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European Journal of Medical Research (2025) 30:206
https://doi.org/10.1186/s40001-025-02473-y

European Journal
of Medical Research

RESEARCH

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Association of systemic inflammatory biomarkers with ocular disease: a large population-based cross-sectional study

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Abstract

Background The aim of this study was to explore the association of systemic inflammatory biomarkers (systemic immune-inflammation (SII) index and systemic inflammatory response index (SIRI)) with the prevalence of ocular disease in the general population of the United States (U.S.).

Methods We conducted a cross-sectional study of subjects in the National Health and Nutrition Examination Survey 2005–2008 years. For the analysis of the association of SII index, and SIRI with the prevalence of ocular disease (glaucoma, cataract, age-related macular degeneration (ARMD), and diabetic retinopathy), the restricted cubic spline (RCS) plot, multivariable logistic regression models, and subgroup analysis were performed.

Results There was a total of 5377 individuals. As shown by the RCS plot, SII index and SIRI were linked with ARMD risk in a U-shaped pattern. Additionally, the SII index and SIRI were linearly positive with glaucoma and cataract. Finally, the risk of diabetic retinopathy was associated with the L-shaped and N-shaped curves of the SII index and SIRI, respectively.

Conclusions Two new systemic inflammatory biomarkers, SII index and SIRI, are closely related to the risk of eye disease. There are different associations between SII index and different ocular diseases. This should raise more concerns and lead to better prevention strategies for systemic inflammation.

Keywords Systemic inflammatory response index, Ocular disease, Systemic immune-inflammation index, United States

Introduction

Ocular diseases refer to a wide range of conditions and disorders that affect the eyes and visual system. These diseases can involve various parts of the eye, including the cornea, conjunctiva, iris, lens, retina, optic nerve, and surrounding tissues [1]. There is a certain correlation between ocular diseases and systemic inflammatory response [2, 3]. Some ocular diseases, especially those related to the immune system, such as ocular autoimmune diseases (dacryoadenitis, iridocyclitis, etc.), are closely related to systemic inflammatory response [4–7]. In these diseases, an increased systemic inflammatory response may lead to inflammation and damage of ocular tissues.

The systemic immune inflammation (SII) index and system inflammation response index (SIRI) are two novel composite indices. SII index is a measure used to assess systemic inflammatory response, which combines the ratio of white blood cells, neutrophils, and platelets in peripheral blood cell count [8]. The elevation of the SII index usually reflects the state of inflammation

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and immune disorders in the body [9]. In addition, the SIRI is used to assess the degree of systemic inflammatory response by calculating the ratio of white blood cell count, neutrophil count, and lymphocyte count [10]. Several studies have also found that the SII index and SIRI may have potential clinical implications in the evaluation of certain ophthalmic diseases. For example, the SII index was significantly higher in pseudo-exfoliative glaucoma patients [11]. Additionally, Alhalwani AY also found that SII index levels are different between all groups of type-2 diabetes-dry eye disease (DM2-DED), dry eye disease, type-2 diabetes, and healthy subjects and higher SII index may be a potential marker for DM2-DED development [12]. Meanwhile, at present, there is a lack of clinical studies to clarify the exact association of SIRI with various ocular diseases. It should be pointed out that the association of ocular diseases with the SII index and SIRI is still being further explored and validated in research. Therefore, the aim of this study was to examine the association of systemic inflammatory biomarkers (SII index, and SIRI) and the risk of ocular diseases (glaucoma, cataract, age-related macular degeneration (ARMD), and diabetic retinopathy) by integrating National Health and Nutrition Examination Surveys (NHANES) data from 2005 to 2008.

Material and methods

Study population

NHANES database is a population-based cross-section survey designed to gather information about the health and nutrition of representative American households. It combines demographics, dietary, examination, laboratory, questionnaire, and limited access data [13]. The NHANES data for the present study from 2005 to 2008 years were used and analysed. Among the 19,488 participants in the total sample, we excluded participants with insufficient, ocular disease data, including ($n=13,922$). Moreover, excluding participants who did not have data on the SII index and SIRI ($n=189$). Finally, a total of 5377 individuals were included in this research (Fig. 1). The National Center for Health Statistics study ethical review board approved all protocols and each participant

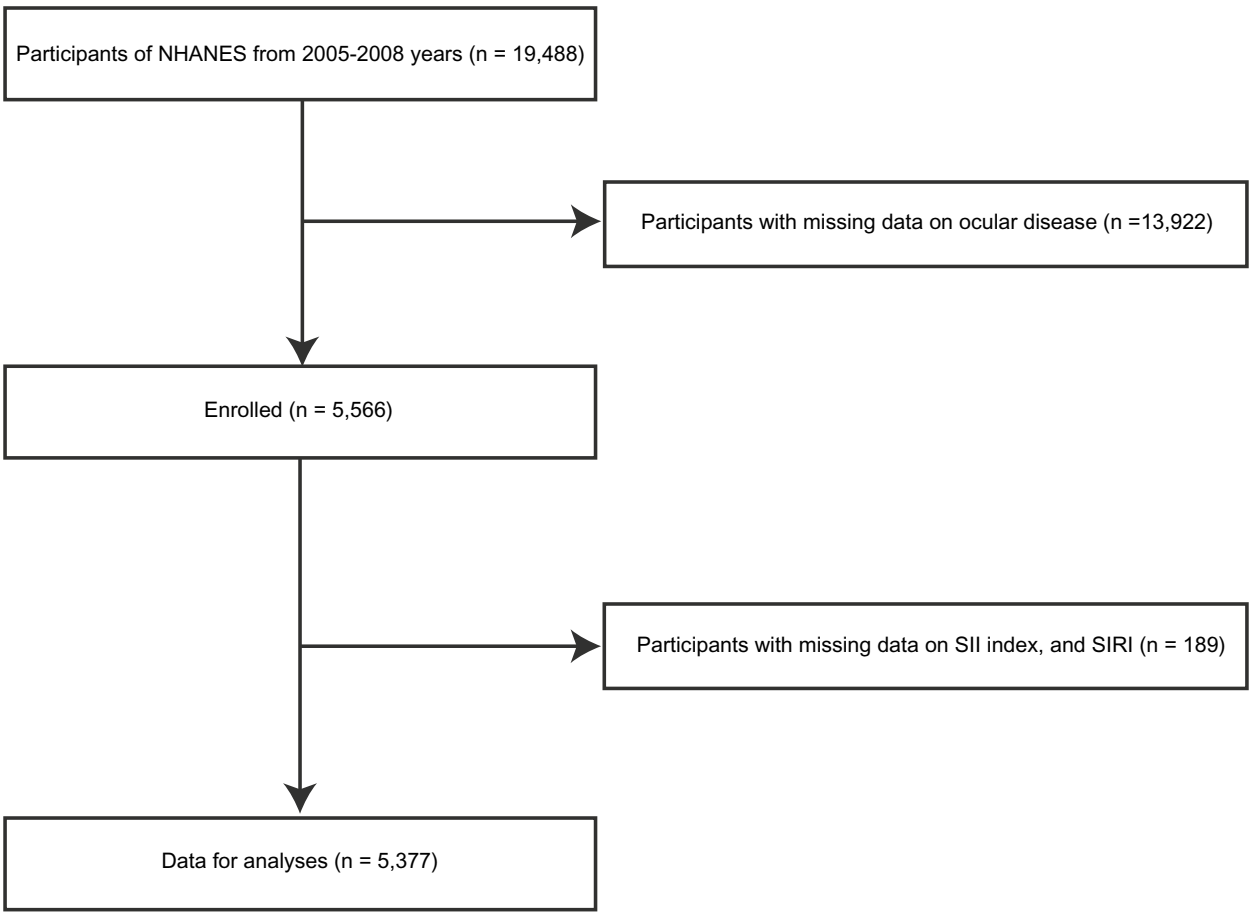

Fig. 1 Study flow chart. SIRI, systemic inflammatory response index; NHANES, National Health and Nutrition Examination Surveys; SII index, systemic immune-inflammation index

provided written informed consent [14]. Detailed study design proposals are publicly available online (https://www.cdc.gov/nchs/nhanes/).

Covariates

According to previous literature, in the study, the covariates were as follows: age, sex (male, and female), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race), family poverty income ratio (PIR), education level (less than high school, high school, and more than high school), marital status (having a partner, no partner, unmarried), the complication of hypertension, and diabetes mellitus (DM), smoker (no, former, now), drinker (never, mild, moderate, heavy), body mass index (BMI), fast glucose (FBG), blood urea nitrogen (BUN), high-density lipoprotein-cholesterol (HDL-C), uric acid (UA), waist circumference, serum creatinine (Scr), total cholesterol (TC), estimated glomerular filtration rate (eGFR) and triglyceride (TG) [1, 15–18]. You can find more information about the variables in this study here www.cdc.gov/nchs/nhanes/.

Calculation of the SII index

The blood samples were collected from fasting participants in the study. The automated hematology analyzing devices (Coulter® DxH 800 analyzer) were used to measure blood count (neutrophil, lymphocyte, and platelet counts). SII index and SIRI were calculated using the following formula. SII index = (platelet count × neutrophil count) /lymphocyte count; SIRI = (neutrophil count × monocyte count) /lymphocyte count [8, 19].

Ocular diseases measurement

There were two methods for determining ocular diseases: self-report or retinal imaging. A total of two digital images per eye were taken to measure retinal thickness using a Canon EOS 10D digital camera (Canon, Tokyo, Japan) and Canon CR6-45NM ophthalmic digital imaging system during the retinal imaging study which was restricted to participants who were 40 years or older. By placing participants in a darkened room for a period of time, participants' pupils were physiologically dilated. Two digital images were taken, the first of which was centered around the macula, and the other of which was centered around the optic nerve. The pictures of the retinas were read at the Ocular Epidemiologic Reading Center, located at the University of Wisconsin in Madison, and they used the worst eye among the two eyes to define ocular diseases. The early treatment diabetic retinopathy study grading standards defined diabetic retinopathy as a condition where one or more of the retina's microaneurysms or retinal hemorrhages were present with or without more severe lesions. In accordance with the modified Wisconsin Age-Related Maculopathy Grading Classification Scheme, ARMD was defined. To identify disc-defined glaucoma, cup-to-disc ratios ≥ 0.6 for each eye from photographs of the optic nerve were graded as no, possible, probable, or definite, with the results being adjudicated whenever necessary. A glaucoma diagnosis of probable or definite in at least one eye was defined by us, as in other studies using NHANES data [1]. The following questions were used to determine whether a self-reported history of ocular diseases existed: "Have you ever been told by an eye doctor that you have glaucoma, sometimes called high pressure in your eyes?"; "Have you ever had eye surgery to treat cataracts?"; "Have you been told by an eye doctor that you have age-related macular degeneration?"; and "Has a doctor ever told you that diabetes has affected your eyes or that you had retinopathy?" Not all participants with self-reported ocular diseases also completed the retinal image testing.

Statistical analysis

The weighted NHANES sample was used to calculate all estimates. All statistical analyses were calculated using R version 3.6.4 and SPSS version 24.0. The P-value < 0.05 was considered statistically significant. The SII index and SIRI were divided into quartiles: SII index (Q1, 13.750–371.875; Q2, 371.876–515.704; Q3, 515.705–729.882; Q4: 729.883–5120.00) and SIRI (Q1, 0.060–0.715; Q2, 0.725–1.050; Q3, 1.051–1.500; Q4: 1.501–20.50), and the lowest quartile (Q1) served as the reference group (Q1). Continuous variables were reported as mean ± SD, while categorical variables were presented as number (%). Continuous variables were analyzed by weighted student t-test and categorical variables were analyzed by the weighted chi-square test. We performed weighted multivariable logistic regression analysis to explore the association of SII index and SIRI with the risk of ocular disease. Model 1 was adjusted for age and sex. Model 2 was adjusted for model 1 variables plus education level, smoking status, marital status, race/ethnicity, family PIR, drinking status, the complication of hypertension, and DM. Model 3 was adjusted for model 2 variables plus BMI, FBG, TC, UA, waist circumference, Scr, eGFR, TG, BUN and HDL-C. Additionally, after adjusting all the covariates of Model 3 above, restricted cubic spline models (RCS) and subgroup analyses stratified by age, sex, hypertension, DM, and BMI also were analyzed to assess the

association of SII index and SIRI with the risk of ocular disease.

Results

Baseline characteristics

The 5,377 subjects were divided into Q1, Q2, Q3 and Q4 groups according to the levels of SII index and SIRI, and their basic clinical characteristics and laboratory test results were given in Tables 1 and 2. We computed that the 5,377 participants in this research may be representative of the total population of 110,679,964 in American.

Association of SII index and SIRI with ocular disease

In the restricted cubic spline (RCS) plot, the SII index and SIRI were linearly positive with glaucoma and cataract (Figs. 2A and C; 3A and B; all *P* for nonlinearity > 0.05).

SII index and SIRI were linked with ARMD risk in a U-shaped pattern (Fig. 2C, P for nonlinearity = 0.023; Fig. 3C, P for nonlinearity = 0.040). Additionally, the SII index and SIRI were associated with the L-shaped and N-shaped association with the prevalence of ARMD, respectively (Fig. 2D, P for nonlinearity = 0.734; Fig. 3D, P for nonlinearity = 0.027). As SIRI increased, the risk of diabetic retinopathy increased significantly. When the SIRI reached 1.782, diabetic retinopathy risk was the highest, and then the curve showed a descend trend. Three multivariate logistic regression models (Model 1, Model 2, and Model 3) were constructed to explore the association of SII index and SIRI with the prevalence of ocular disease (glaucoma, cataract, ARMD and diabetic retinopathy) (Table 3, 4, 5 and 6).

Subgroup analyses

We performed subgroup analyses stratified by age, sex, hypertension, DM, and BMI, to determine the association of SII index and SIRI with risk of ocular disease were shown in Supplementary Fig. 1–8 and Supplementary Table 1–8. The subgroup analysis revealed that the SII index and SIRI all positively associated with the risk of glaucoma in participants who were ≥ 60 years, female, with or without hypertension and with BMI < 30 kg/m^2 (Supplementary Fig. 1 and 5). The linear positive correlation between the SII index as well as SIRI and cataract was found among subjects who were all age groups, male or female, with hypertension, with or without DM and with BMI < 30 or ≥ 30 kg/m^2 (Supplementary Fig. 2 and 6). Additionally, we also observed that the U-shaped associations of SII index and SIRI with ARMD were found among participants who were < 60 years, male, with hypertension, without DM, and with BMI of < 30 kg/m^2. (Supplementary Fig. 3 and 7).

Discussion

This study explored the associations between systemic inflammatory biomarkers, specifically SII index and SIRI, and various ocular diseases in a large, population-based sample from the NHANES 2005–2008. After adjusting for potential risk factors, our findings highlight significant associations between these systemic inflammatory biomarkers and ocular diseases such as glaucoma, cataract, ARMD and diabetic retinopathy. The main risk factors for glaucoma are: advanced age, elevated intraocular pressure, high myopia, a positive family history of glaucoma and ethnicity [20]. Numerous epidemiologic studies have found that the risk factors for age-related cataract formation include age, sex, race and myopia. Modifiable contributors encompass tobacco use, socioeconomic status and ultra-violet light exposure. Emerging evidence further implicates alcohol consumption and suboptimal nutritional status as potential etiological elements. Notably, epidemiological correlations have been documented between cataract progression and systemic pathologies including DM, chronic hypertension, metabolic syndrome, renal dysfunction, and autoimmune disorders [21]. Additionally, several demographic and environmental factors, including age, sex, smoking status, body composition, education level, family history, ethnicity, and the presence of comorbidities such as hypertension, DM, and hyperlipidaemia are all risk factors for developing ARMD [22, 23]. Finally, the development of diabetic retinopathy is strongly associated with longer diabetes duration, higher levels of hyperglycemia, and hypertension [24]. Additionally, other risk factors include nephropathy, dyslipidemia, smoking, and elevated BMI. These factors are modifiable and may help prevent the progression of diabetic retinopathy [25–27].

Systemic inflammatory biomarkers have been associated with ocular diseases via several potential mechanisms [28–31]. In diabetic macular edema (DME), the SII index has been found to correlate with retinal hyperreflective foci (HRF) detected on optical coherence tomography. This correlation highlights the inflammatory nature of HRF and underscores the significance of inflammation in the pathogenesis of DME [32]. Similarly, in diabetic retinopathy, markers such as tumor necrosis factor-alpha (TNF-α) and sVCAM1 exhibit elevated systemic levels as disease severity increases, indicating that a systemic inflammatory state may contribute to the progression of diabetic retinopathy [33]. Furthermore, in primary angle-closure glaucoma, a higher platelet-to-lymphocyte ratio has been associated with the progression of visual field loss, suggesting its potential as a predictive indicator for visual field loss progression in susceptible populations [34]. Within disorders affecting the optic nerve and degenerative conditions of the retina,

Table 1 Characteristics of the study population based on SII index quartiles

SII index	Total ($n=5377$)	Q1 ($n=1345$)	Q2 ($n=1344$)	Q3 ($n=1343$)	Q4 ($n=1345$)	*P*-value
Age, years	56.35 ± 0.38	56.93 ± 0.59	56.29 ± 0.55	55.98 ± 0.32	56.31 ± 0.64	0.458
Sex, %						< 0.001
Male	2695 (50.1%)	742 (13.8%)	673 (12.5%)	655 (12.2%)	625 (11.6%)	
Female	2682 (49.9%)	603 (11.2%)	671 (12.5%)	688 (12.8%)	720 (13.4%)	
Race/ethnicity, %						< 0.001
Mexican American	836 (15.5%)	200 (3.7%)	221 (4.1%)	226 (4.2%)	189 (3.5%)	
Other Hispanic	378 (7.0%)	99 (1.8%)	108 (2.0%)	90 (1.7%)	81 (1.5%)	
Non-Hispanic Black	1044 (19.4%)	441 (8.2%)	242 (4.5%)	197 (3.7%)	164 (3.1%)	
Non-Hispanic White	2945 (54.8%)	563 (10.5%)	735 (13.7%)	779 (14.5%)	868 (16.1%)	
Other race	174 (3.2%)	42 (0.8%)	38 (0.7%)	51 (0.9%)	43 (0.8%)	
Family PIR	3.30 ± 0.07	3.24 ± 0.08	3.42 ± 0.08	3.37 ± 0.10	3.18 ± 0.09	0.003
Education level, %						0.478
Less than high school	1546 (28.8%)	402 (7.5%)	396 (7.4%)	382 (7.1%)	366 (6.8%)	
More than high school	3831 (71.2%)	943 (17.5%)	948 (17.6%)	961 (17.9%)	979 (18.2%)	
Marital status, %						0.004
Having a partner	3461 (64.4%)	891 (16.6%)	890 (16.6%)	867 (16.1%)	813 (15.1%)	
No partner	1552 (28.9%)	350 (6.5%)	368 (6.8%)	388 (7.2%)	446 (8.3%)	
Unmarried	364 (6.8%)	104 (1.9%)	86 (1.6%)	88 (1.6%)	86 (1.6%)	
Hypertension, %						0.450
No	2454 (45.6%)	634 (11.8%)	625 (11.6%)	601 (11.2%)	594 (11.0%)	
Yes	2923 (54.4%)	711 (13.2%)	719 (13.4%)	742 (13.8%)	751 (14.0%)	
DM, %						0.006
No	4169 (77.5%)	1031 (19.2%)	1062 (19.8%)	1040 (19.3%)	1036 (19.3%)	
Yes	1208 (22.5%)	314 (5.8%)	282 (5.2%)	303 (5.6%)	309 (5.7%)	
Smoker, %						0.009
No	2550 (47.4%)	657 (12.2%)	668 (12.4%)	635 (11.8%)	590 (11.0%)	
Former	1736 (32.3%)	442 (8.2%)	431 (8.0%)	436 (8.1%)	427 (7.9%)	
Now	1091 (20.3%)	246 (4.6%)	245 (4.6%)	272 (5.1%)	328 (6.1%)	
Alcohol user, %						0.168
Never	759 (14.1%)	196 (3.6%)	182 (3.4%)	203 (3.8%)	178 (3.3%)	
Former	1379 (25.6%)	353 (6.6%)	334 (6.2%)	344 (6.4%)	348 (6.5%)	
Mild	1852 (34.4%)	450 (8.4%)	469 (8.7%)	481 (8.9%)	452 (8.4%)	
Moderate	712 (3.2%)	172 (3.2%)	187 (3.5%)	168 (3.1%)	185 (3.4%)	
Heavy	675 (12.6%)	174 (3.2%)	172 (3.2%)	147 (2.7%)	182 (3.4%)	
BMI, kg/m^2	29.07 ± 0.14	28.71 ± 0.22	28.75 ± 0.25	29.34 ± 0.24	29.40 ± 0.26	0.094
Waist circumference, cm	100.38 ± 0.38	99.90 ± 0.57	99.32 ± 0.68	101.25 ± 0.60	100.90 ± 0.52	0.153
FBG, mg/mL	109.25 ± 0.51	112.00 ± 1.38	107.25 ± 1.13	109.87 ± 1.01	108.32 ± 0.80	0.017
BUN, mg/dL	13.68 ± 0.13	13.45 ± 0.22	13.92 ± 0.18	13.66 ± 0.18	13.64 ± 0.24	0.268
UA, mg/dL	5.52 ± 0.03	5.54 ± 0.05	5.43 ± 0.06	5.59 ± 0.06	5.53 ± 0.05	0.266
Scr, mg/dL	0.93 ± 0.01	0.93 ± 0.01	0.92 ± 0.01	0.93 ± 0.01	0.93 ± 0.01	0.577
eGFR, $ml/min/1.73m^2$	85.49 ± 0.59	86.18 ± 0.80	85.62 ± 0.73	85.76 ± 0.73	84.54 ± 0.87	0.29
TC, mg/dL	203.71 ± 0.63	199.95 ± 1.60	205.71 ± 1.20	205.83 ± 1.28	202.72 ± 1.43	0.023
TG, mg/dL	148.38 ± 1.67	144.00 ± 4.37	149.24 ± 3.57	151.51 ± 2.88	147.94 ± 3.17	0.491
HDL-C, mg/dL	53.91 ± 0.33	54.01 ± 0.57	54.27 ± 0.69	53.68 ± 0.46	53.73 ± 0.61	0.904
Glaucoma, %						0.245
No	5062 (94.1%)	1269 (23.6%)	1264 (23.5%)	1275 (23.7%)	1254 (23.3%)	
Yes	315 (5.9%)	76 (1.4%)	80 (1.5%)	68 (1.3%)	91 (1.7%)	
Cataract, %						0.010
No	4714 (87.7%)	1209 (22.5%)	1194 (22.2%)	1174 (21.8%)	1137 (21.1%)	

Table 1 (continued)

SII index	Total ($n=5377$)	Q1 ($n=1345$)	Q2 ($n=1344$)	Q3 ($n=1343$)	Q4 ($n=1345$)	*P*-value
Yes	663 (12.3%)	136 (2.5%)	150 (2.8%)	169 (3.1%)	208 (3.9%)	
ARMD, %						0.105
No	4959 (92.2%)	1242 (23.1%)	1253 (23.3%)	1246 (23.2%)	1218 (22.7%)	
Yes	418 (7.8%)	103 (1.9%)	91 (1.7%)	97 (1.8%)	127 (2.4%)	
Diabetic retinopathy, %						0.071
No	4383 (81.5%)	1082 (20.1%)	1107 (20.6%)	1085 (20.2%)	1109 (20.6%)	
Yes	994 (18.5%)	263 (4.9%)	237 (4.4%)	258 (4.8%)	236 (4.4%)	

SII index, systemic immune-inflammation index; Q1, 13.750–371.875; Q2, 371.876–515.704; Q3, 515.705–729.882; Q4: 729.883–5120.00; family PIR, family poverty income ratio; DM, diabetes mellitus; BMI, body mass index; FBG, fast glucose; BUN, blood urea nitrogen; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; ARMD, age-related macular degeneration

such as ARMD and diabetic retinopathy, neutrophils play a significant role in neuroinflammation and tissue injury. This is attributed to their capacity for neutrophil extracellular trap formation and the release of pro-inflammatory mediators [35]. Collectively, these findings emphasize the crucial role of systemic inflammation in the pathogenesis and progression of various ocular diseases, offering insights into the potential biological mechanisms underlying their association with systemic inflammatory biomarkers. SII index and SIRI have been extensively studied in various health conditions, but their associations with glaucoma and cataract remain unclear. Research has shown that the SII index and SIRI are linked to predicting outcomes in acute ischemic stroke [36], cardiovascular diseases (CVDs) [8, 13], and mortality in patients with CVDs [37]. Our results, however, firstly added a linear positive association between both the SII index and SIRI with the prevalence of glaucoma and cataract. The systemic inflammatory state reflected by the SII index and SIRI affects the development and progression of cataract and glaucoma through multiple mechanisms, including inflammatory response, immune cell infiltration, and oxidative stress. Inflammatory cytokines, including TNF-α and interleukin-6, may mediate the association between inflammatory states and the development of cataracts and glaucoma [38, 39]. Furthermore, extended periods of inflammation and oxidative stress can drain the body's antioxidant defenses. For instance, the functioning of antioxidant enzymes like superoxide dismutase and glutathione peroxidase could be impaired. In addition, the total amount of antioxidants might drop, which could hinder the eye's ability to counteract reactive oxygen species. Previous research has shown that SII index is associated with pseudophakic cystoid macular edema (PCME) after cataract surgery, indicating its potential as a predictive tool for PCME in eyes without risk factors [40]. Additionally, the SII index has been evaluated in exfoliative glaucoma (XFG) patients, although no significant differences were found between XFG and exfoliative syndrome groups in terms of SII index parameters [41]. Furthermore, the SII index has been linked to steroid-induced ocular hypertension (SIOH) and steroid-induced posterior subcapsular cataract (SI-PSC) in children undergoing long-term corticosteroid treatment, with SIOH and SI-PSC occurrences starting within the first month and at 6 months, respectively [42]. In addition, while SIRI was not significantly associated with cataracts in previous studies, for example, in a Chinese population, it was notably linked to diabetic retinopathy and polypoidal choroidal vasculopathy, highlighting its role in specific ocular conditions [29]. This suggests that higher levels of systemic inflammation, as indicated by these biomarkers, may be linked to an increased risk of these ocular diseases. These findings collectively suggest that the SII index may play a role in different ocular conditions, highlighting its potential as a marker for predicting and understanding the pathophysiology of ocular diseases such as glaucoma and cataract. Nevertheless, the findings regarding the associations of the SII index and SIRI with ARMD are less conclusive. Studies on patients with dry- and wet-type ARMD did not show significant differences in SII index or SIRI levels compared to controls [37, 43, 44], indicating that these indices may not be sensitive biomarkers for early diagnosis of ARMD, while the association between the SII index and SIRI with ARMD displayed a U-shaped pattern in our study, indicating that both low and high levels of these biomarkers are associated with higher risks of ARMD. This complex relationship suggests that moderate levels of systemic inflammation may be protective against ARMD, whereas both deficient and excessive inflammatory responses could contribute to disease progression. Further exploration of other routine blood markers is suggested to identify inflammatory changes in ARMD patients. SIRI has been identified as a diagnostic biomarker for the occurrence of DME in patients with non-proliferative diabetic

Table 2 Characteristics of the study population based on SIRI quartiles

SII index	Total ($n=5377$)	Q1 ($n=1345$)	Q2 ($n=1354$)	Q3 ($n=1335$)	Q4 ($n=1343$)	*P*-value
Age, years	56.35 ± 0.38	54.77 ± 0.48	55.49 ± 0.43	56.12 ± 0.49	58.75 ± 0.67	< 0.001
Sex, %						< 0.001
Male	2695 (50.1%)	551 (10.2%)	614 (11.4%)	728 (13.5%)	802 (14.9%)	
Female	2682 (49.9%)	794 (14.8%)	740 (13.8%)	607 (11.3%)	541 (10.1%)	
Race/ethnicity, %						< 0.001
Mexican American	836 (15.5%)	227 (4.2%)	233 (4.3%)	231 (4.3%)	145 (2.7%)	
Other Hispanic	378 (7.0%)	103 (1.9%)	124 (2.3%)	81 (1.5%)	70 (1.3%)	
Non-Hispanic Black	1044 (19.4%)	499 (9.3%)	237 (4.4%)	178 (3.3%)	130 (2.4%)	
Non-Hispanic White	2945 (54.8%)	467 (8.7%)	711 (13.2%)	813 (15.1%)	954 (17.7%)	
Other race	174 (3.2%)	49 (0.9%)	49 (0.9%)	32 (0.6%)	44 (0.8%)	
Family PIR	3.30 ± 0.07	3.29 ± 0.08	3.42 ± 0.08	3.37 ± 0.08	3.12 ± 0.09	0.007
Education level, %						0.155
Less than high school	1546 (28.8%)	409 (7.6%)	371 (6.9%)	382 (7.1%)	384 (7.1%)	
More than high school	3831 (71.2%)	936 (17.4%)	983 (18.3%)	953 (17.7%)	959 (17.8%)	
Marital status, %						0.002
Having a partner	3461 (64.4%)	860 (16.0%)	895 (16.6%)	892 (16.6%)	814 (15.1%)	
No partner	1552 (28.9%)	372 (6.9%)	367 (6.8%)	364 (6.8%)	449 (8.4%)	
Unmarried	364 (6.8%)	113 (2.1%)	92 (1.7%)	79 (1.5%)	80 (1.5%)	
Hypertension, %						0.002
No	2454 (45.6%)	666 (12.4%)	662 (12.3%)	591 (11.0%)	535 (9.9%)	
Yes	2923 (54.4%)	679 (12.6%)	692 (12.9%)	744 (13.8%)	808 (15.0%)	
DM, %						0.018
No	4169 (77.5%)	1054 (19.6%)	1080 (20.1%)	1019 (19.0%)	1016 (18.9%)	
Yes	1208 (22.5%)	291 (5.4%)	274 (5.1%)	316 (5.9%)	327 (24.3%)	
Smoker, %						< 0.001
No	2550 (47.4%)	715 (13.3%)	658 (12.2%)	658 (12.2%)	519 (9.7%)	
Former	1736 (32.3%)	380 (7.1%)	440 (8.2%)	421 (7.8%)	495 (9.2%)	
Now	1091 (20.3%)	250 (4.6%)	256 (4.8%)	256 (4.8%)	329 (6.1%)	
Alcohol user, %						0.086
Never	759 (14.1%)	212 (3.9%)	196 (3.6%)	177 (3.3%)	174 (3.2%)	
Former	1379 (25.6%)	361 (6.7%)	330 (6.1%)	335 (6.2%)	353 (6.6%)	
Mild	1852 (34.4%)	417 (7.8%)	471 (8.8%)	474 (8.8%)	490 (9.1%)	
Moderate	712 (13.2%)	183 (3.4%)	192 (3.6%)	192 (3.6%)	145 (2.7%)	
Heavy	675 (12.6%)	172 (3.2%)	165 (3.1%)	157 (2.9%)	181 (3.4%)	
BMI, kg/m^2	29.07 ± 0.14	28.59 ± 0.20	28.57 ± 0.19	29.60 ± 0.25	29.44 ± 0.31	0.001
Waist circumference, cm	100.38 ± 0.38	97.70 ± 0.48	98.68 ± 0.56	101.96 ± 0.61	102.73 ± 0.75	< 0.001
FBG, mg/mL	109.25 ± 0.51	109.50 ± 1.36	107.51 ± 0.99	110.05 ± 0.92	109.99 ± 0.93	0.201
BUN, mg/dL	13.68 ± 0.13	12.70 ± 0.16	13.26 ± 0.13	13.95 ± 0.22	14.62 ± 0.21	< 0.001
UA, mg/dL	5.52 ± 0.03	5.34 ± 0.05	5.37 ± 0.05	5.57 ± 0.04	5.76 ± 0.06	< 0.001
Scr, mg/dL	0.93 ± 0.01	0.89 ± 0.01	0.89 ± 0.01	0.94 ± 0.01	0.98 ± 0.01	< 0.001
eGFR, ml/min/1.73m^2	85.49 ± 0.59	88.51 ± 0.87	87.11 ± 0.53	85.06 ± 0.82	81.80 ± 0.93	< 0.001
TC, mg/dL	203.71 ± 0.63	207.10 ± 1.49	206.80 ± 1.16	203.80 ± 1.33	197.71 ± 0.98	< 0.001
TG, mg/dL	148.38 ± 1.67	146.38 ± 4.57	142.80 ± 2.34	156.80 ± 2.92	147.19 ± 3.14	0.016
HDL-C, mg/dL	53.91 ± 0.33	56.24 ± 0.49	55.22 ± 0.51	52.27 ± 0.60	52.32 ± 0.51	< 0.001
Glaucoma, %						0.010
No	5062 (94.1%)	1285 (23.9%)	1282 (23.8%)	1261 (23.5%)	1234 (22.9%)	
Yes	315 (5.9%)	60 (1.1%)	72 (1.3%)	74 (1.4%)	109 (2.0%)	
Cataract, %						< 0.001
No	4714 (87.7%)	1245 (23.2%)	1220 (22.7%)	1171 (21.8%)	1078 (20.0%)	

Table 2 (continued)

SII index	Total ($n=5377$)	Q1 ($n=1345$)	Q2 ($n=1354$)	Q3 ($n=1335$)	Q4 ($n=1343$)	*P*-value
Yes	663 (12.3%)	100 (1.9%)	134 (2.5%)	164 (3.1%)	265 (4.9%)	
ARMD, %						0.001
No	4959 (92.2%)	1274 (23.7%)	1257 (23.4%)	1244 (23.1%)	1184 (22.0%)	
Yes	418 (7.8%)	71 (1.3%)	97 (1.8%)	91 (1.7%)	159 (3.0%)	
Diabetic retinopathy, %						0.590
No	4383 (81.5%)	1115 (20.7%)	1112 (20.7%)	1075 (20.0%)	1081 (20.1%)	
Yes	994 (18.5%)	230 (4.3%)	242 (4.5%)	260 (4.8%)	262 (4.9%)	

SIRI, systemic inflammatory response index; Q1, 0.060–0.715; Q2, 0.725–1.050; Q3, 1.051–1.500; Q4: 1.501–20.50; family PIR, family poverty income ratio; DM, diabetes mellitus; BMI, body mass index; FBG, fast glucose; BUN, blood urea nitrogen; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; ARMD, age-related macular degeneration

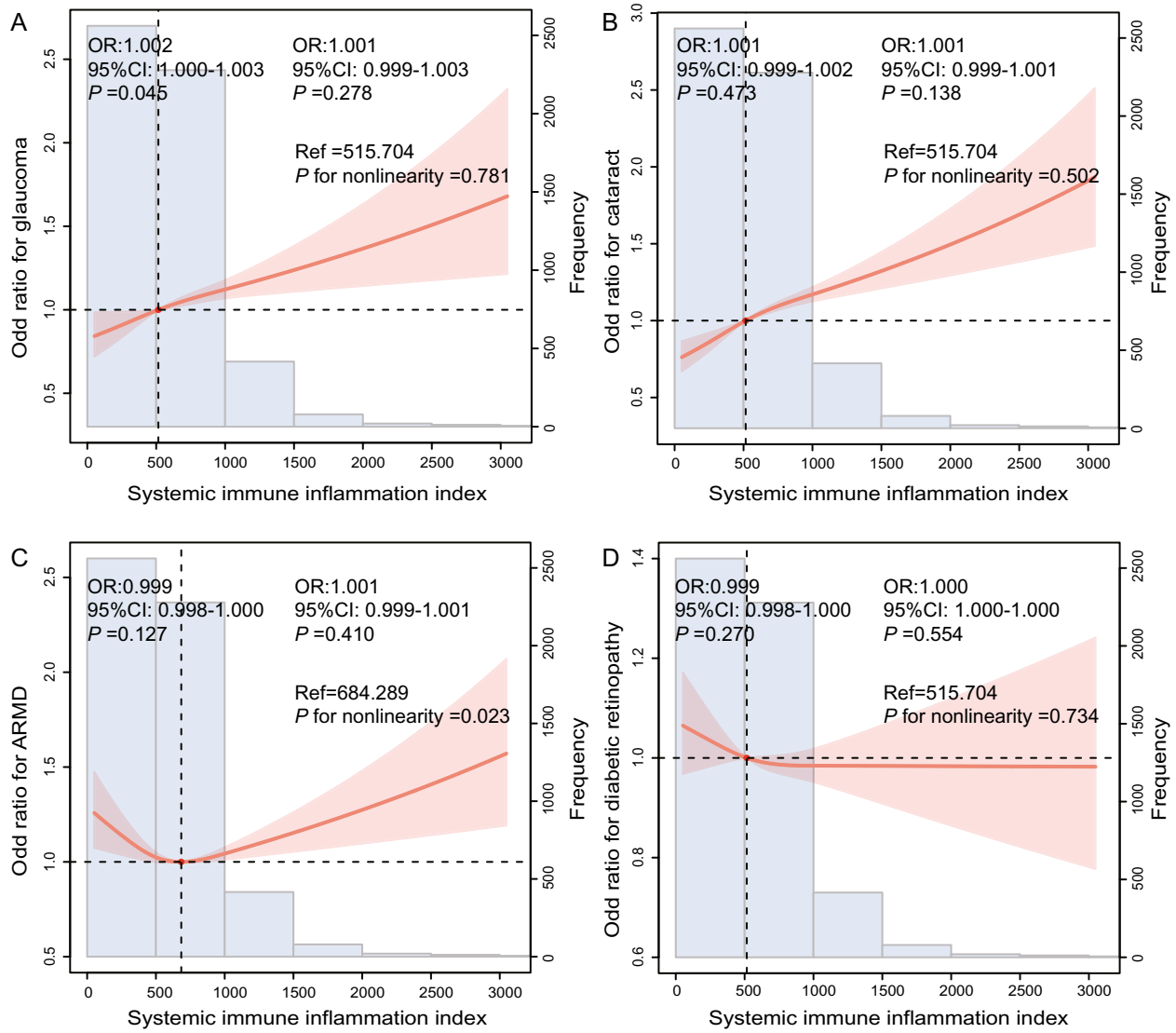

Fig. 2 RCS curve for associations of SII index with ocular disease. **A** SII index and glaucoma; **B** SII index and cataract; **C** SII index and ARMD; **D** SII index and diabetic retinopathy. RCS, restricted cubic spline; SII index, systemic immune-inflammation index; ARMD, age-related macular degeneration

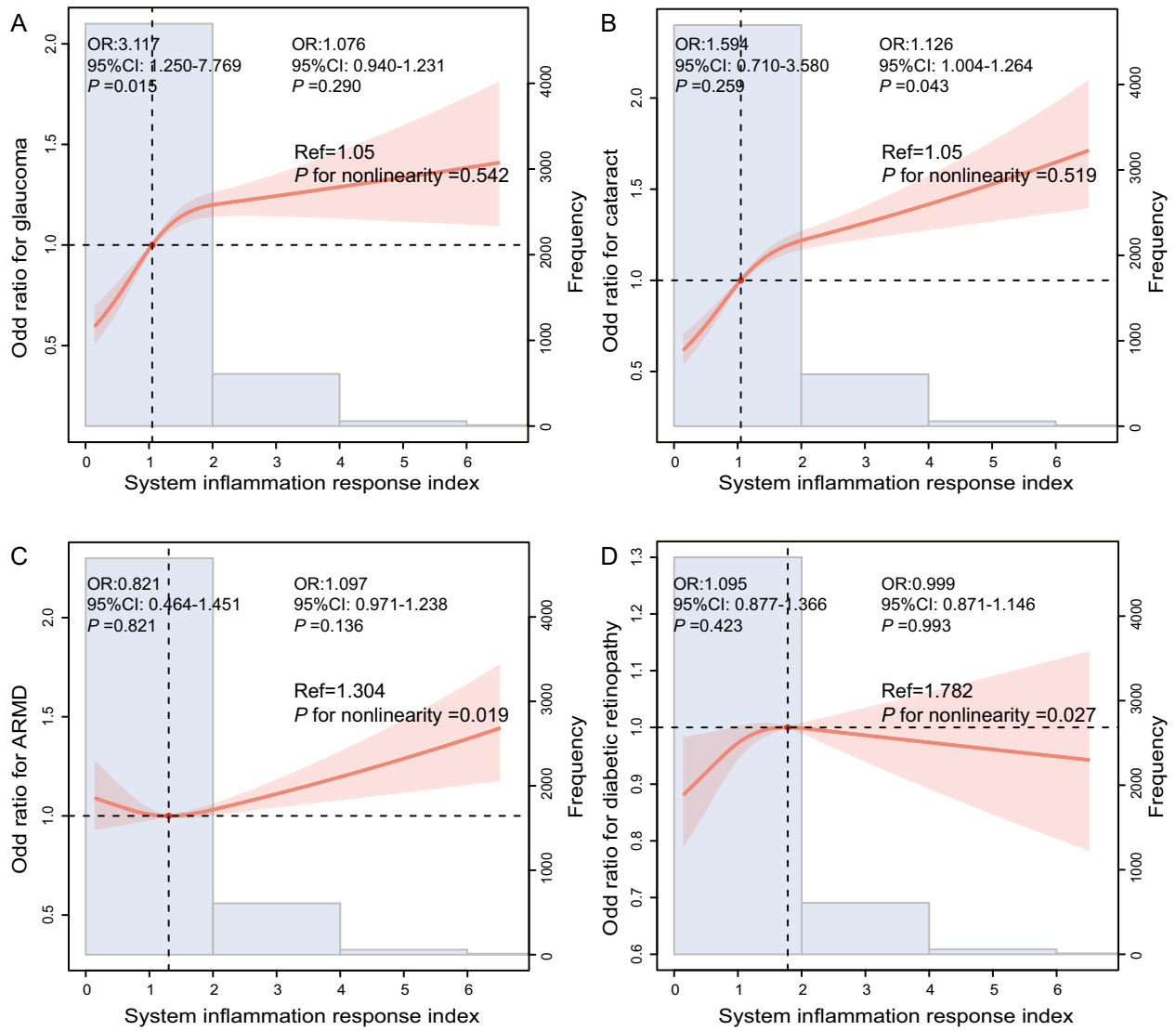

Fig. 3 RCS curve for associations of SIRI with ocular disease. **A** SIRI and glaucoma; **B** SIRI and cataract; **C** SIRI and ARMD; **D** SIRI and diabetic retinopathy

retinopathy, emphasizing its role in risk stratification and management of DME [45]. Additionally, systemic inflammation, as measured by SIRI, has been linked to retinal inflammation in patients with treatment-naïve center-involving DME, suggesting its potential as a marker for DME treatment decisions [32]. In the progression of diabetic retinopathy, inflammation impairs the function of vascular endothelial cells via multiple mechanisms, thereby inducing pathological alterations such as increased vascular permeability and neovascularization. The inflammatory states indicated by the SII index and SIRI are intimately associated with these pathological changes, exerting a significant influence on the onset and progression of diabetic retinopathy (46, 47). A significant increase in the risk of diabetic retinopathy was observed with rising SIRI levels, peaking at a certain SIRI value, after which the risk began to decline. This finding underscores the critical role of systemic inflammation in the development and progression of diabetic retinopathy, emphasizing the need for careful monitoring of inflammatory markers in diabetic patients.

The SII index and SIRI, derived from routine blood examinations, provide convenient and cost-effective biomarkers for the screening and prevention of ocular diseases. Physicians can calculate both the SII index and SIRI during routine blood tests, thereby providing patients with ocular diseases with a more comprehensive health assessment. SII index and SIRI, as emerging

Table 3 Associations of systemic inflammatory biomarkers with prevalence of glaucoma

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend
SII index		0.661		0.277		0.375
13.750–371.875	1.00		1.00		1.00	
371.876–515.704	1.02 (0.73, 1.34)		1.07 (0.78, 1.47)		1.06 (0.77, 1.46)	
515.705–729.882	1.05 (0.76, 1.46)		1.12 (0.80, 1.56)		1.10 (0.79, 1.54)	
729.883–5120.00	1.13 (0.82, 1.56)		1.26 (0.91, 1.76)		1.22 (0.87, 1.70)	
SIRI		0.093		0.009		0.024
0.060–0.715	1.00		1.00		1.00	
0.725–1.050	1.09 (0.77, 1.56)		1.25 (0.87, 1.79)		1.22 (0.85, 1.76)	
1.051–1.500	1.10 (0.77, 1.57)		1.28 (0.88, 1.85)		1.23 (0.85, 1.79)	
1.501–20.50	1.34 (0.95, 1.88)		1.64 (1.14, 2.35) *		1.55 (1.07, 2.24) *	

SII index, systemic immune-inflammation index; SIRI, systemic inflammatory response index; *$P < 0.05$; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty-income ratio, hypertension, diabetes mellitus, smoker, alcohol user; Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, fast glucose, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol

Table 4 Associations of systemic inflammatory biomarkers with prevalence of cataract

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend
SII index		0.003		0.013		0.014
13.750–371.875	1.00		1.00		1.00	
371.876–515.704	1.08 (0.82, 1.43)		1.06 (0.80, 1.40)		1.06 (0.80, 1.41)	
515.705–729.882	1.29 (0.98, 1.70)		1.24 (0.93, 1.64)		1.25 (0.94, 1.66)	
729.883–5120.00	1.45 (1.11, 1.90) *		1.37 (1.04, 1.80) *		1.37 (1.04, 1.80) *	
SIRI		< 0.001		0.003		0.030
0.060–0.715	1.00		1.00		1.00	
0.725–1.050	1.11 (0.81, 1.50)		1.07 (0.78, 1.46)		1.07 (0.78, 1.47)	
1.051–1.500	1.36 (1.01, 1.83) *		1.27 (0.93, 1.73)		1.26 (0.92, 1.72)	
1.501–20.50	1.65 (1.23, 2.19) ***		1.50 (1.11, 2.03) *		1.50 (1.11, 2.04) *	

SII index, systemic immune-inflammation index; SIRI, systemic inflammatory response index; *$P < 0.05$; ***$P < 0.001$; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty-income ratio, hypertension, diabetes mellitus, smoker, alcohol user; Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, fast glucose, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol

inflammation indicators, can be integrated with existing diagnostic tools, including deep learning models and multimodal diagnostic methods, to offer more comprehensive diagnostic information. They are highly valuable for early diagnosis and prognosis assessment, offering high cost-effectiveness and convenience, and can be widely applied in clinical practice. Through these integrated applications, the SII index and SIRI are expected to offer new insights and approaches for the diagnosis and treatment of ocular diseases. Furthermore, these findings support the integration of systemic inflammatory biomarkers into routine clinical practice to identify individuals at higher risk for ocular diseases, thereby facilitating early intervention and management strategies. However, several limitations must be acknowledged. First, this study was unable to establish a causal relationship between systemic inflammatory biomarkers and ocular disease, as it only provided correlational results. Longitudinal analyses or prospective cohort studies can more accurately infer causality by following the same group of participants over time and observing changes in variables. This design allows for a more robust assessment of the impact of systemic inflammation on eye disease and provides a stronger basis for clinical intervention. Therefore, future studies should consider adopting a longitudinal study design to overcome the limitations of cross-sectional studies and further validate the findings of this study. Second, the study population, derived from NHANES data, may not fully represent other populations with differing demographic and clinical characteristics.

Table 5 Associations of systemic inflammatory biomarkers with prevalence of ARMD

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend
SII index		0.282		0.891		0.830
13.750–371.875	1.00		1.00		1.00	
371.876–515.704	0.86 (0.63, 1.16)		0.78 (0.57, 1.06)		0.77 (0.57, 1.05)	
515.705–729.882	0.92 (0.69, 1.25)		0.79 (0.58, 1.08)		0.78 (0.58, 1.06)	
729.883–5120.00	1.14 (0.86, 1.51)		0.95 (0.71, 1.28)		0.94 (0.70, 1.27)	
SIRI		0.038		0.611		0.650
0.060–0.715	1.00		1.00		1.00	
0.725–1.050	0.94 (0.65, 1.35)		0.86 (0.61, 1.21)		0.85 (0.60, 1.21)	
1.051–1.500	1.20 (0.87, 1.67)		1.05 (0.75, 1.46)		1.04 (0.74, 1.45)	
1.501–20.50	1.44 (1.06, 1.97) *		1.12 (0.81, 1.55)		1.11 (0.80, 1.55)	

SII index, systemic immune-inflammation index; ARMD, age-related macular degeneration; SIRI, systemic inflammatory response index; *$P < 0.05$; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty-income ratio, hypertension, diabetes mellitus, smoker, alcohol user; Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, fast glucose, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol

Table 6 Associations of systemic inflammatory biomarkers with prevalence of diabetic retinopathy

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend	OR (95%CI)	*P* for trend
SII index		0.404		0.917		0.777
13.750–371.875	1.00		1.00		1.00	
371.876–515.704	0.98 (0.77, 1.21)		0.97 (0.78, 1.22)		0.96 (0.77, 1.20)	
515.705–729.882	0.89 (0.73, 1.09)		0.95 (0.78, 1.08)		0.93 (0.78, 1.17)	
729.883–5120.00	0.88 (0.72, 1.07)		0.94 (0.77, 1.17)		0.92 (0.76, 1.15)	
SIRI		0.943		0.331		0.597
0.060–0.715	1.00		1.00		1.00	
0.725–1.050	1.01 (0.83, 1.23)		1.14 (0.92, 1.40)		1.13 (0.91, 1.39)	
1.051–1.500	1.07 (0.88, 1.31)		1.19 (0.96, 1.47)		1.17 (0.95, 1.45)	

SII index, systemic immune-inflammation index; SIRI, systemic inflammatory response index; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty-income ratio, hypertension, diabetes mellitus, smoker, alcohol user; Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, fast glucose, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol

Third, the reliance on self-reported ocular disease data for some participants introduces the possibility of misclassification bias. Fourth, the adjustment for confounders is comprehensive, yet residual confounding cannot be ruled out. Finally, additional longitudinal studies are necessary to confirm these findings and elucidate the underlying mechanisms driving these associations.

Conclusion

This study demonstrates significant associations between systemic inflammatory biomarkers and various ocular diseases, providing a basis for future research and potential clinical applications. While these findings highlight the potential value of incorporating systemic inflammatory biomarkers into routine clinical assessments, further investigation is needed to establish causality.

Abbreviations

RCS	Restricted cubic spline
SIRI	Systemic inflammatory response index
ARMD	Age-related macular degeneration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02473-y.

Supplementary material 1
Supplementary material 2
Supplementary material 3
Supplementary material 4
Supplementary material 5
Supplementary material 6
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Supplementary material 8

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Acknowledgements
We would like to express our gratitude to all of the volunteers who participated in the NHANES.

Author contributions
Xue Wang contributed to the hypothesis development and to the drafting of the manuscript; Can Zhang, and Haitao Jiang were responsibility for the data analysis. Xue Wang contributed to the data interpretation and revision of the manuscript. The final manuscript was read and approved by all authors.

Funding
This study was not supported by any project.

Availability of data and materials
Survey data is available for data consumers and researchers all across the globe on the internet (https://www.cdc.gov/nchs/nhanes/).

Declarations

Ethical approval and consent to participate
The National Center for Health Statistics obtained institutional review board approval before collecting data from NHANES participants. Considering that the NHANES data are de-identified and publicly available, Institutional Review Board approval was not required for the analysis presented here.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 June 2024 Accepted: 17 March 2025
Published online: 26 March 2025

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