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

Affective symptoms, cognitive function and inflammation

Amber John, PhD student, EDGE Lab, School of Psychology, University of Sussex, Brighton, United Kingdom

Jennifer Rusted, Professor of Experimental Psychology, School of Psychology, University of Sussex, Brighton, United Kingdom

Marcus Richards, Professor of Psychology and Programme Leader, MRC Unit for Lifelong Health and Ageing at UCL, London, United Kingdom

Darya Gaysina, Senior Lecturer in Psychology, EDGE Lab, School of Psychology, University of Sussex, Brighton, United Kingdom

Key words: Longitudinal; Birth cohort; Epidemiology; Inflammation; Affective symptoms; Cognitive function.

Abstract word count: 267

Main text word count: 3733

Declarations of interest: None

Correspondence to: Amber John, email: A.john@ucl.ac.uk phone: 01273 872547

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 (β=-0.01, SE=0.003, *p*=.03) and delayed memory (β=-0.01, SE=0.004, *p*=.03) via CRP. In addition, there were significant indirect associations between affective symptoms in childhood and immediate memory (β=-0.001, SE=0.00, *p*=.03) and delayed memory (β=-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 (β=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 2) 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 clas 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 disrtributions 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 (β = 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 (β = -0.04, SE = 0.01, p < .001) and delayed memory (β = -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 (β = -0.01, SE = 0.003, p = .03) and delayed memory (β = -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 (β = 0.07, SE = 0.03, p = .03) via adult affective symptoms. Finally, there were significant indirect associations between *childhood affective symptoms* and immediate memory (β = -0.001, SE = 0.00, p = .03) and delayed memory (β = -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 (β = -0.22, SE = 0.04, p < .001), delayed memory, (β = -0.24, SE = 0.05, p < .001), verbal fluency (β = -0.92, SE = 0.18, p < .001), and information processing accuracy (β = 0.55, SE = 0.12, p < .001), but not information

processing speed (β = -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 (β = -0.07, SE = 0.03, p = .01) and of affective symptoms at age 16 (teacher rated) on verbal fluency (β = -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 (β = -0.002, SE = 0.001, p = .03) and delayed memory (β = -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 (β = -0.05, SE = 0.01, p < .001), delayed memory (β = -0.05, SE = 0.01, p = .001), verbal fluency (β = -0.19, SE = 0.05, p < .001), and information processing accuracy (β = -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.

ACKNOWLEDGEMENTS

We would like to thank the Economic and Social Research Council (ESRC) for funding this project (Grant number: ES/J500173/1). We would also like to acknowledge the Centre for Longitudinal Studies (CLS), UCL for use of the data. Finally, we would like to thank the cohort members who have dedicated their time to participating in the National Child Development Study. Data governance was provided by the METADAC data access committee, funded by ESRC, Wellcome, and MRC. (2015-2018: Grant Number MR/N01104X/1 2018-2020: Grant Number ES/S008349/1). This work made use of data and samples generated by the 1958 Birth Cohort (NCDS) , which is managed by the Centre for Longitudinal Studies at the UCL Institute of Education, funded by the Economic and Social Research Council (grant number ES/M001660/1). Access to these resources was enabled via the Wellcome Trust & MRC: 58FORWARDS grant [108439/Z/15/Z] (The 1958 Birth Cohort: Fostering new Opportunities for Research via Wider Access to Reliable Data and Samples). Before 2015 biomedical resources were maintained under the Wellcome Trust and Medical Research Council 58READIE Project (grant numbers WT095219MA and G1001799). Data can be accessed upon application to METADAC.

DECLARATIONS OF INTEREST

None

REFERENCES

1. Jorm AF (2001): History of depression as a risk factor for dementia: an updated review. *Aust New Zeal J Psychiatry*. 36: 776–781.

2. Da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB (2013): Affective disorders and risk of developing dementia: Systematic review. *Br J Psychiatry*. 202: 177–186.

3. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F (2016): Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry*. 24: 823–842.

4. Ownby R, Crocco E, Acevedo A, John V, Loewenstein D (2006): Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. 63: 530–8.

5. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, *et al.* (2017): The Lancet International Commission on Dementia Prevention and Care. *Lancet*. 390: 2673–2734.

6. John A, Patel U, Rusted J, Richards M, Gaysina D (2018): Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis. *Psychol Med*. 49: 353–365.

7. James SN, Davis D, O'Hare C, Sharma N, John A, Gaysina D, *et al.* (2018): Lifetime affective problems and later-life cognitive state: over 50 years of follow-up in a British Birth Cohort Study. *J Affect Disord*. 241: 348–355.

8. John A, James S-N, Patel U, Rusted J, Richards M, Gaysina D (2019): Longitudinal associations of affective symptoms with midlife cognitive function: evidence from a

British birth cohort. *Br J Psychiatry*. In press.

9. Leonard BE, Myint A (2006): Inflammation and depression: Is there a causal connection with dementia? *Neurotox Res*. 10: 149–160.

10. Leonard BE (2007): Inflammation, depression and dementia: Are they connected? *Neurochem Res*. 32: 1749–1756.

11. Byers AAL, Yaffe K (2011): Depression and risk of developing dementia. *Nat Rev Neurol*. 7: 323–331.

12. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ (2002): Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol*. 52: 168–174.

13. Raison CL, Capuron L, Miller AH (2006): Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends Immunol*. 27: 24–31.

14. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008): From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 9: 46–56.

15. Valkanova V, Ebmeier KP, Allan CL (2013): CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *J Affect Disord*. 150: 736–744.

16. Maes M, Song C, Lin A, De Jongh R, Van Gastel A, Kenis G, *et al.* (1998): The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and Th1-like response in stress-induced anxiety. *Cytokine*. 10: 313–318.

17. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R (2003): Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci*. 100: 9090–9095.

18. Steptoe A, Hamer M, Chida Y (2007): The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behav Immun*. 21: 901–912.

19. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ (2012): Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. *Biol Psychiatry*. 71: 15–21.

20. Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, *et al.* (2009): Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-Year follow-up of the Whitehall II study. *Psychol Med*. 39: 413–423.

21. Matthews KA, Schott LL, Bromberger J, Cyranowski J, Everson-Rose SA, Sowers MF (2007): Associations between depressive symptoms and inflammatory/hemostatic markers in women during the menopausal transition. *Psychosom Med*. 69: 124–130.

22. Koyama A, O'Brien J, Weuve J, Blacker D, Metti AL, Yaffe K (2013): The role of peripheral inflammatory markers in dementia and Alzheimer's disease: A meta-analysis. *Journals Gerontol Ser A Biomed Sci Med Sci*. 68: 433–440.

23. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F (2005): Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: Systematic review and meta-analysis. *Lancet Neurol*. 4: 371–380.

24. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, *et al.* (2003): Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology*. 61: 76–80.

25. Power C, Elliott J (2006): Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol*. 35: 34–41.

26. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, Goddard R (1986): CAMDEX: A Standardised Instrument for the Diagnosis of Mental Disorder in the Elderly with Special Reference to the Early Detection of Dementia. *Br J Psychiatry*. 149: 698–709.

27. Brown M, Dodgeon B (2010): *NCDS cognitive assessments at age 50: initial results*. *CLS cohort Stud Work Pap*.

28. Winning A, Glymour MM, McCormick MC, Gilsanz P, Kubzansky LD (2015): Psychological Distress Across the Life Course and Cardiometabolic Risk Findings from the 1958 British Birth Cohort Study. *J Am Coll Cardiol*. 66: 1577–1586.

29. Clark C, Rodgers B, Caldwell T, Power C, Stansfeld S (2007): Childhood and adulthood psychological ill health as predictors of midlife affective and anxiety disorders: the 1958 British Birth Cohort. *Arch Gen Psychiatry*. 64: 668–678.

30. Rodgers B, Pickles A, Power C, Collishaw S, Maughan B (1999): Validity of the Malaise Inventory in general population samples. *Soc Psychiatry Psychiatr Epidemiol*. 34: 333–341.

31. Elliott J, Johnson J, Shepherd P (2008): User Guide to the Biomedical Survey 2002-2004 Dataset. *Natl Child Dev Study User Guid 2006*. 1–7.

32. Tabassum F, Kumari M, Rumley A, Lowe G, Power C, Strachan DP (2008): Effects of socioeconomic position on inflammatory and hemostatic markers: A life-course analysis in the 1958 British birth cohort. *Am J Epidemiol*. 167: 1332–1341.

33. Pepys MB, Hirschfield GM (2003): C-reactive protein: a critical update. *J Clin Invest*. 111: 1805–1812.

34. Lacey RE, Kumari M, Bartley M (2014): Social isolation in childhood and adult

inflammation: Evidence from the National Child Development Study. *Psychoneuroendocrinology*. 50: 85–94.

35. Lacey RE, Kumari M, McMunn A (2013): Parental separation in childhood and adult inflammation: The importance of material and psychosocial pathways. *Psychoneuroendocrinology*. 38: 2476–2484.

36. Richards M, Sacker A (2003): Lifetime antecedents of cognitive reserve. *J Clin Exp Neuropsychol*. 25: 614–624.

37. Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, Polvikoski T, Sulkava R (2010): Education, the brain and dementia: Neuroprotection or compensation? *Brain*. 133: 2210–2216.

38. Richards M, James S-N, Sizer A, Sharma N, Rawle MJ, Davis D, Kuh D (2019): Identifying the lifetime cognitive and socioeconomic antecedents of cognitive state: seven decades of follow-up in a British birth cohort study. *BMJ Open*.

39. Hatch SL, Jones PB, Kuh D, Hardy R, Wadsworth MEJ, Richards M (2007): Childhood cognitive ability and adult mental health in the British 1946 birth cohort. *Soc Sci Med*. 64: 2285–2296.

40. McGurn B, Deary IJ, Starr JM (2008): Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology*. 71: 1051–1056.

41. Kaplan GA, Turrell G, Lynch JW, Everson SA, Helkala E-L, Salonen JT (2001): Childhood socioeconomic position and cognitive function in adulthood. *Int J Epidemiol*. 30: 256–263.

42. Elliott J, Lawrence J (2014): Refining childhood social class measures in the 1958 British cohort study in the 1958 British birth cohort study. *Univ London Cent Longitud Stud Inst*

Educ.

43. Muthén L, Muthén B (2017): Mplus user's guide (eight edition)[Computer software manual]. *Los Angeles, CA*.

44. Enders C (2001): The performance of the full information maximum likelihood estimator in multiple regression models with missing data. *Educ Psychol Meas*. 61: 713–740.

45. Enders C (2001): A primer on maximum likelihood algorithms available for use with missing data. *Struct Equ Model*. 1: 128–141.

46. Enders C, Bandalos D (2001): The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Struct Equ Model*. 8: 430–457.

47. Colman I, Ploubidis GB, Wadsworth MEJ, Jones PB, Croudace TJ (2007): A Longitudinal Typology of Symptoms of Depression and Anxiety Over the Life Course. *Biol Psychiatry*. 62: 1265–1271.

48. Bettcher BM, Wilheim R, Rigby T, Green R, Miller JW, Racine CA, *et al.* (2012): C-reactive protein is related to memory and medial temporal brain volume in older adults. *Brain Behav Immun*. 26: 103–108.

49. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C (2012): Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. *Neurology*. 78: 720–727.

50. Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M, *et al.* (2010): Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. *Neurology*. 74: 1022–1029.

51. Gianaros PJ, Marsland AL, Sheu LK, Erickson KI, Verstynen TD (2013): Inflammatory

pathways link socioeconomic inequalities to white matter architecture. *Cereb Cortex*. 23: 2058–2071.

52. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR (2008): Interleukin-6 Covaries Inversely with Hippocampal Grey Matter Volume in Middle-Aged Adults. *Biol Psychiatry*. 64: 484–490.

53. Verstynen TD, Weinstein A, Marsland AL, Sheu LK, Erickson KI, Gianaros PJ (2013): Competing physiological pathways link individual differences in weight and abdominal adiposity to white matter microstructure. *Neuroimage*. 79: 129–137.

54. Marsland AL, Gianaros PJ, Kuan DCH, Sheu LK, Krajina K, Manuck SB (2015): Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun*. 48: 195–204.

55. Di Filippo M, Sarchielli P, Picconi B, Calabresi P (2008): Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders. *Trends Pharmacol Sci*. 29: 402–412.

56. Salthouse TA (2004): What and When of Cognitive Aging. *Curr Dir Psychol Sci*. 13: 140–144.

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.

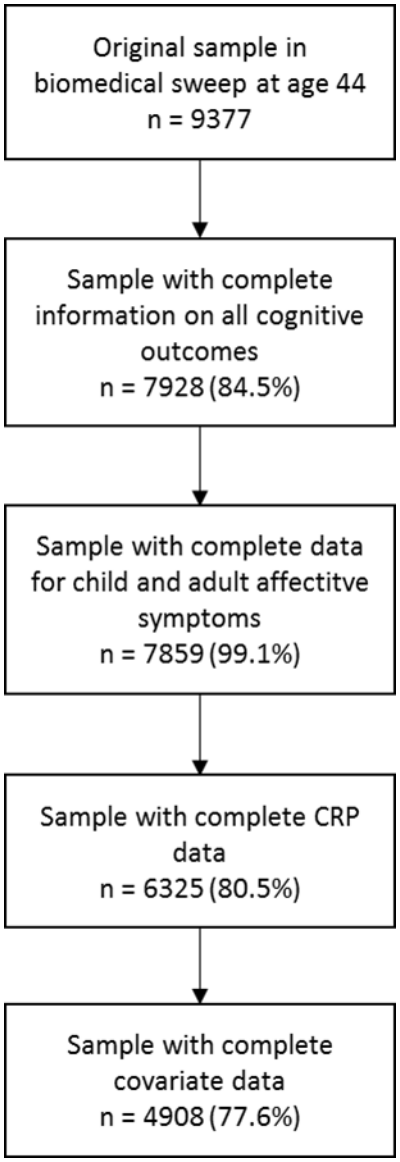

Figure 1: Flow chart to show missing data patterns.

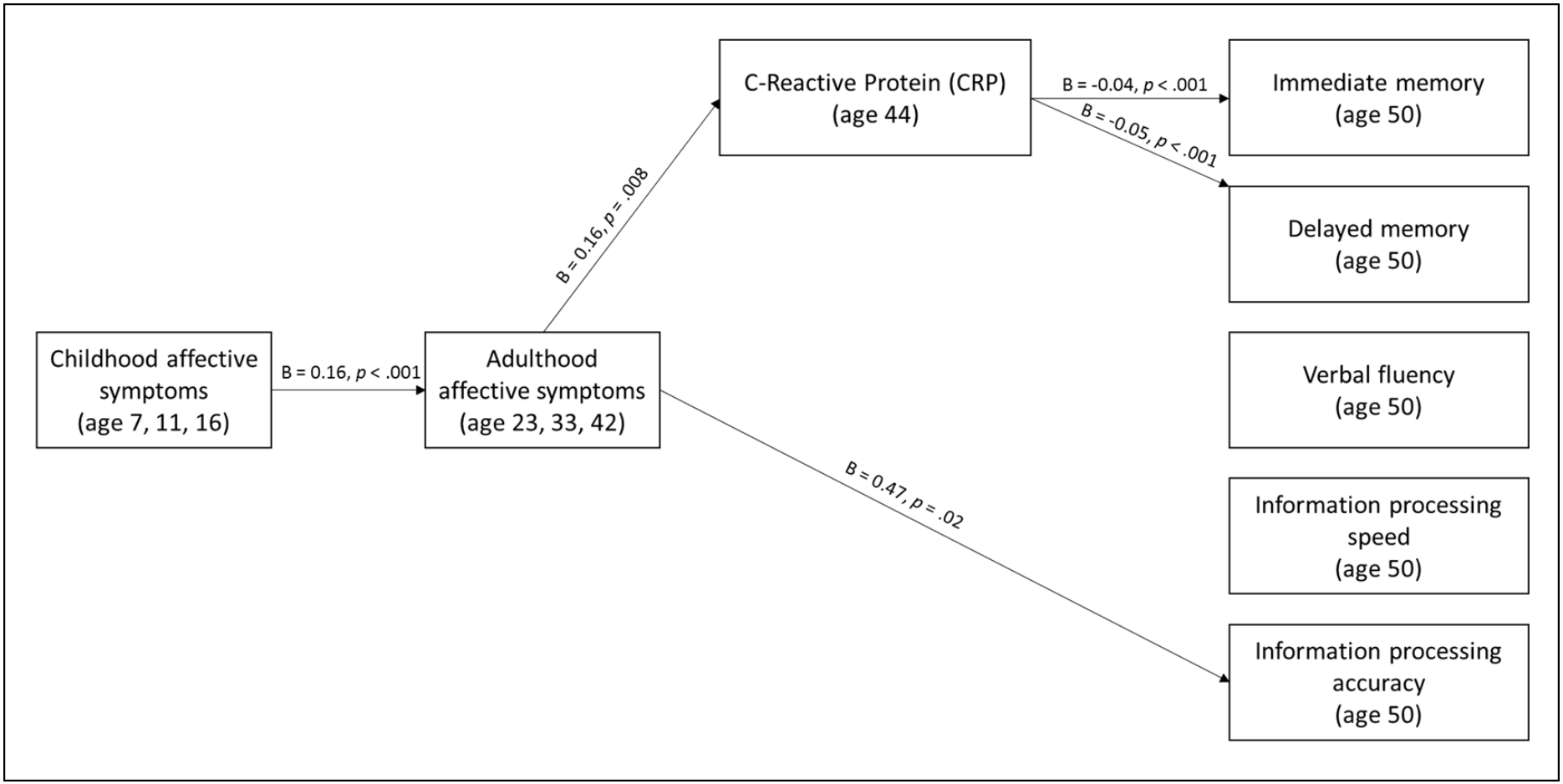

Figure 2: Significant pathways in fully adjusted model.

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 N (%)	Male		3067 (48.9)
	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 N (%)	Degree level		1626 (25.9)
	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 ->	**-0.003, (0.001),**	**-0.004 (0.001),**	**-0.01 (0.003), <.001**	-0.004 (0.04), .91	0.001 (0.002), .40
affective	cognition)	**<.001**	**<.001**			
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	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
symptoms	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

	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
Childhood affective symptoms	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 aeach 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)						
Accumulation of affective symptoms	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
	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