Dementia and Alzheimer Disease Incidence

A Prospective Cohort Study

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**Context:** Age-specific incidence rates for dementia and Alzheimer disease (AD) are important for research and clinical practice. Incidence estimates for the United States are few and vary with the population sampled and study design; we present data that will contribute to a consensus of these rates.

**Objectives:** To provide age-specific incidence estimates for dementia and AD and to estimate the association of sex, educational level, and apolipoprotein E genotype with onset.

**Design:** Prospective cohort study; begun in 1994 with follow-up interviews every 2 years.

**Setting:** Members of community-based, large health maintenance organization with demographics consistent with the surrounding base population; diagnostic evaluation by university-based study clinicians.

**Subjects:** Random sample of subjects aged 65 years or older from the base population; dementia free, nonnursing home residents. Of 5422 who were eligible, 2581 were enrolled, and 2356 had at least 1 follow-up evaluation (10591 person-years of observation).

**Main Outcome Measure:** Dementia and Alzheimer disease diagnoses were based on standard criteria. Age-specific incidence rates were calculated using a person-years approach with Poisson distribution confidence intervals. Cox proportional hazards model analysis was used to examine other factors.

**Results:** Two hundred fifteen cases of dementia and 151 cases of AD were diagnosed. Incidence rates for dementia and AD increase across the 5-year age groups; AD rates rise from 2.8 per 1000 person-years (age group, 65-69 years) to 5.1 per 1000 person-years in the older than 90-year age group. The rates nearly triple from the 75-to-79-year and 80-to-84-year age groups, but the relative increase is much less thereafter. Sex was not associated with AD onset. Educational level (>15 years vs <12 years) was associated with a decreased risk of AD; however, the association was also dependent on the baseline cognitive screening test score.

**Conclusions:** Our dementia and AD incidence rates are consistent with recent US and European cohort studies, providing clinicians and researchers new information concerning the reproducibility of incidence estimates across settings. Increased risk was associated with age and the apolipoprotein E genotype; also with a low baseline cognitive screening test score. Educational level was inversely associated with the risk of dementia and positively associated with the baseline cognitive test score; thus, detection of AD by the screening test could also be influenced by educational level.

Arch Neurol. 2002;59:1737-1746
standing cohorts primarily formed for the study of other diseases have yielded valuable results and will continue to do so. While some of these studies are limited with regard to dementia and AD ascertainment, they often bring to bear unique methods such as extensive follow-up, serial imaging, or serial laboratory measures. A number of longitudinal incidence studies of dementia and cognitive impairment in US population groups have also been published. Non-US investigators have included varying degrees of standardization into study design and diagnosis for their dementia incidence studies. To date perhaps the largest cohort study of dementia incidence, with relatively standardized methods, has resulted from a European consortium effort. A 1998 meta-analysis, which included extant US studies and European studies, showed roughly similar incidence patterns.

Although some consistency across studies has emerged regarding the age-specific incidence of dementia and AD, existing figures still lack general acceptance. Consensus may come as more rigorous, well-designed studies accumulate. We conducted a prospective cohort study specifically designed to observe dementia and AD incidence. We used a 2-stage case identification design with full clinical workup of potential cases followed by criteria-based consensus diagnosis. Our results, along with those of similar, recently reported studies should contribute to the formation of consistent estimates that will be of interest to both clinicians and researchers.

STUDY DESIGN, SETTING, AND SUBJECTS

“Adult Changes in Thought” (ACT) is a prospective cohort study that focuses on dementia. The base population for ACT was the Seattle area members of Group Health Cooperative of Puget Sound (GHC) who were aged 65 years or older. More than 20000 persons fit that general description as we began our study. The demographic composition of GHC mirrors that of the surrounding county: primarily white, middle class, and relatively well educated. Thus, observed incidence rates may reflect the dementia experience of a similar demographic population. The GHC enrollment is stable and the organization long lived (established circa 1949). The University of Washington and GHC institutional review boards reviewed and approved this study base. Consensus may come as more rigorous, well-designed studies accumulate. We conducted a prospective cohort study specifically designed to observe dementia and AD incidence. We used a 2-stage case identification design with full clinical workup of potential cases followed by criteria-based consensus diagnosis. Our results, along with those of similar, recently reported studies should contribute to the formation of consistent estimates that will be of interest to both clinicians and researchers.

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pants.32 Otherwise, nonresponse only affects the power of tests
ing dementia over the course of the study than did partici-
served incidence rates if nonparticipants within each age (or
age interval) could affect the generalizability of the ob-

Risk factor associations and incidence rates.33 However, excessive
subject loss to follow-up after the study begins can cause
risk factor associations to be biased.33,34

The initial refusal rates appear high relative to other re-
cent cohort studies. However, those who refused may include
a number who would have been ruled ineligible if they had ex-
isting dementia that had not been noted in the available med-
ical records. This might push the response rate in line with se-
veral cohort studies that have reported response rates of between
60% and 70% for eligible subjects.8,30,31 Refusal to participate
(nonresponse) could affect the generalizability of the ob-

pation is also used as the end point for subjects who die or
drop out since dementia status is unknown at the time of death
or dropout. Confidence intervals (CIs) for incidence rates were
get rates per 1000 person-years). The number of person-years
is calculated by the time from base-
line to the halfway point between diagnosis and the previous
follow-up examination. This point is also used as the time of
dementia or AD for calculating incidence and for further analy-
sis of relative risks (RRs). The date of the last follow-up ex-
amination is also used as the end point for subjects who die or
don't drop out since dementia status is unknown at the time of death
or dropout. Confidence intervals (CIs) for incidence rates were
were calculated assuming a Poisson distribution for the number of
cases within each age interval. An adjustment to the incidence
rates and CIs to account for 32 subjects failing the CASI screen-
ting test but not given a full diagnostic examination was calcu-
lated by use of multiple imputation based on the probability of
dementia given a failed screening examination.36

Risk factors such as sex, level of education (<12 years, 12-15 years, >15 years), APOE genotype (presence vs absence
of an e4 allele), and race (white, African American, or other)
were examined using Cox proportional hazards regression mod-
els.37 The models adjust for age by using age as the time scale
for the regression model, rather than time-in-study, for ex-
ample, left truncating at the age at baseline. The risk factor
results are reported as RRs (ratios of incidence rates).

A sensitivity analysis34 was conducted to assess the poten-
tial influence on incidence if subjects who died or dropped
out were likely to have dementia at the time. Imputation of
dementia status for those individuals was accomplished by es-
blished techniques.38,39 Hypothetical scenarios are discussed
to further describe the stability of the study’s observed inci-
dence rates. Dementia risk among subjects who dropped out
of the study undiagnosed may have been different from those
subjects who completed the study dementia free. One may sus-
pect the factors leading to death or dropout may be linked
to the same factors that effect incidence. To assess that possibil-
ity, last reported values for risk factors and CASI scores for drop-
outs and deaths were compared with those of subjects who re-

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outs and deaths were compared with those of subjects who re-
mained in the study.

<table>
<thead>
<tr>
<th>Table 1. Percentage Distributions of Sex, Age, and Race Among Those Initially Sampled, Eligible, and Enrolled in the ACT Cohort*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sample of Subjects</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td>65-69</td>
</tr>
<tr>
<td>70-74</td>
</tr>
<tr>
<td>75-79</td>
</tr>
<tr>
<td>80-84</td>
</tr>
<tr>
<td>85+</td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>No. of subjects missing</strong></td>
</tr>
</tbody>
</table>

*Data are given as percentages unless otherwise indicated. ACT indicates Adult Changes in Thoughts.

**STATISTICAL METHODS**

Age-specific incidence of dementia and AD are calculated using
the person-years approach35 by dividing the number of cases
by the number of person-years at risk given as 5-year age in-
ternals starting at age 65 years (these are multiplied by 1000 to
get rates per 1000 person-years). The number of person-years
contributed by each subject who had no dementia is calcu-
lated by taking the time between their baseline examination and
their last follow-up examination. For subjects with dementia
the number of person-years is calculated by the time from base-
line to the halfway point between diagnosis and the previous
follow-up examination. This point is also used as the time of
dementia or AD for calculating incidence and for further analy-
sis of relative risks (RRs). The date of the last follow-up ex-
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were calculated assuming a Poisson distribution for the number of
cases within each age interval. An adjustment to the incidence
rates and CIs to account for 32 subjects failing the CASI screen-
ting test but not given a full diagnostic examination was calcu-

**RESULTS**

**ANALYSIS OF INCIDENCE AND RISK FACTORS**

Of 2356 subjects with at least 1 follow-up examination, 415 subjects screened positive for dementia and re-
ceived full examination and consensus diagnosis. After evaluation and consensus diagnosis, 215 of the 415 sub-
jects were diagnosed as having dementia27 and 146 of those
cases of AD who were diagnosed as having possible AD.29
There were an additional 5 subjects (for a total of 151
cases of AD) who were diagnosed as having possible AD
by the NINCDS-ADRDA (National Institute of Neuro-
logical Disorders and Stroke–Alzheimer’s Disease and Rel-
dated Disorders Association) criteria26 on the basis of a
single severe cognitive deficit, but who did not meet de-
mencia criteria by the Diagnostic and Statistical Manual of
Mental Disorders [DSM]–IV.27 The remaining 69 cases con-
The number of cases of AD and non-AD do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. CI indicates confidence interval.

Table 2. Age-Specific Incidence Rates per 1000 Person-years and Poisson-Based 95% Confidence Intervals for Dementia, Alzheimer Disease (AD), and Non-AD Dementia*

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No. of Person-years</th>
<th>No. of Cases</th>
<th>Rate, % (95% CI)</th>
<th>No. of Cases</th>
<th>Rate, % (95% CI)</th>
<th>No. of Cases</th>
<th>Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>1076</td>
<td>5</td>
<td>4.65 (2.0-10.8)</td>
<td>3</td>
<td>2.78 (1.0-8.2)</td>
<td>2</td>
<td>1.86 (0.5-6.7)</td>
</tr>
<tr>
<td>70-74</td>
<td>3023</td>
<td>27</td>
<td>8.43 (5.8-12.3)</td>
<td>14</td>
<td>4.37 (2.6-7.4)</td>
<td>14</td>
<td>4.37 (2.6-7.4)</td>
</tr>
<tr>
<td>75-79</td>
<td>3082</td>
<td>37</td>
<td>12.01 (8.7-16.6)</td>
<td>24</td>
<td>7.79 (5.2-11.6)</td>
<td>14</td>
<td>4.54 (2.7-7.7)</td>
</tr>
<tr>
<td>80-84</td>
<td>2039</td>
<td>73</td>
<td>35.80 (28.5-45.0)</td>
<td>56</td>
<td>27.46 (21.2-35.7)</td>
<td>19</td>
<td>9.32 (6.0-14.6)</td>
</tr>
<tr>
<td>85-89</td>
<td>906</td>
<td>49</td>
<td>54.05 (40.9-71.5)</td>
<td>38</td>
<td>41.92 (30.5-57.6)</td>
<td>12</td>
<td>13.24 (7.6-23.2)</td>
</tr>
<tr>
<td>90+</td>
<td>285</td>
<td>24</td>
<td>84.19 (56.5-125.6)</td>
<td>16</td>
<td>56.13 (34.7-91.2)</td>
<td>8</td>
<td>28.06 (14.2-55.6)</td>
</tr>
<tr>
<td>Total</td>
<td>10591</td>
<td>215</td>
<td>20.30 (17.8-23.2)</td>
<td>151</td>
<td>14.26 (12.2-16.7)</td>
<td>69</td>
<td>6.51 (5.1-8.3)</td>
</tr>
</tbody>
</table>

*The number of cases of AD and non-AD do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. CI indicates confidence interval.

Figure 1. Age and the incidence of Alzheimer disease (AD) and non-AD dementia; rates per 1000 person-years and Poisson-based 95% confidence intervals for each.
interaction between age and APOE ε4 in the incidence of dementia and AD. Persons with a single copy of APOE ε4 experienced roughly a 3-fold increased risk in successive 5-year age groups (70-85 years old) but showed an RR less than 1 in the oldest age group (90+ years old). There were too few homozygous subjects with APOE ε4 to effectively assess that interaction with age. Incidence rate continues to increase with age past 80 years for subjects with non–APOE ε4 but apparently levels or declines for subjects with APOE ε4 as shown in Figure 2.

Initial analysis given in Table 5 indicates that a higher educational level is associated with decreased risk of both AD and non-AD dementia, or, conversely, a lower educational level is associated with an increased risk. Subjects who have more than 15 years of education were at nearly half the risk of subjects with less than 12 years of education (RR, 0.48; 95% CI, 0.27-0.84) after adjusting for the effects of age, sex, and APOE genotype. Each additional year of education over 11 years the RR decreased approximately 9%. Further analysis revealed that the baseline CASI score was also strongly associated with dementia and with educational level. Of subjects included in this analysis, 203 had an initial CASI score lower than 86; 57 of these subjects later had dementia. The subjects with a low CASI score were also older at enrollment (78.5 vs 74.7 years) and less educated (11.3 vs 14.0 years). Table 6 gives 3 different ways of examining the association between dementia and education based on the initial CASI score. First, when the CASI score is treated as a confounder and adjusted for, the association between education and dementia or AD reduces to the null.

SENSITIVITY ANALYSIS

Table 7 gives a comparison of subjects who died or were lost to follow-up with subjects who were active and had dementia. Subjects who died or were lost to follow-up after cohort enrollment were more similar in age at enrollment and educational level to persons who became demented than to subjects who had no nondementia and who

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**Table 3. Age-Specific Incidence Rates per 1000 Person-years Adjusted by Multiple Imputation to Account for 32 Subjects Failing Cognitive Abilities Screening Instrument but Not Receiving a Full Diagnostic Examination**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>All Dementia Cases</th>
<th>AD Cases</th>
<th>Non-AD Dementia Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate, % (95% CI)</td>
<td>Rate, % (95% CI)</td>
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</tr>
<tr>
<td>65-69</td>
<td>5.39 (1.8-10.8)</td>
<td>3.53 (0.8-8.1)</td>
<td>1.86 (0.2-5.3)</td>
</tr>
<tr>
<td>70-74</td>
<td>9.69 (6.5-13.5)</td>
<td>5.88 (3.4-9.0)</td>
<td>3.81 (1.9-6.9)</td>
</tr>
<tr>
<td>75-79</td>
<td>13.52 (9.7-18.0)</td>
<td>9.36 (6.0-13.4)</td>
<td>4.16 (2.3-6.9)</td>
</tr>
<tr>
<td>80-84</td>
<td>38.00 (29.9-47.1)</td>
<td>29.63 (22.3-38.0)</td>
<td>10.04 (5.9-15.2)</td>
</tr>
<tr>
<td>85-89</td>
<td>58.58 (43.6-75.8)</td>
<td>46.38 (33.0-62.0)</td>
<td>15.53 (8.2-25.2)</td>
</tr>
<tr>
<td>90+</td>
<td>89.39 (57.8-127.9)</td>
<td>61.01 (35.4-93.5)</td>
<td>31.22 (13.8-55.6)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; AD, Alzheimer disease.

**Table 4. Age- and Sex-Specific Rates of Dementia, Alzheimer Disease (AD), and non-AD Dementia Cases per 1000 Person-years of Observation**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Person-years</th>
<th>All Dementia Cases</th>
<th>AD Cases</th>
<th>Non-AD Dementia Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate, %</td>
<td>No. of Cases</td>
<td>Rate, %</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>585</td>
<td>2</td>
<td>3.42</td>
<td>1</td>
</tr>
<tr>
<td>70-74</td>
<td>1855</td>
<td>14</td>
<td>7.55</td>
<td>9</td>
</tr>
<tr>
<td>75-79</td>
<td>1844</td>
<td>18</td>
<td>9.76</td>
<td>13</td>
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<tr>
<td>80-84</td>
<td>1231</td>
<td>45</td>
<td>36.57</td>
<td>39</td>
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<tr>
<td>85-89</td>
<td>638</td>
<td>36</td>
<td>56.41</td>
<td>28</td>
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<tr>
<td>90+</td>
<td>222</td>
<td>19</td>
<td>85.42</td>
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<tr>
<td>Male</td>
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<td>65-69</td>
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<td>85-89</td>
<td>268</td>
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<td>48.45</td>
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<tr>
<td>90+</td>
<td>63</td>
<td>5</td>
<td>79.84</td>
<td>1</td>
</tr>
</tbody>
</table>

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remained in the cohort. Subject's last CASI score, prior to the CASI at diagnosis (for cases), showed an average age-adjusted decline of 5.4 points relative to active subjects with no dementia for subjects with dementia, and declines of 2.7 and 2.1 points, respectively, for those who were lost to follow-up or died. Simple listwise deletion of these subjects, intuitively regarded as "conservative" in the past, can lead to biased incidence estimates when the data are not missing completely at random. 38,39

Table 8 gives the imputed age-specific dementia incidence rates that would result if deaths and dropouts were included in the analysis and if they had experienced rates 1.5 to 3 times higher than those subjects who did not drop out or die. The relative influence is greatest in the oldest age groups since they suffer most deaths.

**COMMENT**

The rates of dementia and AD reported in this study were comparable to the rates reported in other contemporary cohort studies (Figure 1). The rates fall approximately midway between those of the East Boston study 7 and the Framingham study. 3 Interstudy incidence rate differences could have resulted from variations in case detection and diagnosis. Nevertheless, there is still a great deal of consistency among most recent cohort studies.

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*The number of cases of Alzheimer disease (AD) and non-Alzheimer disease do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria.*
Dementia and AD risk factors have not yet been fully explored by cohort studies. Many studies, including ours, have examined the strength of association between dementia onset and sex, education, and APOE genotype, and some have included other risk factors as well (eg, the EURODEM study). We pooled available ethnic groups in this analysis; although our cohort was more than 90% white (this was consistent with the demographics of the area). Ethnicity was included also as a potential confounder of the risk factor associations. Unfortunately, we were unable to examine relationships within ethnic groups because of the sparse number of cases at this time.

The incidence rates for AD and overall dementia in the ACT cohort were similar to those reported by the EURODEM study and the Baltimore Longitudinal Study of Aging, except for appearing slightly higher in the 65- to 74-year age groups and slightly lower in the very oldest age group. While the point estimates at the extremes appear different (Figure 3), there is likely to be inherent instability in the calculated rates owing to small numbers of cases. Higher incidence rates were reported by the East Boston study and the Monongahela Valley study (MoVIES Project) (when MoVIES included mildly impaired cases) across all ages. The ACT cohort age-specific incidence rates were consistently higher than those reported by either the Rochester, Minn, study or, the Framingham study. The Framingham study only included moderate and severe AD cases, and it was not originally designed as a dementia study, perhaps explaining

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-years</th>
<th>All Dementia Cases</th>
<th>AD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Adjusting for Age, Sex, Apolipoprotein E Level, and CASI at Baseline</td>
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<tr>
<td>Educational level, y</td>
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<td>&lt;12</td>
<td>1419</td>
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</tr>
<tr>
<td>12-15</td>
<td>5751</td>
<td>122</td>
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</tr>
<tr>
<td>&gt;15</td>
<td>3407</td>
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<td>Linear 1-y effect</td>
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<tr>
<td></td>
<td>1.03</td>
<td>10.00</td>
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<tr>
<td>Low (&lt;86) vs High Baseline CASI Score Adjusting for Age, Sex, and Apolipoprotein E Level</td>
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<tr>
<td>CASI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9680</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>743</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Excluding Subjects With Low Baseline CASI Score (&lt;86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>12-15</td>
<td></td>
<td>1.07 (0.61-1.86)</td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td></td>
<td>0.88 (0.47-1.62)</td>
<td></td>
</tr>
<tr>
<td>Linear 1-y effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.97</td>
<td>0.97 (0.91-1.03)</td>
<td></td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease; RR, relative risk; and CI, confidence interval.

Table 7. Characteristics of Subjects Deceased and Lost to Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects Lost to Follow-up (n = 180)</th>
<th>Subjects Deceased (n = 430)</th>
<th>Subjects With Dementia† (n = 220)</th>
<th>Subjects With Active Non-Dementia (n = 1719)</th>
<th>Subjects Who Failed CASI‡ but Had No Examination (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of follow-ups</td>
<td>0</td>
<td>72</td>
<td>153</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>65</td>
<td>117</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>43</td>
<td>137</td>
<td>72</td>
<td>857</td>
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<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>23</td>
<td>64</td>
<td>851</td>
</tr>
<tr>
<td>Female, %</td>
<td>61</td>
<td>47</td>
<td>63</td>
<td>61</td>
<td>75</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.7</td>
<td>13.5</td>
<td>12.8</td>
<td>13.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Apolipoprotein E level, %</td>
<td>27</td>
<td>21</td>
<td>38</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
<td>75.6</td>
<td>78.5</td>
<td>79.4</td>
<td>74.0</td>
<td>78.1</td>
</tr>
<tr>
<td>White, %</td>
<td>89</td>
<td>92</td>
<td>93</td>
<td>91</td>
<td>84</td>
</tr>
<tr>
<td>CASI score at baseline</td>
<td>91.8</td>
<td>92.2</td>
<td>88.9</td>
<td>93.8</td>
<td>87.9</td>
</tr>
<tr>
<td>Difference in last CASI relative to active subject adjusting for age</td>
<td>-2.7</td>
<td>-2.1</td>
<td>-5.4</td>
<td>-4.9</td>
<td></td>
</tr>
</tbody>
</table>

*CASI indicates Cognitive Abilities Screening Instrument.
†Subjects with dementia includes the 215 cases diagnosed as having dementia plus the 5 cases of possible Alzheimer disease diagnosed as possible Alzheimer disease but not as having dementia by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria.
‡Of the 32 subjects failing their CASI examination who did not have a full diagnostic examination, 12 are dead, 17 were lost to follow-up, and 3 are still active awaiting a full diagnostic examination.

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and the differences could also be due in part to variability in the details of study design, case ascertainment, and analysis. The EURODEM study reported a higher, though not statistically significant, rate of AD among women. Similarly, Fillenbaum et al reported a higher, though not statistically significant, rate of AD for white women vs white men. The MoVIES study, the Rochester study, the Framingham study, and the Baltimore Longitudinal Study of Aging, and others showed associations of educational level with AD and/or dementia incidence that were somewhat similar to those in the ACT cohort.

In the ACT study the association between educational levels and AD is potentially complex. For example, in our crude analysis a lower educational level was associated with increased risk of AD. However, CASI score at baseline is associated with both dementia diagnosis and educational level. The CASI and other cognitive screening tests are likely to have an education bias. This bias would make it more likely for a highly educated person to have a false-negative result on the screening test. Thus, part of the observed effect of education could be due to under detection of highly educated subjects on screening tests. Analysis of CASI scores, education, and other factors could also be included in future analyses to further explore this relationship.

When the rates of AD and dementia are plotted on the log scale vs age, the rates of nearly all of these cohort studies seem to increase in a roughly linear fashion indicating exponential growth in incidence with age (Figure 2). The slopes of these lines are similar for each of the cohort studies. The ACT study showed a somewhat flatter slope than the comparison studies owing to its relatively high rates in the 65-to-74-year age groups; still, the incidence rate of AD doubled every 5.3 years. A steeper slope of the incidence curve was seen in the Baltimore Longitudinal Study of Aging where the incidence rate of AD doubled every 3.6 years. Compared with AD incidence (except the Rochester study), the incidence rate of non-AD dementias increased more slowly with age.

In the ACT cohort the incidence rate of non-AD dementias doubled every 8.5 years (Figure 2).

Previous reports of the association between sex and AD or dementia have been equivocal. Generally, variation in sex-specific rates is seen at the upper end of the age distribution where few subjects and cases occur and where there are correspondingly wide CIs around the estimated rate. Treating sex as a risk factor in analysis, the EURODEM study reported a 1.5-fold increased risk of AD among women. Similarly, Fillenbaum et al reported a higher, though not statistically significant, rate of AD for white women vs white men. The MoVIES study, the Rochester study, the Framingham study, and the Baltimore Longitudinal Study of Aging, showed associations of educational level with AD and/or dementia incidence that were somewhat similar to those in the ACT cohort.

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mentia is difficult because of how they might be interrelated. Different analyses would be indicated if CASI scores were considered a consequence of education or if CASI scores were considered a proxy for dementia. The analyses we presented generally show that inclusion of this initial cognitive test score in the analysis tends to reduce the observed effect of education on dementia incidence. Racial and ethnic differences could also influence the observed association with education. Although we computed adjusted RR risks for education (to account for confounding by race, age, sex, and *APOE* genotype), strata were too sparse to allow adequate determination of potential effect modification by race of the association between AD and educational level. Future studies should consider evaluating the effect of education not only within ethnic strata but also within strata of the initial cognitive screening examination. Perhaps a clearer specification of the potential for a causal association between education and AD will result.

The ACT cohort has observed an elevated risk of dementia and AD associated with *APOE* ε4 allele of roughly similar magnitude to that observed in other cohort studies.12,45-48 For example, the cohort shows elevated risk for both AD and non-AD dementia when an *APOE* ε4 allele is present. The risk is much greater when there are 2 *APOE* ε4 alleles present for both AD and non-AD dementia. The association between *APOE* ε4 genotype and non-AD dementia is similar to some other studies19,27; however, others have had inconclusive associations.12,48 The AD RR associated with the *APOE* ε4 allele seems to decrease dramatically in the oldest age group while the AD incidence in subjects with non-*APOE* ε4 continues to increase.

The ACT cohort dementia and AD incidence rates are most similar to those of the EURODEM consortium, but are also consistent with other US-based incidence studies. Some may argue that our observed rates are not “representative” because of initial nonparticipation or because our study base was not a statistical sample of some other larger population. We acknowledge that nonparticipation could have affected the observed incidence rates (as described earlier); however, the similarity between our rates and those of other studies indicates that the resulting potential bias may not have been dramatic. Representativeness of the chosen base population with regard to the US population, for example, is also not a requisite for validity unless the task was specifically to provide accurate incidence estimates for the US population as a whole. Cohort studies are often established within specific so-called unrepresentative groups,13,19 such as the Nurses Health Study10 or Framingham, Mass11; Baltimore Longitudinal Study of Aging,12 Baltimore, Md; or the MoVIES Project.10 Monongehela Valley.10 Much has been learned from these studies that has been generalizable to the population-at-large, despite their purported lack of statistical representativeness. Dementia incidence in nonwhite ethnic groups is in need of much greater study; it is not well addressed by our ACT cohort because of small numbers of nonwhite subjects. Other studies are underway (elsewhere) to address the effects of ethnicity on incidence. Choice of a particular study base for a cohort may be done to increase the likelihood of subject retention and complete follow-up, thus, maximizing the study’s internal validity.19 Study results that lack internal validity (eg, resulting from loss to follow-up) are not generalizable regardless of sample representativeness. The effect of ACT loss to follow-up was small. Thus, results contributed by ACT and the several other cohort studies should be viewed as providing multiple, imperfect estimates. The extent to which these estimates converge is additional evidence for their representativeness, generalizability and validity. The addition of the ACT data to the existing pool will contribute to the converging consensus. While much remains to be done, especially in ethnic populations, age-specific incidence estimates are becoming more consistent as studies accumulate; consensus is being approached. Researchers and clinicians now have a stronger foundation from which to address age-associated risks of dementia and AD.

Accepted for publication July 1, 2002.

Author contributions: Study concept and design (Drs Kukull, Bowen, Teri, van Belle, and Larson); acquisition of data (Drs Kukull, Bowen, McCormick, Teri, Schellenberg, van Belle, and Mr Jolley); analysis and interpretation of data (Drs Kukull, Higdon, Bowen, McCormick, van Belle, and Larson); drafting of the manuscript (Drs Kukull, Higdon, van Belle, and Mr Jolley); critical revision of the manuscript for important intellectual content (Drs Kukull, Higdon, Bowen, McCormick, Teri, Schellenberg, van Belle, and Larson); statistical expertise (Drs Higdon, McCormick, and van Belle); obtained funding (Drs Kukull, Teri, van Belle, and Larson); administrative, technical, and material support (Drs Kukull, McCormick, van Belle, Larson, and Mr Jolley); study supervision (Drs Kukull, Schellenberg, and van Belle).

This study was supported in part by grants AG06781 (Dr Larson), AG16976 (Dr Kukull), and AG05136 from the National Institute on Aging, National Institutes of Health, Bethesda, Md.

We thank all of the named and unnamed faculty and staff who have worked on this study and made this article possible. From Group Health Cooperative, Seattle: Andrea LaCroix, PhD, Darlene White, MS, Audra Davis, BA, Sarah Larson, BA, Richard Olson, BA, Jane Steele, BA, Cynthia Thaidigsmann, BA, Russ Bradley, BA, Kathy Plant, BA, Glen Canning, BA, Carol Canfield, BA, Patricia Spaulding, BA, Ryan Finchlom, BA, and John Parker, BA. From the University of Washington, Seattle: Meredith Pfanschmidt, RN, Sheila O’Connell, MS, Duane Beckly, BS, Lisa Millsquag, MS, Duryah Mohameth, BA, Lisa Coons, MS, Zilpha Haycox, BA, Jan Lackey, MA, Jill Thompson, RN, Troy Sukkareigh, BS, Laura Henne, BA, Jan St John, BA, Sara Lynn Salter, BA, Michele Hobart, BA, and Janene Hubbard, BS.

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REFERENCES


