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Prospective study of oral health and risk of primary open-angle glaucoma in men: data from the Health Professionals Follow-up Study

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Abstract

Purpose—Tooth loss or periodontal disease is associated with systemic endothelial dysfunction, which has been implicated in primary open-angle glaucoma (POAG). The relationship between oral health and POAG has received limited attention. Thus, we evaluated the association between oral health history and risk of POAG and POAG subtypes.

Design—Prospective cohort study

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CONFLICT OF INTEREST

No conflicting relationship exists for any author

Participants—Health Professionals Follow-up Study participants (40,536 men) followed biennially from 1986 to 2012. At each 2-year risk period, eligible participants were 40+ years old, free of POAG, and reported eye examinations.

Methods—Using validated questions, we updated participants' status on number of natural teeth, teeth lost, periodontal disease with bone loss and root canal treatments.

Main Outcome Measures—During follow-up, 485 incident cases of POAG were confirmed with medical records and classified into subtypes defined by intraocular pressure (IOP) (≥ or < 22 mm Hg) or by visual field (VF) loss pattern at diagnosis (peripheral loss only or early paracentral loss). Multivariable relative risks (MVRR) and 95% confidence intervals (CIs) were estimated.

Results—Number of natural teeth, periodontal disease or root canal treatment were not associated with POAG. However, compared to no report of tooth loss, a report of losing teeth within the past 2 years was associated with a 1.45 fold increased risk of POAG (95% CI=1.06, 1.97); in particular, a report within the past 2 years of both losing teeth and having a prevalent diagnosis of periodontal disease was associated with 1.85 fold increased risk of POAG (95% CI=1.07, 3.18). The associations with recent tooth loss was not significantly different for the POAG subtypes (p for heterogeneity ≥ 0.36), although associations were strongest in relation to the POAG subtypes with IOP < 22 mm Hg (MVRR = 1.93, 95% CI=1.09, 3.43) and with early paracentral VF loss (MVRR = 2.27, 95% CI=1.32, 3.88).

Conclusion—While the number of natural teeth was not associated with risk of POAG, recent tooth loss was associated with an increased risk of POAG. Because these findings may be due to chance, they need confirmation in larger studies.

Oral infections, leading to tooth loss or periodontal disease, have been related to a multitude of systemic diseases, such as diabetes, cardiovascular disease, rheumatoid arthritis, certain cancers and neurodegenerative diseases.[1–6] There are several mechanisms underlying the association with systemic illnesses, as have been previously reviewed and summarized.[1, 2] Periodontitis, a common bacteria-induced oral inflammatory condition that destabilizes the tooth structural support apparatus, can produce transient bacteremia, which may lead to systemic endothelial dysfunction and chronic inflammatory responses in various extra-oral tissues.[7–9] Second, inflammatory markers generated from the affected periodontal tissue can also travel via the bloodstream to reach other tissue beds. For example, in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, there is growing evidence that peripheral inflammation exacerbates the development of neuronal cell loss.[3, 4] The third mechanism is the immune response to the bacteria, which involves the generation of antibodies to bacteria and their toxins, which may have off-target effects in extra-oral tissues (e.g., cross-reactive antibodies that contribute to atherosclerosis).[10]

Primary open-angle glaucoma (POAG) is a leading cause of blindness worldwide and is a chronic disease characterized by neurodegeneration of retinal ganglion cells and their axons. In a clinic-based case-control study among African-Americans,[11] compared to 45 controls, 58 glaucoma cases showed significantly higher oral bacterial loads and significantly fewer teeth, especially in older persons.[12] The same research group[11] found that when glaucoma animal models were administered low-dose bacterial toxins, glaucomatous neurodegeneration ensued and was accompanied by microglial activation, upregulation of

the complement system and toll-like receptor 4 signaling activity in the optic nerve. These results suggest that oral infections, particularly those that can lead to periodontal disease, may have systemic effects that can contribute to POAG.

We hypothesized that the vascular bed in the base of the tooth may be a conduit for inflammatory cytokines and microbes to access the systemic circulation and consequently the intricate optic nerve head microcirculatory system, leading to endothelial cell dysfunction that would compromise retinal ganglion cell axons. Periodontal disease is associated with impaired flow-mediated vasodilation, and treatment of periodontal disease has been shown to improve flow-mediated vasodilation.[7–9] Importantly, POAG has also been associated with impaired flow-mediated vasodilation, and several studies have reported on genetic and environmental exposures related to endothelial cell function related to early paracentral visual field loss subtype of POAG.[13–16]

To further test the possible link between oral infections and POAG at the population level, we prospectively evaluated self-reported comprehensive analysis of oral health and risk of POAG and POAG subtypes using data from 40,536 men in the Health Professionals Follow-up Study participants followed for 25+ years.

METHODS

Study population

The Health Professionals Follow-up Study (HPFS)[17] is an ongoing cohort study initiated in 1986 when 51,529 U.S. male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians or podiatrists), aged 40–75 years responded to a mailed health questionnaire. In the HPFS, participants are followed every two years with questionnaires that ask about newly diagnosed diseases such as periodontitis and glaucoma as well as other health and lifestyle factors. The follow-up rate for the HPFS cohort is greater than 85%. This work was HIPAA-compliant, and the described research adhered to the tenets of the Declaration of Helsinki. The Human Research Committees of Massachusetts Eye and Ear Infirmary and the Harvard School of Public Health ceded the oversight for this work to the Brigham & Women's Hospital (BWH) Institutional Review Board (IRB), which approved the study. The BWH IRB regarded participants' return of completed questionnaires as implied informed consent.

Ascertainment of primary open-angle glaucoma (POAG) cases and subtype classification

We included 485 confirmed incident cases of primary open-angle glaucoma. Glaucoma case ascertainment occurred every two years; in questionnaires, participants were asked about eye exams and physician-diagnoses of glaucoma. For participants who reported a diagnosis of glaucoma, we sought permission to contact their eye care providers. Eye care providers were asked to send all visual field (VF) tests as well as medical records that established the diagnosis or a completed glaucoma questionnaire that asked about maximal intraocular pressure (IOP), status of the filtration apparatus, optic nerve structural information, ophthalmic surgery, and VF loss. Finally, records were reviewed by a glaucoma specialist

(LRP), masked to participants' oral health history, to confirm POAG cases using standardized criteria.

For the majority of POAG cases (>70% of cases), the following criteria were met: (1) gonioscopy showed that the filtration angle was not occludable in either eye, (2) slit lamp biomicroscopy showed no evidence in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis, and (3) at least 2 reliable tests demonstrated reproducible VF defects consistent with POAG. For the remaining POAG cases, the slit lamp exam and VF criteria were met, but documentation of pupil dilation without subsequent adverse events or of the angle appearing open based on slit lamp biomicroscopy was considered as evidence for non-occludable angles. For VF defects, we did not require a specific type of perimetry; however, full static threshold testing was documented in 95% and kinetic VFs in <1%. For static threshold or suprathreshold tests, we used the following reliability definitions: fixation loss ≤ 33%, false positive rate ≤ 20% and false negative rate ≤ 20%. For kinetic VFs, a VF test was considered reliable unless the examiner noted test circumstances to the contrary.

New glaucoma diagnoses were self-reported by 4,239 HPFS participants. These were confirmed as various types of glaucoma or glaucoma suspect in 52%: potential POAG with VF loss (25%), only elevated IOP or optic disc cupping (15%), and other types of glaucoma/glaucoma suspect (12%). The remaining (48%) were unconfirmed, as participants (16%), or eye care providers (6%) were unreachable, participants denied permission for record review (9%), participants indicated the report was erroneous (15%) or eye care providers refuted the glaucoma diagnosis (2%). Among those classified as potential POAG with VF loss, we included only the POAG cases that met our case definition (485 cases); other confirmed and unconfirmed self-reports were censored in the analyses as of the diagnosis date.

For secondary analyses, we classified cases into subtypes by IOP and by VF loss pattern at diagnosis. We defined subtypes of “high-tension” (n=341) and “normal-tension” POAG (n=144) as those with maximum untreated IOP > or ≤ 21 mm Hg, respectively. We defined subtypes by VF loss pattern: those with peripheral VF loss only (n=260) or early paracentral VF loss (n=147) or undetermined VF loss (n=78) with a method previously described.[18] For POAG with peripheral VF loss only, any combination of nasal step, temporal wedge or Bjerrum area defects were present without any paracentral loss. For POAG 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 zone in the same hemifield, but without any temporal wedge loss. We included the latter paracentral group because cases with only paracentral loss were uncommon (~21%) and cases with clear paracentral loss frequently also showed peripheral loss. Cases (n=78) with undetermined VF loss (i.e., VF loss in the paracentral and any temporal wedge region in the same eye or paracentral in one hemifield with peripheral loss only in the other hemifield) were censored in the analyses as of the diagnosis date.

Ascertainment of oral health

For determining the number of teeth and number of teeth lost, in 1986, we asked about the number of natural teeth, and in the follow-up questionnaires, we asked about any tooth loss during the previous 2 years. In a validation study of a general population sample, self-

reported number of teeth was highly correlated with the actual number of teeth on clinical assessment (r=0.97).[19]

To ascertain periodontal disease history, in 1986, we asked about any periodontal disease with bone loss, and every two years, we asked about any new diagnoses of periodontal disease with bone loss. In the HPFS, we validated this question among dentist participants[20] and other study participants[21] by obtaining radiographs from individuals with and without a self-reported history of periodontal disease. Radiographs were evaluated for bone loss in 32 sites of all posterior teeth present except for the third molars by dentists who were masked to participants' self-report. Bone loss assessed from the radiographs was used as the standard measure of cumulative periodontal disease. We observed overall high validity of positive responses: in dentist participants (n=140), the positive predictive value was 0.76 and the negative predictive value was 0.74;[20] in non-dentist participants (n=212), the positive predictive value was 0.80 and the negative predictive value was 0.68.[21]

Analysis study population

We excluded at baseline (=1986) the following HPFS participants, respectively: 1) 1,596 who did not respond to baseline SFFQs or had outlying total caloric intakes as one of the original aims was to study diet and glaucoma (fewer than 70 out of 131 items blank in the SFFQ, with a total caloric intake <800 or >4200 kcal/day), 2) 1,927 with prevalent cancers excluding nonmelanoma skin cancer, as cancer diagnoses could alter many health behaviors, 3) 1,036 with prevalent glaucoma, 4) 956 lost to follow-up <2 years of baseline, 5) 3,273 who never reported an eye exam during follow-up and 6) 18 who were missing information on oral health history at baseline. After these exclusions, 42,723 were eligible; however, at the beginning of each 2-year risk period, we applied additional provisional exclusions for age and eye exam status. For example, for the 1986–'88 risk period, 29,673 contributed person-time after we provisionally excluded participants (n=13,050) who were age<40 years or reported no eye exam. In later periods, those provisionally excluded were allowed in analyses if they met eligibility criteria during follow-up. Thus, over the study period, 40,536 ever contributed person-time.

Statistical Analysis

Our main exposures of interest were number of teeth, diagnosis of periodontal disease, number of teeth lost (from 1988, when first asked, to 2012) and number of teeth with root canal treatment (from 1996, when first asked, to 2012), which were updated during follow-up with repeated questionnaire information. To reduce misclassification of updated number of teeth, if a participant did not return a questionnaire, then we imputed the value using the updated number of teeth as of the immediately prior questionnaire; if a response was missing for two questionnaire cycles in a row, then the participant was censored at that point in the analyses of number of teeth and number of teeth lost.

Our main outcome of interest was all POAG. We calculated incidence rates of POAG by dividing the incident cases by person-years accrued for each category. For age-adjusted analyses, we conducted Cox proportional hazards analysis stratified by updated age in months and the specific 2-year period at risk,[22] derived the multivariable relative risks

(MVRRs) and 95% confidence intervals (CIs). For multivariable analyses, we ran similar Cox models simultaneously controlling for potential glaucoma risk factors that were time-varying. We conducted tests for trend by evaluating the significance of a variable representing category midpoint values. Similar approaches were taken to evaluate POAG subtypes.

Potential covariates were updated biennially using all information from baseline: glaucoma family history, African ancestry, Asian ancestry, body mass index (BMI; 22–23, 24–25, 26–27, 28–29, 30+ kg/m^2), pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), hypertension, diabetes, physical activity (quartiles of MET [metabolic equivalent]-hours/week), alcohol consumption (g/day) and caffeine intake (mg/day), updated number of eye exams reported during follow-up, self-reported history of cataract diagnosis or extraction, age-related macular degeneration, hypertension, diabetes, and recent report of physical examination (for health maintenance, for medical concerns or no report of a physical exam).

Secondary analyses

We performed several secondary analyses. We separately analyzed the risks of POAG defined by: 1) highest known IOP (high-tension (HTG) and normal-tension POAG (NTG)), and 2) pattern of VF loss (POAG with peripheral VF loss only (Peri-POAG) and early paracentral loss (Para-POAG)). For testing whether the associations with one POAG subtype are different from those with another subtype, we used the Lunn-McNeil approach[23] to derive the p for heterogeneity. Also, we conducted sensitivity analyses, where, for each oral health history variable, we additionally adjusted for other oral health history related variables as appropriate: updated number of teeth (continuous), periodontal disease history (none, diagnosis in past >2 years prior, diagnosis within 2 years), and updated number of teeth lost (0, 1, 2+). To evaluate detection bias, i.e., whether better screening practices leads to both greater dental care and diagnoses of periodontal disease as well as diagnoses of glaucoma, we repeated analyses among those who were 65 years or older (who tend to get more frequent health care overall). We also repeated analyses with a 4-year lag (e.g., 1990 oral health history in relation to risk of POAG in 1994 – 1996 rather than 1994 oral health history), as it is possible that there are delays in POAG diagnosis due to its insidious nature. Furthermore, to test whether dental issues may be just a marker of poor health status that may be related to POAG (e.g., diabetes), we conducted analyses on a subset of participants after excluding those with diabetes, those who were obese, those who smoked ≥ 30 pack-years, those who had reported no physician exams and those who reported having had a physician exam for medical concerns. As dentist participants may best report their oral health history, we also conducted sensitivity analyses restricted to dentist participants to evaluate the robustness of findings. Finally, as oral health history differed by race, we conducted an additional analysis restricted to Caucasians to evaluate whether any associations with oral health history may be due to race differences.

RESULTS

During 528,089 person-years of follow-up accrued over 26 years, we identified 485 incident POAG cases. Those with fewer teeth or who reported lost teeth in the most recent

questionnaire (i.e., in the recent past 2 years) were older and had greater history of periodontal disease (Table 1). They were also more likely to be of African or Asian ancestry, to have a family history of glaucoma, to have a history of diabetes and heavy smoking and to consume more caffeine. They also exercised less and had higher BMI. These differences were adjusted for in multivariable analyses.

Compared to age-adjusted analyses, the multivariable analyses for number of teeth and POAG showed similar associations. We included 408 cases, after excluding those with missing data on number of teeth. Overall, we observed no linear associations with the number of teeth and all POAG or for other POAG subtypes (p for trend≥0.11 across outcomes; Table 2).

Compared with no report of periodontal disease during follow-up, a report of a diagnosis of periodontal disease in the past 2 years was not associated with POAG risk. Interestingly, reported diagnosis of periodontal disease during follow-up but not in the past 2 years was inversely associated with overall POAG: 0.79 (95% CI, 0.63, 0.98; p=0.03) (Table 3). Recent or past history of periodontal disease was not significantly associated with any of the other subtypes of POAG.

We conducted analyses from 1988 among those with at least 1 or more teeth (n=361 POAG cases) to evaluate tooth loss and POAG risk. Compared with those not reporting any teeth lost during follow-up, the MVRR was 1.45 (95% CI, 1.06, 1.97; p=0.02) for reporting 1+ teeth lost within the past 2 years and 1.07 (95% CI, 0.78, 1.46; p=0.69) for reporting 1+ teeth lost sometime during follow-up but not within the past 2 years (Table 4). Furthermore, with a report in the past 2 years of both 1+ teeth being lost and having prevalent periodontal disease with bone loss, the adverse association was stronger (MVRR =1.85; 95% CI, 1.07, 3.18; p=0.03) than with one or more teeth being lost without periodontal disease (MVRR =1.33; 95% CI, 0.94, 1.89; p=0.11). Tooth loss in the past 2 years was also significantly associated with NTG (MVRR= 1.93; 95% CI, 1.09, 3.43; p=0.02) and Para-POAG (MVRR= 2.27; 95% CI, 1.32, 3.88; p=0.003) (Table 4). However, the p for heterogeneity between HTG and NTG (p=0.46) or between Peri-POAG and Para-POAG (p=0.36) were not significant.

In an analysis from 1996 (n= 277 POAG cases), the number of teeth with root canal treatment was not associated with any of the outcomes (Table 5). The p for trend for increasing number of teeth with such treatment was 0.82 for all POAG, and it was ≥ 0.16 for all other subtypes.

In sensitivity analyses of tooth loss in the past 2 years and incident POAG, stronger associations were observed when in multivariable analyses, we further adjusted for current number of teeth and periodontal bone loss status: MVRR= 1.54 (95% CI, 1.11, 2.13; p=0.01) (not shown in tables). When we evaluated age subgroups, we observed that associations tended to be stronger in those <65 years (117 POAG cases; MVRR= 2.13, 95% CI, 1.21, 3.76; p=0.01) versus those who were 65 years and older (247 POAG cases; MVRR=1.25, 95% CI, 0.87, 1.80; p=0.23), with a borderline significant interaction (p for interaction by age = 0.06). Associations for tooth loss and incident POAG were attenuated

when we introduced a 4-year lag period (309 POAG cases; MVRR=1.16, 95% CI, 0.80, 1.68; p=0.44). However, associations were only slightly attenuated when we restricted analyses to Caucasians (349 POAG cases; MVRR= 1.40, 95% CI, 1.02, 1.93; p=0.04) or to dentist participants (210 POAG cases; MVRR=1.45, 0.93, 2.24; p=0.10), and associations seemed stronger in those who were relatively healthy, defined as those who all reported physical exams for health maintenance only (versus for medical concerns), who did not report any diabetes mellitus or obesity, and who reported less than a 30 pack-year history of smoking (157 POAG cases; MVRR= 2.13, 95% CI, 1.33, 3.39; p=0.002).

DISCUSSION

Primary open-angle glaucoma is a neurodegenerative disease that can lead to blindness and for which there are few established risk factors. In this large long-term prospective study among male health professionals, we observed no associations with number of natural teeth, history of periodontitis or number of teeth with root canal treatment. However, we observed that loss of at least one tooth reported in the recent past 2 years was associated with a modestly increased risk of POAG, and in particular, tooth loss accompanied by prevalent periodontal disease with bone loss in the recent past 2 years showed the strongest associations, although the confidence intervals for both estimates of associations were wide. Given that in adults 40+ years old, the most common cause of tooth loss is periodontal disease,[24, 25] this suggests that oral infections that lead to periodontal disease with bone loss severe enough to lead to tooth loss, may be associated with transient increases in risk of POAG. Because this was the first study to link recent tooth loss with POAG, and some of the significant results may be due to chance, these findings should be interpreted with caution and confirmed with other studies.

To date, there has been scarce data linking glaucoma to the oral microbiome.[11, 26, 27] One clinic-based case-control study of 103 African-American subjects[11] observed that those with oral bacteria loads in the upper quartile were over three times more likely to have glaucoma and that glaucoma cases had significantly fewer teeth, especially in older persons.[12] In addition, they observed that in two glaucoma animal models[11] administration of low dose subcutaneous lipopolysaccharide to simulate the condition of chronic subclinical bacterial infection, exacerbated glaucomatous neurodegeneration. The possible mechanisms may be related to upregulation of complement system and toll-like receptor 4 signaling activity along with microglial activation in the optic nerve,[11] which occur early in the glaucomatous process.[28]

In addition to a possible immune-related response in the optic nerve from oral infections, other mechanisms may be operative, especially IOP-independent mechanisms, as we did not observe associations for oral health history and HTG. Another IOP-independent mechanism that may explain the link between oral health and glaucoma may be systemic endothelial cell dysfunction. Periodontitis, the most common oral infection, induces a subclinical systemic inflammatory response leading to endothelial cell dysfunction, and such dysfunction can be reversed over several months with periodontal disease treatment.[7–9] Endothelial dysfunction can lead to impaired flow-mediated vasodilation that affects blood flow to the optic nerve, which has been associated with POAG across the spectrum of IOP.[29, 30] Our observation of

somewhat stronger associations between recent tooth loss and POAG with early paracentral loss, a form of glaucoma linked to vascular endothelial dysfunction,[31, 32] further supports this mechanism. The attenuated association with past tooth loss that occurred >2 years versus that reported in the past 2 years may reflect the possibility that occurrences of tooth loss or periodontitis that occurred > 2 years in the past would likely have been resolved or treated and that such treatment may have led to improvement in endothelial function and long-term better maintenance of good oral health,[8, 9] unlike a recent bout of tooth loss that is accompanied by periodontitis. However, because this result may be due to chance, and our interpretation may be speculative, the modest associations observed need confirmation in studies with greater number of exposed cases.

We observed no associations between number of teeth with root canal treatment and POAG. Root canal treatment generally reflects prior endodontic inflammation, stemming from dental caries, and occasionally, root canal therapies are used to salvage teeth due to a variety of other reasons. The pathophysiology and microbes related to endodontic inflammation are different from periodontal disease; in particular, the dysbiosis associated with periodontitis evokes a strong and direct immune response, whereas the dysbiosis associated with caries promotes demineralization through acidogenic and aciduric mechanisms.[33] Furthermore, endodontic inflammation is less common than periodontal disease, and there is much less evidence for the systemic impact of endodontic inflammation.[34, 35]

Our study had a few limitations. Because we were not able to conduct repeated eye exams on our participants over a 26-year period, we relied on participants' self-report of glaucoma confirmed with medical records. While such a case-ascertainment method would lead to underascertainment of glaucoma, methodologically, bias in the estimation of a relative risk is minimal if the outcome is highly specific (such as our definition of POAG that required reproducible VF loss on reliable VFs), and the ascertainment of disease is unlikely to be related to oral health.[36] To help ensure that ascertainment of glaucoma itself would not be different by oral health status, we included only those who reported eye exams in analyses, adjusted for the following factors: the number of eye exams reported during follow-up; other eye diseases, and whether participants had physician exams for either symptoms or health maintenance. We also censored participants who did not respond to oral health questions on two consecutive questionnaires. Furthermore, to evaluate the possibility of reverse causality, we conducted analyses of whether having POAG itself may later lead to greater tooth loss. We identified 8310 events of incident tooth loss from 1988 to 2012; the multivariable RR for incident tooth loss in relation to prevalent POAG versus no POAG was 0.84 (95% CI= 0.48, 1.46), indicating little support for reverse causation or co-occurrence of frequent eye exams and frequent dental exams explaining the association. Oral health measures were self-reported in our study; however, the self-reports were validated to be accurate when compared against dental radiographic findings in a subset of our participants,[19–21] and similar, although non-significant, associations with recent teeth lost were observed among dentists in our cohort. Given that our participants were all males and predominantly Caucasian, the magnitude of associations observed may not be generalizable to the general population. In our restricted analyses that included only Caucasians, the association with recent tooth loss was slightly attenuated, indicating there might be some differences by race. However, our results are consistent with the findings from studies of Astafurov et al.[11] and

Polla et al.[12] conducted among African-Americans that implicated a role for oral health in POAG. More studies in women and other racial/ethnic groups may help to further shed light on this link, as prevalence of periodontal disease and dental problems differ by gender and race.[37, 38]

Our study has a number of strengths. The prospective design allowed us to examine the relation between oral health and incident POAG and allowed us to minimize recall bias or bias that may arise with including prevalent glaucoma cases if glaucoma treatment could modify the association between oral health and POAG. The number of teeth and periodontal disease status was assessed every 2 years over 25+ years. The results point to periodontal disease, as opposed to tooth loss related to dental caries or other causes, as the key dental exposure linked to POAG (Table 4). The association observed with number of teeth lost is unlikely to be due to tooth loss being a mere marker of overall poor health that may also be linked to glaucoma. After excluding those with diabetes, those who were obese, those who smoked ≥ 30 pack-years, those who had reported no physician exams or reported having had a physician exam due to medical concerns versus only for health maintenance, the association between number of teeth lost and POAG was robust, further supporting an etiologic link between dental pathology and POAG.

In conclusion, while the number of natural teeth and any periodontal disease was not associated with risk of POAG, we observed an adverse association between recent tooth loss, combined with recent periodontal disease, and risk of POAG. The results of this study raise important questions that could be addressed in future studies: how dental pathology, particularly severe periodontitis, may affect glaucoma pathology and whether prompt attention to periodontal disease might alter the development of glaucoma. Because this is the first study to link recent tooth loss with POAG, and some of the significant results may be due to chance, these findings should be interpreted with caution and confirmed with other studies.

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Table 1

Age and age-adjusted updated characteristics of total person-time of follow-up (528,089 person-years of follow-up), accrued from 1986 to 2012 among eligible participants 40 years and older*

	Number of teeth			Teeth lost in recent 2 years	
	17+	1–16	0	0	1+
Person-time, %	92.5	6.4	1.1	90.0	10.0
Age	61.4 ± 10.6	69.7 ± 9.3	69.1 ± 8.9	62.7 ± 10.3	67.8 ± 9.9
African-American, %	0.5	1.0	0.3	0.5	0.4
Asian-American, %	1.4	1.9	0.4	1.3	1.7
Family history of glaucoma, %	11.7	12.1	14.9	11.8	11.9
Cataract diagnosis or extraction, %	13.9	15.2	12.8	15.3	16.1
Age-related macular degeneration diagnosis, %	3.1	3.5	2.9	3.5	3.9
Diabetes, %	5.7	8.4	9.7	6.1	8.2
Hypertension, %	34.4	37.1	35.1	36.2	38.4
Number of eye exams reported†	7.0 ± 3.1	6.2 ± 3.1	5.1 ± 3.1	6.5 ± 3.2	6.3 ± 3.2
Alcohol intake (grams per day)	11.1 ± 13.7	11.1 ± 14.9	10.5 ± 13.9	11.1 ± 13.5	11.1 ± 13.9
Caffeine intake (milligrams per day)	224.6 ± 212.9	276.8 ± 236.1	293.4 ± 262.4	222.6 ± 205.7	254.1 ± 223.6
Body mass index (kg/m^2)	25.5 ± 3.1	26.1 ± 3.3	25.9 ± 3.3	25.5 ± 3.1	26.1 ± 3.3
≥30 years of pack-years of smoking, %	15.3	34.3	36.2	15.4	25.1
Highest quartile of physical activity, %	28.3	23.2	24.3	28.9	25.3
Updated number of natural teeth	24.0 ± 2.3	10.6 ± 5.0	0.0 ± 0.0	23.5 ± 3.8	20.4 ± 5.0
Periodontal disease diagnosed in past 2 years, %	9.6	23.8	16.0	8.3	22.1
Number of teeth lost in past 2 years‡	0.1 ± 0.4	1.0 ± 2.2	0.2 ± 1.4	0.0 ± 0.0	1.6 ± 1.6
Cumulative number of teeth with root canals‖	1.6 ± 2.0	3.2 ± 2.4	1.4 ± 1.9	1.6 ± 2.0	2.7 ± 2.4

*Values are means ± SD or percentages for the entire total accumulated person-time of follow-up and are standardized to the age distribution of the total person-time, unless otherwise noted. Characteristics of person-time were updated every two years and accumulated over follow-up.

†As of the last follow-up period: number reported out of a maximum of 11 total exams over follow-up

‡Among person-time accrued from 1988 (when number of teeth lost was first asked) to 2012

‖Among person-time accrued from 1996 (when number of teeth with root canal treatment was first asked) to 2012

Table 2

Multivariable-adjusted* relative risks (95% confidence intervals) for updated number of natural teeth in relation to risk of primary open-angle glaucoma (1986 – 2012)

	Updated number of natural teeth					
	25+	**17–24**	**11–16**	**1–10**	**0**	**P trend**
Primary analyses						
All cases (n=408 cases)	243	118	24	14	9	
Person-years	309,405	98,302	18,733	9,588	4,807	
ALL: Age-adjusted	1.00 (ref)	1.19 (0.95, 1.50)	1.01 (0.65, 1.57)	1.21 (0.68, 2.17)	1.47 (0.73, 2.95)	0.17
ALL: Multivariable-adjusted*	1.00 (ref)	1.21 (0.96, 1.53)	1.00 (0.64, 1.56)	1.19 (0.66, 2.14)	1.28 (0.63, 2.61)	0.26
Secondary analyses by IOP at diagnosis						
Cases of HTG† (n=292 cases)	177	79	18	11	7	
HTG†: Age-adjusted	1.00 (ref)	1.08 (0.82, 1.42)	0.98 (0.59, 1.64)	1.19 (0.61, 2.32)	1.35 (0.61, 2.96)	0.44
HTG†: Multivariable-adjusted*	1.00 (ref)	1.10 (0.83, 1.46)	0.98 (0.58, 1.65)	1.20 (0.61, 2.36)	1.19 (0.53, 2.68)	0.51
Cases of NTG† (n=116 cases)	66	39	6	3	2	
NTG†: Age-adjusted	1.00 (ref)	1.52 (1.00, 2.30)	1.09 (0.46, 2.61)	1.26 (0.38, 4.14)	1.99 (0.44, 9.02)	0.16
NTG†: Multivariable-adjusted*	1.00 (ref)	1.59 (1.03, 2.45)	1.04 (0.42, 2.56)	1.35 (0.40, 4.57)	2.01 (0.41, 9.86)	0.14
Secondary analyses by type of visual field loss						
Cases of Peri-POAG‡ (n=221 cases)	126	65	18	8	4	
Peri-POAG‡: Age-adjusted	1.00 (ref)	1.26 (0.92, 1.73)	1.38 (0.81, 2.35)	1.17 (0.52, 2.62)	1.10 (0.39, 3.11)	0.22
Peri-POAG‡: Multivariable-adjusted*	1.00 (ref)	1.22 (0.89, 1.68)	1.25 (0.73, 2.16)	1.12 (0.50, 2.53)	0.95 (0.33, 2.73)	0.43
Cases of Para-POAG‡ (n=120 cases)	70	39	4	3	4	
Para-POAG‡: Age-adjusted	1.00 (ref)	1.46 (0.96, 2.22)	0.72 (0.26, 2.00)	1.07 (0.33, 3.47)	2.86 (1.00, 8.20)	0.16
Para-POAG‡: Multivariable-adjusted*	1.00 (ref)	1.56 (1.01, 2.41)	0.74 (0.26, 2.11)	1.21 (0.36, 4.04)	2.88 (0.96, 8.60)	0.11

*All multivariable analyses were stratified by age in months and period at risk, and they were adjusted for the following variables: ancestry (African-American, Asian-American, all others), family history of glaucoma, self-reported history of cataract diagnosis or extraction, age-related macular degeneration, hypertension, diabetes, body mass index (22–23, 24–25, 26–27, 28–29, 30+ kg/m^2), cumulatively averaged intakes of alcohol (g/day) and caffeine (mg/day), dietary nitrate intake (mg/day), pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), physical activity (quartiles of MET-hours [metabolic equivalents] / week), recent report of physician exam (for health maintenance / for medical concerns / no report of physical exam), updated number of eye exams reported during follow-up

†HTG=High tension primary-open angle glaucoma, based on the maximum untreated intraocular pressure (IOP) at diagnosis (IOP > 21 mm Hg); NTG=Normal tension glaucoma (IOP ≤ 21 mm Hg)

‡Peri-POAG=Primary open-angle glaucoma with peripheral visual field (VF) loss, based on VF loss pattern as of the earliest reliable VF at diagnosis that was reproduced at the latest reliable VF. Cases with advanced VF loss at diagnosis (n=67) 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.

Table 3

Multivanable-adjusted* relative risks (95% confidence intervals) for incident periodontal disease in relation to risk of primary open-angle glaucoma (1986 – 2012)

	Periodontal disease status		
	Never diagnosed	**Diagnosed in distant past (>2 years)**	**Diagnosed in past 2 years**
Primary analyses			
All cases (n=485 cases)	259	158	68
Person-years	298,154	174,720	55,215
ALL: Age-adjusted	1.00 (ref)	0.80 (0.64, 0.99)	1.13 (0.85, 1.51)
ALL: Multivariable-adjusted*	1.00 (ref)	0.79 (0.63, 0.98)	1.15 (0.86, 1.55)
Secondary analyses by IOP at diagnosis			
Cases of HTG† (n=341 cases)	189	107	45
HTG†: Age-adjusted*	1.00 (ref)	0.83 (0.64, 1.07)	1.04 (0.74, 1.48)
HTG†: Multivariable-adjusted*	1.00 (ref)	0.82 (0.63, 1.07)	1.05 (0.73, 1.49)
Cases of NTG† (n=144 cases)	70	51	23
NTG†: Age-adjusted*	1.00 (ref)	0.75 (0.51, 1.11)	1.36 (0.81, 2.29)
NTG†: Multivariable-adjusted*	1.00 (ref)	0.70 (0.46, 1.06)	1.45 (0.85, 2.49)
Secondary analyses by type of visual field loss			
Cases of Peri-POAG‡ (n=260 cases)	139	86	35
Peri-POAG‡: Age-adjusted*	1.00 (ref)	0.89 (0.66, 1.19)	0.97 (0.65, 1.44)
Peri-POAG‡: Multivariable-adjusted*	1.00 (ref)	0.82 (0.61, 1.11)	0.90 (0.60, 1.36)
Cases of Para-POAG‡ (n=147 cases)	82	42	23
Para-POAG‡: Age-adjusted*	1.00 (ref)	0.63 (0.42, 0.94)	1.51 (0.91, 2.49)
Para-POAG‡: Multivariable-adjusted*	1.00 (ref)	0.66 (0.43, 1.00)	1.61 (0.95, 2.72)

*All multivariable analyses were stratified by age in months and period at risk, and they were adjusted for the following variables: ancestry (African-American, Asian-American, all others), family history of glaucoma, self-reported history of cataract diagnosis or extraction, age-related macular degeneration, hypertension, diabetes, body mass index (22–23, 24–25, 26–27, 28–29, 30+ kg/m^2), cumulatively averaged intakes of alcohol (g/day) and caffeine (mg/day), dietary nitrate intake (mg/day), pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), physical activity (quartiles of MET-hours [metabolic equivalents] / week), recent report of physician exam (for health maintenance / for medical concerns / no report of physical exam), updated number of eye exams reported during follow-up

†HTG=High tension primary-open angle glaucoma, based on the maximum untreated intraocular pressure (IOP) at diagnosis (IOP > 21 mm Hg); NTG=Normal tension glaucoma (IOP ≤ 21 mm Hg)

‡Peri-POAG=Primary open-angle glaucoma with peripheral visual field (VF) loss; Para-POAG=Primary open-angle glaucoma with paracentral VF loss. This classification is based on VF loss pattern as of the earliest reliable VF at diagnosis that was reproduced at the latest reliable VF. Cases with advanced VF loss at diagnosis (n=78) 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.

Table 4

Multivariable-adjusted* relative risks (95% confidence intervals) for number of incident teeth lost in relation to risk of primary open-angle glaucoma (1988 – 2012)

	Number of teeth lost				
	0	**1+ lost in distant past (>2 years)**	**1+ lost in past 2 years**	**1+ lost in past 2 years with no recent periodontal disease**	**1+ lost in past 2 years with recent periodontal disease**
Primary analyses					
All cases (n=364 cases)	251	57	56	40	16
Person-years	281,777	47,255	34,863	26,827	7,981
ALL: Age-adjusted	1.00 (ref)	1.08 (0.79, 1.47)	1.43 (1.06, 1.94)	1.34 (0.95, 1.90)	1.73 (1.01, 2.95)
ALL: Multivariable-adjusted*	1.00 (ref)	1.07 (0.78, 1.46)	1.45 (1.06, 1.97)	1.33 (0.94, 1.89)	1.85 (1.07, 3.18)
Secondary analyses by IOP at diagnosis					
Cases of HTG† (n=260 cases)	187	34	39	27	12
HTG†: Age-adjusted*	1.00 (ref)	0.88 (0.59, 1.30)	1.34 (0.93, 1.91)	1.23 (0.81, 1.87)	1.67 (0.91, 3.09)
HTG†: Multivariable-adjusted*	1.00 (ref)	0.85 (0.57, 1.27)	1.32 (0.91, 1.90)	1.19 (0.78, 1.82)	1.74 (0.93, 3.25)
Cases of NTG† (n=104 cases)	64	23	17	13	4
NTG†: Age-adjusted*	1.00 (ref)	1.63 (0.97, 2.71)	1.71 (0.97, 3.01)	1.65 (0.88, 3.10)	1.94 (0.66, 5.69)
NTG†: Multivariable-adjusted*	1.00 (ref)	1.65 (0.97, 2.81)	1.93 (1.09, 3.43)	1.81 (0.95, 3.44)	2.46 (0.82, 7.39)
Secondary analyses by type of visual field loss					
Cases of Peri-POAG‡ (n=197 cases)	134	35	28	19	9
Peri-POAG‡: Age-adjusted*	1.00 (ref)	1.24 (0.83, 1.86)	1.29 (0.84, 1.98)	1.16 (0.70, 1.92)	1.71 (0.83, 3.53)
Peri-POAG‡: Multivariable-adjusted*	1.00 (ref)	1.17 (0.78, 1.76)	1.21 (0.79, 1.87)	1.08 (0.65, 1.79)	1.67 (0.80, 3.48)
Cases of Para-POAG‡ (n=107 cases)	71	16	20	15	5
Para-POAG‡: Age-adjusted*	1.00 (ref)	1.13 (0.62, 2.03)	2.04 (1.21, 3.41)	1.88 (1.05, 3.35)	2.71 (1.06, 6.94)
Para-POAG‡: Multivariable-adjusted*	1.00 (ref)	1.23 (0.66, 2.27)	2.27 (1.32, 3.88)	2.02 (1.11, 3.68)	3.52 (1.31, 9.43)

*All multivariable analyses were stratified by age in months and period at risk, and they were adjusted for the following variables: ancestry (African-American, Asian-American, all others), family history of glaucoma, self-reported history of cataract diagnosis or extraction, age-related macular degeneration, hypertension, diabetes, body mass index (22–23, 24–25, 26–27, 28–29, 30+ kg/m^2), cumulatively averaged intakes of alcohol (g/day) and caffeine (mg/day), dietary nitrate intake (mg/day), pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), physical activity (quartiles of MET-hours [metabolic equivalents] / week), recent report of physician exam (for health maintenance / for medical concerns / no report of physical exam), updated number of eye exams reported during follow-up

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‡Peri-POAG=Primary open-angle glaucoma with peripheral visual field (VF) loss; Para-POAG=Primary open-angle glaucoma with paracentral VF loss. This classification is based on VF loss pattern as of the earliest reliable VF at diagnosis that was reproduced at the latest reliable VF. Cases with advanced VF loss at diagnosis (n=60) 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.

Table 5

Multivariable-adjusted * relative risks (95% confidence intervals) for number of teeth with root canal treatment in relation to risk of primary open-angle glaucoma (1996 – 2012)

	Updated number of total teeth with root canals				
	0	**1**	**2–4**	**5+**	**P for trend**
Primary analyses					
All cases (n=277 cases)	99	64	90	24	
Person-years	102,837	58,478	80,290	20,515	
ALL: Age-adjusted	1.00 (ref)	1.01 (0.73, 1.39)	1.03 (0.77, 1.38)	1.04 (0.65, 1.64)	0.94
ALL: Multivariable-adjusted *	1.00 (ref)	1.02 (0.73, 1.41)	1.03 (0.77, 1.39)	1.08 (0.68, 1.72)	0.82
Secondary analyses by IOP at diagnosis					
Cases of HTG † (n=170 cases)	58	45	52	15	
HTG †: Age-adjusted *	1.00 (ref)	1.23 (0.83, 1.84)	1.01 (0.69,1.49)	1.06 (0.59, 1.90)	0.98
HTG †: Multivariable-adjusted *	1.00 (ref)	1.27 (0.85, 1.89)	1.00 (0.68,1.48)	1.14 (0.63, 2.06)	0.85
Cases of NTG † (n=107 cases)	41	19	38	9	
NTG †: Age-adjusted *	1.00 (ref)	0.67 (0.37, 1.20)	1.05 (0.66, 1.66)	0.99 (0.47, 2.09)	0.89
NTG †: Multivariable-adjusted *	1.00 (ref)	0.67 (0.37, 1.22)	1.09 (0.68, 1.73)	0.99 (0.46, 2.12)	0.90
Secondary analyses by type of visual field loss					
Cases of Peri-POAG ‡ (n=152 cases)	60	36	46	10	
Peri-POAG ‡: Age-adjusted *	1.00 (ref)	0.94 (0.61,1.43)	0.84 (0.57, 1.25)	0.71 (0.36, 1.42)	0.21
Peri-POAG ‡: Multivariable-adjusted *	1.00 (ref)	0.90 (0.59,1.39)	0.82 (0.55, 1.23)	0.69 (0.34, 1.40)	0.19
Cases of Para-POAG ‡ (n=79 cases)	25	16	30	8	
Para-POAG ‡: Age-adjusted *	1.00 (ref)	0.92 (0.47, 1.79)	1.41 (0.81, 2.43)	1.43 (0.63, 3.24)	0.20
Para-POAG ‡: Multivariable-adjusted *	1.00 (ref)	0.91 (0.46, 1.80)	1.54 (0.88, 2.69)	1.47 (0.64, 3.40)	0.16

* All multivariable analyses were stratified by age in months and period at risk, and they were adjusted for the following variables: ancestry (African-American, Asian-American, all others), family history of glaucoma, self-reported history of cataract diagnosis or extraction, age-related macular degeneration, hypertension, diabetes, body mass index (22–23, 24–25, 26–27, 28–29, 30+ kg/m^2), cumulatively averaged intakes of alcohol (g/day) and caffeine (mg/day), dietary nitrate intake (mg/day), pack-years of smoking (1–9, 10–19, 20–29, 30+ pack-years), physical activity (quartiles of MET-hours [metabolic equivalents] / week), recent report of physician exam (for health maintenance / for medical concerns / no report of physical exam), updated number of eye exams reported during follow-up

† HTG=High tension primary-open angle glaucoma, based on the maximum untreated intraocular pressure (IOP) at diagnosis (IOP > 21 mm Hg); NTG=Normal tension glaucoma (IOP ≤ 21 mm Hg)

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