Periodontitis and outer retinal thickness

Wagner, Siegfried K; Patel, Praveen J; Huemer, Josef; Khalid, Hagar; Stuart, Kelsey; Chu, Colin; Williamson, Dominic J.; Struyven, Robbert R.; Romero-Bascones, David; Foster, Paul; Khawaja, Anthony; Petzold, Axel; Balaskas, Konstantinos; Cortina-Borja, Mario; Chapple, Iain; Dietrich, Thomas; Rahi, Jugnoo S; Denniston, Alastair; Keane, Pearse A

Link to publication on Research at Birmingham portal

Journal Pre-proof

Periodontitis and outer retinal thickness: A cross-sectional analysis of the UK Biobank cohort

Siegfried K. Wagner, MD PhD, Praveen J. Patel, MD, Josef Huemer, MD, Hagar Khalid, MD PhD, Kelsey V. Stuart, MBBCh MSc, Colin J. Chu, MD PhD, Dominic J. Williamson, MSc, Robbert R. Struyven, MD, David Romero-Bascones, MSc, Paul J. Foster, MD PhD, Anthony P. Khawaja, MD PhD, Axel Petzold, MD PhD, Konstantinos Balaskas, MD, Mario Cortina-Borja, PhD, Iain Chapple, PhD, Thomas Dietrich, PhD, Jugnoo S. Rahi, MD PhD, Alastair K. Denniston, MD PhD, Pearse A. Keane, MD, for the UK Biobank Eye & Vision Consortium
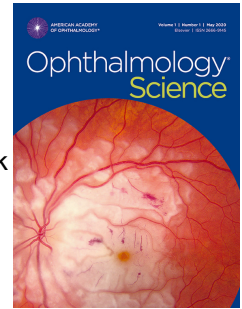
Please cite this article as: Wagner S.K, Patel P.J, Huemer J., Khalid H., Stuart K.V, Chu C.J, Williamson D.J, Struyven R.R, Romero-Bascones D., Foster P.J, Khawaja A.P, Petzold A., Balaskas K., Cortina-Borja M., Chapple I., Dietrich T., Rahi J.S, Denniston A.K, Keane P.A & for the UK Biobank Eye & Vision Consortium, Periodontitis and outer retinal thickness: A cross-sectional analysis of the UK Biobank cohort, *Ophthalmology Science* (2024), doi: https://doi.org/10.1016/j.xops.2024.100472.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1   **Periodontitis and outer retinal thickness: A cross-sectional analysis of the UK Biobank cohort**

2

3   Siegfried K Wagner MD PhD[1, 2], Praveen J Patel MD[1, 2], Josef Huemer MD[2,3], Hagar Khalid MD PhD[2],

4   Kelsey V Stuart MBBCh MSc[1, 2], Colin J Chu MD PhD[1, 2], Dominic J Williamson MSc[1, 2, 4], Robbert R

5   Struyven MD[1, 2, 4], David Romero-Bascones MSc[2, 5], Paul J Foster MD PhD[1, 2], Anthony P Khawaja MD

6   PhD[1, 2], Axel Petzold MD PhD[1, 2, 6], Konstantinos Balaskas MD[1, 2], Mario Cortina-Borja PhD[7], Iain

7   Chapple PhD[8, 12, 13], Thomas Dietrich PhD[8, 12, 13], Jugnoo S Rahi MD PhD[1, 2, 7, 9,10, 11], Alastair K Denniston

8   MD PhD[1, 2, 8, 12, 14] , Pearse A Keane MD[†][1, 2] for the UK Biobank Eye & Vision Consortium

9

10   **Affiliations**

11   [1] Institute of Ophthalmology, University College London, London, UK,
12   [2] NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology London, UK
13   [3] Department of Ophthalmology and Optometry, Kepler University Hospital, Linz 4020, Austria
14   [4] Centre for Medical Image Computing, Department of Computer Science, University College London, UK
15   [5] Biomedical Engineering Department, Faculty of Engineering (MU-ENG), Mondragon Unibertsitatea, Mondragón, Spain.
16   [6] Queen Square Institute of Neurology, University College London, London, UK
17   [7] Great Ormond Street Institute of Child Health, University College London, London, UK,
18   [8] NIHR Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK
19   [9] Great Ormond Street Hospital NHS Foundation Trust, London, UK.
20   [10] Ulverscroft Vision Research Group, University College London, London, UK
21   [11] NIHR Biomedical Research Centre at UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital, London, UK
22   [12] University of Birmingham, Birmingham, UK
23   [13] Birmingham Community Healthcare NHS Foundation Trust, UK
24   [14] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
25
26
27

28   [†]Corresponding author: Professor Pearse Keane, Institute of Ophthalmology, University College London,

29   11-43 Bath Street, London, EC1V 9EL, United Kingdom. Tel: +44 207 253 3411 Email: p.keane@ucl.ac.uk

30

49   **Conflict of Interest Disclosures**

50   Dr Khawaja has acted as a consultant to Abbvie, Aerie, Google Health, Novartis, Reichert, Santen and

51   Thea. Prof Foster has acted as a consultant to Alphasights, GLG, Google Health, Guidepoint, PwC and

52   Santen. No conflicting relationship exists for any other author.

53

54   **Keywords**

55   Periodontitis

56   Age-related macular degeneration

57   Optical coherence tomography

58

59   **Running head**

60 Outer retinal thickness in periodontitis

61 Abstract

62 Purpose: Periodontitis, a ubiquitous severe gum disease affecting the teeth and surrounding alveolar bone

63 can heighten systemic inflammation. We investigated the association between very severe periodontitis

64 and early biomarkers of age-related macular degeneration, in individuals with no eye disease.

65

66 Design: Cross-sectional analysis of the prospective community-based cohort United Kingdom (UK)

67 Biobank.

68

69 Participants: Sixty-seven thousand three hundred eleven UK residents aged 40-70 years recruited between

70 2006-2010 underwent retinal imaging.

71

72 Methods: Macular-centered optical coherence tomography images acquired at the baseline visit were

73 segmented for retinal sublayer thicknesses. Very severe periodontitis was ascertained through a

74 touchscreen questionnaire. Linear mixed effects regression modeled the association between very severe

75 periodontitis and retinal sublayer thicknesses adjusting for age, sex, ethnicity, socioeconomic status,

76 alcohol consumption, smoking status, diabetes mellitus, hypertension, refractive error, and previous

77 cataract surgery.

78

79 Main Outcome Measures: Photoreceptor layer (PRL) and retinal pigment epithelium-Bruch's membrane

80 (RPE-BM) thicknesses.

81

82 Results: Among 36,897 participants included in the analysis, 1,571 (4.3%) reported very severe

83 periodontitis. Affected individuals were older, lived in areas of greater socioeconomic deprivation and

84 were more likely to be hypertensive, diabetic and current smokers (all $p<0.001$). On average, those with

85 very severe periodontitis were myopic (-0.29 ± 2.40 diopters) while those unaffected were hyperopic

86 (0.05 ± 2.27 diopters, *p*<0.001). Following adjusted analysis, very severe periodontitis was associated

87 with thinner PRL (-0.55 μm, 95% CI: -0.97, -0.12, *p*=0.022) but there was no difference in RPE-BM

88 thickness (0.00 μm, 95% CI: -0.12, 0.13, *p*=0.97). The association between PRL thickness and very

89 severe periodontitis was modified by age (*p*<0.001). Stratifying individuals by age, thinner PRL was seen

90 among those aged 60-69 years with disease (-1.19 μm, 95% CI: -1.85, -0.53, *p*<0.001) but not among

91 those under 60 years.

92

93 Conclusions: Among those with no known eye disease, very severe periodontitis is statistically associated

94 with a thinner PRL, consistent with incipient age-related macular degeneration. Optimizing oral hygiene

95 may hold additional relevance for people at risk of degenerative retinal disease.

Introduction

Periodontal disease is a holistic term used to describe a group of common chronic disorders of the gums that are initiated by accumulation of a dental plaque biofilm on the teeth, but which are characterized by inflammation of the periodontal tissues, including the alveolar bone that surrounds the teeth. Typically, periodontal disease progresses from an early reversible form, termed gingivitis, where the gums may swell and bleed, to very severe periodontitis which is a major cause of tooth loss and gingival recession if left untreated[1,2]. Up to half of adults worldwide are estimated to have irreversible periodontitis with a peak prevalence of severe disease in those aged 60-64 years[3–5]. Periodontitis is independently associated with several chronic inflammatory non-communicable diseases of ageing, such as type-2 diabetes[6], atherogenic cardiovascular disease[7] and associated major adverse cardiovascular events[8], chronic kidney disease[9], rheumatoid arthritis[10] and Alzheimer's disease[11]. Biological mechanisms of association include periodontal bacteremia during daily function due to micro-ulcers in the gingival (gum) lining, dissemination inflammation from the periodontal tissues, and post-translational sequelae of periodontal inflammation that generate autoantigens within periodontal tissues and may predispose to systemic autoimmune disease[10].

Given the role of chronic inflammation in the pathogenesis of age-related macular degeneration (AMD), several epidemiological investigations have sought to investigate the link between AMD and periodontal disease[12]. Population-based health surveys in Finland, South Korea and the US have found an increased prevalence of AMD in individuals with periodontitis, particularly among those younger than 60 years of age[13–15], suggesting severe periodontitis may contribute to the premature development of AMD. Supporting this hypothesis, an analysis of National Health Insurance Research Database in Taiwan over a twelve-year period found that individuals with periodontitis had 58% greater hazard of developing AMD compared to those without[16]. However, the findings were based on routinely collected retrospective data where there is risk of residual confounding (e.g. smoking status was not included despite strong links with

121 periodontitis and AMD) and use of diagnostic codes for the case definition may be prone to information

122 bias. Moreover, the specific date of disease codes, such as AMD and periodontitis, which are

123 asymptomatic at their early stages, may not be representative of actual disease development. A further

124 limitation of all the above reports is that the diagnosis of AMD is based on color fundus photography

125 (CFP) yet the detection of disease-related features, such as drusen and atrophy of the retinal pigment

126 epithelium, are greater with optical coherence tomography (OCT)[17,18]. Assessment of OCT-based

127 sublayer thicknesses has increasingly recognized an association between thinning of the outer retinal layer

128 and thickening of the retinal pigment epithelium-Bruch's membrane (RPE-BM) layer in both early and

129 incipient AMD[19–21].

130

131 In this study, we explored the association between very severe periodontitis and outer retinal sublayers

132 using deeply phenotyped data from the prospective community-based research cohort, UK Biobank. Our

133 objective was to investigate whether individuals with very severe periodontitis and no eye disease had

134 outer retinal OCT features suggestive of early AMD. We hypothesized that affected individuals would

135 have reduced thickness of the photoreceptor layer (PRL) and increased thickness of the RPE-BM.

136

Methods

138 Data and Design

139

140 We conducted a cross-sectional analysis of data from the United Kingdom Biobank (UKBB), a

141 prospective epidemiological cohort study of >500,000 participants aged between 40 and 70 years and

142 residing in the United Kingdom (UK). Participants were recruited between 2006 and 2010 and gave

143 informed consent to undergo deep phenotyping for the investigation of health and disease (more

144 information available at: https://www.ukbiobank.ac.uk/). As part of a touchscreen questionnaire at their

145 initial assessment visit, participants were asked about oral/dental problems experienced within the last

146 year. A subset of 67,321 UKBB participants additionally underwent a detailed ophthalmic assessment

147 including retinal imaging with both CFP and OCT at their initial assessment visit[22,23].

148

149 Retinal imaging within UKBB was acquired using the Topcon 3D-OCT 1000 device (Topcon

150 Corporation, Tokyo, Japan). All images covered a 6.0 mm $\times$ 6.0 mm^2 area and had 128 horizontal B-scans

151 and 512 A-scans per B-scan. Images from both eyes, where available, were used. Only participants who

152 had completed the touchscreen questionnaire and undergone retinal imaging were included. Those who

153 had retinal imaging only at the second assessment visit (2012-2013) were excluded as this would be a

154 significant duration from the recording of periodontitis. Those who self-reported any eye disease were

155 also excluded as this may interfere with the retinal imaging measures.

156

157 Outcome variables

158

159 The primary outcome measures were PRL and RPE-BM thickness, derived from automated segmentation

160 of OCT. OCTs were segmented using the Topcon Advanced Boundary Segmentation Tool (TABS,

161 version 1.6.2.6), a software leveraging dual-scale gradient information for automated segmentation of

162 retinal sublayers. PRL thickness was defined as the distance between the inner nuclear layer and retinal

163   pigment epithelium (RPE) while RPE-Bruch's membrane (RPE-BM) was defined as between the RPE

164   and BM (Figure 1). Retinal sublayers for the four parafoveal subfields for PRL and RPE-BM were

165   analysed individually and as an average of all subfields (Figure 1). Standard criteria for quality

166   assessment of OCT in UKBB have been previously described[23,24]. We excluded the poorest 20% of

167   images based on specific image quality metadata, generated by TABS for each OCT volume.

168

169   Exposure variables

170   The primary exposure variable was self-reported periodontitis. Individuals reporting painful gums or

171   loose teeth were considered as having very severe periodontitis based on the findings of previous validity

172   studies[25–27]. We excluded individuals reporting denture wear as they were unable to report the exposure

173   (loose teeth) and the origin of their denture wear is not recorded. We also excluded individuals with

174   bleeding gums as this symptom is common among the general population (>50% in a recent UK-based

175   survey[28]) and previous literature suggests poor diagnostic accuracy for periodontitis with this question[26].

176   We additionally performed a sensitivity analysis including, as cases, just individuals reporting loose teeth

177   as this has previously been shown to have the highest sensitivity and specificity for severe periodontitis

178   among the items in the questionnaire[26]. As controls, we excluded those with dentures and gingival

179   bleeding but also mouth ulcers and toothache.

180

181   Secondary exposure variables were defined a priori and included age, sex, ethnicity, socioeconomic

182   status, diabetes mellitus, hypertension, alcohol drinker status, smoking status, refractive error and

183   previous cataract surgery. Socioeconomic status was measured using the Townsend deprivation scores, a

184   relative measure of material deprivation derived from four areas - unemployment, non-home ownership,

185   non-car ownership and household overcrowding[29]. Hypertension and diabetes mellitus were self-reported

186   by the participant through touchscreen questionnaire. For hypertension, all those who reported having

187   either hypertension or essential hypertension were included. For diabetes mellitus, all those reporting

188   diabetes, type 1 or type 2 diabetes mellitus were categorized into a binary variable of diabetic/non-

189   diabetic. Smoking status was also reported by participants as never, previous or current. The few who

190   preferred not to answer this question at the initial visit were excluded (499,461/501,518, 99.6%

191   complete). Alcohol drinker status was self-reported as 'never', 'previous' or 'current' and was available

192   for 500,757 of 501,512 participants (99.8%). Refractive error, as measured using the spherical equivalent

193   on autorefraction, is strongly associated with retinal thicknesses on OCT[24] and was included as an

194   adjustment variable. Given that refractive error will be influenced by previous cataract surgery, we

195   additionally adjusted for this using the self-reported data in UKBB at the eye level.

196

197   Data analysis

198   Distribution of data was visualized using quantile-quantile plots and assessed statistically with the

199   Anderson-Darling test; homogeneity of variance was through Levene's test. Continuous variables were

200   summarised using mean +/- standard deviation and categorical variables through percentages.

201   Comparison of PRL and RPE-BM thickness between groups was assessed using the independent samples

202   t test (where data from both eyes was available, we averaged the measurement from both for unadjusted

203   analyses). Chi-squared testing was used to assess the proportional association between periodontal disease

204   and categorical secondary exposure variables. For adjusted analyses, we fitted linear mixed effects

205   regression using maximum likelihood estimation with a random effect on the intercept. Models were

206   adjusted for age, sex, ethnicity, socioeconomic status, diabetes mellitus, hypertension, alcohol drinker

207   status, smoking status, refractive error and previous cataract surgery. Degrees of freedom for multilevel

208   modeling were estimated using Satterthwaite's approximation[30]. We assessed for interaction between age,

209   smoking status and diabetes mellitus with very severe periodontitis by comparing models with and

210   without an interaction term using the likelihood ratio test/Wilks test (LRT) to compare model fit[31]. The

211   level of statistical significance was set at $p < 0.05$. All analyses were conducted in R version 4.1.0 (R Core

212   Team, 2021. R Foundation for Statistical Computing, Vienna, Austria) and used the `lme4` and

213   `lmertest` packages[32–34].

214

215   Ethics Committee approval was obtained for UKBB (ref: 06/MRE08/75); specific approval was obtained

216   for this project (application ID: 2112). This study adhered to the ethical standards outlined in the

217   Declaration of Helsinki.

218

219

220   Results

221   From an initial cohort of 67,311 participants who underwent retinal imaging at the initial visit, there were

222   1,571 individuals (2,748 eyes) with very severe periodontitis and 35,326 unaffected individuals (62,221

223   eyes) included in the analysis (prevalence: 4.3%, Figure 2). Individuals with very severe periodontitis

224   were older (56.6 ± 7.8 years versus 55.6 ± 8.1 years, $p < 0.001$) and lived in areas of greater

225   socioeconomic deprivation (Townsend score -0.43 ± 3.2 versus -1.22 ± 2.9, $p < 0.001$). They were also

226   more likely to be current smokers (18.8% versus 8.9%, $p < 0.001$) and have hypertension (26.2% versus

227   22.7%, $p < 0.001$) and diabetes mellitus (5.3% versus 3.3%, $p < 0.001$). On average, those with very

228   severe periodontitis were myopic (-0.29 ± 2.40 diopters) while those unaffected were hyperopic (0.05 ±

229   2.27 diopters, $p<0.001$). On unadjusted analysis, individuals with very severe periodontitis had thinner

230   PRL (severe periodontitis: 164.3 ± 9.0 μm, unaffected: 165.2 ± 8.8 μm, $p<0.001$) but no difference in

231   RPE-BM thickness (severe periodontitis: 23.0 ± 2.1 μm, unaffected: 22.9 ± 2.5 μm, $p=0.40$, Table 1).

232
233
234
235   Adjusting for all confounders, very severe periodontitis was associated with thinner PRL (-0.55 μm, 95%

236   CI: -0.97, -0.12, $p=0.013$). PRL thickness difference was greatest in the superior parafoveal segment (-

237   0.70 μm, 95% CI: -1.14, -0.26, $p= 0.002$, Table S2). Thinner PRL was also associated with older age,

238 non-White ethnicity, diabetes mellitus, hypertension and current smoking (Table 3). There was no

239 significant difference in RPE-BM layer thickness between unaffected individuals and those with very

240 severe periodontitis (0.00 μm, 95% CI: -0.12, 0.13, *p*=0.97). RPE-BM was thicker among older

241 individuals (0.22 μm per decile, 95% CI: 0.19, 0.25, *p*<0.001), men (0.32 μm, 95% CI: 0.27, 0.37,

242 *p*<0.001) and those self-reporting Black (1.57 μm, 95% CI: 1.41, 1.73, *p*<0.001 or South Asian (0.31 μm,

243 95% CI: 0.14, 0.47, *p*<0.001) ethnicity. There was no evidence of interaction between current smoking

244 (LRT *p*=0.26) or diabetes mellitus (LRT *p*=0.56) and very severe periodontitis on PRL thickness.

245 However, there was evidence of interaction between age and very severe periodontitis for PRL thickness

246 (LRT *p*<0.001). When stratifying individuals by age, we found PRL was thinner among those aged 60-69

247 years (-1.19 μm, 95% CI: -1.85, -0.53, *p*<0.001) but not those aged 40-49 years or 50-59 years (Figure 3,

248 Table 4). On the sensitivity analysis, similar direction but more extreme effect estimates were found with

249 affected individuals having a -0.90 μm (95% CI: -1.49, -0.30) thinner PSL. Those with very severe

250 periodontitis also had thicker RPE-BM layer (0.89 μm, 95% CI: 0.33, 1.46, *p*=0.002, Table S5).

251
252
253

Discussion

In this analysis of 36,948 participants in the UKBB who underwent retinal imaging and denied any eye disease, we found individuals with very severe periodontitis had thinner PRL. Thinner PRL was most marked in the superior parafoveal region and was only noted among those aged 60-69 years. Our report, the first to examine retinal OCT in periodontal disease, suggests individuals with very severe periodontitis have outer retinal features consistent with emerging AMD and support further investigation into the role of periodontal disease and oral hygiene in AMD incidence.

Our adjusted analysis showed that the PRL of individuals with very severe periodontitis was, on average, 0.55 μm thinner than that of controls but this was driven predominantly by differences in the 60-69 year age group (-1.19 microns, 95% CI: -1.85, -0.53). For context, this difference in PRL thickness was analogous to approximately 5 years of age and slightly smaller than the estimate for current smoking (-1.44 μm). The replication of similar directions and sizes of effect between PRL thickness and age, sex, ethnicity, hypertension and current smoking reported in previous literature lends validity to our analyses.[35–37]. Although thinner PRL was originally noted as a feature of late AMD, its presence in early disease is increasingly recognized. The German AugUR study showed that, compared to normal eyes, individuals with moderate early AMD had a 1.7 micron thinner PRL within the central fovea subfield while differences in the parafoveal subfield were more subtle (Figure 2 within their report[20]). Individuals with early AMD also have significantly thinner outer nuclear layers compared to controls[20] and recent evidence has suggested that PRL thinning may be the earliest manifestation of emerging AMD[21]. Even among those with normal eyes, Zekavat et al showed that for each SD decrease in PRL thickness, the incident risk of AMD diagnosis was increased by 14% however it should be noted that they did not include the outer nuclear layer in their definition of the PRL[21]. While there has been no previous report examining retinal OCT in individuals with periodontitis, our findings concord with epidemiological

reports that have highlighted an association between periodontitis and AMD, as measured on CFP, in younger individuals. Participants in the US-based National Health and Nutrition Examination Survey, who were aged ≤ 60 years and had periodontal disease, were more likely to have any form of AMD[14]. This was echoed in a similar report in the Korean National Health and Nutrition Examination Survey where those aged ≤ 62 years with severe periodontal disease had 61% greater odds of having AMD[15]. While strengths of both of these reports include robust standardized definitions for AMD (CFP labeled by retinal specialists with expertise in AMD grading) and periodontal disease (through oral health examination by trained dentists according to World Health Organization criteria), there is considerable interobserver variability in CFP-based diagnosis of AMD. For example, in the Age-Related Eye Disease Study, while agreement was good for identifying the presence of advanced AMD (kappa: 0.88), it was more modest when considering features of earlier disease, such as depigmentation in the central zone (weighted kappa: 0.49)[38]. OCT imaging is more sensitive for detecting features of early AMD[39] and the use of a reproducible and quantifiable biomarker in our report not only mitigates the potential bias imparted by human-based dichotomization of a disease spectrum into presence or absence but also allows a deeper exploration into the early stages of AMD.

We did not find an association between very severe periodontitis and RPE-BM thickness in our primary analysis. The mean RPE-BM thickness of control participants (22.9 μm) was similar to that reported in normal eyes elsewhere[40,41] and apart from age, sex, ethnicity, and refractive error we did not find any significant association between RPE-BM thickness and the confounders defined a priori. Similar findings were seen in the population-based Beijing Eye Study. Although age and hypertension were associated with thicker RPE-BM thickness on unadjusted analysis, they found no such link with alcohol consumption or diabetes mellitus[42]. Several reports have noted an increase in RPE-BM thickness with age[43] and in AMD[44] owing to loss of melanin granules, calcification and the accumulation of lipid and residual bodies[45]. However, the sequence of outer retinal layer-specific changes remains unclear (e.g.

whether photoreceptor thinning pre-dates RPE-BM thickening or vice-versa). Although beyond the scope of our cross-sectional analysis, our findings do align with the conclusion of Zekavat et al that PRL thinning may pre-date RPE-BM thickening[21], at least in individuals with very severe periodontitis. To explore the potential causal relationship here, future work should longitudinally explore rates of PRL decline and RPE-BM thickening respectively in those with very severe periodontitis.

Periodontitis is associated with heightened systemic inflammation and addressing it through dental treatments leads to a reduction in inflammatory markers[46–51]. Given the role of systemic inflammation in the pathophysiology of AMD[52–54], it seems plausible that the association between periodontal disease and the outer retinal differences we describe are mediated via this pathway and anti-inflammatory measures may have beneficial effects on outer retinal health. Indeed, lifestyle measures which reduce systemic inflammatory burden, such as smoking cessation and vitamin supplementation, reduce the progression of dry AMD. Current smokers develop neovascular AMD 4.4 years younger than ex-smokers, which suggests cessation may have some benefit even when disease is established[55]. Individuals with intermediate forms of AMD have a reduced risk of developing severe AMD when taking the AREDS antioxidant supplement[110]. Ultimately future work should consider the impact of enhanced oral hygiene in individuals with periodontal disease on AMD onset, progression and transformation from dry disease to choroidal neovascularization (CNV). Whether such measures could also alter the response to intravitreal therapy is also credible - sustained complement activation and inflammation are posited to underlie resistance to anti-vascular endothelial growth factor treatment[56] and intravitreal steroid has demonstrated efficacy in reducing retinal thickness and intraretinal fluid in neovascular AMD[57,58].

Strengths of our report include a large population-based cohort, rich deeply phenotyping data permitting the adjustment for probable confounders, and standardized retinal imaging acquisition with reproducible image segmentation. However, there are also limitations. We defined very severe periodontitis as those self-reporting loose teeth and painful gums based on previously published work on the validity of self-

reporting for periodontitis. While self-reporting loose teeth has high pooled specificity for periodontitis (moderate: 94.7, severe 91.9), the pooled sensitivity is low ranging from 28.3 for moderate disease to 54.9 for severe disease[26]. Thus, while individuals with self-reported loose teeth are likely to have very severe periodontitis, it is likely that some controls may also have periodontitis suggesting a dilution of any measure of effect. Indeed, the prevalence of very severe periodontitis within this cohort was at the lower end of estimates across the UK[4]. Other prospective cohort studies have used oral health examination by licensed dentists or even incorporated dental radiographs for the case definition[13,14] and this may be considered for future work. Similarly, we did not have data on the duration of periodontitis. The UKBB touchscreen questionnaire asks about relevant symptoms within the last year but it is likely that disease duration was heterogeneous among our cases. This report should also be considered in the context of the potential selection bias of UKBB. As a population-based cohort of healthy volunteers with an exceptionally low response rate (~6%), there have been some concerns over extrapolating the findings derived from UKBB participants. Compared to the general population, participants in UKBB are less likely to engage in harmful health behaviors and experience less socioeconomic deprivation[59]. UKBB participants are also predominantly of White ethnicity suggesting our findings should be interpreted with caution in other ethnic groups. However, risk factor associations estimated from UKBB have been found to be generalizable when pooling data from other nationally sampled cohort studies within England[60].

In conclusion, individuals with severe periodontitis and no known eye disease have measurable differences in the thickness of the PRL. While longitudinal analyses are needed to further confirm, the directions of effect are consistent with those seen in emerging AMD and remain significant despite adjustment for known confounding factors, including current smoking. Recommendations on oral hygiene may hold additional relevance for people at risk of degenerative retinal disease.

Author Contributions

Dr Wagner and Dr Keane had full access to all of the data in the study and take responsibility for the

integrity of the data and the accuracy of the data analysis.

Concept and design: Wagner, Patel, Chapple, Dietrich, Denniston, Rahi, Keane

Acquisition, analysis or interpretation of data: All authors

Drafting of the manuscript: Wagner, Patel, Petzold, Chapple, Dietrich, Rahi, Denniston, Keane

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Wagner, Cortina-Borja

Obtaining funding: Patel, Foster, Keane

Supervision: Patel, Cortina-Borja, Petzold, Chapple, Dietrich, Rahi, Denniston, Keane

Data Sharing Statement:

Data from the United Kingdom Biobank is available to approved researchers upon application. Further

information is available at https://www.ukbiobank.ac.uk/.

UK Biobank & Eye Vision Consortium

The UK Biobank Eye & Vision Consortium members are Naomi Allen, Dphil, University of Oxford, Tariq

Aslam, PhD, University of Manchester, Denize Atan PhD, University of Bristol, Konsantinos Balaskas

FRCOphth, Moorfields Eye Hospital, Sarah A. Barman, PhD, Kingston University, Jenny H. Barrett, PhD,

University of Leeds, Paul Bishop, PhD, Manchester University, Graeme Black Dphil, University of Manchester, Tasanee Braithwaite DM, St Thomas' Hospital, Roxana O. Carare, PhD, University of Southampton, Usha Chakravarthy, FRCOphth, Queens University Belfast, Michelle Chan, FRCOphth, NIHR Biomedical Research Centre, Sharon Y.L. Chua, PhD, NIHR Biomedical Research Centre, Alexander Day, PhD, NIHR Biomedical Research Centre, Parul Desai, PhD, NIHR Biomedical Research Centre, Bal Dhillon, FRCOphth, University of Edinburgh, Andrew D. Dick, FRCOphth, University of Bristol, Alexander Doney PhD, University of Dundee, Cathy Egan, FRCOphth, NIHR Biomedical Research Centre, Sarah Ennis, PhD, University of Southampton, Paul Foster, PhD, NIHR Biomedical Research Centre, Marcus Fruttiger, PhD, NIHR Biomedical Research Centre, John E.J. Gallacher, PhD, University of Oxford, David F. Garway-Heath FRCOphth- NIHR Biomedical Research Centre, Jane Gibson, PhD, University of Southampton, Jeremy A. Guggenheim, PhD, Cardiff University, Chris J. Hammond, FRCOphth, King's College London, Alison Hardcastle, PhD, NIHR Biomedical Research Centre, Simon P. Harding, MD, University of Liverpool, Ruth E. Hogg, PhD, Queens University Belfast, Pirro Hysi, PhD, King's College London, Pearse A. Keane, MD, NIHR Biomedical Research Centre, Sir Peng T. Khaw, PhD, NIHR Biomedical Research Centre, Anthony P. Khawaja, DPhil, NIHR Biomedical Research Centre, Gerassimos Lascaratos, PhD, NIHR Biomedical Research Centre, Thoams Littlejohns, PhD, University of Oxford, Andrew J. Lotery, MD, University of Southampton, Robert Luben PhD, UCL, Phil Luthert PhD, UCL, Tom Macgillivray, PhD, University of Edinburgh, Sarah Mackie, PhD, University of Leeds, Bernadette McGuinness, PhD, Queen's University Belfast, Gareth J. McKay, PhD, Queen's University Belfast, Martin McKibbin, FRCOphth, Leeds Teaching Hospitals NHS Trust, Tony Moore, FRCOphth, NIHR Biomedical Research Centre, James E. Morgan, DPhil, Cardiff University, Eoin O'Sullivan, MD, King's College Hospital NHS Foundation Trust, Richard Oram PhD, University of Exeter, Chris G. Owen, PhD, University of London, Praveen Patel, FRCOphth, NIHR Biomedical Research Centre, Euan Paterson, BSc, Queens University Belfast, Tunde Peto, PhD, Queen's University Belfast, Axel

Petzold, PhD, UCL, Jugnoo S. Rahi, PhD, UCL Great Ormond Street Institute of Child Health, Alicja R. Rudnikca, PhD, University of London, Naveed Sattar FRSE, University of Glasgow, Jay Self, PhD, University of Southampton, Panagiotis Sergouniotis PhD, University of Manchester, Sobha Sivaprasad, FRCOphth, NIHR Biomedical Research Centre, David Steel, FRCOphth, Newcastle University, Irene Stratton, MSc, Gloucestershire Hospitals NHS Foundation Trust, Nicholas Strouthidis, PhD, NIHR Biomedical Research Centre, Cathie Sudlow, DPhil, University of Edinburgh, Zihan Sun PhD, UCL, Robyn Tapp PhD, St George's University of London, Dhanes Thomas, FRCOphth, NIHR Biomedical Research Centre, Emanuele Trucco, PhD, University of Dundee, Adnan Tufail, FRCOphth, NIHR Biomedical Research Centre, Veronique Vitart, PhD, University of Edinburgh, Ananth C. Viswanathan, FRCOphth, NIHR Biomedical Research Centre, Mike Weedon PhD , University of Exeter, Cathy Williams, PhD, University of Bristol, Katie Williams, PhD, King's College London, Jayne V. Woodside, MRCOphth, PhD, Queen's University Belfast, Max M. Yates, PhD, University of East Anglia, Jennifer Yip, PhD, University of Cambridge, and Yalin Zheng, PhD, University of Liverpool.

References

1. Ramseier CA, Anerud A, Dulac M, et al. Natural history of periodontitis: Disease progression and tooth loss over 40 years. J Clin Periodontol 2017;44:1182–1191.

2. Löe H, Anerud A, Boysen H, Smith M. The natural history of periodontal disease in man. The rate of periodontal destruction before 40 years of age. J Periodontol 1978;49:607–620.

3. GBD 2017 Oral Disorders Collaborators, Bernabe E, Marcenes W, et al. Global, regional, and national levels and trends in burden of oral conditions from 1990 to 2017: A systematic analysis for the Global Burden of Disease 2017 study. J Dent Res 2020;99:362–373.

4. Anon. Adult Dental Health Survey 2009 - Summary report and thematic series. NHS Digital. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/adult-dental-health-survey/adult-dental-health-survey-2009-summary-report-and-thematic-series [Accessed January 3, 2023].

5. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci 2017;11:72–80.

6. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. J Clin Periodontol 2018;45:138–149.

7. Sanz M, Marco Del Castillo A, Jepsen S, et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol 2020;47:268–288.

8. Van Dyke TE, Kholy KE, Ishai A, et al. Inflammation of the periodontium associates with risk of future cardiovascular events. J Periodontol 2021;92:348–358.

9. Sharma P, Fenton A, Dias IHK, et al. Oxidative stress links periodontal inflammation and renal function. J Clin Periodontol 2021;48:357–367.

10. de Pablo P, Dietrich T, Chapple ILC, et al. The autoantibody repertoire in periodontitis: a role in the induction of autoimmunity to citrullinated proteins in rheumatoid arthritis? Ann Rheum Dis 2014;73:580–586.

11. Asher S, Stephen R, Mäntylä P, et al. Periodontal health, cognitive decline, and dementia: A systematic review and meta-analysis of longitudinal studies. J Am Geriatr Soc 2022;70:2695–2709.

12. Lv X, Li W, Fang Z, et al. Periodontal Disease and Age-Related Macular Degeneration: A Meta-Analysis of 112,240 Participants. Biomed Res Int 2020;2020:4753645.

13. Karesvuo P, Gursoy UK, Pussinen PJ, et al. Alveolar Bone Loss Associated With Age-Related Macular Degeneration in Males. Journal of Periodontology 2013;84:58–67. Available at: http://dx.doi.org/10.1902/jop.2012.110643.

14. Wagley S, Marra KV, Salhi RA, et al. PERIODONTAL DISEASE AND AGE-RELATED MACULAR DEGENERATION. Retina 2015;35:982–988. Available at:

http://dx.doi.org/10.1097/iae.0000000000000427.

15. Shin YU, Lim HW, Hong EH, et al. The association between periodontal disease and age-related macular degeneration in the Korea National health and nutrition examination survey: A cross-sectional observational study. Medicine 2017;96:e6418.

16. Sun K-T, Hsia N-Y, Chen S-C, et al. RISK OF AGE-RELATED MACULAR DEGENERATION IN PATIENTS WITH PERIODONTITIS: A Nationwide Population-Based Cohort Study. Retina 2020;40:2312–2318.

17. Jain N, Farsiu S, Khanifar AA, et al. Quantitative comparison of drusen segmented on SD-OCT versus drusen delineated on color fundus photographs. Invest Ophthalmol Vis Sci 2010;51:4875–4883.

18. Leuschen JN, Schuman SG, Winter KP, et al. Spectral-domain optical coherence tomography characteristics of intermediate age-related macular degeneration. Ophthalmology 2013;120:140–150.

19. Keane PA, Patel PJ, Liakopoulos S, et al. Evaluation of age-related macular degeneration with optical coherence tomography. Surv Ophthalmol 2012;57:389–414.

20. Brandl C, Brücklmayer C, Günther F, et al. Retinal Layer Thicknesses in Early Age-Related Macular Degeneration: Results From the German AugUR Study. Investigative Opthalmology & Visual Science 2019;60:1581. Available at: http://dx.doi.org/10.1167/iovs.18-25332.

21. Zekavat SM, Sekimitsu S, Ye Y, et al. Photoreceptor layer thinning is an early biomarker for age-related macular degeneration: Epidemiologic and genetic evidence from UK Biobank OCT data. Ophthalmology 2022;129:694–707.

22. Keane PA, Grossi CM, Foster PJ, et al. Optical coherence tomography in the UK Biobank study - rapid automated analysis of retinal thickness for large population-based studies. PLoS One 2016;11:e0164095.

23. Patel PJ, Foster PJ, Grossi CM, et al. Spectral-domain optical coherence tomography imaging in 67 321 adults: Associations with macular thickness in the UK Biobank study. Ophthalmology 2016;123:829–840.

24. Khawaja AP, Chua S, Hysi PG, et al. Comparison of Associations with Different Macular Inner Retinal Thickness Parameters in a Large Cohort: The UK Biobank. Ophthalmology 2020;127:62–71.

25. Eke PI, Dye BA, Wei L, et al. Self-reported measures for surveillance of periodontitis. J Dent Res 2013;92:1041–1047.

26. Abbood HM, Hinz J, Cherukara G, Macfarlane TV. Validity of self-reported periodontal disease: A systematic review and meta-analysis. J Periodontol 2016;87:1474–1483.

27. Sharma P, Kristunas C, Chapple IL, Dietrich T. Periodontal health and patient-reported outcomes: A longitudinal analysis of data from non-specialist practice settings. J Clin Periodontol 2023. Available at: http://dx.doi.org/10.1111/jcpe.13776.

28. Anon. [No title]. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/fi

le/891208/AiP_survey_for_England_2018.pdf [Accessed February 20, 2023].

29. Townsend P. Deprivation. J Soc Policy 1987;16:125–146.

30. Satterthwaite FE. An approximate distribution of estimates of variance components. Biometrics 1946;2:110–114.

31. Wilks SS. The Large-Sample Distribution of the Likelihood Ratio for Testing Composite Hypotheses. aoms 1938;9:60–62. Available at: [Accessed January 3, 2023].

32. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models using lme4. arXiv [statCO] 2014. Available at: http://arxiv.org/abs/1406.5823.

33. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. J Stat Softw 2017;82:1–26. Available at: [Accessed January 3, 2023].

34. Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www R-project org/. Available at: https://ci.nii.ac.jp/naid/20001692429/.

35. Ooto S, Hangai M, Tomidokoro A, et al. Effects of age, sex, and axial length on the three-dimensional profile of normal macular layer structures. Invest Ophthalmol Vis Sci 2011;52:8769–8779.

36. Harris J, Subhi Y, Sørensen TL. Effect of aging and lifestyle on photoreceptors and retinal pigment epithelium: cross-sectional study in a healthy Danish population. Pathobiology of Aging & Age-related Diseases 2017;7:1398016. Available at: http://dx.doi.org/10.1080/20010001.2017.1398016.

37. Chua SYL, Dhillon B, Aslam T, et al. Associations with photoreceptor thickness measures in the UK Biobank. Sci Rep 2019;9:19440.

38. Anon. The age-related eye disease study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the age-related eye disease study report number 6. Am J Ophthalmol 2001;132:668–681.

39. Midena E, Frizziero L, Torresin T, et al. Optical coherence tomography and color fundus photography in the screening of age-related macular degeneration: A comparative, population-based study. PLoS One 2020;15:e0237352.

40. Karampelas M, Sim DA, Keane PA, et al. Evaluation of retinal pigment epithelium-Bruch's membrane complex thickness in dry age-related macular degeneration using optical coherence tomography. Br J Ophthalmol 2013;97:1256–1261.

41. Shao L, Zhang QL, Zhang C, et al. Thickness of retinal pigment epithelium-Bruch's membrane complex in adult Chinese using optical coherence tomography. Eye 2022. Available at: http://dx.doi.org/10.1038/s41433-021-01911-5.

42. Shao L, Zhang QL, Zhang C, et al. Thickness of retinal pigment epithelium-Bruch's membrane complex in adult Chinese using optical coherence tomography. Eye 2022. Available at: http://dx.doi.org/10.1038/s41433-021-01911-5.

43. Demirkaya N, van Dijk HW, van Schuppen SM, et al. Effect of age on individual retinal layer

thickness in normal eyes as measured with spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2013;54:4934–4940.

44. Karampelas M, Sim DA, Keane PA, et al. Evaluation of retinal pigment epithelium-Bruch's membrane complex thickness in dry age-related macular degeneration using optical coherence tomography. Br J Ophthalmol 2013;97:1256–1261.

45. Booij JC, Baas DC, Beisekeeva J, et al. The dynamic nature of Bruch's membrane. Prog Retin Eye Res 2010;29:1–18.

46. Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. Clinical and Experimental Immunology 2003;107:347–352. Available at: http://dx.doi.org/10.1111/j.1365-2249.1997.270-ce1162.x.

47. Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. J Periodontol 2007;78:2289–2302.

48. Lee Y-L, Hu H-Y, Huang N, et al. Dental prophylaxis and periodontal treatment are protective factors to ischemic stroke. Stroke 2013;44:1026–1030.

49. Chen Z-Y, Chiang C-H, Huang C-C, et al. The Association of Tooth Scaling and Decreased Cardiovascular Disease: A Nationwide Population-based Study. The American Journal of Medicine 2012;125:568–575. Available at: http://dx.doi.org/10.1016/j.amjmed.2011.10.034.

50. D'Aiuto F, Gkranias N, Bhowruth D, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol 2018;6:954–965.

51. de Pablo P, Serban S, Lopez-Oliva I, et al. Outcomes of periodontal therapy in rheumatoid arthritis: The OPERA feasibility randomized trial. J Clin Periodontol 2022. Available at: http://dx.doi.org/10.1111/jcpe.13756.

52. Kauppinen A, Paterno JJ, Blasiak J, et al. Inflammation and its role in age-related macular degeneration. Cell Mol Life Sci 2016;73:1765–1786.

53. Wang Y, Wang VM, Chan C-C. The role of anti-inflammatory agents in age-related macular degeneration (AMD) treatment. Eye 2011;25:127–139.

54. Parmeggiani F, Romano MR, Costagliola C, et al. Mechanism of inflammation in age-related macular degeneration. Mediators Inflamm 2012;2012:546786.

55. Detaram HD, Joachim N, Liew G, et al. Smoking and treatment outcomes of neovascular age-related macular degeneration over 12 months. Br J Ophthalmol 2020;104:893–898.

56. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. Drug Des Devel Ther 2016;10:1857–1867.

57. Barikian A, Salti H, Safar A, et al. INTRAVITREAL DEXAMETHASONE IMPLANT AS ADJUVANT TREATMENT FOR BEVACIZUMAB- AND RANIBIZUMAB-RESISTANT NEOVASCULAR AGE-RELATED MACULAR DEGENERATION. Retina 2017;37:1337–1344. Available at: http://dx.doi.org/10.1097/iae.0000000000001366.

58. Todorich B, Thanos A, Yonekawa Y, et al. Simultaneous dexamethasone intravitreal implant and anti-VEGF therapy for neovascular age-related macular degeneration resistant to anti-VEGF monotherapy. J Vitreoretin Dis 2017;1:65–74.

59. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 2017;186:1026–1034.

60. Batty GD, Gale CR, Kivimäki M, et al. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ 2020;368:m131.

Figure legends

Figure 1: Example macular optical coherence tomography B-scan showing segmented boundaries of the photoreceptor segment (orange to green) and retinal pigment epithelium-Bruch's membrane (green to red) layers (A). Layer thicknesses were extracted from the parafoveal segments indicated (B). II: inner inferior, IN: inner nasal, IS: inner superior, IT: inner temporal.

Figure 2: Flow chart of included participants.

Figure 3: Difference in photoreceptor layer thickness between those with and without very severe periodontitis grouped by age. Significant differences in thickness of the sublayer was only seen among those aged 60-69 years. Error bars indicate 95% confidence intervals.

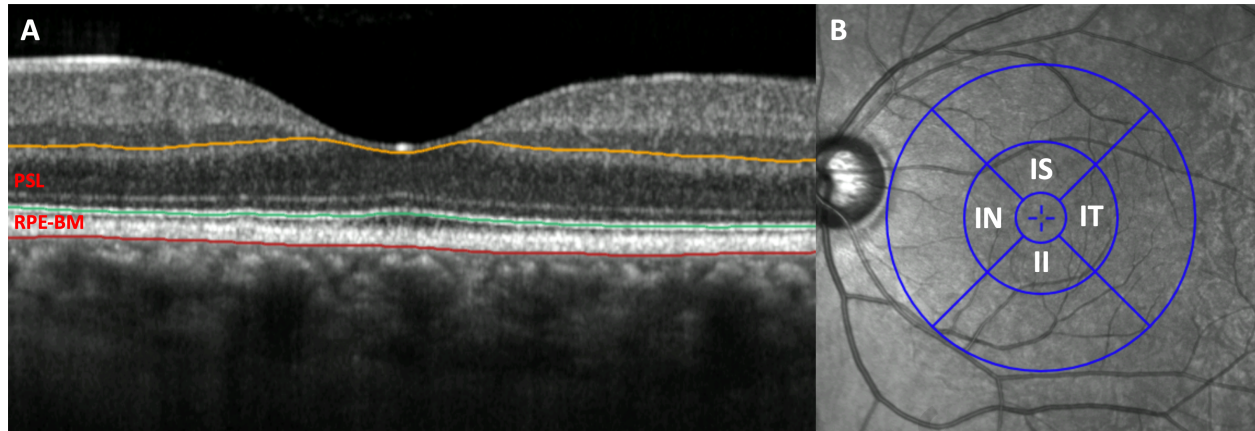| Characteristic[1]		No very severe periodontitis (*n*= 35,326)	Very severe periodontitis (*n*=1,571)	*p*-value
Age mean ± SD (median, IQR)	Years	55.6 ± 8.1 (56, 49.5-62.5)	56.6 ± 7.8 (58, 52-64)	**<0.001**
Sex *n* (%)	Female	19,167 (54.3)	845 (53.8)	0.73
	Male	16,159 (45.7)	726 (46.2)	
Ethnicity *n* (%)	Asian (South)	923 (2.6)	90 (5.7)	**<0.001**
	Black	908 (2.6)	68 (4.3)	
	Other	995 (2.8)	86 (5.5)	
	White	32,500 (92.0)	1,327 (84.5)	
Socioeconomic status mean ± SD (median, IQR)	Townsend score	-1.22 ± 2.9 (-1.84, -3.89, 0.21)	-0.43 ± 3.2 (-1.00, -3.45, 1.45)	**<0.001**
Diabetes mellitus *n* (%)	Absent	34,151 (96.7)	1,487 (94.7)	**<0.001**
	Present	1,175 (3.3)	84 (5.3)	
Hypertension *n* (%)	Absent	27,306 (77.3)	1,159 (73.8)	**0.001**
	Present	8,020 (22.7)	412 (26.2)	
Alcohol drinker status *n* (%)	Never	1,469 (4.2)	110 (7.0)	**<0.001**
	Previous	1,083 (3.1)	77 (4.9)	
	Current	32,774 (92.8)	1,384 (88.1)	
Smoking status *n* (%)	Never	20,553 (58.2)	729 (46.5)	**<0.001**
	Previous	11,649 (33.0)	546 (34.8)	
	Current	3,124 (8.9)	296 (18.8)	
Refractive error mean ± SD	Diopters	-0.29 ± 2.40	0.05 ± 2.27	**<0.001**
Retinal layer thicknesses mean +- SD	PRL (µm)	165.2 +/- 8.8	164.3 +/- 9.0	**<0.001**
	RPE-BM (µm)	22.9 ± 2.5	23.0 ± 2.1	0.40

Table 1: Baseline characteristics of the cohort. Where data on both eyes were available, the values for retinal layer thicknesses and refractive error were averaged. This included 35,326 participants with 62,221 eyes as controls and 1,571 participants with 62,221 eyes as cases. PRL: photoreceptor layer, RPE-BM: retinal pigment epithelium-basement membrane, SD: standard deviation

Variable		PRL (µm)		RPE-BM (µm)	
		Thickness difference (95% CI)	*p*-value	Thickness difference (95% CI)	*p*-value
Very severe periodontitis	Absent	Reference		Reference	
	Present	-0.55 (-0.97, -0.12)	**0.013**	0.00 (-0.12, 0.13)	0.97
Age	Per decile	-0.99 (-1.11, -0.88)	**<0.001**	0.22 (0.19, 0.25)	**<0.001**
Sex	Female	Reference		Reference	
	Male	1.91 (1.74, 2.09)	**<0.001**	0.32 (0.27, 0.37)	**<0.001**
Ethnicity	White	Reference		Reference	
	Asian (South)	-3.94 (-4.49, -3.39)	**<0.001**	0.31 (0.14, 0.47)	**<0.001**
	Black	-5.85 (-6.41, -5.29)	**<0.001**	1.57 (1.41, 1.73)	**<0.001**
	Other	-2.29 (-2.81, -1.77)	**<0.001**	0.47 (0.32, 0.62)	**<0.001**
Socioeconomic status	Per SD increase	-0.28 (-0.37, -0.19)	**<0.001**	0.00 (-0.03, 0.02)	0.92
Diabetes mellitus	Absent	Reference		Reference	
	Present	-1.55 (-2.03, -1.06)	**<0.001**	0.05 (-0.10, 0.19)	0.52
Hypertension	Absent	Reference		Reference	
	Present	-0.82 (-1.04, -0.61)	**<0.001**	-0.02 (-0.08, 0.05)	0.62
Alcohol drinker status	Never	Reference		Reference	
	Previous	0.65 (0.00, 1.30)	0.05	0.00 (-0.19, 0.19)	0.97
	Current	1.09 (0.64, 1.53)	**<0.001**	-0.02 (-0.15, 0.11)	0.81
Smoking status	Never	Reference		Reference	
	Previous	0.07 (-0.13, 0.26)	0.50	0.01 (-0.04, 0.07)	0.60
	Current	-0.73 (-1.04, -0.42)	**<0.001**	-0.12 (-0.21, -0.03)	**0.008**
Refractive error	Per diopter	1.69 (1.62, 1.76)	**<0.001**	-0.12 (-0.14, -0.09)	**<0.001**
Previous cataract surgery	Absent	Reference		Reference	
	Present	0.44 (-0.95, 1.82)	0.54	0.21 (-0.34, 0.77)	0.45

Table 3: Thickness differences of the photoreceptor and retinal pigment epithelium-basement membrane layers estimated through multivariable linear mixed effects models. CI: confidence interval, IMD: index of multiple deprivation, PRL: photoreceptor layer, RPE-BM: retinal pigment epithelium-basement membrane, SD: standard deviation.

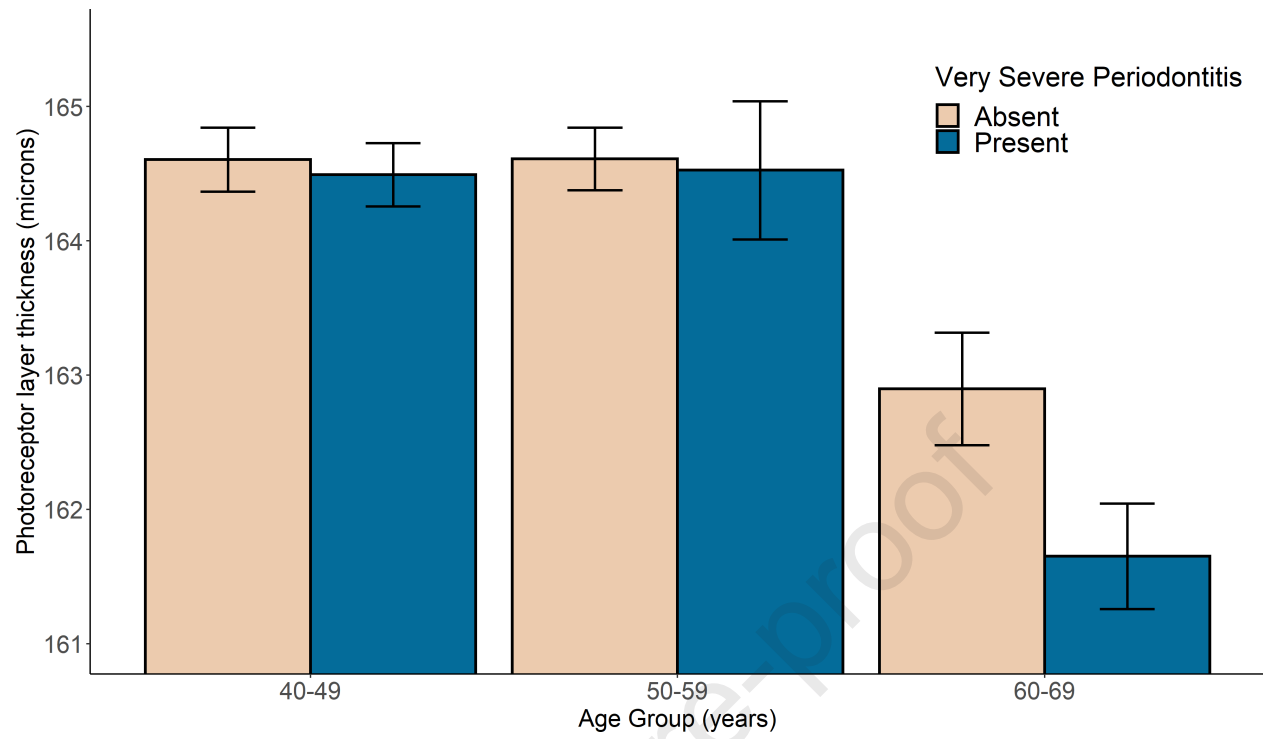| PRL Thickness		40-49 age group (*n*=9,855)		50-59 age group (*n*=12,590)		60-69 age group (*n*=14,452)	
		Thickness difference (95% CI)	*p*-value	Thickness difference (95% CI)	*p*-value	Thickness difference (95% CI)	*p*-value
Very Severe periodontitis	Absent	Reference		Reference		Reference	
	Present	-0.27 (-1.19, 0.64)	0.56	-0.02 (-0.73, 0.69)	0.95	-1.19 (-1.85, -0.53)	**<0.001**
Age	Per decile	0.78 (0.18, 1.37)	**0.010**	-1.11 (-1.55, -0.52)	**<0.001**	-2.30 (-2.81, -1.79)	**<0.001**
Sex	Female	Reference		Reference		Reference	
	Male	2.66 (2.32, 2.99)	**<0.001**	1.56 (1.26, 1.86)	**<0.001**	1.81 (1.53, 2.09)	**<0.001**
Ethnicity	White	Reference		Reference		Reference	
	Asian (South)	-3.41 (-4.26, -2.56)	**<0.001**	-4.22 (-5.17, -3.28)	**<0.001**	-4.20 (-5.32, -3.07)	**<0.001**
	Black	-6.59 (-7.37, -5.81)	**<0.001**	-5.50 (-6.43, -4.57)	**<0.001**	-4.36 (-5.93, -2.80)	**<0.001**
	Other	-2.33 (-3.13, -1.53)	**<0.001**	-2.92 (-3.77, -2.07)	**<0.001**	-1.15 (-2.27, -0.02)	**0.046**
Socioeconomic status	Per SD increase	-0.13 (-0.31, 0.04)	0.13	-0.35 (-0.50, -0.20)	**<0.001**	-0.28 (-0.42, -0.14)	**<0.001**
Diabetes mellitus	Absent	Reference		Reference		Reference	
	Present	-1.52 (-2.84, -0.21)	**0.023**	-2.24 (-3.12, -1.37)	**<0.001**	-1.14 (-1.79, -0.49)	**<0.001**
Hypertension	Absent	Reference		Reference		Reference	
	Present	-0.47 (-1.02, 0.07)	0.09	-0.61 (-0.98, -0.24)	**0.001**	-1.04 (-1.34, -0.74)	**<0.001**
Alcohol drinker status	Never	Reference		Reference		Reference	
	Previous	0.24 (-0.96, 1.44)	0.69	0.73 (-0.39, 1.85)	0.20	0.66 (-0.40, 1.72)	0.22
	Current	1.03 (0.20, 1.85)	**0.015**	1.03 (0.23, 1.82)	**0.012**	1.03 (0.33, 1.74)	**0.004**
Smoking status	Never	Reference		Reference		Reference	
	Previous	0.06 (-0.33, 0.45)	0.77	0.18 (-0.15, 0.51)	0.29	0.05 (-0.24, 0.35)	0.73
	Current	-0.36 (-0.87, 0.15)	0.16	-0.60 (-1.12, -0.07)	**0.026**	-1.44 (-2.02, -0.85)	**<0.001**
Refractive error	Per diopter	1.80 (1.67, 1.92)	**<0.001**	1.69 (1.58, 1.80)	**<0.001**	1.61 (1.50, 1.72)	**<0.001**
Previous cataract surgery	Absent	Reference		Reference		Reference	
	Present	0.57 (-7.57, 8.71)	0.89	-1.33 (-5.43, 2.77)	0.53	0.83 (-0.72, 2.37)	0.29

Table 4: Thickness difference estimates stratified by age groups for the photoreceptor layer. A significant association was only seen for the group aged 60-69 years. CI: confidence interval, IMD: index of multiple deprivation, PRL: photoreceptor layer, RPE-BM: retinal pigment epithelium-basement membrane, SD: standard deviation

```
┌─────────────────┐
│    67,311       │
│  participants   │
└─────────────────┘
         │
         │              ┌──────────────────────────────────────────────┐
         │              │  • Missing periodontal disease data (169)    │
         ├─────────────▶│       • Denture wear (9,528)                 │
         │              │   • Ineligible oral diseases (9,109)         │
         │              │     • Missing alcohol data (56)              │
         │              │   • Missing smoking data (157)               │
         │              │   • Missing refraction data (386)            │
         │              │ • Missing Townsend deprivation data (58)     │
         ▼              └──────────────────────────────────────────────┘
┌─────────────────┐
│    47,848       │
│  participants   │
└─────────────────┘
         │              ┌──────────────────────────────────────────────┐
         │              │  • Insufficient image quality (6,725)        │
         ├─────────────▶│  • Self-reported eye disease (4,226)         │
         │              │                                              │
         ▼              └──────────────────────────────────────────────┘
┌─────────────────┐
│    36,897       │
│  participants   │
└─────────────────┘
       /        \
      /          \
     ▼            ▼
┌──────────┐  ┌──────────┐
│ No very  │  │Very severe│
│ severe   │  │periodontitis│
│periodontitis│ (n =1,571)│
│(n = 35,326)│ └──────────┘
└──────────┘
```
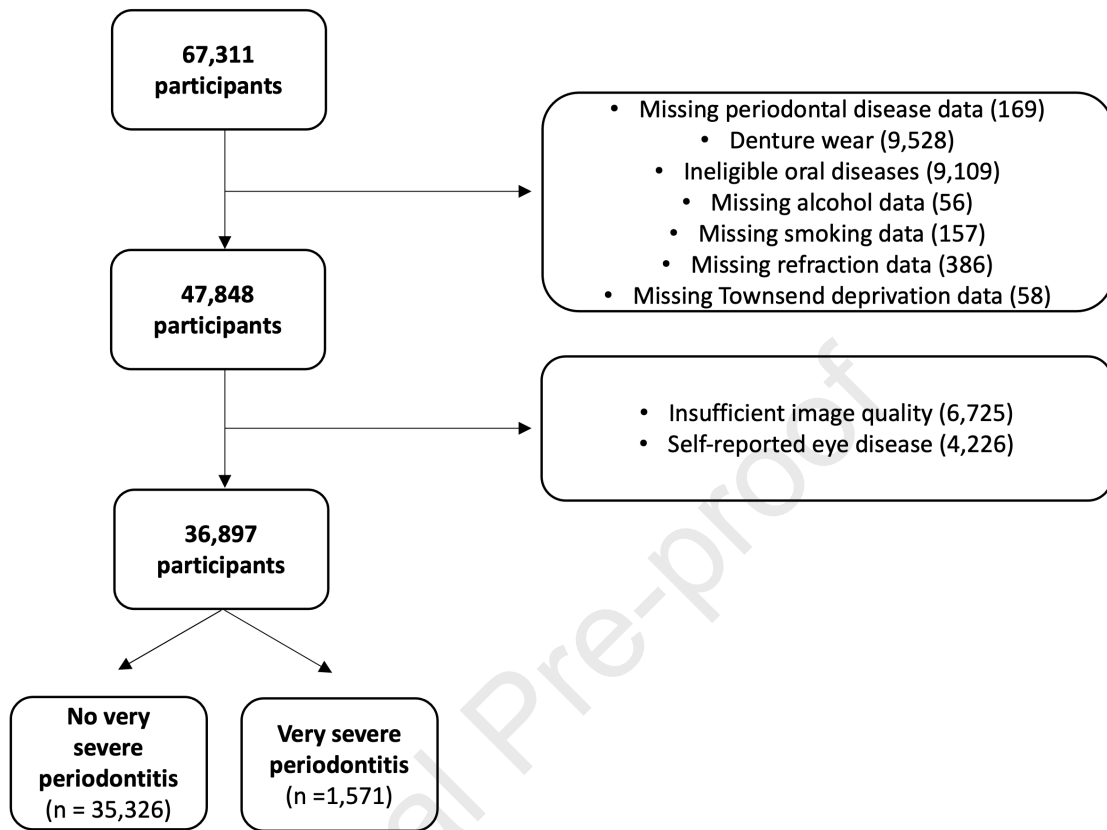
Précis

In this cross-sectional analysis of a prospective community-based cohort, individuals with very severe periodontitis and no eye disease had a thinner photoreceptor layer, suggestive of incipient age-related macular degeneration.

UK Biobank & Eye Vision Consortium

The UK Biobank Eye & Vision Consortium members are Naomi Allen, Dphil, University of Oxford, Tariq Aslam, PhD, University of Manchester, Denize Atan PhD, University of Bristol, Konsantinos Balaskas FRCOphth, Moorfields Eye Hospital, Sarah A. Barman, PhD, Kingston University, Jenny H. Barrett, PhD, University of Leeds, Paul Bishop, PhD, Manchester University, Graeme Black Dphil, University of Manchester, Tasanee Braithwaite DM, St Thomas' Hospital, Roxana O. Carare, PhD, University of Southampton, Usha Chakravarthy, FRCOphth, Queens University Belfast, Michelle Chan, FRCOphth, NIHR Biomedical Research Centre, Sharon Y.L. Chua, PhD, NIHR Biomedical Research Centre, Alexander Day, PhD, NIHR Biomedical Research Centre, Parul Desai, PhD, NIHR Biomedical Research Centre, Bal Dhillon, FRCOphth, University of Edinburgh, Andrew D. Dick, FRCOphth, University of Bristol, Alexander Doney PhD, University of Dundee, Cathy Egan, FRCOphth, NIHR Biomedical Research Centre, Sarah Ennis, PhD, University of Southampton, Paul Foster, PhD, NIHR Biomedical Research Centre, Marcus Fruttiger, PhD, NIHR Biomedical Research Centre, John E.J. Gallacher, PhD, University of Oxford, David F. Garway-Heath FRCOphth- NIHR Biomedical Research Centre, Jane Gibson, PhD, University of Southampton, Jeremy A. Guggenheim, PhD, Cardiff University, Chris J. Hammond, FRCOphth, King's College London, Alison Hardcastle, PhD, NIHR Biomedical Research Centre, Simon P. Harding, MD, University of Liverpool, Ruth E. Hogg, PhD, Queens University Belfast, Pirro Hysi, PhD, King's College London, Pearse A. Keane, MD, NIHR Biomedical Research Centre, Sir Peng T. Khaw, PhD, NIHR Biomedical Research Centre, Anthony P. Khawaja, DPhil, NIHR Biomedical Research Centre, Gerassimos Lascaratos, PhD, NIHR Biomedical Research Centre, Thoams Littlejohns, PhD, University of Oxford, Andrew J. Lotery, MD, University of Southampton, Robert Luben PhD, UCL, Phil Luthert PhD, UCL, Tom Macgillivray, PhD, University of Edinburgh, Sarah Mackie, PhD, University of Leeds, Bernadette McGuinness, PhD, Queen's University Belfast, Gareth J. McKay, PhD, Queen's University Belfast, Martin McKibbin, FRCOphth, Leeds Teaching Hospitals NHS Trust, Tony Moore, FRCOphth, NIHR Biomedical

Research Centre, James E. Morgan, DPhil, Cardiff University, Eoin O'Sullivan, MD, King's College Hospital NHS Foundation Trust, Richard Oram PhD, University of Exeter, Chris G. Owen, PhD, University of London, Praveen Patel, FRCOphth, NIHR Biomedical Research Centre, Euan Paterson, BSc, Queens University Belfast, Tunde Peto, PhD, Queen's University Belfast, Axel Petzold, PhD, UCL, Jugnoo S. Rahi, PhD, UCL Great Ormond Street Institute of Child Health, Alicja R. Rudnikca, PhD, University of London, Naveed Sattar FRSE, University of Glasgow, Jay Self, PhD, University of Southampton, Panagiotis Sergouniotis PhD, University of Manchester, Sobha Sivaprasad, FRCOphth, NIHR Biomedical Research Centre, David Steel, FRCOphth, Newcastle University, Irene Stratton, MSc, Gloucestershire Hospitals NHS Foundation Trust, Nicholas Strouthidis, PhD, NIHR Biomedical Research Centre, Cathie Sudlow, DPhil, University of Edinburgh, Zihan Sun PhD, UCL, Robyn Tapp PhD, St George's University of London, Dhanes Thomas, FRCOphth, NIHR Biomedical Research Centre, Emanuele Trucco, PhD, University of Dundee, Adnan Tufail, FRCOphth, NIHR Biomedical Research Centre, Veronique Vitart, PhD, University of Edinburgh, Ananth C. Viswanathan, FRCOphth, NIHR Biomedical Research Centre, Mike Weedon PhD , University of Exeter, Cathy Williams, PhD, University of Bristol, Katie Williams, PhD, King's College London, Jayne V. Woodside, MRCOphth, PhD, Queen's University Belfast, Max M. Yates, PhD, University of East Anglia, Jennifer Yip, PhD, University of Cambridge, and Yalin Zheng, PhD, University of Liverpool.