Article

Effect of Alzheimer's Disease Risk Genes on Trajectories of Cognitive Function in the Cardiovascular Health Study

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Objective: The trajectory of cognitive decline in patients with late-onset Alzheimer's disease varies widely. Genetic variations in *CLU*, *PICALM*, and *CR1* are associated with Alzheimer's disease, but it is unknown whether they exert their effects by altering cognitive trajectory in elderly individuals at risk for the disease.

Method: The authors developed a Bayesian model to fit cognitive trajectories in a cohort of elderly subjects and test for genetic effects. They first validated the model's ability to detect the previously established effects of *APOE* ε4 alleles on age at cognitive decline and of psychosis on the rate of cognitive decline in 802 subjects from the Cardiovascular Health Cognition Study who did not have dementia at study entry and developed incident dementia during follow-up. The authors then evaluated the effects of *CLU*, *PICALM*, and *CR1* on age and rate of decline in 1,831 subjects who did not have dementia at study entry and then did or did not develop incident dementia by study's end.

Results: The model generated robust fits to the observed cognitive trajectory data, and validation analysis supported the model's utility. *CLU* and *CR1* were associated with more rapid cognitive decline. *PICALM* was associated with an earlier age at midpoint of cognitive decline. Associations remained after accounting for the effects of *APOE* and demographic factors.

Conclusions: Evaluation of cognitive trajectories provides a powerful approach to dissecting genetic effects on the processes leading to cognitive deterioration and Alzheimer's disease.

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Some progress has been made in determining the genetic architecture of late-onset Alzheimer's disease. The association of late-onset Alzheimer's disease with the ε4 variant of apolipoprotein E (*APOE*) is well established (1). More recently, replicated genome-wide associations of late-onset Alzheimer's disease with genetic variation in *CLU*, *CR1*, and *PICALM* have been reported (2, 3). Ultimately, these detected associations must be related to specific neurobiological processes leading to Alzheimer's disease in order for them to translate into meaningful clinical predictors or therapies. Our current understanding of the neurobiology of Alzheimer's disease suggests that disease causation is dependent on a sustained period of pathological accumulation of β-amyloid protein (see reference 4 for a review). The initial accumulation of β-amyloid occurs prior to clinically detectable cognitive impairment, setting off downstream events, including generation of hyperphosphorylated tau, gray matter volume reductions, and synapse loss (5, 6). It is measures of these downstream effectors that appear to change most rapidly during phases of disease characterized by more rapid cognitive decline (4).

Conceptually, genetic variation may thus be linked to cognitive change in Alzheimer's disease in any of several ways. Genetic variations that increase the production of pathological β-amyloid protein, including mutations and duplications of the β-amyloid precursor protein gene (*APP*), and mutations in presenilin 1 and 2 (*PSEN1* and *PSEN2*), all lead to an earlier age at disease presentation (7). Similarly, *APOE* ε4 alleles, which reduce β-amyloid clearance (8), are associated with earlier age at disease presentation (9). Alternatively, one might postulate that genetic variation whose primary role is to interact with the generated or accumulated β-amyloid so as to modify its downstream effects would influence the rate of overt cognitive decline. To date, no such genetic variations have been definitively identified. However, psychotic symptoms in Alzheimer's patients define a genetically determined behavioral phenotype (10) that is strongly associated with a more rapid rate of cognitive decline (11–13).

It would therefore be useful for interpreting the nature of a genetic variation's relationship to Alzheimer's disease risk to be able to measure cognitive trajectories in a way that would allow testing of genetic associations with both age and rate of cognitive decline. Intuitively, it can be seen that an individual traversing the complete course of Alzheimer's disease will have a period prior to disease onset of relatively stable cognitive test performance, followed by a period of declining performance, until reaching a period of scores asymptotically approaching a minimum score. Such a trajectory is readily approximated by a four-parameter logistic curve, but several obstacles exist in practice. These include the fact that few longitudinal data

sets gather complete information on all stages of the cognitive trajectory for individual Alzheimer's patients, although the picture may be complete for the group as a whole. Additionally, it is not uncommon for elderly individuals to have poor cognitive test performance in a given session as a result of factors unrelated to Alzheimer's disease, such as concomitant illness, poor sleep, or medication effects. Trajectory modeling must not be overly sensitive to these outlier values.

To address these issues, we developed a novel Bayesian implementation of a hierarchical nonlinear model using a four-parameter logistic curve. Bayesian hierarchical models have the characteristics of borrowing strength and appropriately modeling multiple sources of error. This means that subjects with fewer data points automatically contribute less to the analysis; that prediction for each subject is based on a combination of whatever information is available for that subject weighted with information from other, similar subjects; and that the degree of uncertainty about parameters is not underestimated (as occurs in two-stage methods that treat the parameters fitted to individual subject curves as having no uncertainty [14]). We evaluated our model's ability to fit trajectories reflecting cognitive deterioration and validated its ability to detect the previously established effects of *APOE* genotype on age at onset of cognitive decline and the effect of psychosis on rate of cognitive decline. We then implemented our approach to examine the effects of single-nucleotide polymorphisms (SNPs) in *CLU, CR1,* and *PICALM* on age at midpoint of cognitive decline and rate of cognitive decline in a large cohort of elderly subjects.

TABLE 1. Demographic and Clinical Characteristics of the Validation and Implementation Cohorts

Variable[a]	Validation Cohort (N=802)		Implementation Cohort (N=1,831)	
	N	%	N	%
Sex				
Male	314	39.2	687	37.5
Female	488	60.8	1,144	62.5
Race				
Caucasian	593	73.9	1,831	100
Non-Caucasian	209	26.1	0	0.0
Education level				
No college	562	70.1	1,100	60.1
Some college	240	29.9	731	39.9
Psychosis status[b]				
Never	388	81.7		
Ever	87	18.3		
APOE ε4 carrier status				
Absent	559	69.7	1,407	76.8
Present	243	30.3	424	23.2
	Mean	SD	Mean	SD
Age at baseline (years)	73.8	5.2	71.7	4.7
Baseline 3MS score	88.6	7.1	92.9	5.6
Baseline DSST score	34.8	12.2	42.6	11.4

[a] 3MS=Modified Mini-Mental State Examination; DSST=Digit Symbol Substitution Test; *APOE*=apolipoprotein E. The age range was 65–95 years for the validation cohort and 65–92.9 years for the implementation cohort. The range for baseline 3MS score was 57–100 for the validation cohort and 45–100 for the implementation cohort, and the range for baseline DSST score was 0–83 for the validation cohort and 3–83 for the implementation cohort.
[b] Of the 802 subjects in the validation cohort, 327 were not assessed for psychosis.

Method

Subjects

Information on the methods of the Cardiovascular Health Study and the Cardiovascular Health Cognition Study has been published previously (15–17). For the validation cohort (Table 1), we analyzed data from participants who by the end of the main study in 1998 and 1999 had developed Alzheimer's disease (with or without comorbid vascular dementia) or had mild cognitive impairment and for whom at least four measurements were available from either the Modified Mini-Mental State Examination (3MS) (18) or the Digit Symbol Substitution Test (DSST) (19) and were thus suitable for trajectory modeling. For the implementation cohort (Table 1), we analyzed data from Caucasian patients who had progressed to Alzheimer's disease (with or without comorbid vascular dementia), had mild cognitive impairment, or had no diagnosis of a cognitive disorder at study endpoint; had at least four 3MS or DSST measurements; and were successfully genotyped for at least one of the SNPs in our genes of interest (20, 21). All participants provided written informed consent to participate in the study. Genetic analyses in this study included data only from participants who provided consent for their samples to be used in research on disorders other than cardiovascular diseases.

Assessments

Cognition was assessed with the 3MS, a measure of global cognition, and the DSST, a measure of attention, which were administered to participants annually. Psychosis was assessed with the Neuropsychiatric Inventory (22), which was completed in 1998 and 1999 in a subset of validation cohort subjects. Classification as ever or never psychotic was done as previously described (16).

Statistical Analysis

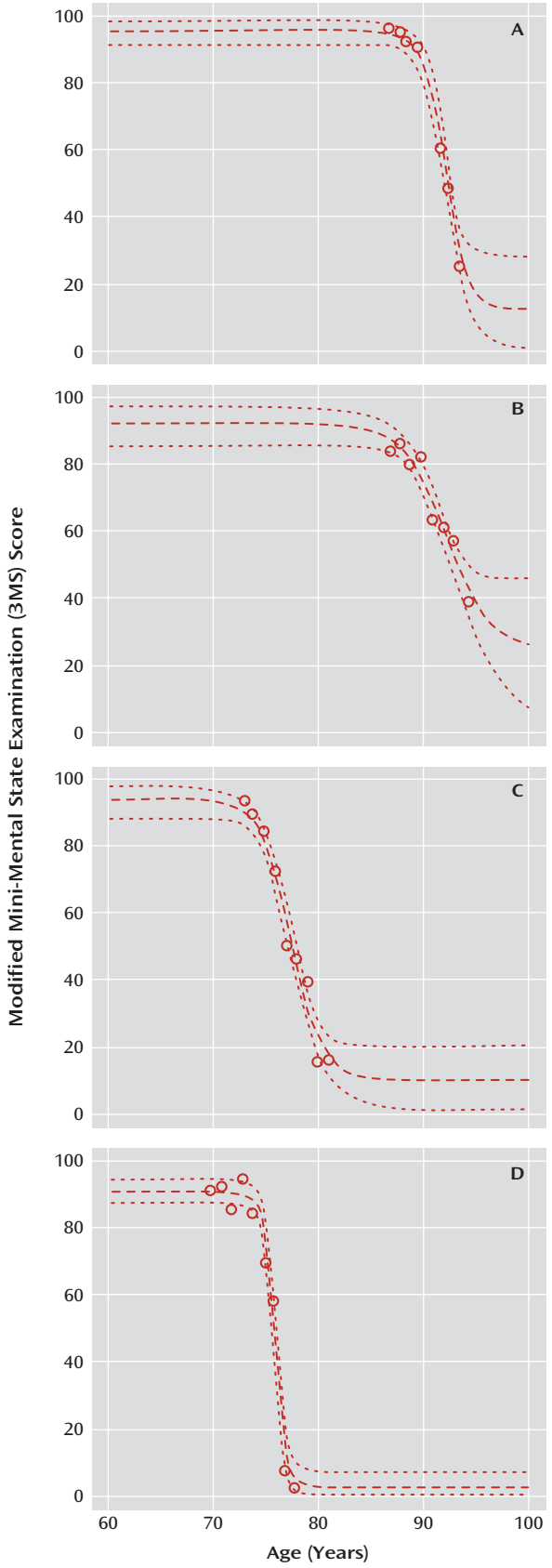
We fit the data to a four-parameter logistic curve in the form

$$E(Y_{it}) = A_i + \frac{B_i - A_i}{1 + \exp\left(\frac{t - M_i}{R_i}\right)}$$

,

where t is the time (age) at measurement, $E(Y_{it})$ is the mean outcome at time t for subject i, A_i is the asymptotic outcome value for subject i at lower ages, B_i is the asymptotic outcome value for subject i at higher ages, M_i is the age at midpoint of cognitive decline—that is, the age at which the trajectory for subject i is halfway between A_i and B_i, or the age at which the fit cognitive score is halfway between the fit maximum and the fit minimum value for that subject. R_i is a measure of the rate of change from A_i to B_i. It can be interpreted as follows: for any given individual, the total change in outcome is $A_i - B_i$, and the time period over which the middle half of that change occurs—that is, the time from 1/4 to 3/4 of the total change—is $2.20(R_i)$. We explicitly modeled the effects of covariates on M and R by replacing the simple mean parameter with a linear combination of an intercept and the products of covariates with corresponding slope parameters. For A and B, we did not model covariate effects but allowed for differences between subjects by modeling the random effects. Effects of covariates are reported as the

FIGURE 1. Examples of Four Parameter Nonlinear Fits of Individual Modified Mini-Mental State Examination Score Trajectories[a]



posterior properties of the difference in the mean of each parameter for a change in level of the covariate. Finally, it should be noted that summaries of the posterior distributions in Bayesian analysis take the place of the p values and confidence intervals of classical statistics. Assuming that we are using an appropriate model and prior distributions, the probability that a parameter is inside its credible interval is 95%.

We tested the effects of *APOE* ε4 status, psychosis status (ever or never psychotic), and individual SNPs that have been associated with Alzheimer's disease risk (*CLU* [rs11136000], *CR1* [rs3818361], and *PICALM* [rs3851179, rs541458] [2, 3]) on *M* and *R*. For *APOE* ε4, we coded the presence or absence of at least one ε4 allele. SNPs were tested individually, examining additive effects of the allele identified as the risk allele in the genome-wide association studies (GWAS). Analysis of *APOE* ε4 included the demographic factors age, sex, education, and race as covariates. Analyses of the effects of psychosis status and of individual SNPs included *APOE* ε4 status, age, sex, education, and (as appropriate) race as covariates.

For additional methodological details, see the data supplement that accompanies the online edition of this article.

Results

Validation Cohort

The basic model, including the effects of demographic variables on 3MS and DSST trajectories (see Table S1 in the online data supplement), was fitted to the data from subjects in the validation cohort. Several 3MS trajectories are shown in Figure 1, along with the 95% credible (curvewise) intervals (CIs). Examples of fitted trajectories for the DSST, and in the face of occasional outlier test scores, are shown in Figure S1 in the online data supplement.

After adjusting for demographic covariates, the presence of an *APOE* ε4 allele was associated with a mean change of −3.36 years (95% CI=−4.58 to −2.16] in age at midpoint on the 3MS and a mean change of −2.26 years (95% CI=−3.41 to −0.92) in age at midpoint on the DSST, both in the predicted directions. In contrast, *APOE* ε4 carriers showed no change in rate of decline on the 3MS (mean=−0.14, 95% CI=−0.46 to 0.16]) or the DSST (mean=−0.14, 95% CI=−0.77 to 0.47). Analysis of the effect of psychosis similarly revealed changes in the predicted directions, with a more rapid rate of decline on the 3MS (mean=−0.42, 95% CI=−0.83 to −0.03) and on the DSST

[a] Each panel shows the trajectory of the observed Modified Mini-Mental State Examination scores over time for a particular subject (open circles). The dashed lines are the median posterior curves, and there is a 95% probability that the whole curve would fit inside the dotted lines. Panels A and B show trajectories for individuals with similar age at midpoint of cognitive decline but with different rates of decline. Panel C shows an example with earlier age at midpoint of decline. Panel D shows an example with both earlier age at midpoint of decline and more rapid decline. In all cases, it can be seen that in the presence of numerous observations—for example, in the falling middle portion of the trajectory—the model estimates the trajectory with good accuracy. In portions of trajectories with less information available (e.g., early and late phases in panel B), limits on the trajectories are set by the constrained maximum and minimum values, but the 95% credible intervals are appropriately wider.

TABLE 2. Effects of Genotype on the 3MS and DSST Age at Midpoint of Cognitive Decline (M) and Rate of Cognitive Decline (R) Parameters in the Implementation Cohort[a]

				3MS	
				M	
Gene, SNP	Minor Allele (Frequency)	Observed Risk Allele	GWAS Risk Allele	Mean	95% CI
CLU, rs11136000	T (40.4%)	T	C	−0.19	−1.17, 0.78
CR1, rs3818361	T (19.1%)	T	T	−0.44	−1.59, 0.71
PICALM, rs3851179	A (37.5%)	G	G	−0.49	−1.45, 0.52
PICALM, rs541458	C (32.1%)	T	T	**−1.15**	−2.33, −0.13

[a] 3MS=Modified Mini-Mental State Examination; DSST=Digit Symbol Substitution Test; SNP=single-nucleotide polymorphism; GWAS=genome-wide association study. Values shown are the posterior mean and 95% credible intervals (CIs) for the change in parameters for the presence of each additional copy of the SNP risk allele. All analyses include *APOE* ε4 genotype and demographic factors in the model. Boldface values are significant.

(mean=−1.06, 95% CI=−1.98 to −0.20). The effect of psychosis resulted in the middle 50% of decline taking a mean of 1.83 fewer years on the 3MS and 2.33 fewer years on the DSST. In addition, analysis of psychosis revealed a change in age at midpoint for the 3MS (mean=−3.74, 95% CI=−5.51 to −2.03]), but not on the DSST (mean=−1.70, 95% CI=−3.67 to 0.42).

Implementation Cohort

We next undertook to examine the effects of SNPs in *CLU, CR1,* and *PICALM* on cognitive trajectory in the larger group of subjects, including individuals with and without incident cognitive impairment (Table 2 and Figure 2). *CLU* SNP rs11136000 was associated with more rapid cognitive decline on the 3MS and nearly reached significance for the DSST. *CR1* SNP rs3818361 was associated with more rapid cognitive decline on the DSST. *PICALM* SNP rs3851179 was not associated with change in either parameter for the 3MS or the DSST. *PICALM* SNP rs541458 was associated with earlier age at midpoint of decline on the 3MS, but not with rate of decline, and it was not associated with either parameter for the DSST. The associations of *CLU* SNP rs11136000 and *CR1* SNP rs3818361 with rate of decline on the DSST did not differ between individuals who carried an *APOE* ε4 allele and those who did not (difference in R between *APOE* ε4 positive and negative subjects for *CLU* SNP rs11136000: mean=0.07, 95% CI=−0.66 to 0.88; for *CR1* SNP rs3818361: mean=0.37, 95% CI=−0.57 to 1.40]). The association of *PICALM* SNP rs541458 with midpoint time on the 3MS did not differ between individuals who carried an APOE ε4 allele and those who did not (difference between APOE ε4 positive and negative subjects for *PICALM* SNP rs541458: mean=−1.32, 95% CI=−3.36 to 0.86). The mean trajectories for *CR1*, *CLU*, and *PICALM* risk allele carriers are shown in Figure 3.

To address whether one or more of the associations of the four Alzheimer's disease risk SNPs (rs11136000, rs3818361, rs3851179, and rs541458) might be a false positive due to multiple testing, we evaluated these SNPs concurrently in additive models for 3MS and DSST trajectory. We again included APOE genotype, age, sex, and education in the models. The approach of evaluating all SNPs concurrently is to widen the 95% credible intervals, creating a more conservative estimate of significance. We found that the significant association of *CR1* SNP rs3818361with DSST rate of decline persisted (mean=−0.61, 95% CI=−1.11 to −0.12), and the nearly significant association of *CLU* SNP rs11136000 with DSST rate of decline now reached significance (mean=−0.50, 95% CI=−0.86 to −0.03)]. These observed effects are strong, equal to 0.83–1.0 of the standard deviation of the random effect for the subject-to-subject variation in DSST rate in our additive model (estimated at 0.60). Significant associations with 3MS did not persist. It should be noted that evaluating the associations with *M* and *R* for a given measure can represent a single two-dimensional test, not two tests, of association with trajectory. We therefore confirmed that the M=0, R=0 origin is not within the 95% posterior ellipsoid for DSST for *CR1* SNP rs3818361and *CLU* SNP rs11136000.

Discussion

We found that a nonlinear model implemented with a Bayesian hierarchical analytic approach generated robust fits to the observed cognitive trajectories of elderly subjects. Validating our approach, *APOE* ε4 alleles were associated with a lower age at midpoint of cognitive decline, and psychosis was associated with a higher rate of cognitive decline. We then implemented our model to test whether SNPs associated with an increased risk for late-onset Alzheimer's disease alter cognitive trajectory after accounting for the effects of *APOE* and demographic factors. We found that rs11136000 in *CLU* and rs3818361 in *CR1* were associated with more rapid cognitive decline. rs541458 in *PICALM* was associated with an earlier age at midpoint of cognitive decline, although this latter association did not persist in an additive model designed to correct, in part, for multiple testing. For all SNPs except *CLU* SNP rs11136000, the allele conferring an adverse cognitive trajectory was the same as that associated with Alzheimer's disease in previous GWAS.

We used a nonlinear model that allowed for censoring at the maximum and minimum values. This choice was

TABLE 2. (*Continued*)

3MS		DSST			
R		M		R	
Mean	95% CI	Mean	95% CI	Mean	95% CI
−0.16	−0.29, −0.01	−0.07	−1.00, 0.90	−0.42	−0.89, 0.00
−0.13	−0.36, 0.11	−0.11	−1.13, 0.83	**−0.64**	−1.09, −0.15
−0.01	−0.22, 0.18	−0.77	−1.62, 0.13	−0.07	−0.50, 0.38
−0.18	−0.46, 0.09	−0.73	−1.61, 0.11	0.00	−0.51, 0.42

based on a common property of cognitive tests, which often have defined maximum and minimum scores. As a result, prior to disease onset individuals may sustain maximal scores, while in end-stage disease sustained minimal scores may be present. Such observations cannot be fitted adequately with a trajectory derived from a linear or quadratic model, although multiple linear fits (e.g., as applied in change-point models), may be used to approximate subsets of points within a longitudinal cognitive trajectory (23). Other psychometric properties of cognitive tests also contribute to nonlinearity. Many tests are admixtures of easier, moderately difficult, and difficult questions, not necessarily in equal proportion. As a consequence, scores may change little during a given phase of cognitive decline, for example, during early illness if there are few difficult questions. Alternatively, scores may show greater change during another phase, such as moderate disease, if there are proportionally more questions of moderate difficulty. Many global cognitive tests, including the 3MS, follow just such a pattern (24). In contrast, the DSST requires repeating the same cognitive function and is scored based on how many times it is successfully completed within a timed interval. However, the overall difficulty of the task results in nonlinearity in moderate to severely impaired individuals, supporting the use of a nonlinear model to fit these data (25). Determining detection of SNP effects would be enhanced by the use of cognitive measurements that demonstrate more consistent linear measurement properties across levels of disease severity.

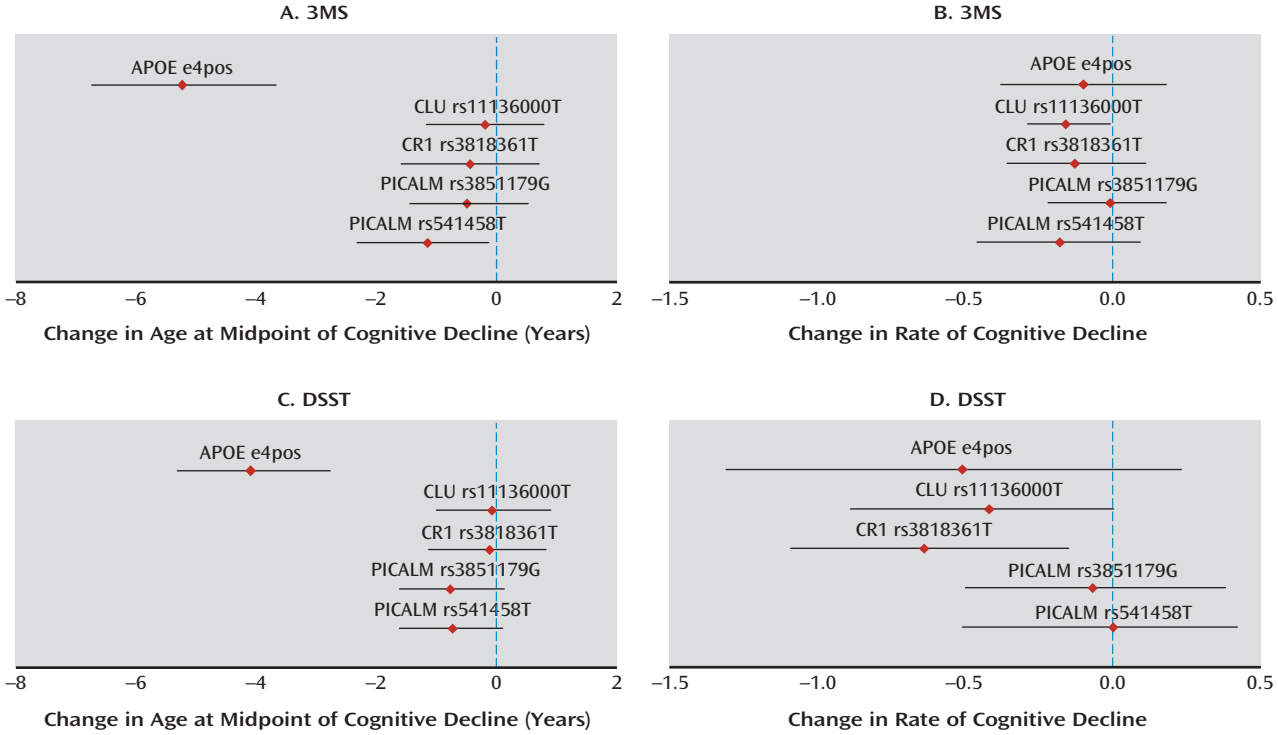
We found that rs11136000 in *CLU* was associated with more rapid cognitive decline, although the risk for more rapid decline was conferred by the allele opposite to that previously associated with Alzheimer's disease (2, 3, 20, 26). Although rate of cognitive decline and presence of Alzheimer's disease are not identical, it seems unlikely that a causal allele would confer different directions of risk for these two outcomes. Several authors have argued that significant allelic association in opposing directions is statistically unlikely (27, 28) and probably reflects true association via one of several underlying mechanisms (27–30). *CLU* encodes the protein clusterin, which is expressed at elevated levels in the brains of individuals with Alzheimer's disease and can serve to prevent fibrillization of β-amyloid and inhibit complement activation (31). In individuals with mild cognitive impairment and Alzheimer's disease, elevated plasma clusterin levels have been found to be correlated with more rapid cognitive decline, although plasma clusterin concentrations were not associated with genetic variants in *CLU*, including rs11136000 (32).

We found that rs3818361 in *CR1* was associated with more rapid cognitive decline. *CR1* is a complement receptor expressed in cerebral cortex. There is emerging evidence that the complement cascade contributes to targeting synapses for elimination during development and in neurodegeneration via astrocyte-mediated opsonization with the complement component 3 fragment, C3b (33). *CR1* supports clearance of opsonized targets by its high affinity for C3b (34). Recent evidence indicates that the reported associations of genetic variation in *CR1* with Alzheimer's disease may arise from linkage disequilibrium between these variants and a low copy repeat that codes for a *CR1* isoform with an additional C3b binding site (35). It is not currently known whether *CR1* contributes to synapse elimination in Alzheimer's disease.

Finally, we found that rs541458 in *PICALM* was associated with an earlier age at midpoint of cognitive decline, although it should be noted that this association did not persist in our additive model. *PICALM* encodes the phosphatidylinositol-binding clathrin assembly (Picalm) protein, an essential factor in clathrin-mediated endocytosis (36). Recent evidence indicates that Picalm is primarily expressed in vascular endothelial cells in human brain (37), where it may affect the clearance of β-amyloid from brain. For example, rs541458 in *PICALM* is significantly associated with CSF levels of β-amyloid 42 (38). This interpretation would be congruent with a mechanism by which variants that result in overproduction or overaccumulation of β-amyloid most strongly affect age at cognitive decline.

These associations of *CLU, CR1,* and *PICALM* were detected in models that accounted for demographic variables and the effect of *APOE* ε4. This finding stands in contrast to a recent analysis of several cohorts, including the Cardiovascular Health Study cohort, which found that rs11136000 in *CLU* and rs3851179 in *PICALM* did not

FIGURE 2. Effect of Genetic Variation on Age at Midpoint of Cognitive Decline and Rate of Cognitive Decline[a]



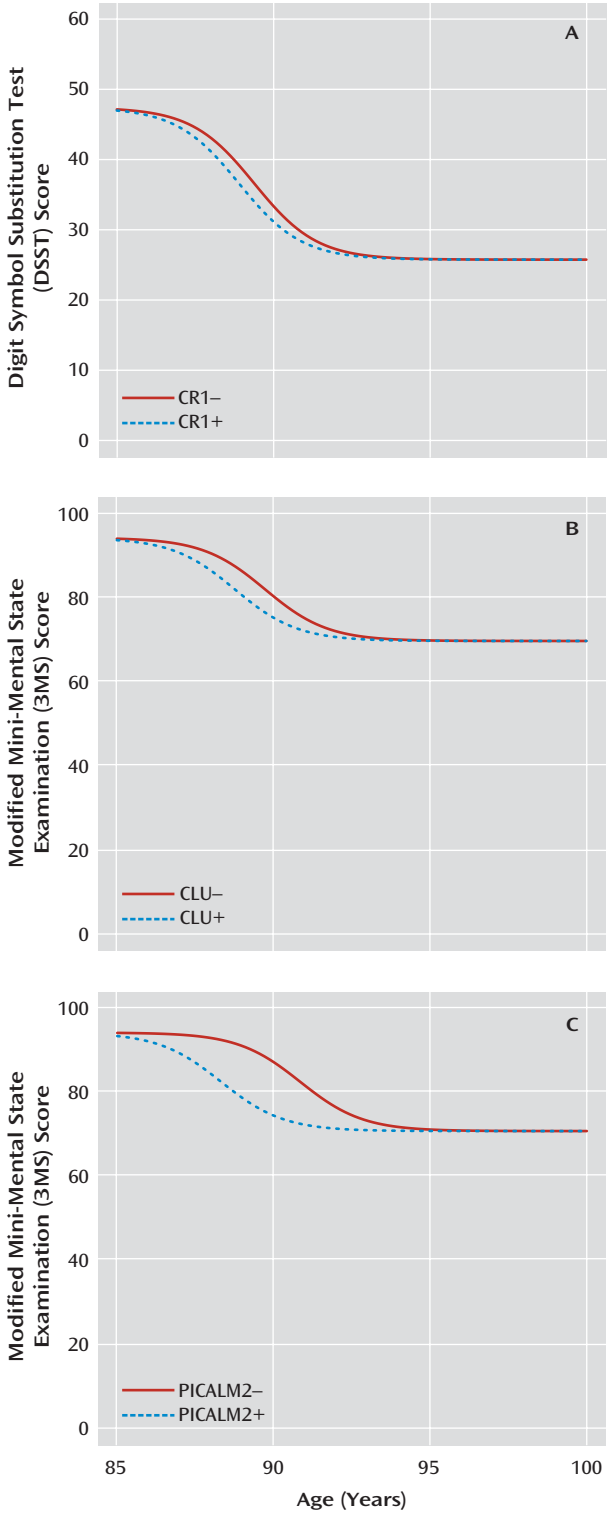
[a] 3MS=Modified Mini-Mental State Examination; DSST=Digit Symbol Substitution Test; APOE e4pos=apolipoprotein E ε4-positive. The graphs plot the mean estimates for change in each parameter associated with the genetic variant, along with 95% credible intervals (horizontal lines). The values plotted are the posterior mean for the change in parameters for the presence of each additional copy of the single-nucleotide polymorphism (SNP) risk allele. All analyses include demographic variables in the model, and for the individual SNPs, analyses also include *APOE* ε4 genotype in the model. Variants for which the horizontal line does not touch the vertical dashed line are significantly associated. The large effect of *APOE* ε4 on age at midpoint of decline (panels A and C) is evident for both cognitive measures. A smaller effect of *PICALM* SNP rs541458 is seen for the 3MS (panel A). Effects on rate of decline are present for variants in *CLU* on the 3MS and DSST (panels B and D) and for *CR1* on the DSST (panel D).

add to the prediction of Alzheimer's disease onset beyond demographic and *APOE* effects (20). This may indicate that there is increased power available in using a cognitive trajectory, rather than a dichotomous diagnosis, to identify SNP associations with longitudinal outcome in subjects at risk for Alzheimer's disease. Of interest, we found that genetic variation in *PICALM* was associated with lower age at midpoint of decline in models that included *APOE*. This is somewhat surprising given recent evidence that *APOE* and *PICALM* genotypes are correlated, resulting in substantial reduction in the association of *PICALM* SNPs with Alzheimer's disease risk after accounting for *APOE* status (26). Unlike *PICALM*, associations of *CLU* and *CR1* with Alzheimer's disease risk did not display confounding with *APOE* genotype (26); thus, it is not surprising that they demonstrated detectable effects after controlling for *APOE* ε4 alleles.

We used a Bayesian approach to fit cognitive trajectories. The principal advantage of Bayesian methods over classical (e.g., mixed-model) analyses is that calculation of posterior distributions is typically straightforward even for complex models. However, Bayesian methods are often computer intensive, creating a potential limitation of our approach; it may not be practical for sequential screening of large numbers of SNPs. Another potential limitation in any model fitting is inadequate model convergence. In Bayesian hierarchical models, completely uninformative prior distributions may result in invalid (improper) posterior distributions. The standard solution to this problem is to incorporate a small amount of prior information to create "weakly informative" prior distributions. In clinical settings such as the ones we modeled, this is simple and effective, because we can put reasonable limits on parameters—for example, we know that for our subjects the age at midpoint of cognitive decline is between 30 and 130 years. The utility of these weak prior distributions can be seen in the fidelity of our trajectory fits to the observed data. Finally, an important modification to our Bayesian implementation was the use of a t-distribution rather than a normal distribution to model deviations of measurements from trajectory means. This approach substantially reduced the effects of occasional outlier values, a not uncommon occurrence in our observed data (see Figure S1 in the online data supplement).

Other possible limitations to our findings should be considered. We selected for testing a limited number of

FIGURE 3. Cognitive Trajectories in Individuals With and Without *CR1*, *CLU*, and *PICALM* Risk Alleles[a]



[a] Each panel shows the mean trajectory for individuals carrying zero (–) or two (+) copies of the risk allele.

SNPs based on replicated evidence of genome-wide significant association in GWAS. Other SNPs in these genes, which did not themselves reach genome-wide significant association with Alzheimer's disease risk, may nevertheless be associated with trajectory of cognitive decline. The same may be true for genetic variation in other genes, including a number of SNPs that have been identified as demonstrating genome-wide significant association in GWAS of Alzheimer's disease. Determining a trajectory requires a minimum number of observed measurements. We chose as inclusion criteria the presence of four measurements on the 3MS and DSST tests. This requirement may have excluded some individuals with more rapid decline, who thus did not complete four tests. Similarly, the individuals who participated in the Cardiovascular Health Cognition Study and were thus available for this analysis were a nonrandom subset of all Cardiovascular Health Study participants, healthier and younger than the parent cohort. Thus, our findings may not fully generalize to the elderly population.

In summary, we developed a Bayesian approach to address several goals for the analysis of cognitive trajectories in aging subjects, including the ability to fit individual as well as group cognitive trajectories; make meaningful descriptive statements about the pattern of change and the variability in that pattern across subjects; develop credible regions for the resultant curves, which include appropriate prediction limits; and evaluate the specific effects of covariates, including genetic covariates, by estimating their impact on trajectory parameters. We validated this approach with two established predictors of different cognitive trajectory parameters, the presence of APOE ε4 alleles and the development of psychosis. We then used our approach to detect effects of recently identified Alzheimer's risk alleles on cognitive trajectories. Replication of this approach using other data sets is warranted.

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