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Feast your eyes: diet and nutrition for optimal eye health

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Feast your eyes: diet and nutrition for optimal eye health

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Table of contents

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Editorial: Feast your eyes: diet and nutrition for optimal eye health

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Editorial on the Research Topic
Feast your eyes: diet and nutrition for optimal eye health

"Let food be thy medicine and medicine be thy food." Hippocrates said these powerful words, and we have indeed strayed far from them in our world of convenience and fast-food diets. This Research Topic focused on arguably one of the most important senses—vision—and perhaps one of the most important topics—nutrition. How does one obtain and maintain optimal eye health? To answer this question, let us look at an example from the recent past. The Age-Related Eye Diseases trials 1 and 2 shed a lot of light on this topic, and have led to recommendations on carotenoid vitamin supplements for the prevention of age-related macular degeneration (AMD) (1–3). Various systematic reviews and meta-analyses have shown that, although effects may vary in different stages of AMD, carotenoid intake may benefit and improve vision in healthy eyes, and all stages of AMD stand to benefit from its intake (4–6). Its benefits are not limited to eyes but also organs like the brain (7–10) and heart (11) and disease states like diabetes (12, 13) that can lead to widespread inflammation. One simple takeaway can be that one needs to increase carotenoid intake. A wider perspective would be that "we are what we eat" and that many other aging and disease states can be controlled by diet.

To this accord, the studies in this Research Topic looked at a wide range of topics dealing with disease states that create burdens of colossal proportions like glaucoma, AMD, diabetic retinopathy, and cataracts. The studies do so by evaluating the effects of deficiencies in nutrients or analyzing a large sample cohort from the National Health and Nutrition Examination Survey (NHANES).

It is not an exaggeration to say we are having a myopia epidemic (14). Whereas in most countries emmetropia was normal, countries like China are now experiencing myopic refractive error becoming the norm (14). Obviously, genetics play an important role, but the effects of epigenetics cannot be underestimated, and researchers (Xiao et al.) have found, using the NHANES data, that cis-β carotene is significantly associated with the risk of myopia and high myopia. The results are indeed fascinating, as they did not find an association with other micronutrient vitamins such as A, D, E, C, α-carotene, trans-β-carotene, or lutein zeaxanthin. Another study performed by Xu et al., using the NHANES data 2005–2008 showed that, although vitamin D and magnesium were protective against diabetic retinopathy, the protective effect of vitamin D primarily benefited

individuals deficient in magnesium. This highlights the complex interplay of nutrients in health and disease states. Bhandarkar et al. looked at low-carbohydrate, high-fat diets in individuals with diabetes and found health benefits going beyond glycemic control, including changing the lipid profile and ocular inflammatory biomarkers. Although not significantly correlated to Hb a1c, this study indeed sows seeds for the need for further investigation in this area, as various biomarkers, such as ICAM-1, IL-17A, IL-1β, and TNF-α, all showed clinically significant changes during the follow-up.

Cataracts is one of the reversible causes of vision loss (15). Most of us have accepted that a complex set of circumstances eventually causes a naturally occurring clear crystalline lens to opacify. If we are what we eat, can there be nutritional methods to prevent the formation of cataracts? Zhang et al., and Feng et al., add to the body of literature already present in this area. Zhang et al., summarized the current body of work in their mini review article, whereas Feng et al., found that famine exposure during the early stages of life is associated with a heightened risk of developing cataracts. This brings another question to mind: although we all would like to be citizens of planet earth, there are significant dietary constraints in various countries and one plan to fix the nutritional requirements of all countries would not work. Thus, studies such as those of Thirunavukkarasu et al., and Nuredin et al., highlight the need for targeted nutritional intervention measures to improve vision health in different regions.

Lastly, AMD (16) and glaucoma (17) are not only the leading causes of irreversible blindness but also pose a huge socioeconomic burden. The current therapy for glaucoma is to lower intraocular pressure (IOP); however, lowering of IOP does not guarantee halting disease progression. Further, glaucoma patients are on multiple medications and require surgery. Both AMD and glaucoma are at high proportions due to the aging population (16–18). Thus, it remains important to look for alternative and adjunct therapies for both these disease states. The work from Yang et al. on vitamin B6 points to a lower risk of glaucoma in the highest quartile and Lee et al. shows that higher intake of omega-3 long chain polyunsaturated fatty acids decreases the risk of AMD. These are easy for patients to implement and, furthermore, these nutrients have many other benefits to the body that also contribute to overall health.

To say that we live in the golden age of science is an understatement. We have more knowledge and technology than our predecessors could ever wish to have. On the other hand, previous clinicians and scientists would not envy the endemic chronic diseases that both developing and developed countries are facing. It will require a conscious change in both physician's and patients' mentality and thinking to counteract these disease trends. We need to stop looking at food as just calories and start looking at food as a flexible spending account to be used for the betterment of our health and quality of life.

Author contributions

PGD: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. AR: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical vitamin A deficiency among preschool aged children in southwest Ethiopia

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Background: The clinical manifestations of vitamin A deficiency (VAD) involve night blindness, bitot's spots, corneal xerosis, and corneal scars. It is the most important cause of preventable childhood blindness among children and causes morbidity and mortality. Even though Ethiopia implemented high-potency vitamin A supplements, the occurrence of VAD remains significant. This study was to identify determinants of clinical VAD among preschool-aged children (PSC) in southwest Ethiopia.

Method: A community-based survey was conducted among 411 randomly selected PSCs. A pretested and structured questionnaire coupled with clinical observation for signs of vitamin A deficiency by a trained ophthalmologist was used to collect the data. An anthropometric measurement of height was taken and analyzed using WHO Anthro to calculate Z-scores for each index. The public health significance of VAD was declared after comparison with international references. A bi-variable and multi-variable logistic analysis was done. We reported the adjusted odds ratio (AOR), 95% confidence interval, and *p*-value.

Result: A total of 411 children were screened for clinical VAD, and the overall prevalence was 2.2% (95% CI: 1.5–2.5). Of which, night blindness affects 1.2%, bitot's spots affects 0.7%, and corneal xerosis affects 0.2%, indicating a major public health problem compared to the international reference. The odds of clinical VAD were 81% lower among children who received vitamin A supplementation (VAS; AOR = 0.19, 95% CI: 0.04–0.92). On the other hand, PSC of mothers who had attended ANC visits were 89% less likely to develop clinical VAD (AOR = 0.11, 95% CI: 0.02–0.53). In addition, the study revealed that the odds of developing clinical VAD are 82% lower among PSC aged 36 to 47 months (AOR = 0.18; 95% CI: 0.03–0.97).

Conclusion: The prevalence of clinical VAD among PSC is a public health problem and is associated with ANC visits, VAS status, and the age of the child, which could be used to target interventions to further reduce existing VAD. Further studies using reliable dietary intake and biomarker data could further depict the burden of subclinical VAD.

KEYWORDS

bitot's spots, clinical vitamin A deficiency, conjunctival xerosis, determinants, night blindness, preschool age children

Introduction

Vitamin A plays a fundamental role in various body functions, including vision, growth, immunity, reproduction, the integrity of epithelial cells, and survival (1). Hence, it is an essential nutrient that cannot be synthesized by the body and should be taken from the diet (2). The average child should consume 500–700 mcg of vitamin A daily to prevent the risk of vitamin A deficiency (VAD) (3, 4). Hence, the World Health Organization (WHO) recommends biannual supplementation of children with 30–60 mg of retinol equivalent to reduce child morbidity and mortality (5, 6).

VAD is a critical concern for children under five, especially in developing countries. To address this issue, a comprehensive dietary approach is necessary. Animal source foods like milk and eggs, which provide retinol directly, are crucial in alleviating VAD in regions with high VAD prevalence (7, 8). Additionally, incorporating orange-fleshed sweet potato (OFSP) into diets can serve as a complementary strategy, as they are rich in beta-carotene, a precursor to retinol (7, 9). However, limited access to both animal source foods and OFSP in low-income areas heightens the risk of VAD, highlighting the urgent need to improve availability and affordability of these vital food sources (8).

Vitamin A Deficiency (VAD) is characterized by various eye manifestations, collectively known as xerophthalmia (10, 11). These manifestations include night blindness, bitot's spots, conjunctival xerosis, corneal dryness, and in severe cases, the destruction of the eyeball leading to blindness. The progression of these symptoms follows a gradual pattern in the natural history of VAD. It typically starts with reduced vision in low-light conditions (night blindness), followed by dryness of the conjunctival mucosa and the appearance of foamy, whitish-gray patches on the conjunctiva (bitot's spots). As the deficiency worsens, the cornea becomes affected, resulting in corneal ulcers, scarring, and eventual loss of the eyeball and vision (xerophthalmia) (4).

VAD is characterized by xeropthalmia, eye manifestations of VAD include night blindness, bitot's spots, conjunctival xerosis, corneal dryness, and destruction of the eyeball leading to blindness (10, 11). These are gradual symptoms of VAD in the natural history where the child can have reduced vision at dark (night blindness), followed by dryness of the conjunctival mucosa and accumulation of keratin in the conjunctiva (bitot's spot), involvement of the cornea (corneal ulcer and scaring) and gradual loss of eye ball and vision at the end (xerophthalmia). Some of these manifestations could be averted through vitamin A supplementation (VAS) (3, 12).

Still, VAD is a major nutritional concern in lower-income countries (11). Both subclinical and clinical VAD are the most important causes of preventable childhood blindness, especially among children (1, 3, 4). Low intake of vitamin A during critical periods, coupled with common childhood illnesses, increases the risk of developing clinical VAD (4). The WHO report showed that VAD affects up to one-third of Preschool-age children (PSC) and contributes to 250, 000–500, 000 cases of blindness (12). It is a severe public health problem in more than 120 countries in the world (3).

Abbreviations: AOR, adjusted odds ratio; ANC, antenatal care; BAZ, body mass index for age; COR, crude odds ratio; VAD, clinical vitamin A deficiency; FAO, food and agricultural organization; HAZ, height for Age Z-score; PSC, preschool-age children; VAS, vitamin A supplementation; WAZ, weight for age Z-score; IECW, integrated eye care worker; DDS, dietary diversity score.

Although the prevalence of VAD has declined from 39% in 1991 to 29% globally, the highest prevalence still exists in sub-Saharan Africa. Moreover, VAD accounts for 1.5% of deaths, and 95% of these deaths are recorded in SS, including Ethiopia (48%) (13). In Ethiopia, VAD leads to 80,000 deaths per year and affects 61% of PSC (14). The risk of VAD reaches 60.3%, and it is closely correlated with food consumption patterns (15). More importantly, maternal vitamin A status and the amount of retinol in breast milk are extremely low, predisposing children to increased risk (16). In addition, 1.7% and 0.8% of children had bitot's spots and night blindness, respectively, indicating significant public health concerns (17). Improving vitamin A status could significantly reduce the risk of mortality from measles by 50%, from diarrhea by 40%, and overall mortality by 25–35% (12).

The practice of VAS can avert an estimated 167,563–376,030 child deaths annually, but the effective VAS coverage could reduce VAD and showed a great variation by wealth and other characteristics (18). Thus, the risks of VAD showed wide variability, mainly due to access to vitamin A-rich foods and VAS coverage (10, 16–18). Hence, the occurrence of VAD could vary from time-to-time between geographic locations and be affected by the season of the study. It could be helpful to study during a very lean season to capture the worst-case scenario for the occurrence of VAD in a population.

Several studies have identified important predictors of Vitamin A Deficiency (VAD) in Ethiopia, including maternal education, family size, droughts, respiratory or diarrheal illnesses, dietary diversity status, availability of latrines, income status, sex of the child, and stunted growth (12, 17, 19, 20). Vitamin A-rich food consumption in the country is seasonal, poor, and geographically clustered (21), and despite periodic high-potency vitamin A supplementation programs, clinical VAD remains a major public health problem (22–24). Access to and consumption of vitamin A-rich foods are low, particularly in southern regions (21), and affordability is decreasing (25). These challenges highlight the need for updated epidemiological evidence and the evaluation of existing interventions to address VAD effectively.

Although sub-clinical VAD could increase the risk of illness and VAS is in place in Ethiopia, the current study would be a valuable input in various ways. Firstly, this study aims to assess the efficacy of national policy and the vitamin A distribution program, partly evaluating the program's impact on reducing vitamin A deficiency and its associated health issues. Secondly, identifying gaps and target populations despite the existence of a national program in place helps to identify high-risk groups and serves as a tool to pinpoint these gaps, facilitating targeted interventions in the study setting. Hence, the current study was to assess the magnitude of different forms of clinical VAD and its potential risk factors in the case of southwest Ethiopia.

Materials and methods

Study design and setting

A community-based survey was conducted during the lean season from March to April 2023 in Cheha district, located in southwest Ethiopia. Cheha is one of the districts found in the Gurage Zone, southwest Ethiopia. Agriculture is the backbone of their economy. Enset, corn, sorghum, chickpeas, teff, and niger seed are the most commonly eaten foods by the community in the district. The availability of vitamin A-rich fruits and vegetables is usually seasonal

and limited (25). The district has 38 kebeles with a total of 26,405 households, six health centers, and 38 health posts. It has a total population of 137,574, of which 49.8% are males and 50.2% are females. The number of children under 5 years old is 21,479, out of which the number of children aged 3 to 5 years old is 10,042 (26).

Population and eligibility

The study population includes all randomly selected eligible PSC aged 36 to 59 months and their mothers or caregivers who were living in randomly selected kebeles. Children who are aged 3 to 5 years (36 to 59 months) and their mother or caretaker who has a mental problem or is critically ill in the absence of a close caregiver were excluded. This study mainly targets children in this age group due to their increased susceptibility and suitability for community-based studies.

Sample size determination

The required sample size was determined by using a single population proportion formula assuming a 95% confidence level, a prevalence of VAD of 2% in Farta district, Ethiopia, and a margin of error of 3% due to the rare nature of the outcome (27). The sample size was 92. Using the StatCalc package in EPiInfo software, the sample for the second objective was calculated. Thus, the sample size was determined by considering various factors that are significantly associated with the outcome variable at 80% power and 5% significance levels and considering the ANC visits of the mother (28) and head of household (29), determinant of clinical VAD. Accordingly, the minimum sample size estimated by ANC visits of mothers was 418 by adding the 10% non-response rate. Hence, a survey of about 418 children was required to assess the determinants of clinical VAD in the study area.

Sampling procedure

A combination of stratified random sampling and systematic random sampling was used to elect the study participants. The 38 kebeles in Cheha district were stratified into seven stratums or clusters based on their geographical location. Then, a total of twelve kebeles were randomly selected from the seven strata. The required sample size was distributed to each of the twelve selected kebele based on proportional allocation, and the study units were selected using systematic random sampling techniques. The first household for the study was selected randomly, and then every third household was included in the study. Where there was no eligible child within the selected household, the adjacent household was visited, and when there was more than one eligible child in a given household, one child was randomly selected.

Study variables

The dependent variable of this study is clinical VAD, which includes night blindness, conjunctival xerosis, corneal xerosis, corneal scars, corneal ulceration, corneal scar, and xeropthalmia. These were assessed by trained and experienced ophthalmology professionals using a history and physical examination. While the socio-demographic characteristics (age, sex, educational status, occupational status, religion, marital status, family size, and income) and health and nutritional factors (stunting, wasting, underweight, dietary diversity, vitamin A-rich vegetables, and child illness) and vaccination-related factors (vitamin A supplementation status and immunization status of the child) were considered independent variables of the current study.

Data collection tools and techniques

Data was collected by three optometrist nurses and two Integrated Eye Care Workers (IECW). Two days of training were given for data collectors and supervisors on the objective of the study, the method of facilitating respondents, and the context of the questionnaire by the principal investigator. A structured and pretested questionnaire, along with clinical observation for signs and symptoms of clinical VAD traced by trained clinicians, was used to collect the data. The questionnaire was adapted from different relevant studies by the WHO and the Food and Agriculture Organization (FAO). First, it was developed in English and then translated into Amharic and the local language, "Guragegna," and back translated to English to check its consistency. The weight and height of children were measured according to standard procedures. The weight of the child was measured using a calibrated electronic weight scale to the nearest 0.1 kg. The height of the child was measured with a standing wooden stadiometer to the nearest 0.1 cm. Height was measured without shoes in the Frankfurt position, where the line of sight was perpendicular to the measuring board. Based on the weight, height, and age of the child, the corresponding anthropometric indices Z-score (WAZ, HAZ, and BAZ) were calculated using the WHO Anthro software (30).

The validated 8-food group dietary diversity tool developed by FAO was used to assess the dietary diversity score of children. The dietary intake was collected over the past 24 h, excluding exceptional fasting and feasting days. These are very predictive of micronutrient adequacy levels (31) and the risk of micronutrient deficiencies, including VAD (31, 32).

Operational definition

In this study, children who are 3 to 5 years (36 to 59 months) of age were considered as PSC. A child with clinical VAD has either a history of night blindness or has a bitot's spots, conjunctival xerosis, corneal xerosis, corneal ulceration, or corneal scar upon examination. In addition, children with a dietary diversity score (DDS) of four or above in the last 24 h of the survey were classified as having a good or adequately diversified diet (33). The clinical signs and symptoms of Vitamin A Deficiency (VAD) in children in this study were assessed using the following operational definitions. Night blindness was defined as the child's inability or difficulty seeing in low-light conditions, which was reported by caregivers. Conjunctival xerosis was identified through clinical examination and characterized by dryness and roughness of the conjunctiva, the clear membrane covering the white part of the eye. Bitot's spots were described as

foamy, whitish-gray patches on the conjunctiva resulting from keratin accumulation, also observed during clinical examination. Corneal xerosis, referring to the drying and clouding of the cornea, and corneal ulceration with scars were evaluated through physical examination conducted by experienced optometrists (3).

Data processing and analysis

The data was edited, coded, and entered into Epi Data version 3.1 and exported to SPSS version 22 statistical software for analysis. After cleaning the data for inconsistencies and missing values in SPSS, descriptive statistical analysis such as mean, median, standard deviation, percent, and frequency was done. A bivariable logistic regression was performed for each independent variable and outcome variable. By considering the result of the bivariable analysis, variables were selected for the multivariable analysis to control for confounding. A variable whose bivariable test has a *p*-value of 0.20 was selected for the multivariable model. Variables that have higher co-linearity were excluded from the regression. Once the variables were identified, multivariable logistic regression analysis with a *p*-value of 0.05 and an AOR with a 95% CI was used to measure the degree of association between independent variables and the outcome variable (33). Multicollinearity among independent variables was evaluated using collinearity diagnostics (33). We have further potential interaction effects among the variables for better modeling (33).

Data quality control measures

In order to assure the quality of the data, training was given to the data collectors on the objective of the study, the data collection process, and the relevance of the study prior to data collection. A pilot study was done before the actual data collection among 21 respondents (5% of the total sample size) on non-selected kebeles. Through the pilot study, the flow of the questions and language usage were modified for the actual data collection. During the data collection process, different WHO-standardized pictures for clinical signs of vitamin A deficiency were used as a golden standard for comparison. The data was checked for completeness, accuracy, and clarity on a daily basis. Throughout the course of the data collection, data collectors were supervised at each site with daily supportive feedback. The calibration of the weight scale and height scale was always checked before measuring every child's weight and height, respectively. The anthropometric measurements were done using standardized procedures and methods (33).

Ethical considerations

Ethical clearance was obtained from the Wolkite University Colleges of Medicine and Health Science, Research Ethics Committee, and a letter of permission was obtained from the Cheha district health office. The purpose of the study was explained to respondents, and verbal informed consent was obtained from the mothers and caregivers. The confidentiality of the information was maintained by omitting any personal identification from the questionnaires. Respondents were informed about the study and the variety of information needed from them. During the data collection process, those children showing signs of clinical VAD were given a therapeutic dose of vitamin A according to the guidelines. A chance was given to the respondent to ask anything about the study, and the right not to participate in the study was kept at any moment.

Results

Socio-demographic characteristics

A total of four hundred eleven (411) children and their mothers or caregivers participated in the study, making the response rate 98.3%. About 215 (52.3%) of the children were female. About 401 (97.6%) households had less than three children under 5 years old. In the majority, 400 (97.3%) of the respondents were married, 166 (40.4%) of the mothers and caregivers did not attend formal education, and 182 (44.3%) attended primary education. About 252 (61.3%) children were aged 36–47 months (Table 1).

TABLE 1 Socio-demographic characteristics of study participants in Cheha District, southern Ethiopia, 2023.

Characteristics of mother/caregiver	Category	*n* (%)
Mother/caregiver age	≤35	344 (83.7%)
	>35	67 (16.3%)
Mother/caregiver marital status	Married	400 (97,3)
	Divorced	6 (1.5%)
	Widowed	5 (1.2%)
Mother/caregiver occupation	Housewife	294 (71.5%)
	Merchant	69 (16.8%)
	Government employer	22 (5.4%)
	Daily labor	13 (3.2%)
	Private employer	12 (2.9%)
	Farmer	1 (0.2%)
Mother/caregiver educational status	Not attend formal education	166 (40.4%)
	Primary education	182 (44.3%)
	Secondary education	44 (10.7%)
	Collages and above	19 (4.6%)
Monthly family income	<2000	273 (66.4%)
	≥2000	138 (33.6%)
Family size	≤4	167 (40.6%)
	>4	244 (59.4%)
Age of the child in month	36–47	252 (61.3%)
	48–59	159 (38.7%)
Sex of the child	Male	196(47.7%)
	Female	215(52.3%)
Number of under 5 children within home	≤2	401(97.6%)
	>2	10 (2.4%)

Health and nutrition-related characteristics of the participants

Most of the mothers (361; 87.8%) had attended antenatal care (ANC) visits for their children. About 350 (85.2%) mothers reported that their children had received vitamin A capsule supplementation, and out of the 350 children, only 188 (53.7%) took the vitamin A capsule supplementation in the last 6 months. Regarding the nutritional status, 18.5%, 16.1%, and 13.6% of the children were stunted, wasted, and underweight, respectively. Most children (84.2%) had inadequate dietary diversity scores. Moreover, 94.2 and 78.3% of the children ate wholegrain and legumes, respectively, in the last 24 h preceding the survey. About three-fourths (304) of the respondents cultivate vitamin A rich vegetables in their garden (Table 2; Figure 1).

TABLE 2 Health and nutrition related characteristics of study participants in Cheha District, southern Ethiopia, 2023.

Characteristics	Frequency (%)
ANC follow up	
Yes	361 (87.8%)
No	50 (12.2%)
Full immunization	
Yes	355 (86.4%)
No	56 (13.6%)
Took vitamin A capsule	
Yes	350 (85.2%)
No	61 (14.8%)
Time of receiving last dose of vitamin A capsule	
≤6 months	188 (53.7%)
>6 months	162 (46.3%)
Child ill 1 week preceding the survey	
Yes	120 (29.2%)
No	291 (70.8%)
Stunting	
Yes	76 (18.5%)
No	335 (81.5%)
Underweight	
Yes	66 (16.1%)
No	345 (83.9%)
Wasting	
Yes	56 (13.6%)
No	355 (86.4%)
Dietary diversity	
Adequate	65 (15.8%)
Inadequate	346 (84.2%)
Cultivate vitamin A rich vegetables	
Yes	306 (74.5%)
No	105 (25.5%)

Prevalence of clinical VAD

The overall prevalence of clinical vitamin A deficiency in the study area was 2.2% (95% CI: 1.7–2.7%). When disaggregated by the clinical form, night blindness affects 1.2%, bitot's spots affects 0.7%, and corneal xerosis affects 0.2%, indicating a major public health problem compared to the WHO cutoff point (Figure 2).

Factors associated with clinical VAD

In the bivariable analysis, the age of the child, vitamin A capsule supplementation, ANC visit, and educational status of the mothers were significantly associated with clinical VAD. The variables that had a *p*-value of 0.25 in the bivariable analysis and relevant determinants of VAD from previous studies were considered for the multivariable logistic regression to adjust for potential confounders and identify independent factors affecting the odds of VAD. The model's fitness was checked by Hosmer and Lemeshow's test, and it was non-significant with a *p*-value of 0.95, which indicates that the model is fit. Hence, in the crude analysis, without considering potential confounders, the age of the child, the mother's education, not having ANC visits, and getting VAS were significant determinants of VAD among PSC.

This study revealed the odds of developing clinical VAD are higher among PSC aged 48–59 as compared to 36–47-month-old children (AOR = 17.3; 1.89–158.7). Moreover, the risk of having a VAD child was higher in households with more than two under-five-year-old children, indicating the potential role of short birth spaces and a larger family size for VAD. The risk of clinical VAD was shown to be concentrated among older children without VAS. Children from mothers who had ANC visits were significantly associated with reduced odds of clinical VAD (AOR = 0.02; 0.001–0.32) as compared to their counterparts. The odds of the occurrence of clinical VAD were 91% lower among children who received VAS (AOR = 0.09; 0.01–0.70) without reporting VAS. On the other hand, the odds of developing clinical VAD were 5.5 times higher among children without growing vegetables in the backyard (AOR = 5.31; 0.34–83.2), and 9 times higher among children with lower estimated monthly income (AOR = 9.39; 0.64–138.7). The occurrence of clinically evident VAD is closely determined by income, the availability of vitamin A-rich foods, and not getting routine VAS. More importantly, having inadequate dietary diversity is associated with higher odds of developing VAD (AOR = 5.50; 0.37–82.6). The same association was also explored, where stunted children (AOR = 2.49; 0.41–15.0) had 2.5-fold increased odds of developing VAD as compared to non-stunted children (Table 3).

Discussion

This study tried to depict the prevalence of clinical VAD and associated factors among PSC aged 3 to 5 years. The overall prevalence of clinical VAD in the study area was 2.2% (1.7–2.7%), which represents a major public health problem according to the WHO cut-off point for public health significance for PSC, which is ≥1.56% (12). Concerning the occurrence of night blindness, bitot's spots are also higher as compared to the WHO recommendations of 1%, 0.5%, and 0.01%, respectively. This could be attributed to low intake of

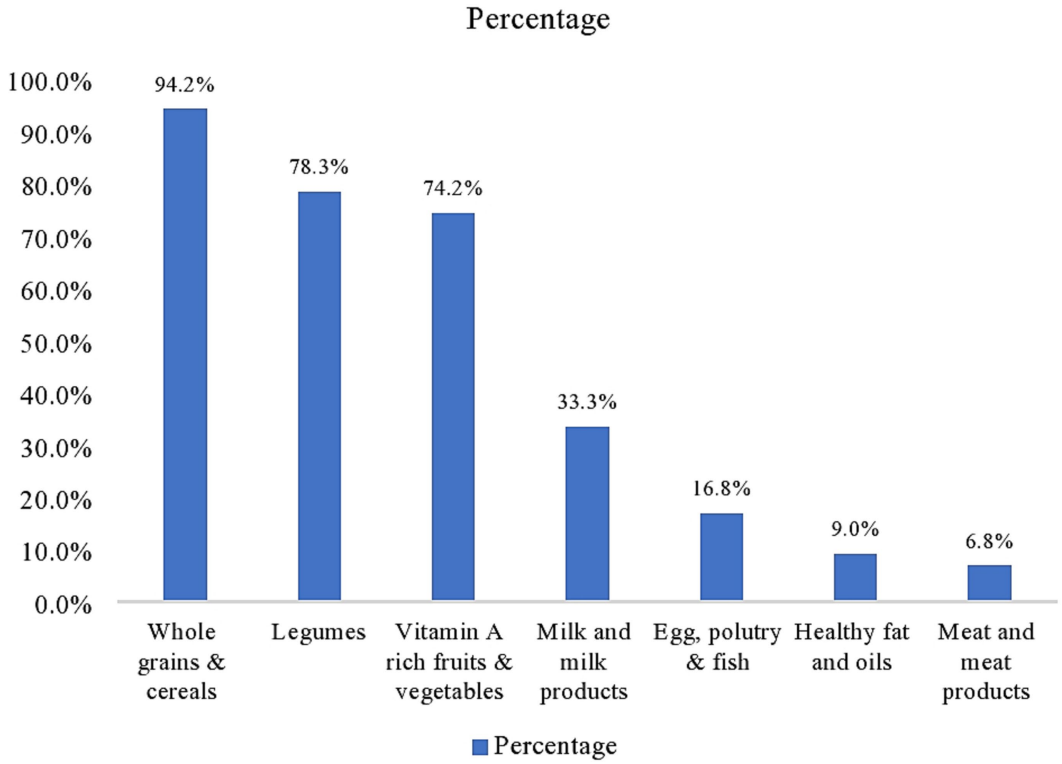

FIGURE 1
Proportion of children 3–5 years old who consumed the seven food groups in last 24 h preceding the survey, Cheha district, Gurage Zone, southern Ethiopia, 2023.

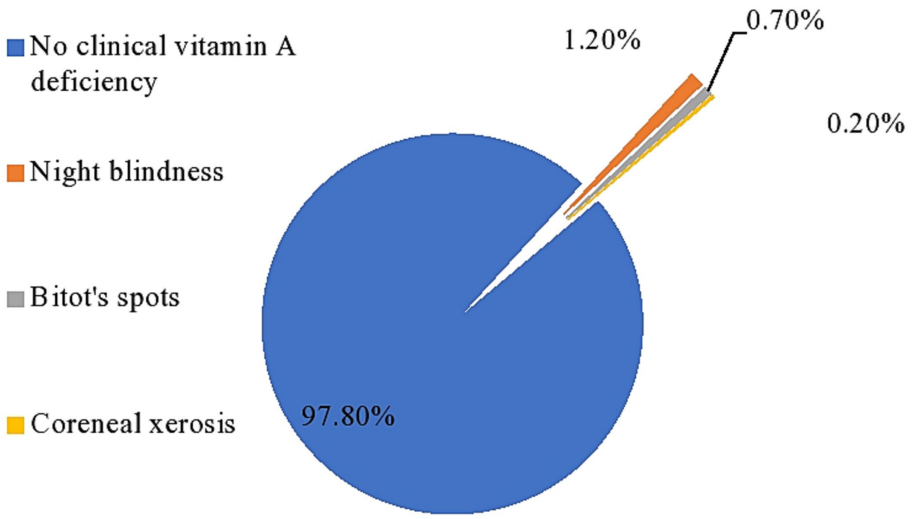

FIGURE 2
Prevalence of clinical vitamin-A deficiency among PSC in Cheha district, southern Ethiopia, 2023.

vitamin A-rich foods and low effective coverage of routine VAS (7). Other studies in the south Gondar zone and north Ethiopia showed that 2 and 2.6% of children had VAD, respectively (27, 34). It was also similar to the studies done in India (35) and Yemen (36).

On the other hand, a higher prevalence of VAD is reported in northwest Ethiopia (8.6%) (28). These variations could be associated with basic variations in demographic factors, socioeconomic classes, VAS coverage (37, 38), and access to and consumption of vitamin A-rich fruit and vegetables. Hence, this emphasizes the spatial variation in the risk of VAD among different geographic locations, driven by local factors (21). Even though routine VAS is in place in Ethiopia, VAD is still a major public health problem that needs to

TABLE 3 Logistic regression analysis for determinants of clinical VAD among children in southwest Ethiopia 2023.

Variables		Clinical VAD		COR (95% CI)	AOR (95% CI)	*p*-value
		Yes	No			
Maternal age	≤35	7	337	1	1	
	>35	2	65	1.48 (0.30–7.29)	3.63 (0.38–34.3)	0.261
Child sex	Male	5	191	1.38 (0.36–5.22)		
	Female	4	211	1		
Age of the child	36–47	2	250	1	1	
	48–59	7	152	5.76 (1.18–28.1)	17.3 (1.89–158.7)	0.012*
Educational status of the mother	Illiterate	7	159	5.35 (1.10–26.08)	9.19 (0.96–88.4)	0.055
	literate	2	243	1	1	
Family size	<=4	2	165	1		
	>4	7	237	2.44 (0.50–11.9)		
Under-five children	≤2	8	393	1	1	
	>2	1	9	5.46 (0.62–48.4)	16.2 (0.81–323.1)	0.069
Illness in the past week	Yes	5	115	3.12 (0.82–11.8)		
	No	4	287	1		
Underweight	Yes	2	64	1.51 (0.31–7.43)		
	No	7	338	1		
Wasting	Yes	1	55	1.27 (0.16–10.3)		
	No	8	347	1		
Income	<2000	8	265	4.14 (0.51–33.4)	9.39 (0.64–138.7)	0.103
	≥2000	1	137	1		
Stunting	Yes	4	72	3.67 (0.96–13.9)	2.49 (0.41–15.0)	0.320
	No	5	330	1	1	
Dietary diversity	Adequate	1	64	1	1	
	Inadequate	8	338	1.52 (0.19–12.3)	5.50 (0.37–82.6)	0.217
Growing vegetables in the backyard	Yes	4	302	1	1	
	No	5	100	3.78 (0.99–14.3)	5.31 (0.34–83.2)	0.235
ANC visit	Yes	3	358	0.06 (0.02–0.25)**	0.02 (0.001–0.32)	0.005**
	No	6	44	1	1	0.005*
Vitamin A supplementation	Yes	3	347	0.08 (0.02–0.33)**	0.09 (0.01–0.70)	0.021*
	No	6	55	1	1	

The symbol asterisks refer to statistically significant determinants of VAD at *p*-value below 0.05 (*) and 0.01(**).

be considered due to the variation in VAS coverage. Enhanced consumption of animal-source foods with a better bioavailability and conversion rate to retinol is needed to tackle VAD. Hence, diversifying our diet is a crucial intervention (39). In addition, intervention measures to increase economic access to vitamin A-rich food sources like OFSP, animal-source foods, and vitamin A-rich fruits and vegetables could improve vitamin A nutrition and its health outcomes. It should be noted that the retinol conversion efficiency of plant-source foods is very limited (9).

The study showed that the odds of developing clinically evident VAD among children aged 36–47 months were relatively lower compared to older children. The finding is consistent with a study from Ethiopia (28), Sudan (40), and India (36). In fact, children aged 36–47 months might be susceptible to VAD since it is a time for the cessation of breast feeding and diversified dietary consumption could be very limited. However, they tend to be asymptomatic in the early stages, as it takes time to develop clinically evident VAD. The risk is expected to be higher among this age group, yet they have hidden VAD. This could be further explained by the higher coverage of VAS for younger children compared to older children. However, a study from northwest Ethiopia (41) showed the reverse. Overall, PSC are very susceptible to VAD, yet the risk might vary by age group, driven by the occurrence of major childhood illnesses like diarrhea, pneumonia, and measles.

Furthermore, the educational status of the mother, rural residence, and family size are important predictors of clinical VAD (34, 35, 42). This might be due to the fact that the number of interviewed mothers who were literate was relatively higher in this study (40.4%) compared to the other study and about two-thirds of the respondents had a family size of >4, which makes most of the respondents fall into that

category. In addition, those variables might be the predictors of subclinical levels of VAD rather than clinical VAD, which is mainly based on serum retinol levels. Hence, the findings of this study would guide targeted interventions to tackle VAD through integrated health and nutrition interventions. For instance, growing vegetables in the backyard could help increase access to vitamin A-rich foods.

The current study found that there is no statistically significant gender-based difference in developing clinical VAD among PSC (COR = 1.38; 0.36–5.22). This was supported by the findings of the study done in Ethiopia (27). However, it was contradicted by reports from other studies in Ethiopia, which showed that males are more susceptible to clinical VAD than females (28, 34). This has been indicated by Israel (43) and India (35). Basically, there might be some baseline differences in immunity, susceptibility to infections, and gender-based feed preference (44). The difference might be related to the slightly higher nutritional requirements of male children, so, they might be highly susceptible to micronutrient deficiency and major childhood illnesses as they tend to be exposed to an external environment.

Additionally, not having ANC follow for the mother was an important risk factor for prevailing VAD among older children. Although routine VAS is not practiced for pregnant women, having ANC follow-up during maternal pregnancy is a baseline for providing nutritional care and counseling and increasing consumption of vitamin A-rich foods (45). This could help ensure adequate postnatal maternal retinol storage and breast milk for the child. This would also encourage the likelihood of receiving other maternal and child health services, and postnatal VAS would help reduce the risk of VAD (46). The finding was consistent with most of the studies conducted in Ethiopia and outside Ethiopia (20, 22, 28). Hence, strengthening the effective utilization of ANC is crucial for maternal and child survival.

Given the effective role of routine VAS, this study also supports the fact that the risk of VAD was 82% lower among those who had routine VAS. This was supported by studies done in Ethiopia and India (2, 22, 28), emphasizing the need for enhanced VAS coverage and targeting vulnerable segments of the population. This might be due to the fact that vitamin A supplementation has been proven effective in reducing the impacts of both clinical and subclinical VAD, particularly among children six months to five years of age (38).

Beyond these, not having growing vegetables in the backyard, children with an inadequately diversified diet, and stunting increase susceptibility to VAD. The former two are closely related to each other, and availability could improve dietary diversity and ultimately access to micronutrient intake (4, 46). On the other hand, being stunted is associated with long-term micronutrient deficiency starting in the uterus, which could increase the risk of VAD. On the other hand, VAD could lead to growth failure and stunting. This emphasizes the need for counseling for dietary diversification and enhancing the production of locally produced fruits and vegetables, which could reduce VAD among children (47, 48). A study from Uganda showed that VAD increases the odds of stunting by 43% (48). However, access to a diversified diet and stunting had a strong discrepancy among different socioeconomic classes (47).

This study has generated new evidence in the study area on the risk factors of VAD in southwest Ethiopia, which has not been investigated before in the study area. However, these findings should be sought in light of some limitations. The clinical assessment to depict VAD only shows the tip of the iceberg, omitting subclinical VAD. These should usually be captured using serum retinol, and the prevalence would be very high. Recall bias and social desirability bias in assessing dietary intakes over the past 24 h could not be excluded. It might have been a risk of recall bias as dietary assessments were made through a 24-h recall, which has a risk of socially desirable bias from the respondent's side. Due to the rare nature of the outcome, the current sample size could not be adequate hence limiting its representativeness and statistical power. This could impact the overall prevalence estimate of clinical VAD.

Conclusions and recommendations

The overall prevalence of clinical VAD among PSC in this study area is a major public health concern that needs enhanced VAS, nutrition education and counseling, and other targeted nutrition-sensitive interventions. The ANC visit of the mother, vitamin A supplementation status, and age of the child were factors that determined clinically overt VAD. Therefore, awareness should be given to the community by primary health care workers, including health extension workers, about dietary sources and prevention methods of VAD. The implementation of postnatal VAS for better childhood vitamin A status should be emphasized. This behavioral intervention should be enhanced during the ANC visits. In addition, the zonal health department and woreda health office should strictly check the implementation status of VAS in the district. Moreover, further investigation of subclinical vitamin A deficiency using reliable biomarkers and dietary intake data with a larger sample size is strongly recommended to inform better decisions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Wolkite University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TM: Supervision, Visualization, Writing – review & editing. AA: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Magnesium status modulating the effect of serum vitamin D levels on retinopathy: National Health and Nutrition Examination Survey 2005 to 2008

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Aim: Magnesium levels may influence the effect of vitamin D levels on the body. This study aimed to assess the combined effect of magnesium status as reflected by magnesium depletion score (MDS) and vitamin D status on the risk of retinopathy.

Methods: This cross-sectional study included participants aged 40 years and older with complete information on vitamin D, MDS, and retinopathy assessment from the 2005–2008 National Health and Nutrition Examination Survey (NHANES). Logistic regression analysis was utilized to analyze the relationship of MDS and vitamin D with retinopathy and expressed as odds ratio (OR) and 95% confidence interval (CI).

Results: Of these 4,953 participants included, 602 (9.53%) participants had retinopathy. Serum vitamin D levels ≤30 nmol/L (vs. >30 nmol/L) (OR = 1.38, 95%CI: 1.05–1.81) and MDS >2 points (vs. ≤2 points) (OR = 1.47, 95%CI: 1.01–2.16) were associated with higher odds of retinopathy. There was an interaction between MDS and vitamin D on the increased odds of retinopathy (OR = 2.29, 95%CI: 1.12–4.68, $P_{interaction}$ = 0.025). In different MDS groups, serum vitamin D levels ≤30 nmol/L increased the odds of retinopathy only in the MDS >2 group (OR = 2.90, 95%CI: 1.16–7.24), but not in the MDS ≤2 group (p = 0.293). Subgroups analyses demonstrated that the interaction between MDS and serum vitamin D on retinopathy was observed in males (OR = 6.88, 95%CI: 1.41–33.66, $P_{interaction}$ = 0.019), people with diabetes (OR = 3.43, 95%CI: 1.78–6.63, $P_{interaction}$ < 0.001), and people with body mass index (BMI) ≥25 kg/m^2 (OR = 2.46, 95%CI: 1.11–5.44, $P_{interaction}$ = 0.028).

Conclusion: Magnesium plays a moderating role in the relationship between serum vitamin D and retinopathy. The protective effect of vitamin D against retinopathy was primarily present among those with inadequate magnesium levels.

KEYWORDS

vitamin D, magnesium, retinopathy, moderating effect, magnesium depletion score

Introduction

Retinopathy is one of the major diseases that cause visual impairment and blindness, among which diabetic retinopathy is the leading cause of blindness in middle-aged and older adults worldwide (1). There is also a 6.7 to 18% prevalence of retinopathy in the population without diabetes, which may be related to advanced age and hypertension (2). Identifying modifiable factors that affect the risk of developing retinopathy is beneficial for disease prevention and reducing the burden of disease.

The retina is susceptible to oxidative stress (3). Vitamin D has been reported to prevent oxidative stress and inflammation in human retinal cells (4). Vitamin D may play a protective role in the retina through antioxidant, anti-inflammatory, anti-angiogenic, and immunomodulatory mechanisms (4, 5). In addition, diabetes is one of the major risk factors for retinopathy, and vitamin D may protect the retina by improving insulin sensitivity and decreasing insulin resistance (6). Magnesium is an essential nutrient that plays an important role in the regulation of blood pressure, glucose metabolism, vascular tone (7, 8), and it is involved in the synthesis and metabolism of vitamin D (9). Several studies have found that the effects of vitamin D on the body may vary depending on magnesium levels (10, 11). For example, the relationship between serum 25-hydroxyvitamin D [25(OH)D] and the risk of death may be altered by the level of magnesium intake, and this negative correlation was found mainly in populations with higher magnesium intake (10). However, the joint effect of serum magnesium levels and vitamin levels on retinopathy is unclear. Furthermore, blood magnesium accounts for approximately 1% of whole-body magnesium, and although serum magnesium measurements can be used for the medical diagnosis of clinically severe magnesium deficiency, they do not reliably represent whole-body magnesium status (12, 13). Since magnesium reabsorption in the kidney plays a crucial role in maintaining magnesium homeostasis (14), the magnesium depletion score (MDS) has been proposed as a new marker of magnesium status (15). MDS has been reported to be associated with self-reported risk of diabetic retinopathy (16).

Thus, this study aimed to assess the combined effect of magnesium status as reflected by MDS and vitamin D status on the risk of retinopathy in the middle-aged and elderly population, and to provide certain references for the prevention and management of retinopathy.

Methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES) dataset from 2005 to 2008 was used for this cross-sectional study. NHANES is an ongoing cross-sectional survey of health and nutrition of the United States noninstitutionalized population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).[1] The NHANES survey utilizes a complex multi-stage probability sampling design with a two-year survey cycle. NHANES collects data through interviews and physical examinations, including demographic, dietary, socioeconomic, and health-related data, as well as medical, physiologic measurements, and laboratory test data. This study was based on two NHANES survey cycles, 2005–2006 and 2007–2008, because only these two cycles included full information on retinopathy based on retinal imaging exam. Participants were included according to the following criteria: (1) aged ≥40 years old; (2) with retinopathy assessment using retinal imaging; (3) with measurement of serum vitamin D; and (4) with complete information to calculate MDS. The excluded criteria were as follows: (1) with renal failure [estimated glomerular filtration rate (eGFR) <15 mL/(min·1.73 m^2)] (17); (2) using anti-angiogenic ophthalmic agents, ophthalmic steroids; and (3) with missing key covariates. Only participants in NHANES aged 40 years and older were included in this study because two-field, non-mydriatic retinal photography was performed only on this age group. The NCHS Research Ethics Review Board approved all NHANES protocols and each participant provided written informed consent.

Assessment of retinopathy

Non-mydriatic digital images of the retina were captured from participants aged ≥40 years using the Canon CR6-45NM ophthalmic digital imaging system and Canon EOS 10D digital camera (Canon USA Inc., One Canon Park, Melville, New York). Two digital images were taken of each eye of the participants in an almost completely dark room, with the first image centered on the macula and the second on the optic nerve. Digital images were evaluated by graders at the University of Wisconsin according to a modified Airlie House classification system (18). Retinopathy severity was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading scale (18). Participants with levels ≥14 were considered to have retinopathy according to the eye with the worse retinopathy level. The detailed assessment process is described in the NHANES database (19).

Assessment of MDS and vitamin D levels

The MDS was used to assess the total body magnesium status and was calculated using 4 factors: (1) diuretic use (current use for 1 point), (2) proton pump inhibitor use (current use for 1 point), (3) kidney function [60 mL/(min · 1.73 m^2) ≤ eGFR <90 mL/(min · 1.73 m^2) for 1 point; eGFR <60 mL/(min · 1.73 m2) for 2 points], and (4) alcohol consumption (heavy drinker for 1 point) (15). Heavy drinkers were defined as >1 drink/day for women and > 2 drinks/day for men. In this study, MDS was categorized as ≤2 and > 2.

Serum vitamin D levels were obtained directly from NHANES records based on laboratory test data. Severe vitamin D deficiency with a serum 25(OH)D concentration below <30 nmol/L greatly increases the risk of mortality and many other diseases (20). In this study, vitamin D levels were categorized as ≤30 nmol/L and > 30 nmol/L.

Covariates

Participants' data were collected including age, gender, race, education, marital status, family poverty-to-income ratio (PIR),

1 https://www.cdc.gov/nchs/nhanes/index.htm

physical activity, smoking, diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD), chronic kidney disease (CKD), dialysis, body mass index (BMI), time of venipuncture (morning, afternoon, evening), season of sample collection (November 1 through April, May 1 through October), vitamin A intake, vitamin D intake, Healthy Eating Index-2015 (HEI-2015), magnesium intake, and total energy intake. CVD includes angina, heart failure, heart attack, coronary heart disease, stroke, and congestive heart failure, and CVD was determined through self-report or the use of CVD medications. Diabetes (21), hypertension (22), and dyslipidemia (23) were identified in the basis of self-report or corresponding biochemical diagnostic indicators or appropriate medications. CKD was identified by a urine albumin to creatinine ratio (UACR) $\geq$ 30 mg/g or an eGFR $\leq$60 mL/min/m^2 (24). Vitamin D intake includes dietary and supplemental intake, and vitamin D intake was categorized as adequate, inadequate, and unknown according to the Dietary Reference Intakes (25).

Statistical analysis

Descriptive statistical analysis was performed in participants with and without retinopathy. Continuous data were described as mean and standard error (S.E.), and independent samples *t*-test was utilized to compare differences between the two groups. Categorical data were presented as frequency and percentage, and chi-square test or rank-sum test was used to compare differences between the two groups.

Variables with more missing values (e.g., physical activity, vitamin D intake, dialysis) were categorized as unknown, and variables with fewer missing values (<10%) were interpolated for missing values by the random forest multiple interpolation method using the "miceforest" package of the Python software. Difference analysis before and after missing value interpolation was performed (Supplementary Table S1). Weighted univariable logistic regression analysis was used to screen for covariates related to retinopathy (Supplementary Table S2). Weighted univariable and multivariable logistic regression analyses were utilized to assess the relationship of MDS and vitamin D with retinopathy: crude model was a univariable analysis; model 1 was a multivariable analysis that adjusted for age, gender, race, education, and PIR; model 2 was a multivariable analysis that adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake. The results were expressed as odds ratio (OR) and 95% confidence interval (CI).

The moderating effect of MDS on the relationship between serum vitamin D and retinopathy was analyzed. Crude model* included variables MDS, serum vitamin D, and interaction term "MDS × serum vitamin D." Model 3 adjusted for age, gender, race, education, and PIR based on crude model*. Model 4 adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake based on crude model*. The interaction term "MDS × serum vitamin D" was used to assess the moderating effect of MDS on the relationship between serum vitamin D and retinopathy. In addition, the effect of the association between serum vitamin D and retinopathy was stratified in two groups of MDS (MDS > 2 and MDS $\leq$ 2). Subgroups analyses were performed based on gender, age, diabetes, and BMI.

Data cleaning and processing of missing values were performed using Python 3.9 (Python Software Foundation, Delaware, United States), and statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, United States). All statistical tests were performed using two-sided tests, and a *p*-value of <0.05 was considered statistically significant.

Results

Characteristics of participants

During 2005–2008 NHANES survey cycle, 5,704 participants aged $\geq$40 years who were evaluated for retinopathy were selected. A total of 651 participants were excluded and 4,953 participants were included in the analysis (Figure 1). The characteristics of 4,953 participants were shown in Table 1. The mean age of the participants was 56.37 (0.39) years, of which 2,473 (35.82%) were $\geq$ 60 years old. There were 2,471 (52.48%) females and 2,723 (78.22%) non-Hispanic Whites. The mean BMI was 29.09 (0.15) kg/m^2, and 3,677 (72.13%) participants had a BMI $\geq$25 kg/m^2. The mean serum vitamin D level was 64.41 (0.76) nmol/L, and 557 (6.90%) participants had vitamin D levels $\leq$30 nmol/L. The mean MDS was 0.99 (0.03) points, and 432 (6.88%) participants had MDS >2 points. There were 602 (9.53%) participants with retinopathy and 4,351 (90.47%) participants without retinopathy.

Association of MDS and vitamin D with retinopathy

Table 2 lists the association of MDS and vitamin D with retinopathy. Serum vitamin D levels $\leq$30 nmol/L (vs. >30 nmol/L) increased the odds of retinopathy in univariable analysis (OR = 1.71, 95%CI: 1.30–2.25) and multivariable analysis [model 1: (OR = 1.38, 95%CI: 1.05–1.81); model 2: (OR = 1.37, 95%CI: 1.01–1.87)]. MDS >2 points (vs. $\leq$2 points) was associated with higher odds of retinopathy in univariable analysis (OR = 1.80, 95%CI: 1.25–2.60). After adjusting for age, gender, race, education, and PIR, MDS >2 points (vs. $\leq$2 points) still increased the odds of retinopathy (OR = 1.47, 95%CI: 1.01–2.16), but not in analysis adjusted for all confounders (p = 0.482).

Moderating effect of MDS on the relationship between serum vitamin D and retinopathy

Table 3 shows the effect of interaction term "MDS × vitamin D" on retinopathy. There was an interaction between MDS and vitamin D on the increased odds of retinopathy [crude model*: (OR = 2.33, 95%CI: 1.17–4.64), $P_{interaction}$ = 0.018; model 3: (OR = 2.76, 95%CI: 1.40–5.45), $P_{interaction}$ = 0.005; model 4: (OR = 2.29, 95%CI: 1.12–4.68), $P_{interaction}$ = 0.025]. Figure 2 shows the interaction between MDS and serum vitamin D on retinopathy. The risk of retinopathy showed a relatively smooth trend with decreasing serum vitamin D levels in the MDS $\leq$2 group, whereas the risk of retinopathy showed a rapid increase with decreasing serum vitamin D levels in the MDS >2 group. These results suggest that MDS plays a moderating role in the relationship between serum vitamin D and retinopathy.

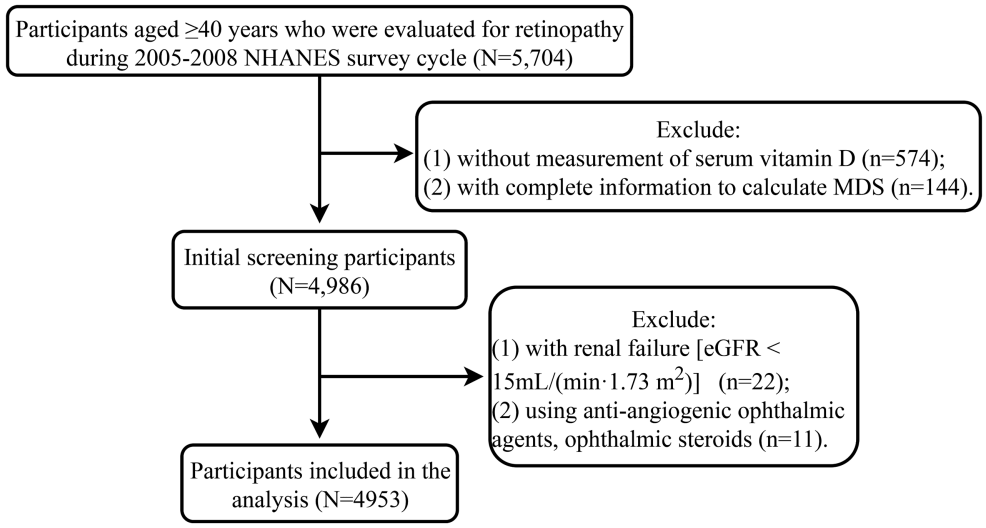

FIGURE 1
Flow chart of the study population. MDS, magnesium depletion score; eGFR, estimated glomerular filtration rate; NHANES, the National Health and Nutrition Examination Survey database.

Table 4 presents the relationship between serum vitamin D and retinopathy in different MDS groups. In the MDS ≤2 group, serum vitamin D levels ≤30 nmol/L (vs. >30 nmol/L) increased the odds of retinopathy only in univariable analysis (OR = 1.47, 95%CI: 1.05–2.07). In the MDS >2 group, serum vitamin D levels ≤30 nmol/L (vs. >30 nmol/L) was related to higher odds of retinopathy both in univariable analysis (OR = 3.43, 95%CI: 2.01–5.86) and multivariable analysis (OR = 2.90, 95%CI: 1.16–7.24).

Because of the effect of age on retinopathy, we excluded 167 participants aged 80 years and older and used data from the remaining 4,786 participants for sensitivity analysis. The results demonstrated that there was still an interaction between MDS and vitamin D on the increased odds of retinopathy [model 4: (OR = 2.48, 95%CI: 1.22–5.05), $P_{interaction} = 0.014$] (Supplementary Table S3). Due to too much missing data for the variable dialysis and the importance of the effect of dialysis on magnesium levels, we performed a sensitivity analysis after excluding the variable dialysis (Supplementary Table S4). The results showed that there was still an interaction between MDS and vitamin D on the risk of retinopathy after the exclusion of the variable dialysis [model 4: (OR = 2.26, 95%CI: 1.11–4.58), $P_{interaction} = 0.025$].

Moderating effect of MDS in different subgroups

The moderating effect of MDS on the association between serum vitamin D and retinopathy in different subgroups were presented in Table 5. In different subgroups, the interaction between MDS and serum vitamin D on retinopathy was observed in males (OR = 6.88, 95%CI: 1.41–33.66, $P_{interaction} = 0.019$), people with diabetes (OR = 3.43, 95%CI: 1.78–6.63, $P_{interaction} < 0.001$), and people with BMI ≥25 kg/m^2 (OR = 2.46, 95%CI: 1.11–5.44, $P_{interaction} = 0.028$). In addition, there may be an interaction between MDS and serum vitamin D on retinopathy in people older than 60 years (OR = 2.13, 95%CI: 0.97–4.66, $P_{interaction} = 0.059$).

Among the different MDS groups, only serum vitamin D levels ≤30 nmol/L (vs. >30 nmol/L) were observed to increase the odds of retinopathy in males (OR = 14.07, 95%CI: 1.61–123.16), people with diabetes (OR = 3.71, 95%CI: 1.99–6.94), people older than 60 years (OR = 3.35, 95%CI: 1.37–8.17), and people with BMI ≥25 kg/m^2 (OR = 2.88, 95%CI: 1.07–7.76) in the MDS >2 group, but not in the MDS ≤2 group ($p > 0.05$) (Supplementary Table S5).

Discussion

This study examined the relationship between magnesium status and serum vitamin D levels and retinopathy in people aged 40 years and older. Serum vitamin D levels ≤30 nmol/L and high MDS (magnesium deficiency) were associated with higher odds of retinopathy. Moreover, MDS plays a moderating role in the relationship between serum vitamin D and retinopathy, and the moderating effect of MDS was observed only in males, people with diabetes, people older than 60 years, and people with BMI ≥25 kg/m^2.

Retinopathy is caused by microangiopathy involving small pre-capillary retinal arterioles, capillaries, and small veins (26). Injury is caused by microvascular leakage and microvascular occlusion resulting from rupture of the blood-retinal barrier (26). Several studies have reported the protective role of vitamin D in the development of retinopathy (4, 5, 27). Vitamin D may exert retinal protective effects through antioxidant, anti-inflammatory, anti-angiogenic, and immunomodulatory mechanisms (5). Vitamin D deficiency has been found to be associated with many eye diseases, such as myopia, age-related macular degeneration, glaucoma, diabetic retinopathy, and dry eye (5). Vitamin D has antioxidant and anti-inflammatory properties and plays a role in anti-angiogenesis, regulation of cell proliferation, differentiation, and apoptosis (28, 29).

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TABLE 1 Characteristics of participants with and without retinopathy.

Variables	Total (*n* = 4,953)	Non-retinopathy (*n* = 4,351)	Retinopathy (*n* = 602)	*p*
Serum Vitamin D, *n* (%)				<0.001
>30 nmol/L	4,396 (93.10)	3,886 (90.85)	510 (9.15)	
≤30 nmol/L	557 (6.90)	465 (85.30)	92 (14.70)	
MDS, *n* (%)				<0.001
≤2	4,521 (93.12)	3,996 (90.89)	525 (9.11)	
>2	432 (6.88)	355 (84.73)	77 (15.27)	
Age, *n* (%)				<0.001
<60 years	2,480 (64.18)	2,244 (92.05)	236 (7.95)	
≥60 years	2,473 (35.82)	2,107 (87.63)	366 (12.37)	
Gender, *n* (%)				<0.001
Male	2,482 (47.52)	2,142 (88.66)	340 (11.34)	
Female	2,471 (52.48)	2,209 (92.10)	262 (7.90)	
Race, *n* (%)				<0.001
Non-Hispanic White	2,723 (78.22)	2,467 (91.55)	256 (8.45)	
Non-Hispanic Black	951 (8.86)	780 (84.57)	171 (15.43)	
Others	1,279 (12.93)	1,104 (87.95)	175 (12.05)	
Education, *n* (%)				<0.001
Less than high school	1,426 (17.36)	1,198 (86.64)	228 (13.36)	
More than high school	3,527 (82.64)	3,153 (91.27)	374 (8.73)	
Marital status, *n* (%)				0.559
Married	3,007 (65.60)	2,638 (90.45)	369 (9.55)	
Never married	337 (6.11)	297 (88.64)	40 (11.36)	
Others	1,609 (28.29)	1,416 (90.89)	193 (9.11)	
PIR, *n* (%)				<0.001
≤1.3	1,221 (14.50)	1,063 (89.57)	158 (10.43)	
1.3–3.5	1906 (33.97)	1,633 (87.32)	273 (12.68)	
>3.5	1826 (51.53)	1,655 (92.79)	171 (7.21)	
Physical activity, *n* (%)				0.002
<450 met*minutes/week	703 (15.22)	619 (91.26)	84 (8.74)	
≥450 met*minutes/week	2,431 (53.59)	2,188 (91.80)	243 (8.20)	
Unknown	1819 (31.19)	1,544 (87.78)	275 (12.22)	
Smoke, *n* (%)				0.707
No	2,362 (48.61)	2075 (90.66)	287 (9.34)	
Yes	2,591 (51.39)	2,276 (90.28)	315 (9.72)	
Diabetes, *n* (%)				<0.001
No	3,821 (83.37)	3,538 (93.44)	283 (6.56)	
Yes	1,132 (16.63)	813 (75.56)	319 (24.44)	
Hypertension, *n* (%)				<0.001
No	2023 (46.62)	1865 (92.83)	158 (7.17)	
Yes	2,930 (53.38)	2,486 (88.40)	444 (11.60)	
Dyslipidemia, *n* (%)				0.714
No	903 (18.38)	808 (90.93)	95 (9.07)	
Yes	4,050 (81.62)	3,543 (90.36)	507 (9.64)	
CVD, *n* (%)				<0.001

(Continued)

TABLE 1 (Continued)

Variables	Total (*n* = 4,953)	Non-retinopathy (*n* = 4,351)	Retinopathy (*n* = 602)	*p*
No	3,517 (75.96)	3,174 (92.29)	343 (7.71)	
Yes	1,436 (24.04)	1,177 (84.71)	259 (15.29)	
CKD, *n* (%)				<0.001
No	4,025 (86.29)	3,635 (91.85)	390 (8.15)	
Yes	928 (13.71)	716 (81.73)	212 (18.27)	
Dialysis, *n* (%)				<0.001
No	142 (2.19)	112 (83.51)	30 (16.49)	
Yes	9 (0.07)	3 (36.98)	6 (63.02)	
Unknown	4,802 (97.74)	4,236 (90.66)	566 (9.34)	
BMI, *n* (%)				<0.001
BMI < 25 kg/m^2	1,276 (27.87)	1,171 (93.38)	105 (6.62)	
BMI ≥ 25 kg/m^2	3,677 (72.13)	3,180 (89.34)	497 (10.66)	
Time of venipuncture, *n* (%)				0.025
Morning	2,394 (48.60)	2077 (89.24)	317 (10.76)	
Afternoon	1892 (35.63)	1,670 (90.90)	222 (9.10)	
Evening	667 (15.77)	604 (93.24)	63 (6.76)	
Season of sample collection, *n* (%)				0.352
November 1 through April	2,128 (36.55)	1857 (89.90)	271 (10.10)	
May 1 through October	2,825 (63.45)	2,494 (90.79)	331 (9.21)	
Vitamin A intake, mcg, Mean (S.E)	637.52 (11.63)	636.71 (11.31)	645.17 (28.78)	0.749
Vitamin D intake, *n* (%)				0.214
Adequate	477 (10.67)	430 (92.47)	47 (7.53)	
Inadequate	2,132 (35.91)	1868 (89.82)	264 (10.18)	
Unknown	2,344 (53.42)	2053 (90.50)	291 (9.50)	
HEI-2015, Mean (S.E)	51.40 (0.43)	51.51 (0.45)	50.43 (0.68)	0.153
Magnesium intake, mg, Mean (S.E)	320.44 (6.81)	321.05 (7.18)	314.59 (12.91)	0.642
Total energy, kcal, Mean (S.E)	2097.52 (21.29)	2098.16 (19.48)	2091.44 (71.57)	0.920

MDS, magnesium depletion score; PIR, family poverty-to-income ratio; CVD, cardiovascular disease; CKD, chronic kidney disease; BMI, body mass index; HEI-2015, Healthy Eating Index-2015.

TABLE 2 Association of MDS and vitamin D with retinopathy analyzed by logistic regression analysis.

Variables	Crude Model		Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Serum vitamin D						
>30 nmol/L	Ref		Ref		Ref	
≤30 nmol/L	1.71 (1.30–2.25)	<0.001	1.38 (1.05–1.81)	0.023	1.37 (1.01–1.87)	0.046
MDS						
≤2	Ref		Ref		Ref	
>2	1.80 (1.25–2.60)	0.003	1.47 (1.01–2.16)	0.049	0.86 (0.57–1.32)	0.482

MDS, magnesium depletion score; OR, odds ratio; CI, confidence interval; Ref, reference; Crude model, univariable analysis. Model 1, multivariable analysis that adjusted for age, gender, race, education, and PIR; Model 2, multivariable analysis that adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake.

In addition, vitamin D prevents oxidative stress and inflammation in human retinal cells and increases the cellular viability of retinal pigment epithelial cells and various tissues (4). This current study analyzed the relationship between serum vitamin D levels and magnesium status and retinopathy. Our results demonstrated that low vitamin D levels and high MDS were related to higher odds of retinopathy. In addition, MDS plays a moderating role in the effect of serum vitamin D on retinopathy. The risk of retinopathy changed insignificantly with decreasing serum vitamin D levels in the low magnesium depletion group, whereas the risk of retinopathy showed

10.3389/fnut.2024.1408497

TABLE 3 Interaction between MDS and serum vitamin D on retinopathy analyzed by logistic regression analysis.

Variables	Crude Model*		Model 3		Model 4	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Serum vitamin D	1.47 (1.05–2.07)	0.026	1.16 (0.83–1.62)	0.380	1.06 (0.72–1.56)	0.767
MDS	1.56 (1.00–2.44)	0.052	1.26 (0.79–2.01)	0.317	0.78 (0.47–1.28)	0.312
MDS × serum vitamin D	2.33 (1.17–4.64)	0.018	2.76 (1.40–5.45)	0.005	2.29 (1.12–4.68)	0.025

Serum vitamin D (≤30, >30 nmol/L) and MDS (≤2, >2) were analyzed as categorical variables; MDS, magnesium depletion score; OR, odds ratio; CI, confidence interval; Crude model*, included variables MDS, serum vitamin D, and interaction term "MDS × serum vitamin D"; Model 3, adjusted for age, gender, race, education, and PIR based on crude model*; Model 4, adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake based on crude model*.

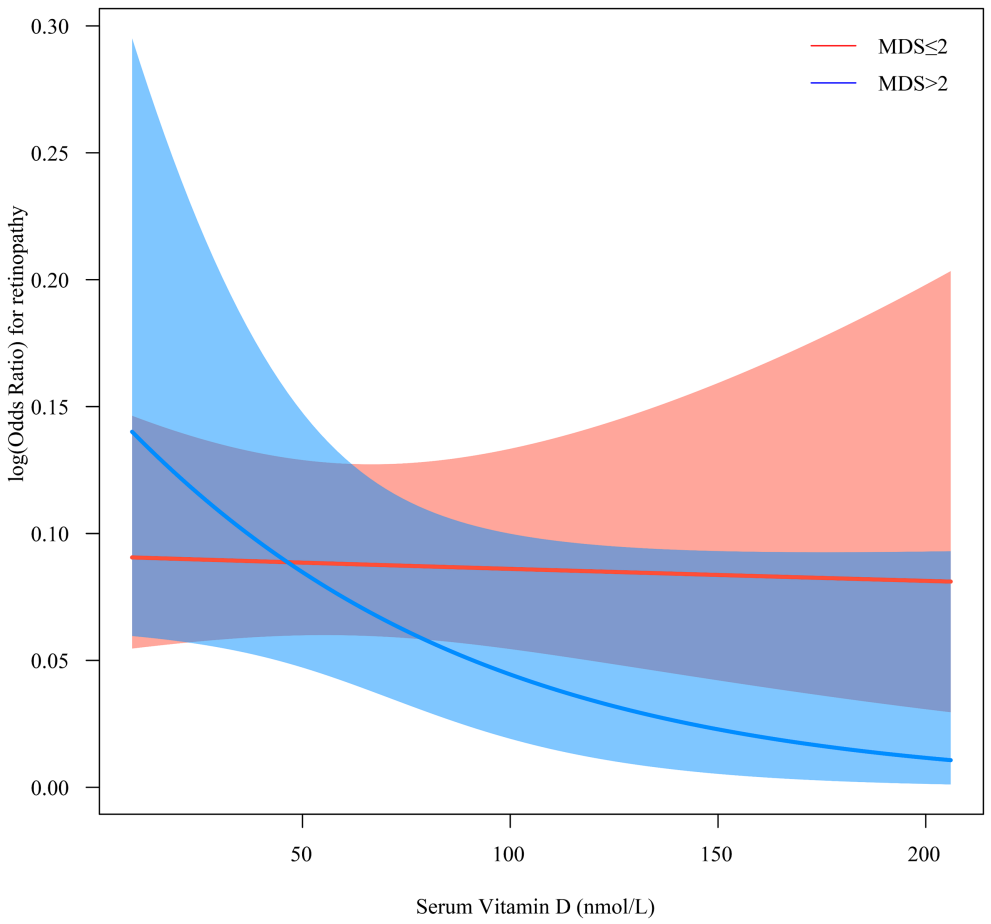

FIGURE 2
The interaction between MDS and serum vitamin D on retinopathy. MDS, magnesium depletion score.

a rapid increase with decreasing serum vitamin D levels in the high magnesium depletion group.

Magnesium plays an important role in maintaining normal metabolism and ionic balance in ocular tissues (30). Membrane-associated ATPases, enzymes for ATP production and hydrolysis are magnesium-dependent (31). In the presence of magnesium deficiency, insufficient activity of antioxidant enzymes leads to lipid peroxidation of polyunsaturated fatty acid-rich membranes by free radicals, thereby impairing retinal function (31). For diabetic retinopathy, insulin resistance decreases intestinal and renal tubular epithelial activity and reduces magnesium absorption by the intestinal and renal epithelium, resulting in low serum magnesium (32). Low serum magnesium levels can further exacerbate insulin resistance, and the two affect each other (33). Magnesium intake can reduce oxidative stress and improve insulin and glucose metabolism (34, 35). In our further analyses, the moderating effect of MDS on the relationship between serum vitamin D and retinopathy was observed only in males, people with diabetes, people older than 60 years, and people with BMI ≥25 kg/m^2. Sex differences in the moderating effect of MDS may be related to sex hormones. Serum magnesium concentrations have been reported to be positively correlated with estradiol (36). The moderating effect of MDS was significant in people with diabetes and people with BMI ≥25 kg/m^2 may be associated with insulin and glucose metabolism due to the role of

TABLE 4 The relationship between serum vitamin D and retinopathy in different MDS groups analyzed by logistic regression analysis.

Variables	Crude Model		Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
MDS ≤ 2 (n = 4,521)						
Serum vitamin D > 30 nmol/L	Ref		Ref		Ref	
Serum vitamin D ≤ 30 nmol/L	1.47 (1.05–2.07)	0.026	1.17 (0.81–1.68)	0.391	1.23 (0.83–1.84)	0.293
MDS > 2 (n = 432)						
Serum vitamin D > 30 nmol/L	Ref		Ref		Ref	
Serum vitamin D ≤ 30 nmol/L	3.43 (2.01–5.86)	<0.001	3.42 (1.65–7.11)	0.002	2.90 (1.16–7.24)	0.024

MDS, magnesium depletion score; OR, odds ratio; CI, confidence interval; Ref, reference; Crude model, univariable analysis. Model 1, multivariable analysis that adjusted for age, gender, race, education, and PIR; Model 2, multivariable analysis that adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake.

TABLE 5 Interaction between MDS and serum vitamin D on retinopathy in different subgroups analyzed by logistic regression analysis.

Variables	Model			
	OR (95%CI)	*p*	OR (95%CI)	*p*
	Age < 60 years (n = 2,480)		Age ≥ 60 years (n = 2,473)	
Serum Vitamin D	1.03 (0.56–1.90)	0.912	1.28 (0.68–2.41)	0.427
MDS	1.88 (0.52–6.88)	0.326	0.54 (0.35–0.85)	0.008
MDS × serum vitamin D	1.12 (0.09–13.52)	0.926	2.13 (0.97–4.66)	0.059
	Male (n = 2,482)		Female (n = 2,471)	
Serum Vitamin D	0.75 (0.43–1.29)	0.290	1.34 (0.76–2.38)	0.303
MDS	0.87 (0.32–2.38)	0.784	0.66 (0.36–1.21)	0.174
MDS × serum vitamin D	6.88 (1.41–33.66)	0.019	1.20 (0.44–3.28)	0.709
	Diabetes-no (n = 3,821)		Diabetes-yes (n = 1,132)	
Serum Vitamin D	1.20 (0.72–1.99)	0.469	0.88 (0.48–1.59)	0.654
MDS	0.99 (0.43–2.29)	0.986	0.58 (0.34–0.99)	0.048
MDS × serum vitamin D	1.84 (0.44–7.66)	0.390	3.43 (1.78–6.63)	<0.001
	BMI < 25 kg/m^2 (n = 1,276)		BMI ≥ 25 kg/m^2 (n = 3,677)	
Serum Vitamin D	1.58 (0.67–3.70)	0.283	0.97 (0.62–1.52)	0.904
MDS	0.39 (0.12–1.26)	0.111	0.83 (0.48–1.44)	0.495
MDS × serum vitamin D	1.68 (0.11–26.86)	0.705	2.46 (1.11–5.44)	0.028

Serum vitamin D (≤30, >30 nmol/L) and MDS (≤2, >2) were analyzed as categorical variables; MDS, magnesium depletion score; OR, odds ratio; CI, confidence interval; Model, included variables MDS, serum vitamin D, and interaction term "MDS × serum vitamin D" and adjusted for age, gender, race, education, PIR, diabetes, hypertension, CVD, CKD, dialysis, BMI, time of venipuncture, and vitamin D intake (corresponding subgroup variables are not adjusted in this subgroup analysis).

magnesium in insulin and glucose metabolism (34, 35). Since magnesium status plays a moderating role in the effect of serum vitamin D on retinopathy, the corresponding mechanism of effect may need to be further explored.

This study is the first to examine the interaction of magnesium and vitamin D status on the risk of retinopathy in the middle-aged and elderly population based on data from a large nationally representative sample. This study provides epidemiologic evidence for the effect of magnesium modulating vitamin D levels on retinopathy. However, some limitations of this study should be noted. First, this was a cross-sectional study that could not infer causality, and residual confounders may have biased the results. Second, the effects of MDS and vitamin D levels on different subtypes of retinopathy could not be assessed because of the lack of appropriate data. Third, some of the information, such as medical history and physical activity, was obtained through self-report, which may have information bias.

Conclusion

This study explored the joint effect of magnesium status and serum vitamin D levels on retinopathy in people aged 40 years and older. Magnesium levels may play a moderating role in the relationship between vitamin D and retinopathy. The protective effect of vitamin D against retinopathy was primarily present among those with inadequate magnesium levels. The mechanisms underlying the moderating effect of magnesium status on the relationship between vitamin D and retinopathy may need to be further explored.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary materials, further inquiries can be directed to the corresponding author/s.

Ethics statement

The requirement of ethical approval was waived by First Affiliated Hospital of Gannan Medical University, for the studies involving humans because First Affiliated Hospital of Gannan Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LeX: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing. PY: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. WL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. LL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. XL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. LiX: Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1408497/full#supplementary-material

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Higher vitamin B_6 dietary consumption is associated with a lower risk of glaucoma among United States adults

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Objective: Although numerous studies have substantiated the neuroprotective effects of vitamin B_6 on the optic nerve and its enhancement of visual function, comprehensive data delineating the correlation between vitamin B_6 and glaucoma at a national demographic scale remain insufficient. This study is designed to explore the link between the dietary consumption of vitamin B_6 and glaucoma.

Methods: This study included 3,850 individuals aged 40 and older from the National Health and Nutrition Examination Survey (NHANES), spanning 2005–2008. Dietary consumption of vitamin B_6 was calculated from the average of two 24-h dietary recall interviews. Glaucoma was diagnosed in accordance with the established Rotterdam criteria. To evaluate the relationship between vitamin B_6 dietary consumption and the risk of glaucoma, we employed Restricted Cubic Splines and weighted multivariable logistic regression analysis. We employed stratified and three other sensitivity analyses to confirm the robustness of our results, and conducted a preliminary exploration of the potential association between vitamin B_6 supplement consumption and glaucoma risk.

Results: After adjusting for covariates, we found a significant inverse correlation between dietary consumption of vitamin B_6 and glaucoma risk ($p_{\text{non-linearity}} = 0.18$; p for trend = 0.02). Stratified analysis and three other sensitivity analyses revealed stability in the outcomes (all p for interaction>0.05). Compared to the lowest quartile of consumption (≤1.23 mg/day), individuals in the highest quartile of vitamin B_6 consumption (>2.34 mg/day) experienced a 75% reduction in glaucoma risk (OR = 0.25, 95% CI 0.07–0.92). However, the effect of vitamin B_6 supplements on glaucoma was inconclusive.

Conclusion: A diet high in vitamin B_6 inversely correlates with glaucoma risk, suggesting that increasing dietary intake of vitamin B_6 could be a viable preventative strategy against glaucoma among adults in the United States.

KEYWORDS

cross-sectional study, glaucoma, vitamin B_6, National Health and Nutrition Examination Survey, nutrition

1 Introduction

Glaucoma, a leading global cause of irreversible vision loss, affects over 80 million individuals worldwide (1, 2). This condition is characterized by the progressive degeneration of retinal ganglion cells (RGCs) and their axons. Key risk factors for glaucoma include advanced age and elevated intraocular pressure (IOP) (3). The prevailing treatment strategy for glaucoma primarily revolves around the reduction of IOP. However, a significant subset of patients who effectively manage their IOP continue to experience progressive visual impairment. This phenomenon has sparked intense scientific investigation into alternative therapeutic approaches.

In glaucoma, RGC death occurs through apoptosis, triggered by various mechanisms such as mechanical damage and ischemic changes due to high IOP, both contributing to oxidative stress. Additional glaucoma risk factors, such as advanced age, genetic predispositions, and inflammatory processes, also precipitate oxidative stress through distinct biological pathways (4–7). RGCs, with their high energy demands, are particularly vulnerable to fluctuations in cellular fuel supply (8). Oxidative stress can lead to mitochondrial dysfunction and compromised ATP synthesis, causing irreparable cellular damage and ultimately resulting in the loss of RGCs (9–13). Furthermore, research suggests that oxidative stress may exacerbate damage to the trabecular meshwork (TM) in the eye, thereby increasing IOP and perpetuating a vicious cycle (14). Hence, oxidative stress is instrumental in the pathogenesis of glaucoma, constituting a crucial element of the alterations associated with glaucoma.

Emerging evidence suggests that antioxidant-rich diets, serving as an alternative therapy, can play a minimally invasive role in managing disease progression and significantly prevent glaucoma (15, 16). Specifically, vitamin B_6, known for its antioxidant properties, shows potential in neuroprotection and improving visual function (15, 17). For instance, animal model experiments by Wang et al. (18) have revealed that vitamin B_6 can counteract neuronal death in adult primate retinas following ischemia. Meanwhile, clinical trials by Mallone et al. (19) indicate that high-dose administration of vitamins B_1, B_6, and B_{12} significantly enhances visual function metrics in cases of chronic visual impairment associated with multiple sclerosis. Furthermore, Ruamviboonsuk et al. (20) have proposed that a 6-month regimen combining vitamins B_6, B_9, and B_{12} significantly enhances retinal sensitivity and thickness in patients with mild to moderate non-proliferative diabetic retinopathy Additionally, a case report by Xuan Cui et al. suggests that supplementation with vitamin B_6 positively affects the delay of Gyrate atrophy (21).

Concurrently, the relationship between vitamin B_6 and the broader group of B vitamins with glaucoma is increasingly being studied and discussed at various levels. Li et al. (22) conducted a meta-analysis to examine the association between serum levels of vitamins B_6, B_{12}, and D across various types of glaucoma. Their findings indicated no significant link between serum vitamin B_6 levels and glaucoma. Similarly, meta-analyses by Xu et al. (23) and Li et al. (24) on non-ocular risk factors for primary glaucoma corroborated these results. In contrast, clinical research led by Rolle et al. (25) demonstrated that supplements containing vitamins B_2, B_6, and folic acid could decelerate the progression of functional impairment in patients with primary open-angle glaucoma and enhance visual function. Additionally, a recent cross-sectional study by Lee et al. (26) exploring the relationship between niacin intake and glaucoma incorporated the intake of vitamins B_2 and B_6 as covariates in their model. However, direct research linking dietary intake of vitamin B_6 to glaucoma is relatively scarce and tends to focus on specific types of the condition (27), such as the prospective study by Walter Willet and others on exfoliative glaucoma and its suspected cases in relation to folic acid, vitamin B_6, and B_{12} (27). As a nationally representative cross-sectional study, this research aims to utilize NHANES data to explore the potential relationship between dietary vitamin B_6 intake and glaucoma in the U.S. population.

2 Materials and methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES), conducted biennially, is a national epidemiological cross-sectional study that utilizes a stratified multistage cluster sampling design to collect health and nutrition data from the U.S. population (28). Additional information about this survey is available on its official website (29). This study adheres to strict ethical standards, ensuring that all participants voluntarily provided informed consent. Our research utilized data collected from 2005 to 2008 by NHANES, involving 7,081 individuals aged 40 and older who underwent eye examinations. We excluded participants who did not attend two dietary interviews or lacked vitamin B_6 dietary data ($n = 1{,}285$), those without gradable fundus photographs ($n = 541$), participants with unavailable or unusable frequency doubling technology (FDT) visual field test results or cup-to-disc ratio data ($n = 487$), and those with abnormal FDT results or cup-to-disc ratios likely due to alternative causes such as cerebrovascular disease ($n = 366$) or various retinal diseases ($n = 552$). After these exclusions, 3,850 participants were included in the final analysis. Given that the missing values in all confounding variables were less than 5% of the final sample size, based on existing literature (30), we considered such a small proportion of missing data unlikely to introduce significant bias into our results. Therefore, we did not exclude these participants from our analysis. Baseline characteristics of included and excluded participants are detailed in Supplementary Table S1. Of the final sample, data on vitamin B_6 supplement intake was available for 615 participants; this data was analyzed to investigate the association between vitamin B_6 supplement intake and the incidence of glaucoma (Figure 1).

2.2 Exposure and outcome variables

The principal exposure in this study is the intake of vitamin B_6 in daily diets, derived from the Dietary Interview component of the dataset. This dataset focuses on collecting and analyzing dietary habits and nutrient intake across the U.S. population (31, 32). In our study, all eligible participants underwent two 24-h dietary recall interviews. These interviews detailed the types and quantities of food consumed in the 24 h preceding each interview. The initial interview was conducted at the Mobile Examination Center (MEC) (32), followed by a second interview via telephone 3 to 10 days later (33). We calculated the average of two interview sessions to estimate the final intake of vitamin B_6, which potentially provides a closer

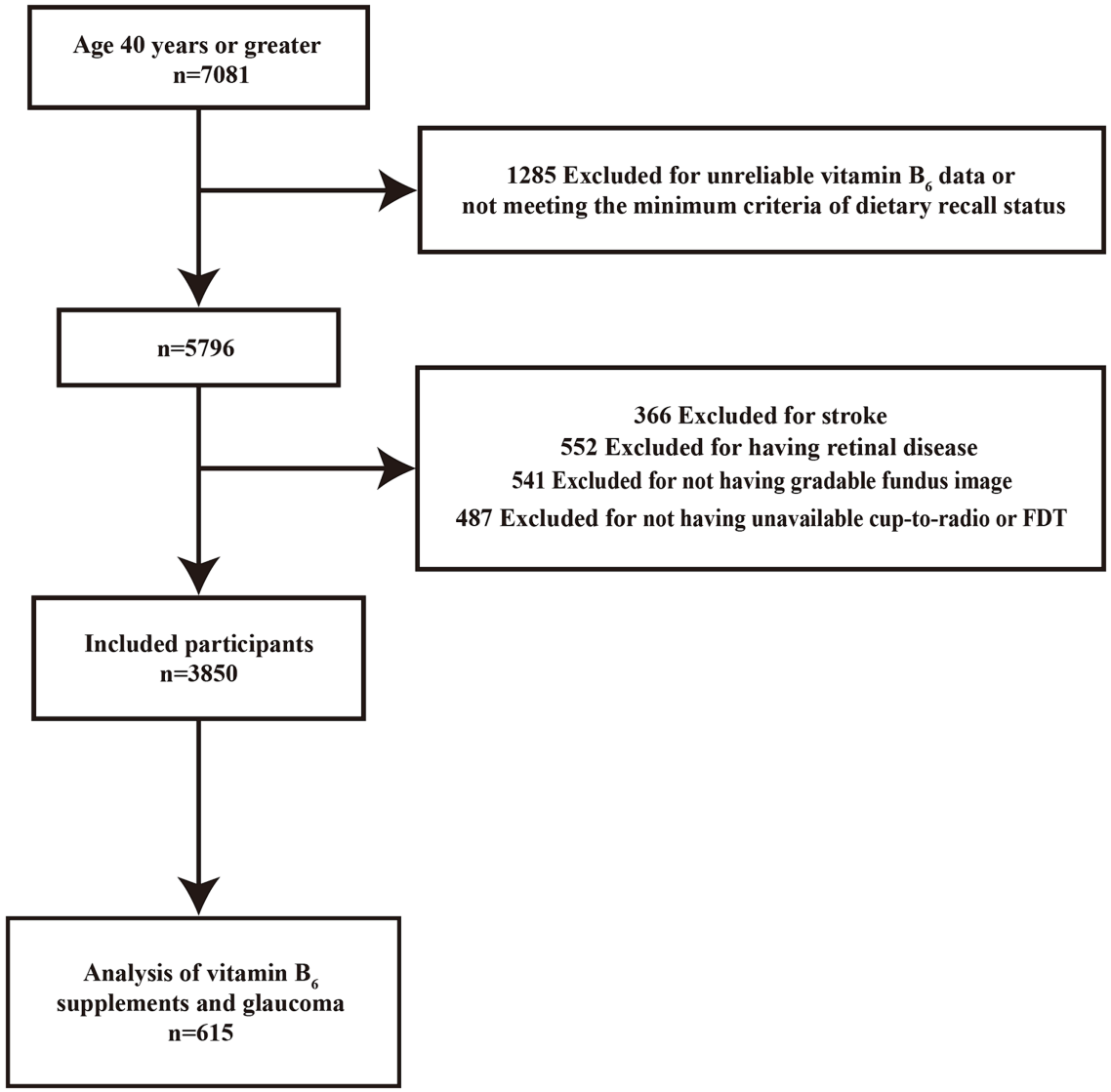

FIGURE 1
Flowchart depicting the selection process for the final inclusion group.

approximation of the participants' usual dietary intake compared to using data from a single interview.

The main result was the identification of glaucoma according to the Rotterdam Criteria, which considered the participants' abnormalities in the visual field and the appearance of the optic nerve. In NHANES, optic nerve morphology was evaluated by optic nerve imaging, and FDT was used to measure glaucoma visual field defects. Glaucoma was clinically diagnosed if at least one eye exhibited a positive FDT result, combined with a CDR in one eye or CDR asymmetry across both eyes, meeting or exceeding 97.5% of the average NHANES population's threshold (34–36).

In NHANES, trained technicians performed the FDT examination under dark conditions. Each eye underwent testing at 19 visual field locations, ensuring comprehensive assessment. The FDT outcome was classified as positive (using the 2–2-1 algorithm) if a minimum of two locations fell beneath the 1% threshold level in both initial and subsequent tests, with at least one identical failed location in both assessments (37). The CDR was ascertained through the analysis of two 45° non-mydriatic retinal digital images, captured by proficient technicians. Each image underwent review by a minimum of three trained graders. If the CDR scores from at least two of the three graders deviated by no more than 0.1, the outcome was established based on the median score. If the score difference between any two graders is greater than 2.2, the image was reviewed again with all graders present to reach a consensus (38).

2.3 Covariates

We conducted an extensive review of existing clinical research and practices related to glaucoma, including 20 potential confounding variables in our model to ensure reliability. These variables include age, sex, race, marital status, education level, household income, total caloric intake, Body Mass Index (BMI), alcohol consumption, waist circumference, diabetes, hypertension, cardiovascular disease (CVD), serum total cholesterol, C-reactive protein (CRP) levels, and dietary

consumption of vitamins B_1, B_2, B_3, B_9, and B_{12} (26, 27, 35, 39, 40). The first six of these variables, pertaining to sociodemographic information, were gathered through personal interviews (41). The intake levels of these vitamins were obtained from dietary interviews, which also accounted for total energy and alcohol consumption (32, 33). For our study, CVD was defined to include any heart-related conditions, such as congestive heart failure, coronary artery disease, angina, or myocardial infarction. Diabetes was classified based on a physician's diagnosis, the use of insulin or oral hypoglycemic agents, fasting plasma glucose levels ≥7.0 mmol/L, or glycated hemoglobin values ≥6.5%. Additionally, hypertension was characterized by a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg, ascertained by the mean of three consecutive readings, a self-disclosed history of hypertension, or the administration of antihypertensive medication (42, 43). Waist circumference measurements and BMI were obtained in the MEC (44), and non-fasting blood samples collected there were sent to laboratory for analysis to obtain total serum cholesterol levels and CRP (45–47). Due to the missing values of the covariate "smoking" reaching 47% of the study population, it could introduce significant bias to the statistical results. Therefore, this variable was not included in the adjusted covariates in this study.

2.4 Exploratory analysis of supplemental consumption of vitamin B_6

Vitamin B_6 supplements were introduced as exploratory variables to evaluate the potential influence of different sources of vitamin B_6 on the risk of glaucoma. The consumption of supplemental vitamin B_6 was determined by averaging data from two 24-h dietary recall interviews with participants.

2.5 Statistical analysis

We conducted weighted analyses using dietary sample weights from NHANES, adapting these to its complex survey sampling design and multilevel clustering. Continuous variables were described using weighted means with accompanying standard errors (SE), and categorical variables were presented as frequencies. The aim was to compare the distribution of potential confounding factors between participants with and without glaucoma. To assess the impact of the distribution of variables, the continuous exposure variables of dietary and supplemental intake of vitamin B_6 were converted into quartiles. This process involves arranging the data in ascending order based on the values of the exposure variables, and then determining the quartiles' cutoff values at the 25th, 50th, and 75th percentiles. These cutoff values divide the dataset into four approximately equal groups, allowing evaluation of the impact of varying levels of exposure variables on the outcome. Similarly, the division into quintiles follows a similar method, with cutoff values at the 20th, 40th, 60th, and 80th percentiles.

Three analytical models were constructed: a base model without adjustment, Model 1 with adjustments for age and sex, and Model 2, which extended these adjustments to include all relevant confounders. Building on Model 2, we first analyzed vitamin B_6 dietary consumption as a continuous variable using Restricted Cubic Splines (RCS) method. By positioning three knots at the 10th, 50th, and 90th percentiles, we used the likelihood ratio test to assess its association with glaucoma risk. Subsequently, we utilized the quartiles of dietary intake and supplemental intake of vitamin B_6, exploring their association with the risk of glaucoma using a weighted logistic regression model.

To bolster the validity of our research outcomes, we used subgroup analysis, accounting for various dimensions including age, race, sex, marital status, household income, education level, diabetes, CVD, and hypertension. This was to assess the consistency and stability of the results across different population groups. Additionally, we conducted three types of sensitivity analyses: (1) an unweighted logistic regression analysis of the sample; (2) an analysis of vitamin B_6 dietary intake divided into quintiles; and (3) an analysis excluding all participants with missing values in the confounding variables.

All statistical tests were conducted as two-tailed, with a significance level set at $p < 0.05$. Analytical procedures were executed using R 4.3.1.

3 Results

3.1 Baseline characteristics

The research included 3,850 unweighted participants and 96,323,492 weighted participants, all aged 40 or above, who participated in dietary interviews and had accessible fundus imaging and FDT test data. Out of these, 151 were identified as having glaucoma as per the study's definition, making up 3.9% of the unweighted population. In the weighted population, the proportion of glaucoma was 2.6% ($n = 2{,}463{,}459$). The findings indicated that among those with glaucoma, there was a significantly higher proportion of participants who were older, non-Hispanic black, not married, and had diabetes, hypertension, CVD, lower CRP, larger waist circumference, and lower total serum cholesterol levels, along with lower intake of vitamins B_3 and B_{12} (all $p < 0.05$). No notable differences were detected among participants in sex, household income, education level, total energy consumption, BMI, alcohol consumption, vitamin B_1, B_2 and B_9 intake, irrespective of their glaucoma status (all $p > 0.05$) (Supplementary Table S2).

3.2 Vitamin B_6 dietary consumption and glaucoma

The average dietary consumption of vitamin B_6 among all eligible participants was 1.96 mg/day (SE 0.02). Notably, the average vitamin B_6 dietary consumption in the glaucoma group [1.82 (SE 0.10) mg/day] was markedly inferior to that in the non-glaucoma group [2.04 (SE 0.03) mg/day] ($p = 0.02$). Based on the fully adjusted Model 2, the RCS analysis indicated no significant non-linear correlation between dietary vitamin B_6 consumption and glaucoma risk ($p_{\text{overall}} = 0.02$, $p_{\text{non-linearity}} = 0.18$) (Figure 2).

To delve deeper into the potential linear correlation between the consumption of dietary vitamin B_6 and glaucoma, we divided vitamin B_6 dietary consumption into four quartiles: Q1 (first) (≤1.23 mg/day), Q2 (second) (>1.23 to ≤1.70 mg/day), Q3 (third) (>1.70 to ≤2.34 mg/day), and Q4 (fourth) (>2.34 mg/day). The outcomes from the logistic regression model revealed a substantial

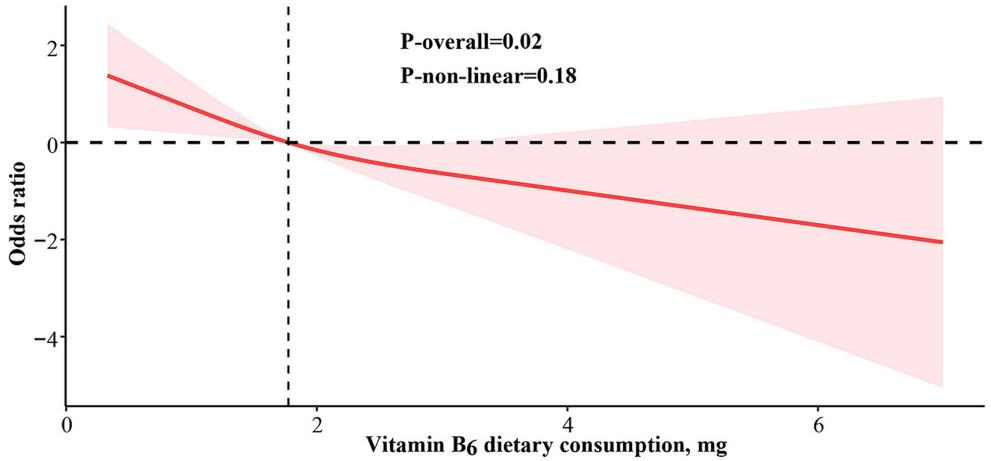

FIGURE 2
Restricted cubic spline analysis of vitamin B_6 dietary consumption and odds ratio of glaucoma based on Model 2, which was adjusted for age, sex, race, marital status, educational level, household income, total energy consumption, BMI (body mass index), alcohol consumption, waist circumference, diabetes, hypertension, cardiovascular disease, serum total cholesterol, C-reactive protein, dietary consumption of vitamin B_1, B_2, B_3, B_9 and B_{12}.

TABLE 1 Results of weighted logistic regressions between vitamin B_6 dietary consumption and risk of glaucoma.

Vitamin B_6 dietary Consumption, mg/day	Glaucoma					
	Crude model		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Q1 (≤1.23)	Ref		Ref		Ref	
Q2 (1.23–1.70)	0.59 (0.34, 1.02)	0.06	0.57 (0.31, 1.02)	0.06	0.50 (0.23, 1.11)	0.08
Q3 (1.70–2.34)	0.53 (0.32, 0.88)	0.02	0.50 (0.29, 0.84)	0.01	0.43 (0.21, 0.86)	0.02
Q4 (>2.34)	0.42 (0.24, 0.75)	0.005	0.38 (0.20, 0.73)	0.01	0.25 (0.07, 0.92)	0.04
P for trend	0.003		0.004		0.02	

Model 1 adjusted for age and sex. Model 2 further adjusted for race, marital status, educational level, household income, total energy consumption, BMI (body mass index), alcohol consumption, waist circumference, diabetes, hypertension, cardiovascular disease, serum total cholesterol, C-reactive protein, dietary consumption of vitamin B_1, B_2, B_3, B_9, and B_{12}. OR (95% CI), odds ratio (95% confidence intervals).

negative linear correlation between glaucoma and vitamin B_6 dietary consumption in the crude model (p for trend = 0.003), with a notable reduction in glaucoma proportion in the higher quartiles of vitamin B_6 dietary consumption compared to the lowest quartile (Q3: OR 0.53, 95% CI 0.32–0.88; Q4: OR 0.42, 95% CI 0.24–0.75). This inverse linear correlation persisted even after controlling for covariates. (Model 1: Q3: OR = 0.50, 95% CI 0.29–0.84; Q4: OR = 0.38, 95% CI 0.20–0.73; p for trend = 0.004; Model 2: Q3: OR = 0.43, 95% CI 0.21–0.86; Q4: OR = 0.25, 95% CI 0.07–0.92 p for trend = 0.02). (Table 1).

3.3 Sensitivity analysis

Subgroup analysis revealed no significant interactions between dietary vitamin B_6 consumption and variables such as age, race, sex, marital status, family income, educational level, diabetes, CVD, and hypertension (all p for interaction >0.05) (Figure 3). Additionally, in our three sensitivity analyses, the results remained robust: (1) unweighted logistic regression analysis was conducted on the sample; (2) dietary intake of vitamin B_6 was analyzed by dividing it into quintiles; (3) analysis was performed after excluding all participants who had missing values in the confounding variables (Supplementary Tables S3–S6).

3.4 Vitamin B_6 supplements shows no negative correlation with glaucoma

To investigate the impact of vitamin B_6 supplement consumption on glaucoma, we conducted a multivariate regression analysis examining the association between vitamin B_6 supplement intake and glaucoma incidence. The results indicated that the vitamin B_6 supplements consumption exhibited no association with glaucoma (Table 2).

4 Discussion

In our study involving 3,850 Americans aged 40 and older, we discovered a significant independent linear negative correlation

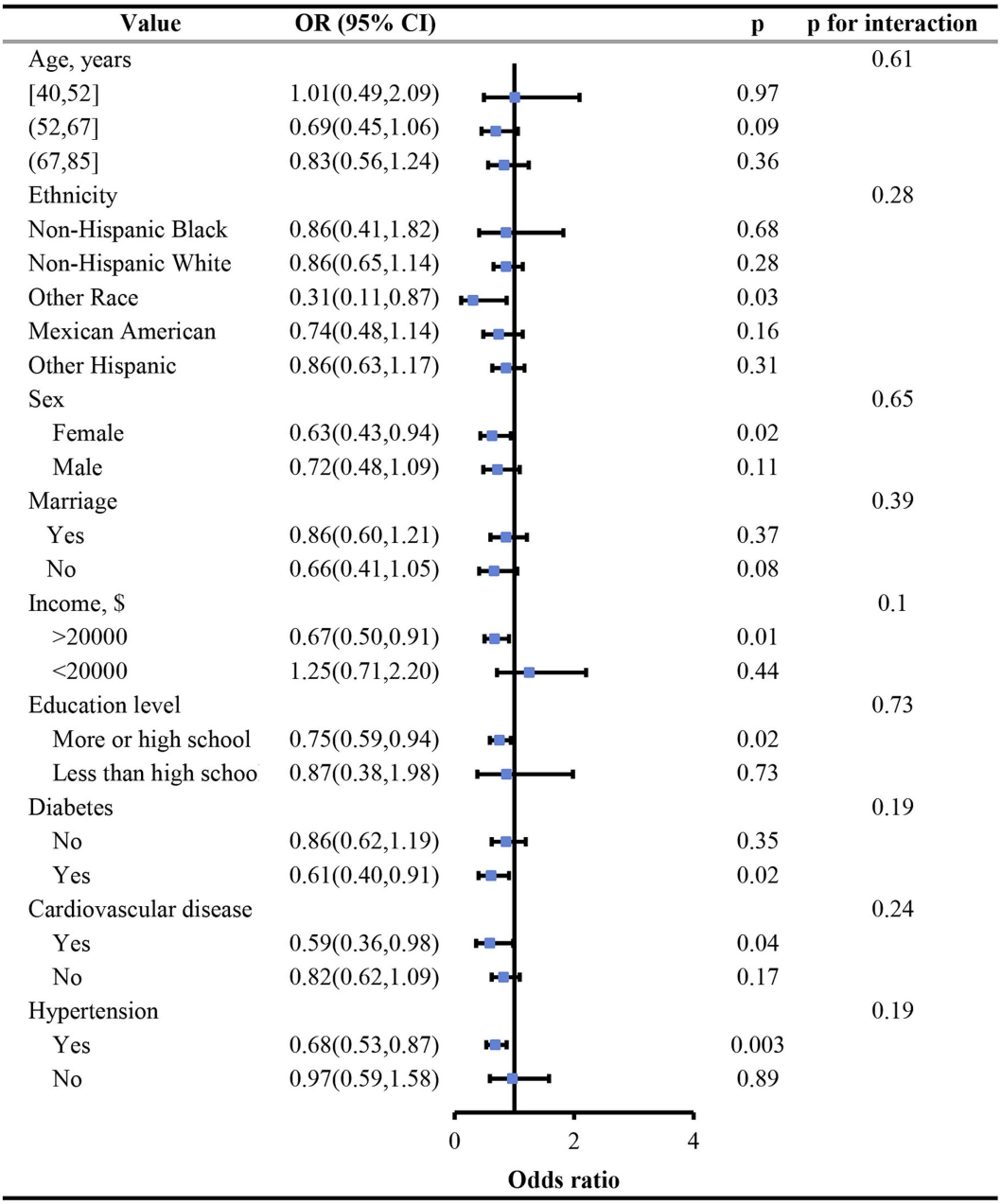

FIGURE 3
Subgroup analysis of correlation between vitamin B_6 dietary consumption and glaucoma stratified by age, race, sex, marital status, household income, education level, diabetes, cardiovascular disease and hypertension.

between dietary intake of vitamin B_6 and the risk of glaucoma. This relationship remained robust even after adjusting for multiple potential confounders. Relative to the first quartile of vitamin B_6 dietary consumption, which falls below the Recommended Dietary Allowance (RDA) of 1.6 mg/day for men and 1.4 mg/day for women, the odds of developing glaucoma dropped by 75% for individuals in the fourth quartile (>2.34 mg/day) (OR = 0.25, 95% CI 0.07–0.92). Additionally, we found no significant correlation between consumption of vitamin B_6 supplements and glaucoma risk.

In light of these results, our review of existing research indicates that there is still debate over whether vitamins from natural dietary sources and synthetic supplements are equivalent in terms of bioavailability and metabolic effects (48). While studies by Nelson et al. (49) suggest that vitamin B_6 from supplements has a higher absorption efficiency, research by Meinrad Lindschinger shows that natural and synthetic B vitamins are roughly equivalent in bioavailability. However, natural vitamin B_6 not only improves serum vitamin B_6 concentrations more effectively compared to its synthetic counterpart but also has a stronger impact on metabolic parameters like homocysteine levels and total antioxidant capacity (48). Additionally, there is currently no evidence to suggest that consuming large amounts of vitamin B_6 from food leads to adverse effects (50). However, multiple reports indicate that long-term excessive use of vitamin B_6

TABLE 2 Associations of vitamin B_6 supplements and risk of glaucoma.

Vitamin B_6 supplements, mg/day	Glaucoma					
	Crude model		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Q1 (≤2)	Ref		Ref		Ref	
Q2 (2, 3)	0.95 (0.24, 3.78)	0.94	0.82 (0.21, 3.18)	0.75	1.03 (0.19, 5.52)	0.97
Q3 (3–6)	0.84 (0.08, 8.95)	0.88	1.00 (0.10, 10.40)	1.00	0.36 (0.04, 3.13)	0.33
Q4(>6)	1.23 (0.45, 3.36)	0.66	1.36 (0.48, 3.83)	0.53	0.87 (0.17, 4.57)	0.87
P for trend	0.60		0.43		0.60	

Model 1 adjusted for age and sex. Model 2 further adjusted for race, marital status, educational level, household income, total energy consumption, BMI (body mass index), alcohol consumption, waist circumference, diabetes, hypertension, cardiovascular disease, serum total cholesterol, C-reactive protein, dietary consumption of vitamin B_1, B_2, B_3, B_9, and B_{12}. OR (95% CI), odds ratio (95% confidence intervals).

supplements can cause adverse reactions (50–53). Additionally, the discrepancy in our findings might be attributed to significant data loss among supplement users, reducing the sample size from 3,850 to 615, potentially introducing substantial bias into the results. Given the limitations of NHANES data, we could not further explore the relationship between these variables. Considering the controversies in existing research, we believe that comparing the efficacy of different sources of vitamin B_6 is a crucial direction for future studies.

Contrarily, our study findings diverge from those reported by JaeH Kang and his colleagues, who conducted a thorough cohort study identifying no significant link between vitamin B_6 intake and the risk of exfoliative glaucoma or its suspected cases. We hold their work in high regard for its rigor and evidential strength (27). The variations in our results likely stem from several key factors: Firstly, our research included all types of glaucoma, not just exfoliative glaucoma, which is estimated to constitute about 25% of all open-angle glaucoma cases (54). Secondly, our method for assessing vitamin B_6 intake, based on 24-h dietary recall interviews, differed from Kang's team, who used a long-term average intake method. Additionally, in the study populations, Kang and colleagues included female registered nurses and male health professionals, whereas our study population is based on NHANES data and broadly involves non-institutionalized civilians across the United States. There may be some degree of demographic and sociological differences between the two study populations. These factors highlight the diversity of research designs, which may explain differences in study outcomes. These key elements are worthy of further exploration and discussion in future research.

Given the discrepancies in existing research findings, a deep understanding of the biochemical roles and mechanisms of vitamin B_6 is particularly crucial. Vitamin B_6, a coenzyme essential for countless biochemical reactions, comprises six compounds (55). These include pyridoxal, pyridoxamine, pyridoxine, and their 5′-phosphate esters (56). Pyridoxal-5′-phosphate (PLP), known as the biologically active form of vitamin B_6 in humans, is often used interchangeably with the term "Vitamin B_6" (57, 58).

One potential protective mechanism of vitamin B_6 against glaucoma may be its antioxidant activity. Pioneering work by Margaret Daub's team has shown that vitamins are highly effective in quenching reactive oxygen species (ROS), with potential comparable to carotenoids and tocopherols (58, 59). Vitamin B_6, by quenching excess ROS, can reduce damage to ocular structures such as RGCs in the eye mitochondria caused by ROS imbalance, and play a certain role in the prevention of glaucoma and intervention in disease progression (13). On the other hand, vitamin B_6 has also been found to be involved in maintaining normal homocysteine (Hcy) levels, and its circulating levels often decrease concurrently with hyperhomocysteinemia (60). High levels of Hcy can promote the progression of glaucoma by stimulating cytochrome c release and ROS production, and by inducing mitochondrial dysfunction and oxidative stress through the ERK1/2 signaling pathway (60). Emerging research increasingly substantiates that hyperhomocysteinemia is a substantial risk factor in the progression of glaucoma (60, 61). A study carried out in Russia involving participants with glaucoma and early-stage cataracts has demonstrated that a 20-day course of low-dose pyridoxine hydrochloride eye drops can impact visual parameters, such as changes in visual acuity and expansion of the visual field. This regimen also showed a reduction in intraocular pressure and the Becker's coefficient (62).

Another potential protective mechanism of vitamin B_6 against glaucoma may be its role in promoting the synthesis of myelin phospholipids, which have been shown to play a significant role in nourishing axons (63, 64). PLP, as a coenzyme in myelin synthesis, plays a positive role in slowing disease progression (63). Considering these potential mechanisms, it's plausible that boosting vitamin B_6 consumption could strengthen the resilience of RGCs against glaucomatous neurodegeneration.

This study's strength lies in its use of stringent inclusion and exclusion criteria to enroll a large, nationally representative sample of American adults, which enhances the reliability of the results to a certain extent. Additionally, we validated the robustness of our conclusions through various sensitivity analyses, including subgroup analyses. On another note, our analysis of the relationship between vitamin B_6 supplements and glaucoma offers a preliminary exploration of the equivalence in efficacy between different sources of vitamin B_6.

This study presents several limitations that warrant consideration. First, to mitigate the impact of confounding factors, we implemented stricter inclusion and exclusion criteria that excluded individuals with stroke and retinal diseases. This approach limited the generalizability of our findings to the excluded groups and potentially introduced selection bias. Moreover, due to the cross-sectional nature of NHANES data, we could not explore causal or temporal associations between dietary vitamin B_6 consumption and glaucoma risk. Dietary intake data, based on self-reporting, may be subject to recall bias. Additionally, given the potential variability in daily food consumption, using data from only two interviews may not accurately reflect participants' regular dietary habits. Furthermore, we defined glaucoma using the Rotterdam criteria,

which, despite being internationally validated, have inherent false positive and negative rates (34). The lack of comprehensive eye examinations to differentiate among the various subtypes of glaucoma also limited our understanding of the correlation between vitamin B_6 dietary consumption and various subtypes of the condition.

To better understand the role of vitamin B_6 in preventing and treating glaucoma, future research should employ less restrictive criteria to include a more diverse group of participants, thereby enhancing the generalizability of the findings. Additionally, more frequent dietary assessments or extended dietary tracking periods could enhance the accuracy of dietary intake estimates. It is also important to take into account other influencing factors such as genetics and environmental conditions, and to conduct further investigations through randomized controlled trials or epidemiological cohort studies. Furthermore, distinguishing between different types and stages of glaucoma will help identify the most effective ways to use vitamin B_6 in prevention and treatment, offering more precise guidance for clinical practice.

5 Conclusion

Our findings indicate an inverse linear correlation between vitamin B_6 dietary consumption and glaucoma risk. Thus, sufficient dietary consumption of vitamin B_6 may serve as a preventive measure against glaucoma.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found a: https://www.jianguoyun.com/p/DagglMEQ_cmbDBjDrqgFIAA.

Ethics statement

The studies involving humans were approved by the NCHS Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

ZY: Formal analysis, Methodology, Writing – original draft. JZ: Conceptualization, Writing – original draft. YZ: Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

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Conflict of interest

The authors affirm that this research was conducted independently, with no commercial or financial affiliations that might be interpreted as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1363539/full#supplementary-material

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Evaluation of dietary patterns and their impact on eye health among Saudi adults—A multi-regional cross-sectional analysis in Makkah, Riyadh, and Qassim

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Background and aim: Nutrition plays a vital role in maintaining and improving vision health. However, little is known about dietary intake habits and their correlation with vision health among adults in the Kingdom of Saudi Arabia (KSA). The present survey was aimed to assess dietary patterns and vision health among Saudi adults and to determine the association between dietary patterns and vision health.

Methods: The present analytical study was carried out among 1,234 Saudi adults in the Makkah, Riyadh, and Qassim regions of KSA. We used the Arabic version of the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) and the diet quality screener (DQS). We applied Mann–Whitney U and Kruskal–Wallis tests to determine the association between vision function score and demographic characteristics. Furthermore, the Spearman correlation test was used to determine the relationship between the DQS and the NEI VFQ-25.

Results: Of the studied population, the highest score obtained through the NEI VFQ-25 was in the social function domain (mean ± SD = 76.64 ± 18.63), followed by the general vision domain (mean ± SD = 75.21 ± 15.16) and was negatively correlated with age. Regarding dietary patterns, the intake of lean protein sources per week was the highest, with a mean intake of 4.17 days per week, followed by that of whole grains and milk or dairy products, with a mean intake of around four days per week. There was a significant correlation between various dietary intakes and visual function scores.

Conclusion: The present survey underscores the significance of understanding regional dietary patterns and their implications for vision health. Furthermore, our study's findings indicate a need for targeted nutritional intervention measures to improve the vision health of this population.

KEYWORDS

nutrition, dietary pattern, Saudi adults, visual health, diet quality screener, lean protein intake

1 Introduction

Vision enables individuals to perform their daily tasks, such as learning, walking, shopping, and personal hygiene, without assistance from others (1, 2). Furthermore, as it affects all quality of life domains, visual problems are commonly associated with difficulties in physical function, emotional distress, and low socialization (personal, psychological, mobility, and social life) (3, 4). Visual impairment can cause substantial burden on the affected individual and the healthcare system (5, 6). The leading causes of visual impairment globally include diabetic retinopathy, cataracts, age-related macular degeneration, and glaucoma (7). The World Health Organization has launched VISION 2020: "The Right to Sight" to eradicate global blindness (8).

Dietary patterns have been linked with different aspects of vision health, including age-related macular degeneration, cataracts, glaucoma, and refractive errors. A nutritious eating regimen comprising fruits, vegetables, fatty fish, nuts, and various other food items has been recognized as advantageous for maintaining good eye health (9, 10). A diet that is rich in proteins and vegetables can reduce the risk of cataracts in middle-aged and elderly people (11). Similarly, a proper dietary regime for glaucoma patients is to maintain a normal weight, reduce excessive coffee intake, and enhance the intake of fruits and vegetables (12). Incorporating potent vitamins, antioxidants, and minerals into one's dietary regimen can enhance vision and contribute to overall eye health. Numerous research findings highlight the potential benefits of lutein and zeaxanthin in mitigating the risk of chronic eye diseases (13, 14). Additionally, the significance of omega-3 fatty acids cannot be understated, as they are vital in supporting proper visual development and maintaining optimal vision health (15).

Traditionally, Saudi Arabia (KSA)'s dietary pattern consisted of dates, whole grains, and meat. However, in recent years, KSA has seen significant changes in lifestyle and nutritional patterns, primarily an increase in the intake of junk food, which is high in salt and high in cholesterol (16, 17). Hence, there is an increasing burden of non-communicable diseases (NCDs). Vision impairments have emerged as one of the most important public health challenges. In the majority of Eastern Mediterranean Region (EMR) countries, including KSA, blindness, and poor vision continue to be major public health concerns (18, 19). A study by Adam et al. (16) stated that the intake of sugar, meat, and animal fat has increased, and fruit and vegetable intake has changed among their study participants. Another study by Hammouh et al. (20) in 2023 revealed that most of their study participants had a higher proportion of low knowledge and poor dietary practices. A recent study by Mulpuri et al. (21) emphasized the importance of diet and vision health, and Francisco et al. (22) ascertained the significant assessment of dietary patterns to improve vision health and quality of life of millions of people and avoid high-cost vision surgeries.

Vision health is the main part of wellbeing, which is the basis of the quality of life and the capacity to do everyday tasks. Nutrition proves to be a key factor in vision health, and its specific dietary patterns are related to the prevention and management of different eye conditions. Hence, assessing the dietary patterns and their association with vision health in the KSA is critical to planning for the necessary dietary intervention programs tailored to the local context. Although the link between diet and vision health is well-known, studies on the relationship between these two factors among adults in the KSA are scarce. Furthermore, dietary patterns are constantly changing among the population. Hence, continuous assessment of the dietary patterns in different cultural settings is essential. Therefore, this research aimed to conduct a nutrition and vision health survey among adults in three regions (Makkah, Riyadh, and Qassim) of Saudi Arabia to assess their dietary patterns and their correlation with vision health.

2 Participants and methods

2.1 Study description

A quantitative cross-sectional study was conducted among adults aged 18 years and older from May to October 2023 in three regions of Saudi Arabia–Qassim, Makkah, and Riyadh. Participants were recruited from public places such as malls, parks, and local community centers in Qassim, Makkah, and Riyadh. We chose this age group to focus on adults who are more likely to make independent dietary choices and experience age-related vision changes. We excluded patients who were diagnosed with chronic diseases, such as diabetes, hypertension, adults with already existing eye problems or injuries, and those aged above 65 years.

2.2 Sample size estimation and sampling method

Considering the limited studies available in this context, we have taken 50% as the expected proportion (p) to estimate the sample size. Numerous authors use this conservative method if the limited study is available to estimate the p in Cochran's sample

size estimation formula to get the largest size and sufficient power to detect significant associations. We used the WHO sample size calculator that uses the same principles of Cochran's formula ($n = z^2pq/e^2$) with a 95% confidence interval and 5% margin of error. The total sample estimated size was 384, and we rounded it to 400. Considering three regions, the research team decided to recruit a minimum of 400 participants from each region (Total = 1,200). The research team applied a convenience sampling method to recruit the participants. In this method, the data collectors made a stall in public places and invited them to participate.

2.3 Data collection procedure

We obtained ethical clearance from the regional research ethics committee, general directorate of health affairs, Gassim region, KSA (Approval number: 607/44/14429, Dated: 03.05.2023). The data collectors invited the participants from public places, as mentioned earlier. Interested individuals were given information about the study and invited to participate. All participants were required to give informed consent before participating in the study. The survey was administered through a Google form link on the data collectors' personal devices to participate in the survey. The survey was administered in the Arabic language. The data were collected anonymously, and the responses were accessed only by the principal investigator to protect the data. The data collection tool for this study was a self-administered survey that consisted of three sections: demographic information, the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), and the Diet quality assessment questionnaire. In the first section of the Google form, the participants filled their background characteristics such as age, gender, occupation, marital status, and level of education of the participants.

NEI VFQ-25 (second section) consists of 25 questions rated on a Likert scale wherein patients were asked to score the degree of difficulty associated with specific visual symptoms or tasks, including reading newspapers or driving (23). The questions were grouped into the following subdomains: general health, general vision, ocular pain, near vision activities, distance vision activities, and social functioning. In the scope of each subdomain, the participants gave answers that showed their individual experiences and views on the issues related to vision. In the domain of general health, the participants rated their overall health in relation to their vision problems, with scores ranging from 0 to 100, and the higher the score, the better the health. For the general vision subdomain, the participants again evaluated the vision aspects, such as vision clarity and satisfaction, on a scale from 0 to 100. Ocular pain was measured by the subjects who reported how often and how severe the pain or discomfort was due to the vision problems on a Likert scale. The near vision activities were assessed by the participants who specified the level of difficulty they had in tasks like reading or using electronic devices, from "No difficulty" to "Unable to do," using a Likert scale. Besides, participants also rated the ability to do distance vision activities like driving or watching television. Finally, the social functioning of the participants was evaluated by the rating of their social interactions and participation in leisure activities despite vision problems. Responses were noted on Likert scales or numerical rating scales; thus, the researchers knew the participants' thoughts on the vision-related quality of life in different domains. According to the NEI VFQ-25 scoring system, the subdomains were assessed and converted to a scale ranging from 0 to 100, where a score of 100 indicated the highest level of function. The composite (overall) score for the NEI VFQ-25 was derived as the mean of all subscale scores except the general health score. The NEI VFQ-25 has been used in various settings and is proven valid and reliable (24–26). Its extensive use in research makes it a suitable choice for capturing the subjective experiences and functional abilities related to vision health among our study participants. In the third section, diet quality was assessed by a dietary quality screener (DQS) consisting of questions regarding the diet intake per typical week, which included frequency of intake of fruit, vegetables, whole grains, and lean protein sources, variety of types of vegetables, and adequacy of milk and dairy product consumption. Participants indicated how often they consumed these items, with response options ranging from "Less than once a week or never" to "Daily or almost daily." The questionnaire was prepared for dietary quality screening from various dietary questionnaires according to the study population through a focused group discussion by the family medicine, public health, and nutrition experts based on previous works of literature (27–29). Hence, these two tools provided a quick and reliable method for examining the relationship between diet and vision health outcomes. The questionnaire was then translated into Arabic language and re-translated to check the appropriateness of the questions. As mentioned earlier, the prepared data collection form consisted of three sections and was initially tested through a pilot study among 30 eligible participants. All pilot study participants have given feedback that the instrument is clear and easy to understand. On average, it took 10 min to complete the questionnaire by the pilot study participants. The coefficient alpha (Cα) value obtained for the data collection tool is above 0.70 for both NEI VFQ-25 (Cα = 0.77) and DQS (Cα = 0.82) The pilot study participants' data were included in the overall analysis.

2.4 Statistical analysis

We analyzed the collected data statistically using IBM SPSS version 21 software. The demographic variables are expressed in frequencies and proportions. The dietary scores and visual function scores were expressed in mean and standard deviation. We applied Mann–Whitney U and Kruskal–Wallis tests to determine the association between vision function score and demographic characteristics. Furthermore, the Spearman correlation test was used to determine the relationship between DQS and NEI VFQ-25 variables. A p-value less than 0.05 derived from a two-tailed test was set as statistically significant.

3 Results

A total of 1,234 participants were included in the study, of which 403 were recruited from Qassim, 417 from Riyadh, and 414 from Makkah. The age of the participants was almost similar in all three regions, with a mean of 35.4 years. The occupation of the participants had almost the same distribution in the three regions with a higher proportion of self-employed and private

10.3389/fnut.2024.1383725

TABLE 1 Demographic characteristics of the study population (n = 1,234).

Demographic characteristics		Region			Total (n = 1,234)
		Qassim (n = 403)	Riyadh (n = 417)	Makkah (n = 414)	
Age (years) (mean ± SD)		34.2 (± 9.2)	34.9 (± 9.1)	37.1 (± 11.1)	35.4 (± 9.9)
Gender	Male	255 (63.3%)	277 (66.4%)	292 (70.5%)	824 (66.8%)
	Female	148 (36.7%)	140 (33.6%)	122 (29.5%)	410 (33.2%)
Occupation	Private sector	113 (28%)	136 (32.6%)	105 (25.4%)	354 (28.7%)
	Unemployed	36 (8.9%)	28 (6.7%)	33 (8%)	97 (7.9%)
	Government sector	76 (18.9%)	72 (17.3%)	122 (29.5%)	270 (21.9%)
	Students	50 (12.4%)	44 (10.6%)	62 (15%)	156 (12.6%)
	Retired	9 (2.2%)	8 (1.9%)	28 (6.8%)	45 (3.6%)
	Self-employed/ business	119 (29.5%)	129 (30.9%)	64 (15.5%)	312 (25.3%)
Marital status	Single	163 (40.4%)	165 (39.6%)	149 (36%)	477 (38.7%)
	Married	179 (44.4%)	188 (45.1%)	232 (56%)	599 (48.5%)
	Divorced	52 (12.9%)	52 (12.5%)	29 (7%)	133 (10.8%)
	Widow	9 (2.2%)	12 (2.9%)	4 (1%)	25 (2%)
Education status	Diploma	164 (40.7%)	172 (41.2%)	96 (23.2%)	432 (35%)
	Bachelor's degree	173 (42.9%)	181 (43.4%)	228 (55.1%)	582 (47.2%)
	Secondary	42 (10.4%)	34 (8.2%)	56 (13.5%)	132 (10.7%)
	Postgraduate	24 (6.0%)	30 (7.2%)	34 (8.2%)	88 (7.1%)
Income (SAR) (1 USD = 3.75 SAR)	< 5,000	67 (16.6%)	44 (10.5%)	53 (12.8%)	164 (13.3%)
	5,000 to 7,000	137 (34.0%)	163 (39.1%)	194 (46.9%)	494 (40.0%)
	> 7,000	199 (49.4%)	210 (50.4%)	167 (40.3%)	576 (46.7%)

sector working people except in Makkah, where the number of people working in the government sector was high, followed by private sector workers and self-employed. Most of the participants were married, followed by single, with less than 15% constituting divorced and widowed. Almost 80% of the study population in all the regions had either a bachelor's degree or diploma, with 6 to 8% having postgraduate degrees. Almost 10% had completed secondary grade of school education (Table 1).

Regarding the visual functioning assessment, the mean general vision score and other vision scores were almost 75, except for general health, which was 65.3. The mean overall vision score was 74.43 (±15.29) and had a negative correlation with age. Near vision activity and general vision had a high negative correlation with increasing age, followed by distant vision activity and social functioning score. The correlation of age with the scores was statistically significant (Table 2).

All the demographic variables were significantly related to the visual function score. Males had a better visual function than females. Government sector employees had a higher visual function, followed by students, those in the private sector, and unemployed individuals. The visual function scores were low among retired people and self-employed. Regarding marital status, single and married people had better visual function than divorced and widowed people. People residing in Makkah had higher visual function scores, followed by Qassim and Riyadh (Table 3).

Lean protein sources' weekly intake was the highest, with a mean intake of 4.17 days per week, followed by whole grains and milk or dairy products, with a mean intake of around four days per week. Mean vegetable intake, dark green vegetable intake, and orange vegetable intake were more than three days per week, and fruit intake was less than three days per week (Table 4).

There was a significant correlation between various dietary intake scores and visual function scores. Vegetable intake, dark green vegetable intake, orange vegetable intake, lean protein sources intake, and milk or dairy products intake significantly correlated with general health, general vision, near vision, distant vision, and social function scores. Fruit intake is positively correlated with general health, distant vision, and social functioning, whereas whole grain intake is positively

TABLE 2 Visual functioning scores and their correlation with age (n = 1,234).

NEI VFQ-25 scores	Mean (± SD)	Correlation with age
General health	65.3 (± 21.35)	−0.127**
General vision score	75.21 (± 15.16)	−0.223**
Ocular pain score	70.46 (± 38.11)	0.068*
Near vision activities score	74.68 (± 17.02)	−0.317**
Distance vision activities score	75.2 (± 16.58)	−0.172**
Social functioning score	76.64 (± 18.63)	−0.173**
Overall visual function score	74.43 (± 15.29)	−0.228**

*Correlation is significant at 0.05 level; **Correlation is significant at 0.01 level.

TABLE 3 Association between visual function score and demographic characteristics.

Variables		Overall Visual function score	Kruskal–Wallis *p*-value
Gender	Male	75.9 (± 15.5)	0.001[#]
	Female	71.5 (± 14.5)	
Occupation	Private sector	72.5 (± 13.3)	0.001
	Unemployed	73.5 (± 15.8)	
	Government sector	80.6 (± 17.8)	
	Students	79.8 (± 13.8)	
	Retired	68.9 (± 20.2)	
	Self-employed/business	69.7 (± 12)	
Marital status	Single	76.6 (± 14.4)	0.001
	Married	74.6 (± 15.7)	
	Divorced	69.6 (± 13.4)	
	Widow	56.2 (± 13)	
Education status	Diploma	71.3 (± 12.8)	0.001
	Bachelor	75.1 (± 16)	
	Secondary	79.3 (± 15.7)	
	Postgraduate	78.5 (± 18)	
Region	Qassim	74.4 (± 15.1)	0.001
	Riyadh	71.5 (± 13.3)	
	Makkah	77.5 (± 16.7)	
Income (SAR)	< 5,000	72.4 (± 13.8)	0.019
	5,000 to 7,000	74.8 (± 14.3)	
	> 7,000	75.6 (± 15.4)	

[#]*p*-value by Mann–Whitney U test.

TABLE 4 Dietary quality screener assessment results (n = 1,234).

Dietary quality screener	Less than once a week or never	1 to 2 times a week	3 to 4 times a week	5 to 6 times a week	Daily or almost daily	Days per week mean (± SD)
Fruits intake	127 (10.3%)	482 (39.1%)	345 (28%)	194 (15.7%)	86 (7%)	2.92 (± 1.99)
Vegetable intake	41 (3.3%)	361 (29.3%)	444 (36%)	261 (21.2%)	127 (10.3%)	3.58 (± 1.92)
Whole grains intake	60 (4.9%)	217 (17.6%)	402 (32.6%)	427 (34.6%)	128 (10.4%)	4.03 (± 1.92)
Lean protein sources intake	39 (3.2%)	184 (14.9%)	451 (36.5%)	419 (34%)	141 (11.4%)	4.17 (± 1.82)
Milk or dairy products intake	45 (3.6%)	248 (20.1%)	425 (34.4%)	357 (28.9%)	159 (12.9%)	4.01 (± 1.93)
Dark green vegetables intake	66 (5.3%)	315 (25.5%)	449 (36.4%)	285 (23.1%)	119 (9.6%)	3.6 (± 1.94)
Orange vegetable intake	40 (3.2%)	311 (25.2%)	437 (35.4%)	309 (25%)	137 (11.1%)	3.77 (± 1.92)

correlated with general vision, near vision, and distant vision scores (Table 5).

4 Discussion

This study aimed to address the gap in understanding the relationship between dietary habits and vision health among Saudi adults, providing valuable insights for public health interventions and strategies to preserve and enhance vision. The current study reported the visual functions among the population and showed that the mean overall vision score was 74.43. Population-based studies showed that the mean visual function score varies from 83 to 93 across the age groups, which signifies that the current study population had a lower visual function score than previous studies (24, 30). The variations across the studies could be attributed to the dietary patterns, lifestyles followed in the Arabian region and variations in data collection tools in the studies as mentioned above.

The age was negatively correlated with the visual function scores, which were statistically significant. Other studies have investigated the impact of age-related declines in visual function on physical health. One study revealed that visual impairment is associated with poor physical health, including physical limitations, difficulty with activities of daily living, and reduced quality of life (31). However, community-based factors could alleviate the effects of vision loss on physical outcomes, highlighting the importance

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TABLE 5 Correlation between dietary intake and visual functions.

	Fruits intake (days/week)	Vegetable intake (days/week)	Whole grains intake (days/week)	Lean protein sources intake (days/week)	Milk or dairy products intake (days/week)	Dark green vegetables intake (days/week)	Orange vegetables intake (days/week)
General health	0.114**	0.138**	−0.030	0.104**	0.070*	0.109**	0.171**
General vision score	−0.004	0.295**	0.126**	0.243**	0.235**	0.116**	0.109**
Ocular pain score	0.021	−0.038	−0.048	−0.057*	−0.024	0.083**	0.060*
Near vision activities score	0.002	0.266**	0.117**	0.234**	0.195**	0.157**	0.141**
Distance vision activities score	0.038	0.287**	0.075**	0.202**	0.202**	0.184**	0.165**
Social functioning score	0.126**	0.234**	0.009	0.221**	0.162**	0.232**	0.233**

*Correlation is significant at 0.05 level; **Correlation is significant at 0.01 level.

of public health endeavors to address visual impairment in older adults (31). One study revealed that decreases in visual function associated with aging significantly affect the health and overall wellbeing of elderly individuals. These declines occur across various levels of sensory and perceptual processing (32).

The visual function scores showed differences for all the demographic variables. Men had better visual function than women. This is supported by the study by Khandekar and Mohammed et al. (33), which showed that the age-adjusted prevalence of blindness in women was 3% higher than that in men. The current study showed that widow and divorced people had low visual function, which is supported by the study by Ezeh et al. (34) which had similar results. The visual function score was low among retired people and self-employed people, which may be attributed more to their age correlation. Region-wide differences in the visual functions may be attributed to their diet and lifestyle practices.

The current study analyzed the dietary patterns followed by the people in three regions of KSA. It was observed that people had a mean of more than four days per week of consumption of lean protein sources, whole grains, and dairy products, followed by a mean intake of vegetables for more than three days per week, followed by fruits, indicating the consumption of a mixed diet with a good source of carotenoids, vitamins, and minerals along with polyunsaturated fatty acids. Reasonable evidence suggests that dark-green leafy vegetables, significantly those high in lutein and zeaxanthin, may help prevent the onset and progression of age-related macular degeneration (AMD) and help lower the risk of some subtypes of cataracts and slow the advancement of glaucoma and diabetic retinopathy (35). Observational studies have revealed that long-chain omega-3 fatty acids, primarily derived from fish, are protective against certain kinds of visual impairment, specifically AMD (15, 36, 37).

The significant correlation between various dietary intakes and visual function scores in the present study further supports this finding. Vegetable intake, especially dark green vegetables and orange vegetables was significantly correlated with general health, general vision, near vision, distant vision, and social function scores. Similarly, the Eye Disease Case-Control Study (EDCC) found that increased intake of dark-green leafy vegetables was associated with a reduced risk of neovascular AMD (OR–0.57) (38). The Age-Related Eye Disease Study 2 (AREDS2) trial examined lutein and zeaxanthin (LZ) supplementation and revealed that sufficient dietary intake of LZ may protect against AMD progression (13). Fruits intake had a positive correlation with general health, distant vision, and social functioning. This is being reflected by many studies. Cross-sectional studies in urban India found a significant association of diabetic retinopathy with low dietary fiber intake in patients with type 2 diabetes (OR–2.24) (39). Blue Mountains Eye research explored that increased consumption of combined vitamins C, E, zinc, and beta-carotene reduces the chances of developing cataracts (OR–0.51) (40). A higher intake of fruits and increased vegetable intake reduced glaucoma risk among the population, as stated by several authors (12, 41).

Lean protein source intake and milk or dairy product intake significantly correlated with general health, general vision, near vision, distant vision, and social function score. In contrast, whole grain intake had a positive association with general vision, near vision, and distant vision scores. These correlations are evidenced

in many studies. Cohort studies have demonstrated that increased fish consumption is negatively associated with neovascular AMD development (OR–0.25) (40), (RR 0.65) (42). A meta-analysis by Chong et al. (43) has demonstrated that eating more than two servings of fish per week decreases the incidence of both early and late AMD, as does consuming high levels of omega-3 fatty acids (OR–0.62). Merle et al. (44) reported that higher dietary intake of vitamin D intake was associated with a lower risk of developing AMD. Reduced consumption of milk products and calcium was significantly linked with adverse retinal vascular symptoms (45, 46).

Oxidative stress and inflammation are believed to be essential in the pathogenesis of AMD, diabetic retinopathy, cataracts, and glaucoma are interconnected, implying that dietary interventions aimed at reducing these conditions could potentially enhance the outcomes of all four disorders simultaneously. Dietary intake of certain foods to decrease these stresses has been well-documented in AMD, diabetic retinopathy (DR), and cataracts (47). Visual impairment has important repercussions for both visually impaired individuals and on the health system. Changes in diet and lifestyle, such as reducing the risk of hyperglycaemia and eating more dark-green leafy vegetables, have the potential to delay or stop the onset of disease and have positive effects on preventing the development of other systemic diseases. Given the current burden of visual impairment on individuals and healthcare systems, further research is needed to determine whether implementing proper dietary and lifestyle measures can effectively reduce the risk of visual impairment.

The survey team performed this vision and nutrition survey using a standard and validated questionnaire. However, we suggest that the readers consider the following constraints while reading the present nutrition survey findings. Firstly, we included only three regions of the KSA. However, the dietary patterns may vary in other regions as sociocultural norms are different in several parts of the KSA. Secondly, we used a convenience sampling method, and the limitations of this method need to be considered. Finally, this nutrition and vision survey used a cross-sectional approach. Hence, the causal association between dietary patterns and vision health cannot be established, as this can be done only through prospective studies.

5 Conclusion

The visual function scores were low among the adults in the Qassim, Makkah, and Riyadh regions of Saudi Arabia. The visual functions were low among women, widowed and divorced people, retired people, self-employed people, and Riyadh residents. The mean days of consumption of lean protein sources, whole grains, and dairy products, followed by a mean intake of vegetables, were between three and four days per week, indicating the participants' poor dietary patterns. We found a significant positive correlation between the NEI VFQ-25 score and fruit and vegetable intake. Hence, there is a need for dietary advice that can be provided through health education, health promotion, and community participation to prevent visual impairment and avoidable blindness. Finally, further exploratory prospective studies are warranted to identify the temporal association between vision health and dietary patterns.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Institutional Review Board, General Directorate of Health Affairs, Al-Gassem Region, Saudi Arabia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft. BA: Conceptualization, Methodology, Resources, Supervision, Visualization, Writing – original draft. AAlf: Conceptualization, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. HA: Conceptualization, Data curation, Formal analysis, Resources, Validation, Visualization, Writing – original draft. SA: Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Writing – original draft. AAlo: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. RA: Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. AAlr: Conceptualization, Data curation, Investigation, Software, Validation, Writing – review & editing. NA: Conceptualization, Data curation, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Famine exposure in early life increases risk of cataracts in elderly stage

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Background: Epidemiological studies have shown that early-life nutritional deficiencies are associated with an increased risk of diseases later in life. This study aimed to explore the correlation between famine exposure during the early stages of life and cataracts.

Methods: We included 5,931 participants from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) 2018 cross-sectional data in our study. Subjects were categorized into three groups by their age during the famine: adulthood group, school age famine exposure group, and teenage famine exposure group. Utilizing binary logistic regression models, we investigated the relationship between early-life famine exposure and cataracts.

Results: Compared to the adulthood group, both the school age exposure group (OR=2.49, 95%CI=1.89–3.27) and teenage exposure group (OR=1.45, 95%CI=1.20–1.76) had a heightened risk of developing cataracts in elderly stage. And the sex differences in the impact of famine during early years on elderly cataract risk were observed, particularly indicating a higher risk among women who experienced childhood famine compared to men with similar exposure.

Conclusion: Famine exposure during the early stages of life is associated with a heightened risk of developing cataracts in old age. To prevent cataracts in elderly individuals, particularly in females, measures should be taken to address nutritional deficiencies in these specific periods.

KEYWORDS

famine, childhood, adolescence, cataract, early-life exposure

1 Introduction

Cataract is a pathological condition of lens opacity, which is prevalent among individuals aged over 60 years old (1, 2). Its prevalence varies globally across regions and age groups, with a global prevalence of approximately 17.20% (2). In China, the prevalence of cataracts among individuals over 50 years old is notably high, reaching 27.45% (3). By 2050, the estimated prevalence of cataracts is expected to reach 33.34%

among individuals aged 45–89 years old, and the total of cataract cases will be more than double to 240.83 million in China (4). Cataracts are the primary reason of blindness and the second most prevalent cause for visual impairment worldwide (5). At present, the primary and effective treatment for cataracts is still cataract surgery, which imposes substantial socioeconomic burdens. For instance, the cost of such surgery can exceed twice the annual income of patients in rural China, significantly diminishing people's quality of life (6). With China's rapid aging population, the disease and economic burden of cataracts are expected to increase, posing significant challenges for both clinical and public health systems.

The famine occurred in 1959–1961 due to food shortages triggered by natural disasters, which is regarded as a "natural experiment." Based on this period, it provided us with an opportunity to explore the enduring consequences of early nutritional deficiencies on individuals' health (7).

The developmental origin hypothesis posits that nutritional deficiencies during early stages of life is linked to a heightened risk for diseases of later life (8, 9). Previous research has linked early-life famine exposure with various chronic conditions such as obesity, hypertension, diabetes, and metabolic syndromes (7, 10–13). The development of cataracts may be attributed to several factors, including nutritional deficiencies, infectious diseases, aging, chemical or drug-induced damage (6, 14). Based upon these observations, this study hypothesizes that individuals who experienced famine during their early years may have a higher risk of cataracts during their elderly age.

To our knowledge, no studies have established a correlation between famine and cataracts. Disclosing a potential correlation between famine experience during early age and cataracts is considerable in terms of understanding origins of the disease and guiding preventive strategies. This article is the first exploration to investigate the correlation between famine and cataracts, concerning school age and teenage famine exposures and utilizing the CLHLS 2018 cross-sectional data. We also conducted separate association analyses in both male and female groups to explore the possibility of sex-specific impacts of exposure to famine on cataracts. Furthermore, additional stratified analyses were performed to delve deeper into this relationship.

2 Methods

2.1 Study design and participants

Data used in the current study were drawn from the Chinese Longitudinal Healthy Longevity Survey (CLHLS). It is a public database that focuses on individuals aged 60 years and above. The aim is to gain a better understanding of the determinable factors of healthy aging among China's aging population. It is a nationally representative survey using a multistage stratified cluster sampling approach across 23 of China's 31 provinces. The survey initiated with a baseline examination in 1998, followed by subsequent surveys in 2000, 2002, 2005, 2008–2009, 2011–2012, 2014, and most recently in 2017–2018. Throughout these periods, trained workers systematically collected and assessed data using structured questionnaires. The specific details have been described before (15).

The present study used the CLHLS 2018 cross-sectional data, and all individuals born from 1935 to 1956 were considered potential candidates. After screening based on specific inclusion and exclusion criteria, the study ultimately enrolled 5,931 participants in total (Figure 1).

2.2 Assessment of famine exposure

The famine exposure period was specified as ranging from 1959 to 1961. According to previous research and life cycle theory, school age and teenage periods are critical stages of growth and development, susceptible to nutritional deficiencies (16, 17). Adulthood follows the teenage period, marking completion of full physical development (18). We designate adults who experienced famine as the reference group and categorize subjects based on their age during the famine as follows: adulthood group (born between 1935 and 1940, aged 21–26 years old), school age famine exposure group (born between 1949 and 1956, exposed between 5 and 12 years old), and teenage famine exposure group (born between 1941 and 1948, exposed between 13 and 20 years old) (19, 20). Adolescence is a transitional period from childhood to adulthood with accelerated growth and development (21, 22). Considering these differences in the developmental period characteristics of sexuality, participants were further categorized as follows: (1) among male participants: unexposed group (born between 1935 and 1940, aged 21–26 years old), childhood famine exposure group (born between 1951 and 1956, exposed between 5 and 10 years old), and adolescence famine exposure group (born between 1941 and 1950, exposed between 11 and 20 years old); (2) among female participants: unexposed group (born between 1935 and 1942, aged 19–26 years old), childhood famine exposure group (born between 1953 and 1956, exposed between 5 and 8 years old), and adolescence famine exposure group (born between 1943 and 1952, exposed between 9 and 18 years old) (23, 24). The specific details showed in Figure 2.

2.3 Assessment of cataracts

Information about cataracts was collected by trained face-to-face interviewers. Participants were asked whether they had cataracts, either by responding personally or by a proxy through a relative. The response options were "1. Yes; 2. No; 3. Unknown."

2.4 Covariates

Demographic, socioeconomic, and lifestyle variables were gathered as covariates. Education level was categorized as middle school or higher and primary or below. Marital status included both married and single (including divorced, widowed, or never married). Residence was classified as urban and rural. Ethnic group was divided as Han and Ethnic Minorities. China's terrain descends from high in the west to low in the east, forming a three-tiered distribution (25). The first step includes regions with an average altitude above 4,000 m, the second step encompasses regions with average altitudes ranging from 1,000 to 2,000 m, and the third step constitutes regions with altitudes below 500 m (25). We divide the regional altitude into three

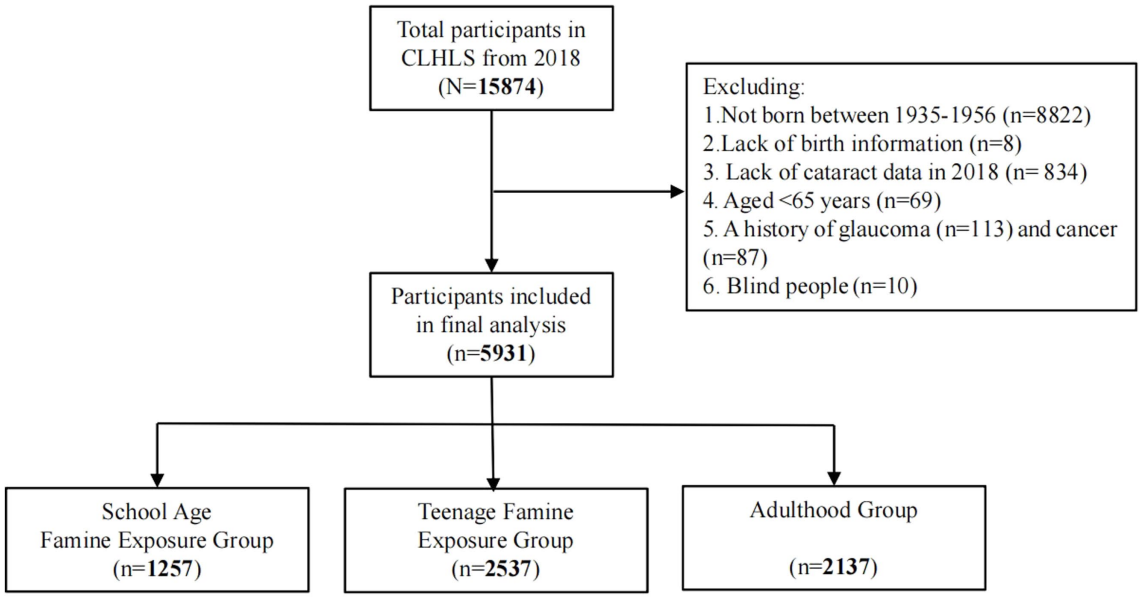

FIGURE 1
Flowchart of participants selected in the study.

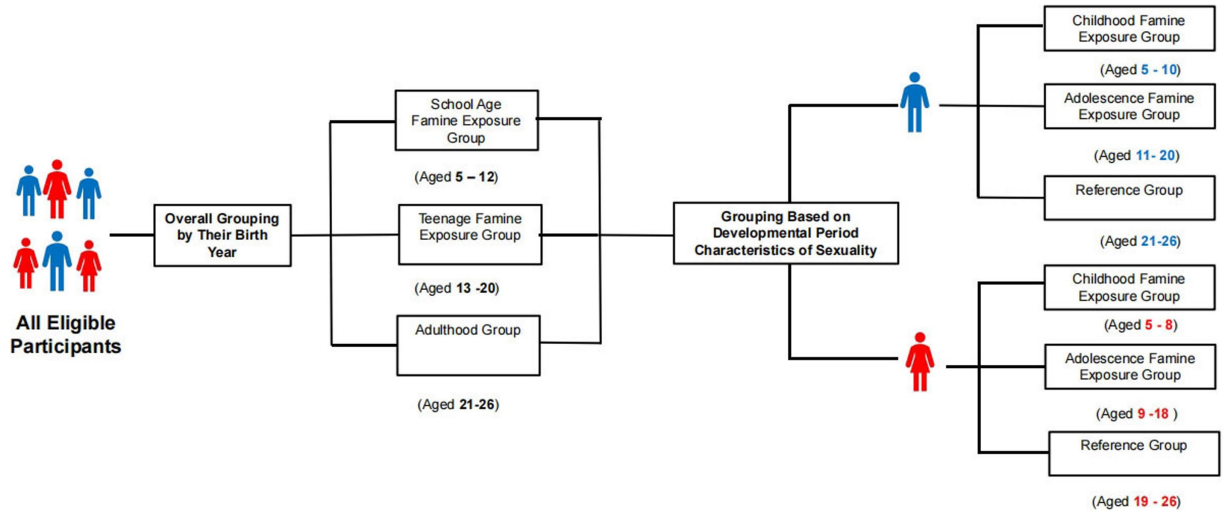

FIGURE 2
Flowchart of grouping after famine exposure assessment.

steps based on each province's geographical distribution, regional altitude was categorized into three classifications: (1) the first step (including Sichuan); (2) the second step (including Shanxi, Shaanxi, Heilongjiang, Beijing, Jiangxi, Hebei, Jilin, Fujian, Hubei, Guangxi, Hunan, Henan, and Chongqing); (3) the third step (including Tianjin, Shanghai, Zhejiang, Guangdong, Jiangsu, Shandong, Liaoning, Anhui, and Hainan) (26). Family income levels were defined as more than 50 k per year and less than 50 k per year. Smoking status encompassed both current smoking and non-smoking, while drinking status involved both current drinking and non-drinking. Exercise status was categorized as currently exercising regularly or not exercising currently. Finally, we used the excess mortality rates from 1959 to 1961 at the provincial level as an index to measure the famine severity (27). Areas with an excess mortality rate of 50% or more were considered severely hit by famine, while areas which with less than 50% were considered less severely hit by famine (28, 29).

2.5 Statistical analyses

To establish the baseline comparisons, categorical variables were presented by percentages and continuous variables were expressed by Mean and Standard Deviation. Utilizing the one-way ANOVA or

Student's *t*-test for continuous variables comparisons and employing the chi square test for categorical variables comparisons.

Employing logistic regression analysis, we evaluated the correlation between famine experience and the risk of cataracts, illustrated through crude and adjusted odds ratios (OR) and their respective 95% confidence intervals (CI). Initially, we implemented three models for an overall analysis. Subsequently, to explore the possibility of sex-specific impacts of famine experience on cataracts, further separate explorations were performed for both males and females. Finally, we performed stratified analyses based on various factors. However, due to the subsequent grouping and stratification, the sample size for each exposure group reduced, potentially limiting the findings for certain variables in the stratified analysis.

All the data were analyzed using IBM SPSS Statistics 25.0. Findings were determined with two-sided tests and considered statistically significant at $p < 0.05$.

3 Results

3.1 Characteristics of participants exposed to early-life famine

Table 1 presents the basic features of each participant based on cataract status. Out of the 5,931 participants, 707(11.9%) had cataracts. The study included 3,014 (50.8%) males and 2,917 (49.2%) females, and the mean age of all the participants was 74.4 ± 5.3 years. Significant differences were observed among gender, age, regional altitude, residence, smoking status, drinking status, exercise status, family income level, education level, famine severity, ethnic group as well as hypertension, diabetes, CHD, and arthritis between the groups with and without cataracts (all $p < 0.05$). Nevertheless, there were no differences within both groups in variables including marital status and the number of offspring (all $p > 0.05$).

Table 2 displays these fundamental characteristics of the subjects categorized by their exposure to famine. 21.2% had experienced famine during school age, while 42.8% had experienced famine during the teenage years. Among different subgroups, significant differences were found for gender, age, smoking, and drinking status, family income level, education level, famine severity, ethnic group, marital status, number of offspring as well as diabetes, CHD, and arthritis (all $p < 0.05$). Nevertheless, there were no notable differences observed in regional altitude, residence, hypertension, and exercise status among the various subgroups (all $p > 0.05$).

3.2 Association of famine exposure in early life stage with cataracts in elderly stage

Table 3 demonstrates the correlation between experience of famine and cataracts using binary logistic regression. In Model 1, without adjusting any variables, the ORs of cataracts were 2.29 (95% CI, 1.80–2.92, $p < 0.001$) for the school age famine exposure group and 1.46 (95% CI, 1.23–1.73, $p < 0.001$) for the teenage famine exposure group compared to the adulthood group. Model 2 further adjusted for gender, family income level, education level, marital status, along with number of offspring, ethnic group, famine severity, regional altitude, as well as residence. The ORs of cataracts were 2.60 (95%CI, 2.00, 3.37, $p < 0.001$) for school age famine exposure group and 1.49 (95%CI, 1.24, 1.79, $p < 0.001$) for teenage famine exposure group, in comparison to adulthood group. In Model 3, the fully adjusted ORs of cataracts were 2.49 (95% CI, 1.89–3.27, $p < 0.001$) within the persons who were in the school age exposure group and 1.45 (95% CI, 1.20–1.76, $p < 0.001$) for the teenage exposure group, in comparison to adulthood exposure group.

Table 4 illustrates the correlation between famine exposure and cataracts using binary logistic regression by gender. For the childhood famine exposure groups in Model 1, the ORs of cataracts were notably higher in the females exposed during the period of childhood (OR = 4.71, 95%CI: 1.47–15.10, $p = 0.009$) compared to the males exposed during the period of childhood (OR = 3.54, 95%CI: 2.05–6.11, $p < 0.001$). And Similar findings could be obviously observed in Model 2 and Model 3, consistently showing higher ORs of cataracts in the female childhood exposure group compared to their male counterparts in the same exposure group. For the adolescence famine exposure groups in Model 1, it was shown that the ORs of cataracts were 1.68 (95% CI, 1.35–2.08, $p < 0.001$) in females, and in males it was 1.74 (95% CI, 1.36–2.23, $p < 0.001$), both as compared to the unexposed group. Similar results were observed in both Model 2 and Model 3.

3.3 Association of famine exposure with cataracts by subgroup

Figure 3 displays the correlation between famine exposure and cataracts through stratified analysis. Our findings highlighted a significant relationship between school age exposure and cataracts among individuals in the first and second steps of regional altitude. Notably, school age exposure demonstrated a consistent relationship with cataracts across various subgroups, regardless of residence, smoking status, drinking status, exercise status, family income level, and famine severity. Teenage famine exposure exhibited a significant association with cataracts among individuals in the first and second steps of regional altitude, as well as non-smokers. Similarly, teenage exposure indicated a significant association concerning residence, drinking status, exercise status, family income level, and famine severity. Similar associations were found between famine exposure and cataracts among male participants, as depicted in Supplementary Figure 1. Additionally, Supplementary Figure 2 illustrates the specific relationship between famine exposure and cataracts among female participants.

4 Discussion

According to our knowledge, it is the first exploration about the correlation of famine exposure during the early stages of life with cataracts, specifically focusing on school age and teenage period. Our findings indicate a significant correlation between exposure to early-life famine and cataracts as adults, markedly stronger when exposed during school age compared to teenage period. Notably, sex differences were observed, with females exhibiting a greater correlation between childhood exposed famine and cataracts compared to males. Overall, individuals who have a history of experiencing famine are more susceptible to have cataracts when residing in higher altitudes, rural

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TABLE 1 Baseline characteristics between subjects with and without cataract group.

Variables	Overall	Without cataracts	With cataracts	*p* values
No. of participants, n (%)	5,931(100.0)	5,224(88.1)	707(11.9)	**<0.001**
Gender, n (%)				**<0.001**
Male	3,014(50.8)	2,714(52.0)	300(42.4)	
Female	2,971(49.2)	2,510(48.0)	407(57.6)	
Age (years), Mean (SD)	74.4(5.3)	74.2(5.3)	76.0(4.9)	**<0.001**
Regional altitude (km), n (%)				**<0.001**
First step	464(7.8)	406(7.8)	58(8.2)	
Second step	2,609(44.0)	2,367(45.3)	242(34.2)	
Third step	2,858(48.2)	2,451(46.9)	407(57.6)	
Residence, n (%)				**<0.001**
Urban	3,253(54.8)	2,770(53.0)	483(68.3)	
Rural	2,678(45.2)	2,454(47.0)	224(31.7)	
Smoking status, n (%)				**0.019**
Current smoking	1,154(19.5)	1,043(20.0)	111(15.7)	
Non-smoking	4,777(80.5)	4,181(80.0)	596(84.3)	
Drinking status, n (%)				**0.017**
Current drinking	1,092(18.4)	987(18.9)	105(14.9)	
Non-drinking	4,839(81.6)	4,237(81.1)	602(85.1)	
Exercise status, n (%)				**<0.001**
Currently exercising regularly	2,403(40.5)	2,042(39.1)	361(51.1)	
Not exercising regularly	3,528(49.5)	3,182(60.9)	346(48.9)	
Family income level, n (%)				**<0.001**
More than 50 k per year	3,898(65.7)	1,709(32.7)	324(45.8)	
Less than 50 k per year	2,033(34.3)	3,515(67.3)	383(54.2)	
Education level, n (%)				**<0.001**
Middle school or higher	1,795(30.3)	1,526(29.3)	269(38.4)	
Primary or below	4,136(69.7)	3,698(70.7)	438(61.6)	
Famine severity, n (%)				**<0.001**
Serious	4,817(81.2)	4,334(83.0)	483(68.3)	
Less severe	1,114(18.8)	890(17.0)	224(31.7)	
Ethnic group, n (%)				**0.004**
Han	4,771(80.4)	4,186(80.1)	585(82.7)	
Ethnic minorities	1,160(19.6)	1,038(19.9)	122(17.3)	
Marital status, n (%)				0.296
Currently married	3,900(65.8)	3,453(66.1)	447(63.2)	
Currently single	2,031(34.2)	1,771(33.9)	260(36.8)	
Of alive children, Mean (SD)	3.4(4.0)	3.5(4.1)	3.3(3.6)	0.205
Hypertension, n (%)				**<0.001**
Yes	2,720(45.9)	2,290(43.8)	430(60.8)	
No	3,211(54.1)	2,934(56.2)	277(39.2)	
Diabetes, n (%)				**<0.001**
Yes	779(13.1)	623(11.9)	156(22.1)	
No	5,152(86.9)	4,601(88.1)	551(77.9)	

(Continued)

TABLE 1 (Continued)

Variables	Overall	Without cataracts	With cataracts	*p* values
CHD, n (%)				**<0.001**
Yes	1,078(18.2)	858(16.4)	220(31.1)	
No	4,853(81.8)	4,366(83.6)	487(68.9)	
Arthritis, n (%)				**<0.001**
Yes	721(12.2)	525(10.0)	196(27.7)	
No	5,210(87.8)	4,699(90.0)	511(72.3)	

Data presented as number (%) for categorical variables and Mean (SD) for continuous variables. CHD, Coronary heart disease. *p* value for Student's *t*-test (continuous variables) or Chi-squared tests (categorical variables). The bold values mean $p < 0.05$, showing significant statistical significance.

TABLE 2 Baseline characteristics among different famine exposure groups.

Variables	Adulthood group	School age famine exposure group	Teenage famine exposure group	*p* values
No. of participants, n (%)	2,137(36.0)	1,257(21.2)	2,537(42.8)	**<0.001**
Gender, n (%)				**0.042**
Male	1,045(48.9)	635(50.5)	1,334(52.6)	
Female	1,092(51.1)	622(49.5)	1,203(47.4)	
Age (years), Mean (SD)	80.1(1.8)	66.9(1.4)	73.3(2.4)	**<0.001**
Regional altitude (km), n (%)				0.752
First step	173(8.1)	104(8.3)	187(7.4)	
Second step	930(43.5)	562(44.7)	1,117(44.0)	
Third step	1,034(48.4)	591(47.0)	1,233(48.6)	
Residence, n (%)				0.092
Urban	1,164(54.5)	723(57.5)	1,366(53.8)	
Rural	973(45.5)	534(42.5)	1,171(46.2)	
Smoking status, n (%)				**<0.001**
Current smoking	358(16.9)	251(20.2)	545(21.7)	
Non-smoking	1,779(83.1)	1,006(79.8)	1,992(78.3)	
Drinking status, n (%)				**<0.001**
Current drinking	326(15.5)	271(21.8)	495(18.7)	
Non-drinking	1,811(84.5)	986(78.2)	2,042(81.3)	
Exercise status, n (%)				0.129
Currently exercising regularly	831(39.4)	541(43.4)	1,031(41.2)	
Not exercising regularly	1,306(60.6)	716(56.6)	1,506(58.8)	
Family income level, n (%)				**0.020**
More than 50 k per year	750(35.1)	461(36.7)	822(32.4)	
Less than 50 k per year	1,387(64.9)	796(63.3)	1,715(67.6)	
Education level, n (%)				**<0.001**
Middle school or higher	510(24.0)	482(38.3)	803(31.7)	
Primary or below	1,627(76.0)	775(61.7)	1,734(68.3)	
Famine severity, n (%)				**0.020**
Serious	1,736(81.2)	989(78.7)	2,092(82.5)	
Less severe	401(18.8)	268(213)	445(17.5)	
Ethnic group, n (%)				**<0.001**
Han	1,602(75.0)	1,109(88.2)	2,060(81.2)	
Ethnic minorities	535(25.0)	148(11.8)	477(18.8)	

(Continued)

TABLE 2 (Continued)

Variables	Adulthood group	School age famine exposure group	Teenage famine exposure group	*p* values
Marital status, n (%)				**<0.001**
Currently married	1,095(51.2)	1,009(80.3)	1,796(70.8)	
Currently single	1,042(48.8)	248(19.7)	741(29.2)	
Of alive children, Mean (SD)	4.0(4.1)	2.6(3.6)	3.4(4.1)	**<0.001**
Hypertension, n (%)				0.060
Yes	1,028(48.3)	542(43.3)	1,150(45.5)	
No	1,109(51.7)	715(56.7)	1,387(54.5)	
Diabetes, n (%)				**0.003**
Yes	265(12.5)	194(15.5)	320(12.7)	
No	1,872(87.5)	1,063(84.5)	2,217(87.3)	
CHD, n (%)				**<0.001**
Yes	437(20.6)	179(14.3)	462(18.3)	
No	1,700(79.4)	1,078(85.7)	2,075(81.7)	
Arthritis, n (%)				**0.049**
Yes	281(13.3)	153(12.2)	287(11.4)	
No	1,856(86.7)	1,104(87.8)	2,250(88.6)	
Cataract, n (%)				**<0.001**
Yes	331(46.8)	283(40.0)	93(13.2)	
No	1,806(53.2)	974(60.0)	2,444(86.8)	

Data presented as number (%) for categorical variables and Mean (SD) for continuous variables. CHD, Coronary heart disease. *p* value for ANOVA (continuous variables) or Chi-squared tests (categorical variables). The bold values mean $p < 0.05$, showing significant statistical significance.

TABLE 3 Binary logistic regression analysis the relationship between famine exposure and cataract among different groups.

Group	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
	p	*p*	*p*
Adulthood group	Ref	Ref	Ref
School age famine exposure group	2.29(1.80,2.92)	2.60(2.00,3.37)	2.49(1.89,3.27)
	<0.001	**<0.001**	**<0.001**
Teenage famine exposure group	1.46(1.23,1.73)	1.49(1.24,1.79)	1.45(1.20,1.76)
	<0.001	**<0.001**	**<0.001**

OR, Odds ratio; CI, Confidence interval.
Model 1: un-adjusted. Model 2: adjusted for gender, family income level, education level, marital status, number of offspring, ethnic group, famine severity, regional altitude, and residence. Model 3: adjusted for variables in model 2 plus hypertension, diabetes, coronary heart disease, Arthritis, drinking status, smoking status, and exercise status. The bold values mean $p < 0.05$, showing significant statistical significance.

areas, among smokers, alcohol consumers, individuals with infrequent exercise, and those with lower income levels.

4.1 Correlation between famine exposure and cataracts

Prior to this, there were no specific studies on famine exposure and cataracts. Only one study suggests a potential connection between famine exposure and eye diseases (30). The finding shows an association between early-life famine exposure and multimorbidity in adults aged 65–71 years, with a significantly increased OR for multimorbidity (OR = 1.39, 95% CI: 1.04–1.87), defined as the presence of two or more chronic diseases out of 14 chronic conditions, including hypertension, eye diseases (cataracts, retinitis pigmentosa, glaucoma, macular degeneration, and diabetic retinopathy), heart diseases, and others (30).

Famine deprives school-age children and teenagers of sufficient nutrients during their periods of rapid growth and development, whereas studies show that high protein intake decreases cataract risk and increased polyunsaturated fat intake lowers the risk of cortical cataracts (31–33). Low protein intake may also indicate a deficiency in specific amino acids required for maintaining lens health, such as tryptophan, which can subsequently lead to lens damage (34, 35).

TABLE 4 Binary logistic regression analysis the relationship between famine exposure and cataract among different groups by gender.

Group	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
	p	*p*	*p*
Men			
Unexposed group	Ref	Ref	Ref
Childhood famine exposure group	3.54(2.05,6.11)	4.72(2.65,8.40)	4.01(2.21,7.26)
	<0.001	**<0.001**	**<0.001**
Adolescence famine exposure group	1.74(1.36,2.23)	1.93(1.47,2.53)	1.77(1.33,2.35)
	<0.001	**<0.001**	**<0.001**
Women			
Unexposed group	Ref	Ref	Ref
Childhood famine exposure group	4.71(1.47,15.10)	5.72(1.75,18.72)	6.21(1.85,20.81)
	0.009	**0.004**	**0.003**
Adolescence famine exposure group	1.68(1.35,2.08)	1.71(1.35,2.17)	1.84(1.43,2.38)
	<0.001	**<0.001**	**<0.001**

OR, odds ratio; CI, confidence interval.
Model 1: un-adjusted. Model 2: adjusted for gender, education level, family income level, marital status, number of offspring, ethnic group, famine severity, regional altitude, residence. Model 3: adjusted for variables in model 2 plus hypertension, diabetes, coronary heart disease, Arthritis, drinking status, smoking status, and exercise status. The bold values mean $p < 0.05$, showing significant statistical significance.

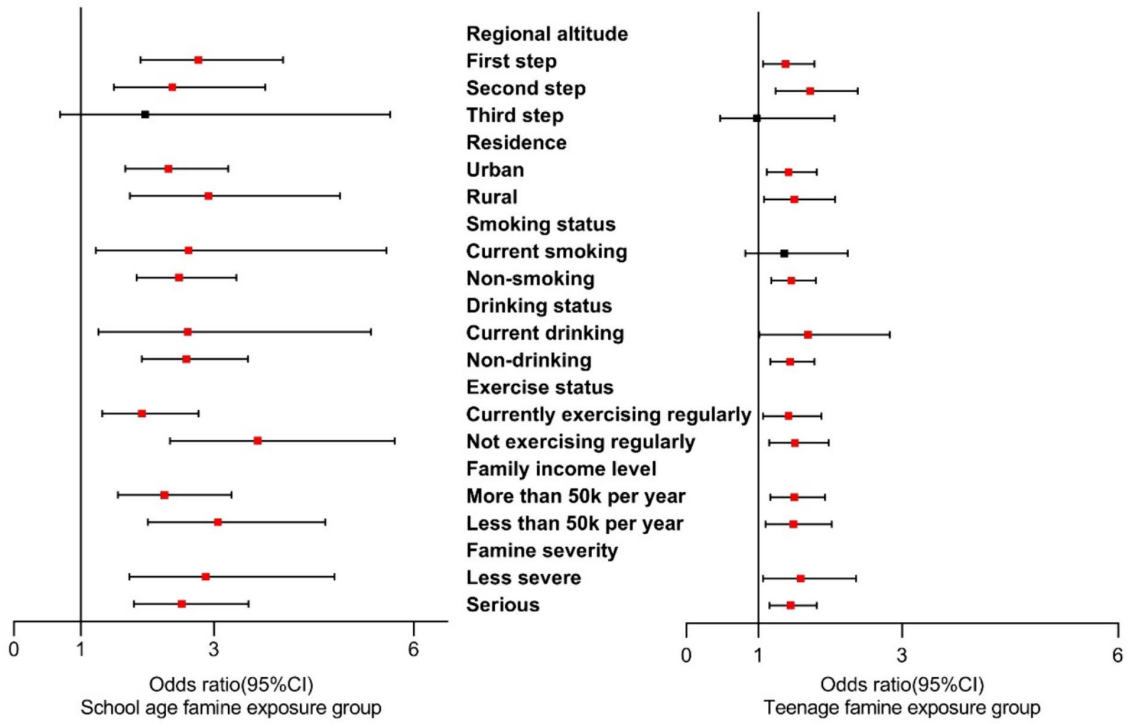

FIGURE 3
Stratified analysis on associations between famine exposure and cataracts in overall grouping.

Most current research on nutrition and cataracts focuses on antioxidant vitamins (36) Firstly, multiple prospective studies indicate that increased vitamin C intake had a long-term protective impact against age-related cataract development (37–39). Participants in the highest quintile of total vitamin C intake (including dietary supplements) had a lower risk of nuclear cataract (OR = 0.55, 95%CI: 0.36–0.86) (37). Oxygen free radicals, formed during normal bodily metabolism, can induce oxidative stress linked to cataract development (40–43). These radicals, including superoxide, hydrogen peroxide, and hydroxyl radicals, can damage lens components (crystalline proteins,

lens fibers, and lipids), potentially accelerating the development of nuclear cataracts (37, 40, 44). Vitamin C, a potent antioxidant that scavenges ROS, exists in high concentrations in the human lens, aqueous humor, and vitreous body (45, 46). This may explain why supplementing with vitamin C can delay the development of cataracts.

Secondly, a hypothesis proposes that antioxidant nutrients may protect against age-related lens damage (47). While most epidemiological studies have not provided evidence for vitamin E's active role in preventing age-related cataracts, one study suggests reduced cataract risk with vitamin E intake from food and supplements, with a multivariate relative risk of 0.86 (95% CI: 0.74–1.00) (48–52). Vitamin E, with its antioxidant capabilities, interacts with selenium and glutathione peroxidase to prevent the formation of oxidation products of polyunsaturated fatty acids and oxidative damage, thus reducing cataract risk (53, 54).

Moreover, carotenoids may reduce the risk of cataracts, particularly lutein and zeaxanthin, which have been shown that these nutrients might have beneficial impacts in decreasing the risk of cataract formation (39, 48). Carotenoids, involved in forming cellular membrane components, maintaining membrane integrity, and facilitating regulated substance transport, can impact the development of posterior subcapsular cataracts if the integrity of the lens's outer layer membrane is compromised (39). Additionally, other nutrients such as riboflavin, tryptophan, and calcium are being explored for their potential roles (34, 55–57).

Therefore, malnutrition and inadequate intake of essential nutrients during famine might contribute to cataract development (31, 32, 37–39, 48, 58, 59). However, further research is crucial to comprehensively grasp the relationship between nutrient deficiencies and cataract development.

4.2 Correlation differences among exposure group

Our results reveal that experiencing famine in the stage of childhood and adolescence heightens the risk of cataracts during the adult age. This aligns with previous research suggesting that individuals in childhood and adolescence may be more vulnerable to famine-related stress than in infancy. Consequently, famine experiences in the stages of childhood and adolescence potentially elevates the likelihood of cataract development during the adult stage (16). One potential explanation could be that individuals enduring famine in extremely early stages of life have opportunities to overturn the effects of nutritional deprivation and attain subsequent catch-up growth. However, childhood and adolescence are critical stages in the process of growth and development, potentially leading to irreversible impacts on long-term health (60).

Therefore, focusing on childhood and adolescence could be crucial in implementing interventions to improve elderly life quality and prevent chronic diseases.

4.3 Sex-based correlation differences

Our research indicates that childhood exposure impacts females more significantly than males. These sex differences might originate from several factors. Firstly, the son preference in traditional Chinese culture might contribute to better health outcomes for boys, as parents prioritize shielding boys from harsh environments and ensuring their access to sufficient food and nutrition (61, 62). Secondly, female health seems more susceptible to the influence of childhood conditions compared to male health, possibly due to different adaptations to early-life events between genders or biological differences in assumed social roles (63–65). Moreover, existing studies generally indicate higher cataract prevalence in females than males (2, 66–70). The only global study found female prevalence at 33.67% (95% CI: 25.90–41.44) and male at 32.57% (95% CI: 26.29–38.85) (2). A US study similarly found higher age-adjusted cataract prevalence in females than males (OR = 1.37; 95% CI, 1.26–1.50) (70). Some studies suggest that female gender is a cataract risk factor due to this gender disparity (2, 66–70).

4.4 Differential results from stratified analysis

UV radiation, excessive smoking and alcohol intake are the significant risk factors for age-related cataracts (71, 72). As altitude increases, the atmosphere's capacity to filter UV rays diminishes, intensifying UV radiation that could potentially harm the lens through thermal and photochemical effects (73). Research has established a direct link between smoking quantity and cataract formation (74). Smoking affects cataract development by inducing oxidative stress on the lens through exposure to tobacco smoke, potential generation for reactive advanced glycation end products, and the direct toxic effects of heavy metals like cadmium, copper, and lead present in tobacco smoke (75). A meta-analysis highlighted that heavy drinking notably amplifies the probability of age-related cataracts (76). Alcohol consumption increases the hazard of developing nuclear, cortical as well as posterior subcapsular cataract due to the lens's high vulnerability to oxidative stress and alcohol's toxic effects (77). Therefore, maintaining a healthy lifestyle serves as a crucial factor in reducing the risk of developing cataracts.

4.5 Limitations

This population-based study displayed that famine exposure significantly heightened the risk of cataracts among the aged population. Nonetheless, it does have several limitations. Firstly, it was not feasible to use a cross-sectional design to establish a causal correlation between famine exposure and cataracts. Secondly, the relying on self-reported cataract data may introduced potential recall bias. Thirdly, the CLHLS 2018 cross-sectional data lacked sufficient participants born after 1956, hindering the analysis of fetal and infant exposure's impacts on cataracts. Additionally, focusing on famine survivors in this study may lead to an overestimation or underestimation of famine effects. Finally, the lack of research on famine exposure and cataracts necessitates further investigation in the future.

5 Conclusion

Exposure to famine during early stages of life is correlated with a significant increased risk of cataracts during the elderly age. The study indicates the status of nutritional deficiencies during school age and teenage period has enduring impacts on people's health outcomes

during the elderly stage. To prevent cataracts in elderly individuals, particularly in females, measures should be taken to address nutritional deficiencies in these specific periods. It also highlights the significance of concentrating on nutritional intake throughout school age and teenage period, emphasizing the importance of promoting nutrition awareness within society.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://opendata.pku.edu.cn/.

Author contributions

JF: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. HN: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SZ: Methodology, Writing – review & editing. WX: Methodology, Writing – review & editing. XL: Writing – review & editing. YD: Writing – review & editing. XX: Writing – review & editing. WY: Conceptualization, Data curation, Writing – review & editing. MC: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1395205/full#supplementary-material

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Association between fatty acid intake and age-related macular degeneration: a meta-analysis

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Objective: The association of age-related macular degeneration (AMD) with the intake of high and low fatty acids (FAs), respectively, remains controversial. To this end, we performed a comprehensive meta-analysis of all the existing studies on the association of various intake levels of FA subtypes with AMD to determine these associations.

Methods: A systematic search of PubMed, Web of Science, Cochrane Library, and EMBASE databases was conducted from inception to September 2023. To compare the highest and lowest groups, odds ratio (OR) with 95% confidence intervals (CIs) was analyzed with a random-effects model/fixed-effects model.

Results: A high intake of omega-3 LCPUFAs (OR:0.67; 95%CI:[0.51, 0.88]; $p = 0.004$), DHA (OR:0.80; 95%CI:[0.70, 0.90]; $p < 0.001$), EPA (OR:0.91; 95%CI:[0.86, 0.97]; p = 0.004), and simultaneous intake of DHA and EPA (OR:0.79; 95%CI:[0.67, 0.93]; $p = 0.035$) significantly reduced the risk of overall AMD. Conversely, a high intake of trans-FAs (OR: 2.05; 95%CI: [1.29, 3.25]; $p = 0.002$) was significantly related to an increased risk of advanced AMD compared to the low-intake group. The subgroup analysis results are shown in the articles.

Conclusion: Increasing dietary intake of omega-3 LCPUFAs, specifically DHA, and EPA, or the simultaneous intake of DHA and EPA, is significantly associated with a reduced risk of overall AMD. Various subtypes of omega-3 also have a significant association with a reduced risk of different stages of AMD. The high intake of trans-fatty acids (TFAs) is significantly and positively correlated with the risk of advanced AMD. This could further support the idea that consuming foods rich in omega-3 LCPUFAs and reducing consumption of foods rich in TFAs may prevent AMD.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42023467227.

KEYWORDS

dietary fatty acids (FAs), long-chain omega-3 polyunsaturated fatty acids (omega-3 LCPUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), trans-fatty acid (TFA), age-related macular degeneration (AMD), meta-analysis

1 Introduction

Age-related macular degeneration (AMD) is the most prevalent cause of irreversible vision loss in older patients and ranks as the fourth leading cause of blindness, mainly affecting people over 55 years of age (1, 2). With the acceleration of population aging, the number of AMD patients has been increasing. According to estimates, the number of individuals with

AMD in the world accounts for 8.69% of the world population and is expected to reach 288 million by 2040, among which more than 60% of the AMD patients are from Asia, imposing huge financial and policy burdens worldwide (1, 3, 4). Although several effective therapeutic drugs are available, repeated and frequent injections and doctor visits increase the financial burden on the healthcare system and patients. Furthermore, treatment-related adverse effects, such as endophthalmitis, retinal detachment, and traumatic lens injury, can reduce patient compliance and further compromise vision as the disease progresses (4–6). Therefore, preventing the development of the disease and delaying its progression is recommended for a better prognosis (4).

In addition to some recognized risk factors for AMD such as age, gender, race, and smoking (1, 3), cumulative oxidative damage to retinal pigment epithelial (RPE) cells is also reported as a major contributor to AMD (4, 7). Therefore, the relationship between lipids and AMD has attracted increasing attention. As people grow older, lipofuscin continues to accumulate in RPE cells and cannot be degraded, which leads to cellular hypoxia and chronic inflammation, thereby resulting in cumulative oxidative damage to cells (4).

Dietary fatty acids (FAs) include saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), and monounsaturated fatty acids (MUFAs). They are vital sources of energy involved in lipogenesis, glycolysis, and protein synthesis (8). PUFAs are primarily obtained from food and are beneficial to anti-inflammatory and antithrombotic processes, as well as for maintaining vision, cognitive function, and glucose and lipid metabolism (8). Long-chain omega-3 polyunsaturated fatty acids (omega-3 LCPUFAs), as the main structural components of the retina, have anti-angiogenic, anti-proliferation of the blood vessel, and neuroprotective effects in terms of the pathogenic factors and processes of proliferative and degenerative retinal diseases. They also protect against oxygen toxicity, inflammation, and age-related retinal damage (9, 10). Many studies have shown that omega-3 FAs are believed to lower the risk of AMD, with a clear difference between high and low intake levels of docosahexaenoic acid (DHA, C22: 6 n-3) in protecting against the development of AMD (11–16), while a small number of studies indicate no difference (17–21). Simultaneously, omega-6 fatty acids are also considered to have a protective effect on the progression of AMD in some studies, but the results of different studies are conflicting; one study suggested that the high and low intake levels of omega-6 were significantly different in reducing the incidence of AMD (22). Another study found a significant difference in increasing the incidence of AMD between the high-omega-6- and low-omega-6-intake groups (23), and three studies concluded that the high and low intake levels of omega-6 did not affect the incidence of AMD (13, 18, 24). Other FA subtypes face a similar situation.

There are many types of FAs, and the effects of various intake levels of different FA subtypes seem to be different in the development and progression of AMD, and the study results are always different among studies, making clinicians confused about how much level of intake of FAs can prevent and delay the development of AMD. To this end, a comprehensive meta-analysis of all existing studies on the association between different intake levels of various FA subtypes and AMD was performed in our study, to investigate the association of the intake of various FA subtypes with the development and progression of AMD.

2 Methodology

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol was followed in the design, performing, and analysis of our research, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the reporting of the results (25, 26). The protocol of our systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42023467227). The current meta-analysis was carried out to analyze the risk factors of AMD, and the exposure factors examined were various FA subtypes. Cohort studies, case–control studies, and cross-sectional studies investigating AMD were included in the present study.

2.1 Literature search

For studies on AMD and dietary FAs, a systematic search of PubMed, Web of Science, Cochrane Library, and EMBASE databases was conducted from the inception of each database up to May 2024. The keywords used for the literature search included fatty acid, age-related macular degeneration, and fish Mediterranean diet, and the search strategy is detailed in the Supplementary material. There were no restrictions on study type, language, or country.

2.2 Selection criteria

We included the following eligible studies in our meta-analysis: (1) studies in which the early, intermediate, and advanced AMD were adequately defined as follows: Normal aging was defined as only having drupelets (small drusen ≤63 μm), while early AMD was defined as having drusen measuring between 63 μm and 125 μm, with no pigment abnormalities associated with AMD. The intermediate AMD was defined as having drusen >125 μm and pigment abnormalities associated with AMD, or without AMD-related pigment abnormalities. Occurrence of neovascular AMD (wet/exudative AMD) or geographic atrophy (dry AMD) indicated advanced AMD (27). The drusen refers to a cell-free, lipid-rich deposit under the RPE (4). (2) All observational studies, such as case–control studies, prospective/retrospective cohort studies, and cross-sectional studies; (3) studies where the intake of different dietary FA subtypes was examined as exposures; (4) studies with data on the association of the highest and lowest levels of FA intake with the risk of AMD in different stages. We excluded the following studies: non-human studies, non-English publications, case reports, overlapping reports, reviews, studies lacking sufficient data, meta-analyses, and publications of which the full texts could not be found.

2.3 Data extraction

Two independent researchers (L. L and Y. L) searched the literature and extracted the data required, separately. First, the two researchers conducted a preliminary screening of the title and abstract separately and then evaluated all eligible studies by reading the full texts, and disagreement, if any, was resolved through group discussion.

After the studies to be included were identified, the following data were extracted separately from each of the included publications: first author, year of publication, study location, study type, gender as well as age of participants, sample size (cases and number of participants), method of assessing intake of dietary FAs, type of dietary FAs, criteria for diagnosing AMD, type of AMD studied, adjusted covariates multivariate analysis, and 95%Cl risk assessment. If multiple multivariate adjustment models were used to report risk assessment in the original studies, data from the model with the most adjustments were extracted.

2.4 Quality assessment

The widely used Newcastle–Ottawa Scale (NOS) was employed to evaluate the quality of case–control studies and cohort studies, and the criteria recommended by the Agency for Healthcare Research and Quality (AHRQ) were adopted to evaluate the cross-sectional studies. The included studies were comprehensively evaluated using the NOS in terms of outcome (cohort studies) or exposure (case–control studies), study selection, and comparability. Each item could be given a maximum of 1 point, and for comparison, some items could be given a maximum of 2 points. The quality of the studies was evaluated as per the following standards: 0 ~ 3 for low quality, 4 ~ 6 for medium quality, and ≥ 7 for high quality (28). The 11-item checklist recommended by the AHRQ includes the definition of information source, period to identify patient and continuity of patient identification, blinding of personnel, inclusion and exclusion criteria, quality assurance assessment, confusing and missing data, and patient response rate and completeness. The maximum score of each item is 1 point. The quality of the studies was evaluated as per the following standards: 0 ~ 3 for low quality, 4 ~ 7 for medium quality, and ≥ 8 for high quality (28).

2.5 Statistical analysis

The OR and 95% CI were believed to be common indicators in the current meta-analysis for the association of each type of dietary FA with the risk of AMD in the studies. Pooled effect estimates were reported with 95% CIs. Before the pooled effect was assessed, the Q test and I^2 test were conducted to examine the heterogeneity among the studies. $I^2 < 50\%$ and $p > 0.1$ indicated the presence of small heterogeneity, and a fixed-effects model was used for meta-analysis; otherwise, a random-effects model was used. In addition, a sensitivity analysis was carried out for each risk factor by eliminating each study from the overall analysis. Egger's test was conducted to estimate the publication bias for FA groups involving 10 or more studies, and $p > 0.05$ indicated that the publication bias was not significant. The publication bias, if any, was corrected to evaluate whether there were consistent results after data with biases were removed.

3 Results

3.1 Study selection process

Our initial screening identified 2,147 records (115 from Cochrane Library, 481 from Embase, 363 from PubMed, and 1,188 from Web of Science) as shown in Figure 1. We excluded 2,121 duplicates and other records not meeting the above inclusion criteria, and finally, 26 studies (14 cohort studies, 3 case–control studies, and 9 cross-sectional studies) were included, involving a total of 241,151 participants.

3.2 Characteristics of the included studies

Table 1 summarizes the descriptive characteristics of the included literature. In the 26 studies included in our research, data on dietary fat intake were based on the Brief Self-administered Diet History Questionnaire (BDHQ) in one study and the Food Frequency Questionnaire (FFQ) in the remaining 25 studies. Of the 26 studies, 15 were carried out in the United States, 5 in Australia, 2 in Europe, 1 in Hong Kong (China), and 3 in Japan.

3.3 Quality assessment results of the included studies

We adopted the NOS and AHRQ to evaluate the quality of different types of studies. The cohort and case–control studies were all awarded ≥7 points, and all the cross-sectional studies were awarded>8 points, suggesting that the included literature was of high quality (Tables 2–4). The FFQ and BDHQ used in these studies to assess dietary FA levels applied to large cohorts and provided information on a variety of foods. However, these tools have several limitations, including incorrect reporting of diet, which can lead to misclassification of dietary intake and/or amount. Therefore, studies evaluated using the NOS were all given a score of 0 for "ascertainment of exposure."

3.4 Meta-analysis

3.4.1 Total fat

In total, 10 of the included studies analyzed the relationship between total fat intake and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 59.1\%$, $P_H = 0.001$) (18, 20, 21, 23, 24, 29–33). We compared the high and low intake levels of total fat and found that the increased intake of total fat did not influence the risk of overall AMD, early AMD, intermediate AMD, or advanced AMD.

3.4.2 Trans-fatty acids

In total, six of the included studies analyzed the association of intake of trans-fatty acids (TFAs) with the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 63.6\%$, $P_H = 0.005$) (20–22, 31, 32, 34). The risk of advanced AMD (OR: 2.05; 95%CI: [1.29, 3.25]; $p = 0.002$) was significantly increased through a high intake of TFAs as shown in Figure 2. Although increasing the intake of TFAs did not affect the risk of overall AMD, early AMD, and intermediate AMD, the OR value increased with the progression of AMD in different stages.

3.4.3 SFAs

In total, 14 of the included studies analyzed the relationship between intake of SFAs and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 55.5\%$, $P_H = 0.001$) (15,

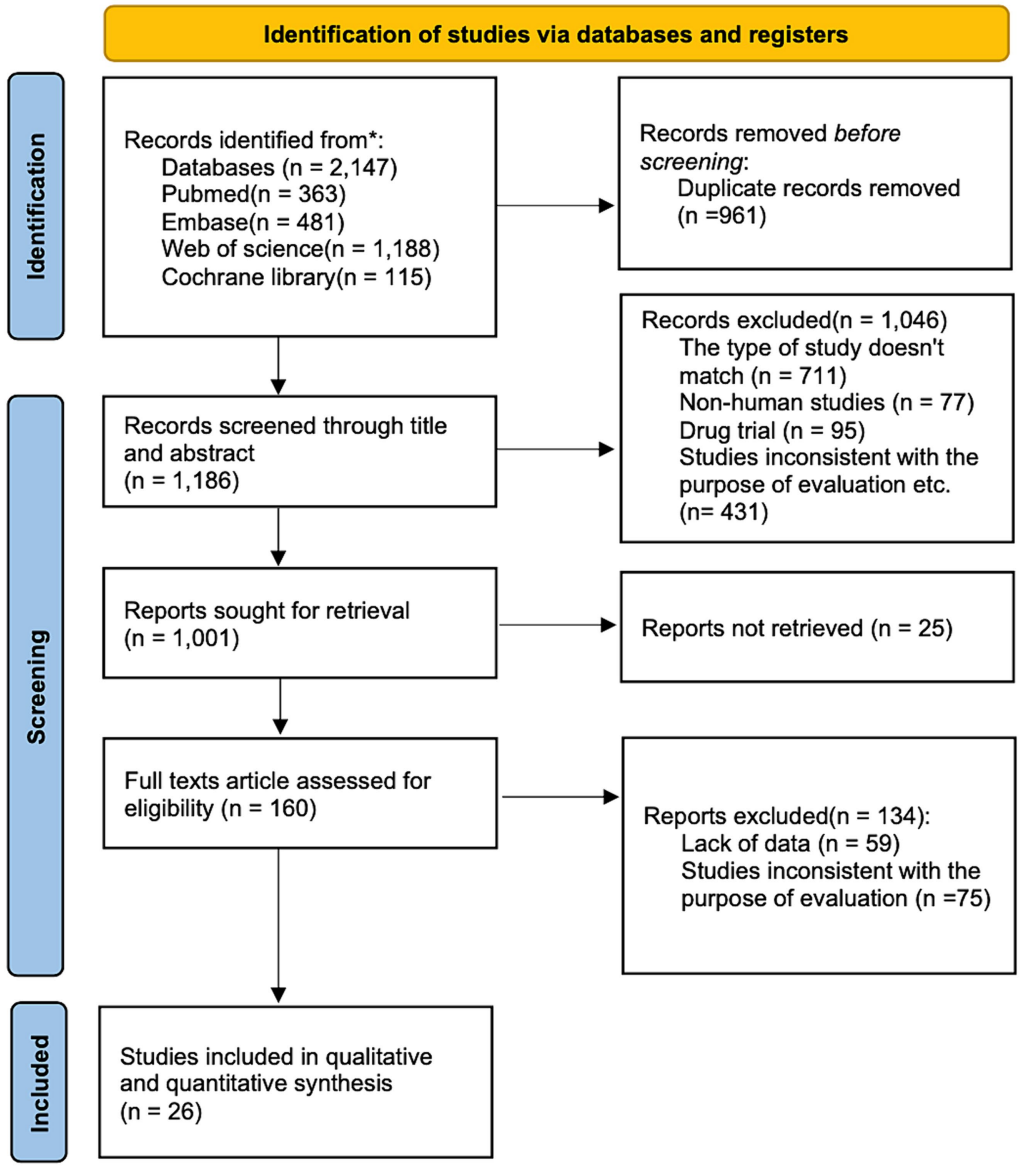

FIGURE 1
Flowchart of literature selection and selection strategy.

18, 20, 24, 29–35). We compared the high and low intake levels of SFAs and found that increasing the intake of SFAs did not influence the risk of overall AMD, early AMD, intermediate AMD, or advanced AMD.

3.4.4 MUFAs

In total, 11 of the included studies analyzed the relationship between intake of MUFAs and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 61.3\%$, $P_H < 0.001$) (15, 18, 20–24, 30–34). We compared the high and low intake levels of MUFAs and found that increasing the intake of MUFAs did not influence the risk of overall AMD, early AMD, intermediate AMD, or advanced AMD.

3.4.5 PUFAs

In total, 11 of the included studies analyzed the relationship between intake of PUFAs and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 53.4\%$, $P_H = 0.006$) (18, 20–22, 24, 30–35). We compared the high and low intake levels of PUFAs and found that increasing the intake of PUFAs did not influence the risk of overall AMD, early AMD, or advanced AMD.

3.4.6 Omega-3 PUFAs family

In total, 10 of the included studies analyzed the association of the intake of omega-3 PUFAs with the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 68.3\%$, $P_H = < 0001$) (13, 18, 21–24, 31, 32, 36, 37). We compared the high and low intake levels of omega-3 PUFAs and observed a significant difference between the intake of high and low omega-3 PUFAs in the risk of early AMD (OR: 0.82; 95%CI: [0.71, 1.05]; $p = 0.148$) as shown in Figure 3A. In contrast, increasing the intake of omega-3 PUFAs showed no difference in the risk of overall AMD, intermediate AMD, or advanced AMD compared to the low-intake group.

TABLE 1 Characteristics of the included studies ($n = 26$).

Characteristics of participants				Characteristics of exposure		Case of AMD	Study quality evaluation[a]
Author, publication year	Study design	Country	Age	Dietary assessment methods	Exposure		
Mares-Perlman et al., 1995	Retrospective cohort study	The United States	45–84	FFQ	Total fat; Saturated fat Oleate Linoleate Cholesterol	314 early AMD, 30 late AMD	High
Smith et al., 2000	Cross-sectional study	Australia	≥49y	FFQ	Total fat Saturated fat Cholesterol Polyunsaturated fat Monounsaturated fat	182 early AMD, 46 late AMD	High
Cho et al., 2001	Perspective cohort study	The United States	≥ 50y	FFQ	Total fat; Saturated fat Monounsaturated fat Polyunsaturated fat (linoleic acid; linolenic acid; arachidonic acid; eicosapentaenoic acid; docosahexaenoic acid) Trans Unsaturated fat	567 AMD (any stages)	High
Seddon et al., 2003	Perspective cohort study	The United States	≥ 60y	FFQ	Saturated fat Monounsaturated fat Polyunsaturated fat Trans unsaturated fat	101 late AMD	High
Chua et al., 2006	Perspective cohort study	Australia	≥ 49y	FFQ	Total dietary fat Saturated fa Monounsaturated fat Polyunsaturated fat (total n-3 polyunsaturated fatty acids; a-linolenic acid; long-chain n-3 polyunsaturated fatty acids; total n-6 polyunsaturated fatty acids; linoleic acid; arachidonic acid) Trans-unsaturated fat	158 early AMD, 26 late AMD	High
Robman et al., 2007	Cross-sectional study	Australia	74±7	FFQ	Omega-3 FA	83 AMD (any stages)	High

(Continued)

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TABLE 1 (Continued)

Characteristics of participants				Characteristics of exposure		Case of AMD	Study quality evaluation[a]
Author, publication year	Study design	Country	Age	Dietary assessment methods	Exposure		
SanGiovanni et al., 2007	Case–control study	The United States	60–80	AREDS FFQ	Omega-3 FA (a-linolenic acid; 18:3–3) eicosapentaenoic acid (20:5 w-3) docosahexaenoic acid (22:6 w-3)) Total w-3 LCPUFAs w-6 Fatty acids (linoleic acid (18:2w-6; arachidonic acid (20:4 w-6)) Monounsaturated fatty acids Saturated fatty acids Dietary cholesterol	657 AMD (any stages)	High
Delcourt et al., 2007	Perspective cohort study	France	>60	FFQ	Total fat Saturated fatty acids Monounsaturated fatty acids Polyunsaturated FA	46 early AMD, 12 late AMD	High
Augood et al., 2008	Cross-sectional study	Europe	≥ 65	FFQ	DHA EPA	105 NV-AMD	High
Chiu et al., 2009	Cross-sectional study	The United States	55–80	FFQ	DHA EPA	4,454 early AMD, 747 late AMD	High
Chong et al., 2009	Perspective cohort study	Australia	40–69	FFQ	Total fat Polyunsaturated fat Monounsaturated fat Saturated fat Trans fat Oleic acid Linoleic acid Arachidonic acid Omega-3 fatty acids Marine omega-3 fatty acids Eicosapentaenoic acid Docosahexaenoic acid Alpha-linolenic acid	1921 early AMD, 77 late AMD	High
Parekh et al., 2009	Perspective cohort study	The United States	50–79	FFQ	Total fat Saturated fat Monounsaturated fat Omega-6 PUFA Omega-3 PUFA;	1787 intermediate AMD	High

(Continued)

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TABLE 1 (Continued)

Characteristics of participants				Characteristics of exposure		Case of AMD	Study quality evaluation[a]
Author, publication year	Study design	Country	Age	Dietary assessment methods	Exposure		
SanGiovanni et al., 2009	Perspective cohort study	The United States	55–80	FFQ	DHA EPA	364 central geographic atrophy, 583 NV-AMD	High
Tan et al., 2009	Perspective cohort study	Australia	>49	FFQ	Saturated FA Monosaturated FA PUFAs Total fat Tans-unsaturated FA Total omega-3 PUFAs Long-chain omega-3 PUFAs Alpha-linolenic acid Total omega-6 PUFAs Linoleic acid Arachidonic acid	220 early AMD, 59 late AMD	High
Christen et al., 2011	Perspective cohort study	The United States	>45	FFQ	Omega-3 FA Omega-6 fatty acid ALA; AA; LA; DPA; DHA; EPA	235 AMD (any stages)	High
Ho et al., 2011	Perspective cohort study	The Netherlands	≥ 55	FFQ	EPA + DHA	517 early AMD	High
Aoki et al., 2016	Case–control study	Japan	AMD: 73.5 ± 7.1 Control: 73.1 ± 5.6	BDHQ	Omega-3 FA	157 AMD (any stages)	High
Wu et al., 2017	Perspective cohort study	The United States	≥ 50	FFQ	ALA Omega-3 FA	1,589 intermediate AMD, 1,356 late AMD	High
Wu et al., 2017	Perspective cohort study	The United States	≥ 50	FFQ	EPA DHA;		High
Ng et al., 2019	Case–control study	Hong Kong	Exudative AMD patient: 73.7 ± 10.2 Control: 67.1 ± 9.3	FFQ	Omega-3 FA Omega-6 FA	99 exudative AMD	High

(Continued)

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TABLE 1 (Continued)

Characteristics of participants				Characteristics of exposure		Case of AMD	Study quality evaluation[a]
Author, publication year	Study design	Country	Age	Dietary assessment methods	Exposure		
Roh et al., 2020	Cross-sectional study	The United States	AMD:74.2 ± 7.9 Control: 68.3 ± 6.7	FFQ	Trans fat Saturated fat PUFA Omega-3 FA Omega-6 FA MUFA	90 early AMD, 201 intermediate AMD 95 late AMD	High
Sasaki et al., 2020	Cross-sectional study	Japan	Early AMD: 62.0 control: 65.3	FFQ	Total fat Saturated fatty acid Monounsaturated FA Polyunsaturated FA n3-polyunsaturated FA; n6-polyunsaturated FA n3-highly unsaturated FA SFA (total, HDL, LDL cholesterol, triglycerides)	447 early AMD	High
Edo et al., 2021	Cross-sectional study	The United States	Early AMD: 66.5 ± 10.3 control: 60.4 ± 13.7	FFQ	SFA; PUFA; cholesterol	111 early AMD,	High
Elmore et al., 2022	Cross-sectional study	The United States	≥ 70	FFQ	EPA, DHA, ALA, LA, AA	378 AMD (any stages)	High
Karger et al., 2022	Perspective cohort study	The United States	45–84	FFQ	DHA, EPA, DHA + EPA	214 early AMD	High
Yasukawa et al., 2023	Cross-sectional study	Japan	62.4 ± 9.4	FFQ	Total fat Saturated fatty acid Monounsaturated fatty acids Polyunsaturated fatty acids Omega-3 FA Linolenic acid Eicosapentaenoic acid (EPA) Docosahexaenoic acid (DHA) Omega-6 FA	1,421 early AMD, 906intermediate AMD 29 late AMD	High

[a]Study quality for cohort and case–control studies was assessed with the use of Newcastle–Ottawa Scale, and cross-sectional studies were assessed with the use of the Agency for Healthcare Research and Quality (AHRQ).

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TABLE 2 Newcastle–Ottawa scale (cohort) for 14 studies included in this meta-analysis.

Study (Author+Year)	Cohort Selection				Comparability	Result			Quality Score
	Representativeness of the Exposed Cohort (high representativeness/ good representativeness)	Selection of the Non-Exposed Cohort (from the same population and community as the exposed cohort)	Ascertainment of Exposure (Strict and accurate records (such as surgical records)/ structured questionnaires)	Demonstration That Outcome of Interest Was Not Present at Start of Study (Yes)	Comparability of Cohorts on the Basis of the Design or Analysis (Select and analyze controls based on the most important factor/ Select and analyze controls based on other important factors such as the second most important factor)	Assessment of Outcome (Independent, blinded measurement or assessment/ based on reliable records)	Was Follow-Up Long Enough for Outcomes to Occur (Yes)	Adequacy of Follow-Up of Cohorts (Adequate follow-up, all study subjects are followed up/follow-up rate > 90%)	
Mares-Perlman et al., 1995	1	1	0	1	2	1	1	1	8
Cho et al., 2001	1	1	0	1	2	1	1	1	8
Seddon et al., 2003	1	1	0	1	2	1	1	1	8
Chua et al., 2006	1	1	0	1	2	1	0	1	7
Delcourt et al., 2007	1	1	0	1	2	1	0	1	7
Chong et al., 2009	1	1	0	1	2	1	1	1	8
Parekh et al., 2009	1	1	0	1	2	1	1	1	8
SanGiovanni et al., 2009	1	1	0	1	2	1	1	1	8
Tan et al., 2009	1	1	0	1	2	1	1	1	8
Christen et al., 2011	1	1	0	1	2	1	1	1	8
Ho et al., 2011	1	1	0	1	2	1	1	1	8
Wu et al., 2017	1	1	0	1	2	1	1	1	8
Wu et al., 2017	1	1	0	1	2	1	1	1	8
Karger et al., 2022	1	1	0	1	2	1	1	1	8

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TABLE 3 Newcastle-Ottawa scale (case–control) for three studies included in this meta-analysis.

Study(Author+Year)	Selection of Cases and Controls				Comparability	Exposure		Quality Score
	Is the Case Definition Adequate? (The definition and diagnosis of the disease are correct, independent and valid)	Representativeness of the Cases (Contiguous cases, or cases of representativeness)	Selection of Controls (community control)	Definition of Controls (No history of disease of interest)	Comparability of Cases and Controls (Select and analyze controls based on the most important factors)	Ascertainment of Exposure (Reliable records; e.g., surgical records)	Are the methods the same for cases and controls? (Yes)	Non-Response Rate (Non-response rates were the same between the two groups)	
SanGiovanni et al., 2007	1	1	0	1	2	0	1	1	7
Aoki et al., 2016	1	1	1	1	2	0	1	1	8
Ng et al., 2019	1	1	0	1	2	0	1	1	7

3.4.7 Omega-3 LCPUFAs and alpha-linolenic acid

In total, two of the included studies analyzed the association of intake of omega-3 LCPUFAs with the risk of overall AMD, and no statistical heterogeneity was observed among studies ($I^2 = 0.0\%$, $P_H = 0.683$) (15, 32). We compared the high and low intake levels of omega-3 LCPUFAs and observed a significant difference in the risk of overall AMD (OR:0.67; 95%CI: [0.51, 0.88]; $p = 0.004$) and advanced AMD (OR:0.60; 95%CI: [0.42, 0.87]; $p = 0.006$) between the increased intake of omega-3 LCPUFAs and the low-intake group as shown in Figures 3B,C.

In addition, eight studies analyzed the relationship between ALA intake and the risk of overall AMD, and there was large statistical heterogeneity among studies ($I^2 = 55.0\%$, $P_H = 0.01$) (13, 15–17, 21, 31, 32, 38). The high intake of ALA had no association with overall AMD, early AMD, intermediate AMD, or advanced AMD.

3.4.8 DHA and eicosapentaenoic acid (EPA, C20: 5 n-3)

In total, seven of the included studies analyzed the relationship between combined intake of DHA and EPA and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 64.5\%$, $P_H = 0.003$) (11, 14, 17, 39, 40). We compared the high and low intake levels of DHA and EPA and observed a difference between the increased intake levels of DHA and EPA and the low-intake group in the risk of overall AMD (OR: 0.79; 95%CI: [0.67, 0.93]; $p = 0.035$) or early AMD (OR: 0.71; 95%CI: [0.53, 0.95]; $p = 0.022$) as shown in Figures 4A,B. In contrast, no difference was found between the two groups in the risk of advanced AMD.

In addition, 12 studies analyzed the relationship between DHA intake and the risk of overall AMD, and large statistical heterogeneity was observed among studies ($I^2 = 66.0\%$, $P_H < 0.001$) (11–21, 40). We compared the high and low intake levels of DHA and observed a difference in the risk of overall AMD (OR:0.80; 95%CI:[0.70, 0.90]; $p < 0.001$), intermediate AMD (OR:0.83; 95%CI:[0.73, 0.95]; $p = 0.005$), or advanced AMD (OR:0.68; 95%CI:[0.52, 0.87]; $p = 0.003$) between the increased intake of DHA and the low-intake group as shown in Figures 4C–E. In contrast, the increased intake of DHA was not related to the risk of early AMD.

Finally, 11 studies analyzed the relationship between EPA intake and the risk of overall AMD, and no statistical heterogeneity was observed among studies ($I^2 = 32.2\%$, $P_H = 0.099$) (11–15, 17–21, 40). We compared the high and low intake levels of EPA and a significant difference was found between the increased intake of EPA and the low-intake group in the risk of overall AMD (OR:0.91; 95%CI: [0.86, 0.97]; $p = 0.004$) and advanced AMD (OR:0.85; 95%CI: [0.70, 1.02]; $p = 0.034$) as shown in Figures 4F,G. In contrast, the increased intake of DHA was not related to the risk of early AMD or intermediate AMD.

3.4.9 Oleic acid, linolenic acid, docosapentaenoic acid (DPA, C22:5n3)

In addition, two of the included studies analyzed the relationship between oleic acid intake and the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 88.6\%$, $P_H = < 0.001$) (16, 21). We compared the high and low intake levels of oleic acid and observed no difference in the risk of overall AMD and advanced AMD between the increased intake of oleic acid and the low-intake group.

TABLE 4 Agency for healthcare research and quality (AHRQ) checklist (cross-sectional) for nine studies included in this meta-analysis.

Study (Author+Year)	Yasukawa et al., 2023	Elmore et al., 2022	Edo et al., 2021	Sasaki et al., 2020	Roh et al., 2020	Chiu et al., 2009	Augood et al., 2008	Robman et al., 2007	Smith et al., 2000
Define the source of information (Survey, record review)	1	1	1	1	1	1	1	1	1
List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	1	1	0	1	1	1	1	1	1
Indicate time period used for identifying patients	1	1	1	1	1	1	1	1	0
. Indicate whether or not subjects were consecutive if not population-based	1	1	1	1	1	1	1	1	1
Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	1	1	1	1	1	1	1	1	1
Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	1	1	1	1	1	1	1	1	1
Explain any patient exclusions from analysis	1	1	1	1	1	1	1	0	0
Describe how confounding was assessed and/or controlled	1	1	1	1	1	1	1	1	1
If applicable, explain how missing data were handled in the analysis	1	1	1	1	1	1	1	1	1
Summarize patient response rates and completeness of data collection	1	1	1	1	1	1	1	1	1
Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	1	1	1	1	1	1	1	1	1
Quality Scores	11	11	10	11	11	11	11	10	9

Additionally, two studies analyzed the relationship between linolenic acid intake and the overall risk of AMD, with no statistical heterogeneity among the studies ($I^2 = 49.8\%$, $P_H = 0.137$) (18, 20). No difference was found in the risk of overall AMD between both groups.

Finally, two studies analyzed the relationship between DPA intake and the risk of overall AMD, and large statistical heterogeneity was observed among the studies ($I^2 = 93.8\%$, $P_H = < 0.001$) (13, 16). The high DPA intake did not influence the risk of overall AMD in comparison with the low-intake group.

3.4.10 Omega-6 PUFAs family

In total, five of the included studies analyzed the association of intake of omega-6 PUFAs with the risk of overall AMD, and the statistical heterogeneity among the studies was large ($I^2 = 69.7\%$, $P_H = 0.006$) (13, 18, 22–24). We compared the high and low intake levels of omega-6 PUFAs and found that increasing the intake of omega-6 PUFAs did not affect the risk of overall AMD, early AMD, or intermediate AMD.

For other subgroups of the omega-6 family, six studies examined the relationship between linoleic acid intake and the risk of overall AMD, and large statistical heterogeneity was observed among studies ($I^2 = 0.0\%$, $P_H = 0.911$) (13, 15, 17, 20, 21, 32). No significant difference was found in reducing the overall AMD, early AMD, or advanced AMD between the high and low intake levels of linoleic acid.

In addition, seven studies examined the relationship between arachidonic acid intake and the risk of overall AMD, and large statistical heterogeneity was observed among studies ($I^2 = 72.7\%$, $P_H = <0.001$) (13, 15–17, 20, 21, 32). The high intake of arachidonic

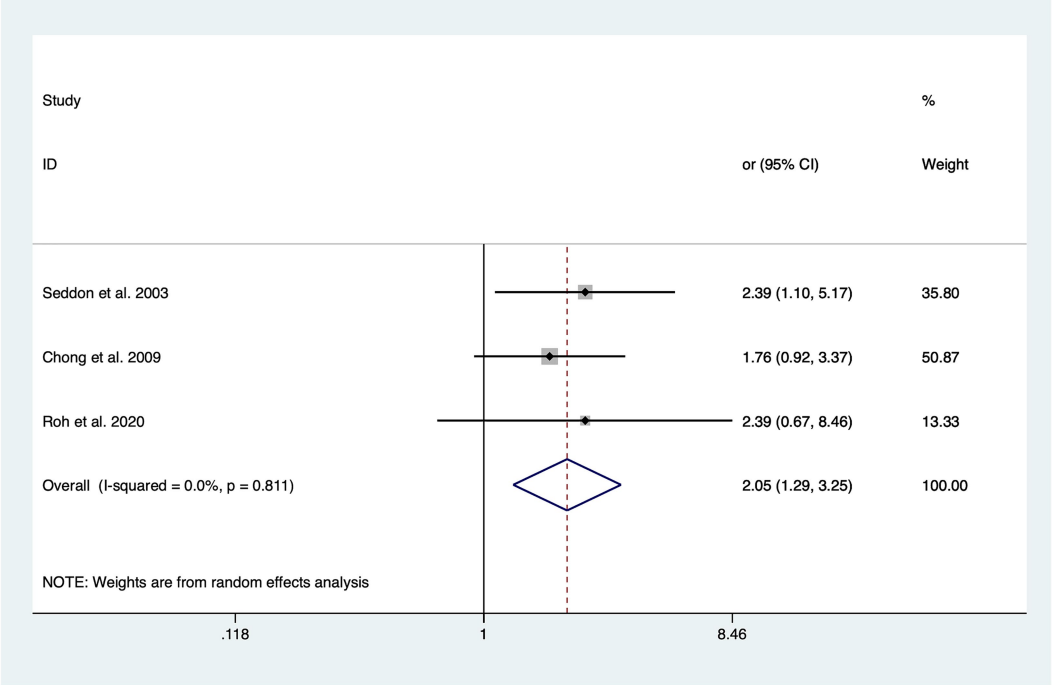

FIGURE 2
Forest plot of the odd risk (OR) of advanced AMD for the highest vs. lowest level intake of trans-fatty acid in studies.

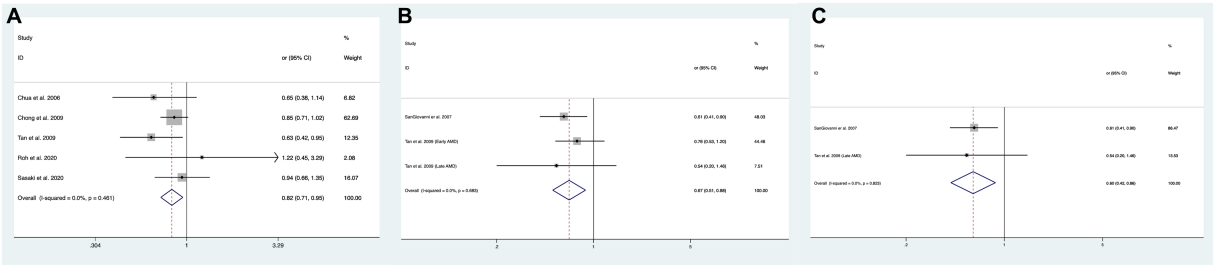

FIGURE 3
Forest plot of the odds risk (OR) of AMD for the highest vs. lowest level intake of omega-3 family in studies. **(A)** The odds risk of omega-3 PUFAs and early AMD; **(B)** the odds risk of omega-3 LCPUFAs and overall AMD; **(C)** the odds risk of omega-3 LCPUFAs and advanced AMD.

acid had no association with reduced overall AMD, early AMD, or advanced AMD compared to the low-intake group.

3.5 Sensitivity analysis and publication bias assessment results

For the studies on overall AMD in the above groups of fatty acids, sensitivity analysis was conducted by removing one study at a time. No individual study was found to affect the pooled effect size, indicating that the results were robust. We used Egger's test to assess the publication bias for total fat, SFAs, MUFAs, PUFAs, omega-3 family, DHA, and EPA (Table 5). Egger's test results suggested the presence of publication bias in DHA ($p = 0.003$) and EPA ($p = 0.017$). Therefore, we corrected the results using the trim-and-fill method and found that no new studies were added to the analysis, indicating that the existing publication bias did not affect the results of the study as shown in Figure 5. Other FA groups did not have publication bias.

4 Discussion

We included 26 studies with 241,151 participants to summarize the relationship between various FA subtypes and AMD in different stages, providing the latest epidemiological evidence. The evidence in this meta-analysis was of high quality and showed that the high intake of omega-3 LCPUFAs, DHA, and EPA as well as the simultaneous intake of DHA and EPA lowered the risk of overall AMD. In contrast, the high and low intake levels of total fat, SFAs, MUFAs, PUFAs, and omega-6 showed no statistical significance in reducing the risk of overall AMD.

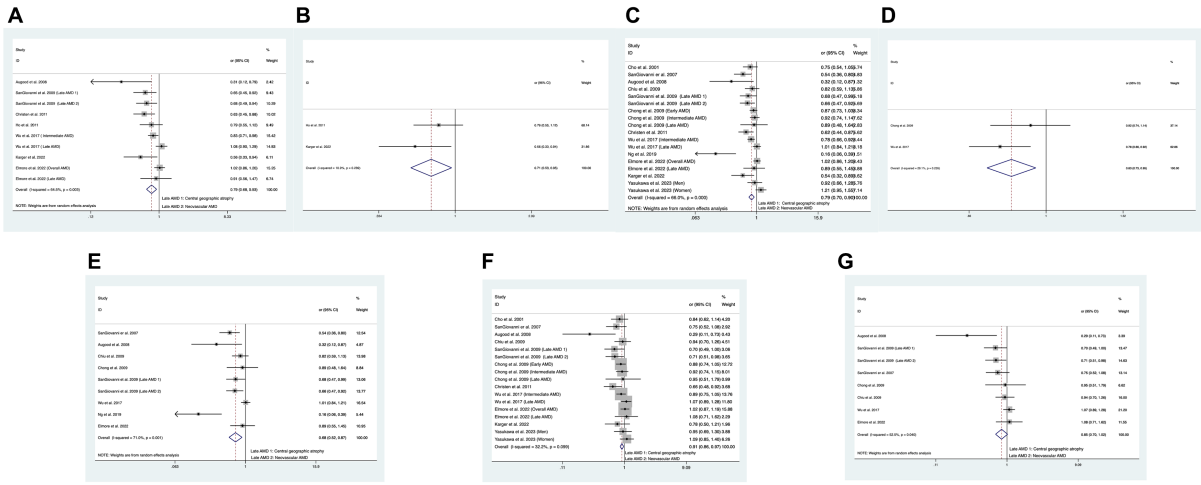

FIGURE 4
Forest plot of the odds risk (OR) of AMD for the highest vs. lowest level intake of DHA and EPA in studies. **(A)** The odds risk of combined intake of DHA and EPA and overall AMD; **(B)** the odds risk of combined intake of DHA and EPA and early AMD; **(C)** the odds risk of DHA and overall AMD; **(D)** the odds risk of DHA and intermediate AMD; **(E)** the odds risk of DHA and advanced AMD; **(F)** the odds risk of EPA and overall AMD; **(G)** the odds risk of EPA and advanced AMD.

The high intake of omega-3 and simultaneous intake of DHA and EPA were statistically significant in reducing early AMD compared to the low-intake group. In addition, a high intake of DHA had a significant protective effect against risk factors for intermediate AMD compared to the low-intake group. Additionally, a high intake of omega-3 LCPUFA, DHA, and EPA significantly reduced the risk of advanced AMD in comparison with the low-intake group. It is worth noting that a high intake of TFAs increased the risk of advanced AMD, and previous meta-analyses have not reported this finding. Studies over the past decades have indicated that a higher intake of TFAs is positively related to a higher incidence of AMD and progression to advanced AMD, and the current meta-analysis has consistent results (21, 22, 34).

Several mechanisms have been suggested to underlie the protective effect of omega-3 LCPUFAs against the occurrence of AMD. The structure and function of the retina are highly dependent on FAs, and lipids make up one-third of the dry weight of the retina (41). FA is among the main nutrients in the human body. As a crucial component of the cell membrane's lipid bilayer, FA participates in the formation of cholesteryl ester (CE) and functions in promoting membrane synthesis, immune signal transduction, gene expression regulation, and other systemic processes (8). In addition, FA can also be mobilized by cells as precursors of lipid mediators involved in many physiological processes, such as inflammation and neuroprotection (42). However, studies have shown that excessive lipid accumulation can promote the accumulation of advanced glycation end products and the activation of the protein kinase C pathway, which results in excessive reactive oxygen species, leading to oxidative stress and cytotoxic effects (43, 44). Accumulation of oxidation derived from lipoprotein in these extracellular deposits and pro-inflammatory lipids may trigger inflammation and innate immune responses through AMD pathophysiology-related complement activation, and the accumulated oxidative damage may lead to changes in the anatomy and physiology of photoreceptors, RPE, drusen, and chorion, thereby causing AMD (4).

PUFAs, including one of the ligands responsible for the activation of PPAR-α, inhibit NF-κB to produce strong anti-inflammatory effects (18). PUFAs contain several FA families, and the two primary families are omega-3 and omega-6. The α-linolenic acid (C18: 3 n-3; ALA) is the precursor of omega-3, and linoleic acid is that of omega-6. The α-linolenic acid and linoleic acid are metabolized to LCPUFAs that contain more double chains and/or carbon atoms *in vivo* after several steps, such as arachidonic acid (AA, C20: 4 n-6), EPA, and DHA, and this is of great significance for maintaining the function and life span of rod cells (42). EPA and DHA are major metabolites of the omega-3 family, with an estimated 8% of ALA converted to EPA and 1% to DHA (42, 45). EPA, as the precursor of DHA, can reduce blood lipids, avoid the formation of atherosclerotic plaque, and inhibit angiogenesis (46). DHA is the main component of membrane phospholipids, and the content of DHA is the highest in synapses and photoreceptors. DHA can regulate gene expression and fight against oxidative stress, inflammation, or apoptosis in retinal cells. DHA is therefore thought to be crucial for regulating inflammation (9, 15, 45, 47). The derivatives of EPA and DHA, such as lysins and neuroprotectins, can also protect photoreceptors from oxidative stress to fight against apoptosis and promote cell differentiation. Therefore, they all have anti-inflammatory properties (48).

The results of our research indicated that a high intake of LCPUFAs effectively lowered the risk of both overall AMD and progression to advanced AMD, and this was consistent with those of the Age-Related Eye Disease Study 2 (AREDS-2) and a 10-year cohort study (15, 32), indicating that a high intake of DHA and EPA may be able to lower the risk of overall AMD or progression to advanced AMD. In addition, a high dietary intake of omega-3 PUFA significantly reduced the risk of early AMD compared to the low-intake group but did not lower the risk of intermediate or advanced AMD as previously reported in some meta-analyses (7, 8). Some studies have hypothesized that this may be because the participants changed their overall diet after they had been diagnosed

TABLE 5 Results of the meta-analysis.

Fatty acid type			Number of studies	Sample size	Heterogeneity, I^2, *p*	Model	OR, 95%CI	*P*	Egger, *P*
Total fat			10	8,248	59.1%, 0.001	Random	0.99(0.84,1.17)	0.881	0.71
		EA	5	2,332	45.2%, 0.104	Fixed	0.99(0.86,1.12)	0.82	N/A
		IM	2	2,697	0.0%, 0.828	Fixed	1.04(0.86,1.26)	0.707	N/A
		LA	5	279	0.0%, 0.822	Fixed	0.85(0.57,1.27)	0.426	N/A
Trans-fatty acid			6	3,515	63.6%, 0.005	Random	1.06(0.85,1.33)	0.061	N/A
		EA	4	2,389	62.1%, 0.048	Random	0.89(0.55,1.44)	0.628	N/A
		IM	2	1,111	65.9%, 0.087	Random	1.31(0,60,2.85)	0.5	N/A
		LA	3	358	0.0%, 0.811	Fixed	2.05(1.29,3.25)	0.002	N/A
Saturated fatty acid			14	8.936	55.5%, 0.001	Random	1.04(0.89,1.22)	0.591	0.343
		EA	8	2,533	72.5%, 0.001	Random	1.01(0.76,1.33)	0.795	N/A
		IM	3	4,898	63.9%, 0.063	Random	0.89(0.52,1.53)	0.675	N/A
		LA	7	1,065	29.6%, 0.202	Fixed	1.17(0.90,1.52)	0.238	N/A
Monounsaturated fatty acid			12	9,048	61.3%, <0.001	Random	0.93(0.78,1.11)	0.422	0.513
		EA	6	4,485	68.2%, 0.008	Random	0.81(0.59,1.11)	0.195	N/A
		IM	2	2,697	91.6%, 0.001	Random	0.45(0.08,2.57)	0.366	N/A
		LA	6	1,035	56.3%, 0.043	Random	1.05(0.68,1.63)	0.827	N/A
Polyunsaturated fatty acid			11	6,715	53.4%, 0.006	Random	0.94(0.80,1.11)	0.452	0.702
		EA	7	3,175	55.8%, 0.035	Random	1.00(0.78,1.29)	0.98	N/A
		LA	5	445	72.6%, 0.006	Random	0.73(0.34,1.58)	0.429	N/A
Omega-3			10	7,912	68.3%, <0.001	Random	0.87(0.72,1.05)	0.148	0.612
		EA	5	1,926	0.0%, 0.461	Fixed	0.82(0.71,0.95)	0.008	N/A
		IM	3	2,898	82.1%, 0.004	Random	1.30(0.72,2.32)	0.383	N/A
		LA	6	497	76.4%, 0.001	Random	0.63(0.29,1.36)	0.241	N/A
	Long-chain omega-3		2	936	0.00%, 0.683	Fixed	0.67(0.51,0.88)	**0.004**	N/A
		LA	2	716	0.0%, 0.823	Fixed	0.60(0.42,0.87)	0.006	N/A
	DHA + EPA		7	5,341	64.5%, 0.003	Random	0.79(0.67,0.93)	**0.035**	N/A
		EA	2	731	10.9%, 0.289	Fixed	0.71(0.53,0.95)	**0.022**	N/A
		LA	7	2,985	66.2%, 0.007	Random	0.85(0.69,1.05)	0.135	N/A
	DHA		12	14,702	66%, 0.000	Random	0.80(0.70,0.90)	**0**	**0.003**
		EA	2	1,225	67.7%, 0.078	Random	0.76(0.46,1.15)	0.173	N/A
		IM	2	2,499	29.1%, 0.235	Fixed	0.83(0.73,0.95)	0.005	N/A
		LA	9	4,366	71.0%, 0.001	Random	0.68(0.52,0.87)	0.003	N/A
	EPA		11	15,603	32.2%, 0.099	Fixed	0.91(0.86,0.97)	**0.004**	**0.017**
		EA	2	2,135	0.00%, 0610	Fixed	0.87(0.73,1.02)	0.082	N/A
		IM	2	2,499	0.0%, 0.815	Fixed	0.90(0.79,1.03)	0.126	N/A
		LA	8	4,267	52.5%, 0.04	Random	0.85(0.70,1.02)	**0.034**	N/A
	Oleic acid		2	2,097	88.6%, 0.000	Random	1.51(0.91,2.51)	0.115	N/A
		LA	2	176	94.0%, 0.000	Random	3.82(0.31,46.92)	0.295	N/A
	Linolenic acid		2	2,923	49.8%, 0.137	Fixed	1.08(0.90,1.28)	0.407	N/A
	ALA		8	6,775	55%, 0.01	Random	1.01(0.89,1.14)	0.937	N/A
		EA	3	1,389	77.9%, 0.011	Random	1.07(0.67,1.71)	0.781	N/A
		IM	2	2,119	75.8%, 0.042	Random	1.10(0.81,1.49)	0.53	N/A
		LA	6	3,556	50.3%, 0.073	Random	0.93(0.74,1.18)	0.548	N/A
	DPA(C22:5n3)		2	334	93.8%, 0.000	Random	0.33(0.06,1.97)	0.225	N/A

(Continued)

TABLE 5 (Continued)

Fatty acid type			Number of studies	Sample size	Heterogeneity, I^2, *p*	Model	OR, 95%CI	*P*	Egger, *P*
Omega-6			5	5,211	69.7%, 0.006	Random	0.93(0.69,1.27)	0.661	N/A
		EA	2	2,193	0.00%, 0.594	Fixed	0.97(0.68,1.38)	0.865	N/A
		IM	2	1,988	92.9%, 0.000	Random	0.69(0.08,6.04)	0.739	N/A
	Linoleic acid		6	4,114	0.00%, 0.911	Fixed	0.95(0.87,1.04)	0.26	N/A
		EA	2	2,141	0.00%, 0.855	Fixed	0.91(0.76,1.08)	0.265	N/A
		LA	4	2,249	0.00%, 0.719	Fixed	1.01(0.79,1.29)	0.926	N/A
	Arachidonic acid		7	4,213	72.7%, 0.000	Random	1.09(0.90,1.33)	0.371	N/A
		EA	2	2,141	0.00%, 0.790	Fixed	0.86(0.74,1.00)	0.053	N/A
		LA	5	2,546	83.9%, 0.000	Random	1.61(0.82,3.14)	0.164	N/A

The bold values indicate *p*-values ≤ 0.05.

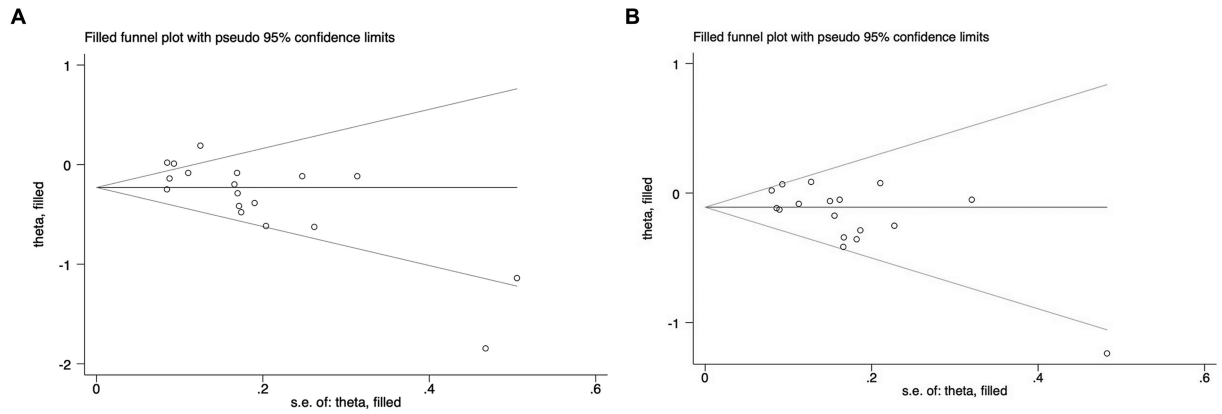

FIGURE 5
Trim-and-fill method for further verification of publication bias among studies.

with AMD, leading to the fact that a high omega-3 PUFA intake did not significantly lower the risk of intermediate and advanced AMD (8).

According to the present meta-analysis, a high intake of DPA and EPA, respectively, reduced the risk of advanced AMD, and this result was consistent with the findings of Meng (49)and Jiang (7), but contrary to the findings of Zhong (8). This may be due to the inconsistency in the type of the studies included in their respective studies. Zhong included only prospective cohort studies and did not include cross-sectional and case–control studies, resulting in inconsistent results (8). Unlike the previously reported studies, this meta-analysis also analyzed the association of increased DHA intake with the risk of intermediate AMD, and a significant difference was found in the high DHA intake group in reducing the risk of intermediate AMD compared to the low-intake group. It is worth noting that simultaneous supplementation of DHA and EPA can effectively reduce the risk of overall and early AMD but cannot reduce the risk of advanced AMD. Among all the included studies, only Wu reported that the risk of advanced AMD had not been lowered for the simultaneous intake of EPA and DHA, we reviewed the study by Wu and found that simultaneous supplementation of DHA and EPA could lower the risk of intermediate AMD but could not lower the risk of advanced AMD. The specific reason may be related to the diet and health awareness of patients. In addition, Wu believed that reducing the incidence of intermediate AMD could ultimately achieve the purpose of reducing the risk of advanced AMD, and at least no harm has been reported in terms of simultaneous supplementation of DHA and EPA (40).

Many studies have shown that the anti-inflammatory mechanism of omega-3 is also related to its ability to inhibit the pro-inflammatory and pro-angiogenic effects of omega-6, and this is due to their competition for the same enzymes in the cyclooxygenase and lipoxygenase pathways (45, 50). Omega-6 produces prostaglandin E2, thromboxane A2, leukotriene B4, and other inflammatory substances after a series of metabolic processes *in vivo*, which further aggravates the oxidative stress of retinal cells and increases the development of AMD (42). This may explain the conflicting conclusions in the included studies that a high omega-6 intake has an increasing or decreasing effect on the risk of AMD. Among the included studies, Roh et al. found that omega-6 reduced the risk of AMD. They believed that this result was because their studies included not only Americans but also Portuguese, who mainly follow the Mediterranean diet (MD). In MD, high consumption of nuts is recommended, and nuts are rich in omega-6, which may slow the progression of AMD (22). However, omega-3 is also one type of rich nutrient in MD, and nuts are also reported to have rich EPA and DHA. Therefore, the MD increases the intake of omega-6 and omega-3 in the diet. This may

have contributed to the protective effect of omega-6 on AMD in some studies (51, 52). In addition, Yasukawa also mentioned that the use of dietary supplements in American men and women was 74 and 79%, respectively, much higher than that in Japanese men and women, which was 30.2 and 38.2%, respectively. This may also lead to inconsistent results (18).

In clinical practice, ophthalmologists should provide different clinical recommendations based on the clinical classification of patients. For early-stage AMD patients, maintaining a healthy lifestyle is recommended, such as smoking cessation, a balanced diet (a diet rich in vegetables, fruits, fatty fish, and various foods rich in omega-3), and moderate physical activity. For patients with mid-stage AMD, in addition to a healthy lifestyle, supplementing antioxidant vitamins and minerals is recommended. According to the supplement formula proposed by AREDS-2, patients with mid-stage AMD should supplement with 500 mg of vitamin C, 400 IU of vitamin E, 10 mg of lutein, 2 mg of zeaxanthin, 80 mg of zinc oxide, and 2 mg of cupric oxide and regularly perform ophthalmologic examinations. For advanced patients, drug treatment is required in addition to the above-mentioned measures. For patients who have ever or currently smoked, lutein and zeaxanthin can be used, instead of β-carotene, to reduce the incidence of lung cancer, as β-carotene, abundant in the formula of AREDS-2, may increase the risk of lung cancer (53).

5 Limitations

First, the sample sizes of studies about some FAs, such as oleic acid, linolenic acid, DPA, and omega-6, are small, and this may lead to a less robust meta-analysis of these FAs, thereby limiting the interpretation of the results. Second, as some of the included studies were published years ago, there are some differences in the staging and diagnosis of AMD in different studies, and some studies did not differentiate AMD in different stages. Therefore, studies on the association of FAs with the risk of AMD in different stages are small in number, and this may lead to underestimation or overestimation of the relationship between intake of FAs and the risk of AMD. Third, the included studies were published within a long time span and involved different clinical factors, including age, country, and population, and this may lead to some biases. Fourth, in all the included studies, the FA intake was assessed using questionnaires that have many limitations, such as incorrect reporting of diet, and measurement errors are inevitable, and these factors may lead to errors in the relationship between FAs and the risk of AMD. Finally, the large number of cross-sectional and case–control studies (13 studies in total) included in this meta-analysis may have led to biases in data.

6 Conclusion

This meta-analysis provides evidence of high quality and showed that a high intake of LCPUFAs, DHA, EPA, or the simultaneous intake of DHA and EPA is strongly related to a decreased risk of overall AMD compared to the low-intake group. The simultaneous intake of high levels of DHA and EPA or high intake levels of omega-3 PUFA effectively decreases the risk of early AMD. In addition, a high intake of DHA has a strong association with a reduced risk of intermediate AMD. It is worth noting that a high intake of TFAs is significantly and positively correlated with advanced AMD, and the intake of TFAs should be reduced in daily diet. In future large-scale prospective studies, cross-sectional studies, or RCTs, more attention should be paid to the association of various intake levels of different FAs with the development and progression of intermediate AMD, to avoid the occurrence of advanced AMD as far as possible. Attention should also be paid to the association between AMD and the study population, dietary habits, and health awareness of the participants, and adjustments should be made accordingly, as this will greatly affect the study results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YL: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. LL: Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation. LZ: Writing – review & editing, Software, Funding acquisition, Formal analysis, Data curation. QZ: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1403987/full#supplementary-material

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Research progress on the correlation between cataract occurrence and nutrition

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Cataract is a common eye disease characterized by lens opacity, leading to blurred vision and progressive blindness of the eye. Factors affecting the development of cataracts include nutrition, oxidative stress, micronutrients and inflammatory factors, and also include genetics, toxicity, infrared exposure, hyperuricemia, and mechanical injuries. Among the nutritional factors, a balanced diet, vegetarian diet, dairy products and vegetables are protective against cataracts; high-sodium diet, high intake of carbohydrates and polyunsaturated fatty acids may increase the risk of cataracts; and increased intake of proteins, especially animal proteins, may prevent nuclear cataracts. Intake of antioxidants such as β-carotene, lutein, or zeaxanthin is associated with a reduced risk of cataracts. Minerals such as zinc, selenium, calcium and sodium have also been associated with cataract development. Oxidative stress plays an important role in the development of cataracts and is associated with several antioxidative enzymes and biomarkers such as glutathione (GSH), superoxide dismutase (SOD), malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Insulin resistance is also an essential risk factor for cataracts, especially in diabetic patients. In conclusion, understanding these influencing factors helps us to better prevent cataracts. And in this article, we will focus on the important factor of diet and nutrition for a detailed discussion.

KEYWORDS

cataract, nutrition, oxidative stress, insulin resistance, micronutrients, inflammatory factors

1 Introduction

Cataract is a common eye disease whose typical symptom is the opacity of the lens, which causes blurred vision and even progressive blindness. According to the World Health Organization (WHO), cataracts affect more than 94 million people worldwide (1), indicating that cataracts have become one of the major causes of global vision impairment. Therefore, exploring the risk factors affecting cataract formation is crucial for the prevention and mitigation of this disease. The object of this study is to comprehensively analyze all known influencing factors, including dietary structure, chronic diseases, to deepen the understanding of the pathogenesis of cataract and providing scientific evidences for the development of effective preventive measures. At the same time, this study will also examine some generally proposed influencing factors, such as nutrient intake, oxidative stress, insulin resistance, etc., in order to expand our knowledge in cataract formation. By systematically analyzing these factors, this study hopes to facilitate

preventive intervention and mitigation of early cataract formation and provide new thoughts and solutions for clinical practice.

2 Correlation of dietary mode and intakes with cataract

2.1 Dietary mode

Falkowska et al. (2) pointed out that a balanced diet (mainly based on calorie restriction of vegetables, grains, legumes and fish, and a nutrient pattern of low animal fats), a vegetables diet, "dairy and vegetables," "traditional diet," "antioxidants" and "Omega-3 (polyunsaturated fatty acids)" have a significant protective effect on age-related cataracts. A large hospital cohort study conducted by Jee and Park (3) assessed lifestyle-related risk factors. Metabolic syndrome (MS) was positively associated with age-related cataract (ARC). In addition, they found that individuals with hyperglycemia and low density lipoprotein (LDL) cholesterolemia were more prone to ARC, and plasma glucose and HbA1c concentrations increased 1.50 and 1.92-fold, in patients with MS exhibiting ARC risk. High carbohydrate intake increased the risk of ARC by 1.4-fold, and high fat (≥15%), protein and calcium intake reduced the risk of ARC by 0.74-fold. Movahedian (4) et al. found a significant and direct relationship between dietary glycemic index, glycemic load, insulin load and cataracts, and speculated that improving the quality of the diet is a key approach to reduce the risk of cataracts.

2.2 Carbohydrate intake

Several studies have shown (5, 6) that carbohydrate intake is positively associated with cataract development. The specific mechanism of the reaction is unknown, and it may be that the slow absorption and utilization of glucose by the ocular aqueous humor leads to prolonged exposure of lens proteins to higher concentrations of glucose, causing the occurrence of protein cross-linking, aggregation, and precipitation, which leads to lens opacity and the development of cataracts (7). In addition, carbohydrates can elevate blood glucose concentrations, increasing the risk of cataract development (8).

2.3 High fat diet

Lu et al. (9) found that intake of large amounts of linoleic or linolenic acid increases the risk of lens opacity, which may ultimately lead to cataracts, because of the susceptibility of unsaturated fatty acids to lipid peroxidation, which results in the susceptibility of lens epithelial cells to oxidative stress, causing cell damage.

3 Correlation of glucose metabolism with cataract

3.1 Association of insulin resistance with cataract

Guo (10) found that in patients with diabetic cataract, high levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and insulin resistance index (HOMA-IR) were negatively correlated with visual acuity, and positively correlated with intraocular pressure (IOP) serum levels of interleukin-6 (IL-6), insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF) levels. This suggests that IL-6, IGF-1, and VEGF are important inflammatory factors promoting insulin resistance, and glucose fluctuations in diabetic cataracts and these factors are closely related to oxidative stress injury. It has been noted (11, 12) that NADPH oxidase-mediated oxidative stress and P53 (p53 is a tumor suppressor protein that regulates the expression of a variety of genes that are involved in apoptosis, growth arrest, inhibition of cell cycle progression, differentiation and accelerated DNA repair or senescence in response to genotoxicity or cell stress.) and Bax/Bcl2-mediated apoptosis signaling pathways are involved in the pathogenesis of cataracts in diabetic rats, and Puerarin may exert a therapeutic effect on diabetic cataract rats by improving the state of insulin resistance and downregulating the level of P53 protein (12).

3.2 The pathogenesis of diabetic cataract

In diabetic patients, prolonged hyperglycemia leads to excessive accumulation of sorbitol in the lens, increased osmotic pressure, influx of aqueous humor, leading to intracellular edema and fiber breakage, ultimately leading to lens turbidity and further worsening the extent of oxidative stress. It has been proposed (13) that cataract formation usually occurs in the several weeks or months after the initiation of insulin treatment in type I diabetes, and insulin autoantibodies are positive within 3 months of the initiation of insulin therapy, which coincided with cataract formation. Martina et al. (14) found that the development of cataracts in type II diabetes mellitus was closely related to the course of diabetes and various metabolic risk factors, especially the coexistence of poor glycemic control, hypercholesterolemia, diastolic blood pressure and diabetic nephropathy.

Decrease in insulin level or inhibition of galactokinase activity in the patients results in increased blood glucose content and the osmotic pressure within the lens. Lens fibers will be swelling and contain fractures, with increased opacity due to excessive osmotic pressure elevation. Early and timely diagnose is mandatory under this situation (15). After testing the serum levels of HbA1c, FPG, and fasting insulin (FINS) in patients with diabetic cataracts and other cataracts, calculating HOMA-IR, and testing the levels of IGF-1 and IL-6, Tang et al. (15) found that the other cataract patients had lower levels of HbA1c, FPG, HOMA-IR, IGF-1, and IL-6 than the patients with diabetic cataracts. Therefore, they believed that these indicators can assist in determining the condition. Guo et al. (10) yielded similar results and also mentioned that the IOP of diabetic cataract patients was higher than other cataract patients. Cai et al. (16) analyzed the relationship between postoperative insulin resistance and changes in inflammatory factor levels and quality of vision in cataract patients with glaucoma. It was mentioned that the patient's preoperative objective scatter index (OSI) was negatively correlated with insulin sensitivity index, that is, the degree of insulin resistance correlated with the degree of lens opacity. Suryanarayana et al. (17) showed that impaired glucose tolerance (IGT), which is suggestive of

insulin resistance, affects cataract development in rat model experiments.

4 Correlation of fat metabolism with cataract

4.1 Correlation of hyperlipidemia and cataract

Yin et al. (18) proposed that hyperlipidemia is the main factor for increased lens density in patients with age-related nuclear cataract. They found that serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDLC) levels in age-related nuclear cataract were correlated with lens density. Zhang et al. (19) suggested that hyperlipidemia promotes the development of galactose cataract to some extent based on data derived from rats experiments and suggested that cataract formation may be involved in the oxidative stress response. The hyperlipidemic cataract group had reduced GSH and higher malondialdehyde contents than the normal cataract group, reflecting reduction of antioxidative capacity and increase of damages caused by free radicals under a hyperlipidemic status (20). This reflects the reduced activity of the antioxidant system in the lens of rats in the hyperlipidemic cataract group, and the increased malondialdehyde content suggests an increased severity of cell attacked by free radicals. Similar results were obtained by Tsutsumi et al. (20) in rats experiments, leading to a conclusion that hyperlipidemia that hyperlipidemia and LDLC are risk factors for the development of diabetic cataracts. In a case–control study conducted by Galeone et al. (21), cataract occurrence was found to associate with hyperlipidemia, central obesity, hypertension and diabetes. Zhang et al. (22) also concluded that age-related cataract patients are often afflicted with hyperlipidemia, hypertension and hyperglycemia. They found that oxidized low-density lipoprotein (oxLDL) can effectively affect lens epithelial cell transcription, leading to differential expression of Rho signaling and ATP1B1, which may be involved in cataract formation.

However, Jiang et al. (23) proposed a different viewpoint, with data showing that only the decrease in HDLC content increased the risk of age-related cataracts in middle-aged and elderly people, and there was no correlation between TC and TG, and they did not discuss LDL. This is inconsistent with the previous view. However, at present, there is not enough research to support the inevitable relationship between hyperuricemia and the development of cataract.

4.2 The relationship between MAFLD and cataract

In a Korean study (24), it was found that metabolism-associated fatty liver disease (MAFLD) was more closely associated with cataracts than non-alcoholic fatty liver disease (NAFLD). MAFLD may be a combined risk factor for cataracts, with significant correlations with all cataract subtypes because cataracts can be caused by various metabolic and inflammatory conditions, and MAFLD covers alcohol-induced cirrhosis and various metabolic diseases. In addition, hepatic factors and the signaling proteins secreted by the liver can reach the eye and cause oxidative stress and inflammation.

5 Correlation of mineral metabolism and cataract

Minerals are also closely related to cataracts, and nutritional dystrophy (lack of macroelement and microelement, insufficient oxygen supply, and reduced hemoglobin) can lead to the development of nuclear cataracts (25).

5.1 Zinc

The content of zinc in ocular tissues, especially in retina, is significantly higher than in other tissues. One study found that combining zinc and vitamin A as a nutrient supplement reduced the incidence of cataracts (26). It can be assumed that oxidative damages cause alterations in the structure of lens proteins, while antioxidant metalloenzymes relied by zinc, such as SOD, protect the lens (27).

5.2 Selenium

Selenium acts as a functional heteroatom in peroxidases and plays an important role in the metabolism of H_2O_2 and other peroxides, effectively preventing free radical production and damages to tissues. If the amount of selenium exceeds the amount required for the synthesis of proteins containing selenium, a redox cycle is initiated, which promotes oxidative damage and ultimately induces cataract development in laboratory animals (28). In addition, Dawczynski (29) et al. found that the amount of selenium in the lens increases with increasing lens opacity, and the amount of selenium in the lens is higher in the mature stage of cataract than in other stages, whereas serum selenium shows the opposite change. But the exact mechanism is still unknown.

5.3 Calcium

When the concentration of calcium ions in the aqueous humor deviates from the normal value, either too high or too low, it will lead to the development of lens opacity, which is named as hypercalcemic cataract and hypocalcemic cataract, respectively. Delamere et al. (30) constructed a model of hypocalcemic cataract in rabbits by feeding a low-calcium diet and divided the hypocalcemic cataracts into three stages, including posterior subcapsule punctate opacity, dense opacity, and extension to the superficial anterior cortical layer, and suggested that aqueous humor calcium can be inferred from the serum calcium. Yang et al. (31) incubated rabbit lens in different concentrations of $CaCl_2$ solution for 36H and found that all the rabbit lenses could develop hypercalcemic cataracts with complete cortical turbidity when the $CaCl_2$ concentration in the culture solution was $\geq$30 mmol/L. The homeostasis of calcium ions plays an important role in maintaining lens transparency. When the cell membrane is damaged, large amounts of calcium ions from the aqueous humor move in to the lens and activate calpain, leading to the degradation of numerous important structural proteins (31).

5.4 Sodium

High intake of sodium is also a factor affecting cataracts (32). When the lens cell membranes are damaged by oxidative stress, the function of Sodium-Potassium Pump that maintains the normal low Na + and high K+ concentrations is altered in the cells, which increases the permeability of sodium ions and the concentration of sodium ions in the lens, exacerbating lens opacity.

6 Correlation of vitamins with cataract

Vitamin A, vitamin C, and vitamin E have been associated with a reduced risk of ARC too. Vitamin C, also named as ascorbic acid, is a strong antioxidant in the body. Its remarkable antioxidant properties have been negatively correlated with the development of cataracts. It can react rapidly with free radicals such as O-, HOO-, and OH- to generate semi-dehydroascorbic acid and be beneficial to the scavenging of single oxygen (33). Ge et al. (34) suggested that the antioxidant efficacy of vitamin C in organisms far exceeds that of the *in vitro*. It may be attributed to its action *in vivo* through a range of indirect mechanisms rather than direct scavenging oxygen radicals. So, increasing the intake of vitamin C can be considered as an effective strategy to improve the antioxidant capacity of the organism and help to prevent cataracts.

In a streptozotocin (STZ)-induced oxidative stress model in senile diabetic rats (35), dietary vitamin C and E supplementation alleviated oxidative stress and increased the antioxidant levels of the lens. The mechanism may be that reduced GSH synergises with antioxidant vitamins to resist oxidative stress. Vitamin E transfers its hydrogen to superoxide radical of polyunsaturated fatty acids, breaking the radical chain reaction and preventing the peroxidation of polyunsaturated fatty acids in the cellular and subcellular membranes. These vitamins can also directly scavenge ROS and increase the activity of antioxidant enzymes.

There is a considerable controversy regarding the effect of vitamin E on cataract formation. Increasing dietary intake of food rich in vitamin E and supplying vitamin E pill to the population may reduce the risk of nuclear cataract development (36), but most studies do not show results in agreement with this hypothesis, especially in studies regarding the role of vitamin E in cortical cataracts (37).

The literature published by Spector et al. (38) mentioned that nutrient interventions may be a solution to reduce cataract risk. They showed that increasing intake of vitamin C, lutein, xanthines and dietary fruit can reduce the incidence of age-related cataracts. Lawrenson and Grzybowski (39) have also shown that a diet containing antioxidants can delay the progression of cataracts. Nutrient factors, particularly vitamins with antioxidant properties, are thought to play a protective role in cataract development and progression. Vitamin A, niacin, riboflavin, thiamin, folic acid and vitamin B12 appear to have a protective effect, either alone or as components of multi-vitamin preparations (26, 40).

7 Analysis of other nutritional factors related to cataract

7.1 The relationship between oxidative stress and cataract

Oxidative stress is a state of imbalance between oxidative and antioxidative effects in the body, with more oxidative stress due to higher oxidative effects. Oxidative stress plays an important role in the pathogenesis of all types of cataracts. The lens derives its energy mainly from the glycolysis, so the lens inevitably generates a large number of oxygen radicals, such as superoxide anion (O^2-), hydroxyl radical (OH-), and hydrogen peroxide (H_2O_2) during metabolism, causing oxidative stress on the membranes and proteins in the lens, affecting lens transparency in different degrees. If the degree of oxidation exceeds the regulatory capacity of the antioxidant system, lens damage occurs, leading to cataract.

7.1.1 Mechanisms of oxidative stress-induced cataract

In almost all types of cataract lens, the amount of GSH decreases with increasing lens opacity, so deficiency of GSH is thought to be one of the causes of cataract. Antioxidant enzyme systems, such as SOD, facilitate to scavenge O^2-, protect cells from oxidative stress damage, and maintain redox balance in the lens. Zhou et al. (41) have shown that H_2O_2 can impair the antioxidant system of the lens, reducing GSH content and decreasing SOD viability to promote the occurrence of cataract.

7.1.2 Methods to mitigate the oxidative damage

The extract of concha haliotidis significantly reduced H_2O_2-induced cataract formation, and its mechanism is to protect lens SOD activity, maintain GSH content, and reduce lens epithelial cell damage (42). In addition, it was found (43) that quercetin improved selenite-induced cataract in rats by enhancing the Nrf-2/HO-1 signaling pathway, through inhibition of oxidative stress. Kang et al. (44) pointed out that nitric oxide synthase (NOS) mRNA was positively correlated with the representative level of oxidative stress in the organism, SOD, in the lens of cortical cataract patients. They further proposed that NOS mRNA is also a factor involved in the process of oxidative stress in patients with cortical cataracts and has a certain effect on the progression of cataracts. It has been shown in the literature (45, 46) that nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2-keap1) is the main mechanism of resistance to oxidative stress, and demethylation of keap1 promoter activates the expression of Keap1 protein, which promotes the degradation of Nrf2 proteasome and attenuates Nrf2 activity, leading to the reduction of resistance to oxidative stress and ultimately causing the cataract occurrence. In addition to Nrf2-keap1, Song et al. (47) proposed that blood suppressor II (BDS-II) inhibits oxidative stress-induced cataract by suppressing oxidative stress-induced reduction of GSH levels and lens epithelial cell death. BDS-II is a blocker of Kv3 channel (voltage gated potassium ion channels), which mainly blocks the oxidation-sensitive channel Kv3.4 to resist oxidative stress.

In normal conditions, Nrf2 is in the cytoplasm, and keap1 protein can maintain the stability of Nrf2 in the cytoplasm. When oxidative stress causes excessive generation of oxygen free radicals, keap1 protein releases Nrf2 through the release of zinc ions, followed by the entrance of Nrf2 into the nucleus to bind to the ARE anti-oxidative stress element sequence, and activates gene transcription downstream of the ARE region, which then initiates the oxidative stress response and reduces the oxidative stress.

Antioxidants have been promoted to delay or prevent cataracts due to their ability to reduce oxidative damage. In a dose–response meta-analysis (48), increasing 5 mg β-carotene daily reduced 10% risk of ARC, and increasing 10 mg lutein or zeaxanthin daily reduced 19%

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TABLE 1 Nutrients related to the cataract.

Nutrients	Dietary structure	Relativity	Influencing mechanism	Reference
Carbohydrate	high carbohydrate diet (rice, noodles and other staple foods)	Carbohydrate intake was positively associated with cataract development.	① The slow absorption and utilization of glucose in the aqueous humor results in prolonged exposure of lens proteins to high concentrations of glucose, leading to protein cross-linking, aggregation, and precipitation that ultimately cause lens opacity and cataract formation.	(5–8, 52–56)
			② Carbohydrate can also increase blood glucose concentration and increase the risk of cataract.	
	high-sugar diet	Glucose metabolism influences the cataract development.	① The fluctuation of blood glucose in diabetic patients leads to oxidative stress response, causing cataract.	(10–16, 57)
			② In diabetic patients, long-term hyperglycemia leads to excessive accumulation of sorbitol in the lens, increased osmotic pressure, and aqueous humor inflow. Osmotic changes lead to intracellular edema and fiber breakage, which eventually makes the lens become turbid and oxidative stress further worsens.	
			③ In diabetic cataract patients, the increasing expression of apoptosis-related factors in lens cells leads to lens opacity.	
			④ In high glucose environment, the lens capsule is damaged, which increases the permeability and loses barrier function, resulting in excessive water absorption of the lens and fiber swelling, fracture, and turbidity.	
			⑤ There is a correlation between the degree of insulin resistance and the degree of lens opacity.	
Protein	high-protein diet	Higher intake of protein, especially animal protein, can reduce the incidence of cataract.	Animal proteins are complete proteins that contain all the amino acids necessary for the human body. Moderate intake of animal protein can provide the specific amino acids needed by the lens to maintain normal renewal and repair of lens proteins. For example, animal viscera are rich in selenoprotein and selenium is an essential trace element for human body. Selenium has an inhibitory effect on oxidative damage of eye lens, and appropriate supplementation of selenium can reduce the incidence of cataract.	(6, 58)
Lipid	high-lipid diet	High blood lipids increase the risk of cataracts.	① Unsaturated fatty acids are prone to lipid peroxidation, leading to oxidative stress in lens epithelial cells, causing cell damage and increasing the risk of lens opacity.	(5, 6, 9, 19–24, 59–62)
			② The activity of antioxidant system is decreased in hyperlipemia.	
			③ Oxidized low-density lipoprotein can effectively affect the transcriptional expression of lens epithelial cells, leading to differences in the expression of Rho signal transduction and ATP1B1, which may increase the incidence of cataract.	
			④ High-fat environment is prone to metabolism-related fatty liver, and liver factors and signal proteins secreted by the liver can also reach the eyes, causing oxidative stress and inflammation.	
Minerals	zinc	Zinc can reduce the incidence of cataract.	Oxidative damage can cause structural changes of lens proteins, and Zinc-dependent antioxidant metalloenzymes such as superoxide dismutase (SOD)， can protect the lens.	(26, 27, 63–67)
	selenium	Selenium has two sides to cataract occurrence.	Appropriate intake of selenium can effectively prevent the production of free radicals and damage to tissues, relieve oxidative stress, and delay the production of cataracts.	(28, 29, 68–74)
			When selenium concentration exceeds the amount required for selenium-containing protein synthesis, the redox cycle starts, which promotes oxidative damage and eventually induces cataract in experimental animals.	

(Continued)

TABLE 1 (Continued)

Nutrients	Dietary structure	Relativity	Influencing mechanism	Reference
	sodium	High intake of sodium increases the incidence of cataract.	Oxidation can damage the cell membrane of lens, change the function of Na + -K-atpase pump, which maintains normal low Na + and high K+ concentration in cells, to increase the permeability of sodium ions and the concentration of sodium ions in the lens, aggravating lens turbidity.	(32, 75–80)
	calcium	High calcium cataracts	A large amount of calcium ions enter the aqueous humor and activate calpain, leading to the destruction of a large number of important structural proteins and eventually causing cataract.	(81–87)
		Low calcium cataract	The decrease of parathyroid hormone results in the disturbance of calcium and phosphorus metabolism. The decrease of calcium increases the permeability of the lens capsule, and electrolyte imbalance in the lens affects its metabolism, leading to the occurrence of cataract.	
Vitamin/dietary fiber	vegetables, fruits, and a vegan diet	Vitamin intake can reduce the incidence of cataract.	① Vitamin C, vitamin E, vitamin A and other vitamins with antioxidant properties: ② B vitamins such as lutein, zeaxanthin, etc.: ③ β-carotene: It is converted to vitamin A in the body, exerting antioxidant effects and reducing cataract incidence	(34–38, 88–97)
Pro-inflammatory factors	inflammatory diet (red meat, sugary drinks, etc.)	Increased dietary inflammatory index may increase the incidence of cataract.	Inflammatory foods can increase cellular inflammatory factors (IL-1, IL-6, TNF-α), affect the transcription of acute phase proteins, which leads to increased mitosis and collagen synthesis of lens epithelial cells, leading to cataract.	(50, 51)

risk of ARC. Lutein and zeaxanthin concentrate in the eye more than any other nutrients and are the only nutrients that have the ability to block blue light and ultraviolet like sunglasses. Blue light and ultraviolet are the primary factors to eye fatigue, blurred vision, and eventually cataracts. Lutein and zeaxanthin are also potent natural antioxidants that resist the destruction of free radical to the eyes. Ma (49) pointed that dietary intake of flavonols (quercetin and isorhamnetin) is associated with the development of age-related cataracts, and increasing dietary intake of quercetin and isorhamnetin may result in a lower risk of age-related cataracts.

8 Dietary inflammation index

Shivappa et al. (50) found that eating red meat, sugary drinks, and high-fat dairy products increased the dietary inflammatory index (DII), and higher DII is more likely to be inflammatory. However, the mechanism between DII and the development of cataracts is unclear. One of the possible mechanisms is that pro-inflammatory foods can increase the effects of pro-inflammatory factors (IL-1, IL-6, TNFα) on the transcription of acute-phase proteins, which leads to increased mitosis and collagen synthesis in lens epithelial cells, triggering cataracts. Studies (51) found differences in the expression of inflammatory factors at different ages, which may be related to the development of immune cells in the uvea stroma. This hypothesis can explain that EGF, IL-3, IL-8, and MCP-1 are positively corrective with age. Among the various pro-inflammatory factors, TNFα can promote the production of extracellular matrix (ECM) and regulate the proliferation and differentiation of lens epithelial cells, but the roles of other factors in cataract formation need to be further investigated.

9 Prospects and outlook

Cataracts have a serious impact on people's quality of life and need to be treated early, but the occurrence is associated with various factors that make it difficult to prevent. Therefore, continuing and deep studies are necessary to better prevent and to develop novel treat regimen for cataracts. In studying the relationship between dietary nutrition and cataract development, Table 1 highlights key nutrients associated with cataract risk. Understanding their roles in maintaining ocular health provides insights into potential preventative measures. Figure 1 illustrates the mechanisms that lead to cataract formation, including oxidative stress, inflammation, and apoptosis. The followings are some suggested actions that can be taken to fight against cataract formation.

The mechanisms of action of various risk factors need to be further clarified. For example, the specific mechanism of the inflammatory factors TNF-α and IL-6 in cataract development remains to be revealed. By resolving these signaling pathways, new targets can be provided for therapy.

Explore MAFLD and other areas that have received less attention, change the research thinking, and explore the occurrence and mechanism of cataract formation from other perspectives.

Enhance nutrient intervention research. Dietary components, such as the antioxidants vitamin C, E and flavonoids, have a protective effect against cataract formation, and personalized diet can be developed for different populations in the future.

In conclusion, cataract is a complex and multi-factorial disease that requires multidisciplinary cooperation to study pathogenesis deeply. With the advancement of science and technology, it is believed that more effective prevention and

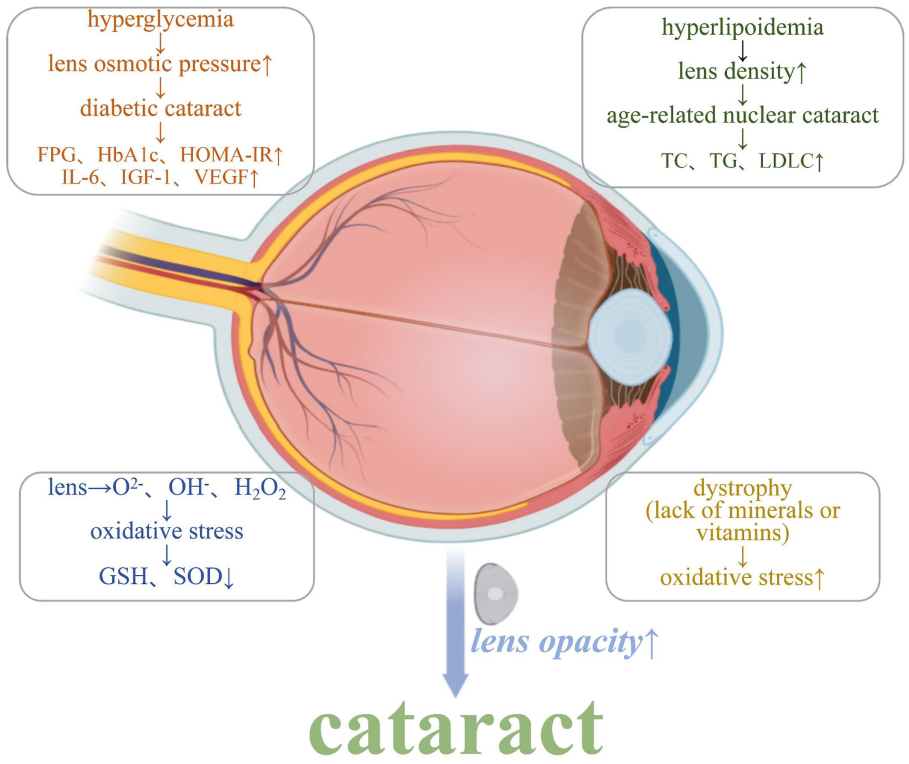

FIGURE 1
Mechanisms that induce cataract development.

therapy can be found in the future to reduce the burden of cataract on human beings.

Author contributions

YZ: Writing – original draft, Writing – review & editing. XQ: Writing – original draft, Writing – review & editing. TX: Writing – review & editing, Writing – original draft. FC: Writing – review & editing, Writing – original draft. BH: Writing – review & editing, Project administration, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comprehensive analysis of systemic, metabolic, and molecular changes following prospective change to low-carbohydrate diet in adults with type 2 diabetes mellitus in India

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Purpose: South Asians, especially Indians, face higher diabetes-related risks despite lower body mass index (BMI) compared with the White population. Limited research connects low-carbohydrate high-fat (LCHF)/ketogenic diets to metabolic changes in this group. Systematic studies are needed to assess the long-term effects of the diet, such as ocular health.

Method: In this prospective, observational study, 465 candidates aged 25–75 years with type 2 diabetes included with institutional ethics approval. A total of 119 subjects were included in the final study assessment based on the availability of pathophysiological reports, tears, and blood samples collected at baseline, 3rd, and 6th months. Serum and tear samples were analyzed by an enzyme-linked lectinsorbent assay, to examine secreted soluble protein biomarkers, such as IL-1β (interleukin 1 Beta), IL-6 (interleukin 6), IL-10 (interleukin 10), IL-17A (interleukin 17A), MMP-9 (matrix metalloproteinase 9), ICAM-1 (intercellular adhesion molecule 1), VEGF-A (vascular endothelial growth factor A), and TNF-α (tumor necrosis factor-alpha). A Wilcoxon test was performed for paired samples. Spearman's correlation was applied to test the strength and direction of the association between tear biomarkers and HbA1c. p-value of < 0.05 was considered significant.

Results: After a 3- and 6-month LCHF intervention, fasting blood sugar decreased by 10% (Δ: −14 mg/dL; $p < 0.0001$) and 7% (Δ: −8 mg/dL; $p < 0.0001$), respectively. Glycated hemoglobin A1c levels decreased by 13% (Δ: −1%; $p < 0.0001$) and 9% (Δ: −0.6%; $p < 0.0001$). Triglycerides reduced by 22% (Δ: −27 mg/dL; $p < 0.0001$) and 14% (Δ: −19 mg/dL; $p < 0.0001$). Total cholesterol reduced by 5.4% (Δ: −10.5 mg/dL; $p < 0.003$) and 4% (Δ: −7 mg/dL; $p < 0.03$), while low-density lipoprotein decreased by 10% (Δ: −11.5 mg/dL; $p < 0.003$) and 9% (Δ: −11 mg/dL; $p < 0.002$). High-density lipoprotein increased by 11% (Δ: 5 mg/dL; $p < 0.0001$) and 17% (Δ: 8 mg/dL; $p < 0.0001$). At the first follow-up, tear proteins such as ICAM-1, IL-17A, and TNF-α decreased by 30% (Δ: −2,739 pg/mL; $p < 0.01$), 22% (Δ: −4.5 pg/mL; $p < 0.02$), and 34% (Δ: −0.9 pg/mL; $p < 0.002$), respectively. At the second follow-up, IL-1β and TNF-α reduced by 41% (Δ: −2.4 pg/mL; $p < 0.05$)

and 34% (Δ: −0.67 pg/mL; $p < 0.02$). Spearman's correlation between HbA1c and tear analytes was not statistically significant.

Conclusion: The LCHF diet reduces the risk of hyperglycemia and dyslipidemia. Changes in tear fluid protein profiles were observed, but identifying promising candidate biomarkers requires validation in a larger cohort.

KEYWORDS

type 2 diabetes mellitus, low-carb diet, hyperglycemia, tear fluid analysis, biomarker discovery

Introduction

Type-2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic diseases. Approximately 537 million adults (20–79 years) are diagnosed with diabetes, and it is estimated that it will increase to 643 million by 2030 and 783 million by 2045. For approximately 116 million diabetic patients, China has the highest contribution. India ranks second with 77 million people, followed by the United States of America with 31 million, indicating that India is one of the most diabetes-risk countries in the coming decades (1, 2). Chronic diabetes-related complications are also a significant risk factor for cardiovascular diseases, chronic renal failure, diabetic retinopathy, and several other allied comorbidities (3). The economic burden of T2DM for treatment and management of its complications contributes to approximately 12% of global health expenditure (2).

Several ocular complications include T2DM, for instance, cataract, glaucoma, retinopathy, punctuate keratitis, and recurrent corneal lesions (4, 5). Patients with diabetes are known to experience dry eye as a common ocular symptom. Dry eye disease (DED) is considerably more common in diabetics than in healthy individuals, and it is also more common in those with T2DM than in those with type 1 diabetes mellitus (T1DM) (6, 7). T2DM is the primary cause of blindness in industrialized countries for individuals aged 25–74 years (8), which is the fourth reason of blindness in developing countries (9). Asia comprises both of the top two nations with the highest number of DM patients, namely, China (116 million) and India (77 million) (10), revealing the decade-long fast economic growth and urbanization in Asia, together with notable dietary and lifestyle changes (11, 12).

Genetic and sedentary lifestyles are crucial factors, especially diet, which play a significant role in the pathogenesis of T2DM. Lifestyle factors are reversible and focused on the effort to lower the T2DM-associated risk (13). Several systematic reviews and meta-analyses (SRMA) of randomized controlled trials (RCT) (14–16) revealed that interventions such as modified diet and/or enhanced level of physical activity can reverse or prevent the onset of T2DM and significantly contribute to the effective management of the disease (7). In RCT and observational studies, low-carbohydrate, high-fat (LCHF) diet or ketogenic diet has revealed promising improvements in glycemic control and weight loss, along with decreases in the quantity and/or doses of anti-diabetic medications (17–19). Low-carbohydrate approaches are supported mainly by the hypothesis that reducing insulin secretion, a critical hormone that creates an anabolic, fat-accumulation state, results in improved cardiometabolic function and induces weight loss (20). This approach has been recently called the carbohydrate–insulin model (21).

People of Indian origin or South Asian origin have a distinct pathophysiological feature with a higher risk of cardiometabolic disorders compared with the White population even though they have lower body mass index (BMI). This phenomenon is known as the "South Asian Phenotype" (21, 22). Distinct features such as abdominal adiposity combined with glucose intolerance and dyslipidemia such as high levels of triglycerides (TGs) and low-density lipoprotein (LDL), low levels of high-density lipoprotein cholesterol (HDL), and high levels of TGs relative to HDL with normal BMI (21–23). Studies have also revealed additional features, such as excess body fat per unit BMI, truncal obesity, higher c-reactive protein, and lower adiponectin as part of the South Asian phenotype (23, 24). Therefore, a myriad of different diabetes-control diets has gained significant popularity in India, including LCHF diets; however, biochemical or molecular data regarding the performance of such diets have not been adequately described.

Even with established ethnic variations in South Asian body composition and metabolic markers, there is a lack of studies connecting low-carbohydrate or ketogenic diets to metabolic alterations in the diabetic population in India and South Asia. Moreover, to understand and document, ocular changes after a switch over to ketogenic diets, though anecdotally described, require systematic long-term prospective trials. The ketogenic diet or low carbohydrate high fat (LCHF) diet-induced metabolic flexibility, adaptive response of an organism's metabolism to maintain energy homeostasis to utilizing available fuels in situations in the shortage of carbohydrates as fuel, allowing the body to switch from using glucose as the chief fuel to using ketones instead, which has been previously documented in starvation as well as ketogenic diets in cases of epilepsy (25–27), causes a reduction in blood insulin, a rise in glucagon and depletion of visceral as well as subcutaneous fat stores and subsequently, leads to recovery in glycaemic factors. We aim to correlate this proposed metabolic reprogramming with changes in body mass index (BMI), body fat measurements, and metabolic parameters in subjects with T2DM. We further hypothesize that the hyperglycemia-induced elevated inflammatory molecular factors will be reduced by the LCHF diet. Such a reduction in the soluble factors in tear and serum may help understand the role of diabetes-associated inflammation in the progression of peripheral organ-specific complications, such as diabetic retinopathy (DR).

Methods and materials

Study design

This was an observational, prospective study performed after it was approved by the Narayana Nethralaya Institutional Ethics Committee (EC reference No: NNIEC/2022/02/01). A written consent form for the study was obtained from the subjects for their participation. For this study, samples from subjects with T2DM adopting the LCHF diet and those receiving standard care were collected. All clinical and disease progression histories were noted before (baseline) and after initiation at 3 and 6 months of home dietary intervention. Subjects with diabetes presenting to the retina clinic were also enrolled in the study (400–600). A total of 465 diabetic subjects were interviewed through counseling and guidance. The subjects with T2DM were treated for their condition as per the standard care with the addition of the LCHF diet. Participants were closely monitored, and their past and current treatment histories were noted in this study. A total of 119 participants and sex-matched diabetic subjects under standard care were finalized and recruited but not on the diet as controls. The inclusion criteria for participants were: person with T2DM, age 18–75 years, and HbA1c > 6.5%, while the exclusion criteria were person with T1DM and had serious diseases such as CKD, IHD, cancers, and DR, and wetting length of <8 mm.

Dietary instruction for the LCHF diet

On recruitment, subjects provided a food log or a list of regularly consumed foods, such as drinks and snacks, to the nutritionist who educated them on carbohydrate metabolism and the role of insulin in lipogenesis and weight gain in simplified terminology. Subjects were recommended to restrict net carbohydrate (total carbohydrates minus fiber) intake to ≤50 g/day or 10–20% of their total calories, which is lower than the guideline of the LCHF diet. The daily recommendation for protein was capped at 20–25% of total calories based on their sex, physical activity level, and ideal body weight. The recommended total fat intake was 65–70% of total calories. Permitted food and beverages include meats, poultry, fish, eggs, low-carbohydrate nuts, seeds, non-starchy (over ground) vegetables, high-fat dairy products, fats, and oils such as olive oil, butter, and coconut oil, and beverages such as water and unsweetened tea or coffee. Sample meals, snack options, and recipes available online were discussed. Subjects were advised to eat only when hungry and avoid eating late at night. No caloric restriction was imposed. All subjects were recommended to drink eight glasses of water per day and encouraged to keep a food log. Food logs were reviewed at subsequent visits to monitor diet adherence.

Clinical examinations

Data were collected longitudinally (0, 3, and 6 months) as part of the follow-up to determine the health status. A general exam was conducted at each visit to document the height, weight, blood pressure (BP), waist, and hip circumference. Following this, a detailed, whole blood serum analysis was performed at each visit.

Sample collections

Blood and tear samples were collected at each visit according to the protocol. Tears were collected and processed according to the standard protocols of the clinical follow-up regime of the institute based on their disease status.

In brief, tear fluid was collected with the help of sterile Schirmer's strips (5 × 35 mm^2; Contacare Ophthalmics and Diagnostics, Gujarat, India) on each visit. The strips were positioned one in each of the conjunctival fornices, simultaneously in both eyes. The strips were collected after a sufficient amount of tear fluid (wetting of strips until the 20 mm mark or more) was absorbed and stored in a sterile microcentrifuge tube at −80°C. For extraction of tear fluid, Schirmer's strips were chopped into small pieces; 300 µL of 1x sterile PBS was added and agitated for 2 h at 4°C at 300 rpm and centrifuged to elute the tear fluid. The elute was collected as tear fluid and used for further processing to examine secreted soluble protein factors in tears as described previously (28).

Blood investigations

Blood samples were collected according to the standard protocol at each visit to monitor the metabolic changes. The following tests were performed: fasting blood sugars (FBS), post-prandial blood sugars (PPBS), glycosylated hemoglobin (HbA1C), renal function tests (RFT), liver function tests (LFT), lipid profile, serum insulin, C peptide, erythrocyte sedimentation rate (ESR), C reactive proteins (CRP), and blood ketones.

Assessment of the diabetic medication effect score (MES)

The medication effect score (MES) was assessed by types (category by drug mechanism) and numbers (total number of oral hypoglycemic agents and injected insulins) at each visit (29).

The MES was the overall consumption of anti-glycemic agents. It was calculated by the sum of the median absolute decline of HbA1c times the percentage of the maximum daily dose for each medication, including insulin (30, 31). The higher the MES shown, the greater the utilization of medication. The assessment was performed at the beginning and the end of the 3-month RCT study.

Tear evaluations

Tear samples were collected using Schirmer's strips according to the standard clinical protocols, which required 2–4 min. The wetting length was noted, and the strips were immediately taken for testing or stored at −80°C in Eppendorf tubes for further evaluation.

Multiplex ELISA

Using a variant of the multiplex ELISA assay (Biomarker Pathfinder, Novomol-Dx, India and Bio-Techne, USA), IL-1β (interleukin 1 beta), IL-6 (interleukin 6), IL-10 (interleukin 10), IL-17A (interleukin 17A), MMP-9 (matrix metalloproteinase 9),

ICAM-1 (intercellular adhesion molecule 1), VEGF-A (vascular endothelial growth factor A), and TNF-α (tumor necrosis factor-alpha) were measured. Schirmer's strips were collected in 1.5 mL tubes, in which 300 µL of phosphate buffer solution (extraction buffer) was added. The cartridge was loaded into an analyzer system, which indicated the measured value based on established internal references for each analyte. In the case of blood samples, serum was prepared for each respective sample. In total, 50 µL of serum was used in the same multiplex ELISA, to test changes in systemic levels of these analytes.

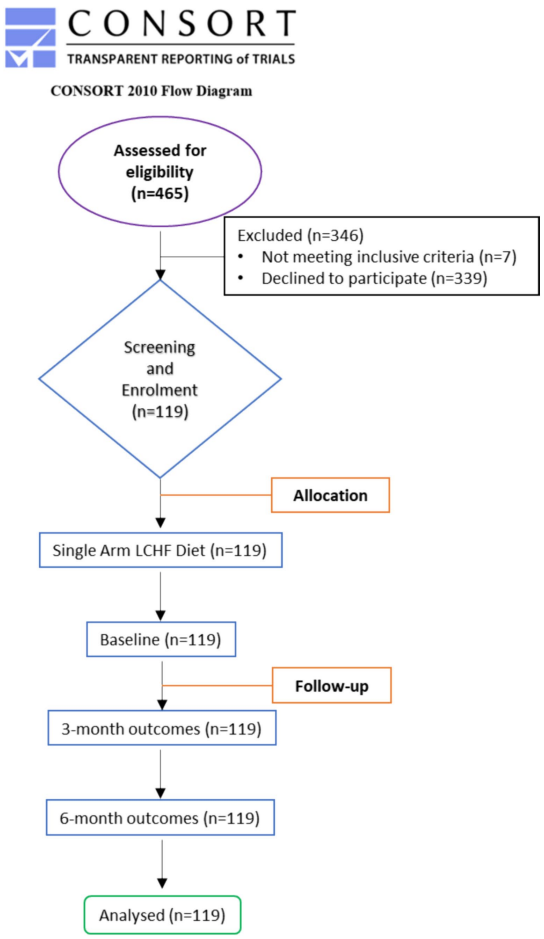

FIGURE 1
CONSORT diagram. Flow diagram of the study through the two time-points (enrolment, intervention allocation, follow-up, and data analysis). Adapted from Schulz et al. (32) licensed under CC BY-NC 2.0.

Follow-up

Data of anthropogenic factors and blood and tear samples were collected longitudinally (0, 3, and 6 months) as part of the follow-up, to determine the disease and the ocular status.

Statistical analyses

The Shapiro–Wilk test was applied to determine the distribution of the data. As the data were not normally distributed, Friedman test with Dunn's multiple comparison test was performed to determine the significant difference in the parameters between baseline and 3- and 6-month follow-up visits and differences or inter-eye correlation, if any, in the tear fluid levels of analytes between the eyes, at all visits. To study the systemic effect of diet on overall ocular conditions, the average value of the analytes of tear from two eyes of the same subject was used. Since the data were not normally distributed, the repeated measure analysis by mixed-effect model-based analysis of variance (ANOVA) was not applicable. Furthermore, Spearman's rank correlation coefficient was performed to determine the association between the various parameters studied. There was no statistical difference between the values of the two eyes in the cohort. All data are presented as median (interquartile range, IQR) distributed variables. A two-tailed p-value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism v.8 and MedCalc MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd., Ostend, Belgium).

Results

Enrollment and participant characteristics

Out of the 465 enrolled participants, 7 dropped out as they did not meet inclusive criteria, and 339 candidates declined to participate in the study. Thus, 119 participants completed 3- and 6-month studies. The flow of the study is presented in Figure 1. In no instance was the primary reason for subject withdrawal attributed to the LCHF study. There were also no adverse events associated with the adoption or maintenance of the LCHF study (Figure 2).

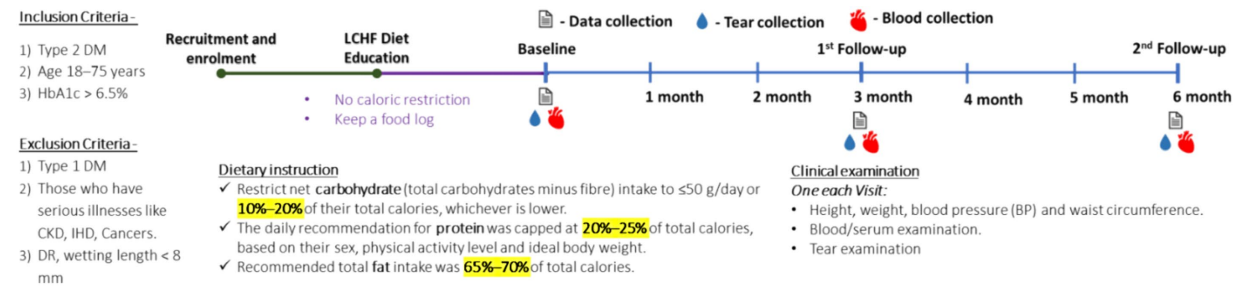

FIGURE 2
Experimental design. Schematic representation of the observational study design.

Anthropogenic factors

The results of anthropogenic parameters are presented in Table 1. All participants lost body weight and BMI at 1st and 2nd follow-up (Figure 3). On average, weight decreased by 1.3% for 1st follow-up (Δ: −1 kg; $p < 0.00001$) and by 2.2% at 2nd follow-up (Δ: −1.6 kg; $p < 0.00001$), while BMI decreased by 1.2% at 1st follow-up (Δ: −0.29 kg/m^2, $p < 0.00014$) and by 1.8% at 2nd follow-up (Δ: −0.46 kg/m^2; $p < 0.00014$) compared with their respective baseline (Table 1).

Glycemic factors

Participants showed a significant reduction in FBS and PPBS at both time-points. FBS was decreased at 1st follow-up by 10% (Δ: −14 mg/dL; $p < 0.00002$) and at 2nd follow-up by 7% (Δ: −8 mg/dL; $p < 0.00002$) from baseline. Similarly, PPBS decreased by 23% (Δ: −42 mg/dL; $p < 0.00001$) and 20% (Δ: −43 mg/dL; $p < 0.00001$) at 1st and 2nd follow-ups, respectively from baseline. Correspondingly, HbA1c reduced by 12% (Δ: −1%; $p < 0.00003$) and 9% (Δ: 0.6%; $p < 0.00003$) at 1st and 2nd follow-ups, respectively, from baseline (Figure 3 and Table 1).

Nevertheless, fasting insulin and insulin resistance/sensitivity parameters such as homoeostasis model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) remained unchanged at both time-points, while C-peptide increased significantly by 39% (Δ: 0.69 ng/mL; $p < 0.00001$) and 51% (Δ: 0.91 ng/mL; $p < 0.00001$) from baseline at 1st and 2nd follow-ups, respectively (Table 1).

Lipid compositions

Serum lipids reported a significant modulation after 3 and 6 months of the LCHF diet. (TG) reduced significantly by 22% (Δ: −27 mg/dL; $p < 0.00001$) and 14% (Δ: −19 mg/dL; $p < 0.00001$) at 1st and 2nd follow-ups, respectively, from baseline. Total cholesterol (TC) decreased by 5% (Δ: −10.5 mg/dL; $p < 0.0436$) at 1st follow-up, and these effects diminished at 2nd follow-up from baseline. Consequently, after 3 and 6 months of the LCHF diet, bad cholesterol, i.e., LDL-c has shown a significant reduction of 9.7% (Δ: −11.5 mg/dL; $p < 0.02485$) and 8% (Δ: −11 mg/dL; $p < 0.02485$), respectively, from baseline. Similarly, VLDL-c decreased at 1st and 2nd follow-up time-points by 21% (Δ: −5 mg/dL; $p < 0.00001$) and 14.5% (Δ: −4 mg/dL; $p < 0.00001$), respectively. Subsequently, good cholesterol, i.e., HDL-c increased by 11% (Δ: 5 mg/dL; $p < 0.00001$) and 17% (Δ: 8 mg/dL; $p < 0.00001$), respectively, from the baseline (Figure 4 and Table 1).

Medication effect score (MES)

Diabetes medication use declined significantly during the 1st follow-up of the LCHF diet, and it remained unchanged at the 2nd follow-up from the baseline. MES decreased at 1st follow-up by 20% (Δ: −0.2; $p < 0.02749$). Nonetheless, at 2nd follow-up time-point, MES did not change from the baseline (Table 1).

Concentration and correlation of tear's secreted soluble protein and HbA1c

Tear's secreted soluble proteins such as IL-6, MMP-9, TNF-α, and VEGF-A remained unchanged at 1st follow-up, while the concentration of IL-10, IL-1β, and IL-17A reduced significantly by 19.5% (Δ: −0.42 mg/dL; $p < 0.02671$), 42% (Δ: −2.9 mg/dL; $p < 0.02947$), and 22% (Δ: −4.5 pg/mL; $p < 0.02$), respectively. At 2nd follow-up, IL-1β reduced significantly by 41% (Δ: −2.4 pg/mL; $p < 0.02947$) from the baseline; nonetheless, other analytes remained unchanged (Figure 5 and Table 2).

The correlation between HbA1c and tear's secreted soluble protein is evaluated at the baseline and 1st and 2nd follow-up time-points, as shown in Table 3. While none of the tear's analytes showed a correlation with HbA1c at either time-points, 1st fold change (1st follow-up/baseline) revealed that only IL-6 showed a weak negative correlation with HbA1c. Nonetheless, the correlation analysis between tear's analytes and HbA1c showed no statistical significance at 2nd fold change (2nd follow-up/baseline). The levels of the various analytes measured were not significantly different between the right and left eyes of the subject at all the visits.

Concentration and correlation of serum's secreted soluble protein and HbA1c

At 1st and 2nd follow-ups, none of the serum analyte concentrations showed significant modulation from the baseline (Table 2).

The correlation between HbA1c and serum's secreted soluble protein is evaluated at baseline and 1st and 2nd follow-up time-points, as shown in Table 3. At the baseline, only ICAM-1 showed a weak positive correlation with HbA1c; however, at 1st follow-up, none of the serum analytes showed any significant correlation with HbA1c. While at 2nd follow-up, TNF-α has shown a significant and moderately positive correlation with HbA1c. At 1st and 2nd fold changes, serum analytes showed no statistically significant correlation with HbA1c.

Discussion

Hyperglycemia and T2DM have been extensively studied in the past, while a low- carbohydrate diet emerged as an attractive approach to prevent and reverse T2DM-associated health disorders. The results of the present study improve the understanding of the effects of the ketogenic diet/LCHF diet in subjects with T2DM for short- and long-term, more preciously in Indian subjects with T2DM. Consistent with the previous studies, in the South-Indian cohort, subjects with T2DM showed improvement in anthropogenic factors, such as weight, BMI, and WHR at the end of the study. Subsequently, there was an improvement in glycemic factors such as FBS, PPBS, and HbA1c, which corresponded to a reduction in dietary carbohydrate intake and elevation in fat intake. All these observations occurred without changing insulin and ketone concentration at the end of the study.

The possible reason for beneficial health delivery of the LCHF diet on subjects with T2DM could be restriction in the carbohydrate intake (Table 4), which leads to a decline in the absorption of sugar or

TABLE 1 Baseline and follow-up characteristics of the participants and changes in anthropometric and biochemistry parameters after LCHF diet intervention#.

Variable	BL[1]			F1[2]			F2[3]			Friedman test (Paired sample)		
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*N*	*p*-value[a]	Multiple comparisons
Anthropogenic												
Gender (male/female)	119	75/44										
Age (years)	119	52	42.3–60									
Weight (kg)	116	68.3	62.4–78	118	67.9	61.1–76.1	119	68	60.05–75.5	115	0.00001	(1) vs. (2); (1) vs. (3)
BMI	116	25.4	23.35–28.12	117	24.97	22.87–27.92	118	24.925	22.79–27.75	114	0.00014	(1) vs. (2); (1) vs. (3)
Waist (cms)	108	95	88.75–103.25	116	94	87–99.5	119	93	86–97.88	106	<0.00001	(1) vs. (2); (1) vs. (3)
HIP (cms)	108	100	96–104.25	116	99	95–105	119	99	93.25–104	106	0.00001	(1) vs. (3)
WHR	108	0.94	0.89–1	116	0.92	0.88–0.98	119	0.93	0.88–0.99	106	0.01113	(1) vs. (2)
Glycaemic factors												
FBS (mg/dL)	119	144	109–191.75	119	129	104–149.75	119	133	109.25–163	119	0.00002	(1) vs. (2); (1) vs. (3)
PPBS (mg/dL)	119	227	156.25–278.75	119	165	124.25–214.75	119	160	130.25–238.75	119	<0.00001	(1) vs. (2); (1) vs. (3)
Serum creatinine (mg/dL)	119	1	0.9–1.1	119	1	0.9–1.1	119	0.9	0.8–1.09	119	0.00102	(1) vs. (3)
SBP (mmHg)	119	130	120–150	119	130	120–140	119	120	120–130	119	<0.00001	(1) vs. (2); (1) vs. (3)
DSP (mmHg)	119	80	80–90	119	80	80–87.5	119	80	80–90	119	0.42064	–
Urea (mg/dL)	119	23	18–28	118	28	22–37	119	28	22–33.75	118	<0.00001	(1) vs. (2); (1) vs. (3)
Serum Insulin (Fasting) (mu/l)	113	10.24	6.88–14.09	109	11.94	6.97–14.7	114	9.65	6.32–13.38	98	0.46745	–
C Peptide (Fasting)	91	1.84	1.31–2.69	100	2.49	1.92–3.25	113	2.62	1.95–3.61	78	<0.00001	(1) vs. (2); (1) vs. (3)
Serum Ketone (mmol/L)	88	0.1	0.1–0.2	108	0.1	0.1–0.2	118	0.1	0.1–0.1	88	0.00079	(1) vs. (3)
QUICKI	113	0.32	0.3–0.34	109	0.32	0.3–0.34	114	0.32	0.31–0.34	98	0.24233	–
HOMA-IR	113	3.4	2.25–5.61	109	3.5	1.98–4.76	114	3.21	2.23–4.34	98	0.27493	–
HBA1C (%)	119	8.7	7.4–10.2	119	7.3	6.7–8.28	119	7.6	6.8–8.88	119	0.00003	(1) vs. (2); (1) vs. (3)
Lipid profile												
Total cholesterol (mg/dL)	119	195	162–232	118	173.5	143–216	119	185	154–216	118	0.0436	(1) vs. (2)
Triglycerides (mg/dL)	119	136	94.25–190.75	118	102	77–129	119	112	82–151	118	<0.00001	(1) vs. (2); (1) vs. (3)
HDL (mg/dL)	119	45	39.25–52	118	50	43–59	119	54	47.25–61.75	118	<0.00001	(1) vs. (2); (1) vs. (3)
LDL (mg/dL)	119	123	85.25–154	118	99.5	71–131	119	106	78–135.75	118	0.02485	(1) vs. (2); (1) vs. (3)
VLDL (mg/dL)	119	26	19–38	118	21	15–27	119	22	16–30	118	<0.00001	(1) vs. (2); (1) vs. (3)
Urine micro albumin (mg/L)	119	12	6.85–26.25	118	10	5–23	119	10	6–19	118	0.00987	(1) vs. (2); (1) vs. (3)
Uric Acid (mg/dL)	119	4.9	4.15–5.9	118	5	4–5.9	119	4.9	4.1–5.9	118	0.28483	–

(Continued)

TABLE 1 (Continued)

Variable	BL[1]			F1[2]			F2[3]			Friedman test (Paired sample)		
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*N*	*p*-value[a]	Multiple comparisons
Liver Function test												
Total Bilirubin (mg/dL)	119	0.7	0.5–0.9	118	0.7	0.5–0.9	119	0.7	0.6–1	118	0.00077	(1) vs. (3)
Direct Bilirubin (mg/dL)	119	0.2	0.2–0.3	118	0.2	0.2–0.3	119	0.2	0.2–0.3	118	0.40908	–
SGOT (U/L)	119	20	17–26	118	20	16–23	119	18	15–22	118	0.00778	(1) vs. (2); (1) vs. (3)
SGPT (U/L)	119	24	18–33.68	118	21.65	17–29.9	119	20.8	15.55–29.23	118	0.0004	(1) vs. (2); (1) vs. (3)
Alkaline phosphatase (U/L)	119	145	100–197	118	76	61–102	119	74	60.25–91	118	<0.00001	(1) vs. (2); (1) vs. (3)
Thyroid profile												
T3 (ng/mL)	119	1	0.9–1.2	118	0.9	0.8–1	119	0.9	0.8–1	118	0.00114	(1) vs. (2); (1) vs. (3)
T4 (ng/mL)	119	8.5	7.2–10.18	118	8.25	6.9–9.1	119	7.9	6.7–9.18	118	0.00037	(1) vs. (2); (1) vs. (3)
TSH (ng/mL)	119	2.2	1.33–3.68	118	2	1.3–3.2	119	1.9	1.2–3.28	118	0.006	(1) vs. (2); (1) vs. (3)
Complete blood count												
Hemoglobin (g/dL)	119	14.1	13–15.3	118	14.15	13.1–15.3	119	14.2	12.9–15.08	118	0.4871	–
WBC count (cell/cumm)	119	7,200	6,400–8,500	118	7,250	6,500–8,400	119	6,900	6,125–8,100	118	0.03982	(1) vs. (3)
Platelet (lakhs/cumm)	119	2.63	2.29–3.11	118	2.575	2.17–2.99	119	2.49	2.09–2.98	118	0.00003	(1) vs. (2); (1) vs. (3)
ESR (mm/h)	119	13	5–24	118	11	5–20	119	12	5–20.75	118	0.02142	(1) vs. (2); (1) vs. (3)
CRP (mg/L)	119	4.5	4.5–4.5	118	4.5	4.5–4.5	119	4.5	4.5–4.5	118	0.29443	–
Serum electrolytes												
Na + (mmol/L)	119	141.5	139.4–143	118	141.3	140.1–142.5	119	140.8	139.9–141.7	118	0.02467	(2) vs. (3)
K+ (mmol/L)	119	4.23	4.06–4.51	118	4.265	4.08–4.47	119	4.19	4–4.39	118	0.28365	–
Cl- (mmol/L)	119	101.8	99.85–103.4	118	103.4	101.4–105.4	119	104.6	103.13–105.9	118	<0.00001	(1) vs. (2); (1) vs. (3)
Medication score												
MEDS	99	1.317	0.9–1.89	79	1.317	0.96–1.61	34	1.25	0.65–1.9	31	0.02749	(1) vs. (2)

[#]Data presented in median (IQR); *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$, [a] Friedman test (paired samples). [1]BL – Baseline, [2]F1 – 1st follow-up at 3 months from baseline, [3]F2 – 2nd follow-up at 6 months from baseline; (1) vs. (2) – BL vs. F1; (1) vs. (3) – BL vs. F2; BMI, Body Mass Index; WHR, Waist Hip ration; FBS, Fasting Blood Sugar; PPBS, Post-Prandial Blood Sugar; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; QUICKI, Quantitative Insulin Sensitivity Check Index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HBA1C, Glycated Hemoglobin; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very Low-Density Lipoprotein; SGOT, Serum Glutamic-Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase; T3, Triiodothyronine; T4, Tetraiodothyronine; TSH, Thyroid Stimulating Hormone; WBC, White Blood Cell; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; MES, Medication Effect Score.

monosaccharides lowering fasting and post-prandial blood glucose and regulating glucose and fatty acid metabolism (33, 34). The current study analyzed subjects at three different time-points, and the results showed a decrease in fasting blood sugar from diabetic range to pre-diabetic range. In addition, PPBS showed a drastic reduction at the end of the study, where approximately PPBS declined by 30%, indicating the effectiveness of the LCHF diet in lowering blood sugar.

HbA1c was analyzed to evaluate the long-term effect of the LCHF diet. HbA1c level indicates crucial clinical significance about average plasma glucose of the previous 2–3 months for assessing the status of blood glucose control, which acts as a diagnostic tool for patients with diabetes and a screening test for persons at a high risk of diabetes progression (35). It has been reported that cardiac infractions and microvascular complications decreased by 14 and 37%, respectively, when HbA1c decreased by 1%. Thus, the HbA1c level established important clinical significance in estimating the blood glucose control, uncovering the potential challenges in the treatment and managing the therapeutic schedule (36, 37). In this study, a reduction in HbA1c occurred after 3 and 6 months of LCHF diet consumption; the changes appeared at −1% and −0.6% time-points; HbA1c reduced by 16 and 12.6%, respectively. The possible explanation for such small changes could be a wide range of ages; thus, the response

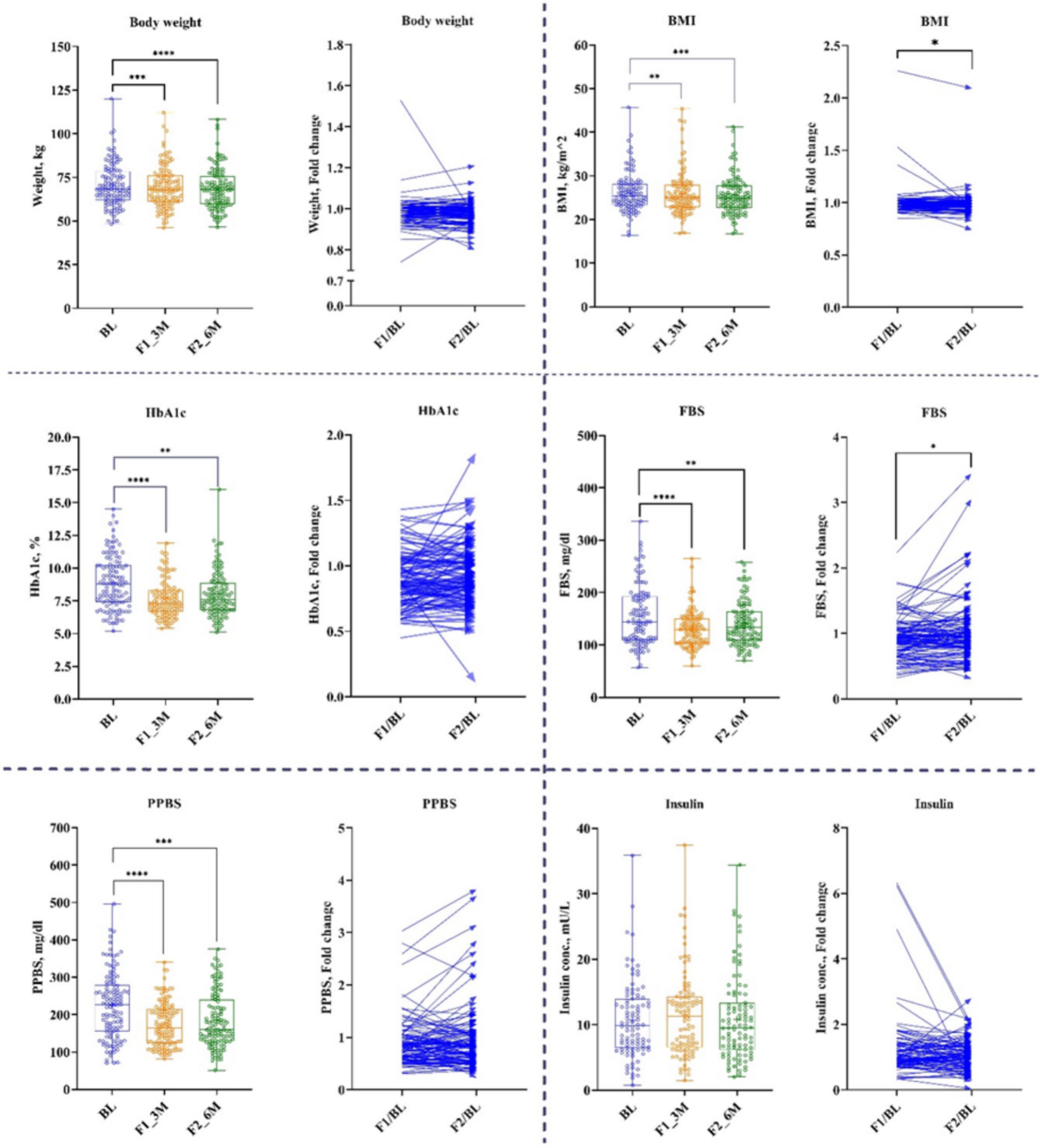

FIGURE 3
Anthropogenic and Glycemic parameters. Baseline – BL; 1st follow-up at 3 months – F1_3M; and 2nd follow-up at 6 months – F2_6M. Data points for body weight, BMI, HbA1c, fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and insulin presented in median (IQR). $N = 119$. p-value of <0.05 is considered significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

of age to treatment cannot be neglected. The average cutoff of HbA1c was 1 in the current study, indicating that diabetes management may also be achieved by ketogenic diet/LCHF diet effects.

The ketogenic diet not only improved glucose metabolism, but several studies reported that the ketogenic diet enhanced lipid metabolism. For instance, Hussain et al. (38) showed that a ketogenic diet decreased TG and TC while increasing the HDL-c level significantly, and as a result, it recovers dyslipidemia-associated conditions. In the current study, at 1st and 2nd follow-ups, the LCHF diet showed that TG was reduced by 27 and 19 mg/dL, TC was reduced by 10.5 and 7 mg/dL, LDL-c was reduced by 11.5 and 11 mg/dL, while HDL-c was increased by 5 and 8 mg/dL, respectively, from the baseline. Similar results have been reported by Dashti et al. (39), where TG decreased by 3.67 mmol/L, TC decreased by 1.88 mmol/L, and LDL decreased by 1.78 mmol/L, while HDL increased by 0.14 mmol/L. Subsequently, the current study showed a reduction in

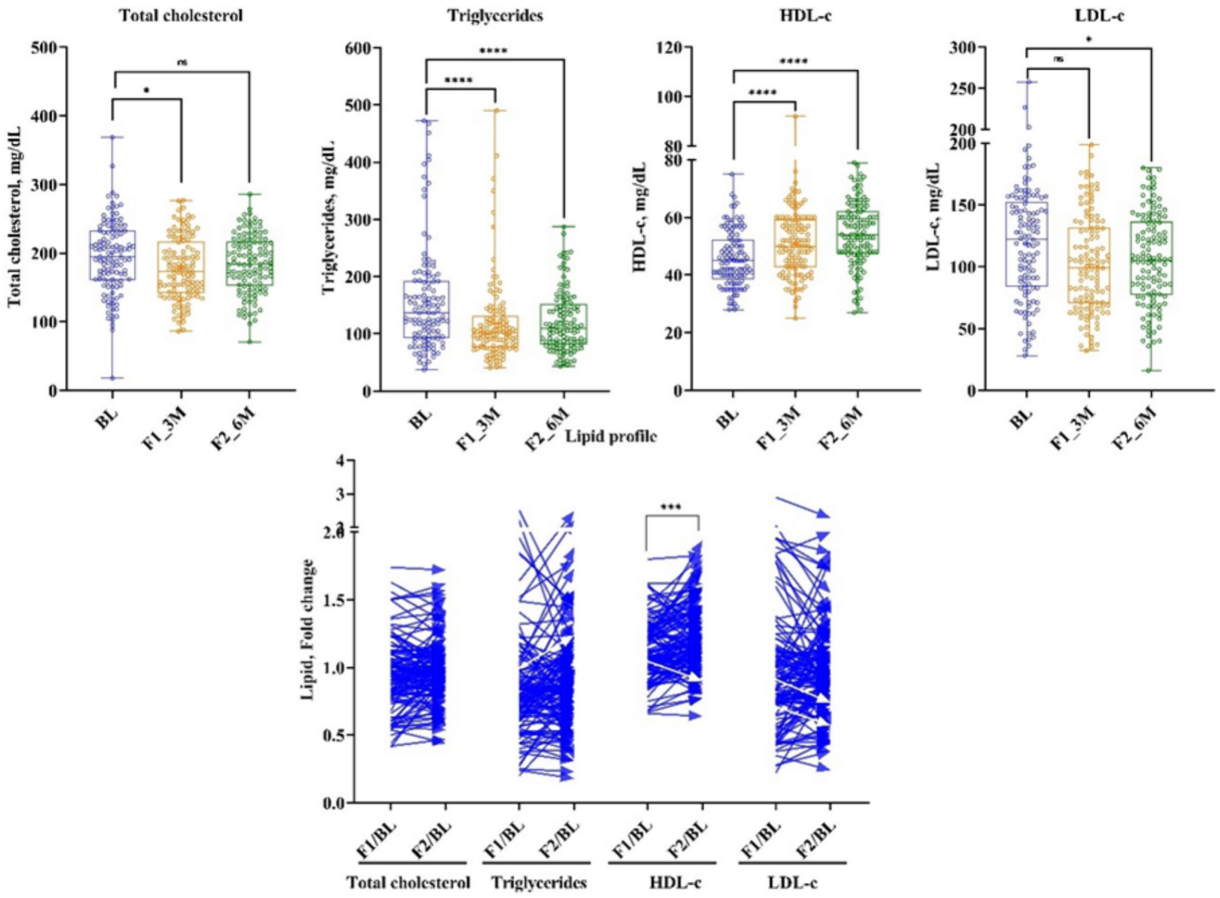

FIGURE 4
The effect of LCHF diet at 1st and 2nd follow-up on lipid profile. Baseline – BL; 1st follow-up at 3 months – F1_3M; and 2nd follow-up at 6 months – F2_6M. Data points for total cholesterol, triglycerides, HDL-c, and LDL-c presented in median (IQR). $N = 119$. p-value of <0.05 is considered significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

systolic blood pressure by 7% (Δ: −10 mmHg; $p < 0.0001$) in subjects with T2DM. LCHF diet intake delivered significant positive effects in subjects with T2DM as elevated TG and free fatty acids (FFAs) are pathogenic factors for insulin resistance and oxidative stress and can lead to the escalation of risk for cardiovascular diseases (40, 41). Hence, recovery from dyslipidaemia is a positive outcome of the current study, which is not only beneficial for regulating insulin sensitivity but also for managing the incident and progression of diabetes-associated heart diseases (42, 43).

The diabetes medication was not restricted in the current study. While diabetes medication schedules are often complicated, with multiple agents, modified dosages, and frequent administration, it does not reduce the dependency on medication (29). There have been numerous studies that have explored reasons associated with non-adherence to anti-diabetic medication such as financial conditions, forgetfulness, younger age, education, ongoing diabetes complications, and problems in taking the medications alone (44, 45). Hence, diet could be a promising approach to maintaining health, reversing, and dependency on diabetes medication. In the current study, the LCHF diet shows a reduction in MES at 1st follow-up ($p < 0.0001$), which remained unchanged at 2nd follow-up from the baseline. However, this could be a possible lack of reporting by participants at 2nd follow-up time-point.

Diet has been proposed as one of the most commonly preferred modes to counter diabetes-associated disorders (46). Indian diet is rich in carbohydrates, ~60% (47), which is a high-carbohydrate diet, and plays a significant role in the development of insulin resistance and T2DM (48). Thus, a low-carbohydrate diet was focused on studying the effects of the LCHF diet on the reversibility of T2DM-associated clinical parameters, such as glycemic parameters, lipid profile, and medication score. To monitor the adherence of subjects to a low-carbohydrate diet, we examine macronutrients such as carbohydrates, fat, and protein at respective time-points. The results have shown that carbohydrate intake was reduced significantly from the baseline, while fatty acid intake elevated significantly (Table 4), and those changes were maintained at the end of the protocol. This revealed that subjects compiled the instruction of the diet throughout the study. To observe the effects of a low-carbohydrate diet at a systemic level, glycemic factors such as FBS, PPBS, HbA1c, and serum ketone were analyzed at respective time-points. At the end of the study, a low-carbohydrate diet reduced glycemic factors at the end of protocol, which supported the significance of a low-carbohydrate diet, consistent with the previous studies (39, 49). Similarly, the lipid profile was monitored to check the dyslipidaemia status of the subject during the study. Several studies have mentioned that dyslipidaemia plays a crucial role in the development of metabolic syndrome and T2DM (50). At the end of the study, total cholesterol,

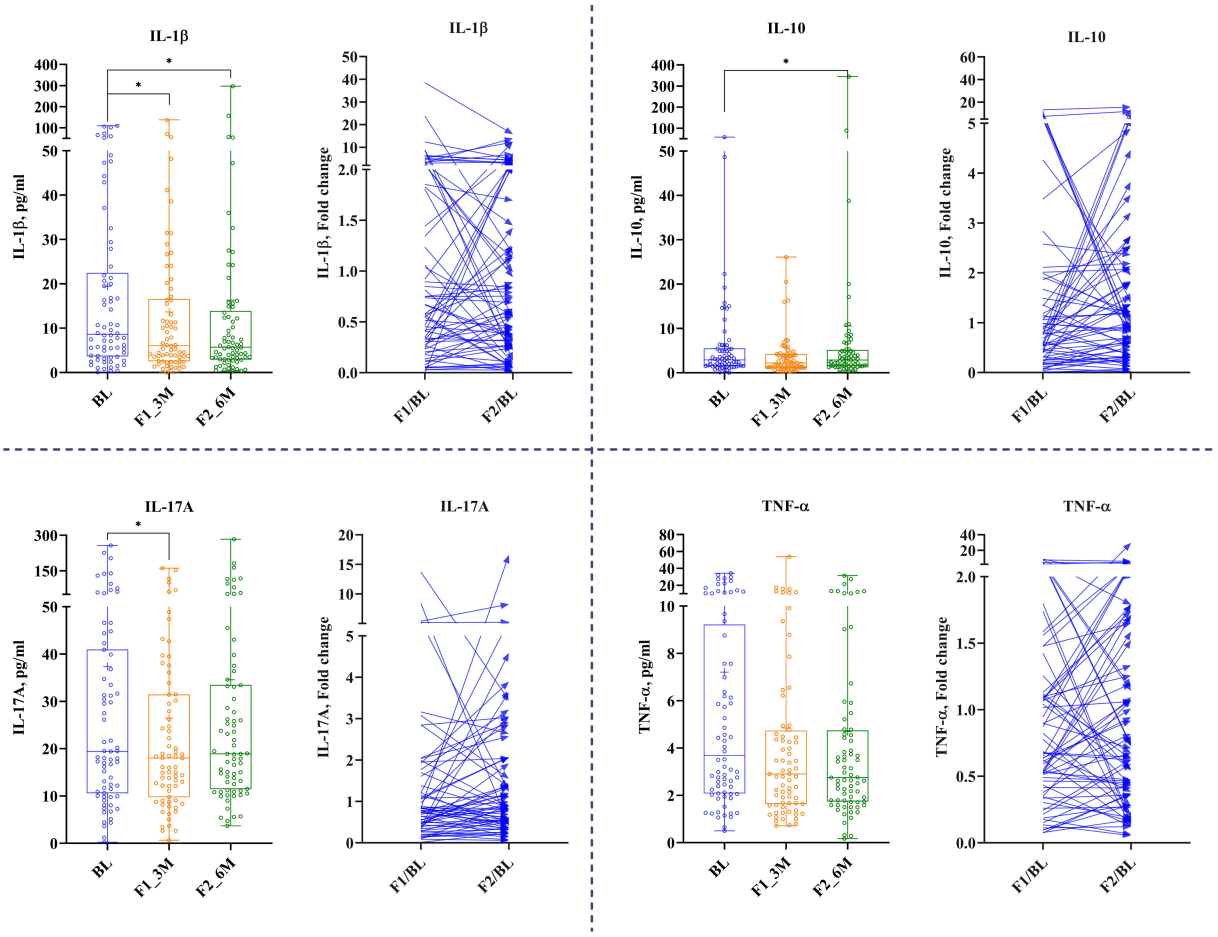

FIGURE 5
The effect of LCHF diet at 1st and 2nd follow-up on tear's secreted soluble protein. Baseline – BL; 1st follow-up at 3 months – F1_3M; and 2nd follow-up at 6 months – F2_6M. Data points for IL-1β, ICAM-1, IL-17A, and TNF-α are presented in median (IQR). $N = 119$. p-value of <0.05 is considered significant. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

triglycerides, and LDL-c were reduced significantly while HDL-c decreased significantly. Medication is one of the effective ways to manage the consequences of T2DM. Nevertheless, as the disease progresses, uses, costs, and complications of glucose-lowering medication increased. For instance, more than 50% of patients with T2DM will require insulin within 10–15 years of diagnosis (51). Our current study revealed the significance of low-carbohydrate diet as it has reduced MES at respective time-points.

Tear fluid has gained prominence as a promising source for biomarker detection regarding the DR status due to its unique components, ease of collection, vicinity to the disease site, and minimal cell contamination (52, 53). Various systemic diseases have also been shown to reflect disease-associated alterations in the tear profiles. Several studies have demonstrated the presence of secreted soluble protein in tears, and alterations in tear quality and quantity have been reported in diabetic patients (54, 55). Furthermore, elevation in tear inflammatory factors has been revealed from various ocular diseases (4, 56). For instance, during inflammation, ICAM-1 expression is upregulated in the vascular endothelium of patients with DED (57). Similarly, a study showed that an elevation of protein and messenger RNA expression of ICAM-1 in lacrimal and conjunctival epithelial cells has been reported in patients with DED (58). In contrast, a study mentioned that diabetic mice deficient of ICAM-1 revealed a decrease in the preliminary lesions linked with DR (such as the damage of pericytes, degeneration, and increased capillary permeability) and leukostasis (59). Moreover, the expression of TNF-α has been associated with the pathogenesis of various chronic inflammatory disorders, such as T2DM (60). Diabetes patients have shown a higher concentration of TNF-α in plasma than non-diabetic, where a strong correlation was found between TNF- α and severity of DR (61). Similarly, TNF-α was found higher in diabetic patient's tears while similar results were observed in serum and vitreous (62). A study revealed that the TNF-α concentration in tears escalates with the severity of DR, the concentration being less in non-diabetic participants than in diabetic, and correspondingly, the correlation of TNF-α was found highly significant with DR severity (63). Interestingly, the intravitreal injection of TNF-α inhibitor resulted in lowering of damage of pericytes and capillary degeneration in diabetic mice (64, 65). Similarly, TNF-α-deficient mice demonstrated a reduction in vascular changes induced by diabetes (66). In summary, soluble secreted proteins of tears such as inhibition of ICAM-1 and TNF-α exert valuable effects on the prevention of early diabetic retinopathy (59, 67). Overall, data propose that inflammation and ocular diabetic complications are interconnected, and that, the concentration of the circulating

TABLE 2 Summary of tear and serum analytes at baseline and follow-up's time-points[#].

Variable	BL[1]			F1[2]			F2[3]			Friedman test (Paired sample)		
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*N*	*p*-value[a]	Multiple comparisons
Tear analytes (pg/mL)												
IL_10	71	2.66	1.55–5.38	72	2.24	1.21–4.2	72	3.01	1.6–5.12	69	0.02671	(1) vs. (2)
IL_1β	72	8.87	3.78–21.6	71	5.96	2.82–16.34	73	5.79	3.21–14.83	70	0.02947	(1) vs. (2); (1) vs. (3)
IL_6	73	48.6	24.69–112.35	73	49.2	21.7–114	73	45.5	19.25–127.8	73	0.60553	–
MMP_9	72	74,826	26679.5–234,010	73	70,953	18771.75–189719.75	73	76,981	28912.75–200894.75	72	0.94667	–
ICAM_1	73	12087.5	7378.63–27218.25	73	10,631	6644.75–21437.5	73	11,361	6829.25–22565.25	73	0.18357	–
IL_17A	73	19.5	10.84–41.25	72	18.05	10.44–30.8	72	18.9	11.35–33.3	71	0.0386	(1) vs. (2)
TNF_α	73	3.86	2.11–8.91	73	2.91	1.66–4.64	72	2.75	1.76–4.68	72	0.0802	–
VEGF_A	73	1910.5	1261.38–3038.75	73	1,674	984.75–2859.75	73	1711	1142.5–2609.5	73	0.77324	–
Serum analytes (pg/mL)												
IL_10	57	4.34	2.07–6.34	57	3.75	2.31–5.59	57	3.65	2.34–5.48	57	0.23	–
IL_1β	8	5.53	0.75–10.26	11	2.03	0.95–4.29	5	0.87	0.64–5.6	2	–	–
IL_6	57	5.12	2.99–6.67	57	4.29	2.75–7.75	56	4.66	2.7–6.78	56	0.98261	–
MMP_9	57	168,813	134858.75–238284.75	57	212,002	156786.5–282198.5	57	172,226	135,186–275491.5	57	0.17365	–
ICAM_1	57	326,628	255,148–436593.75	57	322,566	240,267–381546.75	56	324,576	264699.5–444325.5	56	0.39866	–
IL_17A	15	5.39	2.65–16.23	8	3	2.34–4.6	4	6.36	3.65–9.92	0	–	–
TNF_α	57	32.4	22.65–36.73	57	28.2	21.95–34.18	56	28.1	22.7–34.7	56	0.10293	–
VEGF_A	57	360	216–670.25	57	319	194.75–501.75	55	365	235–754.75	55	0.28997	–

[#]All data are expressed as median (IQR). The *p*-value less than 0.05 considered significant, [a] Friedman test (paired samples). [1]BL – Baseline, [2]F1 – 1st follow-up at 3 month from baseline, [3]F2 – 2nd follow-up at 6 month from baseline; (1) vs. (2) – BL vs. F1; (1) vs. (3) – BL vs. F2; IL-1β (Interleukin 1 Beta), IL-6 (Interleukin 6), IL-10 (Interleukin 10), IL-17A (Interleukin 17A), MMP-9 (Matrix Metalloproteinase 9), ICAM-1 (Intercellular Adhesion Molecule 1), VEGF-A (Vascular endothelial growth factor A), and TNF-A (Tumor Necrosis Factor Alpha).

inflammatory factor may estimate the stages and development of DR. As the tear sample collection technique is non-invasive for patients and easy for technicians (68), so far in Indian population with diabetes, there have been no reports related to the alteration in secreted soluble protein in tears of diabetic subjects treated with low-carbohydrate diet. Hence, in the present study, we demonstrated the outcomes of analysis of soluble secreted protein (IL-1b, IL-6, IL-8, IL-10, IL-17A, MMP-9, ICAM-1, VEGF-A, and TNF- α) in tears, which was collected from Indian subjects with T2DM. At 1st follow-up, IL-10, IL-1β, and IL-17A were decreased significantly, while IL-1β was decreased significantly at 2nd follow-up. In contrast to previous observation, the present study revealed that there was no significant recovery of diabetes corresponding to TNF-α and ICAM-1 in serum and tears. However, a large set of data is needed to verify the outcomes and prediction of biomarkers in tears, indicating the status of DR after diet intervention. Spearman's correlation analysis was performed on HbA1c to evaluate relationship strength with tear analytes, but none of the correlations were statistically significant (Table 3).

Tear protein levels have been associated with a variety of ocular conditions and systemic diseases. In our subject cohort, we aimed to distinguish if specific molecular factors correlated with the HbA1c variability could be used as a monitoring tool to examine T2DM progression. Of course, further studies with a larger number of participants and longer duration are conducted to test the idea of whether tear analytes have a predictive function in the appearance of hyperglycemia. One of the limitations of our study is that more participants are recruited to include further subject stratification into sub-groups. Furthermore, our data illustrate another limitation of the current study that some of the study subjects likely already had insulin resistance, as demonstrated by the data analysis in the results. By having a separate insulin-sensitive or naïve diabetic group, we could have obtained information on the difference between treated and non-treated and T2DM and non-T2DM and their correlation with analytes. Finally, the study cohort lacks advanced diabetic retinopathy subjects, which are difficult to include due to ongoing laser or intravitreal treatments. More studies are required to examine the early changes with possible predictive value, leading to reversibility of hyperglycemia and insulin resistance, and the results should be validated on independent cohorts. It is also important to remark that the current study worked well for dyslipidemia and dysglycemia but did not show significant differences for a set of tear analytes.

TABLE 3 Correlation of tear fluid secreted protein factors level with HbA1c at baseline and follow-up after LCHF diet intervention.

Tear analytes (pg/mL)										
	BL		F1		F2		F1/BL		F2/BL	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
IL-10	−0.0	0.983	−0.1	0.416	−0.0	0.985				
IL-1β	−0.14	0.256	−0.1	0.422	0.17	0.157				
IL-6	−0.03	0.819	−0.1	0.418	0.12	0.303	−0.24*	0.041	−0.08	0.501
MMP-9	−0.03	0.803	−0.07	0.579	0.12	0.322				
ICAM-1	−0.01	0.931	0.0	0.998	0.2	0.098			0.16	0.165
IL-17A	−0.1	0.405	0.09	0.475	0.04	0.728				
TNF-a	−0.19	0.114	0.01	0.922	0.08	0.531	−0.15	0.192	0.13	0.290
VEGF-A	0.15	0.196	−0.03	0.771	0.17	0.162			0.09	0.446
Serum analytes (pg/mL)										
IL-10	0.25	0.064	0.18	0.178	0.08	0.551	0.04	0.750	−0.04	0.779
IL-1β	−0.02	0.955	0.26	0.433			0.6	0.208	−1.0	
IL-6	0.04	0.756	0.25	0.065	0.12	0.396	−0.04	0.792	0.08	0.579
MMP-9	−0.11	0.399	0.14	0.285	0.01	0.949	−0.09	0.521	−0.09	0.485
ICAM-1	0.27*	0.039	0.03	0.842	0.06	0.637	0.09	0.485	0.07	0.624
IL-17A	−0.24	0.386	−0.69	0.060	−0.2	0.800	−1.0			
TNF-a	0.16	0.224	0.25	0.059	0.37**	0.005	0.02	0.901	0.17	0.223
VEGF-A	0.08	0.555	−0.05	0.704	0.15	0.279	0.14	0.296	0.17	0.222

BL – Baseline, F1 – 1st follow-up at 3 months from baseline, F2 – 2nd follow-up at 6 months from baseline, IL-1β (Interleukin 1 Beta), IL-6 (Interleukin 6), IL-10 (Interleukin 10), IL-17A (Interleukin 17A), MMP-9 (Matrix Metalloproteinase 9), ICAM-1 (Intercellular Adhesion Molecule 1), VEGF-A (Vascular endothelial growth factor A), and TNF-A (Tumor Necrosis Factor Alpha). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

TABLE 4 Macronutrient intake at baseline and follow-up by the participants and their changes after LCHF diet intervention[#].

Variable	BL[1]			F1[2]			F2[3]			Friedman test (Paired sample)		
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*N*	*p*-value[a]	Multiple comparisons
Carbohydrate, gm	42	322.9	302.4–341.3	42	115.3	85.0–146.3	42	125.5	95.0–228.9	42	<0.00001	(1) vs. (2); (1) vs. (3)
Fat, gm	42	48.3	42.1–56.0	42	130.6	121.6–141.4	42	125.9	83.3–134.2	42	<0.00001	(1) vs. (2); (1) vs. (3)
Protein, gm	42	55	49.0–60.0	42	59.5	51.0–63.0	42	58	55.0–62.0	42	<0.00001	(1) vs. (2); (1) vs. (3)

[#]Data presented in median (IQR); *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$, a Friedman test (paired samples). [1] BL – Baseline, [2]F1 – 1st follow-up at 3 months from baseline, [3]F2 – 2nd follow-up at 6 months from baseline; (1) vs. (2) – BL vs. F1; (1) vs. (3) – BL vs. F2.

Despite the above-mentioned limitations, our study reveals information that can be used as potential biomarkers for monitoring studies aiming at personalizing therapies and offering alternative solutions for insulin resistance monitored in advanced obesity and T2DM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The clinical data can be shared after de-identification due to ethical clearance.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Narayana Nethralaya (EC reference No: NNIEC/2022/02/01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written

informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NB: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Investigation, Writing – review & editing. KBS: Investigation, Methodology, Resources, Writing – original draft. NS: Writing – review & editing, Investigation, Methodology, Resources. KS: Data curation, Writing – review & editing, Investigation, Methodology. AK: Data curation, Writing – review & editing, Investigation, Methodology. NP: Funding acquisition, Resources, Writing – review & editing, Methodology, Project administration. RS: Supervision, Writing – review & editing, Conceptualization, Funding acquisition, Resources. AG: Project administration, Supervision, Validation, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology.

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In memoriam

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between micronutrients and myopia in American adolescents: evidence from the 2003–2006 National Health and Nutrition Examination Survey

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Purpose: To investigate the associations between circulating micronutrients (vitamins A, C, D, E, and carotenoids) and the risk of myopia.

Methods: A total of 1,620 adolescents from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) were included. Logistic regression was used to analyze the associations of micronutrients with myopia and high myopia. Restricted cubic spline analysis was employed to assess the potential nonlinear relationships.

Results: Among the 1,620 adolescents, 549 were diagnosed with myopia. After adjusting for multiple covariates, only cis-β-carotene was significantly associated with the risk of myopia (OR 1.19, 95% CI 1.03–1.39) and high myopia (OR 1.44, 95% CI 1.03–2.03). No significant associations were found between vitamins A, D, E, C, α-carotene, trans-β-carotene, lutein zeaxanthin, and myopia. No nonlinear relationships were observed between any of the micronutrients and myopia.

Conclusion: Cis-β-carotene is significantly associated with an increased risk of myopia and high myopia. Further research is needed to understand the underlying mechanisms and potential impact of cis-β-carotene on ocular health.

KEYWORDS

micronutrients, myopia, NHANES, Cis-β-carotene, diet

1 Introduction

Myopia has become a significant public health issue among adolescents. In parts of East and Southeast Asia, the prevalence of myopia among high school students is estimated to be around 80 to 90% (1). High myopia can lead to pathological conditions such as retinal detachment, glaucoma, and myopic maculopathy, which may result in irreversible vision loss

(2). Given the increasing incidence and potential for severe ocular complications, it is crucial to understand the factors contributing to the development and progression of myopia.

Recent studies have highlighted the role of various micronutrients in maintaining eye health (3, 4). Micronutrients, including vitamins and minerals, are essential for many physiological functions in the eye. For instance, vitamin A is vital for maintaining normal vision and preventing night blindness (5). High-dose vitamin C and E supplements may delay the progression of age-related macular degeneration and improve vision (6). Carotenoids, by reducing reactive oxygen species, inhibiting inflammation, and suppressing inflammatory markers, have shown significant preventive and therapeutic benefits for age-related ocular abnormalities (7).

Despite the well-recognized importance of micronutrients in eye health, their relationship with myopia remains unclear. Previous studies investigating the association between vitamin D and myopia have produced contradictory results. Yazar et al. (8) found that individuals with vitamin D deficiency have a significantly higher rate of myopia compared with those with sufficient vitamin D levels, while Williams et al. (9) reported no significant association between vitamin D and the risk of myopia. Additionally, evidence on the effects of other micronutrients on myopia is relatively limited.

This study aims to investigate the associations between various serum micronutrient levels (vitamins A, C, D, E, α-carotene, trans-β-carotene, cis-β-carotene, lutein, and zeaxanthin) and myopia among adolescents in the United States, using data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES). By examining this association, we seek to identify specific micronutrients that may influence the risk of myopia. Understanding these relationships could provide insights into potential nutritional interventions to prevent or slow the progression of myopia, ultimately contributing to improved eye health.

2 Methods

2.1 Data source and study population

We used data from the NHANES database, a continuous series of cross-sectional surveys conducted biennially by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. Details on NHANES data collection can be found at the NCHS (10). We utilized data from two independent NHANES cycles (2003–2004 and 2005–2006). The inclusion criteria for our study population were adolescents aged 12–19 years at each recruitment cycle. Each cycle is considered a separate, independent population. Exclusion criteria included: (1) subjects lacking exposure variables, i.e., serum micronutrient levels; (2) subjects without available refractive error data; and (3) subjects missing data on covariates such as age, sex, race, education level, poverty index, height, weight, and mean total cholesterol. All subjects aged 12 years and older underwent examinations at the Mobile Examination Center (MEC). Refractive error was assessed using an automated refraction device. Myopia was defined as a spherical equivalent (SE) of ≤ -1.0 diopters (D) in at least one eye (11). Adolescents with SE ≤ -6.00 D were classified as having high myopia.

2.2 Micronutrients assessment

The assessment of serum micronutrients has been detailed in previous studies (12). Blood samples from participants were collected at the Mobile Examination Center (MEC) and transported to designated laboratories. The serum levels of vitamins A, C, E, and carotenoids were measured using high-performance liquid chromatography and multi-wavelength photodiode array absorbance detection. The serum concentration of vitamin D was measured using the DiaSorin RIA kit (Detailed information about these measurement methods can be found at NHANES Lab Methods). According to previous studies, deficiencies in vitamins A, C, D, and E are defined as less than 0.7 μmol/L (13), 11.4 μmol/L (14), 50 nmol/L (15), and 9 μmol/L (16), respectively. Deficiencies in serum α-carotene, trans-β-carotene, and lutein/zeaxanthin are defined as less than 0.836 μg/dL (12), 4.12 μg/dL (17), and 7.23 μg/dL (6), respectively. Due to the lower quartile of serum cis-β-carotene being below the detection limit, cis-β-carotene deficiency was not analyzed in this study.

2.3 Covariate assessment

Demographic and socioeconomic data, including age, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or Other), education level (less than high school, high school diploma or above), and poverty income ratio (PIR < 1.0, PIR ≥ 1.0), were obtained from interviews. Weight, height, and total cholesterol were measured either at the MEC or in participants' homes. Overweight was defined as a body mass index (BMI) of >25 kg/m^2. Considering that fat-soluble vitamins (such as vitamins A, D, and E) and carotenoids (such as β-carotene) require cholesterol for metabolism and transport, controlling for total cholesterol levels helps reduce potential confounding effects on the relationship between fat-soluble nutrients and myopia.

2.4 Statistical analysis

All analyses were conducted using the statistical software R version 4.4.1, employing NHANES clustering design variables (SDMVSTRA, SDMVPSU) and the full sample 2-year MEC exam weights (WTMEC2YR) for the two cycles (2003–2004, 2005–2006). Weighted methods were used to analyze the associations between demographic factors, myopia, and micronutrients. Continuous data were summarized using means and quartiles, while categorical data were reported using unweighted counts and weighted percentages. Comparisons between subjects with and without myopia employed t-tests for continuous data and design-adjusted Rao-Scott Pearson χ^2 tests for categorical data. A two-sided p-value <0.05 was considered statistically significant. We performed Z-standardization on serum micronutrient levels to calculate the odds ratios (ORs) and 95% confidence intervals (CI) for each 1 standard deviation (SD) increase.

Logistic regression was used to explore the association between each micronutrient and myopia among the subjects. Model 1 was adopted a univariate analysis. Model 2 was adjusted for age, sex,

race PIR, education, weight, and height. Model 3 additionally adjusted for serum total cholesterol to account for the presence of fat-soluble micronutrients (vitamins A, D, E, and carotenoids). Furthermore, the relationship between high myopia and micronutrients was considered. Restricted cubic splines were used to examine the nonlinear associations, with the analysis performed at 4 knots.

3 Results

3.1 Basic characteristics of the study population

From 2003 to 2006, a total of 20,470 participants were included in the NHANES study, of which 4,591 were adolescents aged 12–19 years. After excluding 2,971 participants due to missing core variables and covariates, 1,620 participants were included in the final analysis (Figure 1).

In this study, among the 1,620 participants, 32% (549 individuals, 36 of whom had high myopia) were classified into the myopia group, while 68% (1,071 individuals) were classified into the non-myopia group. As shown in Table 1, the median age of the overall population was 15 years [interquartile range (IQR) 14 to 17 years], with an almost equal gender distribution (48% female and 52% male). The racial distribution was as follows: 12% Mexican American, 14% non-Hispanic Black, 64% non-Hispanic White, 6% Multiracial, and 3.9% other Hispanic. The median weight and height were 62 kg (IQR 53 to 76 kg) and 166 cm (IQR 159 to 174 cm), respectively. Participants with myopia tended to be taller ($p = 0.018$).

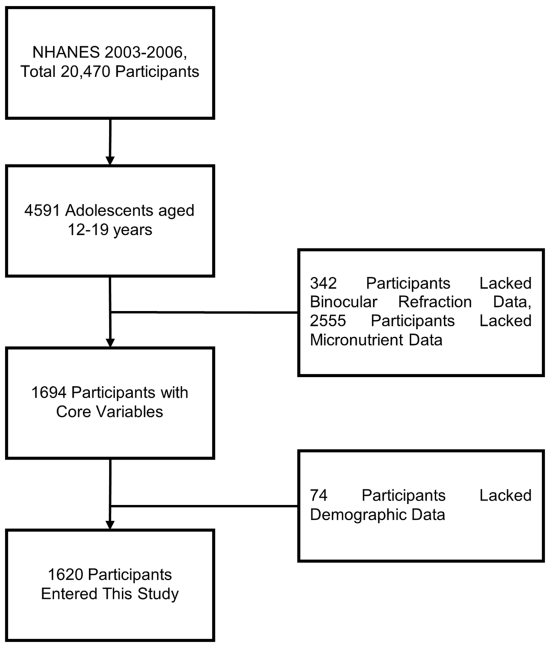

FIGURE 1
Flowchart describing the research process for exploring the association between micronutrients and myopia.

3.2 Micronutrients and myopia

The associations between micronutrients and myopia based on data from the 2003–2006 NHANES are shown in Table 2. Cis-β-carotene was significantly associated with myopia (Model 3: OR = 1.19, 95% CI: 1.03–1.39, $p = 0.026$). Trans-β-carotene showed a significant association in Model 1 (OR = 1.17, 95% CI: 1.01–1.34, $p = 0.036$) but the result did not remain significance in Models 2 and 3. Other micronutrients such as vitamins A, D, E, C, α-carotene, lutein and zeaxanthin were not statistically significantly associated with myopia in the models. Additionally, no nonlinear associations were found in the restricted cubic spline analysis (Figure 2).

3.3 Micronutrients and high myopia

The associations between micronutrients and high myopia based on data from the 2003–2006 NHANES are presented in Table 3.Cis-β-carotene showed a significant association with high myopia (Model 3: OR = 1.44, 95% CI: 1.03–2.03, $p = 0.038$). Other micronutrients did not show statistically significant associations with high myopia.

4 Discussion

The prevalence of myopia among school-aged children in North America is reported to be 42% (18). Parents of children with myopia often seek dietary advice from ophthalmologists (19), but research in this area remains relatively limited. This study systematically evaluated the association between various micronutrients and myopia among adolescents based on data from the NHANES from 2003 to 2006. A total of 1,620 participants were included, with a myopia prevalence of 32% among adolescents aged 12–19 years. Our results indicated that higher serum cis-β-carotene levels were associated with an increased risk of myopia and high myopia in adolescents. Other micronutrients, such as vitamins A, D, E, C, α-carotene, trans-β-carotene, lutein, and zeaxanthin, were not statistically significantly associated with adolescent myopia.

To the best of our knowledge, this is the first report linking higher serum cis-β-carotene levels with an increased risk of myopia. Moreover, since β-carotene is an exogenous rather than endogenous antioxidant (18), caution should be exercised when considering β-carotene supplements for young people. While past research indicated that cis-β-carotene is beneficial for the retina (20, 21), some studies have found adverse effects. One year of treatment with *Dunaliella* containing cis-β-carotene adversely affects full-field electroretinography (ERG) amplitudes in patients with RDH5-related fundus albipunctatus and leads to damage to both cone and rod cells (22). The authors suggested that this may be related to the increased rate of 11-cis retinal photoisomerization, leading to elevated A2E accumulation (22, 23). Interestingly, the accelerated biosynthesis of A2E and its conversion to epoxides have been shown to potentially contribute to myopia (24), which may partially explain our findings. Moreover, although β-carotene as an antioxidant may theoretically protect the retina by reducing oxidative stress (25, 26), high doses of β-carotene supplements were reported to have strong side effects, including mitochondrial dysfunction and increased oxidative stress, negatively impacting retinal cells (27). The National Institutes of

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TABLE 1 Characteristics of participants without and with myopia in the 2003–2006 National Health and Nutrition Examination Survey.

Characteristic	Overall, *N* = 1,620 (100%)	Myopia, *N* = 549 (32%)	Non-myopia, *N* = 1,071 (68%)	*p*- value
Age	15.00 (14.00, 17.00)	16.00 (14.00, 17.00)	15.00 (13.00, 17.00)	0.3
Sex				0.7
Female	811 (48%)	271 (47%)	540 (49%)	
Male	809 (52%)	278 (53%)	531 (51%)	
Race				0.051
Mexican American	535 (12%)	187 (13%)	348 (11%)	
Non-Hispanic Black	529 (14%)	183 (15%)	346 (14%)	
Non-Hispanic White	434 (64%)	131 (59%)	303 (67%)	
Other/Multiracial	79 (6.0%)	31 (6.8%)	48 (5.6%)	
Other Hispanic	43 (3.9%)	17 (6.5%)	26 (2.7%)	
PIR				0.3
At or above poverty line	1,130.00 (80.98%)	395.00 (82.67%)	735.00 (80.17%)	
Below poverty line	490.00 (19.02%)	154.00 (17.33%)	336.00 (19.83%)	
Education				0.10
Below high school	1,344 (84%)	444 (81%)	900 (85%)	
High school or higher	276 (16%)	105 (19%)	171 (15%)	
Weight (Kg)	62 (53, 76)	63 (54, 77)	62 (53, 73)	0.2
Height (cm)	166 (159, 174)	167 (159, 176)	165 (158, 173)	**0.018**
Mean total cholesterol (mg/dL)	157 (137, 176)	156 (135, 178)	158 (140, 175)	0.4
Vitamin A (umol/L)	1.60 (1.38, 1.87)	1.65 (1.41, 1.88)	1.57 (1.37, 1.86)	0.086
Vitamin E(umol/L)	17.54 (15.21, 20.41)	17.65 (14.93, 20.69)	17.51 (15.31, 20.39)	0.6
Cis-β-carotene(umol/L)	0.009 (0.009, 0.015)	0.009 (0.009, 0.015)	0.009 (0.009, 0.015)	0.081
Alpha-carotene (ug/dL)	1.80 (1.00, 3.10)	1.80 (0.90, 3.40)	1.70 (1.00, 3.00)	0.4
Trans-Beta carotene (ug/dL)	9.10 (6.10, 14.10)	9.20 (6.20, 14.50)	8.90 (6.00, 13.80)	0.12
Lutein and zeaxanthin (ug/dL)	10.62 (8.10, 13.80)	10.83 (8.17, 14.40)	10.54 (8.10, 13.50)	0.4
Vitamin D(nmol/L)	61.60 (47.10, 73.80)	61.60 (47.10, 76.20)	61.60 (49.50, 73.80)	0.8
Vitamin C(nmol/L)	60.80 (43.70, 74.90)	60.67 (43.20, 75.50)	60.80 (43.70, 74.40)	0.8
Vitamin A deficiency				0.5
Not	1,619 (100%)	549 (100%)	1,070 (100%)	
Yes	1 (<0.1%)	0 (0%)	1 (<0.1%)	
Vitamin C deficiency				0.6
Not	1,596 (97%)	543 (97%)	1,053 (98%)	
Yes	24 (2.6%)	6 (3.0%)	18 (2.4%)	
Vitamin D deficiency				0.3
Not	821 (70%)	265 (68%)	556 (71%)	
Yes	799 (30%)	284 (32%)	515 (29%)	
Vitamin E deficiency				0.2
Not	1,616 (100%)	548 (99%)	1,068 (100%)	
Yes	4 (0.3%)	1 (0.6%)	3 (0.1%)	
α-carotene deficiency				0.6
Not	1,458 (90%)	492 (91%)	966 (90%)	
Yes	162 (10.0%)	57 (9.2%)	105 (10%)	
Trans-β-carotene deficiency				0.2

(Continued)

TABLE 1 (Continued)

Characteristic	Overall, *N* = 1,620 (100%)	Myopia, *N* = 549 (32%)	Non-myopia, *N* = 1,071 (68%)	*p*- value
Not	1,477 (91%)	506 (93%)	971 (91%)	
Yes	143 (8.7%)	43 (7.2%)	100 (9.3%)	
Lutein and zeaxanthin deficiency				0.2
Not	1,407 (81%)	482 (83%)	925 (79%)	
Yes	213 (19%)	67 (17%)	146 (21%)	

Bold values indicate $p < 0.05$.

TABLE 2 Association between micronutrients and myopia in the 2003–2006 National Health and Nutrition Examination Survey.

Micronutrients	Model 1			Model 2			Model 3		
	OR	95% CI	*p*- value	OR	95% CI	*p*- value	OR	95% CI	*p*- value
Vitamin D, per SD	1.00	0.91, 1.10	>0.9	0.96	0.87, 1.06	0.4	0.96	0.86, 1.07	0.4
Vitamin A, per SD	1.11	0.96, 1.28	0.14	1.08	0.92, 1.27	0.3	1.12	0.97, 1.30	0.11
Vitamin E, per SD	1.03	0.87, 1.21	0.7	0.98	0.78, 1.24	0.9	1.08	0.85, 1.36	0.5
Vitamin C, per SD	1.00	0.89, 1.12	>0.9	0.99	0.85, 1.14	0.8	0.99	0.85, 1.14	0.8
α-carotene, per SD	1.12	0.95, 1.31	0.2	0.99	0.75, 1.31	>0.9	0.99	0.73, 1.32	>0.9
Trans-β-carotene, per SD	1.17	1.01, 1.34	**0.036**	1.14	0.60, 2.15	0.7	1.17	0.62, 2.22	0.6
Lutein and zeaxanthin, per SD	1.06	0.92, 1.22	0.4	1.02	0.84, 1.24	0.8	1.06	0.88, 1.28	0.5
Cis-β-carotene, per SD	1.17	1.01, 1.36	**0.040**	1.18	1.03, 1.36	**0.023**	1.19	1.03, 1.39	**0.026**

Bold values indicate $p < 0.05$.
Model 1: Univariate analysis; Model 2: adjusted for age, sex, race, PIR, education, weight and height; Model 3: adjusted for age, sex, race, PIR, education, weight, height and mean total cholesterol.

Health (NIH) Office of Dietary Supplements also advises that *β*-carotene supplements are not recommended for the general population (28). The existing evidence aligns with our finding that cis-*β*-carotene intake should be carefully controlled in dietary supplements, especially for adolescents aged 12–19 years.

Furthermore, in this study, only cis-β-carotene was significantly positively associated with myopia risk, while trans-*β*-carotene did not show a significant association. Previous studies have indicated that the energy barrier for reverse cis-to-trans isomerization is lower than that for direct isomerization, allowing cis isomers of carotenoids to react more rapidly with free radicals (29, 30). Additionally, *β*-carotene can be metabolized into retinol in the retinal pigment epithelium (RPE) cells and further converted into rhodopsin (31). We hypothesize that the accumulation of cis-β-carotene may lead to increased local oxidative stress, resulting in structural and functional changes in the retina, thereby promoting the development of myopia. Further research is needed to explore the specific mechanisms of cis-β-carotene in the retina, particularly its effects on RPE cells and receptors, and how these effects are related to the pathogenesis of myopia.

Vitamin A is involved in the formation of rhodopsin and the conversion of light signals (32). However, Fletcher et al. (33) proposed that a high intake of vitamin A during adolescence does not necessarily reduce the risk of myopia in early adulthood, which is consistent with our study. Additionally, in the RCS curve of serum vitamin A and myopia, the wider confidence interval may be due to the lack of samples with high vitamin A concentrations. This suggests the need for further research to verify their nonlinear relationship. Similarly, *α*-carotene, a precursor of vitamin A, can also convert into retinal and participate in rhodopsin formation (34). Previous studies have pointed out that the expression of rhodopsin has a relatively limited impact on defocus myopia (35). The impact of vitamin D on myopia remains controversial. Some scholars believe that low blood levels of vitamin D are associated with an increased risk of myopia (8). However, some studies suggest that the contribution of vitamin D levels to myopia is ignorable, with previous results likely confounded by sun exposure during outdoor activity time (36, 37). Therefore, further studies need to control for these confounding factors to more accurately assess the relationship between vitamin D and myopia. Vitamins C and E can prevent oxidative stress-induced cellular damage and help reduce ocular inflammation. In the Age-Related Eye Disease Study (AREDS), supplementation with vitamins C and E was found to reduce the risk of cataracts and glaucoma, among other eye diseases (38). However, Zheng et al. (39) found that in a sample of American adults, vitamin E levels were not associated with an increased or decreased risk of myopia, which is consistent with our study. Furthermore, a study in Hong Kong compared the vitamin C intake of 24 children who developed myopia between the ages of 7 and 10 with that of 68 children who did not develop myopia by the age of 10, and found statistically significant differences (40). This contradicts our findings. On one hand, vitamin C intake may not accurately reflect its bioavailability in the body. On the other hand, the sample size limits the reliability of the study. However, further randomized controlled trials (RCTs) are necessary to validate the true effects of micronutrients on myopia.

This study used a nationally representative sample and comprehensively evaluated the relationship between circulating micronutrients and myopia. However, there are several limitations. First, given the cross-sectional design of the NHANES data, we were not able to infer the longitudinal relationship of

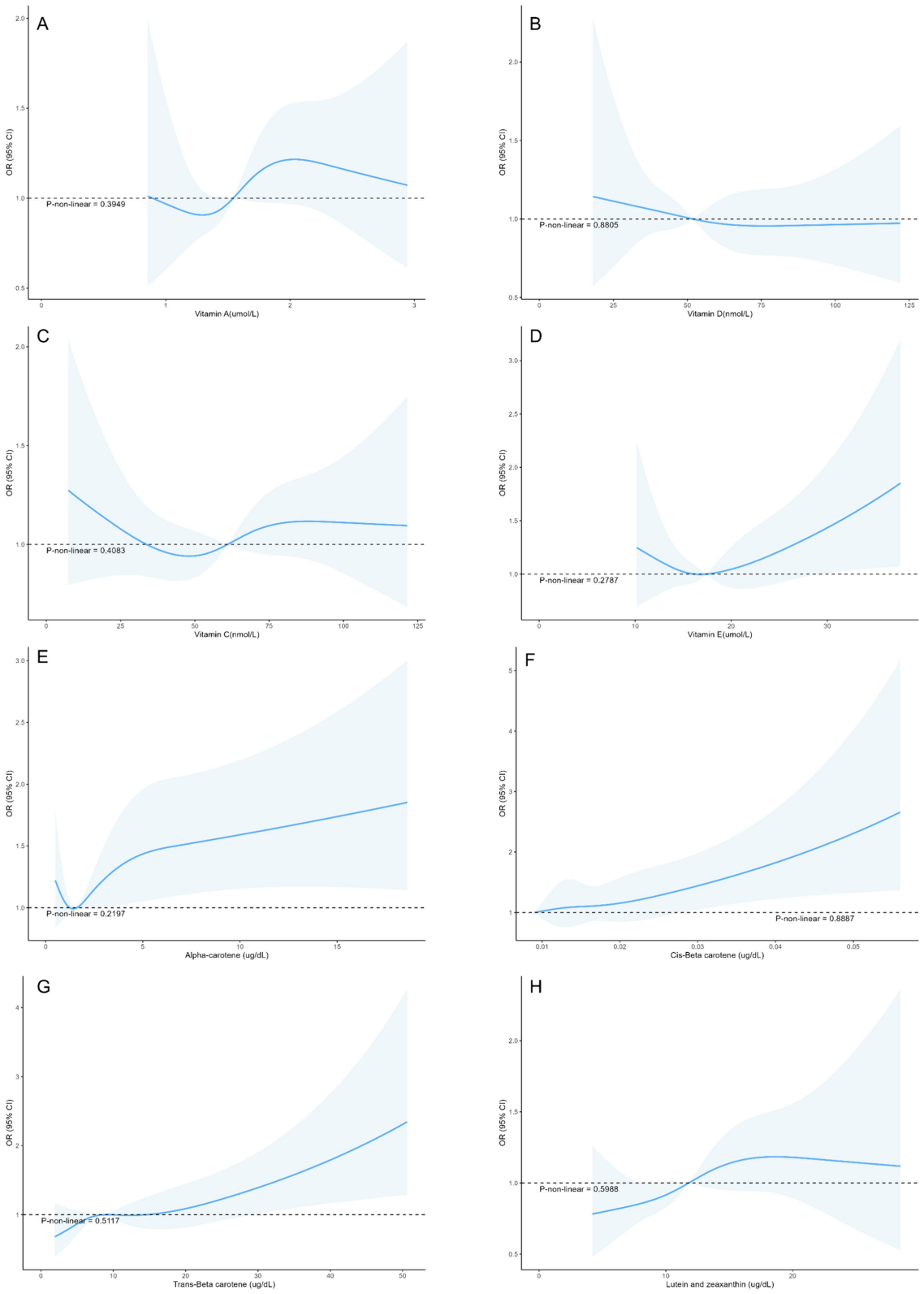

FIGURE 2
Restricted cubic splines between micronutrient levels and the risk of myopia in adolescents **(A)** Vitamin A, **(B)** Vitamin D, **(C)** Vitamin C, **(D)** Vitamin E, **(E)** Alpha-carotene, **(F)** Cis-β-carotene, **(G)** Trans-β-carotene, **(H)** Lutein and zeaxanthin.

micronutrients and future risk of myopia. Secondly, due to the lack of data on outdoor activity time and near-work time in NHANES, our study inevitably has residual confounding. Future longitudinal studies, RCTs, and biological research are needed to

TABLE 3 Association between micronutrients and high myopia in the 2003–2006 National Health and Nutrition Examination Survey.

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	*p*- value	OR	95% CI	*p*- value	OR	95% CI	*p*- value
Vitamin D, per SD	0.98	0.54, 1.80	>0.9	0.95	0.47, 1.93	0.9	0.91	0.43, 1.92	0.8
Vitamin A, per SD	1.09	0.70, 1.69	0.7	1.14	0.65, 2.02	0.6	1.06	0.52, 2.18	0.8
Vitamin E, per SD	1.26	0.92, 1.73	0.13	1.19	0.82, 1.74	0.3	1.22	0.69, 2.14	0.4
Vitamin C, per SD	1.24	0.79, 1.95	0.3	1.09	0.66, 1.80	0.7	1.08	0.64, 1.83	0.7
α-carotene, per SD	1.44	1.16, 1.77	**0.002**	1.15	0.63, 2.12	0.6	1.18	0.61, 2.26	0.6
Trans-β-carotene, per SD	1.39	1.03, 1.87	**0.034**	0.53	0.13, 2.08	0.3	0.49	0.12, 2.01	0.3
Lutein and zeaxanthin, per SD	1.06	0.73, 1.53	0.7	0.75	0.44, 1.28	0.3	0.68	0.37, 1.25	0.2
Cis-β-carotene, per SD	1.47	1.07, 2.01	**0.020**	1.43	1.04, 1.96	**0.032**	1.44	1.03, 2.03	**0.038**

Bold values indicate $p < 0.05$.
Model 1: Univariate analysis; Model 2: adjusted for age, sex, race, PIR, education, weight and height; Model 3: adjusted for age, sex, race, PIR, education, weight, height and mean total cholesterol.

provide a more comprehensive analysis and accurate conclusions. Lastly, the majority of NHANES participants are Non-Hispanic White, which may limit the generalizability of the results in other populations.

5 Conclusion

In summary, this population-based study found that higher serum cis-β-carotene levels were associated with an increased risk of myopia and high myopia in adolescents, indicating that cis-β-carotene is a risk factor for myopia in US adolescents. These findings suggest potential dietary guidance for myopia prevention. However, further research is needed to understand the underlying mechanisms and potential impact of cis-β-carotene on ocular health. Comprehensive evaluation through RCTs is recommended to fully assess the effects of micronutrients on adolescent myopia.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by National Health and Nutrition Examination Survey. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

KX: Conceptualization, Data curation, Writing – original draft. RC: Conceptualization, Data curation, Writing – review & editing. RL: Investigation, Writing – review & editing. WH: Validation, Writing – review & editing. JL: Validation, Writing – review & editing. MY: Validation, Writing – review & editing. YH: Supervision, Writing – review & editing. LL: Funding acquisition, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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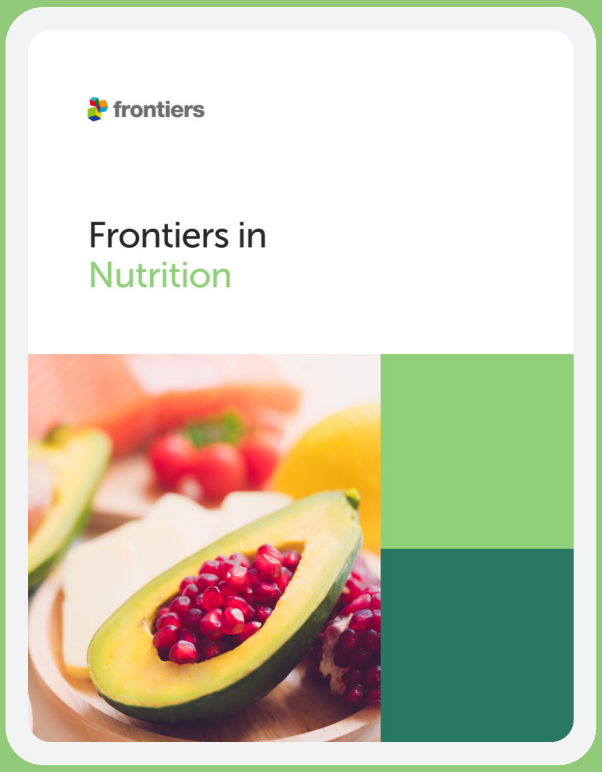

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