Visual Impairment and Risk of Dementia: The UK Biobank Study

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• PURPOSE: **To investigate the relationship between visual impairment (VI) and dementia in the UK Biobank Study.**
• DESIGN: **Prospective cohort study.**
• METHODS: **A total of 117,187 volunteers (aged 40-69 years) deemed free of dementia at baseline were included. Habitual distance visual acuity worse than 0.3 logMAR units in the better-seeing eye was used to define VI. The incident dementia was based on electronically linked hospital inpatient and death records.**
• RESULTS: **During a median follow-up of 5.96 years, the presence of VI was significantly associated with incident dementia (hazard ratio: 1.78; 95% confidence interval: 1.18-2.68; $P = .006$). There was a clear trend between the severity of VI and risk of dementia (P for trend = .002).**
• CONCLUSIONS: **We found VI was associated with increased risk of dementia, with a progressively greater risk among those with worse visual acuity. Our findings suggested that VI might be a modifiable risk factor for dementia and highlighted the potential value of VI elimination to delay the manifestation of dementia. (Am J Ophthalmol 2022;235: 7–14. © 2021 Elsevier Inc. All rights reserved.)**

This study investigated the association between visual impairment and its severity with incident dementia in a total of 117,187 participants of the UK Biobank Study. People with visual impairment had a greater risk of dementia and there was a clear trend between the severity of visual impairment and the risk of dementia. These findings suggested that visual impairment could be modifiable risk factor to control the onset and progression of dementia.

The number of people with visual impairment (VI) and blindness is projected to more than double by 2050, as a result of shifting demographics and an aging population.[1,2] In addition to vision loss, people with VI are more likely to have mental disorders (eg, depression),[3] social isolation,[4] unintentional injuries,[5] functional disabilities,[6] and increased risk of mortality.[7,8]

Dementia is an increasing threat to global health, affecting nearly 46.8 million people worldwide, with this number expected to triple by 2050.[9] Despite this heavy burden, effective treatments for dementia are yet to be developed. Therefore, early prevention, detection, and management are essential to address the enormous burden of dementia.

There is mounting evidence that suggests that VI and cognitive decline may be closely related.[10-22] Nevertheless, the association between VI and the risk of incident dementia has been poorly understood.[23-31] It may be possible that the true association between VI and incident dementia was masked in earlier studies by using relatively small sample size and self-reported visual function, focusing on late-onset dementia, and bias of identifying dementia cases.

Therefore, we aimed to investigate the association of objectively determined VI and VI severity with incident dementia in a large-scale sample aged 40 through 69 years from the United Kingdom (UK) Biobank Study.

METHODS

• STUDY SAMPLE: The UK Biobank is a large-scale prospective cohort study, enrolling more than 500,000 people (aged 40-69 years) from across the UK, with baseline

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Abbreviations: VI, Visual impairment; UK, United Kingdom; logMAR, logarithm of the Minimum Angle of Resolution; VA, Visual Acuity; HR, Hazard Ratios; CI, Confidence Interval; OR, Odds Ratio; SD, Standard Deviation.

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recruitment taking place during 2006-2010. Details of the rationale, design, and assessments used in the UK Biobank Study have been described previously.[32] Briefly, from the UK's National Health Service, approximately 9.2 million people aged 40 to 69 years and residing near 1 of 22 assessment centers were invited. A total of 502,505 people (5.5% response rate) agreed to participate and visited the assessment centers. During the baseline assessment, participants answered comprehensive questionnaires, underwent physical measures, and provided biological samples. They also gave consent to link to their health-related records. Ophthalmic assessments, including logarithm of the Minimum Angle of Resolution (logMAR) visual acuity (VA), autorefraction, intraocular pressure, keratometry, corneal biomechanics, and spectral-domain optical coherence tomography imaging, were introduced to the baseline assessment in 2009 for 6 assessment centers.

The UK Biobank Study's ethical approval had been granted by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee. Because only de-identified data from a public dataset were accessed, the Medical Research Ethics Committee of Guangdong Provincial People's Hospital waived the requirements to obtain ethical approval. The study adhered to the tenets of the Declaration of the Helsinki. Written informed consent was obtained from all participants.

• **VA TESTING:** The detailed procedure for VA testing in the UK Biobank Study has been described elsewhere.[33] Presenting distance VA was measured with the habitual correction (if any) at 4 meters using the logMAR chart (Precision Vision) on a computer screen. Presenting VA was scored as the total number of correctly read lines, converted to logMAR units. In the present analysis, VI was defined as the presenting VA worse than 0.3 logMAR units (Snellen acuity 20/40) in the better-seeing eye. Based on the presenting VA in the better-seeing eye, the severity of VI was classified as mild ($0.3 < \text{logMAR} \leq 0.6$; 20/40 < Snellen acuity $\leq$ 20/80), moderate ($0.6 < \text{logMAR} \leq 0.7$; 20/80 < Snellen acuity $\leq$ 20/100) and severe ($0.7 < \text{logMAR}$; Snellen acuity < 20/100).

• **ASCERTAINMENT OF INCIDENT DEMENTIA:** Dementia cases in the UK Biobank Study were ascertained by combining data from participants' medical history and record linkage to hospital admissions data and the national death register. Detailed information regarding the algorithms used to combine data from different sources to identify dementia can be found at the following link: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_dementia.pdf. In the present analysis of incident dementia, we excluded participants who already had a diagnosis of dementia in the hospital admissions data or self-reported dementia at the point of study entry. Follow-up time was calculated as the duration between the date of the first assessment and censored at the date of incident dementia, date of death, date of loss to follow-up, or March 1, 2016, whichever occurred earliest.

• **COVARIATES:** Factors known to be associated with dementia were included as potential confounders in the present analysis. These confounding variables included age, sex, race (recorded as White and non-White), Townsend Deprivation Index (an area-based proxy measure for socioeconomic status), education attainment (recorded as college or university degree, and others), family history of dementia (a marker of biological vulnerability), smoking status (recorded as current/previous and never), physical activity level (recorded as above moderate/vigorous/walking recommendation or not), and comorbidities (depression, diabetes, hypertension, and hyperlipidemia), which were collected at the same time as the VA data.

Self-reporting and/or score on the Patient Health Questionnaire (the first 2 items) of at least 3 were used to identify participants with depression.[34] Hypertension was defined to include those participants who had self-reported or physician-diagnosed hypertension, were taking antihypertensive drugs, or had a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg averaged over 2 measurements. Diabetes was defined to include those participants who had self-reported or physician-diagnosed diabetes mellitus, were taking antihyperglycemic medications or using insulin, or had a glycosylated hemoglobin level of $\geq$6.5%. Hyperlipidemia was defined to include participants with physician-diagnosed hyperlipidemia, were taking lipid-lowering drugs, or had a total cholesterol level $\geq$6.21 mmol/L.

• **STATISTICAL ANALYSIS:** Descriptive statistics, including means and standard deviations, numbers and percentages, were used to report baseline characteristics of study participants. The unpaired *t* tests were used to compare means between 2 groups on continuous variables, and Pearson χ^2 tests to compare distributions between 2 groups on categorical variables. The log-rank test was used to compare distributions of incident dementia between VI and non-VI groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated based on the Cox proportional hazards regression models. Age- and sex-adjusted Cox proportional hazards regression models were used to identify covariates strongly associated with incident dementia. The covariates that were found to be associated with incident dementia in the age- and sex-adjusted models were then adjusted in the multivariable models.

We performed sensitivity analysis classifying VI using 2 different cutoffs: a presenting VA worse than 0.6 logMAR units (Snellen acuity 20/80) and worse than 0.7 logMAR units (Snellen acuity 20/100) in the better-seeing eye. We also performed a sensitivity analysis using logistic regression to investigate the relationship between VI and dementia.

The proportional hazards assumption for the Cox proportional hazard regression model was satisfied graphically. All tests were 2-sided and statistical significance was set at a P value <.05. All analyses were performed using Stata, version 13 (StataCorp).

RESULTS

• **STUDY SAMPLE:** Of the 502,504 participants enrolled in the baseline UK Biobank Study between 2006 and 2010, VA was measured in 117,252 participants (23.3%). Supplemental Table 1 demonstrates the baseline characteristics of participants with and without VA data. In summary, participants with VA data tended to be slightly older and living in a socioeconomically deprived area compared with those without VA data. There was a similar proportion of men and women, but compared with those without VA data, there was a slightly lower proportion of people who were current/former smokers, a slightly higher representation of non-White race, college or university degree, family history of dementia, below physical activity recommendation, and comorbidities than those without VA data. In the analysis of incident dementia, we excluded participants diagnosed with dementia before baseline assessment (n = 52) and those who self-reported at the baseline nurse interview (n = 13). A total of 117,187 participants were included in the final analysis.

Among the 117,187 participants who were not diagnosed with dementia at the baseline assessment, the mean (standard deviation) age was 56.8 (8.11) years and 54.4% (n=63,745) were female. Other baseline characteristics for the study population are shown in Table 1. A total of 4,018 participants (3.43%) had VI and 113,169 participants (96.6%) did not have VI. Table 1 provides the baseline characteristics for the VI and comparator groups. Participants with VI were more likely to be older, of non-White race, living in a socioeconomically deprived area, and less educated than those without VI. Relative to the comparison group, a slightly lower proportion of participants with VI had a family history of dementia, but a higher proportion had depression, diabetes mellitus, and hypertension.

• **INCIDENT DEMENTIA:** The median follow-up duration post baseline enrollment was 5.96 years (interquartile range: 5.77-6.23 years). A total of 438 participants (0.37%) were ultimately classified as having incident dementia. The baseline characteristics stratified by dementia status at follow-up are shown in Table 2. Age- and sex-adjusted Cox proportional hazards regression models showed that race, education attainment, Townsend Deprivation Index, physical activity level, family history of dementia, and comorbidities (depression and diabetes mellitus) at baseline were significant risk factors for the incident dementia (Table 2).

Participants with VI at baseline were more likely to develop dementia at follow-up compared with those without VI (0.87% vs 0.36%, log-rank test, $z = 28.5$; $P < .001$). After adjusting for potential confounders, the presence of VI was independently associated with a 78% higher risk of incident dementia (95% CI: 1.18-2.68; $P = .006$; Table 3). There was a significant trend toward higher dementia risk across the VI severity groups (P for trend = .002; Table 3), where the greatest risk for dementia was among those with severe VI (HR: 3.53; 95% CI: 1.31-9.49; $P = .013$; Table 3).

• **SENSITIVITY ANALYSIS:** We observed similar findings of sensitivity analyses using different thresholds for classifying VI, where the risk of dementia was greatest among participants with a presenting VA worse than 0.7 logMAR units for VI (HR: 3.42; 95% CI: 1.27-9.19; $P = .015$), followed by a cutoff of 0.6 logMAR units for VI (HR: 2.39; 95% CI: 0.99-5.80; $P = .053$, Supplemental Table 2). Sensitivity analysis using logistic regression models to examine the association of VI and dementia showed similar results to the main analysis (Supplemental Table 3).

DISCUSSION

In this large community-based population of 117,187 initially dementia-free people, we found that participants with VI were more likely to develop incident dementia, even after adjusting for potential confounders. We also found that the increased risk of dementia occurred in a graded fashion by VI severity. Our findings suggested that VI might be a modifiable risk factor for dementia prevention, thus highlighting the importance of vision screening and treatment in older adults. Additional studies are warranted to investigate the causal relationship between VI and dementia.

Our findings have been corroborated by previous studies. The English Longitudinal Study of Ageing,[23] Gingko Evaluation of Memory Study,[24] Health and Retirement Study cohort,[25] and Women's Health Initiative[26] reported that the presence of VI was independently associated with a higher incidence of dementia during follow-up periods of 7 to 18 years. Interestingly, the Three-City Study suggested that poor vision was an indicator of dementia risk at short term (the first 2 years after inclusion) and middle term (from 2 to 4 years after inclusion), but not at long term (beyond 4 years after inclusion).[27] Data from the Korean National Health Insurance database[28] and the cohort of the Hong Kong Elderly Health Centres[29] showed that people with severe VI were at the greatest risk of incident dementia, thereby supporting the association between VI and incident dementia. Nevertheless, other studies presented data refuting these conclusions: in a case-control study in Germany, Michalowsky and associates[30] found that VI was not significantly associated with the risk of dementia. Likewise, the association between poor VA and the risk of developing

TABLE 1. Baseline Characteristics of the Study Participants Stratified by Visual Impairment Status

Baseline Characteristics	Total	Non-VI Group	VI Group	OR (95% CI)[a]
No. of participants	117,187	113,169	4,018	—
Age, y, mean (SD)	56.8 (8.11)	56.8 (8.12)	58.8 (7.57)	**1.03 (1.03-1.04)**
Sex, n (%)				
Female	63,745 (54.4)	61,533 (54.4)	2,212 (55.0)	1 (Reference)
Male	53,442 (45.6)	51,636 (45.6)	1,806 (45.0)	0.96 (0.90-1.02)
Race, n (%)				
White	104,249 (89.0)	100,945 (89.2)	3,304 (82.2)	1 (Reference)
Other	12,938 (11.0)	12,224 (10.8)	714 (17.8)	**2.08 (1.91-2.26)**
Townsend Deprivation Index, mean (SD)	–0.93 (3.01)	–0.96 (3.00)	–0.12 (3.34)	**1.10 (1.09-1.11)**
Education level, n (%)				
College or university degree	40,557 (34.6)	39,504 (34.9)	1,053 (26.2)	1 (Reference)
Other	76,630 (65.4)	73,665 (65.1)	2,965 (73.8)	**1.42 (1.32-1.53)**
Smoking status, n (%)				
Never	64,601 (55.5)	62,410 (55.5)	2,191 (55.4)	1 (Reference)
Former/current	51,795 (44.5)	50,035 (44.5)	1,760 (44.6)	0.96 (0.90-1.02)
Physical activity, n (%)				
Not meeting recommendation	16,867 (17.7)	16,292 (17.7)	575 (18.4)	1 (Reference)
Meeting recommendation	78,268 (82.3)	75,711 (82.3)	2,557 (81.6)	0.93 (0.85-1.02)
Family history of dementia, n (%)				
No	99,228 (84.7)	95,760 (84.6)	3,468 (86.3)	1 (Reference)
Yes	17,959 (15.3)	17,409 (15.4)	550 (13.7)	**0.79 (0.72-0.87)**
History of depression, n (%)				
No	105,197 (89.8)	101,692 (89.9)	3,505 (87.2)	1 (Reference)
Yes	11,990 (10.2)	11,477 (10.1)	513 (12.8)	**1.38 (1.26-1.52)**
History of diabetes, n (%)				
No	109,346 (93.3)	105,706 (93.4)	3,640 (90.6)	1 (Reference)
Yes	7,841 (6.69)	7,463 (6.59)	378 (9.41)	**1.37 (1.23-1.53)**
History of hypertension, n (%)				
No	29,972 (25.6)	29,141 (25.8)	831 (20.7)	1 (Reference)
Yes	87,215 (74.4)	84,028 (74.2)	3,187 (79.3)	**1.17 (1.08-1.27)**
History of hyperlipidemia, n (%)				
No	62,918 (53.7)	60,857 (53.8)	2061 (51.3)	1 (Reference)
Yes	54,269 (46.3)	52,312 (46.2)	1957 (48.7)	0.96 (0.90-1.03)

CI = confidence interval, OR = odds ratio, VI = visual impairment, SD = standard deviation.

[a]Logistic regression models adjusted for age and sex. Bold font indicates statistical significance.

TABLE 2. Baseline Characteristics Stratified by Dementia Status at Follow-up

Baseline Characteristics	Non-Dementia Group	Dementia Group	HR (95% CI)[a]
No. of participants	116,749	438	—
Age, y, mean (SD)	56.8 (8.10)	64.0 (5.13)	**1.18 (1.16-1.21)**
Sex, n (%)			
Female	63,550 (54.4)	195 (44.5)	1 (Reference)
Male	53,199 (45.6)	243 (55.5)	**1.39 (1.15-1.68)**
Race, n (%)			
White	103,857 (89.0)	392 (89.5)	1 (Reference)
Others	12,892 (11.0)	46 (10.5)	**1.49 (1.10-2.02)**
Townsend Deprivation Index, mean (SD)	-0.93 (3.01)	–0.76 (3.17)	**1.06 (1.03-1.09)**
Education level, n (%)			
College or university degree	40,471 (34.7)	86 (19.6)	1 (Reference)
Others	76,278 (65.3)	352 (80.4)	**1.73 (1.36-2.19)**
Smoking status, n (%)			
Never	64,394 (55.5)	207 (47.7)	1 (Reference)
Former/current	51,568 (44.5)	227 (52.3)	1.12 (0.93-1.36)
Physical activity, n (%)			
Not meeting recommendation	16,788 (17.7)	79 (24.7)	1 (Reference)
Meeting recommendation	78,027 (82.3)	241 (75.3)	**0.58 (0.45-0.75)**
Family history of dementia, n (%)			
No	98,897 (84.7)	331 (75.6)	1 (Reference)
Yes	17,852 (15.3)	107 (24.4)	**1.45 (1.16-1.80)**
History of depression, n (%)			
No	104,841 (89.8)	356 (81.3)	1 (Reference)
Yes	11,908 (10.2)	82 (18.7)	**2.75 (2.16-3.50)**
History of diabetes, n (%)			
No	108,988 (93.4)	358 (81.7)	1 (Reference)
Yes	7761 (6.65)	80 (18.3)	**2.30 (1.80-2.94)**
History of hypertension, n (%)			
No	29,909 (25.6)	63 (14.4)	1 (Reference)
Yes	86,840 (74.4)	375 (85.6)	1.14 (0.87-1.50)
History of hyperlipidemia, n (%)			
No	62,738 (53.7)	180 (41.1)	1 (Reference)
Yes	54,011 (46.3)	258 (58.9)	1.08 (0.89-1.31)

CI = confidence interval, HR = hazard ratio, SD = standard deviation.
[a]Cox proportional hazards regression models adjusted for age and sex. Bold font indicates statistical significance.

TABLE 3. Cox Proportional Hazards Models for Incident Dementia by Visual Impairment Status

VI Status	Multivariable Model [a]	
	HR (95% CI)	*P* Value
VI status		
None	1 (Reference)	—
VI	1.78 (1.18-2.68)	.006
VI severity		
None	1 (Reference)	—
Mild	1.66 (1.05-2.62)	.002
Moderate	1.12 (0.16-8.01)	—
Severe	3.53 (1.31-9.49)	—

CI = confidence interval, HR = hazard ratio, VI = visual impairment.

[a]Cox proportional hazards regression models adjusted for age, sex, race, education level, Townsend Deprivation Index, physical activity level, family history of dementia, history of diabetes mellitus, hypertension, and depression.

dementia did not reach significance in the Health, Aging and Body Composition Study.[31] Discrepancy in study design, statistical methodology, demographic characteristics, and definition of VI or poor vision, as well as the detection of dementia, may partly explain the inconsistency among studies' results.

Several mechanisms have been postulated to explain the association between VI and risk of dementia, either in favor of VI being the manifestation of neurodegeneration, greater cognitive load and lower cognitive efficiency, functional disabilities, or shared pathogenesis between VI and dementia. Firstly, it has been suggested that VI may be one of the first manifestations of dementia.[35] Secondly, people with VI may place more stress on neural resources to optimally perform visual tasks, thus increasing cognitive loads.[36] Alternatively, based on the visual deprivation hypothesis, reduced visual inputs and stimulation may compromise cognitive efficiency.[37] It remains possible that the association between VI and dementia may be due to intermediate factors. For instance, people with VI were more prone to social isolation, which, in turn may predispose them to depression, a significant risk factor for dementia.[38] Alternatively, VI could prevent patients from participating in physical activity, which might also contribute to an increased risk of dementia.[39] Additional studies are needed to explore the mediation effects of comorbidities and behaviors in the VI–dementia relationship. Lastly, the shared pathogenesis between the causes of VI and dementia may also explain this association. β-Amyloid deposits and genetic risk factors for dementia have been implicated in patients with age-related macular degeneration, one of the leading causes of VI.[40]

From a health policy perspective, our findings highlight the value of regular vision screening and elimination of VI. Firstly, vision assessment is a widely available and low-cost test. In addition, with the advent of smartphone-based eye care services,[41] the accessibility and uptake of VA testing have improved greatly, particularly in disadvantaged areas. Given the strong evidence of the association between VI and incident dementia, VA testing may be a valuable tool to identify people at high risks of cognitive decline and dementia. Secondly, our findings imply the potential benefits of vision training and VI elimination in delaying the manifestation of dementia, which would have a global economic effect. Notably, it has been indicated that vision-related training (eg, the field of view training) and low vision rehabilitation (eg, cataract surgery) may improve cognitive function.[42,43] Additional studies are needed to investigate the benefits of vision training and vision rehabilitation in dementia prevention.

Despite the advantages of large sample size, long-term follow-up, complete adjustment for confounders, age range in the analytical sample involving cases of early-onset dementia, and use of routinely updated health-related records identifying incident dementia in the present analysis, several limitations should be borne in mind. First, we only explored the association between baseline VA and risk of dementia. Further studies are needed to investigate the effects of VA changes and other components of visual function (eg, contrast sensitivity) on risk of dementia. Second, causes of VI were not available in the present analysis, which prevented us from investigating associations between specific causes of VI and risks of dementia. Third, due to the observational design, we could not draw causal inferences. Additional studies are needed to elucidate a causal relationship between VI and dementia. Fourth, participants included in the present study accounted for approximately one-fifth of the total cohort and demonstrated different baseline characteristics when stratified by availability of VA data, which limited the generalizability of the present study. Nevertheless, given the extensive phenotyping of the participants, valid assessment of a VI–dementia relationship may remain validly generalizable, as included participants being representative of the sampling population is not required.[44] Furthermore, the strong VI–dementia association has been verified by a recent meta-analysis.[45] Fifth, the algorithmically defined dementia outcomes in the UK Biobank Study were based mainly on hospital admissions records, which may have underestimated the incident cases of dementia, especially for those in the mild spectrum. Nevertheless, the incident dementia events captured by the algorithmically defined method were found to balance a high positive predictive value with reasonable case ascertainment.[46] Furthermore, the identified dementia cases were clinically significant, as these are the leading causes of morbidity and mortality. Sixth, given that the status of the covariates, such as depression and physical activity, might change with the status of VI, we cannot exclude the possibility of misclassification of covariates as the study progressed, or a mediation relationship between VI and other covariates. Last but not the least, although a broad array of potential con-

founders were accounted for in the statistical analysis, we could not completely exclude residual confounding. For instance, the lack of adjustments of the accessibility to health care services and insurance might increase bias for the VI–dementia association.

In summary, we found that people with VI were more likely to develop incident dementia, with a progressively greater risk among those with worse VA. Our findings highlight the value of regular vision screening and vision rehabilitation. Additional research is warranted to confirm our findings and further investigate the effects of vision rehabilitation on prevention of dementia.

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