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Research paper

Association of visual impairment with risk for future Parkinson's disease

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ABSTRACT

Background: Although visual dysfunction is one of the most common non-motor symptoms among patients with Parkinson's disease (PD), it is not known whether visual impairment (VI) predates the onset of clinical PD. Therefore, we aim to examine the association of VI with the future development of PD in the UK Biobank Study.
Methods: The UK Biobank Study is one of the largest cohort studies of health, enrolling over 500,000 participants aged 40–69 years between 2006 and 2010 across the UK. VI was defined as a habitual distance visual acuity (VA) worse than 0·3 logarithm of the minimum angle of resolution (LogMAR) in the better-seeing eye. Incident cases of PD were determined by self report data, hospital admission records or death records, whichever came first. Multivariable Cox proportional hazard regression models were used to investigate the association between VI and the risk of incident PD.
Findings: A total of 117,050 participants were free of PD at the baseline assessment. During the median observation period of 5·96 (IQR: 5·77–6·23) years, PD occurred in 222 (0·19%) participants. Visually impaired participants were at a higher risk of developing PD than non-VI participants ($p < 0·001$). Compared with the non-VI group, the adjusted hazard ratio was 2·28 (95% CI 1·29–4·05, $p = 0·005$) in the VI group. These results were consistent in the sensitivity analysis, where incident PD cases diagnosed within one year after the baseline assessment were excluded.
Interpretation: This cohort study found that VI was associated with an increased risk of incident PD, suggesting that VI may serve as a modifiable risk factor for prevention of future PD.
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Abbreviations: PD, Parkinson's disease; VI, visual impairment; VA, visual acuity; LogMAR, logarithm of the minimum angle of resolution; NHS, National Health Service; PHQ-2, Patient Health Questionnaire-2; IQR, interquartile range; HR, hazard ratios; CI, confidence intervals; SD, standard deviations; PPV, positive predictive value; BMI, body mass index

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Research in context

Evidence before the study

Non-motor symptoms of Parkinson disease (PD) have been increasingly recognized to precede the onset of motor symptoms, and may act as markers of preclinical stages of PD. Of note, visual dysfunction as one of the non-motor symptoms of PD have been documented in several studies. The prevalence of this non-motor symptom was higher in PD patients compared with healthy subjects. However, no study to date have longitudinally examined the association of visual impairment (VI), an important indicator of visual dysfunction, with incident PD. Using the North American categorization, VI was defined as a habitual distance visual acuity (VA) worse than 0.3 logarithm of the minimum angle of resolution (LogMAR) in the better-seeing eye.

Added value of this study

In this population-based cohort study of 117,050 individuals, we found that participants with VI had 2.28-fold increased risk of developing future PD compared with those who were not visually impaired during a median follow-up of 5.96 years.

Implications of all the available evidence

VI was identified as a potential risk factor of incident PD in the present study, suggesting that visual screening should be implemented in patients at a high risk of developing PD.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and affects 2 to 3% of the global population aged over 65 [1]. The total burden of disease associated with PD is increasing due to ageing populations, longer disease durations and environmental and social risk factors [2]. Relatively conservative estimates predict over 12 million patients will be affected by PD globally by 2050 [3].

In addition to motor symptoms, clinical features of PD involve many non-motor symptoms exacerbating overall disability [4]. Non-motor symptoms of PD have recently received increased attention as they precede the onset of motor symptoms, and may act as markers of preclinical stages of PD [5]. Visual dysfunction including colour vision, pupil reactivity, stereopsis, eye movements [6], has been reported as one of the most common non-motor symptoms, and increasing evidence has demonstrated higher prevalence of this non-motor symptom in PD patients compared to healthy controls [7–10]. It is yet unknown however whether visual impairment (VI), an important indicator of visual dysfunction [11], predates the onset of clinical PD. Further, understanding the association between VI and future risk of PD may facilitate early diagnosis and intervention of PD prior to manifestation of the full clinical syndrome.

In this context, we sought to examine the association of VI with risk of future PD development using the UK Biobank, a community-based longitudinal sample.

2. Methods

2.1. Study sample

Detailed procedures of the UK Biobank study have been described elsewhere [12]. Briefly, more than 500,000 participants aged between 40 and 69 years were recruited at 22 assessment centers across the UK from 2006 to 2010. Data on lifestyle, environment and medical history were obtained using self-administered questionnaires. Physical measurements and biological specimens including blood, urine and saliva samples were also collected. Detailed follow-up of the health of participants was achieved through linkage to national electronic health record datasets. Ophthalmic examinations for baseline assessment were carried out from 2009 at six assessment centers. Participants with available visual acuity (VA) data (n = 117,252) were included in the present analysis. Baseline characteristics of participants with and without VA data is shown in Supplement Table 1. Relative to participants without VA data, those with available VA data were more likely to be slightly older (56·8 vs. 56·4 years), of non-Caucasian ethnicity, more materially deprived, non-smokers, non-drinkers, physically active, diabetic, hypertensive, less likely to use psychotropic medications and more likely to be cognitively impaired and depressed. For analysis of incident PD, participants diagnosed with PD prior to baseline assessment (n = 174), and those with self-reported PD at the baseline nurse interview (n = 28) were excluded, leading to a final cohort with 117,050 participants included for analysis.

2.2. Standard protocol approvals, registrations, and patient consents

Access to the UK Biobank data was granted after registration. The application ID was 62443. The UK Biobank has obtained Research Tissue Bank approval from its Research Ethics Committee recommended by the National Research Ethics Service (reference 11/NW/0382). Participants provided written informed consent.

2.3. Assessment of visual acuity

Detailed methods for VA testing in the UK Biobank study have been described elsewhere [13]. Habitual distance VA was measured using a logarithm of the minimum angle of resolution (LogMAR) chart (Precision Vision, LaSalle, Illinois, USA). Participants were tested at 4 m with habitual correction if any, or at 1 m if participants were unable to read. Participants were required to read letters sequentially from the top and the total number of correctly identified letters was converted to a logMAR VA. Presenting VA worse than 0·3 logMAR units (equivalent to Snellen 20/40) was defined as VI.

2.4. Ascertainment of PD

The algorithm for ascertaining PD in the UK Biobank Study could be found in detail elsewhere [14]. In brief, ascertainment of PD was based on self-reported data, diagnosis in the hospital admissions data, or cause of death recorded in the national death register, whichever was the earliest. Hospital admission data were retrieved from Health Episode Statistics records (for participants from England and Wales) and the Scottish Morbidity Records (for participants from Scotland). The National Health Service (NHS) Information Centre, and the NHS Central Register Scotland were used to obtain the date and causes of death for participants from England and Wales, and Scotland, respectively. The UK Biobank study conducted a validation study on the accuracy of code sources for identification of PD cases, which achieved a positive predictive value (PPV) of 0·91 (95% confidence interval [CI], 0·83–0·96) when combining all sources (self report, hospital admission records, and death records) [14]. Follow-up length was calculated as the time interval between the date of baseline assessment and the censor date, which is either the date of PD diagnosis, death, lost to follow-up or 1st March 2016.

3. Covariates

Consistent with previous studies [15–18], covariates for the analysis of incident PD included age at baseline assessment (continuous), sex (male/female), ethnicity (Caucasian and non-Caucasian), the Townsend deprivation index (continuous), smoking (current smoker,

past smoker, and never), alcohol consumption (current and past/never drinker), obesity (yes/no), physical activity (above moderate/vigorous/walking recommendation, and not), history of stroke (yes/no), history of diabete mellitus (yes/no), history of hypertension (yes/no), the use of psychotropic medications (yes/no), cognitive impairment (yes/no) and depression (yes/no).

Obesity was defined as body mass index (BMI) $\geq$30 kg/m^2. History of diabete mellitus was defined to include participants with either doctor-diagnosed diabetes, insulin treatment or oral antidiabetic medications. History of hypertension was defined to include participants with either doctor-diagnosed hypertension, antihypertensive agents or measured systolic pressure $\geq$130 mmHg or diastolic pressure $\geq$80 mmHg. The previous use of anti-depressive, anti-migraine and axiolytic medications was defined as the use of psychotropic medications. Cognitive impairment was defined by four cognitive tests in the UK Bionbank including prospective memory, pairs matching, fluid intelligence/reasoning, and reaction time. The failure of tests criteria were consistent with a previous study [19]. We defined cognitive impairment as failure in at least one test. Depression was defined by either a history of depression or with a Patient Health Questionnaire-2 (PHQ-2) score $\geq$3.

4. Statistical analysis

We reported normally distributed variables as means and standard deviation (SD); skewed variables as median and interquartile range (IQR), and categorical variables as number and percentages. Unpaired *t*-test and Pearson's χ^2 test were used to compare continuous and categorical variables, respectively. The log-rank test was used for comparison of incident PD distributions between VI and non-VI groups. The risks of incident PD associated with VI were evaluated using Cox proportional hazards models for estimation of hazard ratio (HR) with 95% confidence interval (CI). The first model was adjusted for age, gender and ethnicity, and the multivariable-adjusted model was additionally adjusted for Townsend deprivation index, smoking status, drinking status, obesity, physical activity, history of stroke, history of diabetes, history of hypertension, psychotropic medications and cognitive impairment.

To exclude the possibility that some patients with depression were not on an anti-depressive treatment, we performed a sensitivity analysis to additionally adjust for depression. To minimize the possibility of including prevalent cases in the present analysis, a sensitivity analysis was performed to exclude PD cases diagnosed in the year immediately following baseline assessment. Schoenfeld residuals were used to test the proportional hazards assumptions for Cox models and all variables were found to be valid. Two-sided p values less than 0·05 were considered statistically significant. All tests were conducted using Stata version 13 (StataCorp LLC, College Station, Texas USA).

5. Data availability statement

The UK Biobank is an open-access resource to researchers through registration of proposed research. This present study was approved and registered as study 62443 with the UK Biobank resource.

Table 1
Baseline characteristics of the study participants stratified by visual impairment status.

Baseline Characteristics	Total	Non-VI Group	VI Group	*P* value
n	117,050	113,039	4,011	–
Age, mean (SD), yrs	56·8 (8·11)	56·8 (8·12)	58·8 (7·57)	<0·001
Gender, *n* (%)				0·361
Female	63,695 (54·4)	61,484 (54·4)	2,211 (55·1)	
Male	53,355 (45·6)	51,555 (45·6)	1,800 (44·9)	
Ethnicity, *n* (%)				<0·001
White	104,128 (89·0)	100,829 (89·2)	3,299 (82·3)	
Other	12,922 (11·0)	12,210 (10·8)	712 (17·7)	
Townsend deprivation index, mean (SD)	−0·93 (3·01)	−0·96 (3·00)	−0·12 (3·33)	<0·001
Smoking status, *n* (%)				<0·001
Never	64,503 (55·5)	62,314 (55·5)	2,189 (55·5)	
Former	40,014 (34·4)	38,750 (34·5)	1,264 (32·0)	
Current	11,744 (10·1)	11,252 (10·0)	492 (12·5)	
Drinking status, *n* (%)				<0·001
Never	6,215 (5·33)	5,877 (5·22)	338 (8·54)	
Former/current	110,352 (94·7)	106,731 (94·8)	3,621 (91·5)	
Obesity, *n* (%)				0·001
No	87,747 (75·4)	84,859 (75·5)	2,888 (73·1)	
Yes	28,640 (24·6)	27,576 (24·5)	1,064 (26·9)	
Physical Activity				0·378
Not meeting recommendation	16,831 (17·7)	16,259 (17·7)	572 (18·3)	
Above moderate/vigorous/walking recommendation	78,195 (82·3)	75,642 (82·3)	2,553 (81·7)	
History of stroke, *n* (%)				<0·001
No	115,275 (98·5)	111,368 (98·5)	3,907 (97·4)	
Yes	1,775 (1·52)	1,671 (1·48)	104 (2·59)	
History of diabetes, *n* (%)				<0·001
No	109,222 (93·3)	105,589 (93·4)	3,633 (90·6)	
Yes	7,828 (6·69)	7,450 (6·59)	378 (9·42)	
History of hypertension, *n* (%)				<0·001
No	29,940 (25·6)	29,113 (25·8)	827 (20·6)	
Yes	87,110 (74·4)	83,926 (74·2)	3,184 (79·4)	
Psychotropic medications, *n*(%)				0·052
No	107,982 (92·3)	104,314 (92·3)	3668 (91·5)	
Yes	9,068 (7·75)	8,725 (7·72)	343 (8·55)	
Cognitive deficit, *n*(%)				<0·001
No	80,603 (69·0)	78,316 (69·4)	2287 (57·4)	
Yes	36,201 (31·0)	34,501 (30·6)	1700 (42·6)	
Depression, *n*(%)				<0·001
No	105,070 (89.8)	101,570 (89.9)	3500 (87.3)	
Yes	11,980 (10.2)	11,469 (10.1)	511 (12.7)	

SD = standard deviation; VI = visual impairment.

6. Role of funding

The funder was not involved in study design, data collection, data analysis, data interpretation, the writing this article or the decision to publish.

7. Findings

A total of 117,050 participants (mean [SD] age: 56·8 [8·11] years; female: 63,695 [54·4%]) who were free of PD at the baseline assessment were included in this present analysis. Baseline characteristics of included participants are described in Table 1. A total of 4011 (3·43%) participants suffered from VI. The visually impaired participants tended to be older, of non-Caucasian ethnicity, more materially deprived, current smokers, non-drinkers, obese, with a history of stroke, diabetes and hypertension, and more likely to be cognitively impaired and depressed. There were no differences in other charateristics between the VI and non-VI group.

During the median follow up period of 5·96 (IQR: 5·77–6·23) years, a total of 222 cases of PD were recorded. The incidence of PD in all participants was 0·19%, with 16 (7·21%) being in the VI group and 206 (92·8%) being in the non-VI group, respectively. The log-rank test demonstrated a significant difference in the incidence of PD between the VI and non-VI groups ($p < 0·001$). Baseline characteristics stratified by the incidence of PD are shown in Table 2. The incident PD group consisted of a greater proportion of participants that were of older age, male gender, former/current smokers, less physically active, with a history of hypertension, use of psychotropic medications, and cognitively impaired at the baseline assessment compared to the non-PD group.

Table 2
Baseline characteristics stratified by incident parkinson disease.

Baseline Characteristics	Non-PD Group	PD Group	*P* value
N	116,828	222	–
Age, mean (SD), yrs	56·8 (8·11)	63·2 (5·42)	<0·001
Gender, *n* (%)			<0·001
Female	63,608 (54·5)	87 (39·2)	
Male	53,220 (45·5)	135 (60·8)	
Ethnicity, *n* (%)			0·452
White	103,927 (89·0)	201 (90·5)	
Others	12,901 (11·0)	21 (9·46)	
Townsend deprivation index, mean (SD)	−0·93 (3·01)	−1·16 (2·89)	0·258
Smoking status, *n* (%)			0·010
Never	64,389 (55·5)	114 (51·4)	
Former	39,919 (34·4)	95 (42·8)	
Current	11,731 (10·1)	13 (5·86)	
Drinking status, *n* (%)			0·123
Never	6,198 (5·33)	17 (7·66)	
Former/current	110,147 (94·7)	205 (92·3)	
Obesity, *n* (%)			0·153
No	87,591 (75·4)	156 (71·2)	
Yes	28,577 (24·6)	63 (28·8)	
Physical Activity			0·007
Not meeting recommendation	16,786 (17·7)	45 (25·4)	
Above moderate/vigorous/ walking· recommendation	78,063 (82·3)	132 (74·6)	
History of stroke, *n* (%)			0·369
No	115,058 (98·5)	217 (97·8)	
Yes	1,770 (1·52)	5 (2·25)	
History of diabetes, *n* (%)			0·054
No	109,022 (93·3)	200 (90·1)	
Yes	7,806 (6·68)	22 (9·91)	
History of hypertension, *n* (%)			0·023
No	29,898 (25·6)	42 (18·9)	
Yes	86,930 (74·4)	180 (81·1)	
Psychotropic medications, *n*(%)			<0·001
No	107,798 (92·3)	184 (82·9)	
Yes	9,030 (7·73)	38 (17·1)	
Cognitive impairment, n(%)			0·003
No	80,470 (69·0)	133 (59·9)	
Yes	36,112 (31·0)	89 (40·1)	
Depression, n(%)			0·164
No	104,877 (89·8)	193 (86·9)	
Yes	11,951 (10·2)	29 (13·1)	

SD = standard deviation; PD = Parkinson's disease.

The risks of developing PD for participants with and without VI based on Cox proportional hazard regression models are shown in Table 3. After adjusting for age, gender and ethnicity, the presence of VI was significantly associated with a higher risk of developing PD (HR=2·13, 95% CI: 1·27–3·56, p = 0·004). The multivariable Cox proportional hazard regression model indicated that VI was associated with a 2·28-fold higher risk of developing subsequent PD (95% CI: 1·29–4·05, p = 0·005). Similar findings were observed in the sensitivity analyses which additionally adjusted for depression (HR=2·28, 95% CI: 1·29–4·04, p = 0.005, Table 3) and excluded participants with PD cases diagnosed in the year immediately following baseline assessment (HR=1·93, 95% CI: 1·07–3·48, p = 0·030, Table 3).

8. Discussion

In this large community-based sample, we found that visually impaired individuals had a 2·28 times greater risk of developing PD compared to those who did not have any VI. Our findings suggest that VI may represent a prodromal feature of PD.

The present study provided additional evidence to the limited knowledge on the longitudinal association between VI and PD. Our findings were in consistency with a recent longitudinal study in the Korean population, which found individuals with low VA had 26.7–35.7% increased risk of developing PD in the future [20]. In cross-sectional studies, it is well established that VI is more common in PD compared to healthy controls. In a cross-sectional study of the European population, PD patients had a greater than double increase in the odds of having self-reported fair or poor eyesight [10]. Worse results of objectively measured VA was also identified in PD patients by Polo et al. [8]. In addition, a case-control study suggested that patients with mild to moderate PD had poorer performance in terms of both near and far VA, which was correlated with worse cognitive function as well [7], indicating that VI was also implicated in cognitive deterioration of PD.

Of note, there have been numerous studies reporting the association between VI and dementia, another important neurodegenerative disease [21–26]. Longitudinal studies with follow-up periods ranging from 3.8 to 14.5 years suggested that visually impaired individuals are at a higher risk of developing dementia [22–24,26]. In a recent meta-analysis of 14 prospective studies, visually impaired individuals had an accumulatively 47% increased risk of developing incident dementia [22].

Given the consistent evidence on associations of VI and neurodegenerative diseases, we could reasonably speculate a neurodegeneration process occurs in the eye as it does in the brain, which could explain the association. Phenotypically, reduced macular thickness and volume were observed in patients with PD and these measures strongly associated with visual parameters including VA [8]. Biologically, the 'bottom-up theory' and the 'top-down theory' could provide plausible explanations. The 'bottom-up theory' postulated that impairment of the retinal dopaminergic system might explain VI in PD [27]. Both animal and clinical studies had suggested that dopaminergic retinal cell loss was commonly seen in PD [28–31]. Further, aggregates of α-synuclein in the retina that mimiced the pathological process of PD, had been reported to cause neurodegeneration of the dopaminergic cells in the retina [32]. The 'top-down theory' might explain VI observed in PD. Support for this hypothesis came from evidence which demonstrated specific dysfunctions of the visual cortex in PD [33]. The depletion of neurotransmitters such as GABA and dopamine, as well as altered lipid metabolism in the visual cortex of PD patients, could account for VI [34–36]. Alternatively, shared

Table 3
Cox Proportional hazards models for incident parkinson disease by visual impairment status.

VI Status	Age-, Gender- and Ethnicity-Adjusted Model		Multivariable Model [a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Main analysis				
VI status				
None	1 [Reference]	–	1 [Reference]	–
VI	2·13 (1·27–3·56)	0·004	2·28 (1·29–4·05)	0·005
Sensitivity analysis I[b]				
VI status				
None	–	–	1 [Reference]	–
VI	–	–	2.28 (1·29–4·04)	0·005
Sensitivity analysis II[c]				
VI status				
None	1 [Reference]	–	1 [Reference]	–
VI	1·79 (1·05–3·03)	0·031	1·93 (1·07–3·48)	0·030

VI = visual impairment; PD = Parkinson's disease; HR = hazard ratio; CI = confidence interval.
[a] Cox proportional hazards regression models adjusted for age, gender, race/ethnicity, Townsend deprivation index, smoking status, drinking status, obesity, physical activity, history of stroke, history of diabetes, history of hypertension, psychotropic medications and cognitive impairment.
[b] Cox proportional hazards regression models adjusted for age, gender, race/ethnicity, Townsend deprivation index, smoking status, drinking status, obesity, physical activity, history of stroke, history of diabetes, history of hypertension, psychotropic medications, cognitive impairment and depression.
[c] Excluding incident PD diagnosed in the year immediately following baseline assessment.

elements in the development of visual-threatening eye diseases and PD could account for the association between VI and PD [37]. Previous studies found that ocular diseases, such as glaucoma, cataract, age-related macular degeneration and diabetic retinopathy [38–40], shared similar pathogenesis [41,42], risk factors [27,43] and proteomics profiles [44] with PD. Further studies are warranted to confirm these speculations.

Our findings have an important implication for research and public health policy. In the present study, VI was identified as a potential risk factor of incident PD, suggesting that visual screening should be implemented in patients at a high risk of developing PD. In addition, the benefits of the VA screening may be expanded beyond its current scope in the prevention of sight-threatening disease.

The strengths of the present study include its large sample size, long-term follow-up duration, and comprehensive adjustments for confounding factors. However, several limitations should be considered. Firstly, the present analysis was solely based on baseline VA. Further studies are needed to examine the impact of vision loss and/or other aspects of visual dysfunction on future risk of PD. Secondly, we did not have sufficient information to differentiate between causes of VI, thus preventing us from investigating associations between specific causes of VI and the risk of developing PD. Thirdly, due to the nature of an observational study, the causal relationship between VI and incident PD cannot be confirmed. Fourth, the UK Biobank participants were relatively younger and might not represent the whole population. Nevertheless, this would not affect the association between VI and incident PD [45]. Lastly, we could not completely exclude the possibility of residual confounding.

In summary, we found that VI was associated with a significantly increased risk of developing PD. Our findings highlighted the importance of vision screening in identifying individuals at high risk of developing PD. Further studies in a distinct population are needed to corroborate our findings, and the causal nature of VI and PD.

Data sharing statement

All statistical outputs in the present study are included in the main text or the supplementary files. Further enquiries could be sent to the corresponding author.

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Author contributions

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Declaration of Competing Interest

The author(s) have no potential conflicts of interest in any materials discussed in this article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101189.

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