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Pain and the aging brain: beyond association toward action

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Abstract

Chronic pain affects more than half of older adults and has been increasingly linked to cognitive decline, a relationship with profound implications for healthy aging. Ramezani and colleagues examined this association in 1,343 Iranian older adults from the Birjand Longitudinal Aging Study, a well-characterised cohort from an understudied population. The study has notable strengths: a large sample size, population-based recruitment, and DAG-guided covariate selection. However, three methodological limitations warrant consideration. First, pain was measured only once, but longitudinal evidence shows that pain trajectories and multisite chronic pain, not single-timepoint intensity, drive cognitive decline. Second, adjusting for employment, wealth, and living arrangement without distinguishing confounders from mediators may have introduced overadjustment bias. Third, the composite cognitive definition (failure on all three tests) has never been validated, raising questions about the 59.6% prevalence reported. Future studies should incorporate repeated pain assessments, distinguish single-site from multisite pain, use careful causal modelling, and validate composite cognitive definitions.

Keywords Chronic pain · Cognitive impairment · Older adults · Longitudinal study

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Dear Editor

We read with interest the article by Ramezani and colleagues examining the association between pain severity, pain interference, and cognitive impairment in community-dwelling older adults from the Birjand Longitudinal Aging Study [1]. The large sample size and the use of a directed acyclic graph (DAG) to guide covariate selection are commendable. However, three methodological issues warrant careful consideration before the findings can be translated into clinical or public health action, as the title of our commentary suggests.

Dynamic nature of pain: why intensity over a single week is insufficient

Chronic pain is fundamentally a dynamic experience that varies over time, and its impact on cognitive health cannot be captured by a single-point measure of intensity. He and colleagues, in a large longitudinal study, demonstrated that distinct trajectories of pain presence over eight to ten years, rather than pain intensity at a single time point, predict the subsequent rate of cognitive decline in older adults [2]. Participants with moderate-increasing or high-stable pain trajectories exhibited significantly steeper declines in global cognition, executive function, and orientation compared to those with low-stable pain trajectories. By using only a cross-sectional measure of pain severity, the present study cannot capture these dynamic pain patterns.

Equally important is the anatomical distribution of pain. Bell and colleagues examined 3,459 older adults without dementia at baseline and found that multisite chronic pain (pain in more than one joint site) was associated with steeper declines in episodic memory and working memory and with increased beta-amyloid deposition in the entorhinal cortex and hippocampus, particularly among APOE- ϵ 4 carriers [3]. Crucially, single-site chronic pain did not differ from no chronic pain on any measure of cognitive decline or Alzheimer's pathology. The authors of the present study did not account for the number of pain sites, thereby potentially conflating clinically inconsequential single-site pain with highly impactful multisite pain. A recent meta-analysis synthesized data from 28 longitudinal cohort studies comprising over 7.9 million participants and confirmed that chronic pain defined by duration (≥ 3 months), not just intensity, is associated with a significantly higher risk of cognitive impairment (pooled adjusted OR = 1.30; 95% CI: 1.14–1.47) [4]. The association was stronger in studies with follow-up of five years or longer (OR = 1.37), underscoring that the long-term persistence of pain, not merely its momentary severity, drives cognitive risk.

Consequently, by reducing pain to a severity score over a single week and ignoring both its temporal trajectory and its anatomical distribution, the authors have likely underestimated the true association between chronic pain and cognitive impairment in vulnerable subgroups (e.g., those with multisite or persistent pain) and overestimated the effect of mild, transient pain. Future studies should incorporate repeated pain assessments and explicitly distinguish between single-site and multisite chronic pain.

Adjusting for mediators as if they were confounders

The most significant methodological concern lies in the interpretation of the sensitivity analysis. While the authors present the attenuation of the pain severity estimate to an odds ratio of exactly 1.00 in the fully adjusted model as evidence of robustness, this pattern is highly suggestive of overadjustment bias, a well-recognised statistical pitfall that occurs when an investigator controls for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome [5]. Unlike controlling for true confounders, which reduces bias, adjusting for mediators removes part of the very effect being studied, biasing estimates toward the null [5]. In the present study, the fully adjusted model (Model 3) included covariates such as employment status, wealth quintile, and living arrangement, variables that are plausibly consequences of chronic pain rather than pure confounders. Chronic pain leads to reduced work capacity, lower income, and social isolation. By adjusting for these factors, the authors may have inadvertently removed the indirect effect of pain on cognitive impairment that operates through these socioeconomic mediators.

The problem is not unique to this study. A meta-research review examined 84 systematic reviews and found that only 5% clearly distinguished confounders from mediators, and a mere 2% incorporated overadjustment into their risk-of-bias assessments [6]. The authors of that review concluded that overadjustment bias has received insufficient consideration and that this is likely to result in biased estimates. In the present study, the authors provide no causal diagram or theoretical justification for treating employment status, wealth, and living arrangement as confounders rather than mediators. Without such justification, the attenuation of pain severity to OR = 1.00 in Model 3 may reflect overadjustment bias rather than true absence of effect. Future studies should construct explicit causal diagrams (directed acyclic graphs) to distinguish confounders from mediators and should report both unadjusted and appropriately adjusted estimates alongside sensitivity analyses that avoid adjusting for known mediators.

Unvalidated composite cognitive definition

The authors classified participants as cognitively impaired only if they failed all three tests (6-CIT, AMTS, and CFT). While each test is individually validated, the specific “AND” rule has never been validated, neither in the original protocol nor in any subsequent psychometric study. The resulting prevalence of 59.6% is substantially higher than typically reported in community-dwelling older adults, suggesting that this unvalidated composite rule may have questionable specificity. Without validation against a gold-standard clinical diagnosis, the degree of misclassification bias remains unknown.

In summary, while the study provides valuable hypothesis-generating data on an understudied population, three limitations should inform its interpretation. First, the single-timepoint measure of pain severity cannot capture the dynamic nature of chronic pain. Second, the inclusion of socioeconomic variables without distinguishing confounders from mediators raises the possibility of overadjustment bias. Third, the composite cognitive definition lacks empirical validation. As our suggests, moving beyond association toward action requires stronger evidence, including repeated pain assessments, distinction between single-site and multi-site chronic pain, careful causal modelling, and validated composite cognitive definitions. We offer these points constructively, in the spirit of scientific dialogue.

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Declarations

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