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Systemic inflammation partially mediates the association between lipid accumulation and osteoarthritis in normal BMI adults

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This study aims to investigate the association between lipid accumulation product (LAP) levels and osteoarthritis (OA) in participants with normal BMI, and the potential role of the systemic inflammation response index (SIRI) in this association. Participants with normal BMI from the national health and nutrition examination survey (NHANES) database (2009–2018) were included. A weighted multivariable logistic regression was used to analyze the association between LAP levels and OA, and mediation analysis was applied to explore the role of SIRI in this relationship. Among 2408 participants with normal BMI, the average age was 43.85 ± 17.68 years, with 1240 (55%) women, and 210 (8.72%) participants recorded as having OA. Compared with the first quartile, the highest quartile of LAP levels was significantly associated with higher OA prevalence and higher SIRI levels [OA (AOR = 1.969, 95% CI 1.035–3.745, *P = 0.039*); SIRI (AOR = 1.174, 95% CI 1.029–1.489, *P = 0.029*)], especially in young women. Compared with the first quartile, the highest quartile of SIRI levels was significantly associated with higher OA prevalence [AOR = 1.542, 95% CI 1.010–2.356, *P = 0.045*], particularly in young women. The highest quartile of LAP levels was significantly associated with higher OA prevalence, with a portion of the association mediated by SIRI (10.30%), with mediation proportions of 8.92% in younger individuals and 8.69% in women. Even with normal BMI, high LAP levels are significantly associated with a higher prevalence of OA, with part of the association mediated by systemic inflammation, especially in young women.

Keywords Lipid accumulation product, Osteoarthritis, NHANES, Systemic inflammation response index, Mediation analysis

Abbreviations

OA	Osteoarthritis
NHANES	National health and nutrition examination survey
LAP	Lipid accumulation product
SIRI	Systemic inflammation response index
WC	Waist circumference
TG	Triglyceride
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
RA	Rheumatoid arthritis
hs-CRP	High-sensitivity CRP

Osteoarthritis (OA) is a chronic joint disease characterized primarily by joint dysfunction, pain, and stiffness[1]. As of 2020, over 500 million people worldwide are affected by OA, making it one of the leading causes of disability[2]. Currently, the treatment of OA is mainly surgical, with joint prostheses being the only effective option[3]. However, there are limitations to the longevity of joint prostheses[4]. Therefore, the prevention and management of OA have become crucial intervention strategies[5]. Obesity is a chronic metabolic disease characterized by a state of low-

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grade systemic inflammation. The lipid accumulation product (LAP) is a novel, sex-specific adiposity indicator based on waist circumference (WC) and triglyceride (TG) levels, used to reflect the accumulation of visceral fat and lipid metabolism abnormalities[6].

The accumulation of visceral fat can lead to metabolic disturbances, which in turn promote a state of systemic inflammation in the body[7]. The systemic inflammation response index (SIRI) is a comprehensive index based on the Neutrophil, Monocyte, and Lymphocyte ratio, which provides a more holistic reflection of the body's inflammatory and immune balance. Our previous studies have already confirmed a significant association between high SIRI levels and an increased risk of OA[8].

This study aims to explore the association between LAP levels and OA risk in individuals with normal BMI in the United States, as well as the role of SIRI in this relationship.

Materials and methods

Study design and population

This study is based on data from the national health and nutrition examination survey (NHANES), including 49,693 participants from the years 2009 to 2018. NHANES is a rigorous, complex, and multi-stage probability sampling study, and all participants provided informed consent and received approval from the NCHS Institutional Review Board. According to the inclusion and exclusion criteria, the final cohort of this study included 2408 U.S. adults with a normal BMI (Fig. 1).

Exposure and outcome

LAP

The calculation of LAP differs by gender, as follows:

(1) LAP (Male) = [WC (cm)−65] × TG (mmol/L).

(2) LAP (Female) = [WC (cm)−58] × TG (mmol/L).

SIRI

In this study, the calculation formula for SIRI[9] = [(neutrophil count × monocyte count)/lymphocyte count], The team found that SIRI did not follow a normal distribution and therefore applied a log2 transformation (Fig. S1).

Waist-height ratio (WHtR)

Classification is made in accordance with the standards proposed by the European Congress on Obesity (CEO, 2019: http://ecoico2020.com/) and NICE (NICE, 2023: https://www.nice.org.uk/guidance/cg189): normal (< 0.5), central obesity (≥ 0.5).

Self-reported OA

In this study, the inclusion of OA and Non-OA participants was based on the self-reported OA status in the survey questionnaire[10]. Specific questions related to OA status are provided in (Table S1).

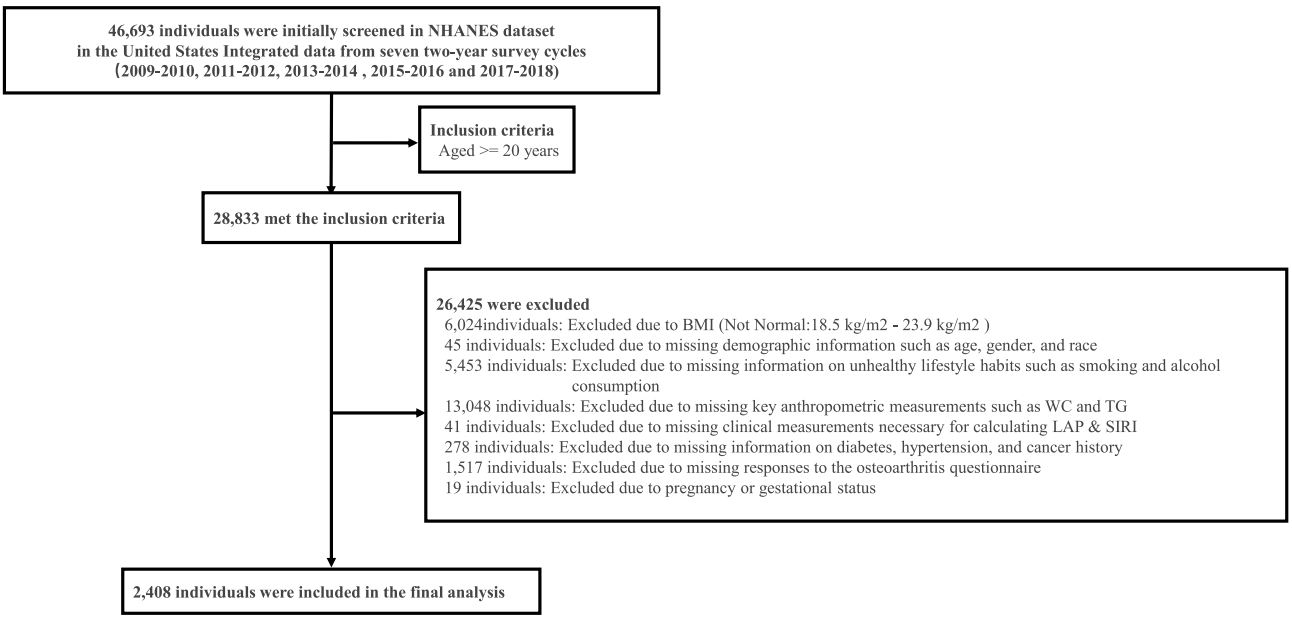

Fig. 1. Flow chart of population screening.

Covariates

The covariates included in this study were selected based on their association with OA and previous similar studies. These covariates encompass a range of demographic and health-related variables[11]. Detailed information on the covariates and their groupings can be found in (Table S2).

Statistical analysis

This study utilized the NHANES database. Due to the complexity of NHANES' sampling design, the sample weights for participants from 2009–2018 were applied in accordance with NHANES analysis and reporting guidelines to ensure national representativeness. Data analysis for this study was performed using R software (version 4.2.1) and Empower Stats (version 2.0).

Continuous variables in the baseline data are presented as means ± standard deviations, and categorical variables are presented as frequencies (percentages). Differences in characteristics between the OA and Non-OA groups were evaluated using Student's t-test for continuous variables and chi-square test for categorical variables. The geometric mean and 95% confidence intervals (CI) for LAP, SIRI, and OA were reported. Survey-weighted linear regression was used for continuous variables, while survey-weighted chi-square tests were used for categorical variables to compare baseline characteristics.

Prior to analysis, the team identified that SIRI was not normally distributed, so a log2 transformation was applied. To ensure uniformity, LAP was also standardized. Three different statistical models were used: Model 1 (unadjusted), Model 2 (adjusted for age, gender, and race), and Model 3 (adjusted for age, gender, race, education level, smoking, drinking, hypertension, and diabetes). Additionally, to further assess whether there is a dose-response relationship between LAP-z (LAP-z refers to the standardized LAP variable, which was derived by applying z-score transformation to the raw LAP values) and OA prevalence across the three models, LAP-z was modeled as both a continuous variable (with logarithmic transformation) and as categorical based on tertiles, exploring the relationship between LAP-z and OA prevalence.

Mediation analysis

To assess whether systemic inflammation (measured by the systemic inflammation response index, SIRI) mediated the association between lipid accumulation product (LAP) and osteoarthritis (OA), we conducted a formal mediation analysis using a counterfactual-based approach. The analysis was performed in accordance with the causal inference framework developed by VanderWeele and implemented using the mediation package in R. We specified LAP as the independent variable (exposure), OA as the binary dependent variable (outcome), and SIRI as the mediator. All continuous variables were standardized (Z-transformed) prior to modeling to facilitate interpretability and model convergence. The natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) were estimated through nonparametric bootstrapping with 1,000 iterations to obtain robust confidence intervals. The mediation proportion was calculated as NIE/TE × 100%, representing the proportion of the total effect of LAP on OA that is mediated by SIRI.

All mediation models were adjusted for potential confounders including age, sex, race/ethnicity, education level, smoking status, alcohol use, hypertension, and diabetes. We also performed stratified mediation analyses by age (< 60 vs ≥ 60 years) and sex to assess effect modification.

All statistical tests were two-tailed, with a significance level set at $P < 0.05$.

Result

Basic characteristics of participants

Table 1 presents data from 2408 participants aged ≥ 20 years with a normal BMI. The mean age was (43.9 ± 17.7) years, with 1,240 (55%) females. Among these, 210 (8.72%) participants were diagnosed with osteoarthritis (OA). Compared to the first tertile, participants in the highest tertile of LAP levels were generally older, more likely to be male, less educated, and predominantly Non-Hispanic White. Additionally, they were more likely to have been diagnosed with hypertension and diabetes. These participants also had a higher likelihood of smoking, excessive alcohol consumption, and higher BMI and WHtR indices.

Association between high LAP levels and increased OA prevalence

Figure 2 shows that, after performing weighted multivariable regression analysis, participants in the highest tertile of LAP levels had a significantly higher risk of OA compared to those in the first tertile (AOR = 1.969, 95% CI 1.035–3.745, *P = 0.039*), particularly among younger women (Tables S3,4).

Association between high LAP levels and elevated SIRI levels

Figure 3 shows that, after performing weighted multivariable regression analysis, participants in the highest tertile of LAP levels had significantly higher SIRI levels compared to those in the first tertile (AOR 1.174, 95% CI 1.029–1.489, *P = 0.029*), particularly among younger women (Table S5).

Association between high SIRI levels and elevated OA prevalence

Figure 4 demonstrates that, after conducting weighted multivariable regression analysis, participants in the highest tertile of SIRI levels had a significantly higher prevalence of OA compared to those in the first tertile (AOR 1.542, 95% CI 1.010–2.356, *P = 0.045*), particularly among younger women (Table S6).

Mediation analysis

Figure 5 shows that, after conducting weighted multivariable regression analysis, participants in the highest tertile of LAP levels had a significantly higher prevalence of OA compared to those in the first tertile. Part of this

Characteristic	N	Overall N = 2408	LAP (group)			P Value
			T1 N = 803	T2 N = 802	T3 N = 803	
Age (years)	2408	43.85 ± 17.68	40.71 ± 16.79	44.68 ± 18.33	46.49 ± 17.39	< 0.001
Sex(group)	2408					< 0.001
Female		1,240 (55%)	803 (100%)	409 (54%)	28 (4.2%)	
Male		1,168 (45%)	0 (0%)	393 (46%)	775 (96%)	
Race(group)	2408					< 0.001
Non-hispanic White		1,031 (69%)	332 (67%)	347 (71%)	352 (70%)	
Other/multiracial		567 (12%)	222 (15%)	149 (9.6%)	196 (13%)	
Non-hispanic black		372 (7.7%)	98 (6.3%)	163 (10.0%)	111 (6.5%)	
Mexican American		223 (5.5%)	65 (4.8%)	78 (5.6%)	80 (6.1%)	
Other hispanic		215 (5.4%)	86 (6.9%)	65 (4.1%)	64 (5.1%)	
Education(group)	2408					< 0.001
Above high school		1,502 (69%)	584 (79%)	475 (67%)	443 (61%)	
Below high school		428 (12%)	91 (6.9%)	143 (11%)	194 (17%)	
High school		478 (19%)	128 (14%)	184 (22%)	166 (22%)	
Smoke(group)	2408					< 0.001
Current smoker		516 (21%)	99 (12%)	194 (22%)	223 (28%)	
Former smoker		442 (20%)	107 (15%)	142 (21%)	193 (23%)	
Never smoker		1,450 (60%)	597 (72%)	466 (57%)	387 (49%)	
Drink(group)	2408					< 0.001
< 12 drinks/year		2,233 (94%)	773 (97%)	758 (96%)	702 (89%)	
≥ 12 drinks/year		175 (5.9%)	30 (3.4%)	44 (4.2%)	101 (11%)	
BMI-z	2408	2.30 ± 0.24	2.18 ± 0.23	2.33 ± 0.24	2.41 ± 0.19	< 0.001
WHtR-z	2408	2.39 ± 0.44	2.21 ± 0.31	2.45 ± 0.50	2.51 ± 0.41	< 0.001
Hypertension(group)	2408					< 0.001
Hypertension		462 (16%)	116 (11%)	161 (18%)	185 (21%)	
Non-hypertension		1,946 (84%)	687 (89%)	641 (82%)	618 (79%)	
DM(group)	2408					< 0.001
DM		128 (3.3%)	15 (0.9%)	41 (3.0%)	72 (6.3%)	
Non-DM		2,280 (97%)	788 (99%)	761 (97%)	731 (94%)	
SIRI	2408	1.08 ± 0.82	0.95 ± 0.64	1.03 ± 0.85	1.27 ± 0.92	< 0.001
log2(SIRI)	2408	0.68 ± 0.30	0.63 ± 0.26	0.65 ± 0.31	0.76 ± 0.32	< 0.001
OA(group)	2408					< 0.001
Non-osteoarthritis		2,198 (90%)	751 (93%)	732 (91%)	715 (89%)	
Osteoarthritis		210 (10%)	52 (6.5%)	70 (8.7%)	88 (11%)	

Table 1. Basic characteristics of participants. BMI-z, WHtR-z, and LAP-z are standardized scores calculated based on the 2005–2012 NHANES weighted overall mean and standard deviation. Standardized weighted means and SDs may not be strictly 0 and 1 due to the complex weighted sampling design.

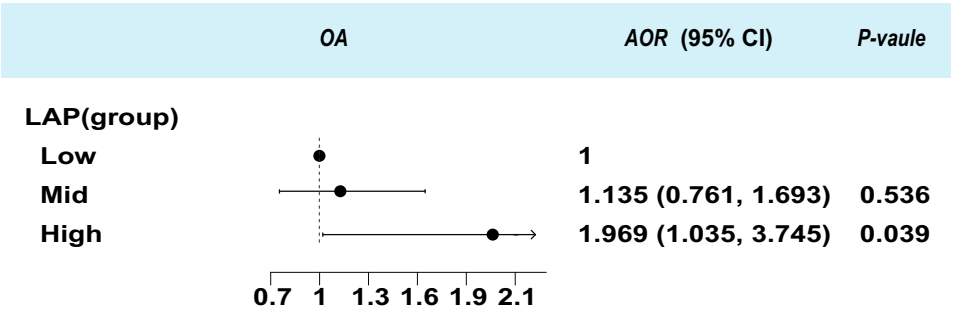

Fig. 2. Association between high LAP levels and increased OA prevalence.

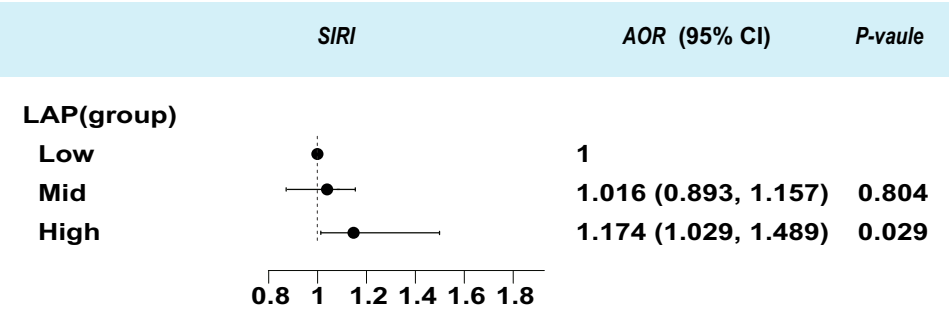

Fig. 3. Association between high LAP levels and elevated SIRI levels.

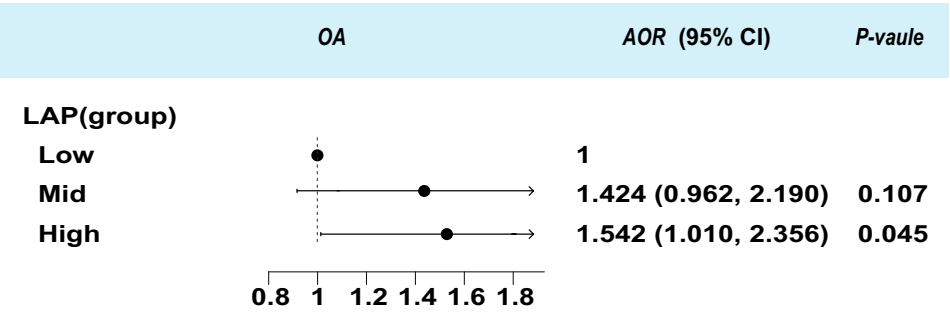

Fig. 4. Association between high SIRI levels and elevated OA prevalence.

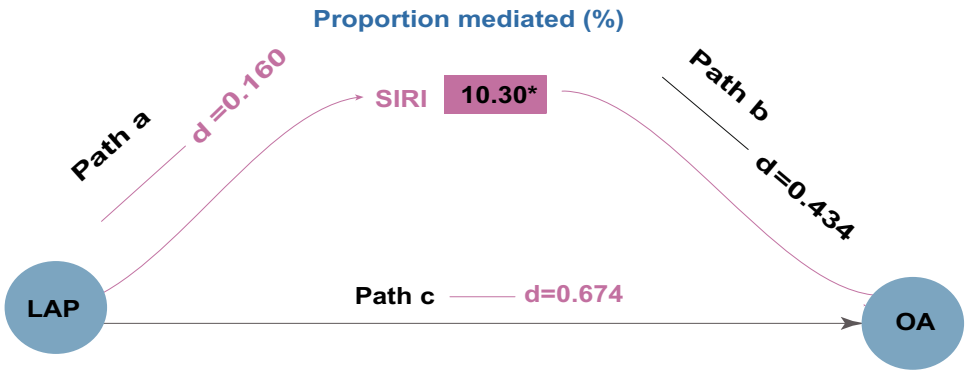

Fig. 5. Mediation analysis.

association (10.30%) was mediated by SIRI, with mediation proportions of 8.92% in younger individuals and 8.69% in women (Fig. S2).

Discussion

In this study, a total of 2,408 participants were included, comprising 1,240 females and 1,168 males, with 210 (8.72%) participants reporting OA. Compared to the first tertile, participants in the highest tertile of LAP levels had a significantly higher prevalence of both OA and SIRI levels [OA (AOR 1.969, 95% CI 1.035–3.745, *P = 0.039*); SIRI (AOR 1.174, 95% CI 1.029–1.489, *P = 0.029*)]. Additionally, compared to the first tertile, participants in the highest tertile of SIRI levels had a significantly higher prevalence of OA [AOR = 1.542, 95% CI 1.010–2.356, *P = 0.045*]. Furthermore, the association between the highest tertile of LAP levels and a higher OA prevalence was partly mediated by SIRI (10.30%).

To date, this study is the first to use the NHANES database to analyze the association between LAP, SIRI, and the prevalence of OA. OA is a degenerative joint disease characterized by cartilage degeneration, osteophyte formation, narrowing of the joint space, and degenerative inflammation, which are the key pathological mechanisms of OA[12]. It is well-established that factors such as gender, age, obesity, and inflammation are closely related to the development of OA[13]. Unlike the irreversible nature of age and gender, obesity is a controllable

environmental factor. Obesity is a risk factor for a variety of diseases, and with the increasing prevalence of obesity, the correlation between obesity and OA has gained more attention[14]. It is widely accepted that excess adipose tissue in obese patients increases biomechanical stress on weight-bearing joints, leading to friction and overload. When the physiological load on the cartilage exceeds normal limits, cartilage damage may occur. Additionally, biomechanical factors can also affect the receptors on the cartilage surface, triggering a cascade of growth factors, cytokines, matrix metalloproteinases, and signaling proteins, further promoting the development of OA. However, biomechanical factors alone cannot explain OA in non-weight-bearing joints[15]. With the advancement of molecular biology, it has become increasingly clear that adipose tissue is not only an energy storage and supply organ but also the largest endocrine organ in the body. Through endocrine, paracrine, and autocrine mechanisms, adipose tissue secretes a variety of adipokines, inflammatory mediators, and signaling proteins that participate in the pathogenesis of OA. Therefore, excess adipose tissue in obese patients has become a risk factor for the development and progression of OA[16]. LAP, a novel adipose tissue function indicator based on WC and TG levels, and gender, is used to estimate fat accumulation and distribution[6]. Unlike LDL-C, which shows limited sensitivity to visceral fat dysfunction, TG levels rise early in metabolic syndrome and better reflect ectopic lipid storage[17]. LAP was therefore intentionally constructed using WC and TG to capture visceral adiposity and lipid metabolic abnormalities in a clinically simple yet pathophysiologically relevant manner. LAP provides a good representation of the body's lipid storage status and has demonstrated better recognition and predictive abilities for cardiovascular diseases and other health conditions in clinical settings[18].

Immune inflammation plays a crucial role in the onset and progression of OA, making the control of inflammatory responses important for both the prevention and treatment of OA. Inflammatory cytokines contribute to the pathogenesis of OA by disrupting the balance between catabolic and anabolic processes in joint tissues. When this balance is disturbed, it leads to the progressive degradation of articular cartilage, which plays a key biomechanical role in the joints, ultimately resulting in the gradual loss of joint function and pain[19]. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most commonly used laboratory markers of systemic inflammatory diseases, and they are elevated in inflammatory joint diseases such as rheumatoid arthritis (RA). OA was once considered a non-inflammatory joint disease, with inflammatory serum markers like CRP not elevated in OA[20]. However, recent studies have shown that high-sensitivity CRP (hs-CRP) and ESR are elevated in OA patients and are closely associated with disease progression and prognosis[21].

In recent years, the SIRI has emerged as a novel marker of systemic inflammation, and its predictive value for disease prognosis has been demonstrated in various types of cancer. SIRI is calculated as (neutrophil count × monocyte count)/lymphocyte count, integrating both pro-inflammatory (neutrophils and monocytes) and anti-inflammatory (lymphocytes) components to reflect the balance between immune activation and suppression. Originally proposed in oncology[22], SIRI has since been widely recognized in metabolic and inflammatory diseases for its superior capacity to characterize systemic immune-inflammatory states compared to single markers like CRP or NLR. In contrast to CRP-which may remain normal in low-grade inflammation-SIRI captures broader immune dysregulation, making it particularly relevant for OA[8], where chronic, subclinical inflammation plays a key pathogenic role. Moreover, SIRI is derived from routine blood counts, offering a practical, low-cost, and scalable biomarker for epidemiologic studies. In this context, our findings support the clinical utility of SIRI in linking visceral adiposity to joint degeneration, highlighting its potential as a mechanistic mediator and early warning tool for OA in populations with normal BMI but hidden metabolic risk.

However, no studies have reported on the relationship between SIRI and OA. In this study, we found that SIRI follows a right-skewed non-normal distribution, and therefore, log transformation was applied before data analysis. The results show that SIRI reflects the systemic inflammation levels in OA patients and has been proven to be a strong predictor of disease activity, joint damage, and radiographic progression. Higher SIRI values were significantly associated with an increased risk of OA, worse disease activity, and poor prognosis. Moreover, the observed associations between higher lipid accumulation product (LAP), elevated systemic inflammation response index (SIRI), and increased OA prevalence remained robust in subgroup analyses, particularly among younger individuals and women. This finding suggests that early metabolic and inflammatory disturbances may contribute to OA risk even before the conventional age threshold. Furthermore, among the 2,408 included participants, 1,240 (55%) were women. The more pronounced associations in females-especially those under age 60-raise the possibility that menopausal transition may play a role. Although the NHANES dataset lacks direct indicators of menopausal status, it is well documented that estrogen decline during menopause may exacerbate adiposity, systemic inflammation, and cartilage degeneration. Therefore, hormonal factors could plausibly influence the relationship between LAP, SIRI, and OA in women. Wang et al. found that excessive obesity leads to inflammatory responses, oxidative stress, and mitochondrial dysfunction[23]. In this study, mediation analysis revealed that part of the association between LAP and OA was mediated by SIRI, with a mediation proportion of 10.30% ($P < 0.001$). This suggests that even in individuals with a normal BMI, high LAP levels are associated with an increased risk of OA, and part of this association is mediated by systemic inflammation.

This study has several notable strengths. First, it leveraged data from NHANES, a large, nationally representative survey with a rigorous multi-stage probability sampling design, which enhances the reliability and generalizability of the findings. Second, by focusing specifically on individuals with normal BMI, the study uniquely isolates the impact of visceral adiposity and systemic inflammation on osteoarthritis (OA) risk, highlighting associations that may be overlooked when relying solely on BMI. Third, the use of mediation analysis offers mechanistic insight, demonstrating that systemic inflammation, as measured by SIRI, partially mediates the relationship between lipid accumulation (LAP) and OA. However, several limitations should be noted. Due to the observational and cross-sectional nature of NHANES, causal relationships between LAP, SIRI, and OA cannot be established, and longitudinal studies are needed to validate the temporal and causal pathways of the observed associations. Additionally, OA diagnosis was based on self-reported survey data rather than clinical or radiographic confirmation, which may lead to recall bias and diagnostic misclassification, particularly

for early-stage or asymptomatic cases. Furthermore, as illustrated in Fig. 1, only 2,408 out of 28,833 eligible participants (8.4%) were included in the final analysis due to missing data on key anthropometric, biochemical, and inflammatory markers. Although these exclusions were essential to ensure analytic rigor and internal validity for multivariable-adjusted and mediation models, the substantial reduction in sample size may introduce potential selection bias and limit generalizability.

Conclusion

This study provides new insights into the relationship between LAP, SIRI, and OA risk in U.S. adults with normal BMI. High levels of LAP are associated with a higher likelihood of OA, with part of this association mediated by systemic inflammation. Therefore, clinical screening, monitoring, and health education focused on LAP levels could be an important public health strategy for adults with normal BMI. The study also observed age- and gender-related differences, suggesting that prevention and intervention strategies for OA should be tailored for younger individuals and women.

Data availability

All data analyzed during this study are available online (https://www.cdc.gov/nchs/nhanes/index.htm).

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Author contributions

Q.H designed and conducted the research; J.M collected and analyzed data; Q.H, D.Z contributed to visualization; Q.H and J.M revised the figures and manuscript. All the authors have read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The NHANES program was approved by the National Center for Health Statistics (NCHS) Ethics Review Board and all participants signed an informed consent form.

Additional information
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