ORIGINAL ARTICLE

Biomarker Changes during 20 Years Preceding Alzheimer's Disease

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ABSTRACT

BACKGROUND

Biomarker changes that occur in the period between normal cognition and the diagnosis of sporadic Alzheimer's disease have not been extensively investigated in longitudinal studies.

METHODS

We conducted a multicenter, nested case–control study of Alzheimer's disease biomarkers in cognitively normal participants who were enrolled in the China Cognition and Aging Study from January 2000 through December 2020. A subgroup of these participants underwent testing of cerebrospinal fluid (CSF), cognitive assessments, and brain imaging at 2-year–to–3-year intervals. A total of 648 participants in whom Alzheimer's disease developed were matched with 648 participants who had normal cognition, and the temporal trajectories of CSF biochemical marker concentrations, cognitive testing, and imaging were analyzed in the two groups.

RESULTS

The median follow-up was 19.9 years (interquartile range, 19.5 to 20.2). CSF and imaging biomarkers in the Alzheimer's disease group diverged from those in the cognitively normal group at the following estimated number of years before diagnosis: amyloid-beta $(A\beta)_{42}$, 18 years; the ratio of $A\beta_{42}$ to $A\beta_{40}$, 14 years; phosphorylated tau 181, 11 years; total tau, 10 years; neurofilament light chain, 9 years; hippocampal volume, 8 years; and cognitive decline, 6 years. As cognitive impairment progressed, the changes in CSF biomarker levels in the Alzheimer's disease group initially accelerated and then slowed.

CONCLUSIONS

In this study involving Chinese participants during the 20 years preceding clinical diagnosis of sporadic Alzheimer's disease, we observed the time courses of CSF biomarkers, the times before diagnosis at which they diverged from the biomarkers from a matched group of participants who remained cognitively normal, and the temporal order in which the biomarkers became abnormal. (Funded by the Key Project of the National Natural Science Foundation of China and others; ClinicalTrials.gov number, NCT03653156.)

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Preclinical Alzheimer's disease has been characterized by the presence of normal cognitive function and abnormal levels of cerebrospinal fluid (CSF) biomarkers.[1] The preclinical stage is typically followed by mild cognitive impairment, which progresses to clinically apparent dementia in some persons. Neuropathologic abnormalities and changes in biomarker levels can begin 15 to 20 years before clinical manifestations of Alzheimer's disease.[2-4]

Changes in CSF biomarkers such as levels of amyloid-beta (Aβ), total tau, phosphorylated tau 181, and neurofilament light chain (NfL) have been indicators in preclinical Alzheimer's disease[5-8] that become abnormal sequentially rather than simultaneously.[9] Some previous studies of the sequential appearance of changes in CSF biomarkers have involved persons with autosomal dominant Alzheimer's disease, which accounts for only a small proportion of Alzheimer's disease cases, and these studies have typically used an estimated number of years before the onset of Alzheimer's disease symptoms to define the timeline of biomarker changes.[10-14]

Determination of the sequence of these changes in sporadic Alzheimer's disease is challenging because a person's clinical course, beginning with normal cognition and progressing to Alzheimer's disease, cannot be predicted.[15] Most studies regarding biomarkers in sporadic Alzheimer's disease have been cross-sectional and may not have reflected alterations of biomarkers over the period from a normal cognitive state to Alzheimer's disease. Longitudinal studies, such as the Alzheimer's Disease Neuroimaging Initiative, have advanced our understanding of preclinical sporadic Alzheimer's disease by exploring these biomarker changes.[16-19]

However, a limitation of these studies has been the underrepresentation of Asian populations, which potentially has limited the generalizability of the results. In addition, the relatively short follow-up periods in previous studies do not reflect the lengthy trajectory over decades of biomarker alterations leading to the onset of Alzheimer's disease. We examined a cohort of participants from one of the nested studies in the China Cognition and Aging Study (COAST) with a goal of estimating the trajectory of changes in several CSF biomarkers in participants who ultimately received a diagnosis of Alzheimer's disease and to assess the biomarker changes in those participants as compared with participants in whom Alzheimer's disease did not develop.

A Quick Take is available at NEJM.org

Methods

Study Design and Participants

COAST was a nationwide prospective cohort study involving multiple subgroups that were assessed for different purposes, the overall aim of which was to establish a large database pertaining to dementia in China. Here we report findings from one of the nested studies within the larger study.

From among the other substudies, we collected data on epidemiology, neuroimaging, and genetic polymorphisms that were associated with cognitive decline in persons in China. We used a multistage cluster-sampling method for enrollment to ensure representation from three primary geographic regions in China (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

From January through June 2000, we enrolled participants 45 to 65 years of age who had no cognitive deficits, as determined by a Clinical Dementia Rating (CDR) score of 0 (scores range from 0 to 3, with 0 representing no dementia).[20] Participants were included in the current study if they had completed the baseline clinical history, medication listing, physical examination, and cognitive and functional assessments; had a Hachinski ischemic score that indicated that they were more likely to have Alzheimer's disease than vascular dementia; and had undergone imaging and laboratory testing. Those who had a family history of Alzheimer's disease, who had any life-threatening disease, or who had hearing or vision loss that could affect neuropsychological testing or biomarker results were excluded.

Follow-up information was obtained from clinical records, CSF samples, neuropsychological tests, and imaging examinations every 2 to 3 years (in 2003, 2006, 2009, 2012, 2015, 2018, and 2020, through Dec. 31, 2020), for a maximum follow-up time of 20 years (Table S1 in the Supplementary Appendix). All the participants provided written informed consent to undergo examina-

tions, including lumbar puncture, and follow-up. The protocol was approved by the ethics committee of Xuanwu Hospital, Capital Medical University, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Participants were not compensated for participating in the study. The sponsors had no role in the study design; collection, analysis, or interpretation of the data; or the writing of the report.

NESTED CASE–CONTROL APPROACH

Our study required that participants be observed for more than 15 years but not more than 20 years. They would undergo at least three assessments that had to include an initial baseline visit, a visit during which the diagnosis was made, and an intermediate follow-up visit between the two. The overarching COAST study had 52,388 participants in 2000, of whom 32,061 were eligible for and enrolled in the current substudy. Of the participants who were enrolled, 30,272 were excluded (6435 discontinued the study, 3172 were untraceable, 10,470 had died, 2759 were cognitively impaired, 4514 were excluded for health-related reasons, 1228 had fewer than three assessments, and 1694 were excluded for other reasons), leaving 1789 participants enrolled.

At the last follow-up, 695 participants had received a diagnosis of Alzheimer's disease and 1094 remained cognitively normal (as assessed by testing as described below). After propensity-score matching on the basis of age, sex, and education level, 648 (93.2%) of the participants with Alzheimer's disease were successfully matched in a 1:1 ratio with participants who remained cognitively normal at the last follow-up, and these two groups form the basis for the current report.

DIAGNOSIS OF COGNITIVE STATUS

The cognitive status of participants was determined at baseline and at each follow-up with the use of three scales. Participants were considered to have no cognitive impairment if they had a score of 27 or higher on the Mini–Mental State Examination (MMSE; range, 0 to 30, with higher scores indicating better performance).[21] Scores of 12 or higher on the Logical Memory Test (LMT), a modification of the episodic memory section of the Wechsler Memory Scale–Revised (scores range from 0 to 25, with higher scores indicating better memory abilities)[22] were considered to indicate normal cognition at baseline. The third scale that was used was the CDR–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). The scores on these scales and participants' medical records were reviewed by neurologists and taken into account when the clinical diagnosis of Alzheimer's disease was made, in accordance with the National Institute on Aging–Alzheimer's Association criteria.[23] Mild cognitive impairment was diagnosed according to the Petersen criteria.[24]

The same tests were used throughout the period of the study; however, the status of cognitively normal at follow-up was defined as consistent maintenance of a score of 0 on the CDR-SB.[20] CDR-SB scores were independently assessed by physicians who were unaware of other cognitive test results. In cases in which no consensus was reached, a diagnosis was determined by subsequent discussion by a group of neurologists, psychiatrists, and neuropsychologists who were experts in Alzheimer's disease.

BIOMARKERS

At each follow-up, CSF and blood samples were obtained under morning fasting conditions for *APOE* genotype and routine biochemical tests. Participants were monitored for signs of discomfort for at least 12 hours after undergoing lumbar puncture. Samples were aliquoted and preserved at −80°C until tested. The same tests were consistently used for each participant throughout the study (see the Supplementary Methods section).

The concentrations of the biomarkers were measured with the use of enzyme-linked immunosorbent assay kits (INNOTEST β-Amyloid 1–40, INNOTEST β-Amyloid 1–42, INNOTEST hTAU Ag, and INNOTEST PHOSPHO-TAU 181P, all Fujirebio; and NF-Light, UmanDiagnostics) according to the manufacturers' instructions. All results had to meet quality-control requirements, including biomarker concentrations falling within the assay ranges of the respective kits and measurement uniformity across plates (ensured by means of a validation control that was used in each plate). Details regarding samples were anonymized to protect participant confidentiality.

Table 1. Characteristic of the Participants at Baseline.*

Variable	Cognitively Normal (N=648)	Alzheimer's Disease (N=648)
Age — yr	61.3±4.1	61.2±4.1
Sex — no. (%)		
Male	328 (50.6)	327 (50.5)
Female	320 (49.4)	321 (49.5)
Education, level and total yr — no. of participants (%)		
Primary school, 6 yr	25 (3.9)	28 (4.3)
Middle school, 7–9 yr	28 (4.3)	26 (4.0)
High school, 10–12 yr	212 (32.7)	210 (32.4)
University, 13–17 yr	334 (51.5)	335 (51.7)
Postgraduate, 18–21 yr	49 (7.6)	49 (7.6)
APOE status — no. (%)		
Noncarrier	516 (79.6)	407 (62.8)
Carrier	132 (20.4)	241 (37.2)
Heterozygous	121 (18.7)	183 (28.2)
Homozygous	11 (1.7)	58 (9.0)
Cognitive score†		
MMSE	29.5±1.0	29.4±1.2
CDR-SB	0	0
LMT	16.8±0.6	16.8±0.7
Biomarker values		
Ratio of $A\beta_{42}$ to $A\beta_{40}$	0.1±0.0	0.1±0.0
Total tau — pg/ml	219.2±52.6	214.6±41.2
Phosphorylated tau 181 — pg/ml	48.8±9.9	48.4±7.8
Neurofilament light chain — pg/ml	633.9±139.3	645.4±140.4
Hippocampal volume — mm^3	7708.3±621.8	7683.0±645.5

* Plus–minus values are means ±SD. Aβ denotes amyloid-beta, and *APOE* apolipoprotein E gene.
† Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better performance. Totals for the Clinical Dementia Rating–Sum of Boxes (CDR-SB) range from 0 to 18, with higher values indicating greater cognitive impairment. Scores for the Logical Memory Test (LMT) range from 0 to 25, with higher scores indicating better memory abilities.

BRAIN VOLUMETRIC IMAGING

Structural magnetic resonance imaging of the brain was performed with 3.0-T scanners (Siemens) with a 20-channel phased-array head–neck coil. The absolute volume of each region of interest was determined with the use of FreeSurfer software, version 5.3.0 (Table S2). The relative region-of-interest volume (the absolute region-of-interest volume as a percentage of the intracranial volume) was calculated to correct for differences in brain size among the participants. Left and right hippocampal volumes were summed to assess the degree of brain atrophy.[25]

STATISTICAL ANALYSIS

Biomarker trajectories were assessed with the use of a backward timescale. In analyses of participants in whom Alzheimer's disease was diagnosed, year 0 was used to denote the year of diagnosis. In analyses of cognitively normal participants, year 0 corresponded to the end of follow-up.

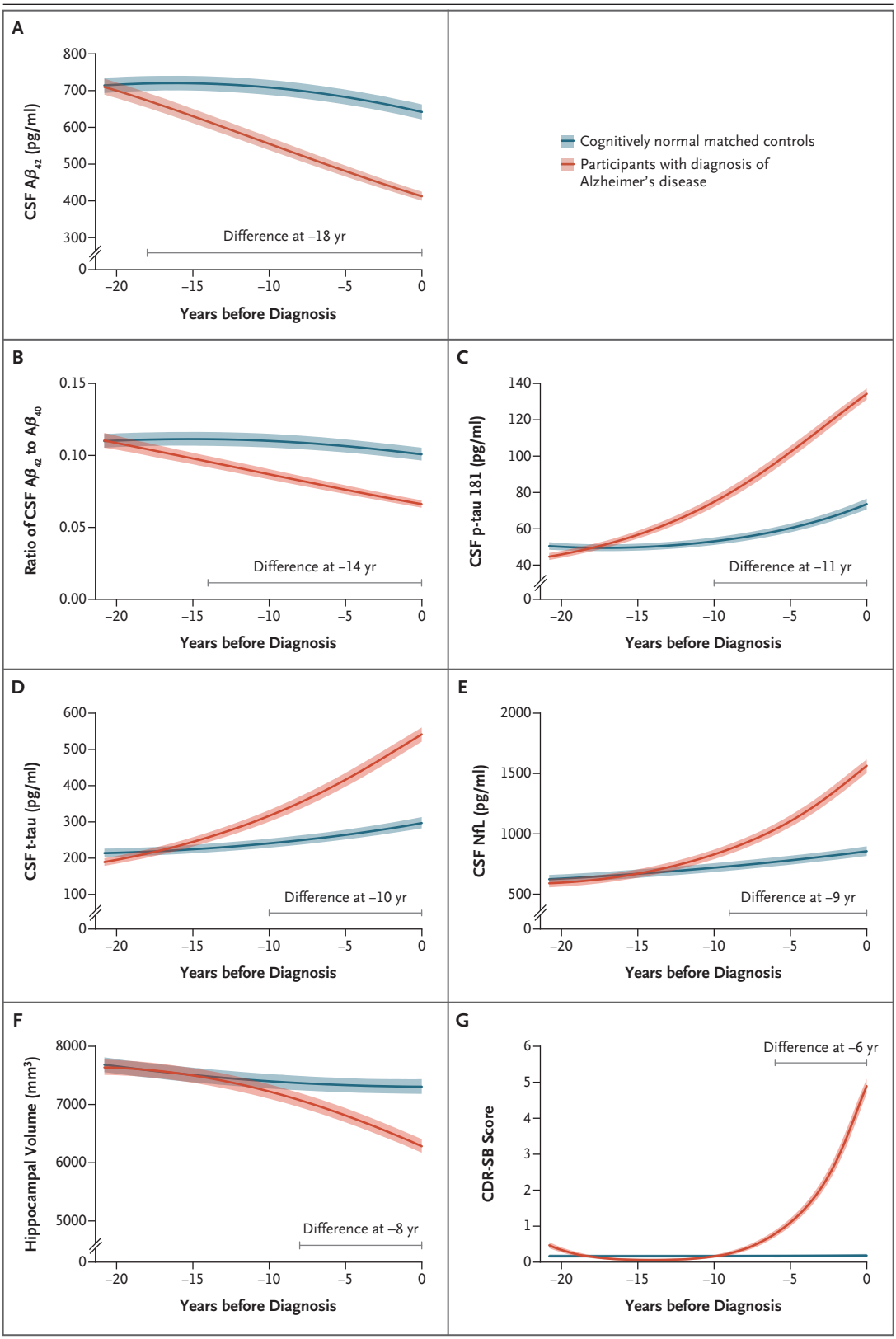

Figure 1 (facing page). Trajectory of Biomarkers before Diagnosis of Alzheimer's Disease.

Shown are the estimated changes in levels of amyloid-beta 42 ($A\beta_{42}$; Panel A), the ratio of $A\beta_{42}$ to amyloid-beta 40 ($A\beta_{40}$) (Panel B), phosphorylated tau 181 (p-tau 181; Panel C), total tau (t-tau; Panel D), neurofilament light chain (NfL; Panel E), and hippocampal volume (Panel F) and scores on the Clinical Dementia Rating–Sum of Boxes (CDR-SB [range, 0 to 18, with higher scores indicating greater impairment]; Panel G) before diagnosis of Alzheimer's disease. Year 0 represents the year of diagnosis. CSF denotes cerebrospinal fluid.

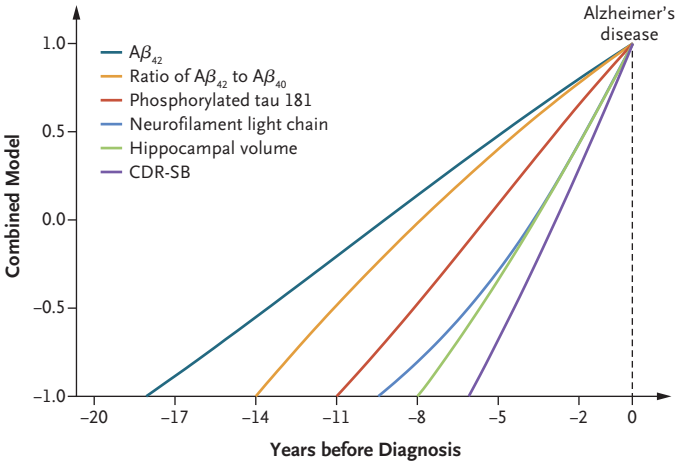

Figure 2. Evolution of Biomarkers before Diagnosis of Alzheimer's Disease.

A combined model shows the temporal evolution of biomarkers in CSF before diagnosis of Alzheimer's disease. Each biomarker trajectory was converted to a scale ranging from −1 to 1 by standardization of fitted values. The first time point at which a group difference was observed was anchored to −1 in order to show superimposed trajectories.

We used the R software, version 4.3.1, lcmm package (R Foundation for Statistical Computing) to establish latent-class mixed models for the estimation of the trajectories of each biomarker over time (see the Supplementary Methods section).[26,27] These models incorporated quadratic functions of retrospective time and were adjusted for case–control status, covariates (e.g., age, sex, education level, and *APOE* status), and their interactions with time and time squared. Within-participant correlations were accounted for by correlated random intercepts and slopes of time and time squares. Spline functions were integrated into the models to capture potential variations in biomarker trajectories over time. The final models with the optimal number of knots were determined with the use of the Akaike and Bayesian information criteria.[28]

Using the R software mvtnorm package for Wald tests, we evaluated the differences in biomarkers between participants with Alzheimer's disease and cognitively normal participants for each year up to year 0; a negative value denoted a lower marker level in the Alzheimer's disease group. Finally, the fitted concentrations of each biomarker were separately scaled and aggregated into a combined model to display the sequence of changes in biomarkers from an inflection time point to Alzheimer's disease diagnosis. We used multiple imputation by chained equations to address the missing data.

Primary analyses were conducted on the imputed data set. For additional analyses, the main analyses were repeated after all missing data were deleted. Participants with data only from baseline and year 0 (no intermediate follow-up data) were also included and the main analyses were repeated. Because there was no prespecified plan for adjusting the widths of confidence intervals for differences in biomarker values between the groups, no P values are presented, and the conclusions that can be drawn from these data are mainly qualitative. The confidence intervals reflect the precision of model estimates for each biomarker at the time the value diverged between groups and are not expressions of confidence intervals for the estimates of time that biomarker differences appeared before diagnosis of Alzheimer's disease.

We further elucidated the longitudinal rate of change for each biomarker per participant by calculating the rate of change between consecutive follow-up visits (subtracting the first measured concentration from the subsequent concentration and dividing the difference by the first concentration). We used the R software rms package to fit restricted cubic splines and plot the rate of change of the biomarker as a function of cognitive decline, adjusted for age, sex, education level, and *APOE* status.

RESULTS

PARTICIPANTS

Table 1 summarizes the characteristics of the Alzheimer's disease group and the propensity-

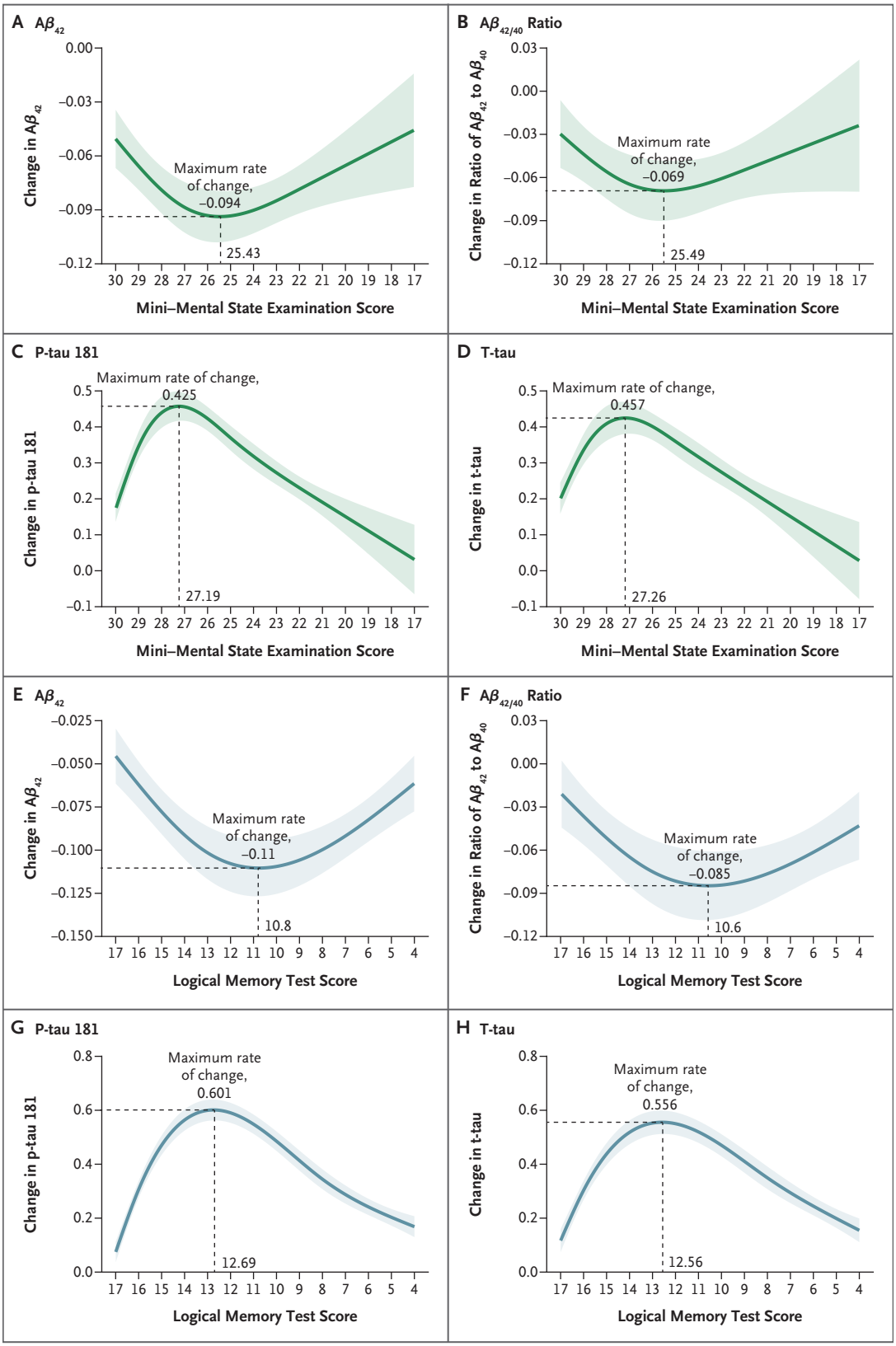

Figure 3 (facing page). Changes in CSF Biomarkers before Diagnosis of Alzheimer's Disease.

Shown are changes in biomarkers according to scores on the Mini–Mental State Examination (range, 0 to 30, with higher scores indicating better performance; Panels A through D) and Logical Memory Test (range, 0 to 25, with higher scores indicating better memory abilities; Panels E through H). The shaded areas represent the confidence intervals of the fitted values.

matched cognitively normal group. The study included only Han Chinese persons. Within both groups, men slightly outnumbered women. Baseline CSF biomarker levels, cognitive scores, and hippocampal volumes were similar in the two groups. Participants in whom Alzheimer's disease ultimately developed were more likely than their matched controls to be carriers of the *APOE* ε4 allele (37.2% vs. 20.4%). Overall, the participants had a level of education that slightly surpassed the educational norms for the general population of older adults in China. The representativeness and other characteristics in the study population as compared with the Chinese general population are shown in Table S3.

The median follow-up was 19.9 years (interquartile range, 19.5 to 20.2). The number of participants whose follow-up times differed from the prespecified schedule and the proportion with missing data at each follow-up are shown in Tables S4 and S5. In general, biomarker and clinical data were missing at one or more visits for less than 16% of the participants in each group.

BIOMARKER CHANGES

Figure 1 shows the modeled estimated biomarker trajectories for each group, and Figure S1 shows spaghetti plots of biomarker changes in each participant. As compared with the level of CSF $A\beta_{42}$ in cognitively normal controls, the level in participants in whom Alzheimer's disease developed differed an estimated 18 years before diagnosis; the difference in mean values at that time (negative values indicate the biomarker was lower in participants with Alzheimer's disease than in normal controls) was −59.13 pg per milliliter (95% confidence interval [CI], −108.08 to −10.18) (Tables S6 and S15). A difference in the ratio of CSF $A\beta_{42}$ to $A\beta_{40}$ between the two groups appeared an estimated 14 years before the diagnosis of Alzheimer's disease (difference in mean values, −0.01 pg per milliliter; 95% CI, −0.02 to −0.001) (Tables S7 and S16). Differences between the two groups in CSF phosphorylated tau 181 and total tau concentrations occurred an estimated 11 years and 10 years before diagnosis, respectively; at those times, the mean differences in phosphorylated tau 181 and total tau concentrations were 7.10 pg per milliliter (95% CI, 1.10 to 13.10) and 87.10 pg per milliliter (95% CI, 45.10 to 129.10), respectively (Tables S8, S9, S17, and S18).

Visual inspection of the curves of concentrations of each CSF marker showed that these differences continued to widen over time. A difference between the groups in CSF NfL was observed 9 years before diagnosis, with visual inspection of the curves showing its trajectory progressively deviating from the concentrations observed in cognitively normal groups at that time to a final mean difference in NfL level of 228.29 pg per milliliter (95% CI, 122.42 to 334.16) (Tables S10 and S19). The combined bilateral hippocampal volume decreased with age in both groups; however, the decrease began to differ between the two groups 8 years before diagnosis, at which time there was a mean difference in volume of −358.94 mm^3 (95% CI, −613.20 to −104.69) in the group with Alzheimer's disease as compared with the control group (Tables S11 and S20).

The Alzheimer's disease group differed from the control group in terms of mean CDR-SB scores at an estimated 6 years before diagnosis (Tables S12 and S21). After exclusion of participants with one or more missing biomarker values across follow-up visits, the times of divergence between groups were similar to those in the main analysis (Table S13). When we included participants who had data only from baseline and the year of diagnosis (80 with Alzheimer's disease and 15 who were cognitively normal), the findings remained similar (Table S14).

We placed each biomarker trajectory on a scale from −1 to 1 by using the standardization of fitted values, anchoring the first time point that showed a group difference to −1 to generate superimposed trajectories (Fig. 2). On visual inspection, an initial increase followed by a decrease was apparent in the rate of change in CSF biomarkers in participants with Alzheimer's dis-

ease; in the control group, the rate of change appeared to have flatter trajectories (Fig. S5).

In individual participants with Alzheimer's disease, the progression of CSF $A\beta_{42}$ concentration, CSF $A\beta_{42/40}$ ratio, total tau concentration, and phosphorylated tau 181 concentration in relation to cognitive decline appeared to initially accelerate and, on visual inspection, peaked at an MMSE score of approximately 25 and an LMT score of approximately 11 (Fig. 3A, 3B, 3E, and 3F). Subsequently, despite further decline in cognitive scores, the rate of change appeared to slow. The rate of change in total tau concentration increased until it reached an MMSE score of 27.26 and an LMT score of 12.56 (Fig. 3D and 3H) and thereafter appeared to slow. The annual rate of change for phosphorylated tau 181 concentration peaked at an MMSE score of 27.19 and an LMT score of 12.69 (Fig. 4C and 4G).

DISCUSSION

In this study assessing change in CSF biomarkers in 648 persons who ultimately received a diagnosis of Alzheimer's disease and the same number of matched persons who remained cognitively normal, the times before Alzheimer's disease diagnosis at which biomarkers diverged between groups ranged from 18 years for CSF $A\beta_{42}$ concentration to 6 years for cognitive decline as measured on the CDR-SB, a scale that has been widely used in clinical trials. The results with regard to changes in the biomarkers in sporadic Alzheimer's disease are similar in most respects to the temporal sequence of the appearance of differences of biomarkers in studies of autosomal dominant Alzheimer's disease, although the alterations in $A\beta_{42}$ concentration became evident nearly a decade later in our study.[10-12] Therefore, the timing of the appearance of changes in biomarkers may differ between sporadic and autosomal dominant Alzheimer's disease.

Consistent with results from previous studies of sporadic Alzheimer's disease,[2,9,15,29-31] the results of our study show an apparent accelerated change in concentrations of CSF biomarkers followed by a slowing of this change up to the time of diagnosis of Alzheimer's disease. We explored associations between the rates of biomarker changes with cognitive function and found that the most rapid change in rate occurs in persons who have MMSE scores in the range of 25 to 27.

The strengths of this study include its prospective and multicenter nature, relatively large sample, long follow-up time, and repeated CSF and imaging assessments. However, our trial has some weaknesses. The participants were Han Chinese, and therefore the results may not be generalizable to other populations. The exclusion of participants with shorter follow-ups might have yielded a group resembling "super-agers" — persons endowed with higher education status, superior health status, and greater health awareness than persons not included in this study.

In addition, we stipulated a minimum of three follow-up visits for enrollment to attempt to capture nonlinear changes in biomarkers. That requirement led to a reduction in the sample size, which affected the reliability and generalizability of the findings. We also excluded persons with a familial history of Alzheimer's disease to characterize the sporadic Alzheimer's disease population and to mitigate the potential confounding effects of genetic factors, thereby diminishing the proportion of *APOE* ε4 carriers within the cohort — a proportion that is inherently low in the Chinese population.[32-34] The inclusion of a lower proportion of these carriers may have attenuated the influence of this genetic factor on biomarkers.

Another drawback is that not all participants who were included in analyses consented to repeated lumbar punctures, which led to a reliance on convenience sampling. This might have affected the representativeness and accuracy of our findings. Finally, the type of biomarker tests and their accuracy changed in the course of the 20 years of the study, which might have introduced inconsistencies in the measurements; however, by preserving frozen samples we were able to use the same test kits for each participant across the duration of the study.

In this longitudinal study in China of CSF markers, magnetic resonance imaging–based hippocampal volume, and measurements of cognition over a period of 20 years, we describe the temporal evolution of biomarkers in a group of persons in whom Alzheimer's disease developed as compared with matched controls who maintained normal cognition through the same period.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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