Conversion to dementia from mild cognitive disorder: The Cache County Study

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Conversion to dementia from mild cognitive disorder
The Cache County Study

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Abstract—Objective: To examine 3-year rates of conversion to dementia, and risk factors for such conversion, in a population-based sample with diverse types of cognitive impairment. Methods: All elderly (aged 65 or older) residents of Cache County, UT, were invited to undergo two waves of dementia screening and assessment. Three-year follow-up data were available for 120 participants who had some form of mild cognitive impairment at baseline. Of these, 51 had been classified at baseline with prodromal Alzheimer disease (proAD), and 69 with other cognitive syndromes (CS). Results: Three-year rates of conversion to dementia were 46% among those with cognitive impairment at baseline. By comparison, 3.3% without impairment converted to dementia in the interval. Among converters, AD was the most common type of dementia. In individuals with at least one APOE ε4 allele, those with proAD or CS exhibited a 22- to 25-fold higher risk of dementia than cognitively unimpaired individuals (vs 5- to 10-fold higher risk in those without ε4). Conclusions: Individuals with all types of mild cognitive impairment have an elevated risk of dementia over 3 years, more so in those with an APOE ε4 allele. These results suggest value in dementia surveillance for broad groups of cognitively impaired individuals beyond any specific category, and utility of APOE genotyping as a prognostic method.

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Since the 1960s, mild cognitive disorders of late life have been described in various terms, with several categories subsuming normal age-related changes as well as neurocognitive entities such as preclinical Alzheimer disease (AD).1 In efforts to facilitate early diagnosis of those at highest risk, many studies have attempted to identify the characteristics of prodromal AD. The well-known classification of mild cognitive impairment (MCI) requires subjective memory complaint and abnormal memory performance for age.2 Other categories emphasize clinical features consistent with AD.3,4 The broadest category, cognitive impairment, no dementia, introduced by the Canadian Study of Health and Aging,5 requires impairment on clinical examination or neuropsychological testing.

Many studies report an increased risk of dementia in various types of late-life cognitive impairment. Rates of conversion to dementia vary,6 but are generally highest among clinical or AD research center samples where annual rates range from 12 to 17%.7,8 Few population-based studies have examined this issue, particularly in the United States. Published population rates of dementia conversion in individuals with late-life cognitive impairment range from 4 to 9% annually.10-13 These population studies have also raised concerns regarding the instability of MCI diagnoses and a failure for some classifications to capture a substantial proportion of individuals with elevated dementia risk. We therefore examined rates...
In addition to a second delayed memory trial and (3MS) examination, a 100-point adaptation of the Mini-Mental knowledgeable informant. The IQCODE inventories cognitive Cognitive Decline in the Elderly (IQCODE) was completed by a

Methods. Design overview, participant sampling, and procedures. The Cache County Study on Memory Health and Aging, conducted in northern Utah, is a longitudinal inquiry into the prevalence and incidence of dementia in relation to genetic and environmental risk factors. The study has attempted to follow prevalence and incidence of dementia in relation to genetic and environmental risk factors. The study has attempted to follow environmental risk factors. The study has attempted to follow environmental risk factors. The study has attempted to follow environmental risk factors.

of conversion to dementia in individuals with mild cognitive disorders in a large population in Cache County, UT. We also examined the influence of major risk factors for dementia such as age, genotype at the polymorphic locus apolipoprotein ε (APOE), and family history of AD or dementia.

Figure. The outcome of the multistage dementia screening and assessment protocol at Waves 1 and 2. Note that the number of incident dementia cases differs from that reported in Miech et al. (n = 185) as the present analysis excludes 19 individuals who were incident cases at Wave 1, one case was later determined to have prevalent dementia, and six cases whose Wave 1 cognitive status was unknown.

Eighteen months after the initial clinical assessment, we re-examined individuals with suspected dementia and others with cognitive disorders thought likely to represent a neurodegenerative illness. After a mean interval from Wave 1 of 3.20 years (SD 0.21, range 1.99 to 4.49), nondemented members of the original cohort, including those with mild cognitive disorders who remained dementia-free at the 18-month follow-up examination, were asked to undergo a second series of dementia screening and assessment procedures (Wave 2; see figure). Wave 2 procedures were identical except for slight modifications to the screening cut scores. Thus, the study design involved follow-up of all participants until they developed dementia or were lost to follow-up.

Because dementia is strongly linked to mortality and refusals are linked to cognitive impairments, we sought to maximize the cognitive status of those otherwise lost to follow-up by interviewing collateral informants of decedents or those who failed to complete all phases of Wave 2 dementia screening. Using this approach, we estimated the cognitive status of an additional 432 individuals (35% of those considered lost to follow-up). All study procedures were approved by the Institutional Review Boards of Utah State University, Duke University, and The Johns Hopkins University. Study participants or their next of kin signed an informed consent document for each stage of assessment.

Participants and definition of mild cognitive symptoms. We relied on the results of the Wave 1 clinical assessment and subsequent diagnostic conferences to identify nondemented individuals with baseline cognitive disorder as indicated by mild difficulty in daily functioning (based on informant report) or objective impairment on neuropsychological testing. Data considered by the diagnosticians included chronology of clinical symptoms, medical history, family history of dementia, neuropsychological interpretation of test data, and physical and neurologic examination results.

All diagnosticians were blinded to participant APOE genotype and screening results from prior study stages. The neuropsychologist was also blinded to any clinical and medical information at the time of interpretation of test results. Data considered by the diagnosticians were blinded to clinical and medical information at the time of interpretation of test results. Data considered by the diagnosticians included chronology of clinical symptoms, medical history, family history of dementia, neuropsychological interpretation of test data, and physical and neurologic examination results.

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category when the pattern of clinical symptoms or results of neuropsychological testing were suggestive of prodromal AD and there were no other medical or neuropsychiatric disorders to preclude an eventual AD diagnosis. Features consistent with this diagnosis included a clinical history of early memory involvement and/or neuropsychological testing consisting of a predominance of memory impairment (1.5 or more standard deviations below age-corrected means or percentile equivalent) with no or lesser impairment of other cognitive domains. When the results of MRI or laboratory work were received, all data were re-examined and, if warranted, diagnoses were modified. With its emphasis on memory impairment, it is likely that the diagnosis of proAD also included MCI classifications from other studies such as amnestic MCI or similar designations. The category of CS was assigned if the participant exhibited significant cognitive impairment that appeared present prodromal AD, for example, performance 1.5 or more standard deviations below age-corrected means (or percentile equivalent) in non-memory cognitive domains or a chronology of symptoms that was associated with an identified condition, including depression, stroke, head injury, chronic alcohol abuse, Parkinson disease without dementia, hypothyroidism, delirium due to medications/infections, or other medical or psychiatric conditions. We did not attempt to identify prodromal states of other dementing illnesses, but it is likely that individuals with such prodromal conditions (e.g., non-amnestic MCI) were also included in the CS group. Unlike the proAD group, individuals with CS were not routinely followed with laboratory or MRI studies. A comparison no impairment (NI) group of 4,285 participants was identified from clinical assessment results that indicated no to minimal functional changes and neuropsychological test results interpreted as broadly normal for the individual's age and level of educational and occupational attainment. For individuals who did not complete a clinical assessment, a designation of NI was assigned for those who screened negative at prior study stages.

Other risk factors for AD or dementia. APOE genotypes were determined using PCR amplification and restriction isotyping following previously described methods. APOE genotypes were unknown to clinicians during the diagnostic process. For analytic purposes, we collapsed across genotypes to dichotomize into those with or without one or more ε4 alleles (ε4 positive or negative). Family history of AD or dementia was assessed by participant interview. When siblings and parents had experienced memory problems, we inquired about the course and features of the problems and whether a physician diagnosed the cause of the memory trouble. Relatives were classified as having suspected dementia if they had received such a physician's diagnosis, or if memory problems caused limitation in daily activities. A family history of suspected AD was coded for relatives who had received this diagnosis, or whose described course specifically suggested AD. Designation of a family history as negative required all relatives of stroke or other cerebrovascular condition, 19 with depression, 15 with other psychiatric conditions such as anxiety, inattention/ frontal lobe symptoms, pain syndrome, 15 with significant medical illness, 10 with cardiovascular conditions, 8 with PD without dementia, 8 with other neurologic conditions, 5 with alcohol abuse or neurotoxin exposure, and 4 with head injuries. Table 1 provides descriptive data. As expected, individuals with mild cognitive disorders had lower baseline 3MS scores than NI and exhibited greater decline on the 3MS at follow-up (p < 0.0001). Those with proAD did not differ from those with CS on baseline 3MS, but exhibited greater decline at follow-up (p = 0.002). The majority of the 1,225 participants unavailable for follow-up either died (39.8%) or refused participation (39.8%), Again, as expected, individuals who did not complete follow-up visits were older (p < 0.0001) and scored lower on the 3MS at baseline (p < 0.0001). Risk for incident dementia with baseline mild cognitive disorders. A disproportionate percentage of those in the CS and proAD groups were ε4 positive (χ² 49.79, df 2, p < 0.0001). In comparison to 3.3% of the NI group, 39.1% of
CS subjects and 54.9% of those with proAD had developed dementia at follow-up ($\chi^2 = 467.15$, df 2, $p < 0.0001$). The majority of those with dementia were classified as AD ($n = 106$), either occurring singly or in combination with some other condition. The remaining 53 with other dementias consisted of 19 with vascular dementia, 5 with PD, 1 each with progressive supranuclear palsy, diffuse Lewy body dementia, and traumatic brain injury, and 26 with a dementia of undetermined etiology. Dementia of undetermined etiology was assigned if clinical or neuropsychological features were not consistent with those of other dementia diagnoses. Table 2 shows that for those classified as proAD at baseline, 86% who developed dementia were classified with AD. Because follow-up diagnoses considered all available data (including clinical assessment information obtained at Wave 1), however, study clinicians were probably more likely to assign a follow-up diagnosis of AD dementia in this subgroup. Among the individuals with cognitive impairments at baseline who did not develop dementia, 64% of CS and 74% of proAD participants remained in a group with cognitive impairment designation at Wave 2. Only 6% of the NI group developed mild cognitive symptoms at Wave 2.

Simple bivariate LR models, individuals with some form of mild cognitive disorder at baseline exhibited substantially higher rates of incident dementia than those without cognitive impairment (OR, 95% CI = 35.61 [19.84, 63.93] for proAD and 18.80 [11.16, 31.68] for CS). Crude associations with dementia were evident in participants with at least one $\varepsilon_4$ allele ($OR = 1.59 [1.15, 2.20]$), older age ($OR = 5.76 [3.71, 8.93]$ and 16.90 [10.29, 27.74]), female sex ($OR = 1.42 [1.02, 1.99]$), and a family history of AD ($OR = 1.46 [1.01, 2.11]$). In multivariable models, baseline cognitive group and age group were retained as significant predictors. Family history of AD was associated with having one or more $\varepsilon_4$ alleles, and was no longer a significant predictor when considered simultaneously with $\varepsilon_4$ status in multivariable models. Results of bivariate and multivariable models are available in table E-1 on the Neurology Web site at www.neurology.org.

The influence of baseline cognitive group was modified by $APOE$ genotype ($p = 0.034$ for the interaction) such that, in the presence of $\varepsilon_4$, CS and proAD exhibited 22 to 25 times the dementia risk of NI (25.46 [11.41, 52.83] for CS and 22.39 [9.15, 54.81] for proAD). In those without $\varepsilon_4$, CS and proAD exhibited only 5 to 10 times the risk of NI (5.33 [2.09, 13.60] for CS and 10.76 [4.19, 27.60] for proAD). Two-way interactions between baseline cognitive group and family history of AD, sex, and education were not significant, nor was the interaction between sex and age group.

Of the 1,212 individuals who did not complete Wave 2 protocols, data on 432 individuals were recovered from informant interviews. Of these, 56 or 13% were determined to have developed dementia (vs 5% among responders to the standard Wave 2 protocol). The occurrence of incident dementia in these nonresponders was similar to those found in the responding sample with proAD or CS, but higher in the NI group (10% vs 3.3% in responders to standard Wave 2 protocol). Inclusion of the additional interview data produced logistic regression models that were broadly consistent with those reported (data not shown).

### Table 2

<table>
<thead>
<tr>
<th>Baseline cognitive group</th>
<th>NI</th>
<th>proAD</th>
<th>CS</th>
<th>AD</th>
<th>Other dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>NI</td>
<td>2,866 (91.1)</td>
<td>103 (3.3)</td>
<td>73 (2.3)</td>
<td>65 (2.1)</td>
<td>39 (1.2)</td>
</tr>
<tr>
<td>proAD</td>
<td>* (11.8)</td>
<td>* (21.6)</td>
<td>* (11.8)</td>
<td>24 (47.1)</td>
<td>* (7.8)</td>
</tr>
<tr>
<td>CS</td>
<td>15 (21.7)</td>
<td>* (5.8)</td>
<td>23 (33.3)</td>
<td>17 (24.6)</td>
<td>* (14.5)</td>
</tr>
</tbody>
</table>

Values are n (%). Table 2 shows the outcome of individuals who at baseline were classified with no impairment (NI), prodromal Alzheimer disease (proAD), or other cognitive syndrome (CS). The majority of those in the three baseline cognitive groups who developed dementia were of the AD type, especially among those with the proAD classification. The majority of those with some cognitive impairment at baseline who did not convert to dementia were found to also be impaired at follow-up. Total percentages that sum less than or greater than 100 are due to rounding.

* Number withheld to comply with privacy policy of Center for Medicare and Medicaid Services.

### Discussion

In a large population-based study, we found that mild cognitive disorders were associated with an increased risk of dementia, with highest risk in those classified with proAD. The presence of at least one $APOE$ $\varepsilon_4$ allele significantly increased dementia risk for those with both proAD and other CS. These results are largely consistent with those previously reported for MCI and cognitive impairment, no dementia (CIND). By contrast, we found that $\varepsilon_4$ did not modify the risk for dementia among those with NI. Predictably, the latter group was younger than those with proAD or CS, and during the 3-year follow-up interval, age was a stronger predictor of dementia in this group than in others. With additional longitudinal follow-up, $APOE$ $\varepsilon_4$ might well emerge as an important risk factor in this group. Other known risk factors such as age and family history of AD, but not of other dementia, increased dementia risk in this population.

Although the category of proAD did not adhere to published criteria for MCI or questionable dementia (CDR 0.5) it resembled these categories of late-life cognitive disorders as memory impairment was an important feature of this category. Predictably, therefore, most proAD participants who developed dementia received diagnoses of AD (86% vs 63% in CS and NI groups). With the exception of a clinic-based sample, incidence rates of dementia and AD were higher here in those with proAD than has been reported elsewhere for either MCI or questionable dementia. Differences might reflect our dementia screening and assessment procedures and our inclusion of other dementia types in the outcome.

Combined, the proAD and the heterogeneous CS groups appear similar to the Canadian Study’s classification of CIND. Nonetheless, our population estimate for both groups combined reflects an overall 3-year conversion rate of 45.8% (roughly 14.3% annually). This rate is higher than the Canadian Study’s 5-year rate of 47% (roughly 9.4% annually); however, our 3.3% incidence of dementia (1% annually) in those without baseline impairment is lower.
than the 5-year rate of 15% (3% annually) in the Canadian Study. Taken together, both the Cache County and the Canadian studies suggest it is important to consider broad groupings of cognitive disorder, and not only those meeting strict criteria, when surveying dementia risk. This idea is gaining support elsewhere.\textsuperscript{31,32} Broadening the scope of late-life mild cognitive disorders and specifying their particular features (i.e., amnestic single domain or multiple domains, non-amnestic single domain or multiple domains) may aid in identifying prodromal states specific to dementias other than AD.\textsuperscript{33}

Among the individuals with proAD and CS who did not progress to dementia, we found 26% in the former group and 36% in the latter reverted after 3 years to a no impairment classification. This percentage reverting back to no impairment is higher than the 10% in MCI reported in clinic samples,\textsuperscript{39} but similar to rates of up to 40% reported in other populations.\textsuperscript{11} Our figures are probably inflated because the non-caseness of a majority of these individuals was inferred from a screen-negative result from a multistage screening protocol with imperfect sensitivity. Future work in Cache County will allow us to examine better the stability of various types of late-life mild cognitive impairment in this population.

The strengths of this study include its population-based sample, relatively thorough evaluation of individuals with cognitive impairment, inclusion of broad types of late-life cognitive impairment, and high initial participation and follow-up rates. Nonetheless, a substantial number of individuals (27% of the original 4,491) were lost to follow-up, the majority owing to deaths and refusals. When we estimated the cognitive status of 452 individuals (35% of those considered lost to follow-up) using informant interviews, we found 56 or 13% were determined to have developed dementia (vs 5% among responders to the standard Wave 2 protocol). The occurrence of incident dementia in these nonresponders was similar to those found in the responding sample with proAD or CS, but higher in the NI group (10% vs 3.3% in responders to standard Wave 2 protocol). Inclusion of the additional interview data produced logistic regression models that were broadly consistent with those reported above.

A potential weakness of our study is its method of categorizing individuals with late-life cognitive impairment. Because our protocol was designed in the mid-1990s, with intent to detect cases of dementia or prodromal AD, many participants with very mild cognitive impairment or those in the prodromal stages of other dementias may have been overlooked. As a result, our methods may have been less sensitive to detecting other dementias such as diffuse Lewy body (DBL) or frontotemporal dementia (FTD). DBL and FTD were rarely identified in this population, possibly reflecting, in part, the higher occurrence of FTD in younger populations.\textsuperscript{34} For DBL, population data on incidence are lacking. A recent review of the prevalence and incidence of DBL reports prevalence of 0 to 5% and incidence of 0.1% per year, the latter based on data from the Cache County Study.\textsuperscript{35} Still, it is possible that some individuals with FTD or DBL were subsumed in the category of dementia, undetermined etiology, which constituted 16% of the dementia diagnoses at follow-up. Unusual presentations of dementia that precluded categorization into traditional diagnostic categories may reflect dementia symptoms more commonly encountered in epidemiologic as compared to clinic-based samples. Finally, the relatively stronger severity of impairment in participants who were detected may explain their increased occurrence of subsequent dementia as compared with similar groups in other studies. Paradoxically, however, the presumed residue of overlooked individuals with milder disorders did not lead to higher dementia incidence in our NI participants than elsewhere. Our relatively high sensitivity and specificity for detection of prodromal dementia may reflect particulars of our screening methods,\textsuperscript{36} but it is possible that these methods might not work as well in less cooperative populations, or in those with different racial or ethnic representation.

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Appendix
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References

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