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Low-carbohydrate-diet scores and the risk of primary open-angle glaucoma: data from three US cohorts

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Abstract

Background/objectives To assess the long-term association between low-carbohydrate dietary patterns and incident primary open-angle glaucoma (POAG), and POAG subtypes defined by highest untreated intraocular pressure (IOP) and by pattern of visual field (VF) loss at diagnosis.

Subjects/methods We followed 185,638 participants of three large US prospective cohorts biennially (1976–2016, 1986–2016 and 1991–2017). Deciles of three low-carbohydrate-diet scores were calculated to represent adherence to diets lower in carbohydrate and higher in protein and fat from any source, animal sources or plant sources. We confirmed POAG cases ($n = 2112$) by medical record review and used Cox proportional hazards models to estimate multivariable-adjusted relative risks (MVRRs) and 95% confidence intervals (CIs).

Results There was no association between the three types of low-carbohydrate-diet scores and POAG: the MVRR for POAG in the highest vs. lowest deciles was 1.13 (95% CI, 0.91–1.39; $P_{trend} = 0.40$) for the overall score; 1.10 (95% CI, 0.89–1.35; $P_{trend} = 0.38$) for the animal score and 0.96 (95% CI, 0.79–1.18; $P_{trend} = 0.88$) for the vegetable score. No differential associations by IOP level was found ($P_{heterogeneity} \geq 0.06$). However, the vegetable score showed a suggestive inverse association with early paracentral VF loss (highest vs. lowest decile MVRR = 0.78 [95% CI, 0.55–1.10]; $P_{trend} = 0.12$) but not with peripheral VF loss only (MVRR = 1.09 [95% CI, 0.83–1.44]; $P_{trend} = 0.14$; $P_{heterogeneity} = 0.03$).

Conclusions Low-carbohydrate diets were not associated with risk of POAG. Our data suggested that higher consumption of fat and protein from vegetable sources substituting for carbohydrates was associated with lower risk of the POAG subtype with initial paracentral VF loss.

Introduction

Primary open-angle glaucoma (POAG) is a chronic and progressive group of optic neuropathies characterized by retinal ganglion cell loss. The neuroprotective effect of a ketogenic diet, which consists of high fat, modest protein and low carbohydrate [1], is well-established for epilepsy

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[2], and has been reported with other neurodegenerative diseases such as Parkinson's disease [3] and Alzheimer's disease [4].

Under a ketogenic diet, ketone bodies are substituted for glucose as a major energy source for the brain [2]. Utilization of ketone bodies results in greater production of adenosine triphosphate per unit of oxygen vs. glucose, and may improve mitochondrial function, reduce free radicals, abate cell apoptosis and stabilize nerve-cell synapse functions, all of which may contribute to slowing neuronal degeneration [5–8]. More recently, however, a low-carbohydrate diet, which can also lead to higher ketone bodies without restricting intakes of protein or total calories, has shown similar neuroprotective properties [9–11], and is recognized as a more practical alternative to a ketogenic diet, for which poor compliance and adverse effects have been reported [12].

The intra-scleral optic nerve, the main site of glaucomatous damage [13], is a relatively long unmyelinated segment (~1 mm) with high energy demands required to support continuous conduction of visual information to the brain, and has a high mitochondrial density to support this conduction [14]. Thus, the low-carbohydrate diet, with its generation of metabolites favourable to mitochondrial function, can be hypothesized to lower POAG risk. To date, the neuroprotective effects of restricted carbohydrate intake in retinal ganglion cells have been reported in a few animal studies [15, 16]; however, human evidence is lacking [17].

Hence, we hypothesized that long-term intake of lower carbohydrate and relatively higher fat and protein would be associated with a lower POAG risk. Furthermore, given that the POAG subtype characterized by early-stage paracentral visual field (VF) loss targets the maculopapillary nerve fibre layer bundles, which are particularly susceptible to metabolic changes (i.e. methyl alcohol toxicity) and impaired mitochondrial function [18]; we also hypothesized that this subtype may show stronger associations with this diet than the more common POAG subtype presenting with peripheral VF loss only. Utilizing data from the large ongoing studies of the Nurses' Health Study (NHS), Health Professionals Follow-up Study (HPFS), and the Nurses' Health Study II (NHSII), we evaluated the association of a low-carbohydrate dietary pattern with the incidence of POAG and POAG subtypes characterized by untreated intraocular pressure (IOP) and VF loss pattern at diagnosis.

Materials and methods

Study population

The NHS enroled 121,700 female nurses aged 30–55 years in 1976 [19]. The HPFS included 51,529 male health professionals aged 40–75 years in 1986 [20]. The NHSII was initiated in 1989 with 116,429 female nurses aged 24–44 at enrolment [21]. Participants responded to biennial mailed questionnaires with high response rates (>85%). Participants were followed until POAG diagnosis, death, cancer, loss-to-follow-up or the end of follow-up (2016 for NHS/HPFS and 2017 for NHSII), whichever came first. The study protocol was approved by the institutional review boards (IRBs) of Icahn School of Medicine at Mount Sinai, the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and the IRBs allowed participants' completion of questionnaires to be considered as implied consent.

For this study, we defined "baseline" as 1980 for NHS, 1986 for HPFS and 1991 for NHSII, when the first food frequency questionnaires (FFQs) were administered. Because carbohydrate intake may be an intermediate factor in the aetiology of diabetes [22], and because diabetes may be a risk factor for glaucoma [23] that can also lead to changes in diet, we excluded individuals with diabetes at baseline and stopped updating the dietary information after a diabetes diagnosis.

At baseline, we excluded: (1) 29,233 NHS women, 1596 HPFS men and 21,180 NHSII women without a complete baseline FFQ; (2) 3622 NHS women, 1927 HPFS men and 602 NHSII women with cancer (except nonmelanoma skin cancer), (3) 855 NHS women, 1037 HPFS men and 228 NHSII women with prevalent glaucoma, (4) Four NHS women, seven HPFS men and one NHSII woman who died before baseline, (5) 764 NHS women, 923 HPFS men and 642 NHSII women whose only questionnaire was at baseline (thus lost to follow-up), (6) 5515 NHS women, 3194 HPFS men and 25,460 NHSII women without an eye exam (in NHSII, the eye exam question was asked once in 2013), (7) 1656 NHS women, 1189 HPFS men and 563 NHSII women with diabetes at baseline and (8) 61 NHS women, 0 HPFS men and 1 NHSII women with missing baseline low-carbohydrate-diet score information. After these exclusions, 79,990 NHS women, 41,656 HPFS men and 67,752 NHSII women were potentially eligible to contribute person-time to the analysis. Among these participants, at each 2-year period of observation, we allowed only those who were ≥40 years old, who reported an eye exam and who had information on dietary intake of carbohydrate, protein, fat and total caloric intake (participants who did not meet these provisional criteria at any time were allowed to contribute person-time at later periods when they met these criteria). Overall, 78,210 NHS women, 41,078 HPFS men and 66,350 NHSII women were included in this analysis.

Assessment of low-carbohydrate diet

Diet was assessed with validated FFQs in 1980, 1984, 1986 and every 4 years thereafter in NHS, and every 4 years since

1986 in HPFS and 1991 in NHSII. In FFQs, participants reported how often ("never/<once per month" to ">6 times per day"), they consumed each food of a standard portion size during the previous year. To compute the daily intake for each nutrient, we multiplied the frequency of consumption of each item by its nutrient content and then summed across items from all contributing foods. All food composition values were obtained from the Harvard University food-composition database, which was derived from the U.S. Department of Agriculture and data from manufacturers [24]. The validity of estimated nutrient intake by FFQ was assessed with multiple dietary records. In the NHS, the Pearson correlation between the FFQ and diet records was 0.73 for carbohydrate, 0.67 for fat and 0.56 for protein intakes [25]; similar results were observed in HPFS [26] and NHSII [27].

We used a previously developed method to derive scores for the adherence to a low-carbohydrate-diet [28]. Briefly, we divided study participants into 11 cohort-specific quantiles separately for total carbohydrate, total fat and total protein intakes (expressed as percentage of total energy consumption). We assigned points on a 0–10 scale for increasing fat intake and for increasing protein intake. Conversely, we assigned points on a scale from 10 to 0 for increasing carbohydrate intake. Points were summed to create the overall low-carbohydrate-diet score with a maximum value of 30 (the highest intake of protein and fat and the lowest carbohydrate intake). Consistent with previous literature [28], we additionally created animal- and vegetable-low-carbohydrate-diet scores, which represent preferential substitution of carbohydrates with fat and protein from animal sources and vegetable sources, respectively. To reduce within-individual variation and to better estimate long-term diet, cumulatively averaged values (i.e. the mean of all available data up to each biennial follow-up cycle) were used and we evaluated deciles of the low-carbohydrate-diet score.

Assessment of POAG cases and subtypes by IOP and VF loss pattern

We included 2112 confirmed incident POAG cases (1357 NHS women, 538 HPFS men and 217 NHSII women). After identifying participants who self-reported diagnoses of glaucoma on biennial questionnaires, we asked these participants for permission to review all VFs with either complete medical records or a completed glaucoma questionnaire with items on maximal IOP, filtration apparatus status, optic nerve structural information, ophthalmic surgery and earliest VF loss date. All records were reviewed using standardized criteria by a glaucoma specialist (LRP), who was unaware of participants' diet scores.

POAG cases were confirmed if: (1) gonioscopy showing that the filtration angle was not occludable in either eye or slit lamp biomicroscopy demonstrated no signs in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma or rubeosis; and (2) reproducible VF defects consistent with POAG on at least two reliable tests. Most cases were detected by a full static threshold testing with age-matched reference sets while <1% were diagnosed with kinetic VFs. For static threshold or supra-threshold tests, we used the following reliability parameters: fixation loss ≤33%, false positive rate ≤20% and false negative rate ≤20%; kinetic VFs were considered reliable unless there were examiners' notes to the contrary.

We further subdivided cases according to highest known untreated IOP and VF loss pattern at diagnosis. We defined subtypes of "high-tension" (n = 1370; 877 in NHS, 378 in HPFS and 115 in NHSII) or "normal-tension" POAG as those with maximum untreated IOP≥ or ≤22 mmHg (n = 742; 480 in NHS, 160 in HPFS and 102 in NHSII), respectively. We defined subtypes by VF loss pattern: those with peripheral VF loss only (n = 1186; 779 in NHS, 279 in HPFS and 128 in NHSII) or early paracentral VF loss (n = 638; 401 in NHS, 168 in HPFS and 69 in NHSII) or undetermined VF loss (n = 288; 177 in NHS, 91 in HPFS and 20 in NHSII), as we previously described [29]. For those with peripheral VF loss only, nasal step, temporal wedge or Bjerrum scotoma was present with no paracentral loss. For a case with early paracentral loss, there was (1) paracentral loss only or (2) paracentral loss with VF loss in the Bjerrum area and/or nasal step area in the same hemifield, but without any temporal wedge loss. We included the latter paracentral group as those with only paracentral loss were uncommon whereas those with clear paracentral loss frequently also showed peripheral loss. Cases with undetermined VF loss patterns were censored.

Statistical analysis

We initially analysed cohort-specific data separately, and in meta-analyses of results, confirmed no heterogeneity by cohorts (p for heterogeneity >0.10) [30]. Thus, we pooled the data across the three cohorts to maximize statistical power.

Cox proportional hazards regression models with time-varying covariates were used [31]. Age-adjusted and multivariable-adjusted (MV) relative risks (RRs) and 95% CIs were computed for the contrast between the highest and lowest deciles of the adherence score ("overall score", "animal-based score" and "vegetable-based score") to a low-carbohydrate-diet and incident POAG risk; for the trend tests across deciles we included and tested the median value for each category as a continuous variable in models.

In alternate analyses, the association with 1-unit increment in the low-carbohydrate-diet score was also evaluated.

To minimize the potential confounding by age, questionnaire cycle, cohort and interactions, we stratified the analysis jointly by these variables. In MV models, we adjusted for a priori-selected confounders: family history of glaucoma, body mass index (BMI, kg/m^2), cigarette smoking (pack-years), hypertension, physical activity, cumulatively averaged intakes of total calories, alcohol and caffeine, race, and among females, age at menopause and postmenopausal hormone use.

In secondary analyses, we evaluated associations with the POAG subtypes by separately analysing the risk of each subtype and testing for heterogeneity using the Lunn–McNeil approach [32]. Finally, we evaluated whether associations might differ by age, gender or glaucoma family history. For interaction testing, the statistical significance of the multiplicative interaction was evaluated by applying the Wald test to the product term of the exposure and the effect modifier. All significance tests were two-sided and $\alpha =$ 0.05. Analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC, USA).

Results

During 3,429,825 person-years of follow-up, we documented 2112 incident POAG cases (mean [standard deviation] age was 65.6 [9.3] years; and mean [standard deviation] mean deviation was −5.5 [5.0] decibels amongst those with computerized automated VF testing). Individuals with a higher overall low-carbohydrate-diet score were more likely to be heavy smokers, had higher BMI and had higher prevalence of diabetes, consumed more caffeine and red meat but were less likely to be physically active. As expected, they had a diet that was lower in glycaemic index and glycaemic load values, total calories, dietary fibre, fruits and vegetables (Table 1). Similar patterns were observed according to the adherence to the animal-based score. For vegetable-based score, participants with higher scores were more likely to exercise and consume more nuts, vegetables, legumes and nitrate (Table 1).

We found no association between the overall score and POAG risk (Table 2). In age-adjusted analyses, the RR comparing those in the 3rd, 5th, 7th and 10th deciles with those in the 1st decile were 0.99 (95% CI, 0.81–1.21), 1.10 (95% CI, 0.91–1.33), 0.97 (95% CI, 0.80–1.19) and 1.01 (95% CI, 0.82–1.25). After controlling for potential confounders, the MVRRs did not differ from the age-adjusted results: the highest vs. lowest decile of overall was 1.13 (95% CI, 0.91–1.39; $P_{\text{trend}} = 0.40$). Similarly, there was no trend in the associations with animal- and vegetable-based scores ($P_{\text{trend}} \geq 0.38$).

When we evaluated low-carbohydrate-diet scores with POAG subtypes characterized by highest known untreated IOP at diagnosis, we observed no significant trends ($P_{\text{trend}} \geq$ 0.08), although there was some suggestion of heterogeneity in association between some low-carbohydrate-diet scores and glaucoma stratified by highest IOP ($P_{\text{heterogeneity}} = 0.06$ for overall and 0.07 for animal-based low-carbohydrate diet scores) (Table 3). When we examined associations with POAG subtypes defined by VF loss pattern, we did not observe associations with either the overall or animal-based scores for either of the subtypes (Table 4). For the vegetable-based score, we observed some suggestions of stronger inverse associations with the early paracentral VF loss subtype vs. the peripheral VF loss subtype ($P_{\text{heterogeneity}} =$ 0.03): compared with the 1st decile of the vegetable-based score, the highest decile MVRR was 0.78 (95% CI, 0.55–1.10; $P_{\text{trend}} = 0.12$) for POAG with early paracentral VF loss and 1.09 (95% CI, 0.83–1.44; $P_{\text{trend}} = 0.14$) for POAG with peripheral loss only. As we had previously observed that dietary nitrate was associated with POAG with early paracentral VF loss [33], when we additionally adjusted for dietary nitrate, results were slightly attenuated for this subtype: MVRR = 0.83 (95% CI, 0.59–1.17 $P_{\text{trend}} = 0.27$).

In exploratory analyses, we evaluated whether associations might differ by age, glaucoma family history or gender. No interactions were observed with any of the scores for these factors (data not shown; p for interaction >0.20).

Discussion

In this large study of 2112 incident POAG cases with 3,429,825 person-years of follow-up, adherence to a low-carbohydrate diet was not associated with the risk of POAG or subtypes of POAG defined by IOP and VF loss pattern. However, we observed a suggestion that greater adherence to a low-carbohydrate diet with high intake of fat and protein from vegetable sources was associated with a moderately lower risk of POAG with early paracentral VF loss, while no such association was observed for POAG with peripheral VF loss only. This is the first population-based study with results suggesting that restricting carbohydrates while increasing intake of plant-based fat and protein is associated with ~20% lower risk of a POAG subtype with initial paracentral VF loss, which arise from the loss of retinal ganglion cells in the maculopapillary bundle and are particularly vulnerable to impairments in vascular autoregulation [33–35] and mitochondrial dysfunction [36]. These results need to be replicated in additional studies.

Emerging evidence suggests that mitochondrial dysfunction and abnormal lipid metabolism may play a key role

Table 1 Age and age-adjusted characteristics of total person-time accrued according to score decile for adherence to a low-carbohydrate diet (1st and 10th deciles) in pooled data from three cohorts: the Nurses' Health Study (1980–2016), the Health Professionals' Follow-up Study (1986–2016) and the Nurses' Health Study II (1991–2017).

Variable[a]	Overall low-carbohydrate-diet score		Animal-based low-carbohydrate-diet score		Vegetable-based low-carbohydrate-diet score	
	Decile 1	Decile 10	Decile 1	Decile 10	Decile 1	Decile 10
No. of person-years	341,332	343,657	343,117	338,039	342,884	346,639
Age, years[b]	56.6 (11.2)	55.6 (10.1)	56.8 (11.3)	55.8 (10.2)	56.8 (11.0)	56.7 (10.6)
Low-carbohydrate-diet score	4.9 (1.9; range: 0–7.4)	24.8 (1.8; range: 22.5–30.0)	3.9 (1.9; range: 0–6.5)	25.6 (1.8; range: 23.1–30.0)	7.6 (1.9; range: 0–9.7)	22.4 (1.7; range: 20.5–30.0)
Total calories, kcal/day	1805 (510)	1698 (498)	1811 (513)	1692 (493)	1789 (490)	1800 (506)
Carbohydrates, % energy	58.6 (5.5)	37.2 (5.8)	58.0 (5.8)	37.5 (6.1)	53.6 (6.8)	43.0 (6.1)
Total protein, % energy	15.6 (2.0)	21.4 (2.4)	15.6 (2.1)	21.6 (2.6)	18.0 (3.1)	18.4 (2.6)
Animal protein, % energy	10.1 (2.3)	17.0 (2.7)	9.6 (2.2)	17.4 (2.7)	13.8 (3.2)	12.6 (2.9)
Vegetable protein, % energy	5.5 (1.6)	4.4 (1.0)	6.0 (1.6)	4.1 (0.9)	4.2 (0.9)	5.8 (1.1)
Total fat, % energy	26.2 (4.4)	40.0 (5.0)	27.1 (5.1)	38.9 (5.4)	28.4 (5.1)	37.4 (4.9)
Animal fat, % energy	13.3 (4.7)	25.9 (7.0)	12.2 (4.3)	26.6 (6.6)	18.6 (5.9)	18.1 (5.7)
Vegetable fat, % energy	12.9 (3.7)	14.1 (4.6)	14.8 (4.4)	12.3 (3.9)	9.7 (2.7)	19.3 (3.8)
Saturated fat, % energy	9.0 (2.3)	14.4 (2.9)	8.9 (2.3)	14.4 (2.9)	10.8 (2.7)	12.2 (2.6)
Trans fat, % energy	1.4 (0.6)	1.8 (0.6)	1.4 (0.6)	1.8 (0.5)	1.4 (0.4)	1.8 (0.7)
Monosaturated fat, % energy	10.0 (2.0)	15.8 (2.6)	10.4 (2.3)	15.3 (2.7)	10.7 (2.3)	15.0 (2.3)
Polysaturated fat, % energy	5.0 (1.1)	6.4 (1.3)	5.6 (1.4)	5.9 (1.2)	4.5 (0.8)	7.4 (1.3)
Glycaemic index[c]	54.2 (3.1)	51.3 (3.6)	53.8 (3.0)	51.4 (3.5)	53.4 (3.6)	52.0 (3.1)
Glycaemic load[d]	140.8 (22.2)	85.4 (18.4)	139.0 (22.6)	86.3 (19.0)	127.2 (24.3)	99.2 (19.5)
Cereal fibre, g/day	6.7 (3.6)	4.1 (1.9)	7.1 (3.7)	4.0 (1.9)	5.0 (2.8)	5.5 (2.4)
Fruits, servings/day	2.8 (1.8)	1.3 (0.9)	2.7 (1.8)	1.3 (0.9)	2.3 (1.6)	1.6 (1.0)
Vegetables, servings/day	3.6 (2.0)	3.1 (1.6)	3.9 (2.2)	3.1 (1.5)	2.9 (1.6)	3.7 (1.9)
Red meat, servings /day	0.4 (0.3)	0.9 (0.5)	0.3 (0.3)	1.0 (0.5)	0.6 (0.4)	0.6 (0.4)
Poultry, servings/day	0.3 (0.2)	0.4 (0.3)	0.3 (0.2)	0.4 (0.3)	0.3 (0.2)	0.4 (0.2)
Fish, servings/week	1.4 (1.3)	1.8 (1.5)	1.5 (1.3)	1.7 (1.5)	1.6 (1.4)	1.8 (1.4)
Nuts, servings/day	0.3 (0.4)	0.4 (0.5)	0.5 (0.5)	0.3 (0.3)	0.2 (0.2)	0.8 (0.8)
Legumes, servings/day	0.5 (0.4)	0.4 (0.2)	0.5 (0.4)	0.4 (0.2)	0.4 (0.2)	0.4 (0.3)
Eggs, servings/week	1.4 (1.5)	2.6 (2.7)	1.4 (1.4)	2.7 (2.7)	1.7 (1.8)	2.0 (1.9)
Caffeine intake, mg/day	224.8 (199.6)	313.6 (231.1)	223.8 (201.6)	310.6 (229.5)	228.7 (197.1)	297.1 (221.9)
Alcohol intake, g/day	4.7 (8.3)	5.9 (8.2)	4.3 (7.3)	7.1 (9.8)	4.3 (8.3)	7.5 (9.9)
Total nitrate intake, mg/day	143.5 (84.2)	142.9 (74.1)	155.0 (92.1)	138.9 (71.6)	119.4 (60.6)	159.4 (83.2)
Family history of glaucoma, %	7.3	7.8	7.4	7.7	7.1	8.1
African ancestry, %	2.3	0.9	1.9	1.0	2.6	0.5
Self-reported diabetes diagnosis, %	3.6	7.8	3.3	7.6	5.0	4.9
Self-reported hypertension diagnosis, %	31.2	37.3	29.4	38.5	35.5	31.5
≥30 pack-years of smoking, %	9.4	17.1	8.2	17.7	12.0	14.0
Body mass index (kg/m^2) ≥30, %	7.7	21.6	7.1	21.3	12.7	13.3
In top 25th percentile for physical activity, %	30.6	19.6	32.7	19.3	24.8	26.2

HPFS Health Professionals Follow-up Study, *NHS* Nurses' Health Study, *SD* standard deviation.

[a]Values are presented as means (SD) for continuous variables and percentages for categorical variables.

[b]All values other than age have been directly standardized to age distribution (in 5-year age group) of all the participants.

[c]Glucose was used as the reference for calculations of glycaemic index. The interquartile range was 50.5–54.3 in the NHS, 51.4–54.8 in the HPFS, 51.2–54.7 in the NHS II.

[d]Glucose was used as the reference for calculations of glycaemic load. The interquartile range was 87.0–109.2 in the NHS, 115.0–143.6 in the HPFS, 109.2–131.3 in the NHS II.

in the development of POAG [37–43], particularly POAG with early paracentral VF loss [37, 42] and in Leber's hereditary optic neuropathy (LHON) [37, 44], an important cause of blindness related to mitochondrial dysfunction. For the less common POAG subset with early paracentral VF loss and LHON, it is common to observe normal ocular tensions (IOP < 22 mmHg) [34, 45], indicating that mitochondrial impairment rather than elevated IOP might play a more important role in neuronal degeneration. In fact, gene-set analyses supported a key role of mitochondrial-encoding proteins (particularly those involved in the degradation of ketone bodies and fatty acid elongation), specifically for

Table 2 Age- and multivariable-adjusted relative risk (95% confidence interval) of primary open-angle glaucoma, by score decile for adherence to a low-carbohydrate diet,[a] using pooled data (Nurses' Health Study: 1980–2016, Health Professionals Follow-up Study: 1986–2016, Nurses' Health Study II: 1991–2017).

Variable	Deciles of scores for adherence to a low-carbohydrate-diet						
	Decile 1	Decile 3	Decile 5	Decile 7	Decile 10	P_{trend}	Per 1 unit increase in adherence score
Overall low-carbohydrate-diet score							
Cases (total $n = 2112$)	189	193	241	199	176		
Person-years	341,332	300,736	362,345	343,220	343,657		
Low-carbohydrate-diet score							
Median	5.3	11.0	14.3	17.3	24.3		
Range	0–7.4	10.1–11.9	13.6–15.0	16.6–18.0	22.5–30.0		
Age-adjusted RR (95% CI)	1 (referent)	0.99 (0.81, 1.21)	1.10 (0.91, 1.33)	0.97 (0.80, 1.19)	1.01 (0.82, 1.25)	0.72	1.00 (0.98, 1.01)
Multivariable-adjusted RR (95% CI)[b]	1 (referent)	1.01 (0.82, 1.24)	1.15 (0.94, 1.40)	1.03 (0.84, 1.27)	1.13 (0.91, 1.39)	0.40	1.01 (0.99, 1.02)
Animal-based low-carbohydrate-diet score							
Cases (total $n = 2112$)	204	213	244	186	182		
Person-years	343,117	349,522	364,860	338,059	338,039		
Low-carbohydrate-diet score							
Median	4.3	10.5	14.3	17.5	25.2		
Range	0–6.5	9.5–11.5	13.4–15.0	16.7–18.4	23.1–30.0		
Age-adjusted RR (95% CI)	1 (referent)	0.90 (0.74, 1.09)	1.03 (0.85, 1.25)	0.85 (0.70, 1.04)	0.98 (0.80, 1.20)	0.63	1.00 (0.98, 1.01)
Multivariable-adjusted RR (95% CI)[b]	1 (referent)	0.92 (0.76, 1.12)	1.08 (0.90, 1.31)	0.90 (0.74, 1.11)	1.10 (0.89, 1.35)	0.38	1.01 (0.99, 1.02)
Vegetable-based low-carbohydrate-diet score							
Cases (total $n = 2112$)	208	197	192	225	198		
Person-years	342,884	315,245	316,682	351,545	346,639		
Low-carbohydrate-diet score							
Median	8.0	12.2	14.7	16.8	22.0		
Range	0–9.7	11.6–12.9	14.1–15.0	16.2–17.3	20.5–30.0		
Age-adjusted RR (95% CI)	1 (referent)	0.88 (0.73, 1.08)	0.88 (0.72, 1.08)	0.92 (0.76, 1.12)	0.97 (0.79, 1.18)	0.86	1.00 (0.99, 1.02)
Multivariable-adjusted RR (95% CI)[b]	1 (referent)	0.89 (0.73, 1.09)	0.87 (0.71, 1.06)	0.93 (0.77, 1.13)	0.96 (0.79, 1.18)	0.88	1.00 (0.99, 1.02)

CI confidence interval, *HPFS* Health Professionals Follow-up Study, *NHS* Nurses' Health Study, *RR* relative risk.

[a]Diet scores were based on cumulatively averaged intakes of macro nutrients (i.e. average of all available intake data from food frequency questionnaires completed before each 2-year period at risk); because diabetes may be an intermediate factor in the aetiology, diet was no longer updated after a diabetes diagnosis.

[b]All multivariable-adjusted analyses were stratified by cohort, age in months and period at risk, and they were adjusted for the following variables: ancestry (African-American, non-African heritage), family history of glaucoma, self-reported history of hypertension, body mass index (22–23, 24–25, 26–27, 28–29, 30+ kg/m²), cumulatively averaged intakes of total energy (kcal/day; quintiles), alcohol (g/day in categories of 0–4, 5–14, 15–29, 30+ g/day), and caffeine (mg/day; quintiles); pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), physical activity (quartiles of metabolic equivalents of task-hours/week), number of eye exams reported during follow-up; and for women only, additionally adjusted for age at menopause (20–44, 45–50, 50–54, 54+ years) and postmenopausal hormone status (premenopausal, current user, past user and non-user).

normal tension glaucoma (NTG) but not high-tension glaucoma [41, 42]. Indeed, a genome-wide association study of NTG in Japan reported strong associations with *ELOVL5*, a gene involved in lipid metabolism pathways [46]. In addition, given that a significant role of mitochondria includes regulation of cell signalling and apoptosis, the pro-apoptotic *p53* polymorphism (the *p53* codon 72 PRO/PRO genotype) [47] being strongly associated with this subtype, further supports a role of optimizing mitochondrial function with aging for neuronal survival.

Restricted carbohydrate consumption is increasingly recognized as a potential therapeutic approach to enhance mitochondrial function in neurodegenerative diseases [48]. A recent study using a murine glaucoma model suggested that ketogenic feeds might significantly increase optic nerve

mitochondrial biogenesis and prolong the survival of retinal ganglion cells and their axons [16]. Also, in rat models, Thaler et al. showed a dose-dependent neuroprotective effect of ketone bodies with retinal ganglion cells [15]. However, these neuroprotective effects of ketone bodies resulted from extremely strict dietary protocols (i.e. 0.1% carbohydrate and 90% fat) [16] which in humans have been linked to poor adherence [48, 49].

We found no association of overall and animal-rich low-carbohydrate-diet scores with risk of POAG overall or subtypes characterized by IOP or VF loss. This overall null association may be due, in part, to possible detrimental effects of higher fat and protein content derived from animal sources. Furthermore, subjects in the highest decile of low-carbohydrate-diet scores in the current analyses derived

Table 3 Multivariable-adjusted relative risk (95% confidence interval) of primary open-angle glaucoma subtypes defined by intraocular pressure[a], by deciles of low-carbohydrate-diet scores,[b] using pooled data (Nurses' Health Study: 1980–2016, Health Professionals Follow-up Study: 1986–2016, Nurses' Health Study II: 1991–2017).

Subtype of POAG	Deciles of scores of adherence to a low-carbohydrate-diet					P_{trend}	Per 1 unit increase in adherence score	$P_{heterogeneity}$[c]
	Decile 1	Decile 3	Decile 5	Decile 7	Decile 10			
Overall low-carbohydrate-diet score								
High-tension glaucoma (intraocular pressure ≥ 22 mmHg)								
Cases (total n = 1370)	107	120	159	137	126			0.06
Multivariable-adjusted RR (95% CI)[d]	1 (referent)	1.18 (0.91, 1.54)	1.40 (1.08, 1.79)	1.27 (0.98, 1.64)	1.31 (1.00, 1.72)	0.08	1.02 (1.00, 1.04)	
Normal-tension glaucoma (intraocular pressure < 22 mmHg)								
Cases (total n = 742)	82	73	82	62	50			
Multivariable-adjusted RR (95% CI)[d]	1 (referent)	0.78 (0.57, 1.08)	0.84 (0.61, 1.15)	0.73 (0.52, 1.02)	0.87 (0.61, 1.26)	0.30	0.99 (0.96, 1.01)	
Animal-based low-carbohydrate-diet score								
High-tension glaucoma (intraocular pressure ≥ 22 mmHg)								
Cases (total n = 1370)	118	134	171	125	130			0.07
Multivariable RR (95% CI)[d]	1 (referent)	1.03 (0.80, 1.32)	1.36 (1.06, 1.73)	1.06 (0.82, 1.38)	1.24 (0.95, 1.61)	0.08	1.02 (1.00, 1.04)	
Normal-tension glaucoma (intraocular pressure < 22 mmHg)								
Cases (total n = 742)	86	79	73	61	52			
Multivariable RR (95% CI)[d]	1 (referent)	0.78 (0.57, 1.07)	0.72 (0.52, 1.00)	0.69 (0.49, 0.97)	0.89 (0.62, 1.28)	0.34	0.99 (0.96, 1.02)	
Vegetable-based low-carbohydrate-diet score								
High-tension glaucoma (intraocular pressure ≥ 22 mmHg)								
Cases (total n = 1370)	138	117	126	143	137			0.47
Multivariable RR (95% CI)[d]	1 (referent)	0.84 (0.65, 1.08)	0.89 (0.69, 1.14)	0.93 (0.73, 1.18)	0.99 (0.78, 1.26)	0.57	1.01 (0.99, 1.03)	
Normal-tension glaucoma (intraocular pressure < 22 mmHg)								
Cases (total n = 742)	70	80	66	82	61			
Multivariable RR (95% CI)[d]	1 (referent)	0.98 (0.71, 1.36)	0.83 (0.59, 1.17)	0.95 (0.68, 1.32)	0.91 (0.64, 1.30)	0.63	1.00 (0.97, 1.02)	

CI confidence interval, *HPFS* Health Professionals Follow-up Study, *NHS* Nurses' Health Study, *POAG* primary open-angle glaucoma, *RR* relative risk.

[a]Based on maximum untreated intraocular pressure at diagnosis.

[b]Diet scores were based on cumulatively averaged intakes of macro nutrients (i.e. average of all available intake data from food frequency questionnaires completed before each 2-year period at risk); because diabetes may be an intermediate factor in the aetiology, diet was no longer updated after a diabetes diagnosis.

[c]For testing whether the associations between low-carbohydrate-diet scores and one POAG subtype is significantly different from that with another subtype, we used the Lunn–McNeil approach to test for heterogeneity in associations and derived the *p* for heterogeneity.

[d]All multivariable-adjusted analyses included the same set of covariates as described in footnote[b] in Table 2.

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Table 4 Multivariable-adjusted relative risk (95% confidence interval) of primary open-angle glaucoma subtypes defined by initial visual field loss pattern[a], by deciles of low-carbohydrate-diet scores,[b] using pooled data (Nurses' Health Study: 1980–2016, Health Professionals Follow-up Study: 1986–2016, Nurses' Health Study II: 1991–2017).

Subtype of POAG	Deciles of scores of adherence to a low-carbohydrate-diet					P_{trend}	Per 1 unit increase in adherence score	$P_{heterogeneity}$[c]
	Decile 1	Decile 3	Decile 5	Decile 7	Decile 10			
Overall low-carbohydrate-diet score								
POAG with peripheral visual field loss only								0.81
Cases (total $n = 1186$)	104	103	130	114	102			
Multivariable-adjusted RR (95% CI)[d]	1 (referent)	0.98 (0.75, 1.30)	1.10 (0.84, 1.43)	1.06 (0.81, 1.39)	1.10 (0.83, 1.46)	0.64	1.00 (0.98, 1.03)	
POAG with early paracentral visual field loss								
Cases (total $n = 638$)	57	61	80	54	49			
Multivariable-adjusted RR (95% CI)[d]	1 (referent)	1.06 (0.73, 1.54)	1.32 (0.93, 1.87)	0.96 (0.65, 1.41)	1.15 (0.78, 1.71)	0.53	1.01 (0.98, 1.04)	
Animal-based low-carbohydrate-diet score								
POAG with peripheral visual field loss only								0.38
Cases (total $n = 1186$)	119	114	144	106	107			
Multivariable RR (95% CI)[d]	1 (referent)	0.84 (0.65, 1.10)	1.08 (0.84, 1.39)	0.85 (0.65, 1.12)	1.01 (0.77, 1.33)	0.91	1.00 (0.98, 1.02)	
POAG with early paracentral visual field loss								
Cases (total $n = 638$)	58	68	68	58	52			
Multivariable RR (95% CI)[d]	1 (referent)	1.04 (0.72, 1.49)	1.08 (0.75, 1.55)	1.04 (0.71, 1.51)	1.24 (0.84, 1.83)	0.24	1.02 (0.99, 1.05)	
Vegetable-based low-carbohydrate-diet score								
POAG with peripheral visual field loss only								0.03
Cases (total $n = 1186$)	101	110	116	135	109			
Multivariable RR (95% CI)[d]	1 (referent)	1.06 (0.80, 1.39)	1.09 (0.83, 1.43)	1.17 (0.90, 1.52)	1.09 (0.83, 1.44)	0.14	1.02 (1.00, 1.04)	
POAG with early paracentral visual field loss								
Cases (total $n = 638$)	78	62	54	61	62			
Multivariable RR (95% CI)[d]	1 (referent)	0.71 (0.50, 0.99)	0.63 (0.44, 0.90)	0.64 (0.45, 0.91)	0.78 (0.55, 1.10)	0.12	0.98 (0.95, 1.01)	

CI confidence interval, *HPFS* Health Professionals Follow-up Study, *NHS* Nurses' Health Study, *POAG* primary open-angle glaucoma, *RR* relative risk, *VF* visual field.

[a]Based on visual field (VF) loss pattern as of the earliest reliable VF at diagnosis that was reproduced at the latest reliable VF. Cases ($n = 288$) with advanced VF loss at diagnosis who could not be categorized based on initial presenting VF loss as either peripheral VF loss only or early paracentral VF loss were censored during analyses. See Methods for how cases were categorized according to initial presenting VF loss.

[b]Diet scores were based on cumulatively averaged intakes of macro nutrients (i.e. average of all available intake data from food frequency questionnaires completed before each 2-year period at risk); because diabetes may be an intermediate factor in the aetiology, diet was no longer updated after a diabetes diagnosis.

[c]For testing whether the associations between low-carbohydrate-diet scores and one POAG subtype is significantly different from that with another subtype, we used the Lunn–McNeil approach to test for heterogeneity in associations and derived the *p* for heterogeneity.

[d]All multivariable-adjusted analyses included the same set of covariates as described in footnote[b] in Table 2.

between 37–43% total energy from carbohydrate, and this intake was much higher than those in pre-clinical ketogenic models of neuroprotection [16] and Atkins-like diets in human weight loss trials [50, 51]. A plausible explanation for the inverse trend between plant-based low carbohydrate intake and paracentral POAG includes the fact that participants with a higher adherence to a vegetable-based (but not the overall or animal-based low-carbohydrate diets) had higher nitrate intake, which we previously observed was inversely associated with this subtype [33]. However, there was minimal attenuation of associations with POAG with early paracentral VF loss, even after nitrate adjustment, indicating that further study with more cases of this subtype is warranted.

The strengths of our investigation include the large, well-characterized study populations with a wealth of updated data on diet, lifestyle, and medical history over a 25+ year follow-up period. The prospective design, high follow-up rate and multiple repeated assessments of exposures and covariates minimized the bias including reverse causation and measurement errors.

Our study had some limitations. First, the case ascertainment of glaucoma was based on the self-reported questionnaire and medical records without repeated eye exams during the follow-up. We acknowledge the under-ascertainment of glaucoma; however, methodologically, bias in estimating a relative risk can be minimized if the outcome is highly specific and the disease is ascertained independent of exposure information [52]. Second, as with all observational studies, we cannot eliminate the possibility of unmeasured or residual confounding. Nonetheless, we were able to adjust for a multitude of covariates. In addition, because the majority of our participants were Caucasians in health-related professions, our data may lack generalizability to those with different underlying POAG risks. We may have lacked power for the subtype analyses; thus, our results need confirmation in larger studies. We did not evaluate optic nerve structure (even though POAG is an optic nerve disease); nonetheless, it was not practical to incorporate a glaucoma definition that included optic nerve structural features in our study as it relied on medical record review. However, we did use a definition related to optic nerve function categorized by reproducible VF loss on reliable tests that could not be explained by disease other than POAG. Also, we have no data on refractive error in our cohorts, thus this might have led to residual confounding as high myopia is a risk factor for POAG [53]. Finally, we did not measure serum ketogenesis, although people who follow low-carbohydrate dietary patterns over several decades likely had higher average levels of ketone bodies [54–56].

In conclusion, low-carbohydrate diets were not associated with risk of POAG overall. There were suggestions that higher consumption of fat and protein from vegetable sources substituting for carbohydrates was modestly associated with lower risk of the POAG subtype with initial paracentral VF loss.

Summary

What was known before

- Evidence suggests that restricted carbohydrate intake may have neuroprotective effects, as established in studies of epilepsy and other neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.
- Little is known about the role of low-carbohydrate-diets (which aim to lower intake of carbohydrates and increase protein and fat intake) on the risk of POAG.

What this study adds

- Among 185,638 participants followed for 25+ years, we observed no association between adherence to an overall low-carbohydrate-diet and POAG risk. However, we observed a suggestive association with a vegetable-rich, low-carbohydrate diet and ~20% lower risk of POAG subtype with early paracentral visual loss.
- Although no association was observed with an overall low-carbohydrate diet, for early paracentral POAG, a diet low in carbohydrates and high in fat and protein from vegetable sources was associated with a suggestive lower risk, indicating that further studies are warranted.

Compliance with ethical standards

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