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

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1 **ABSTRACT**

2 **Background:** Affective symptoms are associated with cognition in midlife and later life.

3 However, the role of cardiometabolic risk in this association has not been examined.

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

6 **Method:** Data were used from the National Child Development Study (NCDS), a sample of
7 people born in Britain during one week in 1958. Affective symptoms were assessed at ages
8 23, 33, and 42 and a measure of accumulation derived. A cardiometabolic risk score was
9 calculated from nine cardiometabolic biomarkers at age 44. Measures of memory, verbal
10 fluency, and information processing were available at age 50.

11 **Results:** After accounting for missing data using multiple imputation, fully adjusted path
12 models indicated significant indirect associations between affective symptoms and midlife
13 immediate memory ($\beta=-0.002$, $SE=0.001$, $p=.009$), delayed memory ($\beta=-0.002$, $SE=0.001$,
14 $p=.02$) and verbal fluency ($\beta=-0.002$, $SE=0.001$, $p=.045$) through cardiometabolic risk.
15 Cardiometabolic risk did not predict subsequent affective symptoms or cognition at age 50.

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

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

1 INTRODUCTION

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

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

3

4

1 **METHOD**

2 **Participants**

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

11 **Measures**

12 *Cognitive outcomes*

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

1 *Affective symptoms*

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

14 *Cardiometabolic risk*

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

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

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

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

9 *Covariates*

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

23 **Analytical procedure**

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

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

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

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

24 **Supplementary analyses**

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

7

1 RESULTS

2 Missing data and descriptive statistics

3 The biomedical sweep at age 44 included 9,377 participants. Of this sample, 3,730 people
4 had complete information for all key variables and covariates (Supplementary Figure 1). This
5 sub-sample was compared to the sample with missing data on key variables (Supplementary
6 Table 2). This revealed that people with missing data had significantly poorer scores for all
7 cognitive tests (including childhood) except processing speed; had reported more episodes of
8 affective symptoms from age 23 to 42 and higher affective symptoms at age 50; were more
9 likely to be categorized as working class, have lower education, and to take cardiovascular
10 medication ; and showed significantly higher levels of all cardiometabolic biomarkers.
11 However, there were no sex differences in probability of missing data. Missing data were
12 addressed using FIML, resulting in an analytic sample of 6,405 people in fully adjusted
13 models. Main models were also conducted on the imputed sample, resulting in a sample of
14 9,377 in fully adjusted models. Demographic information is presented in Table 1.

15 Research question 1: Indirect pathway model

16 Both the unadjusted and adjusted FIML model fit the data well (Unadjusted: N=6682;
17 $\chi^2(1)=5.91, p=.02$; CFI=1.00; TLI=0.99; RMSEA=0.03; Adjusted: N=6403; $\chi^2(2)=1.24,$
18 $p=.54$; CFI=1.00; TLI=1.00; RMSEA=0.00). The model conducted on the imputed sample
19 also fit to the data well (N=9377; $\chi^2(2)=6.22, p=.04$; CFI=1.00; TLI=0.99; RMSEA=0.02)

20 *Direct effects*

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

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

5 *Indirect effects*

6 In the unadjusted FIML model, there were significant indirect effects of affective symptoms
7 on immediate memory, delayed memory, verbal fluency, and information processing speed
8 operating through composite cardiometabolic risk score (immediate memory: $\beta=-0.01$,
9 $SE=0.002$, $p=.008$; delayed memory: $\beta=-0.01$, $SE=0.002$ $p=.008$; verbal fluency: $\beta=-0.003$,
10 $SE=0.001$, $p=.01$; information processing speed: $\beta=-0.003$, $SE=0.001$, $p=.02$). There was no
11 effect for information processing accuracy. After adjustment for covariates, there was still a
12 significant indirect effect of accumulating affective symptoms on immediate memory ($\beta=-$
13 0.002 , $SE=0.001$, $p=.02$), accounting for 4% of the total effect (Table 2; Figure 1). The fully
14 adjusted model run on the imputed sample revealed significant indirect effects of
15 accumulating affective symptoms on immediate memory ($\beta=-0.002$, $SE=0.001$, $p=.009$),
16 delayed memory ($\beta=-0.002$, $SE=0.001$, $p=.02$) and verbal fluency ($\beta=-0.002$, $SE=0.001$,
17 $p=.045$), through the composite cardiometabolic risk score. This accounted for 4%, 4%, and
18 5% of the total effect respectively. There were no significant indirect effects on information
19 processing speed or accuracy (Table 2, Figure 1).

20 *Total effects*

21 In the unadjusted model, there were significant total effects of accumulating affective
22 symptoms on immediate memory ($\beta=-0.09$, $SE=0.01$, $p<.001$), delayed memory ($\beta=-0.08$,
23 $SE=0.01$, $p<.001$), verbal fluency ($\beta=-0.09$, $SE=0.01$, $p<.001$), and information processing
24 accuracy ($\beta=0.05$, $SE=0.01$, $p<.001$), but not information processing speed. After adjusting

1 for covariates, significant total effects remained for immediate memory ($\beta=-0.05$, $SE=0.01$,
2 $p=.001$), delayed memory ($\beta=-0.05$, $SE=0.01$, $p<.001$), and information processing accuracy
3 ($\beta=0.04$, $SE=0.01$, $p=.01$), but not for verbal fluency or information processing speed (Table
4 2; Figure 1). The adjusted model conducted on the imputed sample revealed significant total
5 effects of accumulating affective symptoms on immediate memory ($\beta=-0.05$, $SE=0.01$,
6 $p<.001$), delayed memory ($\beta=-0.05$, $SE=0.01$, $p<.001$), verbal fluency ($\beta=-0.04$, $SE=0.01$,
7 $p=.003$) and information processing accuracy ($\beta=0.04$, $SE=0.01$, $p=.01$), but not on
8 information processing speed (Table 2; Figure 1).

9 **Research question 2: Common cause model**

10 Next, a model was run using cardiometabolic risk score at age 44 as a predictor of affective
11 symptoms and cognitive function at age 50 to test cardiometabolic risk as a potential common
12 cause. The model fit the data well ($N=3847$; $\chi^2(18)=34.27$, $p=.01$; $CFI=1.00$; $TLI=0.99$;
13 $RMSEA=0.02$). Fully adjusted models revealed that cardiometabolic risk significantly
14 predicted immediate memory ($\beta=-0.04$, $SE=0.02$, $p=.008$), but not other cognitive outcomes.
15 Additionally cardiometabolic risk did not significantly predict affective symptoms at age 50
16 ($\beta=0.002$, $SE=0.01$, $p=.90$) (Table 3). The adjusted model conducted on the imputed sample
17 fit to the data well ($N=5288$; $\chi^2(18)=36.23$, $p=.007$; $CFI=1.00$; $TLI=0.99$; $RMSEA=0.01$).
18 The analysis on imputed data revealed that cardiometabolic risk score at age 44 was
19 significantly associated with poorer scores of immediate memory ($\beta=-0.04$, $SE=0.02$,
20 $p=.003$), delayed memory ($\beta=-0.03$, $SE=0.02$, $p=.048$), and verbal fluency ($\beta=-0.03$,
21 $SE=0.02$, $p=.03$) at age 50. However, cardiometabolic risk at age 44 was not significantly
22 associated with affective symptoms at age 50 ($\beta=0.02$, $SE=0.01$, $p=.24$) (Table 3).

23 **Supplementary analysis**

1 The model including nine individual biomarkers as predictors fit the data well (N=6405;
2 $\chi^2(12)=33.29, p<.001$; CFI=1.00; TLI=0.99; RMSEA=0.02). In fully adjusted models
3 including all covariates and individual cardiometabolic biomarkers, there were no significant
4 direct effects of accumulating affective symptoms on cognitive outcomes. There was a
5 significant indirect path between accumulating affective symptoms and delayed memory
6 through fibrinogen ($\beta=-0.003, SE=0.001, p=.03$), accounting for 6% of the total effect. All
7 other indirect paths were not significant at the 5% level in adjusted models. There were
8 significant total effects of accumulating affective symptoms on immediate memory ($\beta=-0.05,$
9 $SE=0.01, p=.001$), delayed memory ($\beta=-0.05, SE=0.01, p<.001$), and information processing
10 accuracy ($\beta=0.04, SE=0.01, p=.01$), but not for verbal fluency or information processing
11 speed (Supplementary Table 3).

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

16

17

1 **DISCUSSION**

2 **Summary of findings**

3 Results across models using two missing data methods (FIML and multiple imputation) both
4 revealed significant indirect associations between accumulation of affective symptoms and
5 immediate memory through a composite cardiometabolic risk score. Additionally, models
6 using multiple imputation revealed significant indirect associations on delayed memory and
7 verbal fluency. Additional associations may have been revealed in the model using imputed
8 data due to extra power associated with increasing the sample size. There were no significant
9 indirect paths observed between symptoms and other cognitive domains (information
10 processing). These results build on previous research which show associations between affect
11 and cardiometabolic risk, and also between cardiometabolic risk and cognitive outcomes
12 (7,23) but had not investigated the role cardiometabolic risk might play in the known
13 relationship between affect and later cognition. These results do not support the common
14 cause hypothesis that cardiometabolic risk may precede both development of affective
15 symptoms and cognitive dysfunction, because in this data cardiometabolic risk score did not
16 predict subsequent level of affective symptoms.

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

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

7 **Strengths and limitations**

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

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

16 **Future research and implications**

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

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

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

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

11

12

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

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REQUIRED STATEMENTS

Declaration of interest: None

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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.

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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)	-

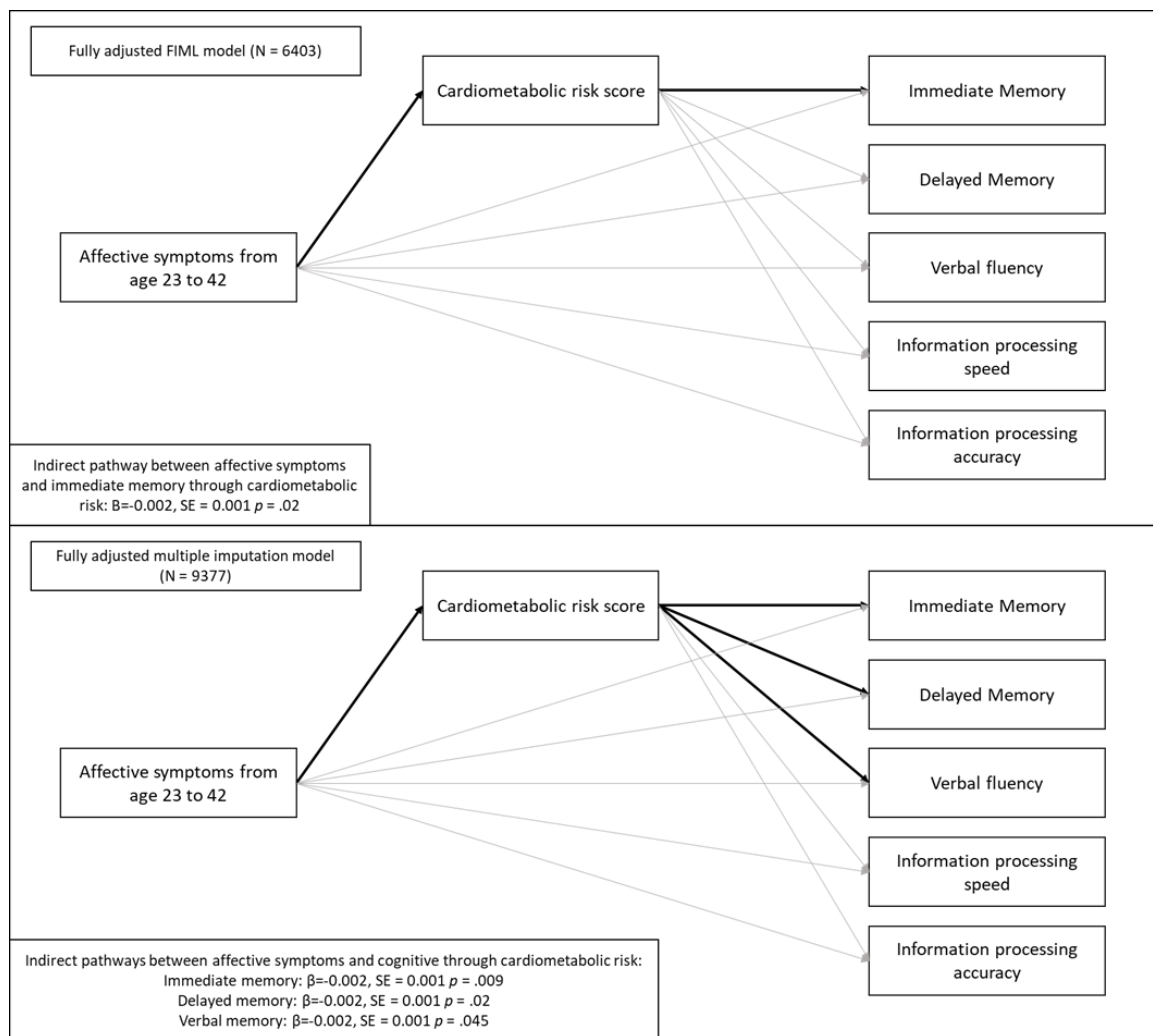
Table 2: Adjusted models testing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, via cardiometabolic risk.

	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; X ² (18)=34.27, p=.01; CFI=1.00; TLI=0.99; RMSEA=0.02	Model using multiple imputation N=5288; X ² (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*.