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Combining Multiple Markers to Improve the Longitudinal Rate of Progression-Application to Clinical Trials on the Early Stage of Alzheimer's Disease

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Abstract

Clinical trials on early stage Alzheimer's disease (AD) are reaching a bottleneck because none of the current disease markers changes appreciably early in the disease process and therefore a huge sample is required to adequately power such trials. We propose a method to combine multiple markers so that the longitudinal rate of progression can be improved. The criterion is to maximize the probability that the combined marker will be decreased over time (assuming a negative mean slope for each marker). We propose estimates to the weights of markers in the optimum combination and a confidence interval estimate to the combined rate of progression through the maximum likelihood estimates and a bootstrap procedure. We conduct simulations to assess the performance of our estimates and compare our approach with the first principal component from a principal component analysis. The proposed method is applied to a real world sample of individuals with preclinical AD to combine measures from two cognitive domains. The combined cognitive marker is finally used to design future clinical trials on preclinical AD, demonstrating a significant improvement in reducing the sample sizes needed to power such trials when compared with individual markers alone.

Keywords

Bootstrap estimate; Delta method; Multivariate random coefficients models; Power; Preclinical Alzheimer's disease (AD); Randomized clinical trials (RCT); Sample size

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1. Introduction

Alzheimer's disease (AD) is an age-related brain-damaging disorder that results in progressive cognitive impairment and death. Accumulating research evidence suggests that neurodegenerative processes associated with AD begin years prior to the symptomatic onset of AD when the disease is clinically at the early prodromal stage or even the latent stage (Katzman, 1976). Many recent clinicopathologic studies have also suggested a time window prior to the symptomatic onset of AD during which no clinical diagnosis could be rendered, but neuropathological changes of AD, notably senile plaques and neurofibrillary tangles, have accumulated (Price et al. 2009, Bennett et al. 2006, Morris and Price 2001). These observations have led to the concept of "preclinical AD", i.e., AD brain pathology develops prior to clinical symptoms. This model suggests an early and insidious pathogenesis of AD, the clinical manifestation of which becomes apparent only after substantial neuronal death and synaptic loss have taken place. To date, there are no pharmaceutical treatments that reverse the pathological processes of AD. A recent report on the neuropathological follow-up of patients with AD who had entered a phase I randomized, placebo-controlled trial of immunization with $A\beta_{42}$ (AN1792, Elan Pharmaceuticals) indicated that, although the immunization resulted in clearance of amyloid plaques in the brain, this clearance did not prevent progressive neurodegeneration (Holmes et al., 2008), suggesting that it may be too late for such treatments to have an effect when given to persons with diagnosed AD (St George-Hyslop and Morris, 2008). Hence, it will be critically important to design randomized clinical trials (RCTs) of individuals at the earliest clinical stages, i.e., mild cognitive impairment (MCI, Petersen et al., 2001), or even preclinical AD prior to the substantial development of clinical symptoms since this is the group of individuals in which targeted therapies may have the greatest chance of preserving normal brain function.

However, because AD markers including cognitive tests and biomarkers have been traditionally designed to track the disease progression after symptomatic onset and to identify cases of fully developed AD, they only exhibit subtle changes during the very early stage or the preclinical stage of AD. Several recent RCTs using existing instruments (e.g., the Alzheimer's Disease Assessment Scale-Cognitive subscale; Mohs et al., 1997) failed to detect significant decline in placebo groups with mild cognitive impairment. Especially for RCTs on early stage or preclinical stage of AD, the lack of progression on existing markers has become an important challenge to the feasibility of such trials because of the need for a huge number of individuals over many years to guarantee that meaningful statistical conclusions can be drawn (Ringman et al., 2009, DeKosky et al., 2006, Launer et al., 2006). Large, long-duration RCTs are time-consuming and prohibitively costly. Whereas emerging cerebrospinal fluid (CSF) markers and neuroimaging markers (Hampel et al., 2010; Fagan et al., 2007; Shaw et al., 2009; Mintun et al., 2006; Chen et al., 2004) have been reported to show early changes in a greater magnitude than existing markers, a major analytic challenge is to combine existing and emerging AD markers in an optimum way so that the rate of longitudinal progression on disease markers can be optimally detected, especially during the very early stages of AD. Appropriate combinations of markers across multiple modalities may improve the feasibility of RCTs on early stage AD.

The purpose of this article is to find a way to combine multiple AD markers so that the longitudinal rate of progression can be improved. We will employ a general linear mixed model for each marker and link the models across multiple markers through a set of correlated random effects. Assuming the disease progression is associated with a decreased level of each marker over time, we will derive the linear combination of multiple markers such that the probability that the combined marker is decreased over time is maximized. We will then provide estimates to the weights of the proposed linear combination as well as confidence intervals to the resulting rate of progression. We will also conduct simulation

studies to compare the rate of progression over time on the combined marker using our proposed method and the traditional approach with a principal component analysis (PCA). Finally, we will demonstrate the proposed methodology by estimating the combined rate of progression through a combination of two cognitive domains using longitudinal data from Washington University (WU) Alzheimer's Disease Research Center (ADRC), and assess the improvement in reducing the sample size of future RCTs on the preclinical stage of AD when the optimum combination of multiple markers is used as the primary efficacy endpoint.

2. Method

We assume a total of *m* disease markers to be longitudinally assessed on individuals. For marker *i*, *i*=1, 2, …, *m*, we use $y_j^i(t)$ to represent the observed value at time *t* for a randomly selected individual *j* and assume a simple linear longitudinal progression:

$$y_j^i(t)=\mu_{0j}^i+\mu_{1j}^i t+e_j^i(t). \quad (1)$$

Let $\mu_j=\begin{pmatrix} \mu_{0j} & \mu_{1j} \end{pmatrix}^T$ (*T*=matrix transpose), where $\mu_{0j}=\begin{pmatrix} \mu_{0j}^1,\cdots & \mu_{0j}^m \end{pmatrix}$ is the vector of intercepts and $\mu_{1j}=\begin{pmatrix} \mu_{1j}^1,\cdots & \mu_{1j}^m \end{pmatrix}$ is the vector of slopes. We assume a random intercept and slope model across *m* biomarkers, i.e., μ_j follows a 2*m*-dimensional normal distribution with mean vector $\mu=\begin{pmatrix} \mu_0 & \mu_1 \end{pmatrix}^T$ and covariance matrix

$$\sum=\begin{pmatrix} \sum_0 & \sum_{01} \\ & \sum_1 \end{pmatrix}.$$

Further, we assume that $\{e_j^i(t), t\geq 0\}$ is a stationary Gaussian process with $E[e_j^i(t)]=0$ and the autocovariance function given by $\gamma_i(h)=\mathrm{cov}[e_j^i(t), e_j^i(t+h)]$, $h\geq 0$. Notice that $\gamma_i(0)=\mathrm{var}(e_j^i(t))$. If $\gamma_i(h)$ is a constant when $h>0$, it corresponds to the compound symmetry covariance structure in longitudinal models (Diggle et al., 2002). If $\gamma_i(h)=\gamma_i(0)\rho_i^h$ when $h>0$, it corresponds to the autoregressive covariance structure in longitudinal models (Diggle et al., 2002). We also assume that, conditional on μ_j, $e_j^{i_1}(t)$ and $e_j^{i_2}(t)$ are independent Gaussian processes for $i_1 \neq i_2$. Thus, conditional on μ_j, $e_j(t)=(e_j^1(t), e_j^2(t), \ldots, e_j^m(t))^T$ follows another *m*-dimensional multivariate normal distribution with 0 mean vector and covariance matrix

$$R=\begin{pmatrix} \gamma_1(0) & 0 & \ldots & 0 \\ 0 & \gamma_2(0) & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & \ldots & \gamma_m(0) \end{pmatrix}.$$

Finally, we assume that μ_j and e_j are independent. Thus, $Y_j(t)=\left(y_j^1(t), y_j^2(t), \ldots, y_j^m(t)\right)^T$ follows a normal distribution with mean $\mu_0{}^T+\mu_1{}^T t$ and covariance matrix $\Omega_t=A_t\sum A_t^T+R$,

where $A_t=(\ I_m \quad tI_m\ )$, and I_m is the m by m identity matrix. Likewise, $Y_j(t+1)=\left(y_j^1(t+1), y_j^2(t+1), \ldots, y_j^m(t+1)\right)^t$ follows a normal distribution with mean $\mu_0{}^T+\mu_1{}^T(t+1)$ and covariance matrix $\Omega_{t+1} = A_{t+1}\Sigma A_{t+1}{}^T + R$, where $A_{t+1}=(\ I_m \quad (t+1)I_m\ )$.

For a vector of constant weights $C = (c_1,c_2,\ldots,c_m)$, we form the linear combination $U_j(t)=\sum_{s=1}^{m} c_s y_j^s(t)$. At $t+1$, $U_j(t+1)=\sum c_s y_j^s(t+1)$. Without loss of generality, we assume that at the population level, each marker is decreased over time, i.e., $\mu_1 < 0$ componentwise. Consider the probability that the combined marker decreases over a time interval of 1 unit for a randomly selected individual, i.e.,

$$P(C)=\Pr\left(U_j(t+1)<U_j(t)\right)=\Phi\left(-\frac{C\mu_1{}^T}{\sqrt{C(\Omega_t+\Omega_{t+1}-2\Omega)C^T}}\right), \quad (2)$$

where $\Omega = A_{t+1}\Sigma A_t{}^T + R_1$, R_1 is the diagonal matrix with the i-th diagonal element equal to $\gamma_i(1)$, and Φ is the distribution function of the standard normal distribution. This probability depends on the weight vector $C = (c_1,c_2,\ldots,c_m)$. One optimum choice of the weight vector is to make the combined marker decrease from t to $t+1$ for as many individuals as possible, i.e., we will maximize $P(C)$ as a function of C. Intuitively, our ultimate goal is to choose weight vector $C = (c_1,c_2,\ldots,c_m)$ such that the expected slope of the combined marker $U_j(t)$ is maximized and at the same time, the variance of the slopes minimized. However, mathematically, these two things can not happen at the same time because if we naively make the weights arbitrarily large so that the mean slope can be enlarged, the standard deviation (SD) of slopes on $U_j(t)$ will be enlarged proportionally at the same time. As a matter of fact, what drives the power of a clinical trial is not the mean or the standard deviation of the slopes individually, but the ratio between them. In another word, maximizing the ratio between the mean and standard deviation of the slopes over all the possible choices of weight vectors will lead to improvement in designing clinical trials, i.e., the most reduced sample sizes. Because Φ is a strictly increasing function, the maximization of $P(C)$ is equivalent to maximizing the ratio between the mean and standard deviation of the slopes over all the possible choices of weight vectors, i.e.,

$$-\frac{C\mu_1{}^T}{\sqrt{C(\Omega_t+\Omega_{t+1}-2\Omega)C^T}}.$$

Notice here we assumed that $\mu_1 < 0$ and $C>0$ componentwise. Because $C\mu_1{}^T< 0$, maximizing $P(C)$ is equivalent to maximizing

$$Q(C)=\frac{C\mu_1{}^T\mu_1 C^T}{C(\Omega_t+\Omega_{t+1}-2\Omega)C^T}.$$

It is well known (Noble and Daniel, 1977) that the maximum is achieved when C is an eigenvector C_0 corresponding to the largest eigenvalue of $(\Omega_t+\Omega_{t+1} - 2\Omega)^{-1}\mu_1{}^T\mu_1$. The maximizing value of $Q(C)$ is the largest eigenvalue λ_0 of $(\Omega_t + \Omega_{t+1} - 2\Omega)^{-1}\mu_1{}^T\mu_1$, which then implies that the maximum probability that the combined marker decreases from t to $t+1$

is $P(C_0)=\Phi\left(\sqrt{\lambda_0}\right)$. Notice that $(\Omega_t + \Omega_{t+1} - 2\Omega) = \Sigma_1 + 2R - 2R_1 = \Delta$. Because $\Delta^{-1}\mu_1{}^T\mu_1$ is a matrix of rank 1, the largest eigenvalue of the matrix is its trace, i.e., $\lambda_0 = \mu_1\Delta^{-1}\mu_1{}^T$. Further, it is straightforward to verify that $C_0 = -\mu_1\Delta^{-1}$ is an eigenvector corresponding to the largest eigenvalue (unique up to a constant). Therefore, the rate of progression from the combined marker is given by (up to a constant)

$$\mu_{opt}=-\mu_1\Delta^{-1}\mu_1{}^T=-\lambda_0. \quad (3)$$

The eigenvector C_0 is unique if it is normalized, i.e., $||C_0||^2=\sum_{i=1}^m c_i^2=1$. As an example, if we assume a compound symmetry (CS, Diggle et al., 2002) structure for the autocovariance function of each marker, i.e., $\mathrm{cov}[e_j^i(t), e_j^i(t+h)]=\rho_i\gamma_i(0)$ for $h > 0$, or an autoregressive (AR, Diggle et al., 2002) structure, i.e., $\mathrm{cov}[e_j^i(t), e_j^i(t+h)]=\rho_i^h\gamma_i(0)$ for $h > 0$, then $\Delta = \Sigma_1 + 2(R - \rho R)$, where ρ is the diagonal matrix with entries ρ_i, and ρR is the Hadamard product or componentwise product between ρ and R.

Example 1: combining 2 markers

In the simple case of combining 2 markers when the autocovariance function for the error process of each biomarker is 0 for $h>0$, i.e., with independent errors over times, let $\mu_1 = (\mu_{11}, \mu_{12})$, $\sigma_i^2=\gamma_i(0)$, $i=1, 2$, and

$$\sum\nolimits_1=\begin{pmatrix} \sigma_{11}^2 & \sigma_{12} \\ \sigma_{12} & \sigma_{22}^2 \end{pmatrix}.$$

The optimum weights are given by $C_0=(c_{01}, c_{02})/[(\sigma_{11}^2+2\sigma_1^2)(\sigma_{22}^2+2\sigma_2^2)-\sigma_{12}^2]$, where $c_{01}=(\sigma_{22}^2+2\sigma_2^2)\mu_{11}-\sigma_{12}\mu_{12}$ and $c_{02}=(\sigma_{11}^2+2\sigma_1^2)\mu_{12}-\sigma_{12}\mu_{11}$. The rate of progression (i.e., the slope) using these weights as given by (3) is

$$\mu_{opt}=-\frac{(\sigma_{22}^2+2\sigma_2^2)\mu_{11}^2-2\sigma_{12}\mu_{11}\mu_{12}+(\sigma_{11}^2+2\sigma_1^2)\mu_{12}^2}{(\sigma_{11}^2+2\sigma_1^2)(\sigma_{22}^2+2\sigma_2^2)-\sigma_{12}^2}.$$

Example 2: combining markers with independent rates of progression

Now we assume that Σ_1 is a diagonal matrix with entries σ_{ii}^2, $i=1,2,\ldots, m$, representing the variances of the slopes from the m markers. Let μ_{1i} be the slope from the i-th marker. Assuming an autoregressive (AR) covariance structure for the error process for each marker, i.e., $\gamma_i(h)=\rho_i^h\sigma_i^2$, the optimum weights are given by $C_0{}^T = -B\mu_1{}^T$, where B is the diagonal matrix with entries $1/(\sigma_{ii}^2+2(1-\rho_i)\sigma_i^2)$, $i=1,2,\ldots, m$. The combined rate of progression (i.e., the slope) as given by (3) is then

$$\mu_{opt}=-\sum\nolimits_i^m \frac{\mu_{1i}^2}{\sigma_{ii}^2+2(1-\rho_i)\sigma_i^2}.$$

3. Estimation and Inferences

We now assume that for a random sample of n individuals, the m markers are longitudinally assessed. Let $y_j^i(t_{jk})$ denote the observation of individual j (j=1,2,..,n) for marker i, i=1,2,…, m, at time t_{jk}. Assume a random intercept and random slope model described above for $y_j^i(t_{jk})$:$y_j^i(t_{jk})=\mu_{0j}^i+\mu_{1j}^i t_{jk}+e_j^i(t_{jk})$, where k=0,1,2,…, K_j, indicates times when the markers are assessed for individual j. The random effects $\mu_j=\begin{pmatrix} \mu_{0j} & \mu_{1j} \end{pmatrix}^T$ can be interpreted as the variations of the intercept and slope across individuals. A multivariate random effects model (Shah, Laird, and Schoenfeld, 1997; Fieuws and Verbeke, 2004; Gao et al., 2006) can be fitted to these data, and the maximum likelihood estimates (MLEs) to $\mu=\begin{pmatrix} \mu_0 & \mu_1 \end{pmatrix}^T$, Σ, and $\gamma_i(h)$,i=1,2,…, m, can be obtained. Let θ denote the set of variance/covariance parameters including these from Σ_1 and $\gamma_i(h)$,i=1,2,…, m. Let $\hat{\mu_1}$ be the maximum likelihood estimate of μ_1, and $\hat{\theta}$ the MLE of θ obtained from fitting the multivariate random coefficients model. If we require that $||C_0||$=1, then the eigenvector C_0 is unique and is a function of μ_1 and θ. Let $\mu_{opt} = f(\mu_1, \theta)$. The MLE to the rate of progression with the optimum weights is $\hat{\mu}_{opt} = \hat{C}_0\hat{\mu_1}^T = f(\hat{\mu_1}, \hat{\theta})$. The sampling distribution of μ_{opt} is complicated to obtain. However, because $\hat{C}_0$ is a continuous function of matrix $\Delta = \Sigma_1 + 2(R - \rho R)$ and vector μ_1, $\hat{\mu}_{opt} = \hat{C}_0\hat{\mu_1}^T$ is a strongly consistent estimator of μ_{opt} due to the strong consistency of the MLEs in the mixed model. Assume that

$$\hat{\Lambda}=\begin{pmatrix} \hat{\Lambda}_{\mu_1} & \hat{\Lambda}_{\mu_1,\theta} \\ \hat{\Lambda}_{\mu_1,\theta} & \hat{\Lambda}_{\theta} \end{pmatrix}$$

is the estimated Fisher information matrix of $(\hat{\mu_1}, \hat{\theta})$ after fitting the multivariate random coefficients model, then asymptotically, $(\hat{\mu_1}, \hat{\theta})$ follows a multivariate normal distribution $N((\mu_1, \theta),\hat{\Lambda^{-1}}/n)$. A simple application of the Delta method implies that $\mu_{opt} = f(\hat{\mu_1}, \hat{\theta})$ follows an asymptotically normal distribution with mean μ_{opt} and variance $\hat{\sigma}^2_{opt}=(Df)^T\hat{\Lambda}Df/n$, where Df is the column vector of the first order derivatives of f evaluated at the MLE $(\hat{\mu_1}, \hat{\theta})$. This then leads to an asymptotic $100(1 - \alpha)\%$ $(0 < \alpha < 1)$ confidence interval (CI) for the combined rate of progression as

$$\hat{\mu}_{opt} \pm z_{\alpha/2}\hat{\sigma}_{opt}, \quad (4)$$

where $z\alpha/2$ is the upper $50\alpha\%$ percentile of the standard normal distribution.

To compute the confidence interval estimate to the combined rate of progression, the estimated covariance matrix $\hat{\Lambda_{\mu_1\theta}}$ has to be available after fitting the multivariate random coefficient model. In standard computer output such as that from PROC MIXED/SAS (Littell et al., 1996), $\hat{\Lambda_{\mu_1}}$ and $\hat{\Lambda_\theta}$ are readily available, but $\hat{\Lambda_{\mu_1\theta}}$ is not. Given that the closed form of $\hat{\Lambda_{\mu_1\theta}}$ is not available, we propose to obtain an estimate through a bootstrap resampling procedure (Davison and Hinkley, 1997):

1. Generate B bootstrap samples (say, B=200) from the observed data with replacement such that each bootstrap sample is of the same sample size of the original sample;

2. Fit the multivariate random coefficients model for each bootstrap sample, and obtain the MLEs ($\hat{\mu_1}$, $\hat{\theta}$). Compute the covariance matrix $\Lambda_{\hat{\mu 1},\hat{\theta}}$ (called $\hat{\Lambda}^B_{\mu_1,\theta}$) from these MLEs;

3. Return back to the original observed data set, use $\hat{\Lambda}^B_{\mu_1,\theta}$ and the estimated $\Lambda_{\hat{\mu 1}}$ and $\Lambda_{\hat{\theta}}$ to compute the CI estimate to μ_{opt}.

Example 1 revisited: CI of the combined rate of progression when combining 2 markers

The MLE to the combined rate of progression (i.e., the slope) is

$$\hat{\mu}_{opt}=-\frac{(\hat{\sigma}^2_{22}+2\hat{\sigma}^2_2)\hat{\mu}^2_{11}-2\hat{\sigma}_{12}\hat{\mu}_{11}\hat{\mu}_{12}+(\hat{\sigma}^2_{11}+2\hat{\sigma}^2_1)\hat{\mu}^2_{12}}{(\hat{\sigma}^2_{11}+2\hat{\sigma}^2_1)(\hat{\sigma}^2_{22}+2\hat{\sigma}^2_2)-\hat{\sigma}^2_{12}}.$$

An asymptotic 100(1 − a)% (0 < a < 1) CI to the combined rate of progression is $\hat{\mu}_{opt} \pm z_{\alpha/2}\sqrt{\hat{D}f^T\hat{\Lambda}\hat{D}f}/\sqrt{n}$, where *Df* is the column vector of derivatives of *f* and $DET=(\sigma^2_{11}+2\sigma^2_1)(\sigma^2_{22}+2\sigma^2_2)-\sigma^2_{12}$, $\partial\mu_{opt}/\partial\mu_{11}=-[2(\sigma^2_{22}+2\sigma^2_2)\mu_{11}-2\sigma_{12}\mu_{12}]/DET$, $\partial\mu_{opt}/\partial\mu_{12}=-[2(\sigma^2_{11}+2\sigma^2_1)/\mu_{12}-2\sigma_{12}\mu_{11}]/DET$, $\partial\mu_{opt}/\partial\sigma^2_{ii}=(\partial\mu_{opt}/\partial\mu_{1i})^2/4$, $\partial\mu_{opt}/\partial\sigma^2_i=(\partial\mu_{opt}/\partial\mu_{1i})^2/2$, *i* = 1,2, and $\partial\mu_{opt}/\partial\sigma_{12}=-2[\sigma_{12}((\sigma^2_{22}+2\sigma^2_2)\mu^2_{11}+(\sigma^2_{11}+2\sigma^2_1)\mu^2_{12})-((\sigma^2_{11}+2\sigma^2_1)(\sigma^2_{22}+2\sigma^2_2)+\sigma^2_{12})\mu_{11}\mu_{12}]/DET^2$.

4. Simulation Results

We ran an extensive simulation study to examine the effect of combining multiple disease markers on the rate of progression over time. Our ultimate goal is to improve the rate of progression utilizing multiple markers and assess how the combined rate will improve the estimated sample sizes of future clinical trials, especially in the early stage of AD. Our method requires, first, estimating the optimum weights to combine multiple markers, and then estimating the combined rate of progression. Using a multivariate random coefficients model, we have proposed a method of estimating the combined rate of progression as well as the associated standard errors. Our proposed estimator is based on a combination of standard asymptotic theory on MLEs and a bootstrap procedure.

Another intuitive way to combine multiple markers is by using the principal components analysis (PCA). Our goal is to improve the rate of progression, so the PCA is conducted on the covariance or correlation matrix of the slopes across multiple markers, i.e., Σ_1. Because Σ_1 is conceptualized on the latent (i.e., not directly observed) slopes, the PCA has to apply to the estimated Σ_1 after fitting the multivariate random coefficients model. Both our proposed approach and the PCA approach use an eigenvector to estimate weights to combine markers, and the weights are only unique up to a constant. Therefore, potentially different scales can be used in the linear combination of multiple markers across different approaches. Hence, a valid comparison on the rate of progression between these two combined markers has to be based on the ratio between the estimated rate of progression and the corresponding standard deviation (SD) or standard error (SE).

Our first simulation study intends to answer the question of which approach, our proposed method, or the simple PCA, provides larger rate of progression over time. Because the intercept parameter of the random coefficients model does not contribute to the rate of

progression through combinations of markers, we used a random slopes model (i.e., with all intercept=0) to generate longitudinal data. We chose two markers (m=2) for the simulation study. The simulated longitudinal study has 6 evenly spaced follow-up occasions for all subjects, i.e., k=0,1,2,3,4,5. The true slope vector was $\mu_1 = (-0.8, -0.8 + \delta)$, $\delta = -0.3, 0, 0.3$, and the true covariance matrix on slopes was

$$\sum_1 = \begin{pmatrix} 1 & c\sqrt{d} \\ c\sqrt{d} & d \end{pmatrix},$$

where d (d=1, 2) is the variance of latent slope of the second marker, and c is the correlation between rates of progression from two markers. We further assumed that the error processes are i.i.d. for both markers and with equal within-subject variances: $\gamma_1(0)=\gamma_2(0)=\sigma_w^2=1, 3, 5, 7, \text{and } 9$. For the selected set of parameters, the true weights C_0 (normalized so that $||C_0||=1$) for combining the two markers with our proposed approach are presented in the forth column of Table 1. Using these true weights, we then computed the combined marker on the longitudinal data simulated from the bivariate random slopes model for 500 subjects. Finally, we fitted a univariate random slope model on the combined marker to estimate the slope. This process was repeated for 500 independently simulated longitudinal data sets, each with a sample size of 500. The ratios between the mean and standard deviation (SD) from 500 independently estimated slopes of the combined marker are given in the sixth column of Table 1. For comparison purposes, we repeated the same process using the weights from the simple PCA, which clearly did not take into account of the difference in mean slopes from two markers (i.e., δ) or the within-subject variances (i.e., σ_w^2). The PCA weights with the assumed parameters are presented in the fifth column of Table 1, indicating the same weight to both markers. The ratios between the mean and standard deviation (SD) from 500 independently estimated slopes of the combined marker with weights from the PCA are given in the seventh column of Table 1. For comparison purpose, we have also computed the ratios between the mean and standard deviation (SD) from 500 independently estimated slopes of the combined marker with equal weights in the eighth column of Table 1. Results from Table 1 show that, when δ= 0, i.e., the two markers have the same mean slope, and the variances of slopes from the two markers are the same, i.e., d=1, the weight vector from our proposed approach is the same as that from the PCA which gives the same weight to combine two markers, resulting in the same ratio between the mean and standard deviation (SD) of the slopes on the two combined markers. On the other hand, when $\delta = -0.3$ or 0.3, i.e., the two markers have different slopes, regardless of the equal variances (d=1) or different variances (d=2) of slopes from the two markers, our proposed weight vector puts more weight on the marker with larger slope (in magnitude), and provides larger ratio in magnitude between the mean and standard deviation (SD) of the slopes than the weights from the PCA. Compared to the equal weights to combine two markers (i.e., with normalized weight vector C=(0.707, 0.707)), when $\delta = -0.3$ or 0.3, i.e., the two markers have different slopes, and regardless of the equal variances (d=1) or different variances (d=2) of slopes from the two markers, our proposed weight vector also provides larger ratio in magnitude between the mean and standard deviation (SD) of the combined slopes except for one occasion. When d=2 and = −0.3, the ratio between the mean and standard deviation (SD) of the estimated slopes δ from the combined marker with equal weights is slightly larger in magnitude (maximum difference=0.324) than that from our proposed weights. The reason behind this remains unknown, and further investigation is needed. Further, Table 1 indicates that as the within-subject variance σ_w^2 increases, if the variances of slopes from the two markers are the same, i.e., d=1, our proposed weight on the marker with smaller absolute slope slightly increases, whereas our proposed weight on the

marker with larger absolute slope slightly decreases. These weights eventually stabilize when the within-subject variance reaches approximately 5 times that of the slopes (i.e., $\sigma_w^2 \geq 5$) in the assumed model. If the variances of slopes from the two markers are different, i.e., d=2, as the within-subject variance σ_w^2 increases, our proposed weight on the marker with smaller variance on the slopes slightly decreases, whereas our proposed weight on the marker with larger variance on the slopes slightly increases, regardless of the differences on the slopes of the two markers (i.e., for all $\delta = -0.3$, 0, or 0.3).

It is important to note that the combined rate of progression (i.e., the slope) by combining the two markers can not be measured directly in real world studies or clinical trials. Instead, it has to be estimated by the repeated measures of both markers over time. The estimated weights from our method depend not only on the covariance matrix Σ_1 of individual slopes, but also on the within-subject (i.e., across times) variances σ_1^2, σ_2^2.

Therefore, the variation associated with estimates to the combined rate of progression has to be taken into account when assessing the power of combining markers.

For a selected sample size n, we generated 200 pairs of data sets of the same size. Each pair contains a training data set and another independent validation data set. For each data set in the pair, we initially simulated n observations of slope vectors $\begin{pmatrix} \mu_{1j}^1 & \mu_{1j}^2 \end{pmatrix}^T$ from the bivariate normal distribution $N_2(\mu_1,\Sigma_1)$. We then simulated n observations of the error vectors $e_j^i=(e_{j1}^i, e_{j2}^i, \ldots, e_{jK}^i)^T$ so that the components were i.i.d. with a normal distribution $N\left(0, \sigma_i^2\right)$ for i=1,2, and were independent of $\begin{pmatrix} \mu_{1j}^1 & \mu_{1j}^2 \end{pmatrix}^T$. Finally we computed the simulated markers by $y_j^i(t_{jk})=\beta_{1j}^i t_{jk}+e_{jk}^i$ for t_{jk} = 0, 1, …, 5.

For each simulated training data set over 2 markers, we then fitted a bivariate random slopes model and estimated the parameters μ_1,Σ_1, σ_i^2, i=1,2. These estimated parameters were used to estimate the optimum weight vector $\hat{C}_0 = (\hat{c}_1, \hat{c}_2)$. These weights were next applied to the validation data set to combine the two markers as $y_j(t_{jk})=\hat{c}_1 y_j^1(t_{jk})+\hat{c}_2 y_j^2(t_{jk})$ for each individual at each time point. We then fitted another random slopes model in the validation data set to obtain the estimated slope on the combined marker and the associated SE. From these results, we obtained the ratio of the slope and its standard error. To compare our proposed weights and those from the PCA on the longitudinal rate of progression from the combined markers, we repeated the same process by applying the PCA on the training data set to obtain weights first and then using these weights to combine the markers in the validation data to estimate the rate of progression. Finally, to assess how the variation in the estimated weights affects the estimate to the longitudinal rate of progression on the combined markers, we repeated the same process by applying the true weights from our method and the PCA (computed from the true model parameters) to the validation data set, and estimated the slope on the combined marker and the associated SE as well as their ratio.

Table 2 presents the mean (SD) of the ratios (i.e., the estimated slope divided by the estimated SE) across 200 independent validation data sets for the combined marker using one of the four sets of weights: our proposed weights estimated by the training data set (column 2), our proposed true weights using true parameters in the model (column 3), weights from the first principal component of the PCA estimated from the training data set (column 4), and true weights from the first principal component of the PCA using the true parameters (column 5). The parameters assumed in Table 2 are d=1, σ_w^2=3, δ= 0.3, and c = 0.5. Results in Table 2 suggest that our proposed weights to combine markers can be

estimated accurately in the training data set and then applied to the validation data set because the mean ratios between the estimated slope and the estimated SE were very close to those when the true weights were used. Further, at least in the simulated scenarios, our proposed weights provide faster rate of decline for the combined marker when compared to that using the weights of the PCA.

Because our model conceptualizes a distribution of subject-specific rates of progression for multiple markers, it is straightforward that the rate of progression from the combined marker depends on the correlations between rates of progression across multiple markers. In traditional regression analyses, multicollinearity can be a potential problem in combining multiple highly correlated markers. Thus, it is necessary to assess the performance of our proposed estimate to the combined rate of progression as a function of the correlation between rates of progression, especially when that correlation is large. Further, because the subject-specific rate of progression can not be directly observed and has to be estimated through repeated measures, within-subject variances around the rate of progression ($\gamma_1(0)=\gamma_2(0)=\sigma_w^2$) also impact the estimation of the rate of progression from the combined marker. It is therefore also important to further assess the performance of our proposed procedure to estimate the combined rate of progression as a function of within-subject variances. To address these, we conducted another simulation study. We used the same model and parameters as above to generate 1000 independent data sets with each selected sample size *n*. We chose a wide range of correlation between two rates of progression (*c*=0.1, 0.5, and 0.9) and within-subject variances ($\sigma_w^2=1$ and 3). For each simulated data set over 2 markers, we fitted the bivariate random slopes model and estimated the parameters μ_1, Σ_1, σ_i^2,*i*=1,2. We used these estimates to estimate the rate of progression for the combined marker as in the last set of simulations described earlier. We obtained the estimated SE for the estimated combined rate of progression using the bootstrap procedure described in Section 3. More specifically, for each data set, 200 bootstrap samples of the same size were obtained, and the same bivariate random slopes model were run on these samples to obtain 200 MLEs ($\hat{\mu_1}$, $\hat{\theta}$), where θ is the set of variance/covariance parameters. From these bootstrap estimates of ($\hat{\mu_1}$, $\hat{\theta}$), we computed the covariance matrix $\hat{\Lambda}^B_{\mu_1,\theta}$ and used it with the original estimates $\hat{\Lambda_{\mu_1}}$ and $\Lambda_{\hat{\theta}}$ from the original sample to compute the CI estimate to μ_{opt} as given by (4). Table 3 presents the empirical coverage of the 95% CI estimate to the true combined rate of progression across 1000 independent simulated data sets for our proposed combination of 2 markers. These coverage probabilities are presented as a function of sample size, the within-subject variance σ_w^2, and the correlation *c* on the slopes between two biomarkers. Results in Table 3 indicate that across a wide range of correlation between two rates of progressions and within-subject variances, our proposed asymptomatic confidence interval estimate (through an embedded bootstrap procedure) to the combined rate of progression achieved a coverage probability close to the nominal 95%, especially when the sample size was relatively large (i.e., >50). On the other hand, the empirical coverage probability showed more variation when sample size was relatively small (i.e., *n*=30).

5. Application to Designing Future Clinical Trials on Preclinical AD

We demonstrate the increased power of the proposed method by applying it to estimate required sample sizes for future clinical trials to evaluate the effectiveness of a hypothetical treatment for preclinical AD. Clinical trials on AD usually require a cognitive outcome as the primary efficacy endpoint. A major challenge in designing modern clinical trials of preclinical or early stage AD is that cognitive outcomes such as the Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog, Mohs et al., 1997) were designed for AD trials rather than for preclinical stages, and thus they may be relatively insensitive at

preclinical stages. The sample sizes required to adequately power such trials are therefore formidable. We hoped that our proposed combination of multiple markers will improve the feasibility of clinical trials on preclinical AD by reducing the sample sizes needed to adequately power these trials.

Several recent studies have reported that cognitive decline begins to accelerate several years prior to the onset of symptomatic AD (Hall et al., 2000; Johnson et al., 2009). Because there are no well established criteria as yet for prospectively identifying at screening a cohort of subjects who are destined to develop AD, we propose to evaluate a hypothetical clinical trial among a population that, without an intervention, is somehow known to be 3 years prior to the onset of symptomatic AD. Existing literature has suggested that several cognitive domains including episodic memory and visuospatial ability are especially sensitive to preclinical progression of AD (Johnson et al. 2009, Hall et al. 2007). We therefore focus on these domains. Our design will be based on real longitudinal data on these cognitive domains from the WU ADRC. Elderly individuals aged at least 65 years from the WU ADRC went through annual clinical and cognitive assessments. The clinical and cognitive assessment procedures have been described previously (Morris et al., 2006; Johnson et al., 2008). From the longitudinal database of the WU ADRC, we identified a total of 180 individuals who were cognitively normal at baseline and subsequently developed AD (defined as receiving a Clinical Dementia Rating (Morris, 1993) of at least 0.5 with a diagnosis of dementia of Alzheimer type) during the longitudinal follow-ups. These individuals all had at least 2 longitudinal assessments 3 years prior to the symptomatic onset of AD, which was our operational definition of the preclinical stage of AD (Johnson et al., 2009). For those with longer follow-up periods, only data points within 3 years of the symptomatic onset of AD were included in the analysis. At baseline, i.e., the assessment 3 years prior to the symptomatic onset of AD, the subjects had a mean age of 81.89 years (SD=7.78 years) and a mean education of 14.31 years (SD=3.41 years). 61% of the sample were female, and 94% were white. Out of 164 subjects with data on apolipoprotein E (APOE) genotype, 33.54% of them had the ε4 allele of apolipoprotein E (APOE4), a major genetic risk factor of AD.

Longitudinal cognitive measures from two domains were available for these individuals: a composite visuospatial score (VS) and the Logical Memory (LM) score from the Wechsler Memory Scale (WMS, Wechsler and Stone, 1973). The visuospatial (VS) composite score included scores from the Wechsler Adult Intelligence Scale Block Design and Digit Symbol subtests (Wechsler, 1955) and Trailmaking A and B (Armitage, 1946). Scores on the four individual tests were converted to z scores using the reference group described previously (Johnson et al., 2009) and then averaged to form the composite. LM was scored according to the Russell criteria (Russell, 1975). Both VS and LM scores were further converted to z-scores using the baseline mean and standard deviation in the current sample.

We fitted a bivariate random slopes model to the longitudinal data on both VS and LM three years prior to the symptomatic onset of AD. We assumed the error processes are i.i.d. for both LM and VS. Table 4 includes the estimated rate of progression (i.e., slopes) as well as the other variance and covariance parameters in the model (i.e., μ_1,Σ_1, σ_i^2,i=1,2) along with their estimated SEs. Based on these estimates, the proposed combination of VS and LM was estimated as 0.6070*VS+ 0.7947*LM (the weight vector C normalized to $||C||=1$). The estimate to the combined rate of change was – 0.1367 per year. Conditional on the estimated weights, an estimated variance for the subject-specific rate of progression for the combined marker was 0.2938, and an estimated within-subject variance for the combined marker was 0.7732.

We used the parameter estimates from these analyses on our pilot data to estimate sample sizes for a future clinical trial among people with preclinical AD. We assumed a future two-arm clinical trial that will be designed for 1.5 years with quarterly assessments for people with preclinical AD. The objective is to detect the difference on the rate of decline between a novel treatment and the placebo on the two cognitive markers, VS and LM. The effect size is expressed as the percentage of improvement on the rate of decline for the treatment arm as compared to the placebo arm. Assuming a sample size ratio of 1:1 for the trial, Table 5 presents the sample size per arm required with 80% statistical power to detect a set of effect sizes using each of the individual cognitive markers as well as using the combined marker with the weights estimated by our proposed method and by the PCA. A significance level of 5% is assumed in the test of efficacy hypothesis. The power analyses were based on a standard normal test on the rate of progression between the treated arm and the placebo arm (Xiong, Zhu, and Yu, 2008). Results from Table 5 indicate that our proposed combination of two cognitive scores significantly reduces the sample sizes needed to adequately power a future clinical trial on people with preclinical AD. More specifically, across the range of effect sizes in Table 5, about 55% and 23% reduction on the sample size can be achieved if our combined marker is used in comparison to the VS and the LM, respectively. For example, with 20% effect size in Table 5, the percentage of sample size reduction with the combined marker is (34163-15442)/34163=54.8% when compared to marker VS, and is (20170-15442)/20170=23.44% when compared to marker LM. We also point out that, compared to individual cognitive scores, the combined marker with weights from the PCA also reduces the sample sizes needed in future clinical trials on preclinical AD, albeit the sample size reduction is to a lesser degree than the combined marker with our proposed approach. Finally, compared to the weights from the PCA, our proposed weights only modestly improve the sample sizes needed for clinical trials on preclinical AD.

Finally, it is clear from Table 4 that cognitive progression in visuospatial and episodic domains is very subtle during the preclinical stage of AD. Hence, although our proposed combination of multiple cognitive scores improves the sample size of future clinical trials on preclinical AD, the required sample size remains very large. These results support the utility of other novel biomarkers than cognitive tests such as CSF and neuroimaging biomarkers in future clinical trials on preclinical AD (Fox et al. 2000).

6. Discussion

There is currently a major conundrum in the search of effective treatments of AD. On the one hand, accumulating research evidence indicates that neurodegenerative processes associated with AD begin years prior to the symptomatic onset of AD (Price et al. 2009, Bennett et al. 2006, Morris and Price 2001), suggesting that the optimum time window for treatment interventions is when the disease is clinically at the early prodromal stage or even the latent or preclinical stage. On the other hand, the lack of detection of progression by currently used disease markers makes the sample size for clinical trials on preclinical AD a formidable task to achieve. This challenge can be partially surmounted by combining multiple markers to optimize the antecedent rate of progression in patients who are at preclinical stage of AD. Of course, these methods could be used in any setting where there was theoretical rationale to combine multiple indicators of change over time.

We proposed a novel methodology to combine data from multiple longitudinal disease markers. We did so by maximizing the probability that the combined marker will be decreased over time across individuals (assuming at the population level, each marker is decreased over time). Because this combination assures a decline as much as possible, it could provide an improvement of estimating the rate of progression across multiple biomarkers. We mathematically derived the optimal combination (i.e., using the optimum

weights) and the combined rate of progression. We further provided both point and confidence interval estimates to the combined rate of progression through the maximum likelihood method. Because the inferential procedure required the estimated covariance matrix between the estimated fixed effects and estimated variance and covariance parameters which is not directly available from standard statistical software such as PROC MIXED/SAS (Littell et al., 1996), we proposed a bootstrap procedure to first estimate the covariance matrix and then proceed to set up the confidence interval estimate for the combined rate of progression.

PCA is another popular approach used to reduce multiple markers into a few principal components that capture most of the variation in the multivariate distributions. Because the PCA is solely based on the covariance structure, it does not involve the mean structure of the multivariate distribution. Given that our main objective is to improve the longitudinal rate of progression across multiple markers, i.e., to achieve larger slope in magnitude by combining multivariate markers, the PCA might be ill-equipped to carry the task. We ran several simulation studies to compare our approach with the PCA approach in terms of providing faster rate of progression and to assess how our proposed confidence interval estimate to the combined rate of progression performs as a function of sample size, within-subject variances, and the correlation between the subject-specific rates of progression across markers. Our simulation was done through a cross-validation approach in which a training data set was used to estimate the weights and an independent validation data set was then used to estimate the optimum combination of markers and its rate of progression. The results indicated that, except for the case when the two markers have exactly the same mean and SD for the slopes as well as the same within-subject variances, our proposed method of combining markers provided faster rate of progression than the PCA approach. The simulation results also indicated that, except for one occasion, our proposed method of combining markers provided faster rate of progression than the combination with equal weights. Further, we found that across a range of within-subject variances and correlations, the empirical coverage probability of our proposed CI estimate to the combined rate of progression was close to the nominal 95%, even when the sample size was as small as 30. As expected, we also observed more variation on the coverage probability when the sample size was small.

Finally, we applied the proposed method to a real world sample of individuals with preclinical AD, and estimated the individual rate of progression in a composite visuospatial score and the score from the WMS Logical Memory (Wechsler and Stone, 1973). We estimated the variance/covariance parameters associated with the rate of progression. We then used these estimates to obtain sample sizes needed for a future clinical trial on preclinical AD. Although the preclinical cognitive progression prior to the onset of AD is in general very slow and hence a large sample is required to power clinical trials on preclinical AD with the cognitive endpoints, our proposed combination of two markers provided a significant improvement in reducing the sample sizes needed to power such trials when compared to each individual marker alone, highlighting the potential use of our proposed methodology in future clinical trials on preclinical AD.

With more progressive novel biomarkers such as CSF and imaging markers (Fox et al. 2000), it is likely that our proposed methodology will provide much more reasonable sample sizes for future clinical trials on preclinical AD. However, our power analyses for a future clinical trial on preclinical AD need to be interpreted with caution. It is well known that the power analysis for any clinical trial depends on the best parameter estimates from existing pilot data available at the designing stage of the trial. Whereas we implemented a retrospective definition of preclinical AD to obtain best estimates to crucial parameters on people who were truly at the preclinical stage of AD, it is very important for trialists to

select subjects with preclinical AD prospectively in future clinical trials. Given that there are no well established criteria as yet to prospectively identify at screening a cohort of subjects who are destined to develop AD, our power analysis has its limitations. Namely, our power analysis will only be valid and provide the improved estimate of the sample sizes in designing a future prospective clinical trial on preclinical AD if prospective data to be collected from the future prospective clinical trial suggest consistent estimates to model parameters as obtained by our pilot data on the retrospectively defined cohort of preclinical AD. Finally, it is important to compare our power analysis results to those with a more standard cognitive endpoints such as ADAS-cog (Mohs et al. 1997). However, a lack of data from the WU ADRC database on ADAS-cog prevented us from doing so. Further investigation is needed using other databases such as those from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

In order to use the proposed methodology to pre-define a better cognitive endpoint for future clinical trials on preclinical AD, weights have to be first estimated to combine multiple cognitive measures. Notice that these weights can not be estimated directly from the unobserved rates of progression (i.e., slopes) in real world studies or clinical trials. Instead, they have to be estimated by the repeated measures of cognitive markers over time. The estimation of these weights hence requires normative and longitudinal data on a comprehensive cognitive battery administered on a large sample of individuals with preclinical AD. For example, the Uniform Data Set (UDS) that National Alzheimer's Coordinating Center (NACC) has been collecting since 2005 can serve as an excellent normative database for this purpose. Application of our proposed methodology to the longitudinal NACC cognitive database on a very large cohort of cognitively normal individuals have the potential to offer a much improved and pre-defined cognitive endpoint that is a linear combination of the entire UDS cognitive battery for future clinical trials on preclinical AD, especially if the stage of preclinical AD can be well defined and operationalized to allow prospective identification of individuals who are truly at the preclinical stage of AD in the NACC database.

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Table 1

Optimum weight vectors and the resulting ratios between the mean and standard deviation (SD) on the slope of the two combined markers as a function of parameters in the bivariate random slopes model (μ_1 = (− 0.8, − 0.8+δ) = individual slopes from two markers. The variance of the latent slope for the first marker=1, and the variance of the latent slope on the second marker=*d*. σ_w^2=shared within-subject variance, *c*=correlation on the slopes of two markers=0.5. Ratios are obtained from 500 independently estimated slopes on the combined markers. Each slope is estimated from longitudinal data simulated for 500 subjects)

d	δ	σ_w^2	Proposed weights	PCA weights	Slope/SD: proposed weights	Slope/SD: PCA weights	Slope/SD: Equal weights
1	−0.3	1.0	(0.538, 0.843)	(0.707, 0.707)	−25.204	−24.505	−24.505
1	−0.3	3.0	(0.569, 0.822)	(0.707, 0.707)	−25.028	−24.492	−24.492
1	−0.3	5.0	(0.576, 0.817)	(0.707, 0.707)	−24.109	−23.537	−23.537
1	−0.3	7.0	(0.580, 0.815)	(0.707, 0.707)	−23.959	−23.490	−23.490
1	−0.3	9.0	(0.581, 0.814)	(0.707, 0.707)	−24.553	−24.093	−24.093
1	0.0	1.0	(0.707, 0.707)	(0.707, 0.707)	−21.326	−21.326	−21.326
1	0.0	3.0	(0.707, 0.707)	(0.707, 0.707)	−19.608	−19.608	−19.608
1	0.0	5.0	(0.707, 0.707)	(0.707, 0.707)	−20.038	−20.038	−20.038
1	0.0	7.0	(0.707, 0.707)	(0.707, 0.707)	−20.616	−20.616	−20.616
1	0.0	9.0	(0.707, 0.707)	(0.707, 0.707)	−19.275	−19.275	−19.275
1	0.3	1.0	(0.890, 0.455)	(0.707, 0.707)	−17.610	−16.564	−16.564
1	0.3	3.0	(0.865, 0.501)	(0.707, 0.707)	−17.045	−16.156	−16.156
1	0.3	5.0	(0.859, 0.512)	(0.707, 0.707)	−16.918	−16.043	−16.043
1	0.3	7.0	(0.856, 0.517)	(0.707, 0.707)	−16.243	−15.654	−15.654
1	0.3	9.0	(0.854, 0.520)	(0.707, 0.707)	−16.147	−15.535	−15.535
2	−0.3	1.0	(0.663, 0.749)	(0.460, 0.888)	−19.669	−18.953	−19.804
2	−0.3	3.0	(0.619, 0.785)	(0.460, 0.888)	−21.256	−20.786	−21.440
2	−0.3	5.0	(0.608, 0.794)	(0.460, 0.888)	−19.247	−18.877	−19.430
2	−0.3	7.0	(0.602, 0.798)	(0.460, 0.888)	−19.337	−18.849	−19.621
2	−0.3	9.0	(0.599, 0.801)	(0.460, 0.888)	−19.508	−18.995	−19.832
2	0.0	1.0	(0.821, 0.571)	(0.460, 0.888)	−17.088	−15.295	−16.523
2	0.0	3.0	(0.757, 0.653)	(0.460, 0.888)	−17.693	−16.022	−17.412
2	0.0	5.0	(0.739, 0.674)	(0.460, 0.888)	−16.866	−15.324	−16.692

d	δ	σ_w^2	Proposed weights	PCA weights	Slope/SD: proposed weights	Slope/SD: PCA weights	Slope/SD: Equal weights
2	0.0	7.0	(0.731, 0.683)	(0.460, 0.888)	−16.819	−15.399	−16.699
2	0.0	9.0	(0.726, 0.688)	(0.460, 0.888)	−17.476	−16.081	−17.386
2	0.3	1.0	(0.950, 0.312)	(0.460, 0.888)	−17.412	−12.194	−14.381
2	0.3	3.0	(0.900, 0.437)	(0.460, 0.888)	−15.996	−11.868	−13.937
2	0.3	5.0	(0.882, 0.471)	(0.460, 0.888)	−14.963	−11.430	−13.335
2	0.3	7.0	(0.874, 0.487)	(0.460, 0.888)	−14.462	−11.284	−13.063
2	0.3	9.0	(0.868, 0.496)	(0.460, 0.888)	−14.692	−11.303	−13.210

Table 2

Mean (SD) ratio between the estimated slope and the estimated SE from 200 simulations for the two combined markers (N=sample size)
(Assumptions for Table 2: d=1, σ_w^2 = within-subject variance=3, c=correlation on the slopes of 2 markers=0.5)

N	Proposed weights estimated from training data sets	True proposed weights	PCA weights estimated from training data sets	True PCA weights
30	−4.244 (1.235)	−4.488 (1.186)	−4.060 (1.240)	−4.268 (1.178)
50	−5.392 (1.196)	−5.752 (1.176)	−5.154 (1.200)	−5.484 (1.157)
100	−7.664 (1.212)	−7.937 (1.127)	−7.333 (1.213)	−7.577 (1.134)
150	−9.338 (1.136)	−9.617 (1.129)	−8.938 (1.144)	−9.179 (1.126)
200	−10.904 (1.188)	−11.060 (1.151)	−10.415 (1.195)	−10.554 (1.123)
250	−12.265 (1.183)	−12.311 (1.084)	−11.708 (1.186)	−11.741 (1.059)
300	−13.436 (1.203)	−13.467 (1.079)	−12.829 (1.199)	−12.845 (1.037)

Table 3

Empirical coverage (in %) of the 95% CI to the combined rate of progression (N=sample size, σ_w^2 = within-subject variance, c = correlation on the slopes of 2 markers)

N	$\sigma_w^2=1$, c = 0.1	$\sigma_w^2=1$, c = 0.5	$\sigma_w^2=1$, c = 0.9	$\sigma_w^2=3$, c = 0.1	$\sigma_w^2=3$, c = 0.5	$\sigma_w^2=3$, c = 0.9
30	93.4	97.8	96.6	94.4	92.5	97.9
50	93.3	95.8	95.9	93.4	93.9	97.2
100	94.9	97.1	94.6	96.6	94.9	95.5
150	96.1	93.8	94.7	94.8	95.3	96.2
200	95.5	96.1	94.4	95.3	95.2	94.3
250	94.6	95.6	95.5	94.7	95.1	94.9
300	95.4	94.9	94.5	95.6	94.7	95.8

Table 4

MLEs to the individual rate of progression per year (i.e., slope) on VS and LM and other variance and covariance parameters

Model parameter	MLE	Standard Error for MLE
Slope of VS (i.e., μ_{11})	−0.0822	0.0528
Variance for the slope of VS (σ^2_{11})	0.1652	0.0381
Within-subject variance for VS (σ^2_{1})	0.7390	0.0583
Slope of LM (i.e., μ_{12})	−0.1093	0.0529
Variance for the slope of LM (σ^2_{22})	0.1608	0.0374
Within-subject variance for LM (σ^2_{2})	0.7931	0.0608
Covariance on the slopes of VS and LM (σ_{12})	0.1362	0.0283

Table 5

Sample size per arm for a 1:1 clinical trial on preclinical AD using individual cognitive scores (LM or VS) and the combined score

Effect size (% of the slope in the control arm)	VS	LM	Combination: Proposed approach	Combination: PCA
20%	34,163	20,170	15,442	15811
25%	21,865	12,909	9,883	10119
30%	15,184	8,965	6,863	7028
35%	11,156	6,586	5,043	5163
40%	8,541	5,043	3,861	3953
45%	6,749	3,985	3,051	3124
50%	5,467	3,228	2,471	2530
55%	4,518	2,668	2,042	2091
60%	3,796	2,242	1,716	1757
65%	3,235	1,910	1,462	1497
70%	2,789	1,647	1,261	1291
75%	2,430	1,435	1,099	1125
80%	2,136	1,261	966	989