



Published in final edited form as:

JAMA Neurol. 2014 August ; 71(8): 961–970. doi:10.1001/jamaneurol.2014.803.

## The Preclinical Alzheimer Cognitive Composite: Measuring Amyloid-Related Decline

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**Group Information:** A list of the researchers of the Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing (AIBL) are provided at <http://aibl.csiro.au/>. A complete listing of the investigators of the Alzheimer's Disease Neuroimaging Initiative (ADNI) can be found at [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf). A list of the investigators of the Alzheimer's Disease Cooperative Study (ADCS) are provided at <http://adcs.org/>.

**Author Contributions:** Dr Donohue had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Donohue, Sperling, Salmon, Raman, Aisen.

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*Obtained funding:* Weiner, Aisen.

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**Conflict of Interest Disclosures:** Drs Donohue and Salmon are consultants for Bristol-Myers Squibb. Dr Aisen serves on a scientific advisory board for NeuroPhase; has served as a consultant to Elan, Wyeth, Eisai, Schering-Plough, Bristol-Myers Squibb, Eli Lilly, NeuroPhase, Merck, Roche, Amgen, Genentech, Abbott, Pfizer, Novartis, Bayer, Astellas, Daiippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, Medivation, Ichor, Toyama, Lundbeck, Biogen Idec, iPerian, Probiobdrug, Somaxon, Biotie, Cardeus, Anavex, Kyowa Hakko Kirin Pharma, and Medtronic; and receives research support from Eli Lilly. Dr Sperling is funded by Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Genentech, Janssen, Lundbeck, Merck, and Roche.

**Additional Information:** Data used in the preparation of this article were obtained from AIBL and were made available at the ADNI database. The AIBL researchers contributed data but did not participate in the analysis or writing of this report. The investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. Private sector contributions are facilitated by the Foundation for the National Institutes of Health ([www.fnih.org](http://www.fnih.org)). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the ADCS at the University of California, San Diego. The Laboratory for Neuroimaging at the University of Southern California disseminates ADNI data (<http://www.loni.usc.edu>). The data collection and sharing for this project were funded by ADNI. The Canadian Institutes of Health Research are providing funds to support ADNI clinical sites in Canada. For AIBL, the design and conduct of the study and the collection and management of the data are funded by the Commonwealth Scientific and Industrial Research Organisation. For the ADCS-PI study, the design and conduct of study; the collection and management of the data; the analysis and interpretation of the data; and the preparation, review, and approval of the manuscript were supported by the National Institute on Aging/National Institutes.

**Additional Contributions:** We would like to acknowledge the invaluable contributions of our ADCS and ADNI collaborators, coinvestigators, volunteers, and their families, none of whom were financially compensated for their work.

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## Abstract

**IMPORTANCE**—As Alzheimer disease (AD) research moves to intervene in presymptomatic phases of the disease, we must develop outcome measures sensitive to the earliest disease-related changes.

**OBJECTIVE**—To demonstrate the feasibility of a cognitive composite outcome for clinically normal elderly participants with evidence of AD pathology using the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The ADCS-PACC combines tests that assess episodic memory, timed executive function, and global cognition. The ADCS-PACC is the primary outcome measure for the first clinical trial in preclinical AD (ie, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study).

**DESIGN, SETTING, AND PARTICIPANTS**—With the ADCS-PACC, we derive pilot estimates of amyloid-related decline using data from 2 observational studies conducted in North America and another conducted in Australia. The participants analyzed had normal cognition and mean ages of 75.81, 71.37, and 79.42 years across the 3 studies.

**MAIN OUTCOMES AND MEASURES**—For the 2 studies that collected data on A $\beta$  levels (ADNI and AIBL), we estimate decline in a preclinical AD “A $\beta$ -positive” placebo group and compare them with an “A $\beta$ -negative” group. For the study that did not include data on A $\beta$  levels (the ADCS Prevention Instrument [ADCS-PI] study), we grouped participants by the presence of *APOE*- $\epsilon$ 4 and by clinical progression.

**RESULTS**—In ADNI, A $\beta$ -positive participants showed more decline than did A $\beta$ -negative participants with regard to the ADCS-PACC score at 24 months (mean [SE] difference,  $-1.239$  [0.522] [95% CI,  $-2.263$  to  $-0.215$ ];  $P = .02$ ). In AIBL, the mean (SE) difference is significant at both 18 months ( $-1.009$  [0.406] [95% CI,  $-1.805$  to  $-0.213$ ];  $P = .01$ ) and 36 months ( $-1.404$  [0.452] [95% CI,  $-2.290$  to  $-0.519$ ];  $P = .002$ ). In the ADCS-PI study, *APOE*- $\epsilon$ 4 allele carriers performed significantly worse on the ADCS-PACC at 24 months (mean [SE] score,  $-0.742$  [0.294] [95% CI,  $-1.318$  to  $-0.165$ ];  $P = .01$ ) and 36 months ( $-1.531$  [0.469] [95% CI,  $-2.450$  to  $-0.612$ ];  $P = .001$ ). In the ADCS-PI study, cognitively normal participants who progress from a global Clinical Dementia Rating score of 0 are significantly worse on the ADCS-PACC than cognitively normal participants who are stable with a global Clinical Dementia Rating score of 0 at months 12, 24, and 36 (mean [SE] ADCS-PACC score,  $-4.471$  [0.702] [95% CI,  $-5.848$  to  $-3.094$ ];  $P < .001$ ). Using pilot estimates of variance and assuming 500 participants per group with 30% attrition and a 5%  $\alpha$  level, we project 80% power to detect effects in the range of  $\beta = 0.467$  to  $0.733$  on the ADCS-PACC.

**CONCLUSIONS AND RELEVANCE**—Analyses of at-risk cognitively normal populations suggest that we can reliably measure the first signs of cognitive decline with the ADCS-PACC. These analyses also suggest the feasibility of secondary prevention trials.

The field of Alzheimer disease (AD) research has evolved to conceptualize AD as a continuum of disease.<sup>1-4</sup> Although, historically, AD was considered to begin with the onset of dementia, a prodementia stage, characterized clinically as mild cognitive impairment and, more specifically, using biomarkers, as prodromal AD, has been widely accepted.<sup>5-7</sup> Most recently, the preclinical stage of AD has been postulated. This asymptomatic stage, believed to precede mild cognitive impairment by years, is characterized by accumulating amyloid pathology and neurodegeneration accompanied by very subtle cognitive decline detectable with sensitive neuropsychological tests and cognitive complaint measures.<sup>1</sup> Individuals with preclinical AD (ie, cognitively normal individuals with biomarker evidence of brain amyloid deposition) represent a group at high risk for decline and an ideal population for a “secondary prevention” trial aimed at delaying the emergence of the clinical syndromes of mild cognitive impairment and dementia.<sup>8</sup>

Drug development strategies in very early stages of the AD process initially focused on biomarkers that might efficiently demonstrate change-occurring years before the onset of symptoms. Examples of such candidate biomarker outcomes have included volumetric magnetic resonance imaging,<sup>9</sup> positron emission tomography (PET) with<sup>18</sup> fluorodeoxyglucose,<sup>10</sup> amyloid PET imaging,<sup>11,12</sup> and cerebrospinal fluid (CSF) markers.<sup>13</sup> Although each of these proposed outcomes reflect disease progression, the impact of therapeutic interventions aimed at disease modification has been surprising. For example, anti-amyloid immunotherapy may paradoxically accelerate brain atrophy as measured by volumetric magnetic resonance imaging.<sup>14</sup> Until a reliable surrogate biomarker is validated, the field must rely on clinical outcome measures that reflect cognitive function.

Studies have shown that cognitive performance, measured using tests ranging from the Mini-Mental State Examination (MMSE) to word list learning tasks, may also show changes many years before the onset of functional decline.<sup>2,15,16</sup> Cognitive measures have important advantages over imaging and biochemical biomarkers: they are closely related to the core symptoms of disease progression and, at later stages, are sensitive to treatment effects. The US Food and Drug Administration has recently indicated support for the potential utility of cognitive composite measures as outcome measures in AD trials conducted at the preclinical stage.<sup>17</sup>

We describe a composite cognitive performance measure, the Alzheimer Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The ADCS-PACC is designed to serve as the primary outcome measure for trials conducted at the asymptomatic phase of AD. We describe, in particular, how the ADCS-PACC will be implemented in the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s study (hereafter referred to as the A4 study), which is being conducted by the ADCS in partnership with Eli Lilly.<sup>18</sup>

## Methods

### The A4 Study Design

The A4 study will be a 168-week placebo-controlled “secondary prevention” trial of an anti- $A\beta$  treatment, aimed at slowing cognitive decline in cognitively normal older individuals

who have elevated brain amyloid levels (ie, “A $\beta$ -positive” individuals), based on florbetapir PET amyloid imaging.<sup>18</sup> The A4 study will include a natural history arm of “A $\beta$ -negative” cognitively normal individuals followed up with longitudinal cognitive outcome measures collected at the same intervals. There are also 2 embedded substudies: (1) an ethics protocol to investigate the impact of disclosure of A $\beta$  status and (2) a novel outcome instrument development protocol to optimize the detection of early decline over the course of preclinical AD.

Eligible participants will be 65 to 85 years of age at the time of screening, with a global Clinical Dementia Rating (CDR-G) score of 0, an MMSE score of 27 to 30, and a Delayed Recall score on the Logical Memory IIa subtest of 8 to 15 for participants with 13 or more years of education, or with an MMSE score of 25 to 30 and a Delayed Recall score on the Logical Memory IIa subtest of 6 to 13 for participants with 12 or less years of education. A study goal is to include approximately 20% of participants from underrepresented minority groups.

The anti-amyloid intervention for the A4 study is solanezumab, a monoclonal antibody targeting the midsequence of monomeric A $\beta$ ; this treatment was selected by the consensus of a panel of experts advising the A4 study team. A total of 1000 A $\beta$ -positive participants will be randomly assigned to solanezumab or placebo. Identifying these A $\beta$ -positive participants will require screening approximately 3000 cognitively normal older individuals by use of florbetapir PET amyloid imaging. This screening process will provide an opportunity to collect plasma biomarkers and imaging and neuropsychological data on a large number of A $\beta$ -negative individuals representing a well-characterized “gold standard” cognitively normal control group.

### The ADCS-PACC

The primary objective of the A4 study is to test the hypothesis that solanezumab, administered as a 400-mg intravenous infusion every 4 weeks for 168 weeks, will slow cognitive decline compared with placebo in participants with preclinical AD. This objective will be assessed using a mixed model of repeated measures (MMRM) analysis of change in the ADCS-PACC score. The specific hypothesis of the A4 study is that there will be less of a decrease in the ADCS-PACC score at the end of the treatment period for participants treated with solanezumab than for participants treated with placebo.

Based on a review of the literature for cohort studies in “normal controls” who progressed to mild cognitive impairment or Alzheimer dementia, we determined that a composite measure sensitive to change in preclinical AD would likely require assessment of 3 key domains: episodic memory, executive function, and orientation. Previous studies<sup>19–21</sup> have reported evidence that both list learning and paragraph recall (measures of episodic memory) tend to decline 7 to 10 years prior to the diagnosis of MCI or Alzheimer dementia. Recent data from amyloid imaging studies<sup>25–29</sup> have reported a decline in multiple cognitive domains looking retrospectively at cognitive trajectories over 8 to 10 years prior to PET amyloid imaging<sup>22–24</sup> and prospectively over 1- to 3-year longitudinal follow-up.

Based on this review, we propose a composite of 4 measures that are well established as showing sensitivity to decline in prodromal and mild dementia, and with sufficient range to detect early decline in the preclinical stages of the disease. The ADCS-PACC includes:

1. The Total Recall score from the Free and Cued Selective Reminding Test (FCSRT) (0–48 words),<sup>20,30</sup>
2. The Delayed Recall score on the Logical Memory IIa sub-test from the Wechsler Memory Scale (0–25 story units),<sup>31</sup>
3. The Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale–Revised (0–93 symbols),<sup>32</sup> and
4. The MMSE total score (0–30 points).<sup>33</sup>

The composite score is determined from its components using an established normalization method.<sup>34</sup> Each of the 4 component change scores is divided by the baseline sample standard deviation of that component, to form standardized z scores. These z scores are summed to form the composite. Thus, a change of 1 baseline standard deviation on each component would correspond to a 4-point change on the composite. In the A4 study, the ADCS-PACC will be administered at baseline and at 24, 48, 72, 96, 120, 144, and 168 weeks, alternating between 3 test versions.

### Sensitivity of the ADCS-PACC

The ideal outcome measure for the A4 study is one that is sensitive to decline that is specific to the A $\beta$ -positive cognitively normal target population, as opposed to decline that is associated with aging. To estimate the rate of A $\beta$ -mediated decline and inform the sample size justification for the A4 study, we examined several natural history data sets. With each data set, a group similar to the A4 study cognitively normal A $\beta$ -positive target population is identified and compared longitudinally with a reference cognitively normal A $\beta$ -negative population. Estimated group differences provide an upper bound on potential treatment effects in our target population. We also explore group differences between those who maintain a CDR-G score of 0 (“CDR-G stable”) vs those who progress from a CDR-G score of 0 to a worse score (“CDR-G pro-gressor”). These progression group differences provide a sense of the clinical interpretation of the composite.

### Data Sets and Measures

**AD Neuroimaging**—The Alzheimer’s Disease Neuroimaging Initiative (ADNI) has followed up with volunteers who were cognitively normal or who had varying degrees of cognitive impairment since 2005.<sup>35</sup> The ADNI battery includes serial neuroimaging, CSF measures, other biomarkers, and clinical and neuropsychological assessments. For the present analysis, we analyze the subset of cognitively normal participants from the initial wave of ADNI with known CSF A $\beta$ 42 levels or Pittsburgh compound B (PiB) PET images. We classify these cognitively normal participants as A $\beta$ -positive participants, with a PiB standardized uptake value ratio (SUVR) above 1.5 and a CSF A $\beta$ 42 level below 192 pg/mL, or as A $\beta$ -negative participants, with a PiB SUVR below 1.5 and a CSF A $\beta$ 42 level above

192 pg/mL. If only 1 of the 2 A $\beta$  measures is known, we use that measure for classification. Data were obtained from the ADNI database on June 7, 2013.

The ADNI battery does not include the FCSRT. In place of the FCRST, we use Delayed Word Recall from the Alzheimer's Disease Assessment Scale–Cognitive Subscale<sup>36</sup> to construct an approximation of the proposed ADCS-PACC. To more closely reflect the inclusion criteria for the A4 study, we exclude ADNI participants with Delayed Recall scores greater than 15 on the Logical Memory IIa subtest.

**Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing**—The Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing (AIBL) is a longitudinal biomarker cohort study,<sup>37</sup> similar to ADNI. We used the same PiB threshold to determine A $\beta$  positivity (PiB SUVR > 1.5). The AIBL battery also does not include the FCSRT, so we use delayed recall from List A of the California Verbal Learning Test<sup>38</sup> to construct the composite in the analysis of AIBL data.

**ADCS Prevention Instrument Study**—The ADCS Prevention Instrument (ADCS-PI) study was a 4-year study of cognitively normal individuals 75 years of age or older to assess potential outcome measures for future prevention studies.<sup>16,30</sup> The ADCS-PI study used New York University Paragraphs,<sup>39</sup> instead of Logical Memory, and the Modified Mini-Mental State Examination,<sup>40</sup> instead of the MMSE. The study data do not include CSF or PET measures of amyloid level. Therefore, as a proxy for A $\beta$  status, we use the presence of at least 1 *APOE*- $\epsilon$ 4 allele, although this is less predictive of decline than A $\beta$  markers.<sup>26</sup> We also compare participants who were CDR-G stable with those who were CDR-G progressors. This last group definition is based on post baseline progression data and is bound to demonstrate larger group differences than the other analyses based on baseline covariates only. However, this analysis of postbaseline progression puts the scale of the composite in perspective relative to clinically meaningful CDR-G change.

The ADNI, ADCS-PI, and AIBL studies were all approved by the institutional review boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

### Sample Size Justification for the A4 Study

For each of the data sets and group comparisons already described, we apply an MMRM to estimate the key variance and covariance parameters that inform sample size calculations. The model includes effects for baseline ADCS-PACC score and age, which is known to be associated with A $\beta$  accumulation in brain. The MMRM treats time as a categorical variable and estimates group differences at each visit while making no assumptions about the shape of trajectories. We use the Akaike information criterion<sup>41</sup> to select the covariance structure between unstructured, compound symmetric, and autoregressive correlations of the order 1. From the final model, we report the difference between the at-risk population and the reference population at the final visit, which is typically the test statistic of primary interest in a clinical trial. We also report *P* values with an adjustment for simultaneous inference<sup>42</sup> and area between the curves using the trapezoid rule.<sup>43</sup> Power calculations assume an MMRM to estimate treatment effect at 36 months, 6-month visit intervals, 500 participants



per group, 30% attrition, and a 5%  $\alpha$  level. We use the formula by Lu et al<sup>44</sup> implemented in the R package *longpower*<sup>45</sup> to project the smallest detectable effect. The formula accommodates general attrition patterns. We assume that attrition accumulates linearly to an overall 30% attrition rate at 3 years with 5% worse attrition in the active arm. We report minimum detectable effects on the raw scale (eg, ADCS-PACC units) and as a percentage of the mean decline in the at-risk group (eg, A $\beta$ -positive individuals, *APOE*- $\epsilon$ 4 carriers, or CDR-G progressors). All analyses are conducted using R version 3.0.1<sup>46</sup> and the *nlme*<sup>47</sup> and *longpower*<sup>45</sup> packages. Graphics are produced using the *ggplot2* package.<sup>48</sup>

### Optimized Item Weights

We explored optimized reweighting of the ADCS-PACC components (see eAppendix in the Supplement for results). We fit Item Response Theory models<sup>49</sup> to a training set composed of ADNI cognitively normal participants with unknown A $\beta$  status to optimize the ADCS-PACC and also search for other items that might improve performance. We also reweighted the ADCS-PACC item z scores based on a logistic regression of AIBL A $\beta$  status and a Nelder-Mead optimization<sup>50</sup> of MMRM power in terms of minimized detectable percentage of A $\beta$  group difference. We also assessed the power of CDR Sum of Boxes and each of the ADCS-PACC items.

## Results

### Baseline Characteristics

Table 1 and Table 2 summarize baseline characteristics for each of the groups analyzed. In ADNI and AIBL, we see that the A $\beta$ -positive groups are significantly older at baseline and have significantly higher percentages of *APOE*- $\epsilon$ 4 carriers compared with the A $\beta$ -negative groups. Not surprisingly in ADNI, the A $\beta$ -positive groups also show significantly lower CSF A $\beta$ 42 levels, higher T-tau levels, higher PiB SUVr, and smaller hippocampi than do the A $\beta$ -negative groups. In AIBL, the A $\beta$ -positive group shows more impairment on Digit Symbol Coding than does the A $\beta$ -negative group. In the ADCS-PI study, the CDR-G progressor group demonstrated greater baseline impairment on the FCSRT and Modified Mini-Mental State Examination than did the CDR-G stable group, and the *APOE*- $\epsilon$ 4 carriers were younger than the noncarriers.

### Longitudinal Analysis of the ADCS-PACC

The Figure, Table 3, and Table 4 summarize the change in the ADCS-PACC scores over time as estimated by the MMRM, controlling for baseline ADCS-PACC score and age. The Akaike information criterion selected the compound symmetric correlation over the other correlation structures considered. In ADNI, there was significant separation of the A $\beta$  groups at 24 months but a reconvergence of the trajectories at 36 months. The mean (SE) area between the curves is  $-26.4$  (13.6) ( $P = .05$ ). In AIBL, we see consistent significant separation at both month 18 and month 36 and area between curves. In the ADCS-PI study CDR-G stable vs progressor analysis, we see highly significant ( $P < .001$ ) separation at months 12, 24, and 36 and area between curves. In the ADCS-PI study *APOE*- $\epsilon$ 4 carriers vs noncarriers analysis, we see significant separation at months 24 and 36 and significant area between the curves.

## Minimum Detectable Treatment Effect on the ADCS-PACC

Based on the variance and correlation estimates in Tables 3 and 4, we can estimate the minimum treatment effect that can be found by assuming 80% to 90% power, a 5%  $\alpha$  level (2-sided), 500 participants in each group, and 30% attrition. The Figure depicts the minimum detectable treatment effect for 80% power.

Using ADNI pilot estimates of variance and correlation (Table 3), we project a minimum treatment difference of  $d = 0.525$  to  $0.607$  units for 80% to 90% power. This is larger than the observed  $A\beta$  group difference in ADNI at month 36 but is  $0.525/1.239 = 42.4\%$  to  $0.607/1.239 = 49.0\%$  of that difference at month 24. Similarly, using the AIBL pilot estimates (Table 3), we project  $d = 0.467$  to  $0.540$  units, or  $0.467/1.404 = 33.3\%$  to  $0.540/1.404 = 38.5\%$  of the  $A\beta$  group difference at month 36. Based on estimates from the analysis of ADCS-PI study CDR-G stable vs progressor groups (Table 4), we project  $d = 0.654$  to  $0.746$  units, or  $0.654/4.471 = 14.6\%$  to  $0.746/4.471 = 16.7\%$  of the group difference at month 36. Based on the analysis of ADCS-PI study *APOE-ε4* carriers vs noncarriers (Table 4), we project  $d = 0.733$  to  $0.847$  units, or  $0.733/1.531 = 47.9\%$  to  $0.847/1.531 = 55.3\%$  of the month 36 group difference. Again, the Figure graphically represents these smallest detectable treatment effects.

## Discussion

Our analyses demonstrate consistent evidence that  $A\beta$ -positive cognitively normal participants demonstrate greater cognitive decline than do  $A\beta$ -negative participants on a composite of verbal list learning, paragraph recall, timed executive function, and global cognition. Moreover, we found that decline on this composite was robust across cohorts, regardless of the exact measures used; however, in ADNI, we did not see significant changes from baseline, and the amyloid group difference was only significant at month 24. The inconsistencies between the various studies used in our retrospective analysis also present some limitations. The particular tests that comprised each study's entire battery, and their order of presentation, varied from study to study. In addition, none of the studies analyzed were treatment trials. Owing to these factors, the ADCS-PACC may behave differently in the A4 study.

These limitations notwithstanding, we project that the A4 study has about 80% power to detect a treatment benefit of 0.5 ADCS-PACC units over 3 years. A quarter standard deviation change in each component of the ADCS-PACC equates to a 1-point change in the ADCS-PACC total score. The ADCS-PACC is standardized according to the baseline distribution of 4 instruments with established face validity in more impaired populations. We believe 0.5 ADCS-PACC units is small enough to be a realistically attainable, yet large enough to suggest benefit to patients, including a reduction in later clinical deterioration.

The Item Response Theory approach applied to ADCS-PACC items did not improve power in ADNI, although a model with 16 items did achieve more consistent decline and  $A\beta$  group separation in ADNI (eFigure and eTable in the Supplement). The logistic regression approach decreased the smallest detectable effect (percentage of  $A\beta$  group difference) at 80% power by 6.5% when applied to same AIBL data that were used to obtain the weights.



The weighting favored list and paragraph recall over MMSE and Digit Symbol Substitution. However, when these weights were applied to the other studies, it performed poorly. The smallest possible effect size was only 1.5% smaller than the logistic regression weights, and this required weighting Digit Symbol Substitution in the wrong direction. We have concerns about the validity of optimized weighting, particularly given that there is no information about treatment response for these items in the target population. It is conceivable, for example, that we would down-weight a particular item that would respond to treatment, but we have no information with which to assess this risk. At this point, we do not find strong evidence to support unequal weighting of the ADCS-PACC items.

Ideally, the A4 study would be powered to detect a clinically meaningful effect. The term *clinically meaningful effect* is somewhat nebulous but presumably indicates an effect on symptoms of importance to the treated individual. In a 3-year study in the clinically normal target population for the A4 study, we will not necessarily observe the emergence of functional impairment seen in late mild cognitive impairment and dementia. However, because a composite measure of memory, orientation, and executive function has face validity as an indicator of AD-related clinical progression, the recent US Food and Drug Administration draft guidance<sup>17,51</sup> suggests that such a measure may serve as a primary outcome measure for the purpose of accelerated approval, with clinical meaningfulness supported by postmarketing study.

The A4 study will include a number of secondary and exploratory measures to inform interpretation of the treatment effect on the primary measure. These include molecular, structural, and functional neuroimaging measures, CSF biochemical markers, and patient- and informant-reported measures of perceived global and specific cognitive function. Experience with such measures in longitudinal studies in the preclinical AD population is limited, and their sensitivity to treatment effects is unknown. However, they may clarify not only the pathophysiological impact of the anti-amyloid intervention but also the implications of the cognitive effects.

## Conclusions

The concept of preclinical AD, a stage of amyloid-mediated neurodegeneration before the emergence of clinical symptoms,<sup>1,8</sup> represents an attractive target for disease-modifying intervention in AD. The relationship of longitudinal change in the ADCS-PACC to the presence of amyloid plaques in the brains of asymptomatic older individuals supports the notion that this measure may be useful in establishing favorable treatment effects. While much remains to be learned about preclinical AD, the enormity of the need for effective therapy requires the rapid initiation of trials. Presumably, the A4 study and other very early interventional studies will further elucidate the trajectory of cognitive decline during the preclinical stages of AD and facilitate the successful development of disease-modifying treatments.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding/Support:** Dr Donohue was supported by National Institute on Aging grant U01-AG10483 (principal investigator) funded by the National Institutes of Health. Dr Donohue was funded by grant 1KL2RR031978 from the National Institutes of Health and was supported by the generous contributions from Abbott; AC Immune; the Alzheimer's Association; the Alzheimer's Diseases Research Center; the University of California, San Diego; the Alzheimer's Drug Discovery Foundation; Amorphix Life Sciences; Araclon; AstraZeneca; Avid Radiopharmaceuticals; Bayer HealthCare; BioClinica; Biogen Idec; Bristol-Myers Squibb; Eisai; Elan; Eli Lilly; F. Hoffmann–La Roche and its affiliated company Genentech; GE Healthcare; Innogenetics NV; IXICO; Janssen Alzheimer Immunotherapy Research and Development, LLC; Johnson & Johnson Pharmaceutical Research and Development LLC; Kenes, International; Medpace; Merck; Meso Scale Diagnostics, LLC; National Brain Research Center, India, for Johns Hopkins Medicine; New York Academy of Sciences; Novartis; Pfizer; sanofi-aventis; Servier; Smartfish AS; Synarc; Takeda; and the University of California, Los Angeles.

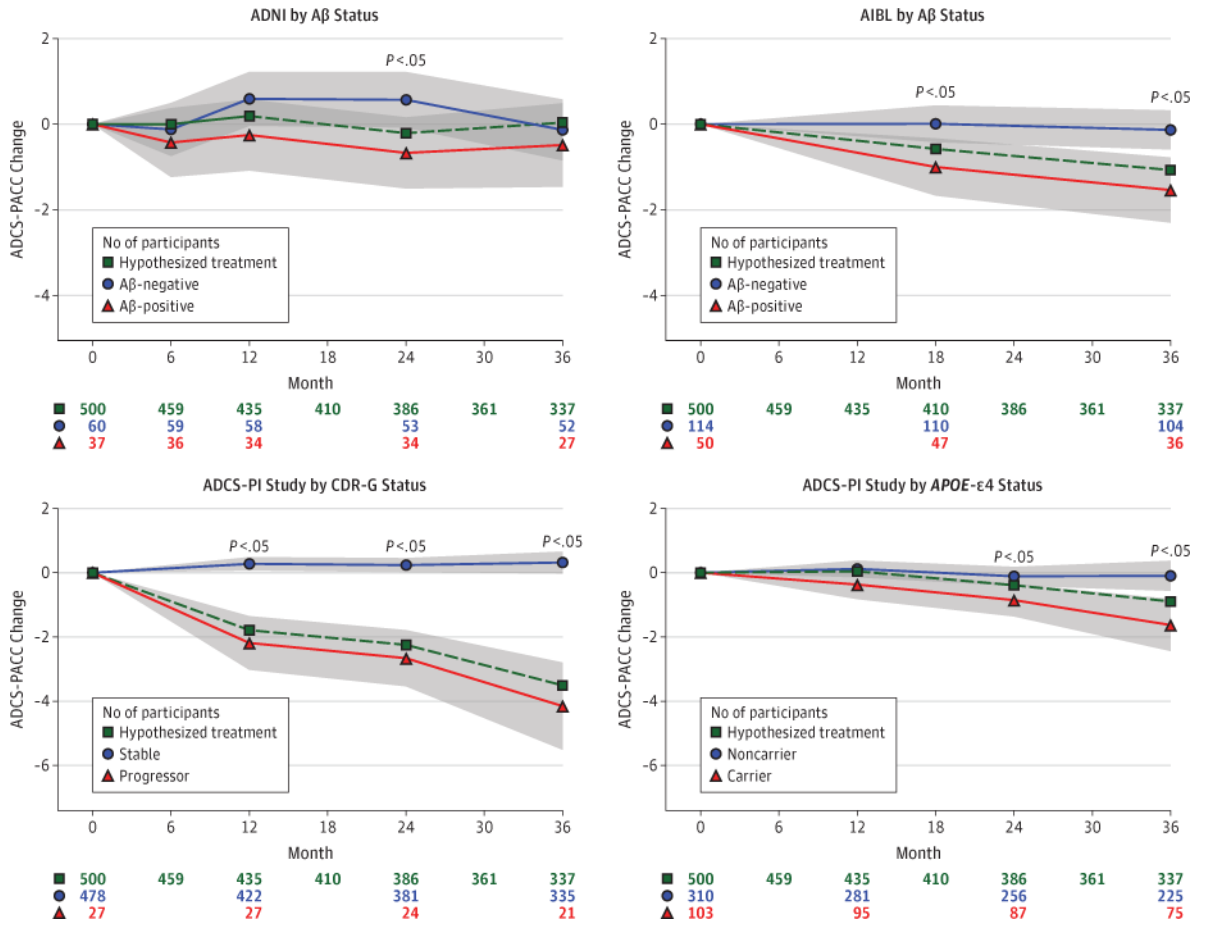
**Role of the Sponsor:** The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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**Figure. MMRM Estimates of Composite Change From Baseline in the ADCS-PACC**

The models assume heterogeneous compound symmetric covariance structure, which allows for a different variance per visit and for a single correlation parameter. Age and composite score at baseline are included as covariates. The dashed line indicates the hypothesized minimum treatment benefit that can be detected with 80% power, a 5%  $\alpha$  level, and the indicated sample size and attrition. The shaded regions depict 95% CIs. Group differences are significant at  $P < .05$ . ADCS-PACC indicates Alzheimer’s Disease Cooperative Study Preclinical Alzheimer Cognitive Composite; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; CDR-G, global Clinical Dementia Rating; MMRM, mixed model of repeated measures; and PI, Prevention Instrument.

**Table 1**

Baseline Characteristics of Participants in ADNI and AIBL, by A $\beta$  Status<sup>a</sup>

| Characteristic                            | Participants With Available Data, No. | A $\beta$ -Negative Participants | A $\beta$ -Positive Participants | All           | P Value <sup>b</sup> |
|---|---------------------------------------|----------------------------------|----------------------------------|---------------|----------------------|
| <b>ADNI</b>                               |                                       |                                  |                                  |               |                      |
| Total No.                                 | 97                                    | 60                               | 37                               | 97            |                      |
| Age, y                                    | 97                                    | 74.80 (5.43)                     | 77.45 (4.74)                     | 75.81 (5.31)  | .006                 |
| Female sex                                | 97                                    | 30 (50)                          | 12 (32)                          | 42 (43)       | .09                  |
| Education, y                              | 97                                    | 15.17 (2.91)                     | 15.46 (3.22)                     | 15.28 (3.02)  | .49                  |
| <i>APOE-<math>\epsilon</math></i> alleles |                                       |                                  |                                  |               |                      |
| 0   | 97                                    | 53 (88)                          | 20 (54)                          | 73 (75)       |                      |
| 1   |                                       | 7 (12)                           | 16 (43)                          | 23 (24)       | <.001                |
| 2   |                                       | 0 (0)                            | 1 (3)                            | 1 (1)         |                      |
| Word List Delayed Recall score            | 97                                    | 3.02 (1.65)                      | 3.24 (1.64)                      | 3.10 (1.64)   | .48                  |
| Logical Memory Delayed Recall score       | 97                                    | 11.10 (2.56)                     | 11.35 (2.68)                     | 11.20 (2.59)  | .62                  |
| MMSE score                                | 97                                    | 28.83 (1.15)                     | 29.05 (1.05)                     | 28.92 (1.11)  | .33                  |
| Digit Symbol Substitution Test score      | 97                                    | 45.60 (9.27)                     | 42.30 (8.49)                     | 44.34 (9.08)  | .09                  |
| ADAS-Cog score                            | 97                                    | 9.96 (3.81)                      | 11.13 (4.12)                     | 10.41 (3.95)  | .12                  |
| CSF A $\beta$ 42 level, pg/mL             | 90                                    | 244.3 (27.2)                     | 144.9 (26.3)                     | 206.8 (55.4)  | <.001                |
| CSF T-tau level, pg/mL                    | 90                                    | 61.2 (19.8)                      | 82.2 (35.8)                      | 69.2 (28.7)   | .005                 |
| PIB SUVR                                  | 15                                    | 1.244 (0.101)                    | 1.900 (0.122)                    | 1.594 (0.356) | <.001                |
| FDG uptake, average intensity score       | 52                                    | 6.500 (0.607)                    | 6.327 (0.703)                    | 6.430 (0.646) | .38                  |
| CDR-SB score of 0.5                       | 97                                    | 5 (8)                            | 1 (3)                            | 6 (6)         | .26                  |
| UCSF hippocampi, %ICV $\times$ 1000       | 87                                    | 485.7 (62.1)                     | 459.4 (50.0)                     | 476.3 (59.1)  | .04                  |
| UCSF ventricles, %ICV $\times$ 1000       | 87                                    | 1989 (980)                       | 2387 (878)                       | 2131 (959)    | .02                  |
| <b>AIBL</b>                               |                                       |                                  |                                  |               |                      |
| Total No.                                 | 164                                   | 114                              | 50                               | 164           |                      |
| Age, y                                    | 164                                   | 69.75 (6.83)                     | 75.06 (6.91)                     | 71.37 (7.26)  | <.001                |
| Female sex                                | 164                                   | 61 (54)                          | 26 (52)                          | 87 (53)       | .86                  |
| Education, y                              | 164                                   | 12.51 (2.53)                     | 12.27 (2.70)                     | 12.44 (2.58)  | .49                  |



| Characteristic                       | Participants With Available Data, No. | Aβ-Negative Participants | Aβ-Positive Participants | All          | P Value <sup>b</sup> |
|--------------------------------------|---------------------------------------|--------------------------|--------------------------|--------------|----------------------|
| <i>APOE-ε4</i> alleles               | 164                                   |                          |                          |              |                      |
| 0                                    |                                       | 77 (68)                  | 17 (34)                  | 94 (57)      |                      |
| 1                                    |                                       | 34 (30)                  | 31 (62)                  | 65 (40)      | <.001                |
| 2                                    |                                       | 3 (3)                    | 2 (4)                    | 5 (3)        |                      |
| Word List Delayed Recall score       | 164                                   | 11.95 (2.97)             | 11.82 (3.16)             | 11.91 (3.02) | .88                  |
| Logical Memory Delayed Recall score  | 162                                   | 11.87 (3.75)             | 10.88 (4.14)             | 11.57 (3.89) | .12                  |
| MMSE score                           | 164                                   | 28.89 (1.20)             | 28.68 (1.17)             | 28.83 (1.19) | .20                  |
| Digit Symbol Substitution Test score | 164                                   | 59.7 (13.2)              | 55.5 (12.9)              | 58.5 (13.2)  | .05                  |

Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale–Cognitive Subscale; ADNI, Alzheimer’s Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; FDG, <sup>18</sup> fluorodeoxyglucose; MMSE, Mini-Mental State Examination; PIB, Pittsburgh compound B; SUVr, standardized uptake value ratio; UCSF, University of California, San Francisco; %ICV, percentage of intracranial volume.

<sup>a</sup> All values are given as mean (SD) values or number (%) of participants, unless otherwise indicated.

<sup>b</sup> Determined by use of the Wilcoxon test for continuous variables and the Pearson  $\chi^2$  test for categorical variables.

**Table 2**

Baseline Characteristics of Participants in the ADCS-PI Study, by Group<sup>a</sup>

| Characteristic                       | Participants With Available Data, No. | Group of Participants                  |                                     |                  | P Value <sup>b</sup> |
|--------------------------------------|---------------------------------------|--|-------------------------------------|------------------|----------------------|
|                                      |                                       | CDR-G Stable<br>(n = 478)              | CDR-G Progressor<br>(n = 27)        | All<br>(n = 505) |                      |
| Age, y                               | 505                                   | 79.36 (3.60)                           | 80.52 (3.82)                        | 79.42 (3.62)     | .08                  |
| Female sex                           | 505                                   | 286 (60)                               | 19 (70)                             | 305 (60)         | .28                  |
| Education, y                         | 505                                   | 15.05 (2.95)                           | 14.15 (3.46)                        | 15.00 (2.98)     | .18                  |
| <i>APOE-ε4</i> alleles               | 305                                   |  |                                     |                  |                      |
| 0                                    |                                       | 223 (77)                               | 13 (76)                             | 236 (77)         |                      |
| 1                                    |                                       | 63 (22)                                | 4 (24)                              | 67 (22)          | .93                  |
| 2                                    |                                       | 2 (1)                                  | 0 (0)                               | 2 (1)            |                      |
| FCSRT Total Free Recall score        | 504                                   | 28.97 (5.53)                           | 25.37 (5.99)                        | 28.77 (5.61)     | .01                  |
| FCSRT Total Recall score             | 504                                   | 47.851 (0.464)                         | 47.556 (0.847)                      | 47.835 (0.495)   | .005                 |
| 3MSE score                           | 505                                   | 95.86 (3.37)                           | 92.04 (4.10)                        | 95.66 (3.51)     | <.001                |
| CDR-SB score of 0.5                  | 505                                   | 90 (19)                                | 8 (30)                              | 98 (19)          | .17                  |
| Digit Symbol Substitution Test score | 495                                   | 42.1 (11.8)                            | 34.2 (10.5)                         | 41.7 (11.9)      | <.001                |
| NYU Paragraph Recall score           | 497                                   | 7.45 (2.80)                            | 5.44 (2.39)                         | 7.34 (2.81)      | <.001                |
|                                      |                                       | <i>APOE-ε4</i> Noncarrier<br>(n = 310) | <i>APOE-ε4</i> Carrier<br>(n = 103) | All<br>(n = 413) |                      |
| Age, y                               | 413                                   | 79.73 (3.63)                           | 78.58 (3.15)                        | 79.44 (3.55)     | .002                 |
| Female sex                           | 413                                   | 170 (55)                               | 59 (57)                             | 229 (55)         | .67                  |
| Education, y                         | 413                                   | 14.94 (3.33)                           | 15.38 (2.76)                        | 15.05 (3.20)     | .43                  |
| <i>APOE-ε4</i> alleles               | 413                                   |  |                                     |                  |                      |
| 0                                    |                                       | 310 (100%)                             | 0 (0%)                              | 310 (75%)        |                      |
| 1                                    |                                       | 0 (0)                                  | 99 (96)                             | 99 (24)          | <.001                |
| 2                                    |                                       | 0 (0)                                  | 4 (4)                               | 4 (1)            |                      |
| FCSRT Total Free Recall score        | 412                                   | 27.99 (6.01)                           | 28.92 (5.71)                        | 28.22 (5.94)     | .06                  |
| FCSRT Total Recall score             | 412                                   | 47.803 (0.554)                         | 47.853 (0.515)                      | 47.816 (0.545)   | .24                  |
| CDR-SB score                         | 413                                   | 0.332 (0.507)                          | 0.403 (0.560)                       | 0.350 (0.521)    | .28                  |

| Characteristic                       | Participants With Available Data, No. | Group of Participants     |                              |                  | P Value <sup>b</sup> |
|--------------------------------------|---------------------------------------|---------------------------|------------------------------|------------------|----------------------|
|                                      |                                       | CDR-G Stable<br>(n = 478) | CDR-G Progressor<br>(n = 27) | All<br>(n = 505) |                      |
| 3MSE score                           | 413                                   | 95.20 (3.88)              | 95.85 (3.15)                 | 95.37 (3.72)     | .27                  |
| Digit Symbol Substitution Test score | 411                                   | 40.7 (12.1)               | 40.4 (11.9)                  | 40.6 (12.0)      | .79                  |
| NYU Paragraph Recall score           | 413                                   | 7.14 (2.82)               | 7.23 (2.72)                  | 7.16 (2.80)      | .65                  |

Abbreviations: ADCS-PI, Alzheimer's Disease Cooperative Study Prevention Instrument; CDR-G progressor, global Clinical Dementia Rating score from 0 to worse score; CDR-G stable, global CDR score of 0; CDR-SB, Clinical Dementia Rating-Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; NYU, New York University; 3MSE, Modified Mini-Mental State Examination.

<sup>a</sup> All values are given as mean (SD) values or number (%) of participants, unless otherwise indicated.

<sup>b</sup> Determined by use of the Wilcoxon test for continuous variables and the Pearson  $\chi^2$  test for categorical variables.

**Table 3**

MMRM Estimates of Composite Change From Baseline, by Study<sup>a</sup>

| Month   | Group                  | Participants, No. | Estimate (SE)  | P Value | Adjusted P Value <sup>b</sup> | 95% CI           | $\sigma$ Value <sup>c</sup> | $\rho$ Value <sup>d</sup> |
|---|------------------------|-------------------|----------------|---------|-------------------------------|------------------|-----------------------------|---------------------------|
| <b>ADNI A<math>\beta</math><sup>+</sup> (n = 36) vs A<math>\beta</math><sup>-</sup> (n = 59)</b>  |                        |                   |                |         |                               |                  |                             |                           |
| 6   | A $\beta$ <sup>-</sup> | 59                | -0.133 (0.310) | .67     |                               | -0.740 to 0.473  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 36                | -0.439 (0.401) | .28     |                               | -1.225 to 0.348  |                             |                           |
|   | Difference             |                   | -0.306 (0.503) | .54     | .94                           | -1.291 to 0.679  | 2.327                       |                           |
| 12  | A $\beta$ <sup>-</sup> | 58                | 0.581 (0.315)  | .07     |                               | -0.037 to 1.199  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 34                | -0.263 (0.414) | .53     |                               | -1.075 to 0.549  |                             |                           |
|   | Difference             |                   | -0.844 (0.516) | .10     | .30                           | -1.857 to 0.168  | 2.358                       |                           |
| 24  | A $\beta$ <sup>-</sup> | 53                | 0.558 (0.325)  | .09     |                               | -0.080 to 1.196  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 34                | -0.681 (0.415) | .10     |                               | -1.494 to 0.132  |                             |                           |
|   | Difference             |                   | -1.239 (0.522) | .02     | .06                           | -2.263 to -0.215 | 2.361                       |                           |
| 36  | A $\beta$ <sup>-</sup> | 52                | -0.145 (0.356) | .68     |                               | -0.843 to 0.553  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 27                | -0.497 (0.487) | .31     |                               | -1.451 to 0.457  |                             |                           |
|   | Difference             |                   | -0.352 (0.599) | .56     | .94                           | -1.527 to 0.823  | 2.578                       | 0.459                     |
|   | Area between curves    |                   | -26.4 (13.6)   | .05     |                               |                  |                             |                           |
| <b>AIBL A<math>\beta</math><sup>+</sup> (n = 47) vs A<math>\beta</math><sup>-</sup> (n = 110)</b> |                        |                   |                |         |                               |                  |                             |                           |
| 18  | A $\beta$ <sup>-</sup> | 110               | 0.009 (0.215)  | .97     |                               | -0.412 to 0.429  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 47                | -1.000 (0.334) | .003    |                               | -1.655 to -0.345 |                             |                           |
|   | Difference             |                   | -1.009 (0.406) | .01     | .02                           | -1.805 to -0.213 | 2.213                       |                           |
| 36  | A $\beta$ <sup>-</sup> | 104               | -0.134 (0.229) | .56     |                               | -0.583 to 0.315  |                             |                           |
|   | A $\beta$ <sup>+</sup> | 36                | -1.538 (0.381) | <.001   |                               | -2.285 to -0.791 |                             |                           |
|   | Difference             |                   | -1.404 (0.452) | .002    | .004                          | -2.290 to -0.519 | 2.315                       | 0.520                     |
|   | Area between curves    |                   | -30.8 (10.1)   | .002    |                               |                  |                             |                           |

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; MMRM, mixed model of repeated measures;

+ , positive;

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<sup>a</sup> , negative.

<sup>a</sup> The models assume heterogeneous compound symmetric covariance structure, which allows different variance parameters ( $\sigma$ ) per visit, and a single correlation parameter ( $\rho$ ).

<sup>b</sup> Adjusted for model-based simultaneous inference.

<sup>c</sup> Residual standard deviation estimate at each visit.

<sup>d</sup> Estimated correlation between visits.

**Table 4**  
MMRM Estimates of Composite Change From Baseline, by ADCS-PI Study Group<sup>a</sup>

| Month   | Group               | Participants, No. | Estimate (SE)  | P Value | Adjusted P Value <sup>b</sup> | 95% CI           | $\sigma$ Value <sup>c</sup> | $\rho$ Value <sup>d</sup> |
|---|---------------------|-------------------|----------------|---------|-------------------------------|------------------|-----------------------------|---------------------------|
| <b>CDR-G Progressor (n = 27) vs Stable (n = 422)</b>                        |                     |                   |                |         |                               |                  |                             |                           |
| 12  | Progressor          | 27                | -2.187 (0.418) | <.001   |                               | -3.006 to -1.367 |                             |                           |
|   | Stable              | 422               | 0.276 (0.105)  | .009    |                               | 0.070-0.482      |                             |                           |
|   | Difference          |                   | -2.463 (0.435) | <.001   | <.001                         | -3.316 to -1.610 | 2.121                       |                           |
| 24  | Progressor          | 24                | -2.661 (0.438) | <.001   |                               | -3.519 to -1.804 |                             |                           |
|   | Stable              | 381               | 0.238 (0.109)  | .03     |                               | 0.024-0.453      |                             |                           |
|   | Difference          |                   | -2.899 (0.455) | <.001   | <.001                         | -3.791 to -2.008 | 3.208                       |                           |
| 36  | Progressor          | 21                | -4.153 (0.679) | <.001   |                               | -5.484 to -2.823 |                             |                           |
|   | Stable              | 335               | 0.318 (0.170)  | .06     |                               | -0.015 to 0.651  |                             |                           |
|   | Difference          |                   | -4.471 (0.702) | <.001   | <.001                         | -5.848 to -3.094 | 2.133                       | 0.542                     |
|   | Area between curves |                   | -91.2 (12.4)   | <.001   |                               |                  |                             |                           |
| <b>APOE-<math>\epsilon</math>4 Carrier (n = 95) vs Noncarrier (n = 281)</b> |                     |                   |                |         |                               |                  |                             |                           |
| 12  | Carrier             | 95                | -0.370 (0.227) | .10     |                               | -0.815 to 0.075  |                             |                           |
|   | Noncarrier          | 281               | 0.117 (0.131)  | .37     |                               | -0.140 to 0.374  |                             |                           |
|   | Difference          |                   | -0.487 (0.263) | .06     | .16                           | -1.003 to 0.028  | 2.197                       |                           |
| 24  | Carrier             | 87                | -0.854 (0.254) | .001    |                               | -1.352 to -0.356 |                             |                           |
|   | Noncarrier          | 256               | -0.112 (0.147) | .45     |                               | -0.400 to 0.176  |                             |                           |
|   | Difference          |                   | -0.742 (0.294) | .01     | .03                           | -1.318 to -0.165 | 3.646                       |                           |
| 36  | Carrier             | 75                | -1.628 (0.406) | <.001   |                               | -2.423 to -0.833 |                             |                           |
|   | Noncarrier          | 225               | -0.098 (0.234) | .68     |                               | -0.557 to 0.362  |                             |                           |
|   | Difference          |                   | -1.531 (0.469) | .001    | .003                          | -2.450 to -0.612 | 2.388                       | 0.547                     |
|   | Area between curves |                   | -23.9 (7.84)   | .002    |                               |                  |                             |                           |

Abbreviations: ADCS-PI, Alzheimer's Disease Cooperative Study Prevention Instrument; CDR-G, global Clinical Dementia Rating score from 0 to worse score; CDR-G stable, global CDR score of 0; MMRM, mixed model of repeated measures.

<sup>a</sup>The models assume heterogeneous compound symmetric covariance structure, which allows different variance parameters ( $\sigma$ ) per visit, and a single correlation parameter ( $\rho$ ).

<sup>b</sup> Adjusted for model-based simultaneous inference.



<sup>c</sup> Residual standard deviation estimate at each visit.

<sup>d</sup> Estimated correlation between visits.

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