Associations of ophthalmic and systemic conditions with incident dementia in the UK Biobank

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ABSTRACT

Aims To examine independent and interactive associations of ophthalmic and systemic conditions with incident dementia.

Methods Our analysis included 12 364 adults aged 55–73 years from the UK Biobank cohort. Participants were assessed between 2006 and 2010 at baseline and were followed up until the early of 2021. Incident dementia was ascertained using hospital inpatient, death records and self-reported data.

Results Over 1 263 513 person-years of follow-up, 2304 cases of incident dementia were documented. The multivariable-adjusted HRs (95% CI) for dementia associated with age-related macular degeneration (AMD), cataract, diabetes-related eye disease (DRED) and glaucoma at baseline were 1.26 (1.05 to 1.52), 1.11 (1.00 to 1.24), 1.61 (1.30 to 2.00) and (1.07 (0.92 to 1.25), respectively. Diabetes, heart disease, stroke and depression at baseline were all associated with an increased risk of dementia. Of the combination of AMD and a systemic condition, AMD-diabetes was associated with the highest risk for incident dementia (HR (95% CI): 2.73 (1.79 to 4.17)). Individuals with cataract and a systemic condition were 1.19–2.29 times more likely to develop dementia compared with those without cataract and systemic conditions. The corresponding number for DRED and a systemic condition was 1.50–3.24. Diabetes, hypertension, heart disease, depression and stroke newly identified during follow-up mediated the association between cataract and incident dementia as well as the association between DRED and incident dementia.

Conclusions AMD, cataract and DRED but not glaucoma are associated with an increased risk of dementia. Individuals with both ophthalmic and systemic conditions are at higher risk of dementia compared with those with an ophthalmic or systemic condition only.

INTRODUCTION

Globally 43.8 million people lived with dementia in 2016[1] and this number is estimated to increase to 152 million by 2050.[2] Dementia accounted for 2.4 million deaths and 28.8 million disability-adjusted life-years in 2016.[1] The epidemic of dementia imposes a tremendous burden on the healthcare systems globally. As there is no effective treatment to stop the progression of dementia, it is imperative to identify modifiable factors for the prevention of dementia.[3 4]

Systemic conditions including obesity, depression, hypertension, diabetes, heart disease and stroke have been identified as the leading risk factors of dementia.[4–7] Recent evidence has suggested that vision impairment is one of the first manifestations of the development of dementia.[8 9] Meanwhile, loss of visual input may lead to reduced activation in central sensory pathways, resulting in an increased risk of cognitive load and brain structure damage,[10 11] which accelerates the development of dementia.[12] Recent studies have linked main causes of vision impairment including age-related macular degeneration (AMD), cataract, diabetic retinopathy (DR) and glaucoma to dementia or cognitive impairment;[13–18] however, the results are inconsistent and the studies are limited by small sample size or case–control design. Ophthalmic and systemic conditions are frequently clustered in pairs,[4 19 20] as they are all heavily age-related conditions. Therefore, an increased risk of dementia associated with ophthalmic conditions may be due to their positive associations with systemic conditions such as obesity and cardiovascular disorders. However, whether ophthalmic conditions are associated with a higher incidence of dementia independent of these systematic conditions and whether this association is mediated by newly developed systematic conditions is unclear.[21–23] It is also unknown whether an ophthalmic condition with a systemic condition as a comorbidity is a stronger predictor of dementia than an ophthalmic or systemic condition only is.

Using the data of the UK Biobank study, we sought to determine the independent associations between ophthalmic conditions and incident dementia. We then examined whether the clustering of ophthalmic and systemic conditions was associated with an increased risk of dementia. The potential mediation effects of newly developed systemic conditions on the association between ophthalmic conditions and incident dementia were also evaluated.

METHODS

Study population

The UK Biobank is a population-based cohort of more than 500 000 participants aged 40–73 years who attended 1 of the 22 assessment centres throughout the UK between 2006 and 2010.[24] The UK Biobank study design and population has been detailed previously elsewhere.[24]

Ophthalmic conditions

Ophthalmic conditions were defined based on the question: 'Has a doctor ever told you that you have any of the following problems with your eyes?' Individuals were classified as AMD, cataract, diabetes-related eye disease (DRED) and glaucoma for those

who selected the corresponding item from a predefined list of answers to the question. DERD includes DR, diabetic AMD, diabetes-related cataract and diabetes-related glaucoma. Additional prevalent cases of ophthalmic conditions were identified using hospital inpatient records.

Systemic conditions

Systemic conditions that are well-known risk factors of dementia were defined based on self-reported data or interviews. Participants were asked whether they had ever been told by a doctor that they had certain common medical conditions, including heart attack, angina, stroke, high blood pressure and diabetes. Heart attack and angina were combined as heart disease. Depression was recorded during the interview with a research nurse. Body mass index (BMI) was computed based on measured height and weight and obesity was defined as BMI ≥30 kg/m^2.[25] Although depression is not a systemic condition, we included depression as an important non-ophthalmic condition in the analysis.

Newly developed systemic conditions during follow-up (before the onset of dementia) were identified using hospital inpatient records and self-reported data during follow-up (the codes for each condition can be seen in online supplemental table e-1).

Ascertainment of incident dementia

Dementia cases in the UK Biobank Study were ascertained using hospital inpatient records, death registers and self-reported data. The codes for international classification diseases were used to identify dementia (detailed in online supplemental table e-2). The earliest recorded code date regardless of sources was used as the onset date of dementia. Person-years were calculated from the date of baseline assessment to the date of onset dementia, date of death or the end of follow-up (31 December 2020 for England and Wales and 18 January 2021 for Scotland), whichever came first.

Covariates

Sociodemographic factors including age, sex, education and income were self-reported. Participants completed a detailed questionnaire on a touch screen computer about their lifestyle, including smoking status, alcohol consumption and dietary intakes. Questions about walking, moderate physical activity and vigorous physical activity, which were similar to those used in the short form of the International Physical Activity Questionnaire, were used to estimate excess metabolic equivalent hours per week of physical activity during work and leisure time.

Statistical analysis

Data were expressed as frequency (percentage) and means±SDs by groups of individuals who had AMD, cataract, DRED and glaucoma and who were free of any ophthalmic conditions at baseline.

Cox proportional hazard regression models were used to examine the association between ophthalmic conditions and incidence of all-cause dementia, Alzheimer's disease and vascular dementia. The following models were tested: (1) age and gender and (2) model 1 plus education, income, smoking, alcohol consumption, physical activity, BMI, cholesterol, glucose and intakes of cooked vegetables, raw vegetables, fresh fruits and dried fruits at baseline. We then examined associations of the clustering of ophthalmic and systemic conditions with incident dementia. For example, HRs (95% CIs) for dementia associated with AMD only, stroke only and both AMD and stroke were estimated with individuals free of AMD and stroke as the reference. Dietary intake, lifestyle, education and BMI were adjusted for in the model because these factors have been linked to dementia in previous studies.[4 26] The association between DRED and incident dementia was conducted among patients with diabetes.

The potential mediation effects of newly developed systemic conditions during follow-up (before onset dementia) on the association between ophthalmic conditions and incident all-cause dementia were estimated using Cox proportional hazards regression models. Percentages of total effects mediated by systemic conditions were computed.

We then tested whether DR was a risk factor of dementia in patients with diabetes. DR was defined as individuals with DRED but not with AMD, cataract or glaucoma (those with DERD and any of AMD, cataract or glaucoma were excluded from the analysis). Sensitivity analysis was conducted to examine the association between ophthalmic conditions and incident dementia by excluding individuals who developed dementia in the first 5 years of follow-up.

Data analyses were conducted using SAS V.9.4 for Windows (SAS Institute) and all p values were two sided with statistical significance set at <0.05.

RESULTS

Baseline characteristics

At baseline, 502 505 participants were assessed. After excluding individuals missing data on ophthalmic conditions (n=3 27 891), those with prevalent dementia (n=112) or those aged <55 years (n=62 138), 112 364 adults (54.0% females) aged 55–73 years (mean±SD: 62.4±4.1) were included in the final analysis (online supplemental figure e-1). The baseline characteristics of the participants are presented in table 1. As shown in online supplemental table e-3, individuals with incident dementia were more likely to be older and males and have APOE4 compared with those without incident dementia.

Incidence of dementia

Over 1 263 513 person-years of follow-up (median (IQR) length of follow-up: 11.0 (10.7–11.7) years), 2304 new cases of incident all-cause dementia, 945 new cases of Alzheimer's disease and 513 new cases of vascular dementia were documented.

Ophthalmic conditions and incident dementia

Of participants with AMD at baseline, 2.94 cases per 1000 person-years developed all-cause dementia compared with 1.78 of those without AMD (multivariable-adjusted HR (95% CI): 1.26 (1.05 to 1.52)). The multivariable-adjusted HRs (95% CI) for dementia associated with cataract and DRED were 1.11 (1.00 to 1.24) and 1.61 (1.30 to 2.00), respectively. Glaucoma was associated with a higher risk of vascular dementia (HR (95% CI): 1.48 (1.13 to 1.94)), but not with Alzheimer's disease (0.89 (0.70 to 1.14)) or all-cause dementia (1.07 (0.92 to 1.25)) after adjustment for confounders (figure 1, online supplemental figures e–2 and 3).

Clustering of ophthalmic and systemic conditions and incident dementia

Stroke only, heart disease only, diabetes only, hypertension only and depression only but not obesity only at baseline were independently associated with an increased risk of dementia. AMD with any systemic condition as a comorbidity was associated with an increased risk of dementia and the risk was larger than AMD only or a systemic condition only. AMD and diabetes among the combination of AMD and a systemic condition had the highest

Table 1 Baseline characteristics of participants according to ophthalmic conditions

	Without any eye disease of interest (n=87 602)	AMD (n=3671)	Cataract (n=15 353)	DR (n=2922)	Glaucoma (n=6386)*
Age (years)	62.0±4.0	63.7±3.9	64.0±3.8	62.9±4.1	63.4±4.0
Gender					
Women	47 094 (53.8)	2222 (60.5)	9076 (59.1)	1047 (35.8)	3044 (47.7)
Men	40 508 (46.2)	1449 (39.5)	6277 (40.9)	1875 (64.2)	3342 (52.3)
APOE4					
Yes	64 443 (73.6)	2732 (74.4)	11 270 (73.4)	2206 (75.5)	4688 (73.4)
No	20 260 (23.1)	845 (23.0)	3604 (23.5)	616 (21.1)	1502 (23.5)
Missing	2899 (3.3)	94 (2.6)	479 (3.1)	100 (3.4)	196 (3.1)
Education					
College/university degree	26 898 (30.7)	1066 (29.0)	4234 (27.6)	583 (20.0)	1729 (27.1)
Upper secondary	8853 (10.1)	367 (10.0)	1402 (9.1)	234 (8.0)	582 (9.1)
Final stage of secondary education	17 583 (20.1)	743 (20.2)	3129 (20.4)	515 (17.6)	1312 (20.5)
Lower secondary	2842 (3.2)	110 (3.0)	364 (2.4)	90 (3.1)	155 (2.4)
First stage of secondary education	6063 (6.9)	232 (6.3)	972 (6.3)	238 (8.1)	472 (7.4)
Vocational qualifications	5615 (6.4)	286 (7.8)	1147 (7.5)	176 (6.0)	449 (7.0)
Others	1274 (1.5)	68 (1.9)	295 (1.9)	71 (2.4)	147 (2.3)
Missing	18 474 (21.1)	799 (21.8)	3810 (24.8)	1015 (34.7)	1540 (24.1)
Household income					
<18 000	20 389 (23.3)	1049 (28.6)	4555 (29.7)	1140 (39.0)	1779 (27.9)
18 000–30 999	21 251 (24.3)	906 (24.7)	3775 (24.6)	657 (22.5)	1590 (24.9)
31 000–51 999	17 051 (19.5)	657 (17.9)	2394 (15.6)	337 (11.5)	1056 (16.5)
52 000–1 00 000	11 212 (12.8)	311 (8.5)	1256 (8.2)	163 (5.6)	596 (9.3)
>1 00 000	2943 (3.4)	77 (2.1)	308 (2.0)	34 (1.2)	132 (2.1)
Unknown	4328 (4.9)	195 (5.3)	1035 (6.7)	218 (7.5)	386 (6.0)
Not answered	10 428 (11.9)	476 (13.0)	2030 (13.2)	373 (12.8)	847 (13.3)
Physical activity (MET minutes/week)	2679±2390	2632±2316	2560±2267	2218±2171	2598±2304
Sleep duration (hours)	7.17±1.14	7.22±1.27	7.21±1.22	7.33±1.61	7.22±1.23
Cooked vegetables (tablespoons/day)	2.91±1.97	3.06±2.29	3.01±2.16	3.08±2.28	2.98±2.03
Raw vegetables (tablespoons/day)	2.30±2.18	2.32±2.25	2.34±2.37	2.34±2.46	2.24±2.22
Fresh fruits (pieces/day)	2.36±1.65	2.50±1.57	2.44±1.65	2.63±2.10	2.38±1.84
Dried fruits (pieces/day)	1.02±1.97	1.17±2.28	1.07±1.94	0.89±2.02	1.00±1.85
Alcohol consumption					
Never	4130 (4.7)	205 (5.6)	1089 (7.1)	328 (11.2)	349 (5.5)
Previous	3506 (4.0)	166 (4.5)	759 (4.9)	300 (10.3)	314 (4.9)
Current	79 820 (91.1)	3299 (89.9)	13 476 (87.8)	2285 (78.2)	5710 (89.4)
Missing	146 (0.2)	1 (0.0)	29 (0.2)	9 (0.3)	13 (0.2)
Smoking					
Never	79 907 (91.2)	3377 (92.0)	14 113 (91.9)	2623 (89.8)	5845 (91.5)
Former	5637 (6.4)	218 (5.9)	961 (6.3)	225 (7.7)	418 (6.5)
Current	1977 (2.3)	72 (2.0)	261 (1.7)	72 (2.5)	121 (1.9)
Missing	81 (0.1)	4 (0.1)	18 (0.1)	2 (0.1)	2 (0.0)
BMI (kg/m^2)	27.5±4.6	27.7±4.8	27.9±4.9	30.9±5.6	27.8±4.7
Cholesterol (mmol/L)	5.74±1.14	5.67±1.18	5.61±1.21	4.45±1.06	5.61±1.19
Glucose (mmol/L)	5.19±0.98	5.31±1.38	5.37±1.56	7.72±3.78	5.31±1.45
Diabetes	3921 (4.5)	312 (8.5)	1636 (10.7)	2454 (84.0)	575 (9.0)
Stroke	1806 (2.1)	112 (3.1)	470 (3.1)	187 (6.4)	184 (2.9)
Heart disease	4966 (5.7)	302 (8.2)	1454 (9.5)	667 (22.8)	555 (8.7)
Hypertension	25 950 (29.6)	1270 (34.6)	5437 (35.4)	1739 (59.5)	2281 (35.7)
Depression	4786 (5.5)	234 (6.4)	895 (5.8)	204 (7.0)	325 (5.1)

Data are mean (SD) or N (%).
*The sum of the sample sizes for all columns exceeded the total participants included in the analysis as some participants had multiple ophthalmic conditions.
AMD, age-related macular degeneration; BMI, body mass index; DRED, diabetes-related eye disease; MET, metabolic equivalent.

risk for incident dementia (HR (95% CI): 2.73 (1.79 to 4.17)), which was followed by AMD and obesity (1.88 (1.35 to 2.63), figure 2.

Cataract only was not independently associated with an increased risk of incident dementia. Cataract with a comorbidity being stroke (HR (95% CI): 2.00 (1.40 to 2.84)), heart disease (1.77 (1.43 to 2.21)), hypertension (1.36 (1.17 to 1.58)), diabetes (2.19 (1.78 to 2.70)), depression (2.29 (1.74 to 3.01)) or any systematic condition (1.57 (1.36–1.81)) was associated with an increased risk of dementia (figure 3).

Of ophthalmic conditions, DRED only had the largest risk for incident dementia. Individuals with DRED and a systemic condition as a comorbidity were 1.50–3.24 times more likely to develop dementia compared with those without DRED and the

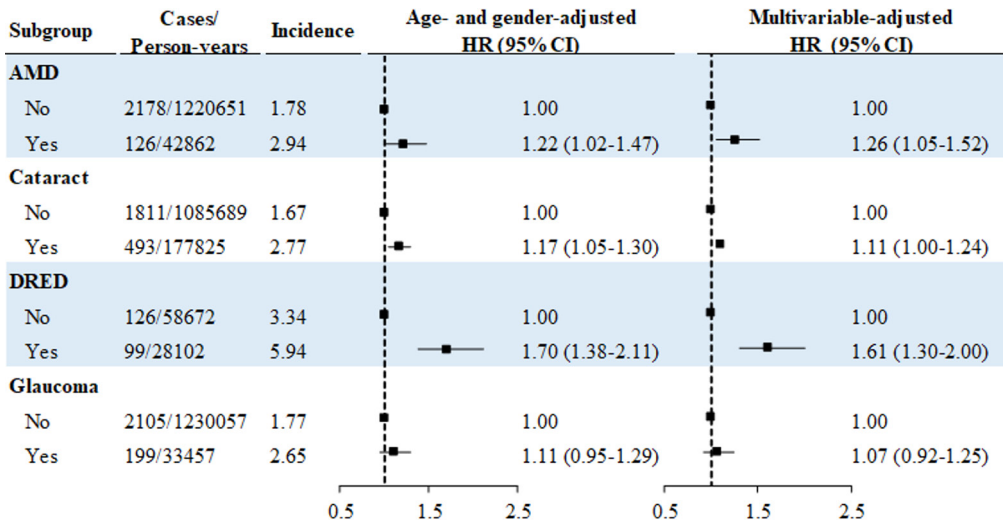

Figure 1 The risk for dementia associated with ophthalmic conditions. Incidence of dementia represents cases per 1000 person-years. HR (95% CI) for incident dementia associated with ophthalmic conditions was estimated using Cox proportional regression models adjusted for age, gender, education, income, cooked vegetables intake, raw vegetables intake, fresh fruits intake, dried fruits intake, smoking, alcohol consumption, physical activity, BMI, cholesterol and glucose at baseline. The analysis for the association between DRED and dementia was conducted among patients with diabetes. AMD, age-related macular degeneration; BMI, body mass index; DRED, diabetes-related eye disease.

corresponding systemic condition. These associations were independent of glucose and duration of diabetes (figure 4).

Glaucoma only was not significantly associated with incident all-cause dementia. However, when it co-occurred with stroke, heart disease, diabetes, hypertension or depression, the risk for dementia increased significantly and was larger than the risk associated with the corresponding systemic condition only (online supplemental figure e-4).

Mediation analysis

The percentage (95% CI) for the association between cataract and incident dementia explained by diabetes, hypertension, heart disease, depression and stroke was 9.2% (95% CI: 2.9% to 25.4%), 7.1% (2.7% to 17.0%), 9.1% (3.3% to 22.5%), 12.0% (4.5% to 28.4%) and 22.4% (8.0% to 48.9%), respectively. This association was fully mediated by these significant mediators combined (65.4% (5.3% to 98.5%). Hypertension, stroke, heart disease, depression and diabetes together explained 10.0% (9.4% to 31.5%) of the association between DRED and incident dementia (online supplemental figure e-5).

Sensitivity analysis

Individuals with DR than those without had an increased risk of dementia in those with diabetes at baseline (HR (95% CI): 1.65 (1.25 to 2.16), online supplemental figure e-6). Among individuals by excluding those who developed dementia in the first 5 years of follow-up, the multivariable-adjusted HRs (95% CIs) for dementia associated with AMD, cataract, DRED and glaucoma were 1.28 (1.06 to 1.55), 1.13 (1.01 to 1.25), 1.56 (1.24 to 1.95) and 1.09 (0.94 to 1.28), respectively (online supplemental figure e-7).

The HRs (95% CI) for dementia associated with 1 and ≥2 ophthalmic conditions were 1.11 (1.01 to 1.22) and 1.55 (1.31 to 1.82), respectively (online supplemental figure e-8).

The incidence of dementia increased with the increasing number of ophthalmic conditions across the number of systemic conditions (online supplemental figure e-9).

DISCUSSION

This prospective cohort study with a large sample size demonstrated that AMD, cataract and DRED but not glaucoma were independently associated with an increased risk of all-cause dementia. Participants with an ophthalmic condition and a systemic condition had a higher risk for dementia compared with those with an ophthalmic or a systemic condition only. Newly developed hypertension, diabetes, stroke, heart disease and depression mediated the association between cataract/DRED and dementia.

Our study is consistent with several cohort studies showing that AMD was associated with an increased risk of dementia. Data from the Adult Changes in Thought (ACT) Study of 3877 participants aged ≥65 years showed that AMD (HR (95% CI): 1.20 (1.02 to 1.40)) was a risk factor of dementia.[21] A longitudinal case–control study of 29 958 participants aged ≥65 years reported that AMD was independently associated with an increased risk of subsequent Alzheimer's disease (HR (95% CI): 1.44 (1.26 to 1.64)) over 4 years.[27] In a cohort study of 308 340 Korean participants aged ≥50 years, those with AMD had a higher risk for Alzheimer's disease (HR (95% CI): 1.48 (1.25 to 1.74)) over 8 years compared with those without.[22] Age is an important marker for dementia,[28] however, these studies included participants with a wide range of age. Our further analysis demonstrated that the positive association between AMD and incident dementia was even significant when the analysis was restricted to those aged 60–70 years. In contrast, a prospective population-based study of 1438 Dutch adults aged ≥75 years demonstrated that AMD at baseline was associated with an increased risk of incident Alzheimer's disease before, but not after adjustment for smoking and atherosclerosis.[13] Two case–control cohort studies did not find a significant association between AMD and incident dementia.[15 16] The case–control design and diagnosis of AMD using hospital admission records only may partly explain why the results of these studies are inconsistent with our findings.[22]

The mechanisms for the positive association between ophthalmic conditions and dementia are largely unknown, but there are several potential pathways for this association. First,

Subgroup	Cases/ person-years	Incidence of dementia	Age- and gender-adjusted hazard ratio (95% CI)	Multivariable adjusted hazard ratio (95% CI)
AMD and stroke				
No AMD and no stroke	2037/1192532	1.71	1.00	1.00
AMD only	120/41513	2.89	1.25 (1.04-1.51)	1.28 (1.06-1.55)
Stroke only	141/28119	5.01	2.29 (1.92-2.73)	1.99 (1.67-2.38)
AMD and stroke	6/1349	4.45	1.75 (0.79-3.91)	1.76 (0.79-3.92)
AMD and heart disease				
No AMD and no heart disease	1860/1140808	1.63	1.00	1.00
AMD only	106/39321	2.70	1.24 (1.01-1.51)	1.27 (1.04-1.55)
Heart disease only	318/79844	3.98	1.85 (1.63-2.09)	1.63 (1.44-1.84)
AMD and heart disease	20/3541	5.65	2.01 (1.26-3.21)	1.83 (1.15-2.91)
AMD and obesity				
No AMD and no obesity	1475/873796	1.69	1.00	1.00
AMD only	77/30527	2.52	1.09 (0.86-1.38)	1.11 (0.88-1.41)
Obesity only	589/312605	1.88	1.12 (1.02-1.24)	1.11 (0.96-1.30)
AMD and obesity	43/11009	3.91	1.77 (1.30-2.41)	1.88 (1.35-2.63)
AMD and hypertension				
No AMD and no hypertension	1336/839815	1.59	1.00	1.00
AMD only	74/28014	2.64	1.23 (0.97-1.56)	1.28 (1.00-1.62)
Hypertension only	842/380836	2.21	1.18 (1.08-1.29)	1.17 (1.06-1.28)
AMD and hypertension	52/14848	3.50	1.43 (1.07-1.90)	1.43 (1.07-1.90)
AMD and diabetes				
No AMD and no diabetes	1837/1137500	1.61	1.00	1.00
AMD only	104/39240	2.65	1.19 (0.97-1.46)	1.22 (1.00-1.50)
Diabetes only	341/83151	4.10	2.18 (1.94-2.46)	1.99 (1.76-2.26)
AMD and diabetes	22/3622	6.07	2.84 (1.86-4.32)	2.73 (1.79-4.17)
AMD and depression				
No AMD and no depression	1976/1152956	1.71	1.00	1.00
AMD only	114/40145	2.84	1.23 (1.02-1.50)	1.28 (1.05-1.55)
Depression only	202/67695	2.98	2.07 (1.79-2.40)	1.82 (1.57-2.12)
AMD and depression	12/2717	4.42	2.27 (1.25-4.11)	1.85 (1.02-3.36)
AMD and any systemic condition				
No AMD and no systemic condition	790/586988	1.35	1.00	1.00
AMD only	42/19089	2.20	1.18 (0.86-1.62)	1.20 (0.87-1.65)
≥1 systemic condition only	1388/633663	2.19	1.44 (1.31-1.57)	1.43 (1.29-1.58)
AMD and ≥1 systemic condition	84/23773	3.53	1.78 (1.41-2.24)	1.83 (1.45-2.31)

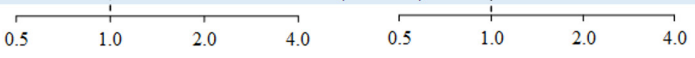

Figure 2 The risk for incident dementia associated with age-related macular degeneration (AMD) and systemic conditions. Incidence of dementia represents cases per 1000 person-years. HR (95% CI) for incident dementia associated with AMD and systemic conditions was estimated using Cox proportional regression models. Multivariable analysis was adjusted for age, gender, education, income, cooked vegetables intake, raw vegetables intake, fresh fruits intake, dried fruits intake, smoking, alcohol consumption, physical activity, body mass index, cholesterol and glucose at baseline. Central squares of each horizontal line represent the HR for each subgroup. Horizontal lines indicate the range of the 95% CI and the vertical dash lines indicate the HR of 1.0.

ophthalmic conditions are associated with well-known risk factors of dementia including diabetes, stroke, heart disease, hypertension and depression.[4 19 20] Second, ophthalmic conditions and dementia have many share risk factors including older age, low levels of education, smoking and physical inactivity.[19 20 29 30] Importantly, vision deprivation may result in reduced activation in central sensory pathways, which is associated with a higher risk of cognitive load and brain structure damage.[10 11] Of note, there are aetiological differences in types of dementia including Alzheimer's disease and vascular dementia, such that the potential effects of ophthalmic conditions might differ among dementia types.

Only several cohort studies have reported the association between cataract and incident dementia. A case–control prospective study showed that cataract was associated with an increased risk of dementia over 14 years.[15] Data from the ACT Study showed that cataract was not significantly associated with dementia (HR (95% CI): 1.21 (0.93 to 1.57)) over 8 years.[21] In the Shanghai Aging Study of 1659 community residents aged ≥60 years, no significant association between cataract and incident dementia was observed.[23] The non-significant association may be attributed to the small number of cataract cases in these two studies.[21] We found that hypertension, diabetes, depression, stroke and heart disease identified during follow-up combined fully mediated the association suggesting that the risk for dementia associated with cataract may depend on these conditions.

Diabetes is a well-known risk factor for dementia,[31] but DRED has been linked to dementia in only two prospective studies.[15 21] DR was associated with an increased risk of dementia in the ACT Study.[21] Similarly, a retrospective case–control study of 126 650 participants showed that those with DR were 1.42 (95% CI: 1.30 to 1.55) times more likely to develop dementia than those without.[15] Our study is consistent with these studies showing that DRED was an independent risk factor of dementia. The association between DRED and dementia may reflect the association

Subgroup	Cases/ person-years	Incidence of dementia	Age- and gender-adjusted hazard ratio (95% CI)	Multivariable-adjusted hazard ratio (95% CI)
Cataract and stroke				
No cataract and no stroke	1698/1061642	1.60	1.00	1.00
Cataract only	459/172404	2.66	1.17 (1.05-1.31)	1.12 (1.00-1.24)
Stroke only	113/24047	4.70	2.30 (1.89-2.81)	2.01 (1.65-2.45)
Cataract and stroke	34/5421	6.27	2.32 (1.64-3.30)	2.00 (1.40-2.84)
Cataract and heart disease				
No cataract and no heart disease	1562/1019085	1.53	1.00	1.00
Cataract only	404/161043	2.51	1.14 (1.02-1.28)	1.09 (0.97-1.23)
Heart disease only	249/66604	3.74	1.81 (1.57-2.08)	1.61 (1.40-1.85)
Cataract and heart disease	89/16781	5.30	2.12 (1.71-2.64)	1.77 (1.43-2.21)
Cataract and obesity				
No cataract and no obesity	1223/781502	1.56	1.00	1.00
Cataract only	329/122820	2.68	1.18 (1.04-1.34)	1.14 (1.00-1.29)
Obesity only	498/274070	1.82	1.17 (1.05-1.30)	1.16 (0.99-1.36)
Cataract and obesity	134/49545	2.70	1.25 (1.04-1.50)	1.19 (0.95-1.48)
Cataract and hypertension				
No cataract and no hypertension	1136/752969	1.51	1.00	1.00
Cataract only	274/114861	2.39	1.08 (0.94-1.24)	1.04 (0.91-1.19)
Hypertension only	675/332720	2.03	1.14 (1.03-1.25)	1.12 (1.02-1.24)
Cataract and hypertension	219/62964	3.48	1.46 (1.26-1.69)	1.36 (1.17-1.58)
Cataract and diabetes				
No cataract and no diabetes	1556/1017658	1.53	1.00	1.00
Cataract only	385/159082	2.42	1.11 (0.99-1.25)	1.07 (0.96-1.21)
Diabetes only	255/68031	3.75	2.14 (1.87-2.46)	1.98 (1.72-2.28)
Cataract and diabetes	108/18743	5.76	2.51 (2.06-3.08)	2.19 (1.78-2.70)
Cataract and depression				
No cataract and no depression	1651/1025586	1.61	1.00	1.00
Cataract only	439/167514	2.62	1.14 (1.02-1.27)	1.09 (0.97-1.21)
Depression only	160/60102	2.66	1.94 (1.64-2.29)	1.71 (1.45-2.03)
Cataract and depression	54/10310	5.24	2.82 (2.15-3.70)	2.29 (1.74-3.01)
Cataract and any systemic condition				
No cataract and no systemic condition	672/530220	1.27	1.00	1.00
Cataract only	160/75857	2.11	1.14 (0.95-1.36)	1.11 (0.93-1.33)
≥1 systemic condition only	1139/555469	2.05	1.43 (1.30-1.58)	1.43 (1.29-1.60)
Cataract and ≥1 systemic condition	333/101968	3.27	1.65 (1.44-1.89)	1.57 (1.36-1.81)

Figure 3 The risk for incident dementia associated with cataract and systemic conditions. Incidence of dementia represents cases per 1000 person-years. HR (95% CI) for incident dementia associated with cataract and systemic conditions was estimated using Cox proportional regression models. Multivariable analysis was adjusted for age, gender, education, income, cooked vegetables intake, raw vegetables intake, fresh fruits intake, dried fruits intake, smoking, alcohol consumption, physical activity, body mass index, cholesterol and glucose at baseline. Central squares of each horizontal line represent the HR for each subgroup. Horizontal lines indicate the range of the 95% CI and the vertical dash lines indicate the HR of 1.0.

between diabetes and dementia. However, these previous studies cannot distinguish whether the risk for dementia associated with DRED was due to diabetes or eye disease. Our further analysis demonstrated that DRED was positively associated with incident dementia in individuals with diabetes. We also observed that hypertension, stroke, heart disease and depression combined did not fully mediate the association highlighting the importance of DRED as an independent risk factor for dementia.

The association between glaucoma and incident dementia has been investigated in some previous studies with conflicting results.[14 15 21 23 32 33] A positive association between glaucoma and dementia has been reported in a case–control study in Taiwan[32] and one in Korea.[33] Data from the Shanghai Aging Study showed that individuals with glaucoma had a higher risk of dementia over 5 years than those without (HR (95% CI): 2.38 (1.08 to 5.23)).[23] However, a retrospective cohort study of older American adults aged ≥68 years demonstrated that glaucoma was inversely associated with the risk of dementia over 14 years.[15] Another prospective cohort study in the USA showed that glaucoma was not significantly associated with the incidence of dementia.[21] A case–control study of 11 721 Danish participants aged 61–77 years did not find a significant association between glaucoma and dementia over 5 years.[14] Our study is in line with the previous studies from Europe and the USA demonstrating that glaucoma was not an independent risk factor for dementia. Further analysis had demonstrated that glaucoma may have the potential to increase the risk of vascular dementia but not Alzheimer's disease.

No previous study has examined the association between combinations of ophthalmic and systemic conditions with incident dementia. As both ophthalmic and systemic conditions examined in our study are aged-related conditions, they are highly likely to be clustered in pairs.[4 19 20 29] We found that all combinations of an ophthalmic condition and a systemic condition were associated with an increased risk of dementia. This risk was greater than that associated with an ophthalmic or a systemic condition only suggesting that there might be an additive effect of ophthalmic and systemic conditions on the development of

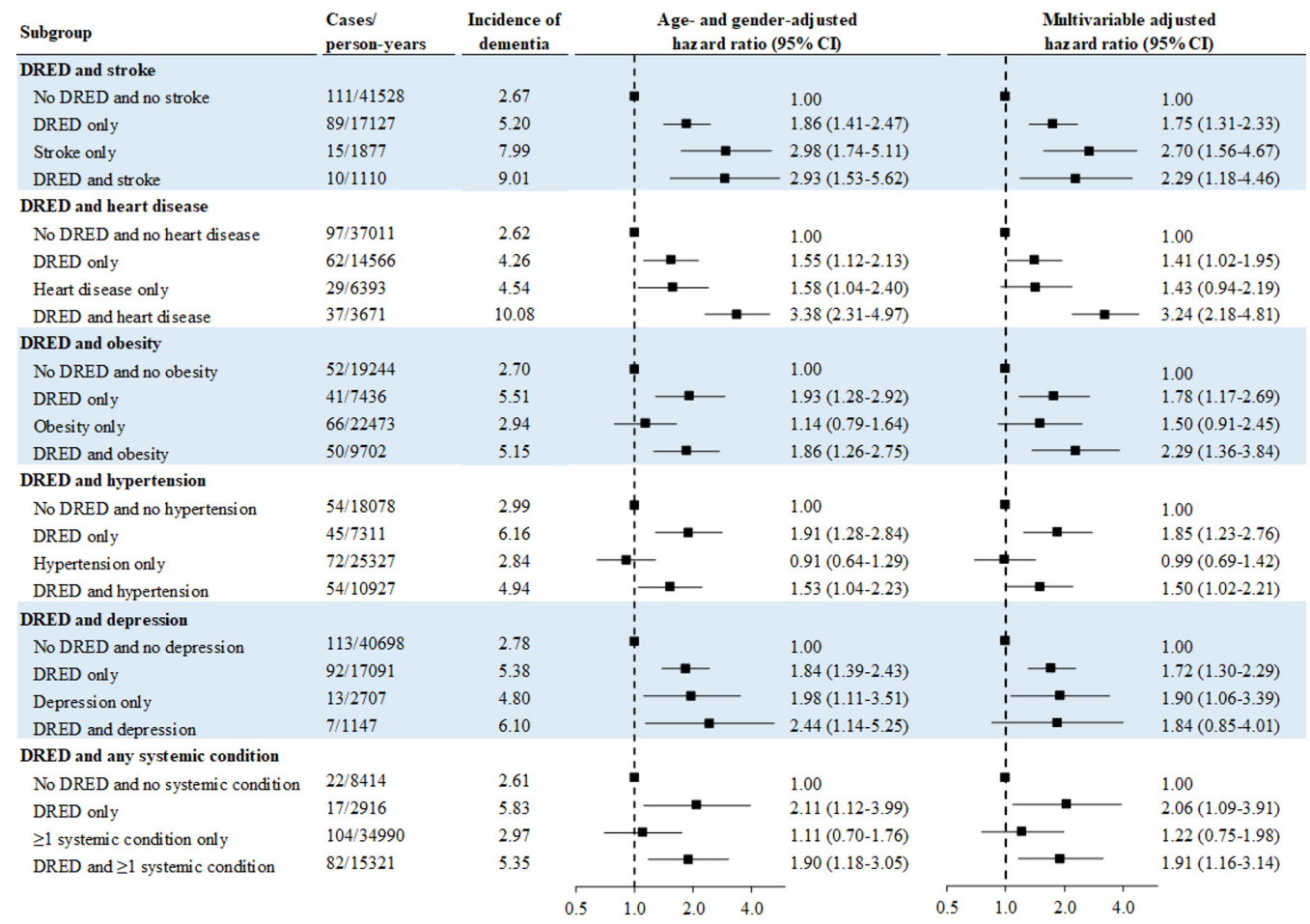

Figure 4 The risk for incident dementia associated with diabetes-related eye disease (DRED) and systemic conditions. Incidence of dementia represents cases per 1000 person-years. HR (95% CI) for incident dementia associated with DRED and systemic conditions was estimated using Cox proportional regression models. The analysis was conducted among patients with diabetes. Multivariable analysis was adjusted for age, gender, education, income, cooked vegetables intake, raw vegetables intake, fresh fruits intake, dried fruits intake, smoking, alcohol consumption, physical activity, body mass index, cholesterol, glucose and duration of diabetes at baseline. Central squares of each horizontal line represent the HR for each subgroup. Horizontal lines indicate the range of the 95% CI and the vertical dash lines indicate the HR of 1.0.

dementia. Underlying mechanisms are unclear, but impairment of multiple organs than a single is more likely to enlarge the risk of dementia. Only one previous study examined multiple ophthalmic conditions and showed that individuals with both glaucoma and cataract were over three times more likely to develop dementia compared with those without ophthalmic conditions.[23] However, this study is limited by the small sample in the subgroup of glaucoma and cataract (n=29). Our study with a much larger sample size demonstrated that individuals with ≥2 ophthalmic conditions had a higher risk of dementia than those with one ophthalmic condition. Notably, individuals with ≥2 ophthalmic and ≥2 systemic conditions were almost three times more likely to develop dementia in our study. This indicates that individuals with both ophthalmic and systemic conditions should be targeted for the prevention and screening of dementia in older adults.

To our knowledge, this is the first prospective study to examine the association between the clustering of ophthalmic and systemic conditions and incident dementia. Our study has several potential limitations. First, ophthalmic conditions were defined based on self-reported and inpatient record data, which may result in misclassification errors. However, these data are more likely to underestimate the prevalence of ophthalmic conditions,[34–36] which is more likely to have biased these findings towards the null. Second, some cases of dementia might not be captured in the medical records or death registers. However, previous research has demonstrated good agreement of dementia case ascertainment with primary care records.[37] Third, dementia documented during follow-up may have occurred before eye diseases, as the prodromal period of dementia can last decades. Therefore, our study may not infer causal relationships although the results by excluding individuals who developed dementia in the first 5 years of follow-up are consistent with those for dementia during the whole follow-up period. Fourth, this sample was restricted to a subgroup of the UK Biobank cohort who had self-reported data on ophthalmic conditions. Individuals excluded from the analysis were more likely to be younger and have a lower prevalence of diabetes, cardiovascular disease and depression compared with those included in the analysis (online supplemental table e-4). However, a previous study has demonstrated that findings regarding exposure–disease relationships may be generalised to other populations.[38]

In conclusion, AMD, cataract and DRED but not glaucoma are associated with an increased risk of dementia. Individuals with both ophthalmic and systemic conditions are at higher risk of dementia compared with those with an ophthalmic or systemic condition only.

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Patient consent for publication Not required.

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