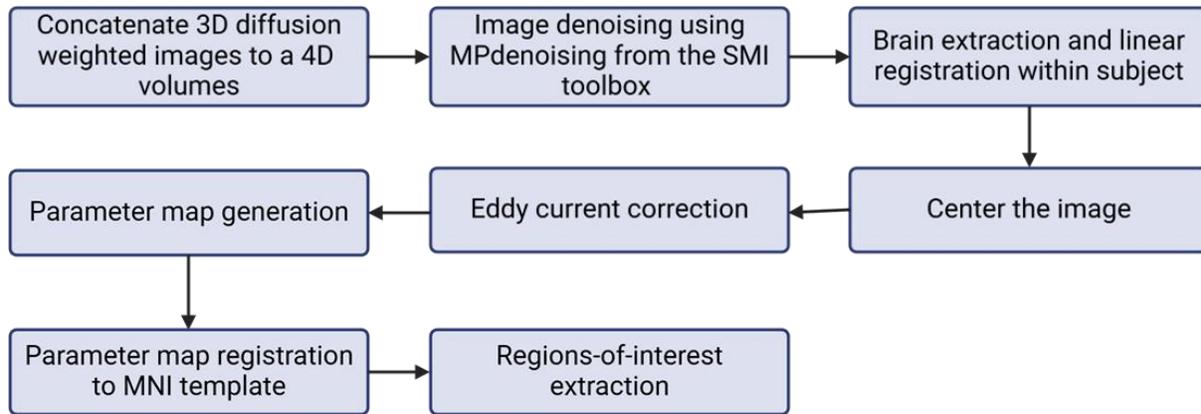


# **Supplementary Material**

## **Early axonal degeneration linked to clinical decline in Alzheimer's disease progression revealed with diffusion MRI**

Zhaoyuan Gong, John P. Laporte, Alexander Y. Guo, Murat Bilgel, Jonghyun Bae, Noam Y. Fox,  
Angelique de Rouen, Nathan Zhang, Aaliya Taranath, Rafael de Cabo, Josephine M. Egan, Luigi  
Ferrucci, Mustapha Bouhrara, and *for the Alzheimer's Disease Neuroimaging Initiative*



**Figure S1.** Flowchart of the diffusion magnetic resonance imaging (dMRI) processing pipeline. After downloading DICOM files from the ADNI site, 3D dMRI were concatenated into a 4D volume. Image denoising was performed using the *MPdenoising.m* MATLAB function from [https://github.com/NYU-DiffusionMRI/mppca\\_denoise](https://github.com/NYU-DiffusionMRI/mppca_denoise). Brain extraction was performed on the dMRI obtained at  $b = 0 \text{ s}^2/\text{mm}$  (aka., b0 image), and all dMRI were brain-masked and linearly registered to the corresponding b0 image. To facilitate later nonlinear registration to the MNI template, all images were also linearly transformed to center the field of view. Eddy current correction was applied using the *eddy* command in FSL. Due to the lack of reverse phase encoding data, susceptibility-induced off-resonance fields were not corrected. Preprocessed data were subsequently fitted to three biophysical diffusion models (NODDI, C-NODDI, and SMI) to derive the corresponding Axonal Density Indices (ADIs). For each model, the resulting ADI map was nonlinearly registered to the MNI template using FSL, and the whole brain white matter region-of-interest (ROI) value was then calculated.

**Table S1.** Linear mixed-effects model results for Figure 2.

The model equation is specified as:

$$ADI_{ij} \sim \beta_0 + \beta_{Age} \times Age_i + \beta_{sex} \times Sex_i + \beta_{Time} \times Time_{ij} + \beta_{Diagnosis} \times Diagnosis_i + \beta_{Time \times Diagnosis} \times Time_{ij} \times Diagnosis_i + b_i + \epsilon_{ij},$$

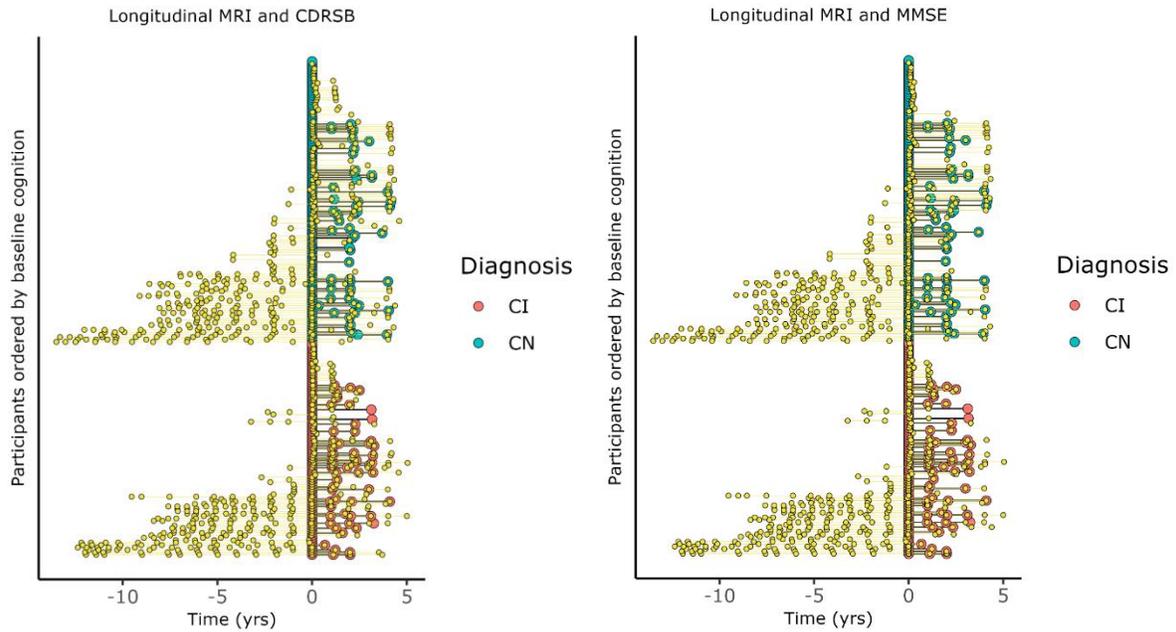
where  $ADI_{ij}$  represents the longitudinal ADI value for subject  $i$  at time point  $j$ ;  $Age_i$  is the age at the first MRI measurement for subject  $i$ ;  $Sex_i$  denotes subject sex;  $Time_{ij}$  is the time since the first MRI measurement for subject  $i$  at time point  $j$ ;  $Diagnosis_i$  indicates the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which includes MCI and AD);  $Time_{ij} \times Diagnosis_i$  is the interaction term representing differential time trajectories of ADI for two diagnosis groups;  $b_i$  is the random intercept for subject  $i$ ;  $\epsilon_{ij}$  is the residual error.  $Age_i$  was standardized using baseline mean and standard deviation, while  $Time_{ij}$  is in the original unit (yrs.) for easier interpretation. Whole brain white matter  $ADI_{NODDI}$ ,  $ADI_{C-NODDI}$ , and  $ADI_{SMI}$  values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-4.21e-01	1.22e-01	2.07e+02	-3.43e+00	7.17e-04
Age	-2.64e-01	6.58e-02	2.06e+02	-4.01e+00	8.39e-05
Time	-1.80e-01	2.69e-02	1.26e+02	-6.68e+00	6.78e-10
Diagnosis-CN	4.44e-01	1.35e-01	2.09e+02	3.30e+00	1.15e-03
Sex-Male	3.95e-01	1.33e-01	2.02e+02	2.98e+00	3.27e-03
Diagnosis-CN × Time	1.19e-01	3.57e-02	1.27e+02	3.35e+00	1.07e-03

	ADI <sub>C-NODDI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.56e-01	1.08e-01	2.14e+02	-3.31e+00	1.10e-03
Age	-4.86e-01	5.78e-02	2.11e+02	-8.40e+00	6.57e-15
Time	-2.08e-01	3.30e-02	1.37e+02	-6.31e+00	3.60e-09
Diagnosis-CN	6.29e-01	1.19e-01	2.18e+02	5.30e+00	2.89e-07
Sex-Male	3.48e-04	1.16e-01	2.04e+02	3.00e-03	9.98e-01
Diagnosis-CN × Time	1.81e-01	4.37e-02	1.38e+02	4.13e+00	6.18e-05

	ADI <sub>SMI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.48e-01	1.32e-01	2.22e+02	-1.12e+00	2.63e-01
Age	-1.62e-01	7.05e-02	2.16e+02	-2.30e+00	2.24e-02
Time	1.05e-01	5.20e-02	1.52e+02	2.02e+00	4.55e-02
Diagnosis-CN	2.17e-01	1.46e-01	2.30e+02	1.49e+00	1.38e-01
Sex-Male	-1.22e-02	1.41e-01	2.03e+02	-8.70e-02	9.31e-01
Diagnosis-CN × Time	-7.04e-02	6.88e-02	1.53e+02	-1.02e+00	3.08e-01

Diagnosis was referenced to the CI group, and sex was referenced to females. P-values were not corrected for multiple comparisons.



**Figure S2.** Available longitudinal diffusion MRI (dMRI) measurements and longitudinal cognitive measurements. Cognitive scores (MMSE or CDR-SB) that occurred after the MRI measurements, or within 0.1 years prior to the MRI measurements, were retained for the analyses presented in the manuscript Figure 3.

**Table S2.** Linear mixed-effects model results for Figure 3.

The model equation is specified as:

$$\begin{aligned} \text{MMSE/CDR-SB}_{ij} \sim & \beta_0 + \beta_{\text{Age}} \times \text{Age}_i + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Time}} \times \text{Time}_{ij} + \beta_{\text{Diagnosis}} \times \\ & \text{Diagnosis}_i + \beta_{\text{ADI}} \times \text{ADI}_i + \beta_{\text{Time} \times \text{ADI}} \times \text{Time}_{ij} \times \text{ADI}_i + \beta_{\text{Time} \times \text{Diagnosis}} \times \text{Time}_{ij} \times \\ & \text{Diagnosis}_i + \beta_{\text{ADI} \times \text{Diagnosis}} \times \text{ADI}_i \times \text{Diagnosis}_i + \beta_{\text{Time} \times \text{Diagnosis} \times \text{ADI}} \times \text{Time}_{ij} \times \\ & \text{Diagnosis}_i \times \text{ADI}_i + b_i + \epsilon_{ij}, \end{aligned}$$

where MMSE/CDR-SB<sub>ij</sub> represents the longitudinal MMSE or CDR-SB scores for subject *i* at time point *j*; Age<sub>*i*</sub> is the age at the baseline MRI measurement for subject *i*; Sex<sub>*i*</sub> denotes the subject sex; Time<sub>ij</sub> is the time of cognitive assessment since the baseline MRI measurement for subject *i* at time point *j*; Diagnosis<sub>*i*</sub> indicates the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, includes MCI and AD) for subject *i*; and ADI<sub>*i*</sub> is the baseline axonal density index. The model includes all two-way interactions among Time<sub>ij</sub>, Diagnosis<sub>*i*</sub>, and ADI<sub>*i*</sub>, as well as the three-way interaction term. b<sub>*i*</sub> is the random intercept for subject *i* and ε<sub>ij</sub> is the residual error. Age<sub>*i*</sub> and ADI<sub>*i*</sub> were standardized using baseline mean and standard deviation, while Time<sub>ij</sub> was kept in the original unit (yrs.) for easier interpretation. Whole brain white matter ADI<sub>NODDI</sub>, ADI<sub>C-NODDI</sub>, and ADI<sub>SMI</sub> values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.63e+01	4.16e-01	2.12e+02	6.32e+01	2.20e-139
Age	-1.39e-01	2.21e-01	1.99e+02	-6.30e-01	5.29e-01
Sex-Male	3.44e-01	4.35e-01	1.86e+02	7.91e-01	4.30e-01
Diagnosis-CN	2.68e+00	4.56e-01	2.26e+02	5.88e+00	1.46e-08
Time	-5.95e-01	1.29e-01	2.32e+02	-4.63e+00	6.18e-06
Whole brain ADI	5.99e-01	3.08e-01	2.22e+02	1.94e+00	5.33e-02
Diagnosis-CN × Time	4.90e-01	1.57e-01	2.31e+02	3.11e+00	2.10e-03
Diagnosis-CN × ADI	-5.96e-01	4.46e-01	2.23e+02	-1.33e+00	1.83e-01
Time × ADI	-6.29e-02	1.32e-01	2.37e+02	-4.77e-01	6.34e-01
Diagnosis-CN × Time × ADI	4.39e-02	1.65e-01	2.33e+02	2.67e-01	7.90e-01

	ADIC-NODDI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.66e+01	4.04e-01	2.15e+02	6.58e+01	2.96e-144
Age	5.27e-02	2.36e-01	1.92e+02	2.23e-01	8.23e-01
Sex-Male	5.19e-01	4.05e-01	1.82e+02	1.28e+00	2.02e-01
Diagnosis-CN	2.30e+00	4.57e-01	2.27e+02	5.04e+00	9.57e-07
Time	-4.23e-01	1.39e-01	2.39e+02	-3.04e+00	2.62e-03
Whole brain ADI	1.23e+00	3.35e-01	2.21e+02	3.68e+00	2.93e-04
Diagnosis-CN × Time	3.24e-01	1.70e-01	2.36e+02	1.91e+00	5.71e-02
Diagnosis-CN × ADI	-1.09e+00	4.56e-01	2.25e+02	-2.39e+00	1.77e-02
Time × ADI	3.17e-01	1.48e-01	2.42e+02	2.15e+00	3.27e-02
Diagnosis-CN × Time × ADI	-3.52e-01	1.80e-01	2.39e+02	-1.96e+00	5.13e-02

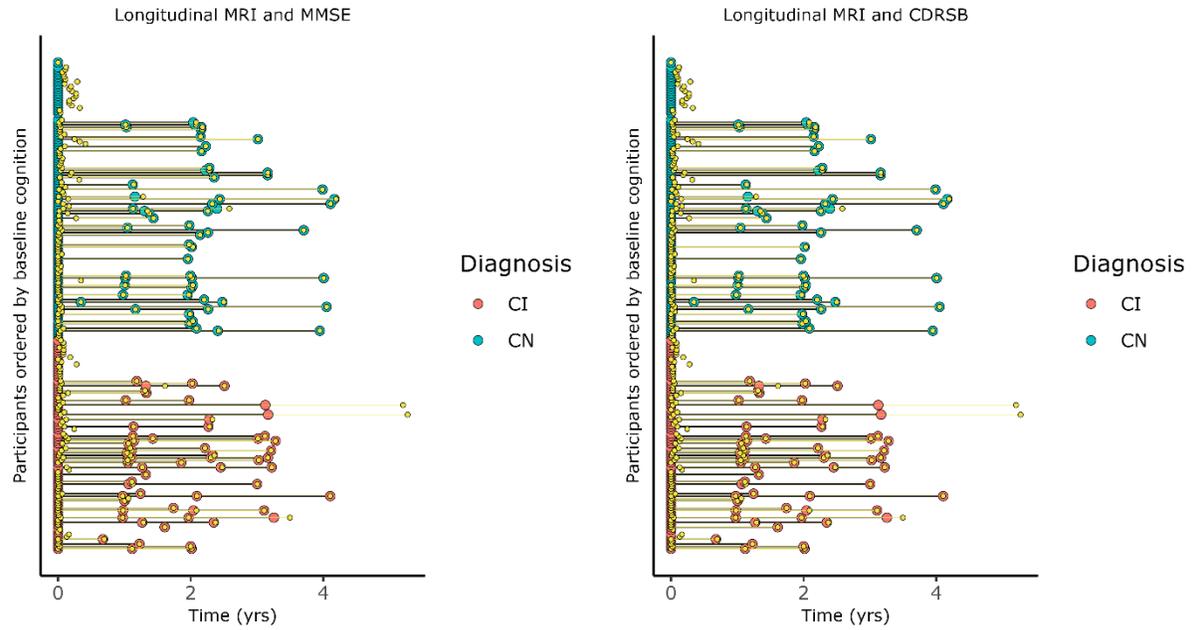
	ADISMI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.61e+01	4.10e-01	2.12e+02	6.37e+01	4.22e-140
Age	-2.07e-01	2.16e-01	1.99e+02	-9.60e-01	3.38e-01
Sex-Male	3.75e-01	4.24e-01	1.86e+02	8.84e-01	3.78e-01
Diagnosis-CN	2.89e+00	4.51e-01	2.26e+02	6.40e+00	8.78e-10
Time	-5.75e-01	1.34e-01	2.34e+02	-4.29e+00	2.64e-05
Whole brain ADI	-4.15e-01	3.67e-01	2.32e+02	-1.13e+00	2.58e-01
Diagnosis-CN × Time	4.78e-01	1.62e-01	2.32e+02	2.96e+00	3.39e-03
Diagnosis-CN × ADI	4.09e-01	4.59e-01	2.32e+02	8.92e-01	3.74e-01
Time × ADI	2.44e-02	1.32e-01	2.32e+02	1.85e-01	8.54e-01
Diagnosis-CN × Time × ADI	-1.04e-01	1.59e-01	2.31e+02	-6.54e-01	5.14e-01

	ADI <sub>NODDI</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.31e+00	2.51e-01	2.18e+02	9.22e+00	2.57e-17
Age	1.22e-01	1.30e-01	1.95e+02	9.38e-01	3.50e-01
Sex-Male	-3.16e-01	2.60e-01	1.89e+02	-1.22e+00	2.24e-01
Diagnosis-CN	-2.20e+00	2.73e-01	2.33e+02	-8.05e+00	4.20e-14
Time	4.78e-01	7.14e-02	2.81e+02	6.69e+00	1.23e-10
Whole brain ADI	-5.77e-01	1.86e-01	2.28e+02	-3.11e+00	2.10e-03
Diagnosis-CN × Time	-4.34e-01	8.70e-02	2.80e+02	-4.99e+00	1.07e-06
Diagnosis-CN × ADI	7.04e-01	2.64e-01	2.32e+02	2.66e+00	8.25e-03
Time × ADI	-3.69e-02	6.96e-02	2.87e+02	-5.30e-01	5.97e-01
Diagnosis-CN × Time × ADI	2.28e-02	8.74e-02	2.83e+02	2.61e-01	7.94e-01

	ADI <sub>C-NODDI</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.10e+00	2.37e-01	2.26e+02	8.85e+00	2.49e-16
Age	-2.01e-02	1.35e-01	1.92e+02	-1.49e-01	8.82e-01
Sex-Male	-4.67e-01	2.33e-01	1.89e+02	-2.01e+00	4.64e-02
Diagnosis-CN	-1.94e+00	2.66e-01	2.38e+02	-7.29e+00	4.63e-12
Time	2.99e-01	7.63e-02	2.88e+02	3.92e+00	1.13e-04
Whole brain ADI	-1.02e+00	1.98e-01	2.34e+02	-5.14e+00	5.78e-07
Diagnosis-CN × Time	-2.57e-01	9.18e-02	2.86e+02	-2.80e+00	5.41e-03
Diagnosis-CN × ADI	1.04e+00	2.63e-01	2.39e+02	3.97e+00	9.41e-05
Time × ADI	-3.72e-01	8.29e-02	2.92e+02	-4.48e+00	1.06e-05
Diagnosis-CN × Time × ADI	3.77e-01	9.94e-02	2.89e+02	3.79e+00	1.81e-04

	ADIS <sub>SMI</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.45e+00	2.52e-01	2.17e+02	9.74e+00	7.87e-19
Age	1.53e-01	1.30e-01	1.94e+02	1.18e+00	2.40e-01
Sex-Male	-3.45e-01	2.59e-01	1.88e+02	-1.33e+00	1.84e-01
Diagnosis-CN	-2.31e+00	2.77e-01	2.31e+02	-8.35e+00	6.30e-15
Time	5.02e-01	7.21e-02	2.81e+02	6.96e+00	2.34e-11
Whole brain ADI	-2.85e-02	2.22e-01	2.30e+02	-1.28e-01	8.98e-01
Diagnosis-CN × Time	-4.64e-01	8.77e-02	2.79e+02	-5.29e+00	2.45e-07
Diagnosis-CN × ADI	5.57e-02	2.78e-01	2.33e+02	2.00e-01	8.42e-01
Time × ADI	1.35e-02	7.84e-02	2.78e+02	1.72e-01	8.64e-01
Diagnosis-CN × Time × ADI	1.53e-02	9.27e-02	2.79e+02	1.65e-01	8.69e-01

Diagnosis was referenced to the CI group, and sex was referenced to females. P-values were not corrected for multiple comparisons.



**Figure S3.** Available longitudinal diffusion MRI (dMRI) measurements and corresponding cognitive measurements (CDR-SB and MMSE). The closest MMSE or CDR-SB measurement to each dMRI measurement was retained for analysis. As visually evident, most cognitive assessments were conducted at or near the time of the MRI measurement. For analysis in Figure 4, the timing of each MMSE or CDR-SB measurement was shifted to align with its nearest dMRI measurement, as outlined in the main manuscript.

**Table S3.** Linear mixed-effects model results for Figure 4.

The model equation is specified as:

$$\text{MMSE/CDR-SB changes}_{ij} \sim \beta_0 + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Age}} \times \text{Age}_{ij} + \beta_{\text{Diagnosis}} \times \text{Diagnosis}_i + \beta_{\text{ADI changes}} \times \text{ADI changes}_{ij} + \beta_{\text{Diagnosis} \times \text{ADI changes}} \times \text{Diagnosis}_i \times \text{ADI changes}_{ij} + \beta_{\text{Baseline ADI}} \times \text{Baseline ADI}_i + \beta_{\text{Diagnosis} \times \text{Baseline ADI}} \times \text{Diagnosis}_i \times \text{Baseline ADI}_i + b_i + \epsilon_{ij},$$

where MMSE/CDR-SB changes<sub>ij</sub> is the longitudinal MMSE or CDR-SB changes for subject *i* at time point *j* from subject *i*'s baseline value; Age<sub>ij</sub> is the age at the MRI measurement for subject *i* at the time point *j*; Sex<sub>*i*</sub> denotes the subject sex; ADI changes<sub>ij</sub> is the change in ADI from baseline ADI for subject *i* at time point *j*; Baseline ADI<sub>*i*</sub> is the baseline ADI value for subject *i*; Diagnosis<sub>*i*</sub> is the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, includes MCI and AD) for subject *i*; b<sub>*i*</sub> is the random intercept for subject *i*, and ε<sub>ij</sub> is the residual error. Two-way interaction terms between diagnosis and ADI changes were included to examine how changes in ADI from baseline are associated with changes in MMSE/CDR-SB from baseline scores. Age<sub>ij</sub> and ADI<sub>ij</sub> values were standardized using the baseline mean and standard deviation. ADI changes<sub>ij</sub> were computed as the difference between the standardized ADI at time *j* and the subject's baseline ADI. Whole brain white matter ADI<sub>NODDI</sub>, ADI<sub>C-NODDI</sub>, and ADI<sub>SMI</sub> values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.79e-01	1.94e-01	2.57e+02	-9.25e-01	3.56e-01
Sex-Male	1.60e-01	2.01e-01	2.34e+02	7.97e-01	4.26e-01
Age	-1.28e-01	1.03e-01	2.62e+02	-1.24e+00	2.16e-01
Diagnosis-CN	1.55e-01	2.08e-01	2.50e+02	7.45e-01	4.57e-01
ADI changes	1.53e+00	3.77e-01	3.05e+02	4.07e+00	6.07e-05
ADI baseline	2.80e-02	1.34e-01	2.22e+02	2.08e-01	8.35e-01
Diagnosis-CN × ADI changes	-1.77e+00	6.37e-01	3.03e+02	-2.78e+00	5.77e-03
Diagnosis-CN × ADI baseline	-8.78e-02	1.98e-01	2.37e+02	-4.43e-01	6.58e-01

	ADIC-NODDI changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.03e-01	1.98e-01	2.63e+02	-5.21e-01	6.03e-01
Sex-Male	1.80e-01	1.95e-01	2.33e+02	9.21e-01	3.58e-01
Age	-1.06e-01	1.14e-01	2.58e+02	-9.30e-01	3.53e-01
Diagnosis-CN	8.55e-02	2.20e-01	2.57e+02	3.88e-01	6.98e-01
ADI changes	1.25e+00	3.85e-01	2.97e+02	3.25e+00	1.27e-03
ADI baseline	2.45e-01	1.55e-01	2.33e+02	1.58e+00	1.15e-01
Diagnosis-CN × ADI changes	-1.75e+00	5.32e-01	3.01e+02	-3.29e+00	1.13e-03
Diagnosis-CN × ADI baseline	-3.40e-01	2.11e-01	2.38e+02	-1.61e+00	1.08e-01

	ADISMI changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.59e-01	1.88e-01	2.41e+02	-1.91e+00	5.68e-02
Sex-Male	1.46e-01	1.98e-01	2.34e+02	7.38e-01	4.61e-01
Age	-1.58e-01	1.01e-01	2.62e+02	-1.56e+00	1.21e-01
Diagnosis-CN	3.61e-01	2.02e-01	2.36e+02	1.79e+00	7.49e-02
ADI changes	4.88e-02	2.55e-01	2.99e+02	1.91e-01	8.48e-01
ADI baseline	5.30e-03	1.59e-01	2.25e+02	3.34e-02	9.73e-01
Diagnosis-CN × ADI changes	3.26e-01	3.69e-01	3.05e+02	8.83e-01	3.78e-01
Diagnosis-CN × ADI baseline	-8.89e-02	2.02e-01	2.37e+02	-4.40e-01	6.60e-01

	ADI <sub>NODDI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.40e-01	9.20e-02	2.44e+02	2.61e+00	9.64e-03
Sex-Male	-4.48e-02	9.46e-02	2.19e+02	-4.73e-01	6.36e-01
Age	6.80e-02	4.89e-02	2.54e+02	1.39e+00	1.66e-01
Diagnosis-CN	-2.12e-01	9.79e-02	2.38e+02	-2.17e+00	3.13e-02
ADI changes	-1.47e+00	1.78e-01	2.92e+02	-8.24e+00	5.91e-15
ADI baseline	3.28e-02	6.25e-02	1.97e+02	5.26e-01	6.00e-01
Diagnosis-CN × ADI changes	1.42e+00	3.10e-01	3.02e+02	4.57e+00	7.26e-06
Diagnosis-CN × ADI baseline	-2.92e-02	9.23e-02	2.23e+02	-3.16e-01	7.52e-01

	ADI <sub>C-NODDI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.38e-01	9.39e-02	2.52e+02	1.47e+00	1.43e-01
Sex-Male	-5.97e-02	9.09e-02	2.17e+02	-6.57e-01	5.12e-01
Age	1.11e-02	5.39e-02	2.51e+02	2.06e-01	8.37e-01
Diagnosis-CN	-9.59e-02	1.04e-01	2.46e+02	-9.25e-01	3.56e-01
ADI changes	-1.42e+00	1.82e-01	3.00e+02	-7.79e+00	1.07e-13
ADI baseline	-2.12e-01	7.21e-02	2.10e+02	-2.94e+00	3.68e-03
Diagnosis-CN × ADI changes	1.42e+00	2.59e-01	3.02e+02	5.48e+00	9.05e-08
Diagnosis-CN × ADI baseline	2.03e-01	9.77e-02	2.24e+02	2.08e+00	3.87e-02

	ADI <sub>SMI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	3.70e-01	9.42e-02	2.23e+02	3.93e+00	1.14e-04
Sex-Male	-1.61e-02	9.88e-02	2.15e+02	-1.63e-01	8.71e-01
Age	8.12e-02	5.13e-02	2.56e+02	1.58e+00	1.15e-01
Diagnosis-CN	-3.55e-01	1.01e-01	2.18e+02	-3.52e+00	5.32e-04
ADI changes	6.87e-02	1.34e-01	3.02e+02	5.13e-01	6.09e-01
ADI baseline	-1.60e-01	7.75e-02	2.01e+02	-2.07e+00	3.98e-02
Diagnosis-CN × ADI changes	-6.80e-02	1.94e-01	2.99e+02	-3.50e-01	7.27e-01
Diagnosis-CN × ADI baseline	1.83e-01	1.01e-01	2.24e+02	1.81e+00	7.15e-02

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

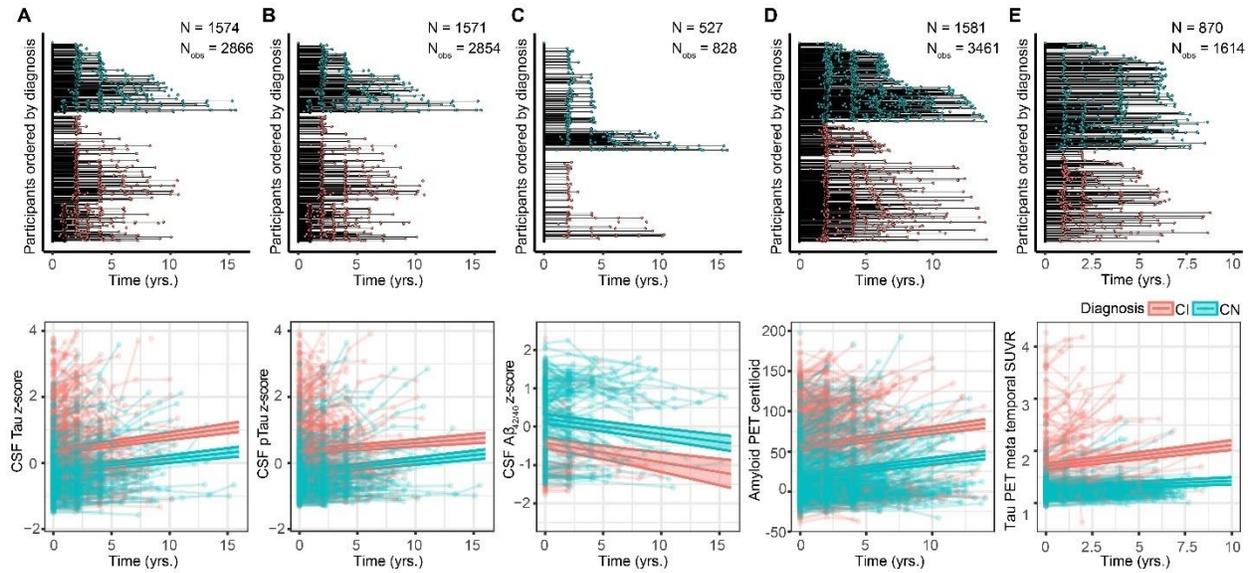


Figure S4. CSF and PET biomarkers longitudinal trajectories of the cognitively normal (CN) and cognitively impaired (CI) groups. Analyses included all available CSF and PET data available at the time of our analysis. Only tau-PET achieved significant group-level differentiation.

**Table S4.** Linear mixed-effects model results for Figure 5.

The model equation is specified as:

$$\text{ADI/PET/CSF}_{ij} \sim \beta_0 + \beta_{\text{Age}} \times \text{Age}_i + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Time}} \times \text{Time}_{ij} + \beta_{\text{Diagnosis}} \times \text{Diagnosis}_i + \beta_{\text{Time} \times \text{Diagnosis}} \times \text{Time}_{ij} \times \text{Diagnosis}_i + b_i + \epsilon_{ij},$$

where ADI/PET/CSF<sub>ij</sub> represents the longitudinal ADI, CSF or PET biomarkers value for subject *i* at time point *j*; Age<sub>*i*</sub> is the age at the first MRI measurement, CSF or PET analysis for subject *i*; Sex<sub>*i*</sub> denotes subject sex; Time<sub>ij</sub> is the time since the first MRI measurement, CSF, or PET analysis for subject *i* at time point *j*, Diagnosis<sub>*i*</sub> is the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which includes MCI and AD) for subject *i*; Time<sub>ij</sub> × Diagnosis<sub>*i*</sub> models differential time trajectories by diagnosis group. *b<sub>i</sub>* is the random intercept for subject *i* and  $\epsilon_{ij}$  is the residual error. Age<sub>*i*</sub> was standardized using baseline mean and standard deviation, while Time<sub>ij</sub> remained in original units (yrs.) for easier interpretation. Whole brain white matter ADI<sub>C-NODDI</sub> values, CSF biomarkers (tau, ptau<sub>181</sub>, Aβ<sub>42/40</sub>), and PET imaging biomarkers (amyloid-PET, tau-PET) were used. Full statistical results are presented below.

	tau trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.62e-01	1.60e-01	1.36e+02	1.01e+00	3.14e-01
Age	3.41e-01	8.56e-02	1.34e+02	3.98e+00	1.13e-04
Time	5.26e-02	2.10e-02	1.03e+02	2.51e+00	1.36e-02
Diagnosis-CN	-2.39e-01	1.78e-01	1.38e+02	-1.34e+00	1.82e-01
Sex-Male	-7.92e-02	1.78e-01	1.33e+02	-4.44e-01	6.57e-01
Time×Diagnosis-CN	9.56e-03	2.80e-02	1.03e+02	3.41e-01	7.34e-01

	ptau <sub>181</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.50e-01	1.62e-01	1.39e+02	9.20e-01	3.59e-01
Age	3.47e-01	8.64e-02	1.36e+02	4.01e+00	1.00e-04
Time	3.93e-02	2.81e-02	1.06e+02	1.40e+00	1.65e-01
Diagnosis-CN	-2.54e-01	1.81e-01	1.42e+02	-1.41e+00	1.62e-01
Sex-Male	-3.03e-02	1.80e-01	1.33e+02	-1.69e-01	8.66e-01
Time×Diagnosis-CN	9.83e-03	3.76e-02	1.06e+02	2.61e-01	7.94e-01

	A $\beta$ <sub>42/40</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-2.47e-01	1.63e-01	1.12e+02	-1.52e+00	1.31e-01
Age	-3.88e-01	8.52e-02	1.11e+02	-4.56e+00	1.34e-05
Time	-5.17e-02	2.65e-02	5.66e+01	-1.95e+00	5.63e-02
Diagnosis-CN	3.68e-01	1.78e-01	1.13e+02	2.07e+00	4.08e-02
Sex-Male	9.12e-02	1.79e-01	1.11e+02	5.10e-01	6.11e-01
Time×Diagnosis-CN	4.62e-02	3.08e-02	5.65e+01	1.50e+00	1.39e-01

	Amyloid-PET trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	4.10e+01	5.13e+00	1.90e+02	7.99e+00	1.28e-13
Age	1.15e+01	2.67e+00	1.86e+02	4.32e+00	2.58e-05
Time	2.08e+00	4.77e-01	1.94e+02	4.35e+00	2.21e-05
Diagnosis-CN	-2.69e+01	5.55e+00	1.91e+02	-4.84e+00	2.63e-06
Sex-Male	-1.14e+00	5.38e+00	1.85e+02	-2.12e-01	8.32e-01
Time×Diagnosis-CN	-1.91e-01	5.95e-01	1.94e+02	-3.20e-01	7.49e-01

	Tau-PET trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.70e+00	6.93e-02	1.78e+02	2.45e+01	5.18e-59
Age	5.41e-03	3.65e-02	1.77e+02	1.48e-01	8.82e-01
Time	4.72e-02	7.81e-03	1.49e+02	6.05e+00	1.14e-08
Diagnosis-CN	-4.14e-01	7.52e-02	1.80e+02	-5.51e+00	1.26e-07
Sex-Male	-1.17e-01	7.34e-02	1.76e+02	-1.59e+00	1.13e-01
Time×Diagnosis-CN	-2.84e-02	1.02e-02	1.49e+02	-2.78e+00	6.09e-03

	ADIC-NODDI trajectory matching tau cohort				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-4.59e-01	1.32e-01	1.42e+02	-3.47e+00	6.78e-04
Age	-4.33e-01	7.05e-02	1.38e+02	-6.14e+00	8.10e-09
Time	-2.41e-01	4.23e-02	1.07e+02	-5.69e+00	1.12e-07
Diagnosis-CN	7.58e-01	1.48e-01	1.46e+02	5.14e+00	8.86e-07
Sex-Male	6.22e-02	1.45e-01	1.33e+02	4.28e-01	6.69e-01
Time×Diagnosis-CN	2.35e-01	5.55e-02	1.07e+02	4.23e+00	4.93e-05

	ADIC-NODDI trajectory matching ptau <sub>181</sub> cohort				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-4.59e-01	1.32e-01	1.42e+02	-3.47e+00	6.78e-04
Age	-4.33e-01	7.05e-02	1.38e+02	-6.14e+00	8.10e-09
Time	-2.41e-01	4.23e-02	1.07e+02	-5.69e+00	1.12e-07
Diagnosis-CN	7.58e-01	1.48e-01	1.46e+02	5.14e+00	8.86e-07
Sex-Male	6.22e-02	1.45e-01	1.33e+02	4.28e-01	6.69e-01
Time×Diagnosis-CN	2.35e-01	5.55e-02	1.07e+02	4.23e+00	4.93e-05

	ADIC-NODDI trajectory matching A $\beta$ <sub>42/40</sub> cohort				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-5.05e-01	1.53e-01	1.19e+02	-3.30e+00	1.29e-03
Age	-3.64e-01	7.94e-02	1.14e+02	-4.59e+00	1.14e-05
Time	-2.63e-01	4.49e-02	8.92e+01	-5.85e+00	8.00e-08
Diagnosis-CN	8.40e-01	1.68e-01	1.21e+02	5.00e+00	1.98e-06
Sex-Male	3.90e-02	1.66e-01	1.12e+02	2.35e-01	8.15e-01
Time×Diagnosis-CN	2.55e-01	5.93e-02	8.94e+01	4.30e+00	4.29e-05

	ADIC-NODDI trajectory matching amyloid-PET cohort				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.67e-01	1.16e-01	1.96e+02	-3.15e+00	1.89e-03
Age	-4.60e-01	6.08e-02	1.93e+02	-7.56e+00	1.61e-12
Time	-2.07e-01	3.31e-02	1.33e+02	-6.26e+00	5.00e-09
Diagnosis-CN	6.46e-01	1.26e-01	2.00e+02	5.10e+00	7.71e-07
Sex-Male	-5.80e-03	1.22e-01	1.87e+02	-4.76e-02	9.62e-01
Time×Diagnosis-CN	1.79e-01	4.40e-02	1.34e+02	4.07e+00	7.90e-05

	ADIC-NODDI trajectory matching tau-PET cohort				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.95e-01	1.16e-01	1.89e+02	-3.39e+00	8.39e-04
Age	-4.69e-01	6.11e-02	1.87e+02	-7.66e+00	9.45e-13
Time	-2.04e-01	3.27e-02	1.30e+02	-6.25e+00	5.36e-09
Diagnosis-CN	6.75e-01	1.27e-01	1.93e+02	5.32e+00	2.79e-07
Sex-Male	2.50e-02	1.22e-01	1.81e+02	2.05e-01	8.38e-01
Time×Diagnosis-CN	1.89e-01	4.42e-02	1.31e+02	4.29e+00	3.50e-05

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

**Table S5.** Linear mixed-effects model results for Figures 6, 7 and 8.

The model equation is specified as:

$$\begin{aligned} \text{MMSE/CDR-SB}_{ij} \sim & \beta_0 + \beta_{\text{Age}} \times \text{Age}_i + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Time}} \times \text{Time}_{ij} + \beta_{\text{Diagnosis}} \times \\ & \text{Diagnosis}_i + \beta_{\text{Biomarker}} \times \text{Biomarker}_i + \beta_{\text{Time} \times \text{Biomarker}} \times \text{Time}_{ij} \times \text{Biomarker}_i + \\ & \beta_{\text{Time} \times \text{Diagnosis}} \times \text{Time}_{ij} \times \text{Diagnosis}_i + \beta_{\text{Biomarker} \times \text{Diagnosis}} \times \text{Biomarker}_i \times \text{Diagnosis}_i + \\ & \beta_{\text{Time} \times \text{Diagnosis} \times \text{Biomarker}} \times \text{Time}_{ij} \times \text{Diagnosis}_i \times \text{Biomarker}_i + b_i + \epsilon_{ij}, \end{aligned}$$

where MMSE/CDR-SB<sub>ij</sub> represents the longitudinal MMSE or CDR-SB scores for subject *i* at time point *j*; Age<sub>*i*</sub> is the age at the baseline CSF, PET or MRI measure for subject *i*; Sex<sub>*i*</sub> is the sex for subject *i*; Time<sub>ij</sub> is the time since the baseline CSF, PET or MRI measure for subject *i* at time point *j*; Diagnosis<sub>*i*</sub> is the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which includes MCI and AD) for subject *i*. The model includes all two-way interactions and the three-way interaction among Time<sub>ij</sub>, Diagnosis<sub>*i*</sub>, Biomarker<sub>*i*</sub>. *b<sub>i</sub>* is the random intercept for subject *i* and  $\epsilon_{ij}$  is the residual errors. Age<sub>*i*</sub> and Biomarker<sub>*i*</sub> were standardized using the baseline mean and standard deviation, while Time<sub>ij</sub> was kept in its original units (yrs.) for easier interpretation. Biomarkers included whole brain white matter ADI<sub>C-NODDI</sub>, CSF-A $\beta_{42/40}$ , amyloid-PET and tau-PET, the best performing biomarkers. Full statistical results are presented below.

Figure 6:

	A $\beta_{42/40}$ predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.58e+01	5.84e-01	1.04e+02	4.41e+01	2.22e-69
Age	-3.00e-01	3.21e-01	9.41e+01	-9.34e-01	3.53e-01
Sex-Male	8.40e-01	6.25e-01	9.46e+01	1.34e+00	1.82e-01
Diagnosis-CN	3.25e+00	6.49e-01	1.10e+02	5.01e+00	2.14e-06
Time	-2.32e-01	1.05e-01	1.87e+02	-2.22e+00	2.77e-02
Biomarker	2.05e+00	4.57e-01	1.07e+02	4.48e+00	1.88e-05
Diagnosis-CN $\times$ Time	1.66e-01	1.32e-01	1.86e+02	1.25e+00	2.13e-01
Diagnosis-CN $\times$ Biomarker	-2.34e+00	6.25e-01	1.09e+02	-3.74e+00	2.94e-04
Time $\times$ Biomarker	2.83e-01	9.45e-02	1.87e+02	3.00e+00	3.08e-03

Diagnosis-CN × Time × Biomarker	-2.22e-01	1.29e-01	1.85e+02	-1.73e+00	8.56e-02
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	ADIC-NODDI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.61e+01	5.81e-01	1.21e+02	4.49e+01	3.37e-77
Age	-1.67e-01	3.06e-01	1.04e+02	-5.46e-01	5.86e-01
Sex-Male	1.38e+00	6.10e-01	1.03e+02	2.27e+00	2.55e-02
Diagnosis-CN	2.84e+00	6.76e-01	1.26e+02	4.21e+00	4.83e-05
Time	-3.17e-01	1.65e-01	1.50e+02	-1.91e+00	5.74e-02
Biomarker	2.02e+00	4.71e-01	1.23e+02	4.30e+00	3.50e-05
Diagnosis-CN × Time	2.95e-01	2.09e-01	1.47e+02	1.41e+00	1.59e-01
Diagnosis-CN × Biomarker	-2.45e+00	6.72e-01	1.24e+02	-3.64e+00	3.95e-04
Time × Biomarker	3.23e-01	1.65e-01	1.50e+02	1.96e+00	5.24e-02
Diagnosis-CN × Time × Biomarker	-4.06e-01	2.12e-01	1.46e+02	-1.91e+00	5.76e-02

	A $\beta$ <sub>42/40</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.43e+00	3.39e-01	1.05e+02	7.17e+00	1.06e-10
Age	2.39e-01	1.82e-01	9.08e+01	1.31e+00	1.93e-01
Sex-Male	-5.16e-01	3.52e-01	9.26e+01	-1.47e+00	1.46e-01
Diagnosis-CN	-2.25e+00	3.76e-01	1.11e+02	-6.00e+00	2.50e-08
Time	3.17e-01	6.37e-02	2.12e+02	4.98e+00	1.34e-06
Biomarker	-1.03e+00	2.73e-01	1.09e+02	-3.77e+00	2.63e-04
Diagnosis-CN × Time	-2.97e-01	8.00e-02	2.09e+02	-3.72e+00	2.60e-04
Diagnosis-CN × Biomarker	1.16e+00	3.59e-01	1.11e+02	3.22e+00	1.68e-03
Time × Biomarker	-2.81e-01	6.10e-02	2.12e+02	-4.61e+00	6.99e-06
Diagnosis-CN × Time × Biomarker	2.68e-01	7.91e-02	2.08e+02	3.39e+00	8.28e-04

	ADIC-NODDI predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.38e+00	3.40e-01	1.26e+02	7.00e+00	1.36e-10
Age	1.97e-01	1.74e-01	1.03e+02	1.13e+00	2.60e-01
Sex-Male	-8.28e-01	3.41e-01	1.03e+02	-2.43e+00	1.70e-02
Diagnosis-CN	-2.19e+00	3.93e-01	1.32e+02	-5.58e+00	1.29e-07
Time	3.93e-01	1.06e-01	1.74e+02	3.71e+00	2.76e-04
Biomarker	-1.20e+00	2.80e-01	1.31e+02	-4.27e+00	3.76e-05
Diagnosis-CN × Time	-3.72e-01	1.29e-01	1.72e+02	-2.89e+00	4.39e-03
Diagnosis-CN × Biomarker	1.43e+00	3.85e-01	1.33e+02	3.71e+00	3.02e-04
Time × Biomarker	-3.13e-01	1.05e-01	1.73e+02	-2.97e+00	3.40e-03
Diagnosis-CN × Time × Biomarker	3.32e-01	1.31e-01	1.71e+02	2.53e+00	1.22e-02

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

Figure 7:

	amyloid-PET predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.73e+01	3.30e-01	1.97e+02	8.27e+01	8.93e-155
Age	-4.82e-03	1.69e-01	1.81e+02	-2.86e-02	9.77e-01
Sex-Male	-3.98e-02	3.24e-01	1.70e+02	-1.23e-01	9.02e-01
Diagnosis-CN	1.91e+00	3.63e-01	2.17e+02	5.26e+00	3.43e-07
Time	-3.47e-01	6.97e-02	3.96e+02	-4.98e+00	9.67e-07
Biomarker	-1.10e+00	2.27e-01	2.09e+02	-4.85e+00	2.41e-06
Diagnosis-CN × Time	2.77e-01	9.33e-02	3.99e+02	2.97e+00	3.19e-03
Diagnosis-CN × Biomarker	1.08e+00	3.60e-01	2.23e+02	3.01e+00	2.90e-03
Time × Biomarker	-3.65e-01	5.76e-02	3.92e+02	-6.33e+00	6.54e-10
Diagnosis-CN × Time × Biomarker	3.25e-01	9.48e-02	3.96e+02	3.43e+00	6.70e-04

	ADIC-NODDI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.64e+01	4.29e-01	1.98e+02	6.16e+01	3.65e-131
Age	1.92e-02	2.40e-01	1.77e+02	8.02e-02	9.36e-01
Sex-Male	6.48e-01	4.20e-01	1.68e+02	1.54e+00	1.25e-01
Diagnosis-CN	2.49e+00	4.76e-01	2.11e+02	5.24e+00	3.89e-07
Time	-2.87e-01	1.46e-01	2.28e+02	-1.97e+00	5.03e-02
Biomarker	1.28e+00	3.54e-01	2.07e+02	3.63e+00	3.61e-04
Diagnosis-CN × Time	1.68e-01	1.76e-01	2.25e+02	9.54e-01	3.41e-01
Diagnosis-CN × Biomarker	-1.21e+00	4.72e-01	2.10e+02	-2.56e+00	1.12e-02
Time × Biomarker	3.49e-01	1.59e-01	2.32e+02	2.20e+00	2.89e-02
Diagnosis-CN × Time × Biomarker	-3.67e-01	1.89e-01	2.29e+02	-1.94e+00	5.38e-02

	amyloid-PET predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.62e+00	2.21e-01	1.97e+02	7.34e+00	5.56e-12
Age	-8.44e-03	1.11e-01	1.79e+02	-7.62e-02	9.39e-01
Sex-Male	1.54e-01	2.17e-01	1.77e+02	7.10e-01	4.79e-01
Diagnosis-CN	-1.58e+00	2.41e-01	2.11e+02	-6.58e+00	3.67e-10
Time	2.44e-01	3.80e-02	4.24e+02	6.41e+00	3.77e-10
Biomarker	5.57e-01	1.52e-01	2.06e+02	3.67e+00	3.08e-04
Diagnosis-CN × Time	-2.39e-01	5.08e-02	4.25e+02	-4.70e+00	3.60e-06
Diagnosis-CN × Biomarker	-6.02e-01	2.35e-01	2.12e+02	-2.56e+00	1.12e-02
Time × Biomarker	2.49e-01	3.11e-02	4.21e+02	8.01e+00	1.13e-14
Diagnosis-CN × Time × Biomarker	-2.15e-01	4.99e-02	4.23e+02	-4.31e+00	2.00e-05

	ADIC-NODDI predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.07e+00	2.55e-01	2.10e+02	8.14e+00	3.49e-14
Age	-5.45e-03	1.38e-01	1.78e+02	-3.96e-02	9.68e-01
Sex-Male	-4.89e-01	2.44e-01	1.76e+02	-2.00e+00	4.71e-02
Diagnosis-CN	-1.90e+00	2.81e-01	2.23e+02	-6.79e+00	1.03e-10
Time	2.86e-01	8.06e-02	2.77e+02	3.54e+00	4.65e-04
Biomarker	-1.06e+00	2.10e-01	2.22e+02	-5.06e+00	8.96e-07
Diagnosis-CN × Time	-2.42e-01	9.62e-02	2.75e+02	-2.52e+00	1.24e-02
Diagnosis-CN × Biomarker	1.11e+00	2.77e-01	2.25e+02	4.02e+00	7.93e-05
Time × Biomarker	-4.28e-01	8.99e-02	2.81e+02	-4.76e+00	3.13e-06
Diagnosis-CN × Time × Biomarker	4.29e-01	1.06e-01	2.78e+02	4.05e+00	6.60e-05

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

Figure 8:

	tau-PET predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.71e+01	4.02e-01	1.96e+02	6.75e+01	8.53e-138
Age	-1.61e-01	1.98e-01	1.71e+02	-8.13e-01	4.18e-01
Sex-Male	-1.17e-02	3.88e-01	1.61e+02	-3.01e-02	9.76e-01
Diagnosis-CN	2.25e+00	4.45e-01	2.18e+02	5.04e+00	9.60e-07
Time	-4.30e-01	9.68e-02	2.72e+02	-4.45e+00	1.27e-05
Biomarker	-1.22e+00	2.70e-01	2.18e+02	-4.53e+00	9.55e-06
Diagnosis-CN × Time	2.62e-01	1.28e-01	2.74e+02	2.04e+00	4.23e-02
Diagnosis-CN × Biomarker	1.56e+00	4.48e-01	2.28e+02	3.48e+00	5.99e-04
Time × Biomarker	-3.19e-01	9.35e-02	2.82e+02	-3.42e+00	7.29e-04
Diagnosis-CN × Time × Biomarker	9.77e-02	1.45e-01	2.89e+02	6.73e-01	5.01e-01

	ADIC-NODDI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.68e+01	4.28e-01	1.97e+02	6.26e+01	8.45e-132
Age	-6.70e-03	2.24e-01	1.75e+02	-2.99e-02	9.76e-01
Sex-Male	4.60e-01	4.08e-01	1.63e+02	1.13e+00	2.61e-01
Diagnosis-CN	2.25e+00	4.83e-01	2.09e+02	4.65e+00	5.83e-06
Time	-3.38e-01	1.41e-01	2.32e+02	-2.40e+00	1.73e-02
Biomarker	1.18e+00	3.50e-01	2.07e+02	3.37e+00	8.88e-04
Diagnosis-CN × Time	2.12e-01	1.75e-01	2.29e+02	1.21e+00	2.28e-01
Diagnosis-CN × Biomarker	-1.16e+00	4.75e-01	2.08e+02	-2.45e+00	1.52e-02
Time × Biomarker	3.83e-01	1.56e-01	2.37e+02	2.46e+00	1.48e-02
Diagnosis-CN × Time × Biomarker	-4.02e-01	1.88e-01	2.33e+02	-2.13e+00	3.39e-02

	tau-PET predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.91e+00	2.58e-01	2.02e+02	7.38e+00	3.93e-12
Age	3.08e-02	1.28e-01	1.77e+02	2.42e-01	8.09e-01
Sex-Male	-1.47e-03	2.49e-01	1.69e+02	-5.91e-03	9.95e-01
Diagnosis-CN	-1.87e+00	2.84e-01	2.21e+02	-6.57e+00	3.46e-10
Time	3.69e-01	5.38e-02	3.07e+02	6.86e+00	3.83e-11
Biomarker	4.83e-01	1.72e-01	2.21e+02	2.80e+00	5.52e-03
Diagnosis-CN × Time	-3.56e-01	7.16e-02	3.09e+02	-4.96e+00	1.14e-06
Diagnosis-CN × Biomarker	-4.98e-01	2.81e-01	2.29e+02	-1.77e+00	7.76e-02
Time × Biomarker	3.50e-01	5.32e-02	3.18e+02	6.58e+00	1.89e-10
Diagnosis-CN × Time × Biomarker	-3.48e-01	8.19e-02	3.19e+02	-4.24e+00	2.89e-05

	ADIC-NODDI predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.01e+00	2.62e-01	2.10e+02	7.66e+00	6.79e-13
Age	-2.05e-02	1.36e-01	1.76e+02	-1.51e-01	8.80e-01
Sex-Male	-3.58e-01	2.46e-01	1.71e+02	-1.46e+00	1.47e-01
Diagnosis-CN	-1.90e+00	2.93e-01	2.20e+02	-6.49e+00	5.67e-10
Time	3.03e-01	8.19e-02	2.73e+02	3.70e+00	2.62e-04
Biomarker	-8.54e-01	2.15e-01	2.21e+02	-3.98e+00	9.49e-05
Diagnosis-CN × Time	-2.70e-01	9.89e-02	2.70e+02	-2.73e+00	6.70e-03
Diagnosis-CN × Biomarker	8.97e-01	2.87e-01	2.21e+02	3.12e+00	2.04e-03
Time × Biomarker	-4.50e-01	9.11e-02	2.77e+02	-4.94e+00	1.35e-06
Diagnosis-CN × Time × Biomarker	4.55e-01	1.08e-01	2.73e+02	4.20e+00	3.59e-05

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

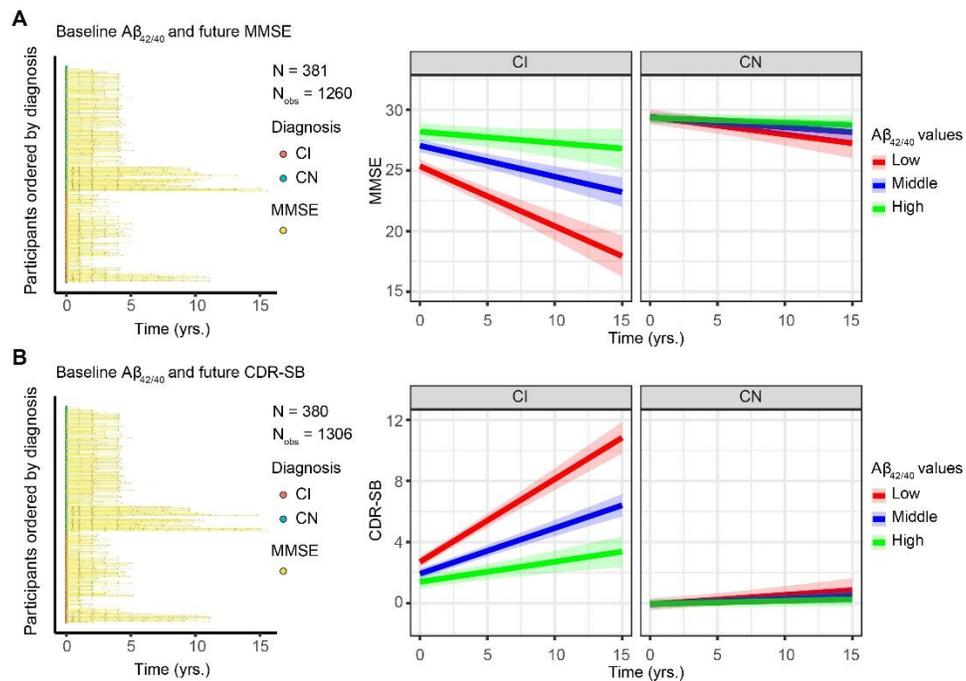


Figure S5. Baseline CSF- $A\beta_{42/40}$  measurements predict prospective changes in cognition and function, as measured using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores. Analyses included all available CSF- $A\beta_{42/40}$  available at the time of our analysis. The longitudinal distributions of MMSE and CDR-SB anchored at the first CSF- $A\beta_{42/40}$  measurement of each subject, with cognitively normal (CN) and cognitively impaired (CI) subjects color-coded.

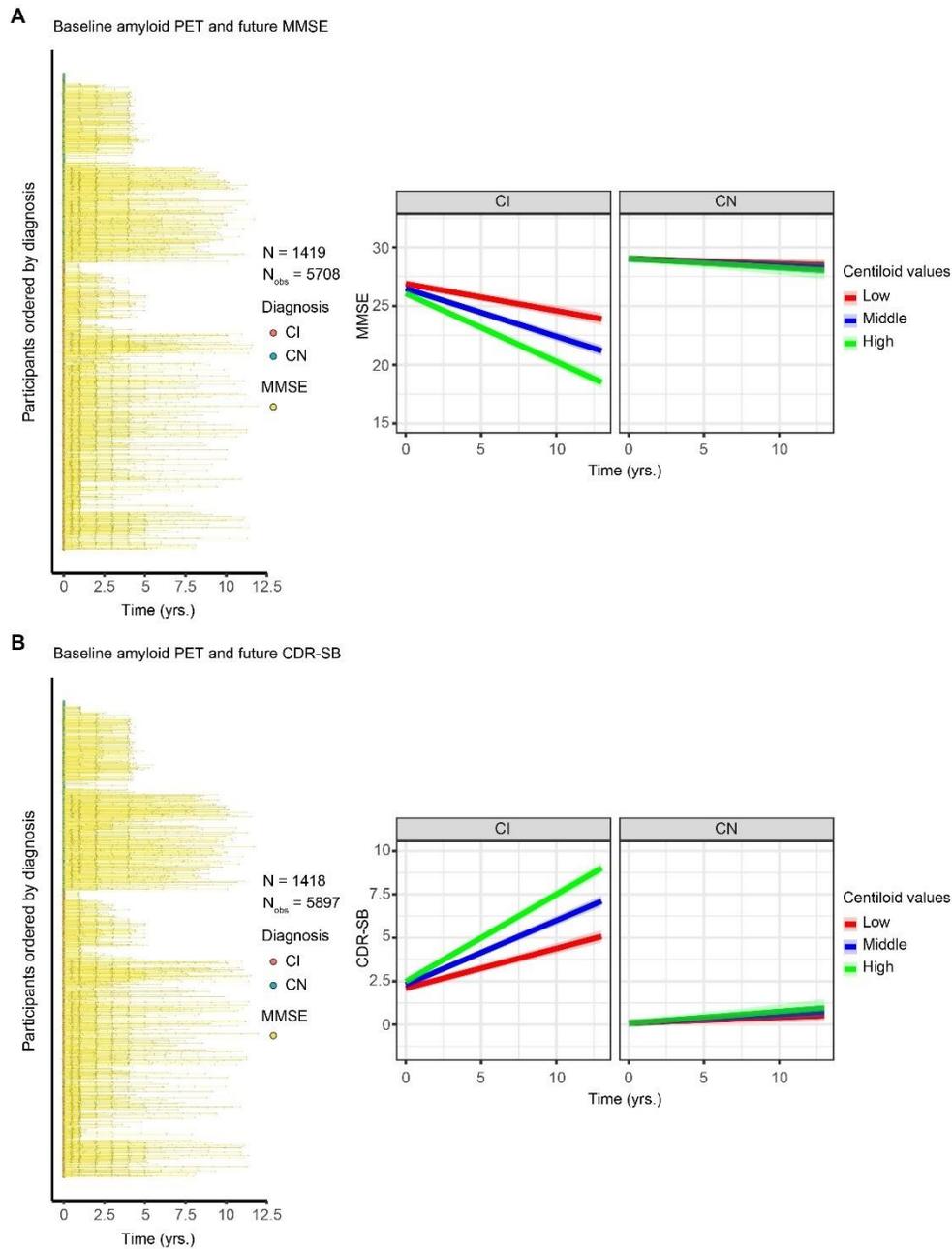


Figure S6. Baseline amyloid-PET measurements predict prospective changes in cognition and function, as measured using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores. Analyses included all available amyloid-PET available at the time of our analysis. The longitudinal distributions of MMSE and CDR-SB anchored at the first amyloid-PET measurement of each subject, with cognitively normal (CN) and cognitively impaired (CI) subjects color-coded.

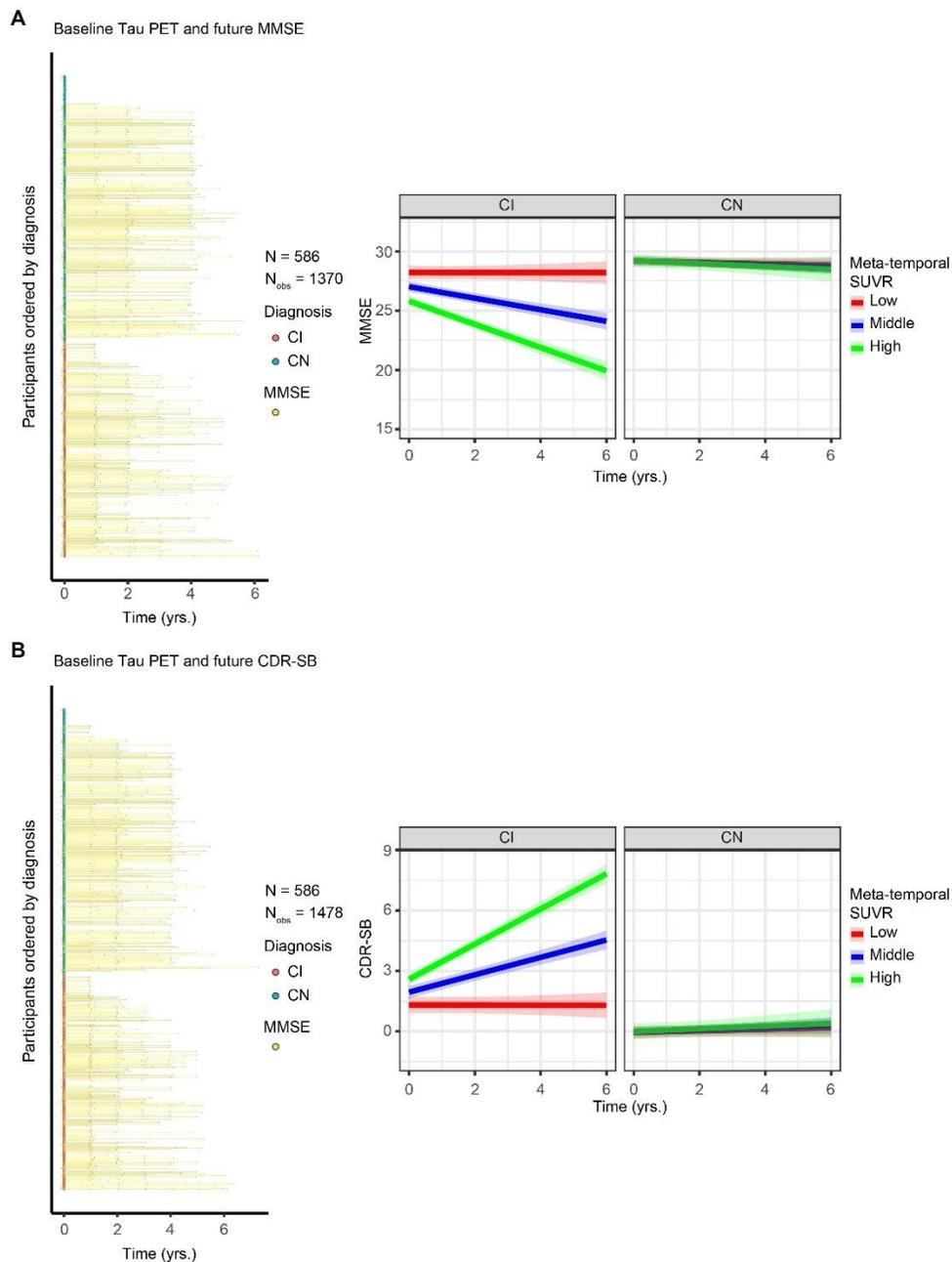


Figure S7. Baseline tau-PET measurements predict prospective changes in cognition and function, as measured using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores. Analyses included all available tau-PET available at the time of our analysis. The longitudinal distributions of MMSE and CDR-SB anchored at the first tau-PET measurement of each subject, with cognitively normal (CN) and cognitively impaired (CI) subjects color-coded.

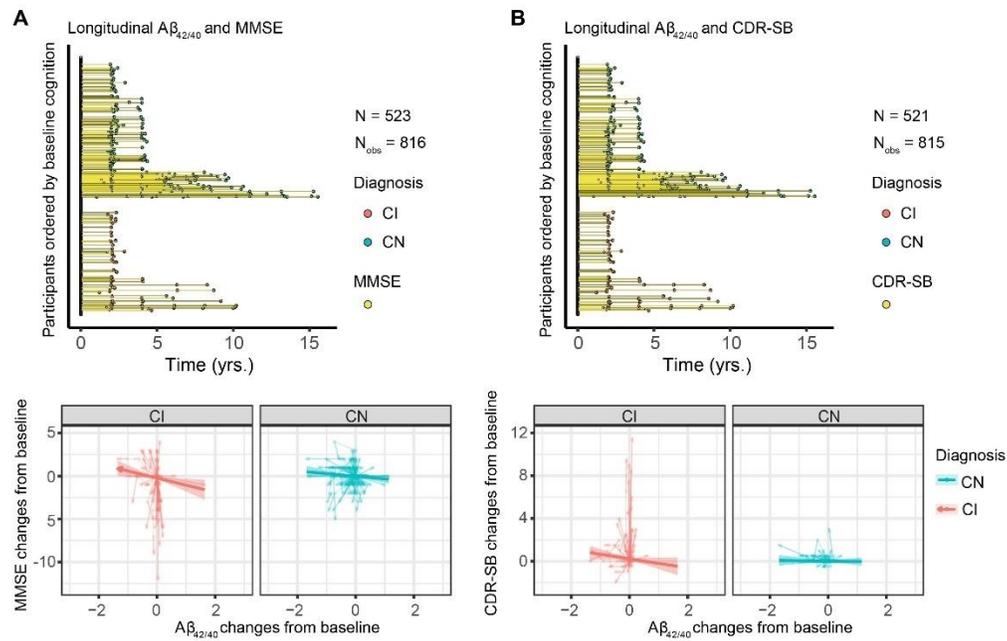


Figure S8. Associations between changes from baseline in CSF- $A\beta_{42/40}$  and changes from baseline in MMSE (A) or CDR-SB (B). The top row shows the longitudinal distribution of MMSE or CDR-SB scores aligned with the nearest CSF- $A\beta_{42/40}$  measurements for linear mixed-effects modeling. Results were derived from all available CSF- $A\beta_{42/40}$  measurements at the time of analysis.

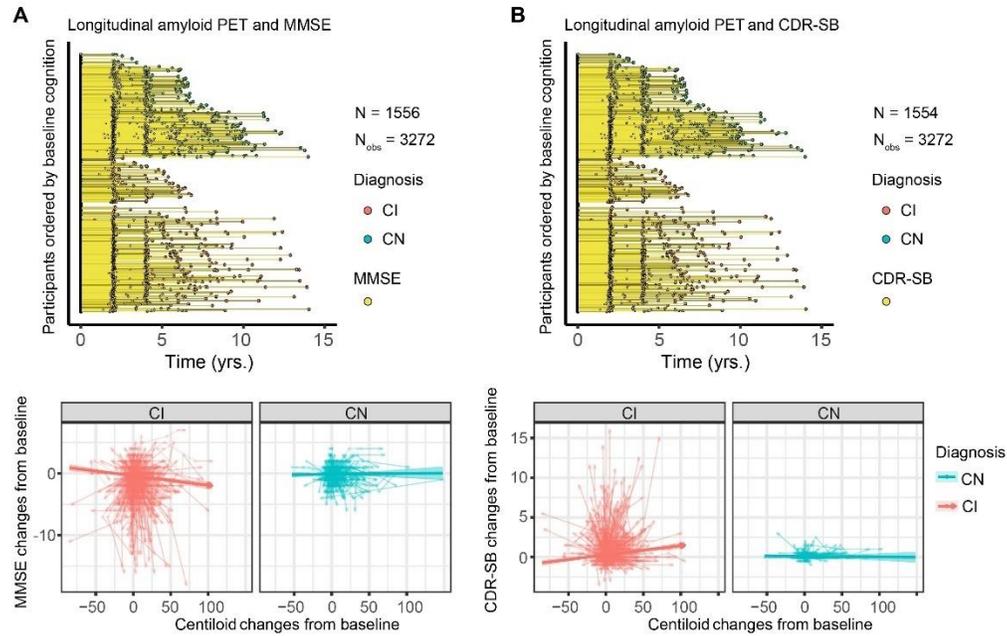


Figure S9. Associations between changes from baseline in amyloid-PET and changes from baseline in MMSE (A) or CDR-SB (B). The top row shows the longitudinal distribution of MMSE or CDR-SB scores aligned with the nearest amyloid-PET measurements for linear mixed-effects modeling. Results were derived from all available amyloid-PET measurements at the time of analysis.

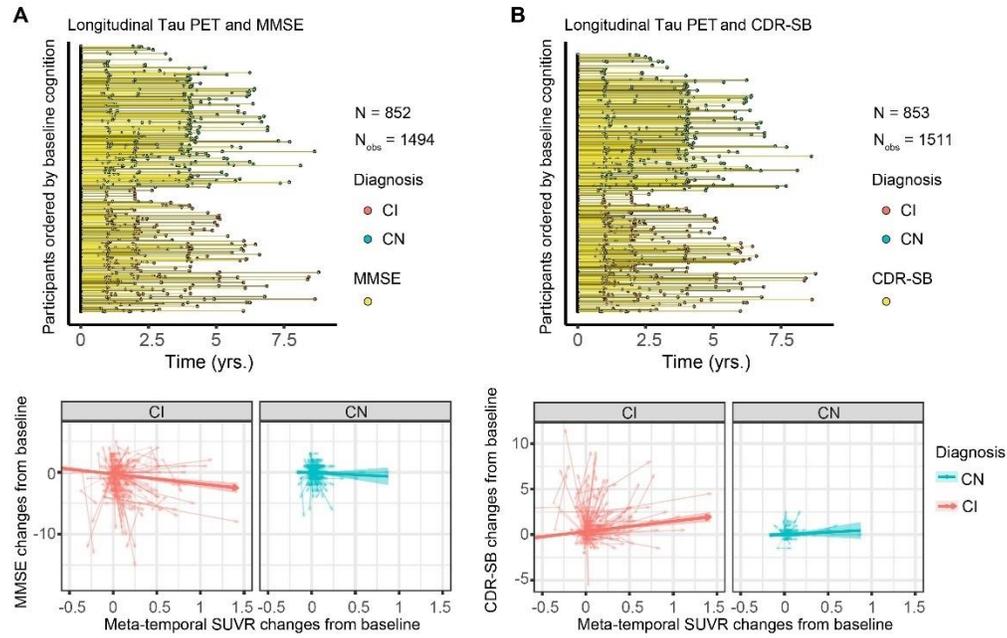


Figure S10. Associations between changes from baseline in tau-PET and changes from baseline in MMSE (A) or CDR-SB (B). The top row shows the longitudinal distribution of MMSE or CDR-SB scores aligned with the nearest tau-PET measurements for linear mixed-effects modeling. Results were derived from all available tau-PET measurements at the time of analysis.

**Table S6.** Linear mixed-effects model results for Figures 9, 10 and 11.

The model equation is specified as:

$$\begin{aligned} \text{MMSE/CDR-SB changes}_{ij} \sim & \beta_0 + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Age}} \times \text{Age}_{ij} + \beta_{\text{Diagnosis}} \times \text{Diagnosis}_i + \\ & \beta_{\text{Biomarker changes}} \times \text{Biomarker changes}_{ij} + \beta_{\text{Diagnosis} \times \text{Biomarker changes}} \times \text{Diagnosis}_i \times \\ & \text{Biomarker changes}_{ij} + \beta_{\text{Baseline Biomarker}} \times \text{Baseline Biomarker}_i + \\ & \beta_{\text{Diagnosis} \times \text{Baseline Biomarker}} \times \text{Diagnosis}_i \times \text{Baseline Biomarker}_i + b_i + \epsilon_{ij}, \end{aligned}$$

where MMSE/CDR-SB<sub>ij</sub> represents the longitudinal MMSE or CDR-SB changes for subject *i* at time point *j* from subject *i*'s baseline value; Age<sub>ij</sub> is the age at the CSF, PET, or MRI measurement for subject *i* at the time point *j*; Sex<sub>*i*</sub> is the sex for subject *i*; Biomarker changes<sub>*ij*</sub> is the difference of Biomarker from its baseline Biomarker for subject *i* at time point *j*; Baseline Biomarker<sub>*i*</sub> is the subject's baseline biomarker value; Diagnosis<sub>*i*</sub> is the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which includes MCI and AD) for subject *i*. *b<sub>i</sub>* is the random intercept for subject *i* and  $\epsilon_{ij}$  is the residual error. Two-way interaction terms between diagnosis and biomarker changes were included to assess how biomarker changes relate to cognitive changes. Age<sub>ij</sub> and Biomarker<sub>ij</sub> values were standardized using baseline mean and standard deviation, while Biomarker changes<sub>ij</sub> were calculated as the difference between the standardized biomarker value at time *j* and the subject's baseline biomarker value. Biomarkers included whole brain white matter ADIC-NODDI, CSF-A $\beta_{42/40}$ , amyloid-PET and tau-PET, the best performing biomarkers. Full statistical results are presented below. Full statistical results are presented below.

Figure 9:

	A $\beta_{42/40}$ changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-5.89e-03	1.72e-01	1.64e+02	-3.42e-02	9.73e-01
Sex-Male	-3.02e-01	1.76e-01	1.64e+02	-1.72e+00	8.78e-02
Age	-1.78e-01	8.84e-02	1.64e+02	-2.02e+00	4.53e-02
Diagnosis-CN	1.53e-01	1.84e-01	1.64e+02	8.33e-01	4.06e-01
Biomarker changes	-3.58e+00	9.29e-01	1.64e+02	-3.85e+00	1.68e-04
Biomarker baseline	1.09e-01	1.41e-01	1.64e+02	7.78e-01	4.38e-01
Diagnosis-CN $\times$ Biomarker changes	3.31e+00	1.12e+00	1.64e+02	2.95e+00	3.67e-03
Diagnosis-CN $\times$ Biomarker baseline	-1.56e-01	1.75e-01	1.64e+02	-8.88e-01	3.76e-01

	A $\beta_{42/40}$ changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.66e-01	1.64e-01	1.58e+02	1.63e+00	1.06e-01
Sex-Male	9.74e-02	1.63e-01	1.58e+02	5.99e-01	5.50e-01
Age	1.27e-01	8.23e-02	1.58e+02	1.55e+00	1.24e-01
Diagnosis-CN	-2.97e-01	1.75e-01	1.58e+02	-1.70e+00	9.11e-02
Biomarker changes	2.57e-01	8.57e-01	1.58e+02	3.00e-01	7.65e-01
Biomarker baseline	-1.56e-01	1.36e-01	1.58e+02	-1.14e+00	2.55e-01
Diagnosis-CN $\times$ Biomarker changes	-2.02e-01	1.05e+00	1.58e+02	-1.93e-01	8.47e-01
Diagnosis-CN $\times$ Biomarker baseline	1.74e-01	1.66e-01	1.58e+02	1.05e+00	2.94e-01

	ADIC-NODDI changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-8.32e-02	2.75e-01	1.65e+02	-3.03e-01	7.62e-01
Sex-Male	2.89e-01	2.70e-01	1.36e+02	1.07e+00	2.87e-01
Age	-7.59e-02	1.37e-01	1.53e+02	-5.56e-01	5.79e-01
Diagnosis-CN	1.31e-01	3.12e-01	1.61e+02	4.21e-01	6.74e-01
Biomarker changes	6.09e-01	4.10e-01	1.81e+02	1.48e+00	1.40e-01
Biomarker baseline	4.13e-01	2.04e-01	1.39e+02	2.02e+00	4.48e-02
Diagnosis-CN × Biomarker changes	-1.42e+00	6.09e-01	1.85e+02	-2.33e+00	2.08e-02
Diagnosis-CN × Biomarker baseline	-5.59e-01	2.84e-01	1.36e+02	-1.97e+00	5.12e-02

	ADIC-NODDI changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.66e-01	1.43e-01	1.56e+02	1.86e+00	6.52e-02
Sex-Male	-2.07e-01	1.35e-01	1.24e+02	-1.53e+00	1.29e-01
Age	6.86e-02	6.99e-02	1.43e+02	9.81e-01	3.28e-01
Diagnosis-CN	-1.96e-01	1.61e-01	1.52e+02	-1.22e+00	2.25e-01
Biomarker changes	-1.03e+00	2.12e-01	1.79e+02	-4.84e+00	2.74e-06
Biomarker baseline	-2.70e-01	1.04e-01	1.19e+02	-2.59e+00	1.08e-02
Diagnosis-CN × Biomarker changes	1.08e+00	3.30e-01	1.81e+02	3.28e+00	1.24e-03
Diagnosis-CN × Biomarker baseline	3.00e-01	1.43e-01	1.23e+02	2.10e+00	3.80e-02

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

Figure 10:

	amyloid-PET changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	5.19e-02	2.45e-01	1.89e+02	2.12e-01	8.32e-01
Sex-Male	1.75e-01	2.05e-01	1.81e+02	8.55e-01	3.94e-01
Age	-9.84e-02	1.02e-01	2.09e+02	-9.68e-01	3.34e-01
Diagnosis-CN	-8.02e-02	2.57e-01	1.91e+02	-3.13e-01	7.55e-01
Biomarker changes	-7.85e-02	1.34e-02	3.03e+02	-5.86e+00	1.21e-08
Biomarker baseline	-1.17e-02	3.24e-03	1.83e+02	-3.61e+00	4.01e-04
Diagnosis-CN × Biomarker changes	7.29e-02	2.10e-02	3.04e+02	3.47e+00	5.86e-04
Diagnosis-CN × Biomarker baseline	1.44e-02	6.29e-03	1.85e+02	2.29e+00	2.30e-02

	amyloid-PET changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.67e-01	1.31e-01	1.67e+02	-2.80e+00	5.67e-03
Sex-Male	9.38e-02	1.07e-01	1.56e+02	8.80e-01	3.80e-01
Age	2.54e-02	5.18e-02	1.74e+02	4.91e-01	6.24e-01
Diagnosis-CN	3.75e-01	1.36e-01	1.67e+02	2.77e+00	6.29e-03
Biomarker changes	5.27e-02	7.13e-03	2.90e+02	7.39e+00	1.59e-12
Biomarker baseline	9.61e-03	1.70e-03	1.54e+02	5.66e+00	7.26e-08
Diagnosis-CN × Biomarker changes	-5.26e-02	1.17e-02	2.95e+02	-4.51e+00	9.56e-06
Diagnosis-CN × Biomarker baseline	-8.82e-03	3.24e-03	1.57e+02	-2.72e+00	7.26e-03

	ADIC-NODDI changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.94e-01	2.29e-01	2.24e+02	-8.46e-01	3.98e-01
Sex-Male	3.87e-01	2.25e-01	1.97e+02	1.72e+00	8.63e-02
Age	-1.87e-01	1.28e-01	2.20e+02	-1.46e+00	1.47e-01
Diagnosis-CN	1.51e-01	2.52e-01	2.20e+02	5.98e-01	5.51e-01
Biomarker changes	1.15e+00	3.97e-01	2.53e+02	2.89e+00	4.13e-03
Biomarker baseline	3.80e-01	1.69e-01	1.99e+02	2.25e+00	2.56e-02
Diagnosis-CN × Biomarker changes	-1.67e+00	6.03e-01	2.55e+02	-2.76e+00	6.16e-03
Diagnosis-CN × Biomarker baseline	-5.51e-01	2.43e-01	2.08e+02	-2.26e+00	2.48e-02

	ADIC-NODDI changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.29e-01	1.08e-01	2.14e+02	2.11e+00	3.62e-02
Sex-Male	-1.10e-01	1.04e-01	1.82e+02	-1.06e+00	2.92e-01
Age	4.71e-02	6.08e-02	2.14e+02	7.75e-01	4.39e-01
Diagnosis-CN	-1.78e-01	1.19e-01	2.11e+02	-1.50e+00	1.35e-01
Biomarker changes	-1.37e+00	1.87e-01	2.54e+02	-7.34e+00	2.88e-12
Biomarker baseline	-2.24e-01	7.85e-02	1.78e+02	-2.85e+00	4.94e-03
Diagnosis-CN × Biomarker changes	1.29e+00	2.99e-01	2.54e+02	4.33e+00	2.16e-05
Diagnosis-CN × Biomarker baseline	2.57e-01	1.13e-01	1.97e+02	2.27e+00	2.40e-02

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

Figure 11:

	tau-PET changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	4.00e-01	4.81e-01	1.93e+02	8.32e-01	4.06e-01
Sex-Male	3.54e-01	2.38e-01	1.79e+02	1.49e+00	1.38e-01
Age	-3.68e-01	1.21e-01	2.08e+02	-3.05e+00	2.55e-03
Diagnosis-CN	-4.53e-01	1.70e+00	1.83e+02	-2.66e-01	7.91e-01
Biomarker changes	-1.01e+00	9.90e-01	2.88e+02	-1.02e+00	3.07e-01
Biomarker baseline	-7.97e-01	2.56e-01	2.10e+02	-3.11e+00	2.10e-03
Diagnosis-CN × Biomarker changes	2.42e+00	2.68e+00	2.87e+02	9.00e-01	3.69e-01
Diagnosis-CN × Biomarker baseline	6.92e-01	1.34e+00	1.78e+02	5.15e-01	6.07e-01

	tau-PET changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-5.46e-03	3.10e-01	1.85e+02	-1.76e-02	9.86e-01
Sex-Male	-1.81e-01	1.54e-01	1.71e+02	-1.18e+00	2.41e-01
Age	2.17e-01	7.72e-02	1.96e+02	2.81e+00	5.47e-03
Diagnosis-CN	1.25e+00	1.10e+00	1.76e+02	1.13e+00	2.59e-01
Biomarker changes	7.18e-01	6.33e-01	2.88e+02	1.13e+00	2.58e-01
Biomarker baseline	3.79e-01	1.65e-01	2.04e+02	2.30e+00	2.24e-02
Diagnosis-CN × Biomarker changes	2.29e-02	1.71e+00	2.88e+02	1.34e-02	9.89e-01
Diagnosis-CN × Biomarker baseline	-1.33e+00	8.68e-01	1.71e+02	-1.53e+00	1.28e-01

	ADIC-NODDI changes associate with MMSE changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.17e-01	2.27e-01	2.21e+02	-5.15e-01	6.07e-01
Sex-Male	2.71e-01	2.26e-01	1.93e+02	1.20e+00	2.32e-01
Age	-1.13e-01	1.30e-01	2.20e+02	-8.72e-01	3.84e-01
Diagnosis-CN	7.06e-02	2.57e-01	2.14e+02	2.74e-01	7.84e-01
Biomarker changes	1.25e+00	4.11e-01	2.56e+02	3.04e+00	2.63e-03
Biomarker baseline	2.76e-01	1.73e-01	1.95e+02	1.60e+00	1.12e-01
Diagnosis-CN × Biomarker changes	-1.86e+00	5.82e-01	2.61e+02	-3.20e+00	1.55e-03
Diagnosis-CN × Biomarker baseline	-3.65e-01	2.44e-01	1.96e+02	-1.49e+00	1.37e-01

	ADIC-NODDI changes associate with CDR-SB changes				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.75e-01	1.04e-01	2.11e+02	1.69e+00	9.31e-02
Sex-Male	-5.12e-02	1.03e-01	1.77e+02	-4.97e-01	6.20e-01
Age	-3.32e-03	6.03e-02	2.11e+02	-5.51e-02	9.56e-01
Diagnosis-CN	-1.33e-01	1.17e-01	2.03e+02	-1.13e+00	2.58e-01
Biomarker changes	-1.41e+00	1.89e-01	2.60e+02	-7.49e+00	1.09e-12
Biomarker baseline	-2.03e-01	7.70e-02	1.77e+02	-2.64e+00	9.14e-03
Diagnosis-CN × Biomarker changes	1.44e+00	2.78e-01	2.62e+02	5.19e+00	4.29e-07
Diagnosis-CN × Biomarker baseline	1.85e-01	1.11e-01	1.85e+02	1.66e+00	9.90e-02

Diagnosis is referenced to CI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.

**Table S7.** Linear mixed-effects model results for Figure 2 without AD subjects.

The model equation is specified as:

$$ADI_{ij} \sim \beta_0 + \beta_{Age} \times Age_i + \beta_{sex} \times Sex_i + \beta_{Time} \times Time_{ij} + \beta_{Diagnosis} \times Diagnosis_i + \beta_{Time \times Diagnosis} \times Time_{ij} \times Diagnosis_i + b_i + \epsilon_{ij},$$

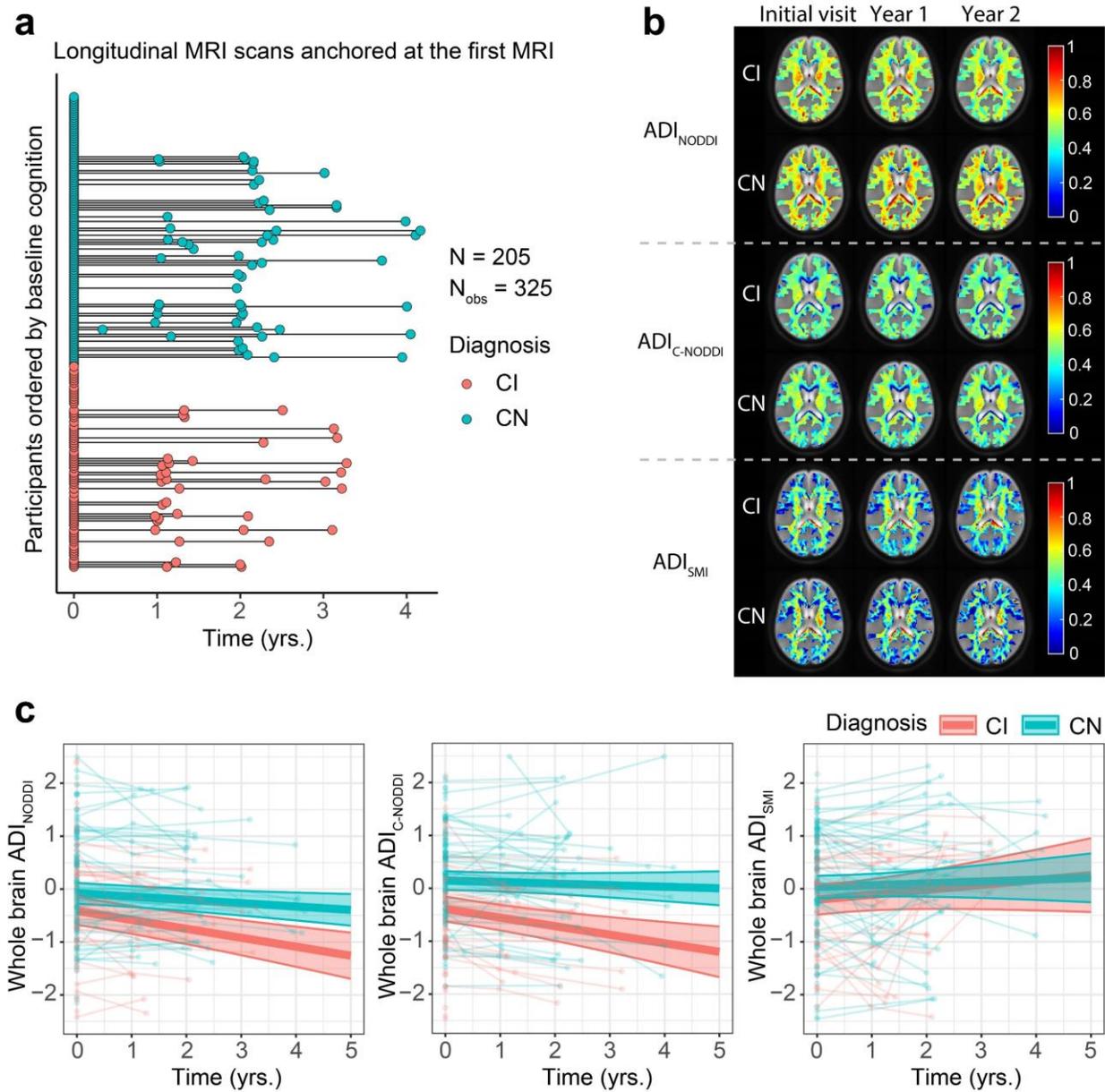
where  $ADI_{ij}$  represents the longitudinal ADI value for subject  $i$  at time point  $j$ ;  $Age_i$  is the age at the first MRI measurement for subject  $i$ ;  $Sex_i$  denotes subject sex;  $Time_{ij}$  is the time since the first MRI measurement for subject  $i$  at time point  $j$ ;  $Diagnosis_i$  indicates the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which only includes MCI);  $Time_{ij} \times Diagnosis_i$  is the interaction term representing differential time trajectories of ADI for two diagnosis groups;  $b_i$  is the random intercept for subject  $i$ ;  $\epsilon_{ij}$  is the residual error.  $Age_i$  was standardized using baseline mean and standard deviation, while  $Time_{ij}$  is in the original unit (yrs.) for easier interpretation. Whole brain white matter  $ADI_{NODDI}$ ,  $ADI_{C-NODDI}$ , and  $ADI_{SMI}$  values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.84e-01	1.33e-01	1.92e+02	-2.89e+00	4.26e-03
Age	-2.83e-01	6.79e-02	1.90e+02	-4.17e+00	4.67e-05
Time	-1.69e-01	3.80e-02	1.00e+02	-4.45e+00	2.23e-05
Diagnosis-CN	3.34e-01	1.41e-01	1.93e+02	2.36e+00	1.92e-02
Sex-Male	4.24e-01	1.38e-01	1.87e+02	3.07e+00	2.47e-03
Diagnosis-CN × Time	1.06e-01	4.56e-02	1.00e+02	2.34e+00	2.15e-02

	ADI <sub>C-NODDI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-3.42e-01	1.19e-01	1.99e+02	-2.87e+00	4.57e-03
Age	-5.08e-01	6.09e-02	1.95e+02	-8.33e+00	1.37e-14
Time	-1.62e-01	4.55e-02	1.11e+02	-3.55e+00	5.59e-04
Diagnosis-CN	5.38e-01	1.27e-01	2.02e+02	4.23e+00	3.60e-05
Sex-Male	3.20e-02	1.23e-01	1.89e+02	2.59e-01	7.96e-01
Diagnosis-CN × Time	1.33e-01	5.45e-02	1.11e+02	2.43e+00	1.65e-02

	ADI <sub>SMI</sub> trajectory				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	-1.89e-01	1.44e-01	2.07e+02	-1.31e+00	1.92e-01
Age	-1.61e-01	7.33e-02	2.00e+02	-2.19e+00	2.94e-02
Time	9.29e-02	6.99e-02	1.26e+02	1.33e+00	1.86e-01
Diagnosis-CN	2.38e-01	1.54e-01	2.13e+02	1.54e+00	1.24e-01
Sex-Male	4.02e-02	1.48e-01	1.89e+02	2.73e-01	7.85e-01
Diagnosis-CN × Time	-5.80e-02	8.37e-02	1.26e+02	-6.93e-01	4.90e-01

Diagnosis was referenced to the MCI group, and sex was referenced to females. P-values were not corrected for multiple comparisons.



**Figure S11.** Characterization of longitudinal trajectories of axonal integrity in CN and MCI subjects. Overall, the results are consistent with those in Figure 2, showing slightly reduced effect sizes and statistical significance. ADI<sub>C-NODDI</sub> remains the best-performing biomarker for distinguishing differential trajectories between CN and MCI groups.

**Table S8.** Linear mixed-effects model results for Figure 3 without AD subjects.

The model equation is specified as:

$$\begin{aligned} \text{MMSE/CDR-SB}_{ij} \sim & \beta_0 + \beta_{\text{Age}} \times \text{Age}_i + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Time}} \times \text{Time}_{ij} + \beta_{\text{Diagnosis}} \times \\ & \text{Diagnosis}_i + \beta_{\text{ADI}} \times \text{ADI}_i + \beta_{\text{Time} \times \text{ADI}} \times \text{Time}_{ij} \times \text{ADI}_i + \beta_{\text{Time} \times \text{Diagnosis}} \times \text{Time}_{ij} \times \\ & \text{Diagnosis}_i + \beta_{\text{ADI} \times \text{Diagnosis}} \times \text{ADI}_i \times \text{Diagnosis}_i + \beta_{\text{Time} \times \text{Diagnosis} \times \text{ADI}} \times \text{Time}_{ij} \times \\ & \text{Diagnosis}_i \times \text{ADI}_i + b_i + \epsilon_{ij}, \end{aligned}$$

where MMSE/CDR-SB<sub>ij</sub> represents the longitudinal MMSE or CDR-SB scores for subject *i* at time point *j*; Age<sub>*i*</sub> is the age at the baseline MRI measurement for subject *i*; Sex<sub>*i*</sub> denotes the subject sex; Time<sub>ij</sub> is the time of cognitive assessment since the baseline MRI measurement for subject *i* at time point *j*; Diagnosis<sub>*i*</sub> indicates the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which only includes MCI) for subject *i*; and ADI<sub>*i*</sub> is the baseline axonal density index. The model includes all two-way interactions among Time<sub>ij</sub>, Diagnosis<sub>*i*</sub>, and ADI<sub>*i*</sub>, as well as the three-way interaction term. b<sub>*i*</sub> is the random intercept for subject *i* and ε<sub>ij</sub> is the residual error. Age<sub>*i*</sub> and ADI<sub>*i*</sub> were standardized using baseline mean and standard deviation, while Time<sub>ij</sub> was kept in the original unit (yrs.) for easier interpretation. Whole brain white matter ADI<sub>NODDI</sub>, ADI<sub>C-NODDI</sub>, and ADI<sub>SMI</sub> values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.75e+01	2.66e-01	2.33e+02	1.03e+02	2.40e-196
Age	3.15e-02	1.22e-01	2.14e+02	2.59e-01	7.96e-01
Sex-Male	-2.70e-01	2.64e-01	1.92e+02	-1.02e+00	3.08e-01
Diagnosis-CN	1.66e+00	2.85e-01	2.54e+02	5.85e+00	1.54e-08
Time	-4.53e-01	9.84e-02	2.65e+02	-4.60e+00	6.43e-06
Whole brain ADI	-4.02e-01	2.06e-01	2.52e+02	-1.95e+00	5.23e-02
Diagnosis-CN × Time	3.49e-01	1.19e-01	2.61e+02	2.94e+00	3.60e-03
Diagnosis-CN × ADI	5.63e-01	2.78e-01	2.54e+02	2.03e+00	4.39e-02
Time × ADI	-1.52e-01	9.85e-02	2.75e+02	-1.54e+00	1.24e-01
Diagnosis-CN × Time × ADI	1.22e-01	1.21e-01	2.67e+02	1.01e+00	3.15e-01

	ADIC-NODDI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.76e+01	2.71e-01	2.35e+02	1.02e+02	1.27e-196
Age	1.33e-01	1.36e-01	2.03e+02	9.80e-01	3.28e-01
Sex-Male	-2.66e-01	2.58e-01	1.88e+02	-1.03e+00	3.04e-01
Diagnosis-CN	1.54e+00	2.97e-01	2.55e+02	5.19e+00	4.27e-07
Time	-3.40e-01	1.08e-01	2.71e+02	-3.14e+00	1.86e-03
Whole brain ADI	2.08e-01	2.33e-01	2.48e+02	8.93e-01	3.73e-01
Diagnosis-CN × Time	2.44e-01	1.30e-01	2.65e+02	1.88e+00	6.10e-02
Diagnosis-CN × ADI	2.99e-02	2.96e-01	2.52e+02	1.01e-01	9.20e-01
Time × ADI	1.28e-01	1.11e-01	2.82e+02	1.16e+00	2.48e-01
Diagnosis-CN × Time × ADI	-1.75e-01	1.32e-01	2.75e+02	-1.33e+00	1.85e-01

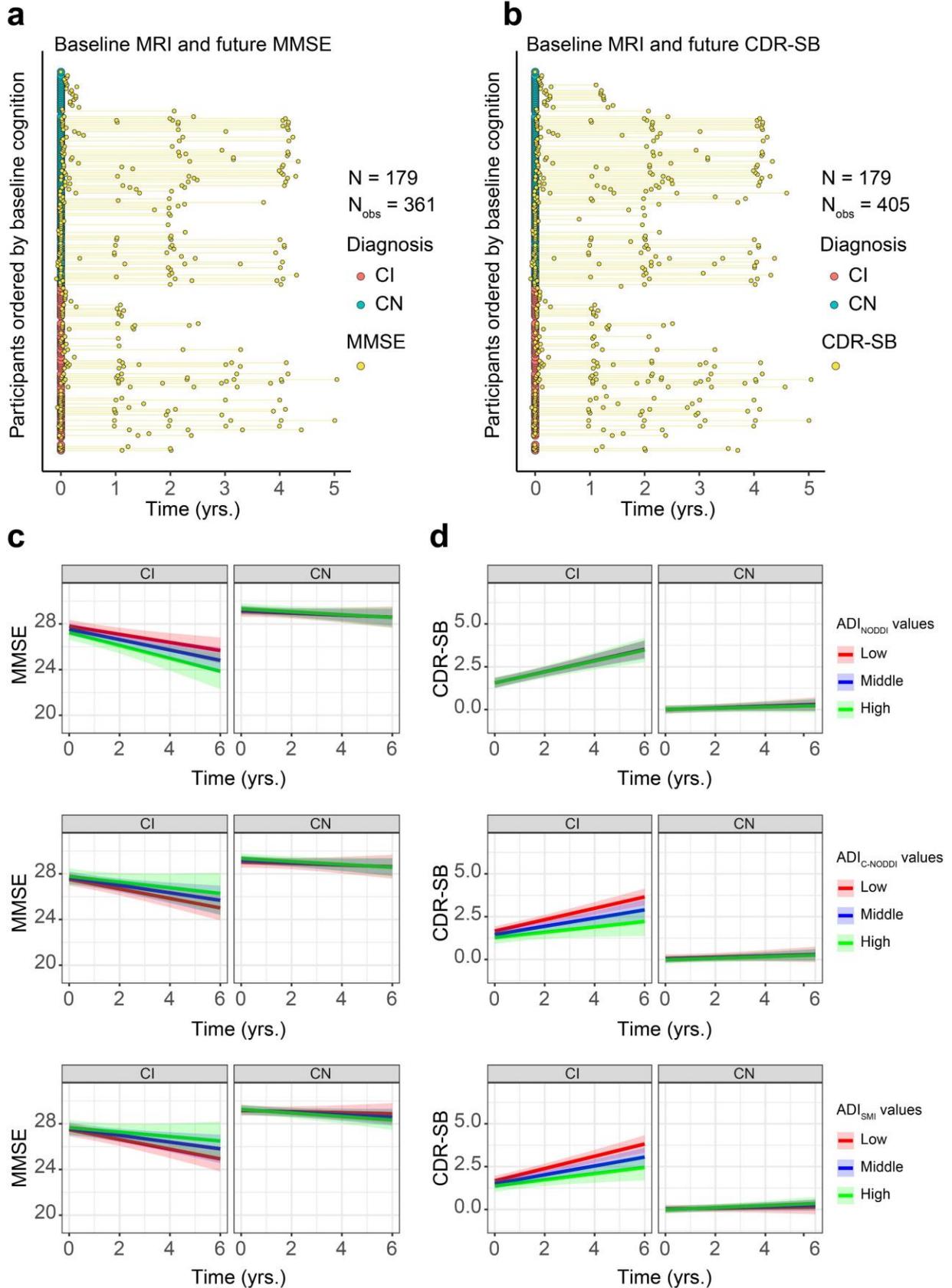
	ADISMI predicts prospective MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.76e+01	2.64e-01	2.32e+02	1.04e+02	8.98e-197
Age	4.43e-02	1.18e-01	2.10e+02	3.76e-01	7.07e-01
Sex-Male	-2.39e-01	2.55e-01	1.89e+02	-9.37e-01	3.50e-01
Diagnosis-CN	1.64e+00	2.85e-01	2.53e+02	5.77e+00	2.30e-08
Time	-3.21e-01	1.03e-01	2.66e+02	-3.12e+00	2.04e-03
Whole brain ADI	1.34e-01	2.43e-01	2.64e+02	5.53e-01	5.81e-01
Diagnosis-CN × Time	2.26e-01	1.23e-01	2.61e+02	1.83e+00	6.79e-02
Diagnosis-CN × ADI	-6.80e-02	2.96e-01	2.63e+02	-2.30e-01	8.18e-01
Time × ADI	1.70e-01	1.03e-01	2.58e+02	1.65e+00	9.97e-02
Diagnosis-CN × Time × ADI	-2.50e-01	1.23e-01	2.55e+02	-2.03e+00	4.29e-02

	ADI <sub>NODDI</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.56e+00	1.42e-01	2.29e+02	1.09e+01	1.06e-22
Age	-5.63e-02	6.58e-02	2.01e+02	-8.56e-01	3.93e-01
Sex-Male	-8.60e-03	1.42e-01	1.94e+02	-6.05e-02	9.52e-01
Diagnosis-CN	-1.55e+00	1.51e-01	2.46e+02	-1.03e+01	7.75e-21
Time	3.24e-01	4.44e-02	2.87e+02	7.31e+00	2.69e-12
Whole brain ADI	9.29e-04	1.11e-01	2.43e+02	8.38e-03	9.93e-01
Diagnosis-CN × Time	-2.80e-01	5.33e-02	2.85e+02	-5.26e+00	2.87e-07
Diagnosis-CN × ADI	9.28e-03	1.46e-01	2.47e+02	6.34e-02	9.49e-01
Time × ADI	-5.88e-03	4.23e-02	2.95e+02	-1.39e-01	8.90e-01
Diagnosis-CN × Time × ADI	-6.54e-03	5.20e-02	2.89e+02	-1.26e-01	9.00e-01

	ADI <sub>C-NODDI</sub> predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.49e+00	1.41e-01	2.37e+02	1.05e+01	1.56e-21
Age	-1.17e-01	7.19e-02	1.99e+02	-1.63e+00	1.04e-01
Sex-Male	-3.84e-02	1.34e-01	1.95e+02	-2.87e-01	7.74e-01
Diagnosis-CN	-1.46e+00	1.53e-01	2.51e+02	-9.57e+00	1.07e-18
Time	2.52e-01	4.90e-02	2.91e+02	5.14e+00	5.04e-07
Whole brain ADI	-2.98e-01	1.22e-01	2.46e+02	-2.43e+00	1.58e-02
Diagnosis-CN × Time	-2.09e-01	5.77e-02	2.89e+02	-3.62e+00	3.47e-04
Diagnosis-CN × ADI	2.37e-01	1.51e-01	2.51e+02	1.57e+00	1.19e-01
Time × ADI	-1.35e-01	5.06e-02	3.00e+02	-2.67e+00	8.02e-03
Diagnosis-CN × Time × ADI	1.39e-01	5.92e-02	2.96e+02	2.36e+00	1.91e-02

	ADISMI predicts prospective CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.53e+00	1.36e-01	2.31e+02	1.12e+01	1.38e-23
Age	-6.46e-02	6.13e-02	2.00e+02	-1.05e+00	2.93e-01
Sex-Male	-1.52e-02	1.32e-01	1.92e+02	-1.16e-01	9.08e-01
Diagnosis-CN	-1.52e+00	1.46e-01	2.50e+02	-1.04e+01	3.13e-21
Time	2.74e-01	4.46e-02	2.92e+02	6.13e+00	2.79e-09
Whole brain ADI	-2.19e-01	1.19e-01	2.51e+02	-1.83e+00	6.79e-02
Diagnosis-CN × Time	-2.35e-01	5.35e-02	2.89e+02	-4.40e+00	1.50e-05
Diagnosis-CN × ADI	1.84e-01	1.46e-01	2.54e+02	1.26e+00	2.08e-01
Time × ADI	-1.28e-01	4.76e-02	2.86e+02	-2.70e+00	7.38e-03
Diagnosis-CN × Time × ADI	1.59e-01	5.57e-02	2.87e+02	2.86e+00	4.58e-03

Diagnosis was referenced to the MCI group, and sex was referenced to females. P-values were not corrected for multiple comparisons.



**Figure S12.** Baseline MRI measurements of axonal density/integrity, assessed using the Axonal Density Index (ADI), predict future changes in cognition and function as measured by MMSE and CDR-SB scores. None of the three ADI metrics significantly predicted MMSE decline within the CN or MCI groups. However, both ADI<sub>C-NODDI</sub> and ADI<sub>SMI</sub> predicted that higher baseline ADI was associated with lower function in the MCI group. These results are not conclusive and may reflect limited sensitivity to the smaller differences between CN and MCI due to the modest sample size. Future studies with larger, multi-cohort datasets are underway.

**Table S9.** Linear mixed-effects model results for Figure 4 without AD subjects.

The model equation is specified as:

$$\text{MMSE/CDR-SB changes}_{ij} \sim \beta_0 + \beta_{\text{sex}} \times \text{Sex}_i + \beta_{\text{Age}} \times \text{Age}_{ij} + \beta_{\text{Diagnosis}} \times \text{Diagnosis}_i + \beta_{\text{ADI changes}} \times \text{ADI changes}_{ij} + \beta_{\text{Diagnosis} \times \text{ADI changes}} \times \text{Diagnosis}_i \times \text{ADI changes}_{ij} + \beta_{\text{Baseline ADI}} \times \text{Baseline ADI}_i + \beta_{\text{Diagnosis} \times \text{Baseline ADI}} \times \text{Diagnosis}_i \times \text{Baseline ADI}_i + b_i + \epsilon_{ij},$$

where MMSE/CDR-SB<sub>ij</sub> is the longitudinal MMSE or CDR-SB changes for subject *i* at time point *j* from subject *i*'s baseline; Age<sub>ij</sub> is the age at the MRI measurement for subject *i* at the time point *j*; Sex<sub>*i*</sub> denotes the subject sex; ADI changes<sub>ij</sub> is the change in ADI from baseline ADI for subject *i* at time point *j*; Baseline ADI<sub>*i*</sub> is the baseline ADI value for subject *i*; Diagnosis<sub>*i*</sub> is the cognitive diagnosis either as cognitive normal (CN) or cognitively impaired (CI, which only includes MCI) for subject *i*; b<sub>*i*</sub> is the random intercept for subject *i*, and ε<sub>ij</sub> is the residual error. Two-way interaction terms between diagnosis and ADI changes were included to examine how changes in ADI from baseline are associated with changes in MMSE/CDR-SB scores. Age<sub>ij</sub> and ADI<sub>ij</sub> values were standardized using the baseline mean and standard deviation. ADI changes<sub>ij</sub> were computed as the difference between the standardized ADI at time *j* and the subject's baseline ADI. Whole brain white matter ADI<sub>NODDI</sub>, ADI<sub>C-NODDI</sub>, and ADI<sub>SMI</sub> values were used. Full statistical results are presented below.

	ADI <sub>NODDI</sub> changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.74e+01	2.30e-01	1.91e+02	1.19e+02	2.62e-181
Sex-Male	-1.75e-01	2.38e-01	1.76e+02	-7.36e-01	4.63e-01
Age	2.54e-02	1.17e-01	1.99e+02	2.16e-01	8.29e-01
Diagnosis-CN	1.67e+00	2.40e-01	1.86e+02	6.95e+00	6.14e-11
ADI changes	7.59e-01	4.32e-01	1.70e+02	1.76e+00	8.07e-02
ADI baseline	-3.27e-01	1.75e-01	1.88e+02	-1.87e+00	6.30e-02
Diagnosis-CN × ADI changes	-8.32e-01	6.07e-01	1.65e+02	-1.37e+00	1.73e-01
Diagnosis-CN × ADI baseline	4.43e-01	2.32e-01	1.83e+02	1.91e+00	5.80e-02

	ADIC-NODDI changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.75e+01	2.38e-01	1.93e+02	1.16e+02	1.91e-180
Sex-Male	-1.65e-01	2.35e-01	1.74e+02	-7.01e-01	4.84e-01
Age	7.00e-02	1.32e-01	1.97e+02	5.29e-01	5.97e-01
Diagnosis-CN	1.61e+00	2.55e-01	1.89e+02	6.31e+00	1.89e-09
ADI changes	1.21e-01	4.99e-01	1.75e+02	2.42e-01	8.09e-01
ADI baseline	4.81e-02	2.00e-01	1.84e+02	2.40e-01	8.11e-01
Diagnosis-CN × ADI changes	-5.44e-01	5.82e-01	1.73e+02	-9.34e-01	3.52e-01
Diagnosis-CN × ADI baseline	7.90e-02	2.50e-01	1.79e+02	3.16e-01	7.53e-01

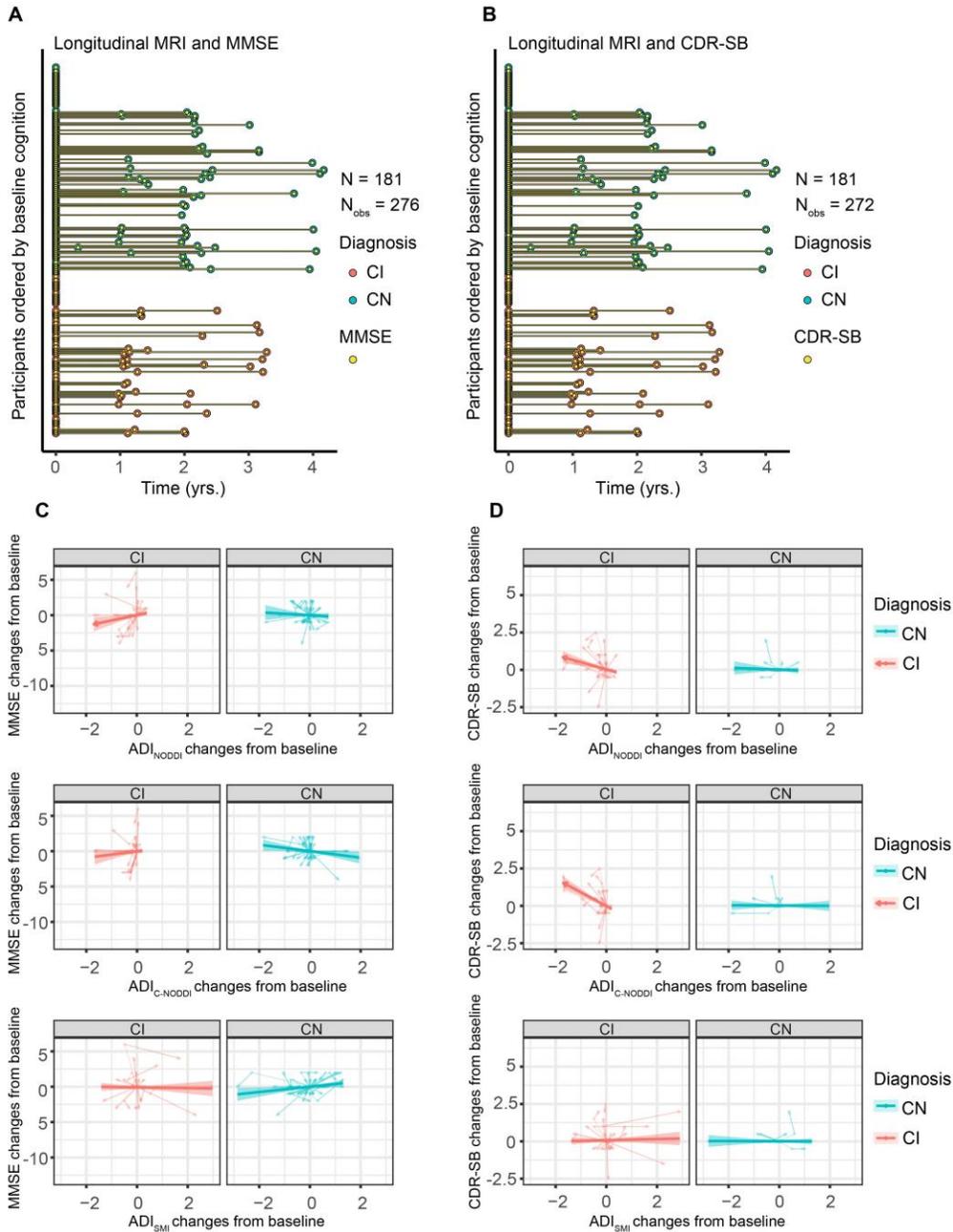
	ADISMI changes associate with MMSE				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	2.75e+01	2.27e-01	1.82e+02	1.21e+02	2.34e-175
Sex-Male	-1.27e-01	2.31e-01	1.73e+02	-5.48e-01	5.84e-01
Age	2.33e-02	1.13e-01	1.95e+02	2.06e-01	8.37e-01
Diagnosis-CN	1.66e+00	2.38e-01	1.74e+02	6.96e+00	6.66e-11
ADI changes	1.40e-01	2.53e-01	1.44e+02	5.52e-01	5.82e-01
ADI baseline	1.85e-01	2.02e-01	1.68e+02	9.17e-01	3.61e-01
Diagnosis-CN × ADI changes	2.86e-01	3.46e-01	1.58e+02	8.27e-01	4.09e-01
Diagnosis-CN × ADI baseline	-1.83e-01	2.43e-01	1.69e+02	-7.53e-01	4.52e-01

	ADI <sub>NODDI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.71e+00	1.16e-01	1.91e+02	1.47e+01	2.75e-33
Sex-Male	-7.29e-02	1.20e-01	1.83e+02	-6.07e-01	5.45e-01
Age	-3.83e-02	5.83e-02	2.04e+02	-6.56e-01	5.12e-01
Diagnosis-CN	-1.65e+00	1.20e-01	1.88e+02	-1.37e+01	5.19e-30
ADI changes	-5.28e-01	1.79e-01	1.38e+02	-2.95e+00	3.75e-03
ADI baseline	1.28e-02	8.82e-02	1.88e+02	1.45e-01	8.85e-01
Diagnosis-CN × ADI changes	4.51e-01	2.56e-01	1.37e+02	1.76e+00	8.06e-02
Diagnosis-CN × ADI baseline	-5.48e-03	1.16e-01	1.87e+02	-4.73e-02	9.62e-01

	ADI <sub>C-NODDI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.59e+00	1.17e-01	1.93e+02	1.37e+01	3.53e-30
Sex-Male	-9.09e-02	1.15e-01	1.84e+02	-7.91e-01	4.30e-01
Age	-1.04e-01	6.41e-02	2.07e+02	-1.62e+00	1.07e-01
Diagnosis-CN	-1.51e+00	1.25e-01	1.91e+02	-1.21e+01	1.55e-25
ADI changes	-8.61e-01	1.96e-01	1.40e+02	-4.38e+00	2.29e-05
ADI baseline	-2.64e-01	1.00e-01	1.88e+02	-2.64e+00	8.94e-03
Diagnosis-CN × ADI changes	8.10e-01	2.33e-01	1.38e+02	3.48e+00	6.69e-04
Diagnosis-CN × ADI baseline	2.18e-01	1.22e-01	1.86e+02	1.78e+00	7.67e-02

	ADI <sub>SMI</sub> changes associate with CDR-SB				
	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	1.69e+00	1.13e-01	1.86e+02	1.50e+01	5.75e-34
Sex-Male	-6.01e-02	1.14e-01	1.81e+02	-5.25e-01	6.00e-01
Age	-3.72e-02	5.53e-02	2.04e+02	-6.73e-01	5.01e-01
Diagnosis-CN	-1.63e+00	1.18e-01	1.83e+02	-1.38e+01	2.89e-30
ADI changes	1.60e-01	1.09e-01	1.27e+02	1.46e+00	1.46e-01
ADI baseline	-2.22e-01	9.73e-02	1.81e+02	-2.28e+00	2.38e-02
Diagnosis-CN × ADI changes	-1.65e-01	1.52e-01	1.36e+02	-1.09e+00	2.79e-01
Diagnosis-CN × ADI baseline	2.27e-01	1.19e-01	1.83e+02	1.90e+00	5.84e-02

Diagnosis is referenced to MCI and Sex is referenced to Female. All p-values are not corrected for multiple comparisons.



**Figure S13.** Changes in axonal integrity, measured using the Axonal Density Index (ADI), are associated with changes in cognition and function, assessed by MMSE and CDR-SB scores. Only changes in ADI<sub>NODDI</sub> significantly associated with MMSE decline within MCI groups. However, decreases in ADI<sub>NODDI</sub> and ADI<sub>C-NODDI</sub> were significantly associated with CDR-SB increases in the MCI group. These results are not conclusive and may reflect limited sensitivity to subtle differences between CN and MCI due to the modest sample size. Future studies involving larger, multi-cohort datasets are underway.

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