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The association between diagnosed glaucoma, cataract and cognitive performance in very old people: Cross sectional findings from the Newcastle 85+ cohort study

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Abstract

Purpose—Common age-related eye diseases including glaucoma, cataract and age-related macular degeneration (AMD) have been proposed to be associated with dementia. Several studies have examined the link between cognition and AMD but few have examined the relationship between cognition and cataract or glaucoma. We explored the association between cognition and cataract and glaucoma diagnoses in community-dwelling 85 year olds.

Methods—Cross-sectional analysis of data from the Newcastle 85+ Cohort study. Diagnoses of eye disease were extracted from family practice records. Cognitive performance was assessed by the standardised mini-mental state examination (sMMSE) and the MMSE-blind (MMblind). The relationships between glaucoma diagnosis or cataract diagnosis and lower cognition were examined using ordinal logistic regression.

Results—Complete data were available for 839 participants. Of these, 36.0% (302/839) had recorded previous cataract surgery, 11.2% (94/839) untreated cataract and 7.9% (66/839) diagnosed glaucoma. Glaucoma diagnosis was associated with lower sMMSE (odds ratio [95% confidence interval]: 1.76[1.05-2.95]); but not with lower MMblind: 1.17[0.65-2.12]. When compared to no cataract, cataract diagnosis (treated and untreated combined) was associated with higher sMMSE: 0.55[0.38-0.79] and MMblind: 0.51[0.34-0.76]. Previously treated cataract was associated with higher sMMSE: 0.72[0.59-0.88] and MMblind: 0.68[0.55-0.85]. Untreated cataract was not significantly associated with sMMSE: 0.65[0.36-1.19] or MMblind: 0.73[0.39-1.36].

Conclusions—This large epidemiological study of 85 year olds found that lower sMMSE but not MMblind was associated with glaucoma diagnosis, suggesting the association may be driven by poor vision. Cataract diagnosis was associated with higher sMMSE and MMblind. Reasons for

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this observation are unclear but may relate to enhanced help seeking behaviour in people with diagnosed cataract.

Keywords

Cataract; glaucoma; cognitive impairment; dementia; Newcastle; 85+; elderly; older people

Introduction

Dementia is a growing problem amongst older populations affecting 24 million people worldwide, with rates predicted to double every 20 years.¹ A number of age-related degenerative eye diseases including cataract, glaucoma and age-related macular degeneration (AMD) have been proposed to share an association with dementia. Although there are a number of studies showing an association of AMD with decreased cognitive function,²⁻⁵ there are few such studies exploring the potential link between cataract, or glaucoma, and cognitive function.

Dementia and cataract have a number of common risk factors including age, female gender, smoking, diabetes and lower socioeconomic class.⁶⁻¹⁴ Cataract and dementia have been proposed to share common aetiological mechanisms^{15,16} and it has even been suggested that cataract could be a potential biomarker for dementia.¹⁷ However two epidemiological studies looking at the association between cataract and cognitive performance found no association.^{18,19} A number of studies have looked at the effect of cataract surgery on cognitive performance; some seem to suggest that cognitive performance can be improved with cataract surgery,^{20,21} but a randomised study using a waiting list control group did not confirm this²² (reviewed in²³).

Common genetic risk factors have been reported in Alzheimer's disease and glaucoma, and similar pathological changes in the optic nerves of glaucoma patients and brains of patients with Alzheimer's disease have been demonstrated.²⁴ A causal relationship between Alzheimer's disease and glaucoma has been proposed.²⁵ A study in the United States examining death certification found an association between dementia and glaucoma,²⁶ and higher rates of glaucoma have been noted in people with Alzheimer's disease in two studies where people with established dementia underwent ophthalmological assessment.^{27,28} A recently reported study of 41 people with glaucoma demonstrated high rates of cognitive impairment and depressive symptoms.²⁹ However, both retrospective and prospective case register based studies in Denmark have shown no association between glaucoma and dementia,^{30,31} and, to our knowledge there has been no comparison of cognitive test scores in those with and without glaucoma.

The Newcastle 85+ study is a population-based cohort study which aims to examine the health trajectories and outcomes of very elderly individuals in the North-East of England aged 85 at recruitment.^{32,33} We have previously shown an association between visual impairment and cognitive scores in the study population.³⁴ The aim of this study was to investigate the cross-sectional relationship between cognitive test scores and cataract or glaucoma diagnoses. We hypothesised that cataract diagnosis (including those who had

undergone previous cataract surgery) and glaucoma diagnosis would be associated with poorer cognitive test scores.

Materials and Methods

The protocol for the Newcastle 85+ Study has been published previously.^{32,33} The investigations adhered to the guidelines of the declaration of Helsinki and ethical approval was obtained from Newcastle and North Tyneside local research ethics committee. In brief, the sampling frame comprised all people born in 1921 who were permanently registered with a participating family practice in Newcastle upon Tyne or North Tyneside NHS Primary Care Trusts, in the UK. Recruitment and assessment took place over a 17 month period during 2006-7, such that all participants were aged around 85 at the time of assessment. Participation at baseline entailed a detailed multidimensional health assessment and a review of medical records held by the family practitioner; participants could decline either element of the protocol. The multidimensional health assessment was carried out in the participant's usual residence (home or institution) by a research nurse. It included questions about years of education and smoking, and the standardised mini-mental state examination (sMMSE).³⁵ The sMMSE is similar to the original mini-mental state examination³⁶ but uses strict guidelines for administration and scoring, with resulting improved intra- and inter-rater variability.³⁵ As part of the review of family practice records, any pre-existing diagnosis of glaucoma, cataract, cataract surgery (unilateral or bilateral) or sight impaired registration was noted and all regular prescription medications, including anti-glaucoma medications, recorded. Details of comorbidities including diabetes and hypertension were extracted from family practice records. A chronic disease count was calculated from the family practice records which was a count of 18 diseases: hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial flutter or fibrillation, arthritis, osteoporosis, chronic obstructive pulmonary disease or asthma, other respiratory disease, diabetes, hypothyroidism or hyperthyroidism, cancer diagnosed within past 5 years (excluding non-melanoma skin cancer), eye disease, dementia, Parkinson's disease, renal impairment and anaemia.³³

The current analysis was based on the 851 participants who were included in both health assessment and review of family practice records (59% of the 1453 eligible to take part). We have previously reported a comparison between participants and non-participants as well as comparisons with local and national census data.³³ Participants and non-participants were compared by gender and index of multiple deprivation score. Deprivation did not differ significantly but there were fewer female participants than non-participants (62.3% (527/846) of participants and 73.1% (396/542) of non-participants). Participants were compared to local census data from 2001 on gender, living arrangements (in institution or living alone), marital status and ethnicity, and this showed the study sample to be broadly representative of the local population, although again with a slight under-representation of women (62.3% (527/846) in this sample and 66.5% in local census data). The population of Newcastle and North Tyneside is broadly representative of the rest of the UK with similar levels of ethnic diversity to Scotland and Wales (2% non-white population) but less ethnic diversity than the rest of England (9% non-white population).³⁷

Statistical analysis

Pearson Chi-square statistic was used to look for associations between ophthalmic diagnosis and sight impairment registration. Pearson chi-square, Fisher's exact test or t-test statistics were used to compare characteristics between groups with and without a recorded diagnosis of cataract and glaucoma.

As sMMSE data distribution was non-normal with a negative skew, it was categorised; sMMSE categories were chosen to be the same as those used in a similar population based study of the oldest old³⁸ and as reported previously for this study.³³ Ordinal logistic regression was used to look for associations between sMMSE score and ophthalmic diagnosis. Ordinal logistic regression provides a useful extension of binary logistic regression where the response variable takes on ordered, categorical values.³⁹

Ordinal logistic regression was performed with sMMSE score, categorised as normal (26-30), mild (22-25), moderate (18-21) and moderate to severe (0-17) impairment, as the dependent variable and recorded glaucoma diagnosis the independent variable. In order to include those with borderline glaucoma or ocular hypertension, ordinal logistic regression was also performed comparing those with either a recorded diagnosis of glaucoma or on anti-glaucoma medications to those with neither a diagnosis of glaucoma nor on anti-glaucoma medications. The same process was repeated for cataract comparing 1) those with no recorded diagnosis of cataract (NC group) to those who had a history of previous cataract surgery (CS group), 2) the NC group with those with a diagnosis of cataract but who had not had previous surgery (CNS group), 3) the NC group with all those with cataract or previous surgery (CS+CNS), and 4) the CNS group with the CS group. The Brant test was used to check the assumption of parallel lines (proportional odds assumption). The odds ratio represents the odds of a lower categorised sMMSE score in the presence of the ophthalmic diagnosis. As the assumption of parallel lines was satisfied, the odds ratio between each pair of categories on the sMMSE is assumed to be the same, regardless of which two adjacent categories are chosen. Models were adjusted for age, gender, ethnicity, smoking, educational level (total years in education), and other comparators found to be significantly different between groups. All reported p-values are two-tailed and a p-value of 0.05 was considered statistically significant.

In order to ascertain if any association could be solely accounted for by poor performance on the tasks requiring vision in the sMMSE, the items requiring vision in the sMMSE (copying, writing a sentence, following a written command, following a 3 stage command and naming 2 objects) were removed to give the blind version of the MMSE (MMblind⁴⁰) with a maximum score of 22. Ordinal logistic regression was repeated as above with the MMblind as the dependent variable categorised as normal (17-22), mild-moderate (12-16) and severe (0-11) cognitive impairment; categories were decided based upon age specific norms.⁴⁰

Data analysis was carried out using the Statistical Package for Social Sciences (SPSS version 17) and STATA version 11 (StataCorp. 2009. Statistical Software: Release 11.0. College Station, TX: Stata Corporation.)

Results

Complete data on ophthalmological diagnoses (from the review of family practice records) and the mini-mental state examination (from health assessment) were available for 839 participants (99% of the 851 who had both health assessment and family practice record review). Reasons for unavailable data were: incomplete family practice records (n=4); withdrawal of consent and request to destroy data (n=2); sMMSE omitted due to interviewer error (n=3); and sMMSE not done due to relative or proxy refusal (n=3).

From the family practice medical records, 36.0% (302/839) had a history of previous cataract surgery in one or both eyes, 11.2% (94/839) had a record of cataract but no previous surgery, 7.9% (66/839) had a recorded diagnosis of glaucoma and 8.6% (72/839) had a diagnosis of glaucoma and/or were on anti-glaucoma medications. Both cataract or previous cataract surgery and glaucoma or anti-glaucoma medications were recorded in 7.3% (61/839) of participants. Registration as severely sight impaired (blind) was recorded in 2.4% (20/839) participants and sight impaired (partially sighted) in 2.9% (24/839). As expected, those with a diagnosis of glaucoma were more likely to be registered sight impaired than those without glaucoma (χ^2 test, $p=0.004$). Neither those with treated nor untreated cataract were more likely to be registered sight impaired than those without cataract (χ^2 test, $p=1.00$ and $p=0.334$ respectively).

A diagnosis of dementia in the family practice medical records was recorded in 8.1% (68/839) of participants. From the sMMSE scores, 71.2% (599/839) had normal cognitive function (sMMSE 26-30); 16.1% (135/839) had mild impairment (sMMSE 22-25); 5.6% (47/839) moderate impairment (sMMSE 18-21) and 6.9% moderate to severe impairment (sMMSE 0-17). From the MMblind scores, 76.5% (642/839) had normal cognitive function (MMblind 18-22); 17.0% (143/839) had mild-moderate impairment (MMblind 12-17) and 6.4% (54/839) severe impairment (MMblind 0-11).

Table 1 shows a comparison of age, gender, ethnicity, educational status, smoking status, medication use, diabetes, hypertension and chronic disease count for those with and without diagnosed cataract and those with and without diagnosed glaucoma.

Table 2 shows the results from ordinal logistic regression with diagnosed glaucoma as a predictor. Those with diagnosed glaucoma were more likely to have lower sMMSE scores ($p=0.032$) than those without diagnosed glaucoma. Those with diagnosed glaucoma or on anti-glaucoma medications were more likely to have lower sMMSE scores than those without a diagnosis or on medication ($p=0.030$). However, when we repeated the ordinal logistic regression using the MMblind scores (without any visual items) these significant relationships were lost.

Table 3 shows the results from ordinal logistic regression with different cataract status as predictors. Those with any history of cataract (treated or untreated) had higher sMMSE scores than those with no cataract ($p=0.001$). Previously treated cataract was a predictor of higher sMMSE scores when compared to the no cataract group ($p=0.001$) whilst untreated cataract was not a significant predictor of sMMSE scores when compared to the no cataract group ($p=0.17$) or when compared to the previously treated cataract group ($p=0.39$). When

the MMblind was examined as the dependent variable, any history of cataract and previously treated cataract remained significant predictors of higher MMblind scores when compared to the no cataract group ($p=0.001$ for each)

Discussion

This large epidemiological study looking at over eight hundred 85 year olds in the North East of England has examined the association between sMMSE/ MMblind scores and cataract or glaucoma diagnoses. We had hypothesised that both cataract and glaucoma diagnoses would be associated with lower cognitive scores, based on common risk factors and pathogeneses. We found that those with a diagnosis of glaucoma scored lower on the sMMSE compared to those without diagnosed glaucoma, in support of this hypothesis.

However, glaucoma diagnosis was not significantly associated with MMblind scores suggesting this relationship may be driven purely by poor vision in the diagnosed glaucoma group as opposed to a common pathogenesis. Contrary to our a-priori hypothesis, we found that those with a diagnosis of cataract (including previously treated and untreated cataract) scored better on the sMMSE and the MMblind than those with no diagnosis of cataract. When those with a diagnosis of cataract were further defined by whether or not they had had previous cataract surgery, we found that those with a history of previous cataract surgery scored better on the sMMSE (and the MMblind) than those without cataract but not significantly differently from those with untreated cataract.

The rates of diagnosed glaucoma we have reported here are similar to previously reported figures in a large epidemiological study in which participants underwent an ophthalmological assessment where 8% of over 80 year olds had “definite open angle glaucoma” and 3% had “probable open angle glaucoma”.⁴¹ Our prevalence of cataract was significantly less than that found in the same epidemiological study in which over 90% of 85-89 year olds were found to have cataract on examination,⁴² although, these may not all have been clinically significant cataracts. We found that women were more likely to have cataract than men, in keeping with previous epidemiological studies.^{43,44} The rates of dementia which were recorded in family practice medical records were lower than those previously reported in a large consensus study on the global prevalence of dementia,¹ although we have previously estimated that 7% of participants who had no diagnosis of dementia recorded in their medical records had an sMMSE score suggestive of dementia.³³ A prevalence of 13% moderate to severe cognitive impairment is similar to the results of the MRC-CFAS study in the UK which used a clinical diagnosis of dementia.⁴⁵

Our findings initially seem to support those who have suggested an association between glaucoma and cognitive impairment²⁵ through the notion of a shared neuro-degenerative process. However, these differences diminished when all visual items were excluded from the analysis, suggesting much of this relationship was driven by poor vision limiting cognitive test performance. Our findings do not support the theory of a combined neurodegenerative mechanism in cataract and cognitive impairment, as we found a positive association between cataract (including treated and untreated) and sMMSE scores. It is not possible to draw conclusions on the effects of cataract surgery on cognition from this cross-

sectional epidemiological study and further study is needed to determine whether cataract surgery can help prevent cognitive decline. If maximising vision with cataract surgery or up to date spectacle prescriptions accounted for improved cognition one would expect to see higher sMMSE scores in those with a previous history of cataract surgery compared to those who had untreated cataract which was not the case. Undiagnosed cataract in the “no cataract” group may also be confusing the results. A more likely explanation for these findings is that those with a diagnosis of cataract or cataract surgery are more likely to visit their optician, more likely to have an up-to-date spectacle prescription, and are more likely to be socially active and help-seeking and that it is these factors which are associated with improved cognition.

These results are from a large population based study, which had reasonable response rates given the age group being assessed and the intensity of the assessment protocol.³²³³ Using a sample of very old individuals meant that we had reasonably high rates of age-related ophthalmic diagnoses and cognitive impairment. The assessments were based in participants’ homes or institutions which is important to achieve a representative sample in a group who may be unwilling or unable to travel for clinic based assessment. The sample is sociodemographically broadly representative of the local population and of England and Wales in this age group, and, importantly included those in institutions and those with cognitive impairment.³²³³ This study was not without limitations. Only cross-sectional analysis has been carried out, limiting scope for assessing causality between eye disease and cognition. We did not measure visual acuity and participants did not undergo an ophthalmological assessment, so some participants may have had undiagnosed glaucoma or cataract. A major limitation of this study was our reliance on family practice medical records for diagnoses of cataract and glaucoma. In the UK, the family practitioner should receive correspondence from all secondary and tertiary care providers (including ophthalmologists) involved in their patients’ care. This means that family practice records should have an accurate and cohesive summary of all the care each patient is receiving, however, they may not have complete details of all secondary/tertiary care consultations. In addition, in some cases participants may have had a mis-diagnosis, as using medical records data for diagnosis of ophthalmic disease means that diagnostic criteria may not be adhered to and physician diagnoses of glaucoma and cataract themselves are often inaccurate. Family practice records will often not distinguish between definite and probable open angle glaucoma. Furthermore, participants did not undergo a formal dementia assessment and although we have demonstrated associations between ophthalmic diagnoses and sMMSE scores, in some cases people with dementia will not be identified by sMMSE scores alone. Whilst reasonable response rates were achieved given the intensity of the assessment protocol, a substantial proportion of the population was not included in this analysis. However, it has been shown in a similar study population that given moderate response rates, additional efforts to increase participation do not necessarily reduce selection bias.⁴⁶

In summary, we found an association between recorded glaucoma diagnosis and cognitive scores which was lost when all visual items were excluded from the cognitive tests, suggesting this association is driven primarily by poor vision limiting test performance as opposed to a shared neuro-degenerative process. We have found an association between a record of previous cataract surgery and better cognition and suggest that this may be due to

factors such as health-seeking behaviour and social activity in those who have had previous cataract surgery.

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Table 1
Shows comparisons for age, gender, education, smoking status and number of medications for those with and without diagnosed cataract and those with and without diagnosed glaucoma

	Diagnosed Cataract [†] (n=396)	No Cataract diagnosis (n=443)	p-value	Diagnosed Glaucoma (n=66)	No Glaucoma diagnosis (n=773)	p-value
Age in years, mean (std)	85.5 (0.43)	85.5 (0.44)	0.24	85.4 (0.41)	85.5 (0.44)	0.42
Gender, %Male	30	44	<0.001*	36	38	0.8
Ethnicity, %White	99.5	99.8	0.60	100	99.6	1.00
Years in education, mean (std)	9.87 (1.82)	9.96 (1.90)	0.49	9.71 (1.88)	9.94 (1.86)	0.34
Smoking, %Current	5.05	6.32	0.43	1.5	6.1	0.17
No of medications, mean (std)	6.30 (3.78)	5.33 (3.09)	<0.001*	6.05 (3.79)	5.76 (3.44)	0.25
Hypertension, % with	55.6	59.1	0.16	59.1	57.3	0.78
Diabetes ^{††} , % with	16	10.6	0.015*	9.1	13.7	0.35
Count of chronic disease (mean, std)	5.4 (1.7)	4.2 (1.7)	<0.001*	5.1 (1.7)	4.7 (1.8)	0.070

[†] Cataract group includes those who have had previous cataract surgery.

^{††} Diabetes includes those with type 1, type 2 and unclassified diabetes. P-values refer to Chi-squared, Fisher's exact test or t-test as appropriate. . .

* p-values of 0.05 are considered significant.

Table 2

Shows median sMMSE and MMblind scores and inter-quartile ranges for those with and without a recorded diagnosis of glaucoma.

It shows the same for those on anti-glaucoma medication and/or with a diagnosis of glaucoma compared to those with no diagnosis of glaucoma and on no anti-glaucoma medications. It also gives the Odds ratio, 95% confidence intervals and p-value derived from the ordinal logistic regression model adjusted for age, gender, ethnicity, smoking and years of education

Glaucoma Status	n	Median sMMSE score	IQR	Odds Ratio [†] (95% Confidence interval)	p-value	Median MMblind score	IQR	Odds Ratio [†] (95% confidence interval)	p-value
No glaucoma diagnosis	773	28	25-29	Ref category		20	18-21	Ref category	
Diagnosed glaucoma	66	27	24-29	1.76 (1.05 to 2.95)	0.032*	20	17-21	1.17 (0.65 to 2.12)	0.60
No glaucoma diagnosis or drops	767	28	25-29	Ref category		20	18-21	Ref category	
Diagnosed Glaucoma or drops	72	27	24-29	1.73 (1.05 to 2.85)	0.030*	20	18-21	1.05 (0.58 to 1.89)	0.87

[†] Odds ratio refers to the odds of a lower sMMSE score compared to the reference group.

* p-values of 0.05 are considered significant. sMMSE: standardised mini mental state examination; MMblind: blind version of the mini mental state examination; IQR: Inter-quartile range.

Table 3
Shows median and inter-quartile range of sMMSE scores for different groups according to their cataract status.

It also gives the odds ratio, 95% confidence intervals and p-values which have been derived from the ordinal logistic regression model, adjusted for age, gender, smoking, years of education, number of medications, chronic disease count and diabetes diagnosis

Comparison categories	n	Median sMMSE score	IQR	Odds Ratio (95% confidence interval)	p-value	Median MMblind score	IQR	Odds Ratio (95% confidence interval)	p-value
No cataract diagnosis	443	27	24-29	Ref category		20	17-21	Ref category	
Cataract, previous surgery (CS)	302	28	26-29	0.72 (0.59 to 0.88)	0.001*	20	18-21	0.68 (0.55 to 0.85)	0.001*
No cataract diagnosis	443	27	24-29	Ref category		20	17-21	Ref category	
Cataract, no previous surgery (CNS)	94	28	24-29	0.65 (0.36 to 1.19)	0.17	20	17.8-21	0.73 (0.39 to 1.36)	0.32
No cataract diagnosis	443	27	24-29	Ref category		20	17-21	Ref category	
All cataract (CS+CNS)	396	28	26-29	0.55 (0.38 to 0.79)	0.001*	20	18-21	0.51 (0.34 to 0.76)	0.001*
Cataract, no previous surgery	94	28	24-29	Ref category		20	17.8-21	Ref category	
Cataract, previous surgery	302	28	26-29	0.76 (0.41 to 1.42)	0.39	20	18-21	0.66 (0.34 to 1.29)	0.22

† Odds ratio refers to the odds of a lower sMMSE score compared to the reference group.

* p-values of 0.05 are considered significant. MMblind: blind version of the mini mental state examination; sMMSE: standardised mini mental state examination; IQR: Interquartile range