**SUPPLEMENTARY MATERIAL**

**Relative Associations of Behavioural and Physiological Risks for Cardiometabolic Disease with Cognition in Bipolar Disorder During Mid and Later-life: Findings from the UK Biobank**

Elysha Ringin, David W Dunstan, Denny Meyer, Roger S McIntyre, Neville Owen, Michael Berk, Mats Hallgren, Susan L Rossell, and Tamsyn E Van Rheenen.

**Table of Contents**

[**Supplementary Methods** 2](#_Toc149733158)

[**Supplementary Appendices** 5](#_Toc149733159)

[**Appendix S1.** Excluded neurological conditions. 5](#_Toc149733160)

[**Supplementary Tables** 6](#_Toc149733161)

[**Table S1.** Associations of the categorical covariates with global cognition 6](#_Toc149733162)

[**Table S2**. Association of continuous covariates (SES) with global cognition 8](#_Toc149733163)

[**Table S3.**  Health risk behaviours regression model for global cognition 9](#_Toc149733164)

[**Table S4.** Anthropometric and clinical risk factors (physiological risk) regression for global cognition 10](#_Toc149733165)

[**Table S5.** Cardiometabolic disease risk biomarkers (physiological risk) regression for global cognition 11](#_Toc149733166)

[**Supplementary Figures** 12](#_Toc149733167)

[**Figure S1.** Effects (bootstrapped standard error in parenthesis) for mediation examining how waist circumference was associated with global cognition 12](file:///C%3A%5CUsers%5Celysh%5CDocuments%5CUnimelb%5CPhD%5CPredictors%20paper%20%284%29%5CCurrent%20drafts%5CFinal%5CBipolar%20Disorders%5CRingin_CMRF%20supplementary%201.11%20mediation.docx#_Toc149733168)

# **Supplementary Methods**

**Full details of cardiometabolic disease risk factors and covariates**

Covariates

Sex, educational level, socio-economic status (SES) - measured by the Townsend Deprivation Index, medication use, and BD subtype (BD I versus BD II) were collected from questionnaires completed during baseline assessments. Educational level was dichotomised into attending or not attending university/college. Medication use was reported to trained research nurses during the verbal interview. In the current study, participants were dichotomised according to whether or not they were taking classes of psychotropic medication (i.e., mood stabilisers, antidepressants, first-generation antipsychotics, second-generation antipsychotics, and sedatives/hypnotics), cholesterol-lowering medication, or hypertensive medication.

Health risk behaviours

*Sedentary Behaviour*

Participants were asked to self-report their hours spent per day in different sedentary behaviours; TV viewing was used a measure of mentally-passive sedentary behaviour, and computer use as a measure of mentally-active sedentary behaviour. Responses of “less than an hour per day” were coded as 0.5 and participants who reported greater than 16 hours per day (indicating implausible levels of sedentary behaviour) of total sedentary behaviour (TV viewing, computer use, and driving) were excluded.

*Physical Activity*

Physical activity was measured using adapted questions from the International Physical Activity Questionnaire (IPAQ) short form. Participants were categorised into low, moderate, and high physical activity groups based on IPAQ data processing guidelines (detailed below). For the purpose of this analyses reported here, participants in the low and moderate groups were grouped together, given evidence from our group of no significant difference in cognitive function between these groups (Ringin et al., 2023).

The below categorisations of physical activity are taken from the IPAQ short-form scoring guidelines.

*Category 1: Low*

Those who do not meet criteria for moderate or high levels of physical activity are included in this group.

*Category 2: Moderate*

Those categorised as completing moderate physical activity must meet one of the following criteria:

a) 3 or more days of vigorous-intensity activity of at least 20 minutes per day

**OR**

b) 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day

**OR**

c) 5 or more days of any combination of walking, moderate-intensity or vigorous activities achieving a minimum Total physical activity of at last 600 MET-minutes per week.

*Category 3: High*

Those categorised as completing high physical activity must meet one of the following criteria:

a) Vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes per week

**OR**

b) 7 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes per week.

*Smoking status*

Participants were dichotomised into current smokers and non-smokers. As this categorisation refers to *current* smoking, past smokers were classed as non-smokers.

*Sleep duration*

Participants were asked to self-report the average number of hours sleep they get in a 24-hour period, including naps. For those whose sleeping time varies a lot, participants were asked to average the time over the past 4 weeks. Answers below 1 and above 23 were rejected, and answers below 3 and above 12 prompted a confirmation from the participant. For the current analyses, sleep duration was dichotomised to reflect adequate sleep (6 – 9 hours) and inadequate sleep (<6 or >9 hours).

Anthropometric and clinical risk factors

*Blood pressure*

Systolic and diastolic blood pressure were measured using an automated monitor (Omron 705). The mean of two measurements is reported.

*Adiposity measures*

Waist circumference measurements were recorded by an on-site research assistant using a Wessex non-stretchable sprung tape during the physical health assessments, as detailed elsewhere (*UK Biobank: Protocol for a large-scale prospective epidemiological resource*, 2007). Body composition measurements were obtained with a Tanita BC-418 MA body composition analyser. Whole-body fat mass and whole-body fat free mass were used to calculate Fat Mass Index (FMI), and Fat Free Mass Index (FFMI), by dividing the respective values by height (in meters) squared.

*Hand-grip strength*

Handgrip strength was measured at the UK Biobank assessment centres using a Jamar J00105 hydraulic hand dynamometer. Measurements were taken by a trained research assistant, in line with standard procedures (Roberts et al., 2011). Participants were seated, with their forearm on an armrest. After selecting the most comfortable of 5 possible handgrip positions, a single score was obtained for each hand which indicated greatest strength. The score from participants self-reported dominant hand was used in the analyses. If handedness was not specified, the highest scoring value was used.

Cardiometabolic disease risk markers

Five biomarkers were analysed: C-reactive protein (CRP), haemoglobin A1c (HbA1c), LDL cholesterol, HDL cholesterol, and triglycerides. Details on serum sample handling and protocol in the UK Biobank have been described previously (Elliott & Peakman, 2008). Serum CRP and lipid traits; LDL cholesterol, HDL cholesterol and triglycerides were measured by immunoturbidimetric analysis on a Beckman automated haematology analyser. HbA1c was measured by high performance liquid chromatography on a Bio-Rad VARIANT II Turbo. Quality control was performed by UKB using standardised laboratory procedures (UK Biobank, 2019).CRP was measured in mg/L, HbA1c in mmol/mol, and cholesterol (both LDL and HDL) and triglycerides in mmol/L. CRP was dichotomised into normal (<5mg/L) (=0) and elevated (≥ 5mg/L) (=1) levels as per the standard reference range provided by the Royal College of Pathologists in Australasia (The Royal College of Pathologists of Australasia, 2019). HbA1c was dichotomised into normal (<39mmol/mol), elevated (>39mmol/mol), in line with reference ranges from the American Diabetes Association and the International Diabetes Federation (International Diabetes Federation, 2021). Lipids were dichotomised into normal (=0) and abnormal (=1) levels, in line with the Australian Institute for Health and Welfare (Australian Institute of Health and Welfare, 2017): LDL cholesterol ≥ 3.5mmol/L; HDL cholesterol <1.00mmol/L for men, <1.3mmol/L for women; triglycerides ≥ 2mmol/L.

**Full details of Cognitive Assessment**

Cognitive functioning was assessed through a brief computerised battery. The current study utilised the measurement of four cognitive domains, listed below. UKB test name in brackets.

1. Visuospatial memory (pairs matching): participants were shown 6 sets of symbol cards for five seconds, which were then turned face down, and asked to remember as many matching pairs as possible in the fewest tries. The outcome of interest was the number of errors made. Higher scores indicate worse performance.
2. Processing speed (reaction time): participants viewed pairs of cards with symbols on them and pressed a button when the cards matched. Participants were instructed to hit the button as quicky as possible with their dominant hand. Twelve pairs were presented in total. The outcome of interest was the mean response time (milliseconds), derived from all trials in which there was a matching pair. Higher scores indicate worse performance.
3. Fluid intelligence (reasoning): participants were asked to solve thirteen numeric and verbal logic problems in two minutes and select the correct answer from an array of prespecified options. These questions were designed to assess logic and reasoning ability, independent of acquired knowledge. The outcome of interest was the number of correct problems solved. Any questions not attempted in the two minutes were scored as zero. Higher scores indicate better performance.
4. Prospective memory: participants were given an instruction during the early stage of the cognitive testing, which they were asked to act on after a delay/distraction period (completion of other cognitive tests described above). The outcome of interest was a dichotomous measure stating whether participants acted correctly or incorrectly in response to the instruction.

**Full details of physical activity and sleep variables included in post-hoc mediation models**

As PROCESS only allows inclusion of continuous mediators, comparable continuous physcial activity and sleep variables were included in the mediation model in place of the categorical variables included in the primary models. Sumed MET minutes of activity per week was used as a physical activity measure. To capture the U-shaped relationship between sleep duration and cognition, sleep duration was recoded with optimal duration (7 hours) as 0, and every hour above and below this as 1 score higher (i.e., 6 or 8 hours = 1, 5 or 9 hours = 2), resulting in a score from 0 – 6. This rescoring was based on a UK Biobank study which demonstrated that seven hours of sleep per day was associated with the highest cognitive performance which decreased for every hour below and above this sleep duration (Tai, Chen, Manohar, & Husain, 2022).

# **Supplementary Appendices**

**Appendix S1.** Excluded neurological conditions. Self-reported by participants; from data fields 6150, 20001 and 20002.

- Brain cancer/primary malignant tumour

- Brain haemorrhage

- Brain/intracranial abscess

- Cerebral aneurysm

- Cerebral palsy

- Chronic/degenerative neurological problem

- Dementia/Alzheimer's disease/cognitive impairment

- Encephalitis

- Epilepsy

- Head injury

- Infection of nervous system

- Ischaemic stroke

- Meningeal cancer/malignant meningioma

- Meningioma (benign)

- Meningitis

- Motor neurone disease

- Multiple sclerosis

- Neurological injury/trauma

- Neuroma (benign)

- Other demyelinating condition

- Other neurological problem

- Parkinson's disease

- Spina bifida

- Stroke

- Subarachnoid haemorrhage

- Subdural haematoma

- Transient ischaemic attack

# **Supplementary Tables**

| **Table S1.** Associations of the categorical covariates with global cognition |
| --- |
| **Domain** | **Comparisonsa** | **Group** | **M** | **SD** | **db** |
| Sex | **F (1,976) = 9.60, p = 0.002\*** | FemaleMale | -0.93-0.56 | 7.438.10 | 0.05 |
| Educational level | **F (1,976) = 23.93, p < 0.001\*** | No universityUniversity  | -1.03-0.45 | 8.576.88 | 0.08 |
| BD subtype  | F (1,976) = 1.34, p = 0.248 | BD IBD II | -0.67-0.82 | 7.398.15 | -0.02 |
| Mood stabilisers  | F (1,976) = 0.80, p = 0.371 | NUU | -0.65-0.83 | 10.513.92 | -0.02 |
| Antidepressants | F (1,976) = 1.86, p = 0.173 | NUU | -0.64-0.85 | 9.884.87 | -0.03 |
| First-generation antipsychotics | F (1,976) = 0.08, p = 0.772 | NUU | -0.82-0.67 | 7.402.02 | 0.03 |
| Second-generation antipsychotics | F (1,976) = 4.17, p = 0.041\* | NUU | -0.45-1.03 | 10.322.89 | -0.08 |
| Sedatives/hypnotics | F (1,976) = 2.46, p = 0.117 | NUU | -0.47-1.02 | 9.842.43 | -0.08 |
| Cholesterol-lowering medication | **F (1,976) = 11.73, p < 0.001\*** | NUU | -0.43-1.05 | 10.174.71 | -0.08 |
| Hypertension medication  | F (1,976) = 1.34, p = 0.248 | NUU | -0.65-0.84 | 9.994.85 | -0.02 |
| Diabetes medication | F (1,976) = 0.001, p = 0.971 | NUU | -0.74-0.75 | 9.952.84 | 0.00 |

NU = Non-users, U = users. An \* indicates significance at p < .05 *before* Benjamini-Hochberg FDR correction for multiple comparisons, and **bolded** values indicate significance *after* Benjamini-Hochberg FDR correction for multiple comparisons.

aResults reported reflect raw values unadjusted for multiple comparisons. \*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons.

bd = Cohen’s d effect sizes.

|  |
| --- |
| **Table S2**. Association of continuous covariates (SES) with global cognition |
|  | **Ba** | **SD** | **B(standardised)b** | **p-value** | **LCIc** | **UCId** |
| SES | -0.10 | 0.02 | -0.1 | <0.001\* | -0.13 | -0.06 |

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons.

a Unstandardised regression coefficient

b Standardised regression coefficient

c 95% confidence interval lower limit

d 95% confidence interval upper limit

|  |
| --- |
| **Table S3.**  Health risk behaviours regression model for global cognition |
|  | **Variable** (category coded as 1) | **Ba** | **SE** | **B(standardised)b** | **p-value**  | **LCIc** | **UCId** |
| *Covariates* | Sex (female) | 0.28 | 0.12 | 0.07 | 0.018\* | 0.05 | 0.51 |
|  | SES  | -0.07 | 0.02 | -0.12 | <0.001\* | -0.11 | -0.04 |
|  | Educational level (attended university) |  0.37 | 0.12 |  0.10 | 0.003\* | 0.13 |  0.61 |
| *Health-risk behaviours* | Mentally-passive sedentary behaviour, hours/day | -0.10 | 0.03 | -0.10 | 0.003\* | -0.16 | -0.03 |
|  | Mentally-active sedentary behaviour, hours/day |  0.12 | 0.03 |  0.11 | <0.001\* | 0.05 |  0.18 |
|  | Physical activity (high physical activity) | -0.40 | 0.12 | -0.10 | <0.001\* | -0.62 | -0.16 |
|  | Smoking status (smoker) | -0.16 | 0.14 | -0.04 | 0.268 | -0.44 | 0.12 |
|  | Sleep duration (6-9 hours) | -0.54 | 0.18 | -0.09 | 0.002\* | -0.88 |  -0.19 |

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1;

Physical activity, low-moderate activity=0, high activity=1; smoking status, non-smoker=0, smoker=1; sleep duration, <6 or >9=0, 6-9=1

a Unstandardised regression coefficient

b Standardised regression coefficient

c 95% confidence interval lower limit

d 95% confidence interval upper limit

|  |
| --- |
| **Table S4.** Anthropometric and clinical risk factors (physiological risk) regression for global cognition  |
|  | **Variable** (category coded as 1) | **Ba** | **SE** | **B(standardised)b** | **p-value**  | **LCIc** | **UCId** |
| *Covariates* | Sex (female) | -0.05 | 0.29 | -0.01 | 0.871 | -0.62 | 0.53 |
|  | SES  | -0.08 | 0.02 | -0.14 | <0.001\* | -0.12 | -0.05 |
|  | Educational level (attended university) |  0.57 | 0.12 |  0.15 | <0.001\* | 0.34 | 0.80 |
| *Anthropometric and clinical risk factors* | Systolic blood pressure, mmHg | -0.02 | 0.01 | -0.21 | <0.001\* | -0.03 |  -0.01 |
|  | Diastolic blood pressure, mmHg | 0.03 | 0.01 | 0.16 | <0.001\* |  0.01 |  0.05 |
|  | Hand-grip strength, kg | 0.04 | 0.01 | 0.25 | <0.001\* | 0.03 | 0.06 |
|  | Waist circumference, cm | -0.03 | 0.01 | -0.19 | 0.011\* | -0.05 | -0.006 |
|  | Fat Mass Index, kg/m2 | 0.06 | 0.04 | 0.12 | 0.083 | -0.008 |  0.13 |
|  | Fat Free Mass Index, kg/m2 | 0.06 | 0.04 | 0.09 | 0.169 | 0.03 | 0.14 |

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1

a Unstandardised regression coefficient

b Standardised regression coefficient

c 95% confidence interval lower limit

d 95% confidence interval upper limit

|  |
| --- |
| **Table S5.** Cardiometabolic disease risk biomarkers (physiological risk) regression for global cognition  |
|  | **Variable** (category coded as 1) | **Ba** | **SE** | **B(standardised)b** | **p-value**  | **LCIc** | **UCId** |
| *Covariates* | Sex (female) | 0.37 | 0.13 | 0.10 | 0.005\* | 0.11 | 0.63 |
|  | SES  | -0.09 | 0.02 | -0.16 | <0.001\* | -0.13 | -0.06 |
|  | Educational level (attended university) |  0.47 | 0.13 |  0.12 | <0.001\* | 0.22 |  0.72 |
|  | Cholesterol-lowering medication (using medication) | -0.71 | 0.18 | -0.14 | <0.001\* | -1.07 | -0.36 |
| *Cardiometabolic disease risk biomarkers* | CRP (elevated) | -0.51 | 0.20 | -0.09 | 0.011\* | -0.91 | -0.12 |
|  | HbA1c (elevated) | 0.09 | 0.18 | 0.02 | 0.619 | -0.26 | 0.43 |
|  | HDL cholesterol (abnormal) | -0.14 | 0.16 | -0.03 | 0.375 | -0.46 |  0.17 |
|  | LDL cholesterol (abnormal) | 0.04 | 0.13 | 0.01 | 0.741 | -0.22 | 0.30 |
|  | Triglycerides (abnormal) | -0.22 | 0.14 | -0.05 | 0.136 | -0.50 |  0.07 |

\*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1;

 Cholesterol-lowering medication, not using medication=0, using medication=1; CRP, normal=0, elevated=1; HbA1c, normal=0, elevated=1; for all lipids, normal=0, abnormal=1

 a Unstandardised regression coefficient

 b Standardised regression coefficient

 c 95% confidence interval lower limit

 d 95% confidence interval upper limit

# **Supplementary Figures**



**Figure S1.** Effects (bootstrapped standard error in parenthesis) for mediation examining how waist circumference was associated with global cognition after controlling for sex, educational level, and SES. \*p <.05. Red lines indicate significant mediation pathways (range of CI did not span 0).

**References**

Australian Institute of Health and Welfare. (2017). Abnormal blood lipids (dyslipidaemia). Retrieved from Risk Factors to Health website: https://www.aihw.gov.au/reports/risk-factors/risk-factors-to-health/contents/abnormal-blood-lipids-dyslipidaemia

Elliott, P., & Peakman, T. C. (2008). The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *International Journal of Epidemiology*, *37*(2), 234–244. https://doi.org/10.1093/ije/dym276

International Diabetes Federation. (2021). *IDF Diabetes Altas (10th edition)*. Retrieved from https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF\_Atlas\_10th\_Edition\_2021.pdf

Ringin, E., Dunstan, D. W., McIntyre, R. S., Owen, N., Berk, M., Rossell, S. L., … Van Rheenen, T. E. (2023). Differential associations of mentally-active and passive sedentary behaviours and physical activity with putative cognitive decline in healthy individuals and those with bipolar disorder: Findings from the UK Biobank cohort. *Mental Health and Physical Activity*, *24*, 100514. https://doi.org/10.1016/j.mhpa.2023.100514

Roberts, H. C., Denison, H. J., Martin, H. J., Patel, H. P., Syddall, H., Cooper, C., & Sayer, A. A. (2011). A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and Ageing*, *40*(4), 423–429. https://doi.org/10.1093/ageing/afr051

Tai, X. Y., Chen, C., Manohar, S., & Husain, M. (2022). Impact of sleep duration on executive function and brain structure. *Communications Biology*, *5*(1), 1–10. https://doi.org/10.1038/s42003-022-03123-3

The Royal College of Pathologists of Australasia. (2019). C-Reactive Protein. Retrieved from https://www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests/C/C-Reactive-protein

*UK Biobank: Protocol for a large-scale prospective epidemiological resource*. (2007). Retrieved from ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf

UK Biobank. (2019). *Biomarker assay quality procedures: approaches used to minimise systematic and random errors (and the wider epidemiological implications)*.