Supplemental material for multivariate functional mixed model with MRI data: an application to Alzheimer's Disease

1 Estimation of covariance matrices C_0 and C_1 for multivariate longitudinal outcomes

We have the following equations for covariance matrices:

$$\begin{aligned}
\text{cov}(X_{ij}(s), X_{ij}(t)) =& C_{jj}(s,t) = \beta_j^2[C_0(s,t) + C_1(s,t)], \\
\text{cov}(X_{ij}(s), X_{ij'}(t)) =& C_{jj'}(s,t) = \beta_j\beta_{j'}C_0(s,t), \text{for } j \neq j', \\
\text{cov}(Y_{ij}(s), Y_{ij}(s)) =& C_{jj}(s,s) + \sigma_j^2.
\end{aligned}$$

If $J = 2$, we solve β_2^2 using least squares of $\hat{C}_{22}(s,t)$ and $\hat{C}_{11}(s,t)$ and determine the sign of β_2 using equation $C_{12}(s,t) = \beta_2 C_0(s,t)$ because $C_0(s,t)$ is a positive semidefinite matrix. After we obtain $\hat{\beta}_2$, we estimate $C_0(s,t)$ by equation $C_{12}(s,t) = \beta_2 C_0(s,t)$, and $C_1(s,t)$ by equation $C_{11}(s,t) = C_0(s,t) + C_1(s,t)$.

If $J > 2$, we have $C_{1j'}(s,t) = \beta_{j'}C_0(s,t)$. Let $j \neq j' \neq 1$, we have $C_{jj'}(s,t) = \beta_j\beta_{j'}C_0(s,t) = \beta_j C_{1j'}(s,t)$. Thus, we solve β_j using least squares of $C_{jj'}(s,t)$ and $C_{1j'}(s,t)$, for $j, j' = 2, \ldots, J$ and $j \neq j'$.

To estimate $C_0(s,t)$, we have $C_{jj'}(s,t) = \beta_j\beta_{j'}C_0(s,t)$. Thus, we solve $C_0(s,t)$ using least squares of $\hat{C}_{jj'}(s,t)$ and $\hat{\beta}_j\hat{\beta}_{j'}$, for $j, j' = 1, 2, \ldots, J$ and $j \neq j'$. To estimate $C_1(s,t)$, we have $C_{jj}(s,t) = \beta_j^2[C_0(s,t) + C_1(s,t)]$. Thus, we solve for $C_1(s,t)$ using least squares of $\hat{C}_{jj}(s,t) - \hat{\beta}_j^2\hat{C}_0(s,t)$ and $\hat{\beta}_j^2$, for $j = 1, \ldots, J$.

2 Estimation of eigenfunctions and scale parameter for the MRI components

We denote covariance functions $C_{jm}(t,v) = \text{cov}(Y_{ij}(t), m_i(v))$ and $C_{mm}(v,v') = \text{cov}(m_i(v), m_i(v'))$. We have the following equations:

$$C_{jm}(t,v) = \text{cov}(\beta_j U_i(t), \beta_m u_{mi}(v)) = \beta_j\beta_m \text{cov}(\sum_{i=1}^{\infty}\xi_{il}\phi_l(t), \sum_{i=1}^{\infty}\xi_{il}\phi_{ml}(v)) =$$
$$= \beta_j\beta_m \sum_{i=1}^{\infty} d_{0l}\phi_l(t)\phi_{ml}(v), \quad (1)$$
$$C_{mm}(v,v') = \text{cov}(\beta_m u_{mi}(v) + f_{mi}(v) + \epsilon_{mi}(v), \beta_m u_{mi}(v') + f_{mi}(v') + \epsilon_{mi}(v')) =$$
$$= \text{cov}(\beta_m \sum_{l=1}^{\infty}\xi_{il}\phi_{ml}(v) + \sum_{l=1}^{\infty}\xi_{mil}\psi_{ml}(v), \beta_m \sum_{l=1}^{\infty}\xi_{il}\phi_{ml}(v') + \sum_{l=1}^{\infty}\xi_{mil}\psi_{ml}(v')) + I(v=v')\sigma_m^2$$
$$= \beta_m^2 \sum_{l=1}^{\infty} d_{0l}\phi_{ml}(v)\phi_{ml}(v') + \sum_{l=1}^{\infty} d_{ml}\psi_{ml}(v)\psi_{ml}(v') + I(v=v')\sigma_m^2. \quad (2)$$

To estimate eigenfunctions $\phi_{ml}(v)$, $\psi_{ml}(v)$, and the scale parameter β_m, we adopt an iterative search procedure:

Step 1: we denote the demeaned MRI matrix as $M^*(v)$ (dimension of N by V) with i-th row being $m_i^*(v)$ and the FPC score matrix as $\hat{\boldsymbol{\xi}}$ (dimension of N by L_0) with i-th row being $\hat{\boldsymbol{\xi}}_i$. We express the demeaned MRI data $M^*(v)$ in a matrix form: $M^*(v) = \beta_m\boldsymbol{\xi}\Phi_m + \boldsymbol{\xi}_m\Psi_m + \boldsymbol{\epsilon}_m$, where Φ_m (dimension of L_0 by V) and Ψ_m (dimension of L_m by V) are eigenfunction matrices with l-th row being $\phi_{ml}(v)$ and $\psi_{ml}(v)$, respectively, $\boldsymbol{\xi}_m = (\xi_{mil})_{i=1,\ldots,N,l=1,\ldots,L_m}$ is the FPC score matrix, and $\boldsymbol{\epsilon}_m = (\epsilon_{mi}(v))_{i=1,\ldots,N,v=1,\ldots,V}$ is the random error matrix. We denote the estimated covariance matrix of $M^*(v)$ as $\hat{C}_M^*(v,v') = \text{cov}(m_i^*(v), m_i^*(v'))$ and we smooth it using bivariate scatter of points via multilevel B-splines. The standard deviation σ_m is estimated using the squared root of the difference of the diagonal elements between the estimated raw covariance matrix and smoothed covariance matrix.

Step 2: we perform an eigendecomposition of the smoothed covariance matrix $\hat{C}_M^*(v,v')$ to obtain the first L_0 eigenvalues $\hat{d}_{0l}^*$ and the eigenfunctions $\phi_{ml}^{(0)}(v)$, which are set as the initial values of the eigenfunctions $\phi_{ml}(v)$. We derive the initial value of the scale parameter β_m^2 by regressing eigenvalues $\hat{d}_{0l}^*$ with $\hat{d}_{0l}$. The sign of the scale parameter β_m is determined by Equation (1), where we regress the covariance matrix $\hat{C}_{jm}(t,v)$ with $\hat{\beta}_j \sum_{l=1}^{L_0} \hat{d}_{0l}\hat{\phi}_l(t)\phi_{ml}^{(0)}(v)$.

Step 3: we compute $M_1^*(v) = M^*(v) - \beta_m^{(0)}\hat{\boldsymbol{\xi}}\Phi_m^{(0)}$, where $\Phi_m^{(0)}$ is the eigenfunction with l-th row being $\phi_{ml}^{(0)}(v)$. We estimate and smooth the covariance matrix of $M_1^*(v)$, denoted as $\hat{C}_{M1}^*(v, v')$. We perform an eigendecomposition of the covariance matrix $\hat{C}_{M1}^*(v, v')$. The number of eigenfunctions L_m is determined using PVE criteria. We obtain the first L_m eigenfunctions $\psi_{ml}^{(1)}(v)$ and eigenvalues $d_{ml}^{(1)}$.

Step 4: we compute and smooth the modified covariance matrix $\hat{C}_{M2}^*(v, v') \approx \hat{C}_M^*(v, v') - \sum_{l=1}^{L_m} d_{ml}^{(1)}\psi_{ml}^{(1)}(v)\psi_{ml}^{(1)}(v')$ as in Equation (2). We perform an eigendecomposition of the covariance matrix $\hat{C}_{M2}^*(v, v')$ and obtain the first L_0 eigenfunctions $\phi_{ml}^{(1)}(v)$ and eigenvalues $\hat{d}_{0l}^*$. The scale parameter $\beta_m^{(1)}$ is estimated from taking the square root of the least squares between the eigenvalues $\hat{d}_{0l}^*$ and $\hat{d}_{0l}$.

Step 5: we iterate Steps 3 and 4 until convergence. The convergence criteria is set as $|\beta_m^{(t+1)} - \beta_m^{(t)}| \leq \epsilon = 1e - 5$. The confidence interval for the scale parameter $\hat{\beta}_m$ and SD $\hat{\sigma}_m$ is derived using the bootstrap method with B replications, by sampling subjects with replacement from the original dataset. From each bootstrap replication b, we obtain the estimated scale parameter $\hat{\beta}_m$. We obtain the standard deviation and 95% confidence interval for scale parameter $\hat{\beta}_m$ and SD σ_m from B bootstrap replications.

3 Expression of Gaussian quadrature approximation

We assume that the baseline hazard function $h_0(t)$ is defined on the time intervals: $[\tau_1, \tau_2]$, $(\tau_2, \tau_3]$, $\ldots$, $(\tau_E, \tau_{E+1}]$, where E is the number of knots, and $\tau_1 = 0$, $\tau_{E+1} = \max(T_i)_{i=1,\ldots,N}$. If $T_i \in (\tau_e, \tau_{e+1}]$, we set $h_0(T_i) = h_{0e}$. Let $H_{i,e}$ denote the change of cumulative hazard function from interval a_{ie} to b_{ie} for subject i, where a_{ie} and b_{ie} are the lower and upper integral bound for subject i at interval e. We have:

$$H_{i,e} = \exp(\log(h_{0e}) + \boldsymbol{Z_i}'\boldsymbol{\alpha} + \boldsymbol{g}'_{mi}\boldsymbol{\gamma_m}) \int_{a_{ie}}^{b_{ie}} \exp(F(\boldsymbol{X_i}, t))dt.$$

Let G denote the number of quadrature nodes, w_g as the weight for node g, and x_g as the node coordinate for node g. We have:

$$H_{i,e} \approx \exp(\log(h_{0e}) + \boldsymbol{Z_i}'\boldsymbol{\alpha} + \boldsymbol{g}'_{mi}\boldsymbol{\gamma_m})\frac{b_{ie} - a_{ie}}{2}\sum_{g=1}^{G} w_g f(\frac{b_{ie} - a_{ie}}{2}x_g + \frac{b_{ie} + a_{ie}}{2}),$$

$$f(s) = \exp(\gamma_0 \sum_{l=1}^{L_0} \xi_{il}\phi_l(s) + \sum_{j=1}^{J} \gamma_{1j} \sum_{l=1}^{L_1} \zeta_{ijl}\psi_l(s)).$$

Thus, the survival probability $S_i(T_i)$ is calculated as $S_i(T_i) = \exp(-\sum_{e=1}^{E} H_{i,e})$. We set the number of quadrature points G as 15.

4 Sensitivity analysis of the number of B-spline functions and knot location

We conduct a sensitivity analysis to explore the number of B-spline functions to approximate the mean function $\mu_j(t)$. We use number of B-spline functions $P = (7, 8, 9, 10, 11)$ and fit Model 2 (the instantaneous model) to compute the model assessment statistics. The results displayed in Table S1 suggest that the model assessment statistics are very close for all choices of number of B-spline functions.

The knots for baseline hazard function $h_0(t)$ are selected as (4, 6, 8) years. This is because the estimated cumulative hazard function displayed in Figure S2 suggests that its slope is slightly different among 0 to 4 years, 4 to 6 years, 6 to 8 years, and 8 years later. We explored other knot selections and obtained very similar results (not shown).

5 Details of Four Candidate Models

Besides Models 1 and 2, we also applies other four candidate models: Model 3 - two stage (Model 3-2S that utilizes two-stage sequential estimation approach for Model 2); Model 3-multivariate joint model with MRI data (Model 3 - MJM-MRI); Model 3 - bCox (the Cox model with baseline longitudinal

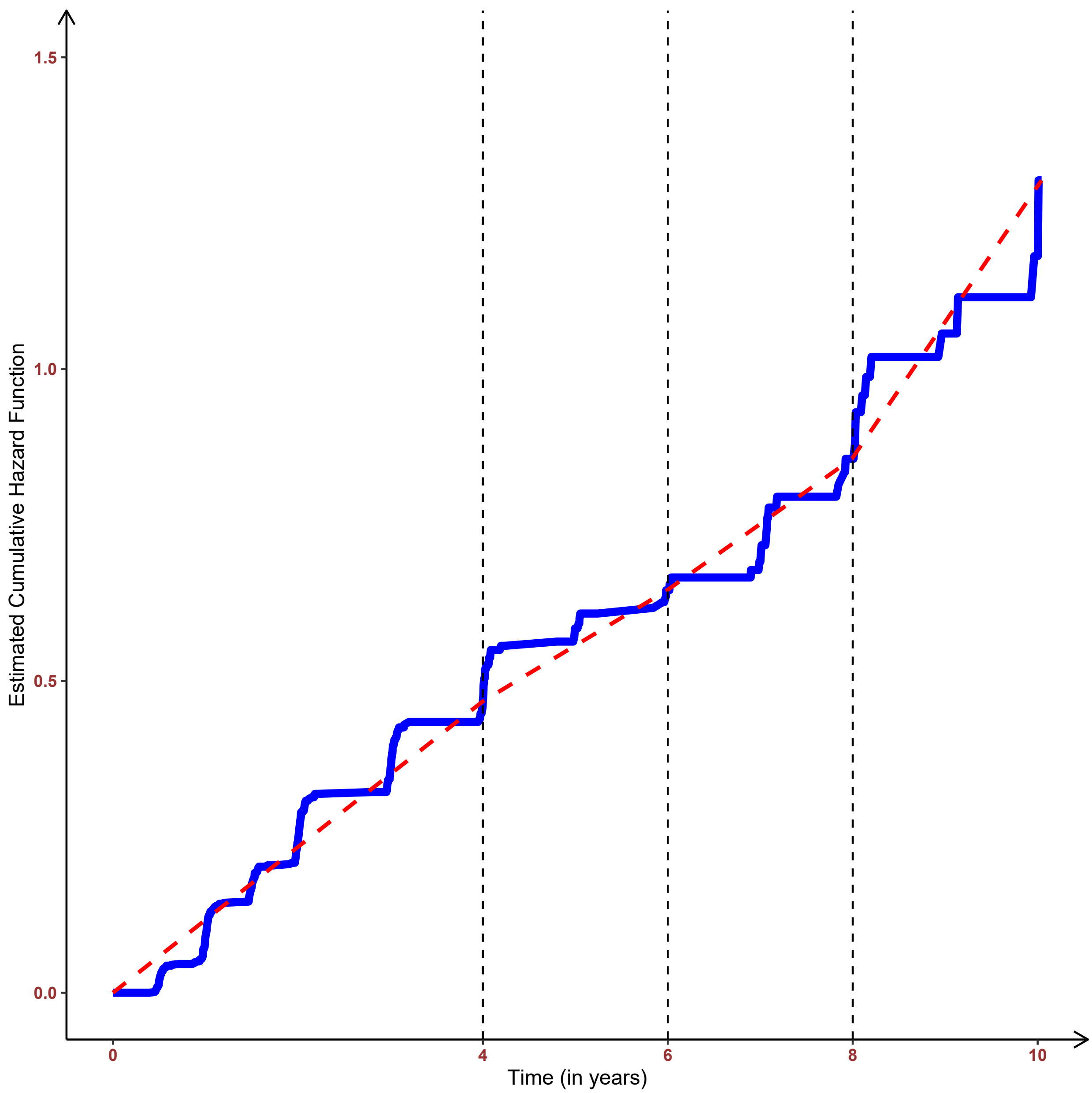

Figure S1: The estimated cumulative hazard function based on the survival model: $h_i(t) = h_0(t)\exp(\boldsymbol{Z}_i'\boldsymbol{\alpha})$. The blue solid curve is the estimated cumulative hazard function. The red dashed curves are the connected lines among knots at (0, 4, 6, 8) years.

Table S1: Model comparison statistics for different numbers of B-spline functions.

Model	EAIC	EBIC	LOOIC	WAIC
$P = 7$	19869	20197	23245	22539
$P = 8$	19871	20221	23258	22560
$P = 9$	19892	20266	23249	22546
$P = 10$	19890	20287	23253	22551
$P = 11$	19872	20291	23232	22517

Notations and abbreviations: EAIC: empirical Akaike information criterion; EBIC: empirical Bayesian information criterion; LOOIC: leave-one-out information criterion; WAIC: widely application information criterion.

outcomes); Model 3 - NM (non-mixed functional model that the longitudinal model is $Y_{ij}(t_{ik}) = \mu_j(t_{ik}) + \epsilon_{ijk}$ and the Cox model includes baseline covariates). The Model 3-bCox has two separate models: (1) a longitudinal model (same as Models 1 and 2); (2) a survival model (a Cox Model that includes age, sex, education, ApoE-ϵ4 alleles, and all J baseline longitudinal outcomes). The Model 3 - MJM-MRI is expressed below:

$$\begin{aligned} Y_{ij}(t_{ik}) =& \mu_{ij}(t_{ik}) + \epsilon_{ijk}, \\ \text{where } \mu_{ij}(t_{ik}) =& \beta_0 + \beta_1 t_{ik} + \int_V m_i^*(v) B_j(v) dv + v_{j0} u_{i0} + v_{j1} u_{i1} t_{ik}, \\ h_i(t) =& h_0(t) \exp(\boldsymbol{Z}_i' \boldsymbol{\alpha} + \int_V m_i^*(v) B_w(v) dv + \sum_{j=1}^{J} \alpha_j \mu_{ij}(t)), \end{aligned}$$

where $m_i^*(v)$ is the de-noised MRI data so that $m_i(v) = m_i^*(v) + \epsilon_{mi}(v)$ and $\epsilon_{mi}(v)$ is the random noise for MRI data $m_i(v)$. We use the same set of covariates $\boldsymbol{Z}_i'$ as Models 1 and 2. We denote (u_{i0}, u_{i1}) as random intercepts and random slopes for subject i, which are assumed to follow a bivariate Normal distribution with a correlation coefficient ρ. We denote the association parameters as v_{j0} and v_{j1} for random effects (u_{i0}, u_{i1}) between outcome j and the first outcome and we set $v_{10} = 1$ and $v_{11} = 1$ for model identifiability. The association parameter α_j quantifies the association between the latent longitudinal mean for outcome j and the risk of AD related dementia.

6 Estimated variances of functional principal components, mean functions, and eigenfunctions

The estimated variances of functional principal components (FPCs) for multivariate longitudinal outcomes and MRI-specific varying pattern are displayed in Table S2 from Model 2 (instantaneous model) with whole-brain voxels. Table S2 suggests that the estimated eigenvalues for the MRI-specific varying pattern $f_{mi}(v)$ have small mean and standard error as compared with the eigenvalues for the longitudinal components. The estimated mean functions and eigenfunctions for multivariate longitudinal outcomes are displayed in Figure S2 from Model 2 (instantaneous model) with whole-brain voxels. Figure S2 suggests that the mean functions and eigenfunctions for the longitudinal outcomes are nonlinear, which suggests that non-parametric functional mixed models are needed to model longitudinal outcomes.

7 Simulation Results for Settings 1 to 4, other Four Candidate Models, and Scenarios 2 and 3

We explore three simulation scenarios to check the robustness of the model:

Scenario 1: The true model is based on Model 2 (the instantaneous model) with whole-brain voxels.

Scenario 2: The true model is based on Model 2, and $\beta_m = 0$, i.e., no correlation between longitudinal outcomes and MRI data.

Scenario 3: The true model is based on Model 1 (the random effects model) and the functional form $F(X_i, t) = \sum_{l=1}^{L_0} \gamma_{0l}\xi_{il} + \sum_{j=1}^{3} \sum_{l=1}^{L_1} \gamma_{1jl}\zeta_{ijl}$, where $L_0 = 2, \gamma_{01} = 0.8, \gamma_{02} = 0.4, L_1 = 1, \gamma_{111} = 0.35, \gamma_{121} = 0.3, \gamma_{131} = 0.1$.

For simulation Scenario 1 (we simulate data from Model 2), we consider four simulation settings

Table S2: Power parameters, estimated mean, standard error (SE) and 95% credible intervals (CI) of variances of FPCs from Model 2 (instantaneous model) with whole-brain voxels.

	Mean	SE	2.5%	97.5%
Power parameters				
λ_1: ADAS-Cog 13	0.6			
λ_2: RAVLT-immediate	0.4			
λ_3: RAVLT-learning	0.8			
λ_4: MMSE	0			
λ_5: CDR-SB	0			
d_{01}	4.805	0.348	4.154	5.505
d_{02}	0.908	0.107	0.711	1.123
d_{11}	2.761	0.134	2.520	3.041
d_{m1}	0.078	0.001	0.076	0.080
d_{m2}	0.048	0.000	0.048	0.049
d_{m3}	0.020	0.000	0.020	0.020
d_{m4}	0.012	0.000	0.012	0.012
d_{m5}	0.011	0.000	0.011	0.011
d_{m6}	0.005	0.000	0.005	0.005
d_{m7}	0.005	0.000	0.005	0.005
d_{m8}	0.004	0.000	0.004	0.004
d_{m9}	0.002	0.000	0.002	0.002
d_{m10}	0.002	0.000	0.002	0.002

Notations and abbreviations: FPCs: functional principal component scores. The parameters d_{01} and d_{02} are variances of the FPCs ξ_{il} $(l = 1, \ldots, L_0)$ of the shared random profile $U_i(t)$. The power parameter used in Box-Cox transformation is denoted as λ. The parameter d_{11} is the variance of the FPC ζ_{ijl} of the subject-outcome specific random profile $W_{ij}(t)$, for $j = 1, \ldots, J$ longitudinal outcomes. The parameters d_{ml} are variances of the FPCs ξ_{mil} $(l = 1, \ldots, L_m)$ of the MRI-specific varying pattern $f_{mi}(v)$. The SE and 95% CI for parameters d_m are derived based on the posterior samples of ξ_{mil}.

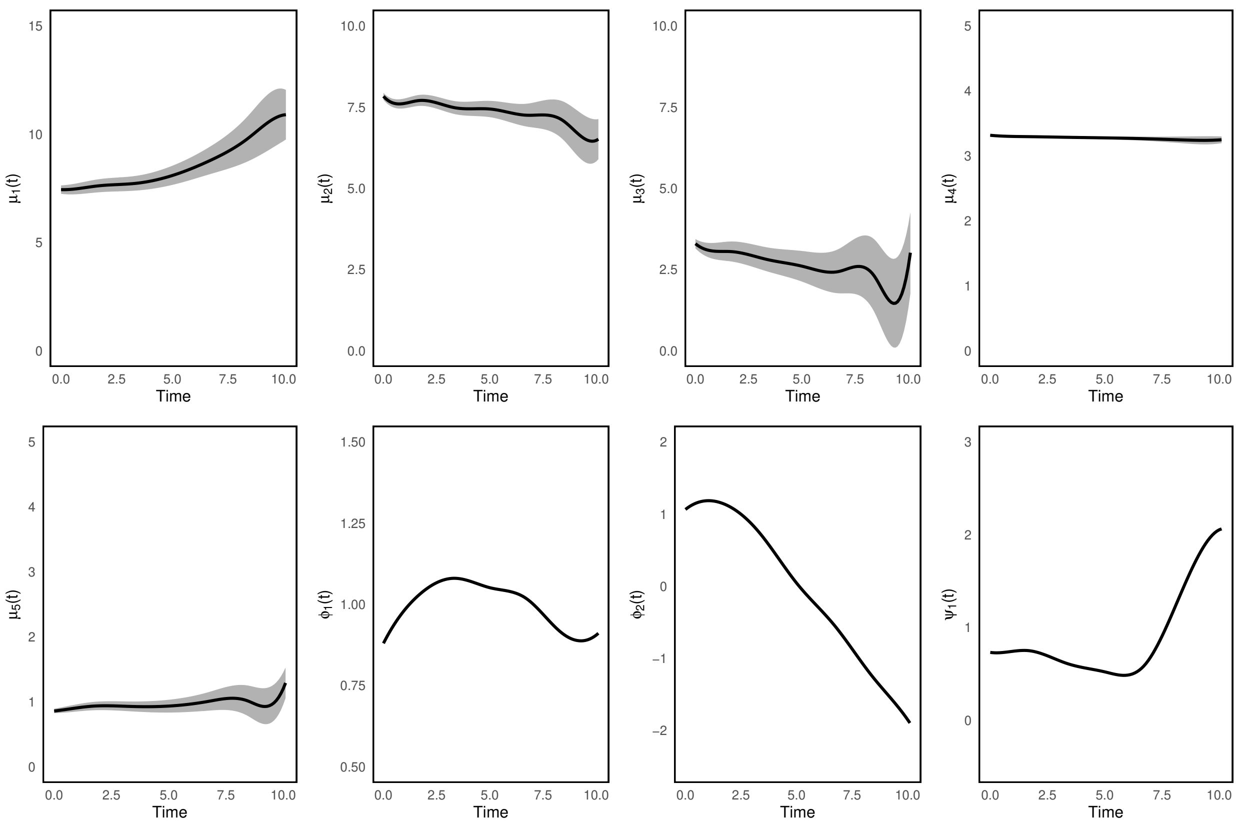

Figure S2: The estimated mean functions and eigenfunctions from Model 2 (instantaneous model) with whole-brain voxels. The shaded areas are 95% point-wise credible intervals.

with different sample sizes and event rate (ER): Setting 1 ($N = 800$ for training set, $N = 300$ for testing set, $h_0(t) = \exp(-1.5)$ so ER = 30%); Setting 2 ($N = 1200$ for training set, $N = 400$ for testing set, $h_0(t) = \exp(-1.5)$); Setting 3 ($N = 800$ for training set, $N = 300$ for testing set, $h_0(t) = \exp(-1)$ so ER = 40%); Setting 4 ($N = 1200$ for training set, $N = 400$ for testing set, $h_0(t) = \exp(-1)$).

We also compare the model with four candidate models: Model 3 - 2S (two-stage approach based on Model 2); Model 3 - MJM-MRI (multivariate joint model with MRI data); Model 3 - bCox (Cox model with baseline longitudinal outcomes); Model 3 - NM (non-mixed functional model).

Table S3: Bias, standard deviation (SD), standard error (SE), coverage probability (CP), and AMSE for simulation Settings 1 and 2 for Scenario 1 based on **Model 2**. Setting 1 (N = 800 for training set, N = 300 for testing set, $h_0(t) = \exp(-1.5)$ so event rate ER = 30%); Setting 2 (N = 1200 for training set, N = 400 for testing set, $h_0(t) = \exp(-1.5)$).

Setting 1: $N.train = 800$, $N.test = 300$, $h_0(t) = \exp(-1.5)$							Setting 2: $N.train = 1200$, $N.test = 400$, $h_0(t) = \exp(-1.5)$						
Parameters	Bias	SD	SE	CP	AMSE		Parameters	Bias	SD	SE	CP	AMSE	
d_{01}=2	−0.055	0.103	0.132	0.980	$\mu_1(t)$	0.000	d_{01}=2	−0.054	0.090	0.108	0.960	$\mu_1(t)$	0.000
d_{02}=1	−0.029	0.065	0.065	0.940	$\mu_2(t)$	0.000	d_{02}=1	−0.024	0.056	0.054	0.910	$\mu_2(t)$	0.000
d_{11}=1	−0.026	0.065	0.045	0.810	$\mu_3(t)$	0.000	d_{11}=1	−0.027	0.053	0.036	0.760	$\mu_3(t)$	0.000
d_{m1}=0.1	0.001				$\mu_m(v)$	0.000	d_{m1}=0.1	0.001				$\mu_m(v)$	0.000
d_{m2}=0.07	0.002				$\phi_1(t)$	0.002	d_{m2}=0.07	0.002				$\phi_1(t)$	0.002
d_{m3}=0.05	0.001				$\phi_2(t)$	0.001	d_{m3}=0.05	0.001				$\phi_2(t)$	0.002
d_{m4}=0.03	0.000				$\psi_1(t)$	0.001	d_{m4}=0.03	0.000				$\psi_1(t)$	0.001
d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.064	d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.055
β_2=−0.55	−0.001	0.008	0.008	0.960	$\phi_{m2}(v)$	0.090	β_2=−0.55	−0.002	0.006	0.007	0.940	$\phi_{m2}(v)$	0.075
β_3=−0.6	−0.001	0.014	0.013	0.930	$\psi_{m1}(v)$	0.003	β_3=−0.6	−0.002	0.011	0.011	0.960	$\psi_{m1}(v)$	0.003
β_m=−0.05	0.002				$\psi_{m2}(v)$	0.003	β_m=−0.05	0.003				$\psi_{m2}(v)$	0.004
σ_1=1.1	0.001	0.010	0.013	0.990	$\psi_{m3}(v)$	0.002	σ_1=1.1	0.001	0.010	0.010	0.980	$\psi_{m3}(v)$	0.001
σ_2=0.6	0.002	0.006	0.007	1.000	$\psi_{m4}(v)$	0.000	σ_2=0.6	0.001	0.005	0.006	0.990	$\psi_{m4}(v)$	0.000
σ_3=1.36	0.002	0.012	0.015	0.970	$\psi_{m5}(v)$	0.000	σ_3=1.36	0.001	0.009	0.012	1.000	$\psi_{m5}(v)$	0.000
σ_m=0.4	−0.000						σ_m=0.4	−0.000					
$\log(h_0)$=−1.5	−0.058	0.141	0.145	0.930			$\log(h_0)$=−1.5	−0.057	0.115	0.117	0.950		
α=0.3	0.009	0.105	0.102	0.950			α=0.3	0.018	0.079	0.082	0.950		
γ_0=0.6	−0.007	0.052	0.055	0.960			γ_0=0.6	−0.002	0.046	0.044	0.950		
γ_{11}=0.35	0.005	0.083	0.090	0.980			γ_{11}=0.35	0.002	0.067	0.073	0.960		
γ_{12}=0.3	−0.013	0.088	0.091	0.970			γ_{12}=0.3	−0.002	0.073	0.073	0.940		
γ_{13}=0.1	0.000	0.095	0.109	0.980			γ_{13}=0.1	0.003	0.089	0.088	0.950		
γ_{m1}=−0.6	0.076	0.232	0.225	0.940			γ_{m1}=−0.6	0.035	0.239	0.181	0.880		
γ_{m2}=−1.1	0.019	0.291	0.270	0.960			γ_{m2}=−1.1	0.011	0.257	0.219	0.880		
γ_{m3}=−0.5	−0.108	0.395	0.316	0.870			γ_{m3}=−0.5	−0.098	0.330	0.256	0.860		
γ_{m4}=0.7	0.109	0.463	0.407	0.900			γ_{m4}=0.7	0.005	0.360	0.331	0.940		
γ_{m5}=−1.8	0.087	0.670	0.701	0.960			γ_{m5}=−1.8	0.067	0.541	0.570	0.970		

Table S4: Bias, standard deviation (SD), standard error (SE), coverage probability (CP), and AMSE for simulation Settings 3 and 4 for Scenario 1 based on **Model 2**. Setting 3 ($N = 800$ for training set, $N = 300$ for testing set, $h_0(t) = \exp(-1)$ so ER = 40%); Setting 4 ($N = 1200$ for training set, $N = 400$ for testing set, $h_0(t) = \exp(-1)$).

Setting 3: $N.train = 800$, $N.test = 300$, $h_0(t) = \exp(-1)$							Setting 4: $N.train = 1200$, $N.test = 400$, $h_0(t) = \exp(-1)$						
Parameters	Bias	SD	SE	CP	AMSE		Parameters	Bias	SD	SE	CP	AMSE	
d_{01}=2	−0.075	0.112	0.138	0.980	$\mu_1(t)$	0.000	d_{01}=2	−0.065	0.101	0.113	0.940	$\mu_1(t)$	0.000
d_{02}=1	−0.036	0.076	0.067	0.890	$\mu_2(t)$	0.000	d_{02}=1	−0.040	0.067	0.054	0.840	$\mu_2(t)$	0.000
d_{11}=1	−0.041	0.081	0.046	0.630	$\mu_3(t)$	0.000	d_{11}=1	−0.036	0.056	0.038	0.690	$\mu_3(t)$	0.000
d_{m1}=0.1	0.002				$\mu_m(v)$	0.000	d_{m1}=0.1	0.001				$\mu_m(v)$	0.000
d_{m2}=0.07	0.002				$\phi_1(t)$	0.002	d_{m2}=0.07	0.002				$\phi_1(t)$	0.002
d_{m3}=0.05	0.002				$\phi_2(t)$	0.001	d_{m3}=0.05	0.001				$\phi_2(t)$	0.001
d_{m4}=0.03	0.001				$\psi_1(t)$	0.002	d_{m4}=0.03	0.001				$\psi_1(t)$	0.002
d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.152	d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.113
β_2=−0.55	−0.002	0.009	0.009	0.940	$\phi_{m2}(v)$	0.178	β_2=−0.55	−0.001	0.007	0.007	0.970	$\phi_{m2}(v)$	0.116
β_3=−0.6	0.000	0.012	0.014	1.000	$\psi_{m1}(v)$	0.008	β_3=−0.6	−0.001	0.012	0.012	0.960	$\psi_{m1}(v)$	0.006
β_m=−0.05	0.003				$\psi_{m2}(v)$	0.010	β_m=−0.05	0.002				$\psi_{m2}(v)$	0.008
σ_1=1.1	0.005	0.011	0.013	0.990	$\psi_{m3}(v)$	0.005	σ_1=1.1	0.001	0.011	0.011	0.950	$\psi_{m3}(v)$	0.003
σ_2=0.6	0.003	0.006	0.007	0.970	$\psi_{m4}(v)$	0.002	σ_2=0.6	0.001	0.005	0.006	0.970	$\psi_{m4}(v)$	0.001
σ_3=1.36	−0.001	0.014	0.015	0.960	$\psi_{m5}(v)$	0.000	σ_3=1.36	0.001	0.011	0.013	1.000	$\psi_{m5}(v)$	0.000
σ_m=0.4	−0.000						σ_m=0.4	−0.000					
$\log(h_0)$=−1	−0.025	0.125	0.121	0.960			$\log(h_0)$=−1	−0.035	0.093	0.098	0.940		
α=0.3	−0.005	0.093	0.087	0.960			α=0.3	0.006	0.069	0.070	0.960		
γ_0=0.6	−0.009	0.047	0.049	0.930			γ_0=0.6	−0.010	0.038	0.040	0.930		
γ_{11}=0.35	−0.012	0.073	0.079	0.980			γ_{11}=0.35	0.004	0.068	0.064	0.970		
γ_{12}=0.3	−0.004	0.087	0.079	0.940			γ_{12}=0.3	0.005	0.062	0.064	0.960		
γ_{13}=0.1	−0.009	0.084	0.095	0.960			γ_{13}=0.1	0.002	0.071	0.076	0.980		
γ_{m1}=−0.6	0.126	0.252	0.192	0.810			γ_{m1}=−0.6	0.084	0.191	0.156	0.870		
γ_{m2}=−1.1	0.036	0.314	0.230	0.840			γ_{m2}=−1.1	0.039	0.224	0.188	0.930		
γ_{m3}=−0.5	−0.094	0.380	0.271	0.800			γ_{m3}=−0.5	−0.053	0.283	0.220	0.840		
γ_{m4}=0.7	0.003	0.368	0.350	0.940			γ_{m4}=0.7	0.044	0.299	0.282	0.940		
γ_{m5}=−1.8	−0.025	0.664	0.595	0.920			γ_{m5}=−1.8	−0.034	0.494	0.487	0.970		

Table S5: True and estimated iAUC and iBS from 100 simulation replications for simulation Settings 1 to 4 and Scenario 1 based on **Model 2**: Setting 1 ($N = 800$ for training set, $N = 300$ for testing set, $h_0(t) = \exp(-1.5)$ so event rate ER = 30%); Setting 2 ($N = 1200$ for training set, $N = 400$ for testing set, $h_0(t) = \exp(-1.5)$); Setting 3 ($N = 800$ for training set, $N = 300$ for testing set, $h_0(t) = \exp(-1)$ so ER = 40%); Setting 4 ($N = 1200$ for training set, $N = 400$ for testing set, $h_0(t) = \exp(-1)$).

Setting 1: $N.train = 800$, $N.test = 300$, $h_0(t) = \exp(-1.5)$					Setting 2: $N.train = 1200$, $N.test = 400$, $h_0(t) = \exp(-1.5)$			
Landmark	True iAUC	Est. iAUC	True iBS	Est. iBS	True iAUC	Est. iAUC	True iBS	Est. iBS
T = 0.4	0.818	0.799	0.063	0.065	0.822	0.805	0.062	0.065
T = 0.5	0.805	0.786	0.060	0.063	0.814	0.799	0.059	0.061
T = 0.55	0.797	0.774	0.058	0.059	0.794	0.776	0.059	0.060
T = 0.6	0.785	0.755	0.056	0.058	0.776	0.750	0.058	0.060
Setting 3: $N.train = 800$, $N.test = 300$, $h_0(t) = \exp(-1)$					Setting 4: $N.train = 1200$, $N.test = 400$, $h_0(t) = \exp(-1)$			
T = 0.4	0.815	0.794	0.082	0.086	0.821	0.803	0.084	0.088
T = 0.5	0.800	0.784	0.080	0.083	0.804	0.794	0.080	0.082
T = 0.55	0.793	0.771	0.077	0.080	0.788	0.775	0.078	0.080
T = 0.6	0.777	0.753	0.077	0.080	0.769	0.747	0.078	0.080

Table S6: True values of parameters, bias, standard deviation (SD), standard error (SE), coverage probability (CP), and mean-squared error (MSE) from 100 simulation replications for Model 3 - 2S (two-stage approach based on Model 2), where we simulate data from Model 2 and estimate the parameters using the two-stage approach.

Parameters	Bias	SD	SE	CP	MSE	
Longitudinal and MRI outcomes						
d_{01}=2	−0.133	0.094			$\mu_1(t)$	0.004
d_{02}=1	−0.038	0.062			$\mu_2(t)$	0.001
d_{11}=1	−0.025	0.065			$\mu_3(t)$	0.000
d_{m1}=0.1	0.001				$\mu_m(v)$	0.000
d_{m2}=0.07	0.001				$\phi_1(t)$	0.002
d_{m3}=0.05	0.001				$\phi_2(t)$	0.002
d_{m4}=0.03	0.000				$\psi_1(t)$	0.001
d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.062
β_2=−0.55	−0.041	0.008	0.004	0.000	$\phi_{m2}(v)$	0.088
β_3=−0.6	−0.110	0.015	0.010	0.000	$\psi_{m1}(v)$	0.003
β_m=−0.05	0.002				$\psi_{m2}(v)$	0.003
σ_1=1.1	−0.120	0.010	0.010	0.000	$\psi_{m3}(v)$	0.002
σ_2=0.6	−0.070	0.005	0.005	0.000	$\psi_{m4}(v)$	0.000
σ_3=1.36	−0.091	0.012	0.012	0.000	$\psi_{m5}(v)$	0.000
σ_m=0.4	−0.000					
Survival outcomes						
α=0.3	0.003	0.105	0.100	0.950		
γ_0=0.6	−0.073	0.041	0.047	0.660		
γ_{11}=0.35	0.004	0.065	0.077	0.990		
γ_{12}=0.3	−0.012	0.069	0.077	0.980		
γ_{13}=0.1	0.007	0.071	0.091	1.000		
γ_{m1}=−0.6	0.051	0.229	0.220	0.960		
γ_{m2}=−1.1	0.098	0.282	0.263	0.910		
γ_{m3}=−0.5	−0.116	0.383	0.310	0.870		
γ_{m4}=0.7	0.119	0.457	0.402	0.910		
γ_{m5}=−1.8	0.071	0.658	0.687	0.960		

Table S7: True and estimated iAUC and iBS from 100 simulation replications for four candidate models (Model 3 - 2S, Model 3 - MJM-MRI, Model 3 - bCox, Model 3 - NM), where we simulate data from Setting 1 based on **Model 2** and estimate the parameters using the candidate models.

	Model 3 - 2S				Model 3 - MJM-MRI			
Landmark	True iAUC	Est. iAUC	True iBS	Est. iBS	True iAUC	Est. iAUC	True iBS	Est. iBS
T = 0.4	0.816	0.796	0.063	0.065	0.817	0.793	0.063	0.066
T = 0.5	0.803	0.783	0.061	0.063	0.805	0.786	0.061	0.066
T = 0.55	0.796	0.772	0.058	0.060	0.796	0.774	0.058	0.065
T = 0.6	0.784	0.752	0.057	0.059	0.783	0.750	0.057	0.067
	Model 3 - bCox				Model 3 - NM			
T = 0.4	0.816	0.487	0.063	0.078	0.816	0.550	0.063	0.075
T = 0.5	0.803	0.468	0.061	0.074	0.803	0.552	0.061	0.070
T = 0.55	0.796	0.465	0.058	0.069	0.796	0.548	0.058	0.066
T = 0.6	0.784	0.469	0.057	0.066	0.784	0.550	0.057	0.063

Table S8: Bias, standard deviation (SD), standard error (SE), coverage probability (CP), and AMSE for simulation Scenarios 2 and 3. Scenario 2: The true model is based on **Model 2**, and $\beta_m = 0$, i.e., no correlation between longitudinal outcomes and MRI data. Scenario 3: The true model is based on **Model 1** (the random effects model) and the functional form $F(X_i, t) = \sum_{l=1}^{L_0} \gamma_{0l}\xi_{il} + \sum_{j=1}^{3}\sum_{l=1}^{L_1}\gamma_{1jl}\zeta_{ijl}$, where $L_0 = 2, \gamma_{01} = 0.8, \gamma_{02} = 0.4, L_1 = 1, \gamma_{111} = 0.35, \gamma_{121} = 0.3, \gamma_{131} = 0.1$.

Scenario 2: $\beta_m = 0$						
Parameters	Bias	SD	SE	CP	AMSE	
d_{01}=2	−0.024	0.107	0.134	1.000	$\mu_1(t)$	0.000
d_{02}=1	−0.024	0.072	0.066	0.900	$\mu_2(t)$	0.000
d_{11}=1	−0.030	0.065	0.045	0.790	$\mu_3(t)$	0.000
d_{m1}=0.1	0.001				$\mu_m(v)$	0.000
d_{m2}=0.07	0.000				$\phi_1(t)$	0.002
d_{m3}=0.05	0.000				$\phi_2(t)$	0.002
d_{m4}=0.03	0.000				$\psi_1(t)$	0.002
d_{m5}=0.01	0.000				$\phi_{m1}(v)$	1.083
β_2=−0.55	0.000	0.009	0.008	0.950	$\phi_{m2}(v)$	0.654
β_3=−0.6	−0.002	0.013	0.013	0.960	$\psi_{m1}(v)$	0.001
β_m=0	−0.021				$\psi_{m2}(v)$	0.002
σ_1=1.1	0.005	0.011	0.013	0.990	$\psi_{m3}(v)$	0.002
σ_2=0.6	0.002	0.006	0.007	0.980	$\psi_{m4}(v)$	0.000
σ_3=1.36	0.000	0.011	0.015	1.000	$\psi_{m5}(v)$	0.000
σ_m=0.4	−0.000					
$\log(h_0)$=−1.5	−0.051	0.167	0.145	0.910		
α=0.3	0.003	0.114	0.101	0.900		
γ_0=0.6	0.011	0.059	0.055	0.950		
γ_{11}=0.35	−0.021	0.091	0.091	0.940		
γ_{12}=0.3	−0.027	0.087	0.091	0.920		
γ_{13}=0.1	0.004	0.113	0.109	0.940		
γ_{m1}=−0.6	−0.004	0.238	0.223	0.950		
γ_{m2}=−1.1	−0.023	0.305	0.272	0.930		
γ_{m3}=−0.5	−0.004	0.380	0.315	0.880		
γ_{m4}=0.7	−0.019	0.423	0.408	0.970		
γ_{m5}=−1.8	0.016	0.799	0.696	0.920		

Scenario 3: $F(X_i, t) = \sum_{l=1}^{L_0} \gamma_{0l}\xi_{il} + \sum_{j=1}^{3}\sum_{l=1}^{L_1}\gamma_{1jl}\zeta_{ijl}$						
Parameters	Bias	SD	SE	CP	AMSE	
d_{01}=2	−0.139	0.104	0.130	0.860	$\mu_1(t)$	0.011
d_{02}=1	0.033	0.067	0.067	0.960	$\mu_2(t)$	0.003
d_{11}=1	−0.007	0.069	0.046	0.770	$\mu_3(t)$	0.004
d_{m1}=0.1	0.001				$\mu_m(v)$	0.000
d_{m2}=0.07	0.002				$\phi_1(t)$	0.009
d_{m3}=0.05	0.001				$\phi_2(t)$	0.009
d_{m4}=0.03	0.001				$\psi_1(t)$	0.002
d_{m5}=0.01	0.000				$\phi_{m1}(v)$	0.108
β_2=−0.55	−0.001	0.009	0.008	0.950	$\phi_{m2}(v)$	0.110
β_3=−0.6	0.002	0.016	0.013	0.920	$\psi_{m1}(v)$	0.006
β_m=−0.05	0.001				$\psi_{m2}(v)$	0.009
σ_1=1.1	0.001	0.010	0.013	0.980	$\psi_{m3}(v)$	0.004
σ_2=0.6	0.001	0.006	0.007	0.960	$\psi_{m4}(v)$	0.000
σ_3=1.36	0.004	0.011	0.015	0.980	$\psi_{m5}(v)$	0.000
σ_m=0.4	−0.000					
$\log(h_0)$=−1.5	0.122	0.145	0.143	0.810		
α=0.3	−0.026	0.106	0.103	0.910		
γ_{m1}=−0.6	−0.028	0.237	0.228	0.940		
γ_{m2}=−1.1	0.350	0.327	0.274	0.710		
γ_{m3}=−0.5	−0.213	0.371	0.318	0.840		
γ_{m4}=0.7	0.206	0.405	0.411	0.940		
γ_{m5}=−1.8	−0.202	0.672	0.713	0.970		

Table S9: True and estimated iAUC and iBS from 100 simulation replications for simulation Scenarios 2 and 3. Scenario 2: The true model is based on **Model 2**, and $\beta_m = 0$, i.e., no correlation between longitudinal outcomes and MRI data. Scenario 3: The true model is based on **Model 1** (the random effects model) and the functional form $F(X_i, t) = \sum_{l=1}^{L_0} \gamma_{0l}\xi_{il} + \sum_{j=1}^{3}\sum_{l=1}^{L_1} \gamma_{1jl}\zeta_{ijl}$, where $L_0 = 2, \gamma_{01} = 0.8, \gamma_{02} = 0.4, L_1 = 1, \gamma_{111} = 0.35, \gamma_{121} = 0.3, \gamma_{131} = 0.1$.

	Scenario 2: $\beta_m = 0$				Scenario 3: $F(X_i, t) = \sum_{l=1}^{L_0} \gamma_{0l}\xi_{il} + \sum_{j=1}^{3}\sum_{l=1}^{L_1} \gamma_{1jl}\zeta_{ijl}$			
Landmark	True iAUC	Est. iAUC	True iBS	Est. iBS	True iAUC	Est. iAUC	True iBS	Est. iBS
T = 0.4	0.823	0.804	0.061	0.064	0.796	0.734	0.052	0.056
T = 0.5	0.807	0.796	0.059	0.061	0.783	0.707	0.050	0.054
T = 0.55	0.804	0.790	0.056	0.057	0.776	0.689	0.051	0.054
T = 0.6	0.789	0.768	0.056	0.058	0.785	0.659	0.049	0.054

8 Dictionary of ROI labels

Table S10: Dictionary of ROI labels 1-90

Label	ROI	Label	ROI	Label	ROI
1	left superior parietal lobule	31	left medial lemniscus	61	left thalamus
2	left cingulate gyrus	32	left superior cerebellar peduncle	62	left globus pallidus
3	left superior frontal gyrus	33	left cerebral peduncle	63	left midbrain
4	left middle frontal gyrus	34	left anterior limb of internal capsule	64	left pons
5	left inferior frontal gyrus	35	left posterior limb of internal capsule	65	left medulla
6	left precentral gyrus	36	left posterior thalamic radiation	66	right superior parietal lobule
7	left postcentral gyrus	37	left anterior corona radiata	67	right cingulate gyrus
8	left angular gyrus	38	left superior corona radiata	68	right superior frontal gyrus
9	left pre cuneus	39	left posterior corona radiata	69	right middle frontal gyrus
10	left cuneus	40	left cingulum (cingulate gyrus)	70	right inferior frontal gyrus
11	left lingual gyrus	41	left cingulum (hippocampus)	71	right precentral gyrus
12	left fusiform gyrus	42	left fornix(cres) stria terminalis	72	right postcentral gyrus
13	left parahippocampal gyrus	43	left superior longitudinal fasciculus	73	right angular gyrus
14	left superior occipital gyrus	44	left superior fronto occipital fasciculus	74	right pre cuneus
15	left inferior occipital gyrus	45	left inferior fronto occipital fasciculus	75	right cuneus
16	left middle occipital gyrus	46	left sagittal stratum	76	right lingual gyrus
17	NA entorhinal area	47	left external capsule	77	right fusiform gyrus
18	left superior temporal gyrus	48	left uncinate fasciculus	78	right parahippocampal gyrus
19	left inferior temporal gyrus	49	left pontine crossing tract	79	right superior occipital gyrus
20	left middle temporal gyrus	50	left middle cerebellar peduncle	80	right inferior occipital gyrus
21	left lateral fronto orbital gyrus	51	left fornix (column and body)	81	right middle occipital gyrus
22	left middle fronto orbital gyrus	52	left genu of corpus callosum	82	right entorhinal area
23	left supramarginal gyrus	53	left body of corpus callosum	83	right superior temporal gyrus
24	left gyrus rectus	54	left splenium of corpus callosum	84	right inferior temporal gyrus
25	left insular	55	left retrolenticular part of internal capsule	85	right middle temporal gyrus
26	left amygdala	56	left red nucleus	86	right lateral fronto orbital gyrus
27	left hippocampus	57	left substancia nigra	87	right middle fronto orbital gyrus
28	left cerebellum	58	left tapatum	88	right supramarginal gyrus
29	left corticospinal tract	59	left caudate nucleus	89	right gyrus rectus
30	left inferior cerebellar peduncle	60	left putamen	90	right insular

Table S11: Dictionary of ROI labels 91-130

Label	ROI	Label	ROI
91	right amygdala	121	right red nucleus
92	right hippocampus	122	right substancia nigra
93	right cerebellum	123	right tapatum
94	right corticospinal tract	124	right caudate nucleus
95	right inferior cerebellar peduncle	125	right putamen
96	right medial lemniscus	126	right thalamus
97	right superior cerebellar peduncle	127	right globus pallidus
98	right cerebral peduncle	128	right midbrain
99	right anterior limb of internal capsule	129	right pons
100	right posterior limb of internal capsule	130	right medulla
101	right posterior thalamic radiation (include optic radiation)		
102	right anterior corona radiata		
103	right superior corona radiata		
104	right posterior corona radiata		
105	right cingulum (cingulate gyrus)		
106	right cingulum (hippocampus)		
107	right fornix(cres) stria terminalis		
108	right superior longitudinal fasciculus		
109	right superior fronto occipital fasciculus		
110	right inferior fronto occipital fasciculus		
111	right sagittal stratum		
112	right external capsule		
113	right uncinate fasciculus		
114	right pontine crossing tract		
115	right middle cerebellar peduncle		
116	right fornix (column and body)		
117	right genu of corpus callosum		
118	right body of corpus callosum		
119	right splenium of corpus callosum		
120	right retrolenticular part of internal capsule		

9 Stan code for the instantaneous model with whole-brain voxels

```
data{
  int n; // number of subjects
  int J; // number of longitudinal outcomes
  int nobs; // number of observations
  int nmiss[J]; // number of missingness
  int id_long[nobs]; // ID
  int L0; // number of eigenvalues for U_i(t)
  int L1; // number of eigenvalues for W_ij(t)
  int Lm; // number of eigenfunctions for f_mi(v)
  int P; // number of cubic B-spline functions
  int P_surv;

  real Y1[nobs]; // Y1
  real Y2[nobs]; // Y2
  real Y3[nobs];
  real Y4[nobs];
  real Y5[nobs];
  int miss_index1[nmiss[1]];
  int miss_index2[nmiss[2]];
  int miss_index3[nmiss[3]];
  int miss_index4[nmiss[4]];
  int miss_index5[nmiss[5]];
  real time[nobs]; // observed time

  matrix[n, P_surv] x;

  real surv_time[n]; // survival time
  real status[n]; // censoring status
  matrix[nobs, P] b; // cubic B-spline matrix
  matrix[nobs, L0] phi; // estimated eigenfunctions for U_i(t)
  matrix[nobs, L1] psi; // estimated eigenfunctions for W_ij(t)
  matrix[n, Lm] m_mat; // m_{ij} matrix
  matrix[L0, Lm] f_l; // \int_V phi_{ml}(v) psi_{mj}(v) dv
  real beta_m;
  matrix[n, L0] phi_surv; // phi_l(T_i)
  matrix[n, L1] psi_surv; // psi_l(T_i)

  int<lower=0> Ltau; // number of knots for baseline hazard function
  real tau[Ltau]; // knots for time
  matrix[n, Ltau+1] h_grid; // observed survival time covariate for survival outcome
  matrix[n, Ltau] h_index; // observed time spline coefficient index for survival outcome

  int<lower=0> G; // number of quadrature points
  vector[G] w; // weights for quadrature
```

```
  matrix[n, Ltau] constant; // (b[i, e] - a[i, e])/2
  row_vector[G] phi1_interval[n, Ltau]; // phi_1 evaluated at G quadrature points for E intervals
  row_vector[G] phi2_interval[n, Ltau]; // phi_2 evaluated at G quadrature points for E intervals
  row_vector[G] psi1_interval[n, Ltau]; // psi_1 evaluated at G quadrature points for E intervals
}
parameters{
  vector[P] A1; // coefficients for mu1
  vector[P] A2; // coefficients for mu2
  vector[P] A3;
  vector[P] A4;
  vector[P] A5;

  vector<lower=0>[L0] sqrt_d0; // standard deviation for FPC scores xi_il
  vector<lower=0>[L1] sqrt_d1; // standard deviation for zeta_ijl

  matrix[L0, n] xi; // FPC scores for U_i(t)
  matrix[L1, n] zeta_1; // FPC scores for W_i1(t)
  matrix[L1, n] zeta_2; // FPC scores for W_i2(t)
  matrix[L1, n] zeta_3;
  matrix[L1, n] zeta_4;
  matrix[L1, n] zeta_5;

  vector[J-1] beta; // beta
  vector<lower=0>[J] sigma;

  vector[Ltau] logh0;
  vector[P_surv] gamma_x; // coefficients for x
  real gamma0; // coefficients for U_i(t)
  real gamma1[J];  // coefficients for W_{ij}(t)
  vector[Lm] gamma_m; // coefficients for zeta_{mil}
  real Y1_imp[nmiss[1]];
  real Y2_imp[nmiss[2]];
  real Y3_imp[nmiss[3]];
  real Y4_imp[nmiss[4]];
  real Y5_imp[nmiss[5]];
}
transformed parameters{
  real Y1_full[nobs] = Y1;
  real Y2_full[nobs] = Y2;
  real Y3_full[nobs] = Y3;
  real Y4_full[nobs] = Y4;
  real Y5_full[nobs] = Y5;

  real mu1[nobs];
  real mu2[nobs];
  real mu3[nobs];
  real mu4[nobs];
  real mu5[nobs];
```

```
matrix[n, Lm] mu_matrix = beta_m*(xi'*f_l); // beta_m * (i,j-th element is sum_l xi_{il}*f_{lj})
matrix[n, Lm] xi_m = m_mat - mu_matrix; // FPC scores for f_mi(v)

vector[L0] d0;
vector[L1] d1;
vector[L0] tmp_xi;

vector[L1] tmp_zeta1;
vector[L1] tmp_zeta2;
vector[L1] tmp_zeta3;
vector[L1] tmp_zeta4;
vector[L1] tmp_zeta5;

real rs_w[n]; // risk score for subject i
real h[n]; // hazard function
matrix[n, Ltau] H; // cumulative hazard in interval (e, e+1)
real LL[n]; // log survival likelihood
row_vector[G] U; // for subject i, interval e, U = tmp_xi[1]*phi_surv[i, e]
row_vector[G] W1; // for subject i, interval e, W1 = tmp_zeta1*psi_surv[i, e]
row_vector[G] W2;
row_vector[G] W3;
row_vector[G] W4;
row_vector[G] W5;
row_vector[G] f; // f = exp(\gamma_0*U_i(t) + \sum_{j=1}^J \gamma_{1j}*W_{ij}(t))

Y1_full[miss_index1] = Y1_imp;
Y2_full[miss_index2] = Y2_imp;
Y3_full[miss_index3] = Y3_imp;
Y4_full[miss_index4] = Y4_imp;
Y5_full[miss_index5] = Y5_imp;

for (i in 1:L0){
  d0[i] = pow(sqrt_d0[i], 2);
}

for (i in 1:L1){
  d1[i] = pow(sqrt_d1[i], 2);
}

for (i in 1:nobs){
  tmp_xi = col(xi, id_long[i]); // FPC scores xi_{i} for subject i

  tmp_zeta1 = col(zeta_1, id_long[i]); // FPC scores zeta_{i1} for subject i
  tmp_zeta2 = col(zeta_2, id_long[i]); // FPC scores zeta_{i2} for subject i
  tmp_zeta3 = col(zeta_3, id_long[i]);
  tmp_zeta4 = col(zeta_4, id_long[i]);
  tmp_zeta5 = col(zeta_5, id_long[i]);
```

```
    mu1[i] = b[i]*A1 + phi[i]*tmp_xi + psi[i]*tmp_zeta1;
    mu2[i] = b[i]*A2 + beta[1]*(phi[i]*tmp_xi + psi[i]*tmp_zeta2);
    mu3[i] = b[i]*A3 + beta[2]*(phi[i]*tmp_xi + psi[i]*tmp_zeta3);
    mu4[i] = b[i]*A4 + beta[3]*(phi[i]*tmp_xi + psi[i]*tmp_zeta4);
    mu5[i] = b[i]*A5 + beta[4]*(phi[i]*tmp_xi + psi[i]*tmp_zeta5);
  }

  for (i in 1:n){
    tmp_xi = col(xi, i);

    tmp_zeta1 = col(zeta_1, i);
    tmp_zeta2 = col(zeta_2, i);
    tmp_zeta3 = col(zeta_3, i);
    tmp_zeta4 = col(zeta_4, i);
    tmp_zeta5 = col(zeta_5, i);

    rs_w[i] = gamma0*(phi_surv[i]*tmp_xi) + gamma1[1]*(psi_surv[i]*tmp_zeta1) +
      gamma1[2]*(psi_surv[i]*tmp_zeta2) + gamma1[3]*(psi_surv[i]*tmp_zeta3) +
      gamma1[4]*(psi_surv[i]*tmp_zeta4) + gamma1[5]*(psi_surv[i]*tmp_zeta5);
    h[i] = exp(h_index[i]*logh0 + x[i]*gamma_x + xi_m[i]*gamma_m + rs_w[i]);

    for (k in 1:Ltau){
      U = tmp_xi[1]*phi1_interval[i, k] + tmp_xi[2]*phi2_interval[i, k];
      W1 = tmp_zeta1[1]*psi1_interval[i, k];
      W2 = tmp_zeta2[1]*psi1_interval[i, k];
      W3 = tmp_zeta3[1]*psi1_interval[i, k];
      W4 = tmp_zeta4[1]*psi1_interval[i, k];
      W5 = tmp_zeta5[1]*psi1_interval[i, k];
      f = exp(gamma0*U + gamma1[1]*W1 + gamma1[2]*W2 + gamma1[3]*W3 + gamma1[4]*W4 + gamma1[5]*W5);
      H[i, k] = exp(x[i]*gamma_x + logh0[k] + xi_m[i]*gamma_m)*constant[i, k]*(f*w);
    }
    LL[i] = status[i]*log(h[i]) + sum(-H[i]);
  }
}
model{
  A1 ~ normal(0, 10);
  A2 ~ normal(0, 10);
  A3 ~ normal(0, 10);
  A4 ~ normal(0, 10);
  A5 ~ normal(0, 10);

  for (i in 1:L0){
    sqrt_d0[i] ~ inv_gamma(0.1, 0.1);
    xi[i] ~ normal(0, sqrt_d0[i]);
  }

  for (i in 1:L1){
    sqrt_d1[i] ~ inv_gamma(0.1, 0.1);
```

```
    zeta_1[i] ~ normal(0, sqrt_d1[i]);
    zeta_2[i] ~ normal(0, sqrt_d1[i]);
    zeta_3[i] ~ normal(0, sqrt_d1[i]);
    zeta_4[i] ~ normal(0, sqrt_d1[i]);
    zeta_5[i] ~ normal(0, sqrt_d1[i]);
  }

  beta ~ normal(0, 10);
  sigma ~ inv_gamma(0.1, 0.1);

  logh0 ~ normal(0, 10);
  gamma_x ~ normal(0, 10);
  gamma0 ~ normal(0, 10);
  gamma1 ~ normal(0, 10);
  gamma_m ~ normal(0, 10);

  target+=skew_normal_lpdf(Y1_full | mu1, sigma[1], 0);
  target+=skew_normal_lpdf(Y2_full | mu2, sigma[2], 0);
  target+=skew_normal_lpdf(Y3_full | mu3, sigma[3], 0);
  target+=skew_normal_lpdf(Y4_full | mu4, sigma[4], 0);
  target+=skew_normal_lpdf(Y5_full | mu5, sigma[5], 0);
  target+=LL;
}
generated quantities{
  vector[Lm] dm;
  for (i in 1:Lm){
    dm[i] = variance(col(xi_m, i));
  }
}
```