

## Periodontitis and outer retinal thickness

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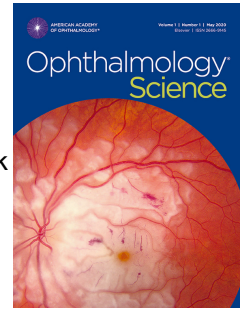
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Periodontitis and outer retinal thickness: A cross-sectional analysis of the UK Biobank cohort

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

2  
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53

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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 ( $-0.29 \pm 2.40$  diopters) while those unaffected were hyperopic  
86 ( $0.05 \pm 2.27$  diopters,  $p < 0.001$ ). Following adjusted analysis, very severe periodontitis was associated  
87 with thinner PRL ( $-0.55 \mu\text{m}$ , 95% CI:  $-0.97, -0.12$ ,  $p = 0.022$ ) but there was no difference in RPE-BM  
88 thickness ( $0.00 \mu\text{m}$ , 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 ( $-1.19 \mu\text{m}$ , 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.

## 96 Introduction

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

111  
112 Given the role of chronic inflammation in the pathogenesis of age-related macular degeneration (AMD),  
113 several epidemiological investigations have sought to investigate the link between AMD and periodontal  
114 disease<sup>12</sup>. Population-based health surveys in Finland, South Korea and the US have found an increased  
115 prevalence of AMD in individuals with periodontitis, particularly among those younger than 60 years of  
116 age<sup>13-15</sup>, suggesting severe periodontitis may contribute to the premature development of AMD.  
117 Supporting this hypothesis, an analysis of National Health Insurance Research Database in Taiwan over a  
118 twelve-year period found that individuals with periodontitis had 58% greater hazard of developing AMD  
119 compared to those without<sup>16</sup>. However, the findings were based on routinely collected retrospective data  
120 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)<sup>17,18</sup>. 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<sup>19-21</sup>.

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



## 137 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<sup>22,23</sup>.

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 × 6.0 mm<sup>2</sup> 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<sup>23,24</sup>. 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<sup>25-27</sup>. 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<sup>28</sup>) and previous literature suggests poor diagnostic accuracy for periodontitis with this question<sup>26</sup>.  
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<sup>26</sup>. 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<sup>29</sup>. 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<sup>24</sup> 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<sup>30</sup>. 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<sup>31</sup>. 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<sup>32-34</sup>.  
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.

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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 ( $56.6 \pm 7.8$  years versus  $55.6 \pm 8.1$  years,  $p < 0.001$ ) and lived in areas of greater  
225 socioeconomic deprivation (Townsend score  $-0.43 \pm 3.2$  versus  $-1.22 \pm 2.9$ ,  $p < 0.001$ ). 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 ( $-0.29 \pm 2.40$  diopters) while those unaffected were hyperopic ( $0.05 \pm$   
229  $2.27$  diopters,  $p < 0.001$ ). On unadjusted analysis, individuals with very severe periodontitis had thinner  
230 PRL (severe periodontitis:  $164.3 \pm 9.0$   $\mu\text{m}$ , unaffected:  $165.2 \pm 8.8$   $\mu\text{m}$ ,  $p < 0.001$ ) but no difference in  
231 RPE-BM thickness (severe periodontitis:  $23.0 \pm 2.1$   $\mu\text{m}$ , unaffected:  $22.9 \pm 2.5$   $\mu\text{m}$ ,  $p = 0.40$ , Table 1).

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235 Adjusting for all confounders, very severe periodontitis was associated with thinner PRL ( $-0.55$   $\mu\text{m}$ , 95%  
236 CI:  $-0.97$ ,  $-0.12$ ,  $p = 0.013$ ). PRL thickness difference was greatest in the superior parafoveal segment ( $-$   
237  $0.70$   $\mu\text{m}$ , 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  $\mu\text{m}$ , 95% CI: -0.12, 0.13,  $p=0.97$ ). RPE-BM was thicker among older  
241 individuals (0.22  $\mu\text{m}$  per decile, 95% CI: 0.19, 0.25,  $p<0.001$ ), men (0.32  $\mu\text{m}$ , 95% CI: 0.27, 0.37,  
242  $p<0.001$ ) and those self-reporting Black (1.57  $\mu\text{m}$ , 95% CI: 1.41, 1.73,  $p<0.001$  or South Asian (0.31  $\mu\text{m}$ ,  
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  $\mu\text{m}$ , 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  $\mu\text{m}$  (95% CI: -1.49, -0.30) thinner PSL. Those with very severe  
250 periodontitis also had thicker RPE-BM layer (0.89  $\mu\text{m}$ , 95% CI: 0.33, 1.46,  $p=0.002$ , Table S5).

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## 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  $\mu\text{m}$  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  $\mu\text{m}$ ). 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<sup>35-37</sup>. 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<sup>20</sup>). Individuals with early AMD also have significantly thinner outer nuclear layers compared to controls<sup>20</sup> and recent evidence has suggested that PRL thinning may be the earliest manifestation of emerging AMD<sup>21</sup>. 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<sup>21</sup>. 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  $\leq 60$  years and had periodontal disease, were more likely to have any form of AMD<sup>14</sup>. This was echoed in a similar report in the Korean National Health and Nutrition Examination Survey where those aged  $\leq 62$  years with severe periodontal disease had 61% greater odds of having AMD<sup>15</sup>. 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)<sup>38</sup>. OCT imaging is more sensitive for detecting features of early AMD<sup>39</sup> 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  $\mu\text{m}$ ) was similar to that reported in normal eyes elsewhere<sup>40,41</sup> 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<sup>42</sup>. Several reports have noted an increase in RPE-BM thickness with age<sup>43</sup> and in AMD<sup>44</sup> owing to loss of melanin granules, calcification and the accumulation of lipid and residual bodies<sup>45</sup>. 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<sup>21</sup>, 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<sup>46-51</sup>. Given the role of systemic inflammation in the pathophysiology of AMD<sup>52-54</sup>, 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<sup>55</sup>. Individuals with intermediate forms of AMD have a reduced risk of developing severe AMD when taking the AREDS antioxidant supplement<sup>110</sup>. 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<sup>56</sup> and intravitreal steroid has demonstrated efficacy in reducing retinal thickness and intraretinal fluid in neovascular AMD<sup>57,58</sup>.

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<sup>26</sup>. 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<sup>4</sup>. Other prospective cohort studies have used oral health examination by licensed dentists or even incorporated dental radiographs for the case definition<sup>13,14</sup> 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<sup>59</sup>. 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<sup>60</sup>.

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.

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*Acquisition, analysis or interpretation of data:* All authors

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## 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/>.

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## 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 <sup>1</sup>		No very severe periodontitis (n= 35,326)	Very severe periodontitis (n=1,571)	p-value
Age mean $\pm$ SD (median, IQR)	Years	55.6 $\pm$ 8.1 (56, 49.5-62.5)	56.6 $\pm$ 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 $\pm$ SD (median, IQR)	Townsend score	-1.22 $\pm$ 2.9 (-1.84, -3.89, 0.21)	-0.43 $\pm$ 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 $\pm$ SD	Diopters	-0.29 $\pm$ 2.40	0.05 $\pm$ 2.27	<0.001
Retinal layer thicknesses mean $\pm$ SD	PRL ( $\mu$ m)	165.2 $\pm$ 8.8	164.3 $\pm$ 9.0	<0.001
	RPE-BM ( $\mu$ m)	22.9 $\pm$ 2.5	23.0 $\pm$ 2.1	0.40

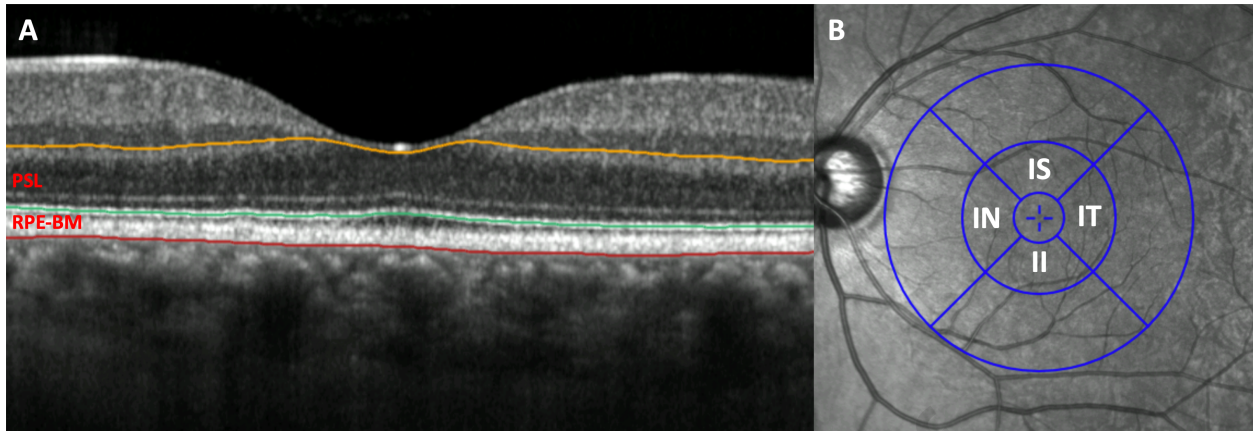
**Table 1:** Baseline characteristics of the cohort. Where data on both eyes were available, the values for retinal layer thicknesses and refractive error were averaged. This included 35,326 participants with 62,221 eyes as controls and 1,571 participants with 62,221 eyes as cases. PRL: photoreceptor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

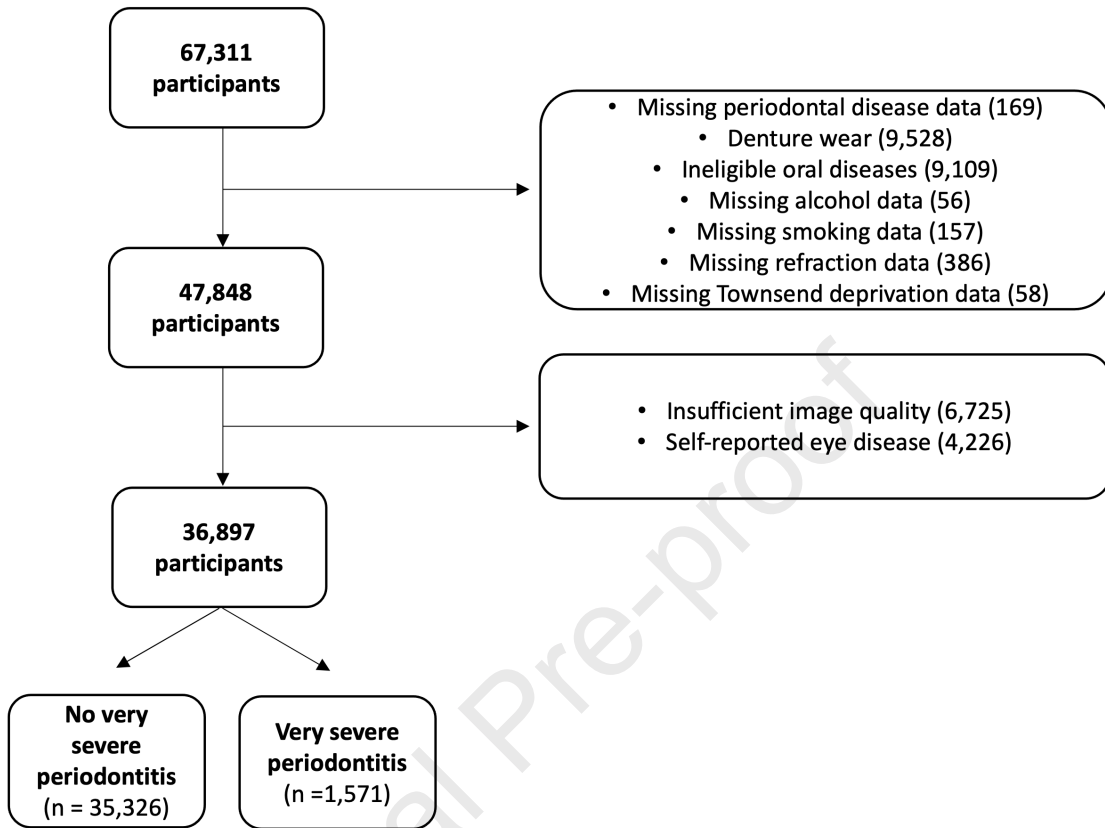
Variable		PRL ( $\mu\text{m}$ )		RPE-BM ( $\mu\text{m}$ )	
		Thickness difference (95% CI)	<i>p</i> -value	Thickness difference (95% CI)	<i>p</i> -value
Very severe periodontitis	Absent	Reference		Reference	
	Present	-0.55 (-0.97, -0.12)	<b>0.013</b>	0.00 (-0.12, 0.13)	0.97
Age	Per decile	-0.99 (-1.11, -0.88)	<b>&lt;0.001</b>	0.22 (0.19, 0.25)	<b>&lt;0.001</b>
Sex	Female	Reference		Reference	
	Male	1.91 (1.74, 2.09)	<b>&lt;0.001</b>	0.32 (0.27, 0.37)	<b>&lt;0.001</b>
Ethnicity	White	Reference		Reference	
	Asian (South)	-3.94 (-4.49, -3.39)	<b>&lt;0.001</b>	0.31 (0.14, 0.47)	<b>&lt;0.001</b>
	Black	-5.85 (-6.41, -5.29)	<b>&lt;0.001</b>	1.57 (1.41, 1.73)	<b>&lt;0.001</b>
	Other	-2.29 (-2.81, -1.77)	<b>&lt;0.001</b>	0.47 (0.32, 0.62)	<b>&lt;0.001</b>
Socioeconomic status	Per SD increase	-0.28 (-0.37, -0.19)	<b>&lt;0.001</b>	0.00 (-0.03, 0.02)	0.92
Diabetes mellitus	Absent	Reference		Reference	
	Present	-1.55 (-2.03, -1.06)	<b>&lt;0.001</b>	0.05 (-0.10, 0.19)	0.52
Hypertension	Absent	Reference		Reference	
	Present	-0.82 (-1.04, -0.61)	<b>&lt;0.001</b>	-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)	<b>&lt;0.001</b>	-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)	<b>&lt;0.001</b>	-0.12 (-0.21, -0.03)	<b>0.008</b>
Refractive error	Per diopter	1.69 (1.62, 1.76)	<b>&lt;0.001</b>	-0.12 (-0.14, -0.09)	<b>&lt;0.001</b>
Previous cataract surgery	Absent	Reference		Reference	
	Present	0.44 (-0.95, 1.82)	0.54	0.21 (-0.34, 0.77)	0.45

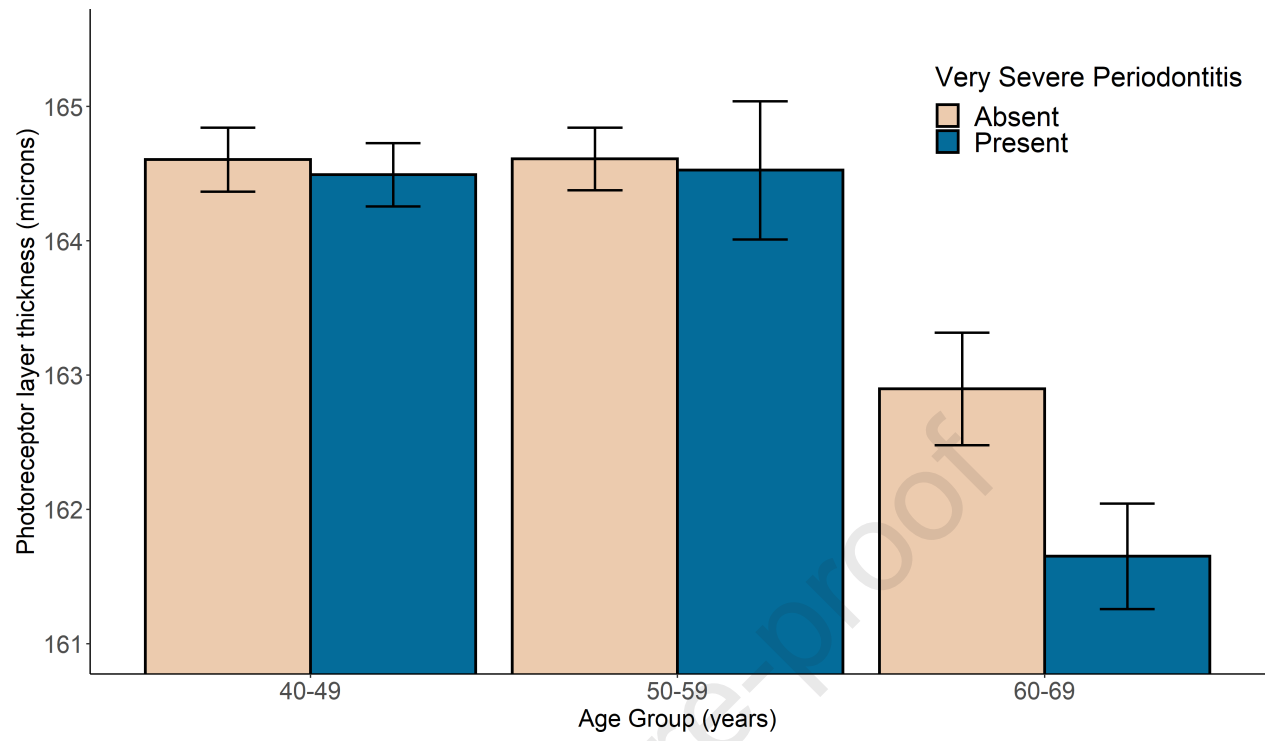
Table 3: Thickness differences of the photoreceptor and retinal pigment epithelium-basement membrane layers estimated through multivariable linear mixed effects models. CI: confidence interval, IMD: index of multiple deprivation, PRL: photoreceptor layer, RPE-BM: retinal pigment epithelium-basement membrane, 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)	<b>0.010</b>	-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)	<b>0.046</b>
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)	<b>0.023</b>	-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)	<b>0.001</b>	-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)	<b>0.015</b>	1.03 (0.23, 1.82)	<b>0.012</b>	1.03 (0.33, 1.74)	<b>0.004</b>
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)	<b>0.026</b>	-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









## 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.

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