Effects of affective symptoms in adolescence and adulthood on trajectories of cognitive function from middle to late adulthood

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ABSTRACT

Background: Little is known about the link between affective symptoms and cognitive function across the life course. This study aims to investigate whether affective symptoms in adolescence and adulthood predict trajectories of cognitive function from middle to late-adulthood.

Methods: Data from the MRC National Survey of Health and Development (NSHD), a cohort of 5362 individuals born in mainland UK in 1946, were utilised. Linear mixed models were used to model cognitive trajectories (memory and processing speed) over a three-decade period (from 43 to 69) and to test effects of affective symptoms in adolescence (ages 13-15) and adulthood (ages 36 and 43) on cognitive function at first testing (age 43) and decline in cognitive function (from 43 to 69). Models were adjusted for sex, childhood cognition, childhood socioeconomic position, and education.

Results: A quadratic model best fitted memory and processing speed data. Models revealed that adolescent affective symptoms were associated with lower memory (b=-1.11, SE=0.53, p=.04) and processing speed (b=-18.17, SE=7.53, p=.02) at first cognitive testing, but not with rates of decline from 43 to 69. There were no significant associations between adult affective symptoms and cognitive trajectories.

Limitations: Missing data is a potential limitation of this study. This was dealt with using maximum likelihood estimation and multiple imputation.

Conclusions: Findings suggest that adolescent, but not adult, affective symptoms are important predictors of cognitive function in midlife, but not rate of cognitive decline. This highlights the importance of early intervention to manage mental health in adolescence to protect later cognitive function.

Keywords: Affective symptoms; Cognitive ageing; Longitudinal; Birth Cohort.

INTRODUCTION

Affective symptoms are common during adolescence and adulthood, with one in six adults and adolescents in the UK reporting symptoms of depression and anxiety (McManus, Bebbington, Jenkins, & Brugha, 2016; Patalay & Fitzsimons, 2017). Recent longitudinal studies have confirmed long-lasting effects of affective disorders and symptoms on a wide range of outcomes later in life, including lower educational attainment (Richards & Abbott, 2009), poorer physical and mental health (Colman, Wadsworth, Croudace, & Jones, 2007; Keenan-Miller, Hammen, & Brennan, 2007), and premature mortality (Archer, Kuh, Hotopf, Stafford, & Richards, 2018). Affective symptoms have also been shown to lead to worse cognitive outcomes, including dementia and faster cognitive decline (Da Silva et al., 2013; James et al., 2018; John et al., 2018; Livingston et al., 2017). However, the majority of existing studies have focused only on the link between affective symptoms and cognitive function in late adulthood (John et al., 2018; Singh-Manoux et al., 2010). Therefore, less is known about the effects of affective symptoms in adolescence and early adulthood on cognitive ageing from middle to late adulthood. The period of middle adulthood could be particularly important for prevention of dementia in relation to depression, before dementia pathology has built up to the clinical threshold for a diagnosis (Exalto et al., 2014). For example, previous research has shown that post-menopausal women may be at increased risk of depression, and this transition is also known to be an important period of increased vulnerability to cognitive impairment and decline (Weber et al., 2014). Specifically, research has shown that higher cognitive function from childhood through to midlife is associated with later menopause (Kok et al., 2006; Kuh et al., 2005; Richards et al., 1999) and that later menopause may be associated with better verbal memory (Richards et al., 2018).

Using data from the Medical Research Council National Survey of Health and Development (MRC NSHD), Richards et al (2014) tested six life course profiles of affective

symptoms (from age 13 to 60-64) in relation to cognitive performance at age 60-64 and decline from 53 to 60-64 (Richards et al., 2014). No associations were found between affective symptoms and cognitive outcomes. Additionally, using NSHD data, Xu et al (2013) investigated adolescent mental health and memory function and decline from age 43 to 60-64. They reported that adolescent self-organisation, but not conduct problems or emotional problems, was associated with lower memory scores at age 43, but not decline from age 43 to 60-64 (Xu et al., 2013). It is possible, however, that participants may have still been relatively young for detection of significant cognitive decline in both of these studies. Indeed, recent evidence shows that in the NSHD cohort, rate of decline in verbal memory accelerates after age 60 (Davis et al., 2017). Therefore, the aim of the present study was to extend existing research by testing associations of affective symptoms in adolescence and adulthood with trajectories of verbal memory and information processing speed from middle to late adulthood (from age 43 through age 69).

METHODS

Participants

Participants were from the MRC NSHD, a nationally representative sample of 5362 individuals born in England, Scotland and Wales during one week of 1946. Since birth, the cohort members have been followed up 24 times, most recently in 2015. At age 69, 80% of participants who were currently alive and with a known address in the UK, took part (N=2148). Of the target sample (N=2698) who were eligible but did not take part (N=550), 298 (54%) refused to take part temporarily, 155 (28%) did not respond, 55 (10%) completed postal questionnaire only, 31 (6%) withdrew from the study, and 11 (2%) were unable to give informed consent. Detailed information about participation patterns, respondent profiles and data collection methods have been published elsewhere (Kuh et al., 2016, 2011; Wadsworth et al., 2006). All participants provided written informed consent at each wave of data collection. Ethical approval for the latest data collection was obtained from NRES Queen Square REC and Scotland A REC.

Measures

Cognitive function

Repeated assessments of verbal memory and information processing speed were available at ages 43, 53, 60-64, and 69 (Davis et al., 2017; Rawle et al., 2018; Richards, Shipley, Fuhrer, & Wadsworth, 2004). Information processing speed was measured using a letter cancellation task, which required cohort members to cross out as many randomly distributed target letters as possible from a grid of other letters within a timed period of 1 minute. Scores ranged from 0-600. Memory function was assessed using a 15-item word recall task, which required participants to recall as many words as possible from a list shown visually at the rate of 1 word per second. Scores ranged from 0-45.

Previously, linear mixed models (linear and quadratic trends) were fit to verbal memory and information processing speed data available from age 43 to age 69 (Davis et al., 2017; Rawle et al., 2018b). The quadratic model was the best fit for both cognitive domains (Davis et al., 2017; Rawle et al., 2018b), and therefore used in the present study to test for associations between affective symptoms in adolescence and adulthood (ages 13-15, 36 and 43) and cognitive trajectories.

Affective symptoms

Affective symptoms were assessed at ages 13, 15, 36, 43, 53, 60-64, and 69 (Richards et al., 2014). For the present study, measures of affective symptoms at ages 13, 15, 36, and 43 were included in order to ensure forward temporal associations. Psychological problems in adolescence (age 13 and age 15) were reported by teachers using a forerunner of the Rutter A scale (Richards & Abbott, 2009). Previous research used exploratory factor analysis on this scale at ages 13 and 15 (Xu et al., 2013), and ten items which loaded strongly onto the factor representing emotional problems at ages 13 and 15 were included in the present study. Confirmatory factor analyses of these items were run to derive latent affective symptoms scores at both ages, and then the mean of these factor scores was calculated to represent the measure of adolescent affective symptoms.

In adulthood, affective symptoms were assessed using the Present State Examination at age 36 (PSE) (Wing et al., 1974), and the Psychiatric Symptom Frequency scale (PSF) at age 43 (Lindelow et al., 1997). Latent trait scores of PSE at age 36, and PSF at age 43 were derived previously (Colman et al., 2007).

The original latent scores were categorised into three percentile groups (1st-50th, 51st-90th, 91th-100th percentiles), which represented no/low, moderate and severe symptoms, as previously described using NSHD data (Archer et al., 2018), as a measure of

symptom severity. Both continuous and categorical measures of affective symptoms were used for the analyses.

Covariates

Key covariates were selected based on previous research: sex, childhood socioeconomic position (SEP) (Kaplan et al., 2001), childhood cognition (McGurn et al., 2008), and educational attainment (Brayne et al., 2010). Childhood SEP was represented by father's occupation. This was coded to correspond to social classes I-V in the Classification of Occupations (1970). Participants were classified by the following: professional; intermediate; skilled non-manual; skilled manual; partly skilled; unskilled. In order to maximise sample size, if SEP at age 4 was missing, this was substituted with SEP at age 11. If SEP at age 4 and 11 were both missing, SEP at age 15 was used. Educational attainment was represented by the highest qualification achieved by age 26. This measure was coded according to the UK Burnham scale and then grouped into 3 categories, including: no educational qualifications; vocational or GCSE; A-Level or higher. Childhood cognition at age 8 was represented by a composite score of four tests of verbal and nonverbal ability, including reading comprehension, word reading, vocabulary, and picture intelligence (Hatch et al., 2007; Richards et al., 2004). In order to maximise sample size, if cognitive function at age 8 was missing it was substituted with z scores of cognitive function at age 11. Where cognitive data was not available at age 8 or 11, z scores of cognitive function at age 15 were used.

Additional covariates were: psychiatric medication use (Rawle et al., 2018a) and externalising problems (Richards & Abbott, 2009; Archer et al., 2018). At ages 36, 43, 53, 60-64, and 69, participants were asked about use of antidepressant and anxiolytic medications. A binary variable was derived, representing participants who were prescribed

these medications during at least one time-point between ages 36 and 69 compared with participants who were never prescribed these medications. Externalising problems were measured with the teacher rated forerunner of the Rutter A scale at ages 13 and 15 (Xu et al., 2013).

Statistical Analyses

Main analyses

STATA version 14 (StataCorp. 2015) was used for all the analyses. Linear mixed models were fitted to model memory and information processing speed trajectories from middle to late adulthood. Intercepts (age 43) and slopes (from age 43 through age 69) were random and an unstructured covariance structure was assumed. These models of cognitive trajectories using NSHD data have been described previously (Davis et al., 2017; Rawle et al., 2018b). Latent scores of affective symptoms in adolescence (ages 13-15), and adulthood (36 and 43) were used to predict cognitive trajectory intercepts and slopes. In order to test for the effect of affective symptom severity on cognitive trajectories, the ordinal measure based on percentile scores of affective symptoms representing no/low, moderate and severe symptoms, were added into the models.

Initial models were unadjusted (Model 1) and subsequent models were adjusted for key covariates: adjusted for sex (Model 2); adjusted for sex, childhood cognition, childhood socioeconomic position, and education by age 26 (Model 3). Because there was no significant interaction at the 5% level between sex and affective symptoms at any of the time-points assessed (age 13-15, 36 and 43) for memory or information processing speed (Supplementary Table 1), sex was used as a covariate, rather than a moderator, in all subsequent analyses. Additionally, the models were adjusted for the use of psychiatric medication (Model 4) and adolescent externalising problems (Model 5).

Sensitivity analyses

The main analyses included participants with cognitive data available in at least one time point between ages 43 and 69 (including participants who might die during this period) with, missing data being accounted for using maximum likelihood estimation. A sensitivity analysis was conducted in order to test whether results might be affected by mortality. For this, the main models we reran on the sub-sample of people who were alive by age 69.

In our main analyses, the sample size was restricted to those with data on all on predictors and covariates available. Therefore, in order to maximise our sample size and to determine that effects observed were not attributable to the method used to account for missing data, an additional sensitivity analysis was conducted, in which a multiple imputation approach was employed using MICE in R (Azur et al., 2011; Buuren and Groothuis-Oudshoorn, 2011). Sixteen imputations were conducted across 11 sweeps over the life course. Multiple imputation techniques have been used frequently with NSHD data (Almoosawi et al., 2013; Jones et al., 2015; Silverwood et al., 2013). The inclusion of a larger number of auxiliary variables in the model maximises the plausibility of the missing at random (MAR) assumption (Coley et al., 2011). To determine whether method used to account for missing data had an effect on our results, all main models were re-run on the imputed sample.

RESULTS

Available study sample and demographic information

Table 1 shows demographic information for the samples included in the main analyses with key covariates. A total of 3395 people had both cognitive measures available in at least one time-point: Verbal memory N=3404; Information processing speed N=3447 (Supplementary Table 2). Of this sample, 2648 (78%) people had complete information on affective symptoms at each time-point assessed. Of this number, 2543 (96%) people also had complete information for covariate data (Supplementary Figure 1). The sample size was slightly larger for those with verbal memory data (N=2546) or information processing speed data (N=2570) than for those with both (N=2543).

The sample with cognitive data (both verbal memory and information processing speed) in at least one time-point and complete predictor and covariate data (N=2543) was compared with the sample with cognitive data in at least one time-point and missing predictor and covariate data (N=852). The sample with missing data did not differ from the sample with complete information on sex (X^2 = 1.29, *p*=.26), education (X^2 = 4.68, *p*=.10), childhood socioeconomic position (X^2 = 9.07, *p*=.11), childhood cognition (t = -0.96, *p*=.34), adolescent affective symptoms (t = -0.03, *p*=.97), information processing speed scores at any age (Age 43: t = 1.58, *p*=.11; Age 53: t = 1.95, *p*=.051; Age 60-64: t = 1.23, *p*=.22; Age 69: t = 1.36, *p*=.17), or verbal memory scores at any age (Age 43: t = 1.44, *p*=.15; Age 53: t = 1.17, *p*=.24; Age 60-64: t = 1.19, *p*=.23; Age 69: t = 1.24, *p*=.21). However, participants with missing predictor and covariate data had significantly higher level of affective symptoms in adulthood (Age 36: t = 3.06, *p*=.002; Age 42: t = 3.58, *p*<.001).

TABLE 1 HERE

Effects of adolescent and adult affective symptoms on cognitive trajectories

Fully adjusted models (Model 3, best fit according to AIC and BIC statistics) revealed that adolescent affective symptoms were significantly associated with cognitive function at first testing (Verbal Memory: b = -1.11, SE = 0.53, *p* = .04; Information Processing Speed: b = -18.17, SE = 7.53, *p* = .02), but not with rate of decline (Verbal Memory: b = 0.01, SE = 0.01, *p* = .30; Information Processing Speed: b = 0.09, SE = 0.13, *p* = .50). There were no significant associations between affective symptoms at ages 36 or 43 and cognitive trajectories between the ages of 43 and 69 (intercept or slope) in unadjusted or adjusted models (Table 2 & Table 3).

TABLE 2 HERE

TABLE 3 HERE

In order to investigate the effect of symptom severity, an ordinal variable based on percentile cuts of the latent score of adolescent affective symptoms (0-50th, 51-90th, 91-100th percentile) was included in the models. Fully adjusted models revealed that both groups with moderate and with severe adolescent symptoms differed significantly at first cognitive testing of memory performance from the group with no/low symptoms. Effect sizes were largest for the highest percentile group of people with the most severe affective symptoms in adolescence (Moderate symptoms: b=-0.87, SE=0.42, *p*=.04; Severe symptoms: b=-1.88,

SE=0.81, *p*=.02). Adolescent affective symptom percentile groups were not significantly associated with the rate of memory decline between the ages of 43 and 69 (b=0.01, SE=0.01, *p*=.14) (Table 4, Figure 1).

In information processing speed models, the moderate symptom group did not differ significantly from the no/low symptom group at the first cognitive testing of information processing speed performance (b=-9.25, SE=5.97, *p*=.12), but the group with the most severe symptoms were significantly poorer at first cognitive testing of information processing speed than the no/low symptom group (b=-23.42, SE=11.55, *p*=.04). Adolescent affective symptom percentile groups were not significantly associated with the rate of processing speed decline between the ages of 43 and 69 (b=0.04, SE=0.10, *p*=.72) (Table 4, Figure 1).

When psychiatric medication use and externalising behaviour in adolescence were controlled for, results were essentially unchanged for both memory and information processing speed (Supplementary Tables 3 & 4).

TABLE 4 HERE

FIGURE 1 HERE

Sensitivity analyses

As a sensitivity analysis, participants who died before age 69 were excluded (N=1028), and main models were re-run on the sample of people who were still living up to

2015 (N=4334). From previous research using this data, it is already known that both affective symptoms (Archer et al., 2018) and cognitive function (memory and processing speed) (Davis et al., 2016; Kuh et al., 2009) can lead to premature mortality.

Fully adjusted models revealed that adolescent affective symptoms significantly predicted processing speed at first testing (b=-16.76, SE=7.98, *p*=.04), but not decline of processing speed between the age of 43 and 69 (b=0.05, SE=0.14, *p*=.71). Affective symptoms at ages 36 and 43 did not significantly predict trajectories of processing speed (intercept or slope). Models including verbal memory showed a slightly different pattern. No effects were observed for affective problems at any age across adolescence and adulthood on memory trajectories (intercept or slope) over the period tested (Supplementary Tables 5 & 6).

Finally, main models were re-run on the imputed sample (N=3404) to maximise sample size and to determine whether effects observed were due to the method used to account for missing data. Effect sizes from the models using the imputed sample were substantially identical to those produced from the main models (Supplementary Tables 7 & 8). Affective symptoms in adolescence significantly predicted lower cognitive scores at first assessment (Memory: b=-1.03, SE=0.47, *p*=.03; Information processing speed: b=-16.81, SE=6.65, *p*=.01), but not decline over the time period tested. Adult affective symptoms did not predict cognitive trajectories.

DISCUSSION

Adolescent affective symptoms predicted lower memory and information processing speed scores in middle adulthood (at age 43). However, adolescent affective symptoms did not predict rate of cognitive decline over the period of three decades. Overall, in this study no effects were observed for adult affective symptoms at ages 36 and 43 on cognitive function or decline from middle to late adulthood. Previous research has reported that affective symptoms in adolescence can have a profound and long-lasting effect on outcomes later in life, including educational attainment (Fletcher, 2010) and premature mortality (Archer et al., 2018). Findings from the current study extend this to include lower memory and information processing speed level in midlife, but not a faster rate of decline from fourth through sixth decade of life.

There was a dose-response between affective symptoms and memory at age 43. Those with moderate and severe symptoms during adolescence differed significantly at first cognitive testing of memory function at age 43 from a group with no/low adolescent symptoms, but effect sizes were largest for the group with severe adolescent symptoms. These results also revealed that participants with moderate adolescent affective symptoms did not differ significantly at first cognitive testing of information processing speed from participants with no/low adolescent symptoms. However, participants with severe adolescent affective symptoms did show significantly poorer information processing speed performance at first testing than participants with no/low adolescent symptoms. This suggests that effects of adolescent affective symptoms on information processing speed performance at first testing may have been largely driven by cohort members with more severe adolescent affective symptoms.

After excluding participants who died before age 69 from the analysis, results revealed that adolescent, but not adult, affective symptoms significantly predicted processing speed scores at first testing, but not decline over fourth to sixth decade. However, after excluding deceased individuals from the analysis, the effect of adolescent affective symptoms on memory was no longer significant. Previous research using NSHD has shown that affective symptoms during adolescence are associated with premature mortality (Archer et al., 2018). It is therefore not entirely surprising that when the sample is restricted to only participants who are alive in 2015, the effects of adolescent affective symptoms on cognitive outcomes is attenuated, as a higher proportion of cohort members with significant adolescent affective symptoms were more likely to have already died by the time of cognitive assessment in adulthood.

These findings are consistent with those of Richards et al (2014), who reported no associations between lifetime latent profiles of affective symptoms on cognitive decline. The present study also found no effects of affective symptoms during adulthood on cognitive performance and no effects of affective symptoms at any time-point on rate of cognitive decline over the time period tested. However, in contrast to Richards et al (2014), in the present study there were significant associations between adolescent affective symptoms and memory and information processing speed level. This may be due to differences in the ages at first testing of cognitive performance between the studies. Richards et al (2014) used cognitive scores at age 60-64 to determine effects of lifetime affective symptoms on cognitive performance, whereas the present study used cognitive scores at age 43 as the baseline. The latter is potentially a more stable baseline uncontaminated by differential age-related decline and prodromal pathological confounders emerging from mid-life. Additionally, the inclusion of additional waves with cognitive data at ages 43 and 69 may explain why these findings in adolescence differ from those of Richards et al (2014).

Importantly, we did not see any effects of adult affective symptoms (age 36 and 43) on performance or rate of decline in either of the cognitive outcomes assessed. This suggests that adolescence is an important sensitive period, during which the presence of more severe affective symptoms may have more profound and lasting long term effects on cognitive health than affective symptoms present during adulthood. Adolescence may therefore be a sensitive period, during which the presence of more severe affective symptoms can impact cognitive health across the life course. It is known that adolescence is an important period of continued brain maturation, characterised by major changes in both brain structure and function (Eiland and Romeo, 2013; Whittle et al., 2014) with long-lasting effects on cognition function and ageing (Andersen, 2003; Spear, 2000). Early developmental changes that accompany the experience of stress or depression during adolescence may therefore be the source of cognitive impairment observed later in life.

Strengths and limitations

Key strengths of the present study include prospectively assessed measurements of affective symptoms available across the life course, spanning from multiple time points in adolescence through to midlife. Additionally, there are multiple repeated assessments of memory and information processing speed from midlife to older adulthood which are consistent over time, allowing for longitudinal modelling of cognitive trajectories.

One potential limitation of the present study is that the NSHD has been collecting data from cohort members for over 70 years, and as such missing data is inevitable. It is therefore possible that characteristics which predict attrition may also be predictive of greater cognitive decline, and as such these individuals may be under-represented in the study. In this analysis, we dealt with missing data using maximum likelihood estimation, minimising issues associated with using a complete case analysis. In order to determine whether this method

influenced results, models were re-run on a sample derived from a multiple imputation approach. Results from models including the imputed sample were substantially identical to those without, suggesting that the method used to account for missing data did not have a considerable impact on these results. Limitations of the psychometric instruments used to assess cognitive and affective symptoms should also be acknowledged. Specifically, although necessarily so, different measures of affective symptoms were used in adolescence and adulthood which may limit comparability of these measures. Additionally, in adolescence, affective symptoms were reported by teachers, whereas for all other time points they were reported directly by the cohort member. Beyond this, cognitive measures were assessed using single assessments, rather than a more comprehensive cognitive battery, and only memory and information processing speed were measured repeatedly over time, although these are key cognitive domains that are sensitive to age- and morbidity-associated decline. Finally, cognitive assessments were only available in adulthood at ages 43, 53, 60-64 and 69, and subsequently associations between affective problems and cognitive function before middle adulthood were not explored.

It is also important to note that affective symptoms were only considered from ages 13 to age 43 in this study and it is possible that affective symptoms later in the life course may also play an important role in predicting cognitive function and decline. Specifically, research has shown that the menopause transition is associated with approximately a 2- to 4-fold increased risk for major depression and that this effect is independent of history of depressive episodes (Bromberger et al., 2011). Additionally, early cognitive ability is associated with age at menopause (Kok et al., 2006; Kuh et al., 2005; Richards et al., 1999) and the menopausal transition has been associated verbal memory function (Richards et al., 2018), and with increased vulnerability to cognitive impairment (Weber et al., 2014). The menopausal transition may therefore be an important period within the association between

affective disorders and cognitive function/decline. This is an interesting avenue for consideration in future research.

Based on population estimates, the relative rates of affective episodes experiences by cohort members were lower than expected. This could suggest that adults with more severe and recurrent affective symptoms were not included in this sample. However, the estimates for lifetime prevalence were consistent with 1 time with elevated symptoms. This may suggest that with more measurements, a larger group with chronic affective symptoms could potentially be identified and analysed. Adolescent affective symptoms are an important marker of future depression recurrence and chronicity.

Affective symptoms during early adulthood were not included and as such we cannot model the role of affective symptoms at this age on cognitive decline in mid to late adulthood. Assessments in this early adulthood period could have more stably estimated differences between age at onset of affective symptoms, recurrence of symptoms, and eventual cognitive difficulties during adulthood.

Implications

With the high prevalence of mental health problems within adolescent populations (24% of girls and 9% of boys report high depressive symptoms by the age of 14 (Patalay and Fitzsimons, 2017), these findings are potentially of great importance for public health. Additionally, there is evidence to suggest that the prevalence of affective symptoms are increasing over time within this adolescent age-group, with depressive symptoms increasing from 13.1% in 2009 to 20.3% in 2014 in adolescent girls (Fink et al., 2015). This high and increasing prevalence is particularly concerning when considered in the context of the results from this study, showing long-lasting effects of adolescent affective symptoms on cognitive health into midlife and beyond, as well as other recent studies demonstrating other negative

adult outcomes of adolescent affective symptoms, including educational attainment (Fletcher, 2010) and premature mortality (Archer et al 2018).

In conclusion, our findings suggest that adolescent affective symptoms are important predictors of cognitive function in midlife, but they do not predict the rate of cognitive decline from middle to late adulthood in cognitively healthy individuals. Taken together, these findings highlight the importance of early intervention to prevent and manage mental health present during adolescence, in order to protect cognitive function later in the life course.

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DECLARATION OF INTEREST

None

DATA STATEMENT

Data used for this study are available to researchers upon request to the NSHD Data Sharing Committee. Further information is available at http://www.nshd.mrc.ac.uk/data. doi: 10.5522/NSHD/Q101; doi: 10.5522/NSHD/Q102;doi: 10.5522/NSHD/S103.

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Table 1: Demographic information for sample included in fully adjusted memory (n=2546) and information processing speed models (n=2570).

Demographic information		**Verbal memory N = 2546**	**Information processing speed N = 2570**
Verbal Memory, Mean (SD)	Age 43	24.65 (6.35)	24.66 (6.35)
	Age 53	23.85 (6.34)	23.85 (6.34)
	Age 60-64	24.17 (6.16)	24.17 (6.16)
	Age 69	22.11 (6.05)	22.11 (6.05)
Processing Speed, Mean (SD)	Age 43	340.94 (75.99)	340.69 (76.15)
	Age 53	279.73 (75.07)	279.55 (75.24)
	Age 60-64	265.74 (71.62)	265.74 (71.62)
	Age 69	261.20 (73.29)	261.08 (73.28)
Continuous Measures of Affective Symptoms, Mean (SD)	Age 13-15	0.02 (0.50)	0.02 (0.49)
	Age 36	0.23 (0.84)	0.23 (0.84)
	Age 43	0.001 (0.64)	0.005 (0.64)
Categorical Measures of Affective Symptoms, N (%)*			
- Low affective symptoms	Age 13-15	1322 (51.92)	1327 (51.63)
	Age 36	1323 (51.96)	1335 (51.95)
	Age 43	1318 (51.77)	1323 (51.48)
- Moderate affective symptoms	Age 13-15	994 (39.04)	1009 (39.26)
	Age 36	987 (38.77)	995 (38.72)
	Age 43	993 (39.00)	1009 (39.26)
- Severe affective symptoms	Age 13-15	230 (9.03)	234 (9.11)
	Age 36	236 (9.27)	240 (9.34)
	Age 43	235 (9.23)	238 (9.26)
Number of episodes of severe affective symptoms between ages 13-42, N (%)	0	1970 (77.38)	1988 (77.35)
	1	465 (18.26)	467 (18.17)
	2	97 (3.81)	100 (3.89)
	3	14 (0.55)	15 (0.58)

Sex N (%)	Male Female	1262 (49.57) 1284 (50.43)	1278 (49.73) 1292 (50.27)
Childhood Cognition, Mean (SD)	Cognitive score	0.05 (0.83)	0.04 (0.83)
Childhood Social Class, N (%)	Professional Intermediate Skilled non-manual Skilled manual Partly skilled Unskilled	140 (5.50) 430 (16.89) 472 (18.54) 786 (30.87) 556 (21.84) 162 (6.36)	141 (5.49) 434 (16.89) 474 (18.44) 799 (31.09) 560 (21.79) 162 (6.30)
Education, N (%)	None attempted Vocational or GCSE A Level or Higher	934 (36.68) 731 (28.71) 881 (34.60)	950 (36.96) 736 (28.64) 884 (34.40)

Notes: * Low symptoms: 0-50th percentile; Moderate symptoms 51-90th percentile; Severe symptoms: 91-100th percentile.

Table 2: Affective symptoms (at ages 13-15, 36, and 43) and verbal memory trajectories.

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-2.08**	**0.54**	**<.001**	**-2.29**	**0.54**	**<.001**	**-1.11**	**0.53**	**.04**
Affective symptoms at age 36	-0.61	0.33	.07	-0.54	0.33	.11	-0.54	0.33	.10
Affective symptoms at age 43	0.87	0.44	.05	0.60	0.44	.18	0.48	0.43	.26
Gender				**2.13**	**0.22**	**<.001**	**2.13**	**0.18**	**<.001**
Childhood cognition							**2.48**	**0.13**	**<.001**
Childhood socioeconomic position							-0.02	0.01	.10
Education							**1.93**	**0.13**	**<.001**
SLOPE TERMS									
Decline per year (linear)	0.36	**0.06**	**<.001**	**0.36**	**0.06**	**<.001**	**0.35**	**0.06**	**<.001**
Decline per year (quadratic)	-0.004	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.21	0.01	0.01	.19	0.01	0.01	.30
Affective symptoms at age 36	0.01	0.01	.18	0.01	0.01	.17	0.01	0.01	.31
Affective symptoms at age 43	-0.01	0.01	.08	-0.01	0.01	.07	-0.01	0.01	.12
N	2652			2652			2546		
AIC	49763.34			49673.18			46636.31		
BIC	49839.82			49755.55			46735.63		

Table 3: Affective symptoms (at ages 13-15, 36, and 43) and information processing speed trajectories.

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-19.66**	**7.38**	**.008**	**-21.56**	**7.33**	**.003**	**-18.17**	**7.53**	**.02**
Affective symptoms at age 36	-1.04	4.56	.82	-0.21	4.53	.96	0.05	4.64	.99
Affective symptoms at age 43	2.95	6.02	.62	0.15	5.99	.98	0.46	6.10	.94
Gender				**21.68**	**2.44**	**<.001**	**21.51**	**2.47**	**<.001**
Childhood cognition							**4.50**	**1.75**	**.01**
Childhood socioeconomic position							**-0.36**	**0.14**	**.01**
Education							**8.44**	**1.75**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**-21.68**	**0.84**	**<.001**	**-21.74**	**0.84**	**<.001**	**-22.02**	**0.85**	**<.001**
Decline per year (quadratic)	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.09	0.13	.46	0.09	0.13	.47	0.09	0.13	.50
Affective symptoms at age 36	-0.002	0.08	.98	-0.001	0.08	.99	-0.002	0.08	.98
Affective symptoms at age 43	-0.04	0.10	.68	-0.05	0.10	.66	-0.05	0.11	.62
	2677			2677			2570		
AIC	93702.93			93627.48			89796.77		
BIC	93779.53			93709.98			89896.25		

Table 4: Effect of adolescent affective symptom percentiles on memory and information processing speed function at age 43.

Severity of adolescent affective symptoms	**Verbal Memory**			**Information Processing Speed**		
	Model 1 **b (SE), *p***	**Model 2** **b (SE), *p***	**Model 3** **b (SE), *p***	**Model 1** **b (SE), *p***	**Model 2** **b (SE), *p***	**Model 3** **b (SE), *p***
No/Low	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Moderate	**-1.11 (0.44), 0.01**	**-1.30 (0.44), 0.003**	**-0.87 (0.42), 0.04**	-8.63 (5.90), 0.14	-10.26 (5.86), 0.08	-9.25 (5.97), 0.12
High	**-3.21 (0.84), <.001**	**-3.51 (0.84), <.001**	**-1.88 (0.81), 0.02**	**-25.53 (11.39), 0.03**	**-27.98 (11.32), 0.01**	**-23.42 (11.55), 0.04**

Figure 1: Cognitive trajectories from ages 43 to 69 by exposure to affective symptoms in adolescence.

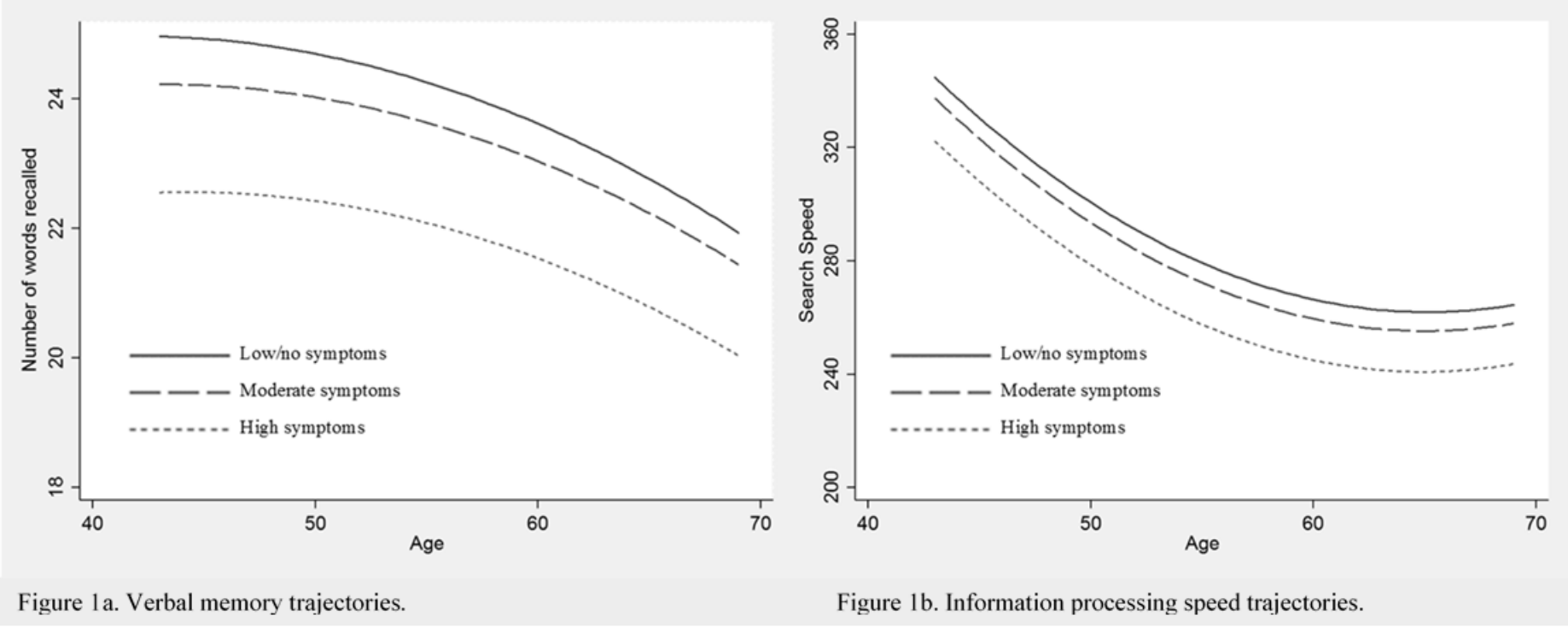

Figure 1a. Verbal memory trajectories.

Figure 1b. Information processing speed trajectories.

Note: Adolescent affective symptoms split into three groups with either 'no/low adolescent affective symptoms', 'moderate adolescent affective symptoms' or 'high adolescent affective symptoms' by dividing participants based on percentiles (0-50th percentile, 51-90th percentile, and 91-100th percentile).