

Dietary inflammatory potential and glaucoma susceptibility: a nationally representative study from NHANES

Hui-Min Shan¹, Yong Tao^{1,2}

¹Department of Ophthalmology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

²National Engineering Research Center for Ophthalmology, Engineering Research Center of Ophthalmic Equipment and Materials, Ministry of Education, Beijing 100111, China

Correspondence to: Yong Tao. Department of Ophthalmology, Beijing Chaoyang Hospital, Capital Medical University, No.8, South Road of Worker's Stadium, Chaoyang District, Beijing 100020, China. taoyong@mail.ccmu.edu.cn

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Abstract

• **AIM:** To evaluate the association between pro-inflammatory dietary patterns, as quantified by the dietary inflammatory index (DII), and the prevalence of glaucoma.

• **METHODS:** This population-based study used data from the National Health and Nutrition Examination Survey (2005-2008). DII scores were calculated based on nutrient data derived from dietary questionnaires. The association between DII scores and glaucoma risk was assessed using sample-weighted, covariate-adjusted multivariable logistic regression models, with further stratified analyses performed across subgroups.

• **RESULTS:** A total of 5659 eligible participants aged 40-85y were included, of whom 383 (6.7%) had glaucoma and 5276 (93.3%) did not. After adjustment for covariates, participants in the highest DII tertile had a 1.35-fold increased risk of glaucoma [odds ratio (OR)=1.35, 95% confidence interval (CI): 1.03-1.79], with a significant linear trend (P for trend=0.034). Restricted cubic spline analysis further verified the association between DII scores and glaucoma risk ($P=0.043$). In subgroup analyses, a significant positive association between higher DII scores and elevated glaucoma risk was observed in males (OR for tertile 3 vs 1=1.48, 95%CI: 1.02-2.15; P for trend =0.049), participants with diabetes (OR=1.56, 95%CI: 1.04-2.34; P for trend =0.028), and participants with obesity (OR=1.66, 95%CI: 1.07-2.58; P for trend =0.023).

• **CONCLUSION:** A pro-inflammatory diet, reflected by higher DII scores, is positively associated with an increased risk of glaucoma among U.S. adults. These findings suggest that anti-inflammatory dietary interventions may serve as a potential preventive strategy against glaucoma.

• **KEYWORDS:** glaucoma; chronic inflammation; diet; dietary inflammatory index; National Health and Nutrition Examination Survey

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INTRODUCTION

Glaucoma represents the leading cause of irreversible blindness worldwide, affecting an estimated over 80 million individuals globally^[1]. Its insidious onset and asymptomatic progression in early stages often result in delayed diagnosis and significant visual impairment, which cannot be restored by current therapeutic interventions, emphasizing the urgent need for evidence-based prophylactic interventions^[2].

Glaucoma, a progressive neurodegenerative disorder, involves the progressive degeneration of retinal ganglion cells (RGCs) and concomitant anatomical deterioration of the optic nerve. While elevated intraocular pressure (IOP) persists as the strongest documented risk factor, emerging evidence suggests that glaucoma pathogenesis involves a complex interplay of vascular, genetic, and inflammatory mechanisms. The pathogenesis and advancement of glaucoma involve multiple underlying pathophysiological pathways and contributory factors, including oxidative stress and mitochondrial dysfunction^[3], neurovascular coupling and ischemia^[4], genetic predisposition^[5], mechanical stress and biomechanics^[6], and immune and inflammatory pathways^[7]. Emerging evidence underscores the pivotal contribution of systemic inflammation to glaucoma pathogenesis, contributing to RGCs damage and optic nerve degeneration^[8].

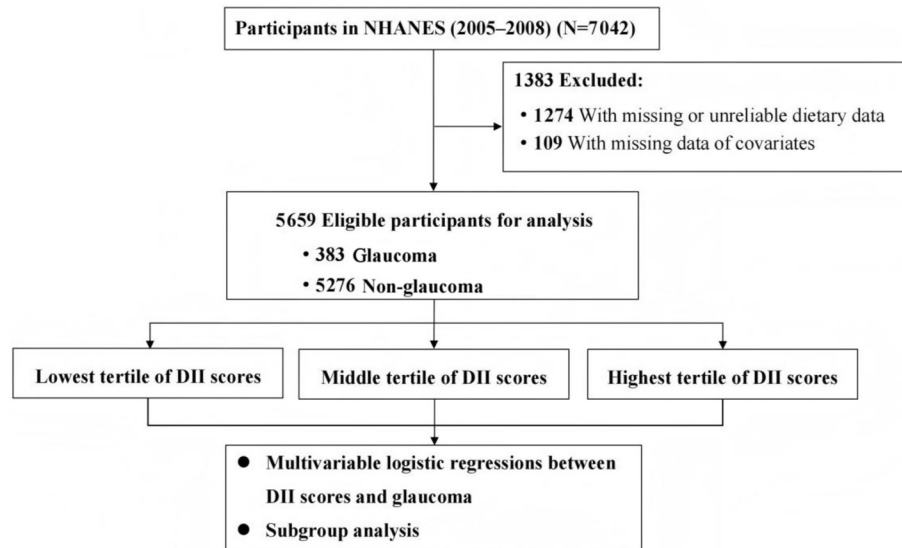


Figure 1 The flowchart of this study NHANES: National Health and Nutrition Examination Survey; DII: Dietary inflammatory index.

Dietary patterns have emerged as key modifiable determinants of systemic inflammation, with profound implications for chronic disease prevention. The dietary inflammatory index (DII) score, a literature-derived dietary assessment tool based on nutritional parameters, serves as a comprehensive metric for evaluating the inflammatory valence of dietary patterns, and is associated with systemic inflammatory biomarkers such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)- α ^[9]. Previous studies have linked high DII scores with an increased risk of various chronic diseases, including diabetes^[10-11], cancers^[11], cardiovascular disease^[11-12], and endometriosis^[13]. However, its association with glaucoma has not been extensively explored.

Therefore, we conducted this study using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to explore the association between DII-quantified proinflammatory dietary profiles and incident glaucoma risk through multivariable-adjusted regression modeling.

PARTICIPANTS AND METHODS

Ethical Approval Ethical approval was waived due to prior ethical approval review from the National Center for Health Statistics. All participants gave written informed consent in accordance with the protocols of the NHANES study.

Data Source and Population The NHANES employs a standardized protocol combining structured interviews, clinical assessments, and biochemical analyses to evaluate population-level health and nutritional parameters in representative American demographic cohorts. This study used open-access datasets spanning the 2005-2008 survey cycles of the nationally representative NHANES. Following the exclusion of 1383 participants (1274 with missing or unreliable dietary data, and 109 with missing covariates), a total of 5659

individuals were included for the final analyses. Figure 1 delineates the detailed participant screening process.

Ascertainment of Glaucoma The diagnosis of glaucoma was based on the “Vision Questionnaire” during the NHANES 2005-2008 survey cycles. Data on glaucoma diagnosis were only collected for individuals aged 40y and older in the “Vision Questionnaire”. Glaucoma cases were defined by self-reported physician diagnosis, ascertained through affirmative responses to the NHANES Vision Questionnaire item “Told by the eye doctor having glaucoma”.

DII Scores and Covariates DII score was calculated using dietary data collected *via* standardized food frequency questionnaires in NHANES. The methodological algorithms for the DII score and its validation protocol have been extensively reported in prior publications^[9,14]. The NHANES database encompasses a comprehensive array of dietary components integral to the DII, systematically incorporating macronutrient profiles (energy, total fat, dietary fiber, protein, carbohydrates), lipid subtypes (saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega-3 and omega-6 fatty acids), cholesterol quantification, micronutrient spectra (vitamins A, C, D, E, B1, B2, B6, B12; β -carotene; niacin; folic acid), essential minerals (magnesium, iron, zinc, selenium), and bioactive compounds including alcohol and caffeine. This multidimensional nutritional dataset provides the foundational variables required for precise DII computation within the NHANES framework. DII scores were calculated by first computing each food parameter’s Z-scores, and then converting them to centered percentiles. Each centered percentile value was weighted using its corresponding inflammatory coefficient. These weighted values were then aggregated across all dietary components to compute the final DII score for each participant. Higher DII scores indicate

a greater intake of pro-inflammatory foods relative to anti-inflammatory foods.

Based on the previous studies^[15-16] and clinical experience, the following covariates were included in the analysis: age, ethnicity, gender and marital status, body mass index, diabetes, and smoking status.

Statistical Analysis Statistical analyses were conducted in adherence to NHANES analytic protocols using R software (version 4.2.2). To account for the complex, multistage, stratified, clustered sampling design of NHANES and to generate nationally representative estimates for the combined 2005-2008 survey cycles, we utilized the 4-year dietary interview sample weight (WTDR4YR). The survey design was fully specified by incorporating the stratum and primary sampling unit variables using the “survey” package in R. This approach ensures accurate calculation of standard errors and confidence intervals, as per the NHANES analytical guidelines. Categorical variables were assessed *via* Chi-square tests, whereas continuous variables were examined through *t*-tests or Wilcoxon rank-sum nonparametric tests based on normality assessment results. Sample-weighted, logistic regression analyses estimated the association of DII score with glaucoma risk, with the results presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). The crude model was adjusted for nothing. Model 1 was adjusted for age, ethnicity, gender, and marital status. Model 2 was adjusted for the covariates of Model 1 with additional adjustments for obesity, diabetes, and smoking status. Additionally, linear trends across tertiles of DII scores were evaluated by modeling the median value of each tertile as a continuous variable in regression models. Nonlinear associations between DII scores and glaucoma risk were explored using restricted cubic splines (RCS) to characterize potential dose-response relationships. Subgroup analyses across demographic and clinical subgroups (gender, diabetes, and obesity) were performed. Additionally, *P* values for interaction across subgroups were also estimated by the likelihood ratio test. All *P* values were derived from two-sided tests, with statistical significance defined at *P*<0.05.

RESULTS

Characteristics of the Study Sample Table 1 provides the baseline characteristics of all included participants stratified by glaucoma status. A total of 5659 eligible participants were finally enrolled, including 383 (6.7%) with glaucoma and 5276 (93.3%) without glaucoma. The age of all included participants ranged from 40 to 85y. Furthermore, glaucoma patients tended to be older, more likely to be female, and exhibited significantly greater diabetes prevalence and current smoking prevalence compared to those without glaucoma. The overall study population exhibited a median DII score of 1.88. Individuals diagnosed with glaucoma demonstrated

a significantly elevated median DII value of 2.18 compared to 1.86 in the non-glaucoma group (*P*=0.022). Furthermore, distribution analysis revealed that glaucoma prevalence demonstrated a gradient increase across DII tertiles, with the highest tertile exhibiting a 38.6% case proportion—significantly exceeding the 29.5% observed in the lowest tertile.

Correlation of DII Scores with Glaucoma Prevalence

Table 2 summarizes the population-level relationships between DII scores and glaucoma risk in the overall cohort. The univariable logistic regression analysis revealed that the highest tertile of DII scores had the strongest association with glaucoma (OR=1.33, 95%CI: 1.04-1.70), compared to the middle tertile (OR=1.03, 95%CI: 0.78-1.35) and the lowest tertile, showing a significant trend (*P* for trend=0.034). Similarly, after adjusting for multiple variables in Models 1 and 2, the analysis revealed a statistically significant elevation in glaucoma risk among participants classified within the highest tertile of DII scores relative to those in the lowest tertile. Specifically, in the fully adjusted model (Model 2), which accounted for all covariates, participants in the highest DII score tertile had a 35% greater likelihood of developing glaucoma relative to those in the lowest tertile (*P*=0.034). We performed a sensitivity analysis restricted to participants aged 60y or older, which yielded results consistent with our main findings (OR_{tertile3vs1}: 1.36, 95%CI: 1.05-1.77; *P*=0.020).

The trend analysis demonstrated a progressive elevation in covariate-adjusted glaucoma risk estimates with ascending DII tertiles across all models (Crude: *P* for trend=0.034, Model 1: *P* for trend=0.039, Model 2: *P* for trend=0.046). Moreover, we examined the association between DII scores and glaucoma risk using a continuous scale through RCS analysis, which corroborated our findings (*P*=0.043; Figure 2).

Subgroup Analysis Subgroup analyses revealed that the positive association between DII scores and glaucoma risk varied by gender, diabetes status, and obesity (Table 3).

The fully adjusted model found no significant link between DII score tertiles and glaucoma risk among female participants (OR=1.24, 95%CI: 0.85-1.79, *P*=0.240), non-diabetic participants (OR=1.15, 95%CI: 0.82-1.63, *P*=0.513), and non-obese participants (OR=1.19, 95%CI: 0.87-1.63, *P*=0.286).

Nevertheless, in male participants, higher tertiles of DII score demonstrated a statistically significant association with elevated glaucoma risk (OR=1.48, 95%CI: 1.02-2.15, *P*=0.049), in diabetic participants (OR=1.56, 95%CI: 1.04-2.34, *P*=0.028), and in participants with obesity (OR=1.66, 95%CI: 1.07-2.58, *P*=0.023). In these subgroups, higher DII tertiles were associated with progressively higher glaucoma risk (all *P* for trend <0.05).

As for interaction terms, no significant interactions of DII with gender, diabetes, and obesity were observed (Table 3).

Table 1 Baseline characteristics between glaucoma and non-glaucoma groups

| Parameters | Total (n=5659) | Non-glaucoma (n=5276) | Glaucoma (n=383) | P |
|-------------------------------|----------------------|-----------------------|----------------------|--------|
| Age, median (IQR) | 60.00 (49.00, 71.00) | 59.00 (49.00, 70.00) | 70.00 (61.00, 78.00) | <0.001 |
| Ethnicity, n (%) | | | | 0.001 |
| Mexican american | 834 (14.7) | 794 (15.0) | 40 (10.4) | |
| Non-hispanic black | 1187 (21.0) | 1079 (20.5) | 108 (28.2) | |
| Non-hispanic white | 3080 (54.4) | 2885 (54.7) | 195 (50.9) | |
| Other races | 558 (9.9) | 518 (9.8) | 40 (10.4) | |
| Marital status, n (%) | | | | <0.001 |
| Never married | 380 (6.7) | 360 (6.8) | 20 (5.2) | |
| Married | 3375 (59.6) | 3181 (60.3) | 194 (50.7) | |
| Other | 1904 (33.6) | 1735 (32.9) | 169 (44.1) | |
| BMI, median (IQR) | 28.35 (24.91, 32.45) | 28.36 (24.90, 32.47) | 28.20 (24.92, 32.33) | 0.914 |
| Obesity, n (%) | | | | 0.876 |
| No | 3486 (61.6) | 3252 (61.6) | 234 (61.1) | |
| Yes | 2173 (38.4) | 2024 (38.4) | 149 (38.9) | |
| Diabetes, n (%) | | | | <0.001 |
| No | 4316 (76.3) | 4080 (77.3) | 236 (61.6) | |
| Yes | 1343 (23.7) | 1196 (22.7) | 147 (38.4) | |
| Smoking status, n (%) | | | | <0.001 |
| Never | 2716 (48.0) | 2541 (48.2) | 175 (45.7) | |
| Former | 1863 (32.9) | 1703 (32.3) | 160 (41.8) | |
| Now | 1080 (19.1) | 1032 (19.6) | 48 (12.5) | |
| DII, median (IQR) | 1.88 (0.42, 3.07) | 1.86 (0.41, 3.06) | 2.18 (0.67, 3.22) | 0.022 |
| DII tertile categories, n (%) | | | | 0.062 |
| Lowest tertile | 1887 (33.3) | 1774 (33.6) | 113 (29.5) | |
| Middle tertile | 1886 (33.3) | 1764 (33.4) | 122 (31.9) | |
| Highest tertile | 1886 (33.3) | 1738 (32.9) | 148 (38.6) | |

Number is the unweighted count of the participants. DII: Dietary inflammatory index; IQR: Interquartile range; BMI: Body mass index; SD: Standard deviation.

Table 2 Associations between the DII and glaucoma in the total cohort

| DII | Cases with glaucoma/n | OR (95% CI) | | | | | |
|----------------------------------|-----------------------|--------------------|-------|----------------------|-------|----------------------|-------|
| | | Crude ^a | P | Model 1 ^b | P | Model 2 ^c | P |
| Continuous values (-5.103-5.065) | 383/5659 | 1.06 (1.00-1.13) | 0.042 | 1.07 (1.00-1.13) | 0.038 | 1.07 (1.01-1.14) | 0.031 |
| Tertile categories | | | | | | | |
| Lowest (-5.103-0.966) | 113/1887 | Reference | | Reference | | Reference | |
| Middle (0.967-2.687) | 122/1886 | 1.03 (0.78-1.35) | 0.841 | 1.03 (0.78-1.37) | 0.824 | 1.04 (0.78-1.38) | 0.788 |
| Highest (2.688-5.065) | 148/1886 | 1.33 (1.04-1.70) | 0.025 | 1.33 (1.02-1.73) | 0.038 | 1.35 (1.03-1.79) | 0.034 |
| P for trend | | 0.034 | | 0.039 | | 0.046 | |

^aCrude model was adjusted for nothing; ^bModel 1 was adjusted for age, ethnicity, gender and marital status; ^cModel 2 included the covariates of Model 1 with additional adjustments for obesity, diabetes, and smoking status. DII: Dietary inflammatory index; OR: Odds ratio; CI: Confidence interval.

DISCUSSION

Through comprehensive analysis of nationally representative epidemiological data, this population-based study provides novel evidence on the significantly positive relationship between dietary inflammatory potential (quantified *via* DII score) and glaucoma prevalence. Multivariable models revealed that participants within the highest DII tertile

demonstrated a 35% elevated risk probability for glaucoma compared to those in the lowest tertile group, following comprehensive adjustment for demographic and clinical confounders. Given that diet is a modifiable factor, our findings underscore the potential importance of anti-inflammatory dietary interventions in the prevention of glaucoma. Glaucoma significantly impacts patients' quality of life through

Table 3 Subgroup analysis of the association between tertiles of DII scores and glaucoma

| Subgroup | DII scores, OR (95%CI) | | | P for trend | P for interaction |
|----------------------|------------------------|------------------|-------------------------------|-------------|-------------------|
| | Lowest tertile | Middle tertile | Highest tertile | | |
| Gender | | | | | 0.489 |
| Male | | | | | |
| Crude ^a | Reference | 1.17 (0.82-1.68) | 1.47 (1.02-2.13) ^e | 0.044 | |
| Model 1 ^b | Reference | 1.18 (0.82-1.68) | 1.46 (1.01-2.12) ^e | 0.048 | |
| Model 2 ^c | Reference | 1.14 (0.80-1.64) | 1.48 (1.02-2.15) ^e | 0.049 | |
| Female | | | | | |
| Crude ^a | Reference | 0.92 (0.63-1.35) | 1.22 (0.85-1.74) | 0.253 | |
| Model 1 ^b | Reference | 0.91 (0.62-1.32) | 1.19 (0.83-1.71) | 0.308 | |
| Model 2 ^c | Reference | 0.92 (0.63-1.34) | 1.24 (0.85-1.79) | 0.240 | |
| Diabetes | | | | | 0.294 |
| No | | | | | |
| Crude ^a | Reference | 0.84 (0.57-1.24) | 1.15 (0.82-1.62) | 0.528 | |
| Model 1 ^b | Reference | 0.83 (0.56-1.22) | 1.12 (0.80-1.57) | 0.616 | |
| Model 2 ^c | Reference | 0.85 (0.58-1.24) | 1.15 (0.82-1.63) | 0.513 | |
| Yes | | | | | |
| Crude ^a | Reference | 1.41 (0.93-2.15) | 1.57 (1.08-2.30) ^e | 0.018 | |
| Model 1 ^b | Reference | 1.42 (0.93-2.16) | 1.55 (1.05-2.29) ^e | 0.026 | |
| Model 2 ^c | Reference | 1.43 (0.93-2.21) | 1.56 (1.04-2.34) ^e | 0.028 | |
| Obesity | | | | | 0.266 |
| No | | | | | |
| Crude ^a | Reference | 1.03 (0.77-1.39) | 1.19 (0.88-1.62) | 0.281 | |
| Model 1 ^b | Reference | 1.02 (0.76-1.38) | 1.17 (0.86-1.58) | 0.343 | |
| Model 2 ^c | Reference | 1.04 (0.77-1.40) | 1.19 (0.87-1.63) | 0.286 | |
| Yes | | | | | |
| Crude ^a | Reference | 1.22 (0.77-1.93) | 1.63 (1.06-2.50) ^e | 0.025 | |
| Model 1 ^b | Reference | 1.23 (0.78-1.96) | 1.64 (1.06-2.55) ^e | 0.026 | |
| Model 2 ^c | Reference | 1.23 (0.77-1.96) | 1.66 (1.07-2.58) ^e | 0.023 | |

^eStatistically significant association. ^aCrude model was adjusted for nothing; ^bModel 1 was adjusted for age, ethnicity, gender and marital status; ^cModel 2 included the covariates of Model 1 with additional adjustments for obesity, diabetes, and smoking status. All Models were not adjusted for the stratified covariates on which the subgroup analyses were conducted. DII: Dietary inflammatory index; OR: Odds ratio; CI: Confidence interval.

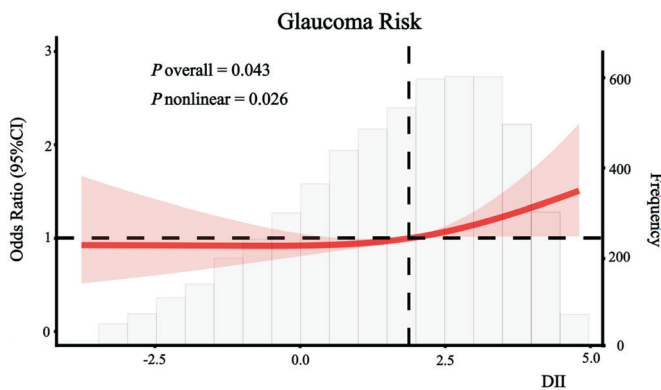


Figure 2 Cubic regression spline of the glaucoma risk by DII scores among the entire population The cubic regression spline was adjusted for age, ethnicity, gender, marital status, obesity, diabetes, and smoking status. ORs are indicated by solid lines and 95% of CIs are presented by shaded areas. DII: Dietary inflammatory index; OR: Odds ratio; CI: Confidence interval.

both physical and psychological burdens, adversely affects interpersonal relationships, and imposes substantial economic costs on healthcare systems^[17]. With growing evidence supporting the critical involvement of chronic inflammation in glaucoma pathogenesis^[7], attention has shifted toward identifying modifiable lifestyle factors, particularly dietary patterns, that may influence inflammatory pathways. Earlier studies have primarily focused on examining the association of individual nutrients or food components with the risk of glaucoma^[18-20]. Based on the existing research, our study utilized the DII scoring system, which comprehensively evaluates the combined inflammatory impact of dietary components, and found a significant relationship between pro-inflammatory dietary patterns and glaucoma risk. The analysis revealed that individuals in the highest DII tertile within the American general population demonstrated a 34% increased

likelihood of glaucoma compared to those in the lowest tertile, following adjustment for multiple confounding factors.

The link between dietary inflammation and glaucoma is multifactorial^[21-22], involving neuroinflammatory processes that contribute to glaucomatous optic neuropathy pathogenesis^[23]. Retinal immune systems (astrocytes, microglia, blood-derived cells) may mediate inflammatory RGCs degeneration^[24-25]. Pro-inflammatory dietary patterns could promote systemic inflammation, potentially elevating IOP and accelerating RGCs loss^[8]. Simultaneously, diet-microbiome interactions drive gut dysbiosis, intestinal inflammation, and barrier dysfunction, which are increasingly recognized as significant contributors to glaucoma progression^[26-29]. The interplay among ocular inflammation, systemic responses, and gut-brain axis interactions might provide a comprehensive framework for understanding the potential role of the DII in the pathogenesis of glaucoma.

Our subgroup analysis further explored the relationship between DII score and glaucoma risk, which revealed that the positive relationship between DII scores and glaucoma risk was particularly strong in male participants, participants with diabetes, and participants with obesity. A Meta-analysis on the epidemiology of glaucoma revealed that the prevalence of glaucoma in the United States in 2022, is 1.62% among all adults (aged ≥ 18 y), 2.56% among those 40y or older. Male adults had a higher age- and race-standardized prevalence of 0.59% compared with a prevalence of 0.55% for female adults^[30]. Overall, males are at higher risk of glaucoma, and these findings underscore the potential contribution of dietary patterns to mediating gender disparity in glaucoma susceptibility. Emerging evidence from prior research highlights the critical role of dietary factors in modulating the risk and progression of primary open angle glaucoma^[31]. The prevalence of primary open angle glaucoma in males is 1.36-fold higher compared to females^[1], which may explain the relationship between DII and glaucoma prevalence observed in the male population in our findings. Diabetes and obesity are both known to be important risk factors for glaucoma, especially for neovascular glaucoma^[32-34]. In the diabetic population, due to the pre-existing chronic inflammatory state, a high DII diet may further exacerbate inflammatory responses, thereby increasing the risk of glaucoma. Studies have shown that pro-inflammatory factors can aggravate oxidative stress and endothelial dysfunction in diabetic mice, subsequently affecting IOP regulation and optic nerve health. Obesity is associated with the development of chronic systemic inflammation, which may progress to insulin resistance, pancreatic β -cell dysfunction, and ultimately culminate in type 2 diabetes mellitus^[35]. Our research findings suggest that the combination of diabetes and a pro-inflammatory dietary

pattern may increase the risk of glaucoma through synergistic effects. Similarly, obesity, which is usually related to chronic low-grade inflammation and metabolic dysfunction, has demonstrated a correlation with an elevated risk of glaucoma, further highlighting the role of systemic inflammation and metabolic disturbances in the pathogenesis of this condition.

A key strength of this study is its use of data from the NHANES project, which utilizes a nationally representative sampling design with stringent weighting procedures. This design improves the applicability of the results to the general population of non-institutionalized adults in the United States. To enhance the reliability of the findings, the analysis rigorously controlled for a wide array of potential confounders were conducted. Additionally, subgroup analyses were performed to examine the association between DII scores and glaucoma within specific demographic groups, offering a more nuanced understanding of this relationship. Importantly, this research is among the first to explore the connection between DII and glaucoma. These findings may provide preliminary insights that could inform future efforts to develop practical dietary intervention strategies aimed at mitigating the public health and economic burden of glaucoma.

Some limitations should be noted. First, despite adjusting for a comprehensive set of demographic, lifestyle, and health-related variables in the multivariable logistic regression models, the potential confounding effect from unmeasured variables such as socioeconomic status, physical activity, and access to healthcare cannot be evaluated. Second, given the cross-sectional design of the NHANES data, causal relationships between DII and glaucoma risk cannot be determined. Third, due to the lack of data on glaucoma subtypes (*e.g.*, primary vs secondary neovascular glaucoma) in NHANES, we examined the association between DII and overall glaucoma only. Meanwhile, another limitation is that the diagnosis of glaucoma was self-reported and was not clinically confirmed for all participants in NHANES, which may have led to potential misclassification. Further well-designed longitudinal studies were necessary.

In conclusion, this nationally representative study found a potential association between anti-inflammatory dietary patterns and a lower risk of glaucoma, underscoring a potential link between dietary inflammatory status and glaucoma risk, which should be further explored in prospective and mechanistic studies.

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Shan HM; Supervision, Tao Y. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Shan HM, None; Tao Y, None.

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