Simultaneously evaluating the effect of baseline levels and longitudinal changes in disease biomarkers on cognition in dominantly inherited Alzheimer’s disease

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Introduction: As the role of biomarkers is increasing in Alzheimer’s disease (AD) clinical trials, it is critical to use a comprehensive temporal biomarker profile that reflects both baseline and longitudinal assessments to establish a more precise association between the change in biomarkers and change in cognition. Because age of onset of dementia symptoms is highly predictable, and there are relatively few age-related comorbidities, the Dominantly Inherited Alzheimer Network autosomal dominant AD population affords a unique opportunity to investigate these relationships in a well-characterized population.

Methods: A novel joint statistical model was used to simultaneously evaluate how a comprehensive AD biomarker profile predicts change in cognition using amyloid positron emission tomography (PET), CSF Aβ42, CSF total tau and Ptau181, cortical metabolism using [F-18] fluorodeoxyglucose–PET, and hippocampal volume from participants enrolled in the Dominantly Inherited Alzheimer Network (n = 262) with mean (SD) duration of follow-up of 2.7 (1.2) years.

Results: Baseline amyloid PET levels and CSF biomarkers were associated with change in cognition in contrast to the rate of change of brain metabolism and hippocampal volume, which predicted change in cognition.

Conclusions: This study suggests that the baseline value of amyloid PET and CSF Aβ42 measures may be useful for screening participants for AD trials; however, brain hippocampus atrophy and hypometabolism are only useful as repeated longitudinal assessments for tracking cognition and disease progression. This suggests that measures of amyloid plaques predict future cognitive decline, but only longitudinal measures of neurodegeneration correlate with cognitive decline. The novel statistical model used in this study can be easily applied to any pair of outcomes and has potential to be widely used by the AD research community.

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1. Background

With the increase of presymptomatic Alzheimer disease (AD) trials comes the need to improve methods for predicting the relatively small decline in cognition expected over a reasonable period. With the increase in biomarkers available for routine use, there is a greater need to use AD biomarkers for enrollment, interim analysis, and/or as the primary outcome at the earliest stage of the disease. For example, the A4 trial [1] used evidence of amyloid accumulation on an initial positron emission tomography (PET) scan to select trial participants, whereas the Dominantly Inherited Alzheimer Network-Trial Unit (DIAN-TU) [2] and the Alzheimer’s Prevention Initiative [3] trials used biomarkers for an interim analysis to determine whether the trial should end early for futility. The assumption is that such biomarker information ultimately relates to cognitive outcomes. Therefore, understanding the association between AD biomarkers and early cognitive changes is critical to validate the legitimacy of using biomarkers as the primary outcome in prevention trials.

Traditionally, the association between biomarkers and cognition has been investigated in three ways: (1) using biomarker values from the baseline assessment to estimate the association with the baseline cognitive performance and/or to predict the change in cognition [4–6]; (2) using longitudinal biomarker values to estimate the correlation in rates of change between biomarkers and cognition [7]; and (3) using a “two-stage” method to obtain the rate of change in biomarkers at the first stage and then use it as a covariate to estimate how it predicts the change in cognition at the second stage [8–10]. However, no studies have simultaneously used both the baseline and longitudinal biomarkers in a single model to predict the change in cognition. Using both predictors in one model offers several advantages: (1) it estimates the significance of both the baseline and longitudinal biomarkers to predict cognitive change simultaneously; (2) provides a comparison of which predictor is relatively more informative; and (3) leads to more accurate estimation because both predictors are adjusted for each other in the same model and each individual serves as its own control (eliminating potential confounders such as age and disease stage). The objective of this study is to evaluate the utility of simultaneously using the baseline value and the longitudinal change in biomarkers to predict cognitive decline in dominantly inherited Alzheimer’s disease in which presence of a disease-causing mutation will invariably lead to dementia.

2. Methods

2.1. Study design and participants

The Dominantly Inherited Alzheimer Network (DIAN) study is a longitudinal, multinational, observational study enrolling participants with at least 50% risk of inheriting a disease-causing, autosomal dominant AD (ADAD) mutation from families with a confirmed genetic mutation in one of three genes: PSEN1, PSEN2, or APP. The presence or absence of an ADAD mutation was determined using PCR-based amplification of the appropriate exon followed by Sanger sequencing. Participants with confirmed mutations are referred to as mutation carriers (MCs); otherwise, they are referred to as mutation noncarriers (NMCs). Participants underwent clinical assessments, cognitive testing, neuroimaging, and CSF assessments at each visit [11,12]. Participants from families that carry the APP E693G (Dutch) mutation were excluded from the analyses because of previous evidence of little neuritic plaque and neurofibrillary tangle pathology [13].

2.2. Clinical and neuropsychological assessments

The Clinical Dementia Rating (CDR) Scale was used to define dementia stage as cognitively normal (CDR = 0), very mild dementia (CDR = 0.5), mild dementia (CDR = 1), and moderate dementia (CDR = 2) [14]. Neuropsychological tests assessing language, memory, attention, executive function, visuospatial function, and general cognitive ability were conducted at each visit [15]. Similar to previous studies [2,16], a composite z-score was calculated using measures of episodic memory (delayed recall of the DIAN 16 word-list learning test and delayed paragraph recall from the Wechsler Memory Scale-Revised Logical Memory Test), complex attention and processing speed (Wechsler Adult Intelligence Scale Digit Symbol Substitution Test), and a general cognitive screen (Mini–Mental State Examination). The composite score covered the major cognitive domains and reflected early cognitive changes in the preclinical stages of ADAD [17].

2.3. Imaging acquisition and process

Magnetic resonance imaging (MRI) scans were obtained using 3 Tesla volumetric T1-weighted MRI scanners following the Alzheimer’s Disease Neuroimaging Initiative (ADNI) protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/) and processed through FreeSurfer, version 5.3 (Martinos Center, Boston, MA), as previously described [18]. The T1-weighted images were used for measurements of hippocampal volumes adjusted for total intracranial volumes using a regression approach, and for measurements of cortical volumes and ventricular volumes.

β-Amyloid (Aβ) imaging with PET was acquired between 40 and 70 minutes after injection of [C-11] Pittsburgh compound B (PiB). A standard uptake value ratio was used to determine levels of Aβ deposition for each region of interest derived using FreeSurfer. Metabolic imaging with [F-18] fluorodeoxyglucose–PET (FDG PET) was performed with a 3D dynamic acquisition starting 30 minutes after a bolus injection of approximately 5 mCi of FDG and lasting 30 minutes. The mean cortical standard uptake value ratio was...
calculated from regions within the prefrontal cortex, precuneus, and temporal cortex as previously described [19].

2.4. CSF biomarker assays

CSF was collected in accordance with ADNI protocols. Briefly, ~15 mL of CSF was collected at 8:00 am following overnight fasting in polypropylene tubes and was immediately frozen on dry ice. Frozen samples were shipped to the DIAN Biomarker Core, thawed, aliquoted (0.5 ml), flash-frozen, and stored at −84°C until analysis.

All assays were performed on aliquots of the same CSF samples. Aβ42, total tau, and Ptau were measured with the corresponding Elecsys immunoassays on the Elecsys cobas e 601 analyzer in the laboratory of Leslie M. Shaw in the ADNI Biomarker Core at the University of Pennsylvania as previously described [20,21]. The Elecsys immunoassays are electrochemiluminescense immunoassays employing a quantitative sandwich principle. A single lot of immunoassay reagents for each analyte was used to measure all samples to avoid drift in the longitudinal measures [22].

2.5. Statistical analyses

We used the concept of joint modeling similar to those that were widely used to model longitudinal data and survival data [23,24] and developed a novel joint model of two general linear mixed-effects (LME) models to simultaneously evaluate how the baseline value and the rate of change (slope) of each biomarker predict decline in cognition. The joint model consisted of two LME submodels and estimated them simultaneously—specifically, a biomarker LME submodel, which included a random intercept for family cluster, random intercepts and random slopes for each individual, and fixed effect of time (years in study), and a cognition LME submodel, which included a random intercept for family cluster, random intercepts and random slopes for each individual, the two-way interaction between time and the individual biomarker random intercept, and the two-way interaction between time and the individual biomarker random slope. For sensitivity analysis, other covariates that were considered potentially associated with cognitive outcomes such as gender, education, baseline age, and apolipoprotein E (APOE) status were also included. Random intercepts for each family-membership cluster were used to account for the within-family cluster correlation. Thus, the joint LME model simultaneously estimates the intercept and the slope of the biomarker, the change in cognition predicted by the baseline biomarker, the change in cognition predicted by the biomarker slope, and the change in cognition not predicted by either the biomarker baseline or slope. Different residual variances and different unstructured covariance matrices for random effects were assumed for biomarkers and cognition. The joint model was estimated using maximum likelihood and connected the same individual’s biomarker and cognition data together, thus controlling for any potential confounders. The model was capable of handling unevenly spaced and unbalanced biomarker and cognition data as well as missing data [25] and thus did not require each individual to have the same amount of biomarker and cognition data. We applied the same analyses separately to NMCs and MCs. We then within the MC cohort conducted follow-up analyses separately on asymptomatic mutation carriers (aMCs; baseline CDR = 0) and on symptomatic mutation carriers (sMCs; baseline CDR >0). All models were implemented using proc nlmixed/SAS (SAS Institute Inc., Cary, NC [23], and their initial values were estimated by applying LME separately to each outcome using proc mixed (SAS Institute Inc.). To avoid nonconvergent problems due to dramatic differences in biomarker measurement scales and the cognitive composite (z-score) [26], CSF total tau, CSF Aβ42, CSF Ptau, and MRI hippocampal volumes were standardized to z-scores with mean 0 and SD 1. Please see Supplemental Materials for more details on the statistical models.

3. Results

3.1. Study participants

We analyzed 293 MCs and 188 NMCs from the DIAN cohort (Table 1). Of the MCs, 225 (76.8%) had PSEN1, 22 (7.5%) PSEN2, and 46 (15.7%) APP mutations. Among the 293 MCs, 186 (63.5%) were asymptomatic (CDR 0) at baseline.

3.2. Cognition rate of change predicted by the biomarker

The cognition rates of change predicted by the biomarker baseline and biomarker slope in the MCs are presented in Table 2. The estimated effect size of the predictability and the comparison between the baseline and the rate of change are summarized in Fig. 1. Overall, the baseline value for CSF total tau, CSF Ptau, CSF Aβ42, and PiB PET is a better predictor of the cognitive decline than their respective longitudinal change, whereas the longitudinal change is a better predictor for MRI hippocampus volume, FDG PET (Fig. 1). MRI hippocampus volume is the only biomarker whose baseline and rate of change are both significantly associated with the change in cognition.

The effect size of baseline PiB was such that a 1-unit increase in amyloid-PiB led to 0.15 z-score greater annual decline in cognitive composite score. Furthermore, after accounting for the change associated with both the baseline and the change in PiB PET, the remaining change in cognition was positive (Table 2) suggesting that below a certain threshold of PiB, (estimated to be 1.3 using the same model) the cognitive change is minimal or slightly positive. Because we have found the precuneus to be an area of very early PiB-PET increase [27], we repeated the analyses limiting it to the precuneus. We found not only was the baseline value more informative than the rate of change but the baseline also
became significant \([-0.26 (0.06), P < .0001\) for PiB baseline; 0.61 (0.62), \(P = .32\) for PiB rate of change].

For all CSF biomarkers, only the baseline value was related to change in cognition. This is not surprising for total tau and Ptau because their rates of change were not significant. The fact that the rate of change of CSF Aβ42 was significant but not related to change in cognition suggests that the rate of change of CSF Aβ42 was much earlier than that of cognition.

For global FDG PET, the longitudinal change predicted change in cognition, but not the baseline (Table 2). Specifically, the annual rate of change in FDG PET was \(-0.009, P = .26 (0.06), P < .0001\) for PiB rate of change. The results for asymptomatic MCs were similar to those for the combined MC group, although some of them were not significant because of the smaller sample size and the decrease in the magnitude of change (Supplemental Table 2). For symptomatic MCs, the results generally demonstrated consistent patterns, although the weight of the predictability in the rate of change for FDG PET largely increases (Supplemental Table 3). In addition, the rate of change of CSF Ptau became negative and significantly associated with the cognitive rate of change (Supplemental Table 3).

4. Discussion

Using the DIAN longitudinal study and a novel mixed-effects model, we simultaneously evaluated/tested the predictability of the biomarker baseline and the biomarker change (slope) on the cognitive change and showed that for different biomarkers, the predictability of the slope vs. baseline values differed. Specifically, change in cognition was better predicted by baseline rather than change in PiB PET and CSF biomarkers, whereas the rate of change for the remaining biomarkers (FDG PET, hippocampal volume) was the better predictor of the cognitive change. To our knowledge, this study represents the first attempt to use the whole biomarker profile (baseline and change) to establish the association between all major AD biomarkers and cognition across the spectrum of disease from preclinical to cognitively impaired. A clear advantage of using the whole biomarker profile is that the model allows comparison of the predictability between the biomarker baseline and the biomarker change.

Consistent with previous reports [4–6], we found that higher cerebral amyloid deposition at baseline predicted longitudinal cognitive decline; however, the individual rate of change in amyloid did not. Xiong et al. [7] previously evaluated the correlation between the change in amyloid deposition and the change in cognition in sporadic AD and concluded that the correlation was not significant, which is indirectly validated by our result in that the former does not predict the latter. For both cerebral amyloid deposition and CSF Aβ42, the baseline value is more informative than the longitudinal change in predicting the cognitive decline. This result further supports using baseline amyloid burden such as PiB PET as an important biomarker inclusion for
Table 2

| Biomarkers | Participants | Change in cognition predicted by the biomarker baseline, mean (SE) | Change in cognition predicted by the biomarker slope, mean (SE) |
|------------|--------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Mean PiB PET | 2.08 (0.08) | P < 0.001 | 0.15 (0.085) |
| Mean FDG PET | 0.12 (0.21) | P < 0.05 | 0.55 (1.13) |
| MRI hippocampal volume | 0.18 (0.15) | P < 0.001 | 0.073 (0.010) |
| Total tau | 0.02 (0.12) | P < 0.05 | 0.01 (0.07) |
| Ptau | 0.13 (0.02) | P < 0.001 | 0.10 (0.06) |

Abbreviations: MC, mutation carrier; FDG, [F-18] fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PIB, (C-11) Pittsburgh compound B.

The change in cognition predicted by the biomarker baseline and the biomarker slope for MCs only.

A decline in hippocampal volume has been demonstrated to be associated with cognitive decline [7,8], but the results with baseline hippocampal volume are inconsistent [7,8]. These differences could be attributed to the different study cohorts (e.g., age of onset, comorbid pathologies). Our results indicate that in this younger population both the baseline and the rate of change in hippocampal volumes predict cognitive decline, which verifies previous results using different cognitive tests [8]. Although other studies have shown that both the baseline and the change in FDG-PET were associated with cognitive decline [9], we found that only the change significantly predicted the cognitive decline. The discrepancy might be due to the study cohorts (sporadic AD vs ADAD), the sample size, or the analytical methods. Again, an important advantage of our analysis is that it takes into account, simultaneously, the baseline (accumulation of pathology at a specific time) and the change (ongoing pathological dynamics) to better account for the total burden of pathology in a disease with a prolonged time course.

Although our study had many strengths, there are also several limitations that warrant mention. First, our analyses are based on an ADAD cohort, and our findings may not extend to the more common sporadic AD where the age of onset is much older and additional pathologies less common in ADAD (e.g., TDP-43, cerebrovascular disease) might influence the associations identified here. Although these merit direct investigation, two recently published articles using a data-driven, event-based modeling technique identified a similar biomarker/cognition profile between ADAD and sporadic AD (initial change in Aβ is most prominent, cognition actually does not decline as fast as when the CSF Aβ42 decline is relatively moderate or plateaued later in the disease).

Secondary prevention trials in AD [1,3], and as a principle component of the newly proposed AD diagnostic criteria [28,29]. Also it has been reported that low baseline CSF Aβ42 leads to significant cognitive decline [7,30], this pattern was consistent in our results. In addition, the rate of change in CSF Aβ42 did not significantly predict the rate of cognitive decline, which is similar to the lack of correlation in previous reports [7]. This finding reveals that at the very early disease stage when the CSF Aβ42 decline is most prominent, cognition actually does not decline as fast as when the CSF Aβ42 decline is relatively moderate or plateaued later in the disease.

Table 2

| Biomarker | Mean PiB PET | Mean FDG PET | MRI hippocampal volume | Total tau | Ptau |
|-----------|--------------|--------------|------------------------|-----------|------|
| MC        | 2.08 (0.08)  | 0.12 (0.21)  | 0.18 (0.15)            | 0.02 (0.12)| 0.13 (0.02) |

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recent work in sporadic AD has suggested that levels of CSF biomarkers may differ between African Americans and non-Hispanic white Americans. Unfortunately, our current numbers of non-Hispanic whites are relatively low limiting our ability to explore these factors. Similarly, specific geographic and socioeconomic differences could contribute to differences in cognitive reserve resulting in differences in cognitive change at similar biomarker levels. Expansion of the DIAN cohort as well as the large kindred from Colombia should provide good opportunities to further explore these potentially important contributors. Future research should also directly analyze a sporadic AD cohort and include subgroup analyses for age and ethnic groups to evaluate whether or not our findings replicate. Second, our cognitive composite score is composed of tests that are different from those used in previous studies; therefore, caution is needed to interpret the discrepancies in various findings, which may be due to the relative sensitivity of various cognitive tests. Third, there are challenges to interpret the findings when using z-scores—primarily, the loss of meaningfulness of the raw score and its standard deviation, magnifying small changes, not reflecting the reality of memory declines. Similar analysis may also be done directly for each individual cognitive/clinical test on their original scales to avoid the interpretation difficulty of using z-scores. Fourth, we assumed that both the cognitive decline and the biomarker change are linear. Although this is valid in our study cohort at the individual level given the relatively short follow-up, such changes may become nonlinear as the follow-up period increases. Exploration of nonlinear longitudinal change in both biomarkers and cognitive tests may provide more accurate evaluation of the associations among them but requires more complicated models and computation times. A further challenge for these future researches is to obtain an appropriate data set, which has adequate follow-up to demonstrate potential nonlinear change and provides sufficient sample size for subgroup analysis. Importantly, the comprehensive protocol followed in DIAN allows for a rich biomarker and clinical characterization of participants at multiple stages in the disease process. Ongoing work to implement novel cognitive test paradigms in DIAN coupled with the extensive biomarkers collected will allow us to explore possible nonlinear cognitive patterns such as practice effects.

Our findings are based on a novel method using the whole biomarker profile (baseline + change) simultaneously and in most cases are consistent with previous results. The method is able to establish the association or lack of between the whole biomarker profile and cognitive decline. It also provides a comparison of the predictability, which helps determine which biomarker to use to identify the “right” trial cohort at enrollment and which biomarker to use at the interim analysis to determine whether a drug is hitting the target in AD clinical trials. Furthermore, the method can be applied to any pair of longitudinal outcomes (e.g., PiB PET and CSF Aβ42) to explore their association or to evaluate their order of change.
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Supplementary data

Supplementary data to this article can be found online at doi.org/10.1016/j.trci.2018.10.009.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the existing literature on establishing the association between biomarkers and cognition. Most studies investigated either only baseline biomarker levels or longitudinal changes in biomarkers. For those studies that used both, they typically used a “two-stage” analytic method, which can lead to biased or inaccurate estimation.

2. Interpretation: An informative comparison between the predictability of the baseline and the rate of change of the biomarkers for cognitive change facilitates the use of biomarkers in Alzheimer’s disease (AD) clinical trials.

3. Future directions: Repeated biomarker assessments are valuable for studies focused on cognitive changes in AD populations. Joint models that incorporate both baseline and longitudinal measures of AD biomarkers are likely to have more accurate predictive power than either method alone and may be extremely useful for primary and secondary prevention trials in AD.
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