Clinical science

Systemic inflammatory biomarkers as risk factors for age-related ocular diseases: a large-scale prospective cohort study

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ABSTRACT

Aims To evaluate associations between systemic inflammation biomarkers and incident age-related ocular diseases while also investigating their correlations with retinal structures.

Methods This population-based prospective cohort study analysed 415 599 UK Biobank participants. Systemic immune-inflammation index (SII) and low-grade inflammation score (INFLA-score) were calculated from baseline haematological parameters. Primary outcomes were incident diagnoses of cataract, primary open-angle glaucoma (POAG), age-related macular degeneration (AMD) and diabetic retinopathy (DR). Multivariable Cox proportional hazards models estimated HRs with 95% CIs. Secondary analyses assessed the associations with optical coherence tomography-derived retinal layer thicknesses and vascular features.

Results Over a median 13.0-year follow-up, we identified 44 906 cataract, 5803 POAG, 7388 AMD and 3319 DR incident cases. Both SII and INFLA-score demonstrated significant, dose-dependent associations with all ocular outcomes (all $p<0.05$). Distinct exposure-response patterns emerged: J-shaped relationships for cataract and POAG (SII threshold >500; INFLA-score threshold >0), versus monotonically positive associations for AMD and DR. Elevated inflammatory markers also correlated with retinal thinning, especially in photoreceptor layers.

Conclusions Systemic inflammation biomarkers could predict incident age-related ocular diseases with disease-specific patterns while concurrently associating with quantifiable retinal structural and vascular pathologies. These findings suggest that anti-inflammatory strategies might have potential to mitigate ocular ageing processes, although further evidence on causal mechanisms and interventions is warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although local ocular inflammation is implicated in age-related eye diseases, the role of systemic inflammation in ocular ageing remains unclear, necessitating further investigation.

WHAT THIS STUDY ADDS

⇒ This study suggests that systemic inflammation biomarkers are associated with major age-related ocular diseases with distinct patterns and are concurrently linked to quantifiable retinal structural and vascular changes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that systemic inflammation may be a modifiable risk factor for ocular ageing, highlighting promising targets for future mechanistic and interventional studies aimed at effective preventive strategies.

INTRODUCTION

Cataract, primary open-angle glaucoma (POAG), age-related macular degeneration (AMD) and diabetic retinopathy (DR) are the most common age-related ocular diseases and the leading causes of vision loss and blindness worldwide.[1] Given the escalating disease burden amid a rapidly ageing global population, identifying modifiable risk factors is critical to inform targeted prevention and early intervention strategies.

Systemic inflammation has been implicated in the pathogenesis of numerous chronic diseases, including cardiovascular disorders, diabetes, cancer and dementia.[2–4] However, in the context of ocular health, the eye—as an immune-privileged organ—has traditionally been considered immunologically isolated from systemic influences.[5 6] Only a specific category of ocular conditions, namely ocular inflammatory diseases such as uveitis and scleritis, is associated with systemic immune dysregulation.[7 8] Nevertheless, emerging evidence suggests that inflammation also contributes to the pathophysiology of ageing,[9] suggesting its potential role in ocular ageing as well.[10–12]

A few studies have investigated potential links between systemic inflammation and the four major age-related ocular pathologies. For instance, analyses of the National Health and Nutrition Examination Survey (NHANES) dataset revealed a linear positive association between the systemic immune-inflammation index (SII) and both glaucoma and cataract.[13] Similarly, findings from the Rotterdam Study demonstrated that pro-inflammatory dietary patterns were associated with elevated risks of cataract and AMD.[14] Furthermore, some studies have

reported associations between serum inflammatory markers (eg, C reactive protein (CRP) and tumour necrosis factor-alpha (TNF-α)) and ocular health.[15 16] Additionally, some studies have regarded retinal thickness as a potential inflammatory marker in systemic autoimmune and inflammatory diseases.[17–19] Notably, existing evidence remains limited by methodological constraints including cross-sectional designs that are vulnerable to reverse causality, small sample sizes and reliance on single inflammatory markers that inadequately reflect the complexity of systemic inflammatory states. These limitations preclude definitive conclusions.

To address these gaps, the UK Biobank offers unique advantages: it enables assessment of comprehensive inflammatory profiles using two novel indices—the SII and the low-grade inflammation score (INFLA-score)—coupled with over a decade of longitudinal follow-up data.[20] This prospective investigation aims to provide high-level evidence, potentially revealing novel strategies for delaying ocular ageing and preventing vision loss through modulation of systemic inflammation.

MATERIALS AND METHODS

Study population

The UK Biobank is a prospective cohort study that enrolled over 500 000 individuals from across the United Kingdom. Participants were aged between 37 and 73 years old during the recruitment phase, which took place from 2006 to 2010. Data for the database were collected using various methods, including touchscreen questionnaires, interviews, physical examinations, biological specimens and imaging.[20] Detailed protocols are available at https://www.ukbiobank.ac.uk/. The UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee, and all participants provided their informed consent electronically at the time of recruitment. This work was reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guideline, and conducted under the approved UK Biobank application number 93 118.

Out of the 502 132 participants, we excluded participants: (1) with missing data or extreme outliers of systemic inflammatory indicators (n=59 026); (2) with a history of any of four age-related ocular diseases at baseline (n=29 549) and (3) with a history of eye injury or trauma (n=3033). Specifically, values exceeding 0.5% of the distribution range were identified as extreme outliers to minimise potential bias.[4 21] Detailed coding information is provided in online supplemental table S1. Ultimately, 415 599 participants were included in the analysis.

Assessment of systematic inflammatory indicators

Peripheral blood samples were processed at the UK Biobank central laboratory. Blood cell counts were measured using the clinically validated Coulter LH 750 analyser, with strict adherence to the manufacturer's quality control protocols. Serum CRP levels were quantified via high-sensitivity immunoturbidimetric assays (Beckman Coulter AU5800 system).

The SII and the INFLA-score are novel, comprehensive markers of systemic inflammation. The SII, calculated as (neutrophils×platelets) / lymphocytes, has been widely used to assess inflammatory status across various clinical conditions.[22 23] The INFLA-score, developed to evaluate chronic low-grade inflammation, integrates four validated inflammatory biomarkers: CRP, white blood cell count, platelet count and the neutrophil-to-lymphocyte ratio. To compute the INFLA-score, each biomarker is assigned a value ranging from −4 to 4 based on its decile ranking.[24] The total score is derived by summing these values, yielding a possible range of −16 to 16, where higher values indicate greater systemic inflammation. Relative coding information is provided in online supplemental table S1. We additionally conducted a Bland-Altman analysis comparing inflammatory marker data from the initial assessment (2006–2010) and the first repeat assessment (2012–2013), as shown in online supplemental figure S1. The results demonstrate that approximately 95% of the samples fall within the 95% limits of agreement, indicating fair longitudinal stability and supporting the use of a single baseline measurement as a reliable proxy for longitudinal inflammatory status.[25]

Age-related ocular diseases

This research examined four major age-related ocular diseases: cataract, POAG, AMD and DR. The incidence dates for these conditions were ascertained using hospital inpatient records and self-reported data. The hospital data were retrieved using International Classification of Diseases (ICD) codes for both ICD-10 and ICD-9, consistent with methodologies employed in prior studies.[26 27] Self-reported data on ocular conditions were obtained through verbal interviews and touchscreen queries, such as 'Has a doctor told you that you have any of the following problems with your eyes?'. Detailed coding information is provided in online supplemental table S2. A Venn diagram (online supplemental figure S2) visualises the number of cases for each disease and their overlapping relationships. The incident age distributions of these diseases are demonstrated in online supplemental figure S3. At the time of this analysis, follow-up data were available until 31 October 2022 for England, 31 August 2022 for Scotland and 31 May 2022 for Wales. The follow-up duration was calculated from the date of recruitment until the occurrence of the event of interest or censoring. The primary event of interest was defined as the first diagnosis of each ocular disease. Participants were right-censored at the earliest of: (1) death from any cause, (2) loss to follow-up or (3) administrative country-specific follow-up endpoints.

Covariates

Potential confounding factors encompass sociodemographic factors, lifestyle factors and health-related status[26]: age at the time of recruitment; sex (male/female); ethnicity (British/others); Townsend Deprivation Index (a score representing the deprivation of the participant's neighbourhood as a reflection of their socioeconomic position); alcohol intake frequency, categorised as low (special occasions only or never), moderate (1–3 times a month to 1 or 2 times a week) and high (more than 3 or 4 times a week); smoking status (never/former/current); physical activity, categorised as low (<600 metabolic equivalent (MET)-min/week), moderate (600 to <3000 MET-min/week) and high (≥3000 MET-min/week) based on the International Physical Activity Questionnaire guidelines; body mass index (BMI, calculated based on the weight and standing height); history of hypertension (no/yes) and history of diabetes mellitus (no/yes). Relative coding information is provided in online supplemental table S1.

Optical coherence tomography-derived retinal layer thicknesses

Spectral-domain optical coherence tomography (OCT) imaging of the macula was performed using the Topcon 3D OCT 1000 Mk2 (Topcon), and automatic segmentation of all scans was conducted using Topcon Advanced Boundary Segmentation (V.1.6.1.1). The thickness of specific retinal layers was determined

by measuring the distance between selected boundary lines. Additional details regarding the OCT imaging protocol are available in prior publications.[28–32] In our analysis, we utilised the thicknesses of seven retinal layers, including retinal nerve fibre layer, ganglion cell-inner plexiform layer, inner nuclear layer, outer plexiform plus outer nuclear layer (OP-ONL), photoreceptor segment (PS, comprising both the inner and outer segments of photoreceptors), retinal pigment epithelium-Bruch's membrane complex and overall macular thickness.

According to established quality control standards,[28 29 31 32] we excluded all images with an image quality score <40 and those falling within the poorest 10% according to the inner limiting membrane quality indicator. Individual-level OCT values were calculated as the mean of the available right and left eye measurements; if only one eye had a valid value, that value was used. Relative coding information is provided in online supplemental table S1.

Colour fundus images-derived quantitative retinal vascular features

Details can be found in the online supplemental methods section and the referenced article.[33]

Statistical analysis

Baseline characteristics were summarised as frequencies with percentages for categorical variables and as means with SDs. Group comparisons were performed using independent t-tests or Mann-Whitney U tests for continuous variables and the Pearson χ^2 test for categorical variables. The assumption of normality for continuous variables was assessed using the Anderson-Darling normality test.

The Cox proportional hazards regression model was used to examine the associations between systemic inflammation indicators and age-related ocular diseases. Proportional hazards assumptions were verified using Schoenfeld residuals, with results confirming the assumptions were adequately met. The results were presented as HRs with 95% CIs. For Cox regression analyses assuming linear relationships, we log-transformed and z-score standardised SII values, while standardising INFLA-scores directly to z-scores.[3 4] To identify non-linear relationships, restricted cubic splines (RCS) models were used.

The analysis employed a stepwise approach, adjusting for different sets of confounders progressively across three models to enhance the transparency of the analysis. In Model 1, age and sex are included as covariates; Model 2 builds on Model 1 by incorporating ethnicity, the Townsend deprivation index, alcohol intake frequency, smoking status and physical activity; Model 3 further includes BMI, a history of hypertension and diabetes mellitus. Missing values of covariates were imputed by multiple imputations using chained equations with five imputations and all other covariates as predictors, as implemented in the R package 'mice'.

Subsequent subgroup analyses were conducted stratified by age at baseline (≤60 years, >60 years) and sex (female, male). Potential interaction effects were identified using likelihood ratio tests by comparing Cox models with or without an interaction term of the stratification factor and exposure.

Eight sensitivity analyses were performed to assess the robustness of our findings: (a) excluding participants with a follow-up time of <2 years to minimise the bias of reverse causality; (b) excluding participants with conditions that could impact inflammatory markers, including certain infectious diseases, malignant neoplasms of the hematopoietic system, blood and blood-forming organ diseases, ocular inflammatory diseases and autoimmune diseases; (c) excluding participants with missing values for any covariate; (d) further adjusting for age-squared to account for potential non-linear relationships between age and the outcomes; (e) incorporating diagnostic data from primary care records documented by general practitioners to better capture early or asymptomatic cases[34]; (f) excluding self-reported data and relying solely on hospital-confirmed cases to avoid misclassification bias; (g) additionally adjusting for systematic use of anti-inflammatory medications and (h) additionally adjusting for dietary patterns, quantified by a healthy diet score based on published protocols.[35] The specific details regarding the processing of medication and diet data can be found in the online supplemental methods (online supplemental tables S3 and S4).

All statistical analyses were performed using R V.4.3.0 (R Foundation for Statistical Computing). The statistical tests were two-sided and a p value <0.05 was considered statistically significant. The analysis of retinal layer thicknesses and vascular features was subjected to false discovery rate (FDR) correction using the Benjamini-Hochberg method.

RESULTS

Baseline characteristics

Among the 502 132 UK Biobank participants at baseline, 415 599 met eligibility criteria for analysis. Figure 1 outlines the study design. Over a median follow-up of 13.0 years, we documented 44 906 cataract cases, 5803 POAG cases, 7388 AMD cases and 3319 DR cases. Baseline characteristics are summarised in online supplemental table S5. Participants who developed incident age-related ocular diseases during follow-up tended to exhibit higher BMI, a history of hypertension and diabetes and elevated SII and INFLA-score at baseline, compared with those without such conditions.

Associations between SII, INFLA-score and the risk of age-related ocular diseases

As demonstrated in table 1, both SII and INFLA-score showed significant relationships with the four age-related ocular diseases across all adjusted models. In the fully adjusted Model 3, each unit increase in SII was independently associated with elevated risks of cataract (HR 1.016, 95% CI 1.007 to 1.026; p<0.001), POAG (HR 1.034, 95% CI 1.007 to 1.061; p=0.012), AMD (HR 1.033, 95% CI 1.009 to 1.057; p=0.006) and DR (HR 1.062, 95% CI 1.027 to 1.098; p<0.001). Similarly, per-unit increment in INFLA-score significantly predicted increased risks of cataract (HR 1.040, 95% CI 1.030 to 1.050; p<0.001), POAG (HR 1.034, 95% CI 1.006 to 1.062; p=0.017), AMD (HR 1.052, 95% CI 1.026 to 1.078; p<0.001) and DR (HR 1.123, 95% CI 1.083 to 1.165; p<0.001).

When analysed as categorical variables, participants in the highest SII category (>1500) exhibited significantly greater disease risks (figure 2A): a 21.0% increased risk for cataract (HR 1.210, 95% CI 1.123 to 1.303; p<0.001) and 29.6% for POAG (HR 1.296, 95% CI 1.063 to 1.581; p=0.010), compared with the reference group (300–600). Relative to the lowest SII category (<300), the >1500 group showed 21.7% higher AMD risk (HR 1.217, 95% CI 1.003 to 1.476; p=0.046) and 35.0% greater DR risk (HR 1.350, 95% CI 1.024 to 1.779; p=0.033). Regarding INFLA-score stratification (figure 2B), individuals in the highest quartile (>8) had 13.0% elevated cataract risk (HR 1.130, 95% CI 1.097 to 1.165; p<0.001) and 10.7% higher POAG risk (HR 1.107, 95% CI 1.015 to 1.207; p=0.021)

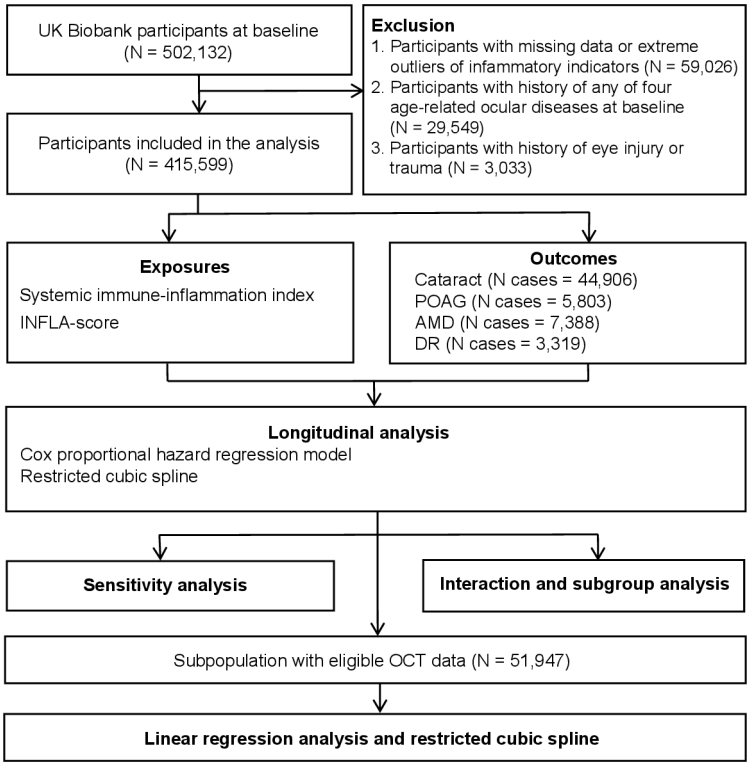

Figure 1 Flow chart of the study design. AMD, age-related macular degeneration; DR, diabetic retinopathy; INFLA-score, low-grade inflammation score; OCT, optical coherence tomography; POAG, primary open-angle glaucoma.

compared with the reference group (−8 to 0). When contrasted with the lowest INFLA-score category (<−8), the >8 group demonstrated more pronounced risk elevations: 26.6% for AMD (HR 1.266, 95% CI 1.130 to 1.419; p<0.001) and 39.1% for DR (HR 1.391, 95% CI 1.161 to 1.667; p<0.001).

Non-linear associations

The RCS analysis presented in figure 3 demonstrates distinct dose-response patterns between inflammatory markers and ocular disease risks. Notably, three significant non-linear relationships emerged: the associations of SII with cataract (P non-linear <0.001) and POAG (P non-linear=0.037), as well as INFLA-score with cataract (P non-linear <0.001). These associations exhibited a J-shaped pattern, with risk curves reaching their inflection point at an SII value of approximately 500, suggesting a potential threshold effect. In contrast, the associations of both SII and INFLA-score with AMD and DR displayed consistently linear trends (all P total <0.01, all P non-linear >0.05), indicating a direct proportional relationship where disease risk escalates progressively with increasing inflammatory marker values.

Sensitivity and subgroup analyses

To assess the robustness of our findings, we performed comprehensive sensitivity analyses employing multiple approaches: exclusion of participants with follow-up duration <2 years (online supplemental figure S4), removal of individuals with baseline immune-related conditions (online supplemental figure S5), elimination of cases with missing covariate data (online supplemental figure S6), additional adjustment for age-squared terms (online supplemental figure S7), incorporation of primary care diagnostic records (online supplemental figure S8), inclusion of only hospital-confirmed cases (online supplemental figure S9),

Table 1 Linear associations between SII, INFLA-score and the risk of age-related ocular diseases

		Model 1		Model 2		Model 3	
Exposure	Outcome	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
SII	Cataract	1.016 (1.007 to 1.026)	<0.001	1.018 (1.009 to 1.028)	<0.001	1.016 (1.007 to 1.026)	<0.001
	POAG	1.033 (1.007 to 1.060)	0.014	1.036 (1.010 to 1.063)	0.007	1.034 (1.007 to 1.061)	0.012
	AMD	1.037 (1.014 to 1.061)	0.002	1.036 (1.012 to 1.060)	0.003	1.033 (1.009 to 1.057)	0.006
	DR	1.069 (1.033 to 1.106)	<0.001	1.073 (1.038 to 1.109)	<0.001	1.062 (1.027 to 1.098)	<0.001
INFLA-score	Cataract	1.077 (1.067 to 1.087)	<0.001	1.060 (1.050 to 1.070)	<0.001	1.040 (1.030 to 1.050)	<0.001
	POAG	1.037 (1.010 to 1.064)	0.007	1.031 (1.004 to 1.059)	0.024	1.034 (1.006 to 1.062)	0.017
	AMD	1.083 (1.058 to 1.109)	<0.001	1.067 (1.042 to 1.093)	<0.001	1.052 (1.026 to 1.078)	<0.001
	DR	1.431 (1.382 to 1.481)	<0.001	1.339 (1.293 to 1.387)	<0.001	1.123 (1.083 to 1.165)	<0.001

SII, systemic immune-inflammation index; INFLA-score, low-grade inflammation score; POAG, primary open-angle glaucoma; AMD, age-related macular degeneration; DR, diabetic retinopathy.

A

Disease	SII	Number of Cases/Person-Years	HR (95%CI)	P value
Cataract	< 300	4403/501990	1.043 (1.010-1.077)	0.010
	300 - 600	23029/2720512	1[Ref]	
	600 - 1500	16750/1946799	1.030 (1.009-1.050)	0.004
	≥ 1500	724/68175	1.210 (1.123-1.303)	< 0.001
POAG	< 300	579/519278	1.061 (0.971-1.160)	0.192
	300 - 600	2930/2810217	1[Ref]	
	600 - 1500	2193/2013024	1.057 (1.000-1.117)	0.050
	≥ 1500	101/71057	1.296 (1.063-1.581)	0.010
AMD	< 300	676/518976	1[Ref]	
	300 - 600	3796/2807341	1.013 (0.933-1.100)	0.754
	600 - 1500	2794/2011121	1.048 (0.963-1.140)	0.275
	≥ 1500	122/71027	1.217 (1.003-1.476)	0.046
DR	< 300	328/520367	1[Ref]	
	300 - 600	1622/2815612	1.009 (0.895-1.136)	0.889
	600 - 1500	1309/2016883	1.098 (0.972-1.241)	0.134
	≥ 1500	60/71216	1.350 (1.024-1.779)	0.033

B

Disease	INFLA-score	Number of Cases/Person-Years	HR (95%CI)	P value
Cataract	< -8	3066/447123	0.996 (0.958-1.035)	0.827
	-8 - 0	16579/2082079	1[Ref]	
	0 - 8	19159/2104187	1.045 (1.023-1.067)	< 0.001
	≥ 8	6102/604089	1.130 (1.097-1.165)	< 0.001
POAG	< -8	450/459016	1.061 (0.958-1.175)	0.257
	-8 - 0	2172/2146260	1[Ref]	
	0 - 8	2461/2179766	1.074 (1.013-1.139)	0.016
	≥ 8	720/628534	1.107 (1.015-1.207)	0.021
AMD	< -8	450/459085	1[Ref]	
	-8 - 0	2761/2144233	1.123 (1.017-1.242)	0.023
	0 - 8	3153/2177598	1.150 (1.041-1.272)	0.006
	≥ 8	1024/627550	1.266 (1.130-1.419)	< 0.001
DR	< -8	152/460150	1[Ref]	
	-8 - 0	973/2151093	1.021 (0.860-1.213)	0.811
	0 - 8	1536/2183841	1.200 (1.013-1.421)	0.035
	≥ 8	658/628995	1.391 (1.161-1.667)	< 0.001

Figure 2 Associations of (A) SII and (B) INFLA-score with incident cataract, POAG, AMD and DR. HRs and 95% CIs were calculated by Cox proportional hazards regression models. AMD, age-related macular degeneration; DR, diabetic retinopathy; INFLA-score, low-grade inflammation score; POAG, primary open-angle glaucoma; SII, systemic immune-inflammation index.

adjustment for systematic use of anti-inflammatory medications (online supplemental figure S10) and adjustment for dietary patterns (online supplemental figure S11). These rigorous sensitivity analyses consistently demonstrated stable effect estimates, with all associations remaining materially unchanged from our primary findings.

Interaction analyses identified significant effect modifications by demographic factors (online supplemental table S6). Age substantially modified the associations of both SII (P-interaction=0.03) and INFLA-score (P-interaction <0.001) with DR risk, with more pronounced detrimental effects observed in younger compared with older populations (online supplemental table S7). Furthermore, sex significantly modified the INFLA-score-DR association (online supplemental table S6), with females exhibiting greater HR than males at equivalent levels of INFLA-score elevation (online supplemental table S7).

The impact of SII and INFLA-score on retinal thickness and vascular features

To provide structural evidence for the aforementioned association, we further analysed the relationship between systemic inflammation and retinal thickness. Figure 4A presents a schematic diagram of retinal layers. Figure 4B demonstrates the linear associations between these two inflammatory markers and the thickness of various retinal layers. The analysis revealed that SII was significantly associated with thinning of the OP-ONL (β −0.120; FDR=0.015), while INFLA-score showed significant correlations with thinning of OP-ONL (β −0.197; FDR <0.001), PS (β −0.130; FDR <0.001) and overall macular thickness (β −0.449; p<0.001). Figure 4C illustrates the association patterns between the two inflammatory markers and overall macular thickness. SII exhibited a non-linear relationship (P non-linear=0.005) similar to the aforementioned findings, where macular thickness decreased with increasing SII values beyond 500. In contrast, INFLA-score demonstrated a consistent linear negative correlation with overall macular thickness (P non-linear=0.079). In addition, the associations between SII,

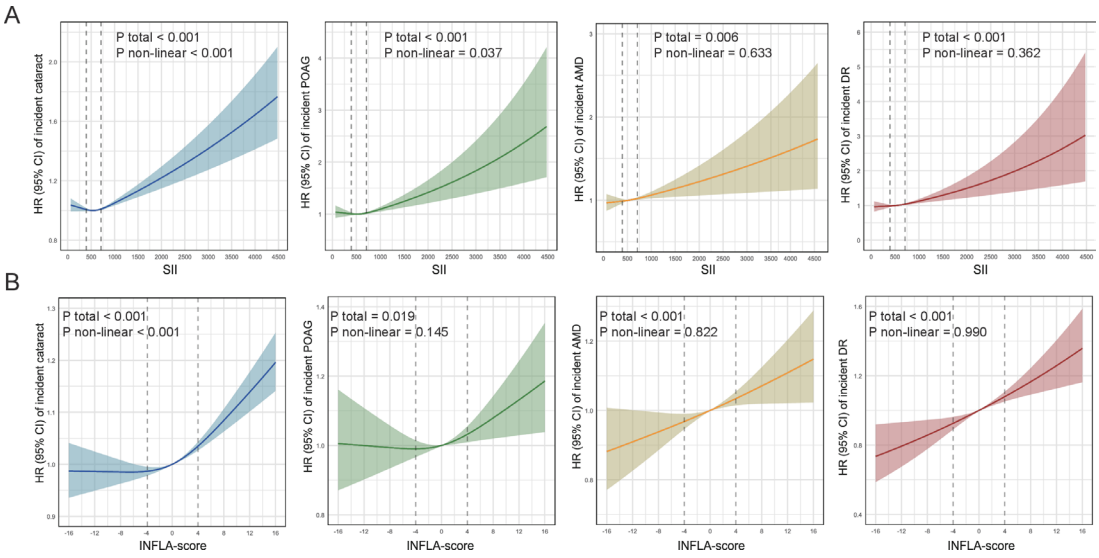

Figure 3 Restricted cubic splines of the associations of (A) SII and (B) INFLA-score with incident cataract, POAG, AMD and DR. Data were fully adjusted for model 3. AMD, age-related macular degeneration; DR, diabetic retinopathy; INFLA-score, low-grade inflammation score; POAG, primary open-angle glaucoma; SII, systemic immune-inflammation index.

INFLA-score and eight quantitative retinal vascular features are presented in online supplemental table 12. Our results show significant positive correlations between SII and the combined tortuosity density of the vasculature (β=0.015; FDR=0.011), as well as between INFLA and the central retinal arteriolar equivalent (β=0.015; FDR=0.019). And both SII and INFLA exhibited significant positive correlations with the central retinal venular equivalent (β=0.027 and 0.079; both FDR <0.001). These findings underscore the potential role of systemic inflammation in retinal neurodegeneration, structural changes and vascular dysfunction.

DISCUSSION

This prospective cohort study comprehensively examined the associations between systemic inflammation indicators and age-related ocular diseases within the large UK Biobank cohort, revealing both linear and non-linear dose-response relationships. Sensitivity analyses confirmed the robustness of our findings, while subgroup analyses highlighted population-specific heterogeneity in these associations. Moreover, the research provides novel structural evidence by demonstrating the effects of systemic inflammation on retinal thickness and vascular parameters.

Due to factors such as the blood-ocular barrier, limited lymphatic drainage, and the local expression of immunosuppressive factors like transforming growth factor-beta (TGF-β) and alpha-melanocyte-stimulating hormone (α-MSH), the human eye has long been recognised for its immune privilege.[6] As a result, it is often shielded from systemic insults. However, emerging evidence has challenged this paradigm, suggesting that chronic inflammation contributes to the pathophysiology of age-related ocular diseases.[10–12] Our findings provide direct epidemiological evidence linking comprehensive systemic inflammation indices (SII and INFLA-score) to both disease onset and structural retinal damage, thereby questioning the absolute nature of ocular immune privilege.[5]

Notably, we observed distinct association patterns: J-shaped relationships for cataract and POAG, vs monotonically positive trends for AMD and DR. This contrasts with previous NHANES findings reporting linear SII-cataract/glaucoma associations and U-shaped (AMD) or L-shaped (DR) relationships.[13] These discrepancies may reflect differences in study design (prospective vs cross-sectional) or sample size (>400 000 vs <6000 participants). The threshold effects observed for cataract and POAG suggest that the eye may maintain immune homeostasis up to certain inflammation levels, beyond which compensatory anti-inflammatory pathways become overwhelmed. Specifically, SII >500 and INFLA-score >0 may represent critical thresholds where systemic inflammation begins to directly impact ocular tissues. The observed associations between inflammatory indices and retinal thickness further provide structural insights, particularly the vulnerability of photoreceptor-related layers. This aligns with known mechanisms of inflammatory-mediated neurodegeneration and suggests these structures may serve as early markers of ocular inflammation.[16 30 36] Moreover, the potential association between systemic inflammation and increased vascular tortuosity, along with thickening or dilation of both arterioles and venules in the retina, may suggest an underlying mechanism related to vascular dysfunction and haemodynamic abnormalities.[37–40] Taken together, these findings suggest that maintaining systemic inflammation within optimal ranges could represent a potential prevention strategy, with SII and INFLA-score serving as biomarkers that could be useful for risk stratification.[14 15]

Mechanistically, several pathways may underlie these observed associations, including disruption of the blood-retinal barrier, adhesion and infiltration of immune cells, release of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β), and activation of inflammation-related cascades (eg, NF-κB and NLRP3 inflammasome pathways).[5 8 10–12 15] These inflammatory processes could collectively lead to structural and functional damage to tissues including lens, trabecular meshwork, retinal ganglion cells, photoreceptors, and vascular endothelial cells.[12 41–44] A groundbreaking recent study has for the first time identified the existence of lymphatic vessels in the eye, specifically within the optic nerve sheath, which provides a potential anatomical pathway for immune communication.[45]

In subgroup analyses, the systemic inflammation-DR association was more pronounced in younger participants compared with older adults, which may be due to the age-related elevation in baseline inflammatory status coupled with reduced inflammatory dynamics,[9] or selective survival

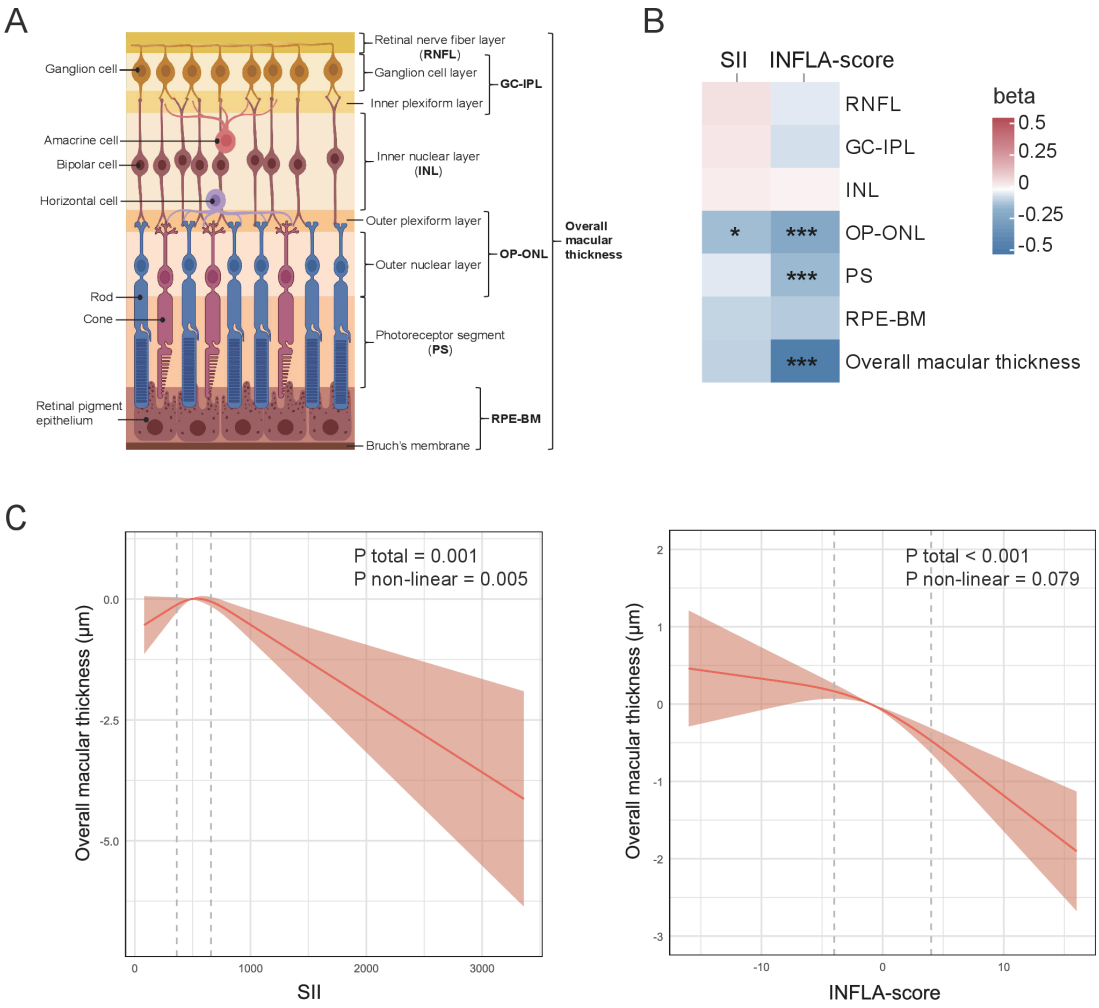

Figure 4 Associations between systemic inflammation biomarkers and retinal thickness parameters. (A) Schematic representation of retinal layer anatomy. (B) Linear correlations between these two inflammatory markers and the thickness of individual retinal layers. (C) Restricted cubic splines of the association patterns between the two inflammatory markers and overall macular thickness. Data were fully adjusted for model 3. The colour represents the β coefficient. *FDR<0.05, ***FDR<0.001. FDR, false discovery rate; INFLA-score, low-grade inflammation score; SII, systemic immune-inflammation index.

bias where high-risk individuals with severe inflammation may have succumbed to competing risks before developing advanced DR.[46 47]

This study has several notable strengths, including its large-scale prospective design with 415 599 participants, comprehensive assessment of both linear and non-linear relationships, potential clinical translation of threshold effects for prevention strategies, and novel structural evidence derived from retinal thickness and vasculature analyses. However, certain limitations should be acknowledged. First, the reliance on single-timepoint measurements of inflammatory markers may lead to exposure misclassification, although the Bland-Altman analysis demonstrated fair longitudinal stability and robustness. Second, while incorporating primary care data, excluding self-reported data, and making extensive adjustments, misclassification bias of outcomes and residual confounding may still exist, though these factors did not substantially alter our conclusions. Third, healthy volunteer bias is inherent in the study design, but research suggests that relative risk estimates may still be broadly applicable.[48 49] Finally, due to the observational nature of the study, clinical translation requires caution. Further mechanistic studies on vascular and inflammatory interactions, along with randomised controlled trials exploring the therapeutic potential of anti-inflammatory agents, represent promising avenues for future research.

CONCLUSIONS

This study demonstrates significant positive associations of systemic inflammation indicators (SII and INFLA-score) with cataract, POAG, AMD and DR, while revealing distinct disease-specific non-linear relationships. Notably, elevated systemic inflammation correlated with retinal thinning, especially in photoreceptor layers and vascular pathology. These findings suggest the potential clinical value of incorporating systemic inflammatory biomarkers into ocular disease risk stratification, as well as the possible therapeutic promise of anti-inflammatory interventions. Further research into causal mechanisms and interventions is crucial for clinical translation.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The UK Biobank study is conducted in accordance with the principles of the Declaration of Helsinki and has received ethical approval from the North West Haydock Research Ethics Committee (#21/NW/0157). The project is registered under the Integrated Research Application System with the ID 299116. Informed consent was obtained from all individual participants during the recruitment process. Participants gave informed consent to participate in the study before taking part.

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