Longitudinal associations of affective symptoms with midlife cognitive function: evidence from a British birth cohort

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ABSTRACT

Background: Affective disorders are associated with poorer cognition in older adults; however, whether this association can already be observed in midlife remains unclear.

Aims: This study investigated effects of affective symptoms over a period of 30 years on midlife cognitive function. First, we explored whether timing (sensitive period) or persistence (accumulation) of affective symptoms predicted cognitive function. Second, we tested how different longitudinal trajectories of affective symptoms were associated with cognitive function.

Method: The study used data from the National Child Development Study. Memory, verbal fluency, information processing speed and accuracy were measured at age 50. Affective symptoms were measured at ages 23, 33, 42, and 50 and used to derive longitudinal trajectories. A structured modelling approach compared a set of nested models to test accumulation versus sensitive period hypotheses. Linear regressions and structural equation modelling were used to test for longitudinal associations of affective symptoms with cognitive function.

Results: Accumulation of affective symptoms was found to be the best fit for the data, with persistent affective symptoms being associated with poorer immediate memory (B=-0.07, SE=0.03, *P*=.01), delayed memory (B=-0.13, SE=0.04, *P*<.001), and information processing accuracy (B=0.18, SE=0.08, *P*=.03), but not with information processing speed (B=3.15, SE=1.89, *P*=.10). Longitudinal trajectories of repeated affective symptoms were associated with poorer memory, verbal fluency, and information processing accuracy.

Conclusions: Persistent affective symptoms can affect cognitive function in midlife. Effective management of affective disorders to prevent recurrence may reduce risk of poor cognitive outcomes and promote healthy cognitive ageing.

Declaration of interest: None

Affective disorders, such as depression and anxiety, have been associated with impaired cognition, dementia and accelerated cognitive decline in late adulthood (1–3). However, there are significant gaps in our understanding of this association. The majority of studies have been conducted in older adults, usually over the age of 60 and have only considered this association in the context of short follow-up periods (<10 years) (4). Therefore, it is unclear how affective symptoms are associated with cognitive function over time. There is some evidence that risk of dementia increases with the number of affective episodes experienced over the life-course; whereby rate of dementia is estimated to increase by around 13% with each additional depressive episode (5). Additionally, evidence shows that individuals with persistent depressive symptoms may be at greater risk for subsequent cognitive deficits than individuals with fewer episodes (4). Another line of evidence suggests that timing, rather than frequency, of affective symptoms can be an important predictor of cognitive outcomes. For example, depressive symptoms in older age only were shown to be associated with increased risk of dementia (6). However, there is limited inconsistent evidence for associations between affective disorders and cognitive function before old age in two studies using data from the MRC National Survey of Health and Development (NSHD). The first study (7) found no associations of affective symptoms measured between ages 13 to 53 with objectively measured cognitive outcomes at age 60-64, whereas the most recent study reported that persistent case-level affective symptoms were associated with poorer cognitive state, verbal memory, and letter search speed and accuracy at age 69 (8). The current study tested for associations of affective symptoms across adulthood (ages 23, 33, 42 and 50) with aspects of cognitive function at age 50. Specifically, two complementary advanced statistical approaches were employed. First, a structured modelling approach comparing a set of nested models was used to investigate whether accumulation or timing of case-level affective symptoms can predict midlife cognition. Second, a latent growth mixture modelling approach

was employed to derive longitudinal trajectories of affective symptoms and to examine how different longitudinal trajectories of affective symptoms were associated with midlife cognition.

METHOD

Participants

Participants were from the National Child Development Study (NCDS), a population representative sample of 18,558 people born during one week of 1958 in England, Scotland and Wales (i.e., British 1958 birth cohort). This sample comprised 98.2% of total births that week. Data were subsequently collected from participants at ages 7, 11, 16, 23, 33, 42, 46, and 50 years. Further information about the study sample, respondent profiles, and data collection methods are described in depth by Power & Elliott (2006) (9). Data are available from the UK Data Service (10–14). Cohort members gave writted informed consent to participate. Ethical approval for the data collection in 2008 was provided by London MREC (REC reference: 08/H0718/29). Ethical approval for the present study was also provided by the University of Sussex (Reference number: ER/AJ316/1).

Detailed information about the sample analysed in the present study is presented in Supplementary Material 1A; Supplementary Figure 1; Supplementary Table 1. There were 9790 people who participated in 2008 data collection (at age 50). A total of 9385 people of this sample completed the cognitive tests at this time point (95.86%). Of the 9385 participants who completed the cognitive tests at age 50, 4625 had complete information for all predictors and covariates (49.28% of those with cognitive measures).

Measures

Cognitive function

Cognitive measures collected at age 50 were verbal memory, verbal fluency, information processing speed and accuracy (15). Memory was assessed using a word-recall test with immediate and delayed components. Verbal fluency was assessed using an animal naming task, in which participants named as many animals as possible in a 1-minute period.

Information processing was assessed using a letter cancellation task. In this task, cohort members crossed as many target letters as possible from a grid of letters in a 1 minute period. This task was split into two scores. The total number of letters scanned represented information processing speed, and the number of target letters missed up to the final letter searched represented information processing accuracy. Accuracy was negatively scored, so higher scores represent poorer performance.

Affective symptoms

Affective symptoms were assessed using the Malaise Inventory Scale, administered at ages 23, 33, 42, and 50 (Supplementary Table 2). This is a measure of psychological distress and comprises 24 self-completion items, which combine to assess levels of emotional disturbance and associated somatic symptoms. The total number of questions answered 'yes' was summed, creating a sum score of affective symptoms out of 24. This score was dichotomised using a standard cut-off threshold score of 7 out of 24 to represent 'case-level' affective symptoms, indicating clinically relevant affective symptoms (16–18). At age 50, a short form of the Malaise Inventory Scale was administered, comprising 9 items. For this time-point, a recommended cut-off score of 3 was used to categorise case-level affective symptoms (19).

As the short form of the Malaise Inventory Scale was used at age 50, the 9 items from this short form were extracted from the longer forms used at ages 23, 33, and 42, in order to make malaise scores over time more comparable to be used for modelling longitudinal trajectories (see Supplementary Table 2 for the information on the included items).

Covariates

Based on previous research, the following factors were included as potential confounders: sex, childhood cognition (20), childhood emotional adjustment (21), childhood

socio-economic position (22), adult socio-economic position (23), and education (24). Childhood cognition was assessed at age 11, using a general ability test administered at the child's school. Childhood emotional adjustment assessed at age 11 using the Bristol Social Adjustment Guides (BSAG) (25). This questionnaire was completed by teachers and is designed to assess behaviour that may be indicative of maladjustment and emotional disturbance. A measure of household socio-economic position at age 11 was derived using guidelines from the Centre for Longitudinal Studies (CLS) (26), based on measures of father's occupation, mother's occupation, and household tenure. Highest educational attainment was derived by combining education data from 1991, 2000, 2004, and 2008 to ascertain the highest academic qualification the cohort member had achieved by age 50. Adult socioeconomic position was based on occupation, with three categories (working, intermediate and middle class). Additional information about these covariates are included in Supplementary Material 1B.

Analytical procedure

First, a structured modelling approach was used to compare a set of nested models corresponding to accumulation and sensitive period hypotheses to a saturated model including all main effects and all possible interactions (8,27,28). The sensitive period model included three measures indicating whether an individual experienced case-level affective symptoms at three time windows across the life-course: early adulthood (age 23); middle adulthood (ages 33 and/or 42); midlife (age 50). The accumulation model included a measure of the sum of the number of time-points (of the three time windows described above) that each individual experienced case-level affective symptoms. The saturated model was also compared with a 'null' model that assumed no effect of affective symptoms on midlife cognition. Partial F tests were used to compare each hypothesis to the fully saturated model.

Where multiple *P* values were > .05, the model with the highest *P* value and lowest F statistic were selected as the best fit for the data. This analysis was conducted in STATA V14.2.

Four variables with case-level affective symptoms were summed up to create a variable for accumulation of adult affective symptoms (ranging from 0 to 4). Linear regression models were fitted to test for associations of accumulation of adult affective symptoms and cognitive function at age 50. For these analyses, four models were fitted: unadjusted (Model 1); adjusted for sex only (Model 2); additionally adjusted for child cognition, emotional disturbance and socioeconomic position (Model 3); and additionally adjusted for highest educational attainment, and adult socioeconomic position (Model 4). This analysis was conducted in R V3.5.1.

To account for missing data, multiple imputation analysis was conducted on the sample with cognitive data, resulting in the imputed dataset for 9385 participants. All analyses described above were re-run using imputed variables for the key predictors. Multiple imputation was conducted in R using the MICE package (29,30). Twenty imputations were conducted using data across 7 sweeps over the life course. This multiple imputation approach includes a large number of covariates and auxiliary variables in the models, which maximises the plausibility of the missing at random (MAR) assumption, and limits possibility of missing not at random (MNAR) data (31). These multiple imputation techniques have been used extensively to address missing data in the National Child Development Study (32–34). Technical details of the multiple imputation process are reported in Supplementary Material 1C.

Second, a confirmatory factor analysis was conducted to generate latent factor scores of malaise symptoms at each time-point (see Supplementary Table 3 for details about model fit). Linear mixed models were then used to examine malaise trajectories over time, using

factor scores from each time-point. Linear and quadratic models were fitted and compared and the model with the best fit according to the Akaike information criterion (AIC) and Bayesian information criterion (BIC) was selected for subsequent analyses. Next, growth mixture models (GMM) were fit to the data to identify trajectory classes. Models with a 2-class, 3-class, 4-class, and 5-class solution were fitted and compared using AIC, BIC, and the Lo-Mendel-Rubin Adjusted likelihood ratio test (Lo-Mendel-Rubin Adjusted LRT). Once longitudinal trajectories were identified using GMM, a structural equation model was used to investigate whether class membership predicted cognitive outcomes at age 50, after controlling for key covariates. One-step estimation approaches have been criticised in recent years on the basis that including distal outcomes into the measurement model in one step may lead to an unintended and problematic circular relationship in which the classes from the trajectory modelling are determined in part by the distal outcome which they are meant to be predicting (35–37). This analysis was therefore conducted in a step-wise fashion to avoid drawbacks associated with one-step estimation methods. Missing data was dealt with using full information maximum likelihood estimation (FIML). Analysis was conducted in Mplus V.8. According to Mplus defaults, variances across classes were held equal.

RESULTS

Missing data and descriptive statistics

Of the sample who completed the cognitive tests at age 50 (n = 9,385), participants with complete information (n = 4625) were compared to the sample with missing data (n = 4,760). Results revealed that participants with missing data did not differ by sex ($P = .54$). However, participants with missing data had significantly lower childhood cognitive scores ($P < .001$), higher levels of childhood psychological maladjustment ($P < .001$), lower level of education ($P < .001$), lower SEP in childhood ($P < .001$) and adulthood ($P < .001$), more case-level affective symptoms at ages 23 ($P < .001$), 33 ($P < .001$), 42 ($P < .001$), and 50 ($P < .001$).

To account for missing data, multiple imputation analysis was conducted resulting in the imputed dataset for the sample of 9385 participants. Socio-demographic information for the sample with complete information for cognitive outcomes, main predictors and covariates (n = 4,625; 50.5% women) and the imputed sample (n = 9,385; 50.8% women) is presented in Supplementary Table 4.

Accumulation of affective symptoms and midlife cognitive function

Results from the analysis using a structured modelling approach revealed that the accumulation model was the best fit for the data. For this model, there were no significant differences observed from the saturated model for any of the cognitive outcomes (Table 1). This was particularly prominent for memory outcomes (immediate memory: F = 1.81; $P = .09$; delayed memory: F = 1.39, $P = .22$), for which none of the other models (i.e., 'no effect' model, or sensitive period models) fit the data well ($P < .05$ for all other models).

Fully adjusted regression models revealed significant linear associations, whereby as the number of case-level affective symptoms increased over the life-course, midlife

immediate memory (B = -0.07, SE = 0.03, *P* = .01), delayed memory (B = -0.13, SE = 0.04, *P* < .001) and information processing accuracy (B = 0.18, SE = 0.08, *P* = .03) decreased (Table 2). No effects were apparent for verbal fluency or information processing speed in fully adjusted models. Results of the analyses using imputed data were similar (Supplementary Tables 5 & 6).

Trajectories of affective symptoms and midlife cognitive function

Linear mixed models revealed that a linear trajectory (AIC = 9020.291; BIC=9065.883), rather than a quadratic trajectory (AIC = 9021.989; BIC = 9075.18), fitted adult affective symptom latent variables scores better and were therefore used to identify trajectory classes. When comparing models with a 2-class, 3-class, 4-class, and 5-class solution, the 5-class solution was found to be the best fit for the data (Supplementary Table 7). Therefore, five different trajectories of adult affective symptoms were identified (Figure 1): 1) no affective symptoms (51.4%); 2) consistent mild/moderate affective symptoms (28.3%); 3) initially low and increasing to high affective symptoms (5.4%); 4) initially high and persistently increasing affective symptoms (7.3%); 5) initially high and decreasing to low affective symptoms (7.5%).

A fully adjusted structural equation model revealed that class membership predicted cognitive function at age 50 (Table 3). Belonging to a trajectory with initially high and increasing affective symptoms was associated with lower midlife immediate memory (B = -0.25, SE = 0.07, *P* < .001), delayed memory (B = -0.23, SE = 0.09, *P* = .006), and verbal fluency scores (B = -0.79, SE = 0.30, *P* = .01), as compared to the trajectory with no affective symptoms. Belonging to a trajectory with initially low and increasing affective symptoms was associated with significantly lower midlife immediate (B = -0.16, SE = 0.07, *P* = .03) and delayed memory (B = -0.23, SE = 0.09, *P* = .007), and information processing accuracy

(B = 0.50 SE = 0.21, *P* = .02). Belonging to a trajectory with initially high and decreasing affective symptoms was associated with poorer immediate memory (B = -0.15, SE = 0.07, *P* = .04). Finally, belonging to a trajectory with consistently mild/moderate affective symptoms was associated with poorer immediate memory (B = -0.09, SE = 0.04, *P* = .03). No associations were found for information processing speed and accuracy. Unadjusted and partially adjusted models are reported in Supplementary Table 8.

DISCUSSION

The present study found that accumulation of affective symptoms across three decades in adulthood (from age 23 through age 50) was associated with poorer cognitive function in midlife: a greater number of case-level affective symptoms was linearly associated with poorer memory and information processing accuracy in midlife. Analysis of longitudinal trajectories of affective symptoms showed that belonging to a trajectory with high and increasing level of affective symptoms across adulthood was significantly associated with poorer verbal memory and fluency in midlife. Belonging to a trajectory with low and increasing affective symptoms was associated with lower verbal memory and information processing accuracy scores at age 50. Belonging to a trajectory with initially high and decreasing affective symptoms or a trajectory with consistently mild/moderate affective symptoms was associated with lower immediate memory scores in midlife.

These findings suggest that associations between affective symptoms and cognitive function may be evident even by midlife, an earlier stage in life course than considered by many previous studies (38). It is now believed that for those experiencing dementia in later life, there is a long pre-clinical period before cognitive impairment becomes evident (39). It is possible that older participants may have already developed cerebral pathology by the time of baseline assessment, even if they are not yet displaying symptoms of cognitive impairment. It is plausible that associations between affective disorders and cognition in older adults may be the result of reverse causality from subtle cognitive changes short of dementia. For this reason, it is important to explore this association earlier in the life course and in a population who have not developed dementia pathology. Midlife may prove a better age to guarantee forward temporal associations between risk factors, such as affective disorders, and subsequent cognitive impairments (40,41). Additionally, if associations between affective disorders and cognitive function are already apparent by midlife, this may be an important

window for early intervention (42). These results advance previous findings, demonstrating that effects may be apparent even many years prior to development of any substantial cognitive deficits and also may be apparent even if no dementia develops. This observation has value in clarifying the temporal order of this association and minimises the issue of reverse causality inherent in studies focussing exclusively on older adults.

These results also suggest that accumulation of multiple, repeated affective episodes can predict poorer cognitive function in midlife. While the late-life trajectory of cognitive decline in this current cohort cannot be modelled, the findings add to previous research which reports a monotonic increase in dementia risk with each additional affective episode, by demonstrating that the pattern of accumulating affective episodes is important in predicting midlife cognitive function in a general population (5). Singh-Manoux et al., (2017) (6) investigated depression trajectories over a period of 28 years for a population of individuals who developed dementia up to 2015 (participants aged 65-85 in 2015), and those who remained cognitively healthy, and found an accelerated growth in depressive symptoms during the decade before dementia diagnosis. Our results complement findings from recent studies using data from the NSHD cohort born in 1946, which reported that recurrent case-level affective symptoms were associated with poorer cognitive state (as measured with ACE), verbal memory, and search speed and accuracy in early old age (8), but not with objectively measured cognitive outcomes in late mid-adulthood (7). Because prevalence of depression and psychological distress has been increasing in the UK over the past few decades (43) it is possible that the effect of mental health problems on cognitive ageing can manifest earlier (by midlife) in younger cohorts, such as NCDS born in 1958.

Taken together, these results suggest that verbal memory is affected by the number of affective episodes experienced and by life-course trajectories with experience of affective symptoms. Information processing accuracy scores are also affected by the number of

affective episodes experienced and by a life-course pattern of initially low and increasing affective episodes. Verbal fluency scores are affected by a pattern of initially high and increasing accumulation affective episodes. Strongest effects of affective symptoms were therefore observed on midlife verbal memory, verbal fluency, and information processing accuracy, while information processing speed was consistently unaffected by affective symptoms. Several studies have found untreated depressive symptoms persistent over the entire life-course may lead to cumulative hippocampal volume loss (44); a key structure associated with verbal memory (45). This could potentially explain why effects of affective problems observed were on memory. It is possible that midlife may be too early for effects to be observed in information processing speed, and that effects of affective disorders may become apparent on this cognitive domain as individuals transition from midlife into older adulthood.

Strengths & limitations

The key strength of the study is a large nationally-representative sample with a long follow-up period (three decades). Moreover, multiple cognitive domains were assessed in midlife, and prospective assessments of affective symptoms using the same instrument from early adulthood through midlife were available for the analyses. However, results should be interpreted with consideration of a number of limitations. Cognitive function was only assessed at one time-point in adulthood (age 50) in the NCDS, and therefore it was not possible to investigate the effects of affective problems on cognitive change over time. Cognitive assessments at this time point were also limited in breadth; single, rather than multiple, cognitive tests were used for each domain (e.g., immediate and delayed memory, verbal fluency, information processing speed and accuracy); and functions in other cognitive domains (e.g., inhibitory processes, attention) known to be affected in people with affective disorders, were not assessed in NCDS. Additionally, although cognitive ability in childhood

was controlled for, this does not completely eliminate the possibility of reverse causality, whereby the association may operate in the opposite direction with lower cognitive function leading to higher affective symptoms across the adult life course (46). We were also unable to take the effect of medications into account, which may play an important role in this association.

Missing data are inevitable in the long-running cohorts such as NCDS, and indeed there was a lot of missing data that could potentially lead to biased estimates. We have dealt with this by imputing missing data using a multiple imputation approach. The benefits of the multiple imputation approach are that missing data can be dealt with prior to analysis (47) using a large amount of additional information from other variables available in the dataset. Specifically, this allows extra information that isn't included in our main models (such as birthweight, parental education etc.) to be used as auxiliary variables to aid with imputing the missing data. This maximises plausibility of the missing at random assumption (31). Notably, these results were substantially identical to the ones obtained using a complete dataset and also were consistent and complementary with the analysis using FIML to account for missing data.

Plausible mechanisms

Both biological and socio-behavioural pathways have been proposed to explain the link between affective disorders and cognitive function. Specifically, hypothalamic pituitary adrenal (HPA) axis function has been proposed as one potential association linking affective problems and subsequent cognitive dysfunction (48). Affective symptoms and chronic stress may give rise to HPA axis activity and lead to increased glucocorticoid production, which in turn may lead to hippocampal atrophy and cognitive dysfunction. Animal studies exploring

response to stress have proposed that conditions of high stress and exogenous glucocorticoids can lead to cognitive impairment (49).

An additional potential pathway is cardio-metabolic risk factors. Affective problems and psychological distress across the life course have been associated with higher cardio-metabolic risk (50). Additionally, cardio-metabolic disorders have also been linked with Alzheimer's disease and cognitive decline (51). Related to this, physical health and health behaviours (52), including physical activity and exercise may also play an important role in the association between affective problems and cognitive ageing. Beyond this, chronic inflammation plays a role in both depression and dementia, and as such may act as an important pathway between the two. Moreover, Aβ deposition is known to play an important role in the pathogenesis of dementia (53) and has additionally been associated with major depression (54). Educational attainment (55) and socioeconomic status (23) may also play a role in the association between affective problems and cognitive ageing. It is more plausible that the association between affective problems and cognitive ageing is underpinned by a complex interaction of biological and socio-behavioural mechanisms, rather than by one single aetiological determinant (2).

Conclusions

In conclusion, the present study suggests that individuals with affective symptoms in adulthood are at increased risk for poorer cognitive outcomes even by midlife. This finding has potential implications for prevention efforts, as the asymptomatic phase before development of dementia pathology may be an important window to target for early intervention (42). Additionally, in the absence of pathological change, one further important avenue of research is to investigate whether effective treatment and management of affective problems early in life can reduce risk of poor cognitive outcomes and promote healthy

cognitive ageing. Future research should focus on determining the biological and socio-behavioural mechanisms that underpin the association between affective and cognitive factors. All interventions to promote and sustain healthy ageing are important to health policy development in an ageing population.

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Figure legend

Figure 1. Life-course trajectories of affective symptoms (estimated from 5-class growth mixture model)

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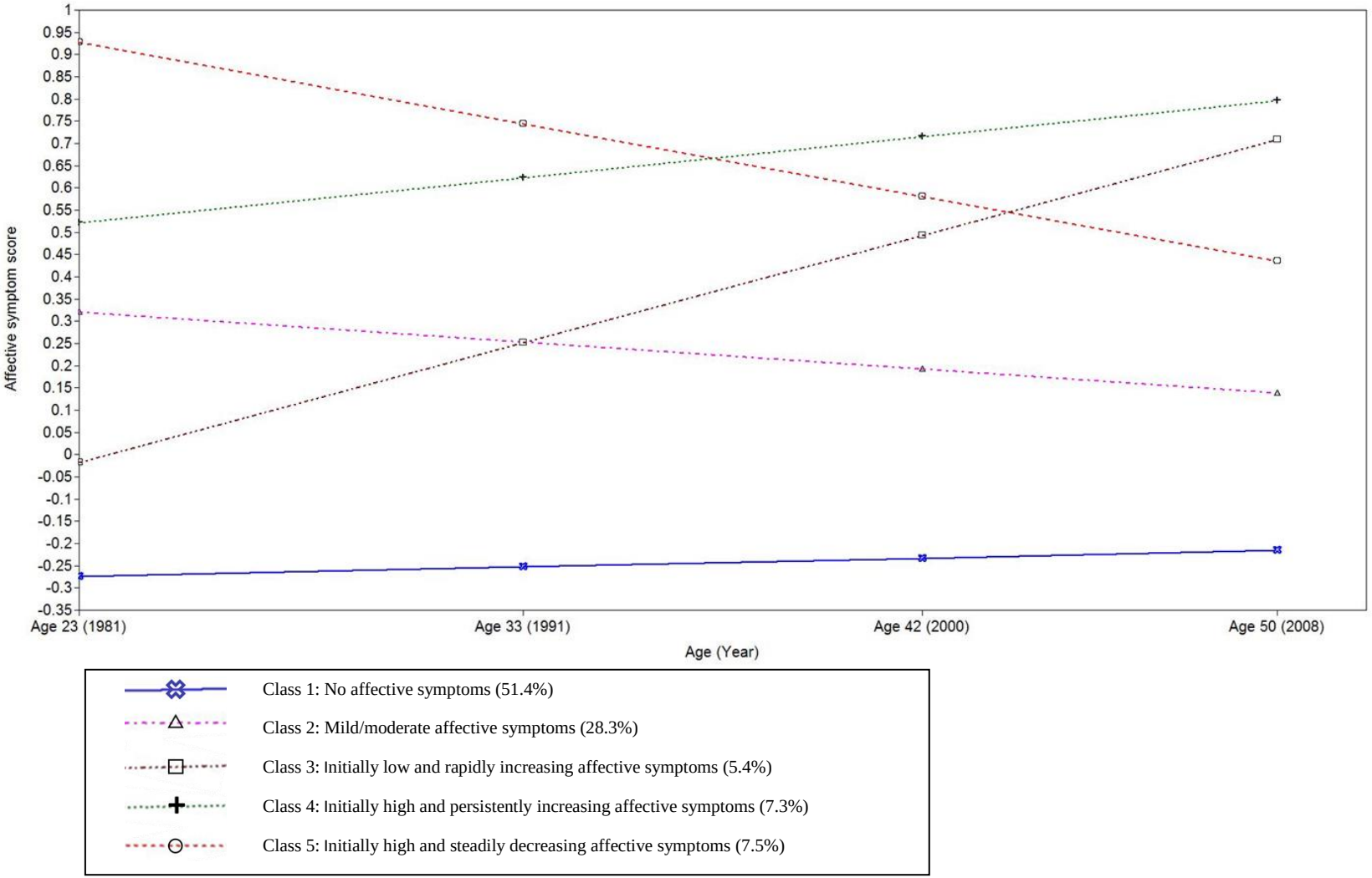

Table 1. A structured modelling approach comparing life-course hypotheses of the association between lifetime affective symptoms and midlife cognitive function (no effect hypothesis, accumulation hypothesis, sensitive period hypothesis).

	Immediate Memory		**Delayed Memory**		**Verbal Fluency**		**Information Processing Speed**		**Accuracy**	
Models	**F**	***P***	**F**	***P***	**F**	***P***	**F**	***P***	**F**	***P***
Saturated model	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No effect	4.15	.0001	5.1	<.0001	2.97	.004	**1.24**	**.28**	2.58	.01
Accumulation	**1.81**[a]	**.09**	**1.39**	**.22**	**0.56**	**.76**	**0.88**	**.51**	**0.66**	**.68**
Sensitive period 1 (age 23)	2.97	.01	3.46	.002	1.86	.08	**1.15**	**.33**	2.19	.04
Sensitive period 2 (age 33-42)	3.51	.002	3.89	.001	**1.35**	**.23**	**1.14**	**.34**	**1.8**	**.10**
Sensitive period 3 (age 50)	3.14	.01	3.23	.004	2.46	.02	**1.12**	**.33**	**1.4**	**.21**
Best fitting model	**Accumulation**		**Accumulation**		**Accumulation**		**Accumulation**		**Accumulation**	

[a] Bold values represent estimates which are non-significant at the $P < .05$ level. Non-significant *P* values represent a good fit for the data. The hypothesis with the smallest F statistic is taken as the hypothesis with the best fit for the data.

Table 2. Life-course accumulation of affective symptoms and cognitive function at age 50

Cognitive Functions	Model 1[a]			Model 2			Model 3			Model 4			Model 5		
	b	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***
Immediate Memory	**-0.14**[b]	**0.03**	**<.001**	**-0.17**	**0.03**	**<.001**	**-0.09**	**0.03**	**.003**	**-0.07**	**0.03**	**.01**	**-0.08**	**0.03**	**.01**
Delayed Memory	**-0.2**	**0.04**	**<.001**	**-0.25**	**0.04**	**<.001**	**-0.14**	**0.04**	**<.001**	**-0.13**	**0.04**	**<.001**	**-0.13**	**0.04**	**<.001**
Verbal Fluency	**-0.51**	**0.13**	**<.001**	**-0.52**	**0.13**	**<.001**	-0.13	0.13	.31	-0.06	0.12	.61	-0.07	0.12	.59
Letter Cancellation - Speed	**3.82**	**1.87**	**.04**	1.45	1.88	.44	2.78	1.89	.14	3.15	1.89	.10	3.25	1.89	.09
Letter Cancellation - Accuracy	**0.32**	**0.08**	**<.001**	**0.3**	**0.08**	**<.001**	**0.17**	**0.08**	**.04**	**0.18**	**0.08**	**.03**	**0.19**	**0.08**	**.02**

[a] Results are presented for model 1 (unadjusted estimates), model 2 (estimates adjusted for sex), model 3 (estimates adjusted for sex, childhood socioeconomic status, childhood emotional adjustment, and childhood cognition), and model 4 (estimates adjusted for sex, childhood socioeconomic status, childhood emotional adjustment, childhood cognition, adult socioeconomic status, and highest educational attainment at age 50). Model 5 is a sensitivity analysis, using all the covariates in Model 4, but excluding childhood emotional adjustment.

[b] Bold values represent estimates significant at the $P < .05$ level. Estimates are based on sample with complete data for all key factors and covariates (N = 4,625).

Table 3. Fully adjusted structural equation model output for class membership predicting midlife cognitive function

Predictors	Immediate memory			Delayed memory			Verbal fluency			Processing Speed			Accuracy		
	b	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**
Affective symptom trajectories: No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**-0.09**	**0.04**	**.03**[a]	0.03	0.05	.58	-0.32	0.18	.08	0.96	2.66	.72	0.10	0.12	.41
Initially low and rapidly increasing affective symptoms	**-0.16**	**0.07**	**.03**	**-0.23**	**0.09**	**.007**	-0.23	0.30	.45	7.02	4.50	.12	**0.50**	**0.21**	**.02**
Initially high and persistently increasing affective symptoms	**-0.25**	**0.07**	**<.001**	**-0.23**	**0.09**	**.006**	**-0.79**	**0.30**	**.01**	-2.80	4.48	.53	0.17	0.21	.42
Initially high and steadily decreasing affective symptoms	**-0.15**	**0.07**	**.04**	-0.17	0.09	.05	-0.59	0.31	.06	3.95	4.69	.40	0.24	0.22	.26
Sex	**0.19**	**0.04**	**<.001**	**0.35**	**0.04**	**<.001**	**-0.33**	**0.16**	**.03**	**23.66**	**2.32**	**<.001**	**0.40**	**0.11**	**<.001**
Childhood affective problems	<.001	0.002	.87	-0.002	0.003	.50	-0.01	0.10	.55	0.05	0.15	.75	**0.02**	**0.01**	**.001**
Childhood cognition	**0.02**	**0.001**	**<.001**	**0.03**	**0.002**	**<.001**	**0.09**	**0.01**	**<.001**	**0.29**	**0.09**	**.001**	**-0.05**	**0.004**	**<.001**
Child socioeconomic position	-0.01	0.02	.60	0.002	0.03	.94	**-0.40**	**0.10**	**<.001**	0.53	1.56	.73	-0.02	0.07	.82
Adult socioeconomic position	**-0.08**	**0.02**	**.001**	**-0.07**	**0.03**	**.02**	**-0.23**	**0.11**	**.03**	**-5.83**	**1.57**	**<.001**	-0.09	0.07	.24
Education	**0.08**	**.009**	**<.001**	**0.11**	**0.01**	**<.001**	**0.37**	**0.04**	**<.001**	**1.96**	**0.58**	**.001**	**0.07**	**0.03**	**.007**

[a] Bold values represent estimates significant at the $P < .05$ level.

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