The role of cardiometabolic risk in the association between accumulation of affective symptoms across adulthood and midlife cognitive function

Amber John[1] PhD

Roopal Desai[1] DClinPsy

Marcus Richards[2] PhD

Darya Gaysina[3]* PhD / Joshua Stott[1]* PhD

*Joint senior author.

1. Research Department of Clinical, Educational, and Health Psychology, UCL, London
2. MRC Unit for Lifelong Health and Ageing at UCL, London
3. EDGE Lab, School of Psychology, University of Sussex, Brighton

Abstract word count: 234

Main text word count: 3379

Address for correspondence: Amber John, 8th Floor Euston House, London. Email: A.john@ucl.ac.uk; phone: 02031 085 868; Twitter: @AmberJohn715.

ABSTRACT

Background: Affective symptoms are associated with cognition in midlife and later life. However, the role of cardiometabolic risk in this association has not been examined.

Aims: The aim of this research was to investigate how cardiometabolic risk contributes to associations between affective symptoms and midlife cognition.

Method: Data were used from the National Child Development Study (NCDS), a sample of people born in Britain during one week in 1958. Affective symptoms were assessed at ages 23, 33, and 42 and a measure of accumulation derived. A cardiometabolic risk score was calculated from nine cardiometabolic biomarkers at age 44. Measures of memory, verbal fluency, and information processing were available at age 50.

Results: After accounting for missing data using multiple imputation, fully adjusted path models indicated significant indirect associations between affective symptoms and midlife immediate memory (β=-0.002, SE=0.001, p=.009), delayed memory (β=-0.002, SE=0.001, p=.02) and verbal fluency (β=-0.002, SE=0.001, p=.045) through cardiometabolic risk. Cardiometabolic risk did not predict subsequent affective symptoms or cognition at age 50.

Conclusions: These findings suggest that cardiometabolic risk may play an important indirect role in the association between affective symptoms and cognitive function (memory and verbal fluency). Results contribute to understanding of biological mechanisms underlying associations between affective symptoms and cognitive ageing, which can have implications for early detection of, and intervention for, those at risk of poorer cognitive outcomes.

Keywords: Depression; Anxiety; Cognitive ageing; Cardiometabolic health; Longitudinal; Birth cohort.

INTRODUCTION

Affective problems, such as depressive and anxiety symptoms and disorders, are important predictors of poorer cognitive function (1), faster cognitive decline (2), and constitute a risk factor for dementia (3) in older age. Understanding the pathways linking affective problems to later cognitive decline and dementia is a key public health priority, with important implications for dementia prevention (4). Various biological mechanisms have been proposed to underlie associations between affective symptoms and cognitive ageing (5), but to date, few of these have been systematically tested. One plausible biological mechanism is the cardiometabolic pathway (5). Cardiometabolic risk is an umbrella term which encompasses a cluster of cardiovascular and metabolic conditions, including insulin resistance, obesity, hypertension, dyslipidemia, and atherosclerosis. A dose-response relationship has been found between severity of depression and cardiometabolic risk (5,6) and persistence of affective symptoms over the life course has been shown to be a strong predictor of midlife cardiometabolic risk in NCDS (7). There is also increasing evidence that cardiometabolic risk factors are associated with accelerated cognitive ageing (8). Despite this, no research has systematically investigated whether the cardiometabolic pathway contributes to the association between affective symptoms and cognitive ageing and precisely how this association may operate. In particular, it is unknown whether the cardiometabolic risk may act as an indirect pathway between affective symptoms and cognitive ageing (indicative of mediation), or alternatively as a common cause contributing to both affective symptoms and cognitive outcomes. Consequently, the aim of this research was to test whether and how cardiometabolic risk may contribute to associations between affective symptoms and cognitive outcomes. Specifically, this study aims to test: 1 if there is an indirect path between accumulating affective symptoms and cognitive outcomes via cardiometabolic risk, something which would possibly be suggestive of a mediational role; and 2: whether

cardiometabolic risk predicts both affective symptoms and cognitive function at age 50, possibly suggestive of common cause.

METHOD

Participants

Data were from the National Child Development Study (NCDS), a sample of 17,415 people born in England, Scotland, and Wales during one week in March 1958. Data have been collected from cohort members a total of 11 times at ages 0, 7, 11, 16, 23, 33, 42, 44, 46, 50, and 55. Comprehensive detail about the sample, data collection methods, and attrition rates are published elsewhere and are freely available online (9). Data were made available upon application by METADAC who manage genetic and biomedical data for NCDS. Written informed consent was obtained from all subjects/patients. Ethical approval for the present study was provided by the University of Sussex (ER/AJ316/2).

Measures

Cognitive outcomes

Measures of immediate memory, delayed memory, verbal fluency, information processing speed, and information processing accuracy were available at age 50. Memory was assessed using a word list recall test, in which 10 words were presented visually and cohort members listed the words they could recall immediately after presentation and then again after a delay. Verbal fluency was assessed using the Animal Naming Task, in which cohort members listed as many animals as they could within a timed period. Information processing speed and accuracy were assessed using a letter cancellation task. The number of letters scanned within a timed period represented information processing speed, with number of errors made used as a measure of processing accuracy. Higher scores represent better performance for all cognitive outcomes, with the exception of information processing accuracy for which higher scores indicate more errors. These cognitive measures have been described in detail and are published elsewhere (10).

Affective symptoms

Affective symptoms in adulthood were measured at age 23, 33, and 42 using the Malaise Inventory scale, a 24 item self-completion questionnaire (11). This is a measure of psychological distress, including emotional disturbance and related physical symptoms. There is a validated cut off for clinical relevance (used in this study). Cohort members scoring 8 and above out of 24, the validated threshold for clinical relevance (11). were coded as having case level affective symptoms (i.e. a high risk of depression), and those scoring 7 and below were coded as having no symptoms. The Malaise Inventory Scale has been used frequently in previous research (7,12) and the internal consistency of this questionnaire is acceptable (11). In line with previous research (12), a measure of accumulating affective symptoms was derived by summing the binary malaise score at age 23, 33, and 42 to represent the number of time points through adulthood with case level affective symptoms (score range 0-3).

Cardiometabolic risk

At age 44, nine measures of cardiometabolic risk were assessed: 1. Total cholesterol; 2. High density lipoprotein (HDL) cholesterol – reverse scored; 3. Triglycerides; 4. Glycosylated hemoglobin (hba1c); 5. Systolic blood pressure; 6. Diastolic blood pressure; 7. C-Reactive Protein (CRP) (excluding values >10mg/l, which may be indicative of recent infection); 8. Fibrinogen; 9. Resting heart rate.

HDL cholesterol was reverse scored, so that for all biomarkers higher scores represent greater cardiometabolic dysfunction. These biomarkers were selected based on the previous research examining cardiometabolic risk in NCDS (7). Specifically, each of these nine variables are components of cardiometabolic risk. Biochemical analyses of blood samples used to collect information on HbA1c, triglycerides, total and HDL cholesterol, fibrinogen, and CRP is

published elsewhere and is described in depth in the NCDS biomedical user guide and the technical report (13,14).

These measures were used both as individual variables and to derive a composite measure of cardiometabolic risk. Measures of CRP and triglycerides were skewed in the direction of low risk and therefore were log transformed. Standardised z scores were derived for all biomarkers and then used in all subsequent analyses. As in previous work (7), z scores for each biomarker were summed to create an overall composite measure of cardiometabolic risk score. Higher scores on this derived measure represent greater cardiometabolic dysfunction.

Covariates

Covariates were selected based on variables known to be associated with cognitive function. Specifically, models were adjusted for sex (3), educational attainment (15), childhood socioeconomic position (16), childhood cognitive function (17), and affective symptoms contemporaneous with measurement of cognitive function (age 50). Education was measured as the highest academic achievement attained by age 50. This was classified into three categories: 1. No education; 2. GCSE to A-Level (or Scottish equivalent); 3. Higher education. Childhood socioeconomic position was derived according to guidelines from the Centre for Longitudinal Studies (CLS) (18), and was based on parental occupation and household tenure. This was coded into three categories: 1. Working class; 2. Intermediate class; 3. Middle class. Childhood cognitive function at age 11 was assessed using a general ability test (19), which cohort members completed at school. Affective symptoms at age 50 were assessed using the short-form of the Malaise Inventory Scale, which encompassed nine items (20), as the 24 item measure is not available at this age.

Analytical procedure

For main analyses, path models were run, estimating direct associations between accumulating affective symptoms and midlife cognitive function and indirect associations through the composite measure of cardiometabolic risk. The use of this composite score allows the model to take into account that combined small variations across multiple biomarkers can confer meaningful change in disease risk, regardless of the signal for any individual biomarker (21).

Next, an additional analysis was run to test whether associations between affective symptoms and cognitive function are driven by cardiometabolic risk as a common cause mechanism. To test this, a path model was conducted using a cardiometabolic risk score to predict cognitive function and affective symptoms at age 50.

Initial models were unadjusted and subsequent models were adjusted for the covariates. All cognitive measures were included together in the models to account for covariances between different cognitive domains. Non-significant covariances were removed from the model to improve fit. Stratifying analyses by sex did not significantly improve model fit (Supplementary Table 1), therefore sex was adjusted for in all subsequent models rather than used as a stratifying variable. Model fit was tested using standard fit statistics: Chi square goodness of fit test, Comparative Fit Index (CFI), Tucker Lewis Index (TLI) and Root Mean Square Error of Approximation (RMSEA). Missing data were accounted for using full information maximum likelihood (FIML) methods, in which model parameters and standard errors are estimated using all available data. All analyses were conducted in Mplus V8.(22)

In order to maximize the analytic sample size, main models were rerun using multiple imputation to impute all covariate data. In total, 21 variables were imputed over five sweeps using the MICE package in R. Main models were re-run on the imputed dataset (N=9377).

Supplementary analyses

To check whether indirect associations between affective symptoms and cognitive outcomes were driven primarily by any particular individual biomarker, an additional model was run in which the nine biomarkers were included in the model individually. This approach allows the effects of each biomarker to be estimated, while simultaneously accounting for covariances between these markers. Following relevant work in NCDS, sensitivity analyses were conducted with models additionally adjusted for cardiovascular medication use (7).

RESULTS

Missing data and descriptive statistics

The biomedical sweep at age 44 included 9,377 participants. Of this sample, 3,730 people had complete information for all key variables and covariates (Supplementary Figure 1). This sub-sample was compared to the sample with missing data on key variables (Supplementary Table 2). This revealed that people with missing data had significantly poorer scores for all cognitive tests (including childhood) except processing speed; had reported more episodes of affective symptoms from age 23 to 42 and higher affective symptoms at age 50; were more likely to be categorized as working class, have lower education, and to take cardiovascular medication; and showed significantly higher levels of all cardiometabolic biomarkers. However, there were no sex differences in probability of missing data. Missing data were addressed using FIML, resulting in an analytic sample of 6,405 people in fully adjusted models. Main models were also conducted on the imputed sample, resulting in a sample of 9,377 in fully adjusted models. Demographic information is presented in Table 1.

Research question 1: Indirect pathway model

Both the unadjusted and adjusted FIML model fit the data well (Unadjusted: N=6682; $\chi^2(1)=5.91$, $p=.02$; CFI=1.00; TLI=0.99; RMSEA=0.03; Adjusted: N=6403; $\chi^2(2)=1.24$, $p=.54$; CFI=1.00; TLI=1.00; RMSEA=0.00). The model conducted on the imputed sample also fit to the data well (N=9377; $\chi^2(2)=6.22$, $p=.04$; CFI=1.00; TLI=0.99; RMSEA=0.02)

Direct effects

Unadjusted FIML models showed significant direct effects of accumulating affective symptoms across adulthood on midlife immediate memory (β=-0.09, SE=0.01, $p<.001$), delayed memory (β=-0.08, SE=0.01, $p<.001$), verbal fluency (β=-0.09, SE=0.01, $p<.001$), and information processing accuracy (β=0.05, SE=0.01, $p<.001$), but not for information

processing speed. However, there were no significant direct effects of affective symptoms on any cognitive domain after adjustment for all covariates (Table 2; Figure 1). Similarly, the fully adjusted model conducted on the imputed sample revealed no significant direct effects of affective symptoms on any cognitive domain (Table 2; Figure 1).

Indirect effects

In the unadjusted FIML model, there were significant indirect effects of affective symptoms on immediate memory, delayed memory, verbal fluency, and information processing speed operating through composite cardiometabolic risk score (immediate memory: β=-0.01, SE=0.002, *p*=.008; delayed memory: β=-0.01, SE=0.002 *p*=.008; verbal fluency: β=-0.003, SE=0.001, *p*=.01; information processing speed: β=-0.003, SE=0.001, *p*=.02). There was no effect for information processing accuracy. After adjustment for covariates, there was still a significant indirect effect of accumulating affective symptoms on immediate memory (β=-0.002, SE=0.001, *p*=.02), accounting for 4% of the total effect (Table 2; Figure 1). The fully adjusted model run on the imputed sample revealed significant indirect effects of accumulating affective symptoms on immediate memory (β=-0.002, SE=0.001, *p*=.009), delayed memory (β=-0.002, SE=0.001, *p*=.02) and verbal fluency (β=-0.002, SE=0.001, *p*=.045), through the composite cardiometabolic risk score. This accounted for 4%, 4%, and 5% of the total effect respectively. There were no significant indirect effects on information processing speed or accuracy (Table 2, Figure 1).

Total effects

In the unadjusted model, there were significant total effects of accumulating affective symptoms on immediate memory (β=-0.09, SE=0.01, *p*<.001), delayed memory (β=-0.08, SE=0.01, *p*<.001), verbal fluency (β=-0.09, SE=0.01, p<.001), and information processing accuracy (β=0.05, SE=0.01, p<.001), but not information processing speed. After adjusting

for covariates, significant total effects remained for immediate memory (β=-0.05, SE=0.01, p=.001), delayed memory (β=-0.05, SE=0.01, p<.001), and information processing accuracy (β=0.04, SE=0.01, p=.01), but not for verbal fluency or information processing speed (Table 2; Figure 1). The adjusted model conducted on the imputed sample revealed significant total effects of accumulating 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=-0.04, SE=0.01, *p*=.003) and information processing accuracy (β=0.04, SE=0.01, *p*=.01), but not on information processing speed (Table 2; Figure 1).

Research question 2: Common cause model

Next, a model was run using cardiometabolic risk score at age 44 as a predictor of affective symptoms and cognitive function at age 50 to test cardiometabolic risk as a potential common cause. The model fit the data well (N= 3847; $\chi^2(18)=34.27$, *p*=.01; CFI=1.00; TLI=0.99; RMSEA=0.02). Fully adjusted models revealed that cardiometabolic risk significantly predicted immediate memory (β=-0.04, SE=0.02, *p*=.008), but not other cognitive outcomes. Additionally cardiometabolic risk did not significantly predict affective symptoms at age 50 (β=0.002, SE=0.01, *p*=.90) (Table 3). The adjusted model conducted on the imputed sample fit to the data well (N=5288; $\chi^2(18)=36.23$, *p*=.007; CFI=1.00; TLI=0.99; RMSEA=0.01). The analysis on imputed data revealed that cardiometabolic risk score at age 44 was significantly associated with poorer scores of immediate memory (β=-0.04, SE=0.02, *p*=.003), delayed memory (β=-0.03, SE=0.02, *p*=.048), and verbal fluency (β=-0.03, SE=0.02, *p*=.03) at age 50. However, cardiometabolic risk at age 44 was not significantly associated with affective symptoms at age 50 (β=0.02, SE=0.01, *p*=.24) (Table 3).

Supplementary analysis

The model including nine individual biomarkers as predictors fit the data well (N=6405; $\chi^2(12)=33.29$, $p<.001$; CFI=1.00; TLI=0.99; RMSEA=0.02). In fully adjusted models including all covariates and individual cardiometabolic biomarkers, there were no significant direct effects of accumulating affective symptoms on cognitive outcomes. There was a significant indirect path between accumulating affective symptoms and delayed memory through fibrinogen (β=-0.003, SE=0.001, $p=.03$), accounting for 6% of the total effect. All other indirect paths were not significant at the 5% level in adjusted models. There were significant total effects of accumulating affective symptoms on immediate memory (β=-0.05, SE=0.01, $p=.001$), delayed memory (β=-0.05, SE=0.01, $p<.001$), and information processing accuracy (β=0.04, SE=0.01, $p=.01$), but not for verbal fluency or information processing speed (Supplementary Table 3).

Additional analyses were conducted additionally adjusting for cardiovascular medication use. The model fit the data well (N= 6370; $\chi^2(3)=12.12$, $p=.007$; CFI=1.00; TLI=0.98; RMSEA=0.02). Results were largely identical to those reported in main models (Supplementary Table 4).

DISCUSSION

Summary of findings

Results across models using two missing data methods (FIML and multiple imputation) both revealed significant indirect associations between accumulation of affective symptoms and immediate memory through a composite cardiometabolic risk score. Additionally, models using multiple imputation revealed significant indirect associations on delayed memory and verbal fluency. Additional associations may have been revealed in the model using imputed data due to extra power associated with increasing the sample size. There were no significant indirect paths observed between symptoms and other cognitive domains (information processing). These results build on previous research which show associations between affect and cardiometabolic risk, and also between cardiometabolic risk and cognitive outcomes (7,23) but had not investigated the role cardiometabolic risk might play in the known relationship between affect and later cognition. These results do not support the common cause hypothesis that cardiometabolic risk may precede both development of affective symptoms and cognitive dysfunction, because in this data cardiometabolic risk score did not predict subsequent level of affective symptoms.

There are several plausible mechanisms, which may account for the observed associations. For example, accumulated affective symptoms may be associated with cardiometabolic risk due to behavioural/lifestyle factors with known associations to dementia and cognitive ageing (e.g. smoking, alcohol, physical activity) (24). Additionally, affective symptoms may be linked with cardiometabolic risk through biological pathways (e.g. through HPA dysregulation, inflammatory processes, sympathetic nervous system activity) (25), which can also be associated with later cognitive health. The mechanisms which underlie these observed associations are likely to be complex and multifaceted.

It should be noted that effect sizes are small and account for only small amounts of the total effects. This suggests that, cardiometabolic risk may be one of multiple underlying pathways and other lifestyle and biomedical factors are likely to play an important role within the association between affective symptoms and cognitive ageing. Further understanding these relationships may be important for appropriate targeting of intervention and advice for amelioration of cognitive risk in the context of high levels of affective symptoms,

Strengths and limitations

Strengths of this research include the use of a large nationally representative cohort, with prospective data available from birth through to midlife over a period of five decades. Additionally, the repeated use of the same instrument to capture affective symptoms over time is a strength of this study. Affective symptoms contemporaneous with cognitive function were included in the models, reducing the possibility that associations between affective symptoms and later cognitive function are simply due to cross sectional associations at age 50. Limitations included missing data, a limitation of most long-running cohort studies. In this study, the sample with missing data differed significantly from the sample with complete information on a range of key variables, including cognitive scores, levels of affective symptoms, and demographic information. The sample with missing data showed higher affective symptoms, poorer cognitive function, and raised cardiometabolic symptoms, and as such associations may be underestimated in this analysis. To address this in these analyses, multiple imputation and FIML were used. It is important to note however that if data is missing not at random (MNAR), these methods may be less appropriate. Additionally, a further limitation of the study is that the number of individuals with case level affective symptoms is relatively small, which may lead to a possible underestimation of effects.

Additionally, cardiometabolic biomarkers were only measured at one time point (age 44). Therefore, the possibility of reverse causality cannot be ruled out. However, we ran a supplementary analysis to partially address this using cardiometabolic risk score as a predictor of later affective symptoms at age 50. These results showed that the association did not operate in the opposite direction and cardiometabolic risk did not predict subsequent affective symptoms. Furthermore, although we adjusted for cardiovascular medication use in a sensitivity analysis, there was no measure of psychotropic medication use, which was consequently not accounted for in the present analyses. Additionally, cognitive data were only available at one time point in this dataset at age 50, so it will be valuable to model cognitive trajectories in a future study. Related to this, it is currently unknown the extent to which midlife cognitive function in this cohort is relevant to dementia risk decades later. This can be tested in this cohort in the future with repeated follow-up assessment of cognitive function and dementia status as participants transition into older adulthood. Finally, the cognitive assessments were limited in breadth, meaning that conclusions cannot be drawn for other cognitive domains not measured in NCDS (e.g. executive functions).

Future research and implications

Overall, these findings provide strong evidence across two missing data methods that cardiometabolic health may contribute to the relationship between accumulating affective symptoms over adulthood and midlife immediate memory. The findings also provide preliminary evidence to suggest that cardiometabolic risk may also contribute to associations between affective symptoms and delayed memory and verbal fluency. Only a small amount of the total effect of affective symptoms on cognitive function was accounted for by the indirect effect through cardiometabolic risk. This suggests that cardiometabolic risk is likely one of multiple pathways operating in this association. Other potential pathways may involve

complex interactions between lifestyle and biological factors. Future research should aim to identify and test these mechanisms.

Affective symptoms present during late life are considered a recognised risk factor for dementia. However, it remains unclear whether this represents a flare-up of earlier depressive symptoms and associated cardiometabolic risk, or whether affective symptoms later in the life course also have direct effects on dementia risk.

These findings have potentially important implications for prevention, specifically the possibility that early intervention to improve cardiometabolic health in people with affective symptoms may help to prevent poorer cognitive outcomes later in the life course. Future research should focus on testing this clinically relevant hypothesis.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the University of Sussex (ER/AJ316/2).

CONSENT STATEMENT

Written informed consent was obtained from all subjects/patients.

AUTHOR DETAILS

Amber John[1] PhD

Roopal Desai[1] DClinPsy

Marcus Richards[2] PhD

Darya Gaysina[3]* PhD / Joshua Stott[1]* PhD

*Joint senior author.

1. Research Department of Clinical, Educational, and Health Psychology, UCL, London
2. MRC Unit for Lifelong Health and Ageing at UCL, London
3. EDGE Lab, School of Psychology, University of Sussex, Brighton

Corresponding author: Amber John, 8th Floor Euston House, London. Email: A.john@ucl.ac.uk; phone: 02031 085 868; Twitter: @AmberJohn715.

REQUIRED STATEMENTS

Declaration of interest: None

Funding: Economic and Social Research Council (DG, AJ: Grant number: ES/J500173/1). Alzheimer's Society (JS, MR: MODIFY Project; Grant number: AS-PG-18-013).

Acknowledgements:

We would like to thank the Economic and Social Research Council (ESRC) for supporting this project (Grant number: ES/J500173/1) and the Centre for Longitudinal Studies (CLS), for allowing use of the data. We would also like to acknowledge Alzheimer's Society for supporting this work (MODIFY Project; Grant number: AS-PG-18-013). Thank you to the NCDS 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. The funder was not involved in the study design; collection, analysis, and interpretation of data; writing the report; or in the decision to submit the article for publication.

Author contributions:

Amber John: Involved in the design of study, running statistical analysis, interpreting results, drafting the article and editing it.

Roopal Desai: Involved in the interpretation of data, and critically evaluating the article for important intellectual content.

Marcus Richards: Involved in the design of the study, the interpretation of data, and critically evaluating the article for important intellectual content.

Darya Gaysina: Involved in the design of the study, the interpretation of data, and critically evaluating the article for important intellectual content.

Josh Stott: Involved in the design of the study, the interpretation of data, and critically evaluating the article for important intellectual content.

Data availability: Data is available upon application to METADAC.

REFERENCES

1. James SN, Davis D, O'Hare C, Sharma N, John A, Gaysina D, et al. Lifetime affective problems and later-life cognitive state: over 50 years of follow-up in a British Birth Cohort Study. J Affect Disord. 2018;241:348–55.

2. John A, Patel U, Rusted J, Richards M, Gaysina D. Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis. Psychol Med. 2018;49(3):353–65.

3. Da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: Systematic review. Br J Psychiatry. 2013;202(3):177–86.

4. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. The Lancet International Commission on Dementia Prevention and Care. Lancet [Internet]. 2017;390(10113):2673–734. Available from: http://discovery.ucl.ac.uk/1567635/1/Livingston_Dementia_prevention_intervention_care.pdf

5. Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci. 2008;10(3):345–57.

6. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: What is the relationship? J Affect Disord. 2004;79(1–3):81–95.

7. Winning A, Glymour MM, McCormick MC, Gilsanz P, Kubzansky LD. Psychological Distress Across the Life Course and Cardiometabolic Risk Findings from the 1958 British Birth Cohort Study. J Am Coll Cardiol. 2015;66(14):1577–86.

8. Bhat NR. Linking cardiometabolic disorders to sporadic Alzheimer's disease: A perspective on potential mechanisms and mediators. J Neurochem. 2010;115(3):551–62.

9. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol. 2006;35(1):34–41.

10. Brown M, Dodgeon B. NCDS cognitive assessments at age 50: initial results. CLS cohort studies, working paper. 2010.

11. Rodgers B, Pickles A, Power C, Collishaw S, Maughan B. Validity of the Malaise Inventory in general population samples. Soc Psychiatry Psychiatr Epidemiol. 1999;34(6):333–41.

12. John A, James S-N, Patel U, Rusted J, Richards M, Gaysina D. Longitudinal associations of affective symptoms with midlife cognitive function: evidence from a British birth cohort. Br J Psychiatry. 2019;215(5):675–82.

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

14. Fuller E, Power C, Shepherd P, Strachan D. Technical report on the National Child Development Study biomedical survey 2002-2004. Natl Cent Soc Res [Internet]. 2006; Available from: http://www.cls.ioe.ac.uk

15. Hatch S, Feinstein L, Link BG, Wadsworth M, Richards M. The Continuing Benefits of Education : Adult Education and Midlife Cognitive Ability in the British 1946 Birth Cohort. J Gerontol. 2007;62(6):404–14.

16. Kaplan GA, Turrell G, Lynch JW, Everson SA, Helkala E-L, Salonen JT. Childhood socioeconomic position and cognitive function in adulthood. Int J Epidemiol.

2001;30(2):256–63.

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

18. Elliott J, Lawrence J. 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. 2014;

19. Douglas JWB. The home and the school: A study of ability and attainment in the primary school. London: MacGibbon & Kee; 1964.

20. Bowling A, Pikhartova J, Dodgeon B. Is mid-life social participation associated with cognitive function at age 50? Results from the British National Child Development Study (NCDS). BMC Psychol. 2016;4(1):58.

21. Winning A, Glymour MM, McCormick MC, Gilsanz P, Kubzansky LD. Childhood psychological distress as a mediator in the relationship between early-life social disadvantage and adult cardiometabolic risk: evidence from the 1958 British Birth Cohort. Psychosom Med. 2016;78(9):1019–30.

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

23. Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, et al. Metabolic syndrome and risk for incident Alzheimer's Disease or vascular dementia. Diabetes Care. 2009;32(1):169–74.

24. Bonnet F, Irving K, Terra JL, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular

disease. Atherosclerosis. 2005;178(2):339–44.

25. Dhar AK, Barton DA. Depression and the link with cardiovascular disease. Front psychiatry. 2016;7:33.

TABLES AND FIGURES

Table 1: Demographic information of the sample who took part in the biomedical sweep of NCDS (N=9,377).

Table 2: Adjusted models testing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, via cardiometabolic risk.

Figure 1: Path analysis models: Fully adjusted models showing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, via cardiometabolic risk.

Table 3: Model using CMR score to predict affective symptoms and cognitive function at age 50.

Table 1: Demographic information of the sample who took part in the biomedical sweep of NCDS (N=9,377).

Measures		Sample in biomedical sweep of NCDS (N=9,377)	
		N (%)	Mean (SD)
Immediate memory		-	6.59 (1.48)
Delayed memory		-	5.47 (1.84)
Verbal fluency		-	22.43 (6.29)
Information processing speed		-	333.61 (88.01)
Information processing accuracy		-	4.32 (3.98)
Number of time points with affective symptoms from age 23 to 42	0 times	5754 (83.3)	-
	1 time	781 (11.3	-
	2 times	266 (3.9)	-
	3 times	105 (1.5)	-
Affective symptoms at age 50		-	1.44 (1.90)
Sex (Female)		4712 (50.3)	-
Childhood cognition		-	45.42 (15.41)
Household socioeconomic position	Working	3238 (41.7)	-
	Intermediate	2880 (37.1)	-
	Middle	1652 (21.3)	-
Education	No academic qualification	1323 (16.1)	-
	GCSE to A Level (or Scottish equivalent)	4781 (58.3)	-
	Higher education	2091 (25.5)	-
Cardiovascular medication (yes)		757 (8.1)	-

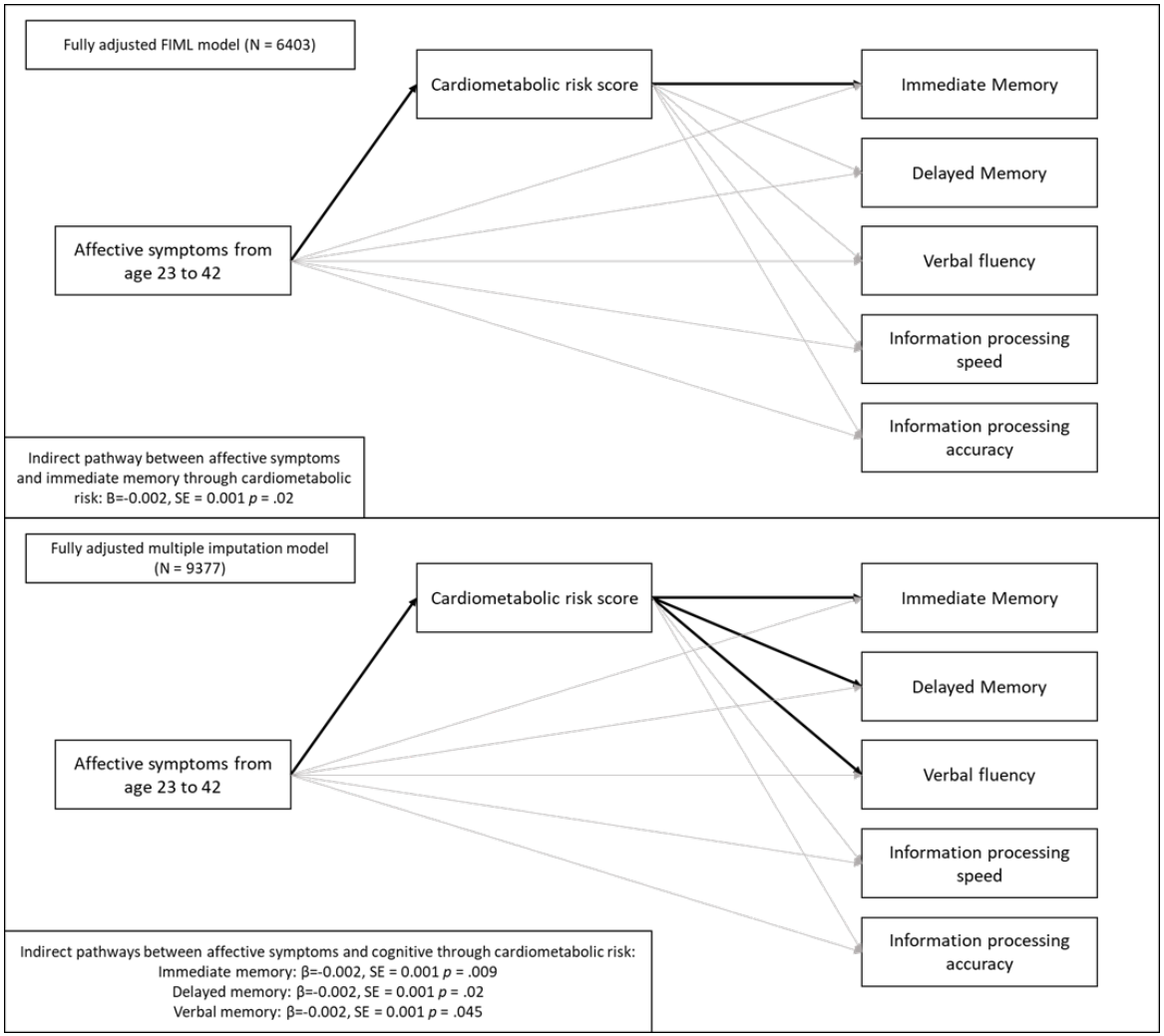
Table 2: Adjusted models testing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, via cardiometabolic risk.

	Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
FIML Model (N=6403; $X^2(2)=1.24$, $p=.54$; CFI=1.00; TLI=1.00; RMSEA=0.00)					
Direct	-0.02 (0.02), .17*	-0.03 (0.02), .10	0.00 (0.02), .98	0.03 (0.02), .06	0.03 (0.02), .11
Indirect	-0.002 (0.001), .02	-0.001 (0.001), .10	-0.001 (0.001), .30	0.00 (0.001), .57	-0.001 (0.001), .23
Total**	-0.05 (0.01), .001	-0.05 (0.01), < .001	-0.02 (0.01), .15	0.02 (0.01), .15	0.04 (0.01), .01
Multiple Imputation Model (N=9377; $X^2(2)=6.22$, $p=.04$; CFI=1.00; TLI=0.99; RMSEA=0.02)					
Direct	-0.03 (0.01), .09	-0.02 (0.01), .12	-0.02 (0.01), .19	0.03 (0.02), .10	0.02 (0.02), .16
Indirect	-0.002 (0.001), .009	-0.002 (0.001), .02	-0.002 (0.001), .045	-0.001 (0.001), .35	-0.001 (0.001), .53
Total	-0.05 (0.01), <.001	-0.05 (0.01), <.001	-0.04 (0.01), .003	0.02 (0.01), .14	0.04 (0.01), .01

* β (SE), *p*.

** Total effects include direct effects of affective symptoms on cognitive outcomes and indirect effects through cardiometabolic biomarkers and affective symptoms at age 50.

Figure 1: Path analysis models: Fully adjusted models showing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, via cardiometabolic risk.



* Significant pathways in bold. Models using FIML and multiple imputation are both presented.

Table 3: Model using CMR score to predict affective symptoms and cognitive function at age 50.

	Model using FIML N = 3847; X2(18)=34.27, p=.01; CFI=1.00; TLI=0.99; RMSEA=0.02	**Model using multiple imputation** N=5288; X2(18)=36.23, p=.007; CFI=1.00; TLI=0.99; RMSEA=0.01
Affective symptoms age 50	0.002 (0.01), .90*	0.02 (0.01), .24
Immediate memory	-0.04 (0.02), .008	-0.04 (0.02), .003
Delayed memory	-0.02 (0.02), .24	-0.03 (0.02), .048
Verbal fluency	-0.01 (0.02), .45	-0.03 (0.02), .03
Information processing speed	0.001 (0.02), .96	-0.01 (0.02), .73
Information processing accuracy	-0.02 (0.02), .37	-0.01 (0.02), .66

*β (SE), *p*.