Associations Between Age-Related Macular Degeneration, Alzheimer Disease, and Dementia
Record Linkage Study of Hospital Admissions

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IMPORTANCE The potential association between age-related macular degeneration (AMD) and Alzheimer disease (AD) is uncertain and has implications for understanding disease pathogenesis, referral, and treatments.

OBJECTIVES To determine whether individuals admitted to the hospital with AMD were significantly more or less likely to develop AD or dementia in the following years, as well as to assess whether people with AD or dementia were significantly more or less likely to be admitted to the hospital for AMD treatment in the years following diagnosis of dementia.

DESIGN, SETTING, AND PARTICIPANTS An AMD cohort of 65,894 people was constructed from English National Health Service, linked hospital episode statistics from January 1, 1999, through February 28, 2011, by identifying computerized record abstracts for all people with an admission or day case for AMD. A dementia cohort (168,092 people) and a reference cohort (>7.7 million people) were constructed in similar ways.

MAIN OUTCOMES AND MEASURES Risk of AD or dementia following AMD and risk of AMD following AD or dementia. Rate ratios were calculated based on standardized rates of AD and dementia in the AMD cohort, as well as standardized rates of AMD in the AD and dementia cohort, relative to those in the reference cohort.

RESULTS The risk of AD or dementia following AMD was not elevated. The rate ratio was 0.86 (95% CI, 0.67-1.08) for AD and 0.91 (0.79-1.04) for dementia. The likelihood of being admitted for AMD following AD or dementia was very low: the rate ratio was 0.04 (0.01-0.10) for people with AD and 0.07 (0.04-0.11) for those with dementia.

CONCLUSIONS AND RELEVANCE These neurodegenerative conditions may share environmental risk factors and histopathologic features. However, considering AD and other dementia after AMD, their coexistence at the individual level is no different from that expected by chance. Our data also suggest that patients in England with dementia may be substantially less likely to receive AMD treatment. Further research is required to determine whether people with dementia receive appropriate investigation and treatment for AMD, as well as identify and address potential barriers.
Age-related macular degeneration (AMD) and Alzheimer disease (AD) are both neurodegenerative diseases strongly associated with increased age. The diseases share environmental risk factors, including cigarette smoking, systemic hypertension, and hypercholesterolemia, as well as histopathologic features, particularly the deposition of amyloid-β in ocular drusen and senile plaques. In addition, oxidative stress, inflammation, and complement activation are thought to be implicated in both diseases.

By contrast, the genetic risk factors for AMD and AD seem to be distinct. Some controversy exists about potential associations between AMD and AD. Several studies have reported an association between AMD and cognitive impairment, based on mental state examination or word fluency scores; another epidemiologic report found no significant association between AMD and dementia or AD. Methodological difficulties are inherent in these studies; in particular, most contained small numbers of AMD and AD cases, which makes it difficult to report accurate estimates of association levels, since the 95% CIs were generally wide.

There is, as yet, no definitive answer to whether AD or dementia is significantly more common in patients with AMD and vice versa. Knowledge about this is important, since it may provide insights into disease pathogenesis and whether treatment for one disease may protect against or even exacerbate the other disease. In addition, it should guide ophthalmologists and other physicians to ensure that patients with one disease receive appropriate counseling and referral for investigation of the other disease.

The main objective of this study was to use record linkage analysis to determine whether individuals admitted to the hospital with AMD were significantly more or less likely than others to develop dementia or AD in the following years. The secondary objective was to determine whether people with AD or dementia were significantly more or less likely to be admitted to the hospital for AMD treatment in the years following diagnosis of dementia.

Methods

Institutional review board and ethics committee approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee, England (index 04/Q2006/176). The research adhered to the tenets of the Declaration of Helsinki.

The National Health Service (NHS) provides most health care in England, including ophthalmology and medical day case and inpatient care. Private medical insurance, held by around 12% of the UK population (using 1997 figures), is mainly used for elective surgery (eg, around 10% of cataract surgery in England from 2004-2005) rather than long-term care for chronic conditions, such as dementia or AMD.

The complete data set of linked English national hospital episode statistics (HES), from January 1, 1999, through February 28, 2011, was used for this analysis. English national HES data are collected by the NHS Information Centre as a statistical database of demographic, medical, and administrative information about all admissions to NHS hospitals in England and admissions funded by the NHS for treatment in non-NHS clinical organizations. Hospital episode statistics include data on hospital day cases as well as inpatients admitted for overnight stays. Record linkage was undertaken by the Oxford record linkage group. Linkage means that data relating to successive episodes of care for each person are collated, so that data about individuals can be analyzed across multiple episodes of care (eg, for AMD and subsequently for AD). In this study, record linkage for the English national file was based on encrypted values of the NHS number (unique for each person registered with the NHS), the HES ID number (a national number used for each person whose hospital care is funded by the NHS), and encrypted postcodes and dates of birth.

The AMD, dementia, AD, and reference cohorts were constructed using methods described previously. We confined all analyses to include only those 50 years and older. The methods of analysis were the same for each pair of conditions investigated for potential association; we describe the methods for AMD followed by dementia as the example.

The AMD cohort was constructed by identifying computerized record abstracts of all people with an admission or day case care for AMD (ie, outpatient attendances were not included). Patients treated in the English NHS receive intravitreal anti–vascular endothelial growth factor (VEGF) therapy in a day case setting (rather than as an office procedure), such that data on these admissions are captured by English national HES. Indeed, in recent years, most admissions for AMD in England have involved day case treatment of neovascular AMD using intravitreal anti-VEGF therapy.

The eligibility criterion for inclusion in the cohort was identification of each person’s first recorded admission with AMD, as the coded principal reason for hospital care, in an NHS hospital during the study period from 1999 through 2011. The reference cohort was constructed by identifying the first admission for each individual with various other, mainly minor medical and surgical conditions (listed in the Table 1 footnote), also coded as the principal reason for hospital care. This is based on a “reference” group of conditions that has been adopted in other studies of associations between diseases, applying the standard epidemiologic practice when using hospital controls of selecting a diverse range of conditions.

People were included in the AMD or reference cohort if they did not have an admission for dementia either before or at the same time as the admission for AMD or the reference condition. We searched the database for subsequent NHS inpatient or day case care for dementia in these cohorts, again identifying only patients for whom the admission was recorded as the principal reason for care. We identified only those admitted for dementia more than 1 year after their entry into the AMD or the reference cohorts. We did this to avoid surveillance bias—namely, the possibility that a person admitted with 1 disease may lead to the identification of another. We considered that rates of care for dementia in the reference cohort would approximate those in the general population of the region while allowing for migration in and out of it (data on migration of individuals were not available). The reverse analysis (ie, dementia
Associations Between AMD, AD, and Dementia

Table 1. Demographics of People Admitted to the Hospital With Age-Related Macular Degeneration and Dementia*

<table>
<thead>
<tr>
<th>Age at Admission, y</th>
<th>People With Age-Related Macular Degeneration</th>
<th>People With Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (% of Total)</td>
<td>Female Sex, %</td>
</tr>
<tr>
<td>50-54</td>
<td>1664 (2.5)</td>
<td>50.6</td>
</tr>
<tr>
<td>55-59</td>
<td>3001 (4.6)</td>
<td>60.4</td>
</tr>
<tr>
<td>60-64</td>
<td>6036 (9.2)</td>
<td>65.7</td>
</tr>
<tr>
<td>65-69</td>
<td>9339 (14.2)</td>
<td>65.4</td>
</tr>
<tr>
<td>70-74</td>
<td>11 422 (17.3)</td>
<td>61.3</td>
</tr>
<tr>
<td>75-79</td>
<td>11 874 (18.0)</td>
<td>58.3</td>
</tr>
<tr>
<td>80-84</td>
<td>10 303 (15.6)</td>
<td>61.4</td>
</tr>
<tr>
<td>&gt;85</td>
<td>8967 (13.6)</td>
<td>68.1</td>
</tr>
<tr>
<td>All ages</td>
<td>65 894 (100)</td>
<td>61.5</td>
</tr>
</tbody>
</table>

* Conditions used in reference cohort, with Office of Population Censuses and Surveys, 4th edition, code for operations and International Classification of Diseases, 10th Revision code for diagnosis (with equivalent codes used for other coding editions): adenoidectomy (E20); tonsillectomy (F34 and F36); appendectomy (H01-H03); dilation and curettage (Q10.3 and Q11.4); total hip replacement (W37-W39); total knee replacement (W40-W42); cataract or media (H60-H67); varicose veins (I83); hemorrhoids (I84); upper respiratory tract infections (J00-J06.9); deflected septum and nasal polyp (J33 and J34.2); impacted tooth and other disorders of the teeth (K00-K03); inguinal hernia (K40); gallbladder disease (K80-K81); ingrowing nail, toenail, and other diseases of the nail (L60); sebaceous cyst (L72.1); bunion (M20.1); internal derangement of knee (M23); and contraceptive management (Z30).

Table 2. Observed and Expected Numbers of Age-Related Macular Degeneration Followed 1 Year or More Later by Dementia or Alzheimer Disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population</th>
<th>Observed</th>
<th>Expected</th>
<th>Rate Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>England</td>
<td>205</td>
<td>224.9</td>
<td>0.91 (0.79-1.04)</td>
<td>.19</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>England</td>
<td>74</td>
<td>85.7</td>
<td>0.86 (0.67-1.08)</td>
<td>.22</td>
</tr>
</tbody>
</table>

* Adjusted, in multivariate analysis, for sex, age in 5-year bands, calendar year of admission, region of residence, and Index of Multiple Deprivation score associated with patients’ area of residence, in quintiles, in the England data set. The rate ratios are calculated as the ratio of the observed to the expected number in the dementia cohort relative to the observed to the expected number in the reference cohort.

followed by AMD) was also performed using similar methods. In this analysis, people were excluded if they had a record of AMD before or at the same time as admission for dementia or the reference condition. This ensured that no one was counted twice (ie, as AMD before dementia and as dementia before AMD).

Rates of dementia were calculated based on person-days “at risk.” Date of entry into each cohort was the date of first admission for AMD or reference condition, and date of exit was the date of first record of dementia, death, or the end of data collection (February 28, 2011), whichever was the earliest. Censoring for death, from the day of death, meant that people who died soon after their first admission for dementia or AMD, when it was the “exposure” condition (or any reference condition), were removed from the study by the day of death.

The expected number of cases in the AMD cohort was calculated, adjusted for age in 5-year bands, sex, calendar year of admission, region of residence, and Index of Multiple Deprivation score—standard English measure of socioeconomic status—as stratified into quintiles. Adjustment for socioeconomic deprivation, as a potential confounder, was made, since previous studies have suggested a higher incidence of dementia in those with higher levels of socioeconomic deprivation. The indirect method of standardization was used, with the combined AMD and reference cohorts as the standard population. Rate ratios were calculated by taking the standardized rate of the occurrence of dementia in the AMD cohort relative to the reference cohort using the formula \( \frac{O_{AMD}/E_{AMD}}{O_{REF}/E_{REF}} \), where \( O \) and \( E \) are the observed and expected numbers of dementia cases in the AMD and reference cohorts, respectively. The CI for the rate ratio of dementia and \( \chi^2 \) statistics for its significance were calculated as described elsewhere.

Results

In total, 65 894 (61.5% female) entered the AMD cohort and 168 092 (61.3% female) entered the dementia cohort. Age distributions are shown in Table 1. More than 7.7 million people entered the reference cohort.

Table 2 shows the number of people in the AMD and reference cohorts who were admitted to the hospital more than 1 year later with dementia or AD. It also shows the expected number of cases of dementia or AD in the AMD cohort, based on the experience of the reference cohort. For people with AMD, there was no significant increase or decrease in the risk of dementia: the rate ratio, comparing observed and expected cases of dementia in the AMD cohort with those of the reference cohort, was 0.91 (95% CI, 0.79-1.04). The rate ratio for AD after AMD was 0.86 (95% CI, 0.67-1.08).
Abbreviations: AD, Alzheimer disease; AMD, age-related macular degeneration.

Limitations include cross-sectional design and small case numbers: there was an association between early age-related maculopathy (ARM) and severe cognitive impairment based on word association tests and early ARM. By contrast, there was no significant association between early AMD and cognitive impairment based on digitsymbol substitution test and early AMD. However, after additional adjustment for smoking and atherosclerosis, no significant risk was observed (relative risk, 1.5; 95% CI, 0.6-3.5). Again, this study was limited by small case numbers (ie, 113 people with advanced ARM), leading to wide confidence intervals.

Baker et al analyzed 2088 people aged 69 to 97 years who participated in the Cardiovascular Health Study in the United States. After multivariate adjustment, they found no association between dementia (OR, 1.0; 95% CI, 0.6-1.7), AD (1.1; 0.6-2.1), or low modified MMSE (1.2; 0.8-1.9) and early AMD. By contrast, they did report a positive association between cognitive impairment based on digit symbol substitution test and early AMD (OR, 2.0; 95% CI, 1.3-3.1). As described earlier, this study is limited by cross-sectional design and small case numbers (324 individuals with early AMD).

Finally, Woo et al conducted a case-control study in Korea, consisting of a battery of cognitive function tests on 170 individuals with AMD and 190 controls without AMD. After multivariate adjustment for age, education, and visual acuity, the authors observed a small difference in MMSE (25.0 in AMD vs 26.0 in non-AMD; P < .001). In addition, the rate of mild cognitive impairment was higher in those with AMD than in controls (52.4% vs 26.8%; P < .001). The authors chose not to exclude the vision-related items from the MMSE (correcting instead for visual acuity afterward) and conceded that the impaired cognitive function of patients with AMD might be related partly to poor vision itself. Furthermore, AMD displays important differences between ethnic groups in its clinical features and underlying genetics, such that the implications of these findings are uncertain for white populations.

The other main finding in our study was that individuals admitted for dementia or AD were substantially less likely to receive anti-VEGF therapy than this and warrants further investigation.

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**Table 3. Observed and Expected Numbers of Dementia or Alzheimer Disease Followed 1 Year or More Later by Age-Related Macular Degeneration**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population</th>
<th>Observed</th>
<th>Expected</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMD after dementia</td>
<td>England</td>
<td>22</td>
<td>304.1</td>
<td>0.07 (0.04-0.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AMD after AD</td>
<td>England</td>
<td>5</td>
<td>118.5</td>
<td>0.04 (0.01-0.10)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AMD, age-related macular degeneration.

* Adjusted, in multivariate analysis, for sex, age in 5-year bands, calendar year of admission, region of residence, and Index of Multiple Deprivations score associated with patients’ area of residence, in quintiles, in the England data set. The rate ratios are calculated as the ratio of the observed or expected number in the dementia cohort relative to the observed or expected number in the reference cohort.
Several factors may contribute to this finding: individuals with dementia may be less likely to attend regular optometrist appointments, less likely to notice or report relevant visual symptoms, and more reliant on carers to act on reported symptoms and allow attendance at ophthalmology appointments. In addition, ophthalmologists may be more reluctant to investigate and treat these patients, and potential barriers might include informed consent and difficulties in obtaining retinal imaging results and arranging regular intravitreal injections, since these generally require a high degree of patient cooperation.

However, few reports in the literature have examined these factors, and we are unaware of any recommendations or guidelines published by national ophthalmology or neurology bodies that deal with the provision of AMD services for patients with dementia. One UK report suggested that most community optometry practices (93% of those surveyed) were willing and able to provide state-funded eye examinations for elderly patients with dementia. However, a report of Medicare participants with diabetes mellitus in the United States found that individuals with dementia were significantly less likely to receive an annual eye examination than those without dementia. Another study of people with AD in nursing homes in the United States found that nearly one-third of residents with visual impairment were not using their required eyeglasses.

Further research across a variety of countries is required to determine whether people with dementia are receiving appropriate investigation and treatment for AMD, as well as identify and address any potential barriers to care. In the United Kingdom, the Macular Disease Society has formed a working party with the Alzheimer Society, the Thomas Pocklington Trust, and the Royal National Institute for the Blind; the Dementia and Sight Loss Interest Group. Its aim is to improve the lives of those with dementia and sight loss, as well as increase awareness that one condition may mask the other and lead to inaction. The group has recommended visual awareness training for staff working with people with dementia, which may prompt a full eye examination at an optometrist or through a domiciliary visit. Ideally, similar national and international groups should join together to perform the research and advocacy work required for this vulnerable group of individuals.

The strengths of this study include the large size of the data set and the prospective nature of the study (through record linkage). Both these factors provide substantial improvements on previous studies described earlier. We have also used this data set in previous studies of ophthalmic disease associations. In addition, we analyzed AMD followed by dementia or AD, as well as dementia or AD followed by AMD, and conducted separate analyses for dementia and AD in all cases.

However, the data set has limitations. The data, based on hospital admissions and day case specialist care for the particular condition, are likely to represent the more severe end of the spectrum of disease. In particular, for AMD, this represents in most cases those patients undergoing admission for intravitreal anti-VEGF therapy, which clearly means that we are examining the potential association between dementia and neovascular AMD (rather than geographic atrophy or early AMD). We have distinguished between AD and dementia of all types, but there is a caveat that clinician terminology and HES coding may not be entirely reliable to make this distinction in all cases. Other potential limitations have been described previously (eg, cohorts based on prevalent cases and the presence of unmeasured migration). In addition, adjustment was made for possible confounding factors, such as socioeconomic deprivation but not for cigarette smoking or other cardiovascular risk factors, since these were unavailable in HES data. However, in the absence of finding a positive association between AMD and AD or dementia, this becomes less relevant. Further research using family practice data would ideally include information on dementia and AMD of all stages, as well as risk factors, such as smoking, hypertension, and hypercholesterolemia.

In conclusion, these data provide evidence that there is no positive association between AMD and dementia or AD. However, people with dementia in England are substantially less likely to undergo treatment for AMD than those without dementia. Potential barriers to care for these vulnerable individuals need to be examined and addressed in the near future.