Osteoarthritis and Cartilage 27 (2019) 1470–1480

Osteoarthritis and Cartilage

Association of osteoarthritis and pain with Alzheimer's Diseases and Related Dementias among older adults in the United States

M. Ikram † *, K. Innes ‡, U. Sambamoorthi §

† Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Robert C. Byrd Health Sciences Center [North], P.O. Box 9510, Morgantown, WV, 26506-9510, USA
‡ Department of Epidemiology, West Virginia University School of Public Health, Morgantown, WV, 26506, USA
§ Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, P.O. Box 9510 Morgantown, WV, 26506-9510, USA

ARTICLE INFO

Article history:
Received 7 December 2018
Accepted 29 May 2019

Keywords:
Osteoarthritis
Pain interference
Alzheimer's disease and related dementias
Dementia
Elderly patients
Pain

SUMMARY

Background: Emerging evidence suggests that Pain Interference (PI) and certain chronic pain conditions, including Osteoarthritis (OA) may be associated with risk for Alzheimer's disease and Related Dementias (ADRD). However, research exploring the relation of OA and PI to ADRD remains sparse.
Objective: To assess the association of OA and PI to ADRD using cross-sectional data from a representative sample of USA adults aged ≥65 years.
Design: Retrospective cross-sectional.
Study sample: Older adults (age ≥ 65 years) drawn from the Medical Expenditure Panel Survey (MEPS, 2009–2015).
Methods: OA was identified using both medical conditions files and participant responses to arthritis-specific queries. ADRD was ascertained using the medical conditions files. PI was defined as reported frequent PI with normal activities (PIA). OA and PIA were categorized as a composite variable: 1) OA with PIA; 2) OA without PIA; 3) No OA with PIA; and 4) No OA and no PIA (reference group). Adjusted associations of OA and PIA to ADRD were assessed using logistic regression and adjusted for biological, demographic, socio-economic, lifestyle, and health conditions.
Results: Overall, 27.1% had OA, of whom 47.6 % reported PIA vs 31.1% of those without OA; 2.8% had diagnosed ADRD. Adults with PIA either with or without OA had significantly higher odds of ADRD relative to those without OA or PIA (Adjusted odd ratios (AOR's) = 1.37, 95%CI − 1.01, 1.86 ($p = 0.04$) and 1.44, 95%CI − 1.13, 1.82 ($p = 0.003$), respectively).
Conclusion: PIA in both the presence and absence of OA remained significantly and positively associated with ADRD after adjustment for multiple confounders.

Introduction

Alzheimer's Disease and Related Dementias (ADRD) is a constellation of neurodegenerative disorders that impose substantial clinical, humanistic, and economic burden on patients and their caregivers, payors, and healthcare systems[1,2]. Many factors have been associated with ADRD risk. These include biological, socio-economic, physical and mental health conditions, genetic factors, health behaviors, and polypharmacy[2–4]. There is also emerging evidence from both cross-sectional[5,6] and longitudinal studies[7,8] that chronic pain and pain interference (PI) with usual activities (PIA) may increase risk for ADRD. For example, in a longitudinal USA study of 1,114 adults (114 new onset dementia cases), PI was associated with significantly increased risk for dementia[7]. Likewise, in a longitudinal survey study of 10,065 older USA adults, persistent pain was associated with both accelerated cognitive decline (a strong predictor of ADRD[9]) and increased risk for probable dementia[8]. In contrast, longitudinal studies in a representative sample of 6,515 British adults[10] and a small USA cohort ($N = 441$)[11] indicated a link only between high pain severity and subsequent deterioration in memory, but not in other cognitive domains.

* Address correspondence and reprint requests to: M. Ikram, Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Robert C. Byrd Health Sciences Center [North], P.O. Box 9510 Morgantown, WV, 26506-9510, USA.
E-mail addresses: mi0018@mix.wvu.edu (M. Ikram), kinnes@hsc.wvu.edu (K. Innes), usambamoorthi@hsc.wvu.edu (U. Sambamoorthi).

https://doi.org/10.1016/j.joca.2019.05.021
1063-4584/

In addition, there are limited data suggesting that risk for ADRD may be increased in adults with certain chronic pain conditions, including osteoarthritis (OA), the second leading cause of chronic pain[12]. To date, only two studies have explored the relationship between OA and cognitive functioning or dementia[13,14]. In a large cross-sectional study of US Appalachian adults, OA and related joint pain were strongly associated with perceived memory loss, suggesting that adults with OA and pain may be at elevated risk for ADRD[13]. Broadly consistent with these findings, a nested case–control study of Taiwanese nationals reported significantly higher risk of dementia in OA patients (HR = 1.25; 95% Confidence Intervals (CI), 1.10–1.43) compared to their age-sex matched non-OA counterparts.[14]

Many patients with OA also report pain that interferes with normal activities[12,15]. In the USA, 80% of adults with OA suffer some mobility limitations, and at least 25% are restricted in major activities of daily living[16]. PI with normal activities (PIA) has been associated with moderate to severe levels of pain intensity[17], suggesting that PI may be a proxy indicator of pain severity and burden that can be used for clinical decision making.[18]

Although the mechanisms underlying the putative association of OA and chronic pain/PIA to the development of ADRD remain unknown, OA may contribute to ADRD pathogenesis via both direct and indirect pathways. For example, chronic musculoskeletal conditions such as OA have been linked to adverse structural and functional changes within the Central Nervous System (CNS)[19], including alterations in brain structures involved in cognitive processing[6] and disruption of brain networks[20] essential to cognitive function. OA has also been associated with activation of central pain processing pathways[21] and hypersensitivity of the CNS[22], factors in turn linked to disruption of cognitive functioning[6,23]. Peripheral factors may also play a role. For example, the proinflammatory soft tissue changes associated with OA, including nociceptor alterations in the joints, have been linked to adverse nociceptive changes in the brainstem, thalamocortical system, and elsewhere[24]; such alterations may, in turn, impair cognitive processing and lead to cognitive dysfunction. In addition, OA may contribute to cognitive decline and the development of dementia via effects on behavioral factors. For example, OA and pain are strongly and reciprocally related to sleep and mood impairment[25–27], both significant risk factors for ADRD.[28–30]

While research to date suggests that chronic pain and certain chronic pain conditions, including OA, may play a role in the development of dementia, the relation of OA and PIA to ADRD remains little explored. To help address this gap, the primary objective of this study was to examine the association of OA and PIA to ADRD among elderly (age $\geq$ 65 years) in the USA, using cross-sectional data from a nationally representative survey. We hypothesize that older adults with OA who reported PIA will have higher odds of ADRD compared to older adults without OA or PIA.

Methods

Study design

We adopted a cross-sectional study design using data from a nationally representative household survey, the Medical Expenditure Panel Survey (MEPS). Data were pooled across multiple years.

Data source

MEPS is a survey of USA non-institutionalized, civilian households and their families, conducted annually since 1996. Households for the survey are selected through a complex survey design described in detail elsewhere[31]. Information on demographics, lifestyle characteristics, socioeconomic status, chronic health conditions, health care utilization and cost, prescription medications, and other factors was collected using the Computer Assisted Personal Interview questionnaire.

Study sample

The study sample comprised adults ≥65 years of age who were alive during the calendar year and who did not have missing information on PIA status. We also excluded participants without health insurance (0.4%). A flow diagram of the study sample selection process is given in Appendix Fig. 1. Because ADRD prevalence in non-institutionalized adults is low[32], we pooled data from multiple calendar years (2009–2015). Pooling data can reduce the relative standard error of estimates, leading to higher reliability and permitting subgroup analyses. This is a standard practice recommended by MEPS investigators and that has been commonly employed in prior studies using MEPS data[33,34]. The final sample size was 25,009 (N's by year = 3450 (2009); 3312 (2010); 3562 (2011); 3881 (2012); 3548 (2013); 3479 (2014); and 3777 (2015)). (See Appendix Fig. 1).

Measures

Dependent variable: ADRD status - yes/no

The presence or absence of ADRD was ascertained using the medical conditions file. Medical conditions were reported for each household member seeking care either from inpatient settings, outpatient clinics, emergency rooms, or other provider settings. These medical conditions were recorded "verbatim and converted by professional coders into fully-specified International Classification of Diseases, ninth Edition, clinical modification (ICD-9-CM) codes"[31]. To protect confidentiality, MEPS releases only 3-digit ICD-9-CM codes. We used ICD-9-CM codes 290.xx, 294.xx, and 331.xx to identify ADRD based on published literature.[35–37]

Key independent variable: OA and PIA categories

Identification of OA. MEPS investigators consider arthritis a priority condition. Therefore, all household members over 18 years of age were queried whether or not they have been ever diagnosed with arthritis and, if so, which type of arthritis (Rheumatoid arthritis vs OA). Participants reporting diagnosed OA in response to these queries or who had a record of OA diagnosis in the medical conditions file were considered to have OA. As MEPS groups ICD-9-CM codes into a manageable number of conditions using clinical classification codes software (CCS)[38], we used the CCS code (203) to identify OA in the medical conditions file.

PIA. A mail survey was administered to collect information on PIA and other domains of health-related quality of life. PIA was measured using the one-item from the MOS Short Form (SF)-12. This item asked how much pain "interfered with normal work (including both work outside the home and housework)" during the past 4 weeks prior to the interview. Responses were recorded using a 5-item Likert scale: 1) 'Not at all'; 2) 'A little bit'; 3) 'Moderately'; 4) 'Quite a bit'; and 5) 'Extremely'. We recoded participant responses into a binary variable indicating presence or absence of PI activity as follows: 1) No PIA (not at all or a little bit); and 2) PIA (moderately, quite a bit, and extremely). Combining PIA using one-item from the MOS SF-12 is a common practice in published literature.[39–41]

We then combined the binary OA and PIA variables to create a composite variable with four categories: 1) OA with PIA; 2) OA without PIA; 3) No OA with PIA and 4) No OA and No PIA.

Other explanatory variables

In our adjusted analyses, we also included other factors previously linked to OA and/or ADRD. These included: biological characteristics, i.e.,: sex (female/male); age category (65–69, 70–74, 75–79, and 80 years and older) and race (Non-Hispanic White, African American, Hispanic, and other); demographics and socioeconomic status, i.e.,: marital status (married, divorced/separated, widowed, single); education (Less than 12 years, 12 years/GED, and >12 years) and income as measured by percentage of federal poverty line (FPL) (poor (<100% FPL), near poor/low income (≥100–<200% FPL), middle income (≥200–<400% FPL), and high income (≥400% FPL)); lifestyle/behavioral factors, i.e.,: current smoking status (smoker/non-smoker), exercise (yes/no); body mass index (BMI, calculated as weight in kg/height in m^2), categorized as underweight/normal (<25), overweight (25–29.9), and obese (≥30)); access to healthcare services, measured by health insurance (private vs public health insurance); chronic conditions, including diabetes, heart disease, high cholesterol, depression, and anxiety (Y/N); and polypharmacy (defined as prescriptions of ≥6 medications (yes/no)). We also included as covariates region of residence (Northeast, Midwest, South, and West) and survey calendar year (2009–2015). In addition, we also added any use of prescribed analgesics during the year (nonsteroidal anti-inflammatory drugs (NSAIDS) and opioids) as covariates in separate ancillary multivariable analyses.

Statistical analysis

Statistically significant subgroup differences in categorical variables by OA and PIA groups with ADRD status were determined by Rao-Scott chi-square tests. Multivariable logistic regression models were used to assess the cross-sectional association of OA and PIA to ADRD. These regression analyses controlled for biological factors (sex, age, race), demographics and socio-economic status (marital status, education, income, and insurance type); chronic physical and mental health conditions (e.g., diabetes, heart disease, depression, anxiety); polypharmacy; and behavioral/lifestyle factors (obesity, smoking, and exercise), as well as region of residence and MEPS year.

As MEPS adopted a complex survey design, all analyses were performed using SAS survey procedures (SAS v 9.4 (SAS Institute, Inc)). To obtain annualized weighted numbers, we divided the annual weights by the number of years pooled, again a standard practice in the published literature[42]. As data for this study included information from self-administered questionnaires, we used weights that were appropriate for responses derived from self-administered questionnaires.[43]

Results

The number of older participants in our study represented an estimated average of 42.7 million older adults (age ≥ 65 years). A majority of the sample were female (55.8%), white (78.4%), and married (56.0%). Only 39.1% had high family income (income ≥ 400% of the FPL). Overall, 27.1% of this study sample of older adults reported having OA and 35.6% reported moderate, severe, and extreme PIA. When examined by the four categories of OA and PIA, 12.9% reported OA with PIA; 14.2% reported OA without PIA; 22.7% reported No OA with PIA; and 50.2% reported No OA and No PIA (Data not presented in tabular form).

In this sample, the four OA and PIA groups (OA with PIA, OA without PIA, No OA with PIA, No OA and No PIA) differed significantly in all measured biological, demographic, and socio-economic characteristics, lifestyle/behavioral factors, and chronic physical and mental health conditions (see Appendix Table I). Notably, those with OA but without PIA had significantly better profiles with respect to certain socioeconomic, behavioral/lifestyle, and health-related factors than those without OA or PIA (and dramatically better profiles with respect to virtually all factors than those with OA and PIA) (Appendix Table I).

Table I summarizes the characteristics of older adults by ADRD status. Overall, 2.8% of older adults had ADRD. Relative to elders with No PIA and No OA, ADRD was significantly more common in those reporting OA with PIA (4.3 vs 2.0%) and those with PIA and No OA (4.6 vs 2.0%) (p's < 0.001). Treated prevalence of ADRD increased significantly with age and was significantly higher in older adults with vs without polypharmacy (4.5 vs 1.8%), diabetes (3.4 vs 2.6%), heart diseases (3.4 vs 2.4%), depression (5.4 vs 2.4%), and anxiety (4.7% vs 2.5%) (p's < 0.05). ADRD was also significantly more common in sedentary than in physically active seniors (4.1 vs 1.1%).

The results of the unadjusted logistic regression indicated a significant association between PIA and ADRD, both in the presence and absence of OA (Table II). Compared to older adults without OA and without PIA, those with both OA and PIA were 2.3 times as likely (OR = 2.28, 95% CI = 1.68, 3.10; $p < 0.0001$) and those with No OA and PIA were 2.4 times as likely (OR = 2.42, 95% CI = 1.92, 3.04; $p < 0.0001$) to report ADRD. Adjustment for biological factors (age, sex, age, and race/ethnicity) only modestly attenuated these associations (AOR's for ADRD, for OA with PIA and No OA and PIA, respectively, = 1.88, (95% CI = 1.39, 2.54) and 1.98 (95% CI = 1.58, 2.49), p's = 0.0001), but strengthened the apparent inverse association OA without PIA to ADRD (AOR = 0.66, 95% CI = 0.44, 0.99; $p < 0.04$).

Additional adjustment for demographics, socio-economic status, behavioral/lifestyle factors, insurance type, chronic physical and mental health conditions, polypharmacy, region, and calendar year further reduced but did not eliminate the significant, positive associations of OA with PIA (AOR = 1.37, 95% CI = 1.01, 1.86; $p = 0.041$) and PIA without OA to ADRD (AOR = 1.44, 95% CI = 1.13, 1.82, $p < 0.003$); however, additional adjustment for these factors did not appreciably alter the inverse association of OA without PIA to ADRD (AOR = 0.66, 95% CI = 0.43, 0.99; $p = 0.046$) (Table II). Inclusion of analgesics in the ancillary adjusted model did not alter any of the observed associations of OA and PIA to ADRD (data not shown).

Other variables significantly and positively associated with ADRD (Appendix Table II) in the fully adjusted analyses included: age (AOR for 80 + vs 65–69 years = 10.90, 95% CI = 6.92, 17.17; $p < 0.01$), African American race (AOR = 1.56, 95% CI = 1.15, 2.11; $p = 0.0045$), lack of physical activity (AOR = 2.36, 95% CI = 1.80, 3.10; $p < 0.001$), and lower education (AOR for less than 12 years = 1.64, 95% CI = 1.17, 2.31; $p = 0.004$). ADRD also showed a significant positive relationship to depression (AOR = 2.06, 95% CI = 1.57, 2.70; $p = 0.0001$), anxiety (AOR = 1.46, 95% CI = 1.04, 2.05; $p = 0.0309$), and polypharmacy (AOR = 1.90, 95% CI = 1.45, 2.47; $p = 0.0001$). In ancillary adjusted analysis (data not presented), any use of prescription analgesic medications (opioids and NSAIDs) was not significantly associated with the odds of ADRD (NSAIDs $p = 0.8516$; opioids $p = 0.6883$).

Discussion

In this first population-based cross-sectional US study on OA, PIA and ADRD, nearly one in four (27.1%) community-dwelling older adults reported osteoarthritis and 2.8% reported ADRD. We found that PIA in OA and no OA was strongly and positively associated with ADRD after adjustment for multiple correlates. Our findings are broadly consistent with those of a nested-case control study of Taiwanese Nationals indicating an increased risk for dementia in adults with OA[14] and a cross-sectional study of

Table I
Selected Characteristics of older adults (≥65 years) by Alzheimer's Diseases and Related Dementia(ADRD) Status Medical Expenditure Panel Survey (MEPS), 2009–2015

ALL	ADRD		No ADRD	
	N	Wt. row %	N	Wt. row %
	727	2.8	24,282	97.2
OA and PIA†				
OA with PIA	134	4.3	2,917	95.7
OA without PIA	44	1.3	3,031	98.7
No OA with PIA	287	4.6	6,092	95.4
No OA and No PIA	262	2.0	12,242	98.0
Biological Factors				
Sex				
Female	447	3.0	13,872	97.0
Male	280	2.5	10,410	97.5
Race/Ethnicity†				
Non-Hispanic White	415	2.7	14,397	97.3
African American	164	3.8	4,308	96.2
Hispanic	89	2.1	3,390	97.9
Other-race	59	3.1	2,187	96.9
Age†				
65–69 Years	55	0.5	8,584	99.5
70–74 Years	93	1.6	5,776	98.4
75–79 Years	120	2.4	4,263	97.6
80 years or older	459	7.1	5,659	92.9
Socio-economic Status				
Poverty Status†,*				
Poor	128	3.2	3,720	96.8
Near Poor	228	3.7	5,968	96.3
Middle Income	223	3.0	7,138	97.0
High Income	148	2.0	7,456	98.0
Education (in years)†				
<12 years	276	4.5	6,139	95.5
12 years/GED	246	3.2	7,539	96.8
>12 years	183	1.8	10,320	98.2
Life-style/Behavioral Factors				
Current Smoking†				
Current smoker	50	2.1	2,292	97.9
Other	661	2.8	21,390	97.2
Obesity				
Underweight/Normal	326	3.6	7,830	96.4
Overweight	244	2.7	8,889	97.3
Obese	145	1.8	7,164	98.2
Exercise†,*				
Yes	117	1.1	10,506	98.9
No	604	4.1	13,607	95.9
Treatment Factors				
Polypharmacy†				
Polypharmacy (>=6 medications))	401	4.5	8,531	95.5
No polypharmacy (<6 medications)	326	1.8	15,751	98.2
Access to Healthcare				
Insurance Coverage†				
Public	260	2.3	11,451	97.7
Private	467	3.3	12,831	96.7
Chronic Conditions				
Diabetes†				
Yes	229	3.4	6724	96.6
No	498	2.6	17,556	97.4
Heart Disease†				
Yes	348	3.4	9307	96.6
No	379	2.4	14,973	97.6
High Cholesterol				
Yes	483	2.8	15,774	97.2
No	244	2.7	8498	97.3
Depression†				
Yes	159	5.4	2651	94.6
No	568	2.4	21,631	97.6
Anxiety†				
Yes	121	4.7	2351	95.3
No	606	2.5	21,931	97.5

Note: Based on pooled data from multiple years older adults (age > 65 years), who were alive during the calendar year, had health insurance and did not have missing values for the PIA variable (N in 2009 = 3450; N in 2010 = 3312; N in 2011 = 3562; N in 2012 = 3881; N in 2013 = 3548; N in 2014 = 3479; and N in 2015 = 3777).

Appalachian adults, which documented a strong association of OA and related joint pain to perceived memory loss[13]. Our findings are also in general agreement with cross-sectional[5,6,23], case–control[44,45], and longitudinal studies[7,8,11] documenting significant associations of non-specific chronic pain[5–8,11] and other (non-OA) chronic pain conditions[5,6,44,45] to impairment in cognitive functioning. Notably, in one recent study of a small US cohort followed for an average of 4.4 years, PI was associated with significantly increased risk for incident dementia[7]. In contrast, in their 4-year longitudinal study of British adults, Veronese *et al.* found no association between non-specific chronic pain and overall decline in cognitive function, although, severe pain was associated with significantly greater memory decline.[10]

While mechanisms underlying the observed association of OA and PIA to ADRD remain unknown, OA and PIA may contribute to cognitive decline and subsequent development of ADRD via both direct and indirect pathways. For example, as discussed above, pain, both in the presence and absence of OA, may lead to adverse changes in brain structure and function and in CNS activation and sensitivity that increase risk for cognitive dysfunction and ultimately, ADRD[6,19,21–23]. PIA in OA may also impair sleep, contribute to depression, and lead to lifestyle changes such as reduced physical activity that further increase the risk for cognitive decline and dementia.

In our study, older adults with OA without PIA appeared to have lower odds of ADRD compared to those without OA and without PIA. The reasons for this finding are not clear. However, it may reflect either effective treatment of OA or asymptomatic OA status. As we could not assess effectiveness of OA treatment, we were unfortunately unable to control for this factor in our analyses. However, we adjusted for prescription analgesics (NSAIDs and opioids) and inclusion of these variables did not appreciably alter odds ratios. It has to be noted that all types of analgesics use are not captured in MEPS (e.g., non-prescription NSAIDS were not recorded). Notably, NSAIDS have been associated with reduced risk for incident cognitive impairment and dementia in several observational studies[46,47] and with lower risk for cognitive decline in a recent meta-analysis of 11 prospective cohort studies[48], although studies regarding the relation of opioid use to subsequent cognitive function have produced inconsistent findings[13]. As most OA patients rely on NSAIDs and other pain medications, failure to control adequately for this factor may have biased observed Adjusted Odds Ratios (AOR) estimates, and may help explain the apparent inverse association of OA to ADRD. In addition, those with OA and without PIA had significantly better profiles with respect to certain socioeconomic, behavioral/lifestyle, and health conditions than those without OA or PIA. Those with OA and without PIA also had dramatically better profiles with respect to virtually all factors than those with OA and PIA (Appendix Table I), which may also have contributed to the observed inverse AOR of ADRD in this group.

Associations of other factors with ADRD observed in this study were consistent with those reported in prior published studies. For example, age was strongly and positively associated with the likelihood of ADRD in this study, consistent with findings of previous epidemiological studies[2,49]. Likewise, the elevated risk of ADRD in African Americans observed in our sample (OR = 1.56) is in

Abbreviations: OA: Osteoarthritis, PIA: Pain interference with usual activity; wt.%: weighted percentage.

* Exercise was measured as 3 or more times/week in 2009 and 2010 and 5 or more times/week in 2011 through 2015.

† Indicates statistical significance ($p < .05$) based on Rao-Scott Chi square tests.

Table II
Unadjusted Odds Ratios (UOR) and Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI) from Logistic Regressions on Alzheimer's Disease and related dementias among Older adults (≥65 years) Medical Expenditures Panel Survey, 2009–2015

Model 1: Unadjusted Model			
	UOR	**95%CI**	***P*-Value**
OA with PIA	2.28	[1.68, 3.10]	0.0001
OA without PIA	0.70	[0.47, 1.05]	0.0856
PIA and No OA	2.42	[1.92, 3.04]	0.0001
No PIA and No OA (ref)	1.00	–	
Model 2: Adjusted for Biological Factors (Sex, Age, and Race/ethnicity)			
	AOR	**95%CI**	
OA with PIA	1.88	[1.39, 2.54]	0.0001
OA without PIA	0.66	[0.44, 0.99]	0.0423
No OA with PIA	1.98	[1.58, 2.49]	0.0001
No PIA and No OA (ref)	1.00	–	
Model 3: Fully adjusted model*			
	AOR	**95%CI**	
OA with PIA	1.37	[1.01, 1.86]	0.0408
OA without PIA	0.66	[0.43, 0.99]	0.0460
PIA and No OA	1.44	[1.13, 1.82]	0.0029
No PIA and No OA (ref)	1.00	–	

Note: Based on pooled data from multiple years older adults (age ≥ 65 years), who were alive during the calendar year, had health insurance and did not have missing values for PIA.
Abbreviations: AOR: Adjusted odds ratios; CI: 95% Confidence Intervals; OA: Osteoarthritis; PIA: Pain interference with usual activity.
* Fully adjusted model controlled for age, sex, race, marital status, poverty status, education, obesity, current smoking, physical activity, polypharmacy, insurance, diabetes, heart disease, high cholesterol, depression, anxiety, region, and calendar year. The fully adjusted model had a c-statistic of 0.81.

agreement with findings of a recent meta-analysis of population-based studies, which indicated increased risk for both prevalent and incident Alzheimer's disease risk in African American vs Caucasian Americans (AOR = 1.56 and 1.64, respectively)[50]. We also observed higher odds of ADRD in older adults who reported less education (AOR = 1.64), physical inactivity (AOR = 2.36), depression (AOR = 2.06), anxiety (AOR = 1.46) and polypharmacy (AOR = 1.90). These findings are consistent with the previous cross-sectional and longitudinal studies.[2–4,51]

This study has several strengths, including the population-based design and the large, nationally representative sample of older, ethnically diverse, community-dwelling USA adults. In our analyses, we were able to adjust for many covariates associated with OA and/or ADRD, reducing the likelihood of confounding. However, our study also has several important limitations. The cross-sectional nature of the data does not allow the determination of causal relationships, and reverse causality, while unlikely, cannot be ruled out. Much of the data gathered were reliant on self-report, introducing the possibility of recall and other forms of information bias. Given that both OA and chronic pain have been linked to increased mortality risk[52–54]. survival bias may also have influenced our findings, potentially attenuating observed risk estimates. Moreover, the differential under-reporting of pain common in patients with dementia[55] may likewise have biased risk estimates toward the null. Furthermore, the PI question captured pain experienced within the past 4 weeks. Our study sample was restricted to adults 65 years and older, limiting generalizability to other age groups. Although we were able to adjust for many potential confounders, we cannot rule out the possibility of unmeasured confounding.

Conclusion

In this large, cross-sectional study in a representative sample of USA adults, PIA both in the presence and absence of OA was associated with significantly increased likelihood of ADRD after adjustment for multiple demographic, socioeconomic, lifestyle, health related, and other factors. Future population-based studies that track individuals over time are needed to confirm and extend these findings and to explore potential underlying mechanisms.

Author contributions

All authors contributed to the conception and design of the research. US/MI conducted the statistical analyses. MI wrote the first draft. MI, US and KI worked on successive iterations. All authors approved the final draft.

Conflicts of interest

The authors report no conflicts of interest.

Acknowledgements

Research reported in this publication was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number 2U54GM104942-02, WVCTSI and in part by the Alzheimer's Research and Prevention Foundation (ARPF). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the ARPF.

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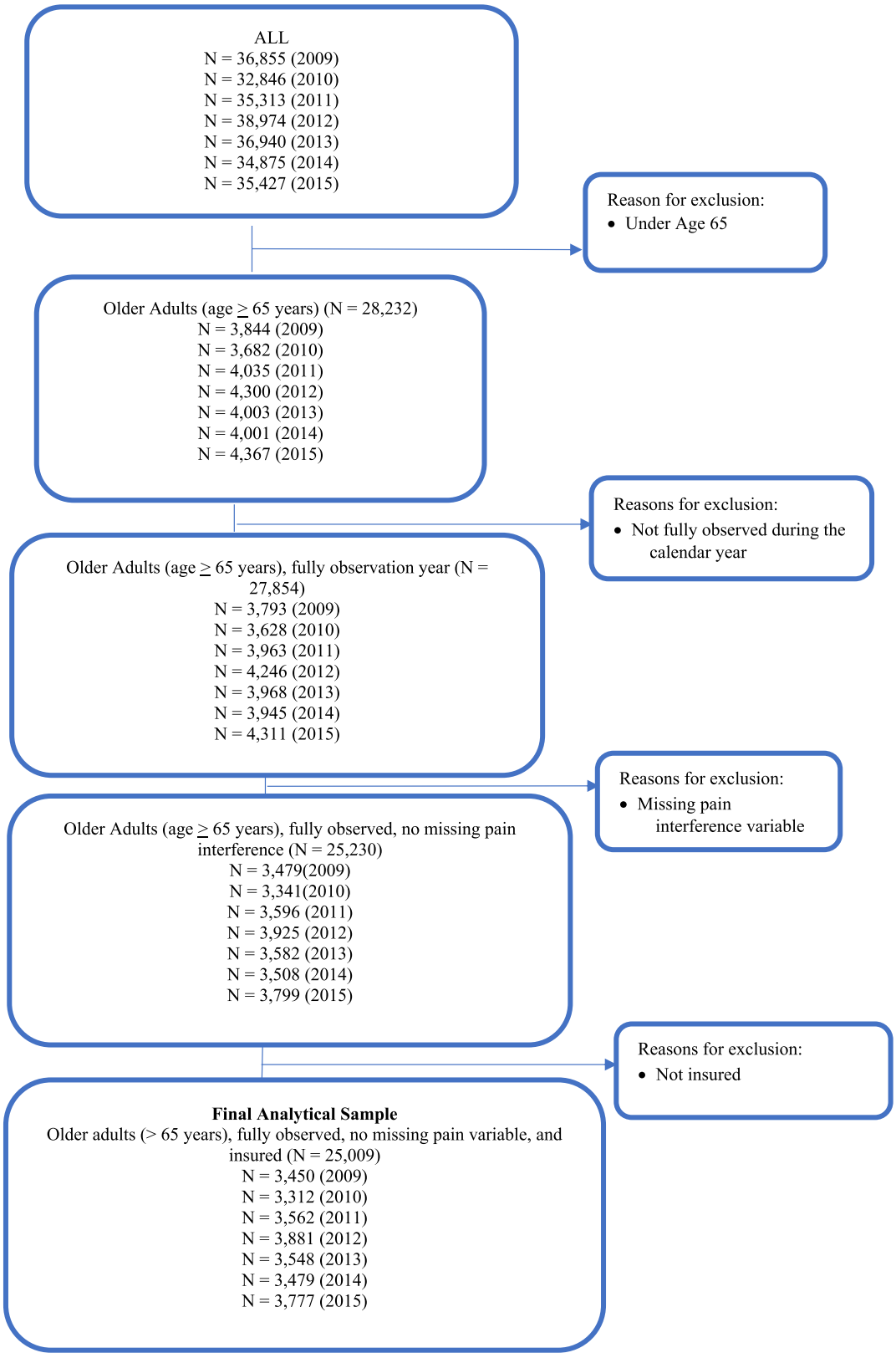
Appendices



Appendix Fig. 1. Study Sample Selection: Medical Expenditure Panel Survey (MEPS), 2009–2015.

Appendix Table I
ICharacteristics of Older Adults (≥65 years) By Osteoarthritis and PIA Status (Column Percentages) Medical Expenditure Panel Survey (MEPS), 2009–2015

ALL	OA with PIA		OA without PIA		No OA with PIA		No OA and No PIA	
	N	Wt. %	N	Wt. %	N	Wt. %	N	Wt. %
	3,051	100	3,075	100	6,379	100	12,504	100
Biological Factors								
Sex*								
Female	2,169	68.2	2,082	66.3	3,654	55.0	6,414	50.1
Male	882	31.8	993	33.7	2,725	45.0	6,090	49.9
Race*								
White	2,081	83.9	2,279	87.1	3,171	71.6	7,281	77.6
African American	455	6.8	375	5.7	1,478	11.5	2,164	8.4
Latino	320	5.1	225	3.3	1,134	10.4	1,800	7.7
Other-race	195	4.3	196	3.8	596	6.4	1,259	6.2
Age*								
65–69 Years	900	27.0	1,024	33.4	1,977	29.7	4,738	36.8
70–74 Years	666	23.1	757	24.9	1,394	21.1	3,052	24.8
75–79 Years	576	19.0	560	17.9	1,158	18.6	2,089	16.7
80 years or older	909	30.9	734	23.8	1,850	30.5	2,625	21.7
Demographic Characteristics								
Marital Status*								
Married	1,394	51.3	1,680	58.8	2,953	50.1	6,816	59.0
Widowed	979	29.9	850	25.3	2,023	30.1	3,173	23.6
Separated/Divorced	531	15.0	415	12.2	1,056	15.4	1,848	13.1
Never married	147	3.8	130	3.7	347	4.4	667	4.3
Socio-Economic Status								
Poverty Status*,†								
Poor	507	10.0	306	6.1	1,357	12.1	1,678	7.5
Near Poor	838	26.3	632	18.6	1,959	29.8	2,767	19.9
Middle Income	865	28.4	897	27.9	1,790	30.4	3,809	29.6
High Income	841	35.2	1,240	47.4	1,273	27.6	4,250	42.9
Education*(in years)								
<12 years	723	17.1	450	10.7	2,357	27.7	2,885	15.8
12 years/GED	1,052	36.8	925	28.9	2,005	33.9	3,803	30.6
>12 years	1,259	45.6	1,686	60.1	1,892	37.0	5,666	52.9
Life-style/Behavioral Factors								
Body Mass Index*								
Underweight/Normal	822	28.1	998	33.8	1,875	30.6	4,461	36.5
Over weight	913	29.4	1,155	38.3	2,140	34.9	4,925	40.9
Obese	1,275	42.5	874	28.0	2,226	34.5	2,934	22.7
Current Smoking*								
Current smoker	270	8.2	168	5.6	715	11.2	1,189	9.2
Other	2,705	89.8	2,852	93.0	5,483	86.4	11,011	88.8
Exercise*,†								
Yes	880	29.2	1,519	50.8	1,937	31.8	6,287	52.2
No	2,156	70.2	1,545	48.9	4,388	67.4	6,122	47.2
Treatment Factor								
Polypharmacy*								
Polypharmacy ≥ 6	1,697	56.5	1,078	35.4	3,051	49.3	3,106	25.0
No polypharmacy <6	1,354	43.5	1,997	64.6	3,328	50.7	9,398	75.0
Access to Healthcare								
Insurance Coverage*								
Public	1,383	52.3	1,725	61.7	2,346	44.9	6,257	57.2
Private	1,668	47.7	1,350	38.3	4,033	55.1	6,247	42.8
Chronic Conditions								
Diabetes*								
Yes	1,015	30.6	630	17.5	2,352	33.7	2,956	20.9
No	2,036	69.4	2,445	82.5	4,026	66.3	9,547	79.1
Heart Disease*								
Yes	1,557	52.9	1,201	40.8	2,964	48.8	3,933	33.4
No	1,493	47.1	1,874	59.2	3,415	51.2	8,570	66.6
High Cholesterol*								
Yes	2,205	72.4	2,038	66.7	4,475	70.2	7,539	61.6
No	844	27.6	1,036	33.3	1,901	29.8	4,961	38.4
Depression*								
Yes	621	20.9	350	12.2	931	15.8	908	8.2
No	2,430	79.1	2,725	87.8	5,448	84.2	11,596	91.8
Anxiety*								
Yes	480	15.9	339	11.7	817	14.0	836	7.4
No	2,571	84.1	2,736	88.3	5,562	86.0	11,668	92.6
Region and Year of Interview								
Region*								
Northeast	499	19.5	560	21.1	922	16.6	2,098	19.1
Midwest	687	23.0	749	24.3	1,111	20.1	2,526	22.3
South	1,226	38.5	1,117	36.5	2,771	40.7	4,631	35.3
West	639	19.1	649	18.1	1,575	22.6	3,249	23.3

Appendix Table I (*continued*)

ALL	OA with PIA		OA without PIA		No OA with PIA		No OA and No PIA	
	N	Wt. %	N	Wt. %	N	Wt. %	N	Wt. %
	3,051	100	3,075	100	6,379	100	12,504	100
Calendar Year								
2009	433	13.5	385	11.7	926	12.9	1,706	12.9
2010	406	13.7	423	13.1	833	12.7	1,650	12.9
2011	443	13.3	451	14.7	904	13.6	1,764	13.5
2012	471	13.8	454	13.9	1,034	15.1	1,922	14.4
2013	422	15.0	445	15.1	873	14.8	1,808	14.6
2014	454	16.3	428	14.9	846	14.8	1,751	15.7
2015	422	14.3	489	16.6	963	16.2	1,903	16.1

Note: Based on pooled data from multiple years older adults (age > 65 years), who were alive during the calendar year, had health insurance and did not have missing values for the PIA variable (N in 2009 = 3450; N in 2010 = 3312; N in 2011 = 3562; N in 2012 = 3881; N in 2013 = 3548; N in 2014 = 3479; and N in 2015 = 3777).
* represent significant group differences by osteoarthritis PIA groups based on Rao-Scott Chi square tests.
† Exercise was measured as 3 or more times/week in 2009 and 2010 and 5 or more times/week in 2011 through 2015.
PIA = Pain Interference with usual activity, wt. = weighted column percentage.

Appendix Table II
Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI) of Biological, Demographic, Socio-economic, Lifestyle/Behavioral, and Health Conditions from Logistic Regression on Alzheimer's Diseases and Related Dementias in adults ≥65 years, Medical Expenditure Panel Survey, 2009–2015

	AOR	95%CI	Significance
Biological Factors			
Sex			
Male (ref)			
Female	0.89	[0.68, 1.16]	0.3903
Race			
White Non-Hispanic (ref)			
African American	1.56	[1.15, 2.11]	0.0045
Hispanic	0.66	[0.43, 1.00]	0.0498
Other-race	1.21	[0.75, 1.96]	0.4280
Age			
65–69 Years (ref)			
70–74 Years	2.97	[1.87, 4.70]	0.0001
75–79 Years	4.12	[2.58, 6.58]	0.0001
GE 80 years	10.9	[6.92, 17.17]	0.0001
Demographic and Socio-Economic status			
Marital Status			
Married (ref)			
Widowed	1.00	[0.76, 1.31]	0.9728
Separated/Divorced	1.19	[0.82, 1.72]	0.3707
Never married	0.77	[0.42, 1.43]	0.4102
Poverty Status			
High Income (ref)			
Poor	0.68	[0.50, 0.93]	0.0167
Low Income	0.83	[0.63, 1.09]	0.1882
Middle Income	0.91	[0.69, 1.21]	0.5137
Education (in years)			
>12 years (ref)			
<12 years	1.64	[1.17, 2.31]	0.0043
12 years/GED	1.34	[1.00, 1.78]	0.0481
Behavioral/Lifestyle Factors			
Obesity			
Underweight/Normal (ref)			
Over weight	0.86	[0.69, 1.07]	0.1704
Obese	0.52	[0.37, 0.74]	0.0003
Current Smoking			
Other (ref)			
Current smoker [Continued]	0.96	[0.65, 1.43]	0.8402
Exercise*			
Yes (ref)			
No	2.36	[1.80, 3.10]	0.0001
Treatment Factor			
Polypharmacy			
<6 prescription meds (ref)			
≥6 prescription meds	1.9	[1.45, 2.47]	0.0001
Access to healthcare			
Insurance Coverage			
Private (ref)			
Public Insurance	0.84	[0.66, 1.08]	0.1734

(*continued on next page*)

Appendix Table II (*continued*)

	AOR	95%CI	Significance
Chronic Conditions			
Diabetes			
No (ref)			
Yes	1.16	[0.88, 1.53]	0.2968
Heart Disease			
No (ref)			
Yes	0.83	[0.65, 1.07]	0.1542
High Cholesterol			
No (ref)			
Yes	0.88	[0.71, 1.09]	0.2492
Depression			
No (ref)			
Yes	2.06	[1.57, 2.70]	0.0001
Anxiety			
No (ref)			
Yes	1.46	[1.04, 2.05]	0.0309

Note: Based on pooled data from multiple years (N in 2009 = 3450; N in 2010 = 3312; N in 2011 = 3562; N in 2012 = 3881; N in 2013 = 3548; N in 2014 = 3479; and N in 2015 = 3777), who were alive during the calendar year, had health insurance and did not have missing values for the PIA variable.
Abbreviations: ADRD: ref = Reference group, *P*-values based on survey logistic regression.
*Exercise was measured as 3 or more times/week in 2009 and 2010 and 5 or more times/week in 2011 through 2015.