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Inverse association between CALLY index and angina pectoris in US adults: a population-based study

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Abstract

Background The C-reactive protein-albumin-lymphocyte (CALLY) index is a significant marker that reflects both inflammatory and nutritional states and has proven to be a valuable tool for assessing prognosis in various medical conditions. However, the connection between it and angina pectoris has not yet been fully examined. This research sought to thoroughly investigate the possible link between the CALLY index and angina pectoris.

Methods This research utilized a cross-sectional approach, drawing data from the 2003–2010 National Health and Nutrition Examination Survey (NHANES), which included 16,291 adults from the U.S. The CALLY index was calculated based on lymphocyte counts, serum albumin concentrations, and C-reactive protein (CRP) levels. The relationship between the CALLY index and angina pectoris was analyzed using multivariate logistic regression and restricted cubic spline (RCS) methods. Subgroup and interaction analyses were also performed.

Results Elevated ln CALLY was inversely correlated with the prevalence of angina (OR: 0.88, 95% CI: 0.82, 0.95). Those in the highest quartile of the ln CALLY (Q4) were 38% less likely to experience angina than those in the lowest quartile (Q1) (OR: 0.62, 95% CI: 0.46, 0.84). RCS analysis revealed an L-shaped curve linking the CALLY index to angina, with a cutoff at 14. The consistency of this relationship was substantiated through subgroup analyses across different population groups.

Conclusions This research highlights a notable inverse relationship between the CALLY index and angina in U.S. adults, suggesting its potential as an innovative tool for evaluating angina.

Keywords NHANES, CALLY index, Angina, Cross-sectional study, Inverse association

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Introduction

Ischemic heart disease (IHD) is a leading cause of global disease burden, responsible for about 49.2% of cardiovascular deaths [1, 2]. IHD-related healthcare expenses in the U.S. are expected to increase from $120 billion to more than $170 billion by 2040 [3]. Angina pectoris, a frequent clinical manifestation of IHD, involves chest discomfort due to insufficient oxygen supply to the heart, primarily characterized by constrictive pain [4]. Angina pectoris affects between 2% and 10% of the adult population, with increasing frequency [5, 6]. Angina not only threatens human life and health but also significantly impairs quality of life and places a substantial economic burden on healthcare systems globally [7, 8]. Therefore, identifying potential risk factors for angina is crucial for developing effective prevention and intervention strategies.

Inflammation is pivotal in the pathophysiology of angina pectoris, with levels of C-reactive protein (CRP), a sensitive systemic inflammation marker, significantly elevated during inflammatory responses, underscoring its clinical relevance in evaluating angina pectoris [9]. Furthermore, malnutrition and immunosuppression, commonly observed in patients with angina, can be assessed using markers like albumin and lymphocytes [10, 11]. Notably, albumin serves as both an indicator of nutritional status and an indirect marker of systemic inflammation [12]. The CRP-albumin-lymphocyte (CALLY) index, a composite of lymphocyte counts, serum albumin, and CRP levels, has gained recognition as a novel and integrated marker of inflammation and nutritional status. Research indicates a strong association between the CALLY index and the prognosis of various cancers and has been linked to sarcopenia, cardiorenal syndrome, and myocardial infarction [13–18]. Currently, there is no research focusing on the link between the CALLY index and angina pectoris.

To address this research gap, we conducted a cross-sectional study to investigate the potential relationship between the CALLY index and angina.

Methods

Study population

The information for this analysis was collected from the National Health and Nutrition Examination Survey (NHANES), supervised by the National Center for Health Statistics (NCHS), which is under the jurisdiction of the Centers for Disease Control and Prevention (CDC) [19]. A stratified, multistage random sampling strategy is employed in the survey to secure a sample that is representative of the national population. Participants underwent detailed physical exams, filled out health and nutrition surveys, and gave samples for laboratory analysis. The NHANES protocol was reviewed and approved by the NCHS Ethics Board.

Data from four consecutive NHANES biennial cycles (2003–2010) were pooled, comprising 41,156 participants. Participants were excluded based on the following criteria: 18,983 individuals under 20 years of age, 77 missing angina-related information, 2,375 with absent CALLY index data, and 3,430 with incomplete covariate data. In total, 16,291 eligible participants were included in the final analysis. Details of the participant selection process are illustrated in Fig. 1.

Outcome variables

The diagnosis of angina was based on the NHANES 'MCQ.Doc' file, which included the question: 'Has a doctor ever diagnosed you with angina or angina pectoris?' Individuals who answered 'yes' to this question were categorized as having a history of angina. Previous research has confirmed the validity of this approach, showing its precision in documenting angina history [20].

Exposed variables

The CALLY index was determined using the formula: lymphocyte count (10^9/L) × albumin concentration (g/dL) ÷ [CRP (mg/dL) × 10]. Lymphocyte counts were assessed using the UniCel DxH 800 analyzer, CRP levels were quantified with the Beckman UniCel analyzer, and albumin concentrations were measured using the DcX800 system. Detailed information on the specific analyzers and laboratory methods can be found in the NHANES laboratory procedures manual.

Covariate definitions

Covariates were identified based on factors found to be linked to both angina and the CALLY index in earlier studies. The factors considered were sociodemographic factors, lifestyle patterns, and health conditions. Covariates included gender, age, race, marital status, education level, poverty-to-income ratio (PIR), body mass index (BMI), smoking status, alcohol use, history of hypertension, diabetes mellitus, and coronary heart disease (CHD), serum alanine aminotransferase (ALT), and serum creatinine (SCr). The definition of smoking status was based on the NHANES Smoking Data Questionnaire SMQ020, where participants were classified as smokers if they reported having smoked at least 100 cigarettes in their lifetime. Alcohol use was defined using the NHANES Drinking Data Questionnaire ALQ101, where participants were classified as alcohol drinkers if they reported consuming at least 12 alcoholic drinks within a year. Participants with a history of hypertension were identified based on their affirmative response to questionnaire BPQ020, indicating a prior diagnosis of high blood pressure by a doctor or health professional.

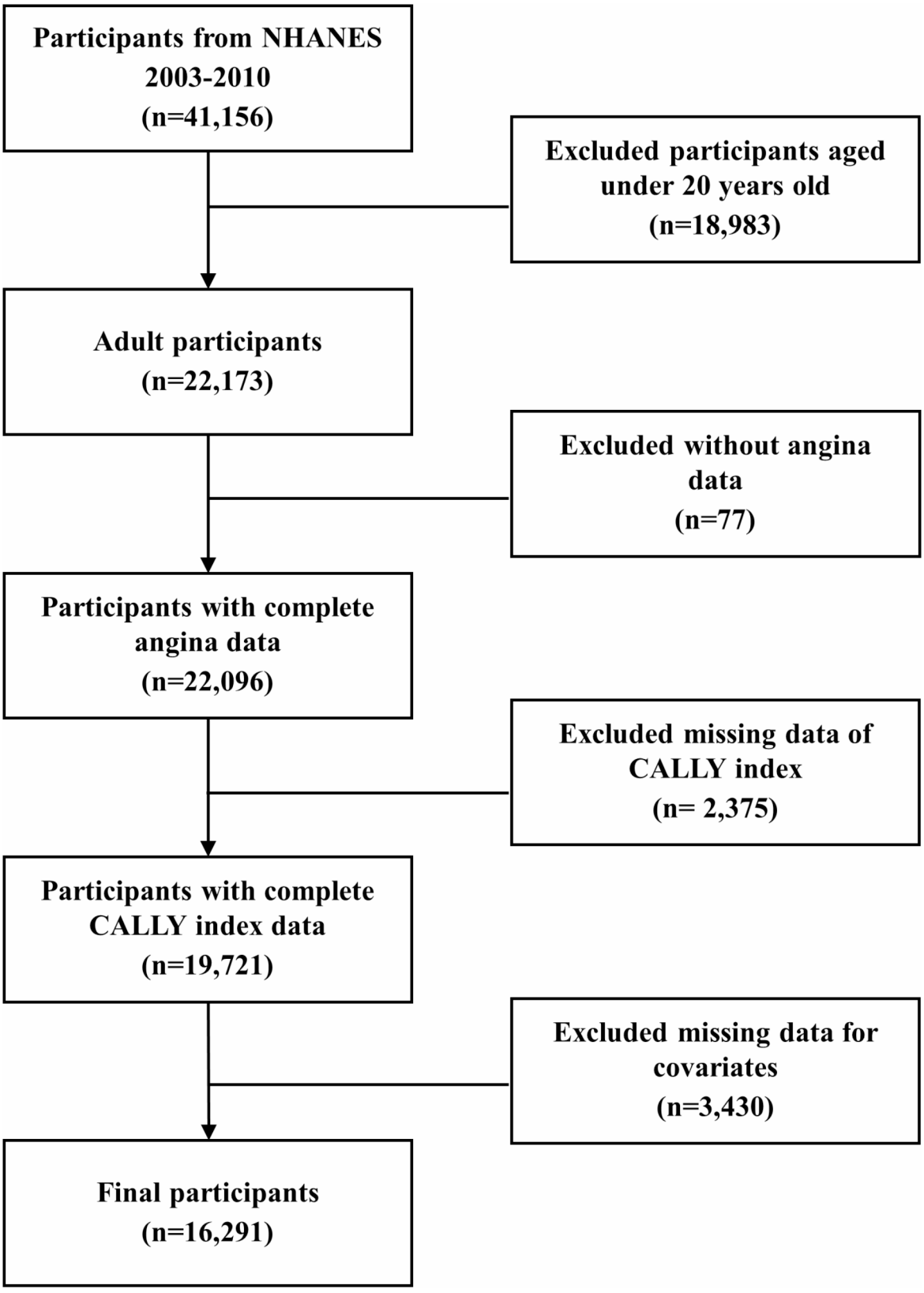

Fig. 1 Flow chart of the study

Participants with a history of diabetes were identified by their affirmative response to questionnaire DIQ010, indicating prior diagnosis by a doctor or health professional. Participants with a history of CHD were identified based on their affirmative response to questionnaire MCQ160C, indicating a prior diagnosis of CHD by a doctor or health professional.

Statistical analysis

Given the substantial skewness in the distribution of the CALLY index, we applied a natural logarithmic transformation (ln CALLY) and stratified the transformed values into quartiles for analysis. Such preprocessing not only improves model fit but also enhances the robustness and interpretability of the results.

At the participant profiling stage, demographic characteristics were assessed using quartiles of ln CALLY. To ensure the study population was nationally representative, sample-specific weighting (WTMEC2YR), stratification (SDMVSTRA), and clustering (SDMVPSU) were applied. For all continuous variables, mean ± standard deviation (SD) was used to accurately represent the data, while frequencies or percentages were used for all categorical variables. To test for significant differences between groups, the weighted chi-square test and weighted Student's t-test were applied.

The link between the CALLY index and angina pectoris was explored using multi-model logistic regression, with outcomes presented as odds ratios (OR) and 95% confidence intervals (CI). The ln CALLY was treated as both continuous and categorical, with the lowest quartile (Q1) as the reference. In Model 1, no covariates were included, while Model 2 included gender, age, and race as adjustments. Model 3, which built on Model 2, incorporated additional covariates, including marital status, education, PIR, smoking, alcohol use, hypertension, diabetes, ALT, and SCr.

To explore the dose-response relationship (linear or nonlinear) between the CALLY index and angina pectoris, we conducted a restricted cubic spline (RCS) analysis on the 10th, 50th, and 90th percentiles of the CALLY index distribution. This analysis adjusted for potential confounders using the same covariates as those in Model 3. This approach facilitated the identification of the optimal cut-off value for the CALLY index and enabled a threshold benefit analysis through segmented logistic regression to clarify the impact of the threshold on angina pectoris.

In addition, after adjusting for factors in the primary analysis Model 3, the results were stratified by gender (male or female), age (< 60 or ≥ 60 years), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races), marital status (married or unmarried and other), education level (less than high school, high school or GED, and Above high school), PIR (< 1.5, 1.5–3.5, and > 3.5), BMI (< 25, 25–30, and > 30 kg/m^2), smoking status (yes or no), Alcohol use (yes or no), hypertension (yes or no), and diabetes (yes or no). Subgroup and interaction analyses were conducted to examine if the relationship between the CALLY index and angina differed across various subgroups, as well as to evaluate the heterogeneity in these associations.

R Studio software was used for data analysis and statistical evaluations, with statistical significance set at a two-sided p-value threshold of under 0.05.

Results

Basic characteristics of participants according to the quartile of CALLY index

The study enrolled 16,291 participants, reflecting a total of 168,073,923 U.S. adults. Baseline data are summarized in Table 1. The mean age of participants was 49.39 ± 18.24 years, comprising 48.7% male, 51.3% female, and 72.7% identified as non-Hispanic white individuals. The mean CALLY index was 9.85 ± 16.87, and 481 participants (2.3%) were diagnosed with angina pectoris. Compared to those in the lowest quartile of the ln CALLY, participants in the highest quartile were more likely to be male, under 60 years old, unmarried, well-educated, have higher incomes, and maintain a normal-range body mass index. Regarding lifestyle factors, the high ln CALLY group exhibited a reduced prevalence of smoking and an increased prevalence of alcohol consumption. The prevalence of hypertension, diabetes, CHD, and angina pectoris was notably lower in this group.

Relationship between the CALLY index and angina pectoris

The multivariate logistic regression analysis in Table 2 shows that higher CALLY index levels were inversely related to the prevalence of angina.

In the continuous variable analysis, both model 1 (OR = 0.78, 95% CI: 0.73, 0.84) and model 2 (OR = 0.82, 95% CI: 0.76, 0.88) demonstrated a negative correlation, which persisted and remained statistically significant in the fully adjusted model (OR = 0.88, 95% CI: 0.82, 0.95). This implies that a 12% decrease in the prevalence of angina is associated with each unit increase in the ln CALLY. The ln CALLY was divided into quartiles, with the reference group being Q1. The fully adjusted model revealed an inverse association for the highest quartile (Q4) (OR = 0.62, 95% CI: 0.46, 0.84, p for trend < 0.05). This suggests that individuals in the highest quartile (Q4) were 38% less likely to develop angina than those in the lowest quartile (Q1).

Additionally, RCS analysis revealed an L-shaped association (p-nonlinear < 0.05), as depicted in Fig. 2. The threshold effect analysis revealed a turning point at a CALLY index value of 14. For a CALLY index less than

Table 1 Baseline characteristics of participants

Characteristics	Overall, *N* = 168,073,923 Overall, *n* = 16,291	Q1 *n* = 4,072	Q2 *n* = 4,073	Q3 *n* = 4,057	Q4 *n* = 4,089	*P*-value
Gender						< 0.001
Male	48.7%	36.6%	45.4%	54.7%	55.1%	
Female	51.3%	63.4%	54.6%	45.3%	44.9%	
Age (years)						< 0.001
< 60	77.1%	71.1%	72.7%	76.9%	85.5%	
≥ 60	22.9%	28.9%	27.3%	23.1%	14.5%	
Race						< 0.001
Mexican American	7.9%	8.8%	7.7%	8.0%	7.3%	
Other Hispanic	3.9%	3.5%	4.2%	3.8%	4.0%	
Non-Hispanic White	72.7%	70.0%	72.9%	74.0%	73.4%	
Non-Hispanic Black	10.3%	14.2%	10.8%	8.7%	8.4%	
Other Race	5.2%	3.5%	4.5%	5.5%	6.8%	
Marital status						< 0.001
Married	58.1%	56.3%	58.8%	61.3%	55.9%	
Unmarried and others	41.9%	43.7%	41.2%	38.7%	44.1%	
Education level						< 0.001
Less than high school	17.5%	20.4%	17.4%	18.4%	14.6%	
High school or GED	24.6%	26.3%	26.2%	24.1%	22.3%	
Above high school	57.9%	53.4%	56.3%	57.5%	63.1%	
PIR						< 0.001
< 1.5	23.0%	27.8%	23.4%	20.7%	21.2%	
1.5–3.5	32.4%	33.8%	32.9%	34.0%	29.6%	
> 3.5	44.6%	38.5%	43.7%	45.3%	49.2%	
BMI (kg/m^2)						< 0.001
< 25	32.1%	15.9%	20.7%	32.9%	52.9%	
25–30	33.9%	26.3%	35.2%	39.1%	33.9%	
> 30	34.0%	57.8%	44.1%	28.0%	13.2%	
Smoking						0.041
Yes	48.0%	49.9%	48.6%	48.3%	46.0%	
No	52.0%	50.1%	51.4%	51.7%	54.0%	
Alcohol use						< 0.001
Yes	75.1%	68.9%	72.5%	77.7%	79.6%	
No	24.9%	31.1%	27.5%	22.3%	20.4%	
Diabetes						< 0.001
Yes	7.9%	13.0%	8.7%	6.2%	4.9%	
No	92.1%	87.0%	91.3%	93.8%	95.1%	
Hypertension						< 0.001
Yes	29.9%	40.4%	33.8%	28.8%	19.8%	
No	70.1%	59.6%	66.2%	71.2%	80.2%	
ALT (U/L)	25.9 ± 17.54	25.6 ± 21.91	27.0 ± 17.39	26.7 ± 16.86	24.7 ± 14.18	< 0.001
SCr (umol/L)	79.2 ± 25.97	78.7 ± 37.39	79.6 ± 25.99	79.9 ± 21.66	78.7 ± 17.80	< 0.001
Angina pectoris						< 0.001
Yes	2.3%	3.4%	2.9%	1.8%	1.4%	
No	97.7%	96.6%	97.1%	98.2%	98.6%	

Continuous variables were showed as mean ± SD, categorical variables were showed as frequency (percentage)

Abbreviations: PIR, poverty index ratio; BMI, body mass index; ALT, alanine aminotransferase; SCr, serum creatinine

14 (OR = 0.94, 95% CI: 0.91, 0.997, $p < 0.05$), the association with the prevalence of angina pectoris was negative, whereas for a CALLY index ≥ 14 (OR = 0.99, 95% CI: 0.98, 1.00, $p > 0.05$), no statistically significant association was observed.

To examine the consistency of the association between the CALLY index and angina across different populations, subgroup analyses and interaction tests were carried out by gender, age, race, marital status, education level, PIR, BMI, lifestyle habits, and disease status. As

Table 2 Association between in CALLY and angina

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
ln CALLY (continuous)	0.78	0.73, 0.84	< 0.001	0.82	0.76, 0.88	< 0.001	0.88	0.82, 0.95	< 0.001
ln CALLY									
Q1	—	—		—	—		—	—	
Q2	0.80	0.64, 1.01	0.063	0.76	0.60, 0.96	0.023	0.86	0.68, 1.09	0.213
Q3	0.60	0.47, 0.77	< 0.001	0.60	0.47, 0.78	< 0.001	0.72	0.56, 0.93	0.012
Q4	0.39	0.30, 0.52	< 0.001	0.48	0.36, 0.65	< 0.001	0.62	0.46, 0.84	0.002
P for trend			< 0.001			< 0.001			< 0.001

Model 1: Unadjusted
Model 2: Adjusted for Gender, Age, and Race
Model 3: Adjusted for Gender, Age, Race, Marital status, Education level, PIR, Smoking, Alcohol use, Diabetes, Hypertension, ALT, and SCr

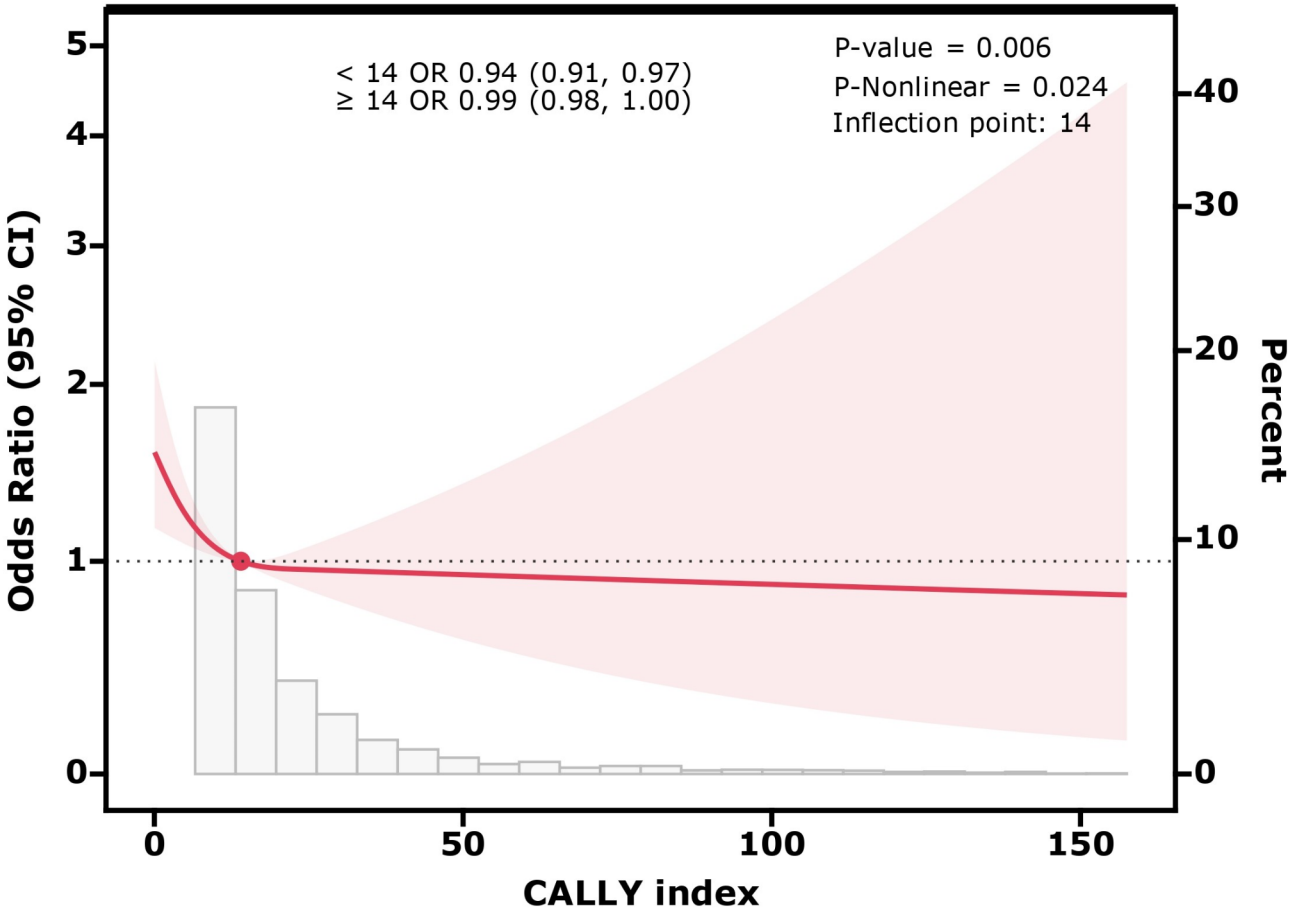

Fig. 2 RCS showing nonlinear relationship between CALLY index and angina pectoris

shown in Fig. 3, the subgroup analyses showed no significant differences in the relationship between the CALLY index and angina across the examined subgroups (p for interaction > 0.05).

Discussion

This research conducted a comprehensive analysis of the relationship between the CALLY index and angina in US adults using NHANES data from 2003 to 2010. Analysis of data from 16,291 participants revealed a significant inverse relationship between the CALLY index and angina prevalence, where a higher CALLY index correlated with a reduced likelihood of angina. Notably, an L-shaped correlation between the CALLY index and angina pectoris was identified, with an inflection point at 14. When the CALLY index was below the inflection point, its increase significantly reduced angina prevalence, demonstrating a robust protective effect. However, once the index reached or exceeded the inflection point, the protective effect plateaued, with further increases

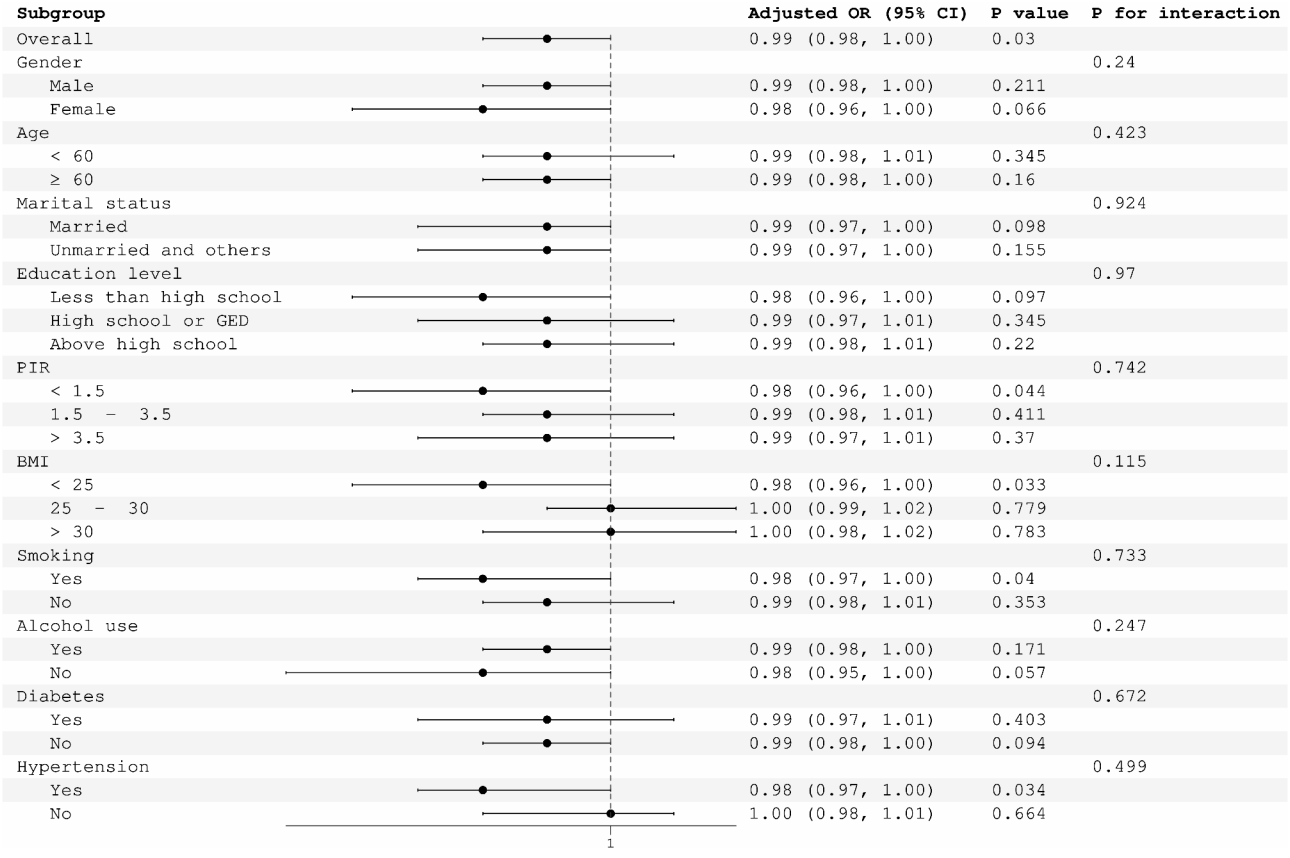

Fig. 3 Subgroup analysis of the association between CALLY index and angina pectoris

showing no significant impact on angina prevalence. Subgroup and interaction analyses supported the robustness of this relationship across multiple groups. To our knowledge, this is the first study to report a strong inverse relationship between the CALLY index and angina pectoris.

The CALLY Index, an integrative measure encompassing inflammatory, nutritional, and immune statuses, was developed by Lida's team and has been shown to correlate strongly with poor survival outcomes after hepatic resection in hepatocellular carcinoma patients [21]. CRP, an effective marker of inflammation, has been extensively confirmed to be linked with a higher risk of angina pectoris. A meta-analysis revealed that CRP levels were, on average, 4.44 times higher in angina patients compared to controls, confirming that elevated CRP serves as an independent risk factor for major adverse cardiac events [22]. Additionally, serum albumin, a critical marker of nutritional status, plays a pivotal role in angina pathogenesis. A cross-sectional study of 5224 Norwegian subjects demonstrated that low serum albumin levels (≤ 47 g/L) significantly correlated with an increased prevalence of angina (OR = 1.44; 95% CI = 1.04–2.01; $p = 0.03$) [23]. Moreover, research on lymphocyte-related indices, such as neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), has highlighted their value as key reference markers for evaluating coronary artery disease severity in angina [24, 25]. Notably, this study, distinct from previous ones, introduced the CALLY index as a comprehensive measure, systematically uncovering, for the first time, the multifaceted impact of inflammation, nutrition, and immunity on angina pectoris. Unlike single biomarkers, which may only reflect one aspect of disease pathophysiology, the CALLY index provides a more holistic assessment of overall health status. For example, while CRP is a well-established marker of inflammation, it does not capture nutritional or immune status. By combining these factors, the CALLY index offers a more comprehensive evaluation of disease risk and prognosis. In the context of angina, the CALLY index may provide a more nuanced assessment of disease risk by capturing the interplay between inflammation, nutrition, and immune function. This holistic approach could help identify high-risk patients who might be missed by traditional biomarkers, enabling earlier intervention and improved outcomes. This offers novel perspectives and robust evidence for exploring its underlying mechanisms and clinical applications.

Inflammation, nutrition, and immunity are intricately interwoven in the pathogenesis of angina pectoris, forming a complex network of interactions. Existing studies

have begun to elucidate the mechanisms linking these factors. Inflammation serves as a pivotal driver of coronary artery disease, inducing endothelial damage, destabilizing atherosclerotic plaques, and culminating in angina [26]. Additionally, inflammation disrupts endothelial regulation of the delicate balance between anticoagulant and coagulation factors, a dysregulation that amplifies the risk of thrombosis, coronary artery obstruction, and angina [27]. CRP and albumin, both liver-derived markers, reflect inflammation levels, though their dynamics during acute inflammation are inverted: CRP levels rise, while albumin levels fall [28]. Hypoalbuminemia intensifies inflammation, oxidative stress, and platelet aggregation, thereby accelerating coronary artery disease progression and worsening angina symptoms [29]. Serum albumin has been identified as an endogenous inhibitor of angiotensin-converting enzyme (ACE), a critical regulator of blood pressure and fluid homeostasis. By inhibiting ACE activity, albumin may significantly reduce angiotensin II production, thereby alleviating angina symptoms [30]. Previous studies have reported significant activation of T-helper 1 (Th1) lymphocytes in patients with unstable angina [31]. Th1 cells secrete IFN-γ to activate macrophages, promoting the rupture of atherosclerotic plaques and thereby contributing to unstable angina [32]. At the same time, Th1 cells are closely associated with elevated CRP levels, highlighting the potential dual role of lymphocytes, as a key component of the CALLY index, in both inflammation and immune regulation in the context of angina pectoris.

Notably, RCS analyses revealed a saturation effect in the relationship between the CALLY index and angina. When the CALLY index is low, it typically indicates substantial inflammation, malnutrition, and immune system dysfunction, all of which collectively heighten the risk of angina. As the CALLY index increases, inflammation and immune function gradually stabilize, and nutritional status improves significantly. However, the protective effect of further increases in the index becomes saturated once it exceeds a certain threshold, possibly reflecting the intricate and dynamic regulation of inflammation, nutrition, and immunity [33].

This study has several notable strengths. Firstly, we utilized a large sample from the NHANES dataset and meticulously accounted for the sample design and weights, thereby improving the national representativeness of the findings. Second, to minimize confounding effects, multiple logistic regression models and RCS analyses were applied, which enhanced the robustness of the findings. Finally, we assessed the between-group consistency of the association between the CALLY index and angina through subgroup analyses. Nevertheless, this study has some limitations. While our study used physician-diagnosed angina as the primary outcome, we acknowledge that the reliability of self-reported disease data in NHANES may be compromised by potential recall bias, as participants might inaccurately remember or report previous medical events or conditions. As the design is cross-sectional, causal inferences between the CALLY index and angina are not possible. Although we adjusted for multiple covariates, the selected covariates may be incomplete, and the effects of other potential confounders cannot be entirely eliminated. Furthermore, given the characteristics of the NHANES dataset, the external validity of these findings, particularly their applicability to populations outside the United States, warrants further investigation.

Conclusion

In summary, our study demonstrates a significant inverse association between the CALLY index and angina pectoris, supported by a large, nationally representative sample. These findings highlight the potential of the CALLY index as a novel tool for assessing angina risk. However, further research is needed to validate these findings in prospective studies, to explore the underlying mechanisms, and to investigate the clinical utility of the CALLY index in other cardiovascular conditions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04544-8 .

Supplementary Material 1

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Author contributions

The study was designed by L.C., D.X. Data analysis and initial drafting of the manuscript were carried out by J.Y. and M.L. The manuscript was revised by R.L., R.L, S.C, and X.H. All authors have read and approved for the final manuscript.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

In accordance with NHANES protocol, all participants in the NHANES study provided written informed consent. As this study utilized publicly available data from the NHANES database, no additional ethical approval or consents were required.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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