regression adjustment, Sobel–Goodman mediation test

Chronic pain is a significant public health concern in the United States (Grol-Prokopczyk, 2017; Grol-Prokopczyk et al., 2025; Zajacova et al., 2021). In 2021, approximately 20.9% of U.S. adults (i.e., 51.6 million) experienced chronic pain, and 6.9% (about 17.1 million) experienced high-impact (i.e., highly disabling) chronic pain (Rikard et al., 2023). Chronic pain is particularly prevalent among middle-aged and older adults, with many reporting pain in multiple sites (Butera et al., 2019; Zelaya et al., 2020). While some of pain's negative consequences are well-established (e.g., pain is strongly linked with functional limitations and disability; see Ruan et al., 2024), findings regarding the link between pain and cognition remain mixed (Innes & Sambamoorthi, 2020; Milani et al., 2023).

Some emerging evidence suggests that experiencing chronic pain is associated with accelerated cognitive decline and an increased risk of memory impairment (e.g., Van Der Leeuw et al., 2016). In contrast to an earlier meta-analysis that found persistent pain at baseline was not associated with subsequent cognitive decline (De Aguiar et al., 2020), a more recent meta-analysis of 37 studies argued that conclusions may vary depending on the cognitive assessment tools employed (Zhang et al., 2021). Specifically, associations between chronic pain and cognitive decline have been observed when certain evaluative methods were used (e.g., Short Form-36 Health Survey questionnaire). The mixed findings across studies may be due to differences in pain and cognitive measures, contexts, statistical approaches, and sample characteristics.

In this study, we evaluate the pain–cognition relationship using longitudinal data from a national sample of middle-aged and older adults and applying a statistical approach specifically designed to address causality in observational studies. In addition to using a dichotomous measure of pain, we explore the pain–cognition association by analyzing the number of pain sites—a measure of pain burden recommended by a growing number of pain epidemiologists (e.g., Natvig et al., 2010). Finally, we use mediation tests to assess five types of pain interference as potential mechanisms underlying the pain–cognition relationship. Overall, we aim to clarify the relationship between pain and cognitive function, both of which significantly impact the ability to live independently and one's overall quality of life.

The pain–cognition link

Although previous research suggests that poor executive function (EF) is associated with a higher risk of chronic pain (Ng & Hartanto, 2022), emerging evidence indicates that chronic

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pain is also linked to cognitive functioning, including worse cognitive function across memory, language, and calculation domains (Sun et al., 2024) and a faster decline in orientation, memory, and semantic fluency (Rong et al., 2021). The underlying pathways linking pain and cognitive function may involve attention competition, as pain requires attentional resources, thereby competing for the brain's limited capacity (Eccleston & Crombez, 1999). Moreover, pain has been associated with reductions in gray matter in key brain regions critical for cognition, including the insular cortex, hippocampus, and ventromedial and dorsolateral prefrontal cortex (Moriarty et al., 2011), which are often considered neurobiological markers of cognitive decline.

Recent research highlights the importance of considering variations in the number of pain sites for both epidemiological and neurobiological reasons. From an epidemiology perspective, pain at one site increases the likelihood of developing pain in additional areas (Natvig et al., 2010), emphasizing that multisite pain is more prevalent than single-site pain. For example, most individuals with musculoskeletal conditions experience pain in multiple locations rather than a single area (Doménech-García et al., 2024). Beyond its impact on physical function (Natvig et al., 2010), multisite pain is also associated with cognitive decline. A population-based cohort study from the United Kingdom (Zhao et al., 2023) found that individuals with multisite chronic pain exhibited a higher risk of dementia onset compared to those with single-site pain or no pain, underscoring the need to account for heterogeneity within the chronic pain population. However, few studies have examined this relationship using American national datasets, which is the primary focus of this study. It is particularly important to understand this in the U.S. context, given its high pain prevalence and leading rate of opioid prescriptions for chronic pain (Grol-Prokopczyk, 2017). From a neurobiological perspective, central sensitization—a condition characterized by heightened excitability of the central nervous system in response to pain stimuli—plays a key role in amplifying pain signals and driving multisite pain (Harte et al., 2018). This widespread pain perception may, in turn, overload cognitive resources, leading to cognitive decline (Eccleston & Crombez, 1999). These perspectives enhance our understanding of the relationship between the number of pain sites and cognitive health.

Accordingly, Croft (2009) has argued that the critical question is not simply "Do you have pain?" but rather, "How extensive is the pain?" This perspective emphasizes the need to attend to intragroup differences in pain burden (Natvig et al., 2010) and argues that research may miss valuable information if it focuses solely on the presence or absence of pain. Doing so obscures potentially meaningful differences among those in pain, including how the number of pain sites (e.g., head, neck, back, arms/hands, legs/feet, shoulders, hips, knees, and other locations) may affect cognitive function. Therefore, beyond examining the relationship between pain presence and cognitive function, our study investigates the association between the number of pain sites and cognitive function using a national American dataset.

Psychosocial mediators of pain–cognition link

Despite intriguing findings about how the number of pain sites predicts cognition, few studies have explored psychosocial interference as a potential mechanism underlying this link. However, individuals experiencing pain at multiple sites may face greater interference in their everyday life (Thomas et al., 2004), and increasing levels of pain interference are associated with cognitive decline (Milani et al., 2023)—suggesting a plausible causal chain. Moreover, previously used measures of pain interference often focus solely on the impact of pain on daily activities (Milani et al., 2023; Ullrich et al., 2008), but pain interference is multifaceted, encompassing not just activity but also mood, enjoyment, social relations, and sleep (Van Der Leeuw et al., 2016). Understanding these varied types of interference may offer deeper insights into the link between pain and cognition.

Each dimension of pain interference may make a unique contribution to cognitive decline. For instance, regarding pain interference with activity, older adults with multisite pain experience reductions in several physical function domains (Butera et al., 2019), a potential predictor of cognitive decline (Erickson et al., 2015). Regarding pain interference with mood, multisite pain among older individuals is linked to psychological dysfunctions, such as anxiety and depression (Butera et al., 2019), which have been identified as mediators in the pain–cognition relationship in patients with rheumatoid arthritis (Brown et al., 2002). Regarding pain interference with social relationships, severe pain is associated with significant losses in friendships (Yang & Grol-Prokopczyk, 2021), which are considered protective factors against cognitive decline (Kremen et al., 2012). In addition, pain's ability to interfere with sleep quality could affect cognition: Individuals with pain in multiple areas are more likely to suffer from sleep disturbances, such as insomnia (Husak & Bair, 2020), and poor sleep quality is linked to declines in aspects of cognition, including working memory, attentional set shifting, and abstract problem-solving (Nebes et al., 2009). Lastly, previous research has shown that pain-related interference with life enjoyment is a key concern for individuals with chronic pain (Turk et al., 2008), while enjoyment itself plays a vital role in maintaining cognitive health (Flatt & Hughes, 2013). By examining the various dimensions of pain interference, our study enhances understanding of how chronic pain, in particular chronic pain in multiple sites, may contribute to declines in cognitive functioning. We thus respond to the call to explore mechanisms underlying the pain–cognition relationship, as highlighted by Van Der Leeuw et al. (2016).

The present study

This study aims to evaluate the association between chronic pain and cognitive function in middle-aged and older adults using data from a national U.S. sample. First, we fit an inverse-probability-weighted regression to rigorously account for potential confounders to obtain robust estimates of how pain predicts cognitive function. Second, we evaluate potential heterogeneity among individuals with chronic pain by examining how cognitive function varies by the number of pain sites. Third, our research seeks to identify the underlying psychosocial mechanisms that help explain the relationship between pain and cognition, with a focus on the role of pain interference (i.e., pain that interferes with daily activities, mood, enjoyment, social relations, and sleep). Taken together, we propose three hypotheses:

Hypothesis 1: After adjusting for selection factors predicting different risks of pain, individuals with chronic pain exhibit poorer cognitive function than those without chronic pain.

Hypothesis 2: After accounting for intra-group heterogeneity within the pain group and weighting for selection factors associated with varying risks of pain sites, individuals without pain exhibit the highest cognitive function scores, those with a low number of pain sites show moderate cognitive function, and those with a high number of pain sites have the lowest cognitive function.

Hypothesis 3: Among individuals with chronic pain, five types of pain interference (i.e., in activity, mood, relations, sleep, and enjoyment) mediate the relationship between the number of pain sites and cognitive function. Individuals with a greater number of pain sites experience greater pain interference, which in turn negatively impacts their cognitive function.

Method

Participants

This study uses longitudinal data from Waves 2 and 3 of the Midlife in the United States study (MIDUS 2 and 3), a national longitudinal survey of non-institutionalized English-speaking American adults aged 25–74 years from 48 states, recruited via random digit sampling (Ng & Hartanto, 2022). MIDUS 1 was conducted in 1995–1996, followed by MIDUS 2 (2004–2006) and MIDUS 3 (2013–2014). Participants completed phone interviews and mailed self-administered questionnaires. In MIDUS 2 and 3, a subset completed 30-min phone-based cognitive tasks (Ng & Hartanto, 2022).

The MIDUS 2 sample consisted of 5,248 participants (Figure 1). We excluded respondents who did not complete the SAQ or skipped the chronic pain question ($n = 1,313$), as well as those with missing values on cognitive function or covariates ($n = 534$) in MIDUS 2. We further excluded participants missing pain-related measures ($n = 1,054$) and cognitive function ($n = 128$) in MIDUS 3. This resulted in 2,219 participants for testing Hypotheses 1 and 2. For Hypothesis 3, we restricted the sample to 797 participants with chronic pain in MIDUS 3. The demographic and health-related differences between included and excluded groups are shown in Supplementary Tables 3–5 (see online supplementary material).

Measures

Cognitive performance at MIDUS 3

Cognitive function was measured in MIDUS 2 and 3 using the Brief Test of Adult Cognition by Telephone (Lachman et al., 2014), which assesses seven domains: (1) verbal fluency (assessed by category fluency), (2) inductive reasoning (assessed by number series completion), (3) processing speed (measured by the 30-Second Counting Task, or 30-SACT), (4) working memory (measured by backward digit span), (5) attention-switching (measured by the Stop and Go Switch Task), (6) immediate recall (measured by word recall), and (7) delayed recall (measured by word recall). Based on prior confirmatory factor analysis (Lachman et al., 2014), two summary scores were created: episodic memory (EM) and EF. The EM was measured by the average of the immediate and delayed word

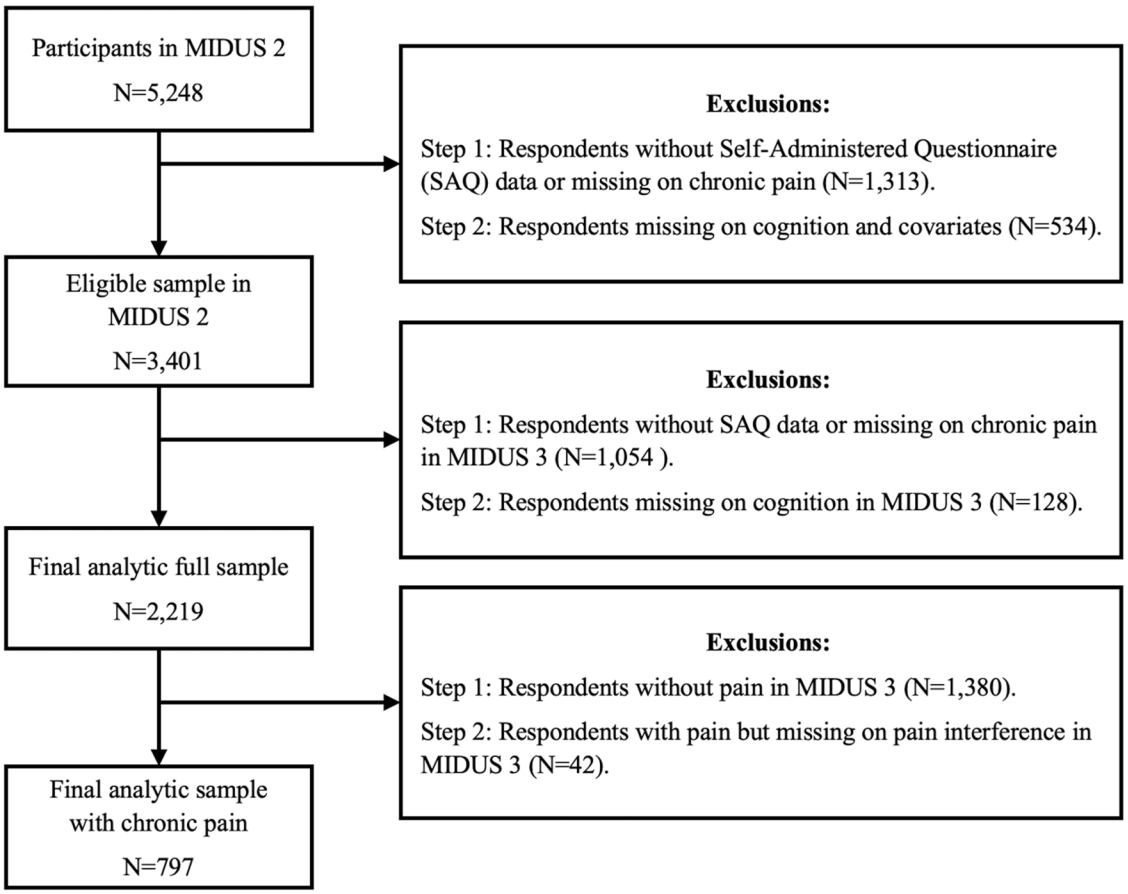

Figure 1. Selection of the analytic sample. MIDUS = Midlife in the United States; MIDUS 2 = Midlife in the United States, Wave 2; MIDUS 3 = Midlife in the United States, Wave 3.

recall scores. The EF score was calculated as the average of the standardized scores for verbal fluency, inductive reasoning, processing speed, working memory, and attention-switching (Lachman et al., 2014). To ensure equal weighting of EM and EF in the overall cognitive function measure, we calculated overall cognition as the average of the standardized EM and EF scores. We then standardized the score for overall cognitive function to a mean of zero and a standard deviation (SD) of one. Higher scores represent better cognitive functioning.

Chronic pain status in MIDUS 3

At both MIDUS 2 and 3, participants were asked, "Do you have chronic pain, that is, do you have pain that persists beyond the time of normal healing and has lasted anywhere from a few months to many years?" We created a binary variable for pain status in both waves, where 1 indicates the presence of chronic pain ("yes") and 0 indicates its absence ("no").

The number of pain sites in MIDUS 3

If respondents have chronic pain, they were asked, "Where is your pain primarily located?" Respondents could select all applicable areas from a list of nine that included the "head, neck, back, arms/hands, legs/feet, shoulders, hips, knees, and other locations." Consistent with previous studies (Bell et al., 2024; Fishbein et al., 2025; Hidalgo-Lopez et al., 2025; Smith et al., 2025), we created a three-level ordinal variable to represent the number of chronic pain sites at MIDUS 3, including no pain, low number of pain sites (1–2 pain sites), and high number of pain sites (3 and above pain sites) (see Section 1.1 of the online supplementary material, as well as Supplementary Tables 1 and 2 (see online supplementary material), for the rationale behind using these categories).

Pain interference in MIDUS 3

Many databases include general dichotomous questions about pain interference (e.g., "Does pain interfere with your daily activities?") (Milani et al., 2023). However, the MIDUS database provides a more detailed measure, capturing multiple dimensions of pain interference and allowing respondents to rate the intensity of interference. Specifically, individuals with chronic pain were asked, "During the past week, how much did your pain interfere with your general activity, mood, relations with other people, sleep, and enjoyment of life?" Respondents rated each dimension on a scale from 0 to 10, where 0 indicated "not at all" and 10 indicated "completely interfere." Using these ratings, we constructed a continuous variable representing the total pain interference score in MIDUS 3, ranging from 0 to 50. Additionally, we created continuous variables for each individual domain, with scores ranging from 0 to 10. A higher score reflects greater levels of pain interference.

Control variables in MIDUS 2

This study leverages the precise temporal sequencing of variable assessments within our dataset to evaluate the role of selection factors in the association between chronic pain, pain interference, and cognitive function. We include only those factors measured prior to the assessment of chronic pain and cognitive function at MIDUS 3, ensuring that these variables may act as confounders but not mediators of the observed relationship. This approach strengthens the ability to draw causal inferences (Zheng, 2017). Hence, all control variables in this study were drawn from MIDUS 2, including socio-demographic characteristics and health status-related variables. Socio-demographic variables included race (White, non-White), education (high school or GED and below, some college, college or more), gender (female, male), annual household income (<$25,000, $25,000–$44,999, $45,000–$69,999, ≥$70,000), marital status (married, not married), and age in years (ranging from 33 to 83). Health status-related variables included obesity (BMI ≥ 30), diabetes (yes or no), asthma (yes or no), lung disease (yes or no), hypertension (yes or no), pain status (yes or no), and standardized cognitive function score (ranging from −2.17 to 2.90). The rationale for including these control variables is provided in Section 1.2 of the online supplementary material.

Statistical analysis

We first present descriptive statistics stratified by pain status (no pain, low number of sites, high number of sites) using one-way ANOVA or *t*-tests for continuous variables and chi-square tests for categorical variables.

To address potential confounding of pain–cognition association by demographic and health characteristics, we used inverse-probability-weighted regression adjustment (IPWRA) models via Stata's *teffects* command (StataCorp., n.d.). The logic of this approach is similar to that of propensity score models, whereby exposure and control groups are equalized on a series of selection factors. Specifically, the exposure group consists of people with chronic pain, and the control group includes those without pain for Hypothesis 1. For Hypothesis 2, the exposure group includes individuals with a low or high number of pain sites, while the control group includes those without chronic pain. Rather than matching based on the propensity scores, however, the IPWRA approach uses weighting by the inverse probability of exposure and can be implemented with multinomial exposure variables (e.g., no pain, low pain sites, high pain sites). The IPWRA estimator uses two models, a selection model predicting exposure status and an outcome model that estimates the outcome conditional on exposure, adjusting for the probability of belonging to each exposure group (Carr et al., 2018). Because the model is doubly robust, only one of the equations must be correctly specified for the estimator to produce unbiased results (Barr & Zhang, 2024; Caldera, 2019; Morgan & Winship, 2014; StataCorp., n.d.).

We employed three IPWRA models to examine Hypotheses 1 (Model 1) and 2 (Models 2 and 3) and six OLS models to explore Hypothesis 3 (Models 4–9). For the first model, we examined the association between chronic pain status and cognitive function using a dichotomous indicator of pain (chronic pain vs. not). The second model examined heterogeneity among the pain group by breaking it into those with a low number of pain sites and a high number of pain sites. Hence, this model uses a three-category measure of pain (no pain, low number of pain sites, high number of pain sites). The third model followed the second but used a two-category pain measure: low number of pain sites and high number of pain sites. Models 4–9 then focus on only those in pain to examine the role of pain interference in the association between pain sites and cognitive functioning. Average effects of the exposure (ATEs) are reported for Models 1–3, while coefficients in OLS are reported for Models 4–9.

Lastly, to further examine how much of the association between chronic pain and cognitive function is mediated by

pain interference, we employed the Sobel–Goodman mediation test (MacKinnon et al., 2002) using Stata's *sgmediation* procedure. This test allows us to quantify the extent to which the total effect of pain sites on cognition is mediated by the overall pain interference score and its specific domains. Because *sgmediation* is not available in the IPWRA framework, we relied on OLS regression for this test. All statistical analyses were conducted using StataCorp LLC Stata software (version 17).

Results

Sample characteristics

Among the 2,219 participants in the full analytic sample, 62.19% reported no chronic pain, 23.03% had a low number of pain sites (1–2), and 14.78% had a high number of pain sites (3+). As shown in Table 1, participants with a high number of pain sites were more likely to be older, female, less educated, have lower annual household income, be unmarried, and have chronic conditions such as diabetes, asthma, lung disease, hypertension, or obesity than those without pain or with a low number of pain sites. They were also more likely to report chronic pain in MIDUS 2 and to exhibit worse cognitive functioning in both MIDUS 2 and MIDUS 3 compared to those with no pain or a low number of pain sites.

Among participants with chronic pain ($n = 797$), 61.10% had a low number of pain sites, while 38.89% had a high number of pain sites. As shown in Supplementary Table 6 (see online supplementary material), sociodemographic and health-related

Table 1. Descriptive statistics for analytic sample, MIDUS 2, and MIDUS 3.

	Total	No pain	1–2 Pain sites	3+ Pain sites	X^2/F	*p*
Variables	(*N* = 2,219)	(*n* = 1,380; 62.19%)	(*n* = 511; 23.03%)	(*n* = 328; 14.78%)		
Age	55.24 (11.11)	54.94 (11.05)	54.49 (11.19)	57.68 (10.95)	9.66	<.001
Sex					16.58	<.001
Female	1,247 (56.20)	754 (54.64)	275 (53.82)	218 (66.46)		
Male	972 (43.80)	626 (45.36)	236 (46.18)	110 (33.54)		
Race					3.77	.15
White	2,054 (92.56)	1,276 (92.46)	481 (94.13)	297 (90.55)		
Non-White	165 (7.44)	104 (7.54)	30 (5.87)	31 (9.45)		
Education					43.77	<.001
≤High school	611 (27.53)	347 (25.14)	127 (24.85)	137 (41.77)		
Some college	448 (20.19)	277 (20.07)	104 (20.07)	67 (20.43)		
College or more	1,160 (52.28)	756 (54.78)	280 (54.79)	124 (37.80)		
Annual household income					35.09	<.001
<$25,000	344 (15.50)	190 (13.77)	76 (14.87)	78 (23.78)		
$25,000–$44,999	364 (16.40)	234 (16.96)	66 (12.92)	64 (19.51)		
$45,000–$69,999	470 (21.18)	282 (20.43)	119 (23.29)	69 (21.04)		
≥$70,000	1,041 (46.91)	674 (48.84)	250 (48.92)	117 (35.67)		
Marital status					7.94	.02
Yes	1,635 (73.68)	1,020 (73.91)	392 (76.71)	223 (67.99)		
No	584 (26.32)	360 (26.09)	119 (23.29)	105 (32.01)		
Diabetes					10.63	.01
Yes	179 (8.07)	93 (6.74)	47 (9.20)	39 (11.89)		
No	2,040 (91.93)	1,287 (93.26)	464 (90.80)	289 (88.11)		
Asthma					18.82	<.001
Yes	219 (9.87)	120 (8.70)	45 (8.81)	54 (16.46)		
No	2,000 (90.13)	1,260 (91.30)	466 (91.19)	274 (83.54)		
Lung disease					15.02	<.001
Yes	46 (2.07)	21 (1.52)	9 (1.76)	16 (4.88)		
No	2,173 (97.93)	1,359 (98.48)	502 (98.24)	312 (95.12)		
Hypertension					39.08	<.001
Yes	612 (27.58)	342 (24.78)	133 (26.03)	137 (41.77)		
No	1,607 (72.42)	1,038 (75.22)	378 (73.97)	191 (58.23)		
Obesity					57.31	<.001
Yes	616 (27.76)	319 (23.12)	154 (30.14)	143 (43.60)		
No	1,603 (72.24)	1,061 (76.88)	357 (69.86)	185 (56.40)		
Chronic pain status at M2					304.75	<.001
Yes	774 (34.88)	304 (22.03)	244 (47.75)	226 (68.90)		
No	1,445 (65.12)	1,076 (77.97)	267 (52.25)	102 (31.10)		
Cognitive function at M2	0.00 (1.00)	0.04 (0.99)	0.04 (1.02)	−0.23 (1.00)	10.22	<.001
Cognitive function at M3	0.00 (1.00)	0.05 (0.98)	0.05 (1.04)	−0.32 (0.96)	20.16	<.001

Note. M = mean; M2/MIDUS 2 = Midlife in the United States, Wave 2; M3/MIDUS 3 = Midlife in the United States, Wave 3; N/n = number of respondents. Mean and standard deviation were provided for continuous variables, whereas frequency and percentage were presented for categorical variables. Differences in descriptive statistics among individuals with no pain, 1–2 pain sites, and 3+ pain sites in MIDUS 3 were assessed using ANOVA tests for continuous variables and chi-square tests for categorical variables. We grouped Blacks, Hispanics, Asians, and other racial categories together as non-White due to their small sample sizes.

differences between these two groups were similar to those just described for the full analytic sample, with one exception: There was no significant difference in diabetes prevalence between the low- and high-pain site groups. Additionally, participants with a high number of pain sites reported higher pain interference scores compared to those with a low number of pain sites. This pattern was consistent for the overall pain interference score as well as across specific domains, including mood, activity, relations, sleep, and enjoyment. Additionally, the correlation matrix of included variables is provided in Supplementary Tables 7 and 8 (see online supplementary material).

Inverse-probability-weighted regression and OLS regression analysis

We next estimated inverse-probability-weighted regression models, which construct counterfactual scenarios and estimate exposure effects unbiased by confounders (Barr & Zhang, 2024). Balance plots in Supplementary Figure 1 (see online supplementary material) illustrate how weighting, conducted using Stata's *tebalance* command, reduced differences in cognitive function in MIDUS 2 across pain groups, making them more comparable at baseline. Postestimation tools (e.g., *tebalance density*) confirmed successful covariate balancing, ensuring the groups were effectively equalized on measured potential confounders, including baseline cognition.

Models 1–3 in Table 2 summarize the results after balancing covariates across pain groups using IPWRA. Recall that cognitive functioning was measured as the sum of standardized EM and EF scores, with higher values indicating better cognitive performance. Model 1 shows no significant difference in standardized cognitive functioning between the no-chronic-pain group and the chronic-pain group (ATE = –0.04, 95% confidence intervals [95% CI: –0.10, 0.03], $p > .05$), which fails to support our Hypothesis 1. Model 2 indicates no significant difference in standardized cognitive functioning between the no-pain group (0 pain sites) and those with 1–2 pain sites (ATE = 0.01, 95% CI [–0.07, 0.08], $p > .05$). However, there is a small, substantial, but statistically significant difference in standardized cognitive function between individuals without pain and those with 3+ pain sites. Specifically, cognition scores among those with 3+ pain sites were, on average, 0.17 SD lower than those among the no-pain group (ATE = –0.17, 95% CI [–0.27, –0.08], $p < .001$). In addition, Model 2 reveals that the null effect observed in Model 1 reflects a lack of consideration of heterogeneity among individuals experiencing pain, i.e., it shows that the null effect in Model 1 was driven by individuals with 1–2 pain sites. Model 3 shows a small but statistically significant difference in standardized cognitive function between individuals with a low number of pain sites (1–2 pain sites) and those with a high number of pain sites (3–9 pain sites), with cognition scores on average 0.11 SD lower among the latter group (ATE = –0.11, 95% CI [–0.21, –0.01], $p < .05$). Overall, Models 2 and 3 provide partial support for Hypothesis 2, as they indicate that individuals with 3+ pain sites have the lowest standardized cognitive scores compared to both the pain-free group and those with 1–2 pain sites (see Figure 2). However, no significant difference in cognitive function was found between the pain-free group and the 1–2 pain-sites group.

Models 4–9 each include one measure of pain interference and adjust for all control variables using OLS regression. Including these measures reduces the association between having 3+ pain sites and standardized cognitive functioning to no significance (suggesting that pain interference indeed mediates the association between a high number of pain sites and worse standardized cognitive scores; we formally test this shortly).

Figure 2. Predicted cognitive scores in MIDUS 3 (Midlife in the United States, Wave 3) across groups with no pain, 1–2 pain sites, and 3+ pain sites (from Model 2).

Table 2. Inverse propensity score weight-adjusted models predicting standardized cognitive function at MIDUS 3.

	Sample with or without chronic pain		Sample with chronic pain						
Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Number of pain locations at M3									
No pain	Ref	Ref	//	//	//	//	//	//	//
Have pain	−0.04 (−0.10, 0.03)	//	//	//	//	//	//	//	//
1–2 pain sites	//	0.01 (−0.07, 0.08)	Ref	Ref	Ref	Ref	Ref	Ref	Ref
3+ pain sites	//	−0.17*** (−0.27, −0.08)	−0.11* (−0.21, −0.01)	−0.04 (−0.14, 0.07)	−0.05 (−0.15, 0.06)	−0.06 (−0.16, 0.04)	−0.04 (−0.15, 0.06)	−0.05 (−0.15, 0.06)	−0.06 (−0.16, 0.05)
Pain interference at M3									
Total interference score	//	//	//	−0.01*** (−0.02, −0.00)	//	//	//	//	//
Interference with mood	//	//	//	//	−0.03** (−0.05, −0.01)	//	//	//	//
Interference with activity	//	//	//	//	//	−0.02** (−0.04, −0.01)	//	//	//
Interference with social relationships	//	//	//	//	//	//	−0.04*** (−0.05, −0.02)	//	//
Interference with sleep	//	//	//	//	//	//	//	−0.02* (−0.04, −0.01)	//
Interference with enjoyment of life	//	//	//	//	//	//	//	//	−0.02** (−0.04, −0.01)
N	2,219	2,219	797	797	797	797	797	797	797

Note. M3 = MIDUS Wave 3; MIDUS = Midlife in the United States; MIDUS 2 = Midlife in the United States, Wave 2; OLS = Ordinary Least Squares; Ref = reference group. Models 1–9 control for pain status, cognition, education, diabetes, asthma, lung disease, hypertension, age, sex, race, marital status, obesity, and income at MIDUS 2. In Models 1–3, the average exposure effect (ATE) is reported (with 95% confidence interval in parentheses) for the number of pain locations at M3. In Models 4–9, the OLS regression coefficient is reported (with 95% confidence interval in parentheses) for the number of pain locations and pain interference at M3.
*$p < .05$. **$p < .01$. ***$p < .001$.

These models reveal that total pain interference (range: 0–50) is significantly associated with lower cognitive function score (β = −0.01, 95% CI [−0.02, −0.00], $p < .001$). Pain interference in specific domains (range: 0–10) also shows small but significant associations with lower standardized cognitive function, including interference with mood (β = −0.03, 95% CI [−0.05, −0.01], $p < .01$), activity (β = −0.02, 95% CI [−0.04, −0.01], $p < .01$), social relations (β = −0.04, 95% CI [−0.05, −0.02], $p < .001$), sleep (β = −0.02, 95% CI [−0.04, −0.01], $p < .05$), and enjoyment of life (β = −0.02, 95% CI [−0.04, −0.01], $p < .01$). These results indicate that each type of pain interference is a significant negative predictor of cognitive functioning.

Sobel–Goodman mediation test

Table 3 presents the results of the Sobel–Goodman mediation tests, which examine the mediating role of total pain interference and its specific components in the relationship between low vs. high number of pain sites and standardized cognitive function. The analyses control for sociodemographic and health covariates, baseline standardized cognitive function, and baseline pain status. To account for Type I error in the multiple tests of mediation, we employed the Bonferroni correction to adjust the significance level (Bland & Altman, 1995) (see details in Section 2.1 of the online supplementary materials). The tests reveal that 53.6% of the total effect is significantly mediated by the total pain interference score, which supports our Hypothesis 3. For individual domains, the percent of the effect mediated is 39.1% for mood, 27.7% for general activity, 45.3% for relations with others, 41.0% for sleep, and 31.3% for enjoyment of life. Note that after applying the Bonferroni correction, only interference with relationships and mood remained significant, while other domains showed marginal significance. These results indicate that all domains of pain interference significantly mediate the negative relationship between the number of pain sites and cognitive function, with pain interference in social relations being the strongest individual mediator.

Sensitivity analyses

Some research (e.g., Natvig et al., 2010) treats the number of pain sites as a continuous variable rather than an ordered categorical variable as done here. Following this guidance, we reanalyzed the data using the number of pain sites as a continuous predictor. The results showed a negative and marginally significant association with cognitive function ($p = .075$). Hence, the linear specification does not have as much predictive power as the ordered categories. These findings suggest that the pain–cognition association does not follow a strictly linear trend in this national sample; instead, the relationship fluctuates across pain site counts.

In addition, a series of sensitivity analyses was conducted using inverse propensity score-weighted models. The results, presented in Supplementary Tables 10–12 (see online supplementary material), examine the relationship between pain presence, the number of pain sites, and different cognitive domains, including EM and EF. Consistent with findings on overall cognition, pain presence alone is not significantly associated with EM or EF. In addition, compared to the pain-free group, individuals with three or more pain sites exhibit significantly worse EM (ATE = −0.145, SE = 0.055, $p < .01$) and EF (ATE = −0.083, SE = 0.030, $p < .01$). When comparing individuals with three or more pain sites to those with 1–2 pain sites, a significant association is observed only for EF (ATE = −0.063, SE = 0.029, $p < .05$). These findings suggest that, among individuals with chronic pain, the impact of multiple pain sites on cognitive function is primarily driven by EF. Given this, Sobel–Goodman mediation tests with adjusted significance levels as described above were conducted specifically for the relationship between the number of pain sites and EF. As shown in Supplementary Table 12 (see online supplementary material), most of the results align with those for overall cognitive function, indicating that total pain interference mediates 39.1% of the association between the number of pain sites and EF. However, after applying the adjusted significance level to account for Type I error, social relations emerged as the strongest mediator, followed by sleep and mood. No statistically significant effect was observed for activity and enjoyment.

Discussion

This study used longitudinal data from a national sample of Americans aged 34 and older to understand how the number

Table 3. Sobel–Goodman mediation test among people with chronic pain, MIDUS 3.

			Indirect effect			
DV	**IV**	**MV (pain interference, M3)**	**Est. (SE)**	***Sig***	**Adjusted *Sig***	**%M**
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Total pain interference	−0.06 (0.02)	<0.001	***	53.60
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Total interference score	−0.04 (0.01)	0.002	*	39.10
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Interference with mood	−0.03 (0.01)	0.010	†	27.70
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Interference with activity	−0.05 (0.01)	<0.001	***	45.30
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Interference with social relationships	−0.04 (0.02)	0.009	†	41.00
Standardized cognition at M3	3+ (vs. 1–2) pain sites, at M3	Interference with sleep	−0.03 (0.01)	0.009	†	31.30

Note. adjusted sig = significance level using Bonferroni correction (†p < .017, *p < .008, ***p < .0001); DV = dependent variable; IV = independent variable; %M = percentage of total effect that is mediated; M3 = MIDUS Wave 3; MIDUS = Midlife in the United States; MIDUS 2 = Midlife in the United States, Wave 2; MV = mediator variable; Sig = significance level. Number of respondents = 797. Models controlled for age, gender, income, education, race, marriage status, obesity, diabetes, asthma, lung disease, hypertension, pain status, and cognitive function at MIDUS 2.

of pain sites is associated with cognitive functioning. It is the first study to examine the relationship between number of pain sites, multidimensional pain interference, and cognitive functioning in the general population by using longitudinal U.S. national data, which allows for adjustment for a wide range of potential confounders, a robust approach to temporal and causal relationships, and estimation of the public health burden (around 40% of individuals with chronic pain reported pain in 3+ sites in MIDUS 3). Our findings highlight that multisite pain (pain in three or more sites), rather than simply the presence of pain, is associated with worse cognitive function, with this relationship mediated by pain's interference with mood, enjoyment, daily activities, social relations, and sleep.

Our findings show that individuals with chronic pain did not show worse cognitive function compared to those without pain (so did not support Hypothesis 1). However, we found that while individuals with a low number of pain sites did not show worse cognitive function than their pain-free peers, those with a high number of pain sites had significantly worse cognitive function than pain-free individuals (supporting Hypothesis 2), which is consistent with findings from Zhao et al. (2023). Taken together, these findings underscore the importance of focusing on the extent of chronic pain—specifically, the number of pain sites—rather than simply pain's presence when examining intragroup differences in the impact of pain on cognitive function (Croft, 2009; Natvig et al., 2010). Multisite pain serves as a critical marker of central sensitization, which amplifies pain perception (Harte et al., 2018) and has been linked to broader neurobiological changes that could contribute to cognitive decline (Eccleston & Crombez, 1999; Moriarty et al., 2011).

Our mediation analysis (Hypothesis 3) shows that pain interference negatively impacts cognitive function, which is consistent with prior research (Milani et al., 2023; Van Der Leeuw et al., 2016). While previous studies primarily examined pain interference with daily activities, our study delves more deeply into this topic by exploring multiple domains of pain interference. Our findings reveal that pain interference mediated over 50% of this association, with social relations being the strongest mediator (45.3%), followed by mood (39.1%). These results align with existing literature, highlighting the critical roles of social relationships (Kremen et al., 2012; Yang & Grol-Prokopczyk, 2021) and mood (Butera et al., 2019) in linking chronic pain to cognitive outcomes.

Our findings may have clinical implications for chronic pain management in middle-aged and older adults, particularly concerning cognitive health. For clinicians, our findings suggest that a more comprehensive pain assessment, including the number of pain sites and pain interference, is important. Interventions targeted for multisite pain could protect patients from a potential decline in cognitive function. Moreover, the role of pain interference—particularly in social relationships and mood—as a significant mediator of the pain–cognition link highlights the need for multidisciplinary interventions that address not just the physical aspects of pain but also its psychosocial dimensions. For instance, cognitive rehabilitation programs could be tailored to incorporate strategies that mitigate the impact of pain on social interactions and mood (Franqueiro et al., 2023; Sturgeon, 2014).

This study has several limitations that should be considered when interpreting the findings. First, the dataset lacks information on pain frequency, intensity, and duration, which often covary with the number of pain sites but reflect distinct pain mechanisms (Larsson et al., 2019). Therefore, we cannot determine whether the observed association between the number of pain sites and cognitive decline is influenced by (or a proxy for) these factors. However, individuals with pain in multiple locations often experience more intense, frequent, and persistent pain than those with pain in a single region (Grimby-Ekman et al., 2015), suggesting that the number of pain sites is an effective indicator of overall pain burden, capturing aspects of pain severity that may not be fully reflected by intensity or frequency alone. Second, as highlighted in a systematic review (Welsh et al., 2019), there is no consensus on how pain sites should be measured. To maintain statistical power given small cell sizes, we followed prior studies (e.g., Bell et al., 2024) and categorized pain sites as 1–2 and 3+ (see online supplementary materials for results using alternative operationalizations). Future research with larger samples should further validate optimal cutoffs. Third, the Brief Test of Adult Cognition by Telephone (BTACT), while validated for use in healthy adult populations, may be less generalizable to individuals with cognitive impairment. It has not been validated as a diagnostic tool for identifying cognitive impairment and is less sensitive to detecting the severity of impairments, such as those resulting from traumatic brain injury, compared to standard neuropsychological assessments (Lachman et al., 2014). These limitations highlight the need for future research to investigate the relationship between multisite pain and cognitive impairment using clinical samples and outcomes. Moreover, our estimates may be biased due to attrition between waves, especially among disadvantaged groups, including non-White individuals, those with less education, lower income, unmarried status, or chronic conditions like diabetes, asthma, and chronic pain. Consequently, our estimates may be biased toward healthier or more advantaged individuals, potentially underestimating the true associations in the broader population. Our results cannot be generalized to the U.S. population, as MIDUS tends to include individuals with higher socioeconomic status, English-speaking backgrounds, and predominantly White participants.

Previous research has shown that individuals with cognitive impairment are more likely to report pain (Defrin et al., 2015). Although we considered prior cognitive functioning in our selection model using the IPWRA approach, this measure was collected 6–7 years before the focal measure of pain. We cannot rule out that cognition changed first in the years between the MIDUS2 and MIDUS3 assessments of pain. Future studies should explore causal ordering using datasets with more waves and/or fewer years between waves. Additionally, daily diary studies suggest that daily pain levels may influence cognition on the same day, independent of chronic pain status (Whibley et al., 2022). However, our dataset does not include information on pain status specifically on the day of cognitive testing, which should be addressed in future data collection efforts. Moreover, due to the limited sample size with available medication data, we could not determine whether participants were taking pain medications with sedative effects (e.g., opioids and anticonvulsants such as gabapentin) or medications with a high anticholinergic load that might influence cognition on the day of testing (Khera & Rangasamy, 2021). Future studies assessing the role of medication in the pain–cognition link would be

beneficial. Finally, while our mediation analysis is cross-sectional, the logical and temporal ordering of pain status, pain interference, and subsequently measured cognition provides a more robust mediation test than purely simultaneous cross-sectional models. However, we acknowledge that longitudinal measurement would further strengthen causal inferences, as recommended by O'Laughlin et al. (2018).

Despite these limitations, this study makes three key contributions to the field of pain–cognition research. First, we leverage data from a national U.S. sample and employ an inverse-probability-weighted regression adjustment approach to address potential confounding factors, providing a more robust analysis of the relationship between chronic pain and cognitive function in middle-aged and older adults. Moreover, the MIDUS measurement may be the most reliable national survey for assessing the presence of chronic pain, as it is the first to align with the International Association for the Study of Pain's definition—chronic pain that persists beyond the normal healing time. Also, although pain in MIDUS is self-reported, at present, this approach is considered the "gold standard" for pain measurement (Grol-Prokopczyk, 2025). Second, we examine intragroup differences among individuals with chronic pain by assessing how the number of pain sites impacts cognitive function. Our findings show that individuals with three or more pain sites have worse cognitive function than those with one or two pain sites, emphasizing the importance of multisite pain in predicting cognitive decline. Third, the study examines the mechanisms underlying the pain–cognition relationship by focusing on the mediating role of pain interference. Specifically, it explores how various dimensions of pain interference—such as its impact on daily activities, mood, social relationships, and sleep—contribute to cognitive outcomes. These findings enhance our understanding of the pathways through which chronic pain affects cognitive function and support the development of targeted interventions to address cognitive decline in individuals with chronic pain.

Supplementary material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of interest

None declared.

Data availability

The data used in this paper, Midlife in the United States (MIDUS), are publicly available. The dataset can be accessed at https://midus.wisc.edu/scopeofstudy.php

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