Published in final edited form as:

Neuropsychology. 2013 January ; 27(1): . doi:10.1037/a0030855.

The Apolipoprotein E Genotype Predicts Longitudinal Transitions to Mild Cognitive Impairment but Not to Alzheimer's Dementia: Findings From a Nationally Representative Study

C. J. Brainerd,

Department of Human Development, Cornell University

V. F. Reyna,

Department of Human Development, Cornell University

R. C. Petersen,

Department of Neurology, Mayo Clinic, Rochester, Minnesota

G. E. Smith,

Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

A. E. Kenney,

Department of Human Development, Cornell University

C. J. Gross,

Department of Human Development, Cornell University

E. S. Taub,

Department of Human Development, Cornell University

B. L. Plassman, and

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

G. G. Fisher

Institute for Social Research, University of Michigan

Abstract

Objective—The $\epsilon 4$ allele of the apolipoprotein E (APOE) genotype is the most widely accepted genetic risk factor for Alzheimer's dementia (AD), but findings on whether it is a risk factor for the AD prodrome, mild cognitive impairment (MCI), have been inconsistent. In a prospective longitudinal design, we investigated (a) whether transitions to MCI and other forms of neurocognitive impairment without dementia (CIND) are more frequent among normal $\epsilon 4$ carriers than among noncarriers and (b) whether subsequent transitions to AD from MCI and from other forms of CIND are more frequent among $\epsilon 4$ carriers than among noncarriers.

Method—The frequency of the $\epsilon 4$ allele was studied in older adults (mean age > 70), who had participated in two or more waves of neuropsychological testing and diagnosis in the Aging, Demographics, and Memory Study (ADAMS) of the United States Department of Health and Human Services, National Institutes of Health, National Institute on Aging's Health and Retirement Study, conducted by the University of Michigan. The association between $\epsilon 4$ and longitudinal transitions to specific types of CIND and dementia can be determined with this data set.

Results—Epsilon 4 increased the rate of progression from normal functioning to MCI (58% of new diagnoses were carriers) but not to other forms of CIND. The rate of progression to AD from MCI or from other forms of CIND was not increased by $\epsilon 4$.

Conclusions—The results support the hypothesis that $\epsilon 4$ is a risk factor for transitions from normal functioning to MCI but not for subsequent transitions to AD. In the ADAMS sample, the reason $\epsilon 4$ is elevated in AD individuals is because it is already elevated in MCI individuals, who are the primary source of new AD diagnoses.

Keywords

mild cognitive impairment; Alzheimer's dementia; APOE genotype

We report a longitudinal extension of prior research on whether the $\epsilon 4$ allele of the apolipoprotein E (APOE) genotype is a genetic marker of mild cognitive impairment (MCI). Epsilon 4 has long been accepted as a genetic marker of Alzheimer's dementia (AD), of course (Corder et al., 1993; Strittmatter et al., 1993), with roughly half of individuals with probable AD diagnoses being carriers of at least one copy of this allele (e.g., Caselli et al., 2009). In contrast, previous research has produced inconsistent findings with respect to whether $\epsilon 4$ is also a genetic marker of MCI (Small, Rosnick, Fratiglioni, & Backman, 2004). That result is puzzling because clinical evidence points to MCI as the AD prodrome (Petersen, 2011; Petersen et al., 2001; Serra et al., 2010; Smith, 2002). If MCI is prodromal to AD, it is natural to suppose that $\epsilon 4$ would be a risk factor for both conditions.

In a review of the methodologies of prior studies (Brainerd et al., 2011), we concluded that salient sources of both Type I error (i.e., uncontrolled variables that could produce spurious $\epsilon 4$ –MCI associations) and Type II error (i.e., uncontrolled variables that could mask $\epsilon 4$ –MCI associations) were present in the designs of these studies. On the Type I error side, no study implemented diagnostic criteria that excluded participants from MCI groups who had other diseases for which $\epsilon 4$ is a risk factor. Thus, associations between $\epsilon 4$ and MCI could be due to $\epsilon 4$'s correlation with other diseases (e.g., see Hayden et al., 2009, for a study of undetected latent dementia that may be responsible for variation in associations between $\epsilon 4$ and MCI). A source of Type II error is that MCI samples were usually small, so that failures to observe reliable $\epsilon 4$ –MCI associations could simply be due to low statistical power. Another source of Type II error is that designs failed to ensure that MCI samples consisted predominantly of individuals with significant impairments in episodic memory (amnesic MCI). MCI is normally divided into amnesic MCI (a-MCI) and nonamnesic MCI (n-MCI; Anderson & Schmitter-Edgecombe, 2010; Bhalla et al., 2009; Bizzozero, Lucchelli, Saetti, & Spinnler, 2009; Johnson, Schmitz, Asthana, Gluck, & Myers, 2008; Schmitter-Edgecombe & Sanders, 2009; Schmitter-Edgecombe, Woo, & Greeley, 2009; Seidenberg et al., 2009; Woodard et al., 2009). Only a-MCI is assumed to be prodromal to AD (Petersen, 2011; Petersen et al., 2001; Serra et al., 2010).

Brainerd et al. (2011) reexamined the $\epsilon 4$ –MCI relation in a data set that minimized the sources of Type I and Type II error in prior studies, the Aging, Demographics, and Memory Study (ADAMS; Health and Retirement Study, 2011). For example, the ADAMS diagnostic procedures excluded participants from MCI diagnoses who had other diseases that seemed to explain cognitive impairment without dementia (CIND; see Plassman et al., 2008), and those procedures produced MCI groups that satisfy the key clinical criterion for a-MCI (see Petersen, 2004), which is episodic memory performance ≥ 1.5 SDs below that of healthy age mates. The ADAMS has the additional advantage that it is the only nationally representative study of cognitive impairment and dementia in older adults in the United States.

Brainerd et al. (2011) used data from the initial wave of ADAMS testing (Wave A), which provided large samples of healthy control (HC), CIND, and demented (D) participants. On an age-adjusted basis, the $\epsilon 4$ allele was found to be a risk factor for MCI (i.e., it was elevated in that diagnostic group, relative to the HC group) but not for other forms of CIND. The $\epsilon 4$ allele was also found to be a risk factor for probable AD (it was elevated in that diagnostic group, relative to all other diagnostic groups), and to be a weaker risk factor for possible AD (it was elevated in that diagnostic group, relative to CIND groups other than MCI and to the HC group).

Longitudinal Transition Patterns

The suggestion of the Wave A ADAMS results for transitions from HC to CIND is that the effect of $\epsilon 4$ is specific to HC $\rightarrow$ MCI transitions, and the suggestion for transitions from CIND to D is that $\epsilon 4$ increases rates of transition to both probable and possible AD, with its effect being larger for probable AD transitions. However, the last result might be due to diagnostic error: A possible AD diagnosis was assigned when an individual's profile was atypical for AD, or there were other conditions that seemed to contribute to cognitive impairment (see Plassman et al., 2008).

The Wave A results fall short of establishing that these suggestions about longitudinal transition rates are correct. With respect to transitions to MCI, although $\epsilon 4$ was correlated with MCI diagnoses in the Wave A data, that might be due to uncontrolled differences between the MCI group and the other groups to which it was compared (e.g., undetected disease in the MCI group; see Brainerd et al., 2011), rather than to differences in longitudinal transition rates. The same is true of the correlation between $\epsilon 4$ frequency and AD diagnoses. The fact that $\epsilon 4$ frequency was elevated in both AD groups and most highly elevated in the probable AD group does not show that transitions to dementia are more likely among $\epsilon 4$ carriers. Because $\epsilon 4$ is so widely accepted as an AD risk factor, the notion that it may not increase longitudinal progression to AD seems an unlikely hypothesis. Consider the following developmental model, however.

First, as individuals convert from HC to various forms of CIND, suppose that $\epsilon 4$ elevates the rate of HC $\rightarrow$ MCI transition, but not rates of transition to other forms of CIND. If so, $\epsilon 4$ will be elevated in new MCI diagnoses, relative to new diagnoses of other forms of CIND and to HC. Second, as older adults convert from various forms of CIND to various forms of dementia, assume that $\epsilon 4$ has no effect on any of the dementia transition rates, but that (a) individuals who convert to probable AD overwhelmingly have MCI diagnoses and (b) individuals who convert to possible AD are more likely to have MCI diagnoses than other CIND diagnoses. It follows from the second assumption that $\epsilon 4$ will be elevated in both forms of AD, and more so in probable AD, even though (by the first assumption) it does not affect rates of longitudinal transition from any form of CIND to any form of dementia.

Thus, the data from Wave A of the ADAMS suggest but do not test two hypotheses about longitudinal transition rates—namely, that $\epsilon 4$ increases the rate of transition from HC to MCI and that $\epsilon 4$ increases the rate of transition from CIND to AD. Both hypotheses can be evaluated using other waves of the ADAMS to investigate longitudinal transition patterns. As noted by Plassman et al. (2011), three subsequent waves of neuropsychological testing and diagnosis were undertaken with portions of the original sample of participants. Wave B occurred 16–18 months after Wave A, and it focused on retesting and rediagnosis of participants who received CIND diagnoses during Wave A. Wave C occurred an average of 44.4 months after a participant's most recent testing wave, and Wave D occurred an average of 21.6 months after a participant's most recent testing wave. Wave C focused on retesting and rediagnosis of all participants whose current diagnosis was either HC or CIND. Wave D

also focused on retesting and rediagnosis of all participants whose current diagnosis was either HC or CIND. Death was again the modal reason for nonparticipation in Wave C and Wave D.

We analyzed data from Waves B, C, and D in order to test hypotheses about how $\epsilon 4$ affects rates of transition to neurocognitive impairment and dementia. Although methodological details are supplied below, the general procedure ran as follows. Because the focus was on genetic risk for different longitudinal transitions, analyses were restricted to Wave A participants who participated in at least one subsequent wave, and hence, received at least one rediagnosis that could be compared to an immediately preceding diagnosis. For each subject, we noted the diagnoses during pairs of consecutive testing waves. The data of participants whose diagnosis was HC during the first wave of a consecutive pair were used to determine whether longitudinal progression to MCI was more likely among $\epsilon 4$ carriers, and if so, whether that increase was specific to MCI. The data of participants whose diagnosis was some form of CIND during the first wave of a consecutive pair were used to determine whether longitudinal progression to probable or possible AD was more likely among $\epsilon 4$ carriers, and if so, whether that increase was greatest for probable AD.

Method

Participants

The full details of the ADAMS subject sample have been provided in several publications (e.g., Langa et al., 2005; Plassman et al., 2007, 2008) and, therefore, will not be extensively reprised here. ADAMS participants are a subsample of the larger HRS (Health and Retirement Study) subject pool, which consists of over 30,000 individuals and was constructed using sampling procedures that ensure that it is fully representative of all geographical regions, ethnic groups, and racial groups in the United States. As mentioned, there were 856 participants who participated in Wave A (10% Hispanic, 19% non-Hispanic Black, and 71% non-Hispanic White). With respect to educational level, 52% had fewer than 12 years of education, 23% had 12 years, and 25% had more than 12 years. Wave A neuropsychological testing and diagnosis yielded a group of 307 HC participants ($M_{age} = 78.0$, $SD_{age} = 5.6$, 141 males), a group of 241 CIND participants ($M_{age} = 80.7$, $SD_{age} = 6.9$, 117 males), and a group of 308 demented (D) participants ($M = 84.3$, $SD = 6.9$, 127 males).

As our interest lies with genetic predictors of HC $\rightarrow$ CIND transitions and CIND $\rightarrow$ D transitions, the subject sample for the present study consisted of all Wave A HC participants who participated in at least one subsequent wave of neuropsychological testing and rediagnosis ($N = 233$; $M_{age} = 77.4$, $SD = 4.68$) and all Wave A CIND participants who participated in at least one subsequent wave ($N = 185$; $M_{age} = 81.1$, $SD = 6.88$). Although these two groups differed in mean age, they did not differ in gender composition or ethnic/racial composition, though the mean years of education was higher in the HC group than in the CIND group (13 vs. 11). It is important to note, however, in the longitudinal transition groups whose data we analyzed, groups of carriers versus noncarriers of $\epsilon 4$ did not differ in any of these variables.

A numerical breakdown of the diagnoses of these groups during all four waves of testing is presented in Table 1. In the first row, it can be seen that, although N s shrank over time, sufficient numbers of HC participants remained to evaluate whether $\epsilon 4$ increased the rate at which individual participants converted to each of the three CIND groups that Brainerd et al. (2011) used to determine the relations between $\epsilon 4$ and different cognitive impairment diagnoses: MCI, cognitive impairment secondary to vascular disease or stroke (VSCI), and all other forms of cognitive impairment without dementia (AOCI). In the second row, it can be seen that sufficient numbers of CIND participants also remained to evaluate whether $\epsilon 4$

increased the rate at which individual participants converted to each of the three D groups that Brainerd et al. used to determine the relations between $\epsilon 4$ and different dementia diagnoses (AD1 = probable AD, AD2 = possible AD, and AOD = all other dementias).

Neuropsychological Testing and Diagnosis of ADAMS Participants

The neuropsychological tests, medical examinations, and diagnostic procedures that were used with ADAMS participants have also been fully described in prior publications (e.g., Langa et al., 2005; Plassman et al., 2007, 2008) and will only be briefly summarized here. Each wave involved an in-person, 3–4-hour structured assessment, which consisted of a battery of neuropsychological tests, a self-report depression instrument, a neurological examination, and a blood pressure measurement. (In addition, during Wave A, buccal tissue samples were gathered for APOE testing.) Proxy respondents (e.g., participants' spouses or adult children) supplied information on cognitive and functional decline, neuropsychiatric symptoms, and medical history, which are important in diagnosing CIND and dementia because diagnostic criteria for these conditions specify that current cognitive performance and functioning represent declines from earlier levels.

The data generated by the structured assessment were then used by an expert consensus panel (neuropsychologists, neurologists, geropsychiatrists, and internists) to classify each subject as HC, CIND, or demented. Participants with a CIND classification were also classified according to one of 12 subtypes (see Langa et al., 2005), some of which contained very few participants. To generate CIND groups with sufficiently large numbers of participants for statistical comparisons, Brainerd et al. (2011) examined these participants' primary ADAMS diagnoses (subtypes) and aggregated diagnoses to create three comparison groups: MCI, VSCI, and AOCI. For the sake of comparability, the same method of aggregation was used in the present study to determine whether $\epsilon 4$ increases the rate of longitudinal transition from HC to MCI. ADAMS participants with a dementia classification were also classified according to one of 18 subtypes, most of which contained very few participants. To generate dementia groups with sufficiently large numbers of participants for statistical comparison, Brainerd et al. (2011) aggregated the subtypes into three groups, based on their primary diagnoses: AD1, AD2, and AOD. Again, for the sake of comparability, the same method of aggregation was used in the present study to determine whether $\epsilon 4$ increases the rate of longitudinal transition from CIND to AD.

Data Analysis

Data from the ADAMS were used to determine whether $\epsilon 4$ is a risk factor for HC $\rightarrow$ MCI transitions (or transitions to other forms of CIND), and to determine whether the allele is a risk factor for MCI $\rightarrow$ AD1 transitions (or other CIND $\rightarrow$ dementia transitions). Three types of data were analyzed.

First, to determine whether $\epsilon 4$ increases the rate of longitudinal transition to MCI, we analyzed rates of transition from HC to each of the four diagnoses that did not involve dementia (HC, MCI, AOCI, and VSCI) for $\epsilon 4$ carriers versus noncarriers, on an age-adjusted basis. The omnibus test of the null hypothesis that $\epsilon 4$ does not affect the rate of transition to any form of CIND was a multinomial logistic regression, with carrier versus noncarrier as the independent variable, type of diagnostic transition as the dependent variable, and age as a covariate. This was followed by a series of pairwise tests of the age-adjusted $\epsilon 4$ frequencies (carrier vs. noncarrier) for the four possible types of transitions (HC $\rightarrow$ HC, HC $\rightarrow$ MCI, HC $\rightarrow$ AOCI, and HC $\rightarrow$ VSCI). Those tests determined whether, as the Wave A data suggest, $\epsilon 4$ only elevates the rate of transition to MCI.

The second type of data analyzed consisted of longitudinal transitions from CIND to dementia to determine whether $\epsilon 4$ increases rates of transition to AD and other forms of dementia. These analyses involved a larger number of transition groups than those for transitions from HC to CIND: Because there are three CIND groups and three dementia groups, nine distinct types of CIND $\rightarrow$ dementia transitions were possible, and nine distinct types of CIND $\rightarrow$ CIND transitions were also possible. The omnibus test of the null hypothesis that $\epsilon 4$ does not affect the rate of transition from CIND to any form of dementia was a multinomial logistic regression, with carrier versus noncarrier as the independent variable, type of diagnostic transition as the dependent variable, and age as a covariate.

The third type of data analyzed did not involve the genetic results, and instead, consisted simply of the rates of transition to each dementia group from each CIND group. The purposes of these analyses were to determine whether (a) longitudinal transitions to AD were generally higher for particular CIND groups (e.g., MCI) and whether (b) longitudinal transitions to specific dementia groups were higher for particular CIND groups (e.g., MCI $\rightarrow$ AD1 transitions). As mentioned, because $\epsilon 4$ frequency is higher in MCI than in other forms of CIND, the Wave A genetic results for dementia could be explained if the rate of transition to AD is higher for MCI participants and if that effect is most pronounced for AD1. The test of the null hypothesis that there was no relation between CIND group and rate of transition to AD was a 2 (CIND group: MCI vs. VSCI/AOCI) $\times$ 2 (dementia group: AD1/AD2 vs. AOD) chi-square (χ^2) test of the age-adjusted frequencies of consecutive diagnoses. The test of the null hypothesis that there was no relation between CIND group and rate of transition to AD1 versus AD2 was a 2 (CIND group: MCI vs. VSCI/AOCI) $\times$ 2 (AD group: AD1 vs. AD2) χ^2 test of the age-adjusted frequencies of consecutive diagnoses. Chi-square tests were appropriate, because in both analyses, $N > 20$, all expected cell frequencies were > 5 , and each subject only appeared once (based on which of the first three waves produced the first CIND diagnosis).

Results

Longitudinal Transitions to CIND for HC $\epsilon 4$ Carriers Versus Noncarriers

The age-adjusted proportions of $\epsilon 4$ carriers among participants who made each type of HC $\rightarrow$ CIND transition, along with the number of transitions on which each entry is based, are displayed in Table 2. (In addition, there were a few transitions from HC to the dementia groups, which are not considered here because the numbers were too small for statistical analysis.) A glance at the first row of data suggests that $\epsilon 4$ did indeed increase the rate of progression from HC to MCI, relative to the chances that participants' diagnoses would remain HC (HC $\rightarrow$ HC), or that participants would progress to one of the other two CIND groups (HC $\rightarrow$ VSCI or HC $\rightarrow$ AOCI) because the proportion of carriers among HC $\rightarrow$ MCI participants was much higher than in any of the other transition groups.

That the proportion of $\epsilon 4$ carriers varied reliably as a function of transition group was confirmed by a multinomial logistic regression in which $\epsilon 4$ carrier status (carrier vs. noncarrier) was the independent variable, transition group was the dependent variable, and age was a covariate. That analysis revealed that carrier status was a highly reliable predictor of transition group, $\chi^2(3) = 16.49$ ($p < .001$) and that age was not (i.e., the four transition groups did not differ reliably in mean age). The effect sizes, 95% confidence intervals, and p values for this analysis appear in Table 3, where it can be seen that the only transition group that yielded a p value that exceeded the conventional .05 level of confidence was the HC $\rightarrow$ MCI group. This pattern was confirmed in a series of follow-up planned comparisons, which showed that the effect of carrier status was wholly due to the fact that $\epsilon 4$ was elevated in HC $\rightarrow$ MCI transitions, relative to the other three types of transitions. Specifically, pairwise χ^2 tests showed that the proportion of carriers was higher in the HC $\rightarrow$ MCI group than in the

HC → HC group, $\chi^2(1) = 14.77$ ($p < .0001$), the HC → VSCI group, $\chi^2(1) = 8.96$ ($p < .003$), and the HC → AOCl group, $\chi^2(1) = 6.17$ ($p < .02$). In contrast, a pairwise χ^2 test showed that $\epsilon 4$ was not elevated in the HC → AOCl group relative to the HC → HC group, $\chi^2(1) < 1$, and of course, it was not elevated in the HC → VSCI group because the proportion of carriers in that group was (nonsignificantly) smaller than in the HC → HC group.

Summing up, when it comes to longitudinal transitions to neurocognitive impairment without dementia, the effect of $\epsilon 4$ in the ADAMS data is highly specific. The allele increases the rate of transition from normal functioning to MCI, but it does not affect rates of transition to other forms of CIND.

Longitudinal Transitions to Dementia for CIND $\epsilon 4$ Carriers Versus Noncarriers

As there were three CIND groups and three dementia groups, there were nine distinct types of CIND → dementia transitions and nine distinct types of transitions that could occur between CIND groups, including remaining in the same CIND group on consecutive testing waves. In all then, beginning in one of the three CIND groups and ending in one of the dementia groups or one of CIND groups, 18 distinct types of transitions were possible. Preliminary power analyses of the CIND data indicated that an N of 10 was required to have a reasonable chance of detecting strong between-groups differences ($\alpha = .01$) in $\epsilon 4$ frequency. Eight transition groups did not satisfy that criterion and were therefore excluded from the analysis. For the remaining transition groups, the proportions of $\epsilon 4$ carriers who made each type of transition, along with the number of transitions on which each entry is based, are displayed in Table 4.

Inspection of this table indicates that, in contrast to the results for conversion to CIND (see Table 2) and to current scientific opinion that $\epsilon 4$ is a genetic marker of AD, $\epsilon 4$ did not increase the rate of longitudinal transition to dementia among ADAMS CIND participants. Note, for instance, that for the transition groups in Table 4, the proportion of $\epsilon 4$ carriers varied within a quite narrow range among these groups, and further, that the proportion of MCI $\epsilon 4$ carriers who transitioned to some form of AD was virtually the same as the proportion who remained MCI. This suggestion was confirmed by an omnibus test of the null hypothesis that the proportion of $\epsilon 4$ carriers did not vary reliably as a function of transition group, which was a multinomial logistic regression with $\epsilon 4$ carrier status (carrier vs. noncarrier) as the independent variable, transition group as the dependent variable, and age as a covariate. That analysis showed that neither the χ^2 test for $\epsilon 4$ carrier status nor the χ^2 test for age was a reliable predictor of transition group. It should be noted in connection with the latter result that Plassman et al. (2011) have previously reported a reliable association between age and transitions to dementia in the Waves B–D of the ADAMS. The difference between their analysis and ours is that ours was restricted to 10 CIND transition groups in which $N \geq 10$, whereas their age analysis encompassed all transition groups (including HC transition groups).

The complete absence of statistical relations between $\epsilon 4$ and rates of longitudinal transition to dementia can be summarized by pooling the data of all participants who remained CIND (i.e., were diagnosed with some form of CIND during both waves of a consecutive pair of testing waves) versus all participants who progressed from CIND to dementia (i.e., were diagnosed with some form of CIND during one wave and with some form of dementia during the next wave). Those two values differed only slightly: The proportion of CIND $\epsilon 4$ carriers who remained CIND was .26, whereas the proportion of CIND carriers who progressed to any form of dementia was .29.

Longitudinal Transitions to Dementia for Different CIND Groups

So far, we have seen that $\epsilon 4$ has a highly specific effect on longitudinal transitions to neurocognitive impairment in the ADAMS sample—namely, it increases the rate of conversion from HC to MCI but has no other effect. This poses an explanatory problem from the perspective of the larger literature on genetic risk factors for neurocognitive impairment in older adults. It is well established that $\epsilon 4$ frequency is elevated in individuals with AD diagnoses, particularly AD1 diagnoses, relative to normal functioning age mates (e.g., Caselli et al., 2009; Corder et al., 1993; Strittmatter et al., 1993). Further, in the ADAMS Wave A data, $\epsilon 4$ frequency was elevated in AD1, relative to HC and *any* form of CIND, and it was also elevated in AD2, relative to HC and *some* forms of CIND (Brainerd et al., 2011). The problem, then, is how to account for the higher frequency of $\epsilon 4$ in individuals with AD diagnoses without the allele increasing the rate of conversion to AD from CIND.

Earlier, we proposed an explanation that turns on the pivotal role of MCI in transitions to AD, together with (a) the present finding that $\epsilon 4$ increases the rate of HC $\rightarrow$ MCI transition and (b) the prior finding that $\epsilon 4$ frequency is elevated in ADAMS Wave A MCI participants. By virtue of the latter two results, $\epsilon 4$ frequency will be elevated in ADAMS MCI participants, relative to VSCI and AOCI participants. In principle, therefore, $\epsilon 4$ need not increase the rate of CIND $\rightarrow$ AD transition for the allele to be elevated in AD participants or for it to be more frequent in the AD1 group than in the AD2 group. It is only necessary for MCI individuals to contribute disproportionately to AD transitions, especially to AD1 transitions.

To evaluate that explanation, we conducted two follow-up analyses with participants who transitioned to some form of dementia from some form of CIND. Because the N exceeded 40 for both analyses and because none of the expected cell frequencies were < 5 , χ^2 tests with continuity corrections were appropriate, rather than Fisher exact probability tests. (However, Fisher's exact tests produce the same qualitative results as the ones we now report.) The first analysis compared the CIND origins (MCI vs. other forms of CIND) of AD transitions, regardless of whether they were AD1 or AD2, to the CIND origins (MCI vs. other forms of CIND) of AOD transitions. We computed a $\chi^2(1)$ test of the null hypothesis that the type of dementia (AD vs. AOD) was unrelated to prior CIND diagnosis. That test produced a null hypothesis rejection at a high level of confidence, $\chi^2(1) = 14.86$ ($p < .0005$). Descriptively, ADAMS MCI participants yielded 60% of new AD diagnoses but only 9% of new AOD diagnoses. Because $\epsilon 4$ frequency is higher in MCI than in other forms of CIND, this accounts for the fact that the allele is more frequent in individuals with AD diagnoses.

The second analysis compared the CIND origins (MCI vs. other forms of CIND) of AD1 transitions to the CIND origins of AD2 transitions. We computed a $\chi^2(1)$ test of the null hypothesis that the type of AD diagnosis (AD1 vs. AD2) was unrelated to the prior CIND diagnosis. That test also produced a null hypothesis rejection at a high level of confidence, $\chi^2(1) = 15.19$ ($p < .0001$). Descriptively, MCI participants yielded 91% of new AD1 diagnoses and 40% of new AD2 diagnoses. Because $\epsilon 4$ frequency is higher in MCI than in other forms of CIND and MCI is a less frequent source of AD2 diagnoses than AD1 diagnoses, this accounts for the fact that the allele is more frequent in AD1 individuals than in AD2 individuals.

Discussion

Our analysis of longitudinal transitions in Waves A–D of the ADAMS produced some instructive new findings on the role of the APOE genotype in neurocognitive impairment. At present, $\epsilon 4$ is widely accepted as the major genetic risk factor for conversion to AD. For

instance, Caselli et al. (2009) recently commented that “ $\epsilon 4$, the most prevalent known genetic risk factor for Alzheimer’s disease, may account for up to half of all sporadic and familial late onset cases of Alzheimer’s disease” (p. 255). In contrast, whether this allele is also a risk factor for conversion from HC to some form of CIND has been controversial. Some studies have identified an $\epsilon 4$ –MCI link (Henderson et al., 1995; Traykov et al., 2002; Zill et al., 2001) and others have not (Bartrés-Faz et al., 2001; Collie, Maruff, & Currie, 2002; Devanand et al., 2005; Heun et al., 2010), which has prompted reviewers to conclude that available data are mixed and inconsistent (Small et al., 2004). However, when salient sources of Type I and Type II error in earlier studies were minimized, using Wave A data from the ADAMS, a clear pattern emerged (Brainerd et al., 2011): Epsilon 4 frequency was elevated in ADAMS MCI participants, relative to HC, VSCI, or AOI participants, and consistent with many prior studies, $\epsilon 4$ was elevated in AD participants.

However, such findings do not unambiguously establish that $\epsilon 4$ affects the probability that an HC individual will transition over time to some form of CIND, nor do they unambiguously establish that $\epsilon 4$ affects the probability that a CIND individual will transition over time to some form of dementia. Therefore, here we investigated the relation between $\epsilon 4$ and longitudinal transitions among different diagnoses, using consecutive diagnoses of participants in Waves A–D of the ADAMS. The results were surprising from the perspective of current scientific opinion about genetic markers of neurocognitive impairment because the APOE genotype was more strongly predictive of progression to MCI than to AD.

On the one hand, longitudinal transitions from HC to the various CIND diagnoses were consistent with what one would anticipate on the basis of our previous finding that the allele’s frequency is elevated in the Wave A MCI group. The proportion of $\epsilon 4$ carriers among participants who made HC $\rightarrow$ MCI transitions (.58) was nearly three times the proportion among participants who made HC $\rightarrow$ VSCI, HC $\rightarrow$ AOI, or HC $\rightarrow$ HC transitions (.20 overall). Thus, the longitudinal data suggest that $\epsilon 4$ was elevated in Wave A MCI participants because individuals who convert to that condition are more likely to be carriers than individuals who convert to other forms of CIND or who remain healthy.

On the other hand, longitudinal transitions to dementia were not consistent with what one would expect on the basis of prior findings that $\epsilon 4$ frequency is elevated in AD participants. The proportion of $\epsilon 4$ carriers among participants who progressed to AD from any form of CIND did not differ reliably from the proportion among participants who remained CIND. Although this is a novel finding about genetic markers of AD, we proposed a developmental model that explains the result and is supported by the ADAMS data. The model posits that $\epsilon 4$ carriers are more common among HC participants who progress to MCI than other forms of CIND, and that CIND participants who then progress to AD are more likely to be MCI than VSCI or AOI, especially those who progress to AD1. Consequently, individuals with AD diagnoses, particularly AD1, are bound to have elevated $\epsilon 4$ frequencies, even though this allele does not increase the chances that individuals with neurocognitive impairment will progress to dementia.

Because the ADAMS longitudinal patterns differ from what one would anticipate on the basis of the prior literature, it is important to note that they are congruent with (a) the role of episodic memory impairment in MCI versus AD diagnoses and (b) research on cognitive functioning in normal $\epsilon 4$ carriers. Concerning the first point, according to the AD cognitive deficit criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994), this diagnosis must involve clinically significant episodic memory impairment, plus impairment in at least one of four other domains (executive function, language, motor function, and object identification). MCI diagnostic criteria (see Petersen, 2004) usually specify impairment in one of these domains,

with a-MCI individuals having memory impairment and n-MCI individuals having impairment in another domain. N-MCI is further divided into multiple-domain (md-MCI) and single-domain (sn-MCI) subtypes (see Panza et al., 2005; Petersen et al., 2010). The key consideration is that MCI individuals with memory impairment predominate over individuals with impairments in other domains 2 to 1, according to some estimates (e.g., Petersen, 2004). Thus, memory declines predominate in conversion to MCI, whereas declines in other cognitive domains (along with further declines in episodic memory) predominate in conversion to AD because memory impairment is usually already present (e.g., Summers & Saunders, 2012).¹ This brings us to our second point.

Neuropsychological testing has tied $\epsilon 4$ to reduced performance in multiple cognitive domains in healthy older adults. For instance, Small et al. (2004) conducted a meta-analysis of prior studies of the relation between $\epsilon 4$ and performance on the cognitive tests that figure in neuropsychological batteries. Of the five cognitive domains specified in the *DSM-IV* (APA, 1994) dementia criteria, the meta-analysis revealed a reliable association between $\epsilon 4$ and reduced performance on tests of episodic memory and executive function, and it also revealed a reliable association between $\epsilon 4$ and reduced performance on tests of global cognitive functioning (e.g., the Mini-Mental State Examination). Extensive recent data on the $\epsilon 4$ –memory association were reported by Caselli et al. (2009).

Tying these two points together with the ADAMS longitudinal data, a viable explanation of the fact that $\epsilon 4$ frequency was a risk factor for HC $\rightarrow$ MCI transitions but not MCI $\rightarrow$ AD transitions is that this allele is a marker of *initial* cognitive declines (e.g., memory, executive function) that are associated with MCI diagnoses but not of *subsequent* declines in cognition or in daily functioning that are associated with AD diagnoses. In that connection, as mentioned, the ADAMS MCI group met the main clinical criterion for a-MCI, and it also displayed statistically significant reductions in the other four cognitive domains (see Footnote 1). When we examined the performance of the AD1 and AD2 groups on the ADAMS neuropsychological battery, we found that, relative to the MCI group, they displayed further significant reductions in performance on tests in all five *DSM-IV* (APA, 1994) cognitive domains. Thus, the predictive power of the $\epsilon 4$ allele appears to lie in its ability to forecast initial declines from normal cognitive functioning—as opposed to later, more severe, declines.

These results have two noteworthy implications for clinical practice, one about MCI and the other about the use of the genetic testing to predict risk of future dementia. Concerning MCI, this condition seems to play an even more central role in neurocognitive impairment than is currently supposed. At present, the clinical importance of MCI lies in the fact that it is the primary candidate for a transitional stage between normal functioning and early AD. That view of MCI, which is consistent with clinical data (Smith, 2002), is supported by the present finding that MCI participants were the predominant source of new AD diagnoses. Beyond this, the key new result is that in ADAMS participants, MCI captured all of the effect of the best genetic predictor of neurocognitive impairment: Epsilon 4 increased the HC $\rightarrow$ MCI transition rate, but it did not affect any other type of transition.

Turning to the second clinical implication, future dementia is, quite naturally, a pressing concern for individuals with CIND diagnoses, whereas future CIND is not a pressing

¹In the ADAMS MCI group (designated as “prodromal AD” in the study), the diagnostic criteria allow for some impairment in cognitive domains other than episodic memory. In addition to objective memory impairment that meets the clinical criterion for a-MCI, examination of the data from the neuropsychological battery revealed statistically significant differences between this group’s performance on tests in the executive function, language, motor function, and object identification domains and the performance of the ADAMS HC group. However, the MCI group’s performance on all of these tests, as well as their performance on the episodic memory tests, was significantly better than the performance of the AD1, AD2, and AOD groups.

concern for most normal functioning individuals. Hence, although testing for the $\epsilon 4$ allele is not currently recommended in routine practice (Petersen, 2011), using genetic tests to identify CIND individuals who are at risk of future dementia is more common than using such tests to identify normal functioning individuals who are at risk of future impairment. Obviously, this is the opposite of what one would recommend on the basis of the ADAMS longitudinal data. According to those data, testing for the $\epsilon 4$ allele can identify normal functioning individuals who are at risk of future MCI, but it lacks predictive value when it comes to identifying CIND individuals who are at risk of future dementia.

In closing, it is important to consider an alternative explanation of why $\epsilon 4$ was a risk factor for HC $\rightarrow$ MCI transitions but not for MCI $\rightarrow$ AD transitions, one that centers on potential lack of separation between ADAMS MCI and AD diagnoses. Diagnostic criteria for MCI have evolved over time. Recent criteria promulgated by the National Institute on Aging (NIA; Albert et al., 2011) now include declines in daily functioning of the sort that have been traditionally identified with dementia. Morris (2012) conjectured that these more inclusive criteria compromise the separation between MCI and AD diagnoses, and he reported data that were consistent with that hypothesis. Morris applied the NIA MCI criteria to the data of over 6,000 individuals who had been previously diagnosed as very mild, mild, moderate, or severe AD. He found that over 90% of individuals with very mild or mild AD diagnoses were reclassified as MCI, and he concluded that those criteria blur the distinction between the MCI and AD.

The fact that $\epsilon 4$ was a risk factor for HC $\rightarrow$ MCI transitions but not for MCI $\rightarrow$ AD transitions would be less surprising, of course, if MCI individuals were actually early AD. In that connection, the question of diagnostic separation between ADAMS CIND and dementia diagnoses figured in a recent article by Fisher et al. (2011). The main point, for present purposes, is that the ADAMS implemented earlier diagnostic criteria, rather than the recent NIA criteria, and that the MCI criteria, in particular, were similar to those in Winblad et al. (2004). Further, two empirical findings of the ADAMS are at variance with the hypothesis that MCI individuals were overwhelmingly early AD—namely, their rate of progression to AD diagnoses on subsequent testing waves and their rate of reversion to HC diagnoses.

With respect to rate of progression to AD, if most MCI individuals were actually early AD, one would expect very high rates of progression to AD diagnoses on consecutive pairs of diagnoses. However, the rate was well under 50% throughout the study. For instance, 28% of the Wave A MCI participants (mean age = 82.5 years) who also participated in Wave B were diagnosed as demented during Wave B. Across all waves, as can be seen in Table 4, the MCI $\rightarrow$ AD transition rate between consecutive diagnoses was 38%. These percentages are similar to AD progression rates in other studies that used the consensual panel approach to diagnosis, coupled with pre-NIA diagnostic criteria (see Plassman et al., 2008). With respect to reversion to HC, if MCI individuals were actually early AD, one would expect that reversions to HC would be extremely rare. However, of the Wave A MCI participants who also participated in Wave B, 9% were diagnosed as HC during Wave B. This percentage is on the low end of the range of reversion rates in other studies that used the consensual panel approach to diagnosis, coupled with pre-NIA diagnostic criteria (see Fisher et al., 2011).

Summing up, that $\epsilon 4$ was a risk factor for HC $\rightarrow$ MCI transitions but not for MCI $\rightarrow$ AD transitions is surprising, given the extant literature on genetic markers of AD. However, this result can be explained by a developmental model that assumes that $\epsilon 4$ increases the rate at which healthy individuals progress to MCI and that MCI individuals are the predominant source of new AD diagnoses. It does not seem that this result can be explained by the hypothesis that MCI individuals were actually early AD. The ADAMS did not use the recent

NIA diagnostic criteria for MCI, and rates of progression to AD and reversion to MCI were not what the hypothesis would expect.

Acknowledgments

Preparation of this article was supported by United States Department of Health and Human Services, National Institutes of Health (NIH) Grant 1RC1AG036915-02 to the first and second authors. The HRS (Health and Retirement Study) is sponsored by the NIH, National Institute on Aging (Grant NIA U01AG009740) and is conducted by the University of Michigan.

References

- Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011; 7:270–279.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed.. Washington, DC: Author; 1994.
- Anderson JW, Schmitter-Edgecombe M. Mild cognitive impairment and feeling-of-knowing in episodic memory. *Journal of Clinical and Experimental Neuropsychology*. 2010; 32:505–514. [PubMed: 19821173]
- Bartrés-Faz D, Clemente IC, Valveny JN, López-Alomar A, Sánchez-Aldeguer J, López-Guillén A, Moral P. APOE and APOC1 genetic polymorphisms in age-associated memory impairment. *Neurogenetics*. 2001; 3:215–219. [PubMed: 11714102]
- Bhalla RK, Butters MA, Becker JT, Houck PR, Snitz BE, Lopez OL, Reynolds CF. Patterns of mild cognitive impairment after treatment of depression in the elderly. *The American Journal of Geriatric Psychiatry*. 2009; 17:308–316. [PubMed: 19307859]
- Bizzozero I, Lucchelli F, Saetti MC, Spinnler H. Mild cognitive impairment does entail retrograde amnesia for public events. *Journal of Clinical and Experimental Neuropsychology*. 2009; 31:48–56. [PubMed: 18608681]
- Brainerd CJ, Reyna VF, Petersen RC, Smith GE, Taub ES. Is the Apolipoprotein E genotype a biomarker for mild cognitive impairment? Findings from a nationally representative study. *Neuropsychology*. 2011; 25:679–689. [PubMed: 21728427]
- Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Reiman EM. Longitudinal modeling of age-related memory decline and the APOE ε4 effect. *The New England Journal of Medicine*. 2009; 361:255–263. [PubMed: 19605830]
- Collie A, Maruff P, Currie J. Behavioral characterization of mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*. 2002; 24:720–733. [PubMed: 12424647]
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GA, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993; 261:921–923. [PubMed: 8346443]
- Devanand DP, Pelton GH, Zamora D, Liu X, Tabert MH, Goodkind M, Mayeux R. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Archives of Neurology*. 2005; 62:975–980. [PubMed: 15956169]
- Fisher GG, Franks MM, Plassman BL, Brown SL, Potter GG, Llewellyn D, Langa KM. Caring for individuals with dementia and cognitive impairment, not dementia: Findings from the Aging, Demographics, and Memory Study. *Journal of the American Geriatrics Society*. 2011; 59:488–494. [PubMed: 21391939]
- Hayden KM, Zandi PP, West NA, Tschanz JT, Norton MC, Corcoran C, Welsh-Bohmer KA. Effects of family history and Apolipoprotein E epsilon 4 status on cognitive decline in the absence of Alzheimer dementia: The Cache County study. *Archives of Neurology*. 2009; 66:1378–1383. [PubMed: 19901170]
- Henderson AS, Eastel S, Jorm AF, Mackinnon AJ, Korten AE, Christensen H, Jacomb PA. Apolipoprotein E allele ε4, dementia, and cognitive decline in a population sample. *The Lancet*. 1995; 346:1387–1390.

- Heun R, Gühne U, Luck T, Angermeyer MC, Ueberham U, Potluri R, Riedel-Heller SG. Apolipoprotein E allele 4 is not a sufficient or a necessary predictor of the development of mild cognitive impairment. *European Psychiatry*. 2010; 25:15–18. [PubMed: 19560323]
- Johnson SC, Schmitz TW, Asthana S, Gluck MA, Myers C. Associative learning over trials activates the hippocampus in healthy elderly but not mild cognitive impairment. *Aging, Neuropsychology, and Cognition*. 2008; 15:129–145.
- Langa KM, Plassman B, Wallace R, Herzog AR, Heeringa S, Ofstedal MB, Willis R. The Aging, Demographics and Memory Study: Study design and methods. *Neuroepidemiology*. 2005; 25:181–191. [PubMed: 16103729]
- Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer disease dementia. *Archives of Neurology*. 2012; 69:700–708. [PubMed: 22312163]
- Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Solfrizzi V. Current epidemiology of mild cognitive impairment and other predementia syndromes. *The American Journal of Geriatric Psychiatry*. 2005; 13:633–644. [PubMed: 16085779]
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*. 2004; 256:183–194. [PubMed: 15324362]
- Petersen RC. Mild cognitive impairment. *The New England Journal of Medicine*. 2011; 364:2227–2234. [PubMed: 21651394]
- Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, Rocca WA. Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic study of aging. *Neurology*. 2010; 75:889–897. [PubMed: 20820000]
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: Early detection of dementia. Mild cognitive impairment: An evidence-based review [Report of the Quality Standards Subcommittee of the American Academy of Neurology]. *Neurology*. 2001; 56:1133–1142. [PubMed: 11342677]
- Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Wallace RB. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*. 2007; 29:125–132. [PubMed: 17975326]
- Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Wallace RB. Prevalence of cognitive impairment without dementia in the United States. *Annals of Internal Medicine*. 2008; 148:427–434. [PubMed: 18347351]
- Plassman BL, Langa KM, McCammon RJ, Fisher GG, Potter GG, Burke JR, Wallace RB. Incidence of dementia and cognitive impairment, not dementia in the United States. *Annals of Neurology*. 2011; 70:418–426. [PubMed: 21425187]
- Schmitter-Edgecombe M, Sanders C. Task switching in mild cognitive impairment: Switch and nonswitch costs. *Journal of the International Neuropsychological Society*. 2009; 15:103–111. [PubMed: 19128533]
- Schmitter-Edgecombe M, Woo E, Greeley DR. Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology*. 2009; 23:168–177. [PubMed: 19254090]
- Seidenberg M, Guidotti L, Nielson KA, Woodard JL, Durgerian S, Zhang Q, Rao SM. Semantic knowledge for famous names in mild cognitive impairment. *Journal of the International Neuropsychological Society*. 2009; 15:9–18. [PubMed: 19128524]
- Serra L, Bozzali M, Cercignani M, Perri R, Fadda L, Caltagirone C, Carlesimo GA. Recollection and familiarity in amnesic mild cognitive impairment. *Neuropsychology*. 2010; 24:316–326. [PubMed: 20438209]
- Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology and Aging*. 2004; 19:592–600. [PubMed: 15584785]
- Smith G. Is mild cognitive impairment bridging the gap between normal aging and Alzheimer's disease? *Journal of Neural Transmission: Supplement*. 2002; 62:97–104. [PubMed: 12456055]
- Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: High avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer's disease. *Proceedings of the National Academy of Science*. 1993; 90:1977–1981.

- Summers MJ, Saunders NLJ. Neuropsychological measures predict decline to Alzheimer's dementia from mild cognitive impairment. *Neuropsychology*. 2012; 26:498–508. [PubMed: 22612573]
- Traykov L, Rigaud AS, Baudic S, Smaghe A, Boller F, Forette F. Apolipoprotein E epsilon 4 allele frequency in demented and cognitively impaired patients with and without cerebrovascular disease. *Journal of Neurological Science*. 2002; 203–204:177–181.
- University of Michigan, Institute for Social Research, & The United States Department of Health and Human Services, National Institutes of Health, National Institute on Aging. Health and retirement study. Ann Arbor, MI: Author; 2011. [Public use dataset]
- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Petersen RC. Mild cognitive impairment: Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*. 2004; 256:240–246. [PubMed: 15324367]
- Woodard JL, Seidenberg M, Nielson KA, Antuono P, Guidotti L, Durgerian S, Rao SM. Semantic memory activation in amnesic mild cognitive impairment. *Brain: A Journal of Neurology*. 2009; 132:2068–2078. [PubMed: 19515831]
- Zill P, Engel R, Hampel H, Behrens S, Bürger K, Padberg F, Bondy B. Polymorphisms in the apolipoprotein E (APOE) gene in gerontopsychiatric patients. *European Archives of Psychiatry and Clinical Neuroscience*. 2001; 251:24–28. [PubMed: 11315514]

Table 1

Composition of the Subject Samples in the Four Waves of the ADAMS

Diagnostic group	Testing wave			
	A	B	C	D
HC	307	59	158	117
CIND	241	136	110	80
D	308	57	47	20

Note. HC = healthy control; CIND = cognitive impairment without dementia; and D = dementia. These values are a combination of incident and prevalent diagnoses.

Table 2

Proportion of $\epsilon 4$ Carriers and Number of Transitions For Each Type of Diagnostic Transition Involving Healthy Control Subjects

Statistic	Diagnostic transition			
	HC → HC	HC → MCI	HC → VSCI	HC → AOCI
$\epsilon 4$ carriers	.22	.58	.08	.30
Number of cases ^a	165	26	13	64

Note. HC = healthy control; MCI = mild cognitive impairment; VSCI = cognitive impairment secondary to vascular disease or stroke; and AOCI = all other forms of cognitive impairment without dementia.

^aNumbers of carriers + noncarriers of $\epsilon 4$.

Table 3

Multinomial Logistic Regression of APOE Prediction of HC → CIND Longitudinal Transitions

Predictors	Statistic		
	OR	95% CI	<i>p</i>
Age	.39	.96–1.08	.53
HC → MCI	6.19	.01–.56	.01
HC → AOCI	2.25	.02–1.64	.13
HC → HC	1.23	.04–2.46	.27

Note. HC = healthy control; CIND = cognitive impairment without dementia; D = dementia; MCI = mild cognitive impairment; VSCI = cognitive impairment without dementia due to vascular disease or stroke; AOCI = all other forms of cognitive impairment without dementia; OR = odds ratio; CI = confidence interval; and *p* = probability value. HC → VSCI was the reference transition group for this analysis.

Proportion of ε4 Carriers and Number of Transitions for Each Type of Diagnostic Transition Involving Subjects Who Were Cognitively Impaired but not Demented

Table 4

First diagnosis	Second diagnosis				
	MCI	VSCI	AOCI	AD1	AD2
MCI ^a					
ε4	.33		.21	.39	.33
N	44		18	23	15
VSCI ^a					
ε4		.23			.18
N		35			11
AOCI ^a					
ε4	.33	.21		.33	.42
N	12	75		16	12

Note. MCI = mild cognitive impairment; VSCI = cognitive impairment secondary to vascular disease or stroke; AOCI = all other forms of cognitive impairment without dementia; AD1 = probable Alzheimer's dementia; AD2 = possible Alzheimer's dementia; and AOD = all other dementias.

^aThe total number of cognitively impaired but not demented (CIND) individuals (MCI, VSCI, and AOCI) who participated in at least two testing waves was 136 (see Table 1). The total number of transitions for CIND participants in rows three, six, and nine exceeds 136 because individuals who participated in three testing waves contributed two transitions (one for each consecutive pair of diagnoses), and individuals who participated in all four testing waves contributed three transitions (one for each consecutive pair of diagnoses).