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Original article

# The inflammatory potential of diet is associated with the risk of age-related eye diseases

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SUMMARY

*Background & aims:* Inflammation is involved in the pathogenesis of cataract, age-related macular degeneration (AMD), and possibly open-angle glaucoma (OAG). We assessed whether the inflammatory potential of diet (quantified using the dietary inflammatory index; DII) affects the incidence of these common blinding age-related eye diseases. Serum inflammation markers were investigated as possible mediators.

*Methods:* Participants aged >45 years were selected from the prospective, population-based Rotterdam Study. From 1991 onwards, every 4–5 years, participants underwent extensive eye examinations. At baseline, blood samples and dietary data (using food frequency questionnaires) were collected. The DII was adapted based on the data available. Of the 7436 participants free of eye diseases at baseline, 4036 developed incident eye diseases during follow-up (cataract = 2895, early-intermediate AMD = 891, late AMD = 81, OAG = 169).

*Results:* The adapted DII (aDII) ranged from −4.26 (i.e., anti-inflammatory) to 4.53 (i.e., pro-inflammatory). A higher aDII was significantly associated with increased inflammation. A higher neutrophil-lymphocyte ratio (NLR) was associated with an increased risk of cataract and AMD. Additionally, complement component 3c (C3c) and systemic immune-inflammation index (SII) were associated with increased risks of cataract and late AMD, respectively. Every point increase in the aDII was associated with a 9% increased risk of cataract (Odds ratio [95% confidence interval]: 1.09 [1.04–1.14]). The NLR and C3c partly mediated this association. We also identified associations of the aDII with risk of AMD (early-intermediate AMD, OR [95% CI]: 1.11 [1.03–1.19]; late AMD, OR [95% CI]: 1.24 [1.02–1.53]). The NLR partly mediated these associations. The aDII was not associated with OAG.

*Conclusions:* A pro-inflammatory diet was associated with increased risks of cataract and AMD. Particularly the NLR, a marker of subclinical inflammation, appears to be implicated. These findings are relevant for patients with AMD and substantiate the current recommendations to strive for a healthy lifestyle to prevent blindness.



## 1. Introduction

Chronic low-grade inflammation plays an important role in the pathogenesis of multiple chronic non-communicable diseases, including several eye diseases. Cataract, age-related macular degeneration (AMD), and open-angle glaucoma (OAG) are

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**Abbreviations**

| | |
|---|---|
| AMD | Age-related Macular Degeneration |
| C3c | Complement component 3c |
| C4 | Complement component 4 |
| (a)DII | (Adapted) Dietary Inflammatory Index |
| eQQ | empirical Quantile–Quantile |
| GA | Geographic Atrophy |
| HFA | Humphrey Field Analyzer |
| IOP | Intraocular Pressure |
| L | Lymphocyte |
| MET | Metabolic Equivalent of Task |
| N | Neutrophil |
| NLR | Neutrophil-Lymphocyte Ratio |
| OAG | Open-Angle Glaucoma |
| OCT | Optical Coherence Tomography |
| P | Platelet |
| RPE | Retinal Pigment Epithelium |
| RS | Rotterdam Study |
| SII | Systemic Immune-inflammation Index |
| SMD | Standardized Mean Difference |
| T | Tertile |
| T2D | Type 2 Diabetes Mellitus |
| WARMGS | Wisconsin Age-related Maculopathy Grading System |

the leading causes of blindness worldwide [1]. Cataract is a common complication of chronic intraocular inflammation (e.g., chronic uveitis) as well as chronic systemic and/or topical corticosteroid therapy [2]. In AMD, soft drusen (the main characteristic of AMD; deposits under the retina) contain many mediators of chronic low-grade inflammation, e.g., C-reactive protein (CRP) and complement-related proteins. The complement system mediates chronic inflammation in intermediate, atrophic, and neovascular AMD [3]. Additionally, recent studies have also suggested that inflammatory responses are involved in the pathogenesis of OAG [4].

The emerging evidence of chronic inflammation playing a role in major degenerative diseases has stimulated research into the influence of nutrition and dietary patterns on inflammatory indices [5]. A traditional Mediterranean dietary pattern, characterized by a high intake of fruits, vegetables, legumes, and grains, has shown anti-inflammatory effects in comparison to typical dietary patterns consumed in North America and Northern Europe. The Mediterranean diet has previously been associated with numerous beneficial health outcomes [6–11]. Nutrition has been suggested to impact the risk of age-related eye diseases as well [12,13]. The Mediterranean diet has been linked to a lower risk of AMD [14]. The evidence regarding associations between nutrition and cataract is inconclusive, and scarce for associations with OAG [13]. Epidemiological nutritional research faces challenges due to the fact that dietary guidelines are typically established based on country or regional considerations. This is due to variations in the prevalence of nutrient imbalances and diet-related public health issues, as well as notable disparities across countries in dietary habits and traditions [15]. This makes it difficult to compare and generalize results to other populations. To address this limitation, the dietary inflammatory index (DII) was developed. This index offers a quantitative method to assess the impact of diet on inflammation-mediated health outcomes. Importantly, it is designed to be applicable to any human population, facilitating comparisons across diverse populations [16]. It is a literature-based index calculated from 45 nutrients and food components that have been associated with inflammation: a high index indicates a pro-inflammatory potential of the diet and a low index indicates anti-inflammatory potential of the diet [17]. Given the relative novelty of the DII, there have not been extensive investigations regarding its association with age-related eye diseases. Only one case–control study has reported an association between the DII and cataract [18].

Therefore, we aimed to investigate the association between the DII and incident cataract, to address causality. Furthermore, we assessed whether the DII was also associated with AMD and OAG. Serum inflammation markers were investigated as possible mediators.

## 2. Material & methods

### 2.1. Ethics statement

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent following the declaration of Helsinki to participate in the study and to have their information obtained from their treating physicians.

### 2.2. Study population

The study population included participants from the Rotterdam Study (RS, combining the first three cohorts); a population-based prospective cohort study designed to assess determinants of age-related diseases in the middle-aged and elderly population (45+ years). Enrolment took place from 1991 onwards with response rates varying between 65 and 78%. Participants underwent extensive examinations at baseline and subsequent follow-up visits that took place every 4–5 years [19]. We included a total of 7436 participants who, at baseline, were free of eye diseases and provided dietary data (Fig. 1). All participants had at least one follow-up visit with a reliable ophthalmic examination. Follow-up duration was calculated from baseline until the last visit with reliable ophthalmic examination or until the first visit in which the eye disease under study was detected.

### 2.3. Ophthalmic assessment

The eye examinations included visual acuity testing, Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland), visual field testing (24-2 SITA standard test, Humphrey Field Analyzer; HFA II 740; Carl Zeiss, Oberkochen, Germany), fundus photography (Topcon TRV-50VT, Topcon Optical Company, Tokyo, Japan for the first three visits of the first cohort and Topcon TRC 50EX, and the Sony DXC-950P digital camera for the remaining visits), and optical coherence tomography (SD-OCT, Topcon Optical Company, since 2007) centered on macula and on optic disc.

Cataract was defined as evidence of lens opacities and best-corrected visual acuity <1.0 (20/20), cataract diagnosed by an ophthalmologist based on slit-lamp examination, or presence of pseudophakia. The severity or type of cataract was not determined. Participants with aphakia were excluded [20].

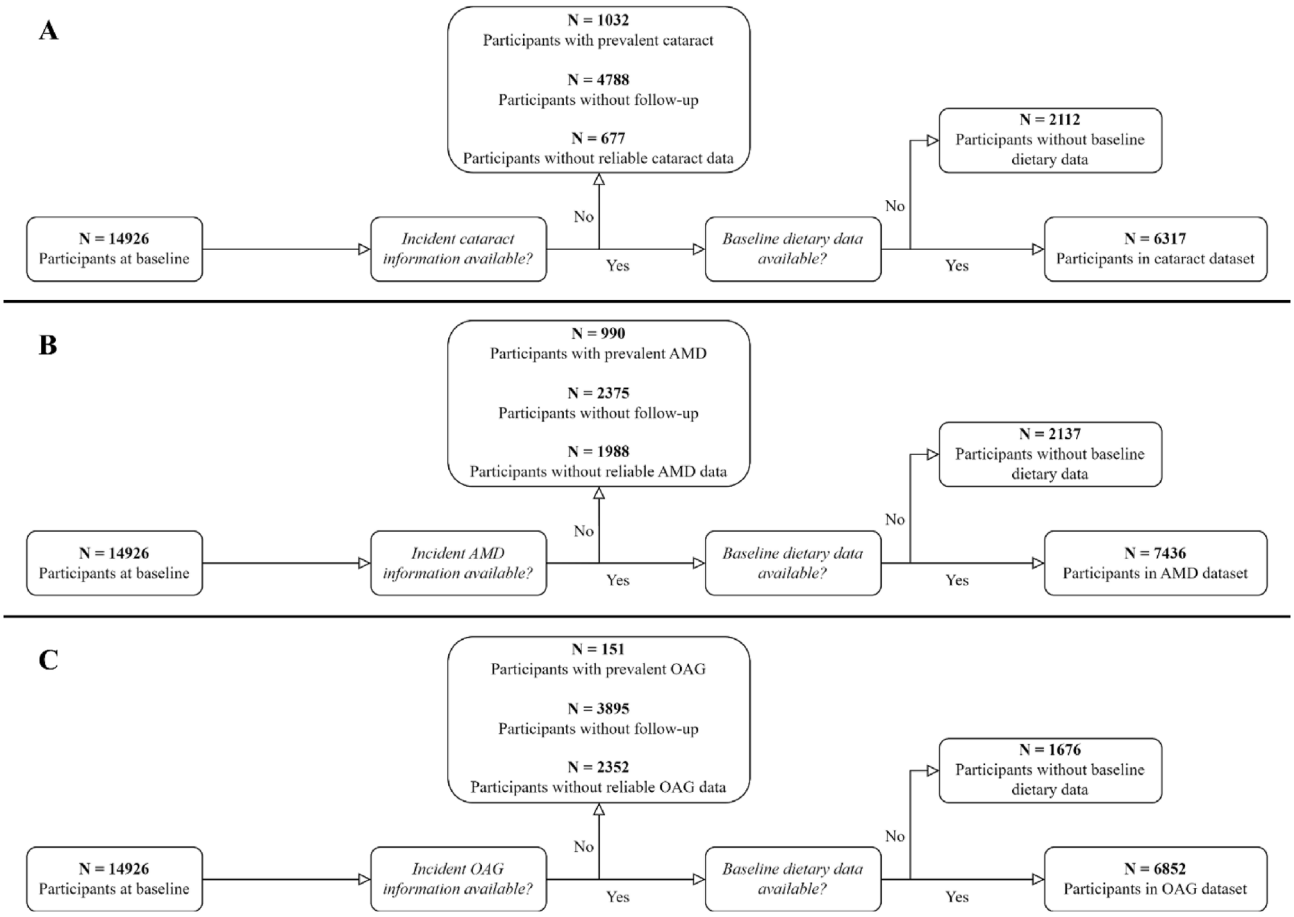


**Fig. 1.** Study design: inclusion of participants in the cataract (A), age-related macular degeneration (AMD; B), and open-angle glaucoma (OAG; C) datasets is described. Participants of the first three independent cohorts of the Rotterdam Study were combined (N = 14,926) and analyzed for incident eye diseases. Participants with eye diseases at baseline (i.e., prevalent cases) were excluded. Additionally, participants without follow-up or without reliable ophthalmic data were removed. Lastly, we excluded participants without (reliable) baseline dietary data. The final dataset for cataract included 6317 participants (3422 controls and 2895 cases); the final dataset for AMD included 7436 participants (3380 controls, 3084 preliminary AMD, 891 early-intermediate AMD, and 81 late AMD); and the final dataset for OAG included 6852 participants (6683 controls and 169 cases).

AMD features – drusen in varying size, type, and area; hyperpigmentation; retinal pigment epithelium (RPE) degeneration; geographic atrophy (GA) [21]; choroidal neovascularization [22]; and mixed late AMD – were graded by experienced graders on color fundus photographs according to a modified version of the Wisconsin Age-related Maculopathy Grading System (WARMGS). Features were confirmed on OCT, near-infrared and fundus autofluorescence. AMD features were grouped into stages according to RS classification [23]: No AMD (absence of lesions), preliminary AMD (or "age-related changes"; only drusen $\leq$63 μm, only soft distinct drusen, or presence of pigment changes without soft drusen), early AMD (presence of only soft indistinct drusen $\geq$125 μm, only reticular pseudodrusen, or soft distinct drusen of 63–125 μm with pigmentary changes), intermediate AMD (presence of soft indistinct drusen with pigmentary changes or reticular pseudodrusen with pigmentary changes), and late AMD (presence of geographic atrophy, choroidal neovascularization, or both). Early and intermediate AMD stages are originally considered sequential AMD severity classes, but are often grouped as they do not have distinct clinical boundaries. Both categories can convert to late AMD, hence not every patient passes through the intermediate stage. We therefore combined the two stages as a common risk category. Any AMD was classified as the presence of early AMD, intermediate AMD, or late AMD. Preliminary AMD represents "age-related changes" without significant clinical morbidity; it would not be classified as AMD in routine clinical practice. Thus, we excluded this stage from our definition of any AMD.

To assess whether visual field loss was present, all participants underwent visual field testing using the HFA. A second supra-threshold test was performed when a visual field defect appeared to be present. Details have been described elsewhere [24]. If the second supra-threshold test showed at least one overlapping abnormality in the same hemifield, Goldmann kinetic perimetry (first and third visit of the first cohort; Haag-Streit, Köniz, Switzerland) or full-threshold HFA (all other cohort visits) was performed on both eyes. If abnormalities were consecutive and reproducible, thus present on the Goldmann or full-threshold test and on both supra-threshold tests, visual field loss was considered to be present. Defects had to be in a consistent hemifield and at least one depressed test point had to have exactly the same location on all fields. Glaucoma specialists examined fundus photographs, ophthalmic examination reports, medical histories, and magnetic resonance imaging (MRI) scans of the brain to exclude all other possible causes of visual field loss. Discrepancies were resolved by consensus. OAG was defined as glaucomatous visual field loss in at least one eye with reproducibility of the defect, independent of the intraocular pressure (IOP, the main risk factor for OAG) [24]. OAG cases had an open anterior chamber angle and no history or signs of secondary glaucoma. The IOP was measured three times per eye, of which the median value was recorded. For OAG cases, we used the

measurement of the affected eye. If both eyes were affected or unaffected, a random eye was selected.

### 2.4. Serum inflammation markers

At baseline, fasting blood samples were collected at the study center. Samples were stored at −80 °C until laboratory measurements were performed. Full blood count measurements were performed using the COULTER® AcT diff2™ Hematology Analyzer (Beckman Coulter, San Diego, California, USA). CRP, complement component 3c (C3c), and complement component 4 (C4) levels were measured using a particle enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). The neutrophil-lymphocyte ratio (NLR) was calculated with the formula: NLR = granulocytes/lymphocytes. The platelet-lymphocyte ratio (PLR) was calculated with the formula: PLR = peripheral platelets/lymphocytes. The systemic immune-inflammation index (SII) was calculated with the formula: SII = peripheral platelets*-granulocytes/lymphocytes. All the inflammatory markers are either ratios or indices and as such do not have a unit. Details have been described earlier [25].

### 2.5. Dietary data

Dietary intake was assessed at baseline using food frequency questionnaires (FFQs) as described in detail elsewhere [26]. In short, dietary intake for the first two cohorts was assessed using a 170-item FFQ, applied as two-stage approach. First, participants indicated which foods they consumed at least twice a month in the preceding year. Second, a trained dietician used this list to identify how often and in which amounts the foods were consumed. For the third cohort, dietary intake data were collected using an extended self-administered 389-item FFQ. Both FFQs were previously validated and showed reasonable to good estimates of nutrient intake [27–29]. All food items were assessed based on the frequency of consumption (in times per month or per week), the number of servings per day (expressed in standardized household measures) as well as on the preparation methods. Participants with unreliable reported dietary intake (energy intake <500 kcal/day or >5000 kcal/day; N = 84) were excluded [30]. In Fig. 1, these participants are included in the group of participants without baseline dietary data. In order to calculate the DII, first, specific overall inflammatory effect indices were calculated for all specific food parameters, indicating whether it was overall considered anti-inflammatory (index below zero) or pro-inflammatory (index above zero). Individuals' consumption was expressed relative to a standard global mean as a Z-score [17]. To minimize the effect of right skewing, this value was converted to a percentile score. To achieve a symmetrical distribution with values centered on 0 (null) and bounded between −1 (maximally anti-inflammatory) and +1 (maximally pro-inflammatory), each percentile index was doubled and then '1' was subtracted. The centered percentile value for each food parameter was then multiplied by its respective 'overall food parameter-specific inflammatory effect index' to obtain the 'food parameter-specific DII'. Finally, all 'food parameter-specific DII' were summed to create the 'overall DII' for an individual. The DII originally consists of a mixture of 8 pro-inflammatory nutrients, 19 anti-inflammatory nutrients, 10 whole foods and spices, caffeine, flavan-3-ol, flavones, flavonols, flavanones, anthocyanidins, and isoflavones [17]. In the present study, we combined the participants from the three cohorts of the Rotterdam Study to improve the sample size and statistical power. As described earlier, different FFQs were used to obtain the dietary data. As a result, data on some of the components was only available in one or two cohorts. Therefore, we opted to include only the 25 components that were available in all three cohorts (Supplemental Table 1). We will refer to this adapted version of the DII (aDII) throughout the remainder of the manuscript. We used the aDII as continuous variable as well as categorical variable, where we divided the participants in tertiles. Participants in the first tertile had an anti-inflammatory aDII with a mean ± standard deviation (SD) of −1.7 ± 0.7. Participants in the second tertile had a neutral aDII with a mean ± SD of 0.0 ± 0.4. Participants in the third tertile had a pro-inflammatory aDII with a mean ± SD of 1.7 ± 0.8. Tertiles were always calculated based on the participants included in the analyses of the respective eye disease and may therefore differ slightly between disease outcomes.

### 2.6. Covariates

All covariates were assessed at baseline. The participants' height and weight were measured at the research center, and their body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters [31]. Physical activity, expressed in metabolic equivalent of task (MET) hours per week, was assessed using a validated adapted version of either the Zutphen Physical Activity Questionnaire (first two cohorts) [32] or the LASA Physical Activity Questionnaire (third cohort) [33]. Since the total activity scores from these questionnaires are not one on one comparable, standardized Z-scores were used instead. Education level was assessed with questionnaires and categorized into: primary education, lower education, intermediate education, or higher education. Questionnaires were also used to assess the smoking status of the participants. Participants were classified as never smoker, previous smoker, or current smoker. Hypertension was defined as a resting blood pressure exceeding 140/90 mmHg or the use of blood pressure-lowering medication (diuretics, beta-blockers, calcium channel blockers, and renin-angiotensin-aldosterone system modifying agents) [34]. Type 2 diabetes mellitus (T2D) was defined as either having a fasting serum glucose exceeding 7.0 mmol/L, a non-fasting serum glucose level exceeding 11.1 mmol/L, or using blood glucose-lowering medication [20]. General practitioners' records and hospital discharge letters were also monitored for presence of T2D. Total cholesterol measurements were done on fasting serum samples with the Hitachi automatic analyzer (Boehringer Mannheim) [35].

### 2.7. Statistical analyses

All serum inflammation markers were log(+1) transformed and standardized preceding the analyses. We addressed the association of the aDII with inflammation markers by performing multivariable linear regression analyses calculating beta's with corresponding 95% confidence intervals (CIs). We modeled the aDII continuously per point increase and in tertiles with the first tertile (T1) serving as reference to test for linear trends. The median value for each category as continuous variable was used in separate linear regression models. Next, we assessed the association between inflammation markers and incident eye diseases, using multivariable logistic regression analyses, calculating odds ratio's (ORs) with corresponding 95% CIs. Subsequently, we analyzed the association between the aDII and incident eye diseases, using a similar approach. To assess potential reverse causality, we also performed these analyses in cumulative follow-up intervals. We modeled the aDII continuously per point increase and in tertiles with T1 serving as reference to test for linear trends. The median value for each category as continuous variable was used in separate logistic regression models. All analyses were adjusted for age, sex, BMI, energy intake, and follow-up time (model 1). We additionally adjusted for lifestyle factors (model 2; smoking status, education level, and physical activity) or comorbidities (model 3;

hypertension, T2D, and total cholesterol). The maximally-adjusted model (model 4) included all aforementioned covariates. Categorical variables were included in the model using dummy coding, creating binary variables for each category of the categorical variables. The reference groups for sex, smoking status, education level, hypertension, and T2D were male, never smoker, primary education, no hypertension, and no T2D, respectively. Furthermore, where appropriate, we tested whether inflammation markers were mediators in the relationship between the aDII and incident eye diseases, using the R package 'mediation'. We implemented a bootstrap approach (with 1000 simulations) to estimate the mediated effect. Mediation was considered present when the average causal mediation effect was significant [36]. Since age has a very strong positive association with all eye diseases under study and a strong inverse association with dietary intake [37,38], and dietary intake is different for females compared to males [39], we also performed propensity score matching on age and sex (Supplemental Methods). Statistical analyses were performed using R v3.6.1 (R Inc., Boston, MA, USA). We considered a P-value <0.05 as statistically significant.

## 3. Results

Among the 7436 participants who did not have any eye disease at baseline, 4036 individuals developed an eye disease during the follow-up period. This included 2895 cases of cataract, 891 cases of early-intermediate AMD, 81 cases of late AMD, and 169 cases of OAG. Additionally, 3084 participants showed preliminary signs of AMD. The aDII in the present study ranged from −4.26 (i.e., maximally anti-inflammatory) to 4.53 (i.e., maximally pro-inflammatory). Baseline characteristics of participants stratified on aDII tertiles are presented in Table 1.

Participants with a higher aDII were older and had a lower energy intake and education level. Additionally, they were more often female. Overall, participants with a pro-inflammatory diet had a worse lifestyle and overall health: their physical activity was lower, they smoked more frequently, they had a higher total cholesterol level, and they were more frequently diagnosed with hypertension and T2D. Moreover, cataract and AMD were more frequently diagnosed in participants with a high aDII.

### 3.1. The aDII and inflammation markers

Every point increase in the aDII was significantly associated with higher CRP (Beta [95% CI]: 0.05 [0.03–0.07], P-trend <0.001), NLR (Beta [95% CI]: 0.06 [0.04–0.08], P-trend <0.001), SII (Beta [95% CI]: 0.05 [0.03–0.07], P-trend <0.001), and C3c (Beta [95% CI]: 0.06 [0.04–0.07], P-trend <0.001). There was no significant association between the aDII and PLR or C4. Only the significant inflammation markers (Table 2, model 4) were included in the subsequent analyses.

### 3.2. Inflammation markers and incident eye diseases

NLR and C3c were significantly associated with an increased risk of cataract (Table 3, model 4; OR [95% CI]: 1.16 [1.08–1.24] per SD and OR [95% CI]: 1.11 [1.03–1.20] per SD, respectively). For AMD, both NLR and SII were associated with increased risks (Table 3, model 4; any AMD, OR [95% CI]: 1.19 [1.08–1.30] per SD and OR [95% CI]: 1.11 [1.01–1.21] per SD). In particular, the NLR tended to increase the risk of more severe AMD (preliminary AMD, OR [95% CI]: 1.10 [1.03–1.18] per SD; early-intermediate AMD, OR [95% CI]: 1.14 [1.04–1.25] per SD; late AMD, OR [95% CI]: 1.61 [1.27–2.04] per SD). When stratifying on disease severity, the SII was only

**Table 1**
Baseline characteristics of participants by tertiles (T) of the adapted dietary inflammatory index.

| | T1 (N = 2454) | T2 (N = 2454) | T3 (N = 2528) | P-value |
|---|---|---|---|---|
| Age, years | 60.3 (7.1) | 63.9 (7.7) | 65.4 (8.0) | <0.001 |
| Female sex, N (%) | 1298 (52.9) | 1391 (56.7) | 1650 (65.3) | <0.001 |
| BMI, kg/m$^2$ | 26.9 (3.8) | 26.7 (3.8) | 26.8 (4.1) | 0.19 |
| Energy intake, kcal/day | 2455.9 (626.1) | 2052.5 (467.0) | 1774.2 (444.9) | <0.001 |
| Adapted dietary inflammatory index[a] | −1.7 (0.7) | 0.0 (0.4) | 1.7 (0.8) | <0.001 |
| Physical activity, MET hours/week | 0.1 (0.9) | 0.1 (0.9) | 0.0 (1.0) | <0.001 |
| Education,[b] N (%) | | | | <0.001 |
| Primary education | 216 (8.8) | 343 (14.0) | 447 (17.7) | |
| Lower education | 916 (37.3) | 1058 (43.1) | 1107 (43.8) | |
| Intermediate education | 698 (28.4) | 732 (29.8) | 695 (27.5) | |
| Higher education | 608 (24.8) | 305 (12.4) | 269 (10.6) | |
| Smoking status, N (%) | | | | <0.001 |
| Never smoker | 734 (29.9) | 798 (32.5) | 874 (34.6) | |
| Previous smoker | 1226 (50.0) | 1125 (45.8) | 964 (38.1) | |
| Current smoker | 481 (19.6) | 519 (21.1) | 681 (26.9) | |
| Hypertension, N (%) | 1250 (50.9) | 1355 (55.2) | 1488 (58.9) | <0.001 |
| Type 2 diabetes mellitus, N (%) | 227 (9.3) | 215 (8.8) | 303 (12.0) | <0.001 |
| Total cholesterol, mmol/L | 5.9 (1.1) | 6.3 (1.2) | 6.6 (1.3) | <0.001 |
| Cataract,[c] N (%) | 723 (32.0) | 1033 (50.2) | 1139 (56.9) | <0.001 |
| AMD, N (%) | | | | <0.001 |
| Preliminary AMD | 915 (37.3) | 1056 (43.0) | 1113 (44.0) | |
| Early-intermediate AMD | 218 (8.9) | 326 (13.3) | 347 (13.7) | |
| Late AMD | 15 (0.6) | 29 (1.2) | 37 (1.5) | |
| Open-angle glaucoma,[d] N (%) | 53 (2.2) | 51 (2.3) | 65 (3.0) | 0.14 |

Data are presented as mean (standard deviation), unless stated otherwise. Data of the complete population (N = 7436) are depicted and tertiles were calculated based on these participants.
Abbreviations: N = number; BMI = body mass index; MET = metabolic equivalent of task; AMD = age-related macular degeneration.
[a] Range: −4.26 to 4.53.
[b] Education: lower education was defined as lower/intermediate general education or lower vocational education; intermediate education was defined as intermediate vocational education or higher general education; higher education was defined as higher vocational education or university.
[c] Only available in a subset of participants (N = 6317; T1 = 2258, T2 = 2058, T3 = 2001).
[d] Only available in a subset of participants (N = 6852; T1 = 2457, T2 = 2237, T3 = 2158).

**Table 2**
Association of the adapted dietary inflammatory index and serum inflammation markers.

| | | Beta[a] (95% CI) | P-value | T1 | T2 | T3 | P-trend[b] |
|---|---|---|---|---|---|---|---|
| CRP | Model 1 | 0.08 (0.06–0.09) | <0.001 | 0.00 | 0.16 (0.10–0.21) | 0.26 (0.20–0.33) | <0.001 |
| | Model 2 | 0.05 (0.04–0.07) | <0.001 | 0.00 | 0.13 (0.07–0.19) | 0.20 (0.13–0.27) | <0.001 |
| | Model 3 | 0.07 (0.05–0.09) | <0.001 | 0.00 | 0.15 (0.09–0.21) | 0.24 (0.17–0.30) | <0.001 |
| | Model 4 | 0.05 (0.03–0.07) | <0.001 | 0.00 | 0.12 (0.06–0.18) | 0.18 (0.11–0.25) | <0.001 |
| NLR | Model 1 | 0.07 (0.05–0.09) | <0.001 | 0.00 | 0.14 (0.07–0.20) | 0.23 (0.16–0.30) | <0.001 |
| | Model 2 | 0.06 (0.04–0.09) | <0.001 | 0.00 | 0.12 (0.06–0.19) | 0.21 (0.13–0.29) | <0.001 |
| | Model 3 | 0.07 (0.05–0.09) | <0.001 | 0.00 | 0.14 (0.08–0.21) | 0.24 (0.16–0.31) | <0.001 |
| | Model 4 | 0.06 (0.04–0.08) | <0.001 | 0.00 | 0.13 (0.06–0.20) | 0.21 (0.13–0.28) | <0.001 |
| PLR | Model 1 | 0.00 (−0.02–0.02) | 0.91 | 0.00 | 0.00 (−0.07–0.06) | −0.01 (−0.08–0.07) | 0.81 |
| | Model 2 | 0.02 (0.00–0.04) | 0.09 | 0.00 | 0.01 (−0.06–0.08) | 0.04 (−0.04–0.12) | 0.32 |
| | Model 3 | 0.00 (−0.02–0.02) | 0.96 | 0.00 | 0.00 (−0.07–0.06) | −0.01 (−0.08–0.07) | 0.85 |
| | Model 4 | 0.02 (−0.01–0.04) | 0.13 | 0.00 | 0.01 (−0.06–0.08) | 0.03 (−0.05–0.11) | 0.44 |
| SII | Model 1 | 0.05 (0.03–0.07) | <0.001 | 0.00 | 0.10 (0.03–0.17) | 0.18 (0.10–0.25) | <0.001 |
| | Model 2 | 0.05 (0.03–0.07) | <0.001 | 0.00 | 0.08 (0.01–0.15) | 0.16 (0.08–0.24) | <0.001 |
| | Model 3 | 0.05 (0.03–0.08) | <0.001 | 0.00 | 0.10 (0.03–0.17) | 0.18 (0.10–0.26) | <0.001 |
| | Model 4 | 0.05 (0.03–0.07) | <0.001 | 0.00 | 0.08 (0.01–0.15) | 0.15 (0.07–0.23) | <0.001 |
| C3c | Model 1 | 0.07 (0.05–0.09) | <0.001 | 0.00 | 0.16 (0.10–0.23) | 0.28 (0.21–0.35) | <0.001 |
| | Model 2 | 0.06 (0.04–0.08) | <0.001 | 0.00 | 0.15 (0.09–0.21) | 0.26 (0.19–0.34) | <0.001 |
| | Model 3 | 0.06 (0.04–0.07) | <0.001 | 0.00 | 0.16 (0.09–0.22) | 0.22 (0.15–0.29) | <0.001 |
| | Model 4 | 0.06 (0.04–0.07) | <0.001 | 0.00 | 0.14 (0.08–0.21) | 0.21 (0.14–0.28) | <0.001 |
| C4 | Model 1 | 0.02 (0.00–0.04) | 0.05 | 0.00 | 0.07 (0.00–0.13) | 0.11 (0.03–0.18) | 0.006 |
| | Model 2 | 0.01 (−0.01–0.04) | 0.20 | 0.00 | 0.06 (−0.01–0.13) | 0.09 (0.01–0.17) | 0.03 |
| | Model 3 | 0.01 (−0.01–0.03) | 0.24 | 0.00 | 0.06 (−0.01–0.13) | 0.07 (−0.01–0.15) | 0.07 |
| | Model 4 | 0.01 (−0.01–0.03) | 0.24 | 0.00 | 0.05 (−0.02–0.12) | 0.05 (−0.03–0.13) | 0.18 |

Model 1: adjusted for age, sex, body mass index, energy intake, and follow-up time. Model 2: model 1 additionally adjusted for smoking status, education level, and physical activity. Model 3: model 1 additionally adjusted for hypertension, type 2 diabetes mellitus, and total cholesterol. Model 4: model 1 additionally adjusted for smoking status, education level, physical activity, hypertension, type 2 diabetes mellitus, and total cholesterol.
Abbreviations: CI = confidence interval; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio; SII = systemic immune-inflammation index; C3c = complement component 3c; C4 = complement component 4.
[a] Beta's (95% confidence interval) for serum inflammation markers by the adapted dietary inflammatory index (as continuous variable) analyzed using linear regression.
[b] Test for trend conducted using median value for each tertile (T1 = −1.60, T2 = 0.04, T3 = 1.60).

**Table 3**
Association of serum inflammation markers and the incident eye diseases.

| | | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Cataract | CRP | 1.04 (0.98–1.11) | 0.20 | 1.05 (0.99–1.12) | 0.12 | 1.04 (0.97–1.10) | 0.27 | 1.05 (0.98–1.12) | 0.15 |
| | NLR | 1.16 (1.09–1.24) | <0.001 | 1.16 (1.08–1.24) | <0.001 | 1.17 (1.09–1.25) | <0.001 | 1.16 (1.08–1.24) | <0.001 |
| | SII | 1.06 (0.99–1.13) | 0.07 | 1.06 (0.99–1.13) | 0.08 | 1.07 (1.00–1.14) | 0.06 | 1.06 (0.99–1.14) | 0.07 |
| | C3c | 1.13 (1.05–1.21) | 0.001 | 1.12 (1.05–1.21) | 0.002 | 1.11 (1.03–1.19) | 0.009 | 1.11 (1.03–1.20) | 0.009 |
| Any AMD | CRP | 1.05 (0.97–1.14) | 0.24 | 1.03 (0.94–1.13) | 0.46 | 1.07 (0.98–1.18) | 0.12 | 1.05 (0.96–1.15) | 0.29 |
| | NLR | 1.16 (1.06–1.27) | <0.001 | 1.18 (1.08–1.29) | <0.001 | 1.18 (1.08–1.29) | <0.001 | 1.19 (1.08–1.30) | <0.001 |
| | SII | 1.07 (0.99–1.17) | 0.11 | 1.10 (1.01–1.21) | 0.03 | 1.09 (1.00–1.20) | 0.05 | 1.11 (1.01–1.21) | 0.03 |
| | C3c | 1.01 (0.91–1.12) | 0.92 | 1.01 (0.91–1.13) | 0.83 | 1.01 (0.91–1.12) | 0.87 | 1.02 (0.91–1.14) | 0.76 |
| Preliminary AMD | CRP | 1.03 (0.98–1.09) | 0.26 | 1.01 (0.95–1.08) | 0.66 | 1.03 (0.96–1.09) | 0.42 | 1.01 (0.95–1.08) | 0.68 |
| | NLR | 1.10 (1.03–1.17) | 0.004 | 1.11 (1.04–1.19) | 0.001 | 1.09 (1.02–1.17) | 0.007 | 1.10 (1.03–1.18) | 0.004 |
| | SII | 1.05 (0.99–1.12) | 0.11 | 1.07 (1.00–1.14) | 0.03 | 1.05 (0.99–1.12) | 0.13 | 1.06 (0.99–1.13) | 0.08 |
| | C3c | 1.02 (0.96–1.10) | 0.49 | 1.03 (0.96–1.10) | 0.48 | 1.03 (0.96–1.10) | 0.46 | 1.02 (0.95–1.10) | 0.51 |
| Early-intermediate AMD | CRP | 1.04 (0.96–1.13) | 0.34 | 1.03 (0.93–1.13) | 0.58 | 1.06 (0.97–1.16) | 0.22 | 1.04 (0.94–1.15) | 0.42 |
| | NLR | 1.12 (1.02–1.22) | 0.02 | 1.14 (1.04–1.25) | 0.007 | 1.14 (1.04–1.25) | 0.006 | 1.14 (1.04–1.25) | 0.007 |
| | SII | 1.03 (0.95–1.13) | 0.47 | 1.06 (0.97–1.16) | 0.20 | 1.06 (0.96–1.16) | 0.24 | 1.07 (0.97–1.17) | 0.18 |
| | C3c | 0.99 (0.89–1.10) | 0.83 | 1.00 (0.89–1.11) | 0.94 | 1.00 (0.89–1.11) | 0.93 | 1.00 (0.90–1.12) | 0.95 |
| Late AMD | CRP | 1.18 (0.93–1.48) | 0.15 | 1.15 (0.89–1.46) | 0.26 | 1.26 (0.99–1.58) | 0.05 | 1.22 (0.94–1.54) | 0.12 |
| | NLR | 1.56 (1.25–1.95) | <0.001 | 1.60 (1.26–2.02) | <0.001 | 1.59 (1.27–2.00) | <0.001 | 1.61 (1.27–2.04) | <0.001 |
| | SII | 1.60 (1.26–2.05) | <0.001 | 1.66 (1.28–2.17) | <0.001 | 1.58 (1.23–2.04) | <0.001 | 1.62 (1.25–2.12) | <0.001 |
| | C3c | 1.18 (0.86–1.61) | 0.30 | 1.19 (0.86–1.62) | 0.30 | 1.17 (0.74–1.61) | 0.36 | 1.18 (0.84–1.63) | 0.33 |
| OAG | CRP | 0.94 (0.79–1.11) | 0.47 | 0.95 (0.79–1.12) | 0.55 | 0.95 (0.79–1.13) | 0.58 | 0.95 (0.79–1.12) | 0.55 |
| | NLR | 1.08 (0.92–1.26) | 0.36 | 1.08 (0.91–1.26) | 0.37 | 1.08 (0.92–1.27) | 0.34 | 1.08 (0.92–1.27) | 0.34 |
| | SII | 0.97 (0.83–1.14) | 0.73 | 0.98 (0.83–1.15) | 0.77 | 0.99 (0.84–1.16) | 0.89 | 0.99 (0.84–1.17) | 0.92 |
| | C3c | 1.06 (0.87–1.29) | 0.55 | 1.06 (0.87–1.29) | 0.55 | 1.05 (0.85–1.29) | 0.65 | 1.06 (0.86–1.30) | 0.60 |

Multi-variable adjusted odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) of cataract, age-related macular degeneration (AMD), and open-angle glaucoma (OAG), as a function of the serum inflammation markers (per standard deviation increase) were determined using logistic regression. Model 1: adjusted for age, sex, body mass index, energy intake, and follow-up time. Model 2: model 1 additionally adjusted for smoking status, education level, and physical activity. Model 3: model 1 additionally adjusted for hypertension, type 2 diabetes mellitus, and total cholesterol. Model 4: model 1 additionally adjusted for smoking status, education level, physical activity, hypertension, type 2 diabetes mellitus, and total cholesterol. Abbreviations: CI = confidence interval; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; SII = systemic immune-inflammation index; C3c = complement component 3c.

associated with late AMD (OR [95% CI]: 1.62 [1.25–2.12] per SD). None of the serum inflammation markers were significantly associated with OAG (Table 3).

### 3.3. The aDII and incident cataract

A pro-inflammatory diet was associated with a higher risk of cataract (Fig. 2A, model 4; OR [95% CI]: 1.09 [1.04–1.14] per point). There was a significant trend between a higher aDII and increased risk of cataract (Fig. 2A, P-trend = 0.02). The NLR and C3c mediated 7.5% (95% CI: 3.1–15.2%, P-value <0.001) and 4.8% (95% CI: 0.8–14.3%, P-value = 0.01) of this association.

### 3.4. The aDII and incident AMD

Every point increase in the aDII was associated with a 12% increase in any AMD (Fig. 2B, model 4; OR [95% CI]: 1.12 [1.04–1.20]). There was a significant trend between a higher aDII and increased risk of any AMD (Fig. 2B, P-trend = 0.007). In particular, the NLR mediated 7.5% (95% CI: 2.0–29.0%, P-value = 0.008) of this association.

When looking at the different stages of AMD, we observed a significant association of the aDII with early-intermediate AMD (Fig. 2E, model 4, OR [95% CI]: 1.11 [1.03–1.19] per point) and late AMD (Fig. 2F, model 4, OR [95% CI]: 1.24 [1.02–1.53] per point), but not preliminary AMD (Fig. 2D, model 4, OR [95% CI]: 1.02 [0.97–1.07] per point). Trends were present for the association of a higher aDII with increased risk of early-intermediate AMD (Fig. 2E, P-trend = 0.01) and late AMD (Fig. 2F, P-trend = 0.06). The NLR showed a significant causal mediation effect in the association of the aDII with early-intermediate AMD (P-value = 0.02) and late AMD (P-value = 0.006). The proportion mediated was significant for the association with early-intermediate AMD (6.2%, 95% CI: 0.6–33.0%, P-value = 0.03), but not late AMD (10.2%, 95% CI: −40.1–94.0%, P-value = 0.11).

### 3.5. The aDII and incident OAG

In the maximally-adjusted model (Fig. 2C, model 4), we observed no significant association between a higher aDII and increased risk of OAG (OR [95% CI]: 1.09 [0.95–1.24] per point). A higher aDII was not associated with higher OAG risk (P-trend = 0.68). We also did not observe a significant association between the aDII and IOP (model 4, Beta [95% CI]: −0.03 [−0.10–0.04] per point).

### 3.6. The aDII and incident eye diseases: cumulative follow-up intervals

All previously reported associations remained consistent across every cumulative follow-up interval (Supplemental Fig. 1).

### 3.7. Associations in age and sex-matched participants

Performing all aforementioned analyses in age and sex-matched participants provided similar results (Supplemental Results).

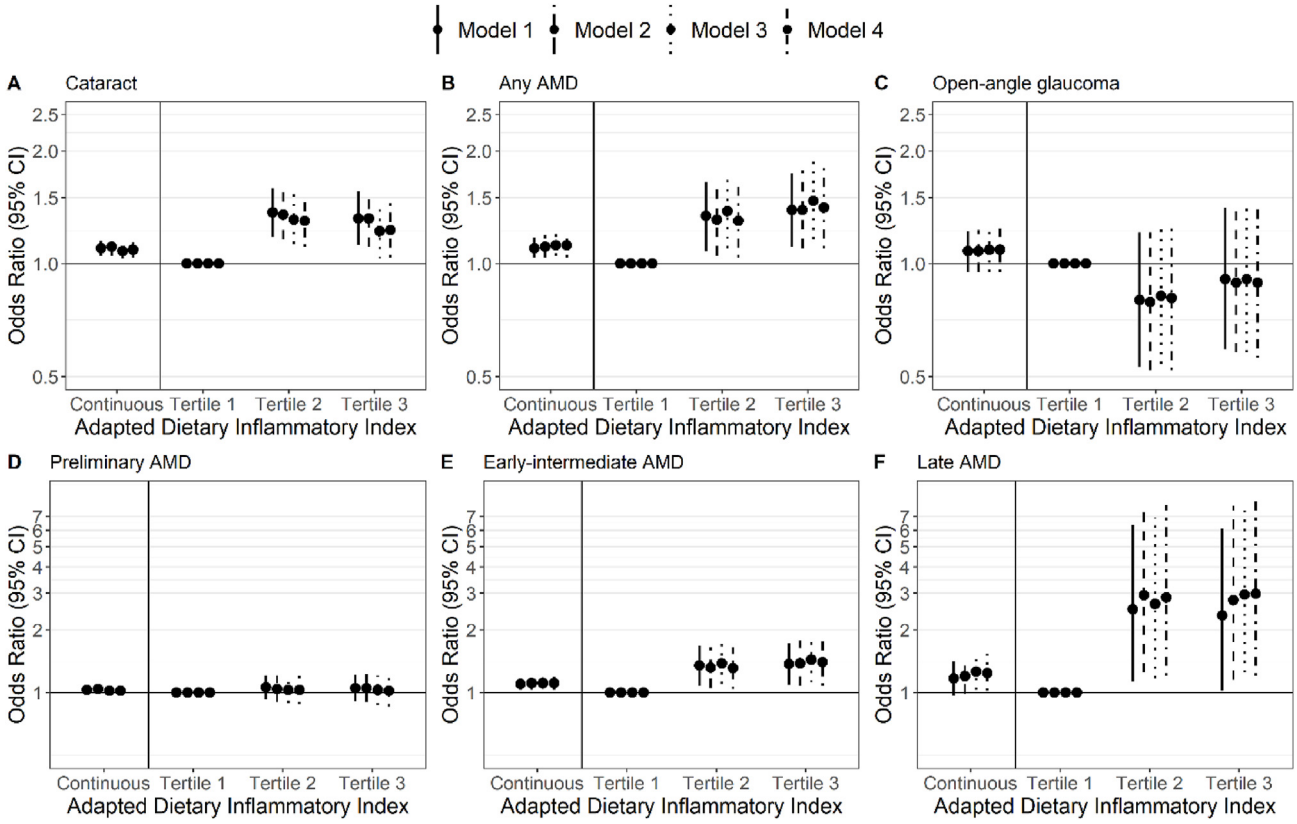


**Fig. 2.** Graphs showing associations between the adapted dietary inflammatory index and incident age-related eye diseases. The top row includes the results of cataract (A), any age-related macular degeneration (AMD; B), and open-angle glaucoma (C). The bottom row shows the results of AMD stratified on disease severity, including the results of preliminary AMD (D), early-intermediate AMD (E), and late AMD (F). Multivariable-adjusted odds ratios with corresponding 95% confidence intervals (CIs) for incident age-related eye diseases are shown as a function of the adapted DII as continuous variable (left side of the graph) and per tertile (right side of the graph), and were determined by logistic regression. Model 1: adjusted for age, sex, body mass index, energy intake, and follow-up time. Model 2: model 1 additionally adjusted for smoking status, education level, and physical activity. Model 3: model 1 additionally adjusted for hypertension, type 2 diabetes mellitus, and total cholesterol. Model 4: model 1 additionally adjusted for smoking status, education level, physical activity, hypertension, type 2 diabetes mellitus, and total cholesterol.

## 4. Discussion

In this large prospective population-based cohort, we observed that a pro-inflammatory diet was associated with an increased risk of cataract. Additionally, a higher aDII was also associated with an increased risk of (more severe) AMD. NLR, a marker that mirrors the balance between acute- and chronic inflammation and the adaptive immune system, partly mediated these associations. This striking finding may be particularly relevant for patients with AMD, and raises the intriguing possibility of inflammation triggering disease pathogenesis.

Previously, an adverse association between the DII and cataract risk (OR [95% CI]: 1.51 [1.13–2.03] per point) was reported [18]. We observed a similar association, while addressing causality. We did not determine the type of cataract. Inflammation may play a more important role in the development of nuclear cataract than posterior subcapsular cataract and cortical cataract [40,41]. While nuclear cataract remains the most prevalent form among the general population, it's important to acknowledge the potential inclusion of other types of cataracts, which could have influenced the observed associations. The associations reported in this study may even be stronger when looking at nuclear cataract only. In the present study, both the NLR and C3c partly mediated the association between the aDII and cataract. NLR, a marker of subclinical inflammation, is emerging as a prognostic biomarker for many diseases, including stroke, lung disease, and cancer [42]. Changes over time are considered a sign of immune system derangement [43]. Previously, significantly increased NLRs were found in diabetic senile cataract, indicating that systemic inflammation may underlie cataract formation [44]. Moreover, the NLR has been associated with retinal artery and retinal vein occlusion [45,46], retinitis pigmentosa [47], dry eye disease [48], keratoconus [49], diabetic retinopathy [50], and glaucoma [51–54]. To date, only one association between serum C3 levels and cataract has been reported [55]. Shao et al. reported that serum C3 levels were lower in participants with cataract, which contradicts our findings. However, their study was hampered by a cross-sectional, case–control study design (e.g., unable to address reverse causality). Moreover, there is a difference between C3 and C3c. Activation of both the classical and alternative pathways lead to C3 conversion with generation of various activation fragments. Activation-related complement split products, such as C3c, may better reflect ongoing inflammation [56].

In this study, we assessed the associations of serum inflammation markers and the aDII with different stages of AMD. Participants with preliminary AMD (or "age-related changes") may or may not progress to more advanced stages of AMD. We were able to show that a more pro-inflammatory diet was not associated with the risk of preliminary AMD (or "age-related changes"), but was associated with a higher risk of more advanced stages of AMD. Moreover, we confirmed previous findings that (late) AMD patients have higher NLRs than those without AMD [57,58]. In contrast to the present study, these cross-sectional studies were not able to address causality. SII is a systemic immune-inflammatory marker of which the underlying physiological processes are not fully understood. The role for SII in the pathogenesis of AMD is unclear. Interestingly, an increased SII has been associated with other eye diseases, such as keratoconus [59], retinal vein occlusion [60], dry eye disease [61], uveitis [62], and retinopathy of prematurity [63]. Lastly, dysregulation of the complement cascade has been implicated in the pathogenesis of AMD [64]. In the present study, we were only able to investigate C3c, for which we did not observe significant associations. Similarly, this product was not associated with AMD in previous literature [65].

Research into dietary interventions and OAG risk are scarce. However, several studies have hinted towards a protective effect of diets, dietary components, and nutrients with anti-inflammatory properties. Vitamin C supplementation [66], greater intake of green leafy vegetables [67], and greater intake of dietary nitrate [68,69], were associated with a decreased risk of glaucoma. Also, greater adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay diet lowered incidence of OAG [70]. This diet is rich in nutrients (e.g., folate, vitamin E, lutein-zeaxanthin, flavonoids) that are known for their anti-inflammatory and antioxidant properties [71]. As data on important components for OAG, e.g., vitamin B9 (folate) and flavonoids, were lacking in the present study (Supplemental Table 1), this may potentially explain our non-significant association (P-value = 0.22) between the aDII and incident OAG.

A limitation of our study is the necessity to adapt the DII to accommodate missing data, thereby restricting the comparability of our study and potentially influencing the observed associations to some extent. This adaptation may also have reduced the representation of certain pro-inflammatory or anti-inflammatory components, potentially affecting the accuracy of the DII calculation. Nevertheless, the aDII was associated with several inflammation markers, suggesting it did predict the anti- and pro-inflammatory potential of diet. We used a 170-item and 389-item FFQ to determine the dietary intake of the participants. Although both FFQs were previously validated and showed reasonable to good estimates of nutrient intake [27–29], it is possible that they do not capture the full dietary diversity and nuances of participants' diets. Nevertheless, this would most likely introduce non-differential misclassification. By utilizing FFQs, we depended on participants' memory to gather information spanning up to a year, posing a risk of either under- or over-reporting of certain components. Also, data collected at baseline may not reflect long-term intake as participants may change dietary habits over time. Specific dietary recommendations are provided for people with or at risk for AMD. If those participants adapted their diet prior to study participation, this could have introduced differential misclassification. Nevertheless, this would have resulted in a bias towards the null, i.e., underestimating the true effect. Although the DII was designed to improve generalizability, it is possible that the association between the DII and age-related eye diseases is different across ethnicities. As our study population is mainly from European descent, our results may not be translatable to all ethnic populations. Lastly, the use of a population-based design limited the number of participants with incident late AMD and OAG.

The prospective population-based design is also an important strength of this study, since randomized intervention studies are not feasible due to the slowly progressing nature of the age-related eye diseases under study. This prospective study plays an important role in generating valuable hypotheses and identifying potential associations in a real-world setting. By measuring the exposure (diet or inflammation) at baseline before the occurrence of any age-related eye disease and then following participants over time, we established a temporal sequence where exposure preceded the outcome. This temporal order is a required criterion for assessing causality in observational studies. Additionally, this approach helped mitigate selection bias, as all participants included in the study were free of eye diseases at the time of exposure determination. By assessing the association between the aDII and incident eye diseases over cumulative follow-up periods (Supplemental Fig. 1), we observed that reversed causality is unlikely as the associations remained consistent over time. The availability of robust data on possible confounders allowed us to reach independent associations between the aDII and incident eye diseases. We used different models with increasing number of covariables. Additional adjustment for lifestyle factors and/or comorbidities did not clearly change the observed associations. Although we adjusted for multiple confounders, it is possible that additional confounding factors

may have influenced the results; however, we were unable to account for these variables, potentially introducing bias into the reported associations in this study. These factors can include, but are not limited to, genetic predisposition for the eye disease under study, use of specific medications, and other (lifestyle) factors. Through the execution of mediation analyses, we demonstrated that specific inflammatory markers are involved in the mechanism through which the aDII impacts the incidence of cataract and AMD. The results of the analyses including propensity score matched participants only (Supplemental Results) were very similar to the results described in the main manuscript. Therefore, we presented the results including the highest number of participants. The similarity between the main results and supplemental results shows that it is very unlikely that our findings were affected by the association of age and sex with dietary intake.

## 5. Conclusion

A higher aDII was significantly associated with higher risks of cataract and AMD, but not OAG. These associations were partly mediated by NLR, a marker that mirrors the balance between acute- and chronic inflammation and the adaptive immune system. These findings are relevant for patients with AMD and substantiate the current recommendations to strive for a healthy lifestyle to prevent blindness.

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## Author contribution

JEV: conceptualization, methodology, formal analysis, writing - original draft, writing - review and editing, visualization. EFT: conceptualization, methodology, writing - original draft. TOEdC: conceptualization, methodology, writing - review and editing. JCKdJ: data curation, methodology, writing - review and editing. MAMS: methodology, writing - review and editing. TV: conceptualization, data curation, methodology, writing - review and editing, funding acquisition. CCWK: data curation, writing - review and editing, supervision, funding acquisition. WDR: conceptualization, methodology, writing - review and editing, supervision, funding acquisition.

## Data availability statement

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Due to restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

## Conflicts of interest

CCWK: Consultant – Bayer, Laboratoires Théa, Novartis.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.10.008.

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