Supplementary Materials

Table E1. Characteristics of eligible and ineligible aMCI subjects at earliest aMCI diagnosis with concomitant MRI

	aMCI subjects without qualifying no. of scans (n = 344)	aMCI patients with qualifying no. of scans		P-value	
		Subjects included in analysis (n= 69)	Subjects excluded from analysis (n= 67)	Subjects in analyses vs. subjects without qualifying no. of scans	Subjects in analyses vs. excluded subjects
No. of women (%)	172 (50)	33 (48)	24 (36)	0.74	0.16
Mean (SD) age, y	78.3 (9.7)	77.0 (6.2)	74.4 (8.7)	0.06	0.10
Mean (SD) number of years of education	13.8 (3.4)	14.2 (3.4)	14.0 (3.5)	0.29	0.62
No. of APOE ε4 carriers (%)	114 (47)	41 (59)	26 (40)	0.07	0.02
Median (min., max.) summed learning over trials 1–5 from AVLT	27 (8, 48)	27 (4, 43)	28 (8, 44)	0.54	0.37
Median (min., max.) CDR sum of boxes	0.5 (0.0, 6.5)	0.5 (0.0, 3.5)	0.5 (0.0, 5.0)	0.78	0.96
Median (min., max.) MMSE	27 (18, 30)	26 (18, 30)	26 (19, 30)	0.11	0.64
Median (min., max.) WMS logical memory II, paragraph recall	4 (0, 30)	3 (0, 17)	5 (0, 26)	0.048	0.10
Median (min., max) WAIS-R block design	6 (1, 14)	7 (1, 17)	7 (4, 14)	0.04	0.96
Median (min., max) WAIS-R picture completion	5 (1, 14)	6 (1, 11)	6 (3, 14)	0.28	0.57

The piecewise-linear mixed effects model was expressed as

$$\begin{aligned} y_{ij} = {} & \beta_0 + \beta_1 \mathrm{TIV}_i + \beta_2 \mathrm{Male}_i \\ & + \beta_3 \mathrm{IndexAge}_i + \beta_4 \mathrm{Time}_{ij} + \beta_5 h(\mathrm{Time}_{ij}) \\ & + b_{0i} + e_{ij} \end{aligned}$$

Here y represents either volume or cognitive test score with ij denoting the value for the ith subject at the jth timepoint. Male_i is 1 if the ith subject is male and zero otherwise. $\mathrm{IndexAge}_i$ is the age of the ith subject at the time of the index scan. Time_{ij} is the years from the index scan for the ith subject at the jth timepoint. For pre-index times, $h(\mathrm{Time}_{ij})$ is zero while for post-index times, $h(\mathrm{Time}_{ij}) = \mathrm{Time}_{ij}$, thus accommodating a change in slope at time zero. The random intercept b_{0i} is normally distributed with mean zero and standard deviations σ_0. The random errors e_{ij} are normally distributed with mean zero and standard deviation σ_e. The correlation between e_{ij} and e_{ik} is modeled as $\exp(-(x_i/a)^2)$ where x_i is the time between observation j and observation k for subject i and a is a parameter estimated from the data.

The age-based model was parameterized as

$$\begin{aligned} y_{ij} = {} & \beta_1 \mathrm{TIV}_i + \beta_2 \mathrm{Male}_i \\ & + \beta_3 \mathrm{CN}_i + \beta_4 (\mathrm{CN}_i \times \mathrm{Age}_{ij}) + \beta_5 (\mathrm{CN}_i \times \mathrm{Age}_{ij}^2) \\ & + \beta_6 \mathrm{aMCI}_i + \beta_7 (\mathrm{aMCI}_i \times \mathrm{Age}_{ij}) + \beta_8 (\mathrm{aMCI}_i \times \mathrm{Age}_{ij}^2) \\ & + \beta_9 \mathrm{aMCI}_i + \beta_{10} (\mathrm{aMCI}_i \times \mathrm{Age}_{ij}) + \beta_{11} (\mathrm{aMCI}_i \times \mathrm{Age}_{ij}^2) \\ & + b_{0i} + e_{ij} \end{aligned}$$

Here the notation is similar to above but with CN_i, $\mathrm{aMCI\text{-}s}_i$, and $\mathrm{aMCI\text{-}p}_i$ representing group indicators that are 1 if the ith subject belongs to the respective group and zero otherwise. In this model, each group has its own intercept term, linear age term, and quadratic age term and all three groups share a common TIV and sex term. The results from these models are shown in tables A1 and A2. For the APOE ε4 analysis, a similar model was fit except the CN subjects were omitted and the three-level group variable was replaced with a binary variable representing carriers and non-carriers.

Table E2. aMCI Progressors. Estimates for pre-index date rate, post-index date rate, and rate change of AVLT sum of words learned of trials 1 to 5, CDR sum of boxes, and MMSE based on piecewise-linear mixed effects models

	Estimate	95% CI	P-value*
Change in AVLT summed learning trials 1−5			
Before index date	−1.7	−2.0 to −1.3	<0.001
After index date	−1.1	−1.6 to −0.6	<0.001
Rate change	0.6	−0.2 to +1.3	0.13
Change in CDR sum of boxes			
Before index date	+0.5	+0.3 to +0.7	<0.001
After index date	+1.8	+1.6 to +1.9	<0.001
Rate change	+1.3	+1.0 to +1.6	<0.001
Change in MMSE			
Before index date	−0.5	−0.7 to −0.2	<0.001
After index date	−2.0	−2.4 to −1.7	<0.001
Rate change	−1.5	−2.0 to −1.0	<0.001

Note: Estimates are adjusted for education, sex, and age at the time of the index scan

CI, confidence interval

* Based on Wald test testing whether coefficient is zero

Table E3. Age-based mixed model estimates for ventricular volume			
Term	Coefficient (SE)	95% CI	P-value
TIV, liters	66.7 (21.0)	25 to 108	0.002
Male sex	−2.89 (5.91)	−15 to 9	0.63
Cognitively normal			
Intercept	−134.1 (64.7)	−262 to −6	0.04
Age	0.942 (1.45)	−1.9 to 3.8	0.52
Age^2	0.0032 (0.0092)	−0.01 to 0.002	0.73
aMCI-stable			
Intercept	−484.5 (157.9)	−797 to −172	0.003
Age	8.92 (3.78)	1.5 to 16.3	0.02
Age^2	−0.0400 (0.0228)	−0.08 to 0.005	0.08
aMCI-progressor			
Intercept	−545.0 (71.9)	−687 to −403	<0.001
Age	9.43 (1.65)	6.2 to 12.7	<0.001
Age^2	−0.0360 (0.0103)	−0.06 to −0.02	<0.001

SE, standard error for coefficient

CI, confidence interval

Table E4. Age-based mixed model estimates for whole brain			
Term	Coefficient (SE)	95% CI	P-value
TIV, liters	674.1 (54.5)	566 to 782	<0.001
Male sex	29.18 (15.29)	−1.1 to 59.5	0.06
Cognitively normal			
Intercept	494.2 (178.4)	141 to 848	0.007
Age	−1.21 (4.07)	−9.2 to 6.8	0.77
Age^2	−0.0179 (0.0256)	−0.07 to 0.03	0.48
aMCI-stable			
Intercept	1512.3 (465.1)	591 to 2434	0.002
Age	−24.87 (11.14)	−47 to −3	0.03
Age^2	0.1187 (0.0669)	−0.013 to 0.25	0.08
aMCI-progressor			
Intercept	1747.9 (194.6)	1362 to 2134	<0.001
Age	−29.12 (4.50)	−38 to −20	<0.001
Age^2	0.1272 (0.0282)	0.07 to 0.18	<0.001

SE, standard error for coefficient

CI, confidence interval

Table E5. Age-based mixed model estimates for AVLT sum of learning over trials 1 to 5			
Term	Coefficient (SE)	95% CI	P-value
Education, years	0.5 (0.2)	0.02 to 0.9	0.04
Male sex	-3.5 (1.4)	-6.3 to -0.7	0.01
Cognitively normal			
Intercept	-81.0 (43.2)	-166 to 4.5	0.06
Age	2.9 (1.1)	0.7 to 5.0	0.008
Age^2	-0.02 (0.01)	-0.03 to 0.00	0.010
aMCI-stable			
Intercept	-134.0 (107.7)	-347 to 79	0.22
Age	4.3 (2.6)	-0.8 to 9.4	0.10
Age^2	-0.03 (0.02)	-0.06 to 0.003	0.07
aMCI-progressor			
Intercept	50.7 (60.3)	-68 to 170	0.40
Age	0.3 (1.5)	-2.7 to 3.3	0.86
Age^2	-0.01 (0.01)	-0.03 to 0.01	0.37

SE, standard error for coefficient

CI, confidence interval

Table E6. Age-based mixed model estimates for CDR sum of boxes*

Term	Coefficient (SE)	95% CI	P-value
Education, years	-0.15 (0.19)	-0.5 to 0.2	0.41
Male sex	-1.9 (1.3)	-4.4 to 0.6	0.14
aMCI-stable			
Intercept	-5.7 (64.4)	-134 to 123	0.93
Age	0.20 (1.6)	-2.9 to 3.3	0.90
Age^2	-0.001 (0.009)	-0.02 to 0.02	0.92
aMCI-progressor			
Intercept	-61.1 (30.1)	-121 to -0.99	0.046
Age	0.76 (0.75)	-0.7 to 2.2	0.31
Age^2	0.001 (0.005)	-0.008 to 0.01	0.78

* The CN group is excluded from this model fit

SE, standard error for coefficient

CI, confidence interval

Table E7. Age-based mixed model estimates for MMSE			
Term	Coefficient (SE)	95% CI	P-value
Education, years	0.16 (0.09)	-0.02 to 0.3	0.08
Male sex	0.37 (0.56)	-0.7 to 1.5	0.51
Cognitively normal			
Intercept	16.8 (25.3)	-33 to 67	0.51
Age	0.27 (0.63)	-1.0 to 1.5	0.68
Age^2	-0.002 (0.004)	-0.01 to 0.01	0.65
aMCI-stable			
Intercept	-7.2 (61.2)	-128 to 114	0.91
Age	0.7 (1.5)	-2.1 to 3.6	0.63
Age^2	-0.004 (0.009)	-0.02 to 0.01	0.65
aMCI-progressor			
Intercept	-21.0 (32.2)	-85 to 43	0.52
Age	1.7 (0.8)	0.06 to 3.3	0.04
Age^2	-0.01 (0.005)	-0.02 to -0.004	0.006

SE, standard error for coefficient

CI, confidence interval