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Association between osteoarthritis and cognitive function: results from the NHANES 2011–2014 and Mendelian randomization study

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Abstract

Background: Previous meta-analyses have demonstrated osteoarthritis (OA) is associated with an increased risk of dementia, but these studies were prone to bias based on residual confounding factors and reverse causality.

Objectives: We aimed to investigate associations between OA and cognitive function using data from the National Health and Nutrition Examination Survey (NHANES) and to investigate the causality using Mendelian randomization (MR).

Design: This is a cross-sectional study and MR study.

Methods: Data from the NHANES 2011–2014 were used. Multiple linear, logistic regressions and stratified analyses were used to determine the association between OA status and cognitive function. Sample weights were used to ensure result generalizability. Two-sample MR analysis was conducted to examine the association between OA and dementia. Mediation analyses were performed to investigate the mediating effects of depression.

Results: We did not demonstrate a significant association between OA and cognitive performance after adjusting for relevant covariates ($p > 0.05$), and the population of individuals with both OA and depression was associated with higher odds of low total word recall cognitive performance (odds ratio (OR) = 4.74, 95% confidence interval (CI): 1.09–20.63; $p = 0.04$). Genetically predicted specific-site OA was not significantly associated with the risk of dementia (OR = 1.12; 95% CI: 0.96–1.32; $p = 0.16$), Alzheimer's disease (OR = 0.95, 95% CI: 0.68–1.31, $p = 0.74$), vascular dementia (OR = 1.32, 95% CI: 0.82–2.13, $p = 0.25$) with accepted heterogeneity and no evidence of directional pleiotropy. Furthermore, major depression was found to mediate the pathway between OA and vascular dementia (β = 0.044, 95% CI: −0.391 to 0.479, $p < 0.05$).

Conclusion: Our findings indicate that there is no significant association or causal relationship between OA and cognitive decline. However, depression may serve as an important factor influencing cognitive outcomes. Future research should further explore the bidirectional causal relationship and underlying mechanisms.

Keywords: Alzheimer's disease, cognitive function, dementia, Mendelian randomization, NHANES, osteoarthritis

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Introduction

Dementia is a general term for the impaired ability to remember, think, or make decisions that interfere with doing everyday activities.[1] Types of dementia include the most common Alzheimer's disease, followed by vascular dementia, dementia

with Lewy bodies, frontotemporal dementia, and other disorders linked to dementia like Huntington's disease, Creutzfeldt–Jakob disease, and Parkinson's disease.[1,2] Due to the proportion of older people increasing, there will be approximately 78 million people with dementia worldwide in 2030 and approximately 139 million in 2050.[3] Osteoarthritis (OA) is also an age-associated degenerative joint disease, and there is growing evidence to suggest a potential link between OA and dementia.[4–6] OA is associated with inflammation, pain, and decreased physical activity, and these would lead to an increased risk of dementia.[7–9] Several epidemiological investigations and meta-analyses have evaluated the relationship between OA and the risk of dementia and cognitive impairment.[10–13] However, existing observational studies are subject to a few limitations, such as small sample size, insufficient adjustment of some important covariates, and potential reverse causality, making it difficult to fully understand the true relationship between OA and dementia. Understanding the impact of OA on cognitive abilities is crucial, as diminished cognitive functions are linked to a decline in daily physical activities.

Therefore, there is still a need for further research to better understand the potential link between OA and dementia and to address these limitations. The National Health and Nutrition Examination Survey (NHANES) is a large, national program that collects data on the health and nutrition status of US civilians. It can help to overcome some of these limitations by providing a larger sample size and collecting information on a wide range of relevant covariates.[14] Mendelian randomization (MR) study is a novel statistical method to use genetic variants as instrumental variables (IVs) to investigate the causal effects of a risk factor on the outcome.[15] Because an individual's genotype is determined at conception and cannot be changed, MR studies are less susceptible to confounding issues than observational studies and capable of making causal inferences.[16] Furthermore, the availability of detailed phenotypes of conditions from large-scale genome-wide association studies (GWAS) allows MR can further explore the etiological dementia subtypes or site-specific OA.[17]

We aimed to use the extensive database of NHANES to conduct a cross-sectional study on the correlation between OA and cognitive performance, followed by conducting an MR study first to verify the causal effect of OA on the pathogenesis of dementia subtypes.

Methods

This study utilized publicly accessible deidentified summary-level data, and ethical approval and informed consent have been obtained in all original studies. This study adheres to the guidelines outlined in the STROBE and STROBE-MR Statement for strengthened reporting of observational studies in epidemiology.[18,19]

Overall study design

The study design was conducted in two stages. Stage 1 utilized data from the NHANES database to demonstrate a link between OA and cognitive function. Stage 2 employed a two-sample MR design that was employed to assess the causal relationship between OA, knee OA, and hip OA, and various subtypes of dementia. To ensure the validity of the MR analysis, three key assumptions must be considered. First, it was assumed that the selected genetic variants were associated with the exposure of interest. Second, the single nucleotide polymorphisms (SNPs) were not associated with any unmeasured confounders between the exposure and outcome. Lastly, genetic variations only affect the outcome through exposure rather than any other pathways.

Data sources and study population

We performed a population-based study of older American adults surveyed in the NHANES 2011–2014 two cycles who underwent cognitive function testing including word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease, the Animal Fluency test, and the Digit Symbol Substitution test (DSST).[20] Our analyses included adults aged ⩾60 years who completed cognitive functioning tests and had information on OA status. Sample weights were adjusted to get unbiased data generalizable to the entire US population.

Variables definition

The definition of OA status was determined based on the response to the medical condition questionnaire: "Has a doctor or other health professional ever told you that you have arthritis?" Participants who answered "no" were classified as without OA. Participants who answered "yes"

will be further asked, "Which type of arthritis was it?" Participants who self-reported having been diagnosed with OA were classified as OA patients.

The definition of cognitive functioning assessment was based on the methods previously described.[21] Scores from cognitive tests were treated as continuous variables and were dichotomized using the lowest non-survey weighted quartile to define low cognitive performance (cognitive impairment).[21]

According to the previous study, we used the following variables as covariates: age, gender, race, education level, family poverty level, body mass index (BMI), smoking status, alcohol intake, history of diabetes, hypertension, hyperlipidemia, anemia, coronary heart disease, myocardial infarction, stroke, and depression.[22,23]

MR analysis

Genetic association dataset source. The IEU OpenGWAS project database (https://gwas.mrcieu.ac.uk) was searched to find relevant data, with "osteoarthritis" and "dementia" being used as keywords, respectively. The source and characteristics of GWAS data for OA and dementia are exhibited in Table S1. The summary-level data for site-specific OA were taken from a GWAS conducted by the UK Biobank including 39,427 cases of OA in the hip or knee, 24,955 cases of knee OA, 15,704 cases of hip OA, and 378,169 controls of European descent.[24] Summary genetic association estimates for the risk of dementia subtypes were obtained from 3 GWAS[25–27] involving a total of 7284 European descent individuals with dementia as well as Alzheimer's disease (2191 cases), vascular dementia (881 cases), Parkinson's disease dementia (267 cases), Lewy body dementia (2591 cases), and frontotemporal dementia (515 cases).

Genetic IVs. We carried out a series of quality control measures on the GWAS summary data to select appropriate instrumental SNPs. First, SNPs were chosen as IVs for the exposure that should meet the requirement of $p < 5 \times 10^{-8}$. Second, to avoid linkage disequilibrium, we selected only the SNP with the lowest p-value from pairs with an r2 threshold of 0.001 and kb threshold of 10,000.

Statistical analysis

All NHANES analyses accounted for the cluster design and used sample weights that corrected for non-response, yielding representative estimates of the non-institutionalized US population. For categorical variables, data were presented as percentages, and Chi-square tests were used for comparison. For continuous variables, data were presented as mean and standard error. Multiple linear or logistic regression was conducted to investigate the association between OA and cognitive scores and low cognitive performance. All models were first adjusted for age and gender and followed for demographics and socioeconomic status (age, gender, race, education level, and family poverty level), then followed the addition of general health conditions and behaviors (BMI, smoking status, alcohol intake, history status of diabetes, hypertension, hyperlipidemia, anemia, coronary heart disease, myocardial infarction, stroke, and depression). Stratified analyses were conducted based on gender, BMI ($<$25.00 or $\geqslant$25.00), and level of physical activity (a high level of PA was defined as $\geqslant$600 MET·min/week, and a low level of PA was defined as $<$600 MET·min/week based on the US PA guidelines),[23,28] and the history of diabetes, hypertension, coronary heart disease, myocardial infarction, stroke, and depression with fully adjusted model. All analyses were carried out with R 4.3.0 and a two-tailed $p < 0.05$ was considered statistically significant.

In the two-sample MR study, we used the standard inverse-variance weighted method to estimate the causal relationship between OA and dementia as primary analysis and MR-Egger regression, weighted median, and weighted mode method as sensitivity analysis. Other sensitivity analysis methods include leave-one-out analysis to assess whether a single SNP of exposure would drive or bias the inverse-variance weighted (IVW) estimate and use all retrieved data from the IEU OpenGWAS project database to perform MR to test the causal relationship between OA and dementia. The Cochran's Q statistic was used to quantify the statistical heterogeneity between SNPs ($p < 0.05$). We also performed a two-step MR analysis to determine the mediation effect of depression on the associations between OA and dementia. All statistical analyses were performed using the "TwoSample MR" packages in R software (Version 4.3.0, R Core Team, Vienna, Austria).

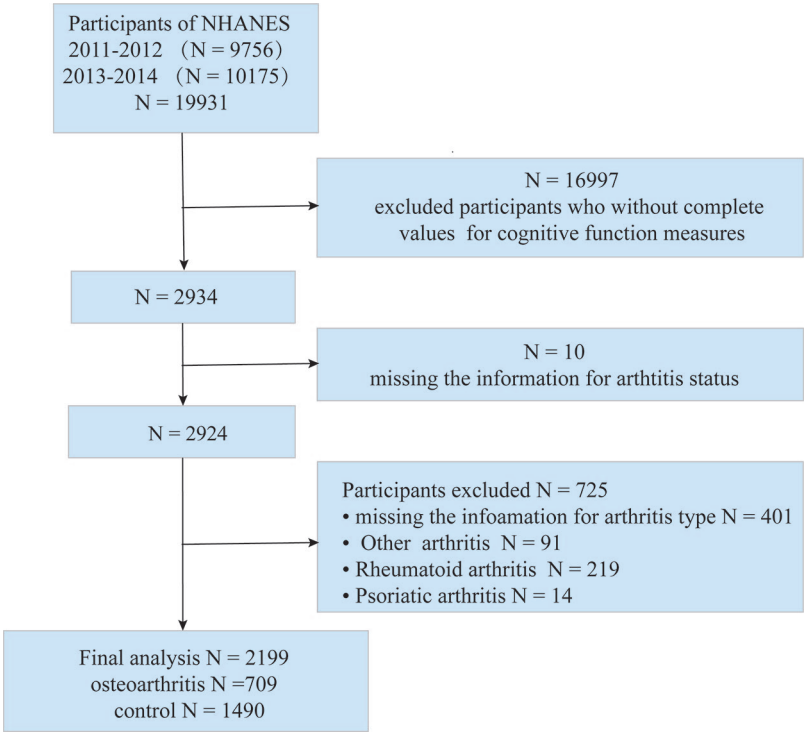

Figure 1. Flow chart for the selection of included sample.

Results

Population characteristics of NHANES

Out of the 19,931 subjects included in the NHANES 2011–2014 database, 2934 individuals aged over 60 completed all cognitive function tests, while 735 individuals were excluded due to other types of arthritis or a lack of reported arthritis status. Consequently, the study included 2199 participants, representing a weighted population of approximately 42.5 million civilian non-institutionalized United States (Figure 1). The weighted average age of participants with OA was 69.76 years, and a higher weight proportion of females (65.39%) with significantly higher BMI was observed in the OA group. In addition, a higher weight prevalence of depression (9.78%) was observed in individuals with OA (Table 1).

Association between OA and cognitive function

Table 2 presents the findings from linear and logistic regression analyses examining the relationship between OA and cognitive performance. Initially, OA was associated with better delayed word recall scores in the linear regression models. However, as subsequent adjustments were made for covariates, this association gradually weakened, and the result was not statistically significant ($\beta = 0.29$; 95% confidence interval (CI): −0.01 to 0.59; $p = 0.06$). There was no significant difference observed in the score of total word recall, animal fluency, and DSST, whether adjustments were not made or were made with full covariate adjustment. In addition, the odds of low cognitive performance in all aspects in the OA group were not significantly higher when compared to those without OA.

Stratified analyses showed no significant interaction between OA and stratified variables on low cognitive performance except for physical activity. However, our findings indicated that depression was found to be associated with higher odds of low total word recall cognitive performance (odds ratio (OR) = 4.74, 95% CI: 1.09–20.63; $p = 0.04$) while being female was associated with higher odds of low animal fluency cognitive performance (OR = 1.78, 95% CI: 1.16–2.75; $p = 0.02$) (Table 3).

MR of the causal effect of OA on dementia

There was no causal relationship detected between the genetically predisposed OA and overall dementia (IVW OR: 1.125, 95% CI: 0.956–1.323, $p = 0.156$, Figure 2) without directional pleiotropy

Table 1. Characteristics of study participants from the NHANES (2011–2014) ($n = 2199$) with recorded cognitive function.

Characteristic	Overall, $N = 2199$[a]	Non-OA group, $N = 1490$[a]	OA group, $N = 709$[a]	p-Value[b]
Age (mean ± SE)	68.94 ± 0.19	68.44 ± 0.27	69.76 ± 0.37	0.01
Gender				<0.001
Male	46.39	53.48	34.61	
Female	53.61	46.52	65.39	
Race				<0.001
Non-Hispanic White	81.56	78.04	87.40	
Non-Hispanic Black	6.86	9.02	4.93	
Non-Hispanic Asian	3.46	4.59	1.58	
Mexican American	3.08	3.44	2.48	
Other Hispanic	3.26	3.95	2.12	
Other	1.78	1.96	1.49	
Education				0.38
<12th grade	13.63	14.02	12.98	
High school graduate	21.67	23.06	19.35	
Some college	30.87	29.87	32.53	
College graduate	33.80	33.00	35.14	
Family poverty income ratio (mean ± SE)	3.20 ± 0.07	3.23 ± 0.07	3.16 ± 0.11	0.44
Smoking status				0.02
Never	50.72	52.47	47.82	
Former	39.32	36.18	44.54	
Current	9.94	11.32	7.64	
Alcohol status				0.32
Never	12.34	12.27	12.46	
Former	21.62	21.25	22.25	
Mild	45.62	46.49	46.84	
Moderate	11.94	11.88	12.03	
Heavy	5.82	6.96	3.94	
BMI (mean ± SE)	28.81 ± 0.25	28.03 ± 0.23	30.12 ± 0.39	<0.001
Hypertension	64.11	61.90	67.78	0.09
Diabetes	26.14	25.86	26.59	0.74

(Continued)

Table 1. (Continued)

Characteristic	Overall, *N* = 2199[a]	Non-OA group, *N* = 1490[a]	OA group, *N* = 709[a]	*p*-Value[b]
Hyperlipidemia	81.83	81.01	83.19	0.27
Anemia	8.65	8.60	8.72	0.53
Depression	5.97	3.68	9.78	0.002
Coronary heart disease	8.85	8.08	10.12	0.24
Myocardial infarction	8.12	7.26	9.53	0.05
Stroke	6.12	6.57	5.38	0.22
Physical activity				0.19
High physical activity	25.14	26.26	23.28	
Low physical activity	9.53	8.53	11.20	

[a]Proportions (%) are presented unless stated otherwise, accounting for NHANES sampling weights. *N* = 2199 weighted *N* in 42,494,040; *N* = 1490 weighted *N* in millions = 26,533,922; *N* = 709 weighted *N* in millions = 15,960,117.
[b]*t*-Test adapted to complex survey samples; Chi-squared test with Rao and Scott's second-order correction.
BMI, body mass index; NHANES, National Health and Nutrition Examination Survey; OA, osteoarthritis; SE, standard error.

($p = 0.363$) and heterogeneity ($p = 0.745$). As for other supplementary MR results, such as weighted median, weighted mode, and MR-Egger, which were consistent with the IVW method (Table S2). Similar results were found for other dementia categories such as Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, and Parkinson's disease dementia. All results found no significant heterogeneity and directional pleiotropy ($p > 0.05$, Figure 2).

Similarly, genetically predisposed knee OA was not significantly associated with overall dementia, Alzheimer's disease, vascular dementia, or Lewy body dementia with no significant heterogeneity and directional pleiotropy. There was a lack of available IVs for knee OA on frontotemporal dementia.

As revealed by the MR analyses for genetically predisposed hip OA, there were significant associations with Alzheimer's disease (OR: 0.808, 95% CI: 0.679–0.963, $p = 0.017$, Figure 2) without heterogeneity ($p = 0.451$). However, the results of our leave-one-out sensitivity analysis indicated that the association between hip OA and Alzheimer's disease was not robust (Figure S1) and could be impacted by the SNP rs79056043 (if it is omitted, the result is OR: 0.840, 95% CI: 0.703–1.003, $p = 0.054$). No significant associations were observed between hip OA and overall dementia, vascular dementia, Lewy body dementia, frontotemporal dementia, and Parkinson's disease dementia (Figure 2).

Sensitivity analysis

We also used all retrieved data from the IEU OpenGWAS project database to perform MR and did not detect a causal relationship between the exposure (genetically predisposed of any site of OA, OA (self-reported), and OA (hospital diagnosed)) with specific outcomes (dementia, Alzheimer's disease, vascular dementia, and Lewy body dementia) (Table S3).

Mediation analysis

Based on previous findings using the NHANES database, we discovered a significantly higher prevalence of depression among individuals with OA compared to the control group. In addition, depression was associated with more pronounced cognitive impairment. Motivated by these findings, we conducted further analysis using MR to investigate the mediating role of depression in the relationship between OA and dementia.

Figure 3 presents the results of our causal analysis, highlighting the mediation effect of major depression. Our findings indicate that OA causally increases the risk of developing depression

Table 2. Linear and logistic regression models of osteoarthritis status for cognitive performance using NHANES.

Adjusted and unadjusted model[a]	β (95% CI)[b]	*p* Value	OR (95% CI)[c]	*p* Value
Delayed word recall				
Unadjusted	0.28 (0.05, 0.51)	0.02	0.74 (0.51, 1.05)	0.09
Adjusted[d]	0.3 (0.08, 0.52)	0.01	0.69 (0.47, 1.00)	0.05
Demographics and SES	0.26 (0.03, 0.49)	0.03	0.70 (0.47, 1.07)	0.09
Health behaviors and conditions	0.29 (−0.01, 0.59)	0.06	0.69 (0.40, 1.18)	0.13
Total word recall				
Unadjusted	0.66 (−0.01, 1.34)	0.05	0.87 (0.64, 1.18)	0.36
Adjusted	0.68 (0.02, 1.33)	0.04	0.84 (0.62, 1.13)	0.23
Demographics and SES	0.41 (−0.29, 1.11)	0.24	0.94 (0.67, 1.32)	0.71
Health behaviors and conditions	0.48 (−0.39, 1.34)	0.22	1.01 (0.69, 1.46)	0.96
Animal fluency				
Unadjusted	0.14 (−0.53, 0.81)	0.67	1.16 (0.84, 1.60)	0.34
Adjusted	0.54 (−0.06, 1.14)	0.08	1.06 (0.77, 1.47)	0.7
Demographics and SES	−0.06 (−0.66, 0.54)	0.84	1.33 (0.95, 1.87)	0.09
Health behaviors and conditions	0.09 (−0.61, 0.79)	0.76	1.27 (0.87, 1.83)	0.16
Digit symbol substitution test				
Unadjusted	1.59 (−0.16, 3.35)	0.07	0.99 (0.75, 1.30)	0.93
Adjusted	2.11 (0.72, 3.50)	0.004	0.89 (0.68, 1.16)	0.38
Demographics and SES	0.62 (−0.54, 1.78)	0.28	1.40 (0.99, 1.97)	0.05
Health behaviors and conditions	0.71 (−0.84, 2.26)	0.29	1.46 (0.89, 2.41)	0.11

[a]Results are adjusted to account for the effect of weighting.
[b]β: differences in cognitive scores in linear regression (negative β coefficients represent lower cognitive scores and worse cognitive performance).
[c]ORs for cognitive impairment based on cognitive scores (delayed word recall <4 indicates cognitive impairment, total word recall <21 indicates cognitive impairment, animal fluency <13 indicates cognitive impairment, digit symbol substitution test <36 indicates cognitive impairment).
[d]Models were sequentially adjusted for age and gender alone; demographics and SES (age, gender, race/ethnicity, education level, and annual family poverty income ratio) alone; demographics and SES plus health behaviors and conditions (body mass index, smoke status, alcohol status, diabetes, hypertension, hyperlipidemia, anemia, depression or coronary heart disease, myocardial infarction, and stroke).
CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SES, socioeconomic status.

(β = 0.056, 95% CI: 0.0008–0.112, $p = 0.047$). Furthermore, we observed that depression acts as a mediator in the pathway between OA and vascular dementia, with a mediated effect (β = 0.044, 95% CI: −0.391 to 0.479, $p < 0.05$, Figure 3).

Discussion

To the best of our knowledge, this study is the first comprehensive investigation of the association between OA and cognitive performance impairment based on the combination of

Table 3. Stratified analyses of cognitive performance impairment in individuals with and without osteoarthritis.[a]

Characteristic	Delayed word recall <4		Total word recall <21		Animal fluency <13		Digit symbol substitution test <36	
	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI), *p*-value	*p* for interaction
Overall effect	0.69 (0.40, 1.18) 0.13		1.01 (0.69, 1.46) 0.96		1.27 (0.87, 1.83) 0.16		1.46 (0.89, 2.41) 0.11	
Stratified analyses								
Sex		0.93		0.58		0.11		0.87
Male	0.67 (0.33, 1.35) 0.21		0.95 (0.49, 1.86) 0.86		0.77 (0.40, 1.49) 0.37		1.52 (0.73, 3.16) 0.21	
Female	0.66 (0.36, 1.20) 0.14		1.05 (0.55, 2.00) 0.86		1.78 (1.16, 2.75) 0.02		1.40 (0.82, 2.39) 0.18	
BMI		0.47		0.43		0.65		0.53
<25	0.68 (0.41, 1.11) 0.1		1.06 (0.70, 1.60) 0.75		1.29 (0.86, 1.93) 0.17		1.65 (0.88, 3.07) 0.1	
⩾25	0.62 (0.23, 1.66) 0.27		0.71 (0.28, 1.78) 0.38		1.17 (0.57, 2.43) 0.59		1.22 (0.54, 2.73) 0.56	
Physical activity		0.66		0.24		0.34		0.01
Low physical activity	0.73 (0.22, 2.41) 0.51		0.95 (0.32, 2.79) 0.89		3.27 (0.96, 11.12) 0.05		1.53 (0.21, 11.22) 0.59	
High physical activity	0.42 (0.08, 2.29) 0.3		0.21 (0.03, 1.33) 0.09		1.11 (0.23, 5.41) 0.89		/	
Diabetes		0.65		0.27		0.42		0.68
Yes	0.56 (0.27, 1.14) 0.09		1.25 (0.70, 2.22) 0.39		0.97 (0.57, 1.68) 0.91		1.69 (0.68, 4.19) 0.21	
No	0.70 (0.38, 1.30) 0.21		0.89 (0.56, 1.42) 0.55		1.42 (0.88, 2.30) 0.13		1.30 (0.68, 2.49) 0.36	
Hypertension		0.05		0.14		0.86		0.1
Yes	0.85 (0.44, 1.63) 0.57		1.13 (0.73, 1.75) 0.53		1.21 (0.78, 1.87) 0.33		1.72 (0.94, 3.15) 0.07	
No	0.29 (0.11, 0.77) 0.02		0.60 (0.22, 1.69) 0.28		1.48 (0.70, 3.12) 0.25		0.74 (0.25, 2.19) 0.52	
Coronary heart disease		0.33		0.88		0.95		0.9
Yes	2.45 (0.78, 7.71) 0.35		0.95 (0.26, 3.41) 0.95		1.66 (0.38, 7.35) 0.61		1.92 (0.45, 8.27) 0.53	
No	0.63 (0.39, 1.04) 0.07		1.02 (0.67, 1.55) 0.93		1.28 (0.85, 1.92) 0.19		1.43 (0.88, 2.33) 0.12	
Myocardial infarction		0.1		0.88		0.39		0.72
Yes	2.04 (0.67, 6.18) 0.2		0.65 (0.22, 1.97) 0.43		1.96 (0.67, 5.71) 0.21		1.01 (0.33, 3.12) 0.98	
No	0.62 (0.36, 1.08) 0.08		1.05 (0.67, 1.64) 0.79		1.22 (0.84, 1.78) 0.24		1.57 (0.92, 2.66) 0.08	

(Continued)

Table 3. (Continued)

Characteristic	Delayed word recall <4		Total word recall <21		Animal fluency <13		Digit symbol substitution test <36	
	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI) *p*-value	*p* for interaction	OR (95% CI), *p*-value	*p* for interaction
Stroke		0.54		0.98		0.45		0.3
Yes	0.30 (0.06, 1.40) 0.12		0.82 (0.13, 5.34) 0.83		0.82 (0.13, 5.09) 0.82		3.36 (0.69, 16.43) 0.13	
No	0.67 (0.39, 1.14) 0.11		0.99 (0.69, 1.41) 0.92		1.21 (0.86, 1.71) 0.22		1.44 (0.86, 2.42) 0.13	
Depression		0.04		0.34		0.82		0.64
Yes	2.10 (0.42, 10.52) 0.35		4.74 (1.09, 20.63) 0.04		1.60 (0.40, 6.44) 0.49		2.38 (0.84, 6.71) 0.1	
No	0.63 (0.37, 1.07) 0.08		0.98 (0.67, 1.43) 0.88		1.22 (0.83, 1.79) 0.25		1.44 (0.88, 2.37) 0.12	

[a]Age, gender, race/ethnicity, education level, annual family poverty income ratio, body mass index, smoke status, alcohol status, diabetes, hypertension, hyperlipidemia, anemia, depression or coronary heart disease, myocardial infarction, and stroke were all adjusted except the variable itself.
BMI, body mass index; CI, confidence interval; OR, odds ratio.

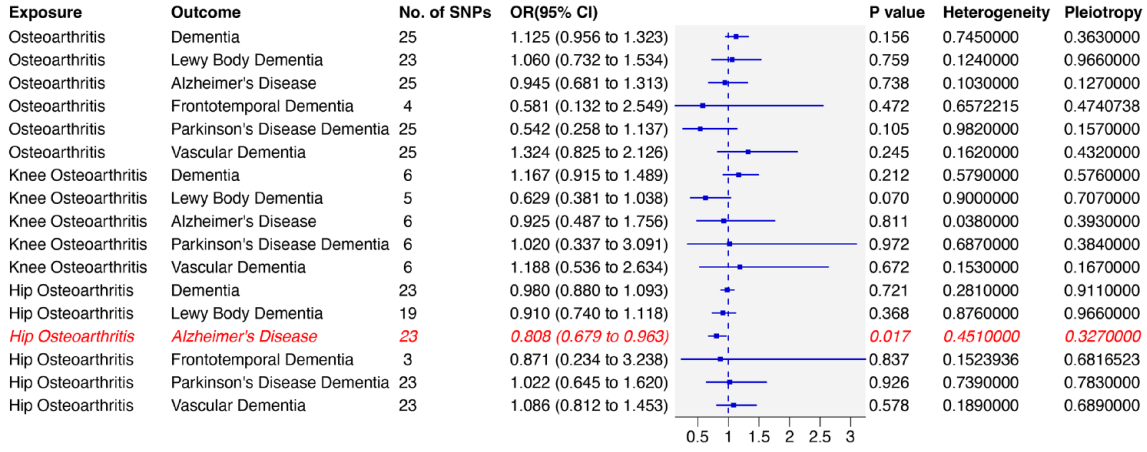

Figure 2. MR estimates of assessing the causal effects of OA on dementia and subtypes.
MR, Mendelian randomization; OA, osteoarthritis.

large-scale observational study and MR design. Also, it explores the mediating effect of depression to provide further insights into the underlying mechanisms. Our findings indicated that OA was not associated with worsened performance in delayed word recall scores, total word recall, animal fluency, and DSST after adjusting for demographic characteristics, health behaviors, and comorbidities. These results were substantiated in MR studies, which were conducted to minimize confounding factors and provided additional evidence that there was no causal relationship between OA and dementia or subtypes. Furthermore, our findings demonstrate that individuals with both OA and comorbid depression exhibit a heightened risk of total word recall cognitive impairment. This observation was further corroborated through subsequent MR analysis,

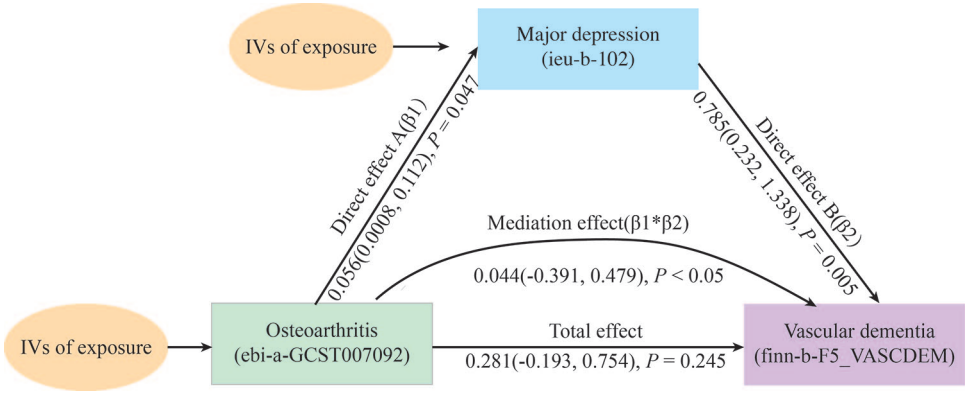

Figure 3. The major depression mediated the causal effect of OA on vascular dementia.
OA, osteoarthritis.

reinforcing the mediating role of major depression in the relationship between OA and vascular dementia.

A recent comprehensive meta-analysis, encompassing 11 prospective studies, revealed that the presence of OA is associated with an overall increased risk of dementia or cognitive decline.[10] However, it is crucial to note that the results of these studies exhibit some instability. Sensitivity analysis indicates that the statistical differences in overall results could potentially be altered by sequentially excluding two specific studies.[29,30] In addition, the observed heterogeneity in the pooled results may arise from variations in factors such as the adjusted covariates, patient characteristics, statistical effect sizes, and sample sizes across the included studies, and may contribute to the lack of confidence in the reliability of the conclusions.[10] Our study provides important insights into the relationship between two common age-related conditions that affect a large proportion of the elderly population. Confounding variables can make it difficult to determine a clear relationship between OA and dementia. These variables, such as the use of NSAIDs, demographic factors (such as gender, age, and obesity), depression, age-related diseases, coexisting medical conditions (such as vascular disease), and physical inactivity, can create false associations and obscure the true relationship between OA and dementia.[12,31–33] The failure of previous cohort studies to fully adjust for these confounding variables resulted in meta-analyses concluding that OA increases the risk of dementia.[10–12] Our analysis provides more robust evidence compared to previous studies as we utilized a complex, multistage, probability sampling design to select participants representative of the civilian, non-institutionalized US population. In addition, we conducted a comprehensive evaluation of cognitive function from four dimensions including delayed word recall scores, total word recall, animal fluency, and DSST, enhancing the depth and breadth of our assessment. Furthermore, we conducted stepwise adjustments and stratified analyses for relevant covariates, and our results revealed no significant association between OA and cognitive decline. The use of MR in this study design has several advantages over traditional observational studies. MR allows for the examination of causality rigorously, reducing the risk of bias and confounding.[16] Our study conducted a comprehensive analysis and concluded that there is no causal relationship between site-specific OA and dementia subtypes. Although hip OA may increase the risk of Alzheimer's disease, sensitivity analysis shows that the conclusion is unstable. rs79056043 is a specific variant of the LRIG3 (leucine-rich repeat-containing G protein-coupled receptor 3) gene, which has been linked to improved injury recovery of hippocampal neurons, and is crucial for memory and learning.[34] However, this information may introduce bias in our analysis. A sensitivity analysis of the MR method was conducted to examine the causal relationship between self-reported, hospital-diagnosed OA, and dementia subtypes. The results again confirmed that there is no relationship between OA and dementia.

Consistent with conventional knowledge, our study findings support the notion that females or individuals with higher BMI are more prone to developing OA, as statistically significant differences were observed in the proportion of females

and elevated BMI within the OA group. Interestingly, we observed a significant increase in the proportion of individuals with depression within the OA group. This phenomenon can be attributed to the pain experienced by those with OA, which exerts both physical and emotional strain. Prolonged exposure to stress can induce alterations in the concentrations of neurochemicals within the brain and nervous system, including cortisol, serotonin, and norepinephrine.[35] Disruptions in the delicate balance of these biochemicals in the body can potentially contribute to the development of depression in specific individuals.[36] In addition, arthritis pain significantly reduces quality of life, contributing to poorer mental health. Fatigue, common among arthritis patients, often leads to notable mood changes. The relationship between fatigue and anxiety can be affected by disease duration, overall health, and comorbidities.[37] Furthermore, our stratified analysis revealed a significantly higher prevalence of low total word recall cognitive performance among individuals with both OA and depression after adjusting for complete covariates. This finding suggests a potential link between OA, depression, and dementia. Depression and dementia are recognized as independently assessable and quantifiable diseases, yet emerging research indicates a significant correlation between them. For instance, one study found that patients with a 6-month history of depression have a 15-fold increased risk of developing dementia compared to the general population.[38] Similarly, veterans with moderate to severe depression have twice the risk of dementia compared to veterans without depression.[39] In addition, studies indicate that major depressive disorder not only affects neurotransmitters and the endocrine system but also impacts the physiological structure of multiple brain networks, especially reduced gray matter volume in the hippocampus and medial prefrontal cortex which plays a crucial role in memory formation and retrieval.[40] Subsequently, we investigated the mediating role of depression in the relationship between OA and dementia. Our MR results established a causal relationship, demonstrating that OA contributes to the development of depression, which, in turn, increases the risk of dementia, thereby providing insights into the possible explanations for previous studies yielding false-positive results. However, whether there is a bidirectional causal relationship between these factors still requires further confirmation in future studies.

Physical activity has demonstrated its capacity to enhance hippocampal function, promote neurogenesis, bolster synaptic plasticity, improve cerebral blood flow, and mitigate cardiovascular risk and inflammation.[41] These benefits contribute to its protective role against cognitive decline in both the general population and individuals with chronic diseases.[42] However, in our analysis, although there was a statistically significant difference (p for interaction) for physical activity, we did not observe this effect in the physical activity subgroup. This may be due to differences in how physical activity was measured and categorized. Further research with larger sample sizes and alternative approaches to categorizing and measuring physical activity is needed to explore this relationship more comprehensively.

Some animal studies are investigating the connection between OA and dementia. In one study, Gupta et al.[43] used a mouse model of Alzheimer's disease and observed that OA in the mice increased levels of inflammatory cytokines in the brain tissue, and led to significant increases in beta-amyloid deposition and neuronal loss. However, it is possible that these findings may not be directly applicable to humans due to species differences. In addition, the level of beta-amyloid deposition may just be a biomarker and may not yet have reached the threshold for dementia in the OA model. Further research is needed to fully understand the relationship between OA and dementia.

The study has some limitations that should be noted. First, our study primarily focused on the association between OA and cognitive decline, specifically in terms of cognitive performance measures. It is important to note that cognitive decline is a broad term that encompasses various aspects of cognitive function, including memory, executive function, attention, and language skills. While our study examined specific cognitive performance measures, it may not capture the entire spectrum of cognitive decline associated with dementia. Second, accurately determining the prevalence of OA is challenging, as many individuals with the condition do not seek medical attention. This reliance on self-reported data may lead to underreporting of the condition. In addition, the diagnosis of depression based on Patient Health Questionnaire (PHQ) scores in our study also may introduce potential misclassification, as these also self-reported conditions. Third, it is

important to consider the population characteristics of the NHANES study, which primarily consisted of US participants, and the MR study, which focused on European individuals. These population-specific samples may limit the generalizability of our findings to other populations and introduce bias. In addition, factors such as cultural differences, disparities in healthcare access, and variations in socioeconomic status can significantly influence the relationship between OA and cognitive decline. Moreover, due to data availability, the study could not analyze the effect of OA at other sites on dementia, such as hand OA, spine OA, and temporomandibular OA, and we could not perform further sensitivity analyses to account for population stratification, pleiotropy that is not properly accounted for, which may affect the conclusions of the MR study. Finally, using SNPs from different large-sample GWAS may increase the risk of sample overlap between exposure and outcome variables, potentially biasing the results.

Conclusion

In conclusion, our study provides comprehensive insights into the association between OA, depression, and dementia. Our findings indicate that there is no significant association between OA and cognitive decline when adjusting for relevant covariates. However, we observed a higher proportion of individuals with depression within the OA group, highlighting the potential impact of pain and emotional strain on mental health. The MR analysis further may support a causal relationship between OA, depression, and increased risk of dementia. Future studies should aim to confirm the bidirectional causal relationship between these factors and explore potential mechanisms underlying this association. In addition, further research is needed to elucidate the role of physical activity and the connection between OA and dementia in animal models and larger human cohorts. Understanding these relationships can contribute to the development of targeted interventions and strategies for preventing cognitive decline in individuals with OA.

Declarations

Ethics approval and consent to participate

This study utilized data from the NHANES database. The Institutional Review Board (IRB) approval number for the dataset used is (IRB number: Protocol #2011-17). Informed consent from participants was obtained by the US National Center for Health Statistics (NCHS) during the conduct of NHANES. As the data were de-identified, no further consent was required for participation in this study.

Consent for publication

Consent for publication of identifiable patient data was not applicable, as the NHANES dataset used in this study contains de-identified data, ensuring participant confidentiality.

Author contributions

Kun Zhao: Conceptualization; Data curation; Formal analysis; Funding acquisition; Software; Visualization; Writing – original draft.

Liuyan Nie: Data curation; Formal analysis; Software.

Jingting Zhao: Validation; Writing – review & editing.

Yankai Dong: Formal analysis; Software; Supervision.

Kaixiu Jin: Formal analysis; Software; Supervision.

Song Wang: Methodology; Visualization.

Xiangming Ye: Project administration; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data source exists in the public domain. Data analyses by the authors are available upon reasonable request by contacting the corresponding author.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work, we used chatGPT to help us polish the language and improve the logic. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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Supplemental material

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