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**Accumulation of affective symptoms and midlife cognitive function: the role of
inflammation**

Affective symptoms, cognitive function and inflammation

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ABSTRACT

Background: The aim of the present study was to test whether C-Reactive Protein (CRP), a proxy measure of inflammation, is elevated in people with higher child and adulthood affective symptoms and whether elevated CRP predicts midlife cognitive function.

Methods: Data were used from the National Child Development Study (n = 6276). Measures of memory, verbal fluency, information processing speed and accuracy were available in midlife (age 50). Affective symptoms were assessed in childhood (ages 7, 11, 16) and in adulthood (ages 23, 33, 42, 50). The level of plasma CRP was measured at age 44. Pathway models, unadjusted and fully adjusted for sex, education, childhood socioeconomic position, childhood cognitive ability and affective symptoms at age 50, were fitted to test direct associations between affective symptoms and midlife cognitive function, and indirect associations via the inflammatory pathway (CRP level).

Results: In a fully adjusted model, there were significant indirect associations between adult affective symptoms and immediate memory ($\beta=-0.01$, $SE=0.003$, $p=.03$) and delayed memory ($\beta=-0.01$, $SE=0.004$, $p=.03$) via CRP. In addition, there were significant indirect associations between affective symptoms in childhood and immediate memory ($\beta=-0.001$, $SE=0.000$, $p=.03$) and delayed memory ($\beta=-0.001$, $SE=0.001$, $p=.03$), via adult affective symptoms and associated CRP. Independent of CRP, there was a significant direct association between adult affective symptoms and information processing errors ($\beta=0.47$, $SE=0.21$, $p=.02$). There were no direct or indirect associations between affective symptoms and verbal fluency or information processing speed.

Conclusions: CRP at age 44 is elevated in people with higher affective symptoms from age 7 to 42, and elevated CRP is associated with poorer immediate and delayed memory at age 50.

INTRODUCTION

Systematic reviews have shown that affective symptoms (depression and anxiety) are associated with faster cognitive decline and an increased risk of dementia in older adulthood (1–6). More recent studies using longitudinal data from British birth cohorts suggest that persistent affective symptoms are associated with poorer cognitive function, specifically verbal memory in early old age (age 69) (7) and midlife (age 50) (8). Taken together, these findings suggest that persistent affective episodes can affect cognitive function as early as midlife.

There is a growing body of research, investigating possible biological mechanisms that may contribute to observed associations between affective symptoms and subsequent cognitive function. One plausible hypothesis is that inflammation plays an important role in the association between affective symptoms and cognition (9–11). Inflammation refers to the immune system's response to threat, such as infection or injury. C-Reactive Protein (CRP) is an acute phase reactant, produced in the liver and released into the bloodstream in response to inflammation. High concentrations of CRP are indicative of elevated levels of inflammation and can therefore be used as an inflammatory marker. There is evidence that peripheral measures correlate with inflammatory markers in the brain (12).

Research has shown a cross-sectional association between depressive symptoms and plasma levels of inflammatory markers, including CRP (13, 14). Converging lines of evidence support the association between depression and inflammation, whereby elevated inflammation can increase vulnerability for depression (15) and psychological stress can increase production of pro-inflammatory cytokines (15–18). Additionally, a growing body of research has also focussed on the association between depression and CRP over time, showing elevated CRP levels in people with cumulative depressive symptoms across

adolescence and early adulthood (19). The timing of this longitudinal association remains unclear, with research showing that inflammation can precede depression onset and contribute to pathogenesis of this condition (20), and also that depressive symptoms are associated with elevated fibrinogen (a biomarker of inflammation) across time (21). It is therefore possible that associations between inflammation and depression may be bidirectional.

In addition to this, research has proposed that inflammatory changes may be an important pathological feature of dementia (9). Specifically, evidence from longitudinal studies have shown that peripheral inflammatory markers measured during midlife are associated with risk of dementia after 25 years, and that these processes are operating long before emergence of clinical symptoms of dementia (12). Systematic reviews have also shown that high concentrations of peripheral inflammatory markers are associated with increased risk of cognitive impairment and dementia (22, 23). In addition to dementia, markers of inflammation including CRP can also prospectively predict poorer cognitive function after follow up and faster cognitive decline over time (24). These converging lines of evidence suggest that inflammation may play an important role within the association between affective symptoms and midlife cognitive function. However, to the best of our knowledge this hypothesis has never been directly tested in a prospective population-based birth cohort.

The aim of the present study was therefore to test whether inflammation, measured with CRP, is elevated in people with higher affective symptoms over the life course and whether elevated CRP is associated with midlife cognitive outcomes. In order to address this aim, direct associations of affective symptoms in childhood and adulthood, as well as their indirect associations with midlife cognitive function, via the inflammatory pathway were estimated. We hypothesised that CRP levels at age 44 will be elevated in people with higher

affective symptoms from age 7 to 42, and that elevated CRP levels at age 44 will be associated with poorer cognitive outcomes at age 50.

METHODS AND MATERIALS

Participants

Data were used from the National Child Development Study (NCDS), a national representative sample of 17,415 people born in England, Scotland and Wales during one week of 1958. Data have been collected at ages 0, 7, 11, 16, 23, 33, 42, 44, 46, 50, and 55 (25). At age 44, biomedical data were collected from a subset of cohort members with informed consent (N=9377), and blood samples were drawn. Of the 9,377 people who took part in the biomedical sweep, 8,753 consented to blood sample collection. Ethical approval for the biomedical sweep at age 44 was provided by the South-East Multi-centre Research Ethics Committee. Additional ethical approval for the present study was obtained from the University of Sussex (Reference number: ER/AJ316/1). Data can be accessed upon application to METADAC.

Measures

Cognitive function

Cognitive data were available at age 50. Short-term and delayed memory were assessed using a word recall task consisting of a list of 10 common words recalled immediately after presentation and again after a 5-minute delay. Verbal fluency was captured by naming as many animals as possible in one minute ((26). Information processing was measured using a letter cancellation task, in which participants are required to cross out as many target letters (Ps and Ws) as possible within a grid of random letters in one minute. Information processing speed is based on the total number of letters searched, and information processing accuracy is based on the number of target letters missed up to the last letter searched (higher scores represent more errors). These cognitive tasks are described in detail elsewhere (27).

Affective symptoms

Affective symptoms were assessed repeatedly in childhood and adolescence using the Rutter Behaviour Child Scale A at ages 7, 11 and 16. These questionnaires were completed by cohort members' parents, usually the mother. At age 16, the Rutter Behaviour scale comprised 18 items, encompassing both internalising and externalising symptoms. At ages 7 and 11, a shorter version of the Rutter Behaviour scale was administered, comprising 14 items. According to previous research, at age 16, 5 items from this scale were used to create a measure of internalising symptoms (worries, solitary, miserable, fearful, fussy). Four of these items were also available at ages 7 and 11 (worries, solitary, miserable, fearful) and these were used to create a measure of internalising symptoms at these time-points. These items in particular were used in order to be consistent with previous research (28, 29). Confirmatory factor analysis (CFA) was used to derive latent scores of affective symptoms at each time-point. This was a good fit to the data (Supplementary table 1). Mean latent score was also calculated across ages 7, 11 and 16 to derive an overall measure of affective symptoms in childhood.

Affective symptoms were assessed repeatedly in adulthood at ages 23, 33, 42, and 50 using the Malaise Inventory Scale (30). At ages 23, 33, and 42, this was a 24-item self-completion questionnaire designed to capture psychological distress. At age 50, the short-form questionnaire (9 items) was used. These 9 items were selected from all four time-points to make scores more comparable over time. CFA was conducted on these 9 items at each available time-point to derive latent scores of affective symptoms at ages 23, 33, 42, and 50. This fitted the data well (Supplementary table 1). Mean latent score was calculated for ages 23, 33, and 42 and this was used to predict CRP at age 44. The latent affective symptom score at age 50 was used as a covariable.

Inflammation

For the purposes of this paper, inflammation status was assessed by recorded level of C-Reactive Protein (CRP) in citrated plasma (mg/L), acquired from blood samples collected during the biomedical sweep at age 44 by trained nurses and analysed by partnered laboratories (Elliott, Johnson, & Shepherd, 2008). CRP was measured on citrated plasma by high-sensitivity nephelometric analysis of latex particles which were coated with CRP-monoclonal antibodies (32). The inter- and intra-assay variation coefficients were > 10% for CRP (8.3% and 4.7% respectively). Further details about the processing of CRP data is available elsewhere (31). CRP values of >10mg/L (N = 230) are indicative of recent infection (33) and as such these cases were excluded from the analysis to be consistent with previous research (34, 35).

Covariables

Covariables selected for the study were based on previous research and comprised measures of sex, educational attainment (36–38), childhood cognition (36, 38–40), and childhood socio-economic position (38, 41). Affective symptoms at age 50 were also included in the model to account for concurrent affective symptoms. Education was captured by cohort member's highest educational qualification achieved by age 50. This was categorised into 1) Low education (up to GCSE level); 2) middle education (up to A Level); and 3) high education (Degree). Two measures of childhood cognitive ability (reading and mathematics) at age 7 were included. Reading ability was captured using the Southgate Group Reading Test, a task designed to assess word recognition and comprehension, producing a score ranging from 0-30. Mathematical ability was measured using the Problem Arithmetic Test, requiring completion of 10 problem questions, producing a score ranging from 0-10. Socio-economic position at age 11 was based on parental occupation and

household tenure, categorised into working, intermediate and middle. The derivation of this variable was based on guidance from the Centre for Longitudinal Studies (CLS) (Elliott & Lawrence, 2014). Specifically, cohort members were coded as middle class if paternal occupation was professional, managerial etc (RGSC class I or II) and they were not living in council accommodation and mother occupation was not manual. Cohort members were coded as intermediate class if paternal occupation was professional/managerial (RGSC class 1 or 2) but either the cohort member was living in council accommodation or mother was in a manual occupation. Cohort members were also coded as intermediate class in paternal occupation was routine non-manual (RGSC class IIIa). Cohort members were also considered to be intermediate class if paternal occupation was manual or in routine service, but they were living in accommodation which was owner occupied. Finally, cohort members were coded as working class, if paternal occupation was manual or routine service and they were not living in accommodation which was owner occupied.

Analytical procedure

A series of models were run, estimating the direct associations between childhood and adult affective symptoms and cognitive function at age 50. Indirect pathways between symptoms and cognitive function through CRP were also estimated. All measures of cognitive function were included in the same model to account for covariances between different cognitive domains; non-significant covariances were removed from the model. Pathway analysis was conducted in Mplus Version 8 (43).

The initial pathway model was unadjusted, and subsequent models were adjusted for sex, education, childhood cognitive ability, childhood socioeconomic position, and affective symptoms at age 50. Including sex as a stratifying variable did not significantly improve model fit, and as such this was used in all analyses as a covariable (Supplementary Table 2).

Model fit was assessed using chi-square goodness of fit, CFI, TLI and RMSEA statistics. All missing data were addressed using full information maximum likelihood (FIML) (44–46).

A sensitivity analysis was conducted to test whether affective symptoms at certain ages were more strongly associated with elevated CRP and cognitive outcomes in adulthood. In order to do this, the model was re-run using the latent scores of affective symptoms at each age as individual predictors in the model. This allows us to identify particular ages at which affective symptoms may have important effects on CRP and cognitive outcomes. In addition to testing each age as a sensitive period, accumulation was also tested in a further sensitivity analysis. Specifically, latent variables of affective symptoms at all ages were dichotomised based a cut-off of the 75th percentile, in line with previous research (47). Participants with scores lower than the 75th percentile were considered to have no/low symptoms and participants with scores higher than 75th percentile were considered to have moderate/high affective symptoms. These scores were then summed to create an overall measure of total accumulation of affective symptoms from age 7 to 42. The range of possible scores was from 0 (no time points with moderate/high affective symptoms) to 6 (moderate/high affective symptoms at all time points). This method of assessing accumulation has been used in previous research using longitudinal birth cohort data (7, 8). The affective symptom accumulation score was then added to the model as a predictor. Additionally, the model was re-run using the MLR estimator, which is robust to non-normal distributions in the model to ensure skew did not affect the results. As, results using MLR estimator were substantially identical to those reported in the main analysis these are not presented.

RESULTS

Missing data and demographic information

The initial sample was comprised of 9377 participants who took part in the biomedical sweep at age 44. Of these 9377 people, 7928 (84.5%) had complete information on all cognitive domains. Within the sample with complete cognitive data, 7859 (99.1%) also had complete information on affective symptoms. There were 6325 (80.5%) people who also had a CRP measure (<10mg/L). Finally, there were 4908 (77.6%) people who also had complete covariable data (Figure 1). This final sample did not differ significantly from the sample with missing data on sex ($p = .94$), childhood affective symptoms ($p = .08$), education ($p = .09$), or childhood socioeconomic position ($p = .27$). However, the sample with complete information showed significantly lower adult affective symptoms ($p < .001$). Additionally, the sample with complete information also had significantly lower CRP levels ($p = .02$), and had significantly higher childhood cognitive scores, based on maths ($p = .002$) and reading ($p < .001$).

Additional analysis was conducted to test how missingness on CRP assessment was associated with other key observed variables. Cohort members with missing CRP data had significantly higher affective symptoms in adulthood ($p < .001$) and in childhood ($p < .001$), and significantly poorer information processing accuracy scores ($p = .01$) than cohort members with available CRP data. Cohort members with missing CRP data did not significantly differ from people with available CRP measures on immediate memory ($p = .75$), delayed memory ($p = .054$), verbal fluency ($p = .96$), or information processing accuracy ($p = .61$) scores. The full information maximum likelihood (FIML) method resulted in the analytical sample of 6276 participants (see Table 1).

Direct associations with midlife cognitive function:

After adjustment for all key covariables, *adult affective symptoms* (age 23 to 42) were directly associated with information processing accuracy ($\beta = 0.47$, $SE = 0.21$, $p = .02$) at age 50, but no other cognitive domains. In this fully adjusted model, there were no significant direct associations between *childhood affective symptoms* and any cognitive domain. There were, however, significant direct associations between *CRP* and immediate memory ($\beta = -0.04$, $SE = 0.01$, $p < .001$) and delayed memory ($\beta = -0.05$, $SE = 0.01$, $p < .001$) at age 50 (Table 2; Figure 2).

Indirect associations with midlife cognitive function:

After adjustment for the covariables, there were significant indirect associations between *adult affective symptoms* on immediate ($\beta = -0.01$, $SE = 0.003$, $p = .03$) and delayed memory ($\beta = -0.01$, $SE = 0.004$, $p = .03$) at age 50, whereby CRP level was elevated in people with higher adult affective symptoms, and this elevated CRP predicted midlife memory outcomes. In this fully adjusted model, there were significant indirect associations between *childhood affective symptoms* and information processing accuracy ($\beta = 0.07$, $SE = 0.03$, $p = .03$) via adult affective symptoms. Finally, there were significant indirect associations between *childhood affective symptoms* and immediate memory ($\beta = -0.001$, $SE = 0.00$, $p = .03$) and delayed memory ($\beta = -0.001$, $SE = 0.001$, $p = .03$) via adult affective symptoms and subsequent CRP level (Table 2; Figure 2).

Total associations with midlife cognitive function:

The fully adjusted model showed a significant total association between *adult affective symptoms* and immediate memory ($\beta = -0.22$, $SE = 0.04$, $p < .001$), delayed memory, ($\beta = -0.24$, $SE = 0.05$, $p < .001$), verbal fluency ($\beta = -0.92$, $SE = 0.18$, $p < .001$), and information processing accuracy ($\beta = 0.55$, $SE = 0.12$, $p < .001$), but not information

processing speed ($\beta = -1.32$, $SE = 2.58$, $p = .61$). There were no significant total associations between *childhood affective symptoms* and any cognitive domains (Table 2).

Sensitivity analysis

Fully adjusted models including latent scores of affective symptoms at each age as individual predictors revealed that there were significant direct effects of affective symptoms at age 23 on immediate memory ($\beta = -0.07$, $SE = 0.03$, $p = .01$) and of affective symptoms at age 16 (teacher rated) on verbal fluency ($\beta = -0.04$, $SE = 0.01$, $p = .002$). However, there were no significant indirect effects of affective symptoms at any age on cognitive outcomes through CRP.

Sensitivity analysis where models were re-run including scores of accumulation of affective symptoms from age 7 through to age 42 showed that there was no significant direct associations between accumulation of affective symptoms and any cognitive outcomes. However, there were significant indirect associations between accumulation of affective symptoms and immediate memory ($\beta = -0.002$, $SE = 0.001$, $p = .03$) and delayed memory ($\beta = -0.002$, $SE = 0.001$, $p = .03$) at age 50, via CRP. There were no significant indirect associations between accumulation of affective symptoms and other cognitive domains through CRP. There were significant total effects of accumulation of affective symptoms on immediate memory ($\beta = -0.05$, $SE = 0.01$, $p < .001$), delayed memory ($\beta = -0.05$, $SE = 0.01$, $p = .001$), verbal fluency ($\beta = -0.19$, $SE = 0.05$, $p < .001$), and information processing accuracy ($\beta = -0.07$, $SE = 0.03$, $p = .02$), but not information processing speed (Table 3).

DISCUSSION

Summary of findings & comparison to previous research

This study suggests that inflammation may contribute to the link between adult affective symptoms and midlife memory. Specifically, CRP levels at age 44 were elevated in people with higher adult affective symptoms and elevated CRP was associated with poorer immediate and delayed memory at age 50. Similarly, there were significant indirect associations between childhood affective symptoms and immediate and delayed memory, through adult affective symptoms and CRP level. There was also a direct association between adult affective symptoms and information processing accuracy, independent of CRP level. There were no significant direct or indirect associations between affective symptoms and verbal fluency or information processing speed. Affective symptoms at individual ages did not significantly predict CRP and cognitive outcomes. However, the number of time points with moderate/high affective symptoms from age 7 to 42 (i.e. accumulation) showed significant indirect associations with immediate and delayed memory, via CRP.

These results support previous research, showing elevated levels of CRP in chronic depression (19). Additionally, findings from the current study also support previous research, showing that peripheral inflammation levels can be associated with poorer verbal memory function in healthy older adults, and that participants with detectable CRP levels had reduced medial temporal lobe volume (48). Indeed, other studies have also shown that chronically high levels of inflammation in healthy older adults may lead to changes in brain morphology, including reduced total grey matter volume (49), white matter integrity (50), and hippocampal volume (49). There is also evidence that the effects of inflammation on brain structure can be observed during midlife (51–54). Therefore, impaired midlife memory function can be a consequence of structural brain changes accompanying chronically elevated

inflammation levels. In the current study, the absence of brain imaging data limits interrogation of the precise biological mechanism behind the observed associations noted here.

In contrast to the association between affective symptoms and memory, there were only significant direct associations between adult affective symptoms and information processing accuracy. No indirect associations were observed between affective symptoms, CRP and information processing accuracy. One potential explanation for this may be related to the differences in brain structures that the information processing accuracy domain draws on compared to memory measures. In addition to this, the inflammation hypothesis is closely linked with hippocampal volume change, so this could potentially explain why CRP level selectively contributed to the association between affective symptoms and memory measures, but not for other cognitive outcomes, including information processing accuracy. Additionally, research shows that neuroinflammation disrupts synaptic plasticity (55), and as such associations observed for memory exclusively are in line with the literature. It is possible that neuroinflammation may be more associated with executive dysfunction or processing speed later in the life course.

Strengths and limitations

Key strengths include the use of data from a large prospective birth cohort followed up until age 50. Multiple measures of affective symptoms were available from age 7 through age 50, testing the effects of persistent affective symptoms on cognitive function, with a follow up period of more than 40 years.

However, there was only one time point in which measurements of CRP were available in this dataset (age 44), meaning that CRP levels from earlier in the life course could not be explored. This means that the specific timing and temporal ordering of associations between

inflammation and affective symptoms cannot be inferred from this study. Additionally, only one single peripheral marker of inflammation (CRP) was used, meaning that caution should be used when interpreting these findings, and that results should be confirmed using other large longitudinal and prospective cohorts. There was also no brain imaging data available in this study and as such the neural mechanisms behind observed associations could not be tested. In addition, measures of cognitive function were only available at one time point in this dataset (age 50), so cognitive trajectories and rate of decline over time could not be modelled in this analysis. An additional limitation is the presence of missing data in the study. Attrition is common in long running cohorts; however, in this study it was addressed using full information maximum likelihood (FIML). Specifically, the sample with missing data showed significantly higher affective symptoms, higher CRP levels, and lower childhood cognitive function. Our results may therefore underestimate associations between affective symptoms, CRP and cognitive outcomes, because people with more severe affective symptoms and poorer childhood cognitive function were less likely to take part. Additionally, participants with higher affective symptoms were less likely to have data for CRP available, which may have contributed to bias in analyses.

Future research & conclusions

These findings show that inflammation may contribute to the observed associations between accumulation of affective symptoms and memory function as early as in midlife, a period when differences in ageing related cognitive trajectories can first be observed prior to the presence of clinical cognitive impairment (56). Results revealed that observed associations between adult affective symptoms and information processing accuracy were independent of CRP level. Further research is needed to identify the particular biological mechanisms which may underlie this association.

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DECLARATIONS OF INTEREST

None

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TABLES AND FIGURE LEGENDS

Figure 1: Flow chart to show missing data patterns.

Figure 2: Significant pathways in fully adjusted model.

Table 1: Demographic information about sample included in fully adjusted model (n = 6276).

Table 2: Unadjusted and adjusted models showing direct, indirect and total associations between child and adult affective symptoms and mid-life cognitive outcomes.

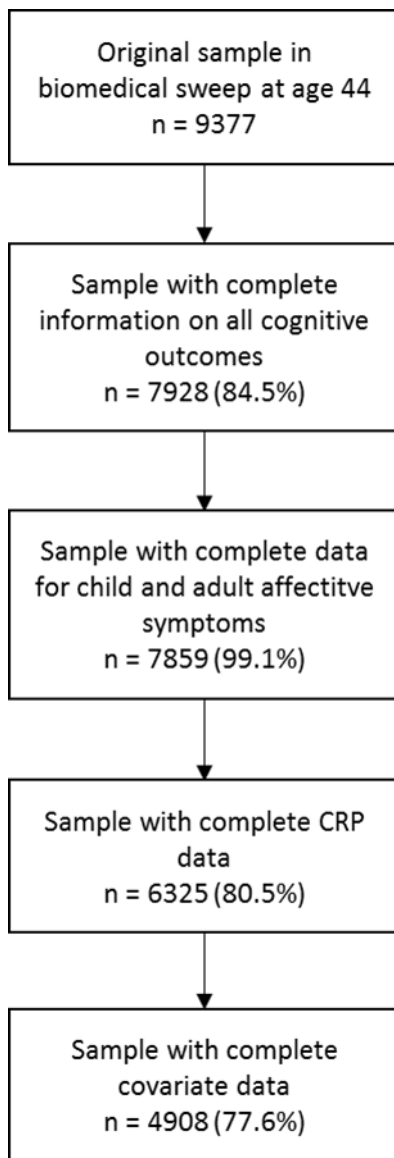


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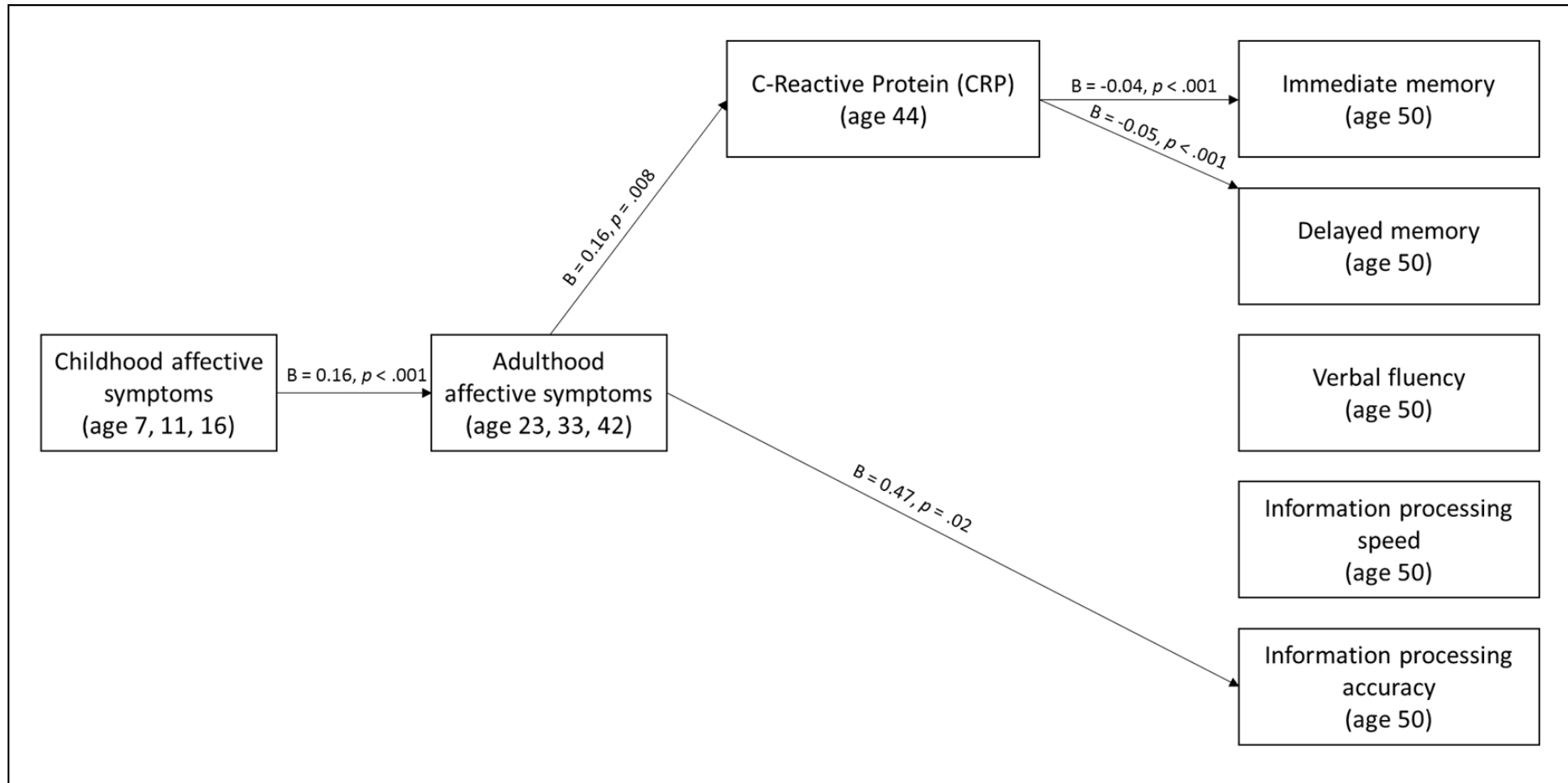


Figure 2: Significant pathways in fully adjusted model.

Measures		N (min/max)	Mean (SD) (unless specified otherwise)
Immediate memory		8131 (0/10)	6.60 (1.47)
Delayed memory		8078 (0/10)	5.49 (1.82)
Verbal fluency		8131 (0/65)	22.54 (6.25)
Information processing speed		7981 (84/780)	333.21 (87.78)
Information processing accuracy		7981 (0/48)	4.26 (3.89)
Child affective symptoms		9292 (-1.00/2.08)	0.03 (0.53)
Adult affective symptoms		9377 (-0.57/1.72)	0.05 (0.46)
Age 50 affective symptoms		9377 (-0.61/2.01)	0.07 (0.54)
CRP level		7462 (0.08/9.96)	1.61 (1.82)
Sex	Male		3067 (48.9)
N (%)	Female		3209 (51.1)
Child SEP N (%)	Middle		1356 (21.6)
	Intermediate		2326 (37.1)
	Working		2594 (41.3)
Childhood cognition	Reading		24.49 (6.32)
	Arithmetic		5.39 (2.43)
Education	Degree level		1626 (25.9)
N (%)	Up to A Level		565 (9.0)
	Up to GCSE Level		4085 (65.1)

Table 1: Demographic information about sample included in fully adjusted model (n = 6276).

		Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
Model 1: Unadjusted (N = 9292) (X2(1)=10.42, p=.001; CFI=1.00; TLI=0.97; RMSEA=0.03)						
	Direct	0.01 (0.03), .83	-0.02 (0.04), .59	-0.02 (0.14), .91	-2.02 (1.98), .31	0.06 (0.09), .53
Childhood/	Indirect (child AS -> CRP -> cognition)	0.00 (0.002), .90	0.00 (0.003), .90	0.001 (0.01), .90	0.00 (0.01), .93	0.00 (0.001), .90
adolescence	Indirect (child AS -> adult AS -> CRP -> cognition)	-0.003, (0.001), <.001	-0.004 (0.001), <.001	-0.01 (0.003), <.001	-0.004 (0.04), .91	0.001 (0.002), .40
affective symptoms	Indirect (child AS -> adult AS -> cognition)	-0.05 (0.01), <.001	-0.04, (0.01), <.001	-0.29 (0.03), <.001	0.64 (0.40), .11	0.11 (0.02), <.001
	Total direct and indirect	-0.04 (0.03), .19	-0.07 (0.04), .09	-0.32 (0.14), .02	-1.39 (1.94), .47	0.17 (0.09), .06
Adulthood	Direct	-0.26 (0.04), <.001	-0.24 (0.05), <.001	-1.61 (0.16), <.001	3.56 (2.22), .11	0.61 (0.10), <.001
affective symptoms	Indirect (adult AS -> CRP -> cognition)	-0.02 (0.004), <.001	-0.02 (0.01), <.001	-0.06 (0.02), <.001	-0.02 (0.19), .91	0.01 (0.01), .40
	Total	-0.28, (0.04), <.001	-0.26 (0.05), <.001	-1.67 (0.16), <.001	3.53 (2.21), .11	0.62 (0.10), <.001
Model 2: Fully adjusted (N = 6276) (X2(3)= 1.41, p=.70; CFI=1.00; TLI=1.00; RMSEA=0.00)						
	Direct	-0.02 (0.03), .59	-0.04 (0.04), .39	-0.03 (0.15), .86	-3.78 (2.14), .08	-0.05 (0.10), .61

Childhood affective symptoms	Indirect (child AS -> CRP -> cognition)	0.00 (0.002), .85	0.001 (0.002), .85	0.001 (0.004), .85	-0.01 (0.03), .85	0.00 (0.00), .94
	Indirect (child AS -> adult AS -> cognition)	-0.02 (0.01), .16	-0.003 (0.01), .82	-0.06 (0.05), .21	0.63 (0.73), .39	0.07 (0.03), .03
	Indirect (child AS -> adult AS -> CRP -> cognition)	-0.001 (0.00), .03	-0.001 (0.001), .03	-0.002 (0.001), .17	0.01 (0.02), .49	0.00 (0.001), .94
	Total	-0.05 (0.03), .12	-0.07 (0.04), .09	-0.17 (0.14), .24	-3.99 (2.10), .06	0.04 (0.10), .69
Adulthood affective symptoms	Direct	-0.10 (0.07), .16	-0.02 (0.09), .82	-0.39 (0.31), .21	4.03 (4.63), .39	0.47 (0.21), .02
	Indirect (adult AS -> CRP -> cognition)	-0.01 (0.003), .03	-0.01 (0.004), .03	-0.01 (0.01), .17	0.08 (0.11), .49	0.00 (0.01), .94
	Total	-0.22 (0.04), <.001	-0.24 (0.05), <.001	-0.92 (0.18), <.001	-1.32 (2.58), .61	0.55 (0.12), <.001
Sex		0.28 (0.04), <.001	0.47 (0.05), <.001	-0.05 (0.16), .74	25.09 (2.34), <.001	0.24 (0.11), .02
Education		0.25 (0.02), <.001	0.35 (0.03), <.001	1.26 (0.09), <.001	8.13 (1.39), <.001	0.11 (0.06), .08
Childhood cognition (maths)		0.06 (0.01), <.001	0.06 (0.01), <.001	0.27 (0.04), <.001	1.12 (0.54), .04	-0.05 (0.02), .05
Childhood cognition (reading)		0.03 (0.003), <.001	0.04 (0.004), <.001	0.08 (0.01), <.001	0.51 (0.21), .02	-0.04 (0.01), <.001
Childhood socioeconomic position		-0.07 (0.03), <.001	-0.06 (0.03), .06	-0.67 (0.11), <.001	-2.68 (1.55), .08	0.02 (0.07), .83
Affective symptoms at age 50		-0.11 (0.06), .07	-0.20 (0.08), .01	-0.51 (0.26), .05	-5.34 (3.78), .16	0.08 (0.17), .64

Table 2: Unadjusted and adjusted models showing direct, indirect and total associations between child and adult affective symptoms and mid-life cognitive outcomes.

			Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
N = 6276; (X2 (1) = 0.98, p = .32; CFI =1.00; TLI = 1.00; RMSEA = 0.00)							
Affective symptoms at each age	Age 7	Direct	-0.01 (0.03), .63	0.01 (0.03), .77	0.04 (0.03), .17	-0.02 (0.03), .57	0.03 (0.03), .34
		Indirect (AS -> CRP -> cognition)	0.003 (0.002), .15	0.003 (0.002), .15	0.001 (0.001), .27	0.00 (0.001), .53	0.00 (0.001), .93
		Total	-0.01 (0.03), .66	0.01 (0.03), .76	0.04 (0.03), .17	-0.02 (0.03), .55	0.03 (0.03), .34
	Age 11	Direct	0.02 (0.03), .66	-0.01 (0.03), .79	-0.06 (0.03), .08	0.04 (0.04), .32	-0.02 (0.04), .51
		Indirect (AS -> CRP -> cognition)	-0.004 (0.002), .06	-0.004 (0.002), .07	-0.002 (0.001), .21	0.001 (0.001), .52	0.00 (0.001), .93
		Total	0.01 (0.03), .72	-0.01 (0.03), .73	-0.06 (0.03), .08	0.04 (0.04), .30	-0.02 (0.04), .51
	Age 16 (mother rating)	Direct	-0.003 (0.03), .90	-0.01 (0.03), .81	0.03 (0.02), .16	-0.04 (0.03), .09	-0.02 (0.03), .54
		Indirect (AS -> CRP -> cognition)	0.002 (0.002), .15	0.002 (0.002), .15	0.001 (0.001), .28	0.00 (0.001), .53	0.00 (0.001), .93
		Total	-0.002 (0.03), .95	-0.01 (0.03), .85	0.03 (0.02), .16	-0.05 (0.03), .08	-0.02 (0.03), .54
	Age 16 (teacher rating)	Direct	-0.02 (0.01), .17	-0.01 (0.01), .37	-0.04 (0.01), .002	-0.01 (0.01), .49	0.02 (0.01), .22
		Indirect (AS -> CRP -> cognition)	-0.001 (0.001), .45	-0.001 (0.001), .45	0.00 (0.00), .49	0.00 (0.00), .61	0.00 (0.00), .93
		Total	-0.02 (0.01), .16	-0.01 (0.01), .36	-0.04 (0.01), .002	-0.01 (0.01), .50	0.02 (0.01), .22
	Age 23	Direct	-0.07 (0.03), .01	-0.04 (0.03), .17	-0.02 (0.03), .51	0.03 (0.03), .34	-0.02 (0.03), .58
		Indirect (AS -> CRP -> cognition)	-0.001 (0.002), .69	-0.001 (0.002), .69	0.00 (0.001), .70	0.00 (0.00), .73	0.0 (0.00), .93
		Total	-0.07 (0.03), .01	-0.04 (0.03), .14	-0.02 (0.03), .47	0.03 (0.03), .35	-0.02 (0.03), .58
Age 33	Direct	0.03 (0.03), .34	0.03 (0.03), .32	-0.003 (0.03), .94	0.00 (0.04), .99	0.04 (0.04), .23	
	Indirect (AS -> CRP -> cognition)	-0.002 (0.002), .46	-0.001 (0.002), .46	-0.001 (0.001), .50	0.00 (0.001), .61	0.00 (0.00), .93	
	Total	0.03 (0.03), .47	0.02 (0.03), .48	-0.01 (0.03), .79	-0.002 (0.04), .95	0.04 (0.04), .23	
Age 42	Direct	0.01 (0.03), .72	0.004 (0.03), .90	-0.004 (0.03), .90	-0.01 (0.03), .77	0.04 (0.03), .24	

	Indirect (AS -> CRP -> cognition)	0.001 (0.002), .53	0.001 (0.002), .53	0.00 (0.001), .56	0.00 (0.00), .64	0.00 (0.00), .93
	Total	-0.03 (0.03), .24	-0.05 (0.03), .07	-0.04 (0.03), .11	-0.03 (0.03), .29	0.04 (0.03), .14
N = 6276; (X2 (2) = 2.61, p = .27; CFI =1.00; TLI = 1.00; RMSEA = 0.007)						
	Direct	-0.02 (0.01), .21	-0.01 (0.01), .62	-0.02 (0.01), .18	-0.02 (0.02), .26	0.003 (0.02), .83
Accumulation of affective symptoms	Indirect (AS -> CRP -> cognition)	-0.002 (0.001), .03	-0.002 (0.001), .03	-0.001 (0.001), .17	0.00 (0.001), .47	0.00 (0.001), .94
	Total	-0.05 (0.01), <.001	-0.04 (0.01), <.001	-0.05 (0.01), <.001	-0.02 (0.01), .08	0.03 (0.01), .02

Table 3: Adjusted models showing direct, indirect and total associations between affective symptoms at each age and accumulation of affective symptoms with mid-life cognitive outcomes