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The Association of Osteoarthritis and Related Pain Burden to Incident Alzheimer's Disease and Related Dementias: A Retrospective Cohort Study of U.S. Medicare Beneficiaries

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Abstract

Background: Emerging evidence suggests osteoarthritis (OA) and related symptom burden may increase risk for Alzheimer's disease and related dementias (ADRD). However, longitudinal studies are sparse, and none have examined the potential mediating effects of mood or sleep disorders.

Objective: To determine the association of OA and related pain to incident ADRD in U.S. elders.

Methods: In this retrospective cohort study, we used baseline and two-year follow-up data from linked Medicare claims and Medicare Current Beneficiary Survey files (11 pooled cohorts, 2001–2013). The study sample comprised 16,934 community-dwelling adults ≥ 65 years, ADRD-free at baseline and enrolled in fee-for-service Medicare. Logistic regression was used to assess the association of OA and related pain (back, neck, joint, neuropathic) to incident ADRD, explore the mediating influence of mood and insomnia-related sleep disorders, and (sensitivity analyses) account for potential survival bias.

Results: Overall, 25.5% of beneficiaries had OA at baseline (21.0% with OA and pain); 1149 elders (5.7%) were subsequently diagnosed with ADRD. Compared to beneficiaries without OA, those with OA were significantly more likely to receive a diagnosis of incident ADRD after adjustment for sociodemographics, lifestyle characteristics, comorbidities, and medications (adjusted odds ratio (AOR) = 1.23 (95% confidence interval (CI) 1.06, 1.42). Elders with OA and pain at baseline were significantly more likely to be diagnosed with incident ADRD than were those without OA or pain (AOR = 1.31, CI 1.08, 1.58). Sensitivity analyses yielded similar findings. Inclusion of depression/anxiety, but not sleep disorders, substantially attenuated these associations.

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SUPPLEMENTARY MATERIAL

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Conclusion: Findings of this study suggest that: OA is associated with elevated ADRD risk, this association is particularly pronounced in those with OA and pain, and mood disorders may partially mediate this relationship.

Keywords

Alzheimer's disease and related dementias; arthritis; cognition; dementia; medicare current beneficiaries survey; mood; pain; sleep

INTRODUCTION

Prevalence of Alzheimer's disease and related dementias (ADRD), which encompass a range of progressive and devastating neurodegenerative disorders, is increasing dramatically worldwide, imposing an enormous clinical, societal, and economic burden and constituting a serious and rapidly growing global public health crisis. For example, Alzheimer's disease (AD), the most common form of dementia and a leading cause of mortality in higher income countries and many developing nations [1–3], affects over 46 million adults worldwide, with prevalence projected to reach over 75 million by 2030 and 135.5 million by 2050 [4]. In the U.S., at least 5.8 million are currently living with AD, at an estimated annual direct cost of \$290 billion for those over age 65 [3], figures that are projected to rise steeply in coming years. Even in high-income countries, the economic costs and associated societal burden of dementia threaten to overwhelm existing resources as the population ages and longevity increases [5].

With effective treatments for cognitive impairment or ADRD still lacking after decades of clinical trials and billions of dollars invested, research is shifting increasingly to prevention and early intervention [6, 7], with large-scale risk reduction trials now underway in multiple countries [7–11], including the U.S. [7, 12]. However, while there has been considerable progress in identifying modifiable risk factors for ADRD, major knowledge gaps remain. Important among these is our still limited understanding regarding the contribution of common chronic pain conditions to the development of cognitive impairment. The former include osteoarthritis (OA), a condition which, like ADRD, continues to increase rapidly in prevalence worldwide, and that itself poses a looming global public health crisis [13–16].

OA is the most common form of arthritis, affecting an estimated 31–52 million (12–20%) U.S. adults [13,17,18]. The global prevalence of OA is expected to rise steeply in coming years due to aging of the population and increasing rates of obesity and physical inactivity [13, 16, 19]. A leading cause of disability worldwide [16, 19, 20], OA is associated with substantial clinical, economic, and societal burden [21, 22], with excess expenditures considerably greater than those for diabetes, hypertension, and other common chronic disorders [21]. OA is also associated with increased risk for medical comorbidity [23, 24], falls [25], and mortality [19, 23, 26, 27]. The second most common cause of chronic pain worldwide [13], OA is linked to significant reductions in physical function [13], productivity [13, 18, 28], mood [13, 29, 30], sleep quality [29, 31], and quality of life (QOL) [21, 26]. In the U.S., 80% of those with OA suffer some degree of mobility limitation due to chronic pain, and at least 25% are restricted in major activities of daily living [20].

While studies remain sparse, emerging evidence from cross-sectional and longitudinal studies by our group and others suggests that OA and OA symptom burden may also be linked to increased ADRD risk. In our recent cross-sectional study of a large Appalachian population, OA and related joint pain showed a strong, dose-response relation to reported memory loss; this association appeared to be partially mediated by impaired sleep and mood, factors strongly and reciprocally associated with OA and linked to increased ADRD risk [32]. Likewise, in our cross-sectional study of a large, representative sample of U.S. elders, we found OA accompanied by moderate to severe pain interference to be strongly and positively associated with ADRD after adjustment for multiple potential confounders [33, 34]. Consistent with these findings, the results of two large nested case-control studies of Taiwanese nationals suggested those with diagnosed OA at baseline were at significantly elevated risk for incident dementia within the maximum 4 [35] to 10 [36] year follow-up period [35, 36].

However, although findings from existing studies suggest OA and related symptom burden may increase risk for incident dementia, interpretation is hampered by some important limitations. These include cross-sectional design [32, 34], potential self-report bias [32, 34]; and failure to assess the influence of OA-associated pain [35, 36], evaluate the potential role of psychosocial factors [35, 36] or survival bias [32, 34–36], or control for several potential confounders known to affect cognition, including certain: lifestyle and demographic factors [34–36], chronic health conditions [35, 36], and medications [35, 36]. In addition, longitudinal studies in U.S. and other western populations are lacking. Clearly, additional rigorous investigations are needed. In this large retrospective cohort study of U.S. community-dwelling fee-for-service (FFS) Medicare beneficiaries, we examine: the relation of OA to incident ADRD; assess the influence of pain symptoms on this association; and explore the potential mediating role of mood and insomnia-related sleep disorders.

METHODS

Study design and data source

We used a retrospective cohort design to assess the association of baseline OA and related pain to incident ADRD using linked, longitudinal data from FFS Medicare Claims and Medicare Current Beneficiaries Survey (MCBS). Initiated in 1991, MCBS is a continuous, in-person, multi-purpose survey of a nationally representative sample of adults enrolled in Medicare, a U.S. government health insurance program for U.S. citizens and permanent residents who are at least 65 years of age or have eligible disabilities. Survey participants are recruited using a complex stratified, three-stage probability sampling design described in detail elsewhere [37, 38]. Structured in-person interviews are administered at baseline and follow-up rounds each year for up to three years.

MCBS generates comprehensive cross-sectional and longitudinal data on healthcare cost and utilization of survey participants using a combination of survey, administrative, and claims-based records. Our study used the MCBS cost and use files (MCBS-CU). These files include information on demographics, lifestyle factors, access to care, insurance coverage, and health status, linked to Medicare FFS claims data, which contain information on medical services, spending, and utilization.

Study sample

The study sample comprised 16,934 community-dwelling adults who were aged 65 years or over, were continuously enrolled in FFS Medicare, and were still alive at end of study, defined as either diagnosis of incident ADRD or end of follow-up period (see below). Participants with diagnosed ADRD at baseline (5.3%) were excluded from the sample, as were institutionalized adults. Based on the recommendations by MCBS investigators [39] and sampling strategies documented in prior published studies using MCBS [40,41], we combined multiple three-year MCBS cohorts (2001–2013) in order to minimize relative standard errors and to enhance the reliability and precision of our study estimates. As illustrated in the sample selection flow chart (Fig. 1), application of all a priori exclusion criteria yielded a final sample size of 16,934 adults (Ns by cohort = 1874 (2001–2003); 1768 (2002_2004); 1884 (2003_2005); 1766 (2004_2006); 1735 (2005_2007); 1650 (2006_2008); 1495 (2007_2009); 1278 (2008_2010); 1034 (2009_2011); 1159 (2010_2012); and 1291 (2011_2013)). All MCBS data received were deidentified.

Measures

Outcome variable: Incident ADRD at follow-up—ADRD status at baseline (year 1) and follow-up (years 2 and 3) were ascertained using the 2001–13 Medicare FFS claims for inpatient (IP), skilled nursing facility (SNF), outpatient (OT), home health agency (HHA), and physician office (PO), as well as MCBS CU self-reported Health Status and Functioning files. To help increase capture of diagnosed ADRD, both claims and survey data were used to identify ADRD [42]. Specifically, the presence of ADRD was defined as 1) one or more FFS claims with any of the following International Classification of Diseases, ninth Edition, clinical modification (ICD-9-CM) diagnostic codes: 290.0–290.3, 331.0–331.2, 331.7, and 331.8 [43, 44]; or 2) an affirmative response to the self-reported Health Status question “Has a doctor ever told you that you had Alzheimer’s?”.

Key independent variable: OA and related chronic pain symptoms—Baseline OA, related chronic pain symptoms (joint, back, and neck pain) were identified using ICD9 codes from FFS Medicare claims; each condition was defined as the presence of two or more outpatient claims, at least 90 days apart, for the specific condition or any one inpatient or skilled nursing facility claim. Eligible claims were identified using clinical classification codes software (CCS) for ICD-9-CM diagnostic codes as follows: CCS code 203 (OA); 201, 204, 211, 212, 54, 225 (Joint pain); 205, 209, 217, 231, 232 (back and neck pain); and 84, 95 (neuropathic pain).

To determine the relation of OA to incident ADRD, we first assessed OA as a binary variable (OA versus no OA). To evaluate the potentially differential associations of OA and related symptom burden to incident ADRD, we also created a composite variable from the above, categorized as follows: no OA, no pain (joint, neck, back, or neuropathic) (referent category); pain present but no OA; OA without pain; and OA with pain.

Covariates

To control for the influence of potential confounding, specific baseline characteristics known or suspected to be associated with ADRD risk and/or OA were selected for inclusion as

covariates in our multivariable models. These included biological factors, i.e., age group (assessed as a categorical variable), sex (female/male), and race/ethnicity (Non-Hispanic White, African American, Hispanic, and other); other demographic characteristics, i.e., education (less than high school, high school, some college, college), marital status (married, widowed, divorce/separated, other), family income, measured as the percentage of federal poverty line (FPL) (poor/low-income (<200%), (middle to high-income (200%)); health insurance status (Medicaid (yes/no); private insurance (yes/no)); rurality (residence in a metropolitan area (yes/no)); and lifestyle factors, i.e., smoking status (current smoker, past smoker, never smoked) and body mass index (BMI, kg/m², categorized as underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI 30)).

We also included as covariates other chronic health conditions reported at baseline (yes/no), including: hypertension, diabetes, heart disease, chronic respiratory illness, history of stroke or traumatic brain injury (TBI), cancer, and certain auto-immune conditions associated with chronic pain, including rheumatoid arthritis (RA, yes/no), and systemic lupus erythematosus (SLE, yes/no), as well as other chronic pain conditions (headache, migraine). As for OA, other chronic health conditions were ascertained using Medicare FFS claims. In analyses of OA as a binary variable, we also assessed the influence of back, neck, joint and neuropathic pain as covariates on the association of OA to incident ADRD. In addition, certain commonly used medications associated with ADRD risk and/or used in chronic pain management were also evaluated as covariates, including opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).

To examine the potential mediating influence of mood and sleep disorders on the relation of OA and associated pain symptoms to incident ADRD, we also evaluated the effects of diagnosed depression and anxiety disorders, as well as insomnia and related sleep disorders both separately and in combination. As detailed above, these disorders were determined using Medicare FFS claims (for ICD-9 codes, see the Supplementary Material)

Statistical analysis

Potential differences in baseline characteristics by OA and ADRD status were assessed using Rao-Scott chi-square tests (categorical variables). Logistic regression was used to assess the unadjusted and independent relation of OA and related pain burden to incident ADRD and to evaluate the potential mediating effects of mood and sleep disorders. All multivariable logistic regression models included demographic and socioeconomic factors; additional models also adjusted for lifestyle factors, chronic physical health conditions, access to care, and medications, including NSAIDs and opioid analgesics. In addition, we also included baseline diagnoses of depression, anxiety, and insomnia, both individually and in combination, in the fully adjusted models to assess the potential mediating influence of these factors on the relation of OA and related pain to ADRD risk. Specifically, to assess the potential mediating influence of these factors, we first determined the associations of sleep and mood disorders both to incident ADRD and to baseline OA and related pain symptoms in adjusted logistic regression models. Following confirmation of these associations, we then included sleep and mood disorders, both separately and together, in the fully adjusted

models to determine the influence of these factors on the associations of OA and related pain symptoms to incident ADRD.

To account for potential survival bias, we also examined, in sensitivity (competing risk of death) analyses, the relation of OA and pain to incident ADRD using multinomial logistic regression; eligible participants who died during the follow-up period ($N = 1479$, including 259 with incident ADRD) were included in these models, with the outcomes categorized as: 1) died, no incident ADRD; 2) died, incident ADRD; 3) alive, incident ADRD; 4) alive, no ADRD.

All bivariate and MVLRA analyses were performed using MCBS complex survey design sampling weights [37,38]. We used 3-year backward longitudinal weights for analysis of our pooled cohorts to yield up to two years of continuous follow-up. All analyses were conducted using SAS survey procedure (SAS version 9.4, SAS Institute, Inc.).

RESULTS

Study population characteristics

Of the 16,934 FFS Medicare beneficiaries included in the study sample, the majority were female (57%), white (83%), married (56.5%), and from metropolitan areas (71%); most reported a family income of at least 200% of the FPL (54.1%). Baseline prevalence of OA was 25.5% (weighted percentage). OA prevalence was similar by cohort year ($p = 0.95$) and did not differ significantly by census region or rurality (p 's > 0.05). As illustrated in Table 1, a significantly higher percentage of beneficiaries with OA were older, female, widowed, lower income, more poorly educated, on Medicaid, and overweight or obese relative to those without OA (p 's < 0.0001). A significantly greater proportion of those with OA also reported a history of chronic physical health conditions associated with ADRD, including hypertension (82.7% versus 70.4%), heart disease (30.8% versus 21.8%), diabetes (22.4% versus 20.2%), chronic respiratory disease (16.2% versus 13.5%), and history of stroke (13.4% versus 10.9%) and TBI (2.1% versus 0.9%), as well as other chronic pain conditions, including RA (6.5 versus 1.6%), lupus (1.5% versus 0.5%), and headache/migraine (9.4% versus 4.5%) (p 's < 0.0001). Presence of chronic pain symptoms, including back and neck, joint, and/or neuropathic pain, were significantly more common in beneficiaries with a history of OA, with 82.5% of the latter indicating pain versus 45.7% of those without OA (Table 1).

In addition, use of prescription analgesics was significantly higher in beneficiaries with than without OA, including NSAIDs (35.5% versus 12.8%) and opioids (33.2% versus 14.6%) (p 's < 0.0001). Elders with prevalent OA were also significantly more likely to report mood disorders, including depression (10.8% versus 5.6%) and anxiety (7.7% versus 4.2%), as well as sleep disorders (23.2% versus 13.3%) relative to those without OA (p 's < 0.0001 (Table 1).

A total of 1,149 beneficiaries (5.7%, weighted percentage) were diagnosed with incident ADRD during the 2-year follow-up period. Incident ADRD rates did not differ by study cohort (range 4.9 to 6.2 per 100 participants, $p > 0.8$), but were significantly higher in

women (6.2% versus 5.0% in men), and in elders who were African American (7.4% versus 5.5% in Non-Hispanic whites), widowed (8.2% versus 4.5% in married), and more poorly educated (p 's < 0.0001) (Supplementary Table 1). Incident ADRD increased strongly with age, from 1.9% in adults 65–69 years to 12% in those 80 and older. The proportion of participants diagnosed with incident ADRD was also significantly higher in those who reported incomes under 200% of the federal poverty level (7.4% versus 4.3%), were on Medicaid (9.1% versus 5.2%) and who lacked private insurance (7.2% versus 5.3%) (p 's < 0.0001). In addition, the percentage diagnosed with incident ADRD was significantly greater in those who indicated a history of specific physical health conditions at baseline, including hypertension, heart disease, stroke, and TBI, as well as in those with certain other chronic pain conditions (including migraine and non-migraine headache) and who reported use of opioid analgesics (p 's < 0.0001). Incident ADRD rates were also significantly higher among those who were diagnosed with depression, anxiety disorders, or insomnia and related sleep disorders at baseline, and notably, were elevated in elders with a history of OA or chronic pain symptoms (p 's < 0.0001).

Association of OA to incident ADRD

As illustrated in Table 2A, OA was strongly and positively associated with likelihood of incident ADRD in unadjusted analyses (odds ratio (OR) = 1.5, 95% confidence interval (CI) 1.31, 1.73, p < 0.0001). Adjustment for sociodemographics, lifestyle factors, other chronic conditions (including RA and lupus), and medications attenuated but did not eliminate this association (adjusted OR (AOR) = 1.23, CI 1.06, 1.42, p = 0.005). Further adjustment for other pain conditions, including those commonly associated with OA (joint, back, neck, and neuropathic) only modestly reduced this risk estimate (AOR = 1.19, CI 1.02, 1.38, p = 0.026), suggesting that accompanying pain only partially explained the observed association of OA to incident ADRD.

Association of OA and pain symptoms to incident ADRD

Table 2B depicts the association of OA and pain, alone and in combination, to incident ADRD. Again, in the unadjusted analysis, OA at baseline, in both the presence and absence of pain, was strongly and positively associated with likelihood of incident ADRD, with the magnitude of risk greatest in those with OA accompanied by pain (ORs for OA with and without pain, respectively = 1.75 (CI 1.46, 2.09) and 1.58 (CI 1.19, 2.09), p 's = 0.001). Baseline back, neck, or joint pain in the absence of OA was likewise associated, albeit more modestly, with elevated ADRD risk (OR = 1.32, CI 1.12, 1.54) (Table 2B). Adjustment for demographic and socioeconomic characteristics attenuated these associations, but did not eliminate the relation of incident ADRD to either OA with pain (AOR = 1.40, CI 1.16–1.68, p = 0.0004) or pain in the absence of OA (AOR = 1.21, CI 1.03, 1.42, p = 0.02). The magnitude of these latter associations was further reduced after additional adjustment for lifestyle factors, other physical health conditions (including other pain conditions), and medications, with only OA accompanied by pain retaining a significant, positive association with incident ADRD (AOR = 1.31, CI 1.08–1.58, p = 0.006).

Potential mediating effects of sleep and mood disorders

As illustrated in Table 3, inclusion of mood disorders attenuated the relation of OA (both with and without pain) to incident ADRD after adjustment for sociodemographics, lifestyle factors, and medical history (AORs for OA versus no OA = 1.14 (0.98, 1.32) and OA with pain versus no OA, no pain = 1.20 (0.99, 1.45). In contrast, the inclusion of insomnia-related disorders alone only modestly affected these associations (AORs for OA versus no OA = 1.18 (1.01, 1.37) and OA with pain versus no OA, no pain = 1.26 (1.05, 1.52) (Table 3). Depression and anxiety disorders, as well as insomnia and related disorders remained significantly and positively associated with incident ADRD (AORs for depression, anxiety, and sleep disorders, respectively = 2.35 (1.86, 2.96), 1.33 (1.04, 1.71), and 1.31 (1.09, 1.58)), p 's = 0.03) and baseline OA (AORs, respectively = 1.46 (1.26, 1.70), 1.38 (1.18, 1.62), 1.44 (1.29, 1.61), p 's < 0.0001)) in the fully adjusted analyses.

Sensitivity analyses

Analyses using competing risk of death models yielded results strongly consistent with findings from our primary analyses (Tables 4A,B). As detailed in Table 4A, relative to elders without baseline OA, those with OA were significantly more likely to be living with incident ADRD at follow-up after adjustment for sociodemographic and lifestyle factors, chronic health conditions, and medications (AOR = 1.22, CI 1.05, 1.41); further adjustment for pain conditions only modestly attenuated this association. In contrast, OA was unrelated to death during the follow up period, either with or without a diagnosis of incident ADRD. Likewise, sensitivity (competing risk of death) analyses regarding the potential mediating influence of mood and sleep disorders yielded findings consistent with those described above (Table 4B). These findings suggest survival bias is unlikely to explain the positive associations observed between baseline OA and incident ADRD, or the apparent partial mediating effects of depression and anxiety disorders.

Other covariates

Several demographic, lifestyle, and health-related factors remained significantly associated with incident ADRD in our fully adjusted model. These include: black (versus non-Hispanic white) race (AOR = 1.41, CI 1.04, 1.90); age (80+ versus 65–69 y, AOR 6.13, CI = 4.72, 7.95); poverty (<200% versus > 200%, AOR 1.16, CI 1.02, 1.34); enrollment in Medicaid (AOR 1.30, 95% CI 1.03, 1.65); and history of diabetes (AOR = 1.21, CI 1.02, 1.44), stroke (AOR 1.87, CI 1.59, 2.19) or TBI (AOR = 1.52, CI = 1.04, 2.23). In contrast, obesity was inversely associated with incident ADRD (AOR = 0.68, CI 0.56, 0.83). Use of neither prescription NSAIDs nor opioids were associated with risk for incident ADRD (AORs = 1.01–1.05, p 's > 0.5).

DISCUSSION

To our knowledge, this is the first study using longitudinal data to examine the association of OA to ADRD in a western population, to assess the potential influence of OA-associated pain on this relationship, and to explore the potential mediating effects of mood and sleep disorders on this association. This study is also among the first to account for the potential influence of survival bias on the association of any pain condition to ADRD. In this

retrospective cohort study of a large sample of 16,934 Medicare beneficiaries, baseline OA was significantly and positively associated with likelihood of incident ADRD within the 3-year study period, an association that was most pronounced in those with OA accompanied by joint, neck, back, or neuropathic pain. However, OA-related pain did not appear to completely explain the link between OA and ADRD, and pain in the absence of OA was unrelated to incident ADRD after adjustment for multiple potential confounders. These findings are broadly consistent with those of our recent cross-sectional study of Appalachian adults [32]; in this investigation, OA and related pain demonstrated a strong, dose-response relation to reported memory loss, with OA retaining a significant, positive association to memory loss even in the absence of joint pain. Likewise, in our large, cross-sectional study of U.S. elders [33, 34], OA was associated with significantly elevated likelihood of ADRD, although only in the presence of pain interference [33, 34]. Our results are also in agreement with those of two large nested case-control studies of Taiwanese nationals indicating significantly elevated likelihood of incident dementia in those diagnosed with OA at baseline (ORs adjusted for age, sex, and certain comorbidities: 1.25 [35]-1.47 [36]), although these studies did not provide information on the relative contribution of OA-related pain or on the potential influence of other chronic pain conditions.

Similarly, our findings parallel those of a growing number of epidemiological studies suggesting certain chronic pain conditions, as well as nonspecific chronic pain symptoms may increase ADRD risk. Notably, recent large retrospective cohort studies in Taiwanese nationals [45–48] and prospective cohort studies Norwegian adults [49, 50] reported significantly increased risk for incident dementia in those diagnosed with fibromyalgia [45] and headache [46–50] after adjustment for demographics, comorbidities, and other factors. While longitudinal studies examining the relation of chronic pain symptoms to adverse cognitive outcomes remain few, and studies, all in U.S. [51–53] and British [54] adults, have varied widely in design, study population, measures, length of follow-up, and other factors, overall findings likewise suggest that persistent pain [51], severe chronic pain [53, 54], and/or reported pain interference [55] may predict subsequent deterioration in memory [53, 54], accelerated cognitive decline [51], and dementia [51, 55].

Potential mediating influence of mood and sleep impairment

OA pain and dysfunction have been bidirectionally linked to sleep impairment [29, 31, 56–58], psychological stress [30, 59–61], depression and anxiety [59, 62–64], and fatigue [30, 64, 65]. Sleep disturbances are common in OA, affecting over 70% of those with symptomatic OA [29, 66]. Likewise OA is often accompanied by serious mood disturbance; e.g., a recent meta-analysis estimated depression to affect 20% of OA patients overall [67], with prevalence rates well over 40% documented in some populations [67–70]. Current evidence from existing experimental, clinical, and epidemiologic studies suggest that the relationships between musculoskeletal pain, inadequate sleep, and psychological distress are strongly reciprocal [71–75]. Chronic pain can lead to significant disruption of both sleep and mood [64, 73, 75, 76]; conversely, growing research suggests that sleep deficits increase sensitivity to noxious stimuli and exacerbate both pain and affective symptoms [71, 74, 75, 77, 78]. Similarly, depression, anxiety, and other distressful states can lead to disordered sleep, as well as increased pain [73, 78–81]. In addition, a substantial body of evidence

indicates that both mood and sleep impairment can significantly and adversely influence cognitive functioning, and are important independent predictors of subsequent cognitive decline, incident cognitive impairment, and ADRD [82–93]. Disruption of mood and sleep may thus in part mediate the documented negative effects of pain on memory and cognitive performance. Consistent with findings from investigations in other chronic pain populations, measures of sleep, depression, and anxiety disorder were significantly inter-related in this study (AORs = 1.7, p 's < 0.0001) and were strongly and positively associated with both OA (AORs = 1.4–1.5) and incident ADRD (AORs = 1.3–2.3) in the fully adjusted models (p 's < 0.0001).

Nonetheless, apart from our recent cross-sectional study of OA and reported memory loss [32], the potential mediating effects of mood and sleep impairment on the association of OA and related pain to ADRD remain little explored. In this study, inclusion of depression and anxiety disorders in the adjusted models attenuated but did not eliminate the association of OA to ADRD, suggesting the observed link between OA and incident ADRD may be partially mediated by these factors. However, in contrast to the findings of our cross-sectional study, we found little evidence for a mediating effect of insomnia and related sleep disorders, with inclusion of the latter only modestly attenuating the risk estimates. The apparent lack of a mediating effect of sleep disturbance in this study may in part reflect the increased prevalence of sleep problems with age; moreover, sleep disturbance and mood impairment are common in prodromal and early ADRD (conditions not captured or likely significantly under-ascertained, respectively, in our study), potentially diluting the effects of both mood and sleep disorders on the association of OA to ADRD, a possibility rendered more likely given the short follow-up period. As indicated above, depression, anxiety, and sleep disorders remained significantly and positively associated with increased ADRD risk after adjustment for pain conditions and multiple other factors.

Potential mechanisms of action

While the mechanisms underlying the observed link between OA and incident ADRD remain incompletely understood, OA may contribute to cognitive decline and the development of ADRD via several pathways. First, the chronic pain associated with OA can have profound effects on neurocognitive function, with potentially significant implications for the development of cognitive impairment and conversion to ADRD. In a recent review of 53 studies of cognitive performance in chronic pain populations, the authors concluded that chronic pain was related to deficits in several key neurocognitive domains, including memory, attention, and processing speed, and, albeit less consistently, executive functioning [94]. The neural systems involved in memory and cognition are closely linked to those involved in pain processing and likely affect one another reciprocally [95, 96], disrupting cognitive processing and contributing to a vicious cycle of continuing pain, adverse neurostructural changes, and deteriorating cognitive function [32]. Patients with chronic pain show changes in brain morphology paralleling those implicated in cognitive decline and cognitive impairment, including grey matter volume reduction in brain regions involved in attention, memory consolidation, and cognitive processing [32, 95–100]. Chronic pain has also been shown to disrupt the functioning of brain networks [99] essential to normal cognitive function. These alterations are thought to help explain the deterioration in

cognitive function documented in many chronic pain populations, including those with OA [95,101], deterioration which may ultimately presage cognitive decline and the development of ADRD.

OA may contribute to ADRD pathogenesis via other pathways as well, e.g., OA has been associated with activation of central pain processing pathways [102] and CNS hypersensitivity [103], factors in turn, linked to disruption of cognitive functioning [95, 104]. Both systemic and peripheral inflammation may also play a role, e.g., systemic increases in Hs-CRP, IL-6, and other proinflammatory mediators have been implicated in the development and progression of both OA and cognitive impairment [105]. Likewise, local proinflammatory changes associated with OA have been linked to neuroinflammation [105], cerebrovascular dysfunction [105], and adverse nociceptive [106] and structural [105] changes in the brain [106], alterations that may, in turn, impair cognitive processing and promote cognitive dysfunction [33, 105]. While some investigators have suggested the putative association between OA and ADRD may be due to use of NSAIDs [107], analgesics associated with reduced ADRD risk in some studies but not others [108–110], adjustment for use of NSAIDs and other prescription analgesics did not substantively alter risk estimates, and NSAID use was not independently associated with incident ADRD in this study.

Consistent with the findings of previous studies [3, 111–113], risk for incident ADRD rose strongly with age, and was increased in elders who were of African American descent, less educated, or poor, as well as those with a history of stroke, diabetes, or TBI in this sample. Likewise, the strong, positive associations between baseline depression, anxiety and sleep disorders, and subsequent likelihood of incident ADRD diagnosis observed in this study are in agreement with numerous prior investigations, including recent meta-analyses [93, 114–116]. Similarly, while midlife obesity has been associated with elevated risk for dementia [117], late life BMI has, in agreement with our findings, shown a generally consistent inverse association with likelihood of ADRD [118–121].

Strengths and limitations

Strengths of this study include the large sample of elderly U.S. FFS Medicare beneficiaries, longitudinal design, and rigorous ascertainment of OA, ADRD, and other chronic health conditions using claims data and validated algorithms. We were able to adjust for a wide array of sociodemographic characteristics, lifestyle factors, and health conditions, as well as use of medications linked to both OA and ADRD risk, reducing the possibility that confounding significantly affected our findings. Information on specific pain conditions commonly associated with OA also allowed us to assess the potential differing influence of OA with and without pain.

This study also carries some important limitations, including the relatively short follow-up period. The development of ADRD is generally insidious, with onset of clinical signs preceded years earlier by perceived and/or objective cognitive decline [122]. Thus, the two year follow up period was likely insufficient to capture the true magnitude of risk associated with OA, especially in light of the often delayed diagnosis of ADRD and the under-ascertainment of ADRD documented in many populations [123], including those on

Medicare [124], which together may have biased estimates towards the null. On the other hand, those with chronic pain may be more likely to seek care, and thus to be diagnosed with dementia, potentially helping to explain the observed associations. However, pain in the absence of OA was not significantly associated with ADRD risk in this study, suggesting that such a detection bias is unlikely to have significantly influenced our findings. As noted above, mood and sleep impairment may have in part reflected signs of prodromal or early ADRD rather than independent riskfactors, potentially reducing our ability to detect a potential mediating role of these factors. Both chronic pain [125] and OA [27] have been linked to increased risk for mortality, raising the possibility that, relative to elders without OA, those with OA may be more likely to die before receiving an ADRD diagnosis and introducing potential survival bias. However, sensitivity analyses accounting for competing risk of death yielded findings consistent with those of our primary analyses, suggesting that survival bias is unlikely to have substantively affected our results. While we were able to adjust for a broad array of factors linked to both OA and ADRD, we lacked information on certain potential confounders, including physical activity and over the counter medications (including non-prescription NSAIDs). In addition, the study was not adequately powered to examine the effects of OA on specific dementia types. Insomnia and related sleep disorders, as well as depression and anxiety, were ascertained using claims data, precluding capture of mood or sleep problems that did not receive a clinical diagnosis and potentially leading to under-ascertainment of these conditions. Our sample was also restricted to community-dwelling elders enrolled in Medicare FFS, potentially limiting generalizability to institutionalized elders, adults enrolled in other insurance plans, younger Medicare beneficiaries, and other populations.

Conclusions

In this retrospective cohort study of community-dwelling Medicare FFS beneficiaries, baseline OA was significantly and positively associated with likelihood of incident ADRD at follow-up; this association was most pronounced in those with OA accompanied by pain and appeared to be partially mediated by depression and anxiety. Clearly, additional rigorous prospective studies are needed to confirm and extend these findings, and to explore potential underlying mechanisms. If confirmed in further longitudinal research, findings of this study could have important clinical and public health implications for the role of OA and associated symptom management in preventing, delaying, or slowing the development of ADRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Study Sample Selection Diagram (linked Medicare Current Beneficiary Survey and Medicare claims, 11 pooled cohorts, 2001–2013). FFS, fee-for-Service; ADRD, Alzheimer’s disease and related dementias.

Table 1

Study sample baseline characteristics stratified by osteoarthritis in a representative sample of community-dwelling Medicare fee-for-service beneficiaries aged 65 years (N = 16,934; linked Medicare Current Beneficiary Survey (MCBS) and fee-for-service Medicare claims, 2001–2013)

	Diagnosed Osteoarthritis				<i>p</i>
	Yes		No		
	N	Weighted %	N	Weighted %	
<i>Total</i>					<0.0001
<i>Incident ADRD</i>					
Yes	4,545	25.5	12,389	74.5	
No	386	7.5	763	5.1	
	4,159	92.5	11,626	94.9	
<i>Sociodemographics</i>					<0.0001
Sex					<0.0001
Female	3,047	67.2	6,622	53.4	
Male	1,498	32.8	5,767	46.6	
Age in Years					<0.0001
65–69	848	23.9	3,340	34.5	
70–74	861	21.8	2,623	22.8	
75–79	1,030	23.5	2,644	20.7	
80 +	1,806	30.7	3,782	22.1	
<i>Mean (SE)</i>	<i>75.90(0.110)</i>		<i>74.14 (0.079)</i>		<0.0001
Race/Ethnicity					0.262
Non-Hispanic White	3,739	82.4	10,346	83.4	
Black/African American	344	7.4	815	6.5	
Hispanic	264	5.8	692	5.6	
Other	194	4.4	515	4.5	
Marital Status					<0.0001
Married	2,255	52.4	6,884	58.0	
Widowed	1,832	36.6	3,971	28.5	
Divorce/separated	322	7.7	1,133	10.2	
Other	135	3.4	397	3.3	
Education					<0.0001

	Diagnosed Osteoarthritis				<i>p</i>
	Yes		No		
	N	Weighted %	N	Weighted %	
<High School	1,066	27.6	3,264	24.1	<0.0001
High School	1,329	35.6	4,553	36.7	
Some College	532	15.1	1,784	15.0	
College	766	21.7	2,752	24.2	
Household Income					<0.0001
<200% Federal Poverty Level	2,374	50.1	5,886	44.5	<0.0001
200% Federal Poverty Level Insurance					
Insurance					
Medicaid	2,171	49.9	6,503	55.5	
Yes	739	15.9	1,408	10.5	0.23
No	3,806	84.1	10,981	89.5	
Private Insurance					
Yes	3,646	80.1	9,772	79.1	
No	899	19.9	2,615	20.9	0.07
Rurality					
Metro	3,127	72.3	8,248	70.0	
Rural	1,418	27.7	4,140	30.0	
<i>Lifestyle Characteristics</i>					<0.0001
Body Mass Index (kg/m2)					
Underweight (<18.5)	66	1.4	246	1.8	
Normal (18.5–24.9)	1,361	29.1	4,506	35.6	
Overweight (25–29.9)	1,768	38.7	4,941	40.5	<0.0001
Obese (≥ 30)	1,295	30.9	2,586	22.1	
<i>Mean (SE)</i>	28.09 (0.086)		26.91 (0.056)		
Smoking Status					
Current	291	6.9	1,303	11.3	<0.0001
Past	2,072	46.5	5,904	47.8	<i>Baseline Health History</i>
Never	2,173	46.6	5,153	40.9	

	<i>p</i>			
	Diagnosed Osteoarthritis			
	Yes		No	
	N	Weighted %	N	Weighted %
Physical Health Conditions				
Hypertension				<0.0001
Yes	3,791	82.7	8,922	70.4
No	754	17.3	3,467	29.6
Ischemic Heart disease				<0.0001
Yes	1,449	30.8	2,908	21.8
No	3,096	69.2	9,481	78.2
History of Stroke				<0.0001
Yes	650	13.4	1,489	10.9
No	3,895	86.6	10,900	89.1
Diabetes				0.003
Yes	996	22.4	2,499	20.2
No	3,549	77.6	9,890	79.8
Chronic Respiratory disease				<0.0001
Yes	719	16.2	1,704	13.5
No	3,826	83.8	10,685	86.5
History of Cancer				<0.0001
Yes	2,017	43.2	5,084	39.4
No	2,528	56.8	7,305	60.6
History of Traumatic Brain Injury				<0.0001
Yes	100	2.1	121	0.9
No	4,445	97.9	12,268	99.1
Other Chronic Pain Conditions				
Rheumatoid Arthritis				<0.0001
Yes	284	6.5	224	1.6
No	4,261	93.5	12,165	98.4
Lupus				<0.0001
Yes	70	1.5	66	0.5
No	4,475	98.5	12,323	99.5
Headache/Migraine				<0.0001

	<i>p</i>			
	Diagnosed Osteoarthritis			
	Yes		No	
	N	Weighted %	N	Weighted %
Yes	422	9.4	567	4.5
No	4,123	90.6	11,822	95.5
<i>Chronic pain symptoms</i>				
<i>Back/neck pain</i>				
Yes	2,051	45.4	2,782	21.9
No	2,494	54.6	9,607	78.1
<i>Joint Pain</i>				
Yes	3,422	76.0	4,967	39.5
No	1,123	24.0	7,422	60.5
<i>Neuropathic Pain</i>				
Yes	332	7.2	439	3.5
No	4,213	92.8	11,950	96.5
<i>Presence of any chronic pain symptoms</i>				
Yes	3,731	82.5	5,773	45.7
No	814	17.5	6,616	54.3
<i>Sleep and Mood Disorders</i>				
<i>Insomnia and related sleep disorders</i>				
Yes	1,055	23.2	1,673	13.3
No	3,490	76.8	10,716	86.7
<i>Depression</i>				
Yes	491	10.8	667	5.6
No	4,054	89.2	11,722	94.4
<i>Anxiety</i>				
Yes	346	7.7	516	4.2
No	4,199	92.3	11,873	95.8
<i>Analgesic medication use</i>				
<i>NSAIDs</i>				
Yes	1,612	35.7	1,629	12.8
No	2,933	64.3	10,760	87.2

	Diagnosed Osteoarthritis			<i>p</i>
	Yes	No		
Opitoid Analgesics				
Yes	1,491	33.2	1,862	14.6
No	3,054	66.8	10,527	85.4
				<0.0001

Table 2A

Relation of OA to incident ADRD in 16,934 Medicare fee-for-service beneficiaries 65 years (linked Medicare Current Beneficiary Survey (MCBS) and fee-for-service Medicare claims, 11 pooled cohorts, 2001–13)

Unadjusted model		Adjusted for sociodemographics [¶]		Also adjusted for lifestyle factor [‡] , chronic conditions ^{¶¶} , medications [‡]		Also adjusted for other chronic pain conditions [‡]	
OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
No OA (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
OA	1.50(1.31,1.73) <0.00001	1.24 (1.07, 1.43) 0.004		1.23 (1.06, 1.42) 0.005		1.19(1.02,1.38) 0.026	

[¶]Including sex, age, race/ethnicity, education, income, supplemental insurance, marital status, region.

[‡]Including smoking status, BMI.

^{¶¶}Including chronic physical health conditions (including RA, lupus), history of stroke, TBI.

[‡]Including joint, back, neck, or neuropathic pain, headache, migraine.

Table 2B

Relation of OA and associated pain[‡] to incident ADRD in 16,934 Medicare fee-for-service beneficiaries 65 years (linked Medicare Current Beneficiary Survey (MCBS) and fee-for-service Medicare claims, 11 pooled cohorts, 2001–13)

	<u>Unadjusted model</u>		<u>Adjusted for sociodemographics[‡]</u>		<u>Also adjusted for lifestyle factors[‡], chronic conditions[‡], medications^{##}</u>	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
No OA, no pain [‡]	1.00 (referent)		1.00 (referent)		1.00 (referent)	
No OA, pain [‡]	1.32(1.12, 1.54)	0.0006	1.21 (1.03, 1.42)	0.02	1.13 (0.96, 1.33)	0.15
OA without pain [‡]	1.58(1.19,2.09)	0.001	1.22 (0.90, 1.66)	0.21	1.23 (0.94, 1.66)	0.16
OA with pain [‡]	1.75 (1.46, 2.09)	<0.00001	1.40(1.16, 1.68)	0.0004	1.31 (1.08, 1.58)	0.006

[‡]Including joint, back, neck, or neuropathic pain.

[‡]Adjusted for sex, age, race/ethnicity, education, income, supplemental insurance, marital status, region.

[‡]Including smoking status, BMI.

^{##}Including diagnosed headache, migraine, and other physical health conditions, history of stroke, TBI.

Table 3

Relation of osteoarthritis (OA) and related pain to incident ADRD in 16,934 community-dwelling Medicare beneficiaries 65 years (linked Medicare Current Beneficiary Survey (MCBS) and fee-for-service Medicare claims, 11 pooled cohorts, 2001–13). Potential mediating influence of diagnosed mood and sleep disorders

	Fully adjusted model [‡]		Adjusted model including depression, anxiety		Adjusted model including sleep disorders		Adjusted model including sleep disorders, depression, and anxiety	
	AOR (95% CI)	p	AOR (95% CI)	p	AOR (95% CI)	p	AOR (95% CI)	p
<i>Diagnosed OA</i>								
No	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Yes	1.23 (1.06, 1.42)	0.005	1.14 (0.98, 1.32)	0.09	1.18 (1.01, 1.37)	0.03	1.13 (0.97, 1.31)	0.11
<i>Diagnosed OA, stratified by presence of pain</i>								
No OA, no pain [†]	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
No OA, pain [†]	1.13 (0.96, 1.33)	0.15	1.09 (0.92, 1.28)	0.06	1.11 (0.94, 1.31)	0.21	1.08 (0.91, 1.27)	0.21
OA without pain [†]	1.23 (0.94, 1.66)	0.16	1.18 (0.90, 1.59)	0.28	1.22 (0.90, 1.65)	0.19	1.18 (0.87, 1.59)	0.29
OA with pain [†]	1.31 (1.08, 1.58)	0.006	1.20 (0.99, 1.45)	0.06	1.26 (1.05, 1.52)	0.01	1.18 (0.97, 1.43)	0.09

[‡] Adjusted for sex, age, race/ethnicity, education, income, insurance, marital status, region; lifestyle factors (smoking, BMI); other chronic conditions, history of TBI, stroke; and medications.

[†] Including joint, back, neck, or neuropathic pain.

Table 4A

Relation of baseline osteoarthritis (OA) to incident ADRD in 18,413 community-dwelling Medicare fee-for-service beneficiaries 65 years, including those who died prior to follow-up (linked Medicare Current Beneficiary Survey (MCBS) and fee-for-service Medicare claims, 11 pooled cohorts, 2001–13): Sensitivity (competing risk of death) analysis

No OA (referent) versus OA	<u>Alive at F/u, no diagnosis of ADRD</u>		<u>Alive at F/u, diagnosed with ADRD</u>		<u>Died with diagnosis of ADRD</u>		<u>Died without diagnosis of ADRD</u>	
Model	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
1 (unadjusted)	1.00 (referent)	-	1.50(1.30, 1.72)	<0.00001	1.11 (0.86, 1.44)	0.41	1.09 (0.94, 1.26)	0.99
2 (including sociodemographics [¶])	1.00 (referent)	-	1.23 (1.07, 1.42)	0.0047	0.87 (0.67, 1.14)	0.31	1.00 (0.85, 1.17)	0.99
3 (+lifestyle factors [‡] , medical hx [‡])	1.00 (referent)	-	1.22 (1.05, 1.41)	0.009	0.88 (0.66, 1.16)	0.36	0.92 (0.78, 1.09)	0.35
4 (+chronic pain conditions ^{##})	1.00 (referent)	-	1.17 (1.00, 1.36)	0.046	0.82 (0.62, 1.09)	0.18	0.88 (0.74, 1.05)	0.15

[¶]Including sex, age, race/ethnicity, education, income, supplemental insurance, marital status, region.

[‡]Including smoking status, BMI.

[‡]Including chronic physical health conditions (including RA, lupus), history of stroke, TBI.

^{##}Including joint, back, and neck pain; neuropathic pain, headache, migraine.

Table 4B

Relation of baseline osteoarthritis (OA) to incident ADRD in 18,413 community-dwelling Medicare fee-for-service beneficiaries 65 years (linked MCBS and fee-for-service Medicare claims, 11 pooled cohorts, 2001–13). Potential mediating influence of diagnosed mood and sleep disorders: Sensitivity (competing risk of death) analysis

<i>Model</i>	<u>Alive at F/u, no diagnosis of ADRD</u>		<u>Alive at F/u, diagnosed with ADRD</u>		<u>Died with diagnosis of ADRD</u>		<u>Died without diagnosis of ADRD</u>	
	AOR (95% CI)	<i>p</i>	AOR (95% CI)	<i>p</i>	AOR (95% CI)	<i>p</i>	AOR (95% CI)	<i>p</i>
Fully adjusted [‡]	1.00 (referent)	-	1.22 (1.05, 1.41)	0.009	0.82 (0.62, 1.09)	0.18	0.88 (0.74, 1.05)	0.15
+depression, anxiety	1.00 (referent)	-	1.12 (0.97, 1.30)	0.13	0.82 (0.61, 1.09)	0.16	0.87 (0.73, 1.04)	0.12
+sleep disorders	1.00 (referent)	-	1.16 (0.99, 1.35)	0.06	0.81 (0.61, 1.07)	0.14	0.87 (0.73, 1.04)	0.13
+ mood and sleep disorders	1.00 (referent)	-	1.11 (0.96, 1.29)	0.16	0.81 (0.61, 1.07)	0.13	0.86 (0.72, 1.03)	0.10

[‡] Adjusted for sex, age, race/ethnicity, education, income, insurance, marital status, region; lifestyle factors (smoking, BMI); other chronic conditions, history of TBI, stroke; and medications.