Supplemental Methods and Results

Supplemental Methods

Cardiovascular Health Study (CHS) and CHS Cognition Study Overview

The CHS was designed to investigate stroke and cardiovascular disease risk factors in a randomly-sampled population-based cohort of individuals over 65 years of age. The CHS Cognition Study included subjects from the CHS who were additionally screened and evaluated for cognitive disorders. Information on the CHS and CHS Cognition Study methods have been published previously (15-17). Institutional review board approval was obtained at each University site and all participants provided written informed consent to participate in the study. Additional written consent was obtained from some subjects to use their genetic material. Genetic analyses in this paper utilize data only from participants who provided consent for their samples to be used in research on disorders other than cardiovascular diseases.

Subjects

In 1989, 5,201 participants were recruited at four sites in the United States (Forsyth Co., NC; Washington Co., MD; Sacramento Co., CA; and Pittsburgh, PA). An additional African American (AA) Cohort of 687 participants was recruited in 1992. Of the total 5,887 participants, 3,608 were recruited into the ancillary CHS Cognition Study (15). Dementia was evaluated using neuropsychological tests, neurological examinations, medical records, physician questionnaires, and proxy/informant interviews. Dementia was classified by neurologist/psychiatrist committee review using National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD and Alzheimer's Disease Diagnostic and Treatment Center's State of California criteria for Vascular Dementia(15).

Dementia was present at study entry in 164 subjects, leaving 3,444 individuals without dementia at study entry from which we selected our validation and implementation cohorts. Four hundred eighty of these individuals developed incident dementia: 69% AD, 16% AD with comorbid Vascular Dementia, 11% Vascular Dementia, and 4% other dementias. Another 577 individuals were classified as Mild Cognitive Impairment (15). For the validation cohort, we analyzed data from 802 subjects who by the end of the main study in 1998-9 had either developed AD (with or without comorbid Vascular Dementia) or had Mild Cognitive Impairment and who had at least four Modified Mini-Mental Status Examination (3MS) or Digit Symbol Substitution Test (DSST) measurements and were thus suitable for trajectory modeling (Table 1). For the implementation cohort, we analyzed data from subjects who had either progressed to AD (with or without comorbid Vascular Dementia), had Mild Cognitive Impairment, or were without a cognitive disorder diagnosis at study endpoint, had at least four 3MS or DSST measurements, had provided consent for genetic testing for non-cerebrovascular disease studies, and were successfully genotyped for at least one of the SNPs in our genes of interest. Because the GWA for these SNPs were detected in samples predominantly of European ancestry, and because we identified significant differences in minor allele frequencies at these loci between the Caucasian and non-Caucasian subjects in our cohort (unpublished observations), we further restricted these analyses to Caucasian subjects, resulting in a final N of 1,831 (Table 1).

Assessments

Cognition. The Modified Mini-Mental Status Examination (3MS) (20), a measure of global cognition, and the Digit Symbol Substitution Test (DSST), a measure of attention (21), were administered to participants annually from 1990-1 through 1998-9 in the original cohort and from 1992-3 through 1998-9 in the AA Cohort. Percentiles of the 1831 subjects in the Implementation Cohort completing annual follow-up testing are shown in Table S2. More than 70% of subjects had at least 8 years of annual testing.

Psychosis. Of the 802 subjects in the validation cohort, 475 (Table 1) completed an additional neuropsychiatric evaluation in 1998-9 that included the Neuropsychiatric Inventory (NPI) (22) administered by raters trained in its use. The NPI is a structured interview of an informant in close contact with the subject on various neuropsychiatric domains including delusions and hallucinations. Delusions were defined as a fixed false belief. Hallucinations were defined as perceptions with no basis in reality. Informants were asked if the subject experienced any delusions/hallucinations in the month prior to the interview or since the onset of memory problems. For our analyses, subjects were classified as Ever Psychotic if informants answered yes to any NPI question regarding delusions and/or hallucinations. Subjects were classified as Never Psychotic if informants answered no to these questions. For two subjects, information on symptoms since the onset of memory problems was missing, but other items were negative, and they were classified as Never Psychotic.

Genotyping

Genotyping methods, including the platform, statistics, and quality control were described previously (18;19).

Statistical Analysis

All of the Bayesian analyses were performed using R (http://www.r-project.org) statistical software and the WinBugs system (http://www.mrc-bsu.cam.ac.uk/bugs/). The analyses also used the R2WinBUGS add-on package in R, as well as the rube package developed by us in parallel with these analyses. Code for performing these or similar analyses are available at http://www.stat.cmu.edu/~hseltman/TrajBUGS/". These analyses use a 2,000 iteration burn in and a 20,000 iteration run thinned to keep every 40th iteration.

We fit 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) of 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 small ages, B_i is the asymptotic outcome value for subject i at large ages, M_i is the age at midpoint of cognitive decline, that is the age at which the trajectory for subject i is half-way between A_i and B_i, i.e. 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. Parameters A, B and M have the advantages of simple clinical interpretation. R_i 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, i.e., the time from ¼ to ¾ of the total change, is 2.20(R_i).

We modeled the individual deviations of measurements from the trajectory mean as a t-distribution with a small degrees of freedom to minimize the effects of an occasional outcome far off the rest of the trajectory (outliers), e.g., due to a temporary illness and assume independence within a subject. We explicitly model the censoring at the ends of the scale. The models were verified with standard Bayesian tools including trace plots, Gelman's R-square, and autocorrelation plots. In addition residual plots and plots of data vs. predicted trajectories confirmed the adequacy of the models.

The hierarchical nature of the model utilized the clinically meaningful idea that any and all of the four logistic parameters may vary from subject to subject (random effects) and with changes in covariates. For M which is unrestricted in the range of its possible values, we used a normal distribution with mean and variance determined by weakly informative higher level distributions. For R we used a half normal distribution defined on all positive values. The use of informative

prior distributions that restrict the majority of the probability to the widest possible range of clinically plausible values ensured that the posterior distributions were proper probability distributions while also letting the data determine the values of the posterior distribution. Sensitivity analysis confirmed that our prior distributions were sufficiently weak as to have no observable effect on the inferences.

The prior distributions of the *A* and *B* parameters for the 3MS (which is on the 0 to 100 scale) and the DSST (which ranged from 0 to 90) were each set to 100 times a beta distribution. The beta family of distributions gives a flexible range of shapes for the subject-to-subject variability in the *A* and *B* parameters while requiring that all values are between 0 and 100. A technical problem arises with high posterior correlation of the two parameters of the beta distribution, usually called alpha and beta. We solved this problem by using the parameters alpha/beta and beta instead. Gamma distributions were used as the very weakly informative prior distributions on the (transformed) parameters of the beta distribution.

The final component of the model was accommodation of covariate effects on the parameter values. Theoretically, covariates such as demographics, genetics, and experimental manipulations could affect any of the four logistic parameters. Because our hypotheses involved predictions for *M* and *R*, we explicitly modeled the effects of covariates on these two parameters by replacing the simple mean parameter in the usual way with a linear combination of an intercept and the products of covariates with corresponding slope parameters. Again, weakly informative prior distributions were placed on these slopes. For *A* and *B*, we did not attempt to model covariate effects, but allowed for individual differences between subjects by modeling the random effects. Effects of covariates are reported as the 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 versus Never Psychotic), and individual SNPs which have been associated with AD risk: *CLU* (rs11136000), *CR1* (rs3818361), and *PICALM* (rs3851179, rs541458) (2;3) on the age at midpoint and rate of decline trajectory parameters. 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 GWA studies. Analysis of *APOE* ε4 included demographic factors as covariates. Analyses of the effects of psychosis status and of individual SNPs included *APOE* ε4 and demographic factors as covariates.

TABLE S1. **Posterior distribution summaries for parameters of 3MS and DSST trajectories from the model including demographic covariates, as assessed in the Validation Cohort.** The baseline demographic group is white females with high school education or less. For each variable, values shown are the Posterior Mean [95% Credible Interval] for the change in parameters relative to the baseline demographic group.

Variable	3MS		DSST	
	M	**R**	**M**	**R**
Baseline Group	86.8 [85.6, 88.1]	1.9 [1.6, 2.21]	80.5 [79.0, 82.0]	4.19 [3.37, 5.03]
Male	0.65 [-0.63, 2.0]	0.08 [-0.23, 0.39]	**-2.23 [-3.67, -0.88]**	**0.91 [0.22, 1.55]**
Some College Education	**1.89 [0.52, 3.4]**	**-0.55 [-0.87, -0.23]**	**5.81 [4.48, 7.24]**	**-2.07 [-2.76, -1.4]**
Non-Caucasian	**6.38 [3.91, 9.14]**	**4.12 [2.89, 5.31]**	**-6.98 [-9.16, -5.1]**	**3.51 [2.15, 5.03]**

3MS: Modified Mini-Mental Status Examination; DSST: Digit Symbol Substitution Test; M: age at midpoint; R: rate of fall; >H.S.: some college education or higher

TABLE S2. Percentiles of Implementation Cohort Subjects completing annual follow-up evaluations on the 3MS and DSST

Percent of Subjects	**90%**	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**	**20%**	**10%**
Follow-up, Yrs 3MS	5.45	6.84	8.69	8.82	8.86	8.90	8.93	8.97	9.03
Follow-up, Yrs DSST	4.96	6.73	8.57	8.8	8.85	8.9	8.93	8.97	9.02

3MS: Modified Mini-Mental Status Examination; DSST: Digit Symbol Substitution Test

FIGURE S1. Examples of four parameter non-linear fits of individual 3MS trajectories and DSST trajectories. Each panel shows the observed test 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. (A - D) and (E - H) show examples of fits for the 3MS and DSST, respectively. Several individuals in which outlier values occur at one or more test points are shown (e.g. Panels B-D, G, H). It can be seen that our fits continue to demonstrate high fidelity to the underlying trajectories without undue influence from outliers.