Visual impairment and risk of dementia in two population-based prospective cohorts: UK Biobank and EPIC-Norfolk

Thomas J. Littlejohns, PhD, Shabina Hayat, PhD, Robert Luben, PhD, Carol Brayne, PhD, Megan Conroy, MSc, Paul J. Foster, PhD, Anthony P. Khawaja, PhD, Elżbieta Kuźma, PhD

Nuffield Department of Population Health, University of Oxford, Oxford, UK (T.J.L., M.C.); Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (S.H., R.L., C.B.); NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK (P.J.F., A.P.K.); MRC Epidemiology Unit, University of Cambridge, Cambridge, UK (A.P.K.); Albertinen-Haus Centre for Geriatrics and Gerontology, University of Hamburg, Hamburg, Germany (E.K.)

Corresponding author: Thomas J. Littlejohns, Big Data Institute, University of Oxford, Old Road Campus, Oxford, UK, OX3 7LF. E-mail: thomas.littlejohns@ndph.ox.ac.uk. Tel: +44 (0) 1865 743645

Abstract

Visual impairment has emerged as a potential modifiable risk factor for dementia. However, there are a lack of large studies with objective measures of vison and with more than ten years of follow-up. We investigated whether visual impairment is associated with an increased risk of incident dementia in UK Biobank and EPIC-Norfolk. In both cohorts, visual acuity was measured using a "logarithm of the minimum angle of resolution" (LogMAR) chart and categorised as no (≤0.30 LogMAR), mild (>0.3 - ≤0.50 LogMAR), and moderate to severe (>0.50 LogMAR) impairment. Dementia was ascertained through linkage to electronic medical records. After restricting to those aged ≥60 years, without prevalent dementia and with eye measures available, the analytic samples consisted of 62,206 UK Biobank and 7,337 EPIC-Norfolk participants, respectively. In UK Biobank and EPIC-Norfolk. respectively, 1,113 and 517 participants developed dementia over 11 and 15 years of follow-up. Using multivariable cox proportional-hazards models, the hazard ratios for mild and moderate to severe visual impairment were 1.26 (95% Confidence Interval [CI] 0.92-1.72) and 2.16 (95% CI 1.37-3.40), in UK Biobank, and 1.05 (95% CI 0.72-1.53) and 1.93 (95% CI 1.05-3.56) in EPIC-Norfolk, compared to no visual impairment. When excluding participants censored within 5 years of follow-up or with prevalent poor or fair self-reported health, the direction of the associations remained similar for moderate impairment but were not statistically significant. Our findings suggest visual impairment might be a promising target for dementia prevention, however the possibility of reverse causation cannot be excluded.

Keywords: prevention, visual acuity, longitudinal, epidemiology

Introduction

Visual acuity is the ability to see clearly and is typically used to assess visual impairment, which can range from mild impairment to complete blindness (1). An estimated 440 million individuals worldwide live with visual impairment, with the prevalence of blindness projected to triple between 2020-2050 (2). However, visual impairment is often preventable or treatable through eye care programmes, surgery and corrective lenses (3). Recently, sensory impairments have emerged as potential risk factors for dementia, with the Lancet 2017 and 2020 Commissions on dementia prevention identifying hearing loss as a key modifiable risk factor (4,5). Visual impairment could increase dementia risk through mechanisms similar to hearing loss, such as the reallocation of cognitive resources to handle increased perceptual demands, or mediation through depression, social isolation and physical inactivity (6–9).

A recent meta-analysis found that visual impairment was associated with a 47% increased risk of dementia when pooling data from fourteen prospective studies (10). Despite promising findings for visual impairment as a target for dementia prevention, there is a lack of studies that combine a large sample size with a long follow-up period and an exposure ascertained using distance visual acuity. This is the clinical standard and underpins international taxonomies of visual impairment (11). Interpreting previous findings is further complicated by the heterogeneity of different study designs, methodological approaches and exposure/outcome definitions. This could be addressed by replicating analyses in different populations, with similar exposure, covariate and outcome ascertainment.

To address these limitations, we investigated the association between objectively measured visual impairment and the risk of incident dementia in two large population-based cohorts over 11 and 15 years of follow-up, respectively. We hypothesised that visual impairment would be associated with an increased risk of developing dementia compared to no visual

impairment. We also hypothesised that there would be a dose-response effect, with increasing severity of visual impairment associated with greater dementia risk.

Methods

UK Biobank

UK Biobank is a population-based prospective cohort study that recruited 503,317 women and men aged 40-69 from England, Scotland and Wales between 2006-10 (5.5% response rate) (12,13). At baseline, all participants provided electronic signed consent, answered questions on sociodemographic, lifestyle and health-related factors and completed a range of physical examinations. Eye measures were incorporated into the physical examinations at baseline assessment between 2009 and 2010 and were completed by approximately 117,252 participants. A further 16,016 participants who did not undergo the eye examination at baseline had eye measures collected during a repeat of baseline assessment between 2012-13 (14). For the current study, date of first eye examination is defined as 'baseline', whether 2009-10 or 2012-13.UK Biobank received ethical approval from the National Health Service North West Centre for Research Ethics Committee (Ref: 11/NW/ 0382).

EPIC Norfolk

The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) is a population-based prospective cohort study of 25,639 women and men aged 40-79 years recruited between 1993-1997 (33% response rate) (15,16). Additional participants also joined the study at follow-up waves. Eye measures were introduced as part of a third health examination (EPIC-Norfolk 3 - baseline for current study) between 2006 and 2011, including data from a pilot phase 2004-2006 (15,17). At examination, all participants provided written informed consent and completed a questionnaire on sociodemographic, lifestyle and health-

related factors. Ethical approval for EPIC-Norfolk core study was provided by the Norwich District Health Authority ethics committee (Rec Ref: 98NC01). EPIC-Norfolk 3 was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney National Health Service (NHS) Research Governance Committee (2005EC07L).

Visual function

The eye examinations in UK Biobank and EPIC-Norfolk included visual acuity, the most common clinical measurement of visual function. Visual acuity was measured in both eyes using "logarithm of the minimum angle of resolution" (LogMAR) characters (Precision Vision, LaSalle, Illinois, USA), displayed on a computer screen in UK Biobank and on a light box in EPIC-Norfolk, both under standard illumination (17,18). The test in both cohorts was carried out with participants wearing usual, available, correction at 4 metres, or at 1 metre if participants were unable to read any letters. Participants were asked to read each letter from the end of each line going from top to bottom, until hesitation. In UK Biobank the test was terminated when ≥2 letters were incorrect. In EPIC-Norfolk the test was terminated when the participant was able to read ≤3 letters on a line and testing was repeated using pinhole-correction if participants were unable to read 3 letters on the 0.3 line. Standard letter by letter scoring was used to derive LogMAR visual acuity.

Dementia

In UK Biobank, dementia status recorded using hospital inpatient records obtained from Hospital Episode Statistics (HES) for England, Scottish Morbidity Record for Scotland and Patient Episode Database for Wales as well as death registry records obtained from NHS Digital for England and Wales and Information and Statistics Division for Scotland. In EPIC-Norfolk, dementia was ascertained using hospital inpatient records obtained from HES, death registry records as well as the following mental healthcare datasets which capture information on individuals in contact with mental health services and memory clinics; Mental Health Minimum Data Set, Mental Health and Learning Disabilities Data Set and the Mental Health Services Data Set. All diagnoses were recorded using the International Classification of Diseases (ICD) coding system (see **eTable 1** for list of ICD codes).

Covariates

In both cohorts, Townsend deprivation score was used as an indicator of material deprivation and was assigned to each participant corresponding to the output area of their residential postcode at recruitment (19). Educational qualifications, ethnicity, smoking status, alcohol consumption, diabetes and cardiovascular disease were collected via paper questionnaire in EPIC-Norfolk. The same variables were collected via the touchscreen questionnaire in UK Biobank, except diabetes and cardiovascular disease, which were captured during a verbal interview conducted by a trained nurse. In both cohorts, body mass index (BMI; kg/m2) was derived from weight (kg) using scales and standing height (metres) measured during the physical examinations (see **eTable 2** for more information on covariate collection). In UK Biobank, the covariates were collected at both baseline (2009-10) and repeat assessment (2012-13). Covariates collected at the time of first eye measure were used in all analyses.

Statistical analysis

Person years were calculated from the date of visual acuity measure until the first incident diagnosis of dementia, date of death, date lost-to follow-up or end of follow-up, whichever came first. End of follow-up was based on the last possible date of electronic medical record availability. For UK Biobank this was 30 November 2020 for England, 31 October 2020 for Scotland, 28 February 2018 for Wales; for EPIC-Norfolk this was 31 March 2019. Cox proportional-hazards models were used to assess the association between visual impairment and risk of incident dementia. Visual impairment was categorised using the World Health Organisation classification based on visual acuity in the better eye of 'no impairment' (≤0.30 LogMAR), 'mild impairment' (>0.3 - ≤0.50 LogMAR) and 'moderate to severe impairment' (>0.50 LogMAR) (20). All models were assessed for the proportionality of hazards assumption using Schoenfeld residuals. In basic adjusted models we controlled for age in years, sex, ethnicity (white, non-white) and educational qualifications (no qualifications, lower-secondary (i.e. CSE/O-Level/GCSE or equivalent), upper secondary (i.e. AS/A-Level or equivalent), higher education, or other equivalent professional qualification). In fully adjusted models we additionally controlled for socioeconomic status using Townsend deprivation score (quintiles), smoking status (never, former, current), alcohol intake (never, former, current), BMI (<25, ≥25–<30, ≥30 kg/m^2) diabetes (no, yes) and cardiovascular disease (no, yes). Multiple imputation by chained equations with 100 imputations were used to impute missing values and values where participants responded "prefer not to answer" or "do not know", for any covariates. The main exposure, outcome and covariates were entered into the imputation model.

In a sensitivity analysis, the main models were repeated using a Fine-Gray subdistribution hazard model with death considered as a competing event (21).

Two separate sensitivity analyses were performed to explore reverse causation due to preclinical dementia potentially influencing visual and other health-related factors. These included 1) excluding participants with less than five years of follow-up and 2) excluding participants who reported their health as poor or fair at baseline assessment.

In secondary analyses, the main analysis was repeated with visual acuity entered as a continuous variable to investigate the association with incident dementia per 0.10 LogMAR unit, which is equivalent to five letters or one line on a LogMAR chart. We also repeated the main model using a complete case analysis to investigate whether the results differed compared to using multiple imputation. Stratification by age was performed in UK Biobank to investigate effect modification by late-middle age (60-64 years) or early-older age (≥65 years). This analyses was not performed in EPIC-Norfolk due to older age structure of the cohort. Furthermore, because the UK Biobank outcome adjudication working group's recommended definition of dementia includes additional ICD codes compared to EPIC-Norfolk (**eTable 1**) (22), the UK Biobank analyses were repeated with the same ICD codes used to define dementia as EPIC-Norfolk. Due to the availability of genetic data in UK Biobank, the main analyses were repeated with additional adjustment for Apolipoprotein E (APOE) -ε4 carrier status (absence of ε4 alleles, presence of 1 or 2 ε4 alleles), a strong risk factor for dementia (23,24).

All *p* values were 2-sided, and the type I error rate for statistical significance was set at 0.05. Analyses were performed using Stata SE version 15.1 (StataCorp, College Station, TX).

Results

Of 502,506 UK Biobank and 30,445 EPIC-Norfolk participants, 130,218 and 8,380 participants had complete visual acuity data, respectively. After excluding participants less than 60 years old at baseline or with prevalent dementia, the final sample size in UK Biobank and EPIC-Norfolk was 62,206 and 7,337 participants, respectively (**Figure 1**).

In UK Biobank, a total of 1,113 newly recorded hospital inpatient dementia cases or dementia-registered deaths were captured over 616,117 person-years of follow-up (mean = 9.9 years, standard deviation = 1.8), while in EPIC-Norfolk, a total of 517 incident dementia cases were captured over 68,709 person-years of follow-up (mean = 9.4 years, standard deviation = 2.5). In UK Biobank and EPIC-Norfolk, respectively, 1,549 (2.5%) and 216 (2.9%) participants had mild visual impairment, and 463 (0.7%) and 49 (0.7%) participants had moderate to severe visual impairment. Baseline characteristics by visual impairment status for both cohorts are provided in **Table 1**.

A Nelson-Aalen cumulative hazards plot of dementia demonstrates clear differences in risk by visual impairment status after 1-2 years of follow-up in both cohorts (**Figure 2**). In basic adjusted models, the risk of dementia increased monotonically by visual impairment status in both cohorts, although the association between mild visual impairment and incident dementia was not statistically significant in either cohorts (**Table 2,** see **eTable 3** for effect of each additional covariate on the model estimates). The observed associations remained similar in fully adjusted models. Compared to those with no visual impairment, the Hazard Ratios (HR) in UK Biobank and Epic-Norfolk, respectively, were 1.26 (95% Confidence Interval [CI] 0.92-1.72) and 1.05 (95% CI 0.72-1.53) for mild impairment, and 2.16 (95% CI 1.37-3.40) and 1.93 (95% CI 1.05-3.56) for moderate to severe impairment. The direction of the associations remained similar when repeating the fully adjusted models with death as a

competing event, although the effect sizes were attenuated for those with moderate impairment in both cohorts (**eTable 4**).

In sensitivity analyses, the main findings were attenuated in both cohorts when excluding participants with less than five years follow-up (**Table 3**). For instance, the HRs for moderate to severe impairment were 1.51 (95% CI 0.83-2.74) and 1.51 (95% CI 0.71-3.24) in UK Biobank and EPIC-Norfolk, respectively, compared to no impairment. After excluding participants with poor or fair self-reported health in UK Biobank, compared to no impairment, the associations remained similar to the main findings for mild impairment (HR=1.44, 95% CI 0.97-2.16) but was weaker for moderate to severe impairment (HR=1.29, 95% CI 0.58-2.88) (**Table 3**). Whereas after excluding participants with poor or fair self-reported health in EPIC Norfolk, the strength of the association for moderate to severe impairment was similar to the main findings, albeit attenuated, (HR=2.01, 95% CI 0.89-4.57), compared to no impairment.

In fully adjusted models, the risk of dementia increased by 15% (HR=1.15, 95% CI 1.11-1.19) and 6% (HR=1.06, 95% CI 1.01-1.13) per 0.1 increase in LogMAR in UK Biobank and EPIC-Norfolk, respectively. In complete cases analyses, the direction of the associations remained similar to the main findings, although the strength was attenuated, in particular for those with moderate visual impairment (**eTable 5**). In analyses stratified by age in UK Biobank, the associations were stronger in late-middle aged participants (60-64 years) and weaker in early-older aged participants (≥65 years, **eTable 6**). In UK Biobank, when restricting to the same ICD codes used to ascertain dementia as EPIC-Norfolk there were 959 incident cases, and the HRs were 1.23 (95% CI 0.90-1.69) and 2.05 (95% CI 1.29-3.28) for mild and moderate to severe impairment, respectively, compared to no impairment in a fully adjusted model. In UK Biobank, the findings remained similar when additionally adjusted for

APOE-ε4 carrier status (HR=1.29, 95% CI 0.93-1.78 and HR=2.12, 95% CI 1.35-3.35 for mild and moderate impairment, respectively).

Discussion

In two large cohorts of middle to older aged women and men recruited from the general population, moderate to severe visual impairment was associated with double the risk of incident dementia compared to normal vision. Mild visual impairment was associated with approximately 25% increased risk of dementia in UK Biobank, although the association was not statistically significant. There was limited evidence for an association between mild visual impairment and dementia in EPIC-Norfolk. In both cohorts, the main findings were attenuated when excluding those with less than five years of follow-up or prevalent poor or fair self-reported health and therefore reverse causation cannot be ruled out.

Our main findings are consistent with results from a meta-analysis of 14 prospective studies by Shang and colleagues, which found an increased risk of dementia in those with visual impairment compared to no impairment (Relative Risk [RR] = 1.47, 95% CI: 1.36-1.60) (10) . This included unpublished UK Biobank results of similar strength to the current study (RR = 1.78, 95% CI: 1.18-2.68), though not directly comparable to our findings due to the lack of detail on the study design and apparent differences in sample composition (e.g. unpublished results had a bigger analytic sample but fewer dementia cases).

The meta-analysis included studies that used various methods to define visual impairment, such as self-report (25–28), medical records (29,30) and colour vision (31). In UK Biobank and EPIC-Norfolk, a distance visual acuity test, the clinical standard for determined visual impairment, was used. To our knowledge, three previous population-based studies have used the same method to ascertain visual impairment (32–34). In 2,008 US-based adults, mild visual impairment or worse was associated with a non-significant increased risk of dementia

(HR=1.26, 95% CI 0.90-1.77) over 10 years follow-up (32). In 1,061 US-based adults, mild visual impairment or worse was associated with an increased risk of dementia (HR=2.14, 95% CI 1.08-4.21) over 7 years follow-up (34). In 15,506 Hong Kong-based adults, a monotonic association was observed in relation to dementia risk for mild (HR=1.56, 1.17-2.06), moderate (HR=2.27, 95% CI 1.68-3.06), and severe or worse (HR=10.84, 95% CI 6.60-17.81) impairment over 6 years follow-up (33).

Previous studies generally indicate that mild visual impairment is associated with an increased dementia risk. However, we observed a weak association between mild visual impairment and incident dementia in UK Biobank (HR=1.26, 95% CI 0.92-1.72) and a lack of association in EPIC-Norfolk (HR=1.05, 95% CI 0.72-1.53). It is possible that age modifies the associations between milder forms of visual impairment and dementia risk, as the strongest associations were observed in those who were 60-64 years at baseline compared to participants 65 years or older in UK Biobank, whilst the overall associations in the older EPIC-Norfolk population were weaker than the younger UK Biobank population. This is consistent with findings that certain risk factors, such as hearing impairment, are hypothesised to increase the likelihood of dementia primarily at mid- rather than late-life (5). Alternatively differential responses might exist across age groups, more studies exploring the effect of age on associations between vison and dementia risk are necessary.

One explanation is that the findings are driven by reverse causation. The long prodromal period of dementia can affect exposures measured several years prior to a clinical dementia diagnosis, which in turn, can produce spurious associations in studies with short follow-up(35–37). The meta-analysis by Shang and colleagues found similar associations between visual impairment and incident dementia when restricting to studies with 10 or more years follow-up (HR=1.53, 95% CI 1.30-1.80) and less than 10 years follow-up (HR=1.50, 95% CI 1.23-1.83) (10). However, even in studies with longer follow-up periods, the overall

associations could be driven by cases that develop within the first few years. In the current study, when excluding participants with less than five years follow-up, the direction of associations remained the same but were substantially weaker. Lee and colleagues found that an increased risk of dementia remained for those with moderate and severe, but not mild, visual impairment when excluding cases within three years of follow-up (33). Whilst Naël and colleagues found that mild and moderate near visual impairment were significantly associated with dementia risk before, but not after, four years of follow-up follow-up (38). There are several other potential explanations for the observed associations between visual impairment and dementia. Visual impairment is related to a poorer quality of life, a decline in physical and functional activities, social isolation and an increased risk of depression (6–9,39,40), and these factors could in lead to an increased risk of dementia (5,38,41). Impaired visual processing could adversely affect cognitive functioning directly through various mechanisms, such as sensory deprivation, increased perceptual load or information degradation (42–44). Alternatively, visual and cognitive impairment and dementia risk could be linked by a 'common cause' (43). In this scenario, impaired visual acuity could represent a promising predictive marker for dementia risk rather than a target for prevention. Certain visual conditions have been previously proposed as biomarkers for dementia, such as retinal nerve fibre layer thinning, abnormal pupillary response, and contrast sensitivity (45,46). An additional non-causal explanation is potential detection bias, such as performing worse on visually-based cognitive tests or through increased utilisation of health services.

In addition to visual impairment, studies have explored the link between specific eye diseases and risk of dementia, although the evidence is mixed. A meta-analysis of prospective studies found that cataracts and diabetic retinopathy, but not glaucoma or age-related macular degeneration, were associated with dementia risk (47). Similar associations have been observed in UK Biobank, although in contrast, age-related macular degeneration was weakly

associated with dementia risk (48). The potential mechanisms underlying the associations between eye diseases and dementia are complex, for instance they could increase the risk of dementia via visual impairment, be confounded by other factors (i.e. diabetes in the case of diabetic retinopathy) or share similar neurodegenerative pathways as dementia (i.e. glaucoma) (49). Due to this complexity, we investigated visual impairment independently of eye diseases in the current study. Studies which explore whether associations between certain eye diseases and dementia are mediated by visual impairment or driven by other factors are warranted.

Our study has several strengths. Both cohorts utilised a similar eye assessment protocol, measured the same covariates, and captured dementia using longitudinal hospital and death registry records. This enabled us to replicate the analysis using standardised criteria in two separate populations with different age structures and population characteristics. Both studies captured dementia through ongoing linkage to cohort-wide electronic medical records minimising loss to-follow-up. Participants were assessed with habitual correction (i.e. glasses or contact lenses) which should provide an accurate measure of usual day-today visual function.

Our study also has several limitations. Despite the large sample size in both cohorts, the proportion of individuals with moderate visual impairment was small. This limited the potential for additional analyses due to lack of statistical power, such as investigating whether the associations were mediated through other factors. As there was no information on how long participants have been visual impaired or repeat visual acuity measures we were unable to investigate whether the results were affected by time impaired or account for exposure change over time.

We did not investigate specific dementias, such as Alzheimer's disease or vascular dementia, due to the poor positive predictive value of the hospital inpatient and death records for

ascertaining subtypes (50). However, validation studies have found that these are reliable for ascertaining all-cause dementia , with a positive predictive value of 84.5% in UK Biobank when compared with expert clinical adjudication (50,51). Nevertheless, the hospital inpatient and death records are likely to capture dementia cases in the later stages. For instance, one study found that dementia cases originally diagnosed in primary care are captured in hospital records an average of 1.6 years later (52). A degree of misclassification bias is likely whereby dementia cases not captured in the available medical records are treated as controls, which could bias the effect sizes towards the null.

Both cohorts were volunteer-based, with strong evidence of a 'healthy volunteer effect' in UK Biobank (13,15). A recent study found that similar exposure-outcome associations were observed in UK Biobank compared to a representative cohort for cause-specific deaths, nevertheless selection bias could remain (53,54). Due to the observational design, a degree of residual confounding is likely and causality cannot be inferred.

Mild and moderate to severe visual impairment was monotonically associated with an increased likelihood of developing dementia. Visual impairment has a high prevalence, especially in middle-later life, but is often treatable or preventable and consequently could be a promising target for dementia prevention. However, further research is needed to disentangle whether visual impairment is a dementia risk factor, an early sign of dementia or whether the timing of onset of visual impairment or its duration play a differential role.

Funding: A.K. was funded by a UKRI Future Leaders Fellowship. E.K. was supported by the Nicolaus and Margrit Langbehn Foundation. The EPIC-Norfolk study (DOI 10.22025/2019.10.105.00004) has received funding from the Medical Research Council (MR/N003284/1 and MC-UU_12015/1) and Cancer Research UK (C864/A14136). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest: A.K. has performed consultancy work for Aerie, Allergan, Google Health, Novartis, Reichert, Santen and Thea. The other authors have no conflicts of interest to disclose.

Ethics: UK Biobank received ethical approval from the National Health Service North West Centre for Research Ethics Committee (Ref: 11/NW/ 0382).

Ethical approval for EPIC-Norfolk core study was provided by the Norwich District Health Authority ethics committee (Rec Ref: 98NC01). EPIC-Norfolk 3 was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney National Health Service (NHS) Research Governance Committee (2005EC07L).

Acknowledgements: We are grateful to all the participants who have been part of both projects and to the many members of the study teams at UK Biobank as well as the University of Cambridge for EPIC-Norfolk who have enabled this research. This research has been conducted using the UK Biobank Resource under Application Number 41115. TJL, SH, RL, APK and EK conceived and designed the study. TJL analysed the UK Biobank data. SH and RL analysed the EPIC-Norfolk data. TJL wrote the manuscript. All authors were involved interpreting the data, critically revising the manuscript and providing final approval for the work to be published.

References

1. Bourne R, Steinmetz JD, Flaxman S, et al. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the Global Burden of Disease Study. *Lancet Glob Heal*. 2021;9(2):e130-e143. doi:10.1016/S2214-109X(20)30425-3.

2. Bourne RRA, Flaxman SR, Braithwaite T, et al. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Glob Heal*. 2017;5(9):e888-e897. doi:10.1016/S2214-109X(17)30293-0.

3. GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Heal*. 2021;9(2):e144-e160. doi:10.1016/S2214-109X(20)30489-7.

4. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;6736(17). doi:10.1016/S0140-6736(17)31363-6.

5. Livingston G, Sommerlad A, Orgeta V, et al. The Lancet Commissions Dementia prevention, intervention, and care. *Lancet*. 2020;390(17):2673-2734. doi:10.1016/S0140-6736(20)30367-6.

6. Choi HG, Lee MJ, Lee SM. Visual impairment and risk of depression: A longitudinal follow-up study using a national sample cohort. *Sci Rep*. 2018;8(1):1-8. doi:10.1038/s41598-018-20374-5.

7. Brunes A, B Hansen M, Heir T. Loneliness among adults with visual impairment:

prevalence, associated factors, and relationship to life satisfaction. *Health Qual Life Outcomes*. 2019;17(1):24. doi:10.1186/s12955-019-1096-y.

8. Ong SR, Crowston JG, Loprinzi PD, Ramulu PY. Physical activity, visual impairment, and eye disease. *Eye*. 2018;32(8):1296-1303. doi:10.1038/s41433-018-0081-8.

9. Wayne R V., Johnsrude IS. A review of causal mechanisms underlying the link between age-related hearing loss and cognitive decline. *Ageing Res Rev*. 2015;23(Pt B):154-166. doi:10.1016/j.arr.2015.06.002.

10. Shang X, Zhu Z, Wang W, Ha J, He M. The association between vision impairment and incidence of dementia and cognitive impairment: a systematic review and meta-analysis. *Ophthalmology*. January 2021:104947. doi:10.1016/j.ophtha.2020.12.029.

11. World Health Organisation. Universal Eye Health: A global action plan 2014–2019.

12. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779.

13. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*. 2017;186(9):1026-1034. doi:10.1093/aje/kwx246.

14. Repeat Assessment : Participant Characteristics of responders vs . non-responders. https://biobank.ndph.ox.ac.uk/~bbdatan/repeat_assessment_characteristics_v1.pdf. Published 2014. Accessed March 1, 2021.

15. Hayat SA, Luben R, Keevil VL, et al. Cohort profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of

men and women in Norfolk (EPIC-Norfolk 3). *Int J Epidemiol*. 2014;43(4):1063-1072. doi:10.1093/ije/dyt086.

16. Day N, Oakes S, Luben R, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer*. 1999;80 Suppl 1:95-103.

17. Khawaja AP, Chan MPY, Hayat S, et al. The EPIC-Norfolk eye study: Rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. *BMJ Open*. 2013;3(3):1-10. doi:10.1136/bmjopen-2013-002684.

18. Chua SYL, Thomas D, Allen N, et al. Cohort profile: design and methods in the eye and vision consortium of UK Biobank. *BMJ Open*. 2019;9(2):e025077. doi:10.1136/bmjopen-2018-025077.

19. Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. London: Croom Helm; 1988.

20. *World Health Organisation. World Report on Vision.* Genva; 2019.

21. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144.

22. Definitions of Dementia and the Major Diagnostic Pathologies, UK Biobank Phase 1 Outcomes Adjudication. http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_dementia.pdf. Published 2018. Accessed July 17, 2020.

23. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep

phenotyping and genomic data. *Nature*. 2018;562(7726):203-209. doi:10.1038/s41586-018-0579-z.

24. Loy CT, Schofield PR, Turner AM, Kwok JBJ. Genetics of dementia. *Lancet*. 2014;383(9919):828-840. doi:10.1016/S0140-6736(13)60630-3.

25. Rogers MAM, Langa KM. Untreated poor vision: A contributing factor to late-life dementia. *Am J Epidemiol*. 2010;171(6):728-735. doi:10.1093/aje/kwp453.

26. Davies HR, Cadar D, Herbert A, Orrell M, Steptoe A. Hearing Impairment and Incident Dementia: Findings from the English Longitudinal Study of Ageing. *J Am Geriatr Soc*. 2017;65(9):2074-2081. doi:10.1111/jgs.14986.

27. Lipnicki DM, Crawford J, Kochan NA, et al. Risk Factors for Mild Cognitive Impairment, Dementia and Mortality: The Sydney Memory and Ageing Study. *J Am Med Dir Assoc*. 2017;18(5):388-395. doi:10.1016/j.jamda.2016.10.014.

28. Hwang PH, Longstreth WT, Brenowitz WD, et al. Dual sensory impairment in older adults and risk of dementia from the GEM Study. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2020;12(1):P196. doi:10.1002/dad2.12054. eCollection 2020.

29. Paik J, Ha M, Jung YH, Kim G, Han K, Kim H. Low vision and the risk of dementia : a nationwide population-based cohort study. *Sci Rep*. 2020:1-10. doi:10.1038/s41598-020-66002-z.

30. Maruta M, Tabira T, Sagari A, et al. Impact of sensory impairments on dementia incidence and symptoms among Japanese older adults. *Psychogeriatrics*. 2020;20(3):262-270. doi:10.1111/psyg.12494.

31. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism

in idiopathic REM sleep behaviour disorder: A multicentre study. *Brain*. 2019;142(3):744-759. doi:10.1093/brain/awz030.

32. Brenowitz WD, Kaup AR, Lin FR, Yaffe K. Multiple sensory impairment is associated with increased risk of dementia among black and white older adults. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2019;74(6):890-896. doi:10.1093/gerona/gly264.

33. Lee ATC, Richards M, Chan WC, Chiu HFK, Lee RSY, Lam LCW. Higher Dementia Incidence in Older Adults with Poor Visual Acuity. *J Gerontol A Biol Sci Med Sci*. 2020;75(11):2162-2168. doi:10.1093/gerona/glaa036.

34. Tran EM, Stefanick ML, Henderson VW, et al. Association of Visual Impairment With Risk of Incident Dementia in a Women's Health Initiative Population. *JAMA Ophthalmol*. 2020;138(6):624-633. doi:10.1001/jamaophthalmol.2020.0959.

35. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003.

36. Singh-Manoux A, Dugravot A, Shipley M, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimer's Dement*. 2018;14(2):178-186. doi:10.1016/j.jalz.2017.06.2637.

37. Sabia S, Dugravot A, Dartigues J-F, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ*. June 2017:j2709. doi:10.1136/bmj.j2709.

38. Naël V, Pérès K, Dartigues JF, et al. Vision loss and 12-year risk of dementia in older adults: the 3C cohort study. *Eur J Epidemiol*. 2019;34(2):141-152.

doi:10.1007/s10654-018-00478-y.

39. Tseng Y-C, Liu SH-Y, Lou M-F, Huang G-S. Quality of life in older adults with sensory impairments: a systematic review. *Qual Life Res*. 2018;27(8):1957-1971. doi:10.1007/s11136-018-1799-2.

40. Lin MY, Gutierrez PR, Stone KL, et al. Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. *J Am Geriatr Soc*. 2004;52(12):1996-2002. doi:10.1111/j.1532-5415.2004.52554.x.

41. Hämäläinen A, Phillips N, Wittich W, Pichora-Fuller MK, Mick P. Sensory-cognitive associations are only weakly mediated or moderated by social factors in the Canadian Longitudinal Study on Aging. *Sci Rep*. 2019;9(1):1-8. doi:10.1038/s41598-019-55696-5.

42. Monge ZA, Madden DJ. Linking cognitive and visual perceptual decline in healthy aging: The information degradation hypothesis. *Neurosci Biobehav Rev*. 2016;69:166-173. doi:10.1016/j.neubiorev.2016.07.031.

43. Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging*. 1997;12(1):12-21. doi:10.1037//0882-7974.12.1.12.

44. Lindenberger U, Baltes PB. Sensory functioning and intelligence in old age - A strong connection. *Psychol Aging*. 1994;9(3):339-355. doi:10.1037//0882-7974.9.3.339.

45. Murphy C. Olfactory and other sensory Impairments in Alzheimer's disease. *Nat Rev Neurol*. 2018. doi:10.1038/s41582-018-0097-5.

46. Albers MW, Gilmore GC, Kaye J, et al. At the interface of sensory and motor

dysfunctions and Alzheimer's disease. *Alzheimer's Dement*. 2015;11(1):70-98. doi:10.1016/j.jalz.2014.04.514.

47. Kuźma E, Littlejohns TJ, Khawaja AP, Llewellyn DJ, Ukoumunne OC, Thiem U. Visual Impairment, Eye Diseases, and Dementia Risk: A Systematic Review and Meta-Analysis. Peters R, ed. *J Alzheimer's Dis*. August 2021:1-15. doi:10.3233/JAD-210250.

48. Shang X, Zhu Z, Huang Y, et al. Associations of ophthalmic and systemic conditions with incident dementia in the UK Biobank. *Br J Ophthalmol*. 2021:bjophthalmol-2021-319508. doi:10.1136/bjophthalmol-2021-319508.

49. Mancino R, Martucci A, Cesareo M, et al. Glaucoma and Alzheimer Disease: One Age-Related Neurodegenerative Disease of the Brain. *Curr Neuropharmacol*. 2018;16(7):971-977. doi:10.2174/1570159X16666171206144045.

50. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019:1-9. doi:10.1007/s10654-019-00499-1.

51. Wilkinson T, Ly A, Schnier C, et al. Identifying dementia cases with routinely collected health data: A systematic review. *Alzheimer's Dement*. 2018;(April):1-14. doi:10.1016/j.jalz.2018.02.016.

52. Brown A, Kirichek O, Balkwill A, et al. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. *Emerg Themes Epidemiol*. 2016;13:11. doi:10.1186/s12982-016-0053-z.

53. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ*. 2020;368:m131. doi:10.1136/bmj.m131.

54. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. *Int J Epidemiol*. 2018;47(1):226-235. doi:10.1093/ije/dyx206.

Figure 1 – Flow chart for final analytic sample sizes in UK Biobank and EPIC-Norfolk

Figure 2 - Cumulative hazard of dementia by visual impairment status

Table 1 – Baseline characteristics of 62,206 UK Biobank and 7,337 EPIC-Norfolk participants by visual impairment status

Characteristic, N (%)	UK Biobank			Epic-Norfolk		
	Visual Impairment (LogMAR)			Visual Impairment (LogMAR)		
	None (≤0.3) N=60,194	Mild (>0.3-≤0.5) N=1,549	Moderate to severe (>0.5) N=463	None (≤0.3) N=7,072	Mild (>0.3-≤0.5) N=216	Moderate to severe (>0.5) N=49
Age in years, mean (SD)	64.5 (3.1)	65.0 (3.1)	64.7 (3.1)	70.2 (6.9)	76.0 (7.2)	76.1 (7.8)
Women	31,217 (51.9)	812 (52.4)	239 (52.6)	3,813 (53.9)	126 (58.3)	27 (55.1)
Townsend deprivation score, quintiles						
1 (least deprived)	12,143 (20.2)	249 (16.1)	65 (14.0)	1,806 (25.5)	48 (22.2)	10 (20.4)
2	12,100 (20.1)	238 (15.4)	76 (16.4)	1,453 (20.5)	41 (19.0)	10 (20.4)
3	12,049 (20.0)	299 (19.3)	81 (17.5)	1,408	37 (17.1)	7 (14.3)

				(19.9)		
4	12,015 (20.0)	316 (20.4)	103 (22.3)	1,218	48 (22.2)	10 (20.4)
				(17.2)		
5 (most deprived)	11,845 (19.7)	445 (28.7)	138 (29.8)	1,168	42 (19.4)	12 (24.5)
				(16.5)		
Missing	42 (0.1)	2 (0.1)	0 (0)	19 (0.3)	0 (0)	0 (0)
Education						
No qualifications	12,656 (21.0)	483 (31.2)	143 (30.9)	1,935	68 (31.5)	29 (59.2)
				(27.4)		
Lower secondary	9,536 (15.8)	232 (15.0)	79 (17.1)	804 (11.4)	26 (12.0)	1 (2.0)
Upper secondary	2,907 (4.8)	75 (4.8)	17 (3.7)	3,159	94 (43.5)	12 (24.5)
				(44.7)		
Higher education or other	34,373 (57.1)	716 (46.2)	213 (46.0)	1,173	27 (12.5)	7 (14.3)
professional				(16.6)		
qualification or equivalent						
Missing/prefer not to answer	722 (1.2)	43 (2.8)	11 (2.4)	1 (0)	1 (0.5)	0 (0)

Ethnic background						
White	56,936 (94.6)	1,369 (88.4)	402 (86.8)	7,033 (99.4)	214 (99.1)	47 (95.9)
Non-white	2,885 (4.8)	153 (9.9)	54 (11.7)	20 (0.3)	0 (0.0)	1 (2.0)
Missing/prefer not to answer/do not know	373 (0.6)	27 (1.7)	7 (1.5)	19 (0.3)	2 (0.9)	1 (2.0)
Alcohol intake frequency						
Never	2,821 (4.7)	118 (7.6)	42 (9.1)	358 (5.1)	7 (3.2)	3 (6.1)
Former	2,177 (3.6)	76 (4.9)	12 (2.6)	790 (11.2)	29 (13.4)	5 (10.2)
Current	55,045 (91.5)	1,339 (86.4)	405 (87.5)	5,551 (78.5)	165 (76.4)	33 (67.35)
Missing/prefer not to answer	151 (0.3)	16 (1.0)	6 (0.9)	373 (5.3)	15 (6.9)	8 (16.3)
Smoking status						
Never	30,919 (51.4)	787 (50.8)	240 (51.8)	3,410 (48.2)	99 (45.8)	15 (30.6)
Former	24,681 (41.0)	588 (38.0)	173 (37.4)	3,294	102 (47.2)	28 (57.1)

				(46.6)		
Current	4,236 (7.0)	152 (9.8)	44 (9.5)	264 (3.7)	11 (5.1)	3 (6.1)
Missing/prefer not to answer	358 (0.6)	22 (1.4)	6 (1.3)	104 (1.5)	4 (1.9)	3 (6.1)
BMI						
<25	18,712 (31.1)	448 (28.9)	150 (32.4)	2,444 (34.6)	81 (37.5)	21 (42.9)
25-29.9	26,694 (44.4)	666 (43.0)	196 (42.3)	3,258 (46.1)	95 (44.0)	22 (44.9)
≥30	14,517 (24.1)	410 (26.5)	108 (23.3)	1,358 (19.2)	38 (17.6)	6 (12.2)
Missing	271 (0.5)	176 (11.4)	50 (10.8)	12 (0.2)	2 (1.0)	0 (0)
Diabetes	4,425 (7.4)	142 (9.2)	40 (8.6)	233 (3.3)	6 (2.8)	0 (0.0)
Cardiovascular disease	6,150 (10.2)	176 (11.4)	50 (10.8)	351 (5.0)	19 (8.8)	10 (20.4)
Overall health rating						
Poor/fair	15,776 (26.2)	1,054 (68.0)	307 (66.3)	1,090 (15.4)	34 (15.7)	16 (32.7)

Good/excellent	44,130 (73.3)	479 (30.9)	150 (32.4)	5,825 (82.4)	178 (82.4)	29 (59.2)
Missing/prefer not to answer/ do not know	288 (0.5)	16 (1.0)	6 (1.3)	157 (2.2)	4 (1.9)	4 (8.2)

Note. BMI, Body Mass Index, LogMAR, Logarithm of the Minimum Angle of Resolution, SD, Standard Deviatio

Table 2 – Cox-proportional-hazards models for the association between visual impairment and incident dementia

		Visual impairment (LogMAR)					
		None (≤0.3)		Mild (>0.3-≤0.5)		Moderate to severe (>0.5)	
Cohort	**Cases/Population**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**
UK Biobank							
Model A[a]	1,113/62,206	61,194	1 (reference)	1,549	1.32 (0.96-1.80)	463	2.17 (1.38-3.41)
Model B[b]	1,113/62,206	61,194	1 (reference)	1,549	1.26 (0.92-1.72)	463	2.16 (1.37-3.40)
EPIC-Norfolk							
Model A[a]	517/7,337	7072	1 (reference)	216	1.10 (0.76-1.59)	49	1.86 (1.02-3.39)
Model B[b]	517/7,337	7072	1 (reference)	216	1.05 (0.72-1.53)	49	1.93 (1.05-3.56)

Note. CI, Confidence Interval, HR, Hazard Ratio, LogMAR, Logarithm of the Minimum Angle of Resolution

[a] Adjusted for age, sex, ethnicity and education

[b] Adjusted for age, sex, ethnicity, education, Townsend deprivation score, alcohol, smoking, body mass index, diabetes and cardiovascular disease

Table 3 – Cox proportional-hazards models for the association of visual impairment and incident dementia accounting for reverse causation

		Visual impairment (LogMAR)					
		None (≤0.3)		Mild (>0.3-≤0.5)		Moderate to severe (>0.5)	
Cohort	**Cases/Population**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)[a]**	**N**	**HR (95% CI)[a]**
Excluding participants with <5 years follow-up							
UK Biobank	915/60,384	58,466	1 (reference)	1,489	1.18 (0.83-1.68)	429	1.51 (0.83-2.74)
EPIC-Norfolk	411/6,827	6609	1 (reference)	180	0.82 (0.51-1.30)	38	1.51 (0.71-3.24)
Excluding participants with poor/fair self-reported health							
UK Biobank	627/45,801	44,418	1 (reference)	1,070	1.44 (0.97-2.16)	313	1.29 (0.58-2.88)
EPIC-Norfolk	379/6,032	5825	1 (reference)	178	1.00 (0.65-1.55)	29	2.01 (0.89-4.57)

Note. CI: Confidence Interval; HR, Hazard Ratio, LogMAR, Logarithm of the Minimum Angle of Resolution

[a] Adjusted for age, sex, ethnicity, education, Townsend deprivation score, alcohol, smoking, body mass index, diabetes and cardiovascular disease

Figure 1

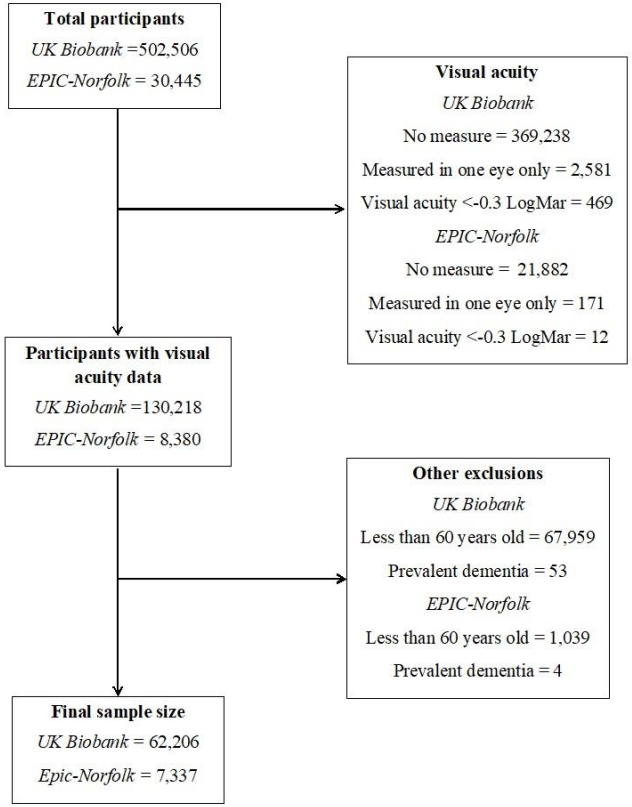

Figure 2