Trajectory models

There are several approaches to trajectory modeling. Hierarchical modeling and latent curve analysis assume that all individuals in the sample are drawn from the same population, their trajectories have a continuous distribution, and these can all be modeled using the same set of parameters. Group-based approaches, on the other hand, such as the group-based trajectory model and the growth mixture model, assume that the sample is drawn from a discrete set of subpopulations, each defined by a unique trajectory pattern, and each modeled using a unique set of parameters via a finite mixture model. Since in the case of depression and the cognitive domains we do not expect individuals to vary continuously from a mean population developmental trajectory, but rather expect there to be subgroups with distinct trajectories, we chose a group-based approach.

The growth mixture model and group-based trajectory model differ in the ways they handle within-group variation. The growth mixture model explicitly models individual variation from the subgroup mean trajectories using random effects, which can result in the identification of fewer trajectory groups, while the group-based trajectory model does not use random effects, but instead aims at approximating the structure of developmental trajectories at the level of the population. In contrast to the growth mixture model, the group-based trajectory model does not commit to the assumption that the groups are literally distinct, but uses a discrete set of trajectories to approximate what may be in reality an underlying continuous distribution with a complex structure. Since we are interested in the structure at the population level and remain uncommitted to the notion that there are literally distinct trajectory groups in the population, we chose the group-based trajectory model. For a good nontechnical overview of trajectory modeling approaches, see Nagin and Odgers (2010) [1].

The dual group-based trajectory model is an extension of the univariate case in that it allows assessment of the relationships between two sets of trajectories [2, 3, 4]. Fitting a dual trajectory model involves maximizing a joint likelihood function which specifies both sets of trajectories simultaneously. Similarly to the univariate model, the dual model outputs include the optimal number of trajectory groups, the shapes of trajectories, and estimates of the percentage of the population belonging to each trajectory group. For each of the two sets of trajectories, a posterior probability of membership in each of the

trajectory groups is determined for each individual in the sample, and the maximum posterior probability assignment rule assigns each individual in the sample to the trajectory group with the highest probability. In addition, the dual models give estimates of joint and conditional probabilities of trajectory group membership. These probabilities link the two sets of trajectories, and can help to indicate an association between two developmental domains.

We fit five dual trajectory models to relate trajectories of depression (measured by modified Center for Epidemiological Studies-Depression scale (mCES-D) score, which takes integer values from 0-20) to trajectories of cognitive function (measured by cognitive domain composite z-score) one for each cognitive domain: (1) attention, (2) executive function, (3) language, (4) memory, and (5) visuospatial skill. We followed the dual trajectory model-fitting procedure recommended by Nagin (2005) [4], which involves two stages: Since the trajectories in the fitted dual models tend to look very similar to those in the univariate models, the model search space is reduced by first finding the best univariate trajectory models, and then using the trajectory parameters from these as starting values for the dual model. Hence, first the best univariate trajectory models (i.e. the optimal number of groups and orders of the corresponding polynomial functions modeling the group mean trajectories, and the parameter estimates) were found for mCES-D and each of the five cognitive domains. Model choice was based on a combination of maximum Bayesian information criterion (BIC), Wald tests, and clinical plausibility. The dual trajectory models were then fit using starting parameters from the final univariate models.

In order to find unadjusted trajectory patterns, trajectory models were fit using mCES-D and cognitive z-scores alone; covariate information was not incorporated. We sought to find unadjusted trajectory patterns so that we could later investigate associations between covariates and specific trajectory groups. We used a zero-inflated Poisson model [5] for mCES-D since it was count data with excess zeros. Normal models were used for each of the five cognitive domain z-scores. The software only fits censored normal models, so we chose min=-50, max=50 so as to be essentially equivalent to an uncensored normal distribution, given that the cognitive z-score data were well within these limits.

To identify the optimal number of trajectory groups for depression and each of the cognitive domains, we tried from three up to a maximum of ten groups in each of the univariate models, using all second-order polynomial trajectories at this stage as per the recommended method [4]. In all cases, the

BIC tended to increase with increasing number of groups. Consequently, we decided to use the alternative criterion suggested by Nagin (2005) [4], which is to choose the minimum number of groups needed in order to capture the important features the data. The depression univariate model was fixed at five groups because adding more groups increased model complexity without identifying any additional meaningfully distinct groups. For example, the trajectory structure of the six-group depression model was very similar to the five-group model, except that there were now two low-increasing depressive symptom trajectory groups with approximately parallel trajectories, separated by 1 to 2 points on the mCES-D scale in their means, and composed largely of members of the five-group low-increasing trajectory. For the cognitive domains, more than six groups resulted in groups with very small group membership probabilities and appeared sensitive to outliers, suggesting overfitting. Because of this, we chose to use six groups for each cognitive domain. Also, we decided to use the same number of groups for each cognitive domain to help facilitate comparisons between models.

Once the numbers of groups were chosen, we determined the best orders for the polynomials in the univariate models based on the highest BIC criterion. Many of the second-order polynomial trajectories were reduced to first- or zero-order trajectories with resulting increased BIC. Visual inspection of plots of the individual-level trajectories did not suggest a need for third-order trajectories. After the best univariate models were found for depression and the five cognitive domains, the dual trajectory models were fit using the starting parameter values obtained from the univariate models.

Model diagnostics

We examined model diagnostics for all of the univariate and dual trajectory models using three criteria [4]: (1) average posterior probability of group membership at least 0.7 for all groups, (2) odds of correct classification greater than 5.0 for all groups, and (3) estimated group probabilities reasonably close to the proportion of the sample assigned to the group based on the maximum posterior probability assignment rule.

Analysis of trajectory groups

We calculated descriptive statistics to characterize the sample at baseline, years of follow-up, and antidepressant use during the course of the study, both for the overall sample and stratified by depression trajectory group. We performed global tests of association of these variables with the depression trajectory groups, using a chi-squared test for most categorical variables (age group, education group, gender, antidepressant use), Fisher's exact test for categorical variables with any cell sizes of five or less (race), and a Kruskal-Wallis test for continuous and count variables (continuous age, MMSE, mCES-D, years of follow-up). We did all pairwise comparisons of proportion antidepressant use among the depression trajectory groups using Fisher's exact tests with Holm-adjusted p-values to correct for multiple comparisons.

With regard to cognition, we defined as "persistently low" the cognitive trajectories with a composite z-score of -1 or lower during the majority of the study period. We performed pairwise comparisons of proportions of persistently low cognitive trajectory membership among the depression trajectory groups against the top-ranked group, i.e. the depression trajectory group with the largest proportion of members classified into a persistently low cognitive trajectory, using Fisher's exact tests with Holm-adjusted p-values to correct for multiple comparisons within each cognitive domain.

We also fit logistic regression models for each cognitive domain to model the log odds of persistently low cognition as a function of depressive symptom trajectory group (as unordered categorical variable), both with and without adjustment for baseline demographics (age group, education group, gender, race). Due to complete separation in the case of attention (the low-decreasing depression group had 0% classified as persistently low), we used Firth's penalized likelihood method to fit the unadjusted and adjusted logistic regression models for the attention domain [6, 7].

Post-hoc sensitivity analyses

When data is missing at random, the maximum likelihood estimates from the group-based trajectory model are asymptotically unbiased [1]. However, we expect that attrition is correlated with our outcomes of interest, depression and cognitive function. Indeed, we found that the high-grade depressive

symptom group had a shorter median follow-up time (2 years) than the other groups (4 or 5 years). To assess whether this introduced bias into our estimates, we refit the five depression group dual trajectory models using only the first four time points (3 year follow-up) in a post-hoc analysis.

Also, to determine whether results were influenced by the small group size for the persistently low attention group, we investigated whether incorporating the next-lowest trajectory into the persistently low group altered our conclusions.

Statistical software

Trajectory model fitting was performed using the SAS procedure TRAJ [8, 9] in SAS 9.3 [10]. The PROC TRAJ program can be downloaded from the website http://www.andrew.cmu.edu/user/bjones. Example SAS code is given below. The remainder of the analyses were carried out using R version 3.1.3 [11].

Example SAS PROC TRAJ code

Univariate mCES-D trajectory model

```
* BEST mCES-D 5 group model;
* mCESD vs. Cycle ZIP model;
proc traj data=depcog outstat=os outest=oe outplot=op itdetail ci95m;
  id researchid;
  var mcesdscore_c1-mcesdscore_c6;
  indep c1-c6;
  model zip; ngroups 5; order 1 2 2 2 2;
run;

%TRAJPLOT(OP,OS,'mCES-D vs. Time','ZIP Model', 'mCES-D', 'Years from baseline')
%TRAJPLOTNEW(OP,OS,'mCES-D vs. Time','ZIP Model', 'mCES-D', 'Years from baseline')
```

Univariate executive function trajectory model

```
* BEST Executive 6 group model;
* Executive vs. Cycle CNORM model;
proc traj data=depcog outstat=os outest=oe outplot=op itdetail;
  id researchid;
  var rexecutive1-rexecutive6;
  indep c1-c6;
  model cnorm; min -50; max 50; ngroups 6; order 2 1 1 0 0 0;
run;

%TRAJPLOT(OP,OS,'Executive z-score vs. Time','Cnorm Model', 'Executive z-score', 'Years from baseline')
%TRAJPLOTNEW(OP,OS,'Executive z-score vs. Time','Cnorm Model', 'Executive z-score', 'Years from baseline')
```

Dual trajectory model for mCES-D and executive function

```
* Dual Trajectory for mCES-D (Model 1) and EXECUTIVE (Model 2);
* using starting values to match best univariate trajectory models;
proc traj data=depcog out=b outstat=ost outplot=opl outstat2=ost2 outplot2=opl2 itdetail;
  id researchid;
  var mcesdscore_c1-mcesdscore_c6;
  indep c1-c6;
  model zip; ngroups 5; order 1 2 2 2 2;
  var2 rexecutive1-rexecutive6;
  indep2 c1-c6;
  model2 cnorm; min2 -50; max2 50; ngroups2 6; order2 2 1 1 0 0 0;
  start     -1.235094     0.479515    -2.431718    -0.528150     0.075744
             0.929868     0.608688    -0.203230     0.703371    -0.689590
             0.043112     1.950256    -0.192341     0.029827                  /* Model 1 trajectory parameters */
             9.631360    60.467051     7.350804    18.50616      4.044625       /* Model 1 group percentages */
            -2.253636    -0.620265     0.095969    -1.034139    -0.246534
            -0.544709    -0.047107    -0.006713     0.634784     1.306596    /* Model 2 trajectory parameters */
             0.451101                                                              /* Model 2 sigma */
             16.67 16.67 16.67 16.67 16.66 16.66
             16.67 16.67 16.67 16.67 16.66 16.66
             16.67 16.67 16.67 16.67 16.66 16.66
             16.67 16.67 16.67 16.67 16.66 16.66
             16.67 16.67 16.67 16.67 16.66 16.66       /* Model 2 given group 1 conditional group percentages */
  ;
run;

%TRAJPLOT(OPL,OST,'mCES-D vs. Time','ZIP Model', 'mCES-D', 'Years from baseline')
%TRAJPLOTNEW(OPL,OST,'mCES-D vs. Time','ZIP Model', 'mCES-D', 'Years from baseline')

%TRAJPLOT(OPL2,OST2,'Executive z-score vs. Time','Cnorm Model', 'Executive z-score', 'Years from baseline')
%TRAJPLOTNEW(OPL2,OST2,'Executive z-score vs. Time','Cnorm Model', 'Executive z-score', 'Years from baseline')
```

References

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Supplemental Digital Content 2. Logistic regression odds ratios for persistently low cognitive trajectory membership

Parameter	Cognitive domain					
	Attention[a]		Executive function		Language	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Intercept	0.03 (0.02, 0.04)***	0.00 (0.00, 0.01)***	0.06 (0.05, 0.07)***	0.01 (0.01, 0.02)***	0.06 (0.05, 0.07)***	0.01 (0.00, 0.01)***
Depression group						
Rare	---	---	---	---	---	---
Low, decreasing	0.05 (0.00, 0.32)***	0.04 (0.00, 0.29)***	1.80 (1.17, 2.73)**	1.69 (1.08, 2.61)*	1.80 (1.17, 2.72)**	1.63 (1.04, 2.52)*
Low, increasing	4.77 (2.56, 8.58)***	3.59 (1.84, 6.75)***	3.43 (2.06, 5.56)***	2.46 (1.42, 4.16)***	2.89 (1.72, 4.73)***	2.07 (1.18, 3.52)**
Moderate	2.03 (0.78, 4.49)	1.74 (0.66, 3.99)	6.61 (4.19, 10.35)***	6.15 (3.75, 10.02)***	4.42 (2.66, 7.17)***	3.64 (2.10, 6.17)***
High	2.00 (0.63, 4.97)	1.48 (0.44, 3.98)	2.15 (0.97, 4.27)*	1.63 (0.69, 3.49)	3.14 (1.55, 5.89)***	2.71 (1.26, 5.47)**
Age group at baseline						
65-74		---		---		---
74-85		2.92 (1.21, 8.36)*		3.83 (2.18, 7.20)***		7.38 (3.72, 16.81)***
85+		11.38 (4.87, 32.10)***		13.73 (7.79, 25.94)***		21.85 (10.93, 50.14)***
Education						
High school or less		1.79 (0.99, 3.44)		1.54 (1.06, 2.27)*		1.67 (1.14, 2.50)*
More than high school		---		---		---
Sex						
Male		1.53 (0.89, 2.64)		1.21 (0.85, 1.71)		1.05 (0.73, 1.50)
Female		---		---		---
Race						
White		---		---		---
Non-white		4.14 (1.87, 8.58)***		4.28 (2.18, 7.20)***		4.49 (2.52, 7.83)***

Notes: Significance codes for Wald test of the null hypothesis that the corresponding regression coefficient is equal to zero: *** P < 0.001; ** P < 0.01; * P < 0.05

--- denotes reference level.

[a] For the Attention domain, there was complete separation in the case of the low, increasing depression trajectory group, so Firth's penalized likelihood method was used (Firth D. (1993). Bias reduction of maximum likelihood estimates. Biometrika 80: 27-38.)

Supplemental Digital Content 2. Logistic regression odds ratios for persistently low cognitive trajectory membership

Parameter	Cognitive domain			
	Memory		Visuospatial skill	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Intercept	0.19 (0.16, 0.22)***	0.02 (0.01, 0.04)***	0.06 (0.05, 0.08)***	0.02 (0.01, 0.03)***
Depression group				
Rare	---	---	---	---
Low, decreasing	1.32 (0.98, 1.76)	1.27 (0.92, 1.74)	1.81 (1.20, 2.69)**	1.66 (1.09, 2.50)*
Low, increasing	1.59 (1.04, 2.40)*	1.26 (0.79, 1.98)	2.24 (1.26, 3.78)**	1.56 (0.85, 2.75)
Moderate	2.52 (1.69, 3.70)***	2.12 (1.37, 3.25)***	5.84 (3.70, 9.10)***	5.41 (3.34, 8.66)***
High	2.39 (1.43, 3.89)***	2.43 (1.38, 4.20)**	3.98 (2.13, 7.07)***	3.39 (1.73, 6.35)***
Age group at baseline				
65-74		---		---
74-85		6.02 (4.00, 9.43)***		2.44 (1.57, 3.90)***
85+		18.51 (12.04, 29.52)***		5.20 (3.25, 8.56)***
Education				
High school or less		1.54 (1.18, 2.02)**		1.45 (1.02, 2.08)*
More than high school		---		---
Sex				
Male		1.33 (1.03, 1.71)*		1.00 (0.71, 1.40)
Female		---		---
Race				
White		---		---
Non-white		1.84 (1.09, 3.06)*		6.20 (3.75, 10.13)***

Notes: Significance codes for Wald test of the null hypothesis that the corresponding regression coefficient is equal to zero: *** P < 0.001; ** P < 0.01; * P < 0.05

--- denotes reference level.

Supplemental Digital Content 3. Joint and Conditional Probabilities of Group Membership

Table A. Joint probability of cognition and depression trajectory groups

Cognition group	Depression group	Attention	Executive	Language	Memory	Visuospatial
1 Low	1 Rare	0.02	0.00	0.01	0.03	0.04
	2 Low, decreasing	0.00	0.00	0.00	0.01	0.02
	3 Low, increasing	0.02	0.00	0.00	0.01	0.01
	4 Moderate	0.00	0.01	0.01	0.01	0.02
	6 High	0.00	0.00	0.00	0.00	0.01
2	1 Rare	0.07	0.03	0.02	0.06	0.13
	2 Low, decreasing	0.04	0.02	0.01	0.02	0.04
	3 Low, increasing	0.02	0.01	0.02	0.02	0.04
	4 Moderate	0.02	0.01	0.01	0.01	0.02
	6 High	0.01	0.00	0.01	0.01	0.01
3	1 Rare	0.19	0.10	0.06	0.11	0.21
	2 Low, decreasing	0.05	0.04	0.03	0.04	0.08
	3 Low, increasing	0.03	0.03	0.01	0.03	0.04
	4 Moderate	0.02	0.02	0.01	0.02	0.02
	6 High	0.02	0.02	0.00	0.01	0.02
4	1 Rare	0.18	0.23	0.14	0.16	0.13
	2 Low, decreasing	0.06	0.07	0.05	0.05	0.03
	3 Low, increasing	0.02	0.04	0.05	0.02	0.01
	4 Moderate	0.01	0.02	0.02	0.02	0.01
	6 High	0.01	0.01	0.01	0.01	0.00
5	1 Rare	0.12	0.18	0.22	0.16	0.06
	2 Low, decreasing	0.02	0.04	0.06	0.04	0.00
	3 Low, increasing	0.01	0.01	0.02	0.02	0.00
	4 Moderate	0.02	0.02	0.01	0.01	0.00
	6 High	0.00	0.01	0.01	0.01	0.00
6	1 Rare	0.02	0.05	0.14	0.07	0.02
	2 Low, decreasing	0.01	0.01	0.03	0.02	0.00
	3 Low, increasing	0.00	0.00	0.01	0.00	0.00
	4 Moderate	0.00	0.00	0.01	0.01	0.00
	6 High	0.00	0.00	0.00	0.00	0.00

Notes: Pr(Depression group, Cognition group)
Shaded cells indicate cognition trajectory groups that are persistently low, i.e. the majority of the trajectory is less than or equal to a z-score of -1.

Supplemental Digital Content 3. Joint and Conditional Probabilities of Group Membership

Table B. Conditional probability of depression group given cognition group

Cognition group	Depression group	Attention	Executive	Language	Memory	Visuospatial
1 Low	1 Rare	0.42 (0.09)	0.18 (0.10)	0.53 (0.09)	0.43 (0.06)	0.40 (0.05)
	2 Low, decreasing	0.00 (0.00)	0.25 (0.12)	0.00 (0.00)	0.12 (0.05)	0.12 (0.04)
	3 Low, increasing	0.39 (0.09)	0.18 (0.09)	0.09 (0.07)	0.21 (0.05)	0.20 (0.05)
	4 Moderate	0.12 (0.06)	0.30 (0.10)	0.37 (0.09)	0.20 (0.05)	0.20 (0.04)
	6 High	0.07 (0.05)	0.09 (0.06)	0.00 (0.00)	0.03 (0.02)	0.08 (0.03)
2	1 Rare	0.46 (0.05)	0.38 (0.06)	0.34 (0.06)	0.51 (0.04)	0.55 (0.03)
	2 Low, decreasing	0.24 (0.04)	0.19 (0.05)	0.24 (0.06)	0.13 (0.03)	0.15 (0.03)
	3 Low, increasing	0.13 (0.04)	0.22 (0.05)	0.21 (0.06)	0.18 (0.04)	0.19 (0.03)
	4 Moderate	0.10 (0.03)	0.17 (0.04)	0.13 (0.05)	0.10 (0.03)	0.07 (0.02)
	6 High	0.07 (0.02)	0.04 (0.02)	0.09 (0.03)	0.08 (0.03)	0.04 (0.02)
3	1 Rare	0.60 (0.03)	0.50 (0.04)	0.52 (0.05)	0.52 (0.03)	0.58 (0.03)
	2 Low, decreasing	0.17 (0.03)	0.16 (0.03)	0.08 (0.03)	0.14 (0.03)	0.09 (0.02)
	3 Low, increasing	0.11 (0.02)	0.19 (0.03)	0.25 (0.04)	0.19 (0.03)	0.22 (0.02)
	4 Moderate	0.07 (0.02)	0.08 (0.02)	0.10 (0.03)	0.10 (0.02)	0.06 (0.02)
	6 High	0.06 (0.01)	0.07 (0.02)	0.05 (0.02)	0.05 (0.02)	0.05 (0.01)
4	1 Rare	0.64 (0.03)	0.61 (0.03)	0.51 (0.03)	0.62 (0.03)	0.71 (0.03)
	2 Low, decreasing	0.23 (0.03)	0.11 (0.02)	0.17 (0.02)	0.09 (0.02)	0.08 (0.02)
	3 Low, increasing	0.08 (0.02)	0.19 (0.02)	0.18 (0.03)	0.19 (0.03)	0.15 (0.03)
	4 Moderate	0.03 (0.02)	0.06 (0.01)	0.08 (0.02)	0.06 (0.02)	0.06 (0.02)
	6 High	0.03 (0.01)	0.03 (0.01)	0.05 (0.01)	0.03 (0.01)	0.01 (0.01)
5	1 Rare	0.70 (0.03)	0.70 (0.03)	0.68 (0.03)	0.69 (0.03)	0.88 (0.04)
	2 Low, decreasing	0.14 (0.03)	0.04 (0.01)	0.07 (0.02)	0.07 (0.02)	0.02 (0.02)
	3 Low, increasing	0.06 (0.02)	0.17 (0.02)	0.19 (0.02)	0.17 (0.02)	0.06 (0.03)
	4 Moderate	0.09 (0.02)	0.06 (0.01)	0.03 (0.01)	0.04 (0.01)	0.03 (0.02)
	6 High	0.01 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)	0.02 (0.02)
6	1 Rare	0.75 (0.07)	0.77 (0.05)	0.72 (0.03)	0.71 (0.04)	0.74 (0.08)
	2 Low, decreasing	0.00 (0.00)	0.04 (0.02)	0.04 (0.01)	0.05 (0.02)	0.08 (0.05)
	3 Low, increasing	0.18 (0.06)	0.13 (0.04)	0.15 (0.03)	0.16 (0.04)	0.14 (0.07)
	4 Moderate	0.05 (0.03)	0.06 (0.03)	0.07 (0.02)	0.06 (0.02)	0.00 (0.00)
	6 High	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.02 (0.01)	0.04 (0.03)

Notes: Pr(Depression group | Cognition group) (Standard error)
Shaded cells indicate cognition trajectory groups that are persistently low, i.e. the majority of the trajectory is less than or equal to a z-score of -1.

Supplemental Digital Content 3. Joint and Conditional Probabilities of Group Membership

Table C. Conditional probability of cognition group given depression group

Depression group	Cognition group	Attention	Executive	Language	Memory	Visuospatial
1 Rare	**1 Low**	0.03 (0.01)	0.01 (0.00)	0.02 (0.00)	0.05 (0.01)	0.07 (0.01)
	2	0.12 (0.02)	0.05 (0.01)	0.04 (0.01)	0.11 (0.01)	0.22 (0.02)
	3	0.32 (0.02)	0.18 (0.02)	0.10 (0.01)	0.18 (0.02)	0.36 (0.02)
	4	0.29 (0.02)	0.38 (0.02)	0.23 (0.02)	0.27 (0.02)	0.22 (0.02)
	5	0.20 (0.02)	0.31 (0.02)	0.37 (0.02)	0.27 (0.02)	0.10 (0.01)
	6 High	0.04 (0.01)	0.08 (0.01)	0.24 (0.02)	0.12 (0.01)	0.03 (0.01)
2 Low, decreasing	**1 Low**	0.00 (0.00)	0.02 (0.01)	0.01 (0.01)	0.08 (0.02)	0.12 (0.03)
	2	0.20 (0.03)	0.09 (0.02)	0.08 (0.02)	0.13 (0.03)	0.25 (0.04)
	3	0.29 (0.05)	0.22 (0.03)	0.15 (0.03)	0.21 (0.03)	0.44 (0.04)
	4	0.34 (0.04)	0.39 (0.04)	0.27 (0.03)	0.28 (0.03)	0.15 (0.03)
	5	0.13 (0.03)	0.24 (0.03)	0.33 (0.04)	0.21 (0.03)	0.02 (0.01)
	6 High	0.03 (0.01)	0.04 (0.01)	0.16 (0.03)	0.09 (0.02)	0.02 (0.01)
3 Low, increasing	**1 Low**	0.17 (0.05)	0.05 (0.03)	0.00 (0.00)	0.08 (0.03)	0.13 (0.04)
	2	0.19 (0.06)	0.13 (0.04)	0.15 (0.04)	0.17 (0.04)	0.35 (0.06)
	3	0.34 (0.06)	0.31 (0.05)	0.09 (0.03)	0.30 (0.05)	0.35 (0.06)
	4	0.21 (0.05)	0.38 (0.05)	0.46 (0.05)	0.23 (0.04)	0.14 (0.04)
	5	0.10 (0.03)	0.10 (0.03)	0.22 (0.05)	0.17 (0.04)	0.01 (0.01)
	6 High	0.00 (0.00)	0.02 (0.01)	0.07 (0.03)	0.05 (0.02)	0.02 (0.01)
4 Moderate	**1 Low**	0.08 (0.04)	0.09 (0.03)	0.09 (0.03)	0.17 (0.04)	0.29 (0.06)
	2	0.23 (0.07)	0.16 (0.04)	0.12 (0.04)	0.16 (0.05)	0.23 (0.06)
	3	0.33 (0.07)	0.21 (0.05)	0.16 (0.04)	0.26 (0.05)	0.30 (0.07)
	4	0.12 (0.06)	0.28 (0.06)	0.30 (0.05)	0.22 (0.05)	0.16 (0.05)
	5	0.22 (0.05)	0.21 (0.05)	0.14 (0.05)	0.11 (0.04)	0.03 (0.02)
	6 High	0.02 (0.01)	0.05 (0.02)	0.20 (0.04)	0.07 (0.03)	0.00 (0.00)
5 High	**1 Low**	0.07 (0.05)	0.05 (0.03)	0.00 (0.00)	0.05 (0.04)	0.23 (0.07)
	2	0.24 (0.09)	0.07 (0.04)	0.16 (0.05)	0.24 (0.08)	0.23 (0.09)
	3	0.45 (0.09)	0.38 (0.08)	0.14 (0.06)	0.28 (0.08)	0.46 (0.09)
	4	0.18 (0.07)	0.29 (0.08)	0.36 (0.08)	0.20 (0.07)	0.03 (0.05)
	5	0.04 (0.04)	0.19 (0.06)	0.23 (0.07)	0.18 (0.06)	0.03 (0.03)
	6 High	0.02 (0.02)	0.02 (0.02)	0.12 (0.05)	0.04 (0.03)	0.02 (0.02)

Notes: Pr(Cognition group | Depression group) (Standard error)
Shaded cells indicate cognition trajectory groups that are persistently low, i.e. the majority of the trajectory is less than or equal to a z-score of -1.

Supplemental Digital Content 4. Model Diagnostics

Model	Group	$\hat{\pi}$	P	$AvePP$	OCC
Depression	1 Rare	60.47	63.09	0.9286	8.50
	2 Low, decreasing	18.51	19.97	0.7774	15.38
	3 Low, increasing	9.63	6.57	0.8895	75.50
	4 Moderate	7.35	6.37	0.8582	76.25
	5 High	4.04	3.99	0.8903	192.55
Attention	1 Low	4.38	3.13	0.8070	91.30
	2	15.27	15.62	0.7279	14.85
	3	32.24	34.13	0.7527	6.40
	4	27.58	27.40	0.7387	7.43
	5	17.26	16.78	0.8114	20.63
	6 High	3.28	2.93	0.9116	304.23
Executive	1 Low	2.20	2.17	0.9137	470.64
	2	7.37	6.67	0.8496	71.03
	3	20.96	20.22	0.8070	15.77
	4	37.20	39.64	0.8138	7.38
	5	26.17	25.78	0.8595	17.26
	6 High	6.11	5.51	0.8918	126.74
Language	1 Low	1.79	1.77	0.9666	1591.65
	2	6.66	6.62	0.8600	86.04
	3	11.49	10.82	0.8112	33.11
	4	27.24	27.20	0.8334	13.36
	5	32.71	34.83	0.7946	7.96
	6 High	20.11	18.76	0.8649	25.45
Memory	1 Low	6.50	6.57	0.9029	133.78
	2	12.82	12.44	0.8355	34.54
	3	20.97	21.03	0.8158	16.69
	4	26.13	27.05	0.8039	11.58
	5	23.40	23.26	0.8386	17.01
	6 High	10.18	9.66	0.8875	69.64
Visuospatial	1 Low	10.93	9.38	0.8535	47.51
	2	23.85	21.80	0.7833	11.54
	3	37.07	44.15	0.7342	4.69
	4	18.92	16.40	0.8234	19.98
	5	6.85	6.05	0.8758	95.91
	6 High	2.38	2.22	0.9110	419.30

Notes:

$\hat{\pi}$ is estimated percentage of population belonging to the trajectory group
P is the percentage of the sample assigned to the trajectory group by the maximum posterior probability assignment rule
$AvePP$ is the average posterior probability of assignment
OCC is odds of correct classification; $OCC = \frac{AvePP/(1-AvePP)}{\hat{\pi}/(1-\hat{\pi})}$

Supplemental Digital Content 5. Depression and cognitive trajectories, three years of follow-up

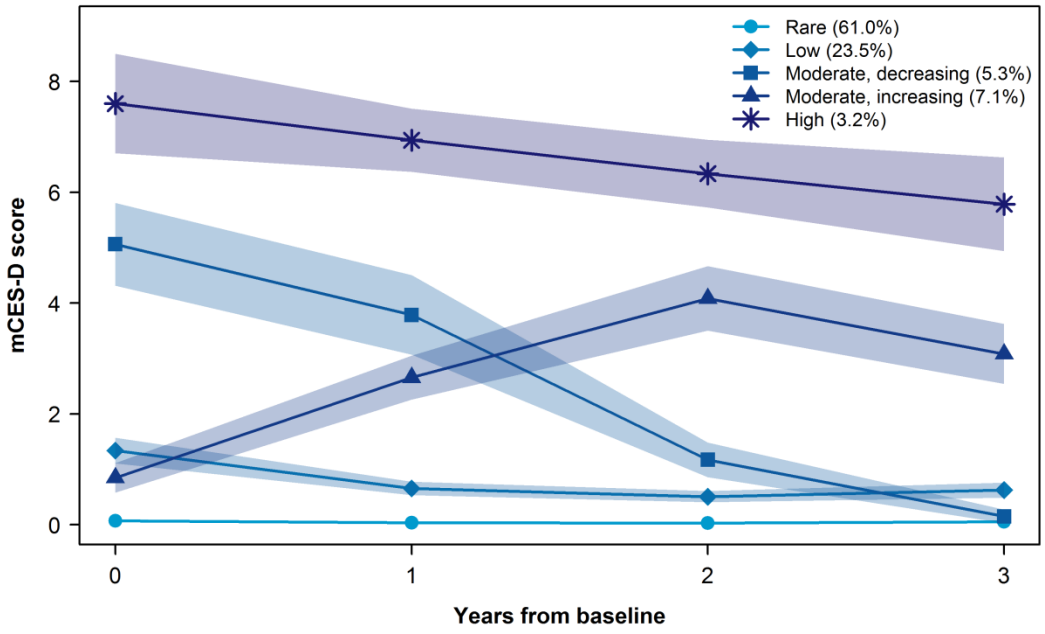

FIGURE 1. Trajectories of depressive symptoms, with 95% confidence bands, three years of follow-up.
Note: mCES-D: modified Center for Epidemiologic Studies-Depression scale.

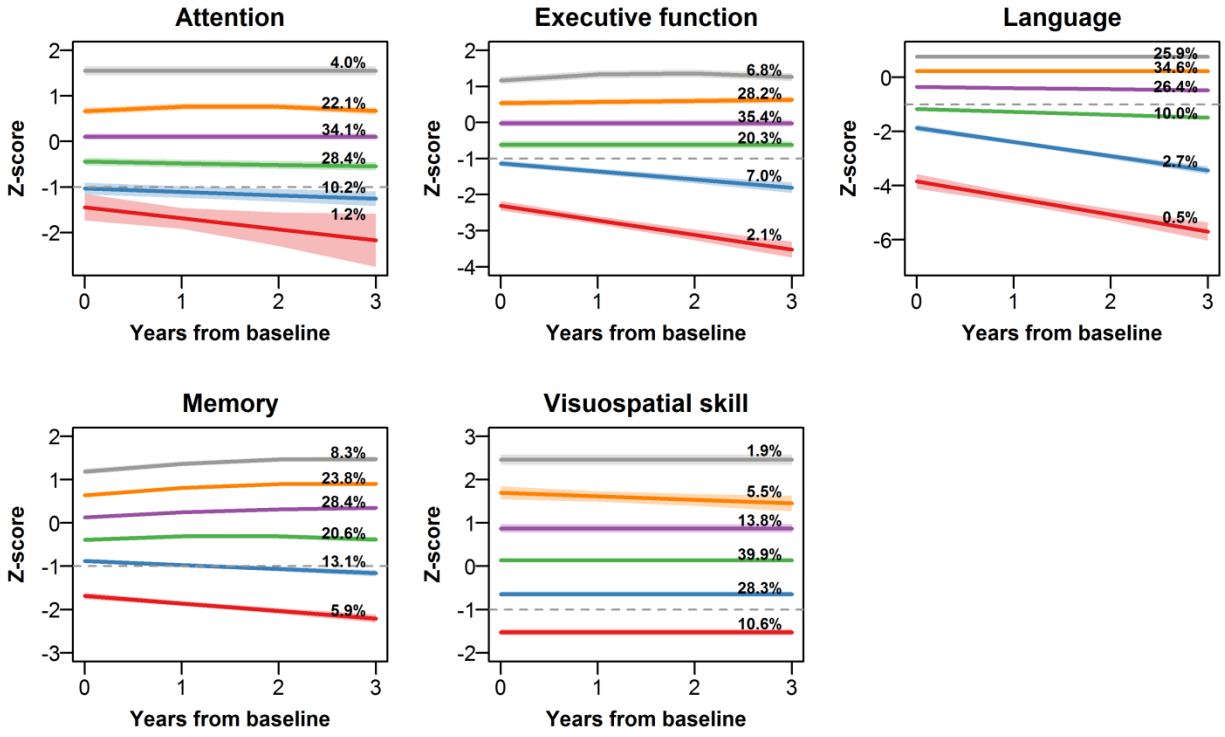

FIGURE 2. Trajectories of cognitive functioning, with 95% confidence bands, three years of follow-up.
Note: Dotted gray lines indicate z-score of -1. Trajectories were designated as persistently low if they had a z-score of -1 or below for the majority of the study period. This included the two lowest trajectories for attention and executive function, the three lowest trajectories for language, and the lowest trajectory for memory and visuospatial skill.

Supplemental Digital Content 5. Depression and cognitive trajectories, three years of follow-up

Table 1. Rank-ordering of depression trajectory groups by proportion with persistently low cognition; three years of follow-up

Rank	Attention	Executive	Language	Memory	Visuospatial
1	Moderate, incr (24%)	Moderate, incr (21%)	Moderate, incr (24%)	Moderate, incr (13%)	Moderate, incr (26%)
2	Low (15%); P = 0.0529	High (20%); P = 1.000	Moderate, decr (21%); P = 0.6367	High (10%); P = 0.6296	Moderate, decr (22%); P = 0.5365
3	Moderate, decr (13%); P = 0.0529	Low (12%); P = 0.0780	Low (19%); P = 0.5918	Low (8%); P = 0.2884	High (16%); P = 0.3517
4	*High (9%); P = 0.0498	Moderate, decr (9%); P = 0.0780	High (17%); P = 0.5918	*Rare (5%); P = 0.0019	*Low (11%); P = 0.0002
5	*Rare (7%); P < 0.0001	*Rare (6%); P < 0.0001	*Rare (8%); P < 0.0001	*Moderate, decr (3%); P = 0.0163	*Rare (6%); P < 0.0001

Notes: incr: increasing; decr: decreasing

* Significant difference (P < 0.05) from the Rank 1 group; one-sided Fisher's exact test of difference in proportions.

P-values within each cognitive domain were adjusted using Holm's correction.

Supplemental Digital Content 5. Depression and cognitive trajectories, three years of follow-up

Table 2. Logistic regression odds ratios for persistently low cognitive trajectory membership, three years of follow-up

Parameter	Cognitive domain					
	Attention[a]		Executive function		Language	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Intercept	0.08 (0.06, 0.10)***	0.01 (0.01, 0.02)***	0.06 (0.05, 0.08)***	0.01 (0.00, 0.02)***	0.09 (0.07, 0.11)***	0.01 (0.00, 0.02)***
Depression group						
Rare	---	---	---	---	---	---
Low	2.26 (1.61, 3.16)***	1.95 (1.36, 2.80)***	2.26 (1.55, 3.27)***	1.88 (1.26, 2.78)**	2.62 (1.91, 3.58)***	2.11 (1.50, 2.95)***
Moderate, decreasing	1.84 (0.97, 3.25)*	1.85 (0.94, 3.42)	1.68 (0.79, 3.21)	1.54 (0.71, 3.07)	3.05 (1.81, 4.97)***	2.64 (1.49, 4.56)***
Moderate, increasing	4.01 (2.46, 6.39)***	3.69 (2.17, 6.17)***	4.20 (2.51, 6.84)***	3.75 (2.16, 6.37)***	3.63 (2.25, 5.72)***	3.18 (1.88, 5.29)***
High	1.29 (0.49, 2.84)	1.08 (0.39, 2.56)	3.95 (1.93, 7.52)***	3.63 (1.68, 7.37)***	2.25 (1.05, 4.40)*	1.97 (0.87, 4.10)
Age group at baseline						
65-74		---		---		---
74-85		3.31 (2.03, 5.65)***		5.01 (2.78, 9.83)***		6.99 (4.06, 12.97)***
85+		11.85 (7.22, 20.38)***		15.31 (8.43, 30.27)***		21.21 (12.16, 39.87)***
Education						
High school or less		1.66 (1.18, 2.38)**		1.47 (1.02, 2.16)*		1.63 (1.18, 2.28)**
More than high school		---		---		---
Sex						
Male		1.47 (1.06, 2.03)*		1.20 (0.84, 1.70)		0.95 (0.70, 1.30)
Female		---		---		---
Race						
White		---		---		---
Non-white		4.77 (2.80, 7.99)***		3.71 (2.08, 6.45)***		5.06 (2.99, 8.49)***

Notes: Significance codes for Wald test of the null hypothesis that the corresponding regression coefficient is equal to zero: *** P < 0.001; ** P < 0.01; * P < 0.05

--- denotes reference level.

Supplemental Digital Content 5. Depression and cognitive trajectories, three years of follow-up

Table 2. Logistic regression odds ratios for persistently low cognitive trajectory membership, three years of follow-up

Parameter	Cognitive domain			
	Memory		Visuospatial skill	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Intercept	0.05 (0.04, 0.06)***	0.00 (0.00, 0.01)***	0.06 (0.05, 0.08)***	0.02 (0.01, 0.03)***
Depression group				
Rare	---	---	---	---
Low	1.91 (1.23, 2.94)**	1.65 (1.04, 2.57)*	1.83 (1.24, 2.68)**	1.52 (1.00, 2.25)*
Moderate, decreasing	0.58 (0.14, 1.59)	0.54 (0.13, 1.53)	4.48 (2.65, 7.37)***	4.17 (2.38, 7.14)***
Moderate, increasing	3.21 (1.70, 5.73)***	2.93 (1.51, 5.40)***	5.47 (3.36, 8.73)***	5.08 (3.03, 8.39)***
High	2.33 (0.87, 5.25)	2.26 (0.82, 5.36)	2.94 (1.31, 5.95)**	2.65 (1.14, 5.57)*
Age group at baseline				
65-74		---		---
74-85		8.59 (3.76, 24.78)***		2.69 (1.71, 4.37)***
85+		22.08 (9.58, 64.09)***		5.81 (3.59, 9.68)***
Education				
High school or less		1.17 (0.77, 1.80)		1.43 (1.01, 2.06)*
More than high school		---		---
Sex				
Male		1.34 (0.90, 2.00)		0.99 (0.69, 1.39)
Female		---		---
Race				
White		---		---
Non-white		1.73 (0.76, 3.52)		6.11 (3.67, 10.02)***

Notes: Significance codes for Wald test of the null hypothesis that the corresponding regression coefficient is equal to zero: *** P < 0.001; ** P < 0.01; * P < 0.05

--- denotes reference level.

Supplemental Digital Content 5. Depression and cognitive trajectories, three years of follow-up

Table 2. Model diagnostics, three years of follow-up

Model	Group	$\hat{\pi}$	P	$AvePP$	OCC
Depression	1 Rare	60.96	64.21	0.9210	7.47
	2 Low	23.45	21.54	0.8234	15.22
	3 Moderate, decreasing	5.34	5.56	0.7642	57.47
	4 Moderate, increasing	7.05	5.81	0.8818	98.35
	5 High	3.20	2.88	0.8967	262.61
Attention	1 Low	1.23	0.76	0.8028	327.97
	2	10.24	9.71	0.7647	28.47
	3	28.37	29.52	0.7597	7.98
	4	34.12	34.88	0.7683	6.40
	5	22.09	21.54	0.8281	16.99
	6 High	3.96	3.59	0.8875	191.52
Executive	1 Low	2.14	2.17	0.9139	485.66
	2	7.04	6.57	0.8490	74.28
	3	20.33	19.67	0.8014	15.81
	4	35.41	37.11	0.7924	6.96
	5	28.25	28.51	0.8314	12.52
	6 High	6.83	5.97	0.8953	116.70
Language	1 Low	0.52	0.51	0.9812	10069.21
	2	2.66	2.58	0.9280	470.99
	3	9.99	9.40	0.9090	90.01
	4	26.40	26.90	0.8475	15.50
	5	34.58	35.44	0.8014	7.63
	6 High	25.86	25.18	0.8655	18.45
Memory	1 Low	5.92	5.92	0.9118	164.39
	2	13.13	13.09	0.8471	36.68
	3	20.58	20.22	0.8248	18.17
	4	28.36	29.42	0.8248	11.89
	5	23.77	23.51	0.8630	20.21
	6 High	8.25	7.84	0.8832	84.11
Visuospatial	1 Low	10.59	9.30	0.8573	50.73
	2	28.30	26.04	0.8172	11.32
	3	39.93	46.16	0.7716	5.08
	4	13.82	11.83	0.8129	27.09
	5	5.59	4.95	0.8325	85.57
	6 High	1.87	1.72	0.9028	486.25

Notes:

$\hat{\pi}$ is estimated percentage of population belonging to the trajectory group
P is the percentage of the sample assigned to the trajectory group by the maximum posterior probability assignment rule
$AvePP$ is the average posterior probability of assignment
OCC is odds of correct classification; $OCC = \frac{AvePP/(1-AvePP)}{\hat{\pi}/(1-\hat{\pi})}$