Relationship between oral health and glaucoma traits in the United Kingdom

Short title: Oral health and glaucoma

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Precis:

In this cross-sectional analysis of UK Biobank participants, we find no adverse association between self-reported oral health conditions and either glaucoma or elevated intraocular pressures.

Abstract:

Purpose

Poor oral health may cause inflammation that accelerates the progression of neurodegenerative diseases. We investigated the relationship between oral health and glaucoma.

Patients

United Kingdom (UK) Biobank participants

Methods

This is a cross-sectional analysis of participants categorized by self-reported oral health status. Multivariable linear and logistic regression models were employed. Primary analysis examined the association with glaucoma prevalence. Secondary analyses examined associations with IOP, macular retinal nerve fiber layer (mRNFL), and ganglion cell inner plexiform layer (mGCIPL) thicknesses, and interaction terms with multi-trait glaucoma polygenic risk scores (MTAG PRS) or intraocular pressure (IOP) PRS.

Results

170,815 participants (34.3%) reported current oral health problems, including painful or bleeding gums, toothache, loose teeth, and/or denture wear. 33,059, 33,004, 14,652, and 14,613 participants were available for analysis of glaucoma, IOP, mRNFL, and mGCIPL, respectively. No association between oral health and glaucoma was identified

(odds ratio (OR): 1.04, 95% confidence interval (CI): 0.95, 1.14). IOPs were slightly lower among those with oral disease (-0.08 mmHg, 95% CI: -0.15, -0.009); specifically, among those with loose teeth (p=0.03) and denture-wearers (p<0.0001). mRNFL measurements were lower among those with oral health conditions (-0.14 microns, 95% CI: -0.27, -0.0009), but mGCIPL measurements (p=0.96) were not significantly different. A PRS for IOP or glaucoma did not modify relations between oral health and IOP nor glaucoma (p-for-interactions≥0.17).

Conclusions

Self-reported oral health was not associated with elevated IOP nor increased risk of glaucoma. Future studies should confirm the null association between clinically diagnosed oral health conditions and glaucoma.

Keywords: oral health; dental health; glaucoma; intraocular pressure

I. Introduction

A growing body of research suggests that oral infections may lead to chronic inflammation of distant tissues. Poor oral health has been linked to a variety of systemic diseases, including heart disease, dementia, diabetes, chronic kidney disease, rheumatoid arthritis, and several malignancies.[1] Two possible mechanisms for these associations have been described previously. First, it is postulated that chronic periodontitis could allow oral bacteria to enter the systemic circulation, thereby enabling damage to distant organs,[1] including cardiovascular tissues. Additionally, chronic periodontitis may serve as a source of chronic inflammation, thus accelerating other disease processes,[2,3] including neurodegenerative conditions such as Alzheimer's disease.[4]

Glaucoma is a chronic neurodegenerative disease that may lead to permanent vision loss and blindness. To date, intraocular pressure (IOP) is the only known modifiable risk factor for glaucoma. Thus, all medical and surgical interventions for glaucoma aim to lower IOP. The discovery of additional modifiable risk factors for glaucoma would therefore be significant.

Several studies suggest there is a relationship between oral health and glaucoma. A prospective cohort study conducted using data from the Health Professionals Follow-up Study found that a history of tooth loss during the preceding two years was associated with a 1.5-fold increase in the risk of primary open-angle glaucoma.[5] A study based on Taiwan's National Health Insurance Research Database reported that patients with a history of periodontitis were found to have a 30% increased risk of developing glaucoma as compared to those without dental disease.[6] In line with these findings, a cross-sectional study conducted in Korea noted over a three-fold increase in odds of glaucoma among patients with a history of periodontitis.[7] Although these initial studies are somewhat consistent, conclusions on the specific types of oral diseases associated with glaucoma vary from study to study. Furthermore, it is unknown whether individuals with poor oral health have higher IOPs.

Importantly, the mechanism underlying the potential link between oral health and glaucoma is also not fully understood. Previously, two studies investigated the possibility that dental health might affect the oral microbiome, and thereby increase the risk of glaucoma. While one study found that an increased total oral bacterial load was associated with glaucoma,[8] the other suggested that the prevalence of specific bacterial strains contributed to glaucomatous disease.[9] Therefore, while changes in the oral microbiome may be associated with an increased risk of glaucoma, an alternative and/or complementary mechanism to explain a possible link between poor oral health and glaucoma is also plausible.

The goal of this study was to investigate a possible relationship between poor oral health and glaucoma by leveraging data from the UK Biobank. We hypothesized that poor oral health may be linked to an altered metabolome,[10,11] that could lead to an upregulated inflammatory response, impaired microvascular flow, and ultimately elevated IOP and/or glaucoma. Therefore, we examined the association between poor oral health and the prevalence of glaucoma in the UK Biobank. We also investigated the relationship between oral health and intraocular pressures and ocular coherence tomography measurements.

II. Methods

This study was exempt from review by the Mount Sinai Hospital Institutional Review Board due to the utilization of de-identified data. The North West Multi-Center Research Ethics Committee approved the study, according to the principles of the Declaration of Helsinki and the Icahn School of Medicine has entered into a data use agreement with the UK Biobank under UK Biobank application number 36741 for the use of the de-identified data files.

A. Design

The UK Biobank is a cohort study including 502,389 adults recruited between 2006 and 2010. Participants completed questionnaires, in-person interviews, physical measurements, and the collection of biospecimens, including blood, urine, and saliva samples. Consent was obtained to link baseline data to health records. The UK Biobank, therefore, includes data on participant demographics, self-reported and clinician-confirmed health status and diseases, biometric measurements including IOPs, as well as genomes, proteomes, and metabolomes.

B. Participants

Subjects included for analysis were between the ages of 37 and 73 years at the time of recruitment. Those participants missing data on oral health or ophthalmic measurements/glaucoma disease status were excluded from the analysis. Those participants with missing covariable data were excluded from the analysis, given small rates of missing data across the majority of covariables (0-3.5%). Data on metabolic equivalents (METS) and calorie intake were only available for ~80% and 14% of participants, respectively, but were included in analyses.

C. Oral health and other exposure variables

Oral health history was ascertained based on data from baseline health questionnaires. Subjects were presented with a touchscreen question, “Do you have any of the following? (You can select more than one answer).” The choices included the presence of mouth ulcers, painful gums, bleeding gums, loose teeth, or toothache, none of the above, or prefer not to answer. Prior studies have suggested that bleeding and/or painful gums, and tooth mobility have acceptable validity in detecting moderate to severe periodontitis; self-reported toothache has validity in identifying patients with periodontitis and pulpitis.[12–15] Because periodontal disease is the leading cause of tooth loss leading to denture wear, and self-reported denture wear has been associated with excellent validity and reliability,[16,17] this variable was also included for analysis. Therefore, for this study, the presence of painful or bleeding gums, loose teeth, toothache, or denture wear was analyzed both as a composite exposure variable for ‘poor oral health’ and as individual exposures. Participants without oral health issues

were defined by the lack of self-reported toothache, bleeding or painful gums, tooth loss, or denture wear.

Baseline demographic characteristics including age, sex, and self-reported ethnicity, were recorded. The Townsend deprivation index, a single numerical value quantifying material deprivation including unemployment, lack of car or home ownership, and household overcrowding,[18] was also documented for each subject. Additionally, data on multiple covariables including diagnosis of diabetes, alcohol use, smoking history, systolic blood pressure, body mass index, estimated caloric intake, and physical activity levels (as estimated via metabolic equivalents in hours per week, or METS), spherical equivalents, and use of systemic beta-blockers were extracted and derived from the database for analysis.

D. Outcome variables

Ophthalmic data was obtained from 122,143 participants in 2009 and 2010 at UK Biobank assessment centers. A single IOP measurement was recorded for each eye using the Reichert Ocular Response Analyzer noncontact tonometer. Corneal-compensated IOP measurements of the right and left eyes were averaged to calculate a subject-level outcome. Subjects were excluded from analysis if they reported a history of eye surgery within four weeks of the measurement, or if they reported an eye infection at the time of measurement. The lowest and highest 0.5% of measurements were discarded to minimize bias due to artefactual extreme measures. For those patients on IOP-lowering therapy, pretreatment IOPs were imputed by dividing the measured IOP by 0.7.[19–21] Patients with a history of glaucoma surgery and laser were excluded from the analysis.

Baseline health questionnaires included the query, “Has a doctor told you that you have any of the following problems with your eyes?” Study participants were categorized as having self-reported glaucoma if the response “glaucoma” was selected for this query. Patients whose health records also revealed an associated ICD-9 or ICD-10 diagnosis code of open-angle glaucoma were also categorized as having diagnosis-confirmed glaucoma (ICD-9 codes 365.0*, 365.1*, 365.7*; ICD-10 codes H40.1*).

Retinal ocular coherence tomography (OCT) measurements in the macula region were obtained in 67,321 subjects. High-resolution spectral domain OCT images of undilated nerves and retinas were performed using the Topcon 3D OCT 1000 Mk2. Quality control steps for included OCT scans have been previously described.[22,23] In brief, scans with poor signal strength, and/or those with scan quality or segmentation indices in the bottom 20% of all images were also excluded.

E. Genetic data, Glaucoma, and IOP polygenic risk scores

Genotyping data were obtained on 488,377 subjects using Affymetrix UK BiLEVE Axiom Array (49,950 participants) and the Affymetrix UK Biobank Axiom Array (438.427 participants). As described previously, quality control and imputation were performed jointly, as the two arrays shared over 95% of genetic markers.[24] In total, 92,693,895

genetic markers of 487,442 participants were made available for analysis in the UK Biobank database.

Data from genome-wide association studies (GWAS) of individuals of European descent were used to create a multi-trait glaucoma polygenic risk score (MTAG PRS) for each patient, consisting of 2,673 independent genetic loci.[25] We also created an IOP PRS consisting of 111 independent genome-wide significant loci based on results from the largest IOP GWAS to date.[20] Each PRS served as a single numeric score that summarizes the genetic risk for POAG for each subject. The methods for creating a glaucoma PRS has been described previously.[20,25] Additional analyses including glaucoma PRS as a covariable and evaluating whether a glaucoma PRS modifies the relationship between oral health and glaucoma were evaluated. In addition to treating the PRS as a continuous variable, we conducted a sensitivity analysis where we classified participants into two genetic risk groups: those with the highest 25% genetic risk scores and those in the lowest 25% genetic risk scores. The remaining 50% of participants were excluded from the sensitivity analysis. Interaction terms between categorical PRS variables and oral health were calculated, and used to determine whether extremes of genetic risk scores modified the relationship between oral health and glaucoma.

F. Statistical analysis

Baseline characteristics were compared among subjects in the poor oral health group versus the comparison group using the student's T-test and 1-proportion Z-test. To evaluate associations with poor oral health as a risk factor for glaucoma, multiple logistic regression models were used, adjusting for multiple covariables extracted from baseline health survey questionnaire data and measurements: age, sex, self-reported ethnicity, smoking history, alcohol use, physical activity, Townsend deprivation index, BMI (kilograms per square meter), systolic blood pressure, diabetes, and total calorie intake.[26] Similarly, to determine whether poor oral health is associated with IOPs or differences in macula region retinal nerve fiber layer thickness (mRNFL) or ganglion cell inner plexiform layer (mGCIPL) thickness, multiple linear regression models were conducted, adjusting for the same covariables. Finally, for each glaucoma trait, we examined whether a glaucoma or IOP PRS modified the relation between oral health and the outcomes of interest by evaluating interaction variables (oral health variable * genetic variable). The significance of the interaction term was assessed with a p-for interaction test statistic. Since total caloric intake and physical activity had a high missingness rate, a sensitivity analysis excluding these covariates was performed.

All statistical analyses were conducted using SAS 9.4 and R software.

III. Results

A. Demographics

A total of 498,713 subjects completed the oral health questionnaire. Of these, a total of 170,815 (34%) subjects reported a history of oral health conditions including

bleeding or painful gums, toothache or loss, or need for dentures. Please see **Figure 1** for details on subject inclusion details.

Subjects with a history of self-reported oral health conditions were older, more likely to be female, of non-Caucasian descent, and were more likely to experience material deprivation than those without a history of oral health conditions. Additionally, those with self-reported oral health conditions were more likely to have a history of diabetes, reported consuming less alcohol, were more likely to report smoking, and had higher BMIs than those without oral health problems. Those with oral health conditions were also more likely to have increased calorie intake and were less sedentary than those without oral health conditions (**Table 1**). We adjusted for all these covariables in multivariable analysis.

B. Association with glaucoma prevalence

A total of 33,059 subjects had data available for all covariables for analysis on the relationship between oral health and glaucoma. A total of 4,801 subjects (2.81%) with self-reported oral health conditions and 6,842 subjects (2.30%) without oral health conditions also had a history of glaucoma at the time of survey collection. A statistically significant difference in the proportion of patients with glaucoma was noted in univariate analysis ($p<0.0001$).

After controlling for covariables, oral health conditions were not associated with an increased likelihood of glaucoma (**Table 2**). The overall odds of glaucoma among subjects with oral health conditions as compared to those without in this cohort was 1.04 (95% confidence interval (CI): 0.95, 1.14; $p=0.39$). The relationship between each oral health variable and glaucoma was also analyzed. None of the five oral health variables—the presence of painful gums, bleeding gums, toothache, loose teeth, or denture wear—were associated with increased odds of glaucoma (**Supplemental Table 1**). Sensitivity analysis excluding variables for physical acitivity and caloric intake showed that oral health problems resulted in no material differences (data not shown).

Each standard deviation increase in PRS was associated with a nearly 2.5-fold increased odds of glaucoma (odds ratio: 2.48, 95% confidence interval: 2.34, 2.63, $p<0.0001$). Overall, the MTAG PRS did not modify the relationship between oral health problems and glaucoma (p for interaction=0.84; **Table 2**). Furthermore, no significant modification was noted for any of the five oral health variables in relation to glaucoma (p for interaction$\geq$0.34, **Supplemental Table 1).** Finally, no significant interaction between dental health problems and MTAG PRS were noted when only considering those in the lowest vs highest quartile of glaucoma risk ($p=0.98$, **Supplemental Table 2**).

C. Association of oral health conditions with IOP

A total of 33,004 subjects had IOP data available for analysis. The average IOP among patients without oral health problems was 16.0 ± 3.3 mmHg, while the average IOP among patients with oral health conditions was 15.9 ± 3.3 mmHg ($p=0.03$ on univariate analysis). Self-reported oral health conditions were associated with a small, but statistically significant lower IOP, after adjusting for multiple covariables ($p=0.03$, **Table 3**).

The relationship between each oral health variable with IOP was assessed. We found that participants reporting loose teeth or wearing dentures had lower IOPs than those without loose teeth (p=0.03) or without dentures (p<0.0001, **Supplemental Table 3**). By contrast, painful or bleeding gums, toothache, and loose teeth were not associated with IOP differences (p≥0.09; **Supplemental Table 3**). Sensitivity analysis excluding variables for physical activity and caloric intake showed that oral health problems resulted in no differences to the results described above (data not shown).

Every point increase in standardized IOP PRS was associated with a 0.72mmHg increase in IOP (p<0.0001). The interaction between IOP PRS and oral health conditions was neither significant among patients across the spectrum of IOP PRS (**Table 3**; p=0.37), nor among those of the top 25% genetic risk score as compared to the lowest 25% risk scores (p=0.32, **Supplemental table 4**). Interaction terms with each of the individual oral health variables were also not statistically significant (p-for-interaction≥0.10; **Supplemental table 3**).

D. Association of oral health conditions and macula region retinal nerve fiber layer (mRNFL) and macula region ganglion cell inner plexiform layer (mGCIPL)

14,652 and 14,613 subjects had mRNFL and mGCIPL data available for analysis, respectively. The average mRNFL thickness was 28.0 ± 3.8 microns among subjects with oral health problems and 28.4 ± 3.8 microns among those without oral health problems (p=0.38 on univariate analysis). The average mGCIPL thickness was 74.5 ± 5.2 microns among subjects with oral health problems and 74.7 ± 5.1 microns among those without oral health problems (p=0.14 on univariate analysis). There was an inverse association between self-reported oral health conditions and mRNFL thickness, after adjusting for multiple covariables (-0.14 microns, p=0.04, **Table 4**), but no association between oral health conditions and mGCIPL thickness (p=0.96, **Table 5**).

The MTAG PRS did not modify the relationship between oral health conditions and macula inner retinal parameters (mRNFL and mGCIPL) (p for interaction ≥ 0.17; **Tables 4 and 5**). The interaction between the MTAG PRS and oral health conditions was weakly significant among those of the top 25% of MTAG PRS as compared to the lowest 25% risk scores for mGCIPL thickness (0.48 microns; p for interaction=0.04; **Supplemental Table 4**).

Bleeding gums were associated with a small, but statistically significant decrease in mRNFL thickness (-0.21 microns, p=0.02, **Supplemental Table 5).** All other individual oral health problems were not associated with mRNFL nor mGCIPL (p≥0.13; **Supplemental Tables 5 and 6**). The MTAG PRS modified the relationship between toothache and mRNFL (p=0.003 for interaction) despite a null primary relationship between toothache and mRNFL (p=0.14, **Supplemental Table 5**). The MTAG PRS did not modify the associations between all other oral health variables and mRNFL nor mGCIPL (**Supplemental Tables 5 and 6**). Sensitivity analysis excluding variables for physical activity and calorie intake revealed that oral health problems were associated with a small -0.11 ± 0.04 microns (p=0.01) decrease in mRNFL thickness and -0.13 ± 0.05 microns (p=0.01) decrease in mGCIPL thickness. Among the individual oral health variables, dentures were associated with slightly thinner mRNFL (p=0.01) and mGCIPL

(p=0.005) thicknesses, and bleeding gums were associated with thinner mRNFL thickness (p=0.03, data not shown)

IV. Discussion

In this cross-sectional study of over 500,000 participants of the UK Biobank, we investigated a possible relationship between oral health and glaucoma. Consistent with prior reports outside the UK Biobank Study, over one-third of the study population reported some history of oral health conditions including loose teeth, use of dentures, and tooth or gum pain.[27] After controlling for multiple covariables, we found that self-reported oral health conditions were not associated with increased odds of glaucoma (odds ratio: 1.04; p=0.39).

Oral health problems were weakly associated with lower IOP (**Table 3**; -0.08 mmHg, p=0.03). We found that this difference in IOP was driven by an association between both loose teeth and denture wear with IOP (**Supplemental Table 3**; -0.13 mmHg, p=0.03, and -0.22 mmHg, p<0.0001, respectively). Self-reported oral health conditions were also associated with a small decrease in mRNFL thickness (**Table 4**; -0.14 microns, p=0.04), but this difference in mRNFL was not consistently reproducible among the other component oral health variables. Furthermore, oral health conditions did not appear to affect the risk of glaucoma or elevated IOP among patients with low versus high genetic risk for glaucoma or elevated IOP. Thus, while oral health conditions may result in a small decrease in intraocular pressures, this is not protective against glaucoma. Additionally, oral health problems may be associated with thinning of inner retinal layers in a pressure-independent mechanism.

While prior studies suggest that recent loose teeth or periodontal disease is associated with an increased risk of primary open-angle glaucoma,[5–7] we suspect that these results likely reflect variations in the study population, covariable inclusion, and variable definitions. One study examined subjects who were older, male, and had more stringent glaucoma diagnosis criteria, including a review of visual fields.[5] That study reported that tooth loss within the last two years was associated with an increased risk of glaucoma. We found no association between loose teeth and glaucoma in this cross-sectional study—these differences may be attributed to differences in data collection. For instance, while patients in the UK Biobank reported a history of loose teeth or denture wear, data on the recency of tooth loss or denture requirement were not collected. Two other studies implicated an association between periodontal disease and glaucoma: one study examined a Taiwanese national health database without access to covariables including smoking, alcohol use, physical activity, and diet,[6] while a third study leveraged data from a Korean national health database.[7] Among our younger European population, we find that after accounting for multiple covariables, there is no consistent association between self-reported oral health problems and glaucoma in cross-sectional analysis.

The results here expand upon a prior study conducted by Lehrer *et al* on the association between dental disease and glaucoma utilizing the UK Biobank database.[28] In their work, Lehrer *et al* report that the presence of bleeding gums was associated with a decreased risk of primary open-angle glaucoma, and with lower IOP. Discrepancies in our results are likely related to differences in variable definitions and

covariable inclusion. In their study, Lehrer *et al* defined glaucoma by the ICD-10 codes for primary open-angle glaucoma alone. In the UK Biobank, ICD-10 codes for POAG are recorded among individuals who undergo a procedure; therefore, the inclusion of individuals with an ICD-10 diagnosis of POAG likely excludes a significant number of patients with glaucoma. In our work, we defined glaucoma not only by the associated ICD-10 codes for glaucoma but also by self-reported glaucoma or the usage of glaucoma medications. Additionally, while the multivariate analysis conducted by Lehrer *et al* included age, gender, diabetes, and smoking history as covariables, our analysis includes a more comprehensive list of known risk factors for glaucoma, including ethnicity and component genetic PRS, among others. Finally, we examined the relationship between oral health conditions and glaucoma in detail, by also using imaging proxies including mRNFL and mGCIPL data. We found inconsistent relations between oral health problems and inner retinal biomarkers – participants with oral health problems had lower mRNFL but the relationship between oral health problems and mGCIPL was null.

The strengths of our study include the large sample available through the UK Biobank, a comprehensive collection of covariable and genetic data, availability of imaging data, and consistency with prior studies. Our results are supported by data collected previously on dental health in the United Kingdom outside of the UK Biobank. For instance, in line with data collected from the National Dental Public Health Team, we found that roughly 16% of participants wear dentures. Similarly, we found that over 4.4% of participants reported loose teeth in the UK Biobank, comparable to the percentage of adults reporting missing anterior teeth according to data from the National Dental Public Health Team (7.6%), providing further indirect validation for the touchscreen questionnaire instrument used to assess oral health.[29] Furthermore, our univariate analysis suggests that oral health conditions may be more prevalent among patients with smoking history or diabetes, consistent with prior studies that link smoking to periodontiits,[30–32] and those that suggest a relationship between diabetes and oral health disease.[33–36] Additionally, despite the inclusion of self-reported glaucoma, we still found strong correlations between glaucoma PRS scores and patients with self-reported glaucoma. Finally, we did explore whether associations between oral health and glaucoma-related outcomes were modified by a genetic predisposition to higher IOP or glaucoma. Overall, our analyses revealed the minimal impact of our PRSs on the relationship between oral health problems and glaucoma traits.

This work is limited by the reliance upon self-reported oral disease. History of prior dental or oral problems may have been affected by recall bias by participants. Our study likely underestimates the prevalence of oral health problems, particularly among those individuals with prior or minimal symptoms. Additionally, while our data are consistent with estimated rates of oral health problems in the United Kingdom, oral health problems were not confirmed by a clinician. Any misclassification of oral health may have decreased the power of our study to determine an association between oral disease and glaucoma, and may have biased our results towards the null. Similarly, misclassification of glaucoma due to improper use of diagnostic codes or errors in self-reported disease may have led to over or under-reporting of true glaucoma cases, and biased our results. Furthermore, because pretreatment IOPs were not available for all patients, these were estimated by imputation, as described previously.[19-21] Additionally,

secondary subgroup analyses contained smaller sample sizes and may have been underpowered to determine associations. Although the majority of covariables had low missing rates, calorie intake and METS data were available for only a fraction of the participants, and may have affected results. Finally, results from this study are limited by a relatively homogenous population and may not be representative of more diverse populations.

In summary, in this large-scale cross-sectional study, we report no clear association between oral health and glaucoma. Although self-reported denture wear was associated with a small, clinically insignificant change in IOP, this was not protective against a diagnosis of glaucoma or in objective measures—including mRNFL and mGCIPL thickness—related to glaucoma.

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Figure 1. Flowchart of participant inclusion. Out of 497,720 participants with oral health status available, a fraction of patients had glaucoma, IOP, RNFL, GCIPL, and covariable data available for analysis.