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RESEARCH PAPER

Retinal age gap as a predictive biomarker of future risk of Parkinson's disease

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Abstract

Introduction: retinal age derived from fundus images using deep learning has been verified as a novel biomarker of ageing. We aim to investigate the association between retinal age gap (retinal age–chronological age) and incident Parkinson's disease (PD).
Methods: a deep learning (DL) model trained on 19,200 fundus images of 11,052 chronic disease-free participants was used to predict retinal age. Retinal age gap was generated by the trained DL model for the remaining 35,834 participants free of PD at the baseline assessment. Cox proportional hazards regression models were utilised to investigate the association between retinal age gap and incident PD. Multivariable logistic model was applied for prediction of 5-year PD risk and area under the receiver operator characteristic curves (AUC) was used to estimate the predictive value.
Results: a total of 35,834 participants (56.7 ± 8.04 years, 55.7% female) free of PD at baseline were included in the present analysis. After adjustment of confounding factors, 1-year increase in retinal age gap was associated with a 10% increase in risk of PD (hazard ratio [HR] = 1.10, 95% confidence interval [CI]: 1.01–1.20, $P = 0.023$). Compared with the lowest quartile of the retinal age gap, the risk of PD was significantly increased in the third and fourth quartiles (HR = 2.66, 95% CI: 1.13–6.22, $P = 0.024$; HR = 4.86, 95% CI: 1.59–14.8, $P = 0.005$, respectively). The predictive value of retinal age and established risk factors for 5-year PD risk were comparable (AUC = 0.708 and 0.717, $P = 0.821$).
Conclusion: retinal age gap demonstrated a potential for identifying individuals at a high risk of developing future PD.

Keywords: retinal age, Parkinson's disease, prediction, older people

Key Points

- It remains to be answered whether ageing biomarkers could provide clues for Parkinson's disease (PD) risk stratification.
- Retinal age generated by the deep learning algorithm using fundus images accurately predicts age.
- Retinal age gap (retinal age-chronological age) was independently associated with the incident PD.
- Retinal age demonstrated similar predictive value for 5-year PD risk compared with established risk factors.
- Retinal age gap demonstrated the potential as a novel biomarker to identify high-risk individuals for PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease [1] affecting approximately 6.1 million people worldwide in 2016 [2]. The prevalence and incidence of PD increases exponentially with age [3], and ageing is the single most significant factor affecting the onset, progression and clinical presentations of PD. [4, 5]

Ageing can be described as a heterogenous process [6]. Compared with chronological age which merely indicates postnatal life, biological age measures health status in respect to the ageing process [6]. An accurate quantification of the biological ageing process is clinically important for risk stratification and early intervention for age-related diseases. Leukocyte telomere length [7], and epigenic clock based on DNA methylation levels [8], and brain age derived from brain imaging data [9, 10] are a few ageing biomarkers developed to describe the ageing process, however this area remains a fluid and ongoing area of research.

Due to its insidious onset and extensive loss of dopamine neurons (approximately 70–80%) prior to diagnosis [11], a few biomarkers of ageing have been proposed for the early detection of PD in hopes of inciting early interventions for preventing further PD progression. As early as 1985, Marttila *et al*. noted similar but quantitatively exaggerated immune abnormalities in individuals with PD compared with normal ageing [12]. These observations have led investigations into leukocyte telomere length [13–17], epigenetic age [18] and brain age [19, 20] for their associations with PD, albeit their associations remain ambiguous [13–17]. Further, whether biomarkers of ageing could reflect early changes in PD preceding diagnosis remain to be answered. Furthermore, with the high cost of microchips and invasive sampling procedures necessary to estimate the epigenetic clock, the time-consuming and costly features of neuroimaging have limited their application as feasible population-based methods for risk prediction. Therefore, development of biomarkers with the potential to detect early PD during the asymptomatic period is critical.

Recently, we developed a deep learning algorithm based on retinal images, which could accurately predict chronological age. In addition, the retinal age gap, i.e. the difference between age predicted by retinal image and chronological age, was identified as a viable ageing biomarker that could provide important prognostic information [21]. As an extension of the central nervous system, the retina offers a unique and accessible 'window' to visualise cerebral neurons and microvasculature [22, 23]. Dopaminergic deficiency and microvascular abnormalities in the retina have been implicated in patients with PD. [24–26] Further, visual dysfunction, such as abnormal colour vision, pupil reactivity, impaired eye movement and stereopsis, have been reported as one of the most common non-motor symptoms in the prodromal phase of PD. [27]

Taken together, the retinal age has the potential to be utilised as a single biomarker and/or alongside other clinical risk factors/biomarkers to identify people at high risk of PD. Therefore, the current study aimed to investigate the association between retinal age gap and incident PD using the large-scale population-based sample of the UK Biobank.

Methods

Study population

We analyse the data from UK Biobank, a population-based cohort of over 500,000 UK residents aged 40–69 years. All the participants were enrolled between 2006 and 2010 with detailed health-care questionnaires administered to obtain information on lifestyle, environment, medical history and demographic data at baseline. In addition, comprehensive physical and functional measurements including ophthalmic examinations were performed and biological samples of blood, urine and saliva were collected for further analysis. Health-related events were determined using data linkage to Hospital Episode Statistics (HES) and death registers. Details on the overall study protocol and the protocols for each test have been described elsewhere [28].

This study was granted approval by The National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (11/NW/0382). With the UK Biobank application number 62443, all investigations were conducted in accordance with the tenets of the Declaration of Helsinki, with written informed consent obtained from all participants.

Ophthalmic measures

In the UK Biobank vision cohort [29], comprehensive ophthalmic examinations were conducted including the logarithm of the minimum angle of resolution (LogMAR) visual acuity, autorefraction and keratometry (Tomey RC5000, Tomey GmbH, Nuremberg, Germany), intraocular pressure (IOP, Ocular Response Analyzer, Reichert, New York, USA), and paired retinal fundus and optical coherence tomography imaging (OCT, Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan) in 2010. Fundus photography for each eye obtained the 45° non-mydriatic and non-stereo fundus images both optic disc- and macular-centred. We collected 131,238 images from 66,500 participants from the UK Biobank study, among which 80,170 images from 46,970 participants passed image quality checks.

Deep learning model for age prediction

Among 80,169 images of 46,969 participants, 19,200 fundus images of 11,052 participants who reported no previous disease were used to train the DL model for age prediction. To maximise the data available, we utilised images from both eyes if available. Of the remaining 35,917 participants, 83 had a history of PD prior to the baseline examination, yielding 35,834 participants eligible for analysis to examine the association between retinal age gap and risk of PD. If available, images from the right eye were included in the

prediction of retinal age; otherwise, images from the left eye would be used. Details of the training and verification process of the DL model for age prediction have been provided elsewhere [21].

Definition of retinal age gap

We defined the difference between retinal age predicted by the DL model and chronological age as the retinal age gap. A positive retinal age gap suggests that the retina appears 'older' than the patient's chronological age, while a negative retinal age gap suggests that the retina appears 'younger'.

Parkinson's disease ascertainment

PD was determined via hospital administration data in England, Scotland and Wales, the national death register data and self-reported data. PD was defined by self-report codes collected and the International Classification of Diseases Version 9 (ICD-9) code 332.0 and ICD-10 code G20. History of PD was defined as the presence of PD prior to the baseline examination by ICD codes recorded before the recruitment date or self-reported history of PD in the questionnaire at baseline. Incident PD was defined as the first occurrence of PD during the follow-up period, from baseline examination to the 29 February 2016, using a UK Biobank algorithm (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/alg_outcome_pdp.pdf). It integrated sources from hospital admissions records and death registry. The earliest ICD code for PD recorded in the hospital admissions record were defined as the onset date of the incident PD case and date of death was treated as a proxy of PD onset date if ICD code of PD were recorded for the first time in the death registry.

Covariates

According to previous studies [30–33] PD has been associated with various factors including age (continuous), gender (female/male), ethnicity (white/others), Townsend deprivation indices (continuous), smoking status (never/former smoker/current smoker), drinking status (never/former or current), obesity (no/yes), physical activity (meeting recommendation/not meeting recommendation), history of diabetes mellitus (no/yes), hypertension (no/yes), stroke (no/yes) and the use of psychotropic medication (no/yes). These factors were considered as potential confounding factors in our study and were adjusted for to minimise the effects of these variables.

Obesity was defined as body mass index (BMI) 30 kg/m^2 or over. History of diabetes was defined as a diagnosis of diabetes, the use of insulin treatment or diabetic medication, or HbA1C $\geq$48 mmol/mol. History of hypertension was defined as a diagnosis of hypertension, the use of antihypertensive treatment, or measured systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$80 mmHg. History of stroke was defined as having had a UK Biobank algorithm-defined prior stroke according to self-report and hospital admissions data. The use of psychotropic medication was defined as the use of anti-depressant, anti-migraine or anxiolytic medications.

Statistical analyses

The baseline characteristics of all participants were presented as means and standard deviations (SDs) for normally distributed variables, or numbers and percentages for categorical variables. Unpaired *t*-test or ANOVA, and Pearson's χ^2 test or Fisher's exact test were used to compare continuous variables and categorical variables, respectively. To examine the relationship between retinal age gap and the incidence of PD, Cox proportional hazards models were fitted. The associations of both 1-year increase in retinal age gap and the quartiles of it (i.e. retinal age gap data points ranked from the smallest to the largest into four equal parts) with future PD risk were investigated. Utilising two Cox models, we performed a multivariable analysis adjusting for age, gender and ethnicity (Model I); and additionally deprivation, smoking status, drinking status, obesity, physical activity, history of stroke, diabetes mellitus, hypertension and use of psychotropic medication (Model II). Hazards ratio (HR) and 95% confidence interval (CI) were calculated as major measurements for the association. To model the potential non-linear association between retinal age gap and incident PD, a restricted cubic spline was fitted. Retinal age gap of zero was set as the reference. Sensitivity analyses were conducted to validate the results. Sensitivity analysis was performed by adjusting for age square in addition to the co-variates included in Model II (Model III) to overcome the potential non-linear relationship. Participants with PD diagnosed within 1 year of the baseline assessment were excluded for another sensitivity analysis. Multivariable logistic regression models were applied to estimate the predictive value of retinal age, and established risk factors including age, gender and smoking status [34] for 5-year PD risk. Area under the receiver operator characteristic curves (AUC) was used to estimate the discrimination. A two-sided *P*-value of $<0{\cdot}05$ was defined as statistically significant. Statistical analyses were conducted using R (version 3.3.0, R Foundation for Statistical Computing, www.R-project.org, Vienna, Austria) and Stata (version 13, StataCorp, Texas, USA).

Results

Study populations

A total of 35,834 participants were included in the analysis with a mean age of 56.7 $\pm$ 8.04 years at baseline, and 55.7% of the participants were female (Table 1). During the median follow-up period of 5.83 (5.74–5.97) years, 63 (0.18%) incident PD cases were identified. Tables 1 and 2 showed the baseline characteristics of the study population stratified by quartiles of retinal age gap and by incident PD. There were significant differences in age, gender, ethnicity, Townsend index, smoking status, drinking status, obesity,

Table 1. Baseline characteristics of the study participants and stratified by quantiles of retinal age gap

Baseline characteristics	Total	Retinal age gap			
		Q1	Q2	Q3	Q4
N	35,834	8,959	8,958	8,959	8,958
Age, mean (SD), years	56.7 (8.04)	63.1 (4.81)	59.3 (6.43)	54.7 (7.34)	49.8 (6.43)
Gender, No. (%)					
Female	19,969 (55.7)	4,565 (51.0)	5,000 (55.8)	5,156 (57.6)	5,248 (58.6)
Male	15,865 (44.3)	4,394 (49.0)	3,958 (44.2)	3,803 (42.4)	3,710 (41.4)
Ethnicity, No. (%)					
White	33,400 (93.2)	8,456 (94.4)	8,411 (93.9)	8,297 (92.6)	8,236 (91.9)
Others	2,434 (6.79)	503 (5.61)	547 (6.11)	662 (7.39)	722 (8.06)
Townsend index, mean (SD)	−1.09 (2.96)	−1.45 (2.79)	−1.22 (2.88)	−0.99 (3.02)	−0.70 (3.08)
Smoking status, No. (%)					
Never	19,735 (55.4)	4,854 (54.5)	4,841 (54.3)	4,871 (54.6)	5,169 (58.0)
Former smoker	12,642 (35.5)	3,458 (38.8)	3,355 (37.6)	3,104 (34.8)	2,725 (30.6)
Current smoker	3,277 (9.19)	594 (6.67)	721 (8.09)	943 (10.6)	1,019 (11.4)
Drinking status, No. (%)					
Never	1,582 (4.43)	441 (4.93)	357 (3.99)	394 (4.41)	390 (4.37)
Former/current	34,143 (95.6)	8,497 (95.1)	8,586 (96.0)	8,535 (95.6)	8,525 (95.6)
Obesity, No. (%)					
No	26,528 (74.4)	6,766 (76.0)	6,641 (74.5)	6,605 (74.1)	6,516 (73.1)
Yes	9,121 (25.6)	2,141 (24.0)	2,276 (25.5)	2,309 (25.9)	2,395 (26.9)
Meeting PA recommendation, No. (%)					
No	5,289 (18.0)	1,126 (15.6)	1,270 (17.4)	1,379 (18.8)	1,514 (20.2)
Yes	24,036 (82.0)	6,084 (84.4)	6,031 (82.6)	5,950 (81.2)	5,971 (79.8)
History of stroke, No. (%)					
No	35,222 (98.3)	8,750 (97.7)	8,807 (98.3)	8,826 (98.5)	8,839 (98.7)
Yes	612 (1.71)	209 (2.33)	151 (1.69)	133 (1.48)	119 (1.33)
History of diabetes, No. (%)					
No	33,486 (93.5)	8,376 (93.5)	8,370 (93.4)	8,407 (93.8)	8,333 (93.0)
Yes	2,348 (6.55)	583 (6.51)	588 (6.56)	552 (6.16)	625 (6.98)
History of hypertension, No. (%)					
No	8,714 (24.3)	1,549 (17.3)	1,920 (21.4)	2,373 (26.5)	2,872 (32.1)
Yes	27,120 (75.7)	7,410 (82.7)	7,038 (78.6)	6,586 (73.5)	6,086 (68.0)
Use of psychotropic medication, No. (%)					
No	31,934 (89.1)	8,091 (90.3)	8,045 (89.8)	7,930 (88.5)	7,868 (87.8)
Yes	3,900 (10.9)	868 (9.69)	913 (10.2)	1,029 (11.5)	1,090 (12.2)

SD = standard deviation; PA = physical activity; Q = quartile. The first quartile (Q1) is defined as the set of data between the smallest value and the 25th retinal age gap. The second quartile (Q2) is the set of data between the 25th and median value. The third quartile (Q3) is set of data between the median value and the 75th retinal age gap. The fourth quartile (Q4) is defined as the set of data between the 75th and the maximum of the retinal age gap.

physical activity, history of stroke, hypertension and use of psychotropic medication across the four quartiles of retinal age gap (Table 1). Participants in the non-PD group were similar to those in the PD group except for age ($P < 0.001$), gender ($P = 0.040$) and smoking status ($P = 0.047$) (Table 2).

Retinal age gap and Parkinson's disease

After adjusting for multiple confounding factors each 1-year increase in retinal age gap was associated with a 10% increase in the risk of future PD (hazard ratio [HR] = 1.10, 95% confidence interval [CI]: 1.01–1.20, $P = 0.023$; Table 3). Meanwhile, the risk of PD in participants with retinal age gap in the third and fourth quartiles (HR = 2.66, 95% CI: 1.13–6.22, $P = 0.024$; HR = 4.86, 95% CI: 1.59–14.8, $P = 0.005$, respectively) was significantly higher than that of the lowest quartile. The risk of incident PD in the second quartile was similar to that of the lowest quartile. In the restricted cubic spline model no non-linear association were found between retinal age gap and incident PD (P non-linear = 0.322).

Sensitivity analyses

As shown in Table 3, after further adjustment of age square the association between retinal age gap and incident PD remained significant. After excluding participants diagnosed of PD within 1 year of the baseline examination similar findings were observed.

Predictive value of retinal age and established risk factors for PD risk

Figure 1 shows the receiver operator characteristic (ROC) curves of using retinal age and established risk factors including age, gender and smoking status as predictors of 5-year

Table 2. Baseline characteristics stratified by incident Parkinson disease

Baseline characteristics	Non-PD group	PD group	*P* value
N	35,771	63	–
Age, mean (SD), years	56.7 (8.04)	62.8 (5.63)	<0.001[a]
Gender, No. (%)			
Female	19,942 (55.8)	27 (42.9)	0.040[b]
Male	15,829 (44.2)	36 (57.1)	
Ethnicity, No. (%)			
White	33,343 (93.2)	57 (90.5)	0.388[b]
Others	2,428 (6.79)	6 (9.52)	
Townsend index, mean (SD)	−1.09 (2.96)	−1.65 (2.77)	0.134[a]
Smoking status, No. (%)			
Never	19,701 (55.4)	34 (54.0)	0.047[c]
Former smoker	12,614 (35.4)	28 (44.4)	
Current smoker	3,276 (9.20)	1 (1.59)	
Drinking status, No. (%)			
Never	1,578 (4.42)	4 (6.35)	0.362[c]
Former/current	34,084 (95.6)	59 (93.7)	
Obesity, No. (%)			
No	26,483 (74.4)	45 (71.4)	0.587[b]
Yes	9,103 (25.6)	18 (28.6)	
Meeting PA recommendation, No. (%)			
No	5,279 (18.0)	10 (20.0)	0.718[b]
Yes	23,996 (82.0)	40 (80.0)	
History of stroke, No. (%)			
No	35,160 (98.3)	62 (98.4)	1.000[c]
Yes	611 (1.71)	1 (1.59)	
History of diabetes, No. (%)			
No	33,427 (93.4)	59 (93.7)	1.000[c]
Yes	2,344 (6.55)	4 (6.35)	
History of hypertension, No. (%)			
No	8,701 (24.3)	13 (20.6)	0.495[b]
Yes	27,070 (75.7)	50 (79.4)	
Use of psychotropic medication, No. (%)			
No	31,881 (89.1)	53 (84.1)	0.203[b]
Yes	3,890 (10.9)	10 (15.9)	

SD = standard deviation; PA = physical activity; PD = Parkinson disease; HR = hazard ratio; CI = confidence interval. [a]Student's *t*-test. [b]Chi-squared test. [c]Fisher's exact test.

PD risk. The predictive value of the retinal-age-based model (AUC = 0.708, 95% CI: 0.638–0.778) and the risk-factor-based model (AUC = 0.717, 95% CI: 0.633–0.802) was similar ($P = 0.821$).

Discussion

The present study found each 1-year increase in retinal age gap was independently associated with a 10% increase in the risk of incident PD. Compared with the lowest quartile, participants in the third and fourth quartiles of retinal age gap had a 2.66- and 4.86-fold increased risk of developing PD, respectively. Further, the predictive value of retinal age and the well-established risk factors for PD were comparable in our analysis. Our findings suggest the retinal age gap has the potential to be utilised as a standalone biomarker, or conjunctively alongside other clinical risk factors/biomarkers for risk stratification to assist in clinical decision making.

To estimate a summary marker of individual neurodegeneration and microvascular ageing we employed the retinal age

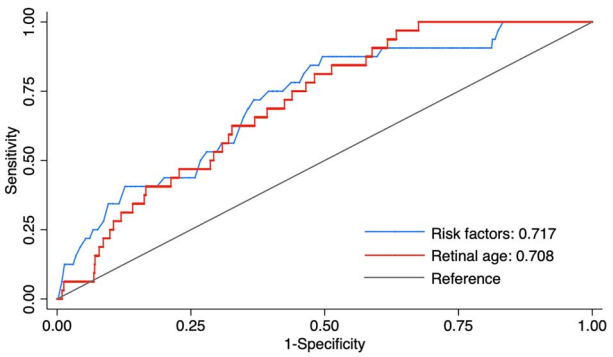

Figure 1. ROC curves of the retinal-age-based model and the risk-factor-based model. All models used PD status in 5 years from baseline as the response variable. The predictor variables were risk factors including age, gender and smoking status and retinal age at baseline. The AUC was comparable between the risk-factor-based model and the retinal-age-based model (0.717 and 0.708, $P = 0.821$).

Table 3. Association between retinal age gap with incident of PD

		Model I[a]		Model II[b]		Model III[c]	
Retinal age gap		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All participants	Mean (SD)						
Retinal age gap, per one age (years)	−1.31 (4.82)	1.06 (0.99–1.13)	0.090	**1.10 (1.01–1.20)**	**0.023**	**1.11 (1.01–1.21)**	**0.023**
Retinal age gap							
Quartile 1	−7.36 (3.44)	1 [Reference]	–	1 [Reference]	–	1 [Reference]	–
Quartile 2	−2.62 (0.86)	0.94 (0.48–1.84)	0.863	1.42 (0.63–3.19)	0.398	1.47 (0.65–3.36)	0.356
Quartile 3	0.26 (0.86)	1.74 (0.83–3.65)	0.142	**2.66 (1.13–6.22)**	**0.024**	**2.87 (1.17–7.03)**	**0.022**
Quartile 4	4.48 (2.35)	**3.53 (1.40–8.91)**	**0.008**	**4.86 (1.59–14.8)**	**0.005**	**5.15 (1.63–16.3)**	**0.005**
Excluding incident PD within 1 year							
Retinal age gap, per one age (years)	−1.31 (4.82)	1.05 (0.98–1.12)	0.147	**1.09 (1.00–1.19)**	**0.046**	**1.09 (1.00–1.19)**	**0.048**
Retinal age gap							
Quartile 1	−7.36 (3.44)	1 [Reference]	–	1 [Reference]	–	1 [Reference]	–
Quartile 2	−2.62 (0.86)	0.88 (0.44–1.75)	0.722	1.33 (0.58–3.05)	0.508	1.34 (0.58–3.13)	0.492
Quartile 3	0.26 (0.86)	1.81 (0.86–3.80)	0.120	**2.82 (1.20–6.64)**	**0.018**	**2.90 (1.18–7.15)**	**0.020**
Quartile 4	4.48 (2.35)	**3.46 (1.33–9.00)**	**0.011**	**4.80 (1.50–15.3)**	**0.008**	**4.90 (1.50–16.0)**	**0.009**

PD = Parkinson diseases; HR = hazard ratio; CI = confidence interval. The first quartile (Q1) is defined as the set of data between the smallest value and the 25th retinal age gap. The second quartile (Q2) is the set of data between the 25th and median value. The third quartile (Q3) is set of data between the median value and the 75th retinal age gap. The fourth quartile (Q4) is defined as the set of data between the 75th and the maximum of the retinal age gap. [a]Model I adjusted for age, gender and ethnicity. [b]Model II adjusted for age, gender, ethnicity, deprivation, smoking status, drinking status, obesity, physical activity, history of stroke, diabetes mellitus, hypertension and use of psychotropic medication. [c]Model III adjusted for age, age square, gender, ethnicity, deprivation, smoking status, drinking status, obesity, physical activity, history of stroke, diabetes mellitus, hypertension and use of psychotropic medication. Significant associations ($P<0.05$) are bolded.

concept based on retinal images which holds advantages of being fast, safe, non-invasive and cost-effective. We noted that the MAE of 3.55 years for retinal age compared well with the current literature reporting MAEs of 3.6–7.8 years for healthy individuals [8, 35, 36]. Further, the retinal age gap has previously been proven a reliable and valid biomarker of ageing which can predict mortality risk [21]. Results from the present study suggest that retinal age gaps may also be a potential ageing biomarker for the early detection of PD.

Our findings provided novel insights regarding ageing biomarkers currently associated with PD. To date, most studies investigating associations of multiple ageing biomarkers with PD were cross-sectional studies. For example, compared with healthy controls PD patients were more likely to have longer telomere length [14] but the association remains inconsistent across studies [15–17]. Accelerated epigenetic age of the immune system [18] and accelerated brain age gaps ranging from 1.5–3.3 years are also associated with PD in cross-sectional studies [19, 20]. Disappointingly, only one prospective study has examined a longitudinal association of ageing biomarker with future PD risk, which leaves counterintuitive associations regarding telomere length and PD warranting further corroboration [13].

Our findings support the hypothesis that retinal ageing may be an indicator for PD. Although mechanisms underlying the association remain to be elucidated, several plausible explanations can be proposed. Firstly, accelerated neurodegeneration observed in the retina might reflect the similar process in PD. Both animal [37] and population-based studies [38, 39] have provided evidence that the retina mirrors the ageing brain. When compared with subjects without PD, PD patients showed more prominent neuronal changes in the retina independent of age and other risk factors, such as increased reduction of retinal nerve fibre layer thickness [40–42]. In addition, retinal vascular alterations have been observed in PD, including decreased vessel density, perfusion density and capillary complexity [43–47]. These findings could be explained by the homogeneity of the retinal and cerebral circulation [23], and consequences of vascular ageing including mitochondrial oxidative stress on both retinal and brain vasculature [48].

Our findings shed light on the potential for retinal age gap to be utilised as a novel biomarker for identifying individuals at a high risk of developing PD. Retinal age gap which can be predicted through fundus photography lends itself as a potential large-scale screening tool, which could be further empowered by incorporation of smartphone-based teleophthalmology assessment [49]. Considering PD is just one of many factors potentially influencing the retinal age gap, the observed association between the retinal age gap and

the incident PD could be biased by such factors. Our analysis attempted to overcome these potential biases by adjusting for a wide array of confounding factors in the final model. A persistent significant association suggests that retinal age gap is a true biomarker for PD, independent from other known factors.

The specificity of the retinal age gap for early detection of PD is an important factor for its future application. Our findings, specifically that the increased retinal age gap was significantly associated with the greater risk of PD, has been interpreted as a byproduct of accelerating neurodegeneration and cerebral vascular ageing, however we suspect distinct patterns could be observed for other neurodegenerative diseases, such as Alzheimer's disease [50]. Thus, the concept of retinal age gap offers a unique opportunity to objectively quantify the deviation of high-dimensional morphometric patterns in neurons and the microvasculature from their age-related norm in a single measurement. Despite these innovative findings, further work is needed to disentangle specific physiological and pathological patterns from raw retinal age gaps to obtain sensitive, specific and clinically useful biomarkers of PD.

Strengths and limitations

The present study demonstrated several strengths including a large sample, standardised ascertainment of incident PD, standardised protocol for capturing fundus images and comprehensive adjustment of confounding factors. However, this study also had several limitations. First of all, the UK Biobank study included healthier and younger participants than the general population they were derived from due to the health selection bias [51], which may bias the association. Nevertheless, we have performed several sensitivity analyses to verify the robustness of our findings. Secondly, the limited number of incident PD cases prevented us from performing further subgroup analyses. Thirdly, due to the lack of follow-up data on fundus images, we could not investigate the association between dynamic changes of retinal age gap and incident PD. Further studies are warranted to examine the association of longitudinal retinal age gap changes and the risk of incident PD. Lastly, the possibility of residuals confounders could not be excluded.

Conclusion

In conclusion, we found that retinal age gap was associated with the future risk of incident PD. The retinal age gap can be considered a biological ageing marker that may be applied for the identification of preclinical PD patients. Further studies are necessary to investigate the association between the dynamic changes of retinal age gaps over time and the risks of PD to further validate our findings.

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